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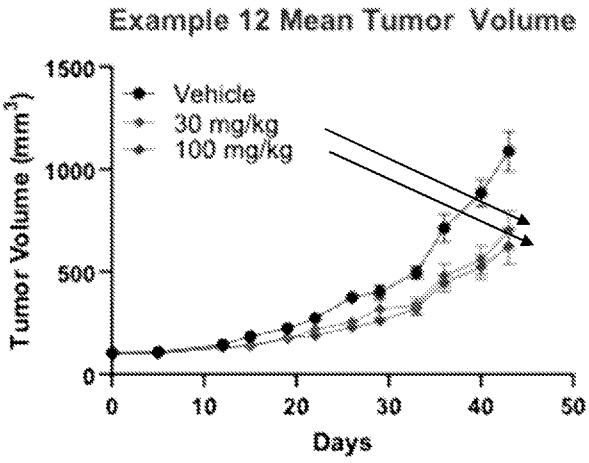
(54) Title: COMPOSITIONS COMPRISING USP1 INHIBITORS AND METHODS OF USING THE SAME

FIG. 1



(57) Abstract: The subject matter described herein relates to compositions comprising Ubiquitin- Specific Protease 1 (USP1) inhibitors and methods of using the same.

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COMPOSITIONS COMPRISING USP1 INHIBITORS AND METHODS OF USING THE SAME

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 63/610,860 filed December 15, 2023, the contents of which are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The subject matter described herein relates to compositions comprising Ubiquitin-Specific Protease 1 (USP1) inhibitors and methods of using the same.

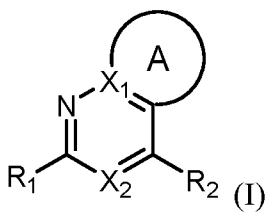
BACKGROUND

The USP1 gene encodes a deubiquitinase that is directly involved in DNA damage repair by regulating the ubiquitination of key regulators like PCNA and FANCD2. Overexpression of USP1 is commonly observed in osteosarcoma, colorectal, non-small cell lung, and gastric cancers, and blockade of USP1 induces apoptosis in many cancers. Moreover, several USP1 inhibitors sensitize cancer cells to platinum-, DNA-damaging-, and radiation-induced death. Given the well-established role USP1 as a selective anti-cancer target for inhibition, there remains a need in the art for new USP1 inhibitors for use in the treatment of such cancers.

SUMMARY OF THE INVENTION

In certain aspects, the compositions and methods described herein relate to compositions comprising USP1 inhibitors and methods of their use in treating disease, e.g., cancer.

In certain embodiments, the compositions and methods described herein relate to a compound of formula (I), or a pharmaceutically acceptable salt thereof:



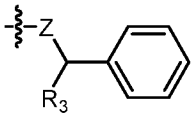
(I)

wherein:

R_1 is selected from C_3-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-OCD_3$, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, - COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

R_2 is selected from:



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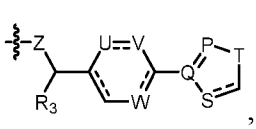

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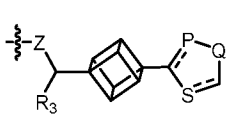
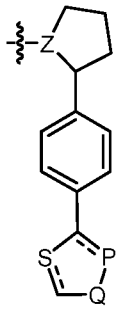
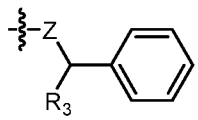


, and


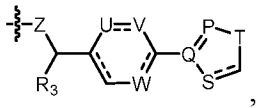
;

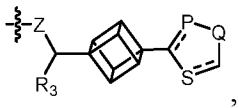
R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S;

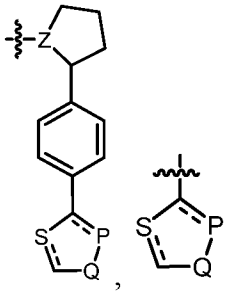
wherein Z, U, V, W, P, Q, S, and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is 

, the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is  , the 5- or 6-membered ring is saturated or unsaturated;

wherein when R_2 is  , the 5-membered ring is saturated or unsaturated;

wherein when R_2 is  , is saturated or unsaturated;

X_1 is selected from C and N;

X_2 is selected from C and N;

wherein when X_2 is C, the said C is optionally substituted with hydrogen, halogen, -CN, $-OR_4$, $-SR_4$, $-N(R_5)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, wherein R_4 and R_5 are independently selected from C_1-C_6 alkyl; and

Ring A is a C_6-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring;

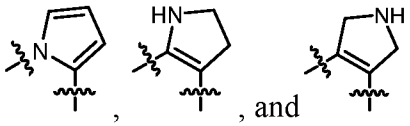
wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

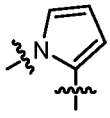
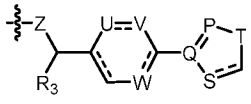
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

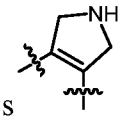
wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S;

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ;

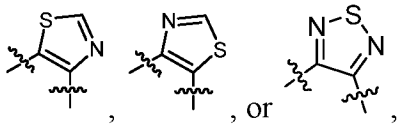
wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

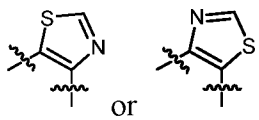
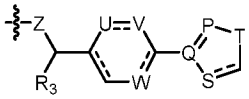
wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

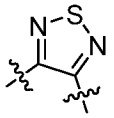
wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  , where Z is N;

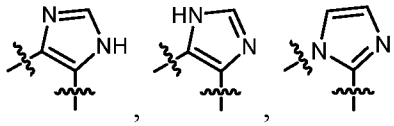
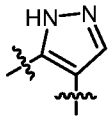
wherein when ring A is selected from  , Z is N, and R_2 is  where S and P are N, wherein:

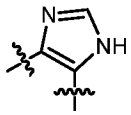
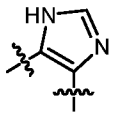
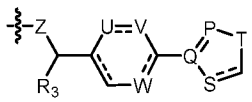
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

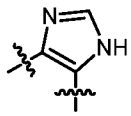
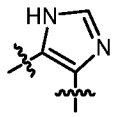
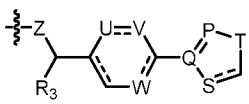
(ii) S or P are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

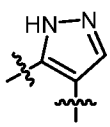
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring, 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

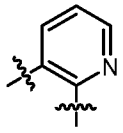
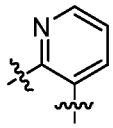
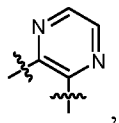
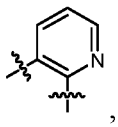
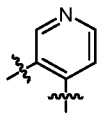
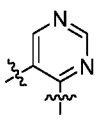
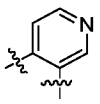
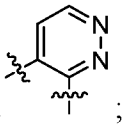
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  , and  ;

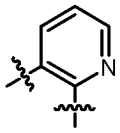
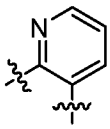
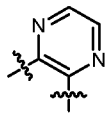
wherein when ring A is  or  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

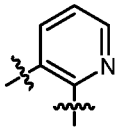
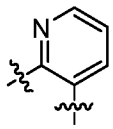
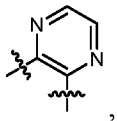
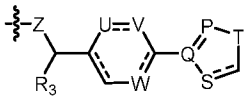
wherein when ring A is  or  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

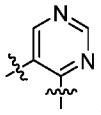
wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen,

C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ,  ,  ,  ,  ,  ,  , and  ;

wherein when ring A is  ,  or  , Z is O;

wherein when ring A is  ,  , or  , Z is O and R_2 is  , P and S are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

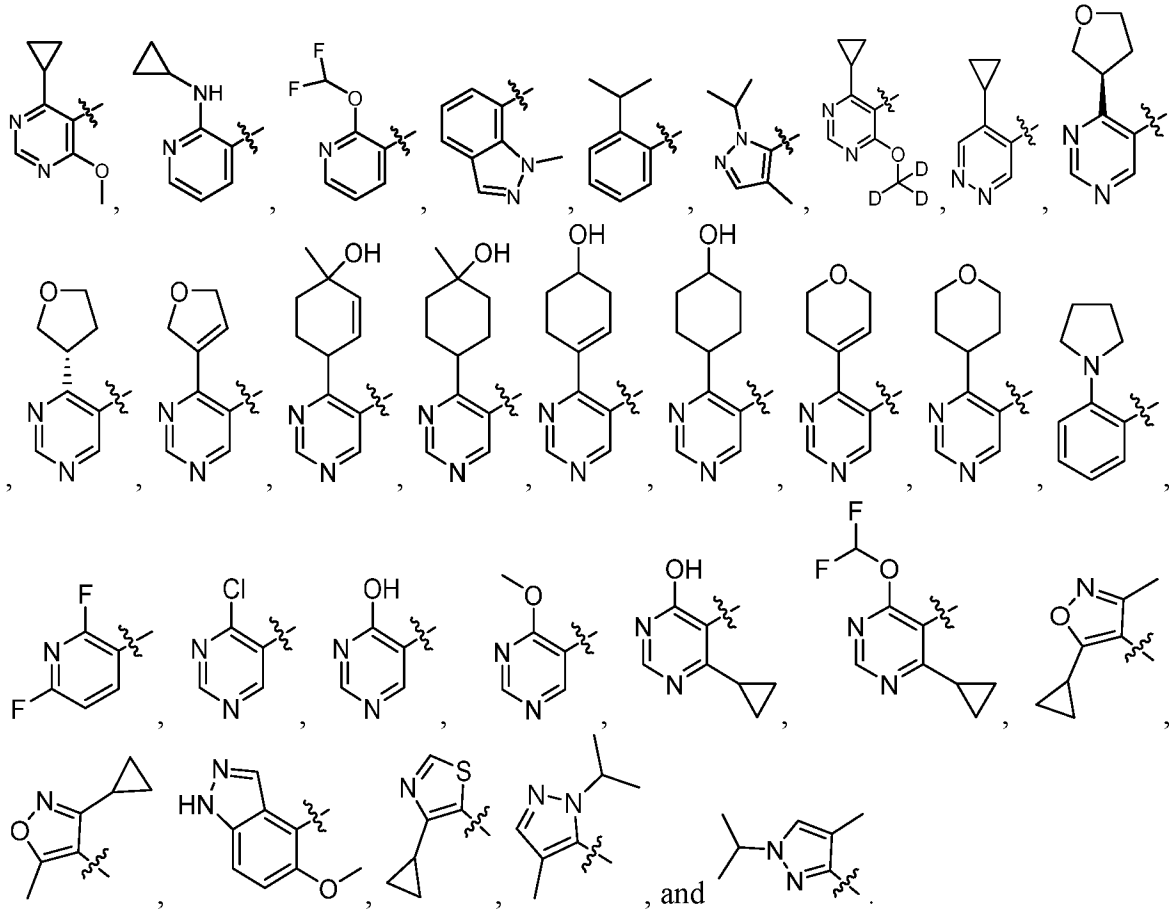
wherein when ring A is  , Z is N and ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_1 is selected from C_3-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; and wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-OCD_3$, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each

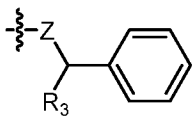
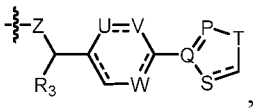
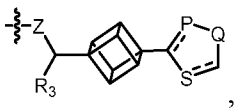
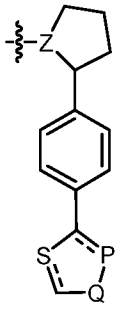
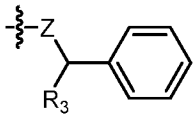
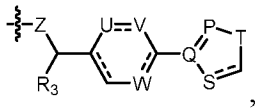
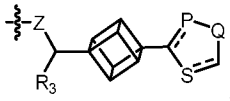
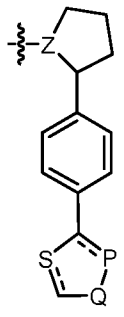
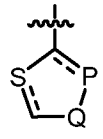
independently optionally substituted with one or more substituents selected from the group consisting of -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl.

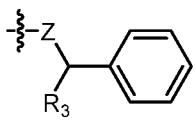
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_1 is selected from C_6 aryl, 5- or 6-memered heterocyclic ring and C_6 aryl fused with 5-membered heterocyclic group; and wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -OCD_3, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_1 is selected from:

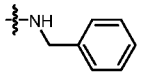
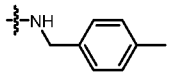
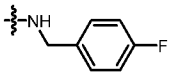


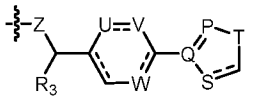
, and .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when R_2 is  ,  ,  , and  ; and R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S, wherein Z, U, V, W, P, Q, S, and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when R_2 is  , the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when R_2 is  , the 5- or 6-membered ring is saturated or unsaturated; wherein when R_2 is  , the 5-membered ring is saturated or unsaturated; wherein when R_2 is  , wherein  is saturated or unsaturated.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:wherein R_2 is  , Z is selected from C, O, N, and S; and R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-}

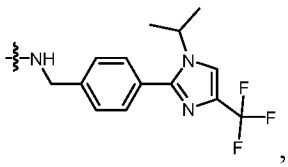
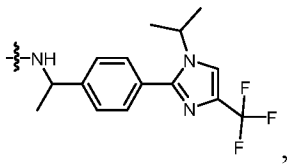
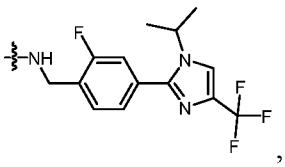
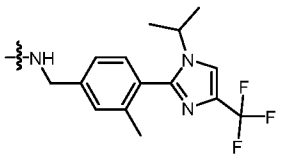
$_6$ alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; wherein the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

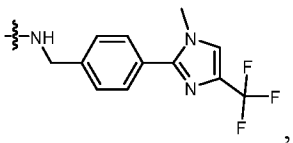
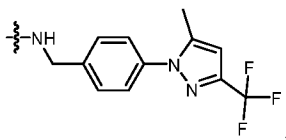
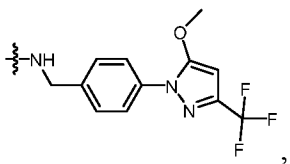
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:  ,  , and  .

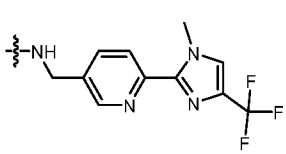
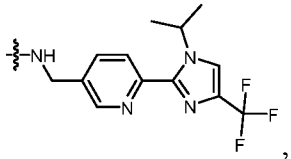
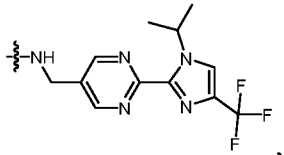
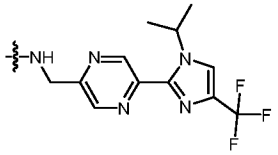
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  and the 5 or 6 membered ring is saturated or unsaturated; R_3 is selected from H, D, -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S; wherein Z, U, V, W, P, Q, S and T are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

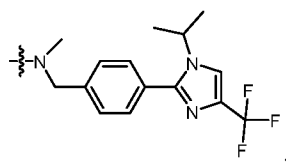
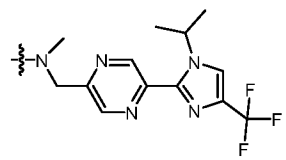
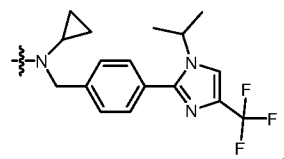
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

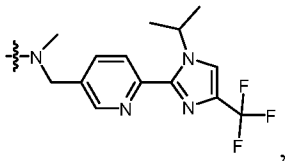
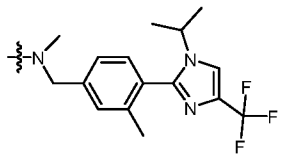
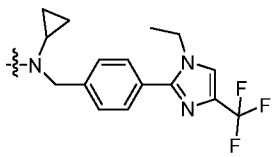
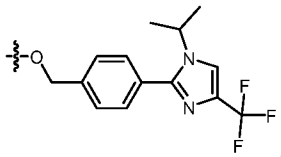
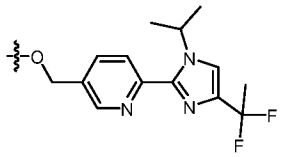
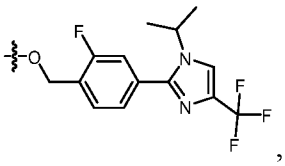
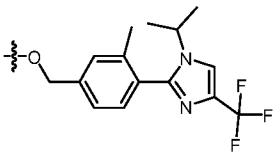
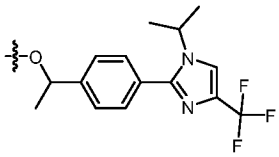
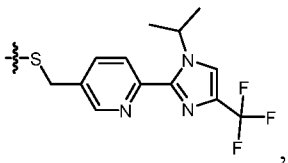
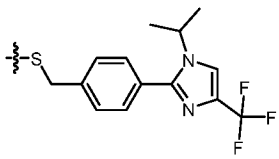
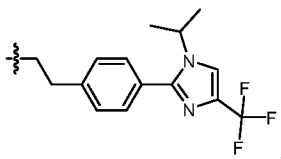
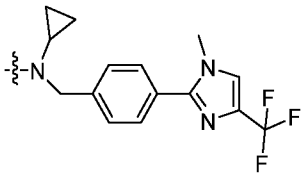
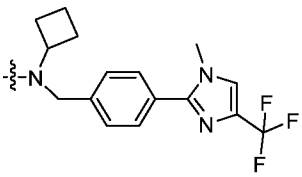
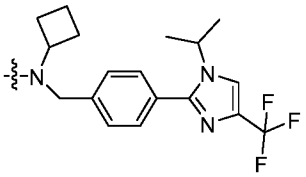
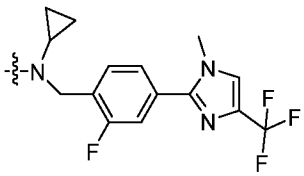
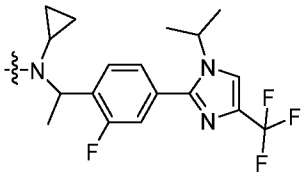
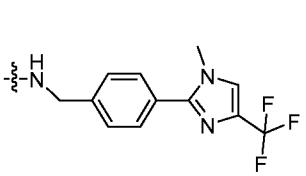
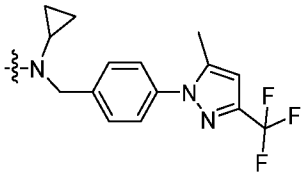
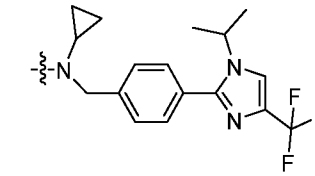
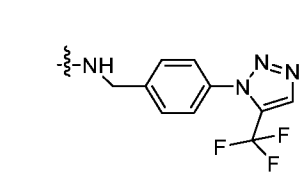
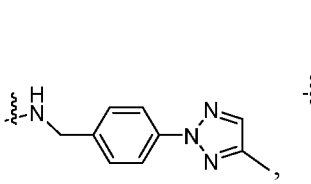
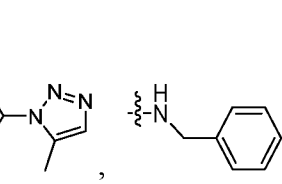
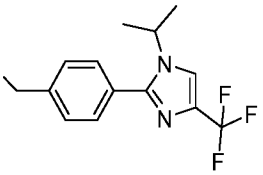
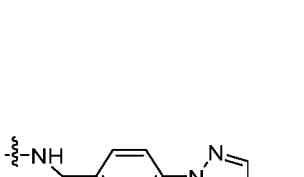
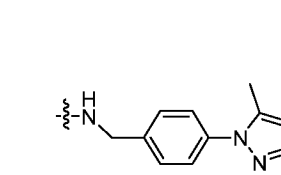
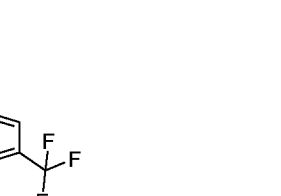
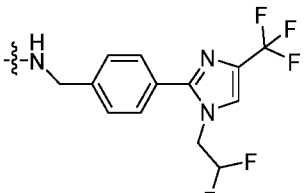
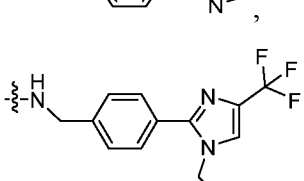
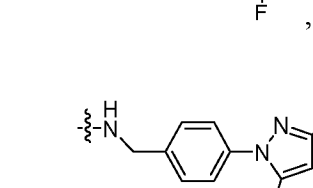
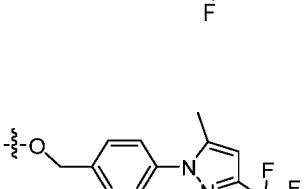
wherein R_2 is selected from:

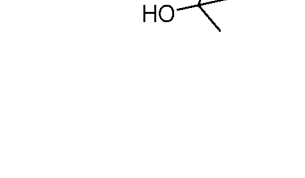
 ,  ,  ,  ,

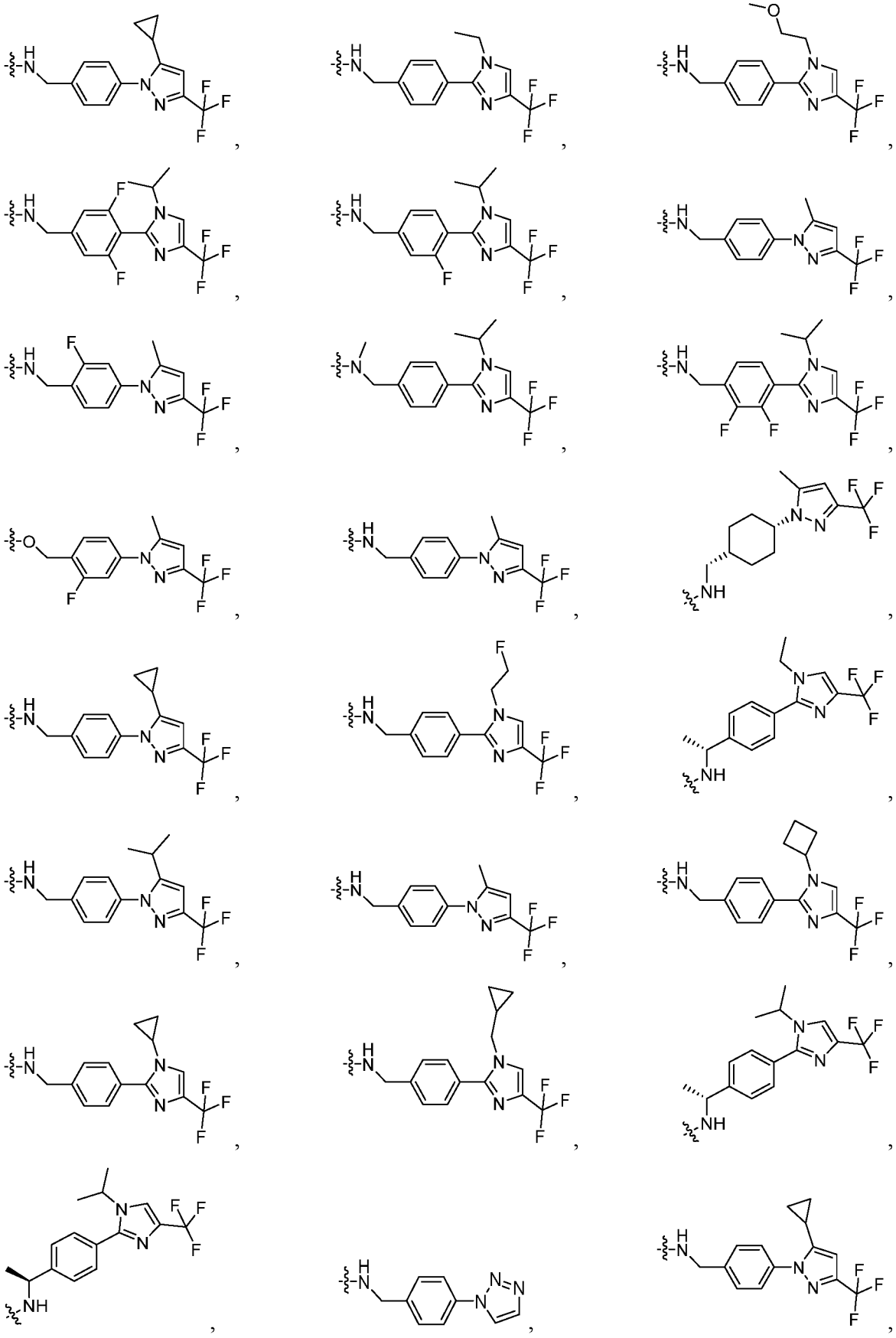
 ,  ,  ,

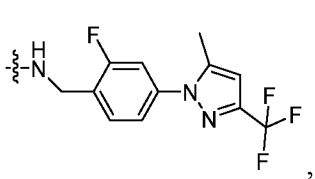
 ,  ,  ,  ,

 ,  ,  ,

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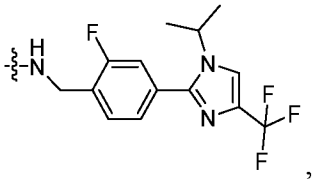
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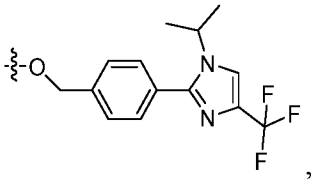
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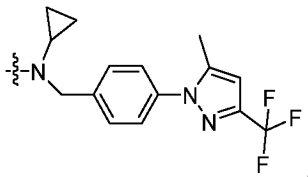
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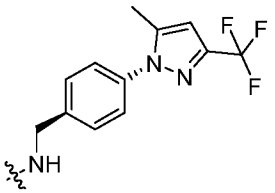
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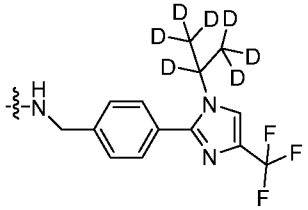
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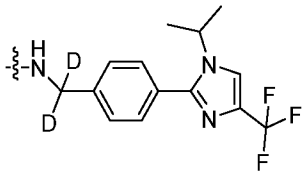
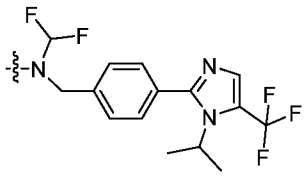
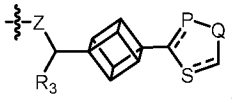
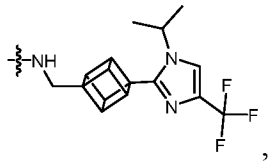

, and

.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  , and the 5-membered ring is saturated or unsaturated; R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and Z, P, Q, and S are independently selected from C, O, N, and S; wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from: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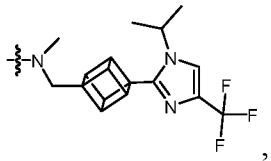
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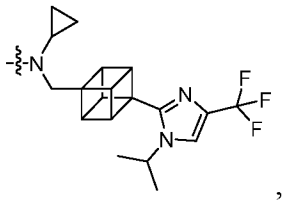
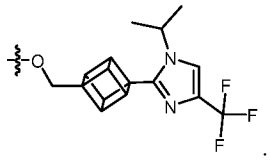
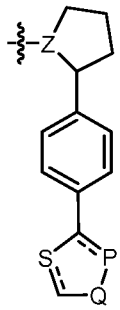
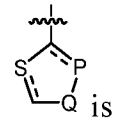
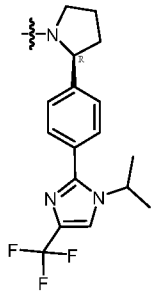

, and

.

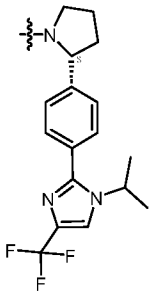
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  , and  is

saturated or unsaturated; Z, P, Q, and S are independently selected from C, O, N, and S, wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

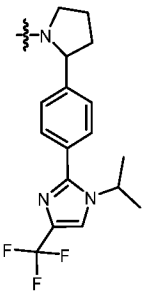
In certain embodiments, the present disclosure is directed to a compound of formula



(I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:



, and



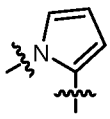
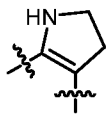
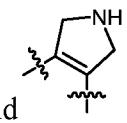
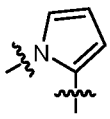
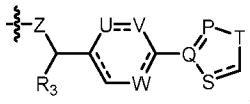
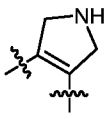
.

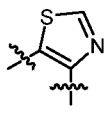
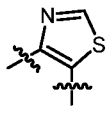
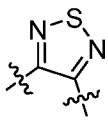
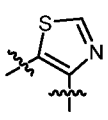
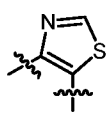
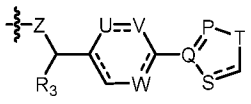
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein X_1 is selected from C and N.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein X_2 is selected from C and N; wherein when X_2 is C, the said C is optionally substituted with hydrogen, halogen, -CN, -OR_4, -SR_4, -$N(R_5)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, wherein R_4 and R_5 are independently selected from C_1-C_6 alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a C_6-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl,

C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

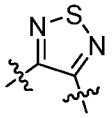
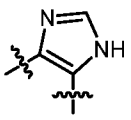
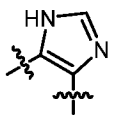
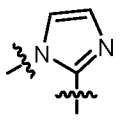
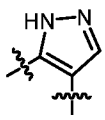
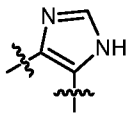
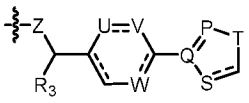
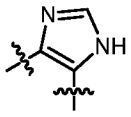
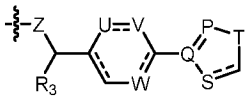
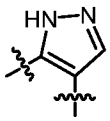
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ; wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

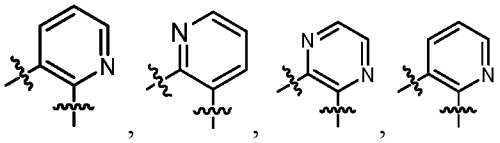
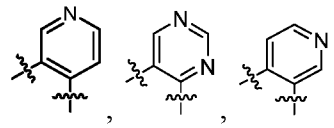
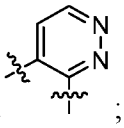
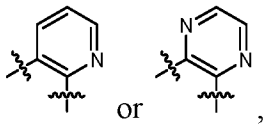
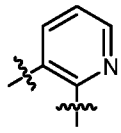
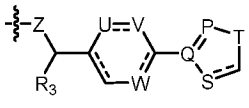
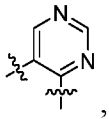
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N; wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

(ii) S or P are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

(iii) V or W are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

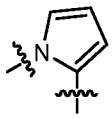
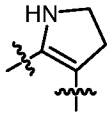
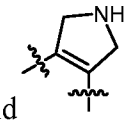
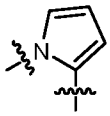
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  , and  ; wherein when ring A is  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is a 6-membered heterocyclyl ring and contains one or two

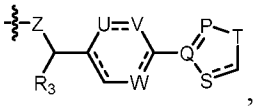
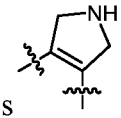
heteroatoms selected from N, ring A is selected from  ,  ,  ,  ; wherein when ring A is  or , Z is O; wherein when ring A is , Z is O and R_2 is  , P and S, are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is  , Z is N, ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

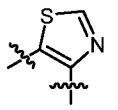
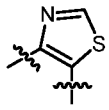
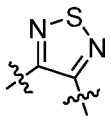
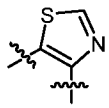
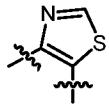
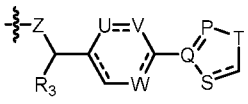
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a 5-membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide;

wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from

N, ring A is selected from  ,  , and  ; wherein when ring A is 

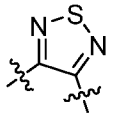
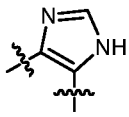
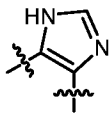
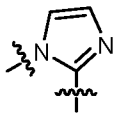
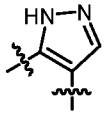
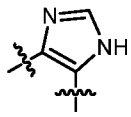
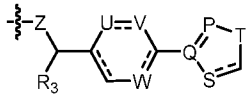
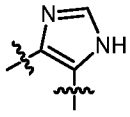
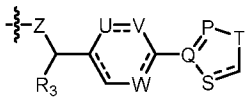
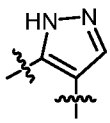
and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N; wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

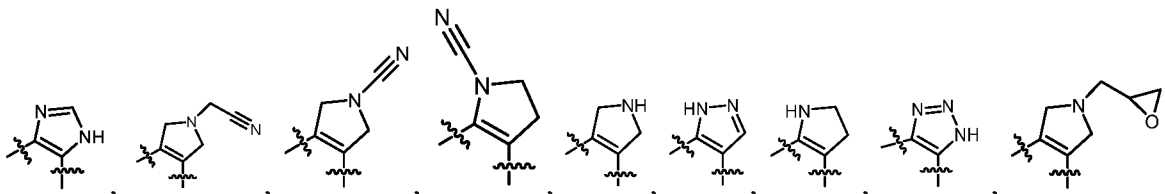
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

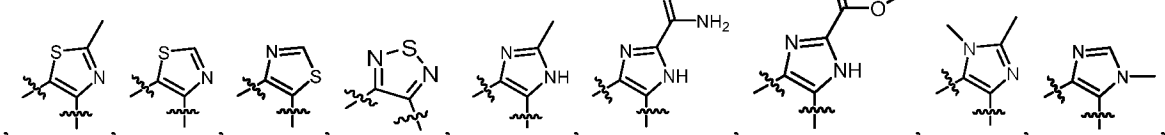
(ii) S or P are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

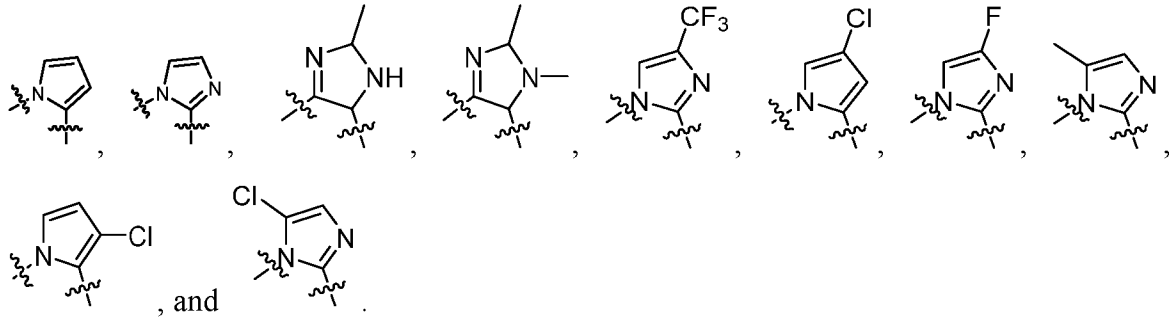
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

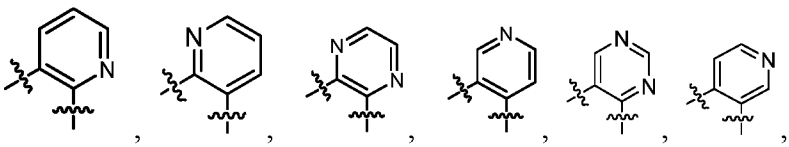
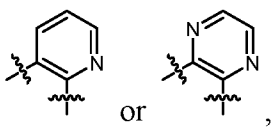
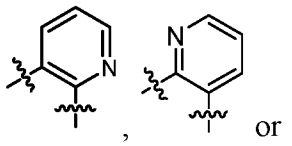
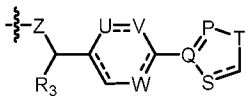
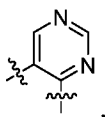
wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  , and  ; wherein when ring A is  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from:

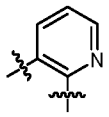
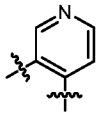
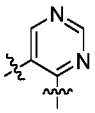
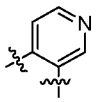
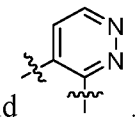




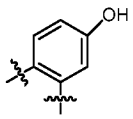


In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a 6-membered heterocyclyl ring, wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl; wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ; wherein when ring A is  , Z is O; wherein when ring A is  , Z is O and R_2 is  , P and S are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is  , Z is N and ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH,

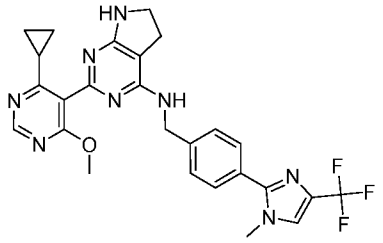
halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from:  ,  ,  ,  , and  .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a C_6-C_{10} aryl; wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is  .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein the compound is selected from: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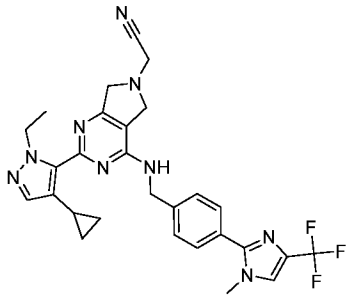
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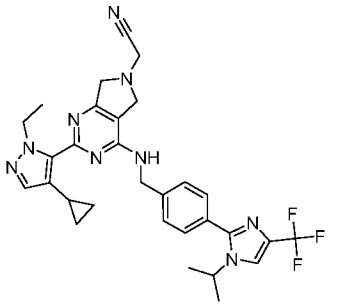
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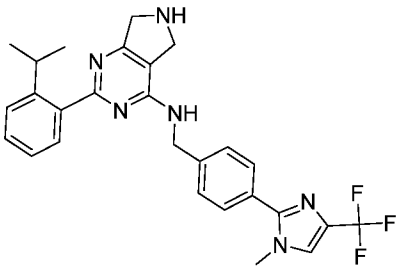
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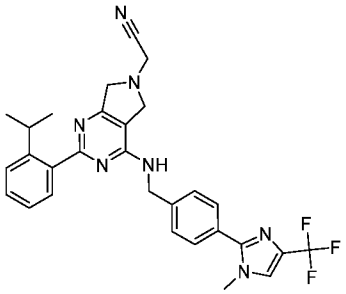
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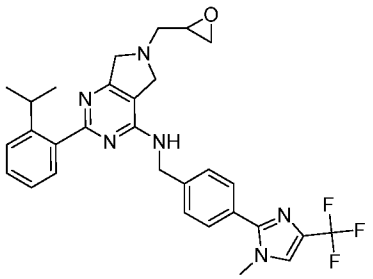
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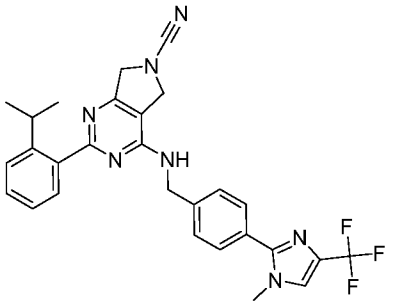
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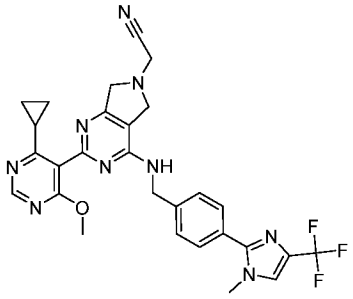
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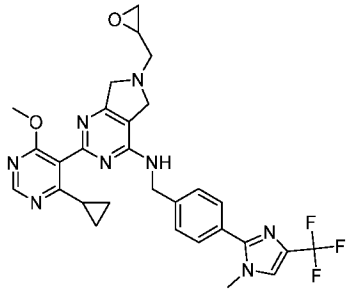
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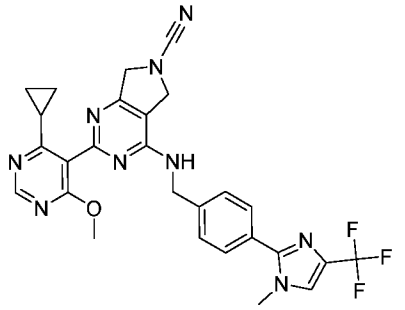
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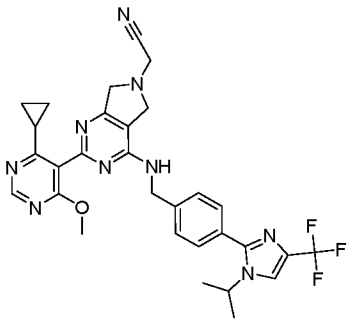
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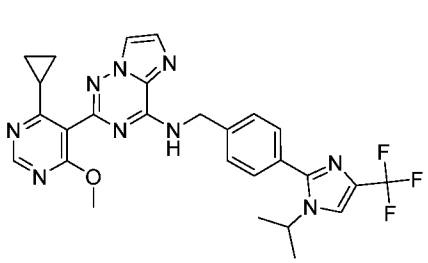
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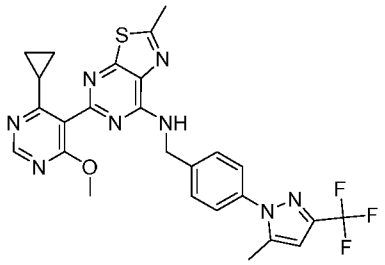
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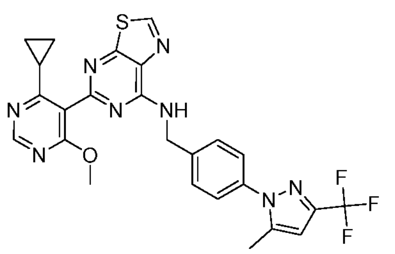
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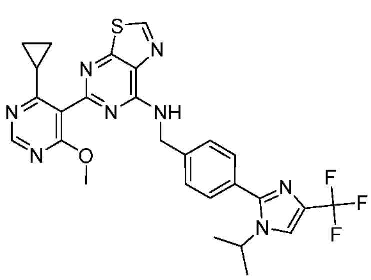
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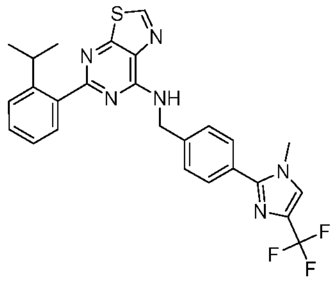
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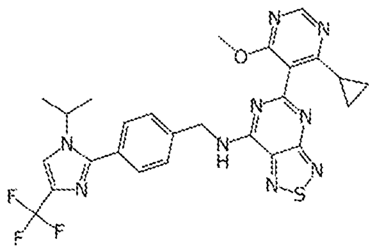
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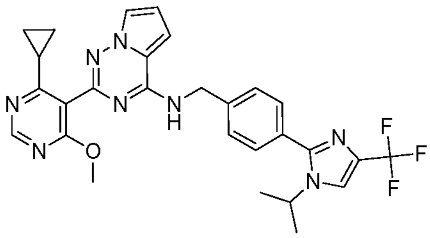
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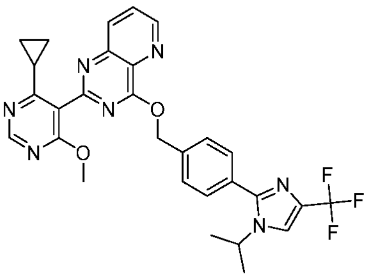
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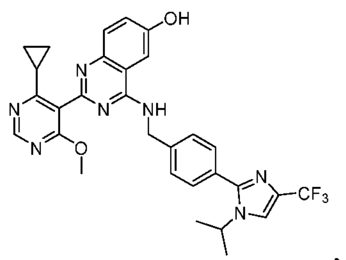
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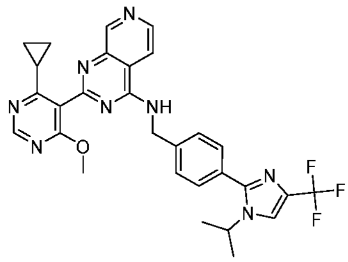
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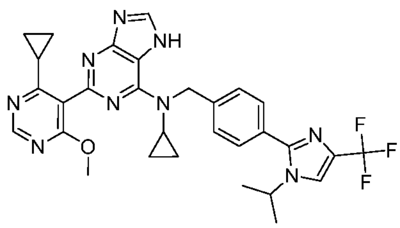
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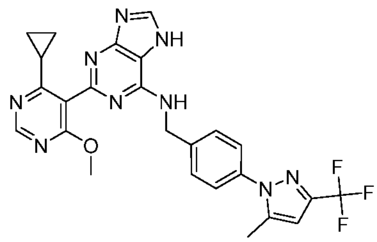
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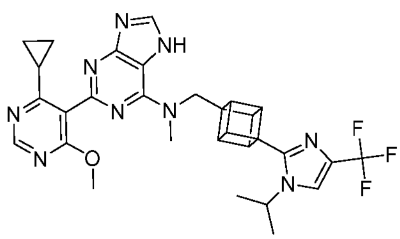
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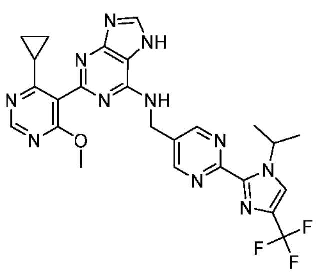
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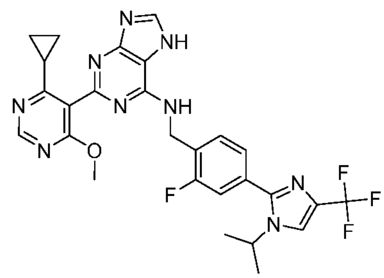
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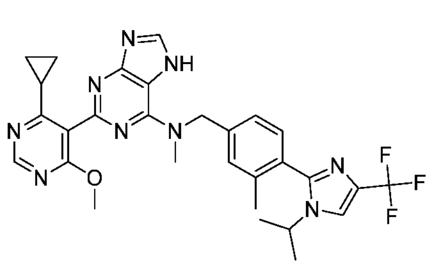
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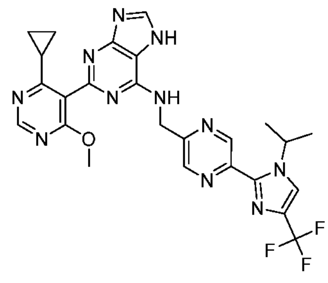
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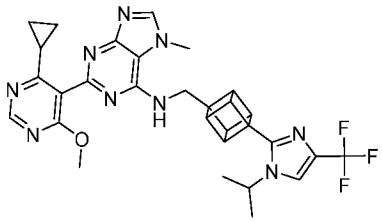
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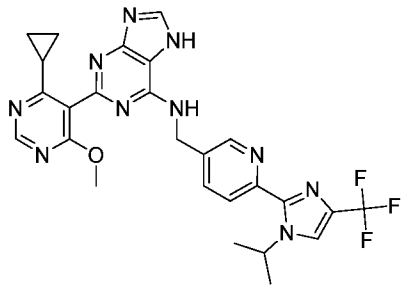
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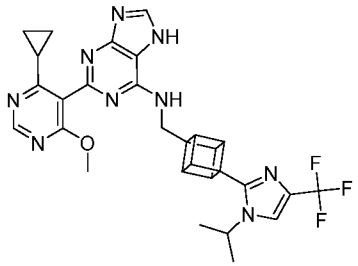
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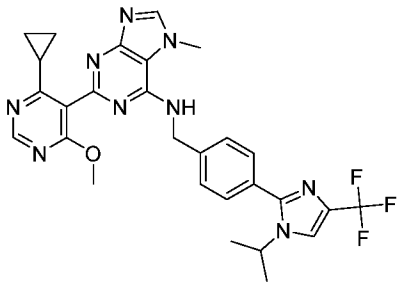
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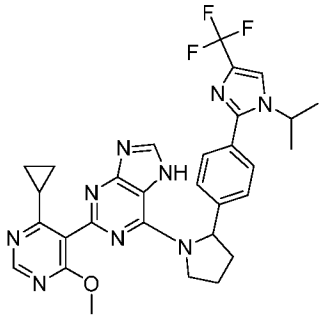
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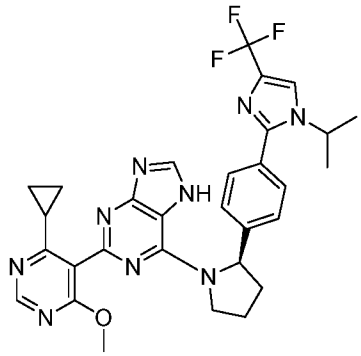
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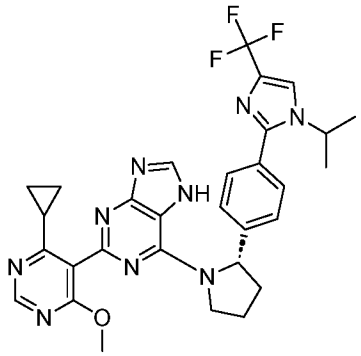
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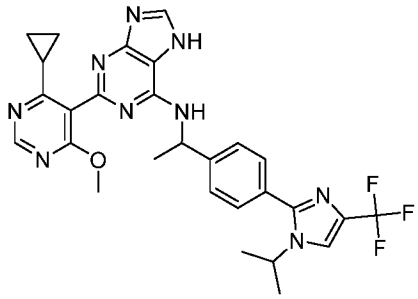
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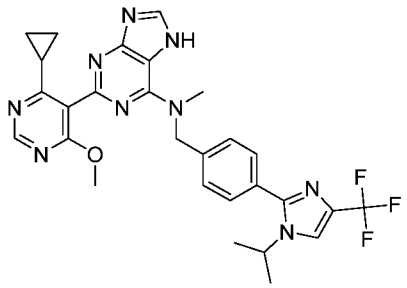
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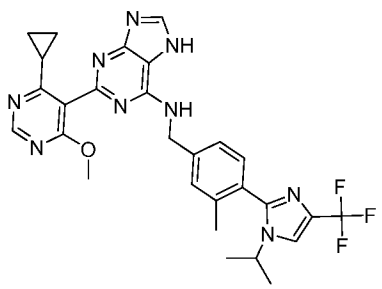
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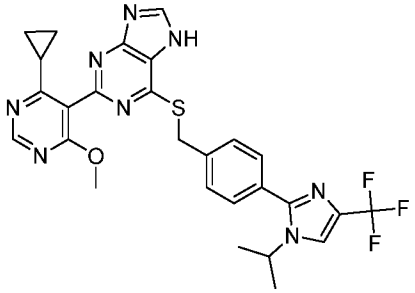
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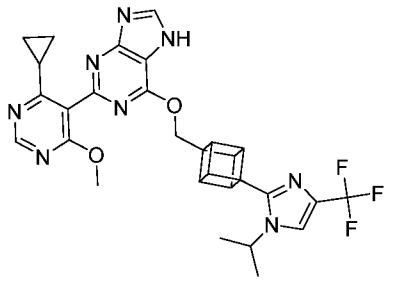
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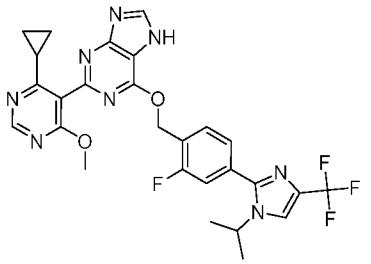
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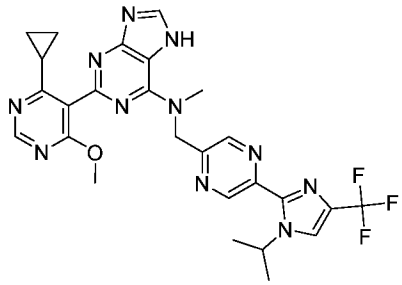
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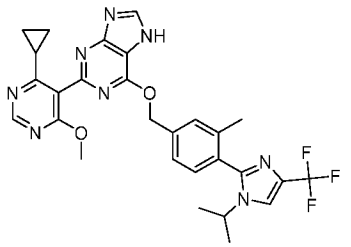
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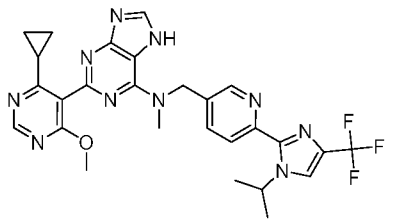
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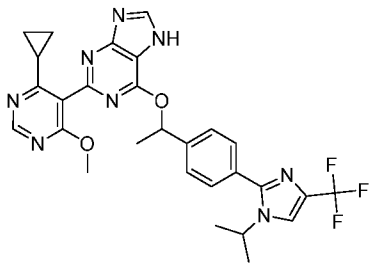
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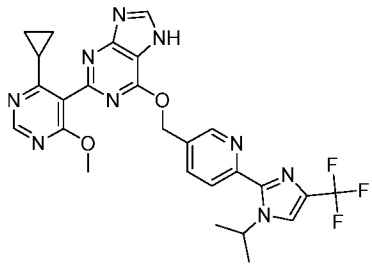
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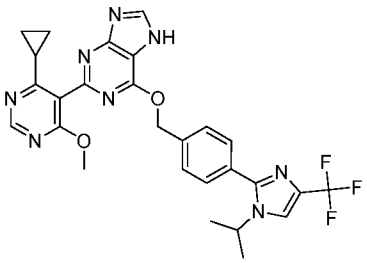
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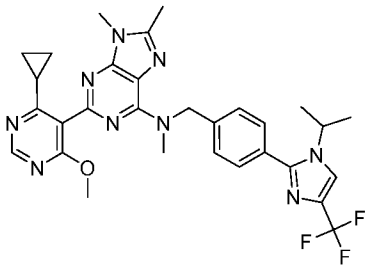
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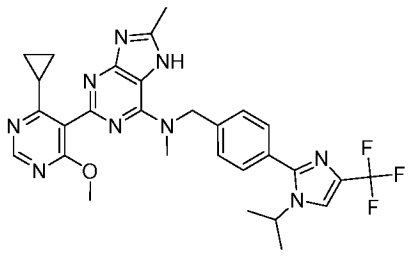
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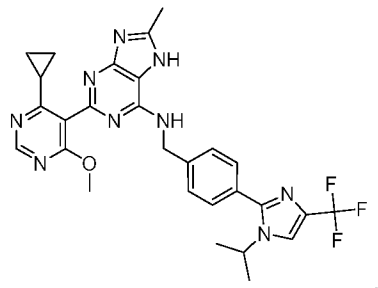
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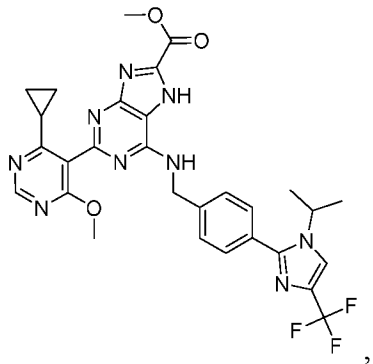
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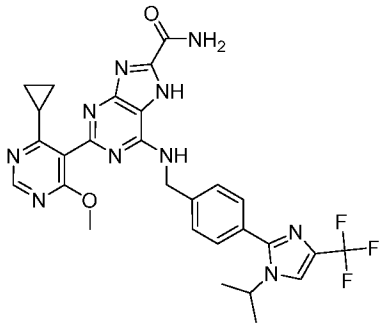
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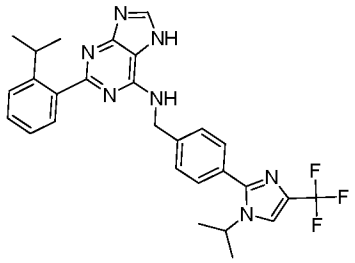
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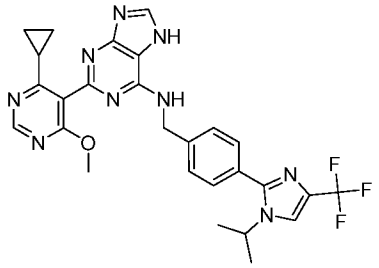
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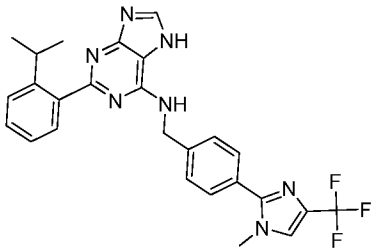
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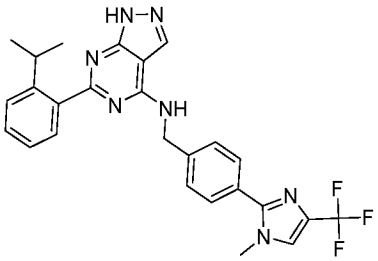
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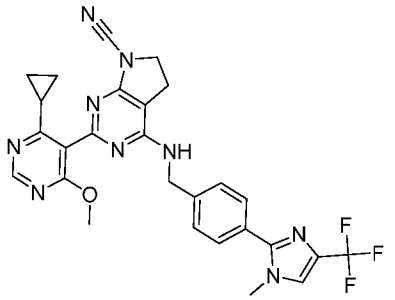
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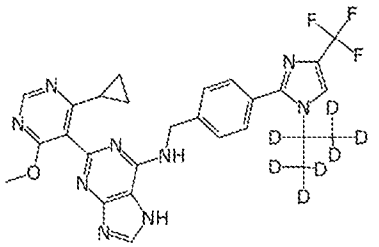
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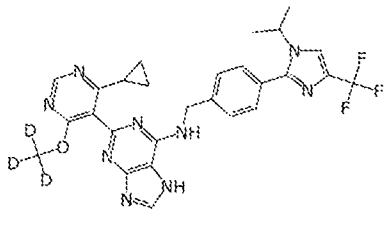
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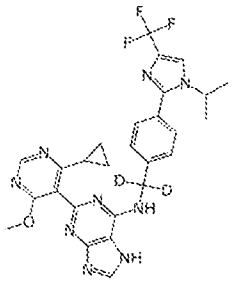
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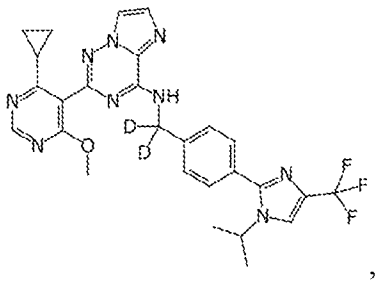
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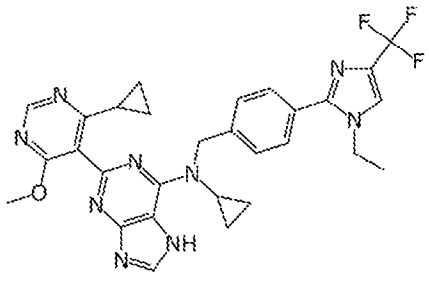
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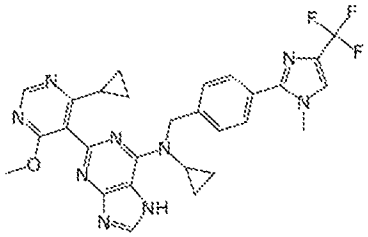
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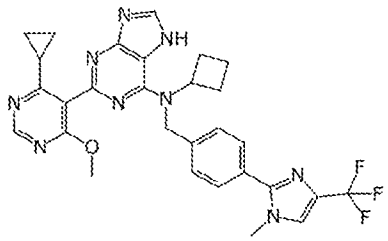
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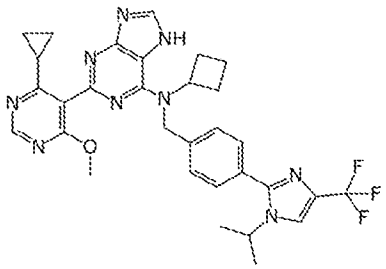
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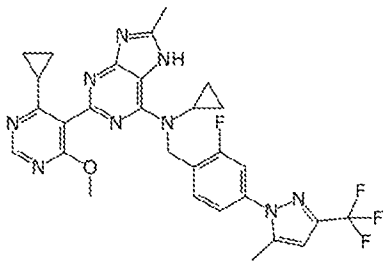
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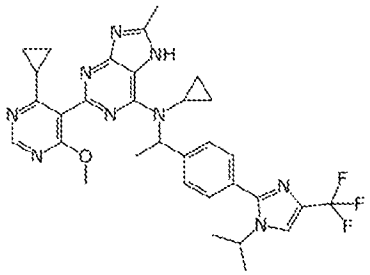
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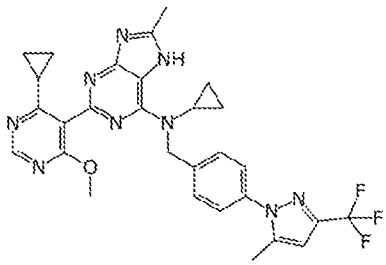
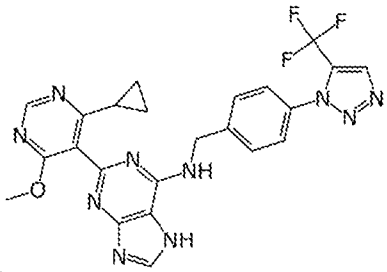
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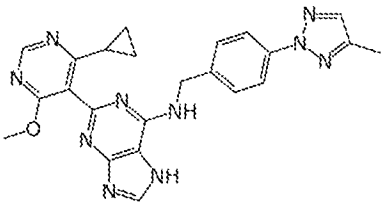
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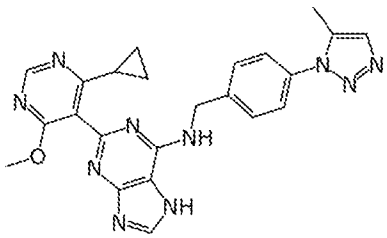
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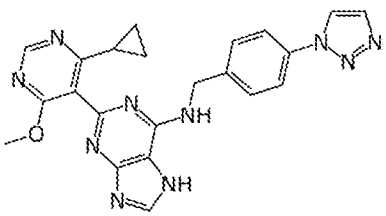
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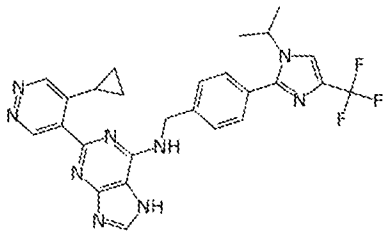
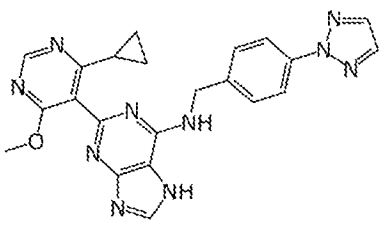
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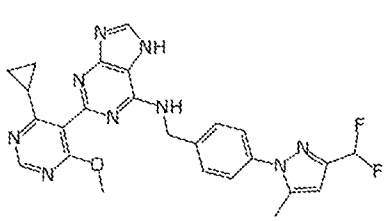
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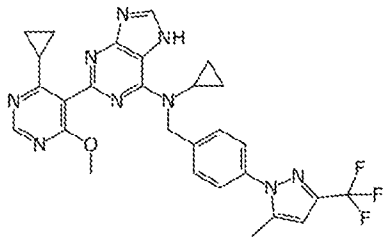
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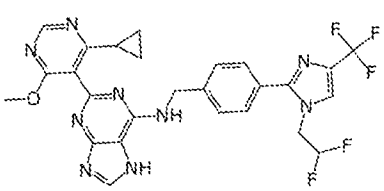
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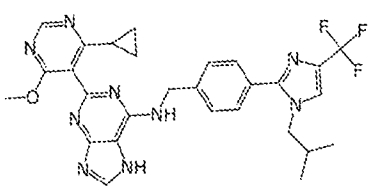
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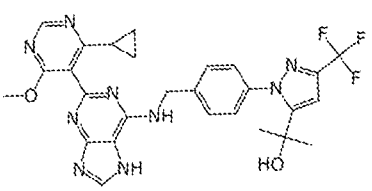
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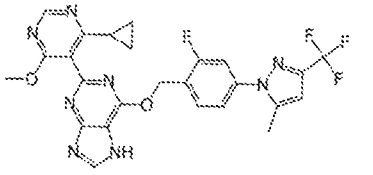
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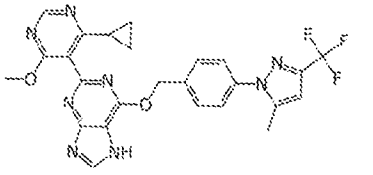
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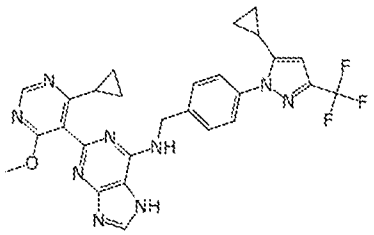
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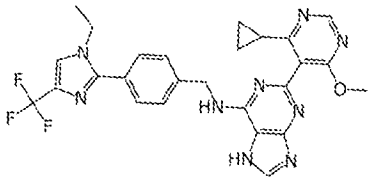
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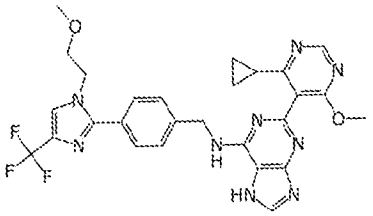
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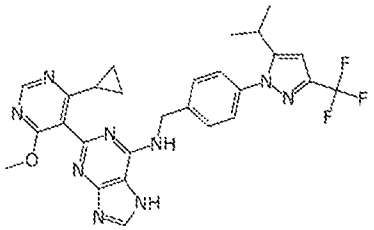
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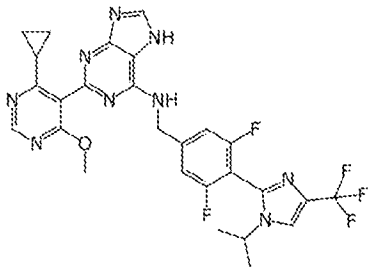
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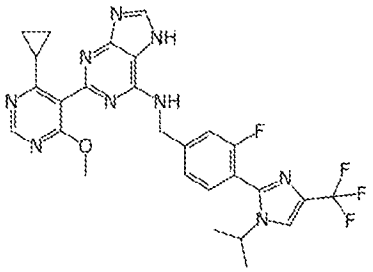
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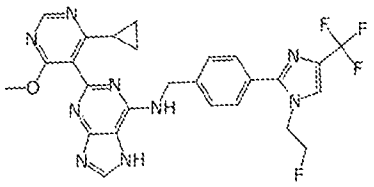
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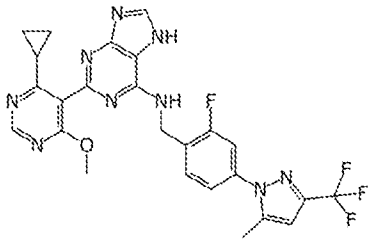
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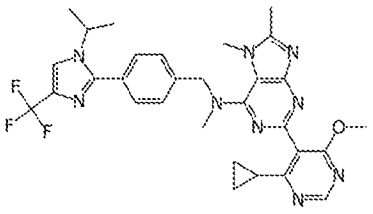
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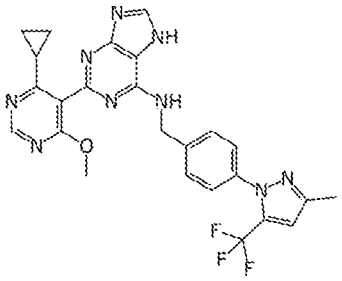
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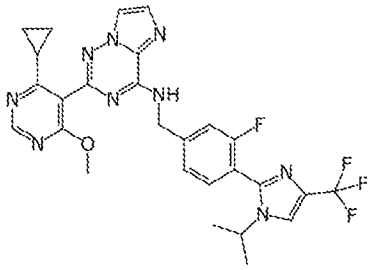
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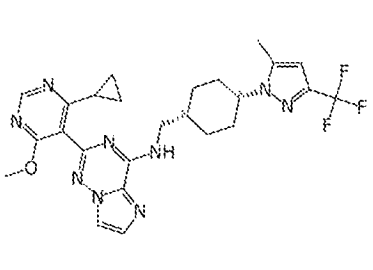
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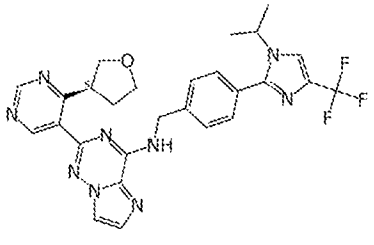
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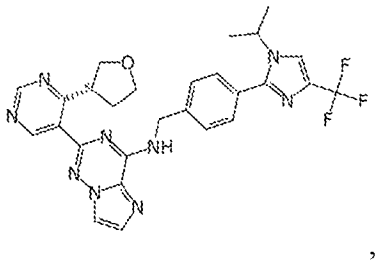
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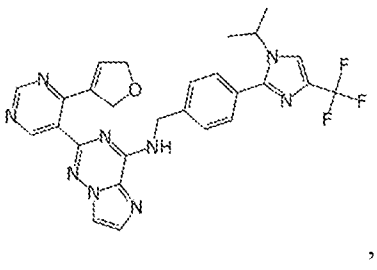
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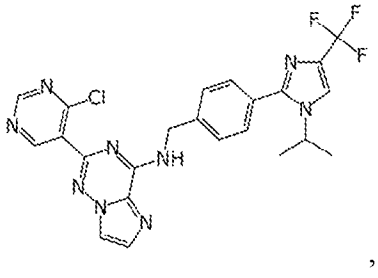
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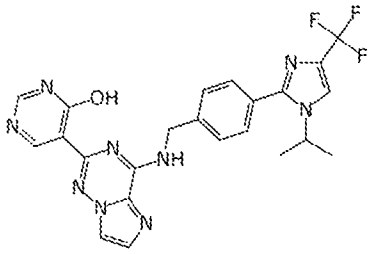
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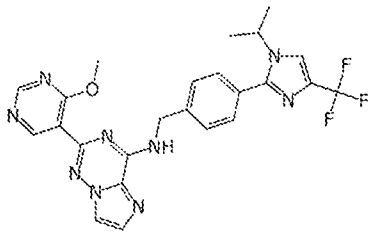
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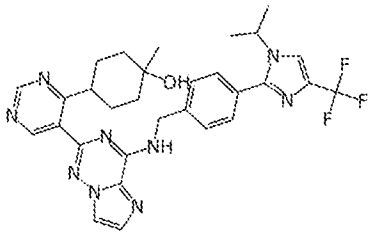
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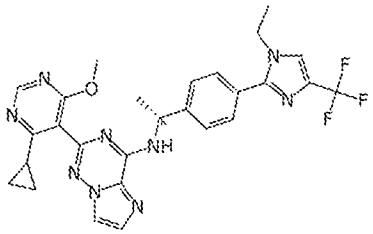
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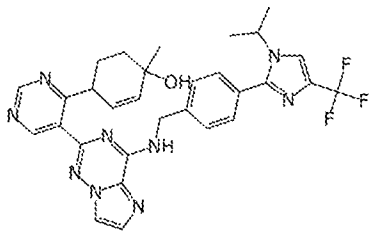
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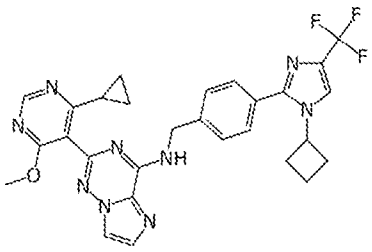
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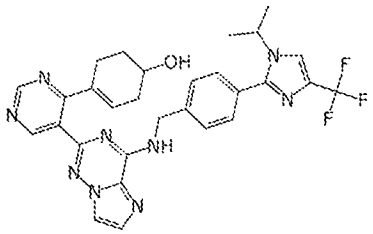
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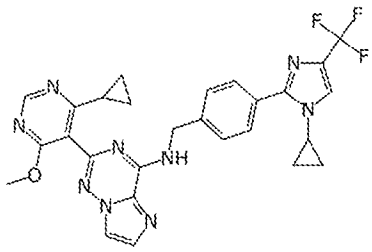
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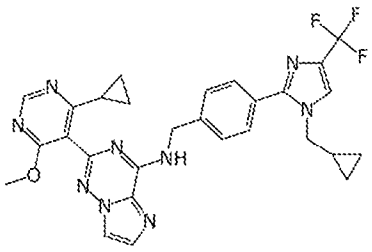
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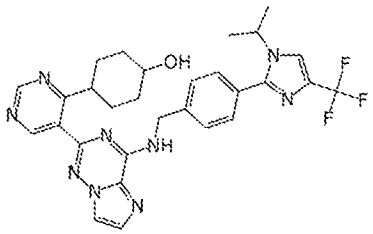
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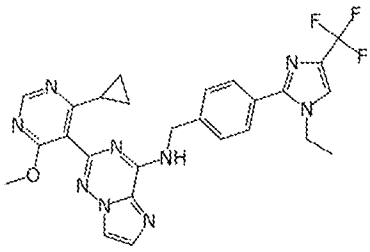
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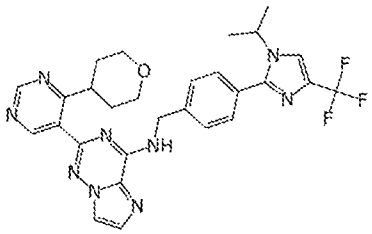
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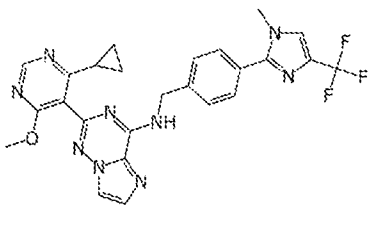
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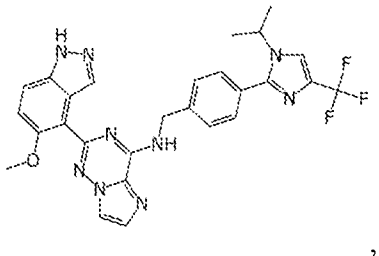
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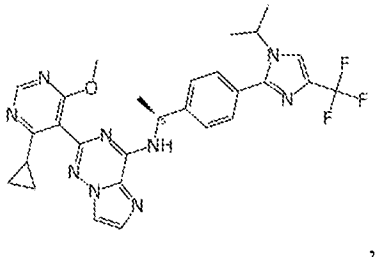
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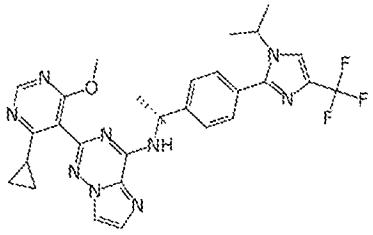
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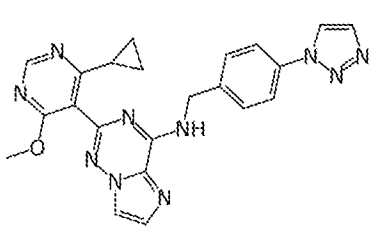
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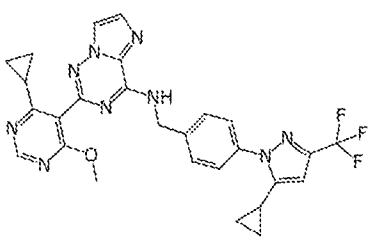
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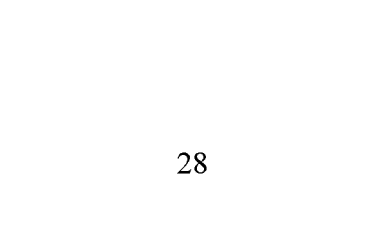
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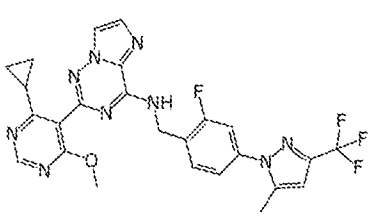
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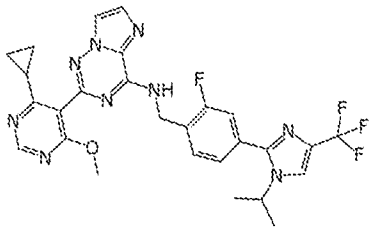
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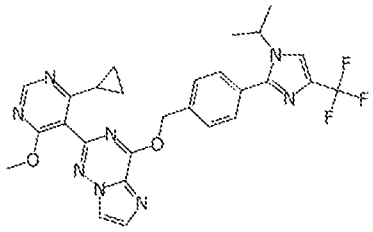
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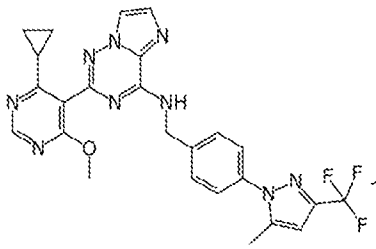
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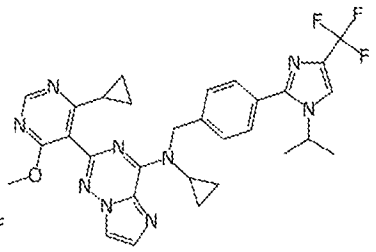
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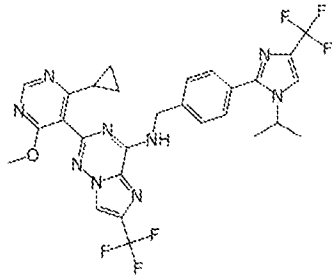
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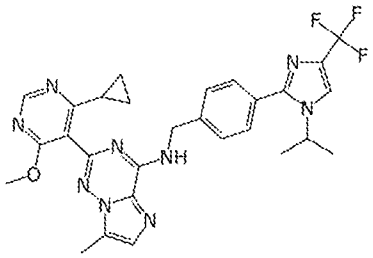
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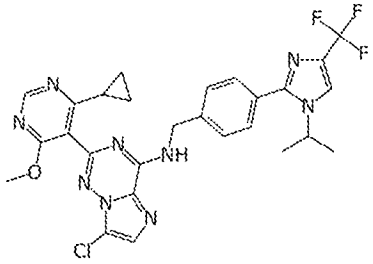
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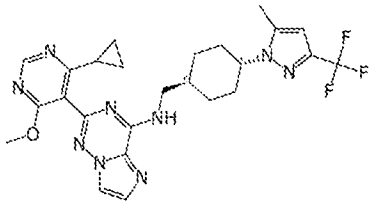
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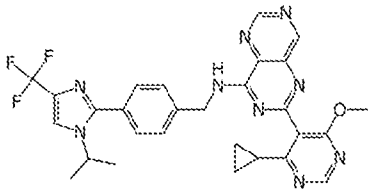
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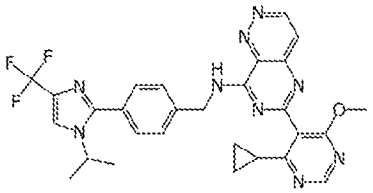
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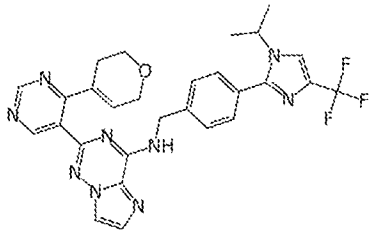
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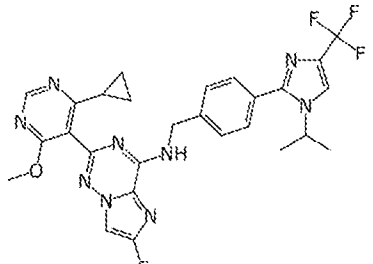
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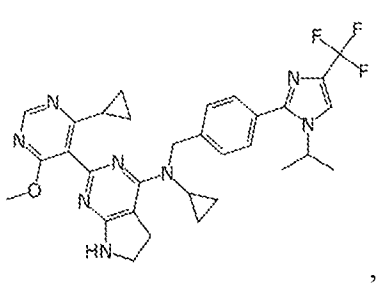
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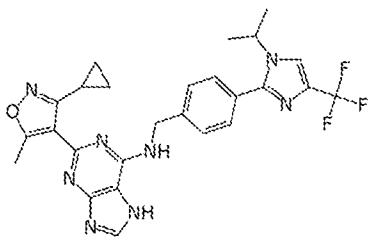
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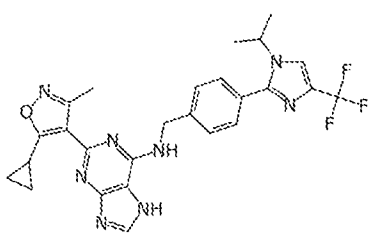
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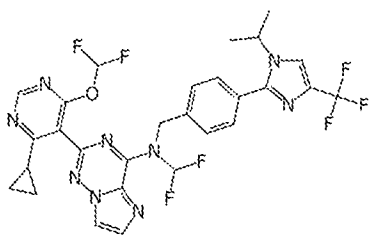
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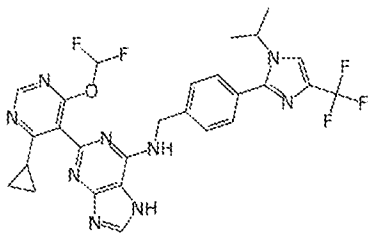
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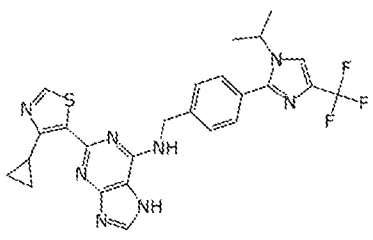
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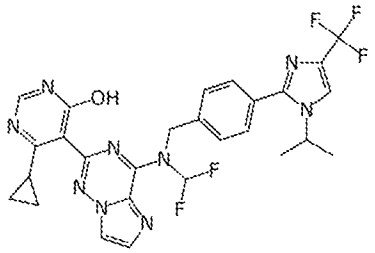
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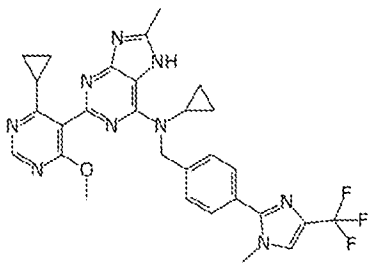
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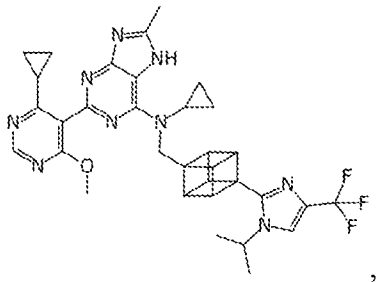
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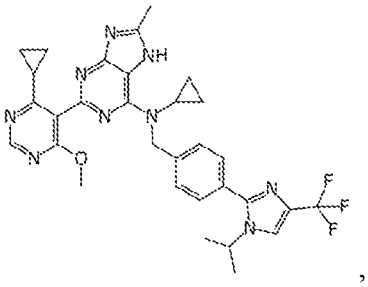
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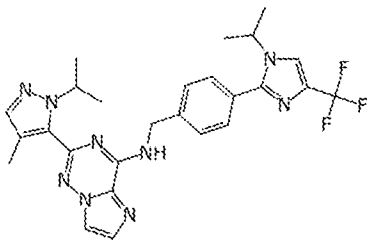
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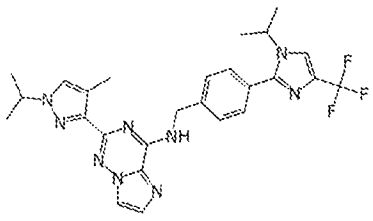
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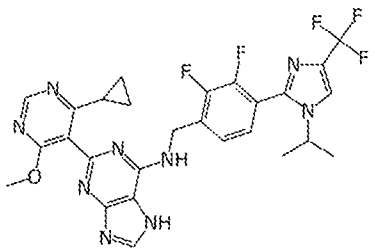
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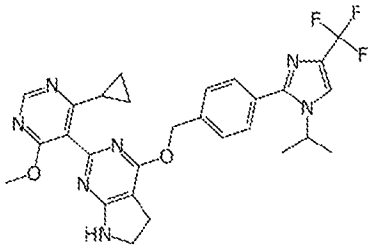
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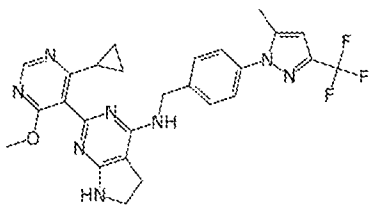
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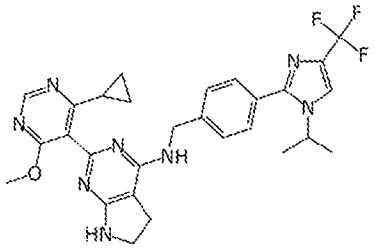
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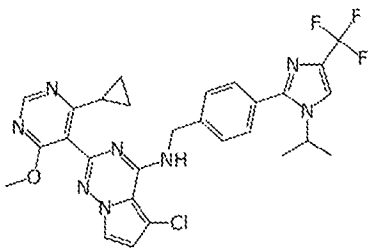
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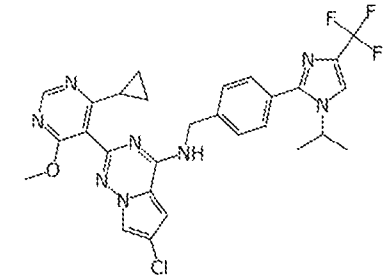
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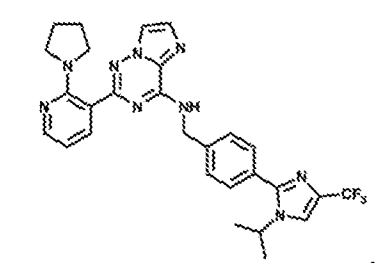
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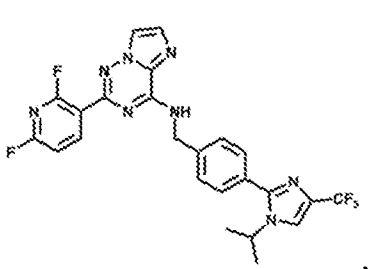
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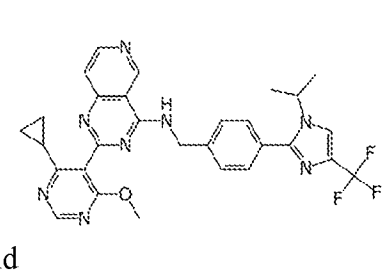
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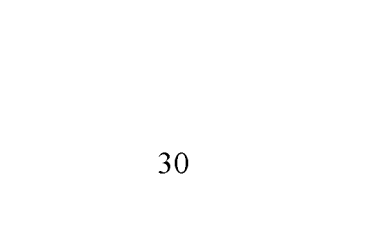
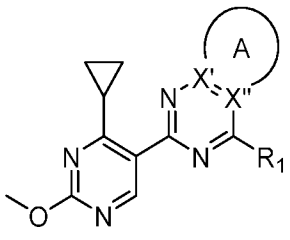
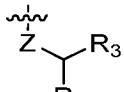
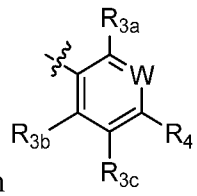
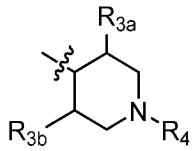
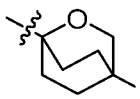
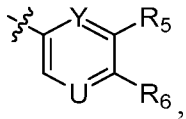
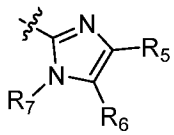
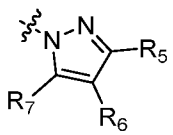
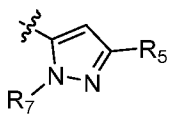
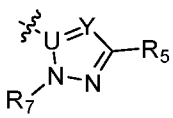
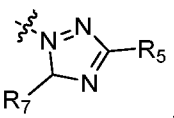
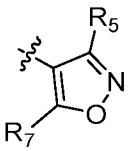
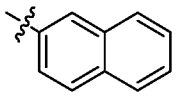
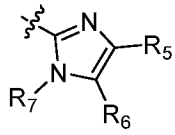
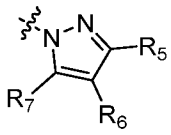
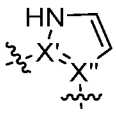
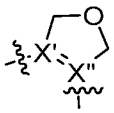
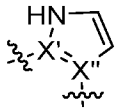
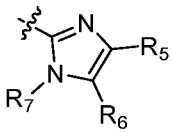
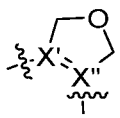
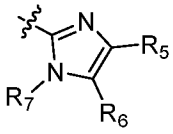
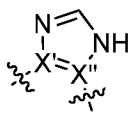
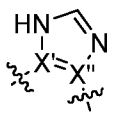
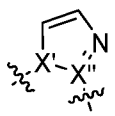

, and .

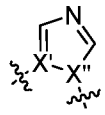
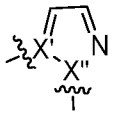
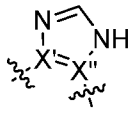
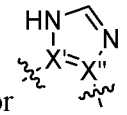
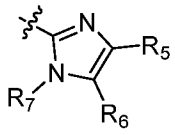
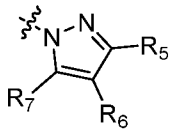
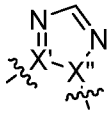
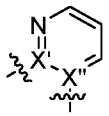
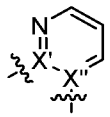
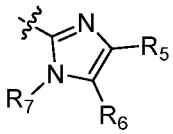
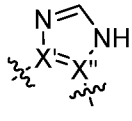
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof:

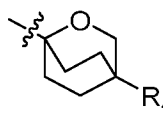
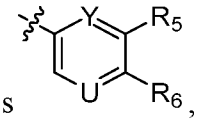
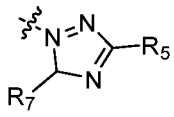
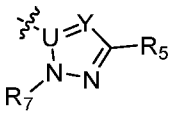
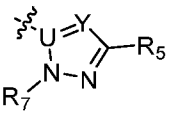
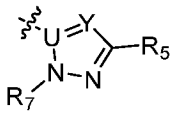
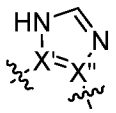
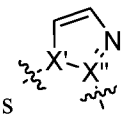
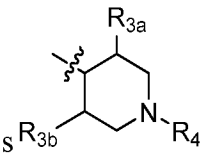
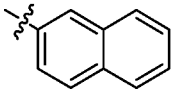
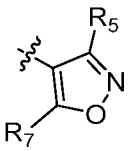
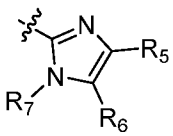


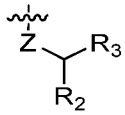
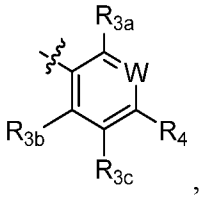
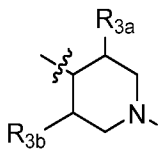
(II)

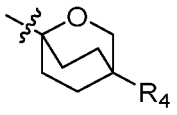
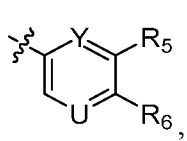
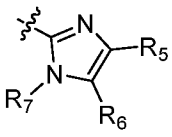
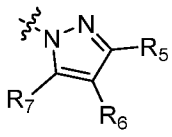
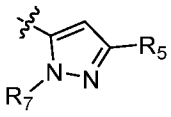
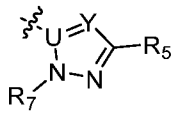
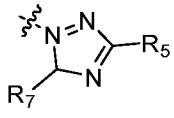
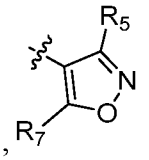
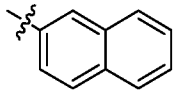
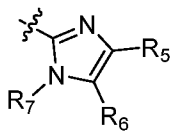
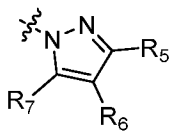
wherein: X' and X" are independently selected from N or C; R_1 is  wherein Z is selected from O or N optionally substituted with R_{1a} or $-CH_2R_{1a}$, wherein R_{1a} is C_3-C_6 cycloalkyl or 4-, 5-, or 6- membered heterocyclyl; wherein R_2 is selected from H or deuterium; R_3 is selected from  ,  , and  , wherein W is selected from C or N, and wherein R_{3a}, R_{3b}, and R_{3c} are independently selected from -H or halogen, R_{3a} and R_2 optionally form a bond to form a 5- or 6-membered heterocyclyl, or R_{3a} and R_{3b} optionally combine to form a bridge; R_4 is selected from  ,  ,  ,  ,  ,  ,  , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C; wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when

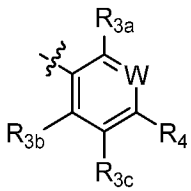
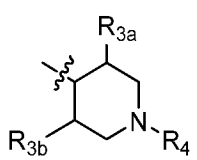
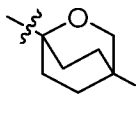
R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  ;and wherein R_{3c} optionally forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen; Ring A is a 5- or 6-membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C; wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, -NH_2, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, -NH_2, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is

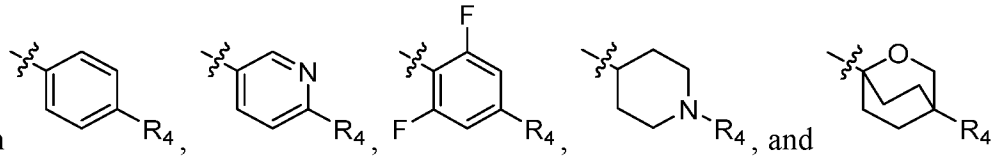
N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N; wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N; wherein when ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N; wherein when ring A is  where X' and X" are C, Z is N, and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl; wherein when ring A is  where X' and X" are C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of: Z is substituted with R_{1a} or $-CH_2R_{1a}$, R_{3a} and R_{3b} are halogen, R_5, R_6, or R_7 is a 4-

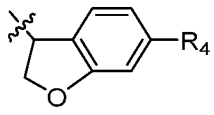
, 5-, or 6- membered heterocyclyl ring, R_3 is  , R_4 is  ,  , or  where U and Y are C,  where U is C and Y is N, or R_3 is  where U is N and Y is C, or a combination thereof; wherein when ring A is  where X' and X" are C , the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises a ring A substituted with a C_2-C_6 alkenyl; wherein when ring A is  where X' is N and X" is C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of: R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_{3a} and R_{3b} combine to form a bridge, R_3 is  , R_4 is  ,  , or  , R_5, R_6, or R_7 a 4-, 5-, or 6- membered heterocyclyl ring, R_{3c} forms a bond with R_5 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, or a combination thereof.

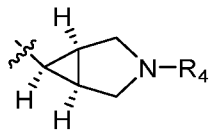
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_1 is  wherein Z is selected from O or N optionally substituted with R_{1a} or -CH_2R_{1a}, wherein R_{1a} is C_3-C_6 cycloalkyl or 4-, 5-, or 6- membered heterocyclyl; wherein R_2 is selected from H or deuterium; R_3 is selected from  ,  , and

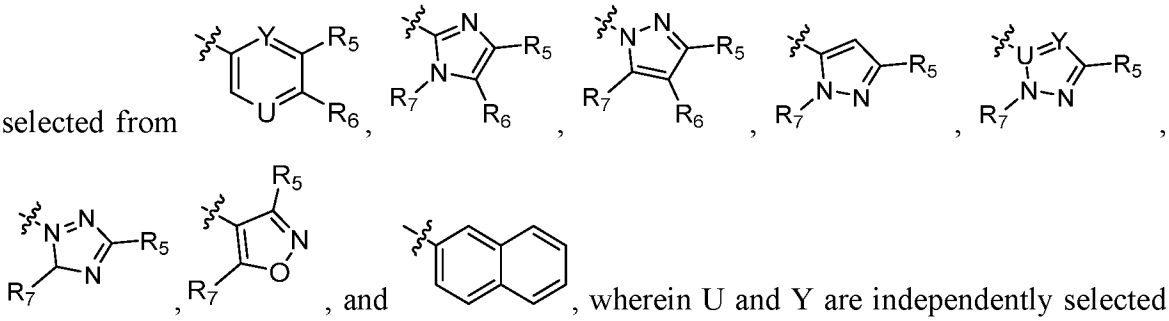
 , wherein W is selected from C or N, and wherein R_{3a}, R_{3b}, and R_{3c} are independently selected from -H or halogen, R_{3a} and R_2 optionally form a bond to form a 5- or 6-membered heterocyclyl, or R_{3a} and R_{3b} optionally combine to form a bridge; R_4 is selected from  ,  ,  ,  ,  ,  ,  , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C; wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  ;and wherein R_{3c} optionally forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen.

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_3 is selected from  ,  , and  , wherein W is selected from N or C.

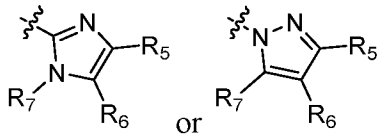
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_3 is selected from  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_3 is  .

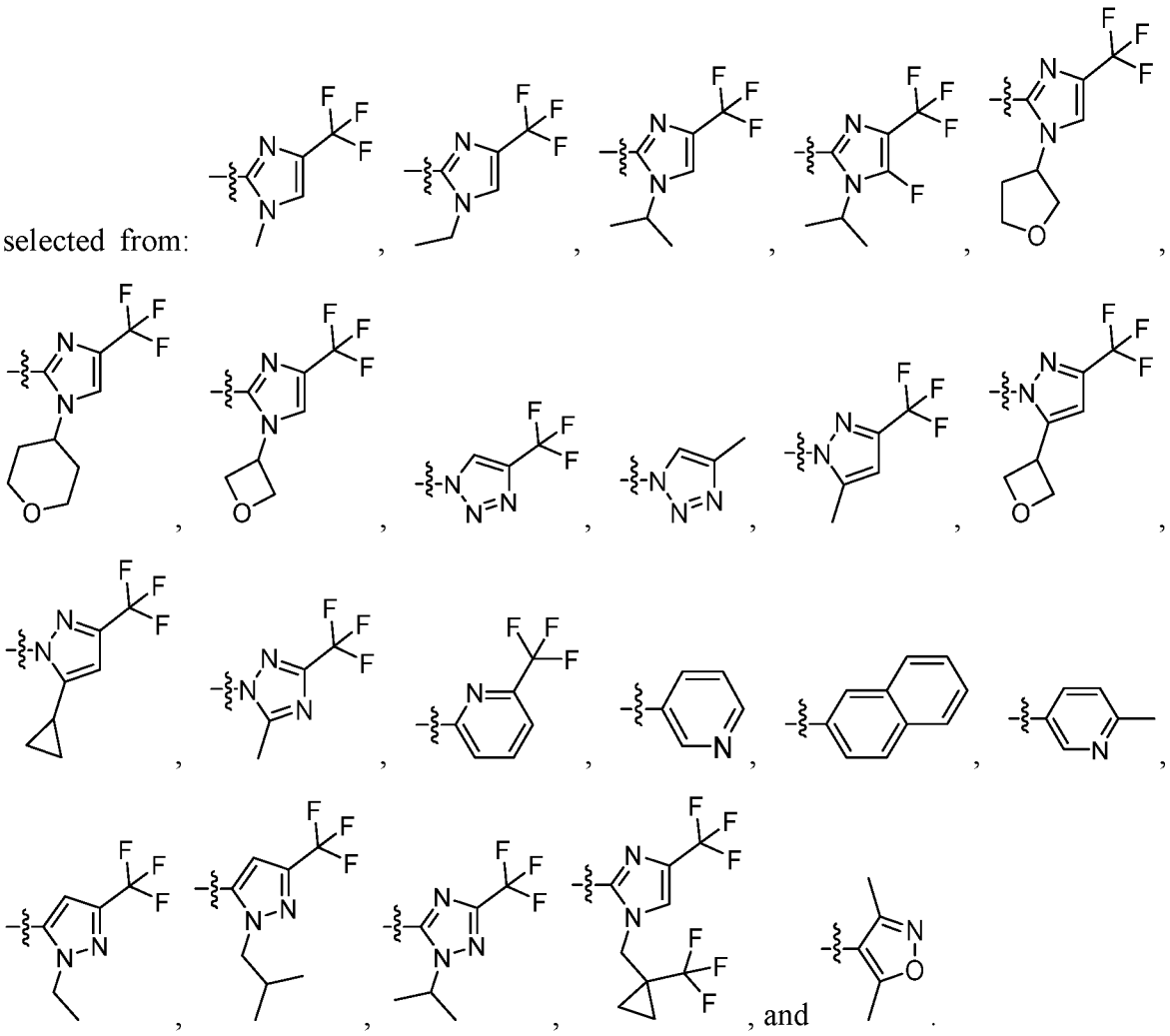
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_{3b} combine to form a bridge, R_3 is  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_4 is selected from  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C; wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered

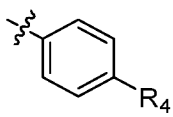
heterocyclyl ring; wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is

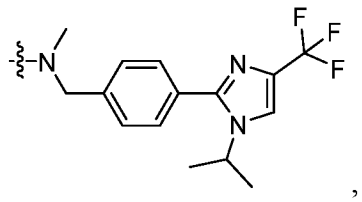
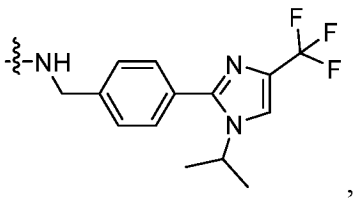
 or .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_4 is selected from:



, and .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is selected from:


,

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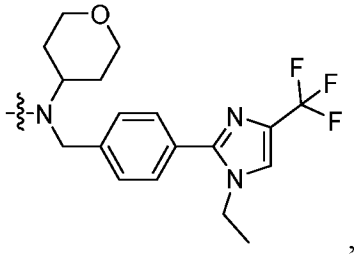
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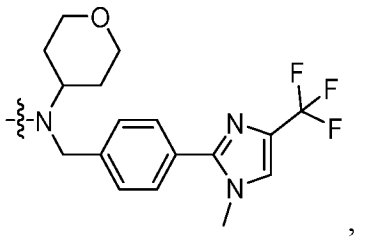
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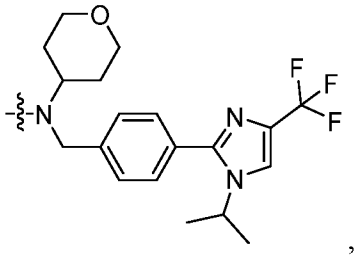
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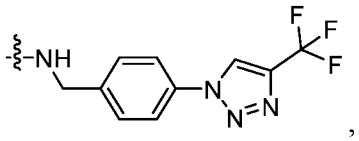
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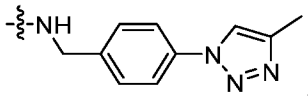
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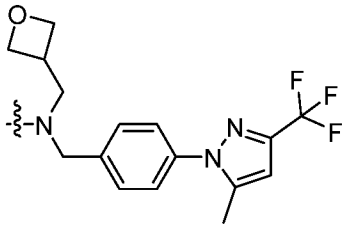
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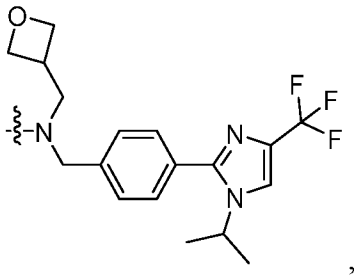
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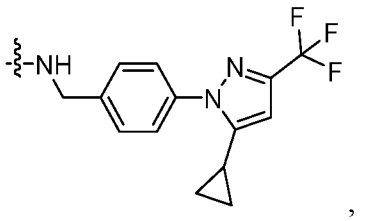
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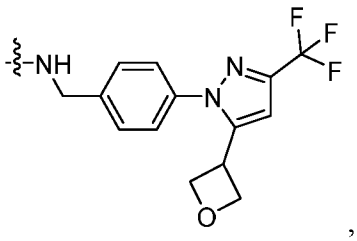
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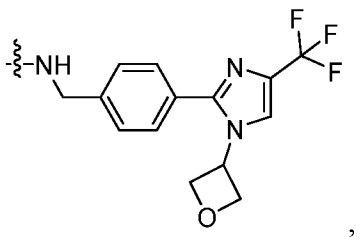
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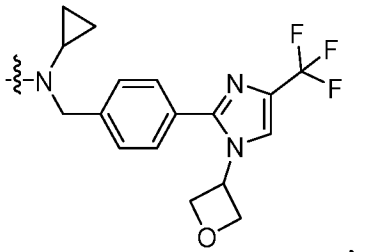
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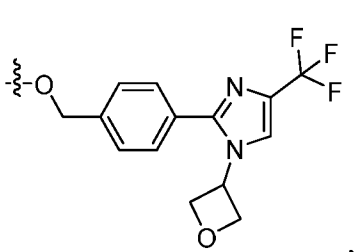
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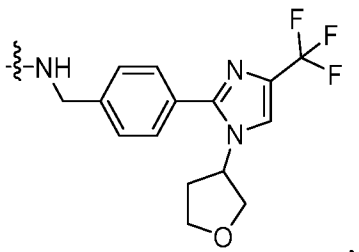
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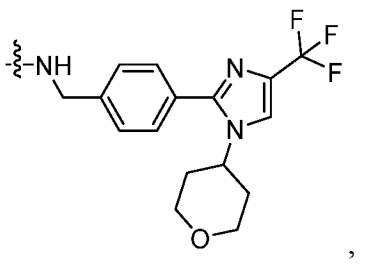
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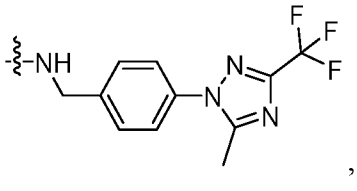
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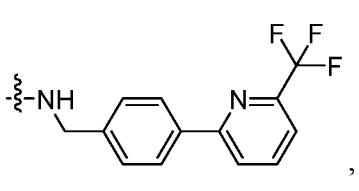
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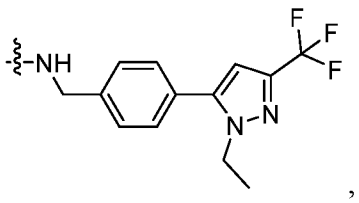
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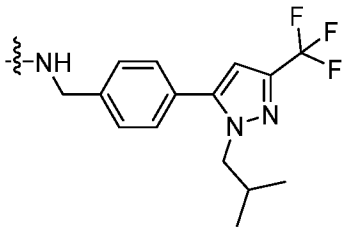
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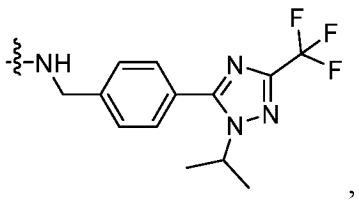
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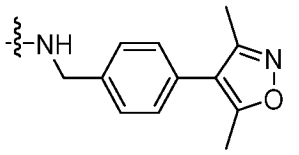
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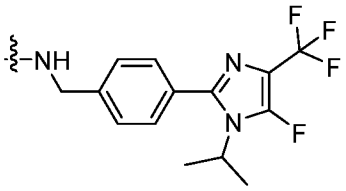
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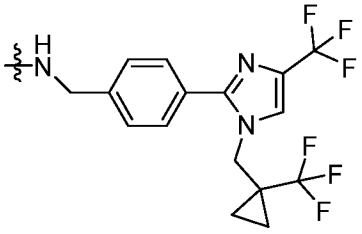
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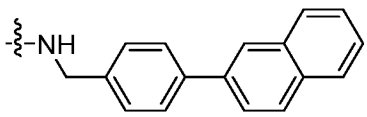
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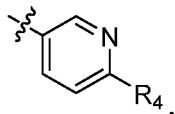
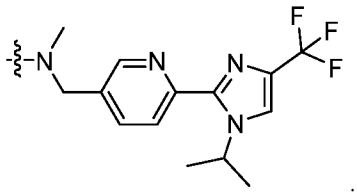
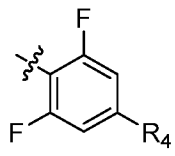
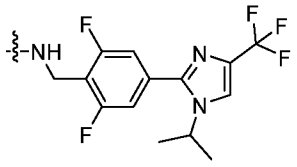
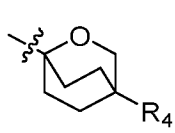
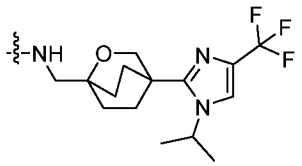
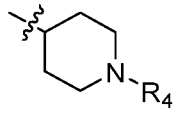
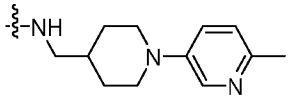
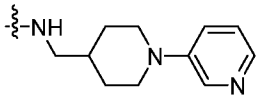
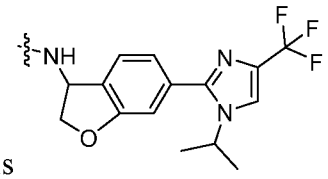
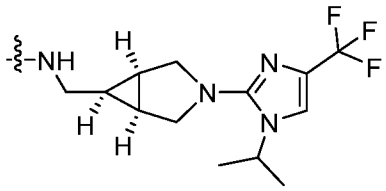
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  .

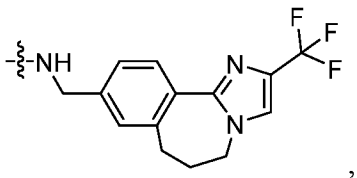
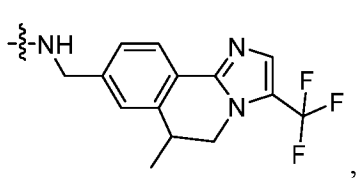
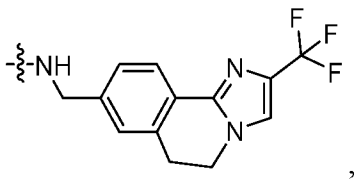
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  .

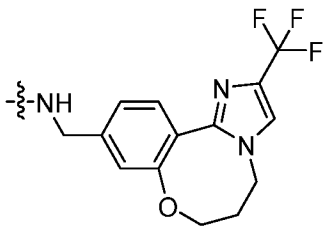
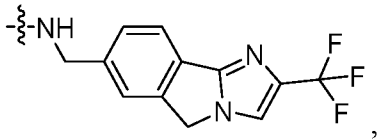
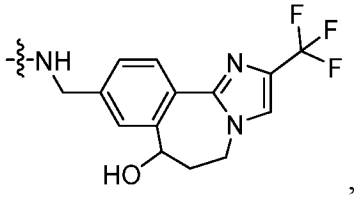
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is selected from  and  .

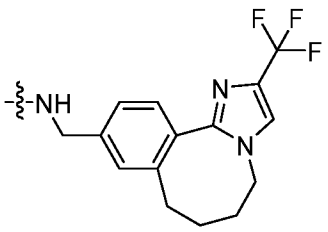
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_1 is  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_{3b} combine to form a bridge, R_1 is  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3c} forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen, R_1 is selected from:

 ,  ,  ,

 ,  ,  ,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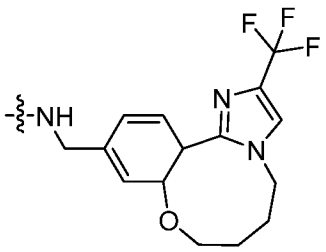
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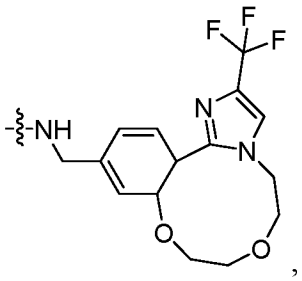
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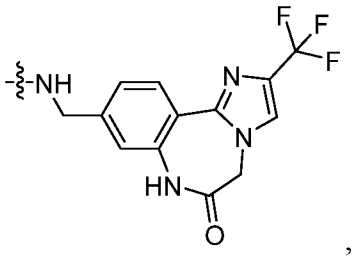
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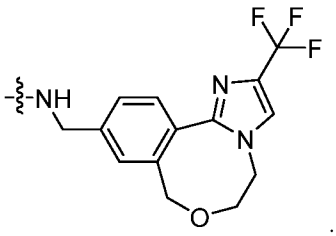
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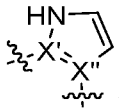
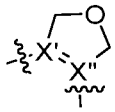
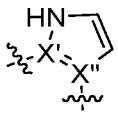
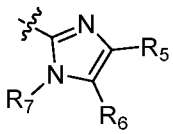
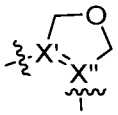
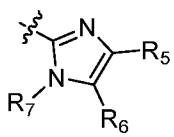
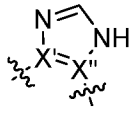
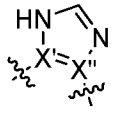
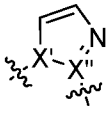
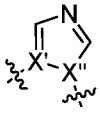
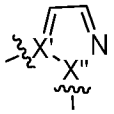
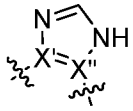
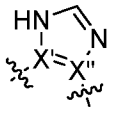
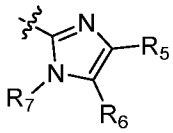
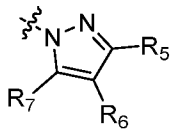
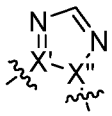
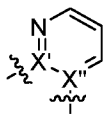
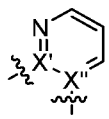
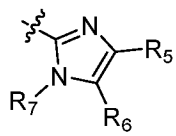
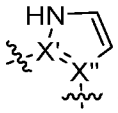
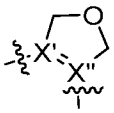
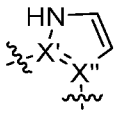
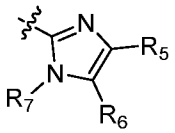
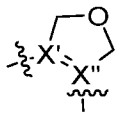
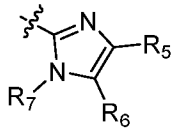
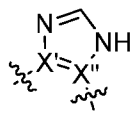
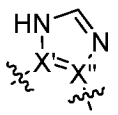
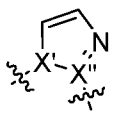
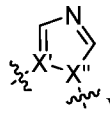
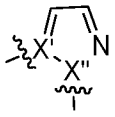
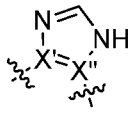
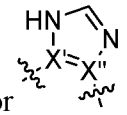
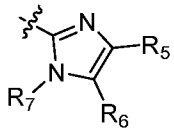
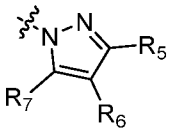
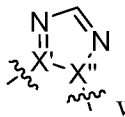
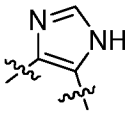
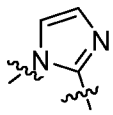
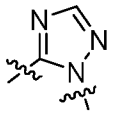
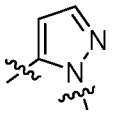
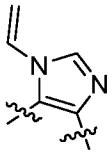
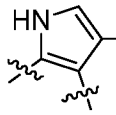
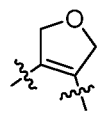
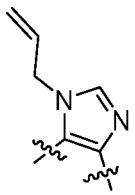
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is a 5- or 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C; wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is are

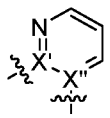
optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N; wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, -NH_2, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{2-6} alkyl, C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N; wherein when R ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, -NH_2, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6}

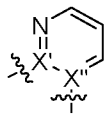
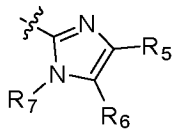
haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

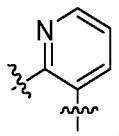
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein Ring A is a 5- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C; wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is

N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N; wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

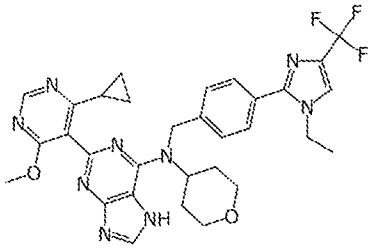
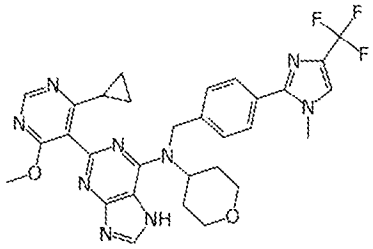
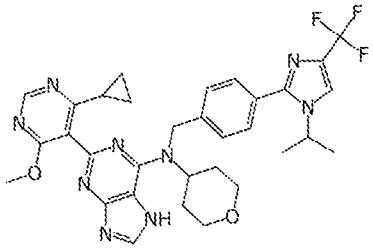
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from:  ,  ,  ,  ,  ,  ,  ,  and .

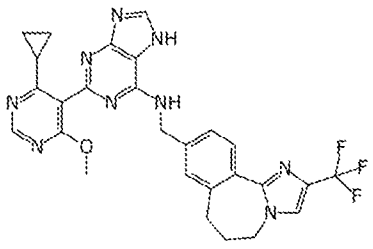
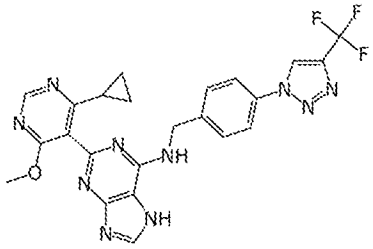
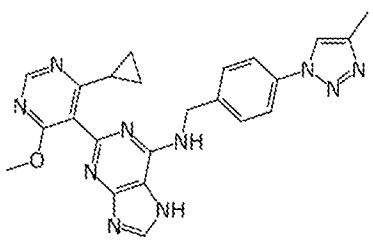
In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein Ring A is a 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when R ring A is 6-membered heterocyclyl ring, ring A is  where X'

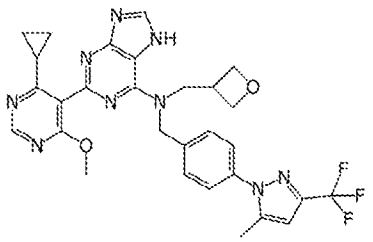
and X" are C and Z is N; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is  .

In certain embodiments, the compositions and methods described herein relate to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein the compound is selected from:

 ,  ,  ,

 ,  ,  ,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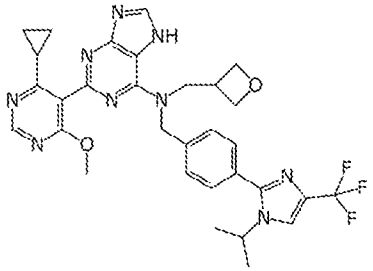
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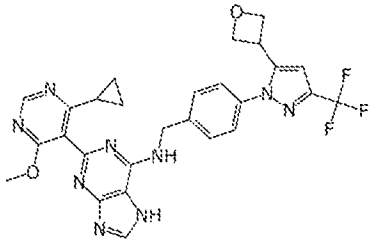
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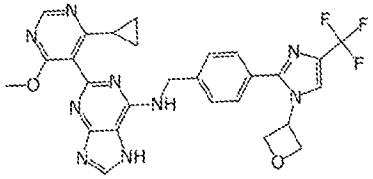
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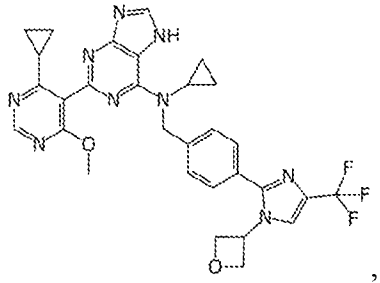
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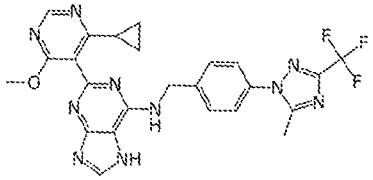
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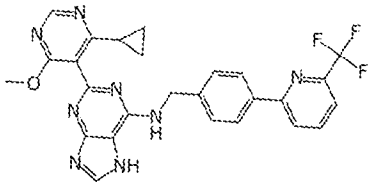
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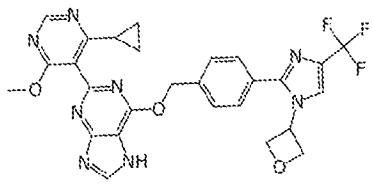
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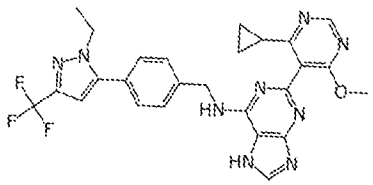
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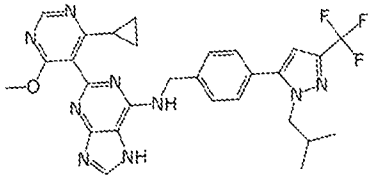
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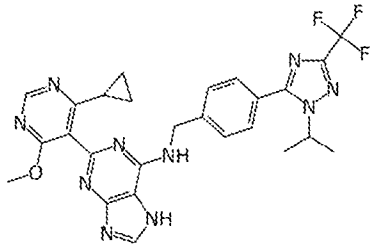
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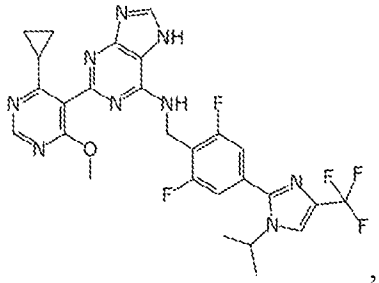
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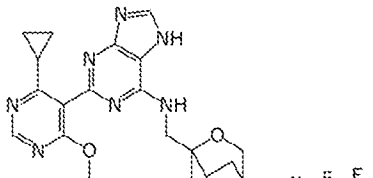
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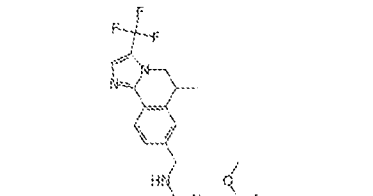
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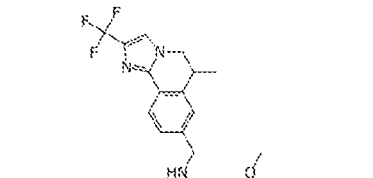
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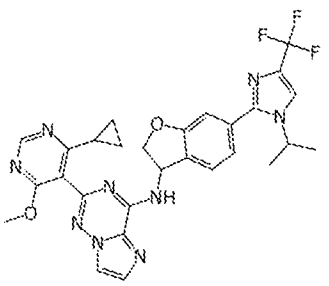
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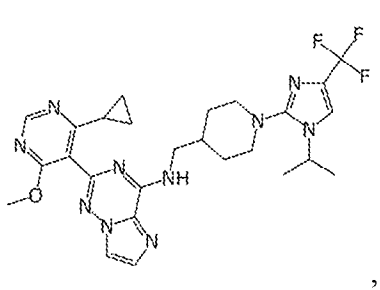
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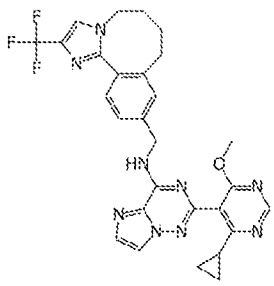
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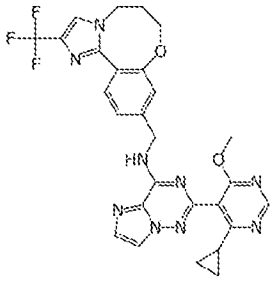
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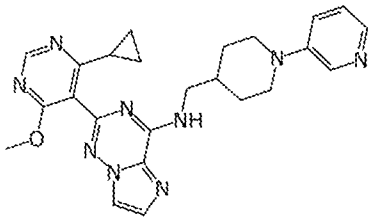
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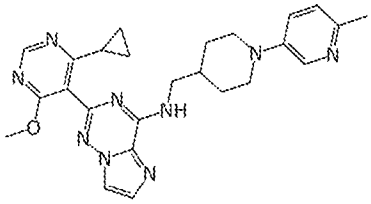
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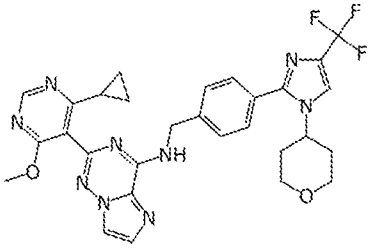
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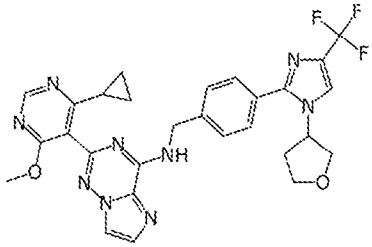
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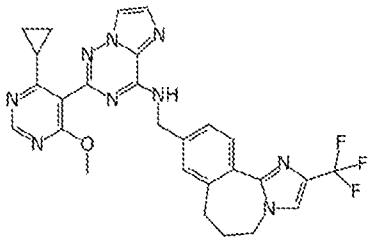
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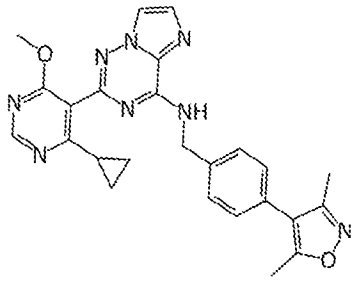
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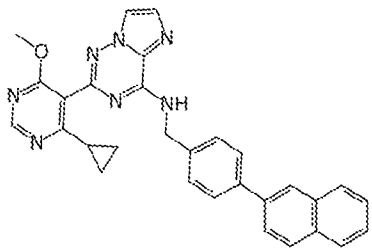
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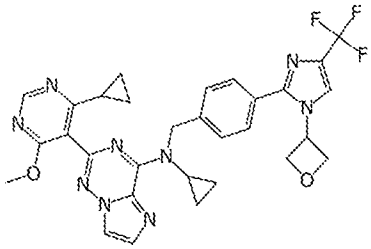
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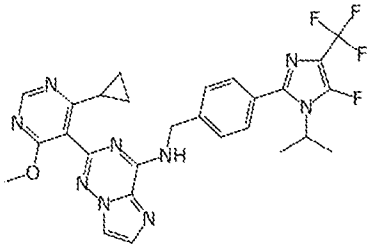
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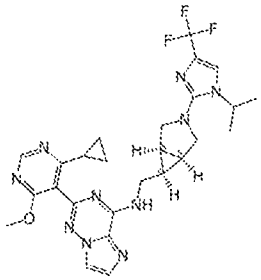
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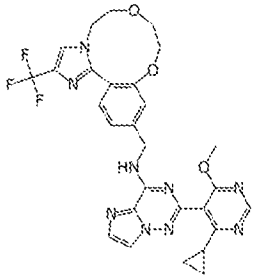
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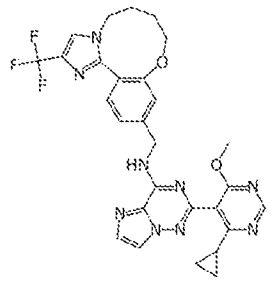
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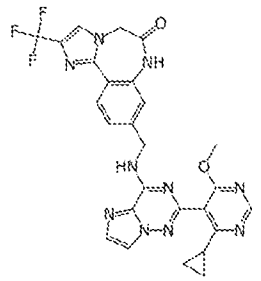
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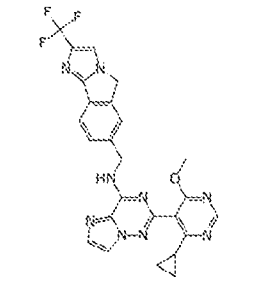
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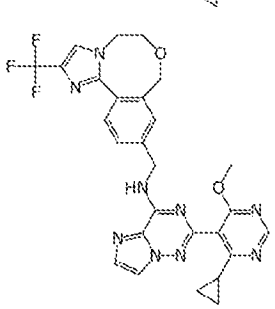
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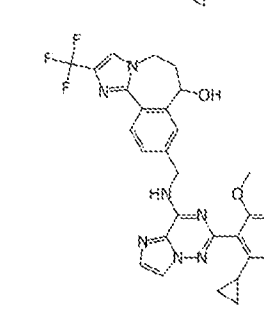
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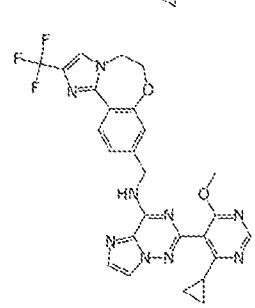
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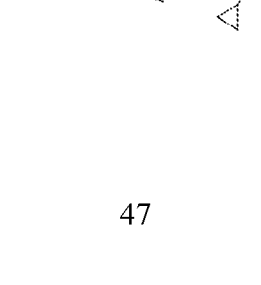
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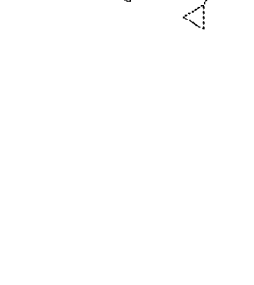
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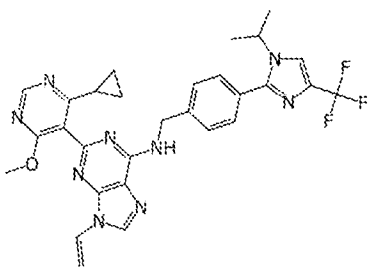
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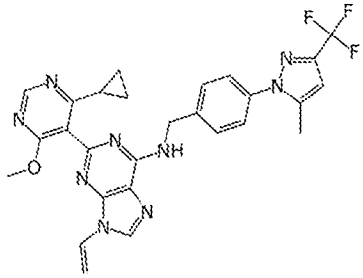
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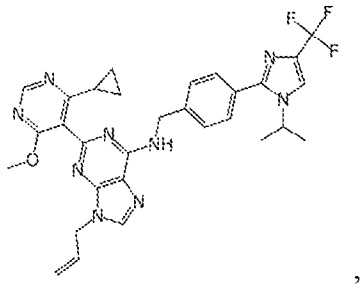
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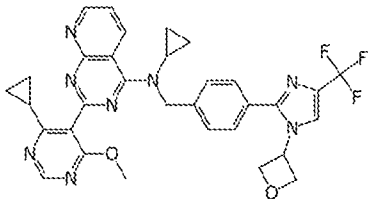
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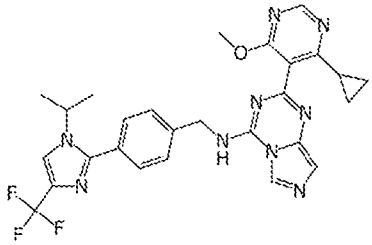
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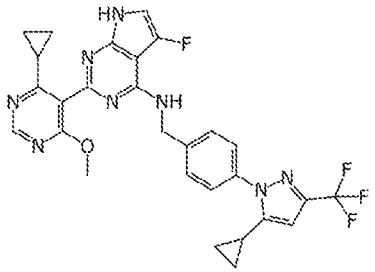
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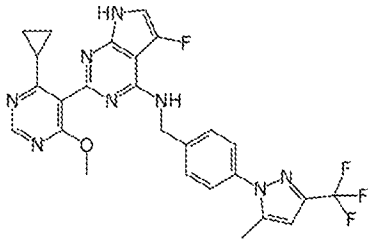
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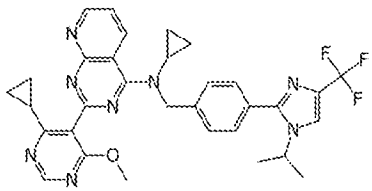
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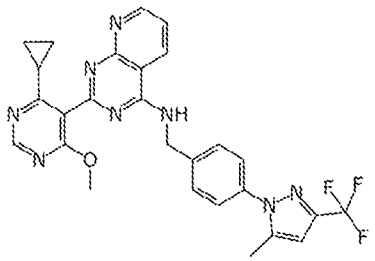
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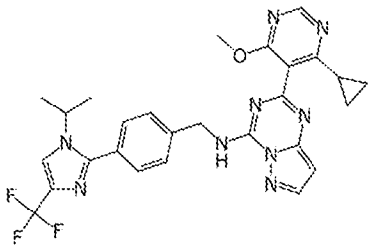
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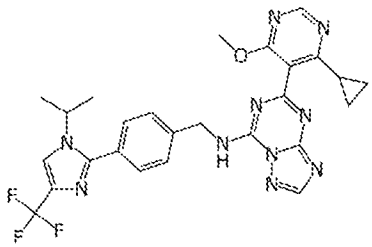
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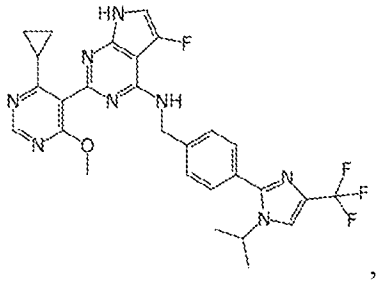
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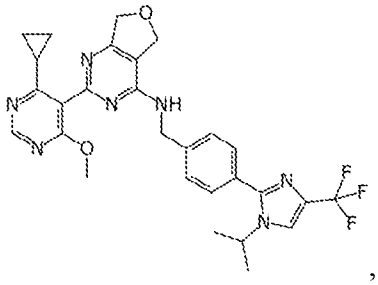
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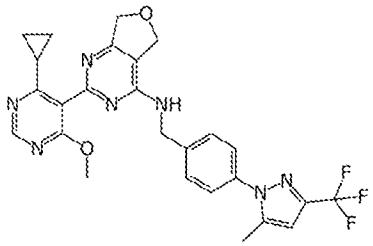
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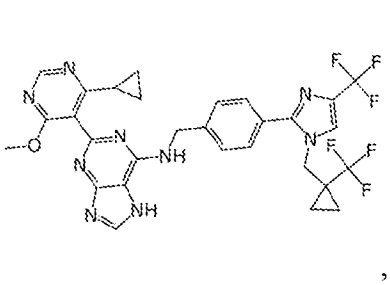
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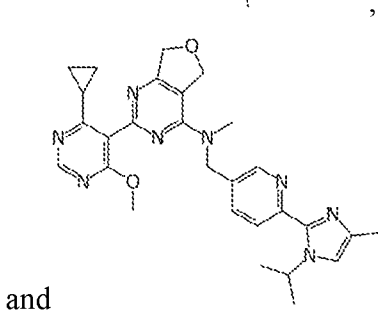
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and .

In certain embodiments, the present disclosure is directed to a method of modulating USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of inhibiting USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating a disorder or disease with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating cancer with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating cancer with a USP1 inhibitor in a subject, comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the cancer is characterized by over expression of USP1.

In certain embodiments, the present disclosure is directed to a method treating cancer with a USP1 inhibitor in a subject, comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the cancer characterized by overexpression of USP1 is selected from prostate, breast, ovarian, non-small cell lung cancer, mesothelioma, Merkel cell carcinoma, synovial sarcoma, renal cell carcinoma, and osteosarcoma.

In certain embodiments, the present disclosure is directed to a use of a compound of formula (I), or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

In certain embodiments, the present disclosure is directed to a use of a compound of formula (I), or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, wherein the cancer is characterized by overexpression of USP1.

In certain embodiments, the present disclosure is directed to a process to manufacture a compound of formula (I), or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

The subject matter of the application will be more readily understood from the following detailed description when read in conjunction with the accompanying drawings.

FIG. 1 shows the mean tumor volume over a period of time in mice treated with 30 mg/kg and 100 mg/kg of Compound 12.

FIG. 2 shows the mean tumor volume over a period of time in mice treated with 30 mg/kg and 100 mg/kg of Compound 21.

FIG. 3 shows the mean tumor volume over a period of time in mice treated with 30 mg/kg and 100 mg/kg of Compound 129.

FIG. 4 shows the mean tumor volume over a period of time in mice treated with 30 mg/kg and 100 mg/kg of Compound 133.

DETAILED DESCRIPTION

The presently disclosed subject matter relates to compositions comprising USP1 inhibitors and methods of their use in treating cancer. For purposes of clarity of disclosure and not by way of limitation, the detailed description is divided into the following subsections:

1. Definitions

2. Compositions of Matter

3. Methods of Use

4. Examples

1. Definitions

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. In case of conflict, the present document, including definitions, will control. Preferred methods and materials are described below, although methods and materials similar or equivalent to those described herein can be used in practice or testing of the presently disclosed subject matter. All publications, patent applications, patents and other references mentioned herein are incorporated by reference in their entirety. The materials, methods, and examples disclosed herein are illustrative only and not intended to be limiting.

The terms "comprise(s)," "include(s)," "having," "has," "can," "contain(s)," and variants thereof, as used herein, are intended to be open-ended transitional phrases, terms, or words that do not preclude the possibility of additional acts or structures. The singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. The present disclosure also contemplates other instances "comprising," "consisting of", and "consisting essentially of," the instances or elements presented herein, whether explicitly set forth or not.

For the recitation of numeric ranges herein, each intervening number within the range is explicitly contemplated with the same degree of precision. For example, for the range of 6-9, the numbers 7 and 8 are contemplated in addition to 6 and 9, and for the range 6.0-7.0, the number 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, and 7.0 are explicitly contemplated.

As used herein, the term "about" or "approximately" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. For example, "about" can mean within 3 or more than 3 standard deviations, per the practice in the art. Alternatively, "about" can mean a range of up to 20%, preferably up to 10%, more preferably up to 5%, and more preferably still up to 1% of a given value. Alternatively, particularly with respect to biological systems or processes, the term can mean within an order of magnitude, preferably within 5-fold, and more preferably within 2-fold, of a value.

As used herein, "modulate" or "modulating" refers to increasing or decreasing, e.g., modulation of the activity of an enzyme includes increasing the activity of the enzyme as well as decreasing the activity of the enzyme.

As used herein, "treat" or "treating" refers to an effort to alter the natural course of a disease, including prophylaxis of the disease, alleviation of symptoms and/or ameliorating pathology associated with the disease.

As used herein, "alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and may be unsubstituted or substituted. Thus, C_1-C_n as in "C_1-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement. For example, C_1-C_6, as in "C_1-C_6 alkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, and octyl.

As used herein, "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present, and may be unsubstituted or substituted. For example, "C_2-C_6 alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and up to 1, 2, 3, 4, or 5 carbon-carbon double bonds respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present, and may be unsubstituted or substituted. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having 2 or 3 carbon atoms and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl.

As used herein, "heteroalkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and at least 1 heteroatom within the chain or branch.

As used herein, "cycloalkyl" shall mean cyclic rings of alkanes of three to eight total carbon atoms, or any number within this range (i.e., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl).

As used herein, the term "heterocyclyl" or "heterocyclic" refers to a mono- or poly-cyclic ring system which can be saturated or contains one or more degrees of unsaturation and contains one or more heteroatoms. Preferred heteroatoms include N, O, and/or S, including N-oxides, sulfur oxides, and dioxides. Preferably the ring is three to ten-membered and is either saturated or has one or more degrees of unsaturation. The heterocycle may be unsubstituted or substituted, with multiple degrees of substitution being allowed. Such rings may be optionally fused to one or more of another "heterocyclic" ring(s), heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s). Examples of heterocycles include, but are not limited to, tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane, piperidine, piperazine, pyrrolidine, morpholine, thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene, 1,3- oxathiolane, and the like. The alkyl, alkenyl, alkynyl, aryl, heteroaryl and heterocyclyl substituents may be substituted or unsubstituted, unless specifically defined otherwise.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic,

and may be unsubstituted or substituted. Examples of such aryl elements include phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

As used herein, the term "halogen" refers to F, Cl, Br, and I.

As used herein, the term "haloalkyl" means an alkyl group that is substituted with one or more fluorine, chlorine, bromine or iodine atoms. Examples of such haloalkyl include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, 1,1-difluoroethyl, chloromethyl, chlorofluoromethyl and trichloromethyl groups.

As used herein, the term "alkoxy" means an -O-alkyl group in which alkyl is defined herein. Preferably the alkoxy is a C_1-C_6 alkoxy. Examples include, but are not limited to, methoxy and ethoxy. The group may be a terminal group or a bridging group.

The term "substitution," "substituted" and "substituent" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups described herein, and halogens (i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, and trifluorom ethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure result.

The compounds of the subject invention may have spontaneous tautomeric forms. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers,

each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

This invention also provides isotopic variants of the compounds disclosed herein, including wherein the isotopic atom is ^{2}H and/or wherein the isotopic atom ^{13}C. Accordingly, in the compounds provided herein hydrogen can be enriched in the deuterium isotope. It is to be understood that the invention encompasses all such isotopic forms.

In the compound structures depicted herein, hydrogen atoms are not shown for carbon atoms having less than four bonds to non-hydrogen atoms. However, it is understood that enough hydrogen atoms exist on said carbon atoms to satisfy the octet rule.

Except where otherwise specified, if the structure of a compound of this invention includes an asymmetric carbon atom, it is understood that the compound occurs as a racemate, racemic mixture, and isolated single enantiomer. All such isomeric forms of these compounds are expressly included in this invention. Except where otherwise specified, each stereogenic carbon may be of the R or S configuration. It is to be understood accordingly that the isomers arising from such asymmetry (e.g., all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis.

The compounds of the present invention include all hydrates, solvates, and complexes of the compounds used by this invention. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. The compounds described in the present invention are in racemic form or as individual enantiomers.

In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e., R_1, R_2, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

The compounds used in the method of the present invention may be in a salt form. As used herein, a “salt” is a salt of the instant compounds which has been modified by making acid or base salts of the compounds. In the case of compounds used to treat an infection or disease caused by a pathogen, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid

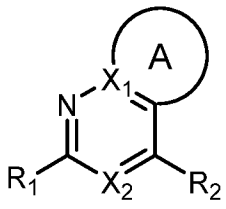
salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkali earth metal salts, sodium, potassium or lithium. The term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like.

The compounds used in the method of the present invention can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or in carriers such as the novel programmable sustained-release multi-compartmental nanospheres (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, nasal, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone or mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow- inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents,

preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

2. Compositions of Matter

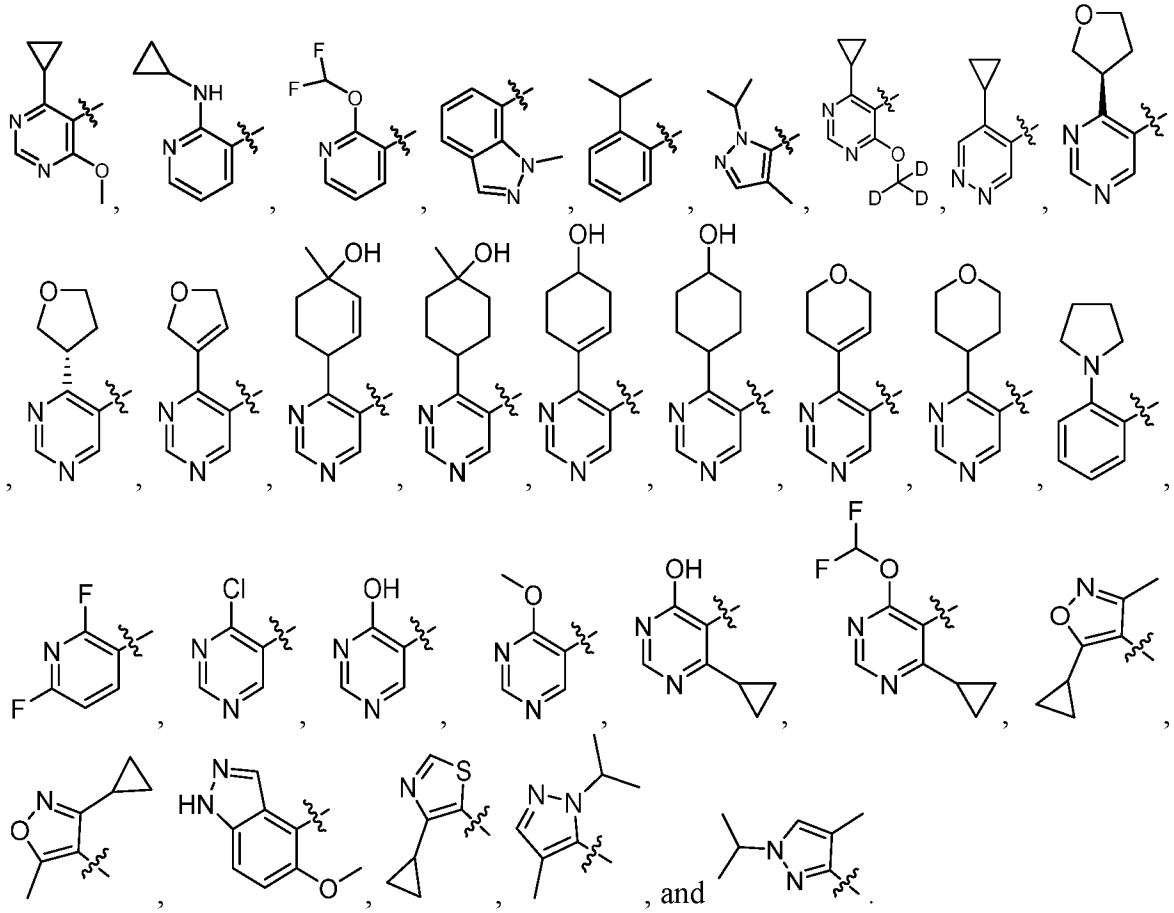
The presently disclosed subject matter relates to compositions comprising USP1 inhibitors and methods of using the same. For example, but not by way of limitation, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:



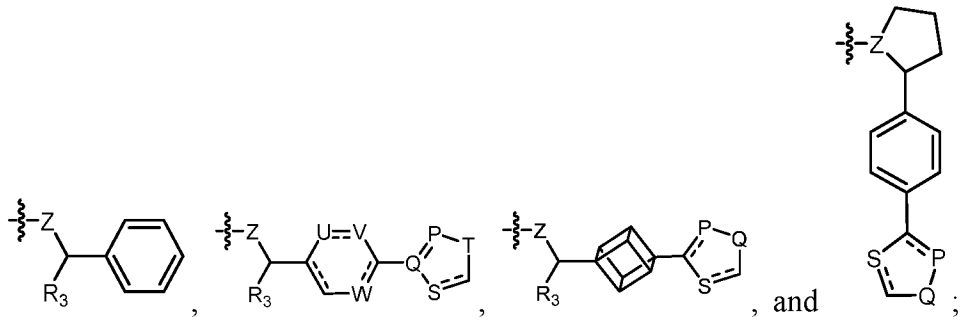
(I).

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_1 is selected from C_3-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-OCD_3$, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, - COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

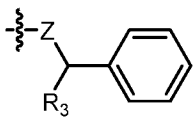
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_1 is selected from:



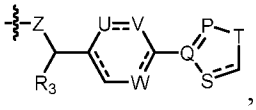
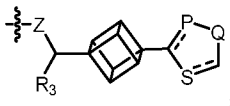
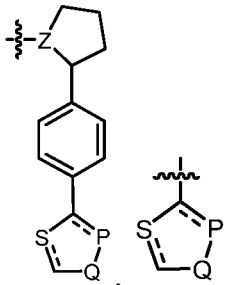
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:

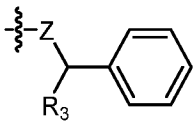


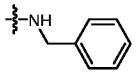
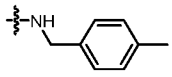
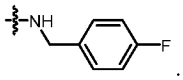
; R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S; wherein Z, U, V, W, P, Q, S, and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when R_2 is

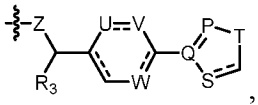


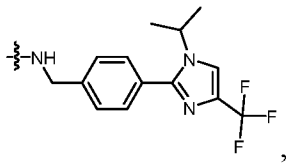
, the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6}

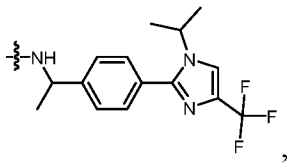
alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when R_2 is  , the 5- or 6-membered ring is saturated or unsaturated; wherein when R_2 is  , the 5-membered ring is saturated or unsaturated; wherein when R_2 is  , is saturated or unsaturated.

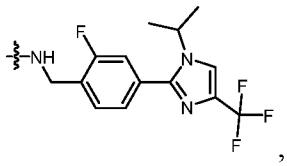
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  , Z is selected from C, O, N, and S; and R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; wherein the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

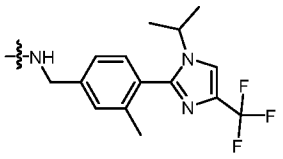
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:  ,  , and  .

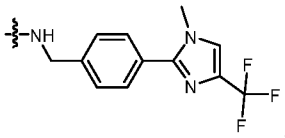
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  , the 5 and 6 membered ring are saturated or unsaturated; R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S, wherein Z, U, V, W, P, Q, S and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6}

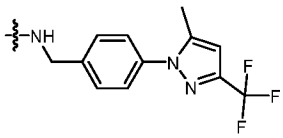


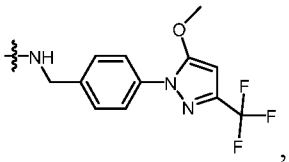


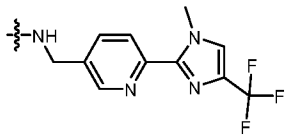


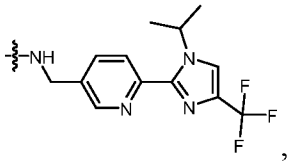


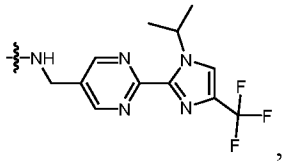


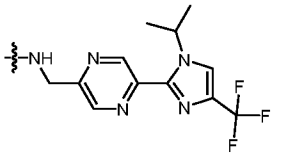


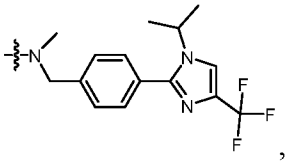


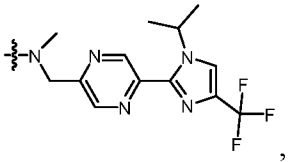


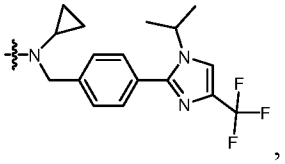


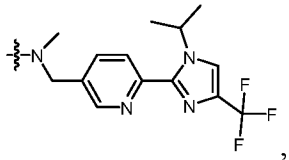


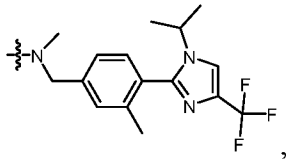


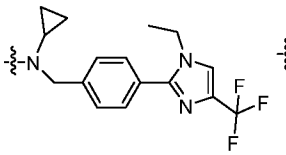


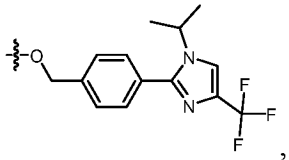


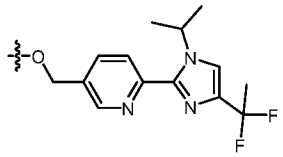


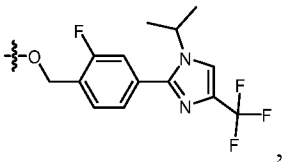


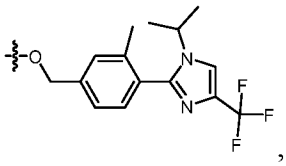


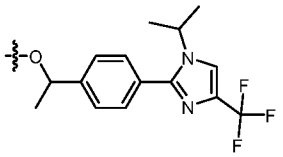


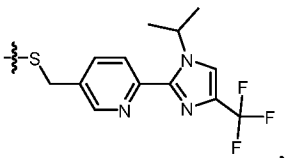


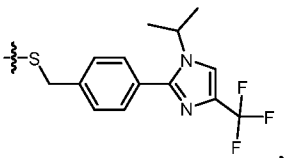


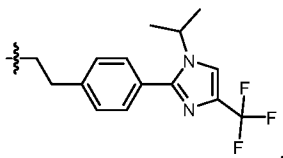


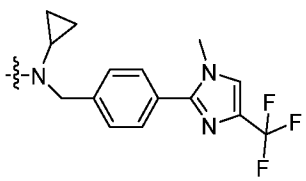


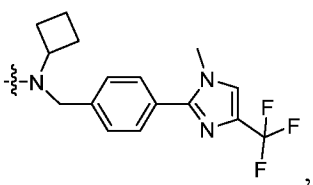


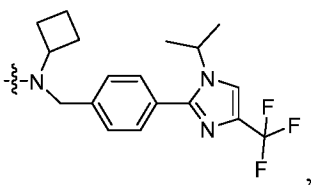












alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof:

wherein R_2 is selected from:

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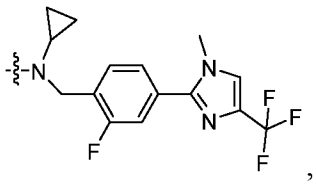
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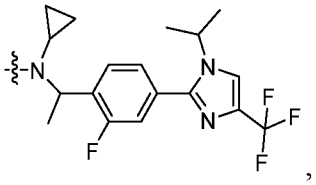
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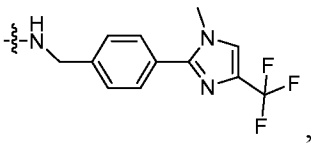
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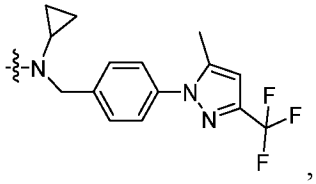
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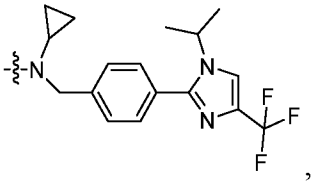
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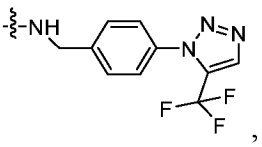
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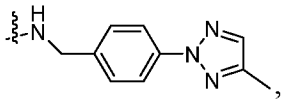
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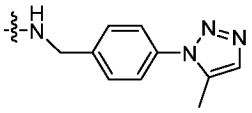
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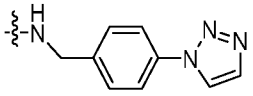
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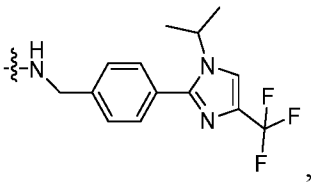
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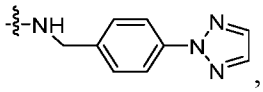
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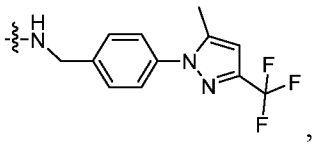
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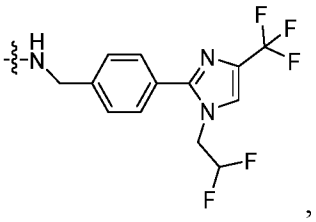
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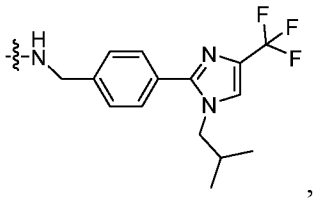
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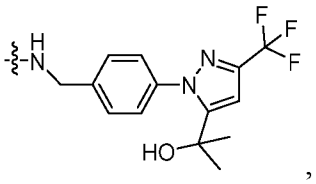
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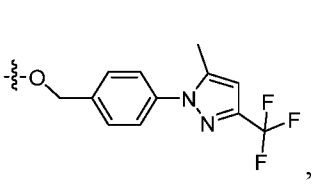
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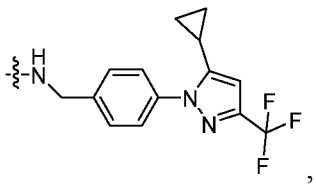
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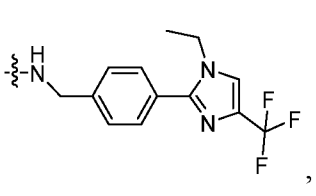
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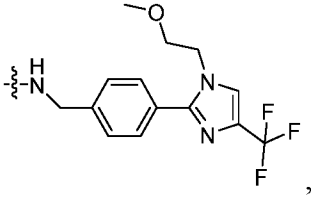
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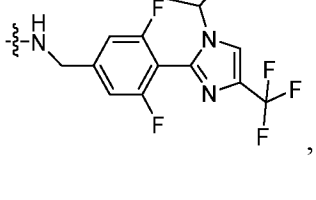
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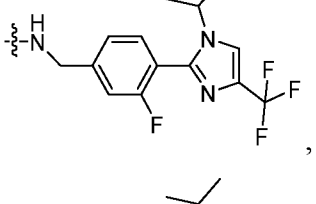
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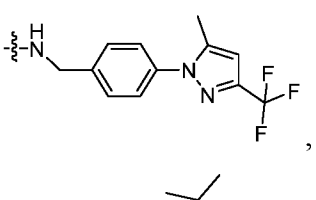
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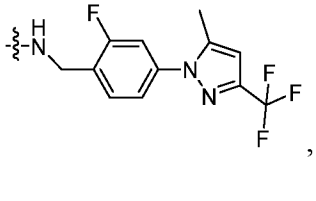
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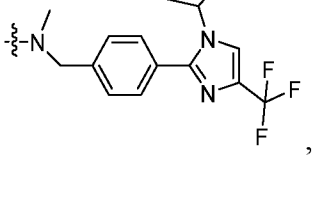
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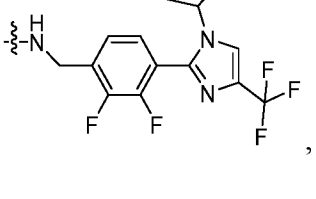
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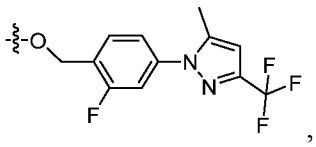
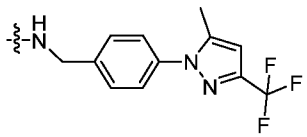
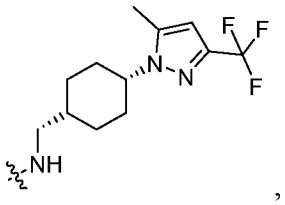
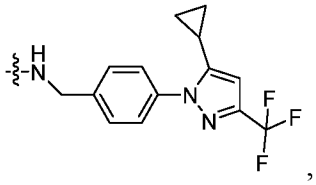
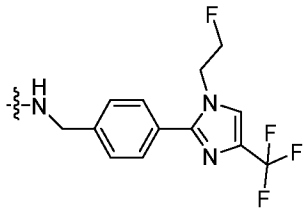
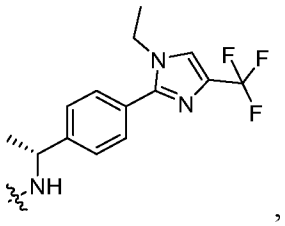
 ,

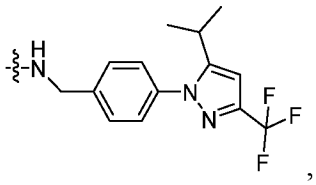
 ,

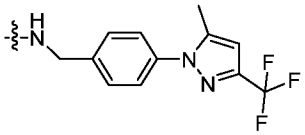
 ,

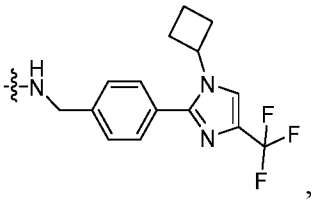
 ,

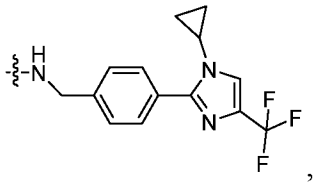
 ,

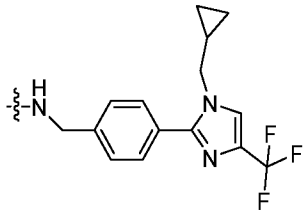
 ,

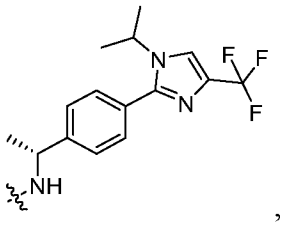
 ,

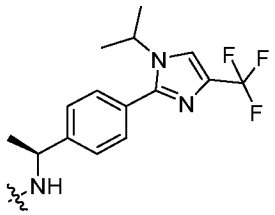
 ,

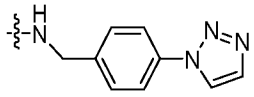
 ,

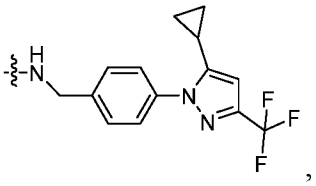
 ,

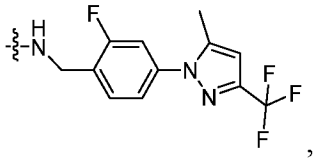
 ,

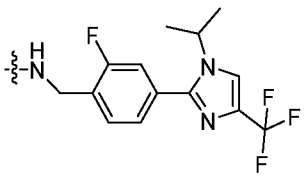
 ,

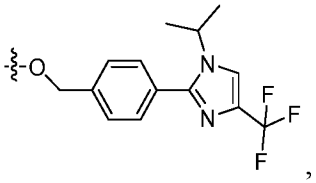
 ,

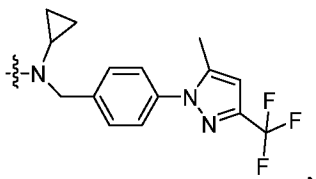
 ,

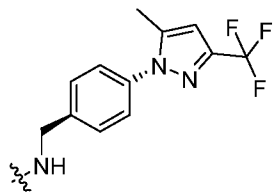
 ,

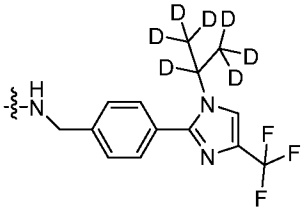
 ,

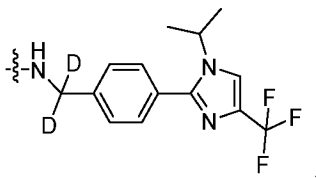
 ,

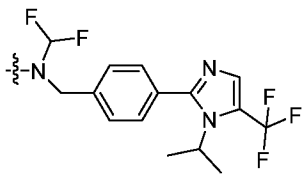
 ,

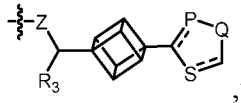
 ,

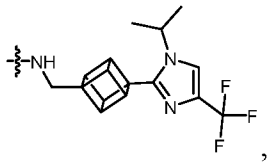
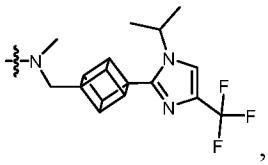
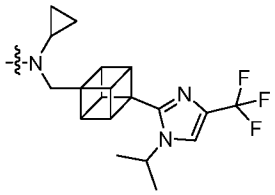
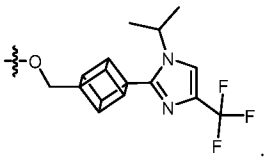
 ,

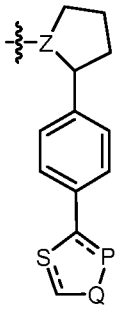
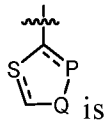
 ,

 , and

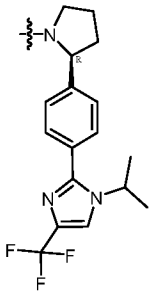
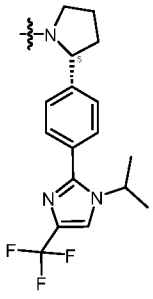
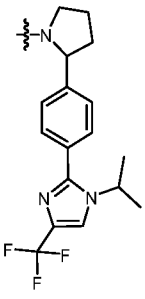
 .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  ,the 5-membered ring is saturated or unsaturated; R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and Z, P, Q, and S are independently selected from C, O, N, and S, wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:  ,  ,  , and  .

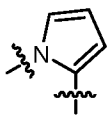
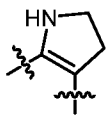
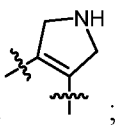
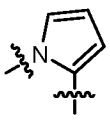
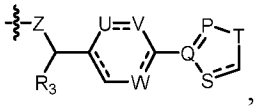
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is  , and  is saturated or unsaturated; Z, P, Q, and S are independently selected from C, O, N, and S, wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

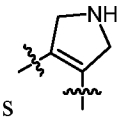
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein R_2 is selected from:

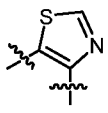
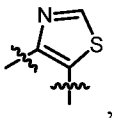
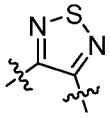
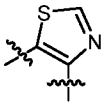
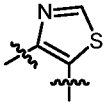
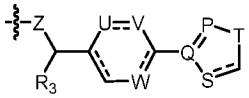
 ,  , and  .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein X_1 is selected from C and N.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein X_2 is selected from C and N; wherein when X_2 is C, the said C is optionally substituted with hydrogen, halogen, -CN, -OR_4, -SR_4, -$N(R_5)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, wherein R_4 and R_5 are independently selected from C_1-C_6 alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a C_6-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl; wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ; wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6}

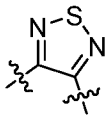
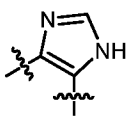
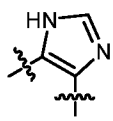
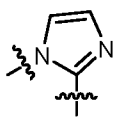
hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

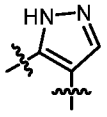
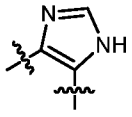
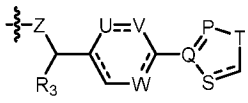
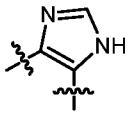
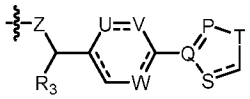
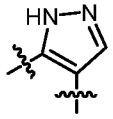
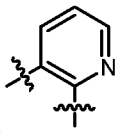
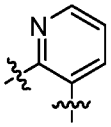
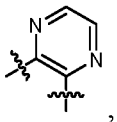
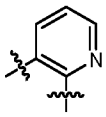
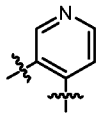
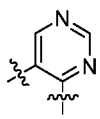
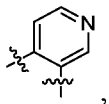
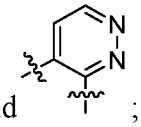
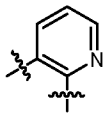
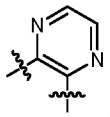
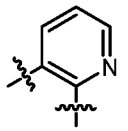
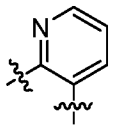
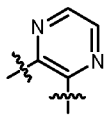
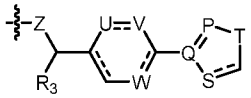
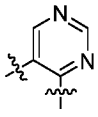
wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl; wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N; wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

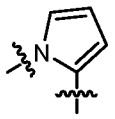
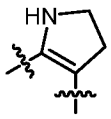
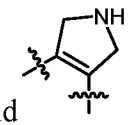
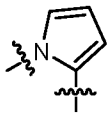
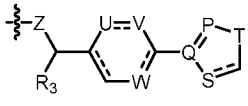
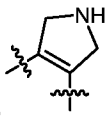
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

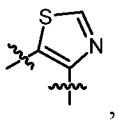
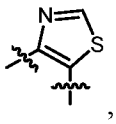
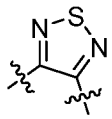
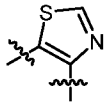
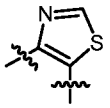
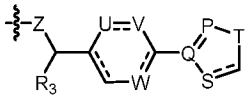
(ii) S or P are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

(iii) V or W are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  ,

and  ;wherein when ring A is  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ,  ,  ,  ,  ,  ,  , and  ; wherein when ring A is  or  , Z is O; wherein when ring A is  ,  or  , Z is O and R_2 is  , P and S, are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is  , Z is N, ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl. wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ; wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl; wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from

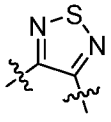







, , or , where Z is N; wherein when ring A is selected from or , Z is N, and R_2 is where S and P are N, wherein:

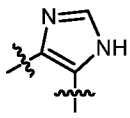
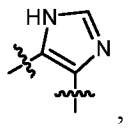
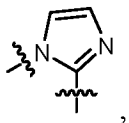
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

(ii) S or P are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

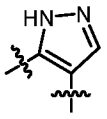
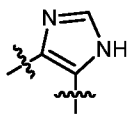
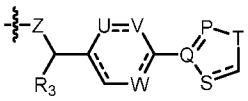
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;



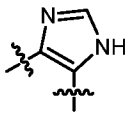
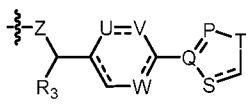
wherein when ring A is and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from

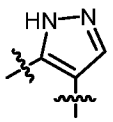
, , ,

and ; wherein when ring A is , Z is O, and R_2 is where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A

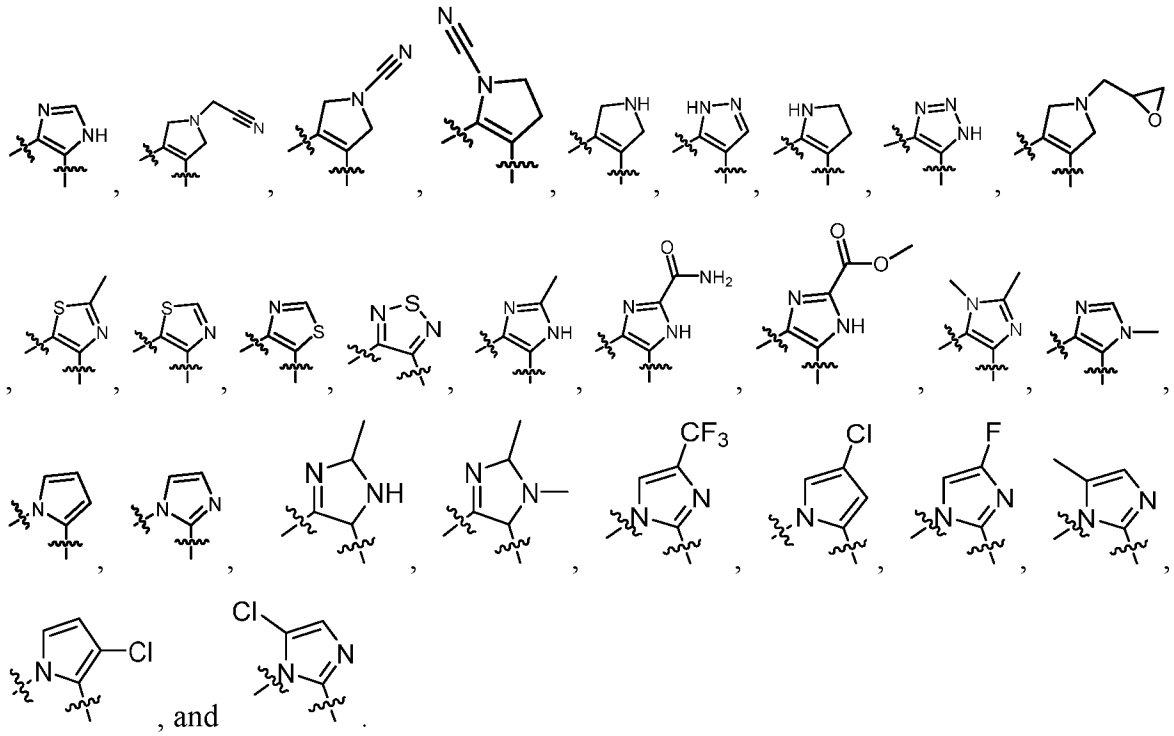



is , Z is O, and R_2 is where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring; wherein when ring A is and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$,

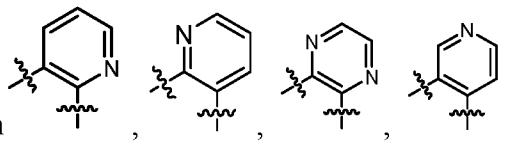


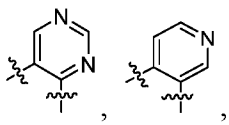
halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring.

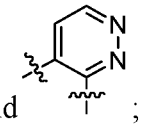
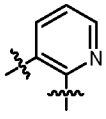
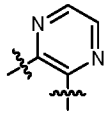
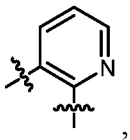
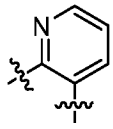
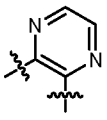
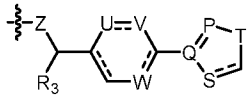
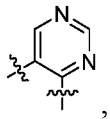
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from:

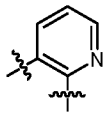


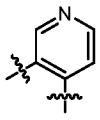
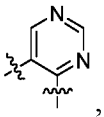
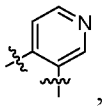
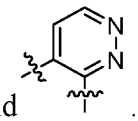
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from



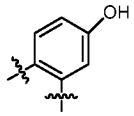



; wherein when ring A is  or  , Z is O; wherein when ring A is  ,  or  , Z is O and R_2 is  , P and S, are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring; wherein when ring A is  , Z is N, ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

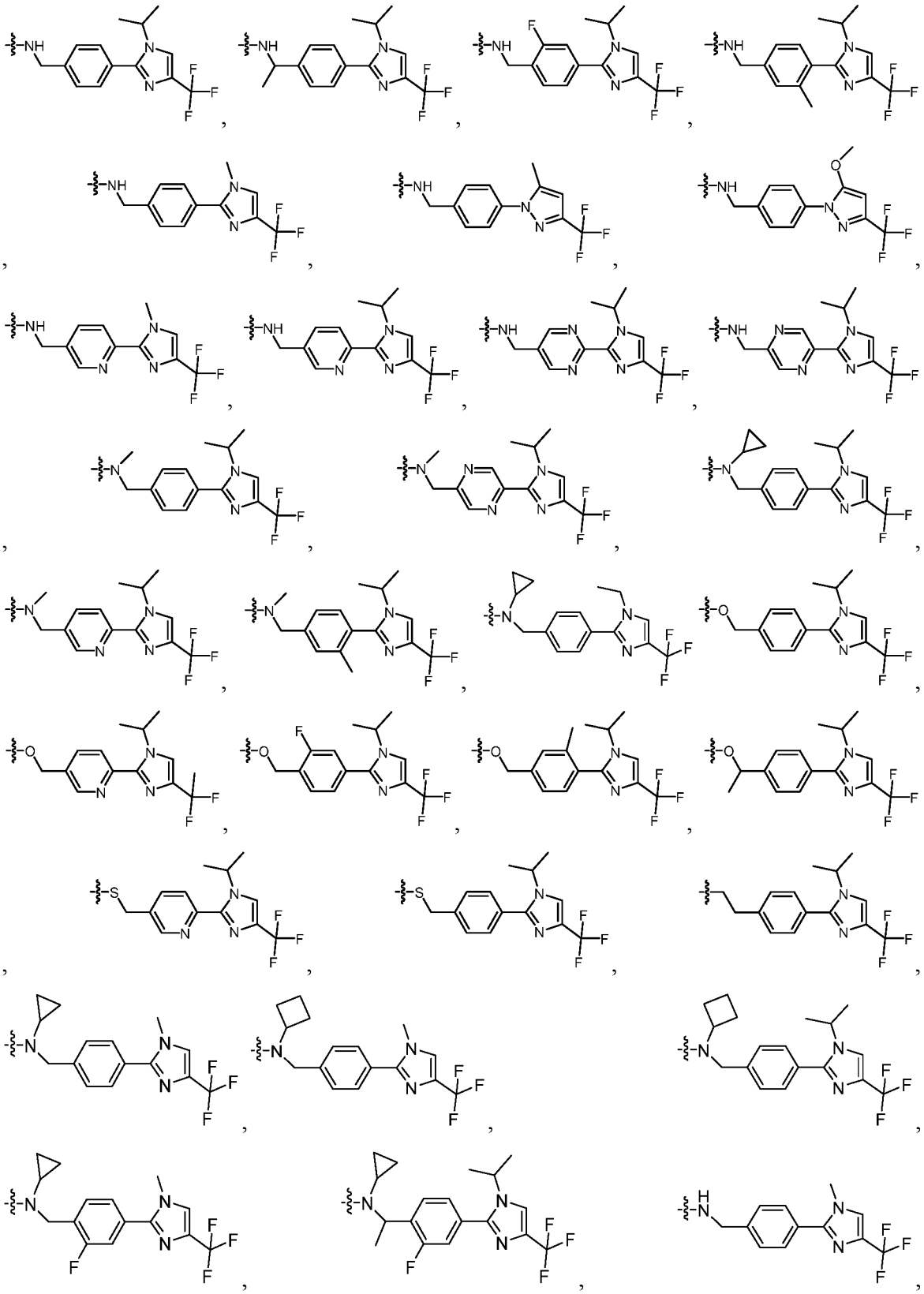
In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from: 

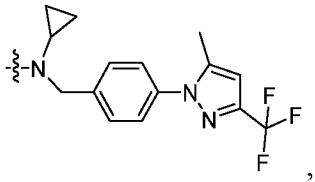



, and  .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is a C_6-C_{10} aryl; wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide; wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl; wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide; wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein ring A is  .

In certain embodiments, the present disclosure is directed to a compound of formula (I), or a pharmaceutically acceptable salt thereof: wherein the compound is selected from:

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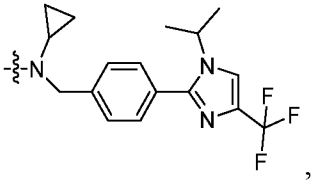
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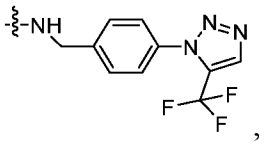
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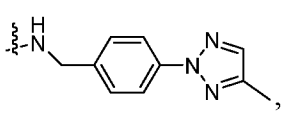
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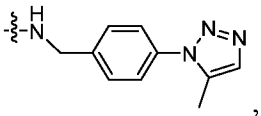
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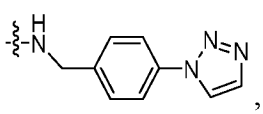
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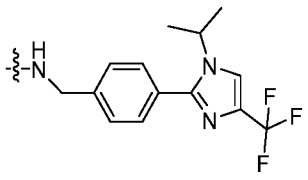
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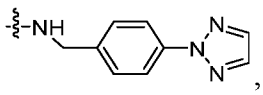
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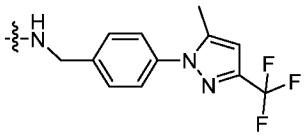
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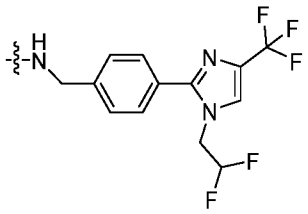
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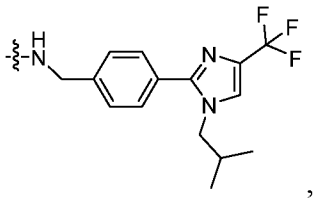
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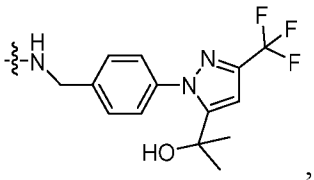
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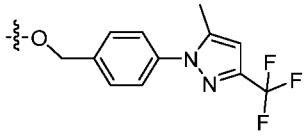
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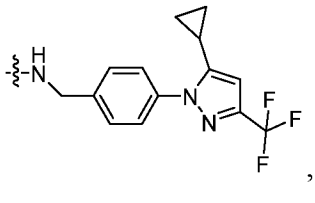
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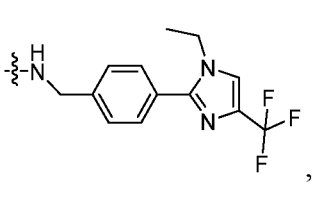
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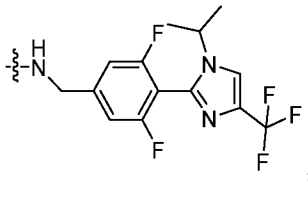
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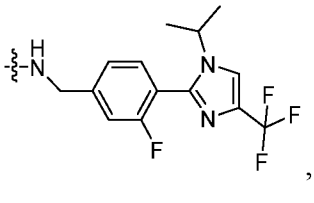
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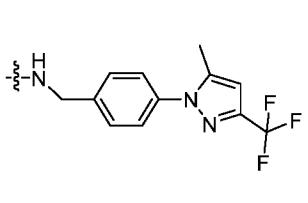
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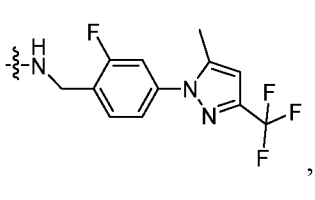
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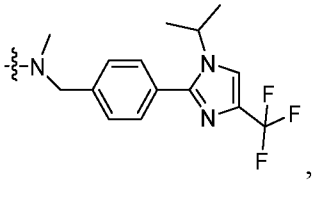
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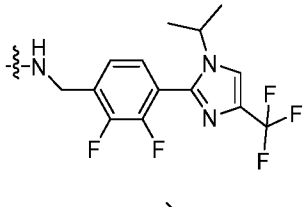
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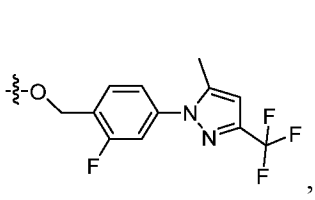
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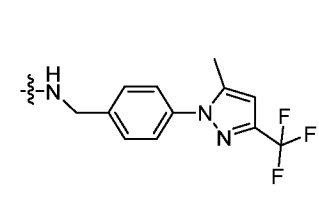
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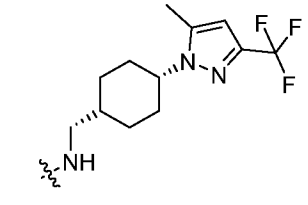
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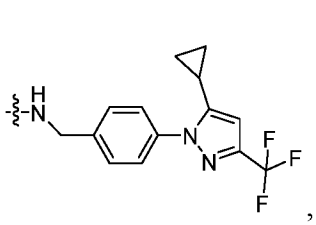
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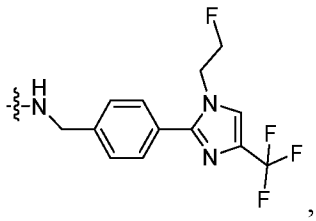
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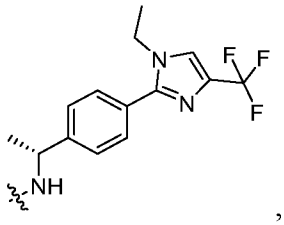
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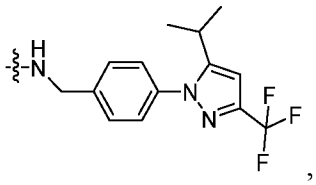
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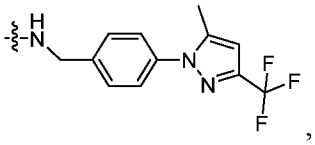
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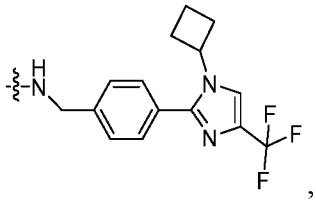
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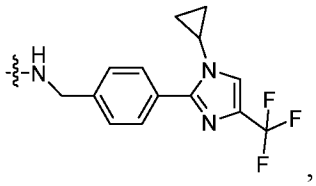
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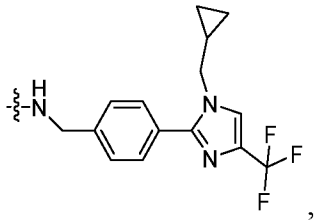
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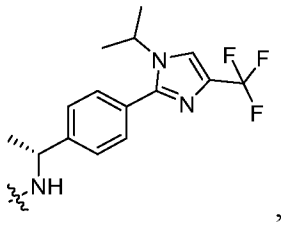
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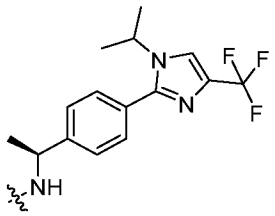
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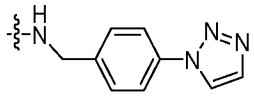
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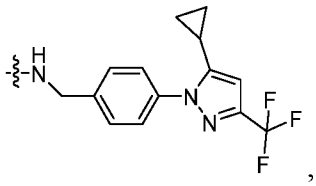
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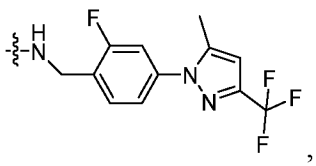
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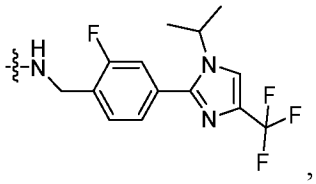
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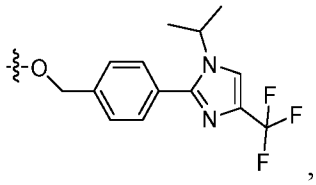
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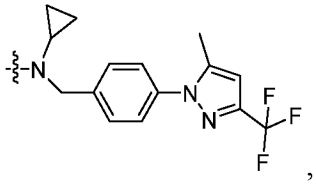
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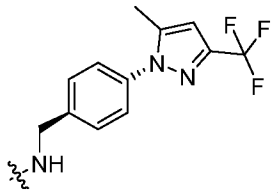
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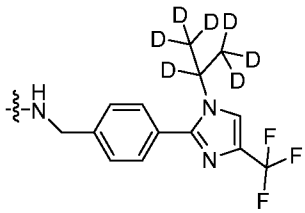
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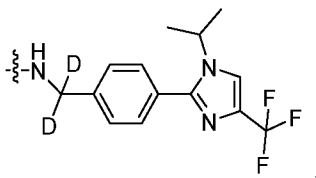
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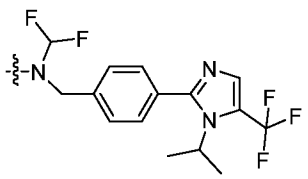
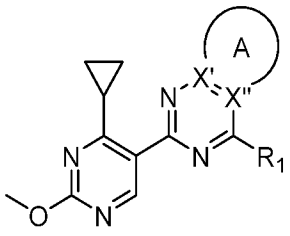
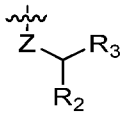
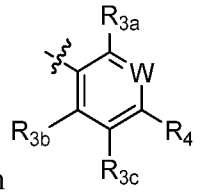
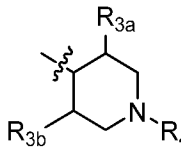
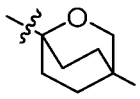
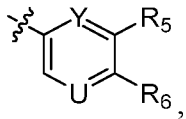
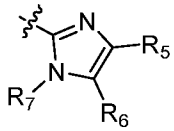
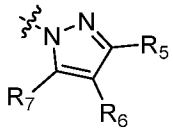
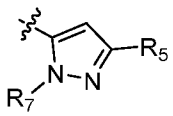
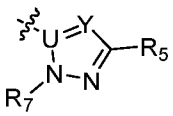
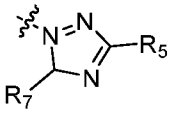
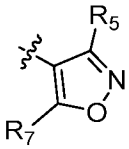
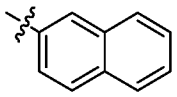

.

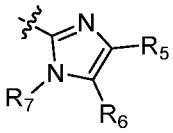
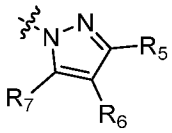
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof:

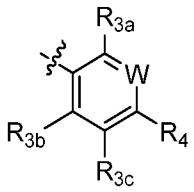
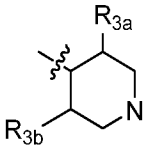
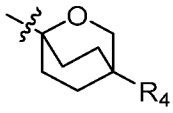


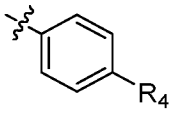
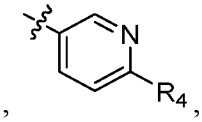
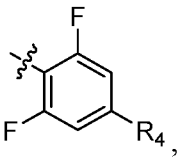
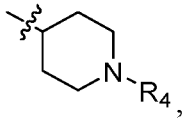
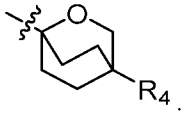
(II).

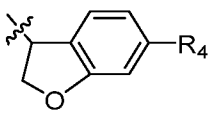
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: X' and X" are independently selected from N or C.

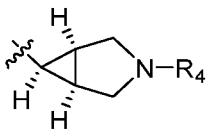
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_1 is  wherein Z is selected from O or N optionally substituted with R_{1a} or $-CH_2R_{1a}$, wherein R_{1a} is C_3-C_6 cycloalkyl or 4-, 5-, or 6- membered heterocyclyl; wherein R_2 is selected from H or deuterium; R_3 is selected from  ,  , and  , wherein W is selected from C or N, and wherein R_{3a}, R_{3b}, and R_{3c} are independently selected from -H or halogen, R_{3a} and R_2 optionally form a bond to form a 5- or 6-membered heterocyclyl, or R_{3a} and R_{3b} optionally combine to form a bridge; R_4 is selected from  ,  ,  ,  ,  ,  ,  , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C; wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl

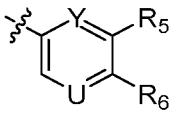
ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  ;and wherein R_{3c} optionally forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen.

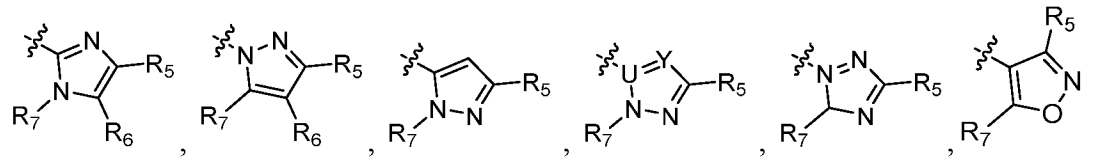
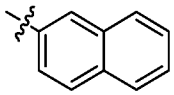
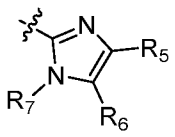
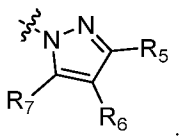
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_3 is selected from  ,  , and  , wherein W is selected from N or C.

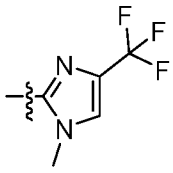
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_3 is selected from  ,  ,  ,  , and  .

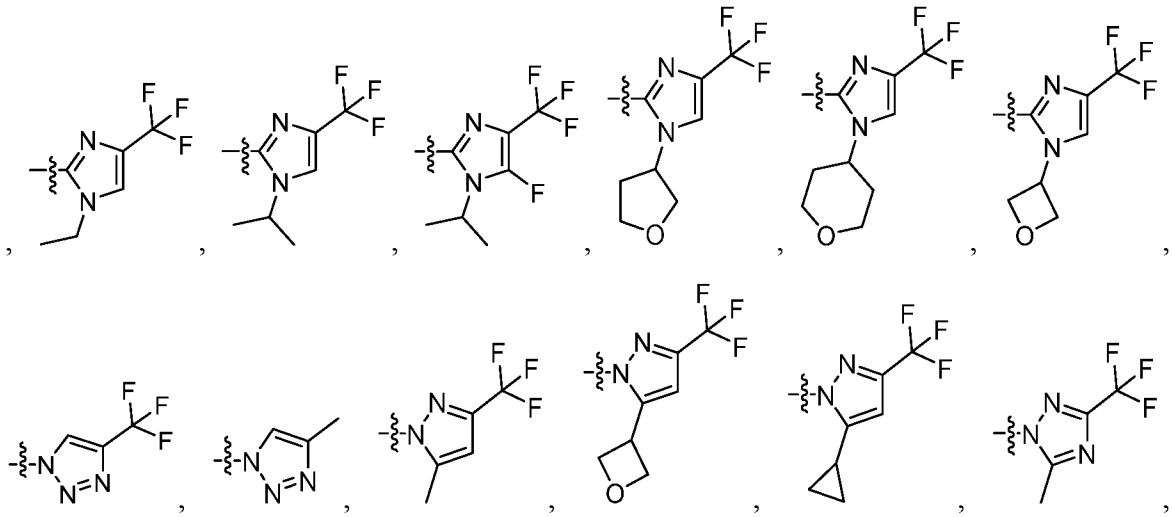
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_3 is  .

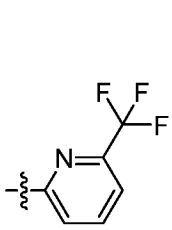
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_{3b} combine to form a bridge, R_3 is  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_4 is selected from 

 , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C; wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein R_4 is selected from: 

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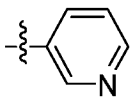
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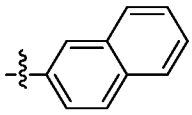
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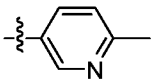
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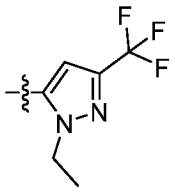
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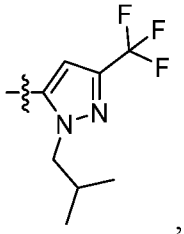
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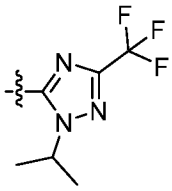
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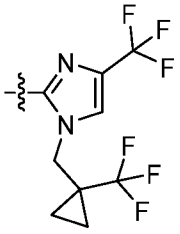
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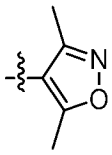
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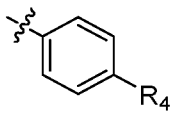
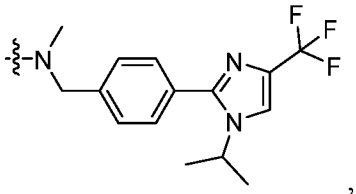
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is selected from: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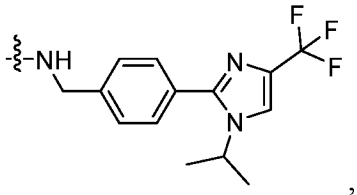
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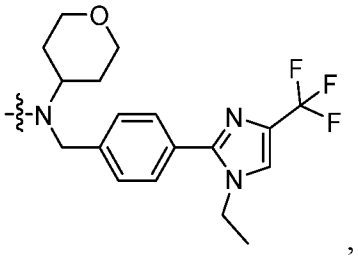
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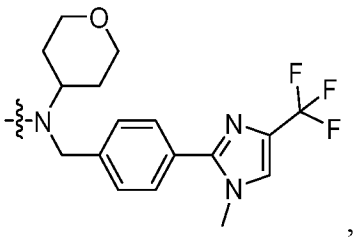
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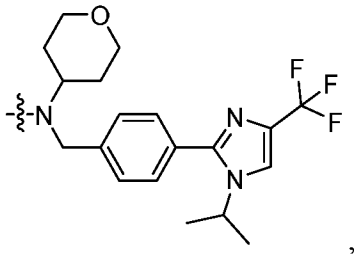
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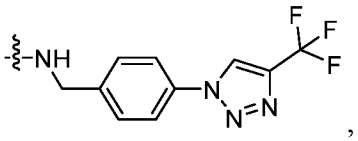
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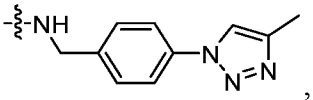
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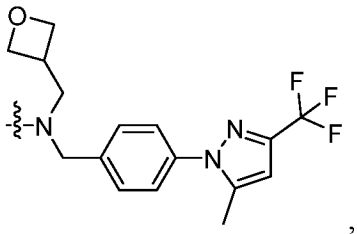
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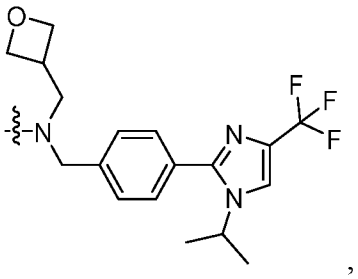
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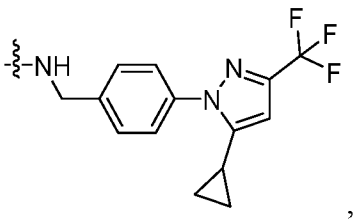
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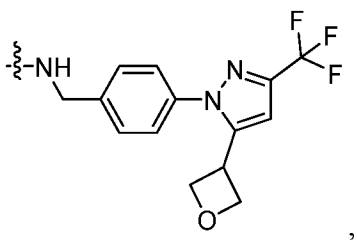
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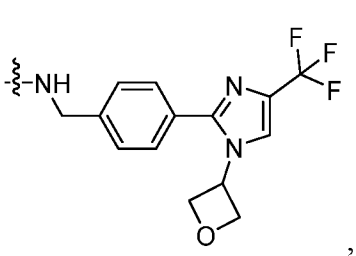
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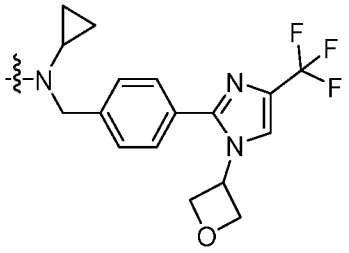
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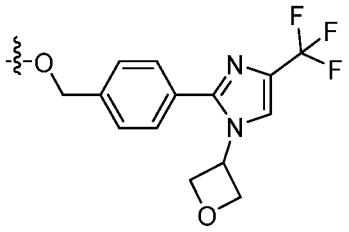
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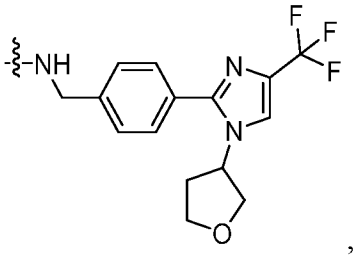
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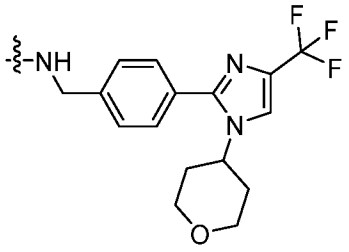
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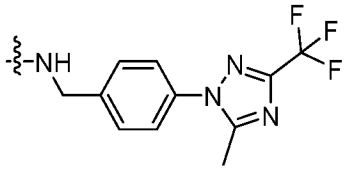
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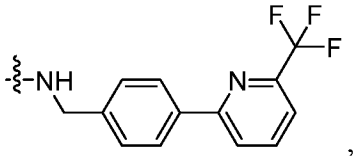
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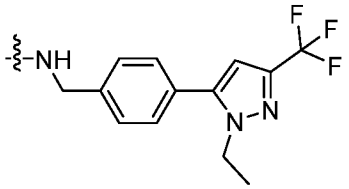
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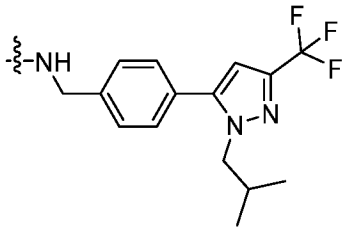
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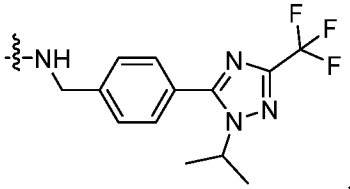
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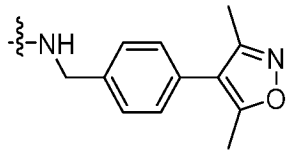
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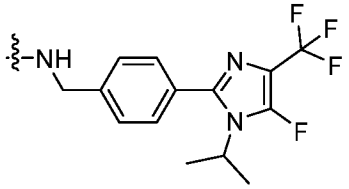
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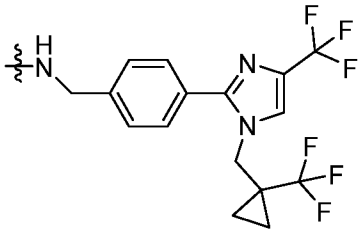
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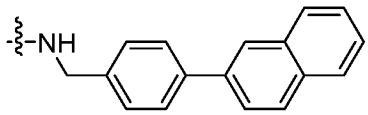
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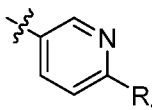
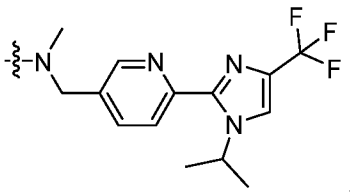
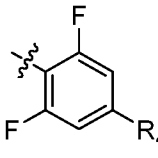
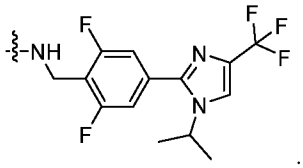
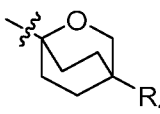
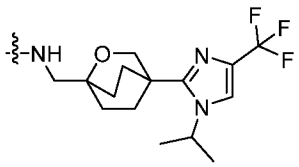
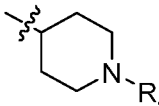
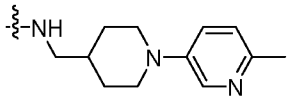
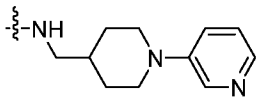
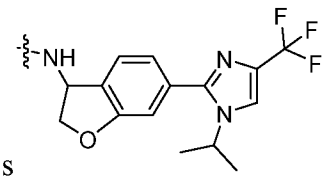
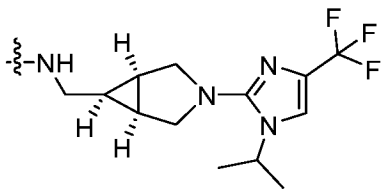
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is  ,

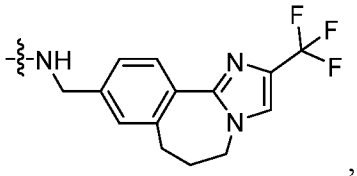
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_3 is  , R_1 is selected from  and  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_1 is  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3a} and R_{3b} combine to form a bridge, R_1 is  .

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when R_{3c} forms a bond with R_5

or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen, R_1 is selected from: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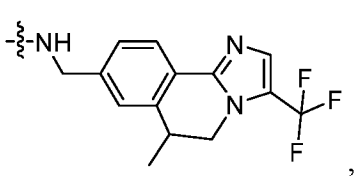
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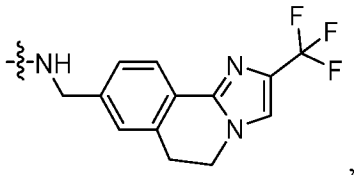
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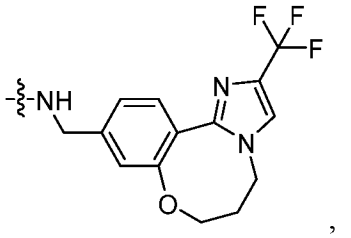
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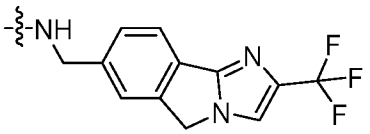
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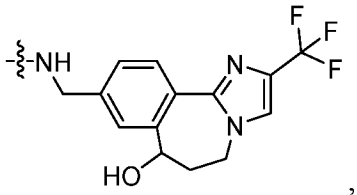
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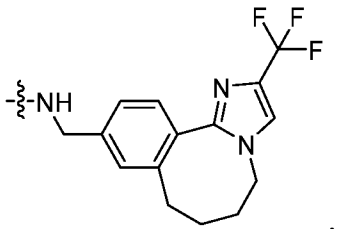
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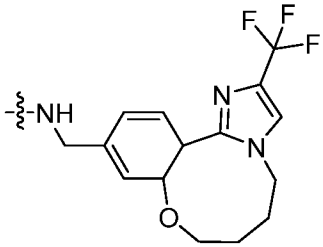
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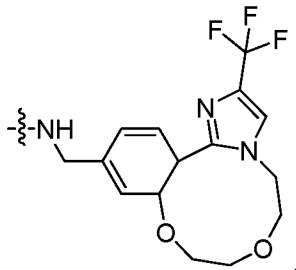
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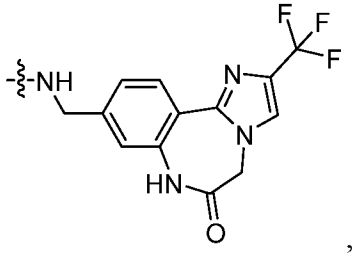
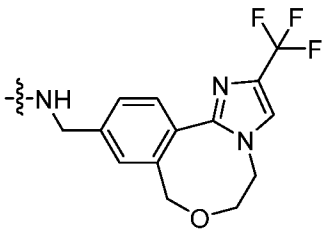
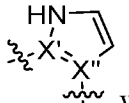
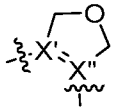
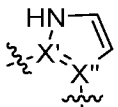
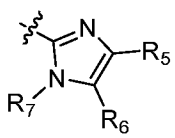
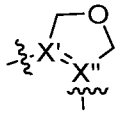
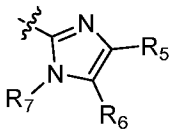
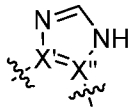
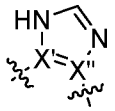
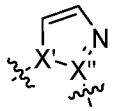
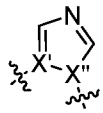
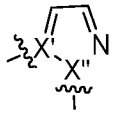
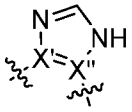
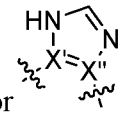
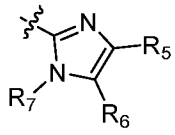
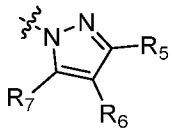
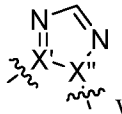
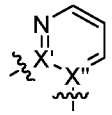
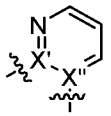
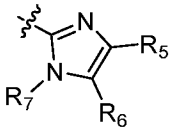
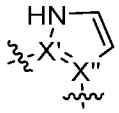
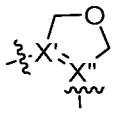
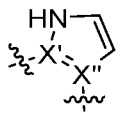
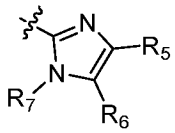
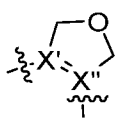
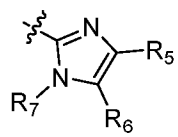
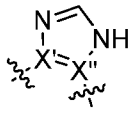
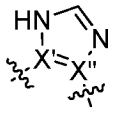
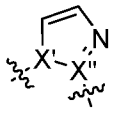
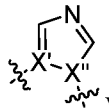
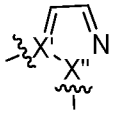
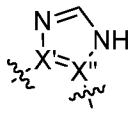
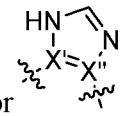
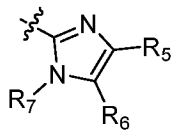
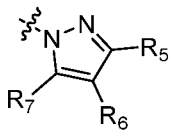
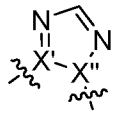

, and

.

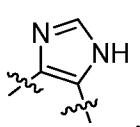
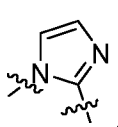
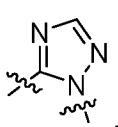
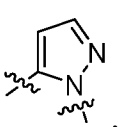
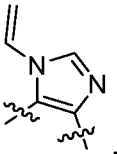
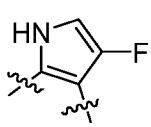
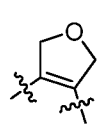
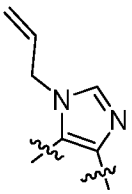
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is a 5- or 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C; wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl,

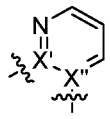
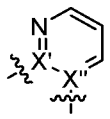
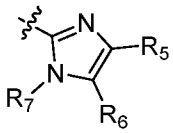
C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N; wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N; wherein when R

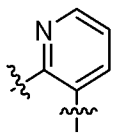
ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

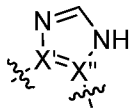
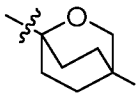
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein Ring A is a 5- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C; wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered

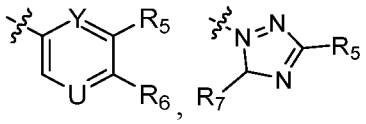
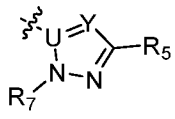
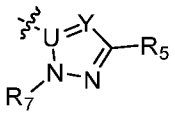
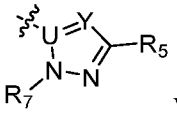
heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N; wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

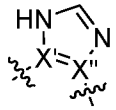
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is selected from:  ,  ,  ,  ,  ,  ,  , and  .

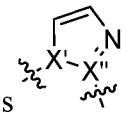
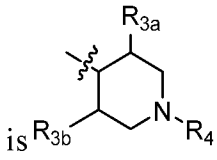
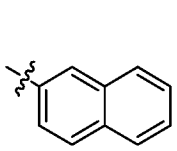
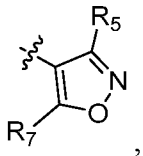
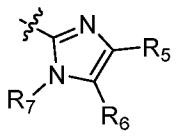
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein Ring A is a 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S; wherein when R ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N; wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring; wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein ring A is  .

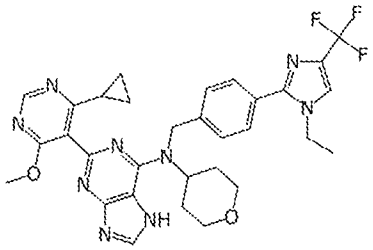
In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when ring A is  where X' and X" are C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of: Z is substituted with R_{1a} or $-CH_2R_{1a}$, R_{3a} and R_{3b} are halogen, R_5, R_6, or R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_3 is  , R_4 is

 , , or  where U and Y are C,  where U is C and Y is N, or R_3 is  where U is N and Y is C, or a combination thereof.

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when ring A is  where X' and X" are C , the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises a ring A substituted with a C_2-C_6 alkenyl.

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein when ring A is  where X' is N and X" is C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of: R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_{3a} and R_{3b} combine to form a bridge, R_3 is  , R_4 is  ,  , or  , R_5, R_6, or R_7 a 4-, 5-, or 6- membered heterocyclyl ring, R_{3c} forms a bond with R_5 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12-membered heterocyclyl or C_5-C_{12} cycloalkyl, or a combination thereof.

In certain embodiments, the present disclosure is directed to a compound of formula (II), or a pharmaceutically acceptable salt thereof: wherein the compound is selected from: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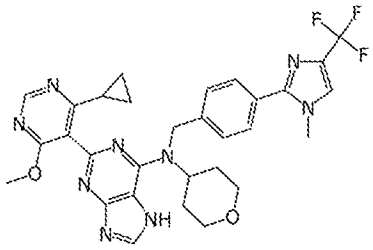
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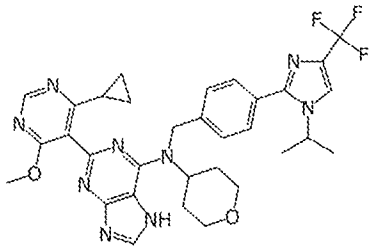
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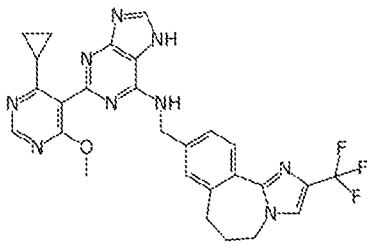
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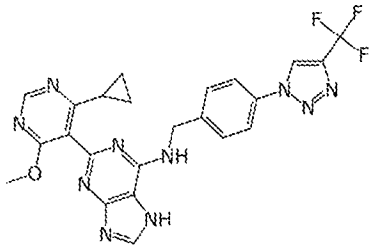
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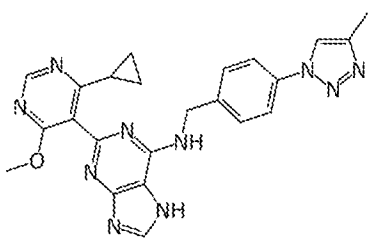
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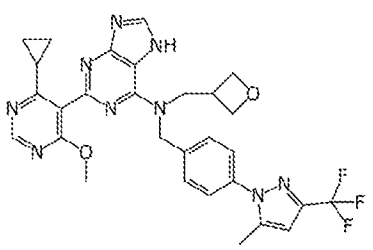
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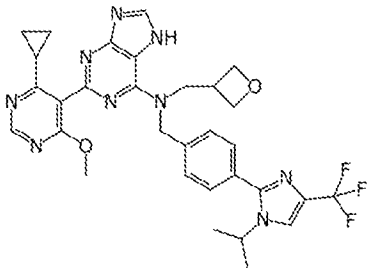
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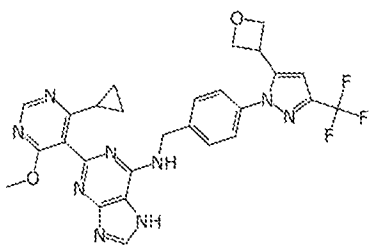
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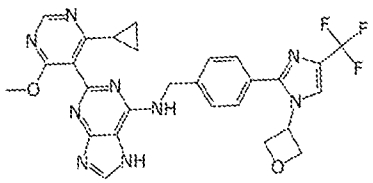
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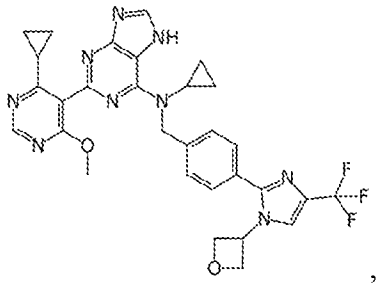
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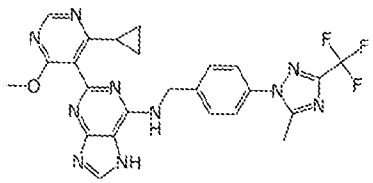
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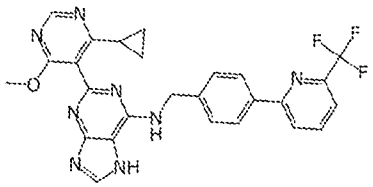
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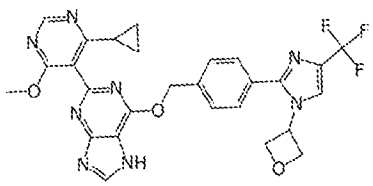
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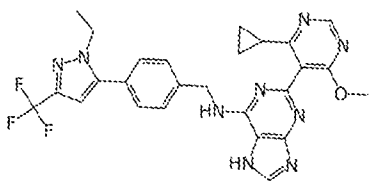
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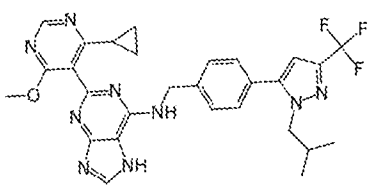
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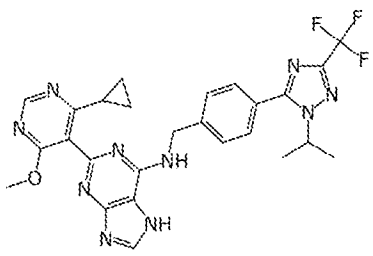
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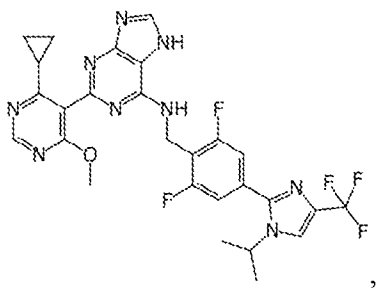
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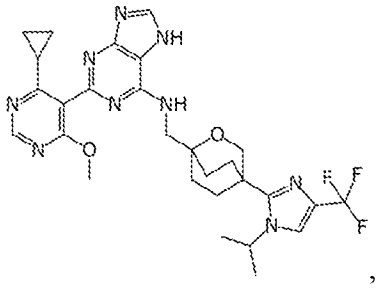
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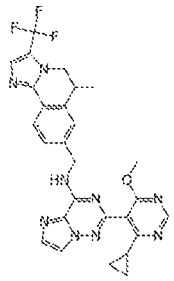
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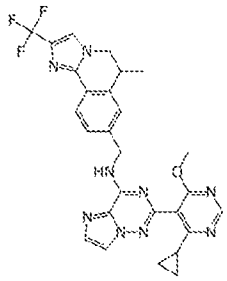
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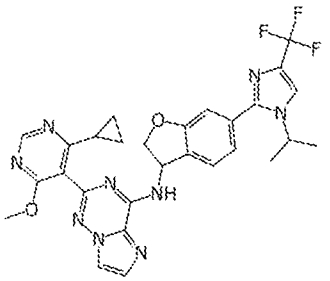
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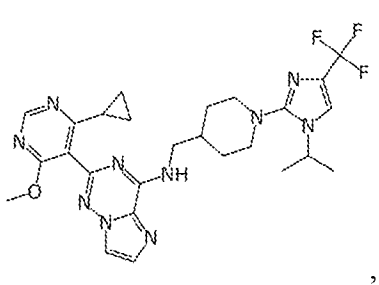
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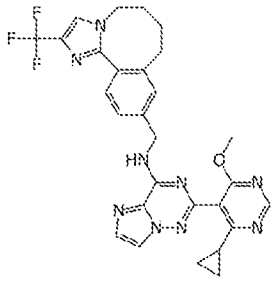
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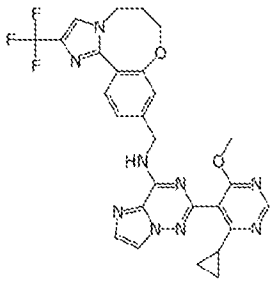
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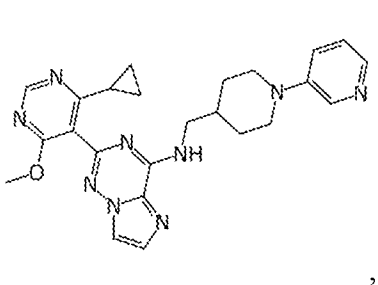
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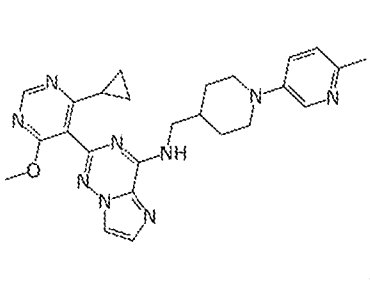
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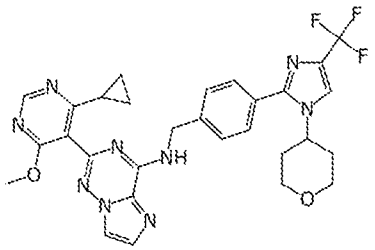
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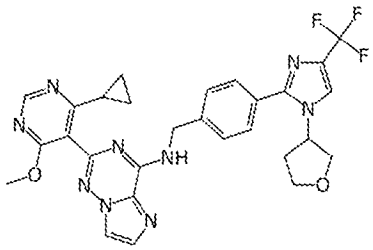
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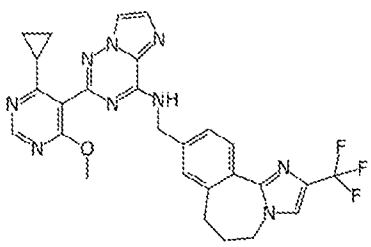
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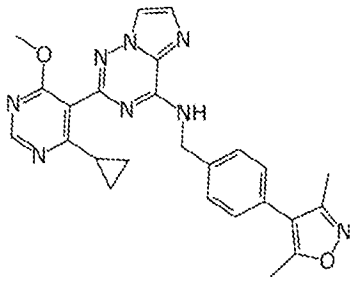
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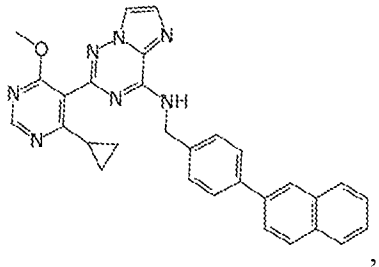
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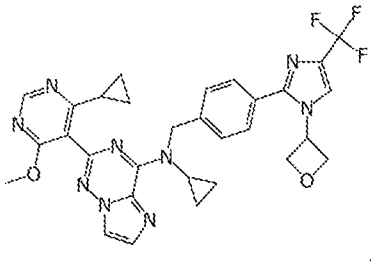
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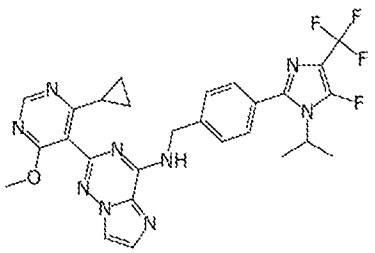
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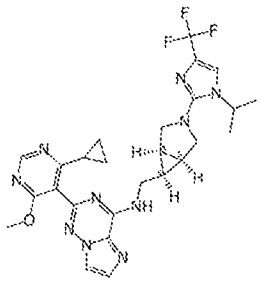
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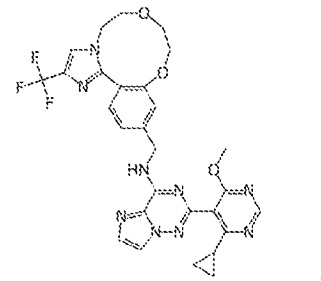
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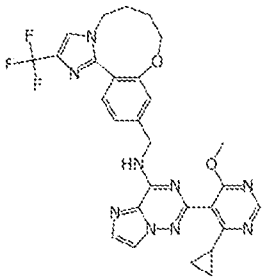
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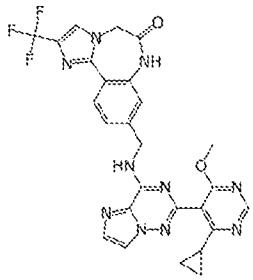
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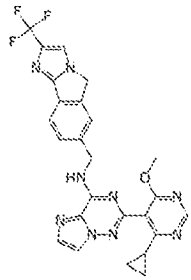
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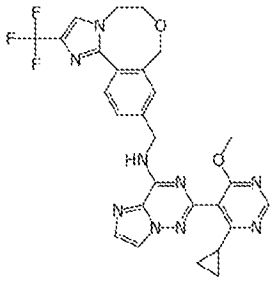
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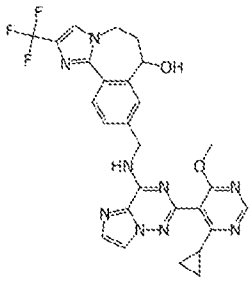
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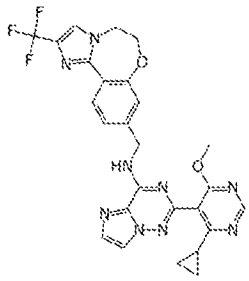
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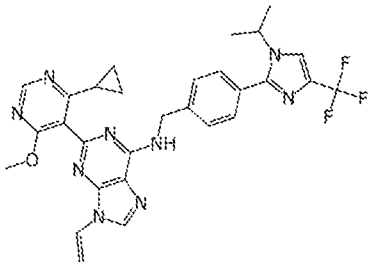
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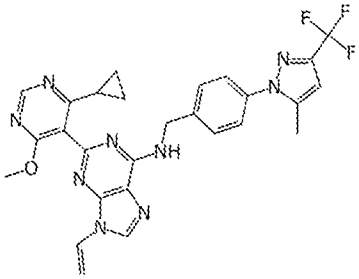
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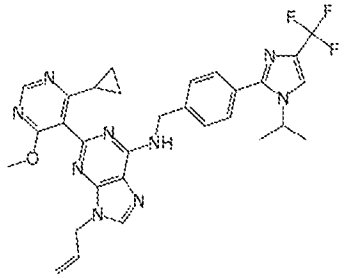
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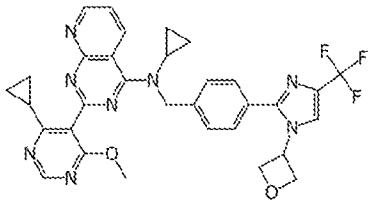
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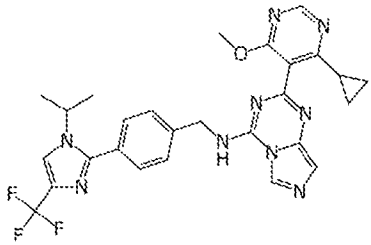
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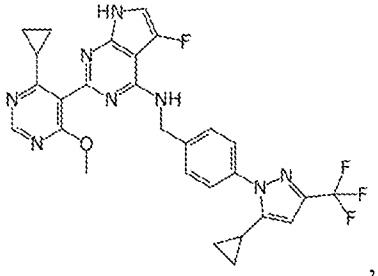
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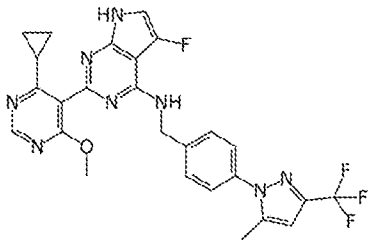
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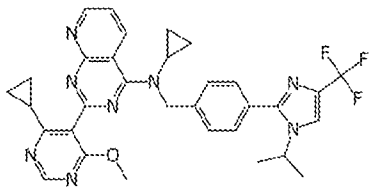
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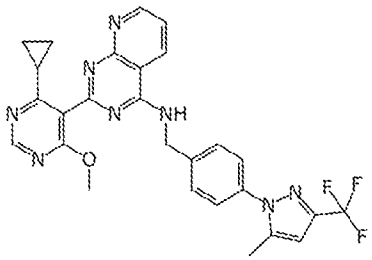
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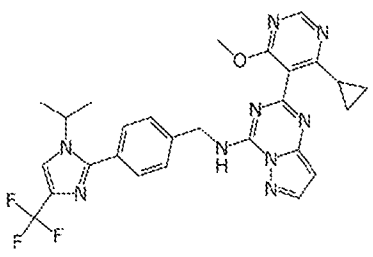
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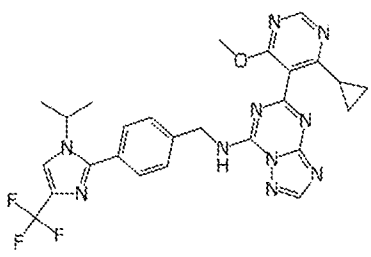
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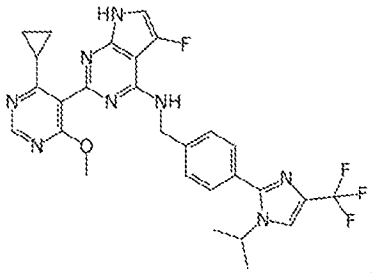
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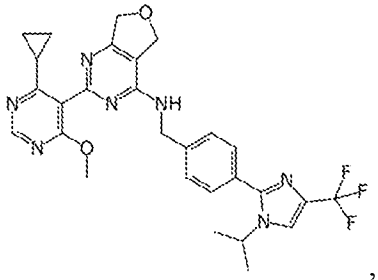
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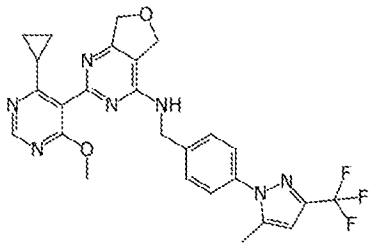
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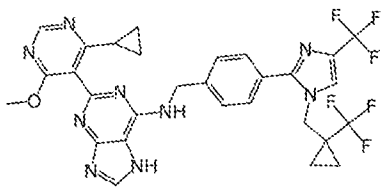
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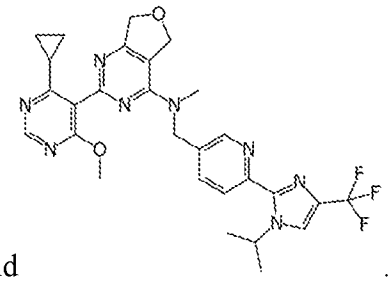

and .

3. Methods of Use

In certain embodiments, the present disclosure is directed to a method of modulating USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of inhibiting USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating a disorder or disease with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating cancer with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present disclosure is directed to a method of treating cancer with a USP1 inhibitor in a subject, comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein the cancer is characterized by over expression of USP1.

In certain embodiments, the present disclosure is directed to a method treating cancer with a USP1 inhibitor in a subject, comprising administering a compound of formula (I), or

a pharmaceutically acceptable salt thereof, wherein the cancer characterized by overexpression of USP1 is selected from prostate, breast, ovarian, non-small cell lung cancer, mesothelioma, Merkel cell carcinoma, synovial sarcoma, renal cell carcinoma, and osteosarcoma.

In certain embodiments, the present disclosure is directed to a use of a compound of formula (I), or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer.

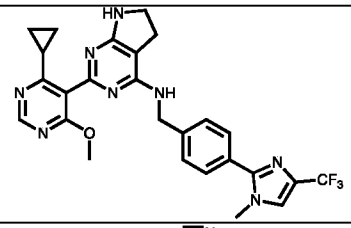
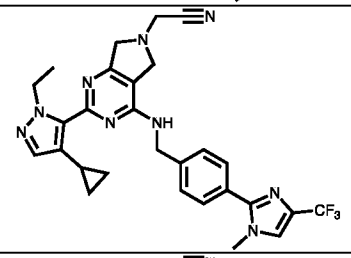
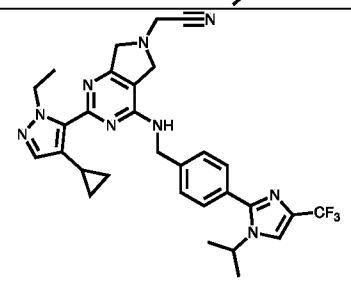
In certain embodiments, the present disclosure is directed to a use of a compound of formula (I), or pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer, wherein the cancer is characterized by overexpression of USP1.

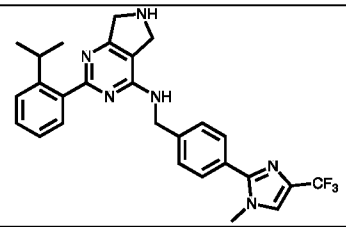
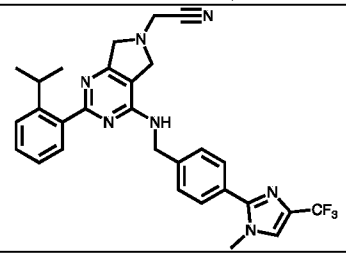
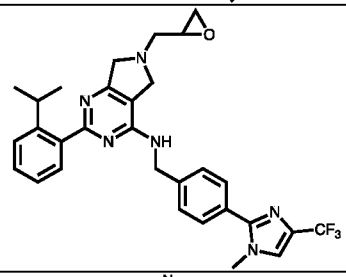
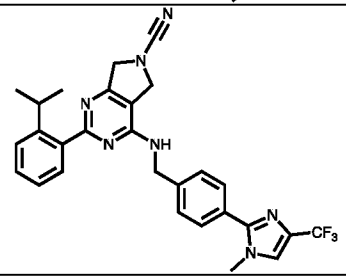
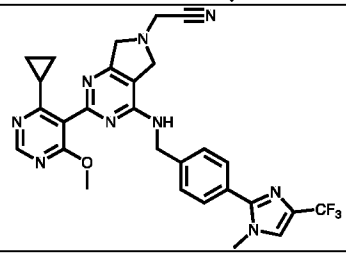
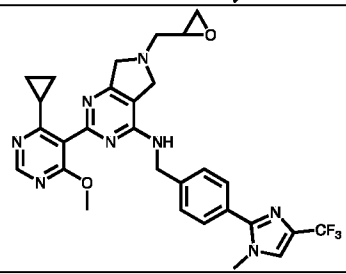
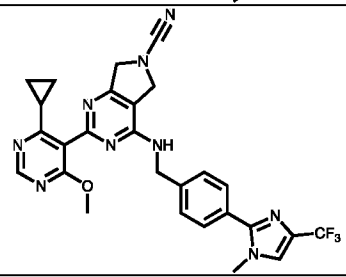
In certain embodiments, the present disclosure is directed to a process to manufacture a compound of formula (I), or a pharmaceutically acceptable salt thereof.

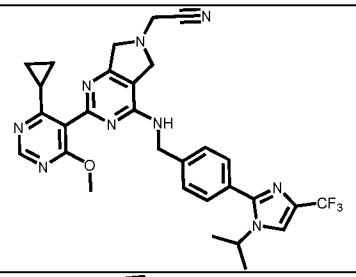
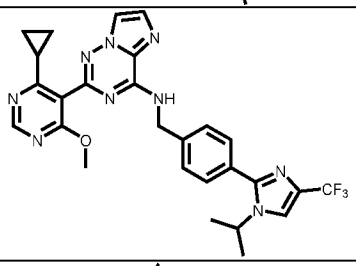
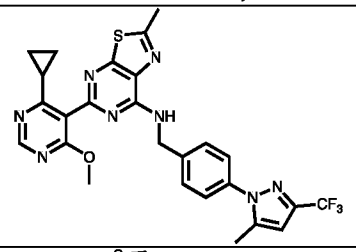
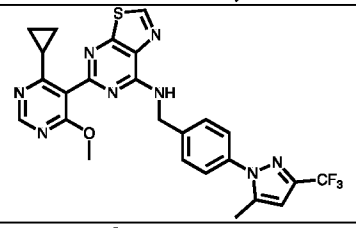
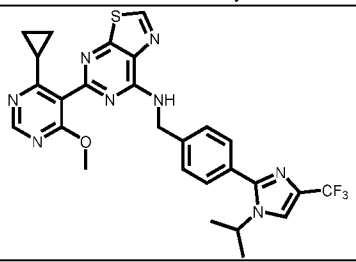
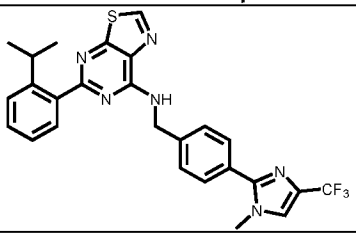
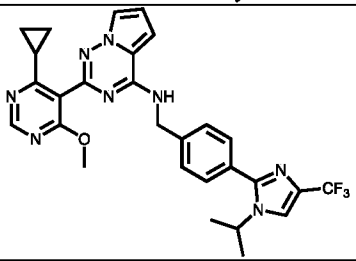
4. Examples

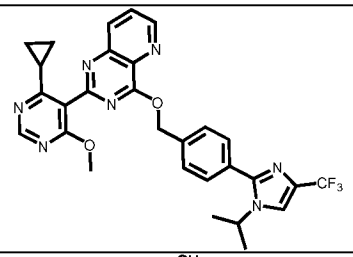
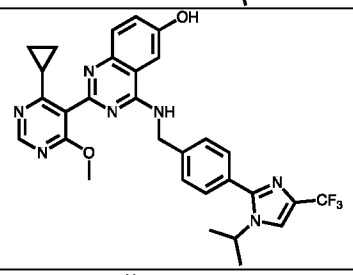
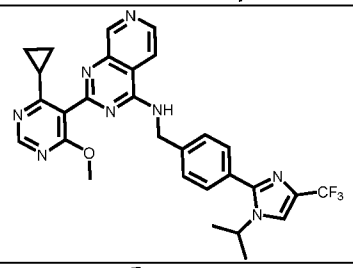
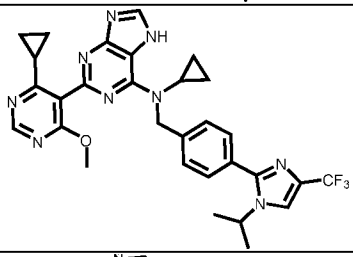
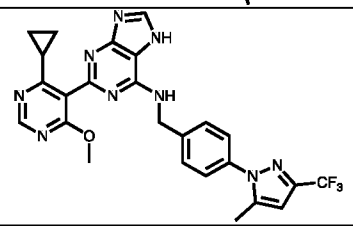
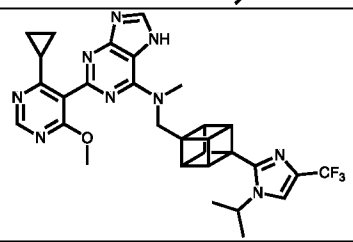
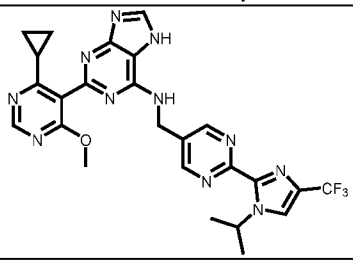
The following Examples are presented by way of illustration, not limitation. One skilled in the art can modify the procedures set forth in the illustrative examples to arrive at the desired products.

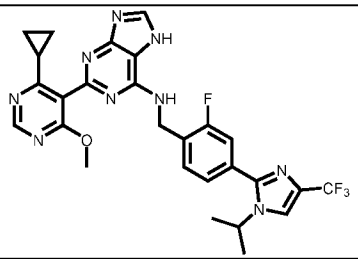
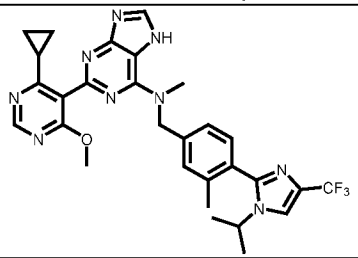
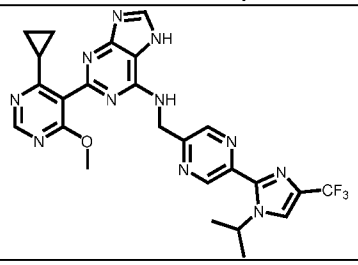
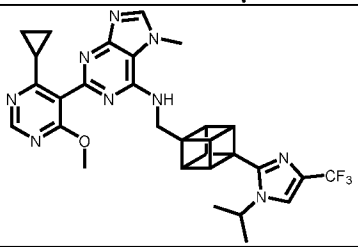
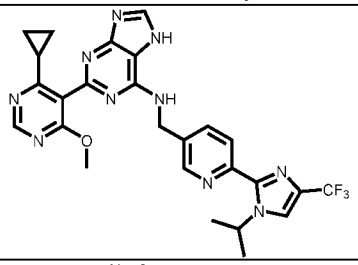
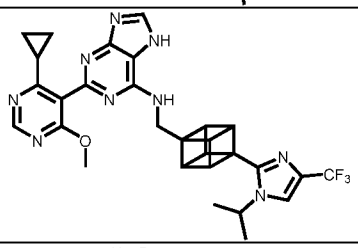
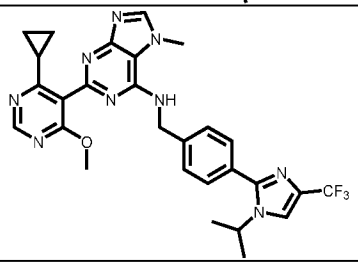
[0001] Table 1: Exemplary compounds.

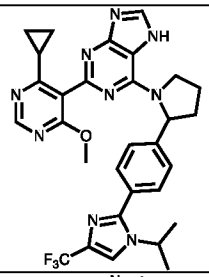
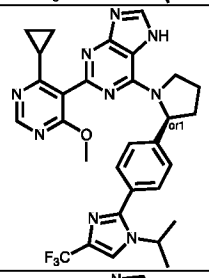
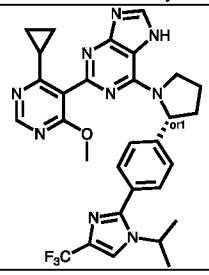
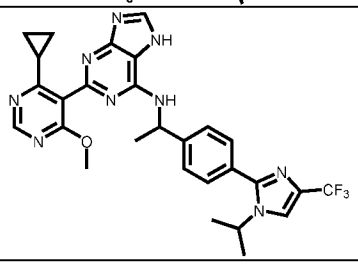
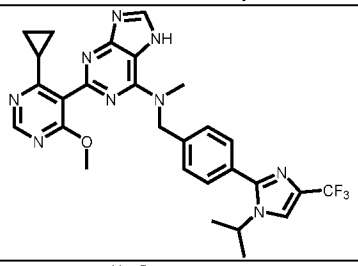
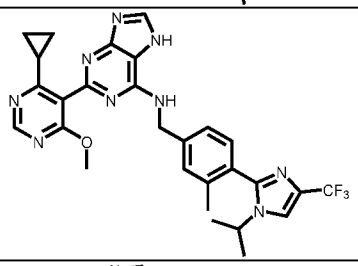
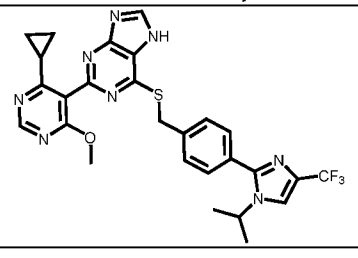
Example	Structure	MS	^{1}H NMR
1		523.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.67 (s, 1H), 8.16 (brs, 1H), 7.93 (s, 2H), 7.66 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 4.66 – 4.65 (m, 2H), 3.88 (s, 3H), 3.76 – 3.71 (m, 5H), 2.96 – 2.95 (m, 2H), 1.83 – 1.82 (m, 1H), 0.99 – 0.98 (m, 2H), 0.83 – 0.82 (m, 2H).
2		548.5	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.03 (t, J = 6.0 Hz 1H), 7.913 – 7.91 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.04 (s, 1H), 4.73 (d, J = 6.0 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 4.02 (s, 2H), 3.95 (s, 2H), 3.75 (s, 3H), 2.22 – 2.15 (m, 1H), 1.09 (t, J= 7.0 Hz, 3H), 0.63 – 0.60 (m, 2H), 0.43 – 0.39 (m, 2H).
3		576.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.16 (d, J = 0.8 Hz, 1H), 8.03 (t, J = 6.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 4.73 (d, J = 2.8 Hz, 2H), 4.47 – 4.40 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 4.02 (s, 2H), 3.95 (s, 2H), 2.21 – 2.14 (m, 1H), 1.40 – 1.38 (m, 6H), 1.09 (t, J = 7.2 Hz, 3H), 0.61 – 0.56 (m, 2H), 0.44 – 0.39 (m, 2H).

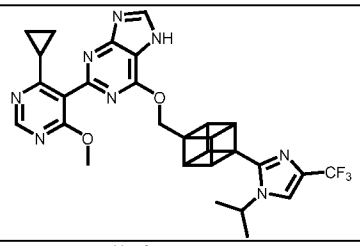
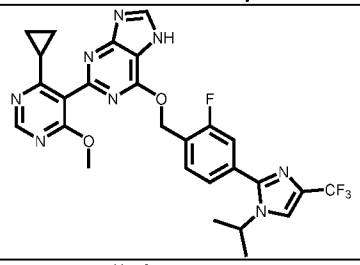
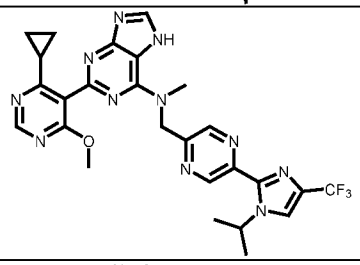
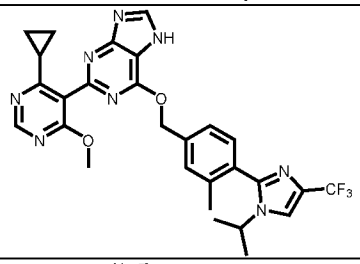
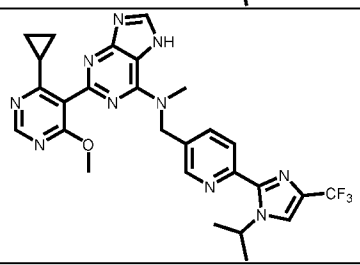
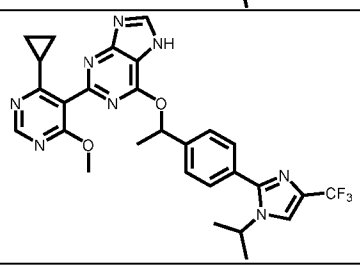
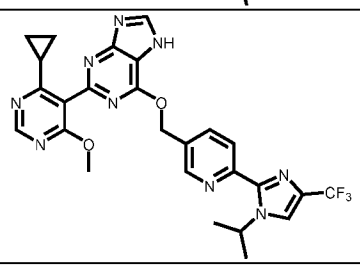
4		493.6	^{1}H NMR (400 MHz , DMSO-d_6) δ 9.39 (s, 2H), 8.20 (t, J = 6.0 Hz, 1H), 7.93 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.45 – 7.38 (m, 5H), 7.23 – 7.19 (m, 1H), 4.76 (d, J = 5.6 Hz, 2H), 4.47 – 4.43 (m, 4H), 3.76 (s, 3H), 3.49 – 3.48 (m, 1H), 1.04 – 1.02 (m, 6H).
5		532.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.87 (m, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.43 – 7.41 (m, 3H), 7.35 – 7.31 (m, 2H), 7.20 – 7.16 (m, 1H), 4.72 (d, J = 5.6 Hz, 2H), 4.06 (s, 2H), 4.00 (s, 2H), 3.93 (s, 2H), 3.75 (s, 3H), 3.49 – 3.42 (m, 1H), 1.02 – 1.00 (m, 6H).
6		549.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 0.8 Hz, 1H), 7.81 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.42 – 7.40 (m, 3H), 7.35 – 7.31 (m, 2H), 7.20 – 7.16 (m, 1H), 4.70 (d, J = 6.0 Hz, 2H), 4.00 – 3.90 (m, 4H), 3.75 (s, 3H), 3.50 – 3.43 (m, 1H), 3.14 – 3.10 (m, 1H), 3.08 – 3.03 (m, 1H), 2.78 – 2.76 (m, 1H), 2.71 – 2.67 (m, 1H), 2.59 – 2.58 (m, 1H), 1.01 – 1.00 (m, 6H).
7		518.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, J = 6.0 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.43 – 7.41 (m, 3H), 7.37 – 7.32 (m, 2H), 7.21 – 7.17 (m, 1H), 4.74 – 4.68 (m, 6H), 3.75 (s, 3H), 3.51 – 3.40 (m, 1H), 1.02 – 1.0 (m, 6H).
8		562.6	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.99 (t, J = 6.0 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 4.05 (s, 2H), 3.98 (s, 2H), 3.93 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.70 – 1.64 (m, 1H), 0.97 – 0.94 (m, 2H), 0.80 – 0.79 (m, 2H).
9		579.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.92 – 7.89 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.63 (d, J = 6.0 Hz, 2H), 3.98 – 3.89 (m, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 3.12 – 3.08 (m, 1H), 3.07 – 3.03 (m, 1H), 2.76 (t, J = 4.6 Hz, 1H), 2.70 – 2.67 (m, 1H), 2.58-2.50 (m, 1H), 1.68 – 1.64 (m, 1H), 0.95-0.94 (m, 2H), 0.78 – 0.75 (m, 2H).
10		548.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.15 (t, J = 6.0 Hz, 1H), 7.92 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.70 – 4.66 (m, 6H), 3.81 (s, 3H), 3.75 (s, 3H), 1.68 – 1.64 (m, 1H), 0.97 – 0.96 (m, 2H), 0.79 – 0.76 (m, 2H).

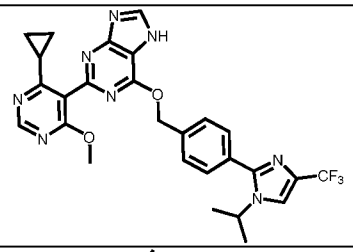
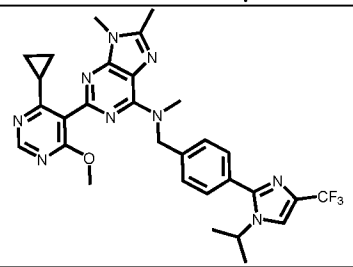
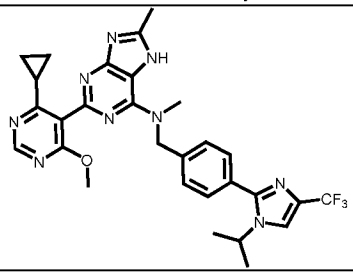
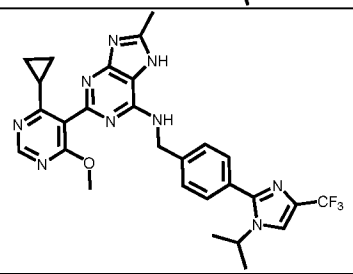
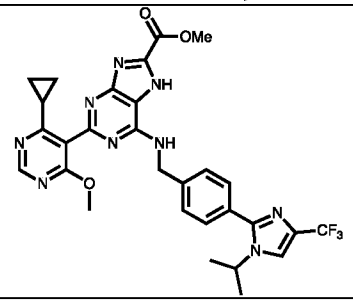
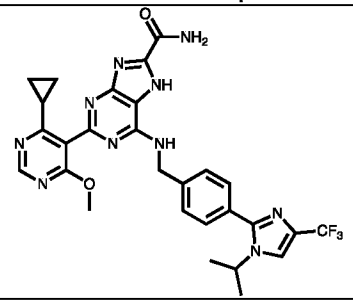
11		590.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.00 (t, J = 6.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 6.0 Hz, 2H), 4.47 – 4.40 (m, 1H), 4.06 (s, 2H), 3.98 (s, 2H), 3.93 (s, 2H), 3.81 (s, 3H), 1.70 – 1.63 (m, 1H), 1.40 – 1.38 (m, 6H), 0.94 – 0.93 (m, 2H), 0.80 – 0.70 (m, 2H).
12		550.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 2H), 7.68 (s, 1H), 7.50 (s, 4H), 4.77 (d, J = 6.4 Hz, 2H), 4.46 – 4.40 (m, 1H), 3.85 (s, 3H), 1.89 – 1.83 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10 – 0.98 (m, 2H), 0.83 – 0.80 (m, 2H).
13		553.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 4.87 (s, 2H), 3.90 (s, 3H), 2.83 (s, 3H), 2.32 (s, 3H), 1.73 (tt, J = 8.6, 4.7 Hz, 1H), 1.12 – 1.03 (m, 2H), 0.90 – 0.74 (m, 2H).
14		539.6	^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.57 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 6.57 (s, 1H), 4.91 (s, 2H), 3.91 (s, 3H), 2.32 (s, 3H), 1.74 (tt, J = 8.5, 4.7 Hz, 1H), 1.12 – 1.05 (m, 2H), 0.88 – 0.80 (m, 2H).
15		567.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.57 (s, 1H), 7.94 – 7.88 (m, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.46 (m, 2H), 4.92 (s, 2H), 4.53 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.83 – 1.69 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.14 – 1.04 (m, 2H), 0.90 – 0.76 (m, 2H).
16		509.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.08 (s, 1H), 7.67 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.26 – 7.20 (m, 1H), 4.95 (s, 2H), 3.75 (s, 3H), 3.42 (hept, J = 6.8 Hz, 1H), 1.10 (d, J = 6.8 Hz, 6H).
17		549.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 7.90 (s, 1H), 7.57 – 7.49 (m, 5H), 6.94 – 6.91 (m, 1H), 6.73 – 6.70 (m, 1H), 4.88 (s, 2H), 4.58 – 4.48 (m, 1H), 3.94 (s, 3H), 1.94 – 1.86 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H), 1.12 – 1.08 (m, 2H), 0.90 – 0.85 (m, 2H).

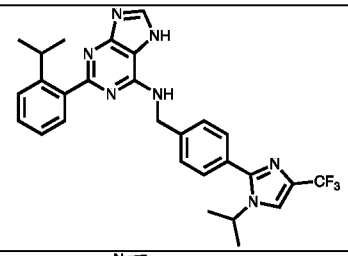
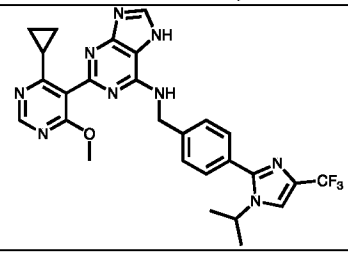
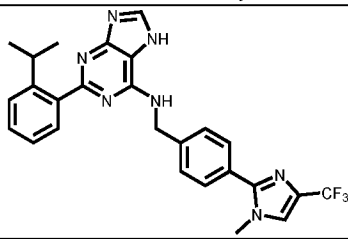
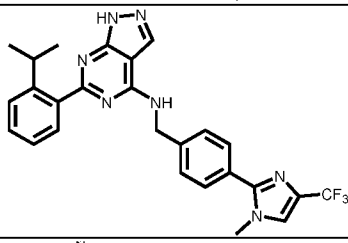
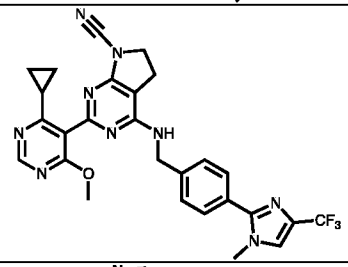
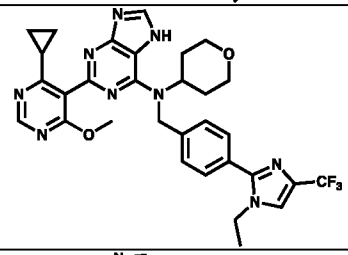
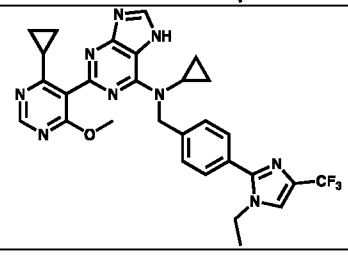
18		562.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 3.2 Hz, 1H), 8.72 (s, 1H), 8.44 (dd, J = 8.6, 1.2 Hz, 1H), 8.20 (s, 1H), 8.03 (dd, J = 8.6, 4.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 5.74 (s, 2H), 4.53 – 4.46 (m, 1H), 3.87 (s, 3H), 1.86 – 1.81 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.31 – 1.24 (m, 2H), 0.93-0.84 (m, 2H).
19		576.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 7.90 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (dd, J = 5.6, 2.7 Hz, 3H), 7.39 (dd, J = 8.9, 2.6 Hz, 1H), 4.93 (s, 2H), 4.52 (h, J = 6.7 Hz, 1H), 3.90 (s, 3H), 1.75 (tt, J = 8.6, 4.7 Hz, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.07 (m, 2H), 0.79 (m, 2H).
20		561.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (t, J = 5.8 Hz, 1H), 9.16 (s, 1H), 8.70 (d, J = 5.6 Hz, 1H), 8.64 (s, 1H), 8.24 (d, J = 5.6 Hz, 1H), 8.16 (s, 1H), 7.50 (s, 4H), 4.86 (d, J = 6.0 Hz, 2H), 4.45 – 4.41 (m, 1H), 3.82 (s, 3H), 1.78 – 1.72 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.78 – 0.75 (m, 2H).
21		590.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.59 (s, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.35 (br s, 2H), 4.48 – 4.41 (m, 1H), 3.80 (s, 3H), 3.15 (br s, 1H), 1.83 (br s, 1H), 1.39 (d, J = 6.4 Hz, 6H), 0.98 – 0.80 (m, 8H).
22		522.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 6.57 (s, 1H), 4.87 (s, 2H), 3.90 (d, J = 1.0 Hz, 3H), 2.33 (s, 3H), 1.72 (tt, J = 8.5, 4.8 Hz, 1H), 1.08 (m, 2H), 0.84 (m, 2H).
23		590.6	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.05 (s, 1H), 7.72 (s, 1H), 4.87 (s, 2H), 4.28 (t, *J* = 5.0 Hz, 3H), 4.23 – 4.13 (m, 1H), 4.02 (t, *J* = 5.0 Hz, 3H), 3.92 (s, 3H), 3.73 – 3.54 (m, 3H), 1.80 – 1.72 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 6H), 1.16 – 1.10 (m, 2H), 0.95 – 0.88 (m, 2H).
24		552.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 2H), 8.56 (s, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 5.72 (hept, J = 6.8 Hz, 1H), 4.90 (s, 2H), 3.89 (s, 3H), 1.74 – 1.62 (m, 1H), 1.51 (d, J = 6.7 Hz, 6H), 1.12 – 1.03 (m, 2H), 0.91 – 0.81 (m, 2H).

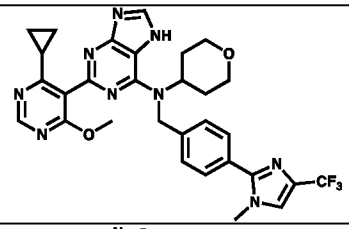
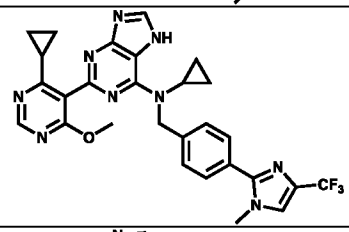
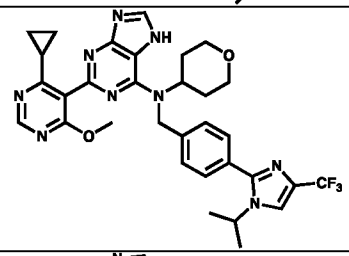
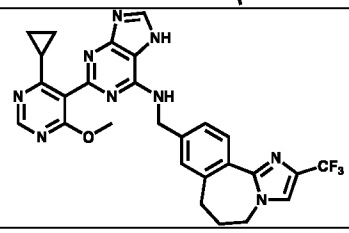
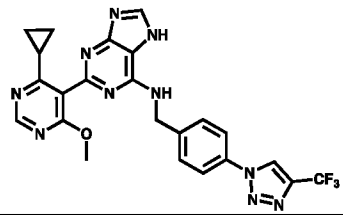
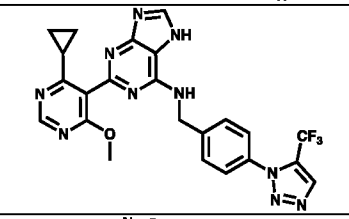
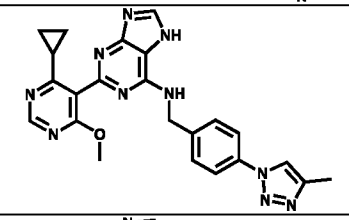
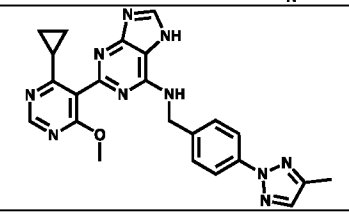
25		568.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.92 (s, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.32 (t, J = 10.7 Hz, 2H), 4.96 (s, 2H), 4.55 (hept, J = 6.6 Hz, 1H), 3.90 (s, 3H), 1.77 – 1.69 (m, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.13 – 1.05 (m, 2H), 0.90 – 0.74 (m, 2H).
26		578.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.35 (s, 1H), 7.33 – 7.25 (m, 2H), 5.35 (s, 2H), 4.12 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 3.53 (s, 3H), 2.13 (s, 3H), 1.89 – 1.78 (m, 1H), 1.39 (d, J = 6.7 Hz, 6H), 1.16 – 1.08 (m, 2H), 0.93 – 0.81 (m, 2H).
27		552.2	^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.74 (s, 1H), 8.55 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 5.62 (hept, J = 6.6 Hz, 1H), 5.01 (s, 2H), 4.58 (s, 1H), 3.87 (s, 3H), 1.72 – 1.62 (m, 1H), 1.50 (d, J = 6.7 Hz, 6H), 1.16 – 0.99 (m, 2H), 0.87 – 0.75 (m, 2H).
28		590.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.15 (s, 1H), 7.72 (s, 1H), 4.26 – 4.20 (m, 3H), 4.20 – 4.13 (m, 4H), 4.06 – 3.99 (m, 3H), 3.93 (s, 2H), 3.90 (s, 3H), 1.78 – 1.69 (m, 1H), 1.46 (d, J = 6.7 Hz, 6H), 1.17 – 1.10 (m, 2H), 0.95 – 0.86 (m, 2H).
29		551.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.56 (s, 1H), 8.14 (s, 1H), 8.00 – 7.88 (m, 3H), 5.66 (hept, J = 6.8 Hz, 1H), 4.91 (s, 2H), 3.90 (s, 3H), 1.75 – 1.66 (m, 1H), 1.48 (d, J = 6.7 Hz, 6H), 1.15 – 1.03 (m, 2H), 0.89 – 0.79 (m, 2H).
30		576.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.18 – 8.10 (m, 1H), 7.77 – 7.69 (m, 1H), 4.87 (s, 2H), 4.31 – 4.25 (m, 3H), 4.20 (hept, J = 6.6 Hz, 1H), 4.07 – 4.01 (m, 3H), 3.92 (s, 5H), 1.80 – 1.70 (m, 1H), 1.47 (d, J = 6.7 Hz, 6H), 1.18 – 1.10 (m, 2H), 0.96 – 0.88 (m, 2H).
31		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 7.56 – 7.43 (m, 4H), 4.81 (d, J = 5.9 Hz, 2H), 4.41 (hept, J = 6.7 Hz, 1H), 4.15 (s, 3H), 3.80 (s, 3H), 1.73 – 1.64 (m, 1H), 1.39 (d, J = 6.6 Hz, 6H), 1.01 – 0.90 (m, 2H), 0.75 – 0.64 (m, 2H).

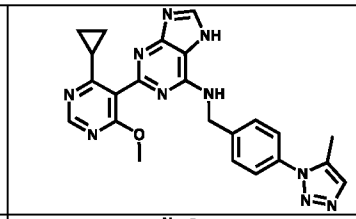
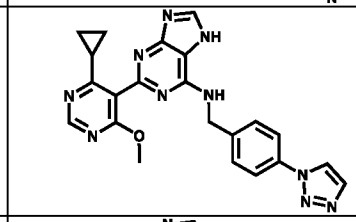
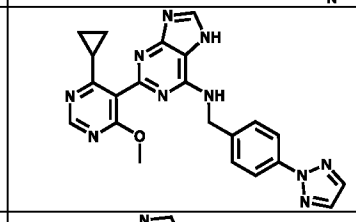
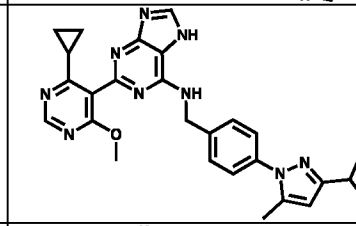
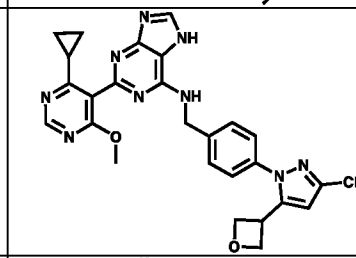
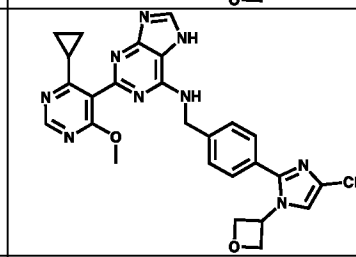
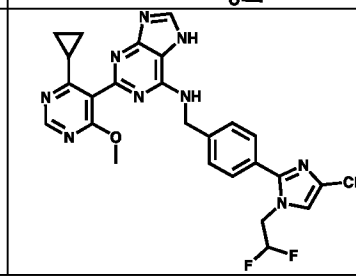
32		590.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H).
33		590.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H).
34		590.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H).
35		564.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.15 (s, 1H), 7.89 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.55 – 7.47 (m, 2H), 5.62 (s, 1H), 4.54 (hept, J = 6.7 Hz, 1H), 3.87 (s, 3H), 1.67 (m, J = 7.0 Hz, 4H), 1.44 (dd, J = 6.7, 4.6 Hz, 6H), 1.04 (m, J = 4.5 Hz, 2H), 0.87 – 0.77 (m, 1H), 0.69 (m, 1H).
36		564.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.51 (s, 4H), 5.37 (s, 2H), 4.54 (hept, J = 6.7 Hz, 1H), 3.91 (s, 3H), 3.63 (s, 3H), 1.88 – 1.75 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H), 1.16 – 1.02 (m, 2H), 0.95 – 0.75 (m, 2H).
37		564.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.47 – 7.34 (m, 2H), 7.31 – 7.23 (m, 1H), 4.93 – 4.87 (m, 2H), 4.10 (hept, J = 6.8 Hz, 1H), 3.92 (s, 3H), 2.13 (s, 3H), 1.81 – 1.71 (m, 1H), 1.38 (d, J = 6.7 Hz, 6H), 1.13 – 1.07 (m, 2H), 0.90 – 0.81 (m, 2H).
38		567.3	^{1}H NMR (400 MHz, DMSO-d_6) 13.80 (br s, 1H), 8.69 (s, 1H), 8.52 (s, 1H), 8.16 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H), 4.47 – 4.41 (m, 1H), 3.87 (s, 3H), 1.74 – 1.70 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.19 – 1.15 (m, 2H), 1.07 – 1.06 (m, 2H).

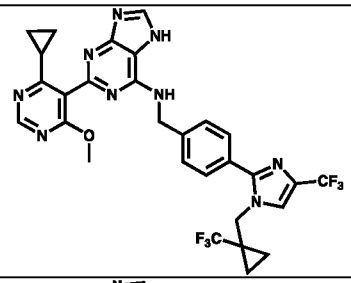
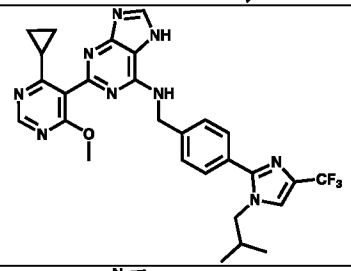
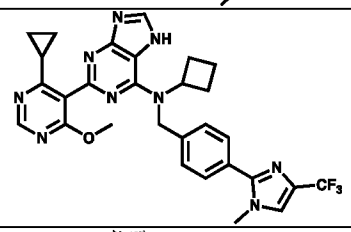
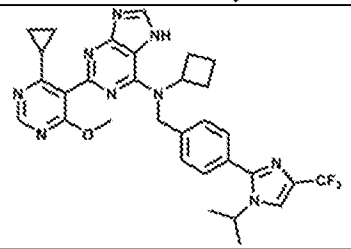
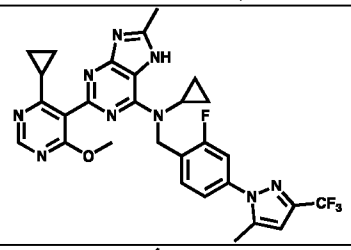
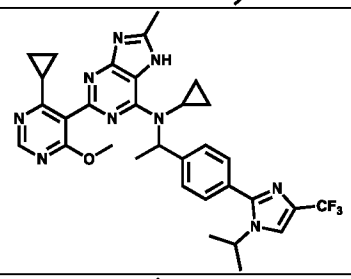
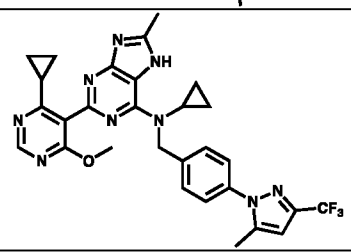
39		577.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.38 (s, 1H), 7.74 (s, 1H), 4.87 (s, 2H), 4.38 – 4.27 (m, 3H), 4.21 (hept, J = 6.7 Hz, 1H), 4.14 – 4.03 (m, 3H), 3.91 (s, 3H), 1.78 – 1.67 (m, 1H), 1.48 (d, J = 6.7 Hz, 6H), 1.21 – 1.09 (m, 2H), 0.97 – 0.82 (m, 2H).
40		569.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.39 (s, 1H), 7.95 (s, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 10.1 Hz, 2H), 5.82 (s, 2H), 4.57 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.79 – 1.68 (m, 1H), 1.47 (d, J = 6.6 Hz, 6H), 1.19 – 1.10 (m, 2H), 0.94 – 0.85 (m, 2H).
41		566.3	^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.72 (s, 1H), 8.57 (s, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 5.62 (hept, J = 6.2 Hz, 1H), 5.39 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 1.83 – 1.70 (m, 1H), 1.51 (d, J = 6.7 Hz, 6H), 1.13 – 1.03 (m, 2H), 0.92 – 0.77 (m, 2H).
42		565.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.39 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 5.73 (s, 2H), 4.11 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 2.17 (s, 3H), 1.77 – 1.70 (m, 1H), 1.40 (d, J = 6.7 Hz, 6H), 1.18 – 1.11 (m, 2H), 0.93 – 0.86 (m, 2H).
43		565.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.98 – 7.89 (m, 3H), 5.67 (hept, J = 6.7 Hz, 1H), 5.33 (s, 2H), 3.92 (s, 3H), 3.61 (s, 3H), 1.84 – 1.74 (m, 1H), 1.49 (d, J = 6.7 Hz, 6H), 1.16 – 1.06 (m, 2H), 0.93 – 0.84 (m, 2H).
44		565.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.40 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.54 (d, 2H), 6.64 (q, J = 6.5 Hz, 1H), 4.53 (hept, J = 6.8 Hz, 1H), 3.86 (s, 3H), 1.79 (d, J = 6.5 Hz, 3H), 1.66 – 1.55 (m, 1H), 1.44 (dd, J = 9.8, 6.7 Hz, 6H), 1.12 – 1.03 (m, 2H), 0.91 – 0.64 (m, 2H).
45		552.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.10 (dd, J = 8.2, 2.2 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.95 (s, 1H), 5.78 (s, 2H), 5.71 (hept, J = 6.7 Hz, 1H), 3.90 (s, 3H), 1.76 – 1.65 (m, 1H), 1.49 (d, J = 6.7 Hz, 6H), 1.20 – 1.07 (m, 2H), 0.95 – 0.81 (m, 2H).

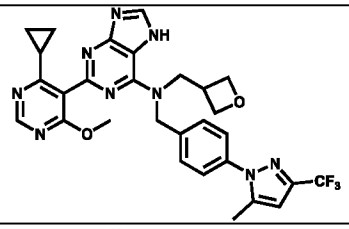
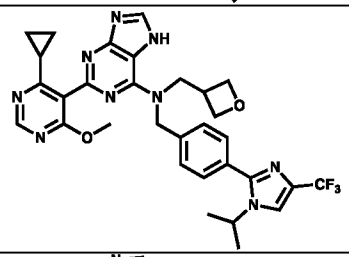
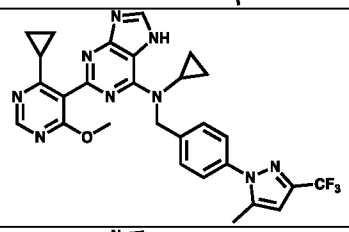
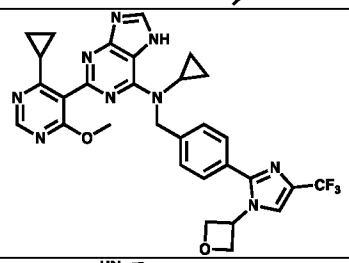
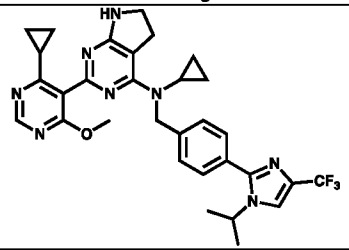
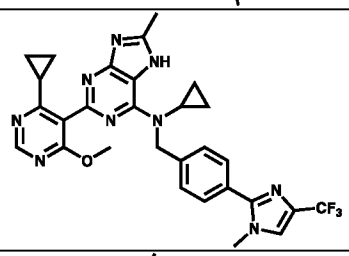
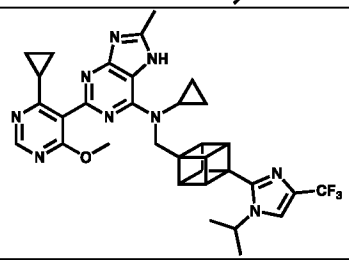
46		551.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (br s, 1H), 8.68 (s, 1H), 8.47 (br s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 5.69 (s, 2H), 4.51 – 4.45 (m, 1H), 3.85 (s, 3H), 1.76 – 1.70 (m, 1H), 1.42 – 1.40 (d, J = 6.8 Hz, 6H), 1.05 – 1.03 (m, 2H), 0.90 – 0.80 (m, 2H).
47		592.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.16 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 5.50 (br s, 2H), 4.47 – 4.43 (m, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.57 (br s, 3H), 2.53 (s, 3H), 1.73 – 1.72 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10 – 0.98 (m, 2H), 0.96 – 0.70 (m, 2H).
48		578.5	^{1}H NMR (400 MHz, DMSO-d_6) 12.84 (s, 1H), 8.60 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 5.16 (br s, 2H), 4.49 – 4.43 (m, 1H), 3.83 (s, 3H), 3.46 (br s, 3H), 2.47 (s, 3H), 1.80 – 1.82 (m, 1H), 1.35 (d, J = 7.2 Hz, 6H), 0.98 – 0.89 (m, 2H), 0.84 – 0.81 (m, 2H).
49		564.5	^{1}H NMR (400 MHz, DMSO-d_6) 12.81 (br s, 1H), 8.60 (s, 1H), 8.30 (br s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.47 (br s, 4H), 4.73 (br s, 2H), 4.46 – 4.40 (m, 1H), 3.81 (s, 3H), 2.49 (s, 3H), 1.73 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.96 (m, 2H), 0.82 – 0.75 (m, 2H).
50		608.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 14.06 (br s, 1H), 9.06 (br s, 1H), 8.61 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.47 (s, 4H), 4.74 (d, J = 4.8 Hz, 2H), 4.46 – 4.40 (m, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 1.73 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96 – 0.95 (m, 2H), 0.26 – 0.24 (m, 2H).
51		593.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.63 (br s, 1H), 8.61 (s, 1H), 8.38 (br s, 1H), 8.15 (s, 1H), 7.92 (br s, 2H), 7.49 (s, 4H), 4.77 (br s, 2H), 4.47 – 4.42 (m, 1H), 3.82 (s, 3H), 1.72 – 1.70 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 0.90 – 0.88 (m, 2H), 0.41 – 0.21 (m, 2H).

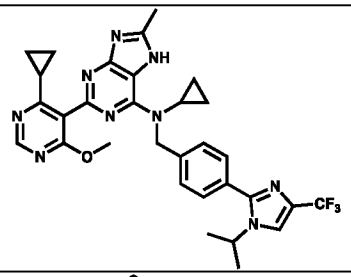
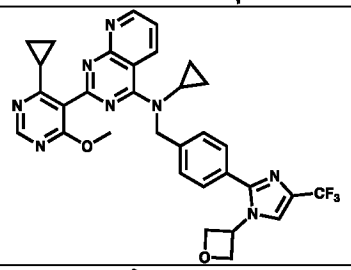
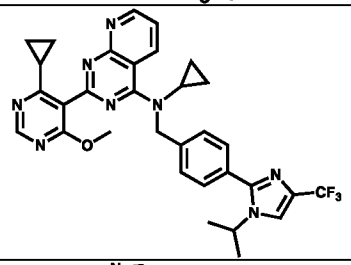
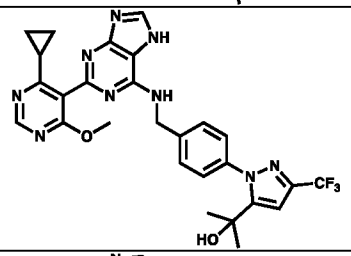
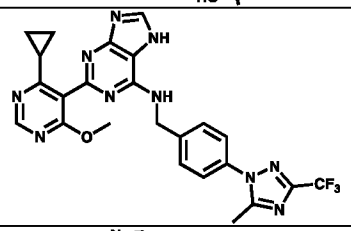
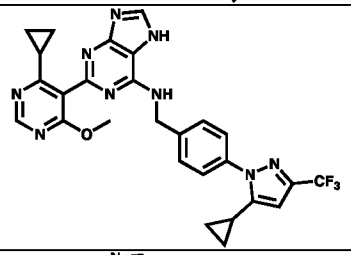
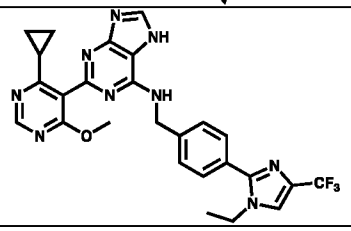
52		520.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.36 (br s, 1H), 8.16 – 8.15 (m, 2H), 7.50 – 7.44 (m, 5H), 7.36 – 7.30 (m, 2H), 7.21 – 7.17 (m, 1H), 4.81 (s, 2H), 4.48 – 4.41 (m, 1H), 3.58 – 3.51 (m, 1H), 1.38 – 1.37 (m, 6H), 1.01 – 1.0 (m, 6H).
53		550.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.48 (s, 4H), 5.16 – 4.74 (m, 2H), 4.47 – 4.40 (m, 1H), 3.81 (s, 3H), 1.76 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96 – 0.94 (m, 2H), 0.75 – 0.73 (m, 2H).
54		492.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.67 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46 – 7.33 (m, 3H), 7.21 (t, J = 7.0 Hz, 1H), 4.95 (s, 2H), 3.75 (s, 3H), 3.39 (hept, J = 6.9 Hz, 1H), 1.11 (d, J = 6.8 Hz, 6H).
55		492.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 11.1 Hz, 2H), 7.69 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.24 (t, J = 6.9 Hz, 1H), 4.95 (s, 2H), 3.78 (s, 3H), 3.43 (hept, J = 6.9 Hz, 1H), 1.22 – 1.11 (m, 6H).
56		548.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.94 – 7.90 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 4.14 (t, J = 8.6 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.05 (t, J = 8.4 Hz, 2H), 1.70 – 1.64 (m, 1H), 0.97 – 0.86 (m, 2H), 0.81 – 0.79 (m, 2H).
57		620.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H), 8.58 (s, 1H), 8.24 (br s, 1H), 8.00 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 5.05 (br s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 3.91 – 3.80 (m, 5H), 3.40 – 3.40 (m, 2H), 1.90 – 1.78 (m, 3H), 1.78 – 1.67 (m, 2H), 1.33 (t, J = 5.6 Hz, 3H), 1.29 – 1.23 (m, 4H).
58		576.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 8.61 (s, 1H), 8.22 (br s, 1H), 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.34 (br s, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.16 – 3.16 (m, 1H), 1.83 – 1.83 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.98 – 0.80 (m, 8H).

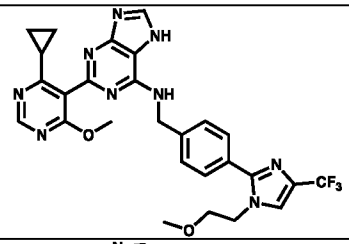
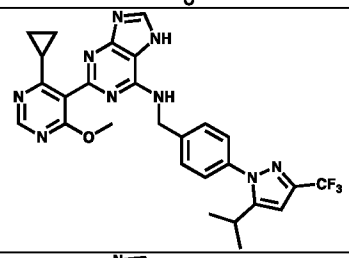
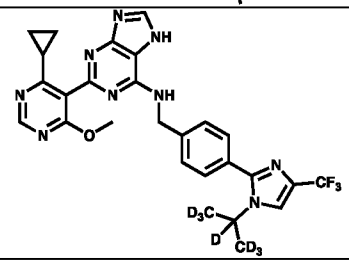
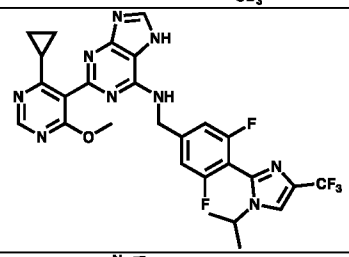
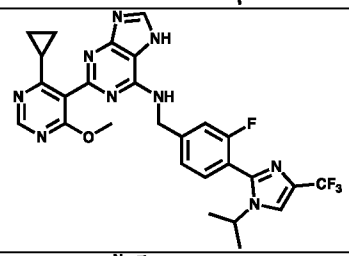
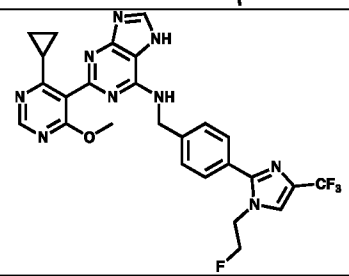
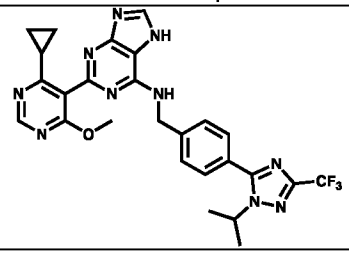
59		606.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 1H), 8.58 (br s, 1H), 8.24 (br s, 1H), 7.91 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.01 – 5.06 (m, 3H), 3.91 – 3.89 (m, 2H), 3.80 – 3.75 (m, 6H), 3.42 – 3.40 (m, 2H), 1.84 – 1.64 (m, 5H), 0.93 – 0.75 (m, 4H).
60		562.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (br s, 1H), 8.62 (s, 1H), 8.30 (br s, 1H), 7.91 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.30 (br s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.17 – 3.17 (m, 1H), 1.83 – 1.83 (m, 1H), 0.99 – 0.92 (m, 4H), 0.82 – 0.82 (m, 4H).
61		634.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.58 (s, 1H), 8.25 – 8.16 (m, 2H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 6.02 – 5.06 (m, 3H), 4.45 – 4.42 (m, 1H), 3.92 – 3.90 (m, 2H), 3.80 (s, 3H), 3.40 (br s, 2H), 1.84 – 1.82 (m, 5H), 1.39 (d, *J* = 6.4 Hz, 6H), 0.93 – 0.73 (m, 4H).
62		548.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.54 (s, 1 H), 8.14 (s, 1H), 7.73 (s, 1H), 7.63 – 7.59 (m, 1H), 7.47 – 7.41 (m 1H), 7.40 (m. 1H), 3.99 (t, J = 6.9 Hz, 2H), 3.91 (s, 3H), 2.70 (t, J = 7.1 Hz, 2H), 2.34 (pent., J = 7.0 Hz, 2H), 1.78 – 1.66 (m, 1H), 1.11 – 1.05 (m, 2H), 0.85 – 0.77 (m, 2H).
63		509.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.55 (s, 1H), 8.60 (s, 1H), 8.49 (br s, 1H), 8.19 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.58 – 7.58 (m, 2H), 4.74 (br s, 2H), 3.81 (s, 3H), 1.74 – 1.68 (m, 1H), 0.85 – 0.96 (m, 2H), 0.65 – 0.76 (m, 2H).
64		509.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.47 (br s, 1H), 8.20 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.56 – 7.56 (m, 2H), 4.74 (s, 2H), 3.80 (s, 3H), 1.71 – 1.68 (m, 1H), 0.94 – 0.83 (m, 2H), 0.73 – 0.65 (m, 2H).
65		455.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.60 (s, 1H), 8.47 (s, 2H), 8.19 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.51 – 7.51 (m, 2H), 4.71 (br s, 2H), 3.81 (s, 3H), 2.31 (s, 3H), 1.73 – 1.69 (m, 1H), 0.95 – 0.95 (m, 2H), 0.74 – 0.74 (m, 2H).
66		455.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.60 (s, 1H), 8.42 (br s, 1H), 8.19 (s, 1H), 7.88 – 7.84 (m, 3H), 7.48 – 7.48 (m, 2H), 4.70 (br s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 1.73 – 1.69 (m, 1H), 0.95 – 0.95 (m, 2H), 0.74 – 0.74 (m, 2H).

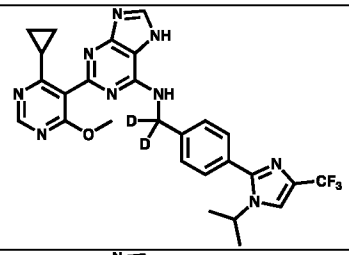
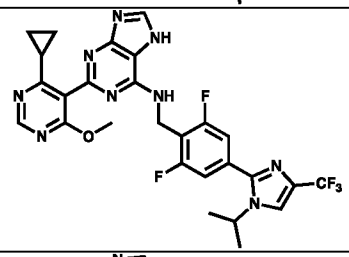
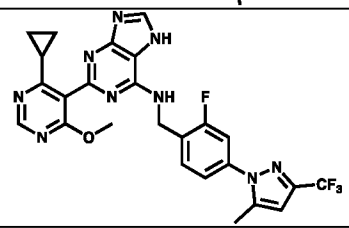
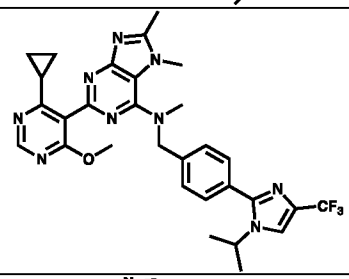
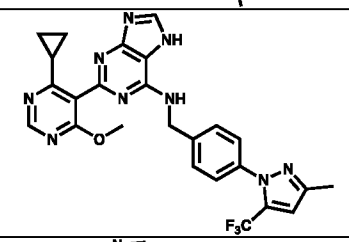
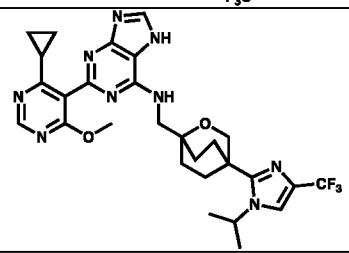
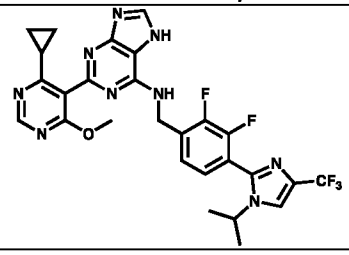
67		455.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.60 (s, 1H), 8.49 (brs, 1H), 8.20 (s, 1H), 7.67 (s, 1H), 7.52 – 7.52 (m, 4H), 4.76 (s, 2H), 3.81 (s, 3H), 2.29 (s, 3H), 1.74 – 1.69 (m, 1H), 0.96 – 0.96 (m, 2H), 0.75 – 0.75 (m, 2H).
68		441.3	^{1}H NMR (400 MHz, DMSO-d_6) 8.79 – 8.77 (m, 2H), 8.61 (d, J = 12.0 Hz, 2H), 8.29 (s, 1H), 7.96 (d, J = 0.8 Hz, 1H), 7.83 (d, J = 12.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 4.75 (br s, 2H), 3.82 (s, 3H), 1.71 (s, 1H), 0.97 (br s, 2H), 0.76 (br s, 2H).
69		441.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (br s, 1H), 8.60 (s, 1H), 8.39 (br s, 1H), 8.19 (s, 1H), 8.09 (s, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 4.72 (br s, 2H), 3.80 (s, 3H), 1.74 – 1.67 (m, 1H), 1.00 – 0.90 (m, 2H), 0.85 – 0.60 (m, 2H).
70		504.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.61 – 7.53 (m, 2H), 7.46 – 7.37 (m, 2H), 6.89 – 6.40 (m, 2H), 4.91 (s, 2H), 3.90 (s, 3H), 2.32 (s, 3H), 1.78 – 1.67 (m, 1H), 1.13 – 1.03 (m, 2H), 0.90 – 0.76 (m, 2H).
71		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.61 (s, 1H), 8.45 (br s, 1H), 8.21 (s, 1H), 7.49 (d, J = 5.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 4.74 – 4.62 (m, 5H), 4.31 – 4.27 (m, 1H), 3.82 (s, 3H), 1.75 – 1.71 (m, 1H), 0.97 – 0.97 (m, 2H), 0.87 – 0.87 (m, 3H).
72		564.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.29 – 8.24 (m, 1H), 8.14 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 – 7.41 (m, 2H), 5.52 (tt, J = 7.3, 6.0 Hz, 1H), 4.96 (t, J = 7.4 Hz, 2H), 4.91 (s, 2H), 4.84 – 4.80 (m, 2H), 3.91 (s, 3H), 1.77 – 1.68 (m, 1H), 1.12 – 1.05 (m, 2H), 0.91 – 0.78 (m, 2H).
73		572.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.13 (s, 1H), 7.79 (s, 1H), 7.56 (q, J = 8.4 Hz, 4H), 6.14 (tt, J = 54.5, 3.2 Hz, 1H), 4.92 (s, 2H), 4.50 (td, J = 15.1, 3.2 Hz, 2H), 3.91 (s, 3H), 1.78 – 1.69 (m, 1H), 1.13 – 1.05 (m, 2H), 0.89 – 0.79 (m, 2H).

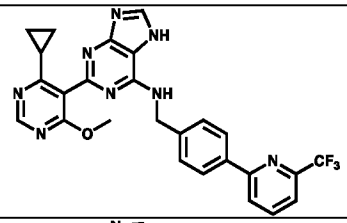
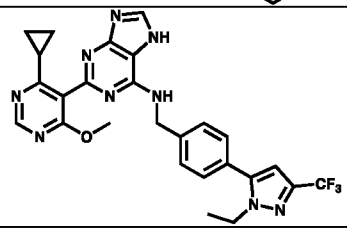
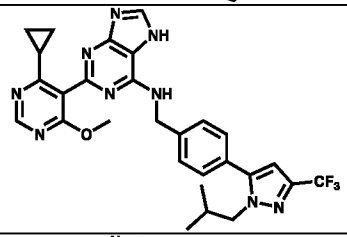
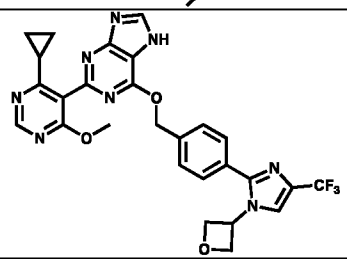
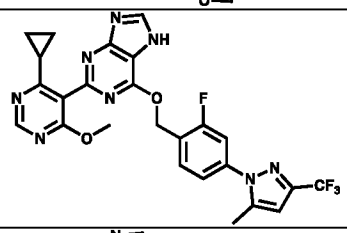
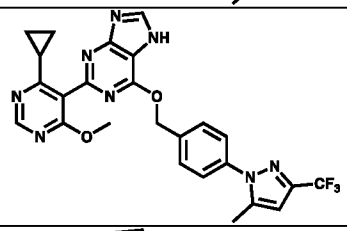
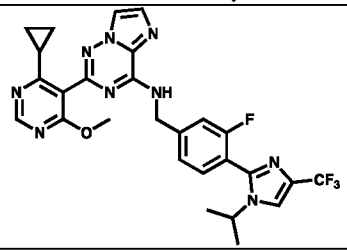
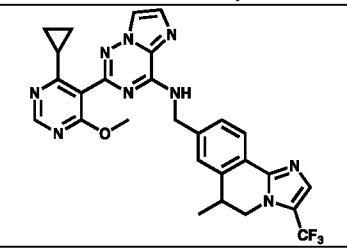
74		630.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.83 – 7.80 (m, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.53 – 7.49 (m, 2H), 4.95 (s, 2H), 4.35 (s, 2H), 3.91 (s, 3H), 1.79 – 1.70 (m, 1H), 1.13 – 1.07 (m, 2H), 1.04 – 1.00 (m, 2H), 0.89 – 0.83 (m, 2H), 0.82 – 0.78 (m, 2H).
75		564.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.75 – 7.73 (m, 1H), 7.58 – 7.51 (m, 4H), 4.92 (s, 2H), 3.93 – 3.89 (m, 5H), 1.99 – 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.12 – 1.03 (m, 2H), 0.88 – 0.81 (m, 2H), 0.76 (d, J = 6.7 Hz, 6H).
76		576.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.67 (s, 1H), 7.59 – 7.55 (m, 2H), 7.42 – 7.38 (m, 2H), 5.83 (br s, 1H), 5.45 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 2.34 – 2.22 (m, 4H), 1.77 – 1.67 (m, 3H), 1.07 – 1.01 (m, 2H), 0.81 – 0.76 (m, 2H).
77		604.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 2H), 5.84 (br s, 1H), 5.47 (s, 2H), 4.54 (sept., J = 6.8 Hz, 1H), 3.88 (s, 3H), 2.34 – 2.22 (m, 4H), 1.77 – 1.67 (m, 3H), 1.44 (d, J = 6.7 Hz, 6H), 1.07 – 1.01 (m, 2H), 0.81 – 0.76 (m, 2H).
78		594.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.35 (dd, J = 10.5, 2.2 Hz, 1H), 7.26 (dd, J = 8.1, 2.2 Hz, 1H), 6.58 (s, 1H), 5.29 (br s, 2H), 3.89 (s, 3H), 3.21 (br s, 1H), 2.61 (s, 3H), 2.36 (s, 3H), 1.76 – 1.68 (m, 1H), 1.10 – 1.00 (m, 4H), 0.93 – 0.85 (m, 2H), 0.85 – 0.79 (m 2H).
79		618.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 7.90 (s, 1H), 7.59 – 7.54 (m, 2H), 7.51 – 7.46 (m, 2H), 6.37 (br s, 1H), 4.54 (sept, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.08 (m, 1H), 2.61 (m, 3H), 1.92 (d, J = 7.2 Hz, 3H), 1.85 – 1.78 (m, 1H), 1.45 (dd, J = 6.6, 2.5 Hz, 6H), 1.13 – 1.04 (m, 2H), 1.01 – 0.91 (m, 1H), 0.91 – 0.84 (m, 2H), 0.83 – 0.68 (m, 2H), 0.59 – 0.42 (m, 1H).
80		576.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.39 (m, 2H), 6.57 (s, 1H), 5.42 – 5.06 (m, 2H), 3.90 (s, 3H), 3.19 (br s, 1H), 2.59 (br s, 3H), 2.32 (s, 3H), 1.75 (m, 1H), 1.12 – 1.04 (m, 3H), 1.04 – 0.92 (m, 2H), 0.90 – 0.78 (m 3H).

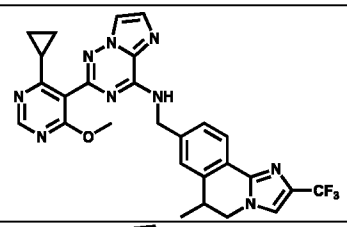
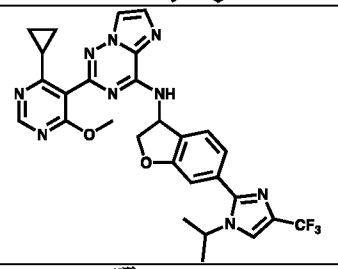
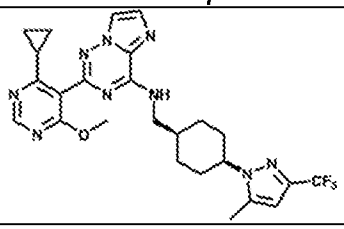
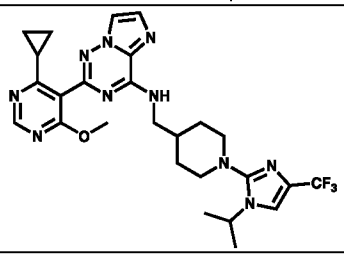
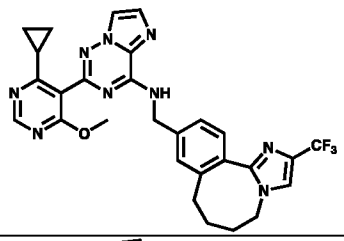
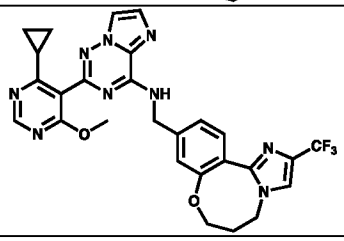
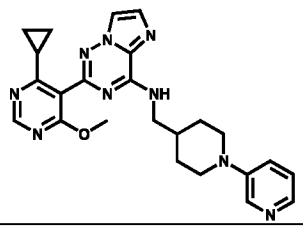
81		592.3	^{1}H NMR (400 MHz, CD_3OD) δ8.66 (s, 1H), 8.55 (s, 1H), 7.59 – 7.54 (m, 2H), 7.52 – 7.48 (m, 2H), 6.60 (s, 1H), 5.31 (br s, 2H), 4.72 (m, 1H), 4.40 (dd, J = 13.4, 9.4 Hz, 1H), 4.03 – 3.99 (m, 1H), 3.98 (m, 3H), 3.95 – 3.88 (m, 1H), 3.67 – 3.58 (m, 2H), 2.69 – 2.60 (m, 1H), 2.35 (s, 3H), 1.98 – 1.91 (m, 1H), 1.19 – 1.14 (m, 2H), 0.91 – 0.86 (m 2H).
82		620.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.35 (s, 1H), 7.92 (s, 1H), 7.57 – 7.49 (m, 4H), 5.25 – 5.16 (m, 2H), 4.63 – 4.56 (m, 1H), 4.54 (hept, J = 6.8 Hz, 1H), 4.28 (dd, J = 13.1, 9 Hz, 1H), 3.91 (s, 3H), 3.88 – 3.84 (m, 1H), 3.75 – 3.70 (m, 1H), 3.61 – 3.56 (m, 2H), 2.59 – 2.51 (m, 1H), 1.85 – 1.79 (m, 1H), 1.46 (d, J = 6.8 Hz, 6H), 1.11 – 1.07 (m, 2H), 0.85 – 0.80 (m, 2H).
83		562.3	^{1}H NMR (400 MHz, DMSO-d_6) δ13.15 (s, 1H), 8.61 (s, 1H), 8.23 (s, 1H), 7.52 – 7.48 (m, 2H), 7.44 – 7.38 (m, 2H), 6.73 (s, 1H), 5.35 (br s, 2H), 3.83 (s, 3H), 3.25 – 3.08 (s, 1H), 2.31 (s, 3H), 1.88 – 1.77 (m, 1H), 1.02 – 0.95 (m, 2H), 0.93 – 0.86 (m, 2H), 0.84 – 0.76 (m 4H).
84		604.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.40 (s, 1H), 8.22 (s, 1H), 7.39 – 7.36 (m, 2H), 7.34 – 7.30 (m, 2H), 5.42 (p, J = 6.9 Hz, 1H), 5.25 (s, 2H), 4.78 (t, J = 7.3 Hz, 2H), 4.71 (t, J = 6.8 Hz, 2H), 3.77 (s, 3H), 3.08 (s, 1H), 1.77 (s, 1H), 0.93 (s, 2H), 0.88 – 0.83 (m, 2H), 0.75 (s, 4H).
85		591.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.16 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 6.87 (s, 1H), 6.66 (s, 1H), 4.84 (s, 2H), 4.57 – 4.40 (m, 2H), 3.81 (s, 3H), 3.48 – 3.46 (m, 4H), 2.88 (t, J = 5.0 Hz, 1H), 2.1 – 2.04 (m, 2H), 2.0 – 1.97 (m, 1H), 1.75 – 1.72 (m, 1H), 1.59 – 1.39 (m, 6H), 1.23 (s, 1H), 0.99 – 0.96 (m, 2H), 0.90 – 0.86 (m, 2H).
86		576.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.68 (s, 1H), 7.62 – 7.58 (m, 2H), 7.48 – 7.43 (m, 2H), 5.28 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.19 (s, 1H), 2.61 (s, 3H), 1.80 – 1.71 (m, 1H), 1.10 – 1.06 (m, 2H), 1.05 – 0.96 (m, 2H), 0.94 – 0.80 (m 4H).
87		630.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 7.72 (s, 1H), 4.33 (br s, 2H), 4.28 – 4.23 (m, 3H), 4.16 (sept., J = 6.7 Hz, 1H), 3.99 – 3.92 (m, 3H), 3.92 (s, 3H), 3.24 (br s, 1H), 2.61 (s, 3H), 1.78 (m, 1H), 1.45 (d, J = 6.7 Hz, 6H), 1.16 – 1.10 (m, 2H), 1.11 – 1.03 (m 2H), 0.95 – 0.87 (m 2H), 0.86 – 0.72 (m, 2H).

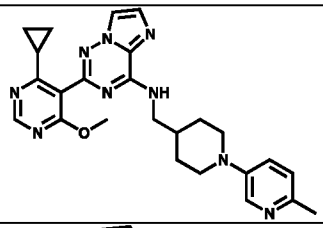
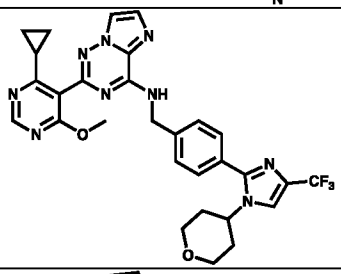
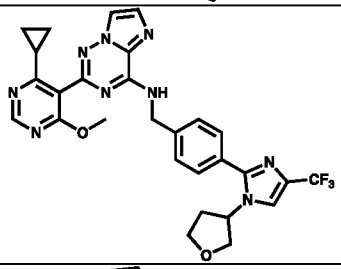
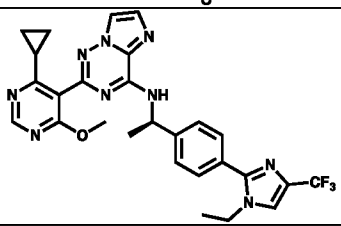
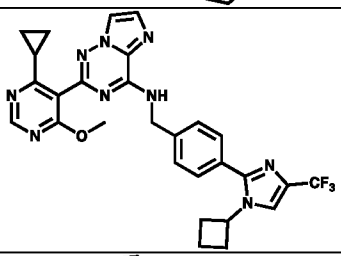
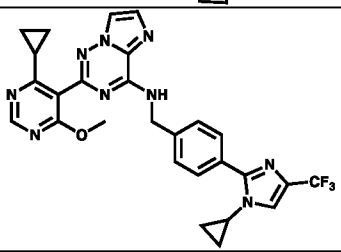
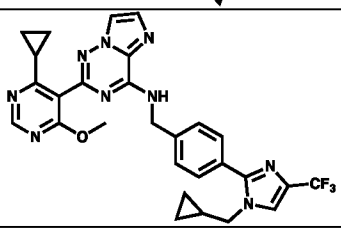
88		604.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.90 (s, 1H), 7.47 (m, 4H), 5.36 – 5.13 (m, 2H), 4.52 (sept., J = 6.6 Hz, 1H), 3.90 (s, 3H), 3.18 (s, 1H), 2.59 (m, 3H), 1.75 (s, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.20 – 1.05 (m, 3H), 1.05 – 0.92 (m, 2H), 0.91 – 0.78 (m, 3H).
89		615.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (dd, J = 8.6, 1.8 Hz, 1H), 9.03 (dd, J = 4.4, 1.6 Hz, 1H), 8.63 (s, 1H), 8.47 (d, J = 0.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.48 – 7.43 (m, 4H), 5.53 – 5.46 (m, 1H), 5.18 (s, 2H), 4.86 – 4.77 (m, 4H), 3.80 (s, 3H), 3.56 – 3.52 (m, 1H), 1.80 – 1.75 (m, 1H), 1.00 – 0.98 (m, 4H), 0.81 – 0.77 (m, 4H).
90		601.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.57 (dd, J = 4.8, 1.6 Hz, 1H), 8.31 (dd, J = 7.8, 1.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.03 (d, J = 8.0 Hz, 2H), 5.36 – 5.23 (m, 2H), 4.44 – 4.41 (m, 1H), 3.80 – 3.73 (m, 4H), 1.93 – 1.89 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.11 – 1.07 (m, 1H), 0.98 – 0.95 (m, 1H), 0.79 – 0.73 (m, 4H), 0.67 – 0.66 (m, 2H).
91		566.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.57 – 7.51 (m, 2H), 7.50 – 7.44 (m, 2H), 6.69 (s, 1H), 4.92 (s, 2H), 3.91 (s, 3H), 1.78 – 1.70 (m, 1H), 1.41 (s, 6H), 1.13 – 1.06 (m, 2H), 0.92 – 0.85 (m, 2H).
92		523.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.65 – 7.59 (m, 2H), 7.55 – 7.49 (m, 2H), 4.93 (s, 2H), 3.90 (s, 3H), 2.52 (s, 3H), 1.76 – 1.65 (m, 1H), 1.12 – 1.03 (m, 2H), 0.89 – 0.76 (m, 2H).
93		548.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (bs, 1H), 8.61 – 8.56 (m, 2H), 8.26 (s, 1H), 7.58 – 7.54 (m, 4H), 6.60 (s, 1H), 4.77 (brs, 2H), 3.82 (s, 3H), 1.81 – 1.72 (m, 2H), 0.97 – 0.94 (m, 4H), 0.93 – 0.92 (m, 4H).
94		536.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.16 (s, 1H), 7.82 – 7.76 (m, 1H), 7.63 – 7.53 (m, 4H), 4.94 (s, 2H), 4.12 (q, J = 7.3 Hz, 2H), 3.93 (s, 3H), 1.80 – 1.70 (m, 1H), 1.38 (t, J = 7.3 Hz, 3H), 1.17 – 1.05 (m, 2H), 0.91 – 0.78 (m, 2H).

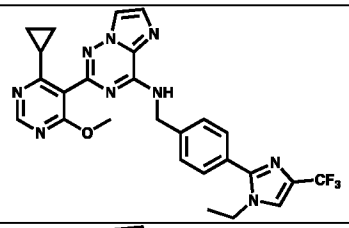
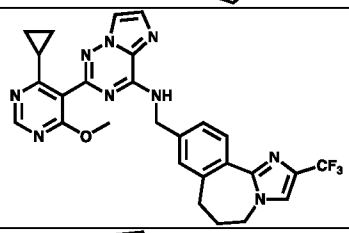
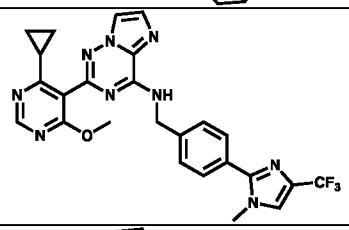
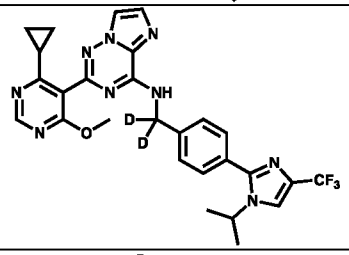
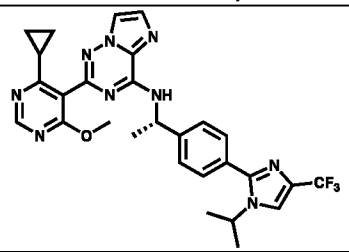
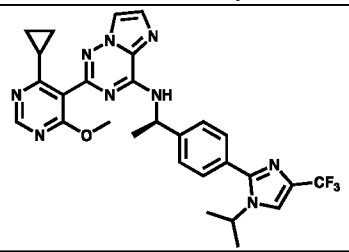
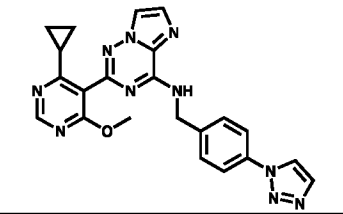
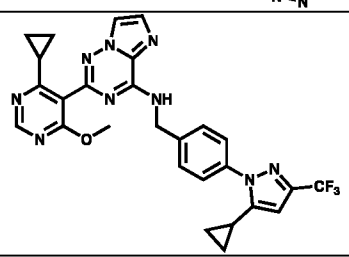
95		566.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.79 – 7.73 (m, 1H), 7.62 – 7.53 (m, 4H), 4.91 (s, 2H), 4.20 (t, 2H), 3.91 (s, 3H), 3.64 (t, J = 4.6 Hz, 2H), 3.28 (s, 3H), 1.82 – 1.68 (m, 1H), 1.12 – 1.04 (m, 2H), 0.90 – 0.78 (m, 2H).
96		550.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.60 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.48 (s, 4H), 4.74 – 5.30 (m, 2H), 4.45 – 4.40 (m, 1H), 3.81 (s, 3H), 1.74 – 1.70 (m, 1H), 1.34 – 1.29 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.90 (m, 2H), 0.89 – 0.70 (m, 2H).
97		557.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.50 (s, 2H), 8.19 (s, 1H), 8.14 (d, J = 0.8 Hz, 1H), 7.48 (s, 4H), 4.73 (br s, 2H), 3.81 (s, 3H), 1.74 – 1.70 (m, 1H), 0.99 – 0.94 (m, 2H), 0.78 – 0.73 (m, 2H).
98		586.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 4.91 (s, 2H), 4.25 – 4.10 (m, 1H), 3.90 (s, 3H), 1.79 – 1.66 (m, 1H), 1.41 (d, J = 1.8 Hz, 6H), 1.16 – 1.05 (m, 2H), 0.93 – 0.79 (m, 2H).
99		568.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.31 (m, 2H), 4.92 (s, 2H), 4.25 (p, J = 6.8 Hz, 1H), 3.91 (s, 3H), 1.81 – 1.67 (m, 1H), 1.41 (d, J = 6.7 Hz, 6H), 1.15 – 1.00 (m, 2H), 0.91 – 0.78 (m, 2H).
100		554.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.81 (s, 1H), 7.56 (t, J = 2.2 Hz, 4H), 4.91 (s, 2H), 4.73 (t, J = 4.8 Hz, 1H), 4.61 (t, J = 4.8 Hz, 1H), 4.40 (t, J = 4.9 Hz, 1H), 4.33 (t, J = 5.0 Hz, 1H), 3.91 (s, 3H), 1.79 – 1.66 (m, 1H), 1.15 – 1.05 (m, 2H), 0.94 – 0.77 (m, 2H).
101		551.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.60 (s, 1H), 8.45 (br s, 1H), 8.20 (s, 1H), 7.63 – 7.55 (m, 4H), 4.76 – 4.68 (m, 3H), 3.81 (s, 3H), 1.75 – 1.68 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 0.95 – 0.95 (m, 2H), 0.73 – 0.73 (m, 2H).

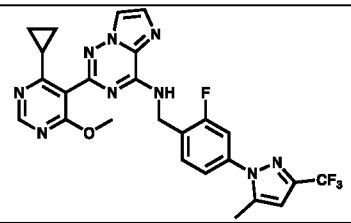
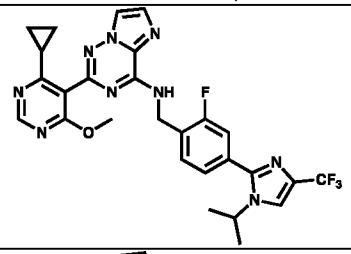
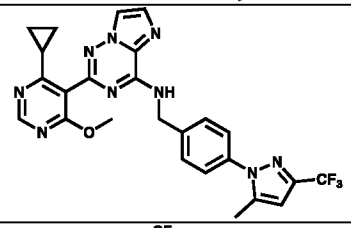
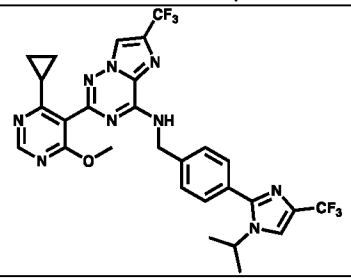
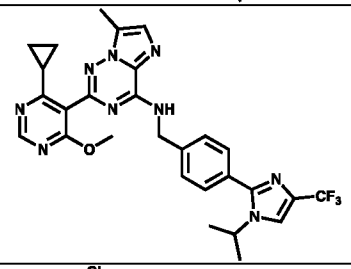
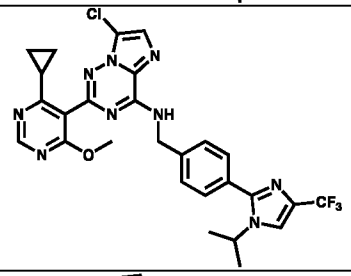
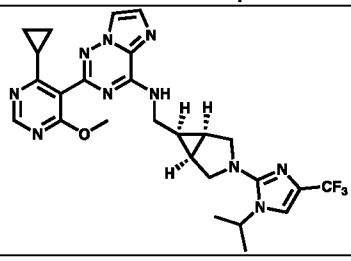
102		552.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (br s, 1H), 8.60 (s, 1H), 8.44 (br s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.48 (s, 4H), 4.45 – 4.40 (m, 1H), 3.81 (s, 3H), 1.76 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96 – 0.94 (m, 2H), 0.75 – 0.72 (m, 2H).
103		586.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.23 (d, J = 7.3 Hz, 2H), 4.98 (s, 2H), 4.57 (p, J = 6.6 Hz, 1H), 3.91 (d, J = 1.7 Hz, 3H), 1.74 (d, J = 8.3 Hz, 1H), 1.47 (d, J = 6.6 Hz, 6H), 1.15 – 1.09 (m, 2H), 0.89 (d, J = 7.6 Hz, 2H).
104		540.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.60 (t, J = 8.2 Hz, 1H), 7.32 (dd, J = 26.0, 9.4 Hz, 2H), 6.58 (s, 1H), 4.94 (s, 2H), 3.89 (s, 3H), 2.37 (s, 3H), 1.74 – 1.67 (m, 1H), 1.08 (q, J = 3.9 Hz, 2H), 0.88 – 0.79 (m, 2H).
105		592.4	^{1}H NMR (400 MHz, DMSO-d_6) 8.62 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.73 (s, 2H), 4.49 – 4.42 (m, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.00 (s, 3H), 2.58 (s, 3H), 1.65 – 1.61 (m, 1H), 1.40 (d, J = 6.4 Hz, 6H), 1.00 – 0.96 (m, 2H), 0.80 – 0.79 (m, 2H).
106		522.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 5.00 – 4.90 (m, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.72 (tt, J = 8.5, 4.6 Hz, 1H), 1.08 (p, J = 4.0 Hz, 2H), 0.84 (dq, J = 7.2, 3.9 Hz, 2H).
107		584.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.15 (s, 1H), 7.70 (s, 1H), 4.96 – 4.90 (m, 1H), 4.26 (s, 2H), 3.92 (s, 3H), 3.65 (s, 2H), 2.34 – 2.23 (m, 2H), 2.10 – 2.00 (m, 4H), 1.89 – 1.79 (m, 2H), 1.79 – 1.70 (m, 1H), 1.46 (d, J = 6.5 Hz, 6H), 1.16 – 1.10 (m, 2H), 0.95 – 0.89 (m, 2H).
108		586.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 8.60 (s, 1H), 8.41 (br s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.29 (s, 2H), 4.84 (br s, 2H), 4.21 – 4.14 (m, 1H), 3.79 (s, 3H), 1.74 – 1.68 (m, 1H), 1.36 (d, J = 6.4 Hz, 6H), 1.02 – 0.96 (m, 2H), 0.87 – 0.75 (m, 2H).

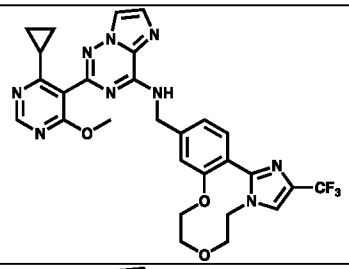
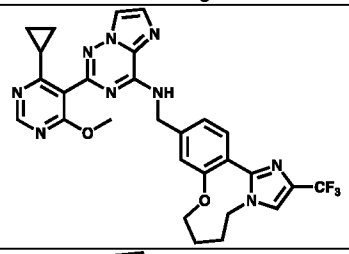
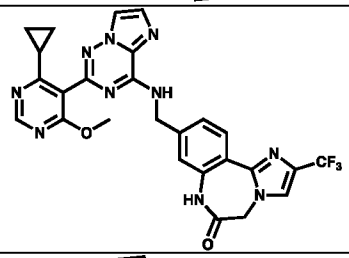
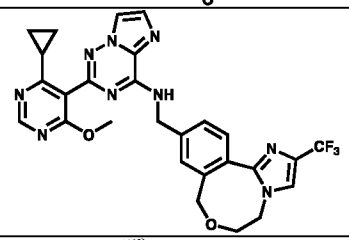
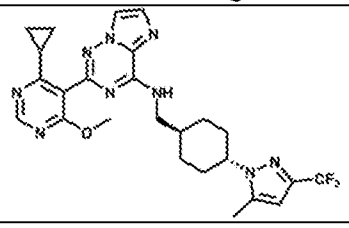
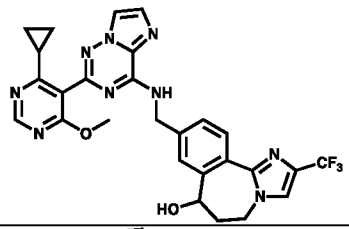
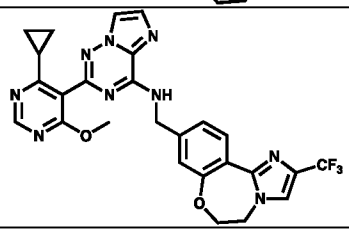
109		519.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.12 – 8.02 (m, 4H), 7.69 (dd, J = 7.4, 1.0 Hz, 1H), 7.56 – 7.50 (m, 3H), 4.88 (s, 2H), 3.90 (s, 3H), 1.75 – 1.64 (m, 1H), 1.09 – 1.01 (m, 2H), 0.85 – 0.73 (m, 2H).
110		536.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.13 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.60 (s, 1H), 4.90 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.78 – 1.65 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.12 – 1.03 (m, 2H), 0.81 (m, 2H).
111		564.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.18 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.43 (d, 2H), 6.60 (s, 1H), 4.93 (s, 2H), 4.01 (d, J = 7.5 Hz, 2H), 3.91 (s, 3H), 2.09 (hept, J = 6.9 Hz, 1H), 1.82 – 1.68 (m, 1H), 1.14 – 1.04 (m, 2H), 0.86 – 0.78 (m, 2H), 0.74 (d, J = 6.7 Hz, 6H).
112		565.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.39 (s, 1H), 8.29 (d, J = 1.4 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 5.77 (s, 2H), 5.61 – 5.47 (m, 1H), 4.98 (t, J = 7.3 Hz, 2H), 4.86 (s, 2H), 3.91 (s, 3H), 1.77 – 1.66 (m, 1H), 1.18 – 1.10 (m, 2H), 0.92 – 0.83 (m, 2H).
113		541.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.37 (s, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.48 – 7.35 (m, 2H), 6.60 (s, 1H), 5.81 (s, 2H), 4.86 (s, 2H), 3.92 (s, 3H), 2.40 (s, 3H), 1.77 – 1.67 (m, 1H), 1.18 – 1.10 (m, 2H), 0.95 – 0.81 (m, 2H).
114		523.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.39 (s, 1H), 7.78 – 7.68 (m, 2H), 7.57 – 7.49 (m, 2H), 6.59 (s, 1H), 5.77 (s, 2H), 4.85 (s, 2H), 3.91 (s, 3H), 2.35 (s, 3H), 1.75 – 1.65 (m, 1H), 1.17 – 1.09 (m, 2H), 0.94 – 0.81 (m, 2H).
115		568.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.95 (m, 2H), 7.65 (s, 1H), 7.51 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H), 4.91 (s, 2H), 4.24 (sept, J = 6.6 Hz, 1H), 3.93 (s, 3H), 1.94 – 1.85 (m, 1H), 1.41 (d, J = 6.6 Hz, 6H), 1.16 – 1.08 (m, 2H), 0.95 – 0.85 (m, 2H).
116		548.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.66 (m, 2H), 7.38 – 7.40 (m, 2H), 4.74 (m, 2H), 4.29 – 4.25 (m, 1H), 4.04 – 3.99 (m, 1H), 3.81 (s, 3H), 3.37 – 3.32 (m, 1H), 1.91 – 1.59 (m, 1H), 1.23 (d, J = 6.4 Hz, 3H), 0.99 – 0.81 (m, 4H).

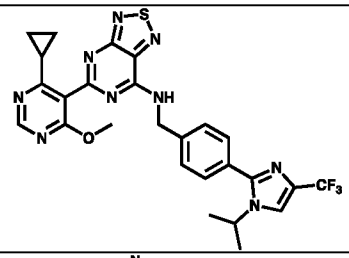
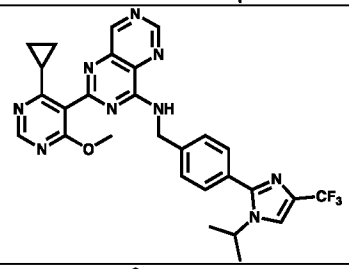
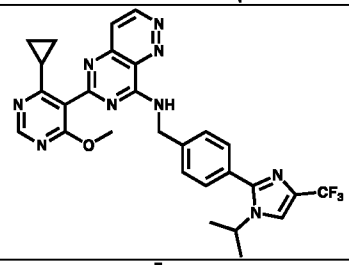
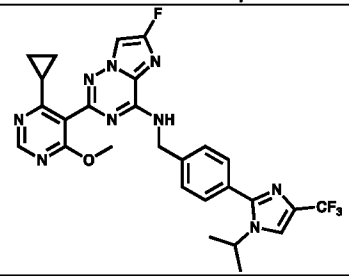
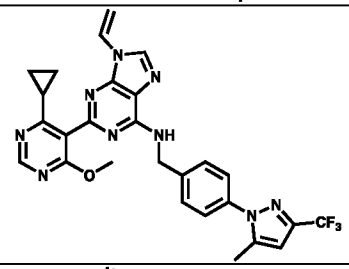
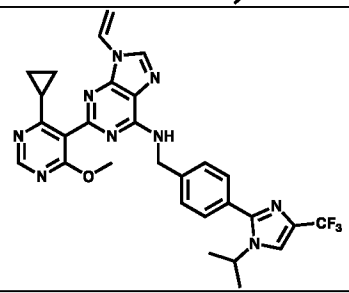
117		548.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 – 9.54 (m, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.88 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.33 (s, 1H), 7.36 (d, J = 10.4 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.27 – 4.22 (m, 1H), 4.04 – 4.00 (m, 1H), 3.77 (s, 3H), 3.31 – 3.26 (m, 1H), 1.69 (m, 1H), 1.15 (d, J = 7.2 Hz, 3H), 1.00 – 1.00 (m, 2H), 0.83 – 0.82 (m, 2H).
118		578.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, J = 7.2 Hz, 1H), 8.70 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.03 – 7.01 (m, 2H), 6.17 – 6.14 (m, 1H), 4.85 – 4.76 (m, 2H), 4.48 – 4.42 (m, 1H), 3.94 (s, 3H), 2.07 – 2.01 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10 – 1.06 (m, 4H).
119		528.9	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (t, J = 5.8 Hz, 1H), 8.64 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.63 (s, 1H), 6.44 (s, 1H), 4.25 – 4.19 (m, 1H), 3.85 (s, 3H), 3.62 (t, J = 6.8 Hz, 2H), 2.50 (s, 3H), 2.29 – 2.00 (m, 3H), 1.95 (t, J = 7.4 Hz, 1H), 1.88 – 1.82 (m, 6H), 1.00 – 1.00 (m, 2H), 0.99 – 0.86 (m, 2H).
120		557.5	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.2 Hz, 1H), 8.67 (s, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 4.38 – 4.31 (m, 1H), 3.87 (s, 3H), 3.46 (t, J = 6.6 Hz, 2H), 3.09 (d, J = 12.0 Hz, 2H), 2.73 – 2.68 (m, 2H), 1.93 – 1.88 (m, 2H), 1.74 – 1.71 (m, 2H), 1.41 – 1.38 (m, 2H), 1.33 (d, J = 6.4 Hz, 6H), 1.05 – 1.04 (m, 2H), 0.90 – 0.99 (m, 2H).
121		562.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.2 Hz, 1H), 8.67 (s, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 4.38 – 4.31 (m, 1H), 3.87 (s, 3H), 3.46 (t, J = 6.6 Hz, 2H), 3.09 (d, J = 12.0 Hz, 2H), 2.73 – 2.68 (m, 2H), 1.93 – 1.88 (m, 2H), 1.74 – 1.71 (m, 2H), 1.41 – 1.38 (m, 2H), 1.33 (d, J = 6.4 Hz, 6H), 1.05 – 1.04 (m, 2H), 0.90 – 0.99 (m, 2H).
122		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.21 – 7.09 (m, 2H), 4.72 (d, J = 6.0 Hz, 2H), 4.05 (t, J = 4.8 Hz, 4H), 3.85 (s, 3H), 1.93 – 1.84 (m, 3H), 1.01 – 1.01 (m, 2H), 0.86 – 0.83 (m, 2H).
123		458.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.26 (d, J = 2.8 Hz, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.94 (d, J = 4.0 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.19 – 7.15 (m, 1H), 3.87 (s, 3H), 3.74 – 3.71 (m, 2H), 3.44 (t, J = 8.0 Hz, 2H), 2.67 (t, J = 11.4 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.76 – 1.73 (m, 2H), 1.35 – 1.25 (m, 2H), 1.06 – 1.03 (m, 2H), 1.06 – 1.03 (m, 2H).

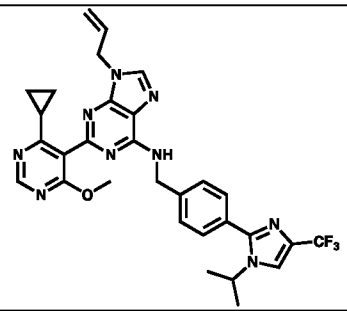
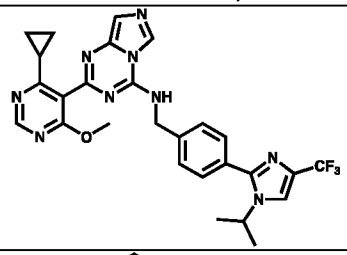
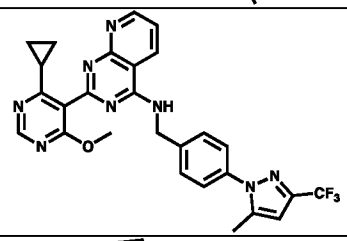
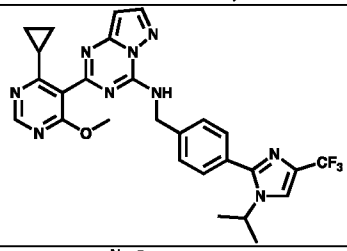
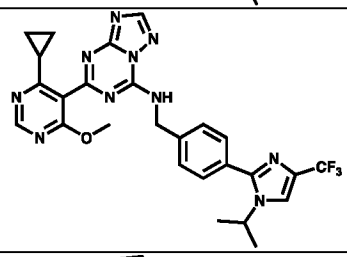
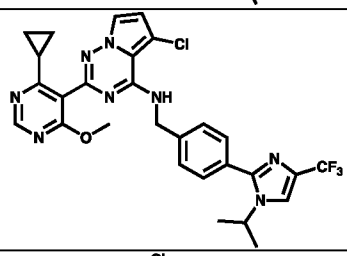
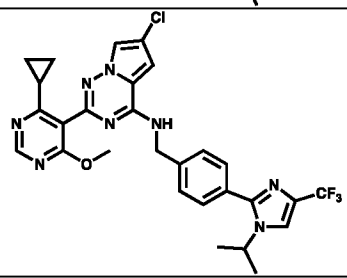
124		472.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.0 Hz, 1H), 8.67 (s, 1H), 8.11 (s, 2H), 7.63 (s, 1H), 7.20 (dd, J = 8.6, 3.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.63 (d, J = 12.4 Hz, 2H), 3.44 – 3.42 (m, 2H), 2.63 – 2.57 (m, 2H), 2.33 (s, 3H), 1.92 – 1.87 (m, 2H), 1.73 (d, J = 11.6 Hz, 2H), 1.35 – 1.25 (m, 2H), 1.06 – 1.04 (m, 2H), 0.94 – 0.93 (m, 2H).
125		592.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.23 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.54 – 7.48 (m, 4H), 4.78 (d, J = 6.0 Hz, 2H), 4.33 – 4.27 (m, 1H), 3.92 – 3.86 (m, 5H), 3.28 (s, 1H), 2.07 – 1.97 (m, 2H), 1.91 – 1.86 (m, 3H), 1.28 – 1.24 (m, 1H), 1.00 – 0.99 (m, 2H), 0.88 – 0.88 (m, 3H) .
126		578.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 – 9.55 (m, 1H), 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.55 – 7.49 (m, 4H), 4.89 – 4.87 (m, 1H), 4.77 (d, J = 6.0 Hz, 2H), 4.10 (q, J = 3.5 Hz, 1H), 3.90 – 3.86 (m, 5H), 3.72 (q, J = 3.6 Hz, 1H), 2.46 – 2.44 (m, 1H), 2.19 – 2.08 (m, 1H), 1.88 – 1.85 (m, 1H), 1.01 – 0.99 (m, 2H), 0.85 – 0.82 (m, 2H).
127		550.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 8.4 Hz, 1H), 8.66 (s, 1H), 8.14 (d, J = 0.8 Hz, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 – 7.57 (m, 4H), 5.60 – 5.53 (m, 1H), 4.09 – 4.07 (m, 2H), 3.82 (s, 3H), 1.81 – 1.75 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 0.99 – 0.98 (m, 2H), 0.87 – 0.87 (m, 1H), 0.84 – 0.84 (m, 1H).
128		562.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.49 (t, J = 9.4 Hz, 4H), 4.78 – 4.73 (m, 3H), 3.86 (s, 3H), 2.38 – 2.33 (m, 4H), 1.89 – 1.87 (m, 1H), 1.78 – 1.63 (m, 2H), 1.01 – 1.00 (m, 2H), 0.85 – 0.82 (m, 2H).
129		548.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 0.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.74 – 3.68 (m, 1H), 1.91 – 1.85 (m, 1H), 1.01 – 0.93 (m, 8H).
130		562.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 3.91 – 3.86 (m, 5H), 1.89 – 1.89 (m, 1H), 1.13 – 1.13 (m, 1H), 1.00 – 1.00 (m, 2H), 0.84 – 0.84 (m, 2H), 0.50 – 0.50 (m, 2H), 0.29 – 0.29 (m, 2H).

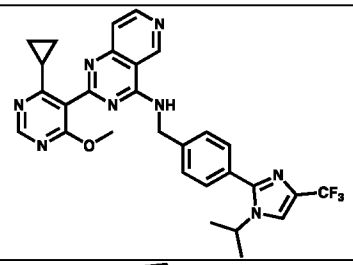
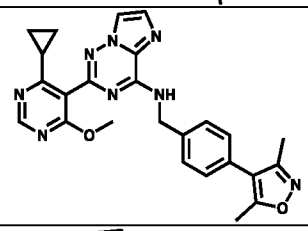
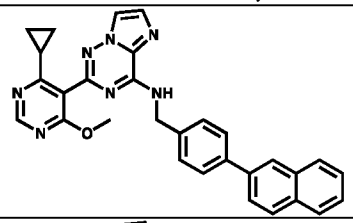
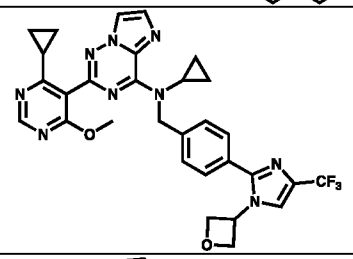
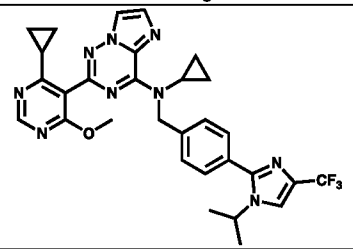
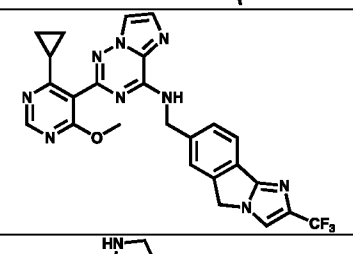
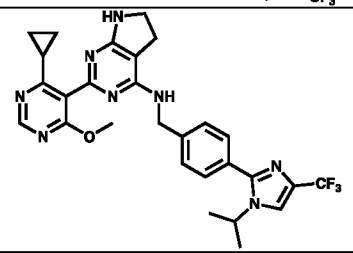
131		536.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 4.06 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.88 – 1.85 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.02 – 0.99 (m, 2H), 0.85 – 0.84 (m, 2H).
132		548.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.67 – 7.61 (m, 2H), 7.47 – 7.43 (m, 1H), 7.41 (s, 1H), 3.99 (t, J = 6.9 Hz, 2H), 3.93 (s, 3H), 2.71 (t, J = 7.1 Hz, 2H), 2.35 (pent, J = 7.00 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.14 – 1.08 (m, 2H), 0.91 – 0.84 (m, 2H).
133		522.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.93 (s, 1H), 7.68 (s, 1H), 7.62 (d, J = 6.7 Hz, 3H), 7.59 – 7.56 (m, 2H), 4.90 (s, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 1.92 – 1.85 (m, 1H), 1.14 – 1.09 (m, 2H), 0.92 – 0.87 (m, 2H).
134		552.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.93 (s, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.61 – 7.57 (m, 2H), 7.54 – 7.50 (m, 2H), 4.53 (sept, J = 6.6 Hz, 1H), 3.93 (s, 3H), 1.92 – 1.86 (m, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.14 – 1.10 (m, 2H), 0.91 – 0.87 (m, 2H).
135		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.60 – 5.53 (m, 1H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H), 1.79 – 1.75 (m, 1H), 1.63 (d, J = 7.2 Hz, 3H), 0.70 (d, J = 7.2 Hz, 6H), 1.10 – 0.99 (m, 2H), 0.98 – 0.98 (m, 1H), 0.97 – 0.96 (m, 1H).
136		564.3	^{1}H NMR (400 MHz, DMSO-d_6) 9.53 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.60 – 5.53 (m, 1H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H), 1.79 – 1.75 (m, 1H), 1.63 (d, J = 7.2 Hz, 3H), 0.70 (d, J = 7.2 Hz, 6H), 1.10 – 0.99 (m, 2H), 0.98 – 0.98 (m, 1H), 0.97 – 0.96 (m, 1H).
137		441.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.78 (d, J = 0.8 Hz, 1H), 8.65 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 9.54 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 3.84 (s, 3H), 1.88 – 1.82 (m, 1H), 1.01 – 0.99 (m, 2H), 0.84 – 0.81 (m, 2H).
138		548.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 1.2 Hz, 1H), 7.61 – 7.56 (m, 4H), 6.38 (s, 1H), 4.91 (s, 2H), 3.93 (s, 3H), 1.88 (tt, J = 8.4, 4.7 Hz, 1H), 1.80 (ddd, J = 13.4, 8.4, 5.1 Hz, 1H), 1.14 – 1.09 (m, 2H), 1.04 – 0.97 (m, 2H), 0.93 – 0.86 (m, 2H), 0.83 – 0.77 (m, 2H).

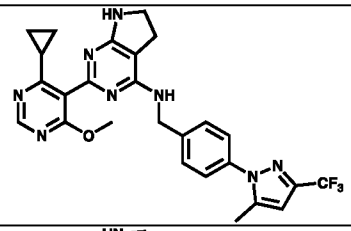
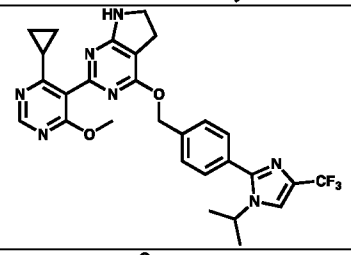
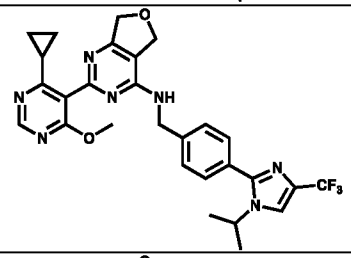
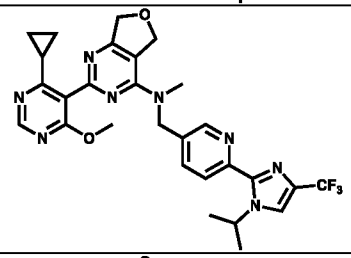
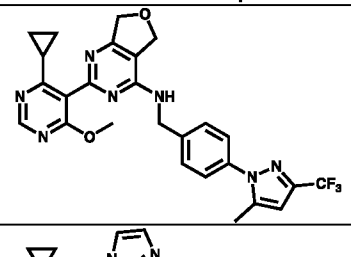
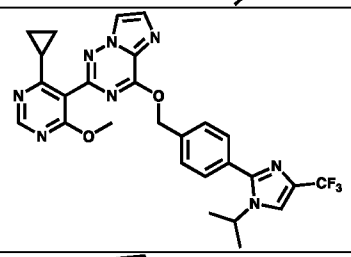
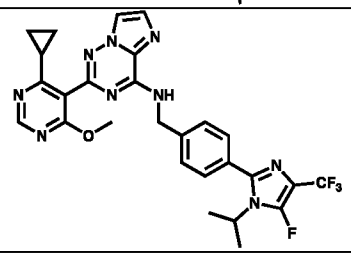
139		540.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (s, 1H), 7.66 – 7.58 (m, 2H), 7.34 (ddd, J = 20.6, 9.2, 2.1 Hz, 2H), 6.58 (s, 1H), 4.94 (s, 2H), 3.91 (s, 3H), 2.37 (s, 3H), 1.86 (tt, J = 8.3, 4.6 Hz, 1H), 1.15 – 1.06 (m, 2H), 0.93 – 0.84 (m, 2H).
140		568.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.98 – 7.90 (m, 2H), 7.67 – 7.58 (m, 2H), 7.40 – 7.29 (m, 2H), 4.95 (s, 2H), 4.55 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.88 (tt, J = 8.3, 4.6 Hz, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.15 – 1.07 (m, 2H), 0.92 – 0.84 (m, 2H).
141		522.5	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.57 (s, 1H), 4.91 (s, 2H), 3.93 (s, 3H), 2.33 (s, 3H), 1.91 – 1.84 (m, 1H), 1.14 – 1.09 (m, 2H), 0.92 – 0.87 (m, 2H).
142		618.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (br s, 1H), 8.88 (s, 1H), 8.67 (s, 1H), 8.16 (s, 1H), 7.50 (s, 4H), 4.78 (s, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 2.01 – 1.94 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 (s, 2H), 0.83 – 0.82 (m, 2H).
143		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.54 – 7.46 (m, 5H), 4.76 (d, J = 6.4 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.85 (s, 3H), 2.42 (s, 3H), 1.88 – 1.81 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.94 (m, 2H), 0.84 – 0.82 (m, 2H).
144		584.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.67 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.81 (s, 1H), 7.49 (s, 4H), 4.78 (d, J = 4.8 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 1.93 – 1.86 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.03 – 1.00 (m, 2H), 0.83 – 0.83 (m, 2H).
145		555.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (br s, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.32 – 7.31 (m, 1H), 4.33 – 4.26 (m, 1H), 3.86 (s, 3H), 3.42 – 3.33 (m, 6H), 1.92 – 1.88 (m, 1H), 1.64 (d, J = 8.4 Hz, 2H), 1.36 – 1.34 (m, 6H), 1.04 – 1.11 (m, 2H), 0.91 – 0.90 (m, 2H).

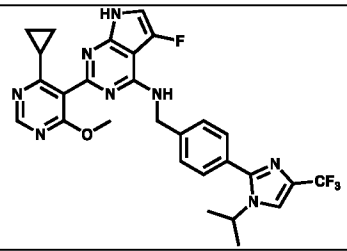
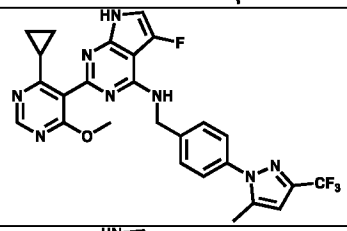
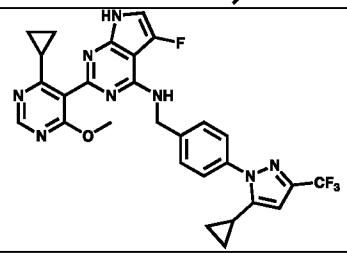
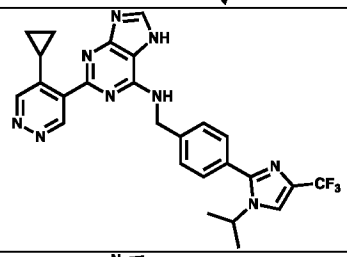
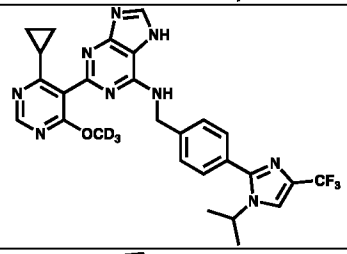
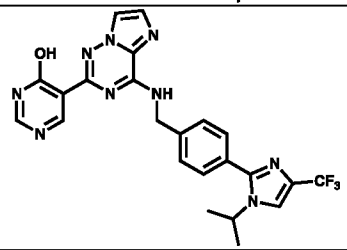
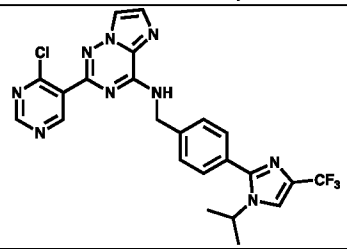
146		594.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.98 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.31 (s, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 1.2 Hz, 1H), 4.76 (d, J = 6.4 Hz, 2H), 4.18 – 4.11 (m, 2H), 3.94 (s, 3H), 3.87 (d, J = 5.2 Hz, 4H), 3.56 – 3.54 (m, 2H), 1.91 – 1.87 (m, 1H), 1.03 – 1.00 (m, 2H), 0.88 – 0.85 (m, 2H).
147		578.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.13 (dd, J = 7.6, 1.2 Hz, 1H), 4.75 (d, J = 6.4 Hz, 2H), 4.16 (t, J = 5.0 Hz, 2H), 3.85 (s, 3H), 3.70 – 3.67 (m, 2H), 1.91 – 1.89 (m, 4H), 1.72 – 1.68 (m, 3H), 1.03 – 0.99 (m, 2H).
148		563.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.58 (t, J = 6.2 Hz, 1H), 8.65 (s, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 4.75 (d, J = 10.4 Hz, 4H), 3.84 (s, 3H), 1.91 – 1.87 (m, 1H), 1.02 – 0.97 (m, 2H), 0.77 – 0.75 (m, 2H).
149		564.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.68 – 7.51 (m, 1H), 7.43 – 7.42 (m, 2H), 4.78 (d, J = 6.0 Hz, 2H), 4.34 – 4.34 (m, 2H), 3.99 – 3.99 (m, 2H), 3.85 (s, 3H), 3.82 – 3.76 (m, 2H), 1.91 – 1.84 (m, 1H), 1.00 – 0.98 (m, 2H), 0.88 – 0.80 (m, 2H).
150		528.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (t, J = 5.8 Hz, 1H), 8.68 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 6.43 (s, 1H), 4.22 – 4.16 (m, 1H), 3.88 (s, 3H), 3.41 (t, J = 6.0 Hz, 2H), 2.30 (s, 3H), 1.92 – 1.68 (m, 8H), 1.26 – 1.18 (m, 2H), 1.08 – 1.05 (m, 4H).
151		564.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.94 (s, 1H), 7.68 – 7.61 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 4.4 Hz, 1H), 4.78 (d, J = 6.4 Hz, 2H), 4.59 – 4.57 (m, 1H), 4.17 – 4.12 (m, 1H), 3.85 (s, 3H), 3.81 – 3.77 (m, 1H), 2.61 – 2.57 (m, 1H), 2.09 – 2.04 (m, 1H), 1.89 – 1.85 (m, 1H), 1.01 – 0.99 (m, 2H), 0.85 – 0.83 (m, 2H).
152		550.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 0.8 Hz, 1H), 7.10 (dd, J = 8.4, 1.6 Hz, 1H), 7.00 (d, J = 1.2 Hz, 1H), 4.68 (d, J = 6.4 Hz, 2H), 4.44 (s, 4H), 3.85 (s, 3H), 1.89 – 1.83 (m, 1H), 1.02 – 0.99 (m, 2H), 0.87 – 0.86 (m, 2H).

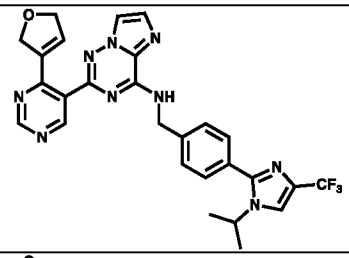
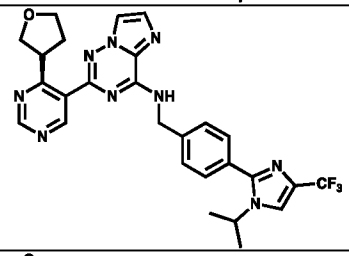
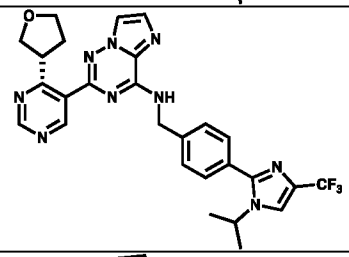
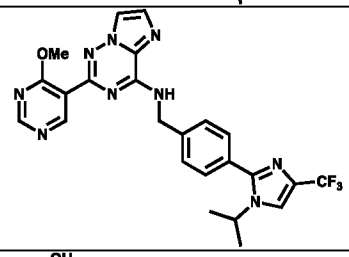
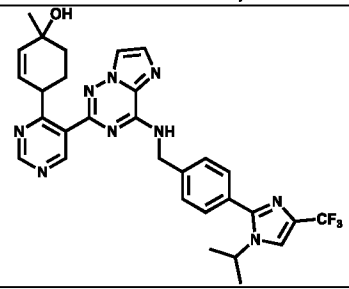
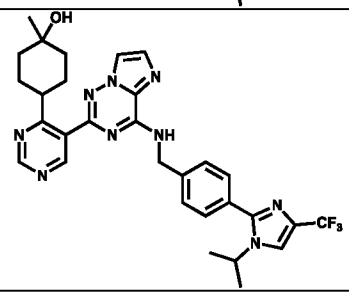
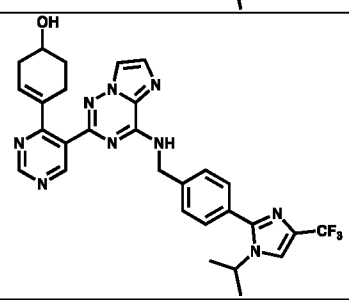
153		568.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.65 (s, 1H), 8.16 (s, 1H), 7.64 – 7.51 (m, 4H), 4.85 (d, J = 4.8 Hz, 2H), 4.44 – 4.41 (m, 1H), 3.84 (s, 3H), 1.91 – 1.86 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.00 – 0.99 (m, 2H), 0.80 – 0.77 (m, 2H).
154		562.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (t, J = 6.4 Hz, 1H), 9.44 (s, 1H), 9.41 (s, 1H), 8.65 (s, 1H), 8.15 (s, 1H), 7.52 – 7.47 (m, 4H), 4.83 (d, J = 6.0 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.83 (s, 3H), 1.84 – 1.78 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.80 – 0.75 (m, 2H).
155		562.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (t, J = 6.2 Hz, 1H), 9.57 (d, J = 6.0 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.98 (d, J = 6.0 Hz, 1H), 7.52 (q, J = 8.5 Hz, 4H), 4.88 (d, J = 6.0 Hz, 2H), 4.46 – 4.40 (m, 1H), 3.84 (s, 3H), 1.88 – 1.82 (m, 1H), 1.40 (d, J = 7.6 Hz, 6H), 1.01 – 0.99 (m, 2H), 0.79 – 0.78 (m, 2H).
156		568.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.51 – 7.46 (m, 4H), 4.75 (d, J = 6.0 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.85 (s, 3H), 1.90 – 1.85 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.03 – 0.97 (m, 2H), 0.84 – 0.82 (m, 2H).
157		548.3	^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (br s, 1H), 8.61 (s, 2H), 7.49 (s, 4H), 7.32 (dd, J = 16.0, 9.2 Hz, 1H), 6.74 (s, 1H), 6.02 (d, J = 16.0 Hz, 1H), 5.13 (d, J = 8.8 Hz, 1H), 4.76 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H), 1.72 – 1.70 (m, 1H), 0.85 – 0.77 (m, 2H), 0.79 – 0.75 (m, 2H).
158		576.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (br s, 1H), 8.62 (s, 2H), 8.15 (d, J = 1.2 Hz, 1H), 7.50 – 7.44 (m, 4H), 7.32 (dd, J = 16.0 Hz, J = 9.2 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.12 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 4.4 Hz, 2H), 4.43 (t, J = 6.4 Hz, 1H), 3.82 (s, 3H), 1.74 – 1.68 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.99 – 0.93 (m, 2H), 0.78 – 0.73 (m, 2H).

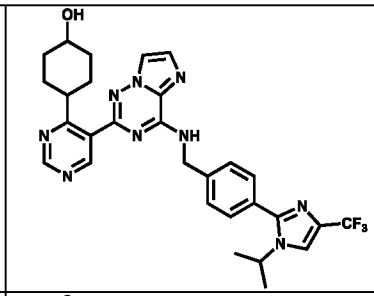
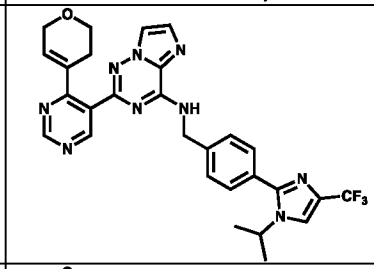
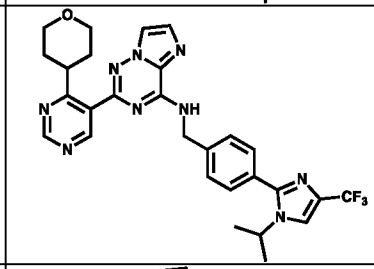
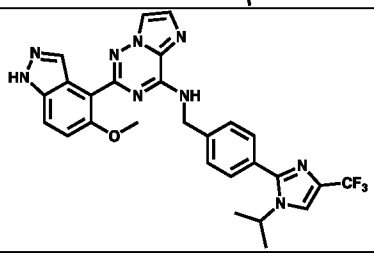
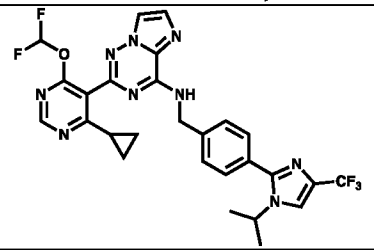
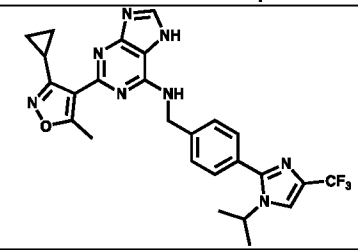
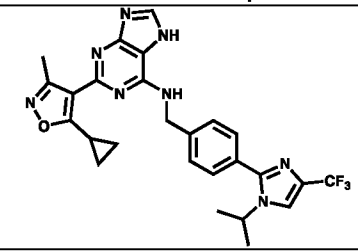
159		590.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 – 8.56 (m, 2H), 8.21 (s, 1H), 8.15 (s, 1H), 7.48 – 7.48 (m, 4H), 6.12 – 6.03 (m, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.13 – 5.13 (m, 1H), 4.81 – 4.74 (m, 4H), 4.45 – 4.41 (m, 1H), 3.81 (s, 3H), 1.71 – 1.67 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.85 – 0.84 (m, 2H), 0.74 – 0.74 (m, 2H).
160		550.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (br s, 1H), 8.58 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 6.99 (s, 1H), 4.74 (s, 2H), 4.49 – 4.43 (m, 1H), 3.84 (s, 3H), 1.98 – 1.98 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.98 – 0.97 (m, 2H), 0.85 – 0.83 (m, 2H).
161		533.5	^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (dd, J = 4.4, 1.8 Hz, 1H), 8.71 (dd, J = 8.3, 1.9 Hz, 1H), 8.57 (s, 1H), 7.63 – 7.60 (m, 1H), 7.60 – 7.56 (m, 2H), 7.47 – 7.42 (m, 2H), 6.57 (s, 1H), 4.96 (s, 2H), 3.90 (s, 3H), 2.32 (s, 3H), 1.87 – 1.78 (m, 1H), 1.13 – 1.07 (m, 2H), 0.87 – 0.81 (m, 2H).
162		550.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.64 (s, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.51 (s, 4H), 6.56 (d, J = 2.0 Hz, 1H), 4.79 (s, 2H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.92 – 1.88 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.90 – 0.86 (m, 2H).
163		551.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.5 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.80 (s, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 2.04 – 1.99 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 1.02 – 1.01 (m, 2H), 0.82 – 0.81 (m, 2H).
164		583.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.16 (t, J = 6.0 Hz, 2H), 7.81 (d, J = 3.2 Hz, 1H), 7.49 (t, J = 5.2 Hz, 4H), 6.82 (d, J = 3.2 Hz, 1H), 4.83 (d, J = 6.0 Hz, 2H), 4.47 – 4.41 (m, 1H), 3.84 (s, 3H), 1.86 – 1.82 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.98 – 0.98 (m, 2H), 0.97 – 0.97 (m, 2H).
165		583.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (t, J = 6.0 Hz, 1H), 8.64 (s, 1H), 8.17 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.06 (s, 1H), 4.79 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.87 – 1.80 (m, 1H), 1.81 (d, J = 4.4 Hz, 6H), 1.40 – 1.40 (m, 2H), 1.38 – 1.38 (m, 2H).

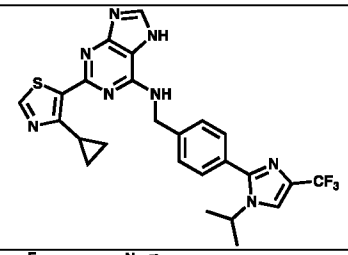
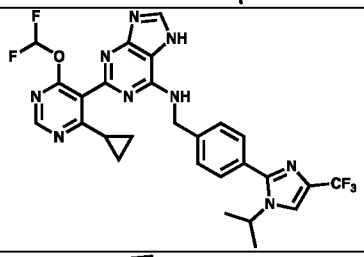
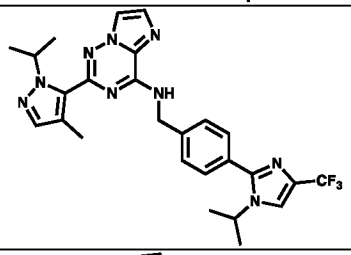
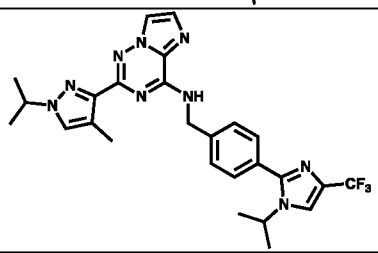
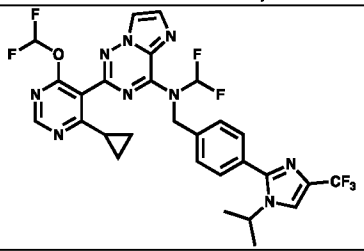
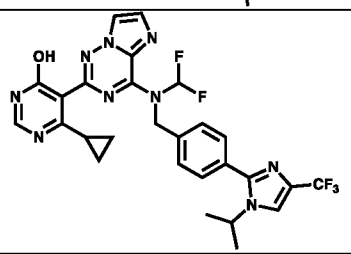
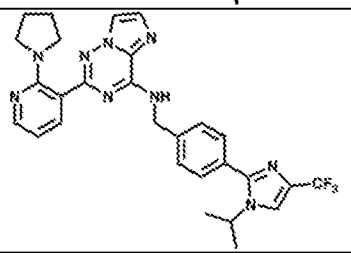
166		561.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.75 (br s, 1H), 9.61 (t, J = 5.6 Hz, 1H), 8.89 (br s, 1H), 8.64 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.65 (s, 1H), 7.51 (s, 4H), 4.88 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H), 1.78 – 1.71 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.78 – 0.75 (m, 2H).
167		469.4	^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 4.85 (s, 2H), 3.92 (s, 3H), 2.37 (s, 3H), 2.21 (s, 3H), 1.87 (tt, J = 8.3, 4.7 Hz, 1H), 1.10 (dq, J = 6.5, 3.9 Hz, 2H), 0.85 (dq, J = 7.0, 3.7 Hz, 2H).
168		500.1	^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.98 – 7.84 (m, 5H), 7.80 – 7.71 (m, 3H), 7.63 (s, 1H), 7.54 – 7.47 (m, 4H), 3.93 (s, 3H), 1.91 – 1.84 (m, 1H), 1.13 – 1.09 (m, 2H), 0.88 (dd, J = 7.9, 3.2 Hz, 2H).
169		604.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (s, 1H), 8.23 (d, J = 0.8 Hz, 1H), 7.73 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 5.89 – 5.86 (m, 1H), 5.10 – 5.05 (m,1H), 5.54 – 5.47 (m, 1H), 4.85 (t, J = 7.2 Hz, 2H), 4.79 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.28 – 3.35 (m, 1H), 2.10 (s, 1H), 1.04 – 0.75 (m, 8H).
170		590.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.24 (d, J = 0.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.74 (br s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 5.90 (br s, 1H), 5.07 (br s, 1H), 4.47 – 4.44 (m, 1H), 3.87 (s, 3H), 3.00 – 2.91 (m, 1H), 2.07 – 1.99 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 1.04 – 0.89 (m, 8H).
171		520.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H), 4.79 (d, J = 6.4 Hz, 2H), 3.85 (s, 3H), 1.88 – 1.86 (m, 1H), 0.99 – 0.99 (m, 2H), 0.81 – 0.78 (m, 2H).
172		551.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 6.4 Hz, 1H), 6.57 (s, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.81 (s, 3H), 3.50 (t, J = 9.0 Hz, 2H), 2.84 (t, J = 8.8 Hz, 2H), 1.77 – 1.71 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 0.91 – 0.90 (m, 2H), 0.75 (m, 2H).

173		523.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.49 –7.43 (m, 4H), 7.07 (t, J = 6.2 Hz, 1H), 6.74 (s, 1H), 6.58 (s, 1H), 4.59 (d, J = 6.4 Hz, 2H), 3.81 (s, 3H), 3.50 (t, J = 8.8 Hz, 2H), 2.84 (t, J = 8.8 Hz, 2H), 2.31 (s, 3H), 1.24 (s, 1H), 0.92 – 0.92 (m, 2H), 0.78 – 0.77 (m, 2H).
174		552.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.18 (s, 1H), 7.55 (s, 4H), 7.28 (s, 1H), 5.44 (s, 2H) 4.50 – 4.45 (m, 1H), 3.84 (s, 3H), 3.59 (t, J = 9.0 Hz, 2H), 2.97 (t, J = 8.8 Hz, 2H), 1.75 – 1.69 (m, 1H), 1.41 (d, J = 6.4 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.85 – 0.85 (m, 2H).
175		552.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.90 (s, 1H), 7.53 – 7.46 (m, 4H), 5.08 (s, 2H), 4.95 (s, 2H), 4.79 (s, 2H), 4.57 – 4.48 (m, 1H), 3.91 (s, 3H), 1.77 – 1.67 (m, 1H), 1.44 (d, J = 1.6 Hz, 6H), 1.11 – 1.03 (m, 2H), 0.87 – 0.78 (m, 2H).
176		567.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1H), 8.55 (s, 1H), 7.97 – 7.93 (m, 2H), 7.88 – 7.83 (comp m, 1H), 5.67 (h, J = 6.8 Hz, 1H), 5.45 (s, 2H), 4.96 (s, 2H), 4.92 (s, 2H), 3.91 (s, 3H), 3.24 (s, 3H), 1.78 – 1.72 (m, 1H), 1.48 (d, J = 6.8 Hz, 6H), 1.11 – 1.05 (comp m, 2H), 0.90 – 0.84 (comp m, 2H).
177		524.2	^{1}H NMR (400 MHz, CD_3OD) 8.54 (s, 1H), 7.53 – 7.49 (comp m, 2H), 7.45 – 7.40 (comp m, 2H), 6.56 (s, 1H), 5.09 – 5.04 (m, 2H), 4.95 – 4.91 (m, 2H), 4.78 (s, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.74 – 1.66 (m, 1H), 1.09 – 1.02 (m, 2H), 0.87 – 0.78 (m, 2H).
178		551.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.46 (d, J = 0.8 Hz, 1H), 8.19 (s, 1H), 7.88 (d, J = 0.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 5.74 (s, 2H), 4.52 – 4.46 (m, 1H), 3.89 (s, 3H), 2.02 – 1.97 (m, 1H), 1.41 (d, J = 6.4 Hz, 6H), 1.10 – 1.08 (m, 2H), 0.95 – 0.94 (m, 2H).
179		568.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.50 (s, 4H), 4.77 (d, J = 6.0 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.87 – 1.84 (m, 1H), 1.45 (d, J = 6.0 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.83-0.80 (m, 2H).

180		567.3	^{1}H NMR (400 MHz, CD_3OD) δ8.53 (s, 1H), 7.89 (s, 1H), 7.56 – 7.51 (m, 2H), 7.50 – 7.43 (m, 2H), 6.93 (s, 1H), 4.52 (hept, J = 6.5 Hz, 1H), 3.88 (s, 3H), 1.75 – 1.69 (m, 1H), 1.43 (d, J = 6.5 Hz, 6H), 1.06 – 1.02 (m, 2H), 0.79 – 0.75 (m, 2H).
181		539.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.59 (s, 1H), 7.85 (t, J = 6.3 Hz, 1H), 7.51 – 7.46 (m, 4H), 7.17 – 7.13 (m, 1H), 6.73 (s, 1H), 4.75 (d, J = 6.3 Hz, 2H), 3.80 (s, 3H), 2.30 (s, 3H), 1.75 – 1.69 (m, 2H), 0.97 – 0.92 (m, 2H), 0.77 – 0.72 (m, 2H).
182		565.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (d, J = 2.9 Hz, 1H), 8.58 (s, 1H), 7.89 – 7.80 (m, 1H), 7.57 – 7.48 (m, 4H), 7.15 (t, J = 2.6 Hz, 1H), 6.61 (s, 1H), 4.75 (d, J = 6.3 Hz, 2H), 3.80 (s, 3H), 1.83 – 1.68 (m, 2H), 0.97 – 0.90 (m, 4H), 0.84 – 0.78 (m, 2H), 0.76 – 0.70 (m, 2H).
183		520.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 9.29 (s, 1H), 8.74 (s, 1H), 8.63 (br s, 1H), 8.28 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.49 (m, J = 7.2 Hz, 4H), 4.82 (s, 2H), 4.48 – 4.42 (m, 1H), 2.89 (s, 1H), 1.37 (d, J = 6.8 Hz, 6H), 0.94 – 0.94 (m, 2H), 0.84 – 0.84 (m, 2H).
184		553.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.60 (s, 1H), 8.45 (br s, 1H), 8.20 – 8.15 (m, 2H), 7.48 (s, 4H), 4.74 (s, 2H), 4.45 – 4.42 (m, 1H), 1.74 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.95 – 0.95 (m, 2H), 0.73 – 0.73 (m, 2H).
185		496.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 9.42 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 0.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 4.82 (s, 2H), 4.49 – 4.43 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H).
186		514.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 – 9.76 (m, 1H), 9.15 – 9.11 (m, 2H), 8.23 (d, J = 0.8 Hz, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.52 (s, 4H), 4.84 (d, J = 5.6 Hz, 2H), 4.48 – 4.41 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H).

187		548.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.70 (t, J = 6.4 Hz, 1H), 9.23 (s, 1H), 8.90 (s, 1H), 8.18 (dd, J = 12.8, 1.2 Hz, 2H), 7.70 – 7.68 (m, 1H), 7.54 – 7.47 (m, 4H), 6.32 – 6.31 (m, 1H), 4.83 – 4.76 (m, 4H), 4.52 – 4.43 (m, 3H), 1.39 (d, J = 6.8 Hz, 6H).
188		550.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.66 (bs, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.52 (s, 4H), 4.86 (s, 2H), 4.48 – 4.45 (m, 1H), 4.14 – 4.10 (m, 1H), 3.91 – 3.87 (m, 2H), 3.73 (t, J = 7.4 Hz, 1H), 3.59 (q, J = 7.3 Hz, 1H), 2.14 – 2.11 (m, 1H), 2.07 – 2.01 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H).
189		550.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.68 (s, 1H), 9.20 (s, 1H), 9.02 – 8.96 (m, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.15 (s, 1H), 7.70 – 7.68 (m, 1H), 7.54 – 7.50 (m, 4H), 4.86 – 4.77 (m, 2H), 4.49 – 4.43 (m, 1H), 4.15 – 4.11 (m, 1H), 3.92 – 3.84 (m, 2H), 3.72 (t, J = 7.6 Hz, 1H), 3.60 (q, J = 7.3 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.38 (d, J = 6.4 Hz, 6H).
190		510.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.59 (t, J = 6.2 Hz, 1H), 8.86 (d, J = 13.6 Hz, 2H), 8.17 – 8.15 (m, 2H), 7.67 (d, J = 1.2 Hz, 1H), 7.57 – 7.52 (m, 4H), 4.82 (d, J = 6.0 Hz, 2H), 4.49 – 4.42 (m, 1H), 3.97 (s, 3H), 1.38 (d, J = 6.8 Hz, 6H).
191		590.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.69 (t, J = 6.2 Hz, 1H), 9.18 (s, 1H), 8.95 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.15 (s, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.52 – 7.52 (m, 4H), 5.61 – 5.59 (m, 1H), 5.49 – 5.46 (m, 1H), 4.84 (d, J = 6.0 Hz, 2H), 4.49 – 4.42 (m, 2H), 4.29 – 4.25 (m, 1H), 2.07 – 2.01 (m, 1H), 1.88 – 1.70 (m, 2H), 1.61 – 1.55 (m, 1H), 1.38 (d, J = 5.6 Hz, 6H), 1.19 (s, 3H).
192		592.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.66 (s, 1H), 9.18 (s, 1H), 8.90 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.15 (s, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.53 – 7.48 (m, 4H), 4.85 (d, J = 4.8 Hz, 2H), 4.47 – 4.44 (m, 1H), 4.26 (s, 1H), 3.39 – 3.36 (m, 1H), 1.74 – 1.74 (m, 4H), 1.59 – 1.56 (m, 2H), 1.38 – 1.34 (m, 6H), 1.24 – 1.23 (m, 2H), 1.17 – 1.14 (m, 3H).
193		576.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.60 – 9.57 (m, 1H), 9.17 – 9.16 (m, 1H), 8.89 (s, 1H), 8.17 – 8.15 (m, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.52 – 7.46 (m, 4H), 5.80 (s, 1H), 4.85 – 4.80 (m, 2H), 4.66 – 4.65 (m, 1H), 4.46 – 4.41 (m, 1H), 3.61 (br s, 1H), 2.24 – 2.19 (m, 2H), 1.91 – 1.84 (m, 1H), 1.72 – 1.69 (m, 1H), 1.48 – 1.42 (m, 6H), 1.39 – 1.23 (m, 2H).

194		578.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.66 (s, 1H), 9.16 (s, 1H), 8.91 (s, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.55 – 7.48 (m, 4H), 5.76 (s, 1H), 4.86 (s, 2H), 4.49 – 4.43 (m, 1H), 3.33 (s, 2H), 1.85 – 1.64 (m, 6H), 1.38 (d, J = 6.4 Hz, 6H), 1.17 – 1.10 (m, 2H).
195		562.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.61 (t, J = 6.4 Hz, 1H), 9.21 (s, 1H), 8.91 (s, 1H), 8.19 – 8.15 (m, 2H), 7.68 – 7.67 (m, 1H), 7.55 – 7.47 (m, 4H), 6.11 (s, 1H), 4.81 (d, J = 6.4 Hz, 2H), 4.48 – 4.42 (m, 1H), 4.07 – 4.02 (m, 2H), 3.62 (t, J = 5.4 Hz, 2H), 2.33 – 2.33 (m, 2H), 1.38 (d, J = 6.8 Hz, 6H).
196		564.4	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.66 (br s, 1H), 9.21 (s, 1H), 8.94 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.71 (s, 1H), 7.54 – 7.49 (m, 4H), 4.86 (s, 2H), 4.47 – 4.40 (m, 1H), 3.79 – 3.75 (m, 2H), 3.67 – 3.61 (m, 1H), 3.11 – 3.05 (m, 2H), 1.90 – 1.79 (m, 2H), 1.61 – 1.59 (m, 2H), 1.39 – 1.37 (m, 6H).
197		548.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.98 (s, 1H), 9.45-9.44 (m, 1H), 8.15 (s, 2H), 7.70 (s, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.53 – 7.48 (m, 4H), 7.30 (d, J = 9.2 Hz, 1H), 4.80 (d, J = 5.2 Hz, 2H), 4.54 – 4.47 (m, 1H), 3.76 (s, 3H), 1.39 (d, J = 6.8 Hz, 6H).
198		586.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.71 (t, J = 6.0 Hz, 1H), 8.79 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.99 – 7.64 (m, 2H), 7.49 – 7.49 (m, 4H), 4.78 (d, J = 5.6 Hz, 2H), 4.46 – 4.40 (m, 1H), 2.05 – 1.99 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.07 – 1.01 (m, 2H), 0.93 – 0.91 (m, 2H).
199		523.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.95 (s, 1H), 8.41 (s, 1H), 8.15 (s, 2H), 7.51 – 7.44 (m, 4H), 4.82 (s, 1H), 4.47 – 4.40 (m, 1H), 2.60 (s, 3H), 2.03 – 1.97 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 0.87 – 0.75 (m, 5H).
200		523.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 12.94 (s, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.51 – 7.44 (m, 4H), 4.81 (s, 2H), 4.47 – 4.40 (m, 1H), 3.06 (s, 1H), 2.40 (s, 3H), 1.38 (d, J = 6.4 Hz, 6H), 1.05 – 0.92 (m, 4H).

201		525.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.83 (s, 1H), 8.54 (s, 1H), 8.15 (d, J = 6.8 Hz, 2H), 7.50 (s, 4H), 4.78 (s, 2H), 4.48 – 4.41 (m, 2H), 1.38 (d, J = 6.8 Hz, 6H), 1.32 – 1.24 (m, 1H), 1.18 – 1.14 (m, 4H). One extra proton observed due to the presence of TFA
202		586.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.73 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.79 (s, 1H), 7.61 – 7.47 (m, 4H), 5.32 (s, 2H), 4.47 – 4.40 (m, 1H), 1.89 – 1.83 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.03 (s, 2H), 0.83 (s, 2H).
203		524.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (t, J = 6.2 Hz, 1H), 8.15 (d, J = 0.8 Hz, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.54 – 7.46 (m, 4H), 7.33 (s, 1H), 5.09 – 5.03 (m, 1H), 4.84 (d, J = 6.0 Hz, 2H), 4.47 – 4.41 (m, 1H), 2.09 (s, 3H), 1.38 (d, J = 6.4 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H).
204		524.4	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (t, J = 6.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.61 (s, 2H), 7.53 (q, J = 8.3 Hz, 4H), 4.86 (d, J = 6.0 Hz, 2H), 4.51 – 4.39 (m, 2H), 2.16 (s, 3H), 1.37 (d, J = 6.4 Hz, 6H), 1.42 (d, J = 6.4 Hz, 6H).
205		636.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 – 9.14 (m, 1H), 8.81 (s, 1H), 8.53 (d, J = 1.2 Hz, 1H), 8.16 (s, 1H), 7.97 – 7.62 (m, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 5.26 (s, 2H), 4.45 – 4.39 (m, 1H), 2.04 – 2.03 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 1.00 – 1.04 (m, 2H), 0.86 – 0.84 (m, 2H).
206		586.3	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (br s, 1H), 9.40-9.12 (m, 1H), 8.45 – 8.41 (m, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.13 (s, 1H), 7.91 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 5.25 (s, 2H), 4.47 – 4.40 (m, 1H), 1.69 (t, J = 4.0 Hz, 1H), 1.39 (d, J = 6.4 Hz, 6H), 0.91 – 0.85 (m, 2H), 0.66 – 0.65 (m, 2H).
207		548.3	^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.1 Hz, 1H), 7.90 (s, 2H), 7.76 (d, J = 7.4 Hz, 1H), 7.63 – 7.49 (m, 5H), 6.73 (dd, J = 7.1, 5.1 Hz, 1H), 4.92 (s, 2H), 4.54 (p, J = 6.9 Hz, 1H), 3.28 – 3.17 (m, 4H), 1.76 (d, J = 6.3 Hz, 4H), 1.44 (d, J = 6.6 Hz, 6H).

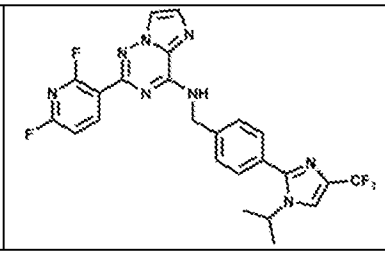
208		515.2	^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (q, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.69 – 7.58 (m, 3H), 7.53 (d, J = 7.8 Hz, 2H), 7.10 (dd, J = 8.2, 2.7 Hz, 1H), 4.98 (s, 2H), 4.52 (p, J = 6.8 Hz, 1H), 1.42 (d, J = 6.6 Hz, 6H).

Table 2: Abbreviations Used.

Abbreviation:	Meaning:
DMSO	Dimethyl sulfoxide
MeOH	Methanol
$NaBH_4$	Sodium borohydride
$LiAlH_4$	Lithium aluminum hydride
DIBAlH	Diisobutylaluminum hydride
DMF	*N,N*-Dimethylformamide
DME	Dimethoxyethane
MeCN/ACN	Acetonitrile
EtOAc	Ethyl acetate
NaH	Sodium hydride
THF	Tetrahydrofuran
CD_3OD	Deuterated MeOH
$CDCl_3$	Deuterated chloroform
DIPEA	*N,N*-Diisopropylethylamine
cataCXium-A	Di(1-adamantyl)-*n*-butylphosphine
Boc	*Tert*-butyloxycarbonyl
THP	Tetrahydro-2*H*-pyran-2-yl
NaOAc	Sodium acetate
NH_4OH	Ammonium hydroxide
Cs_2CO_3	Cesium carbonate

Synthetic Examples

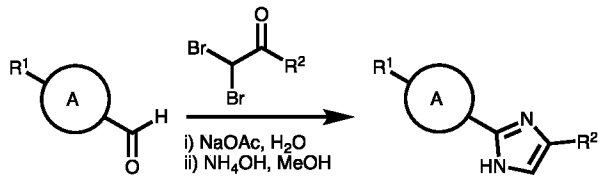
General Procedures

LCMS are recorded for the ion observed and could include $M+H^+$, $M+Na^+$, $M+NH_4^+$ as well as common fragmentations like –Boc, –*t*Bu, $–NH_3$, –OH. ^{1}H NMR

spectra is reported as observed, samples run in protic solvents or $CDCl_3$ may lack signals for exchangeable protons.

General Procedure A

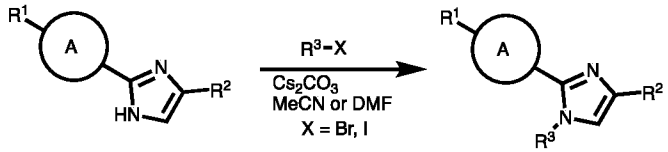
Imidazole Formation



To a stirred suspension of dibromoketone (1.40 equiv.) in water (1.05 M) was added sodium acetate (1.60 equiv.) and the mixture was stirred at 100 °C for 1 h. The reaction was cooled to 23 °C and a solution of aldehyde (1.0 equiv.) in MeOH and 25% aqueous ammonia solution (1:1, 0.4 M) was added. The reaction mixture was stirred at room temperature for 1 h and then stirred at 100 °C for 2 – 16 h. The reaction was cooled to 23 °C and the MeOH was removed under reduced pressure. The aqueous phase was extracted with EtOAc and the organics were washed with sat. sodium bicarbonate, brine, dried over magnesium or sodium sulfate, filtered and concentrated under reduced pressure.

General Procedure B

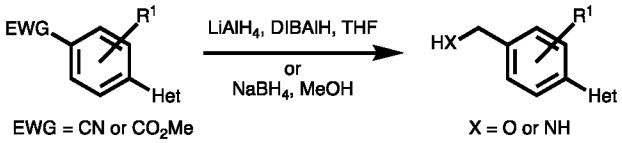
Imidazole Alkylation



To a stirred solution of imidazole in acetonitrile or *N,N*-dimethylformamide (0.4 M) was added Cs_2CO_3 (3.0 equiv.) at 0 °C followed by the alkyl halide (3.0 equiv.) and the mixture was heated at 90 °C for 24 h. The reaction was cooled to 23 °C and extracted with EtOAc. The organics were washed with sat. sodium bicarbonate, brine, dried over magnesium or sodium sulfate, filtered and concentrated under reduced pressure. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under reduced pressure.

General Procedure C

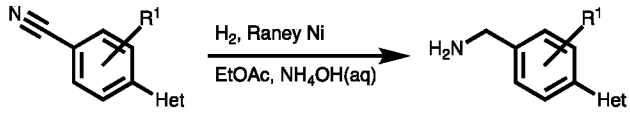
Reduction of Nitriles or Esters



To a stirred solution of the benzonitrile (1.0 equiv.) in THF (0.3 M) was added $LiAlH_4$ (1.2 equiv, 2.0 M in THF) or diisobutylaluminum hydride (1.0 M in hexane, 3.0 equiv.) at 0 °C and the reaction mixture was warmed to 23 °C and stirred for 1 – 4 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under reduced pressure.

General Procedure D

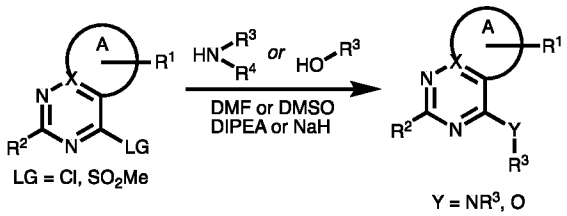
Raney Ni Reduction of Nitriles



To solution of the benzonitrile (1.0 equiv.) in EtOAc and 25% aq. ammonia solution (5:1, 0.3 M final concentration) stirring at 23 °C was added Raney nickel (85%, 5.0 equiv.) and the mixture was stirred under H_2 (Parr reactor, 60 psi) for 16 h. The mixture was filtered through celite and the bed was thoroughly washed with ethanol followed by EtOAc. The filtrate was concentrated under reduced pressure.

General Procedure E

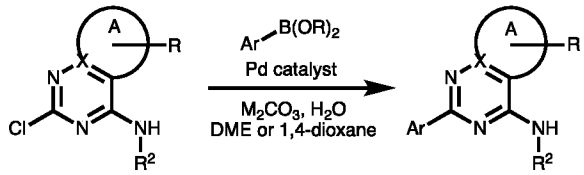
SNAr Substitution



To a stirred solution of amine (1.0 equiv.) dissolved in *N,N*-dimethylformamide (0.15 M) or acetonitrile (0.15 M) at 23 °C was added *N,N*-diisopropylethylamine (3.0 equiv) followed by the substituted pyrimidine (1.0 equiv.) and the reaction mixture was stirred at 50-100 °C for 16 h. Alternatively, to the alcohol (1.0 equiv.) dissolved in *N,N*-dimethylformamide was added sodium hydride (1.5 equiv.) and the mixture was stirred at 23 °C for 15 min. The substituted purine was added (1.0 equiv.) and the reaction was heated at 50-100 °C for 1 – 16 h. The reactions were concentrated under reduced pressure or extracted with EtOAc then washed with water, brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under reduced pressure.

General Procedure F

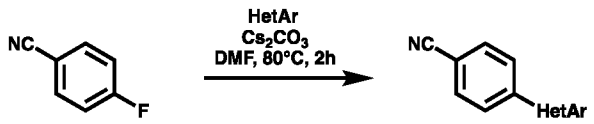
Suzuki Coupling



To a stirred solution of the aryl halide (1.0 equiv.) and the boronic acid or ester (2.0 equiv.) in 1,2-dimethoxyethane/water (6:1, 0.1 M), or 1,4-dioxane/water (6:1, 0.1 M) was added potassium carbonate (2.5 equiv.) or Cs_2CO_3 (2.5 equiv.) at 23 °C. The reaction mixture was degassed with nitrogen gas for 10 min before adding the Pd catalyst (0.10 equiv.). The reaction mixture was further degassed with nitrogen gas for an additional 5 min and then heated at 100 °C for 1 – 16 h. The reactions were concentrated under reduced pressure or extracted with EtOAc then washed with water, brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under reduced pressure.

General Procedure G

SNAr Substitution



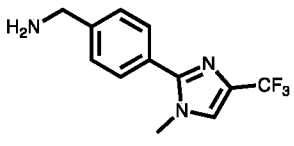
To a stirred solution of heteroaryl (1.0 equiv) in dimethylformamide (10.0 mL), was added Cs_2CO_3 (1.5 equiv) and ArylFluoride (1.0 equiv) at 25 °C. The reaction mixture was stirred at 80 °C for 2 h. The reactions were concentrated under reduced pressure or extracted with EtOAc then washed with water, brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under reduced pressure.

Synthesis of Intermediates:

Intermediate A

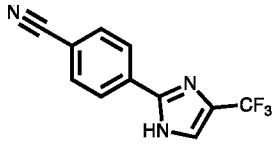
Synthesis of (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine.

Intermediate A



Step 1: Preparation of 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile.

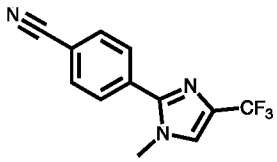
Intermediate A.1



To a stirred suspension of 3,3-dibromo-1,1,1-trifluoropropan-2-one (173 g, 641 mmol) in water (600 mL) was added sodium acetate (60.1 g, 732 mmol) and stirred at 100 °C for 1 h. The reaction mixture was cooled to 23 °C and a solution of 4-formylbenzonitrile (60.0 g, 457 mmol) in MeOH (600 mL) and 25% aqueous ammonia solution (600 mL) was added. The resulting reaction mixture was stirred at room temperature for 1 h and then stirred at 100 °C for 2 h. The reaction mixture was cooled to room temperature and the MeOH was removed under reduced pressure. The resulting solution was diluted with water (1000 mL) and extracted with EtOAc (2 x 1000 mL). The combined organic phases were washed with water (200 mL), brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (30% EtOAc in petroleum ether) to afford 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile (51.0 g) as a pale yellow solid. LCMS observed *m/z* = 238.07 $[M+H]^+$.

Step 2: Preparation of 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile.

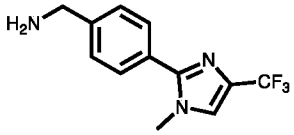
Intermediate A.2



To a stirred solution of 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile (20 g, 84.32 mmol) in tetrahydrofuran (200 mL) was added sodium hydride (6.07 g, 252.97 mmol) at 0 °C and stirred for 15 minutes before adding methyl iodide (7.9 mL, 126.48 mmol). The reaction mixture was stirred at 0 °C for 5 h. After completion, the reaction mixture was quenched with cold water (50 mL), extracted with EtOAc (500 mL x 2). The combined organic layer was washed with water (200 mL), brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (30% EtOAc in petroleum ether) to afford 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile (15.5 g) as a pale yellow solid. LCMS observed *m/z* = 252.15 $[M+H]^+$.

Step 3: Preparation of (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-methanamine.

Intermediate A

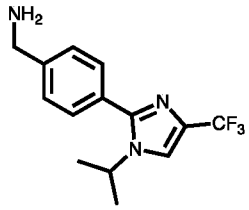


To a solution of 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile (15.5 g, 61.70 mmol) in EtOAc (150 mL) and 25% aq. ammonia solution (30 mL) stirring at 23 °C was added Raney nickel (85%, 15 g) and the mixture was stirred under H_2 (Parr reactor, 60 psi) atmosphere for 16 h. Upon completion, the mixture was filtered through celite and the bed was thoroughly washed with ethanol followed by EtOAc. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (10% MeOH in dichloromethane eluent) to afford (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-methanamine (9.60 g) as a pale yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.92 (d, J = 0.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 3.82 (s, 2H), 3.77 (s, 3H). LCMS observed *m/z* = 256.06 $[M+H]^+$.

Intermediate B

Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine.

Intermediate B

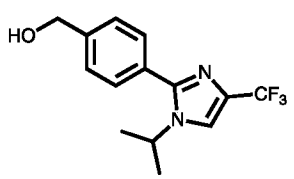


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 2-iodopropane and using general procedure C to reduce the nitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 1.2 Hz, 1H), 7.55 – 7.50 (m, 4H), 4.50 – 4.43 (m, 1H), 4.29 – 4.27 (m, 2H, D_2O exchange protons), 3.88 (s, 2H), 1.40 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 284.32 $[M+H]^+$.

Intermediate C

Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl).

Intermediate C



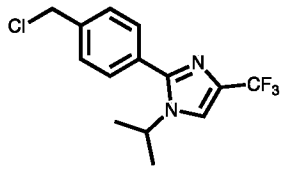
The title compound was prepared using a similar procedure as Intermediate A, replacing

4-formylbenzonitrile with methyl 4-formylbenzoate and using General Procedure C (diisobutyl aluminum hydride) to reduce the ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 5.31 (t, J = 5.8 Hz, 1H), 4.58 (d, J = 5.6 Hz, 2H), 4.51 – 4.44 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 285.18 $[M+H]^+$.

Intermediate D

Preparation of 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole.

Intermediate D

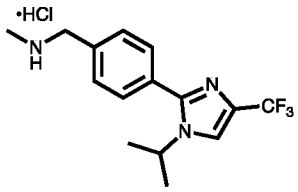


To a solution of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (7.00 g, 24.6 mmol, Intermediate C) in 1,2-dichloroethane (140 mL) was added thionyl chloride (5.35 mL, 73.9 mmol) at 23 °C and reaction mixture was heated to 50 °C for 1 h. After completion, the reaction mixture was evaporated under vacuum and quenched with cold-water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 10% EtOAc in petroleum ether) to afford 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (7.2 g) as an off-white solid. ^{1}H NMR (400 MHZ, DMSO-d_6) δ 8.19 (d, J = 1.2 Hz, 1H), 7.59 (s, 4H), 4.86 (s, 2H), 4.52 – 4.45 (m, 1H), 1.41 (d, J = 6.4 Hz, 6H). LCMS observed *m/z* = 303.32 $[M+H]^+$.

Intermediate E

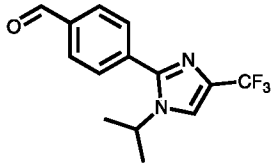
Synthesis of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methyl-methanamine•HCl.

Intermediate E



Step 1: Preparation of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde.

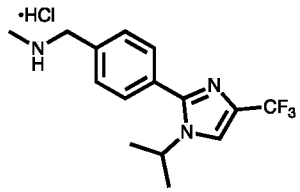
Intermediate E.1



To a stirred solution of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (1.80 g, 6.33 mmol, Intermediate C) in dichloromethane (25.0 mL) at 0 °C under a nitrogen atmosphere, Dess-Martin periodinane (0.990 g, 9.50 mmol) was added. The resulting reaction mixture was stirred at 23 °C for 2 h. After completion, the reaction mixture was quenched with a saturated ammonium bicarbonate solution (20 mL). The product was extracted with dichloromethane (50 mL x 2). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was triturated with pentane to afford 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde (1.70 g) as an off-white solid. LCMS observed *m/z* = 283.24 $[M+H]^+$.

Step 2: Preparation of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methyl-methanamine•HCl.

Intermediate E



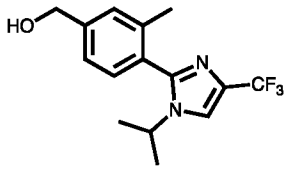
To a stirred solution of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde (1.70 g, 6.02 mmol) and methylamine hydrochloride (0.810 g, 12.0 mmol) in MeOH (25.0 mL) at 0 °C and stirred for 30 min before adding sodium cyanoborohydride (1.14 g, 18.1 mmol). The resulting reaction mixture was stirred at 23 °C for 16 h. After completion, the reaction mixture was quenched with cold water (25 ml) and then the MeOH was concentrated under reduced pressure. The material was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in 4 M HCl in dioxane (5.0 ml) and the resulting reaction mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was triturated with diethyl ether (5 mL)

to afford 1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)-N-methylmethanamine•HCl (1.20 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (br s, 2H), 8.21 (d, J = 0.8 Hz, 1H), 7.68 – 7.64 (m, 4H), 4.50 – 4.43 (m, 1H), 4.20 (t, J = 5.8 Hz, 2H), 2.59 (t, J = 5.2 Hz, 3H), 1.42 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 298.22 [M+H]$^+$.

Intermediate F

Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)methanol.

Intermediate F

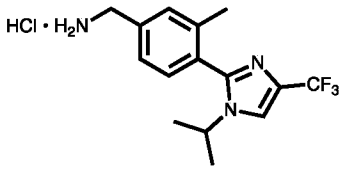


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with methyl 4-formyl-3-methylbenzoate and using General Procedure C to reduce the ester ($NaBH_4$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 1.2 Hz, 1H), 7.32 (s, 1H), 7.25 (s, 2H), 5.27 (t, J = 5.4 Hz, 1H), 4.55 (d, J = 5.2 Hz, 2H), 4.03 – 3.97 (m, 1H), 2.09 (s, 3H), 1.32 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 299.13 [M+H]$^+$.

Intermediate G

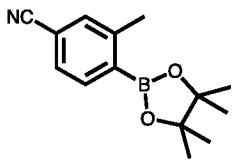
Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-methanamine•HCl.

Intermediate G



Step 1: Preparation of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile.

Intermediate G.1

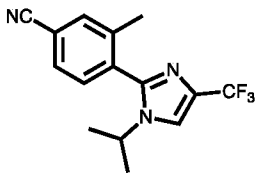


To a stirred solution of 4-bromo-3-methylbenzonitrile (5.00 g, 25.5 mmol) in *N,N*-dimethylformamide (50.0 mL) was added bis(pinacolato)diboron (7.12 g, 28.1 mmol),

followed by the addition of potassium acetate (5.00 g, 51.0 mmol) at 23 °C. The resultant suspension was purged with nitrogen gas for 20 min and subsequently [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (1.04 g, 1.27 mmol) was added. Then the reaction mixture was stirred at 100 °C for 16 h. The reaction was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (50 mL), brine (50.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified using flash chromatography (silica gel, 10% EtOAc in petroleum ether) to afford 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (3.50 g) as a light green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 3.0 Hz, 2H), 2.55 (s, 3H), 1.35 (s, 12H).

Step 2: Preparation of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methyl-benzonitrile.

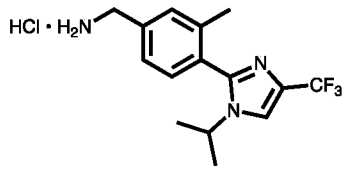
Intermediate G.2



To a stirred solution of 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (1.00 g, 4.11 mmol) in 1,4-dioxane (10.0 mL) and water (1.00 mL) was added 2-bromo-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (1.16 g, 4.50 mmol), followed by the addition of potassium carbonate (1.13 g, 8.22 mmol) at 23 °C. The reaction mixture was then purged with nitrogen gas for 20 min. Subsequently [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (0.336 g, 0.411 mmol) was added and the resultant mixture was stirred at 90 °C for 6 h. The reaction mixture was quenched with cold-water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzonitrile (1.10 g) as a brown solid. LCMS observed *m/z* = 294.26 $[M+H]^+$.

Step 3: Preparation of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-methanamine•HCl.

Intermediate G

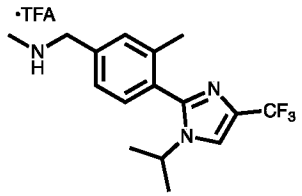


To a stirred solution of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzonitrile (1.10 g, 3.75 mmol) in tetrahydrofuran (17.0 mL) was added lithium aluminum hydride (15.0 mL, 1M solution in THF, 15 mmol) at 0 °C. Then the reaction mixture was brought to 25 °C and stirred for 2 h. On completion, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in 4M hydrochloric acid solution in dioxane (10 mL). The mixture was stirred at 25 °C for 1 h and then concentrated under reduced pressure. Subsequently diethyl ether (5 mL) was added to the residue and the precipitated solid was filtered. The filtered residue was washed further with n-pentane (2 x 10 mL) and dried to afford (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)methanamine•HCl (0.87 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6,) δδ 8.35 (br s, 3H), 8.18 (s, 1H), 7.50 (s, 1H), 7.45 – 7.40 (m, 2H), 4.08 (q, J = 5.7 Hz, 2H), 4.00 – 3.93 (m, 1H), 2.13 (s, 3H), 1.34 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 298.18 $[M+H]^+$.

Intermediate H

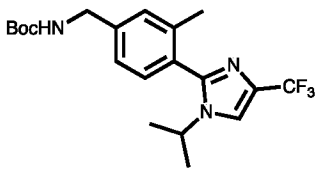
Synthesis of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-*N*-methylmethanamine•TFA.

Intermediate H



Step 1: Preparation of *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)carbamate.

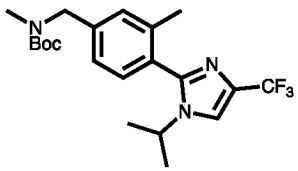
Intermediate H.1



A stirred solution of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)methanamine (1.80 g, 6.05 mmol) in tetrahydrofuran (36.0 mL) was prepared and cooled to 0 °C. Triethylamine (2.50 mL, 18.2 mmol) was added followed by 4-dimethylaminopyridine (0.0740 g, 0.600 mmol) to the reaction mixture. Then, di-*tert*-butyl dicarbonate (1.45 mL, 6.66 mmol) was added, and the mixture was stirred at 25 °C for 4 h. After completion of the reaction, the mixture was diluted with cold water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)carbamate (1.20 g) as a yellow liquid. LCMS observed *m/z* = 398.83 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)(methyl)carbamate.

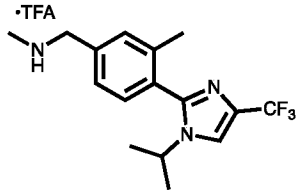
Intermediate H.2



To a solution of *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)carbamate (1.30 g, 3.27 mmol) in tetrahydrofuran (10.0 mL) was added sodium hydride (0.400 g, 9.82 mmol) at 0 °C, and the mixture was stirred for 20 min at the same temperature. Next, iodomethane (0.460 g, 3.27 mmol) was added to the reaction mixture, which was then stirred at room temperature for 16 h. After completion of the reaction, the mixture was quenched with a saturated ammonium chloride solution (5 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 15–20% EtOAc in petroleum ether) to afford *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)-(methyl)carbamate (1.12 g) as a brown solid. LCMS observed *m/z* = 412.86 $[M+H]^+$.

Step 3: Preparation of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-*N*-methylmethanamine•TFA.

Intermediate H



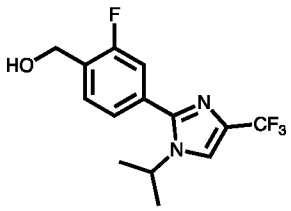
A stirred solution of *tert*-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)carbamate (1.12 g, 2.81 mmol) in dichloromethane (23.0 mL) was treated with trifluoroacetic acid (0.400 g, 5.63 mmol) at 0 °C. The mixture was then stirred at 23 °C for 2 h. After completion of the reaction, the mixture was concentrated under reduced pressure, and the resulting residue was triturated with diethyl ether (10 mL). The solid precipitate was filtered and dried to afford 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-N-methylmethanamine (1.10 g) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (br s, 2H), 8.19 (s, 1H), 7.49 (s, 1H), 7.46 (s, 2H), 4.18 (t, *J* = 5.8 Hz, 2H), 4.01 – 3.95 (m, 1H), 2.61 (t, *J* = 5.4 Hz, 3H), 2.13 (s, 3H), 1.34 (d, *J* = 6.8 Hz, 6H). LCMS observed *m/z* = 312.34 $[M+H]^+$.

Intermediate I

Synthesis of (2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol.

Intermediate I

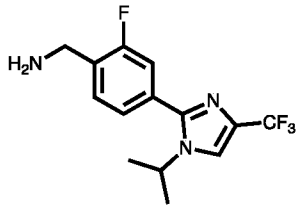


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with methyl 2-fluoro-4-formylbenzoate and using General Procedure C to reduce the ester ($LiAlH_4$). ^{1}H NMR (400 MHz, CD_3OD) δ 7.95 (s, 1H), 7.70 – 7.66 (m, 1H), 7.41 – 7.38 (m, 1H), 7.34 – 7.31 (m, 1H), 4.76 (s, 2H), 4.58 (septet, *J* = 6.6 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 6H). LCMS observed *m/z* = 303.1 $[M+H]^+$.

Intermediate J

Synthesis of (2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-methanamine.

Intermediate J

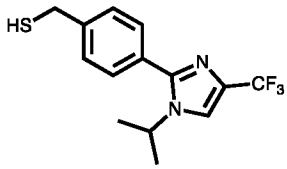


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 2-fluoro-4-formylbenzonitrile and using General Procedure C to reduce the nitrile ($LiAlH_4$). ^1H NMR (400 MHz, CD_3OD) δ 7.94 (s, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 4.5 (septet., J = 6.6 Hz, 1H), 3.94 (s, 2H), 1.48 (d, J = 6.6 Hz, 6H). LCMS observed m/z = 302.2 $[M+H]^+$.

Intermediate K

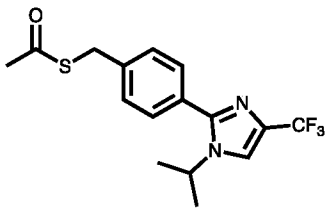
Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanethiol.

Intermediate K



Step 1: Preparation of *S*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl) ethanethioate.

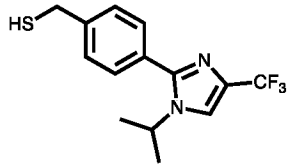
Intermediate K.1



To a stirred solution of 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (80.0 mg, 0.264 mmol, Intermediate D) in dimethyl sulfoxide (1.00 mL) was added potassium iodide (46.0 mg, 0.281 mmol) followed by potassium thioacetate (35.0 mg, 0.310 mmol). The reaction mixture was stirred at 23 °C for 16 h. Upon completion, reaction mixture was quenched with cold water (3 mL) and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with water (10 mL), brine (5 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure to afford *S*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl) ethanethioate (0.600 g) as a tan solid. The material was used in the subsequent reaction. LCMS observed m/z = 343.4 $[M+H]^+$.

Step 2: Preparation of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanethiol.

Intermediate K

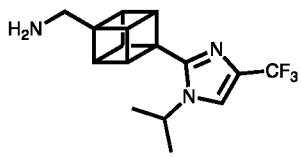


To a solution of *S*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl) ethane-thioate (60.0 mg, 0.175 mmol) in MeOH (2.0 mL) and water (1.0 mL) stirring at 23 °C was added potassium carbonate (72.0 mg, 0.526 mmol) and the reaction mixture was stirred for 16 h. Upon completion, reaction mixture was concentrated under reduce pressure and the residue was dissolved in EtOAc (30 mL) and washed with water (10 mL), brine (5 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20–25% EtOAc in petroleum ether) to afford (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanethiol (30.0 mg) as a white solid. LCMS observed *m/z* = 301.3 $[M+H]^+$.

Intermediate L

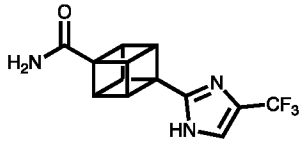
Synthesis of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanamine.

Intermediate L



Step 1: Preparation of 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide.

Intermediate L.1

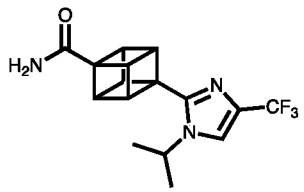


To a stirred solution of 3,3-dibromo-1,1,1-trifluoropropan-2-one (15.3 g, 56.8 mmol) in water (100 mL) was added sodium acetate (46.6 g, 56.8 mmol) at 0 °C. The reaction mixture was heated to 100°C for 1 h. The reaction was cooled to 0 °C and a solution of methyl 4-formylcubane-1-carboxylate (9.00 g, 47.3 mmol) in MeOH (180 mL)

and ammonia (180 mL, 25% in water) was added. The reaction mixture was stirred at 23 °C for 16 h. After completion, the precipitated solid was filtered off and dried to 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide (4.50 g) as an off-white solid. The compound was used in the next step without further purification. LCMS observed *m/z* = 280.19 $[M-H]^-$.

Step 2: Preparation of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide.

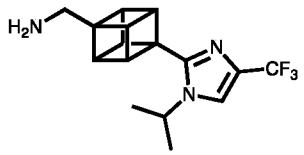
Intermediate L.2



To a stirred solution of 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide (4.50 g, 16.0 mmol) in *N,N*-dimethylformamide (50.0 mL) stirring at 0 °C were added Cs_2CO_3 (7.82 g, 24.0 mmol) and 2-iodopropane (3.26 g, 19.2 mmol). The reaction mixture was warmed to 60 °C and stirred for 12 h. After completion, the reaction mixture was concentrated and the residue was diluted with water (100 mL) and the solids were collected via filtration. The solid was washed with *n*-pentane and dried to afford 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide (2.80 g) as white solid. The material was used without further purification. LCMS observed *m/z* = 324.41 $[M+H]^+$.

Step 3: Synthesis of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanamine.

Intermediate L



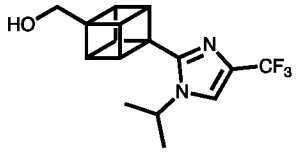
To a stirred solution of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxamide (2.80 g, 8.66 mmol) in dichloromethane (30.0 mL) was added chlorotrimethylsilane (1.66 mL, 13.0 mmol) at 0 °C and the mixture was stirred for 10 min. Lithium aluminium hydride (8.66 mL, 2.0 M solution in THF, 17.3 mmol) was added and the reaction mixture was warmed to 23 °C and stirred for 3 h. After completion, the reaction mixture was quenched with sat. aq. sodium sulfate solution (25 mL) and diluted with dichloromethane (100 mL). The resulting mixture was filtered through celite washing

thoroughly with dichloromethane (2 x 50 mL). The filtrate was concentrated under reduced pressure and the residue was purified by reverse phase chromatography (mobile phase: 20-100% acetonitrile in water w/ 0.1% formic acid) to afford 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanamine (0.900 g, formate salt) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (s, 1H), 8.00 (s, 1H), 3.70 – 3.21 (br s, 2H), 4.20 – 4.17 (m, 3H), 4.06 – 3.99 (m, 4H), 3.04 (s, 2H), 1.43 – 1.41 (m, 6H). LCMS observed *m/z* = 310.321 $[M+H]^+$.

Intermediate M

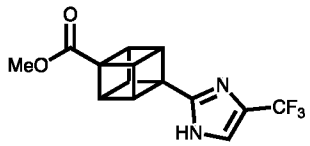
Synthesis of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol.

Intermediate M



Step 1: Preparation of methyl 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate.

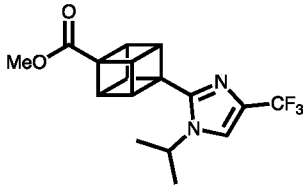
Intermediate M.1



A stirred solution of 3,3-dibromo-1,1,1-trifluoropropan-2-one (30.0 g, 110 mmol) in water (210 mL) was prepared and cooled to 0 °C. Sodium acetate (9.60 g, 118 mmol) was then added to the reaction mixture, which was subsequently stirred at 100 °C for 1 hour, then cooled to 0 °C. A solution of methyl 4-formylcubane-1-carboxylate (14.0 g, 73.6 mmol) in MeOH (210 mL) and 25% aqueous ammonia solution (210 mL) was added to the reaction and the mixture was stirred at 0 °C for 1 hour. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove MeOH. The material was then extracted with EtOAc (3 x 250 mL), and the combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was triturated with *n*-pentane to afford methyl 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate (12.0 g) as an off-white solid. LCMS observed *m/z* = 296.97 $[M+H]^+$.

Step 2: Preparation of methyl 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate.

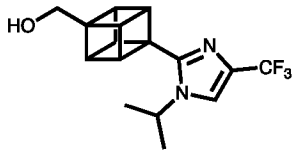
Intermediate M.2



To a stirred solution of methyl 4-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate (12.0 g, 40.5 mmol) in *N,N*-dimethylformamide (120 mL) stirring at 0 °C were added Cs_2CO_3 (39.6 g, 122 mmol) and 2-iodopropane (34.4 g, 203 mmol). The reaction mixture was then heated at 90 °C for 16 h. After completion, the reaction mixture was quenched with cold water (250 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford methyl 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate (5.50 g) as a pale brown solid. LCMS observed *m/z* = 339.62 $[M+H]^+$.

Step 3: Preparation of 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol.

Intermediate M



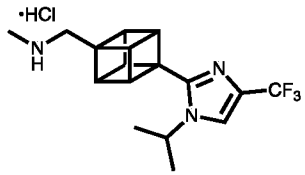
A solution of methyl 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cubane-1-carboxylate (2.00 g, 5.91 mmol) in tetrahydrofuran (20 mL) and MeOH (2.0 mL) was prepared at 0 °C. $NaBH_4$ (0.670 g, 17.7 mmol) was then added to the solution, and the reaction mixture was stirred at 23 °C for 16 h. After completion, the reaction mixture was diluted with cold water (25 mL) and concentrated under reduced pressure to remove MeOH. The mixture was extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (25 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 35–50% EtOAc in petroleum ether) to afford (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol (1.10 g) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 1.2 Hz, 1H), 4.57 (t, J = 5.4 Hz, 1H), 4.16 (t, J = 5.0 Hz, 3H), 4.08 – 4.03 (m, 1H), 3.87 (t, J = 4.8 Hz, 3H), 3.57 (d, J = 5.2 Hz, 2H), 1.41 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 311.22 $[M+H]^+$.

Intermediate N

Synthesis of 1-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)-*N*-methylmethanamine•HCl.

Intermediate N

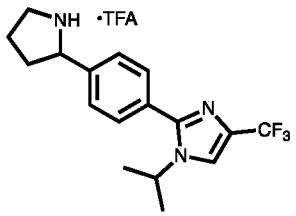


The title compound was prepared using a similar procedure as Intermediate E, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol (Intermediate M). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 0.8 Hz, 1H), 4.26 – 4.16 (m, 3H), 4.09 – 4.02 (m, 1H), 3.89 – 3.87 (m, 3H), 2.74 (s, 2H), 2.33 (s, 3H), 1.41 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 324.38 $[M+H]^+$.

Intermediate O

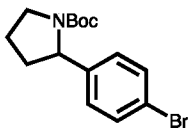
Synthesis of 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole•TFA.

Intermediate O



Step 1: Preparation of *tert*-butyl 2-(4-bromophenyl)pyrrolidine-1-carboxylate.

Intermediate O.1

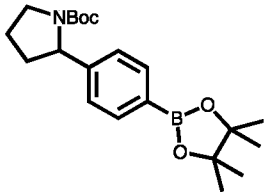


To a stirred solution of 2-(4-bromophenyl) pyrrolidine (1.00 mg, 4.42 mmol) and *N,N*-diisopropylethylamine (1.54 mL, 8.84 mmol) in dichloromethane (40.0 mL) at 0 °C was added di-*tert*-butyl bicarbonate (1.21 mL, 5.30 mmol) and the mixture was warmed to 23 °C and stirred for 2 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2 x 60 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The material was purified by flash

chromatography (silica gel, 8–10% EtOAc in petroleum ether) to afford *tert*-butyl 2-(4-bromophenyl) pyrrolidine-1-carboxylate (1.10 g) as a white solid. LCMS observed *m/z* = 270.1 $[M-56+H]^+$.

Step 2: Preparation of *tert*-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-pyrrolidine-1-carboxylate.

Intermediate O.2

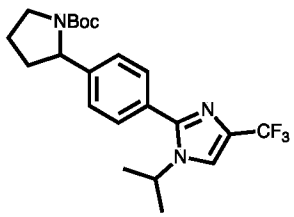


A stirred solution of *tert*-butyl 2-(4-bromophenyl) pyrrolidine-1-carboxylate (900 mg, 2.75 mmol) in 1,4-dioxane (30 mL) was prepared at 23 °C. Bis(pinacolato)diboron (840 mg, 3.31 mmol) and potassium acetate (670 mg, 6.89 mmol) were added and the mixture was purged with nitrogen gas for 30 minutes. 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium(II) (200 mg, 0.276 mmol) was added, and the reaction was heated at 90 °C in a sealed tube for 16 h. After completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 90 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford *tert*-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyrrolidine-1-carboxylate.

(900 mg) as a brown solid. The material was used without further purification. LCMS observed *m/z* = 374.2 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-pyrrolidine-1-carboxylate.

Intermediate O.3

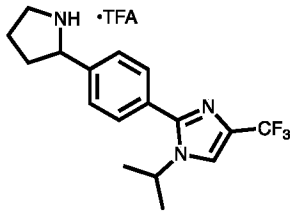


To a solution of *tert*-butyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl) pyrrolidine-1-carboxylate (800 mg, 2.14 mmol) in dioxane (24.0 mL) and water (6.0 mL) stirring at 23 °C was added 2-bromo-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (660 mg, 2.57 mmol) and Cs_2CO_3 (1.74 g, 5.35 mmol). The mixture was purged with nitrogen gas for 30 minutes, then tetrakis(triphenylphosphine)palladium(0) (284 mg,

0.214 mmol) was added, and the reaction was heated in a sealed tube at 90 °C for 16 h. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 90 mL). The combined organic phases were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to afford *tert*-butyl 2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl) phenyl)pyrrolidine-1-carboxylate (700 mg) as a brown solid which was used without further purification. LCMS observed *m/z* = 424.7 $[M+H]^+$.

Step 4: Preparation of 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole•TFA.

Intermediate O

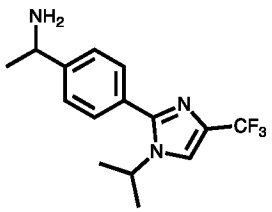


To a stirred solution of *tert*-butyl 2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl) phenyl)pyrrolidine-1-carboxylate (700 mg, 1.65 mmol) in dichloromethane (20 mL) at 0 °C was added trifluoroacetic acid (2.00 mL). The reaction mixture was warmed to 23 °C and stirred for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure to afford 1-isopropyl-2-(4-(pyrrolidin-2-yl) phenyl)-4-(trifluoromethyl)-1*H*-imidazole•TFA (510 mg) as a brown solid. The material was used without further purification. LCMS observed *m/z* = 324.65 $[M+H]^+$.

Intermediate P

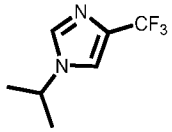
Synthesis of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine.

Intermediate P



Step 1: Preparation of 1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole.

Intermediate P.1

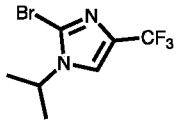


To a stirred solution of 4-(trifluoromethyl)-1*H*-imidazole (12.5 g, 91.8 mmol) in *N,N*-dimethylformamide (125 mL) at 0 °C was added Cs_2CO_3 (119 g, 367 mmol) and 2-iodopropane (27.0 mL, 275 mmol). The reaction mixture was then stirred at 23 °C for 16 h. After completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 100 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford the product. The material was further purified by flash chromatography (12–15% EtOAc/petroleum ether eluent) to afford 1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (11.3 g) as a yellow liquid.

LCMS observed *m/z* = 179.2 $[M+H]^+$.

Step 2: Preparation of 2-bromo-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole.

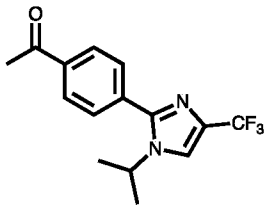
Intermediate P.2



To a stirred solution of 1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (6.00 g, 33.6 mmol) in tetrahydrofuran (120 mL) at –78 °C, a 2.6M solution of *n*-butyllithium in THF (26.1 mL, 84.1 mmol) was carefully added. The reaction mixture was then gradually warmed to 0 °C and stirred for 1.5 h. Next, *N*-bromosuccinimide (6.59 g, 37.0 mmol) was added at -78 °C, and the reaction mixture was subsequently brought to 23 °C and stirred for 16 h. After completion, the reaction mixture was quenched with a saturated ammonium chloride solution (25 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The material was purified by flash chromatography (8–10% EtOAc/petroleum ether eluent) to afford 2-bromo-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (2.10 g) as a yellow liquid. LCMS observed *m/z* = 257.0 $[M+H]^+$.

Step 3: Preparation of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-one.

Intermediate P.3

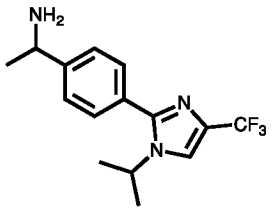


A stirred solution of 2-bromo-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (700 mg, 2.72 mmol) and (4-acetylphenyl)boronic acid (535 mg, 3.26 mmol) in 1,4-dioxane (8.00 mL) and water (2.00 mL) was prepared. The solution was purged with nitrogen gas for 10 minutes, followed by the addition of Cs_2CO_3 (2.04 g, 6.26 mmol). Tetrakis(triphenylphosphine)palladium(0) (346 mg, 0.300 mmol) was added to the reaction and the mixture was heated at 150 °C for 30 minutes in a microwave reactor. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-one (690 mg) as a yellow solid.

LCMS observed *m/z* = 297.05 $[M+H]^+$.

Step 4: Preparation of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine.

Intermediate P

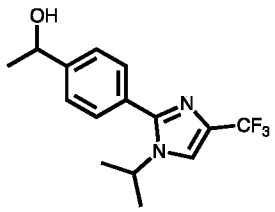


To a stirred solution of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl) ethan-1-one (1.40 g, 4.72 mmol) in MeOH (14.0 mL) was added ammonium acetate (3.60 g, 47.2 mmol) at 23 °C. The reaction mixture was stirred for 30 min at 23 °C, followed by the addition of sodium cyanoborohydride (1.48 g, 23.6 mmol). The reaction mixture was then heated to 60 °C and stirred for 4 h. After completion, the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 25 mL). The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The material was purified by flash chromatography (silica gel, 5–10% MeOH in dichloromethane) to afford 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine (0.600 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20 (s, 1H), 7.63 (br s, 2H), 7.60 (s, 4H), 4.46 – 4.38 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H), 1.41 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 298.37 $[M+H]^+$.

Intermediate Q

Preparation of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-ol.

Intermediate Q



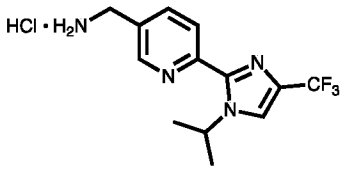
A stirred solution of 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl) phenyl) ethan-1-one (1.20 g, 4.05 mmol, Intermediate P.3) in MeOH (25.0 mL) was prepared and cooled to 0 °C. $NaBH_4$ (0.306 g, 8.10 mmol) was then carefully added to the reaction mixture, which was subsequently stirred for 1 h at 0 °C. Once the reaction was complete, it was quenched with a saturated ammonium chloride solution (20 mL) and concentrated under reduced pressure. The resulting residue was extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The material was purified by flash chromatography (silica gel, 25–30% EtOAc in petroleum ether) to afford 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl) phenyl)ethan-1-ol (0.800 g) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 1.2 Hz, 1H), 7.52 – 7.50 (m, 4H), 5.28 (d, J = 4.0 Hz, 1H), 4.83 – 4.77 (m, 1H), 4.52 – 4.45 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.37 (d, J = 6.4 Hz, 3H). LCMS observed *m/z* = 299.017 $[M+H]^+$.

Intermediate R

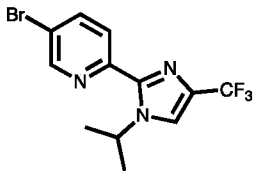
Synthesis of (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanamine•HCl.

Intermediate R



Preparation of 5-bromo-2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridine.

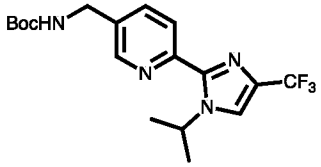
Intermediate R.1



The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 5-bromo-2-pyridinecarboxaldehyde and following General Procedures A and B. LCMS observed *m/z* = 334.19 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl ((6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)carbamate.

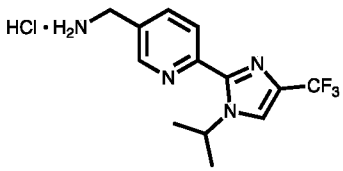
Intermediate R.2



To a stirred solution of 5-bromo-2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridine (2.90 g, 8.68 mmol) in 1,4-dioxane (26.0 mL) and water (3.0 mL) was added potassium (((tert-butoxycarbonyl)amino)methyl)trifluoroborate (2.47 g, 10.4 mmol), followed by the addition of Cs_2CO_3 (7.07 g, 21.7 mmol) at 23 °C. The reaction mixture was purged with nitrogen gas for 30 min. Then cataCXium A Pd G3 (0.63 g, 0.87 mmol) was added under nitrogen atmosphere and the resulting reaction mixture was heated at 100 °C for 16 h. After completion, the reaction mixture quenched with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 60% EtOAc in petroleum ether) to afford *tert*-butyl((6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)carbamate (1.57 g) as a yellow solid. LCMS observed *m/z* = 385.5 $[M+H]^+$.

Step 4: Preparation of (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanamine•HCl.

Intermediate R



To a stirred solution of *tert*-butyl ((6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)carbamate (1.57 g, 4.08 mmol) in dichloromethane (20 mL) was added 4M hydrochloric acid solution in 1,4-dioxane (2.0 mL, 8.00 mmol) at 0 °C. Subsequently the reaction mixture was brought to 23 °C and stirred for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was

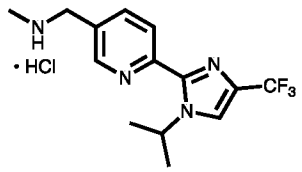
triturated with pentane (5 mL) to afford (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanamine hydrochloride (1.10 g) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, J = 1.2 Hz, 1H), 8.45 (br s, 3H), 8.27 (d, J = 0.8 Hz, 1H), 8.13 – 8.06 (m, 2H), 5.77 – 5.71 (m, 1H), 4.17 – 4.13 (m, 2H), 1.46 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 285.23 $[M+H]^+$.

Intermediate S

Synthesis of 1-(6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)-*N*-methyl-methanamine•HCl.

Intermediate S

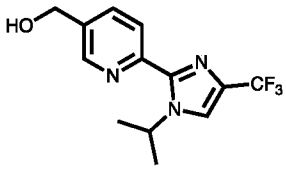


The title compound was prepared using a similar procedure as Intermediate H, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)methanamine with (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanamine hydrochloride (Intermediate R). ^{1}H NMR (400 MHz, DMSO-d_6) 9.42 (br s, 2H), 8.81 (s, 1H), 8.28 (s, 1H), 8.12 (d, J = 1.2 Hz, 2H), 5.80 – 5.70 (m, 1H), 4.21 (br s, 2H), 2.58 (t, J = 5.4 Hz, 3H), 1.47 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 299.17 $[M+H]^+$.

Intermediate T

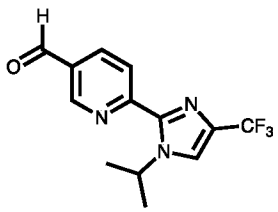
Synthesis of (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanol.

Intermediate T



Step 1: Preparation of 6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)nicotinaldehyde.

Intermediate T.1

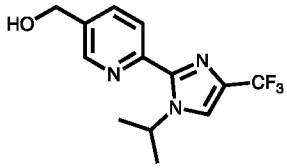


To a stirred solution of 5-bromo-2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridine (2.10 g, 6.28 mmol, Intermediate R.1) in diethyl ether (21.0 mL) at -78 °C was added n-butyl lithium (11.7 mL, 1.6 M in hexanes, 18.8 mmol) drop wise and the mixture was stirred for 15 min. *N,N*-dimethylformamide (9.7 mL, 31.4 mmol) was added and the reaction mixture was stirred at –78 °C for 3 h. The reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford 6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)nicotinaldehyde (1.40 g) as an off-white solid.

LCMS observed *m/z* = 283.98 $[M+H]^+$.

Step 2: Preparation of (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanol.

Intermediate T

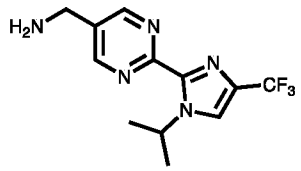


To a stirred solution of 6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)nicotinaldehyde (1.40 g, 4.94 mmol) in MeOH (14.0 mL) was added $NaBH_4$ (0.380 g, 9.88 mmol) at 0 °C portion wise and the reaction mixture was warmed to 23 °C and stirred for 2 h. After completion, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic phases were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and filtered. The solvent was removed under reduced pressure and The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanol (1.05 g) as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.60 (d, J = 1.6 Hz, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.88 (dd, J = 8.2, 2.2 Hz, 1H), 5.78-5.71 (m, 1H), 5.42 (t, J = 5.6 Hz, 1H), 4.60 (d, J = 5.2 Hz, 2H), 1.45 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 286.09 $[M+H]^+$.

Intermediate U

Preparation of (2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrimidin-5-yl)methanamine•TFA.

Intermediate U



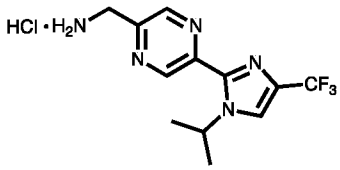
The title compound was prepared using a similar procedure as Intermediate R, replacing 5-bromo-2-pyridinecarboxaldehyde with 5-bromo-2-pyrimidinecarboxaldehyde.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 2H), 8.34 (s, 1H), 8.26 (br s, 3H), 5.52 – 5.45 (m, 1H), 4.20 (q, J = 5.5 Hz, 2H), 1.47 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 286.33 $[M+H]^+$.

Intermediate V

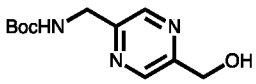
Synthesis of (5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methanamine•HCl.

Intermediate V



Step 1: Preparation of *tert*-butyl ((5-(hydroxymethyl)pyrazin-2-yl)methyl)carbamate.

Intermediate V.1

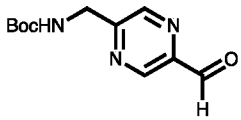


To a stirred solution of (5-chloropyrazin-2-yl)methanol (2.00 g, 13.8 mmol) and *tert*-butyl ((trifluoro-l-boraneyl)methyl)carbamate, potassium salt (8.20 g, 34.6 mmol) in 1,4-dioxane (50.0 mL) and water (10.0 mL), Cs_2CO_3 (9.02 g, 27.7 mmol) was added. The reaction mixture was purged with nitrogen gas for 20 minutes, followed by the addition of palladium(II) acetate (0.310 g, 1.38 mmol) and cataXCium-A (0.990 g, 2.77 mmol). The reaction mixture was then heated at 105 °C for 16 h in a sealed tube. The reaction was filtered through a celite bed and washed with EtOAc (100 mL). The filtrate was further washed with water (50 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 70–90% EtOAc in petroleum ether) to afford

tert-butyl ((5-(hydroxymethyl)pyrazin-2-yl)methyl)carbamate (2.50 g) as an off-white solid. LCMS observed *m/z* = 240.31 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl ((5-formylpyrazin-2-yl)methyl)carbamate.

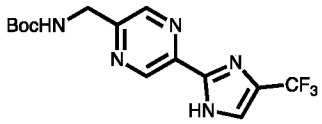
Intermediate V.2



To a stirred solution of *tert*-butyl ((5-(hydroxymethyl)pyrazin-2-yl)methyl)carbamate (2.40 g, 10.0 mmol) in dichloromethane (25.0 mL) at 0 °C under a nitrogen atmosphere, Dess-Martin periodinane (1.57 g, 15.1 mmol) was added slowly. The resulting reaction mixture was then stirred for 3 h at 0 °C. After completion, the reaction mixture was diluted with saturated ammonium bicarbonate solution and extracted with dichloromethane (100 mL x 2). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was then triturated with pentane to afford *tert*-butyl ((5-formylpyrazin-2-yl)methyl)carbamate (2.00 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 9.09 (s, 1H), 8.76 (s, 1H), 5.43 (br s, 1H), 4.59 (s, 2H), 1.47 (s, 9H).

Step 3: Preparation of *tert*-butyl ((5-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate.

Intermediate V.3

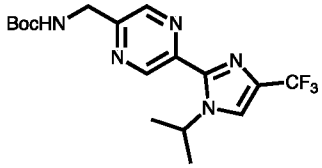


A stirred solution of 3,3-dibromo-1,1,1-trifluoropropan-2-one (2.73 g, 10.1 mmol) in water (50.0 mL) was prepared at 0 °C. Anhydrous sodium acetate (0.830 g, 10.1 mmol) was then added to the solution, and the mixture was stirred at 100 °C for 1 h. The mixture was cooled to 0 °C and *tert*-butyl ((5-formylpyrazin-2-yl)methyl)carbamate (2.00 g, 8.43 mmol) in MeOH (50 mL) and 25% aqueous ammonia solution (20 mL) was added to the reaction mixture. The mixture was then stirred at 25 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure, and the residue was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50–70% EtOAc in petroleum ether) to afford *tert*-butyl ((5-(4-(trifluoromethyl)-1*H*-imidazol-

2-yl)pyrazin-2-yl)methyl)carbamate (2.30 g) as an off-white solid. LCMS observed *m/z* = 344.23 $[M+H]^+$.

Step 4: Preparation of *tert*-butyl ((5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate.

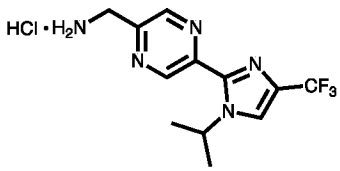
Intermediate V.4



To a stirred solution of *tert*-butyl ((5-(4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate (2.30 g, 6.70 mmol) in *N,N*-dimethylformamide (25.0 mL) were added Cs_2CO_3 (6.55 g, 20.1 mmol) and 2-iodopropane (3.42 g, 20.1 mmol) at 0 °C. The reaction mixture was then stirred at 80 °C for 16 h. After completion, the reaction mixture was quenched with cold water (30 mL) and extracted with EtOAc (2 x 100 mL). The combined organics were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in petroleum ether) to afford *tert*-butyl ((5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate (2.10 g) as a pale brown solid. LCMS observed *m/z* = 386.80 $[M+H]^+$.

Step 5: Preparation of (5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methanamine•HCl.

Intermediate V



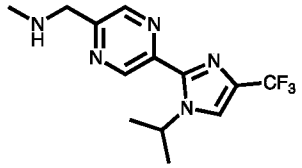
A stirred solution of *tert*-butyl ((5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate (1.50 g, 3.89 mmol) in dichloromethane (15.0 mL) was treated with a 4.0 M solution of hydrochloric acid in dioxane (2.00 mL, 8.00 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 2 h. After completion, the reaction mixture was concentrated under reduced pressure. The residue was subsequently triturated with pentane (5 mL) to afford (5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methanamine•HCl (1.01 g) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 (d, J = 1.2 Hz, 1H), 8.86 (d, J = 1.2 Hz, 1H), 8.57 (br s, 3H), 8.38 (d, J = 0.8 Hz, 1H), 5.59 – 5.52 (m, 1H), 4.35 (q, J = 5.7 Hz, 2H), 1.48 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 286.17 $[M+H]^+$.

Intermediate W

Preparation of 1-(5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)-*N*-methyl-methanamine•HCl.

Intermediate W

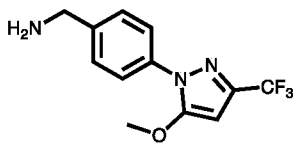


The title compound was prepared using a similar procedure as Intermediate S, replacing *tert*-butyl ((6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)carbamate with *tert*-butyl ((5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (d, J = 1.2 Hz, 1H), 9.24 (br s, 2H), 8.85 (d, J = 1.2 Hz 1H), 8.39 (s, 1H), 5.60 – 5.53 (m, 1H), 4.44 (s, 2H), 2.67 (s, 3H), 1.48 (d, J = 6.4 Hz, 6H). LCMS observed *m/z* = 300.33 $[M+H]^+$.

Intermediate X

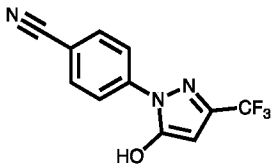
Synthesis of (4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine.

Intermediate X



Step 1: Preparation of 4-(5-hydroxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzonitrile.

Intermediate X.1

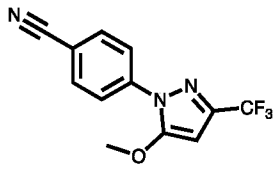


A solution of 4-hydrazineylbenzonitrile (4.0 g, 30 mmol) and sodium hydroxide (1.22 g, 30.0 mmol) in ethanol (60 mL) was stirred at 23 °C for 40 min. To this was added a solution of ethyl 4,4,4-trifluoro-3-oxobutanoate (6.64 g, 36.1 mmol) in ethanol (20 mL) was added and the reaction mixture was refluxed for 24 h. The reaction

mixture was cooled to room temperature and filtered through celite, the filtrate was concentrated under reduced pressure and the residue was dissolved in toluene (200 mL) and *para*-toluenesulfonic acid (0.57 g, 3.0 mmol) was added. The reaction mixture was stirred at 120 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was triturated with pentane (100 mL x 3) to afford 4-(5-hydroxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl) benzonitrile (4.0 g) as an off-white solid. LCMS observed *m/z* = 254.05 $[M+H]^+$.

Step 2: Preparation of 4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzonitrile.

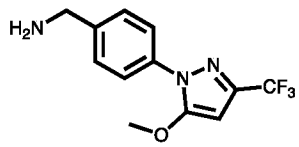
Intermediate X.2



To the stirred solution of 4-(5-hydroxy-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (3.0 g, 12 mmol) in *N,N*-dimethylformamide (30 mL) was added sodium hydride (0.28 g dispersion in mineral oil, 12 mmol) at 0 °C and the mixture was stirred for 10 min. Iodomethane (0.89 mL, 14 mmol) was added and the reaction was warmed to 23 °C and stirred for 16 h. The reaction mixture was quenched with cold water (100 mL), extracted with EtOAc (100 mL x 2). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by flash chromatography (silica gel, 30% EtOAc in petroleum ether) to afford 4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzonitrile (1.5 g) as an off-white solid. LCMS observed *m/z* = 268.30 $[M+H]^+$.

Step 3: Preparation of (4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-methanamine.

Intermediate X



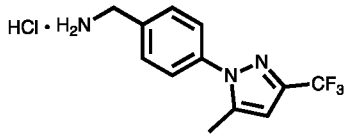
To a stirred solution of 4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzonitrile (5.3 g, 20 mmol) in THF (60 mL) was added $LiAlH_4$ (15 mL, 2.0 M in THF, 24 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. The reaction

mixture was quenched with saturated ammonium chloride solution (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed with water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and filtered. Filtrate was concentrated under reduced pressure. The residue was triturated with diethyl ether (300 mL x 3) and concentrated under reduced pressure to afford (4-(5-methoxy-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-methanamine (2.3 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57 – 7.55 (m, 2H), 7.48 – 7.46 (m, 2H), 6.45 (s, 1H), 3.99 (s, 3H), 3.77 (s, 2H). LCMS observed *m/z* = 272.10 $[M+H]^+$.

Intermediate Y

Synthesis of (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine•HCl.

Intermediate Y

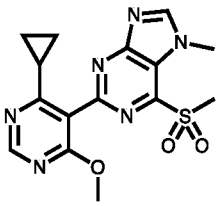


The title compound was prepared using a similar procedure as Intermediate X, replacing 4, 4, 4-trifluoro-3-oxobutanoate with 1,1,1-trifluoropentane-2,4-dione and using general procedure E to reduce the nitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 – 7.18 (m, 4H), 6.75 (s, 1H), 3.85 (s, 2H), 2.33 (s, 3H). LCMS observed *m/z* = 256.06 $[M+H]^+$.

Intermediate Z

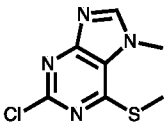
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylsulfonyl)-7*H*-purine.

Intermediate Z



Step 1: Preparation of 2-chloro-7-methyl-6-(methylthio)-7*H*-purine.

Intermediate Z.1

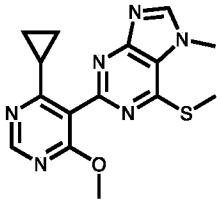


To a stirred solution of 2,6-dichloro-7-methyl-7*H*-purine (5.00 g, 24.6 mmol) in tetrahydrofuran (100 mL) at 0 °C was added sodium thiomethoxide (1.73 g, 24.6 mmol) and

the mixture was warmed to 23 °C and stirred for 16 h. The reaction mixture was diluted with cold water (100 mL) and extracted with EtOAc (2 x 250 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford 2-chloro-7-methyl-6-(methylthio)-7*H*-purine (4.50 g) as a white solid. LCMS observed *m/z* = 215.11 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylthio)-7*H*-purine.

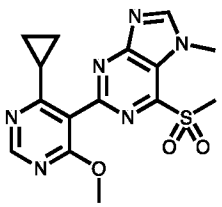
Intermediate Z.2



A stirred solution of 2-chloro-7-methyl-6-(methylthio)-7*H*-purine (4.50 g, 9.31 mmol) in 1,2-dimethoxyethane (38.0 mL) and water (2.00 mL) was prepared at 23 °C. (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid (1.98 g, 10.2 mmol) and potassium carbonate (3.21 g, 23.2 mmol) were added and the reaction mixture was purged with nitrogen gas for 20 min. Tetrakis(triphenylphosphine)palladium(0) (1.08 g, 0.930 mmol) was added and the reaction mixture was heated at 110 °C for 16 h. The reaction was cooled to 23 °C and the solid precipitate was filtered, washed with water (2 x 50 mL), and concentrated under reduced pressure. to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylthio)-7*H*-purine (3.5 g) as a grey solid. LCMS observed *m/z* = 329.33 $[M+H]^+$.

Step 3: 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylsulfonyl)-7*H*-purine.

Intermediate Z



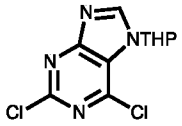
A solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylthio)-7*H*-purine (3.50 g, 10.6 mmol) in dichloromethane (70.0 mL) was prepared and cooled to 0 °C. 3-chloroperbenzoic acid (5.52 g, 32.0 mmol) was slowly added and the mixture was maintained at 0 °C for 5 h. The mixture was diluted with a saturated sodium

bicarbonate solution (40.0 mL) and extracted with EtOAc (2 x 100 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by flash chromatography (silica gel, 50–70% EtOAc in petroleum ether) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylsulfonyl)-7*H*-purine (2.14 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 9.01 (s, 1H), 8.73 (s, 1H), 4.17 (s, 3H), 3.86 (s, 3H), 3.57 (s, 3H), 1.83-1.76 (m, 1H), 1.11-1.07 (m, 2H), 0.93-0.92 (m, 2H). LCMS observed *m/z* = 361.15 $[M+H]^+$.

Intermediate AA

Preparation of 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

Intermediate AA

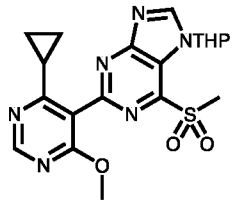


To a stirred solution of 2,6-dichloro-7H-purine (3 g, 15.87 mmol) in EtOAc (30 mL) were added p-toluenesulfonic acid monohydrate (0.03 g, 0.16 mmol) and 3,4-dihydro-2H-pyran (2.0 g, 23.81 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to afford 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (2.5 g) as a white solid. LCMS observed *m/z* = 189.03 $[M-THP+H]^+$.

Intermediate AB

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

Intermediate AB



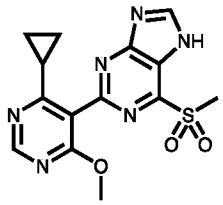
The title compound was prepared using a similar procedure as Intermediate Z, replacing 2,6-dichloro-7-methyl-7*H*-purine with 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-

yl)-7*H*-purine (Intermediate AA). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.57 (s, 1H), 5.90 (dd, J = 10.4, 2.4 Hz, 1H), 4.22 – 4.20 (m, 1H), 3.91 (s, 3H), 3.80 – 3.79 (m, 1H), 3.50 (s, 3H), 2.23 – 2.21 (m, 1H), 2.20 – 2.02 (m, 2H), 1.83 – 1.80 (m, 2H), 1.79 – 1.65 (m, 2H), 1.26 – 1.24 (m, 2H), 0.93 – 0.90 (m, 2H). LCMS observed *m/z* = 431.25 $[M+H]^+$.

Intermediate AC

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine.

Intermediate AC

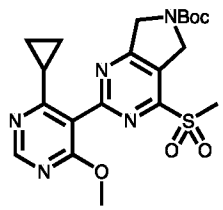


To a solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7-(tetra-hydro-2*H*-pyran-2-yl)-7*H*-purine (4.00 g, 9.29 mmol, Intermediate AB) in dichloromethane (50.0 mL) stirring at 0 °C was added trifluoroacetic acid (10.0 mL) and the resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated under reduced pressure at 10 °C and the residue was triturated with diethyl ether to afford the desired product 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine (2.50 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (br s, 1H), 8.97 (s, 1H), 8.73 (s, 1H), 3.86 (s, 3H), 3.54 (s, 3H), 1.76-1.70 (m, 1H), 1.09-1.07 (m, 2H), 0.90-0.87 (m, 2H). LCMS observed *m/z* = 347.18 $[M+H]^+$.

Intermediate AD

Synthesis of *tert*-butyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-(methylsulfonyl)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate.

Intermediate AD



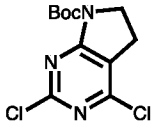
The title compound was prepared using a similar procedure as Intermediate Z, replacing 2,6-dichloro-7-methyl-7*H*-purine with *tert*-butyl 2,4-dichloro-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 4.94 (d, J = 9.6 Hz, 2H), 4.76 (d, J = 10.4 Hz, 2H), 3.88 (s, 3H), 3.37 (s, 3H), 1.79 – 1.76

(m, 1H), 1.49 – 1.47 (m, 9H), 1.11 – 1.08 (m, 2H), 0.95 – 0.85 (m, 2H). LCMS observed *m/z* = 448.36 $[M+H]^+$.

Intermediate AE

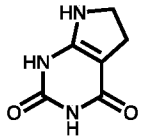
Synthesis of *tert*-butyl 2,4-dichloro-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate.

Intermediate AE



Step 1: Preparation of 1,5,6,7-tetrahydro-2*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*)-dione.

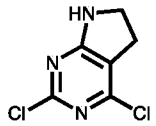
Intermediate AE.1



To the stirred solution of 1,7-dihydro-2*H*-pyrrolo[2,3-d]pyrimidine-2,4(3*H*)-dione (4.00 g, 26.5 mmol) dissolved in trifluoroacetic acid (80.0 mL) was added triethylsilane (12.7 mL, 79.4 mmol) at 0 °C and stirred the reaction mixture at room temperature for 16 h. After completion, the reaction mixture was concentrated and the residue was neutralized with sat. sodium bicarbonate solution. The precipitated solid was filtered off and the solid was dried under vacuum to afford 1,5,6,7-tetrahydro-2*H*-pyrrolo[2,3-d]pyrimidine-2,4(3*H*)-dione (4.00 g) as a brown solid. LCMS observed *m/z* = 154.03 $[M+H]^+$.

Step 2: Preparation of 2,4-dichloro-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine.

Intermediate AE.2



To the stirred solution of 1,5,6,7-tetrahydro-2*H*-pyrrolo[2,3-d]pyrimidine-2,4(3*H*)-dione (1.00 g, 6.53 mmol) in phosphorus(V)oxychloride (12.2 mL, 131 mmol) was added *N,N*-diisopropylethylamine (2.34 mL, 13.1 mmol) at 0 °C and the reaction mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was concentrated under reduced pressure and the residue was quenched with saturated sodium bicarbonate solution and extracted with EtOAc (30 mL x 3), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to afford 2,4-dichloro-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidine (0.30 g). LCMS observed *m/z* = 190.01 $[M+H]^+$.

Step 3: Preparation of *tert*-butyl 2,4-dichloro-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate.

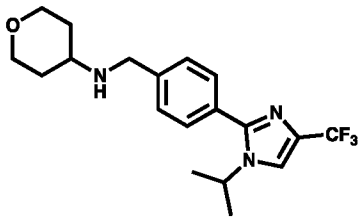
Intermediate AE

The stirred solution of 2,4-dichloro-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidine (0.30 g, 1.58 mmol) in dichloromethane (10.0 mL) was added triethylamine (0.66 mL, 4.74 mmol) followed by di-tert-butyl dicarbonate (0.36 mL, 1.58 mmol) and the reaction mixture was stirred at 23 °C for 16 h. After completion, the reaction mixture was diluted with diluted with water (10 mL) and extracted with dichloromethane (30 mL x 2). The combined organic layer was washed with water (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 10% EtOAc in petroleum ether) to afford *tert*-butyl 2,4-dichloro-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (0.20 g). LCMS observed *m/z* = 234.06 $[M-56+H]^+$.

Intermediate AF

Synthesis of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)tetrahydro-2*H*-pyran-4-amine.

Intermediate AF



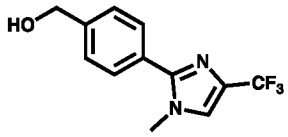
To a stirred solution of 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzaldehyde (1 g, 3.54 mmol Intermediate E.1) and tetrahydro-2H-pyran-4-amine (0.71 g, 7.08 mmol) in MeOH (20 mL) was added acetic acid (0.1 mL) at 0 °C and allowed to stir at room temperature for 2 h. Then sodium cyanoborohydride (0.44 g, 7.08 mmol) was added at 0 °C and allowed to stir at room temperature for 16 h. The progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was diluted with water (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layer was washed by saturated sodium bicarbonate solution (100 mL x 2), dried over anhydrous sodium sulfate and concentrated

under reduced pressure. The crude product was purified by flash chromatography using silica gel (devisil silica, 10% MeOH in dichloromethane) to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)tetrahydro-2H-pyran-4-amine (0.76 g) as yellow solid. LCMS observed *m/z* 368.32 $[M+H]^+$.

Intermediate AG

Synthesis of (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol.

Intermediate AG

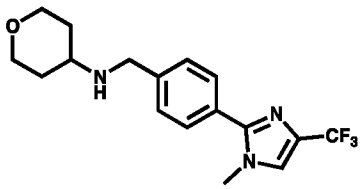


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with methyl 4-formylbenzoate and using General Procedure C (diisobutyl aluminum hydride) to reduce the ester. LCMS observed *m/z* = 257.125 $[M+H]^+$.

Intermediate AH

Synthesis of *N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)tetrahydro-2*H*-pyran-4-amine.

Intermediate AH

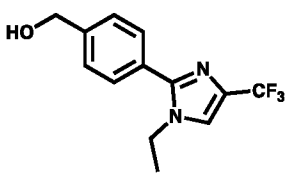


The title compound was prepared using a similar procedure as Intermediate AF, replacing 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzaldehyde (Intermediate E.1) with (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate AG). LCMS observed *m/z* 340.77 $[M+H]^+$.

Intermediate AI

Synthesis of (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol

Intermediate AI

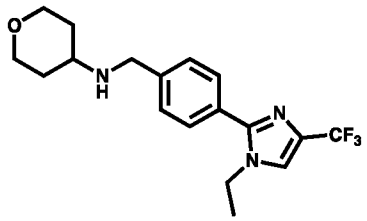


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with methyl 4-formylbenzoate, methyl iodide with ethyl iodide, and using General Procedure C (diisobutyl aluminum hydride) to reduce the ester. LCMS observed *m/z* = 271.10 $[M+H]^+$.

Intermediate AJ

Synthesis of N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)tetrahydro-2H-pyran-4-amine.

Intermediate AJ

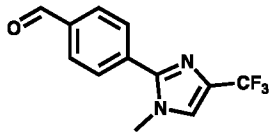


The title compound was prepared using a similar procedure as Intermediate AF, replacing 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzaldehyde (Intermediate E.1) with (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate AI). LCMS observed *m/z* = 354.33 $[M+H]^+$.

Intermediate AK

Synthesis of 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde

Intermediate AK

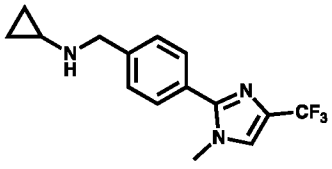


The title compound was prepared using a similar procedure as Intermediate E.1, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (intermediate C) with (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate AG). LCMS observed *m/z* = 255.24 [M+H]+.

Intermediate AL

Synthesis of N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)cyclopropanamine

Intermediate AL

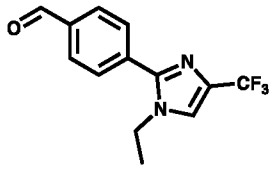


The title compound was prepared using a similar procedure as Intermediate AF, using replacing 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzaldehyde (Intermediate E.1) with 4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde (Intermediate AK) and tetrahydro-2H-pyran-4-amine with cyclopropylamine. LCMS observed *m/z* = 296.23 $[M+H]^+$.

Intermediate AM

Synthesis of 4-(1-ethyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde

Intermediate AM

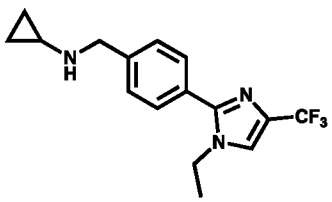


The title compound was prepared using a similar procedure as Intermediate E.1, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate AI). LCMS observed *m/z* = 269.61 $[M+H]^+$.

Intermediate AN

Synthesis of *N*-(4-(1-ethyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)cyclopropanamine

Intermediate AN

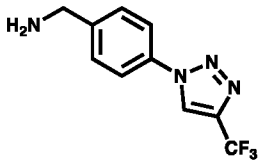


The title compound was prepared using a similar procedure as Intermediate AF, replacing 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzaldehyde (Intermediate E.1) with 4-(1-ethyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzaldehyde (Intermediate AM) and tetrahydro-2H-pyran-4-amine with cyclopropylamine. LCMS observed *m/z* = 310.27 $[M+H]^+$.

Intermediate AO

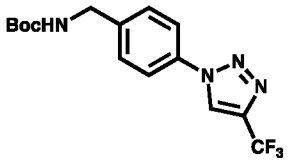
Synthesis of (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AO



Step 1: Preparation of tert-butyl (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)carbamate

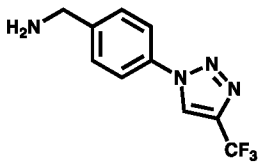
Intermediate AO.1



To a stirred solution of 4-(trifluoromethyl)-2H-1,2,3-triazole (0.85 g, 6.20 mmol) and (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (2.33 g, 9.30 mmol) in 1,2-dichloroethane (50 mL) were added copper(II) acetate (1.69 g, 9.30 mmol) followed by pyridine (0.10 mL, 12.40 mmol) and molecular sieves 13 X, 4 to 8 mesh (2.73 g, 6.20 mmol) at 25° C. The reaction mixture was stirred at 25 °C for 12 h in presence of air. Upon completion of reaction, the reaction mixture was filtered through celite and diluted with cold water (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over Anhydrous sodium sulfate, filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20–30% EtOAc in petroleum ether) to afford tert-butyl (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)carbamate (0.25 g) as an off-white solid. LCMS observed *m/z* 343.21 $[M+H]^+$.

Step 2: Preparation of (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AO



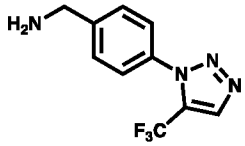
To a stirred solution of tert-butyl (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)carbamate (0.25 g, 0.730 mmol) in dichloromethane (5 mL) was added hydrogen chloride, 4M in 1,4-dioxane (5 mL) at 0 °C and the reaction mixture was stirred at 25 °C for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was triturated with pentane (10 mL) to afford (4-(4-(trifluoromethyl)-1H-1,2,3-

triazol-1-yl)phenyl)methanamine (175 mg) as an off-white solid. LCMS observed *m/z* = 243.12 $[M+H]^+$.

Intermediate AP

Synthesis of (4-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AP

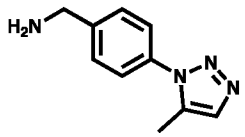


The title compound was prepared using a similar procedure as Intermediate AO, replacing tert-butyl (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)carbamate with tert-butyl (4-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)carbamate. LCMS observed *m/z* = 243.16 $[M+H]^+$.

Intermediate AQ

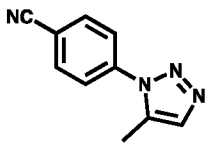
Synthesis of (4-(5-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AQ



Step 1: Preparation of 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile

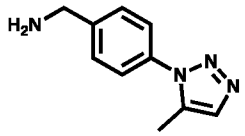
Intermediate AQ.1



To a stirred solution of 5-methyl-1H-1,2,3-triazole (1.0 g, 12.0 mmol) in dimethylformamide (10.0 mL), was added Cs_2CO_3 (5.89 g, 18.1 mmol) and 4-fluorobenzonitrile (1.46 g, 12.0 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 2 h. After completion (monitored by TLC, R_f: 0.50, mobile phase: 50% EtOAc in hexanes), the reaction mixture was diluted with water (90.0 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by SFC prep to afford 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile (3A) (120 mg) as an off-white solid, 4-(4-methyl-2H-1,2,3-triazol-2-yl)benzonitrile (3B) (1.0 g) as an off-white solid and 4-(4-methyl-1H-1,2,3-triazol-1-yl)benzonitrile (3C) (0.5 g) as an off-white solid.. LCMS observed *m/z* 185.20 $[M+H]^+$.

Step 2: Preparation of (4-(4-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AQ

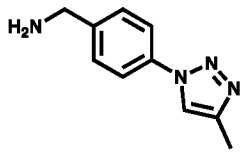


To a stirred solution of 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile (110 mg, 0.597 mmol) was added lithium aluminium hydride 1.0 M in THF (1.8 mL, 1.79 mmol) drop-wise at 0 °C under nitrogen atmosphere and the reaction mixture was stirred at 25 °C for 3 h. After completion (monitored by TLC, Rf: 0.2, mobile phase: 10% MeOH in dichloromethane), the reaction mixture was quenched with aq.NH_4Cl solution (20 mL) and extracted with EtOAc (2 x 30 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford (4-(5-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine (0.1 g). The crude was material was forwarded to next step without any further purification. LCMS observed *m/z* = 188.97 $[M+H]^+$.

Intermediate AR

Synthesis of (4-(4-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AR

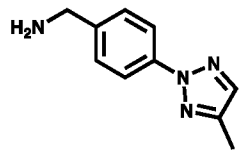


The title compound was prepared using a similar procedure as Intermediate AQ, replacing 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile with 4-(4-methyl-1H-1,2,3-triazol-1-yl)benzonitrile. LCMS observed *m/z* = 188.97 $[M+H]^+$.

Intermediate AS

Synthesis of (4-(4-methyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine

Intermediate AS

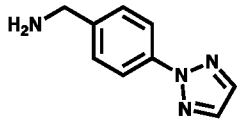


The title compound was prepared using a similar procedure as Intermediate AQ, replacing 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile with 4-(5-methyl-2H-1,2,3-triazol-2-yl)benzonitrile. LCMS observed *m/z* = 189.33 $[M+H]^+$.

Intermediate AT

Synthesis of (4-(2H-1,2,3-triazol-2-yl)phenyl)methanamine

Intermediate AT

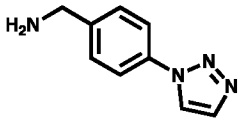


The title compound was prepared using a similar procedure as Intermediate AQ, replacing 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile with 4-(2H-1,2,3-triazol-2-yl)benzonitrile. LCMS observed *m/z* 175.3 $[M+H]^+$.

Intermediate AU

Synthesis of (4-(1H-1,2,3-triazol-1-yl)phenyl)methanamine

Intermediate AU

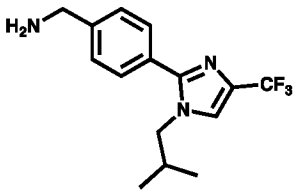


The title compound was prepared using a similar procedure as Intermediate AQ, replacing 4-(5-methyl-1H-1,2,3-triazol-1-yl)benzonitrile with 4-(1H-1,2,3-triazol-1-yl)benzonitrile. LCMS observed *m/z* = 175.2 $[M+H]^+$.

Intermediate AV

Synthesis of (4-(1-isobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine.

Intermediate AV

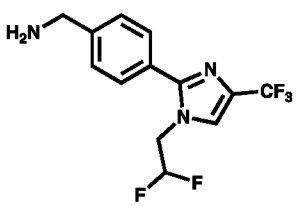


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 1-iodo-2-methylpropane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 298.27 $[M+H]^+$.

Intermediate AW

Synthesis of (4-(1-(2,2-difluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine.

Intermediate AW

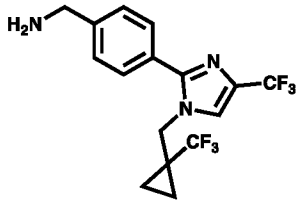


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 1,1-difluoro-2-iodoethane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 306.23 $[M+H]^+$.

Intermediate AX

Synthesis of (4-(4-(trifluoromethyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)-1H-imidazol-2-yl)phenyl)methanamine.

Intermediate AX

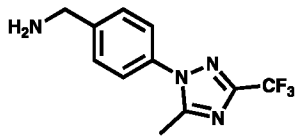


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with [1-(bromomethyl)cyclopropyl]trifluoromethane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 364.32 $[M+H]^+$.

Intermediate AY

Synthesis of (4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)phenyl)methanamine.

Intermediate AY

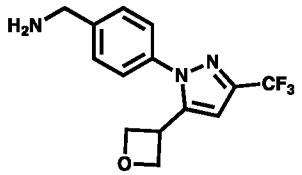


The title compound was prepared using a similar procedure as Intermediate AO, replacing 4-(trifluoromethyl)-1H-1,2,3-triazole with 5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazole. LCMS observed *m/z* = 257.32 $[M+H]^+$.

Intermediate AZ

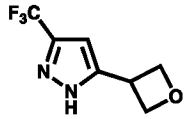
Synthesis of (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate AZ



Step 1: Preparation of 5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazole

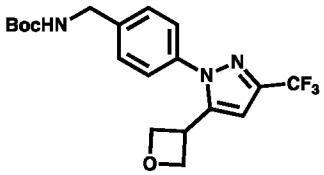
Intermediate AZ.1



To a stirred solution of 2-bromo-3,3,3-trifluoroprop-1-ene (5 g, 28.58 mmol) and oxetane-3-carbaldehyde (4.92 g, 57.16 mmol in toluene (100 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (13.05 g, 85.74 mmol) followed by p-toluenesulfonyl hydrazine (7.83 g, 34.30 mmol) at 25 °C. The reaction mixture was stirred at 60 °C for 12 h. Upon completion, the reaction mixture was concentrated under reduced pressure, diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over Anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by normal phase flash chromatography (silica gel, 50–60% EtOAc in petroleum ether) to afford 5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazole (2 g) as a yellow solid. LCMS observed *m/z* 193.24 $[M+H]^+$.

Step 2: Preparation of tert-butyl (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)carbamate

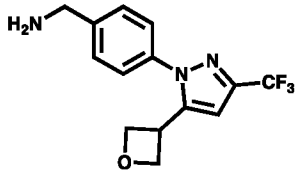
Intermediate AZ.2



To a stirred solution of 5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazole (2.1 g, 10.93 mmol) and (4-(((tert-butoxycarbonyl)amino)methyl)phenyl)boronic acid (4.11 g, 16.39 mmol) in 1,2-dichloroethane (50 mL) were added copper(II) acetate (2.98 g, 16.394 mmol) followed by pyridine (1.76 mL, 21.86 mmol) at 25° C. The reaction mixture was stirred at 25 °C for 6 h in air. Upon completion of reaction, the reaction mixture was filtered through celite and quenched with cold water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine (20 mL), dried over Anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel & EtOAc: petroleum ether = 2:8) to afford tert-butyl (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)carbamate (1.5 g) as an off-white solid. LCMS observed *m/z* = 398.24 $[M+H]^+$.

Step 3: Preparation of (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate AZ

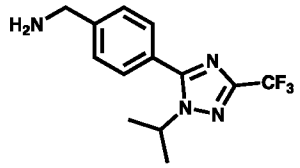


To a stirred solution of tert-butyl (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)carbamate (1.5 g, 3.77 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (15 mL, 37.74 mmol) at 0 °C and the reaction mixture was stirred at 25 °C for 3 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The residue was triturated with pentane (50 mL) to afford (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (1 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (br s, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.25 (s, 1H), 4.77-4.73 (m, 2H), 4.68-4.64 (m, 2H), 4.39-4.31 (m, 1H), 4.15 (s, 2H) LCMS observed m/z = 298.32 $[M+H]^+$.

Intermediate BA

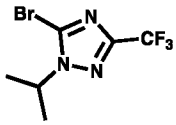
Synthesis of (4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)phenyl)methanamine

Intermediate BA



Step 1: Preparation of 5-bromo-1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazole

Intermediate BA.1

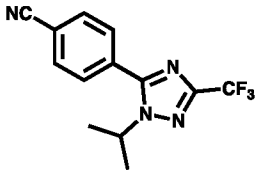


To a stirred solution of 5-bromo-3-(trifluoromethyl)-1H-1,2,4-triazole (1.0 g, 4.63 mmol) in N,N-dimethylformamide (DMF, 10 mL) was added sodium hydride, 60% dispersion in mineral oil (333 mg, 13.9 mmol) at 0 °C and stirred for 15 minutes. Then 2-iodopropane (2.36 g, 13.9 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. After completion, the reaction mixture was quenched with cold water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 10–20% EtOAc in petroleum ether) to afford 5-bromo-

1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazole (800 mg). Note: The isomeric mixture was used moving forward. LCMS observed *m/z* = 257.87 $[M+H]^+$.

Step 2: Preparation of 4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)benzonitrile

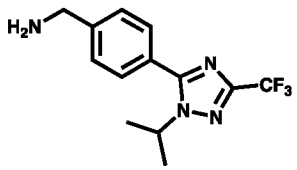
Intermediate BA.2



To a stirred solution of 5-bromo-1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazole (mixture of two regio-isomers) (800 mg, 3.10 mmol) in 1,4-dioxane (8 mL) and water (2 mL), (4-cyanophenyl) boronic acid (683 mg, 4.65 mmol) followed by potassium carbonate (1.28 g, 9.3 mmol) were added, and the mixture was purged with nitrogen gas for 30 min. Tetrakis(triphenylphosphine)palladium(0) (358 mg, 0.31 mmol) was added to the reaction mixture and stirred at 110 °C for 16 h. After completion, the reaction mixture was diluted with water (2 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 10–20% EtOAc in petroleum ether) to afford 4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)benzonitrile (600 mg) as a white solid and 4-(1-isopropyl-5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl) benzonitrile (200 mg). LCMS observed *m/z* = 281.31 $[M+H]^+$.

Step 3: Preparation of (4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)phenyl)methanamine

Intermediate BA



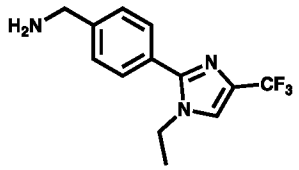
To the stirred solution of 4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl) benzonitrile (800 mg, 2.85 mmol) in tetrahydrofuran (10 mL) was added $LiAlH_4$ powder (325 mg, 8.56 mmol) at 0 °C and stirred at room temperature for 16 h. After completion, the reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford (4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)

phenyl) methanamine (600 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 3H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 4.69-4.75 (m, 1H), 4.15 (s, 2H), 1.48 (d, *J* = 12.0 Hz, 6H) LCMS observed *m/z* = 285.04 $[M+H]^+$.

Intermediate BB

Synthesis of (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine.

Intermediate BB

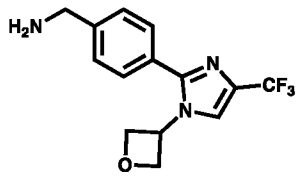


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with ethyl iodide and using general procedure C to reduce the nitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (bs, 2H), 8.06 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.13-4.08 (m, 4H), 1.32 (t, J = 7.2 Hz, 3H). LCMS observed *m/z* = 271.3 $[M+H]^+$.

Intermediate BC

Synthesis of (4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine.

Intermediate BC

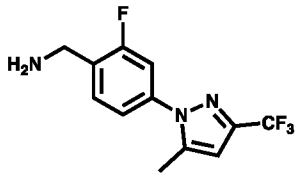


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with iodocyclobutane and using general procedure C to reduce the nitrile. 1H NMR (400 MHz, DMSO-d6) δ 8.42 (bs, 2H), 8.06 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 4.13-4.08 (m, 4H), 1.32 (t, J = 7.2 Hz, 3H). LCMS observed *m/z* = 298.19 $[M+H]^+$.

Intermediate BD

Synthesis of (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate BD

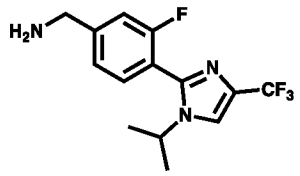


The title compound was prepared using a similar procedure as Intermediate X, replacing 4,4,4-trifluoro-3-oxobutanoate with 1,1,1-trifluoropentane-2,4-dione, 4-hydrazineylbenzonitrile with 2-fluoro-4-hydrazineylbenzonitrile, and using general procedure E to reduce the nitrile. LCMS observed *m/z* = 274.35 $[M+H]^+$.

Intermediate BE

Synthesis of (3-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate BE

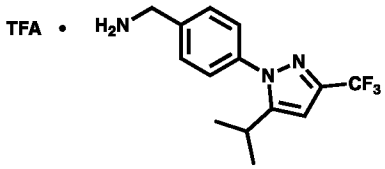


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 3-fluoro-4-formylbenzonitrile and methyl iodide with isopropyl iodide. LCMS observed *m/z* = 302.2 $[M+H]^+$.

Intermediate BF

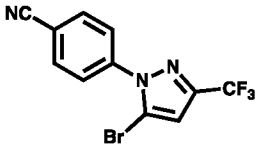
Synthesis of (4-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine.

Intermediate BF



Step 1: Preparation of 4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile

Intermediate BF.1

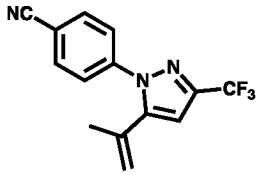


To a stirred solution of (4-cyanophenyl)boronic acid (2.2 g, 14.97 mmol) and 5-bromo-3-(trifluoromethyl)-1H-pyrazole (3.86 g, 17.96 mmol) in 1,2-dichloroethane (44

mL), copper(II) acetate (4.08 g, 22.46 mmol) was added, followed by pyridine (2.41 mL, 29.94 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 12 hours in air. Upon completion, the mixture was filtered through Celite, diluted with cold water (100 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20–30% EtOAc in hexanes) to afford 4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (2.7 g) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H). LCMS observed *m/z* 315.9 $[M+H]^+$.

Step 2: Preparation of 4-(5-(prop-1-en-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile

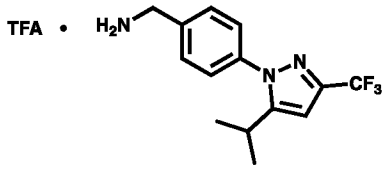
Intermediate BF.2



To a stirred solution of 4-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (2.5 g, 7.91 mmol) in 1,4-dioxane (50.0 mL) and water (5.0 mL), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (2.66 g, 15.82 mmol) and potassium carbonate (3.3 g, 23.73 mmol) were added. The reaction mixture was purged with nitrogen gas for 10 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.91 g, 0.79 mmol) was then added, and the mixture was stirred at 110 °C for 16 hours. Upon completion, the reaction was quenched with cold water (25 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layer was washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (100-200 mesh silica gel, eluent: 4-6% EtOAc in hexanes) to afford 4-(5-(prop-1-en-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (1.8 g) as a pale brown solid. LCMS observed *m/z* = 278.15 $[M+H]^+$.

Step 3: Preparation of (4-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate BF

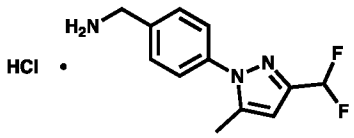


To a stirred solution of 4-(5-(prop-1-en-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzonitrile (1.8 g, 6.5 mmol) in EtOAc (50 mL), palladium on carbon (50% wet basis, 1.8 g), platinum(IV) oxide (0.2 g), and acetic acid (0.5 mL) were added. The reaction mixture was stirred in a Parr shaker under hydrogen atmosphere (85 psi) for 16 hours at 25 °C. Upon completion, as monitored by TLC (Rf: 0.6, mobile phase: 30% EtOAc in hexanes), the mixture was filtered through a Buchner funnel. The filtrate was concentrated under reduced pressure. The crude product was purified by reverse-phase chromatography (Mobile Phase A: 0.1% TFA in H_2O; Mobile Phase B: Acetonitrile = 1:4) to afford (4-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl) phenyl) methanamine (0.75 g) as a pale brown solid. The compound is in the form of a TFA salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (br s, 3H), 7.67-7.61 (m, 4H), 6.85 (s, 1H), 4.16 (d, J = 5.6 Hz, 2H), 3.01-2.94 (m, 1H), 1.15 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 284.38 $[M+H]^+$.

Intermediate BG

Synthesis of (4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate BG

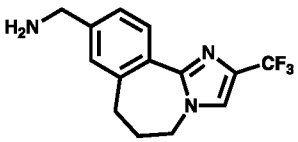


The title compound was prepared using a similar procedure as Intermediate AO, replacing 4-(trifluoromethyl)-2H-1,2,3-triazole with 3-(difluoromethyl)-5-methyl-1H-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (br s, 3H), 7.67-7.57 (m, 4H), 7.19-6.87 (m, 1H), 6.58 (s, 1H), 4.12 (d, J = 4.8 Hz, 2H), 2.35 (s, 3H). LCMS observed *m/z* = 238.33 $[M+H]^+$.

Intermediate BH

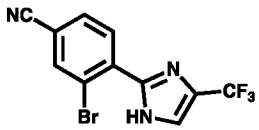
Synthesis of (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methanamine

Intermediate BH



Step 1: Preparation of 3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

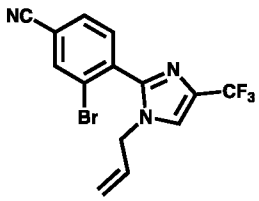
Intermediate BH.1



To a mixture of 3,3-dibromo-1,1,1-trifluoro-2-propanone (619 µL, 1.1 eq., 5.02 mmol) in water (2.13 mL, 118 mmol) was added potassium acetate (497 mg, 1.1 eq., 5.07 mmol) and the mixture was heated to 100 °C for 1 h. The mixture was cooled to 23 °C, then a solution of 3-bromo-4-formylbenzonitrile (950 mg, 4.52 mmol) in MeOH (22.6 mL, 558 mmol) and ammonium hydroxide (5 mL, 128 mmol) (pre-stirred for 1 h) was added and stirred at 23 °C for 45 min, then warmed to 100 °C for 18 h. The reaction was cooled to 23 °C and diluted with water (75 mL) and EtOAc (50 mL). The mixture was filtered, and the phases were separated. The organic was dried over MgSO4, filtered and concentrated under reduced pressure to afford 3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile as a yellow solid (1.43g). The material was used without purification. LCMS observed *m/z* = 316.0 $[M+H]^+$.

Step 2: Preparation of 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-bromobenzonitrile

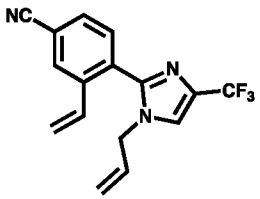
Intermediate BH.2



To a solution of 3-bromo-4-[4-(trifluoromethyl)-2-imidazolyl]benzonitrile (1.43 g, 4.52 mmol) in dimethylformamide (9.04 mL, 117 mmol) was added dipotassium carbonate (1.25 g, 2 eq., 9.04 mmol) followed by 3-bromopropene (586 µL, 1.5 eq., 6.78 mmol) and the mixture was stirred at 23 °C for 3 h. The reaction was poured into LiCl (20 mL, 10% aq) and extracted with EtOAc (2 x 15 mL). The combined organics were washed with water (15 mL), brine (15 mL), dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–25% EtOAc in hexanes eluent, 12 g Gold column) to afford 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-bromobenzonitrile (0.78 g) as an amber oil. LCMS observed *m/z* = 356.1 $[M+H]^+$.

Step 3: Preparation of 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-vinylbenzonitrile.

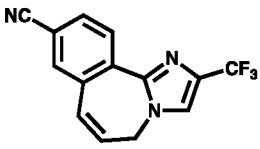
Intermediate BH.3



To a suspension of 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-bromobenzonitrile (356 mg, 1 mmol), Cs_2CO_3 (977 mg, 3 eq., 3 mmol), and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (509 µL, 3 eq., 3 mmol) in 1,4-dioxane (4 mL, 46.9 mmol) and water (1 mL, 20 eq., 20 mmol) was added dichloro-palladamethane—dichloromethane—iron—1λ³,2λ³,3λ³,4λ³,5λ³-cyclopentyldiphenylphosphine (1/1/1/2) (81.7 mg, 0.1 eq., 0.1 mmol) and the mixture was degassed with N2 via vacuum/N2 backfill (5x). The vial was sealed and heated at 85 C for 16 h. The reaction was not complete at this time. An additional 2.0 equiv of the vinyl borane was added followed by $Pd(dppf)Cl_2$ (100 mg) and the reaction was heated to 100 C for 24 h. At this point the starting material was consumed. The reaction was diluted with water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 10–20% EtOAc in hexanes eluent, 40 g Gold column) to afford the product 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-vinylbenzonitrile (0.56 g) as a pale yellow oil. LCMS observed m/z = 304.2 $[M+H]^+$.

Step 4: Preparation of 2-(trifluoromethyl)-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile.

Intermediate BH.4

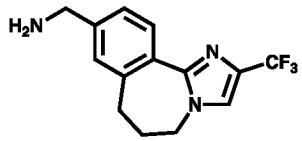


To a solution of 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-vinylbenzonitrile (716.6 mg, 2.33 mmol) in dichloromethane (3.22 mL, 50.3 mmol) was added ruthenium o-isopropoxymethanediidyltoluene 1,3-bis(mesityl)-2,2-imidazolidinediide dichloride (74.0 mg, 0.05 eq., 118.1 µmol) and the mixture was stirred at 23 °C for 16 h. The reaction was filtered through a plug of SiO2, washing with 50% EtOAc in hexanes (5 mL) and the resulting solution was concentrated under reduced

pressure. The crude product was purified by flash chromatography (silica gel, 80–90% EtOAc in hexanes eluent, 24g column) to afford the product 2-(trifluoromethyl)-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile (0.48 g) as a yellow solid LCMS observed m/z = 276.1 $[M+H]^+$.

Step 5: Preparation of (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methanamine.

Intermediate BH

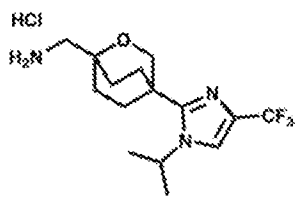


To a solution of 4-(trifluoromethyl)-3,6-diazatricyclo[8.4.0.0^{2,6}]tetradeca-1(14),2,4,8,10,12-hexaene-12-carbonitrile (473 mg, 1.72 mmol) in tetrahydrofuran (10 mL, 123 mmol) and MeOH (10 mL, 247 mmol) at 0 °C was added nickel dichloride (81.8 mg, 0.2 eq., 344 µmol) followed by $NaBH_4$ (309 mg, 3 eq., 5.16 mmol). The mixture was warmed to 23 °C and stirred for 3 h at which point it was complete by LCMS. The reaction was quenched with water (10 mL) and stirred for 10 min. The mixture was extracted with EtOAc (2 x 10 mL) and the combined organics were washed with water (10 mL), brine (10 mL), dried over MgSO4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–10% MeOH in dichloromethane, 12 g column) to afford the product (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methanamine (243 mg) as an off-white solid. LCMS observed m/z = 282.1 $[M+H]^+$.

Intermediate BI

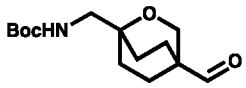
Synthesis of ({4-[1-isopropyl-4-(trifluoromethyl)-2-imidazolyl]-2-oxabicyclo[2.2.2]oct-1-yl}methyl)amine—hydrogen chloride (1/1).

Intermediate BI



Step 1: Preparation of tert-butyl ((4-formyl-2-oxabicyclo[2.2.2]octan-1-yl)methyl)carbamate

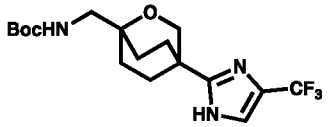
Intermediate BI.1



To a solution of {4-(hydroxymethyl)-2-oxabicyclo[2.2.2]oct-1-yl}methyl 2-methyl-2-propanecarbamate (407 mg, 1.5 mmol) in dichloromethane (15 mL, 234 mmol) stirring at 23 °C was added 1,1-diacetoxy-3-oxo-1,3-dihydro-1λ⁵,2-benziodaoxol-1-yl acetate (0.7 g, 1.1 eq., 1.65 mmol) and the reaction was stirred at 23 °C for 1 h. The reaction was quenched with sat. $Na_2S_2O_3$ (5 mL) and stirred for 5 min. The mixture was diluted with dichloromethane (10 mL) and the phases were separated. The organic was washed with water (10 mL), brine (10 mL), dried over MgSO4, filtered and was concentrated under reduced pressure to afford the crude product as a colorless oil. The material was used without further purification assuming 100% conversion. LCMS observed *m/z* = 292.2 $[M+Na]^+$.

Step 2: Preparation of tert-butyl ((4-(4-(trifluoromethyl)-1H-imidazol-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)methyl)carbamate

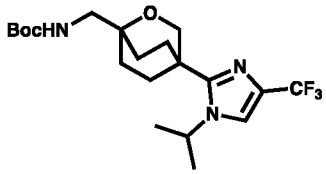
Intermediate BI.2



To a solution of 3,3-dibromo-1,1,1-trifluoro-2-propanone (206 µL, 1.1 eq., 1.67 mmol) in water (869 µL, 48.2 mmol) was added sodium acetate (138 mg, 1.1 eq., 1.68 mmol) and the mixture was heated to 100 °C for 1 h. The mixture was cooled to 23 °C and a solution of (4-formyl-2-oxabicyclo[2.2.2]oct-1-yl)methyl 2-methyl-2-propanecarbamate (404 mg, 1.5 mmol) in MeOH (6.52 mL, 161 mmol) and ammonium hydroxide (1.5 mL) was added and the mixture was heated to 100 °C for 20 h. The reaction was cooled to 23 °C and the mixture was extracted with EtOAc (2 x 20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried over MgSO4, filtered and concentrated under reduced pressure to afford the crude imidazole as a brown resin. The material was used in the next step without purification (370 mg crude). LCMS observed *m/z* = 376.2 $[M+H]^+$.

Step 3: Preparation of tert-butyl ((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)methyl)carbamate

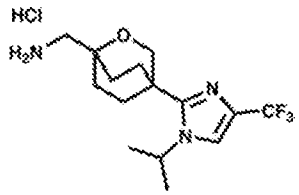
Intermediate BI.3



To a suspension of tert-butyl ({4-[4-(trifluoromethyl)-2-imidazolyl]-2-oxabicyclo[2.2.2]oct-1-yl}methyl)carbamate (563 mg, 1.5 mmol) and dicaesium carbonate (1.47 g, 3 eq., 4.5 mmol) in acetonitrile (6 mL, 115 mmol) stirring at 23 °C was added 2-iodopropane (0.6 mL, 4 eq., 6 mmol) and the mixture was heated to 70 °C for 18 h. LCMS indicated conversion to the desired product. The reaction was cooled to 23 °C and filtered, washing with EtOAc (10 mL). The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 0–75% EtOAc in hexanes, 12 g Column) to afford the product (205 mg) as a pale yellow oil that solidified on standing. LCMS observed *m/z* = 418.3 $[M+H]^+$.

Step 4: Preparation of ({4-[1-isopropyl-4-(trifluoromethyl)-2-imidazolyl]-2-oxabicyclo[2.2.2]oct-1-yl}methyl)amine—hydrogen chloride (1/1)

Intermediate BI

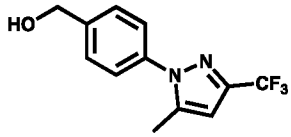


To a solution of tert-butyl ({4-[1-isopropyl-4-(trifluoromethyl)-2-imidazolyl]-2-oxabicyclo[2.2.2]oct-1-yl}methyl)carbamate (201 mg, 481 µmol) in 1,4-dioxane (481 µL, 5.64 mmol) stirring at 23 °C was added HCl in 1,4-dioxane (4M, 3.0 mmol, 3.0 mL and the reaction was stirred at 23 °C for 1 h. The reaction was concentrated under reduced pressure as an azeotropic mixture with heptanes (5 mL) to afford the product as a white solid. 1H NMR (CD3OD, 400 MHz): 8.04 (s, 1H), 5.00 (sept. J = 6.5 Hz, 1H), 4.26 (s, 2H), 2.38 – 2.30 (m, 2H), 2.20 – 2.12 (m, 2H), 2.09 – 1.99 (m, 2H), 1.89 – 1.80 (m, 2H), 1.49 (d, J = 6.5 Hz, 6H). 2H obscured by dioxane solvent impurity. LCMS observed *m/z* = 318.3 $[M+H]^+$.

Intermediate BJ

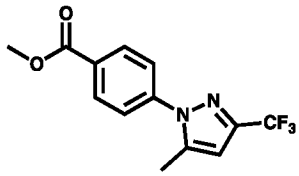
Synthesis of (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol

Intermediate BJ



Step 1: Preparation of methyl 4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoate

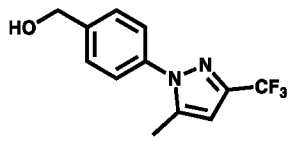
Intermediate BJ.1



To a stirred solution of 5-methyl-3-(trifluoromethyl)-1H-pyrazole (4.5 g, 30.00 mmol) and (4-(methoxycarbonyl)phenyl)boronic acid (9.00 g, 44.97 mmol) in 1,2-dichloroethane (50 mL) was added copper(II) acetate (8.17 g, 44.97 mmol) followed by pyridine (4.83 mL, 59.96 mmol) at 25° C. The reaction mixture was stirred at 25 °C for 12 h. After completion of reaction, the reaction mixture was filtered through celite, diluted with cold water (100 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 10–15% EtOAc in petroleum ether) to afford methyl 4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzoate (6.5 g) as an off-white solid. LCMS observed m/z = 285.3 $[M+H]^+$.

Step 2: Preparation of (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol

Intermediate BJ



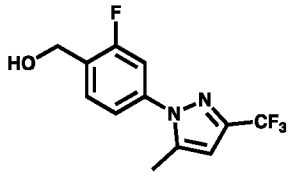
To a stirred solution of methyl 4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoate (6.5 g, 22.87 mmol) in tetrahydrofuran (60 mL) was added diisobutylaluminium hydride, 1M solution in hexane (91 mL, 91.47 mmol) at 0° C. The reaction mixture was stirred at 25 °C for 2 h and the progress of the reaction was monitored by TLC and LCMS. After completion of reaction, the reaction mixture was quenched with saturated ammonium chloride solution (200 mL), diluted with EtOAc (300 mL), stirred for 15 min and filtered through celite. The organic layer was partitioned and the aqueous layer was extracted with

EtOAc (200 mL). The combined organic layer was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 5–10% EtOAc in petroleum ether) to afford (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl) phenyl) MeOH (4.3 g) as yellow gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53-7.48 (m, 4H), 6.75 (br s, 1H), 5.35 (t, J = 5.8 Hz, 1H), 4.59 (d, J = 5.6 Hz, 2H), 2.33 (s, 3H). LCMS observed *m/z* = 257.0 $[M+H]^+$.

Intermediate BK

Synthesis of (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol

Intermediate BK

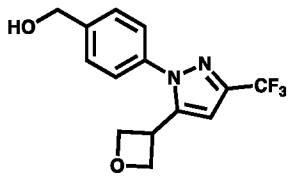


The title compound was prepared using a similar procedure as Intermediate BJ, replacing (4-(methoxycarbonyl)phenyl)boronic acid with [3-Fluoro-4-(methoxycarbonyl)phenyl]boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (t, J = 8.2 Hz, 1H), 7.51-7.43 (m, 2H), 6.78 (s, 1H), 5.43 (t, J = 5.6 Hz, 1H), 4.62 (d, J = 5.6 Hz, 2H), 2.37 (s, 3H). LCMS observed *m/z* = 275.1 $[M+H]^+$.

Intermediate BL

Synthesis of (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol

Intermediate BL



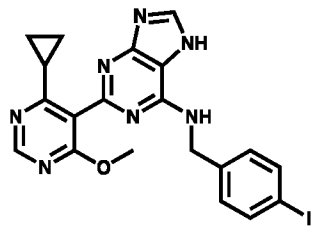
To a stirred solution of 5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazole (Intermediate AZ.1) (2 g, 10.41 mmol) and (4-(hydroxymethyl) phenyl) boronic acid (1.18 g, 7.8 mmol) in 1,2-dichloroethane (100 mL), copper(II) acetate (1.42 g, 7.8 mmol) was added, followed by pyridine (0.84 mL, 10.41 mmol) at 25 °C. After completion, the reaction mixture was filtered through celite and diluted with cold water (100 mL), then extracted

with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 15–20% EtOAc in petroleum ether) to afford (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) phenyl) MeOH (198 mg) as a colorless gum. 1H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.21 (s, 1H), 5.36 (t, J = 5.8 Hz, 1H), 4.77-4.73 (m, 2H), 4.67-4.64 (m, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.40-4.29 (m, 1H). LCMS observed *m/z* = 299.1 $[M+H]^+$.

Intermediate BM

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-iodobenzyl)-7H-purin-6-amine

Intermediate BM

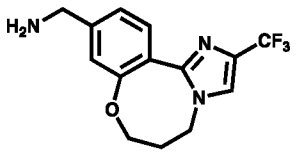


The title compound was prepared according to General Procedure E, using 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7H-purine as the substituted pyrimidine and using (4-iodophenyl)methanamine as the amine. LCMS observed *m/z* = 500.2 $[M+H]^+$.

Intermediate BN

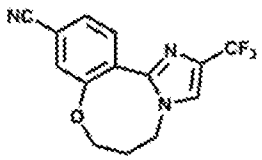
Synthesis of (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methanamine

Intermediate BN



Step 1: Preparation of 2-(2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)acetonitrile

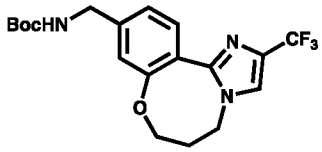
Intermediate BN.1



To a stirred solution of 3-fluoro-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (2.0 g, 7.84 mmol) in DMF (20.0 mL), were added Cs_2CO_3 (7.64 g, 23.51 mmol) followed by (3-bromopropoxy)(tert-butyl)dimethylsilane (2.38 g, 9.41 mmol) and reaction mixture was stirred at 60 °C for 16 h. On completion, the reaction mixture was diluted with ice cold water (80 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 30–35% EtOAc in petroleum ether) to afford 2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocine-10-carbonitrile (2.0 g) as an off-white solid. LCMS observed *m/z* = 294.1 $[M+H]^+$.

Step 2: Preparation of tert-butyl ((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methyl)carbamate

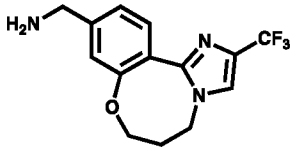
Intermediate BN.2



To the stirred solution of 2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocine-10-carbonitrile (1.8 g, 6.14 mmol) in EtOAc (30 mL) and MeOH (30 mL) was added palladium on carbon (50% wet basis) (1.8 g) and di-tert-butyl dicarbonate (8.03 g, 36.83 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 16 h under H_2 gas (80 psi). After completion, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica & EtOAc: petroleum ether = 3:7) to afford tert-butyl ((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methyl)carbamate (1.8 g) as an off-white solid. LCMS observed *m/z* = 398.7 $[M+H]^+$.

Step 3: Preparation of (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methanamine

Intermediate BN

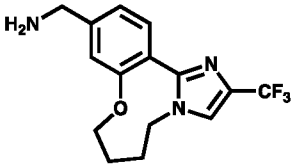


To a stirred solution of tert-butyl ((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methyl)carbamate (1.0 g, 2.156 mmol) in dichloromethane (10 mL) was added TFA (1.0 mL) at 0 °C and reaction mixture was allowed to stir at 25 °C for 4 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with pentane (10 mL) and diethyl ether (10 mL) to afford (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methanamine (1.0 g) as an off-white solid. LCMS observed *m/z* = 298.6 $[M+H]^+$.

Intermediate BO

Synthesis of (2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[b]imidazo[2,1-d][1,5]oxazonin-11-yl)methanamine.

Intermediate BO

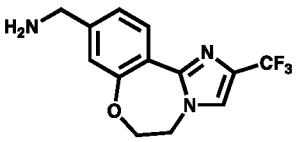


The title compound was prepared using a similar procedure as Intermediate BN, replacing (3-bromopropoxy)(tert-butyl)dimethylsilane with (4-bromobutoxy)(tert-butyl)dimethylsilane. LCMS observed *m/z* = 312.8 $[M+H]^+$.

Intermediate BP

Synthesis of (2-(trifluoromethyl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)methanamine

Intermediate BP

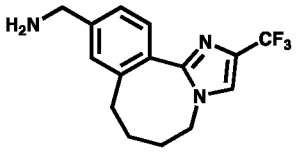


The title compound was prepared using a similar procedure as Intermediate BN, replacing (3-bromopropoxy)(tert-butyl)dimethylsilane with (4-bromoethoxy)(tert-butyl)dimethylsilane. LCMS observed *m/z* = 284.3 $[M+H]^+$.

Intermediate BQ

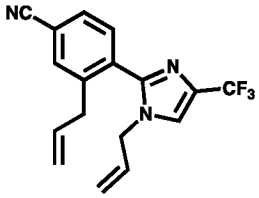
Synthesis of (2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methanamine

Intermediate BQ



Step 1: Preparation of 3-allyl-4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile.

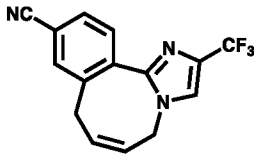
Intermediate BQ.1



A stirred solution of 4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-bromobenzonitrile (1.5 g, 4.21 mmol, Intermediate BH.2) in 1,4-dioxane (15 mL) and water (1 mL) was prepared. Allylboronic acid (1.80 g, 21.05 mmol) and potassium phosphate (2.23 g, 10.52 mmol) were added, and the reaction was purged with nitrogen gas for 30 minutes. Next, XPhos Pd G3 (0.17 g, 0.21 mmol) and CataCXium A (0.075 g, 0.21 mmol) were added. The reaction mixture was stirred at 70 °C for 4 hours. Upon completion, the reaction mixture was diluted with water (15 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 15%–20% EtOAc in petroleum ether) to afford 3-allyl-4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (0.8 g) as a pale brown liquid. LCMS observed *m/z* = 318.0 $[M+H]^+$.

Step 2: Preparation of (Z)-2-(trifluoromethyl)-5,8-dihydrobenzo[c]imidazo[1,2-a]azocine-10-carbonitrile

Intermediate BQ.2

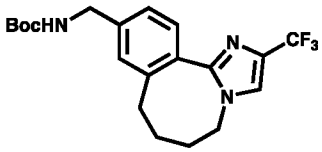


A stirred solution of 3-allyl-4-(1-allyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzonitrile (0.8 g, 2.52 mmol) in DCE (25 mL) was prepared, and 1,3-dimesitylimidazolidin-2-ylidene)(2-isopropoxybenzylidene)ruthenium(VI) chloride (0.31

g, 0.50 mmol) was added under a nitrogen atmosphere. The resulting reaction mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was filtered through celite, and the filtrate was concentrated under reduced pressure to afford the crude product (0.2 g). The crude product was used directly in the next step without further purification. LCMS observed *m/z* = 289.9 $[M+H]^+$.

Step 3: Preparation of tert-butyl ((2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methyl)carbamate

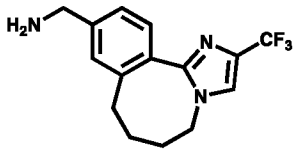
Intermediate BQ.3



A stirred solution of 2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocine-10-carbonitrile (0.2 g, 0.68 mmol) in MeOH (3 mL) and THF (3 mL) was cooled to 0 °C, and nickel(II) chloride hexahydrate (0.016 g, 0.06 mmol) was added. $NaBH_4$ (0.10 g, 2.74 mmol) was then added portion-wise, and the reaction mixture was allowed to stir at room temperature for 1 hour. Upon completion, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the crude product (0.12 g). The crude product was used directly in the next step without further purification. LCMS observed *m/z* = 396.1 $[M+H]^+$.

Step 4: Preparation of (2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methanamine

Intermediate BQ

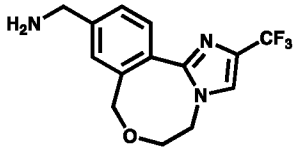


A stirred solution of tert-butyl ((2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methyl)carbamate (0.12 g, 0.30 mmol) in dichloromethane (3 mL) was cooled to 0 °C, and TFA (1.5 mL) was added. The reaction mixture was allowed to stir at room temperature for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with diethyl ether (50 mL) to afford (2-(trifluoromethyl)-5, 6, 7, 8-tetrahydrobenzo[c]imidazo [1, 2-a] azocin-10-yl) methanamine (0.075 g) as a pale brown gum. LCMS observed *m/z* = 296.2 $[M+H]^+$.

Intermediate BR

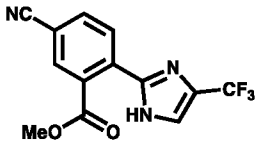
Synthesis of (2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methanamine

Intermediate BR



Step 1: Preparation of methyl 5-cyano-2-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate

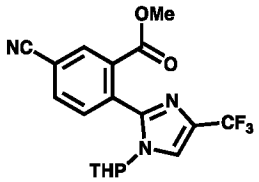
Intermediate BR.1



To the stirred solution of 3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (3 g, 9.49 mmol) in MeOH (30 mL) was added N,N-diisopropylethylamine (4.93 mL, 28.47 mmol) purged with nitrogen gas for 20 min. [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II).dichloromethane (0.69 g, 0.95 mmol) was added and the reaction vessel (steel bomb) was filled with CO gas (120 psi) and stirred at 70 °C for 6 h. After completion, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica & EtOAc: petroleum ether =3:7) to afford methyl 5-cyano-2-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate (1.2 g) as yellow gum. LCMS observed *m/z* = 296.1 $[M+H]^+$.

Step 2: Preparation of methyl 5-cyano-2-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate

Intermediate BR.2

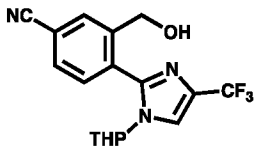


To a solution of methyl 5-cyano-2-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate (3 g, 10.16 mmol) in toluene (30 mL), p-toluenesulfonic acid monohydrate (0.38 g, 2.03 mmol) followed by 3,4-dihydropyran (1.79 mL, 20.32 mmol) were added at room temperature and the reaction mixture was stirred at 80 °C for 12 h. Upon completion, the

reaction mixture was concentrated under reduced pressure, diluted with water (60 mL), and extracted with EtOAc (3 x 60 mL). The combined organic layer was washed with brine (80 mL), dried over Anhydrous sodium sulfate, filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel & EtOAc: petroleum ether = 2:8) to afford methyl 5-cyano-2-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate (2 g) as a yellow gum. LCMS observed *m/z* = 380.4 $[M+H]^+$.

Step 3: Preparation of 3-(hydroxymethyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

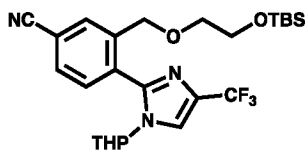
Intermediate BR.3



To a stirred solution of methyl 5-cyano-2-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzoate (2.5 g, 6.59 mmol) in tetrahydrofuran (25 mL), MeOH (25 mL) was added $NaBH_4$ (0.997 g, 26.36 mmol) at 0 °C. The reaction mixture was stirred at 50 °C for 6 h. On completion, the reaction mixture was diluted with ice cold water (50 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica-gel) using 40% EtOAc in petroleum ether as an eluent to afford 3-(hydroxymethyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (2.3 g) as a pale yellow gum. LCMS observed *m/z* = 352.4 $[M+H]^+$.

Step 4: Preparation of 3-((2-((tert-butyldimethylsilyl)oxy)ethoxy)methyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

Intermediate BR.4

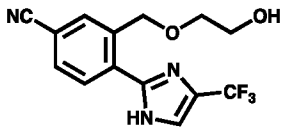


To a stirred solution of 3-(hydroxymethyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (450 mg, 1.28 mmol) in THF (5 mL), was added sodium hydride (60%, dispersion in paraffin liquid) (0.12 g, 5.12 mmol) at 0°C. After 10 min (2-bromoethoxy)(tert-butyl)dimethylsilane (0.36 mL, 2.56 mmol) was added at 0 °C and the reaction mixture was stirred at 50 °C for 12 h. On completion, the reaction

mixture was diluted with ice cold water (80 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica-gel) using 20% EtOAc in petroleum ether as an eluent to afford 3-((2-((tert-butyldimethylsilyl)oxy)ethoxy)methyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (0.4 g, 13.79%) as a pale yellow gum. LCMS observed *m/z* = 510.6 $[M+H]^+$.

Step 5: Preparation of 3-((2-hydroxyethoxy)methyl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

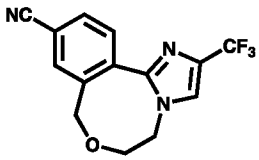
Intermediate BR.5



To a stirred solution of 3-((2-((tert-butyldimethylsilyl)oxy)ethoxy)methyl)-4-(1-(tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (2.0 g, 3.92 mmol) in dichloromethane (10 mL) was added TFA (4.0 mL) at 0°C and allowed to stirred at 25 °C for 4 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with pentane (20 mL) and diethyl ether (20 mL) to afford 3-((2-hydroxyethoxy)methyl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (1.0 g) as a yellow gum. LCMS observed *m/z* = 312.1 $[M+H]^+$.

Step 6: Preparation of 2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocine-10-carbonitrile

Intermediate BR.6

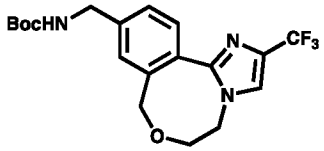


To a stirred solution of 3-((2-hydroxyethoxy)methyl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (1.3 g, 4.17 mmol) in toluene (20 mL) was added 2-(tributyl-l5-phosphaneylidene)acetonitrile (1.16 g, 4.82 mmol) at 25°C and allowed to stirred at 100 °C for 6 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure, diluted with ice cold water (60 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product

was purified by flash chromatography (Davisil silica-gel) using 20% EtOAc in petroleum ether as an eluent to afford 2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocine-10-carbonitrile (0.5 g) as a brown gum. LCMS observed *m/z* = 294.3 $[M+H]^+$.

Step 7: Preparation of tert-butyl ((2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methyl)carbamate

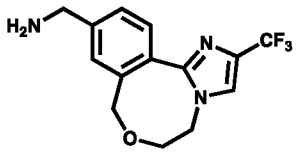
Intermediate BR.7



To the stirred solution of 2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocine-10-carbonitrile (0.5 g, 1.71 mmol) in EtOAc (50 mL) and Methanol (50 mL) was added di-tert-butyl dicarbonate (0.78 mL, 3.41 mmol) followed by palladium 10% on carbon (wetted with ca. 55% Water) (0.5 g) at 25 °C. The resulting reaction mixture was stirred at 25 °C under H_2 gas (80 psi) for 16 h. After completion, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica & EtOAc: petroleum ether =3:7) to afford tert-butyl ((2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methyl)carbamate (0.5 g) as a pale brown solid. LCMS observed *m/z* = 398.5 $[M+H]^+$.

Step 8: Preparation of (2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methanamine

Intermediate BR

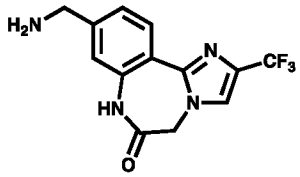


To a stirred solution of tert-butyl ((2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methyl)carbamate (0.230 g, 0.579 mmol) in dichloromethane (5 mL) was added TFA (0.5 mL) at 0 °C and allowed to stirred at 25 °C for 4 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with pentane (10 mL) and diethyl ether (10 mL) to afford (2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methanamine (0.2 g) as a colorless liquid. LCMS observed *m/z* = 298.5 $[M+H]^+$.

Intermediate BS

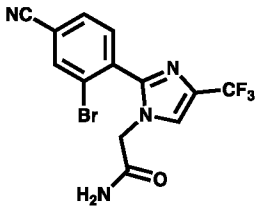
Synthesis of 9-(aminomethyl)-2-(trifluoromethyl)-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-6(7H)-one.

Intermediate BS



Step 1: Preparation of 2-(2-(2-bromo-4-cyanophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamide

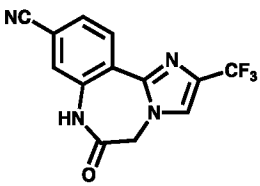
Intermediate BS.1



To a stirred solution of 3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (2 g, 6.33 mmol) in DMF (20 mL), was added Cs_2CO_3 (6.19 g, 18.98 mmol) at 0 °C. The reaction mixture was stirred for 30 minutes, after which 2-bromoacetamide (1.75 g, 12.6 mmol) was added. The mixture was then stirred at room temperature for 2 hours. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel 35–40% EtOAc in petroleum ether) to afford 2-(2-(2-bromo-4-cyanophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamide (1.8 g) as a pale yellow solid. LCMS observed m/z = 373.2 $[M+H]^+$.

Step 2: Preparation of 6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepine-9-carbonitrile.

Intermediate BS.2

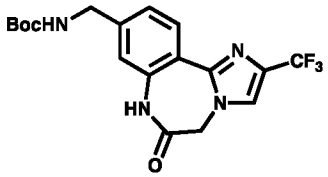


To a stirred solution of 2-(2-(2-bromo-4-cyanophenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamide (1.8 g, 4.82 mmol) in N,N-Dimethylformamide (20 mL) was added copper iodide (2.756 g, 14.47 mmol), Cs_2CO_3 (0.157 g, 0.48 mmol), and trans-N,N'-Dimethylcyclohexane-1,2-diamine (3.81 mL, 24.12 mmol). The reaction mixture was

heated at 100 °C for 16 hours. Upon completion, the mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 40–45% EtOAc in petroleum ether) to afford 6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepine-9-carbonitrile (0.3 g) as a brown gum. LCMS observed *m/z* = 293.2 $[M+H]^+$.

Step 3: Preparation of tert-butyl ((6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-9-yl)methyl)carbamate

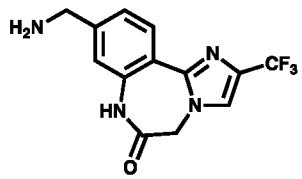
Intermediate BS.3



To a stirred solution of 6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepine-9-carbonitrile (0.3 g, 1.03 mmol) in a mixture of EtOAc (25 mL) and MeOH (25 mL), palladium on carbon (10%, wetted with approximately 55% water) (0.33 g, 3.08 mmol) and di-tert-butyl dicarbonate (0.71 mL, 3.08 mmol) were added. The reaction mixture was stirred at room temperature in a parr shaker under a hydrogen atmosphere (80 psi) for 16 hours. Upon completion, the mixture was filtered through a celite pad and washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to afford tert-butyl ((6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-9-yl)methyl)carbamate (0.2 g) as a yellow gum. LCMS observed *m/z* = 397.3 $[M+H]^+$.

Step 4: Preparation of 9-(aminomethyl)-2-(trifluoromethyl)-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-6(7H)-one

Intermediate BS



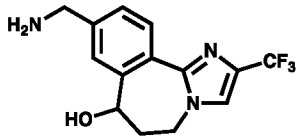
To a stirred solution of tert-butyl ((6-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-9-yl)methy (0.2 g, 0.51 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.155 mL, 2.02 mmol) at 0 °C and stirred at rt for 2 h. On completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with diethyl ether and dried to afford 9-

(aminomethyl)-2-(trifluoromethyl)-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-6(7H)-one (0.14 g) as a pale brown solid. LCMS observed *m/z* = 297.1 $[M+H]^+$.

Intermediate BT

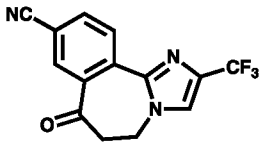
Synthesis of 9-(aminomethyl)-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-7-ol

Intermediate BT



Step 1: Preparation of 7-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile

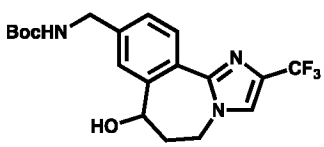
Intermediate BT.1



To a stirred solution of 2-(trifluoromethyl)-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile (Intermediate BH.4) (2.0 g, 7.27 mmol) in ethanol (100 mL) under an oxygen atmosphere, anhydrous iron(III) chloride (2.36 g, 14.53 mmol) was added, followed by phenylsilane (1.79 mL, 14.5 mmol) at 25°C. The reaction mixture was stirred at 25 °C for 16 hours. Upon completion, the reaction mixture was quenched with cold water (100 mL) and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 25–30% EtOAc in petroleum ether) to afford 7-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile (1.1 g) as a pale brown solid. LCMS observed *m/z* = 292.2 $[M+H]^+$.

Step 2: Preparation of tert-butyl ((7-hydroxy-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)carbamate

Intermediate BT.2

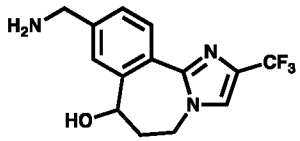


A solution of 7-oxo-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepine-9-carbonitrile (1.3 g, 4.46 mmol) in a mixture of EtOAc (150 mL) and MeOH

(150 mL) was stirred, and di-tert-butyl dicarbonate (2.05 mL, 8.93 mmol) was added, followed by 10% palladium on carbon (wet with approximately 55% water; 1.5 g). The reaction mixture was stirred under hydrogen gas pressure (80 psi) in a Paar shaker at room temperature for 16 hours. Upon completion, the reaction mixture was filtered through a celite bed, which was then washed with THF (100 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 75–80% EtOAc in petroleum ether) to afford tert-butyl ((7-hydroxy-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)carbamate (0.80 g) as an off-white solid. LCMS observed *m/z* = 398.3 $[M+H]^+$.

Step 3: Preparation of 9-(aminomethyl)-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-7-ol

Intermediate BT

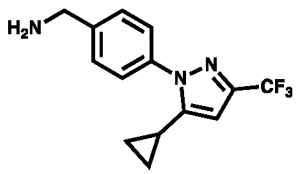


To a stirred solution of tert-butyl ((7-hydroxy-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)carbamate (500 mg, 1.26 mmol) in dichloromethane (15 mL), trifluoroacetic acid (2.0 mL) was added at 0 °C. The reaction mixture was stirred at 25 °C for 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure and triturated with pentane (2 × 5 mL). The resulting solid was dried under vacuum to afford 9-(aminomethyl)-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-7-ol (350 mg) as a pale brown gummy substance. LCMS observed *m/z* = 298.2 $[M+H]^+$.

Intermediate BU

Synthesis of (4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate BU



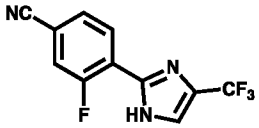
The title compound was prepared using a similar procedure as Intermediate BF, replacing 5-bromo-3-(trifluoromethyl)-1H-pyrazole with 5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58-7.54 (m, 4H), 6.61

(s, 1H), 3.81 (s, 2H), 2.03 (br s, 2H), 1.83-1.79 (m, 1H), 0.98-0.94 (m, 2H), 0.84-0.83 (m, 2H), LCMS observed *m/z* 282.2 $[M+H]^+$.

Intermediate BV

Synthesis of 3-fluoro-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

Intermediate BV

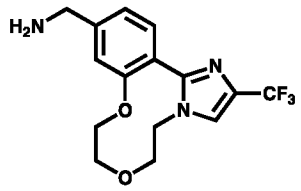


The title compound was prepared using a similar procedure as Intermediate BH.1, replacing 3-bromo-4-formylbenzonitrile with 3-fluoro-4-formylbenzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58-7.54 (m, 4H), 6.61 (s, 1H), 3.81 (s, 2H), 2.03 (br s, 2H), 1.83-1.79 (m, 1H), 0.98-0.94 (m, 2H), 0.84-0.83 (m, 2H), LCMS observed *m/z* 256.9 $[M+H]^+$.

Intermediate BW

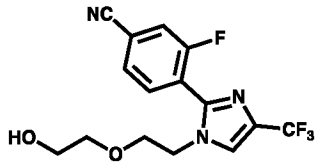
Synthesis of (2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methanamine

Intermediate BW



Step 1: Preparation of 3-fluoro-4-(1-(2-(2-hydroxyethoxy)ethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

Intermediate BW.1

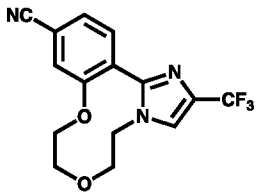


To a stirred solution of 3-fluoro-4-(4-(trifluoromethyl)-1H-imidazol-2-yl) benzonitrile (Intermediate BV) (1 g, 3.91 mmol) in DMF (10 mL) was added Cs_2CO_3 (2.55 g, 7.83 mmol) followed by (2-(2-bromoethoxy) ethoxy) (tert-butyl) dimethylsilane (2.2 g, 7.8 mmol) at 25 °C. The reaction mixture was stirred at 100 °C for 16 hours. Upon completion, the reaction mixture was diluted with ice water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (50 mL × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (30–50% EtOAc/petroleum ether eluent) to

afford 3-fluoro-4-(1-(2-(2-hydroxyethoxy)ethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (1.1 g) as a pale yellow gum. LCMS observed *m/z* = 344.0 $[M+H]^+$.

Step 2: Preparation of 2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecine-12-carbonitrile

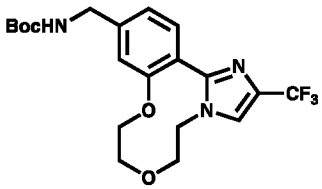
Intermediate BW.2



To a stirred solution of 3-fluoro-4-(1-(2-(2-hydroxyethoxy)ethyl)-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzonitrile (0.9 g, 2.62 mmol) in DMF (9 mL) was added Cs_2CO_3 (1.7 g, 5.24 mmol) and the reaction was heated at 100 °C for 6 h. Upon completion, the reaction mixture was diluted with water (100 mL) and product was precipitated out. The mixture was filtered, washed with cold water (25 mL), and dried to afford 2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecine-12-carbonitrile (0.57 g) as white solid. LCMS observed *m/z* = 324.1 $[M+H]^+$.

Step 3: Preparation of tert-butyl ((2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methyl)carbamate

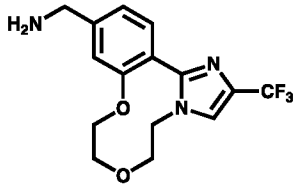
Intermediate BW.3



In a Parr shaker, a stirred solution of 2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecine-12-carbonitrile (0.5 g, 1.54 mmol) in MeOH (10 mL) and EtOAc (10 mL) was combined with Boc-anhydride (2.02 g, 9.28 mmol), followed by 10% palladium on carbon (50% wet basis, 0.5 g). The reaction mixture was stirred at room temperature under H_2 gas (80 psi) for 16 hours. Upon completion, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 30–35% EtOAc in petroleum ether) to afford tert-butyl ((2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[b]imidazo[2,1-d][1,5]oxazonin-11-yl)methyl)carbamate (0.5 g, 75.63%) as a white solid. LCMS observed *m/z* = 428.1 $[M+H]^+$.

Step 4: Preparation of (2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methanamine

Intermediate BW

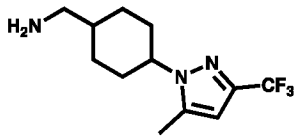


To a stirred solution of tert-butyl ((2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methyl)carbamate (0.5 g, 1.17 mmol) in dichloromethane (10 mL) at 0 °C under an argon atmosphere, TFA (3 mL) was added. The reaction mixture was stirred at 0 °C for 1 hour. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with diethyl ether (2 × 20 mL) to afford (2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methanamine (0.38 g) as a white solid. LCMS observed *m/z* = 328.2 $[M+H]^+$.

Intermediate BX

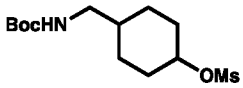
Synthesis of (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanamine

Intermediate BX



Step 1: Preparation of 4-(((tert-butoxycarbonyl)amino)methyl)cyclohexyl methanesulfonate

Intermediate BX.1

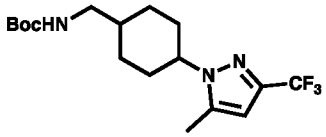


To a stirred solution of tert-butyl ((4-hydroxycyclohexyl)methyl)carbamate (0.2 g, 0.87 mmol) in dichloromethane (5 mL) was added Triethylamine (0.269 mL, 2.00 mmol) followed by Methane sulfonyl chloride (0.078 mL, 0.95 mmol) at 0 °C and reaction mixture was allowed stir at room temperature for 1 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 4-(((tert-

butoxycarbonyl)amino)methyl)cyclohexyl methane sulfonate) (0.2 g, 74.60 %) as a semi solid. LCMS observed *m/z* = 308.2 $[M+H]^+$.

Step 2: Preparation of tert-butyl ((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)carbamate

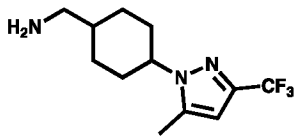
Intermediate BX.2



To a stirred solution of 5-methyl-3-(trifluoromethyl)-1H-pyrazole (1 g, 6.66 mmol) in DMF (10 mL) were added Cs_2CO_3 (6.512 g, 19.98 mmol) followed by 4-(((tert-butoxycarbonyl)amino)methyl)cyclohexyl methanesulfonate (3.072 g, 9.99 mmol) at 0 °C and reaction was allowed to stir at 80 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was cooled, diluted with water (500 mL) and extracted with EtOAc (300 mL x 3). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica-gel, 20 % EtOAc in petroleum ether) to afford tert-butyl ((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)carbamate (0.8 g, 33.23%) as a pale yellow liquid. LCMS observed *m/z* = 362.1 $[M+H]^+$.

Step 3: Preparation of (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanamine

Intermediate BX

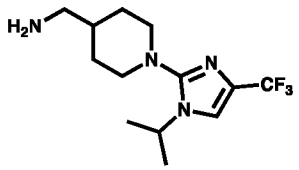


To a stirred solution of tert-butyl ((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)carbamate (0.8 g, 2.21 mmol) in dichloromethane (10 mL) was added TFA (2 mL) at 0 °C and reaction mixture was stirred the at room temperature for 2 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was triturated with diethyl ether (20 mL) to afford (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanamine (0.8 g) as a semi solid. LCMS observed *m/z* = 262.6 $[M+H]^+$.

Intermediate BY

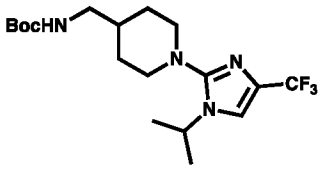
Synthesis of (1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methanamine

Intermediate BY



Step 1: Preparation of tert-butyl ((1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methyl)carbamate

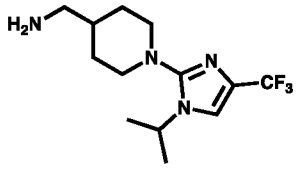
Intermediate BY.1



A solution of tert-butyl (piperidin-4-ylmethyl)carbamate (2.0 g, 9.33 mmol) and 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (2.98 g, 14.0 mmol) in N,N-diisopropylethylamine (20.0 mL) was stirred at 140 °C for 4 days. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 25–30% EtOAc in petroleum ether) to afford tert-butyl ((1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methyl)carbamate (0.3 g, 8% yield) as a pale brown gum. LCMS observed *m/z* = 391.7 $[M+H]^+$.

Step 2: Preparation of (1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methanamine

Intermediate BY



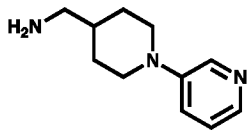
To a stirred solution of tert-butyl ((1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methyl)carbamate (0.3 g, 0.77 mmol) in dichloromethane (10 mL), trifluoroacetic acid (2.0 mL) was added at 0 °C. The reaction mixture was then stirred from 0 °C to 25 °C for 2 hours. Upon completion, the mixture was concentrated under reduced pressure and triturated with pentane (2 × 10 mL). The resulting product was concentrated again under reduced pressure to afford (1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-

yl)piperidin-4-yl)methanamine (0.22 g) as a pale brown gum. LCMS observed *m/z* = 291.7 $[M+H]^+$.

Intermediate BZ

Synthesis of (1-(pyridin-3-yl)piperidin-4-yl)methanamine

Intermediate BZ

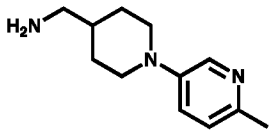


The title compound was prepared using a similar procedure as Intermediate BY, replacing 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 3-bromopyridine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (d, *J* = 2.8 Hz, 1H), 8.17 (d, *J* = 5.2 Hz, 1H), 8.07 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.85-7.78 (m, 3H), 3.98 (d, *J* = 13.2 Hz, 2H), 2.92 (t, *J* = 11.8 Hz, 2H), 2.77 (t, *J* = 6.0 Hz, 2H), 1.84-1.82 (m, 3H), 1.27-1.25 (m, 2H), LCMS observed *m/z* 192.1 $[M+H]^+$.

Intermediate CA

Synthesis of (1-(6-methylpyridin-3-yl)piperidin-4-yl)methanamine

Intermediate CA

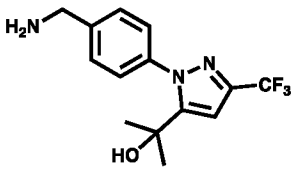


The title compound was prepared using a similar procedure as Intermediate BY, replacing 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 5-bromo-2-methylpyridine. LCMS observed *m/z* 206.4 $[M+H]^+$.

Intermediate CB

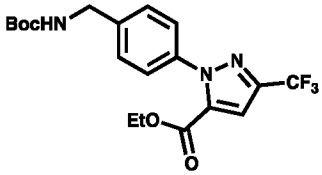
Synthesis of 2-(1-(4-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)propan-2-ol

Intermediate CB



Step 1: Preparation of ethyl 1-(4-(((tert-butoxycarbonyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate

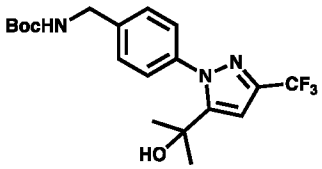
Intermediate CB.1



To a stirred solution of ethyl 3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (5.0 g, 24.0 mmol) in acetonitrile (80.0 mL), 4-(((tert-butoxycarbonyl)amino)methyl)phenyl boronic acid (6.03 g, 24.0 mmol) and pyridine (5.70 g, 72.0 mmol) were added, and the mixture was purged with oxygen gas. Copper(II) acetate (0.873 g, 4.80 mmol) was then added, and the reaction was stirred for 24 hours at 60 °C. Upon completion, the reaction mixture was concentrated under reduced pressure and extracted with EtOAc (2 × 250 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica, 25–30% EtOAc in petroleum ether) to afford ethyl 1-(4-(((tert-butoxycarbonyl) amino) methyl) phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (7.00 g). LCMS observed m/z = 358.3 $[M–C_4H_9+H]^+$.

Step 2: Preparation of tert-butyl (4-(5-(2-hydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)carbamate

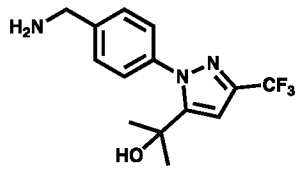
Intermediate CB.2



To a stirred solution of ethyl 1-(4-(((tert-butoxycarbonyl) amino) methyl) phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (6.0 g, 41.3 mmol) in tetrahydrofuran (80.0 mL), was added methylmagnesium bromide (1.4 M, 103 mL, 145 mmol) dropwise at -78 °C. The reaction mixture was stirred for 8 hours at -20 °C. Upon completion, the reaction was quenched with saturated ammonium chloride solution (150 mL) and extracted with EtOAc (2 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 20–25% EtOAc in petroleum ether) to afford ethyl 1-(4-(((tert-butoxycarbonyl) amino) methyl) phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (3.00 g). LCMS observed m/z = 400.3 $[M+H]^+$.

Step 3: Preparation of 2-(1-(4-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)propan-2-ol

Intermediate CB

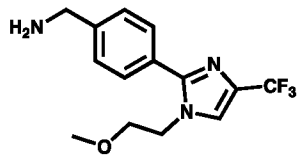


To a stirred solution of tert-butyl (4-(5-(2-hydroxypropan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl) benzyl) carbamate (3.3 g, 8.26 mmol) in dichloromethane (20 mL), was added trifluoroacetic acid (5 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 2 hours. Upon completion, the mixture was evaporated and diluted with cold water (50 mL), then extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), and dried over anhydrous sodium sulfate, then filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 8–10% MeOH in dichloromethane) to afford 2-(1-(4-(aminomethyl) phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl) propan-2-ol (1.5 g). LCMS observed *m/z* = 300.3 $[M+H]^+$.

Intermediate CC

Synthesis of (4-(1-(2-methoxyethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CC

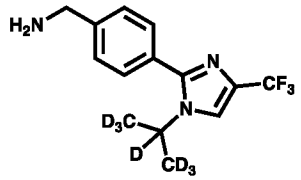


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 1-iodo-2-methylpropane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 300.2 $[M+H]^+$.

Intermediate CD

Synthesis of (4-(1-(propan-2-yl-d7)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CD

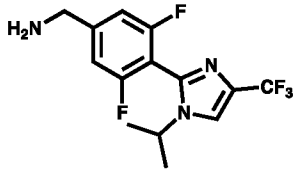


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 2-iodopropane-1,1,1,2,3,3,3-d_7 and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 291.2 $[M+H]^+$

Intermediate CE

Synthesis of (3,5-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CE

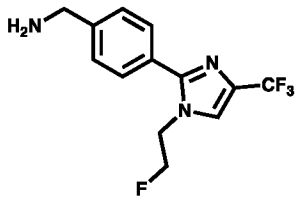


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 3,5-difluoro-4-formylbenzonitrile, methyl iodide with 2-iodopropane, and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 320.1 $[M+H]^+$.

Intermediate CF

Synthesis of (4-(1-(2-fluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CF

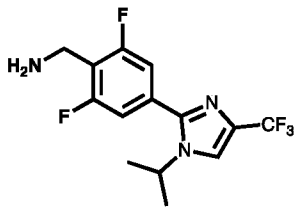


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 1-fluoro-2-iodoethane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 288.2 $[M+H]^+$.

Intermediate CG

Synthesis of (2,6-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CG



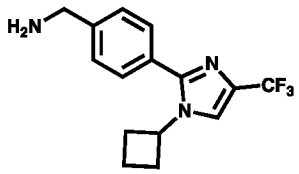
The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 2,6-difluoro-4-formylbenzonitrile, methyl iodide with

2-iodopropane, and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 320.1 $[M+H]^+$.

Intermediate CH

Synthesis of (4-(1-cyclobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CH

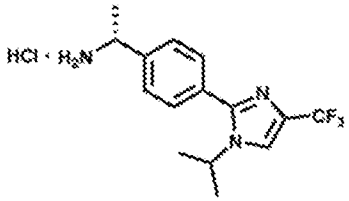


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with bromocyclobutane and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 296.2 $[M+H]^+$.

Intermediate CI

Step 1: Preparation of *tert*-butyl (*R*)-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethyl)carbamate–HCl.

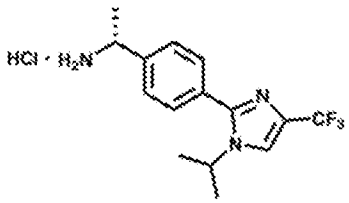
Intermediate CI.1



To a stirred solution of 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (1.5 g, 5.83 mmol, Intermediate P.2) in 1,4-dioxane (15 mL) and water (3 mL) was added (R)-(4-(1-((tert-butoxycarbonyl)amino)ethyl)phenyl)boronic acid (1.70 g, 6.41 mmol) followed by potassium phosphate (0.20 g, 0.97 mmol) and the mixture was purged with nitrogen gas for 30 min. XPhosPdG3 (0.033 g, 0.03 mmol) was added and reaction mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted with water (25 mL) and the product was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (20-25% ethyl acetate/petroleum ether eluent) to afford tert-butyl (R)-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)carbamate (1.5 g, 64 %) as an off-white solid. LCMS observed *m/z* = 398.4 $[M+H]^+$.

Step 2: Preparation of (*R*)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine–HCl.

Intermediate CI

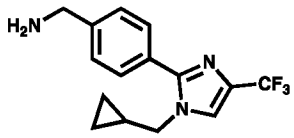


To a stirred solution of tert-butyl (R)-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)carbamate (1 g, 2.51 mmol) in DCM (10 mL) was added hydrogen chloride (3.14 mL, 4.0 M in 1,4-dioxane 12.58 mmol) at 0 °C and reaction mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to afford crude product. The crude was triturated with diethyl ether (25.0 mL) and n-pentane (25.0 mL) to afford (R)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethan-1-amine (0.8 g, 95%) as a pale brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (br s, 3H), 8.21 – 8.21 (m, 1H), 7.67 – 7.63 (m, 4H), 4.52 – 4.42 (m, 2H), 1.55 (d, J = 6.8 Hz, 3H), 1.42 (d, J = 6.8 Hz, 6H). LCMS observed m/z = 298.4 $[M+H]^+$.

Intermediate CJ

Synthesis of (4-(1-(cyclopropylmethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CJ

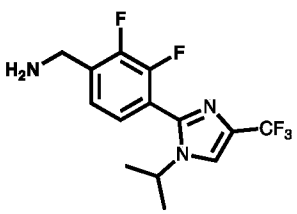


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with (bromomethyl)cyclopropane and using general procedure C to reduce the nitrile. LCMS observed m/z = 296.1 $[M+H]^+$.

Intermediate CK

Synthesis of (2,3-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CK

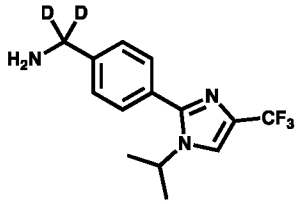


The title compound was prepared using a similar procedure as Intermediate A, replacing 4-formylbenzonitrile with 2,3-difluoro-4-formylbenzonitrile and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 320.1 $[M+H]^+$.

Intermediate CL

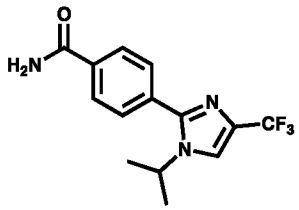
Synthesis of (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methan-d2-amine

Intermediate CL



Step 1: Preparation of 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzamide

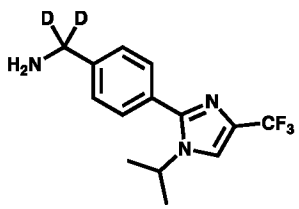
Intermediate CL.1



To a stirred solution of methyl 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzoate (10.0 g, 32.0 mmol) in MeOH (200 mL), was added saturated aqueous ammonia (200 mL) at 25 °C, and the reaction mixture was stirred for 16 hours at this temperature. Upon completion, the mixture was concentrated under reduced pressure and extracted with EtOAc (2 × 250 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was triturated with diethyl ether (25 mL) to afford 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzamide (6.5 g) as an off-white solid. The crude material was then forwarded to the next step without further purification. LCMS observed *m/z* = 298.2 $[M+H]^+$.

Step 2: Preparation of (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methan-d2-amine

Intermediate CL

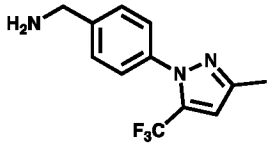


The title compound was prepared using a similar procedure to Intermediate BA, replacing 4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl) benzonitrile with 4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzamide and using $LiAlD_4$ to reduce the carboxamide. LCMS observed *m/z* = 286.4 $[M+H]^+$.

Intermediate CM

Synthesis of (4-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

Intermediate CM

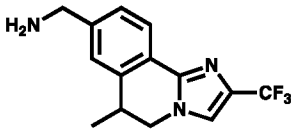


The title compound was prepared using a similar procedure as Intermediate X, replacing 4,4,4-trifluoro-3-oxobutanoate with 1,1,1-trifluoropentane-2,4-dione and using general procedure E to reduce the nitrile. LCMS observed *m/z* = 256.3 $[M+H]^+$.

Intermediate CN

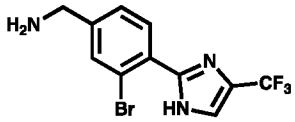
Synthesis of (6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine

Intermediate CN



Step 1: Preparation of (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CN.1

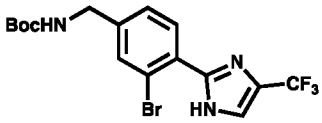


A stirred solution of 3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (Intermediate BH.1) (3 g, 9.4 mmol) in THF (25 mL) was cooled to 0 °C, and Borane-DMS (5 mL) was added. The reaction mixture was then allowed to stir at room temperature for 16 hours. Upon completion, the reaction was quenched with water (100 mL) and extracted with EtOAc (2 × 200 mL). The combined organic layers were washed with ice-cold water (100 mL) and saturated sodium bicarbonate solution (100 mL), then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The resultant residue was washed with pentane and diethyl ether before being concentrated under

reduced pressure to afford (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (2.5 g) as a brown solid. LCMS observed *m/z* = 320.2 $[M+H]^+$.

Step 2: Preparation of tert-butyl (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate

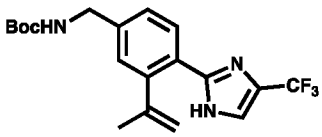
Intermediate CN.2



A stirred solution of (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (2 g, 6.2 mmol) in dichloromethane (20 mL) was cooled to 0 °C, and N,N-diisopropylethylamine (2.4 g, 18.7 mmol), 4-(dimethylamino)pyridine (0.076 g, 0.625 mmol), and di-tert-butyl dicarbonate (2.7 g, 12.4 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 16 hours. Upon completion, the reaction was diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with ice-cold water (100 mL) and brine (100 mL), then dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 30–50% EtOAc in petroleum ether) to afford tert-butyl (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (1.5 g) as a white solid. LCMS observed *m/z* = 420.4 $[M+H]^+$.

Step 3: Preparation of tert-butyl (3-(prop-1-en-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate

Intermediate CN.3

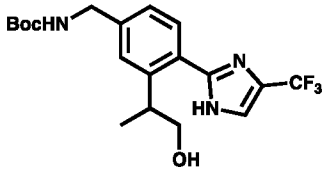


To a stirred solution of tert-butyl (3-bromo-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (1.5 g, 3.5 mmol) and potassium trifluoro(prop-1-en-2-yl)borate (2.6 g, 17.8 mmol) in 1,4-dioxane (20 mL) and water (5 mL), was added K_3PO_4 (2.273 g, 10.708 mmol), and the reaction mixture was purged with argon gas for 15 minutes. XPhosPd(G2) (0.2 g, 0.35 mmol) was introduced, and the reaction mixture was stirred at 70 °C for 2 hours. Upon completion, the reaction was diluted with water (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash

chromatography (silica gel, 70% EtOAc in petroleum ether) to afford tert-butyl (3-(prop-1-en-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (1.5 g) as an off-white solid. LCMS observed *m/z* = 382.5 $[M+H]^+$.

Step 4: Preparation of tert-butyl (3-(1-hydroxypropan-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate

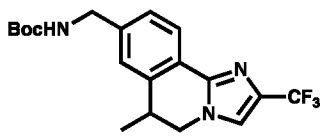
Intermediate CN.4



A stirred solution of tert-butyl (3-(prop-1-en-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (1 g, 2.6 mmol) in THF (10 mL) was cooled to 0 °C, and 1 M borane in THF (10 mL, 7.86 mmol) was added. The reaction mixture was stirred at 0 °C for 1 hour. After 1 hour, hydrogen peroxide (35% in water) (0.76 mL, 7.8 mmol) was added, followed by potassium carbonate (0.725 g, 5.24 mmol), and the mixture was stirred at room temperature for 1 hour. Upon completion, the reaction was quenched with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 70% EtOAc in petroleum ether) to afford tert-butyl (3-(1-hydroxypropan-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (0.8 g) as an off-white solid. LCMS observed *m/z* = 400.4 $[M+H]^+$.

Step 5: Preparation of tert-butyl ((6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methyl)carbamate

Intermediate CN.5

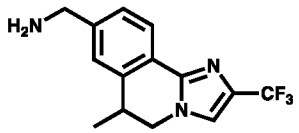


A stirred solution of tert-butyl (3-(1-hydroxypropan-2-yl)-4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (0.8 g, 2.0 mmol) in toluene (10 mL) was heated to 100 °C, and 2-(tributylphosphoranylidene)acetonitrile (1.2 g, 5.0 mmol) was added. The reaction mixture was stirred at 100 °C for 16 hours. Upon completion, the reaction was quenched with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 70% EtOAc in petroleum ether) to afford tert-butyl ((6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-

a]isoquinolin-8-yl)methyl)carbamate (0.6 g) as an off-white solid (two inseparable regio-isomers which were carried forward and separated at the final step). LCMS observed *m/z* = 382.2 $[M+H]^+$.

Step 5: Preparation of (6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine

Intermediate CN

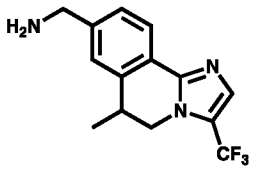


To a stirred solution of tert-butyl ((6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methyl)carbamate (0.5 g, 1.311 mmol) in dichloromethane (10 mL) was added TFA (2 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 2 hours. Upon completion, the mixture was concentrated under reduced pressure. The residue was triturated with diethyl ether to afford (6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine (0.3 g) as a white solid. LCMS observed *m/z* = 282.2 $[M+H]^+$.

Intermediate CO

Synthesis of (6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine

Intermediate CO

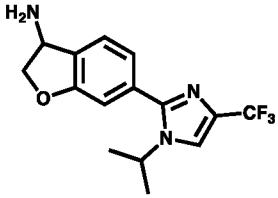


The title compound is the regioisomer that formed during the synthesis of Intermediate CN. LCMS observed *m/z* = 282.2 $[M+H]^+$.

Intermediate CP

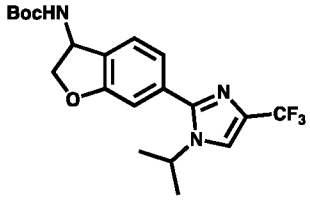
Synthesis of 6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-amine

Intermediate CP



Step 1: Preparation of tert-butyl (6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-yl)carbamate

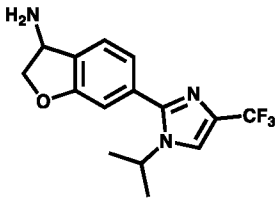
Intermediate CP.1



To a stirred solution of tert-butyl (6-bromo-2,3-dihydrobenzofuran-3-yl)carbamate (0.5 g, 1.59 mmol) in 1,4-dioxane (15 mL), bis(pinacolato)diboron (0.61 g, 2.39 mmol), 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (0.41 g, 1.59 mmol), and potassium acetate (0.312 g, 3.18 mmol) were added, and the mixture was purged with nitrogen gas for 30 minutes. XPhos Pd G2 (0.13 g, 0.16 mmol) was then added, and the reaction was stirred at 100 °C for 16 hours. Upon completion, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 5–10% EtOAc in petroleum ether) to afford tert-butyl (6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-yl)carbamate (0.15 g) as a colorless liquid. LCMS observed m/z = 412.3 $[M+H]^+$.

Step 2: Preparation of 6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-amine

Intermediate CP

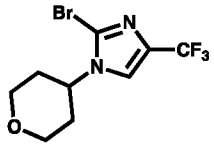


To a stirred solution of tert-butyl (6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-yl)carbamate (180 mg, 0.44 mmol) in dichloromethane (10 mL), TFA (0.5 mL) was added, and the reaction mixture was stirred at room temperature for 4 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude material was triturated with pentane (10 mL) and diethyl ether (10 mL) to afford 6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-amine (60 mg) as a colorless liquid. LCMS observed m/z = 312.3 $[M+H]^+$.

Intermediate CQ

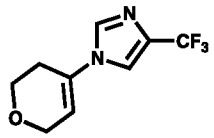
Synthesis of 2-bromo-1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole

Intermediate CQ



Step 1: Preparation of 1-(3,6-dihydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole

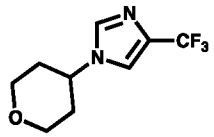
Intermediate CQ.1



To a stirred solution of 4-(trifluoromethyl)-1H-imidazole (5 g, 36.7 mmol) and (3,6-dihydro-2H-pyran-4-yl) boronic acid (7.05 g, 55.1 mmol) in 1,2-dichloroethane (50 mL) was added copper(II) acetate (7.3 g, 40.4 mmol) followed by the addition of 2,2'-bipyridine (5.73 g, 36.7 mmol) and sodium carbonate (7.78 g, 73.4 mmol) at 25° C. The reaction mixture was stirred at 70 °C for 16 h. the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was filter through celite, diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 25% EtOAc in hexanes) to afford 1-(3,6-dihydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (2.2 g) as pale-yellow liquid. LCMS observed *m/z* = 219.1 $[M+H]^+$.

Step 2: Preparation of 1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole

Intermediate CQ.2

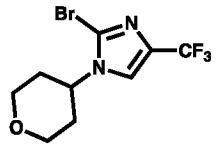


To a stirred solution of 1-(3,6-dihydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (2.2 g, 10 mmol) in EtOAc (22 mL) was added palladium hydroxide, 20% on carbon (wet) (3.11 g, 22.1 mmol) at room temperature under nitrogen atmosphere and reaction mixture was allowed to shake in parr shaker under 50 psi of hydrogen pressure at rt for 16 h. Progress of reaction was monitored by TLC and LCMS. The reaction mixture

was filtered through celite, washed with EtOAc (33 mL) and concentrated to afford crude 1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (2 g) as a white solid, which was used in next step without further purification. LCMS observed *m/z* = 220.9 $[M+H]^+$.

Step 3: Preparation of 2-bromo-1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole

Intermediate CQ

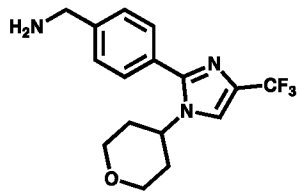


To a stirred solution of 1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (2 g, 9.08 mmol) in anhydrous tetrahydrofuran (10 mL) was added n-butyl lithium, 1.6 M in hexane (0.75 g, 11.8 mmol) dropwise at -78 °C and reaction mixture was allowed to stir 30 min as same temperature. N-bromosuccinimide (1.77 g, 9.99 mmol) in tetrahydrofuran (Dry) (10 mL) was added and reaction mixture was stirred at -78 °C for 2 h. Reaction progress was monitored by TLC, LCMS. Upon completion, the reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with EtOAc (2 × 40 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to get afford crude. The crude was purified by flash chromatography (silica gel, 25% EtOAc in hexanes) to afford 2-bromo-1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (0.85 g) as a pale brown solid. LCMS observed *m/z* = 299.2 $[M+H]^+$.

Intermediate CR

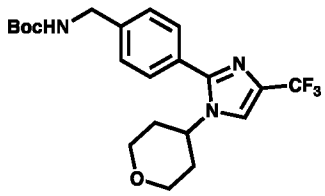
Synthesis of (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CR



Step 1: Preparation of tert-butyl (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate

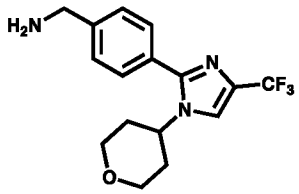
Intermediate CR.1



To a stirred solution of 2-bromo-1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazole (0.1 g, 0.33 mmol) in 1,4-dioxane (0.8 mL) and water (0.2 mL) were added (4-(((tert-butoxycarbonyl) amino) methyl)phenyl) boronic acid (0.07 g, 0.43 mmol) followed by potassium phosphate (0.21 g, 1.003 mmol) and degassed the reaction mixture with nitrogen for 10 minutes. XPhosPdG3 (0.02 g, 0.03 mmol) was added and the reaction mixture was heated at 70 °C for 16 h. The progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20–25% EtOAc in hexanes) to afford tert-butyl (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (0.085 g) as a pale yellow gum. LCMS observed *m/z* = 426.5 $[M+H]^+$.

Step 2: Preparation of (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CR

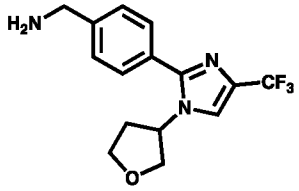


To a stirred solution of tert-butyl (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (0.085 g, 0.20 mmol) in dichloromethane (0.8 mL) was added trifluoroacetic acid (0.306 mL, 3.99 mmol) at 0° C. The reaction mixture was allowed to stir at room temperature for 2 h. The progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction mixture was concentrated under reduced pressure, diluted with saturated sodium bicarbonate (10 mL), and extracted with dichloromethane (3 × 15 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl) phenyl) methanamine as a pale-yellow solid (0.06 g) which was used in the next step without further purification. LCMS observed *m/z* = 326.2 $[M+H]^+$.

Intermediate CS

Synthesis of (4-(1-(tetrahydrofuran-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CS

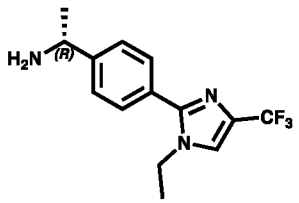


The title compound was prepared using a similar procedure as Intermediate A, replacing methyl iodide with 3-bromotetrahydrofuran and using general procedure C to reduce the nitrile. LCMS observed *m/z* = 312.0 $[M+H]^+$.

Intermediate CT

Synthesis of (R)-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethan-1-amine

Intermediate CT

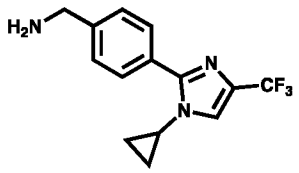


The title compound was prepared using a similar procedure as Intermediate CP, replacing 2-bromo-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 2-bromo-1-ethyl-4-(trifluoromethyl)-1H-imidazole and replacing tert-butyl (6-bromo-2,3-dihydrobenzofuran-3-yl)carbamate with (R)-(4-(1-aminoethyl)phenyl)boronic acid. LCMS observed *m/z* = 384.7 $[M+H]^+$.

Intermediate CU

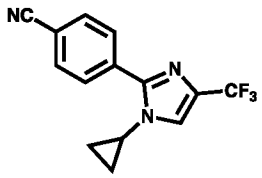
Synthesis of (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CU



Step 1: Preparation of 4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile

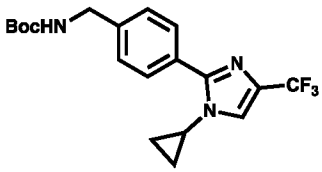
Intermediate CU.1



To a stirred solution of methyl 4-(4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (25 g, 105.403 mmol) and cyclopropylboronic acid (45.269 g, 527.015 mmol) in DCE (500 mL) under oxygen atmosphere was added Sodium carbonate (27.929 g, 263.507 mmol), 2,2'-Bipyridine (16.462 g, 105.403 mmol) followed by $Cu(OAc)_2$ (21.63 g, 119.10 mmol). The reaction mixture was stirred at 70 ° C for 24 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was diluted with water (800 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 25% EtOAc in petroleum ether) to afford methyl 4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzoate (6 g) as an off-white solid. LCMS observed m/z = 278.3 $[M+H]^+$.

Step 2: Preparation of tert-butyl (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate

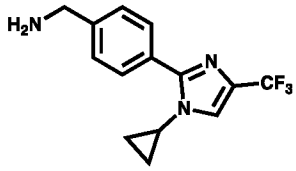
Intermediate CU.2



In a paar shaker, the stirred solution of 4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzonitrile (9 g, 32.462 mmol) in EtOAc (150 mL) and MeOH (150 mL) were added Di-tert-butyl Dicarbonate (ca. 30% in Tetrahydrofuran) (14.915 mL, 64.923 mmol) followed by Palladium 10% on carbon (wetted with ca. 55% Water) (8.636 g, 81.154 mmol) and stirred the reaction mixture at rt for 16 h under hydrogen 80 psi. The progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction was filtered through celite and concentrated under reduced pressure. The crude product was purified by flash chromatography (Davisil silica gel, 30% EtOAc in petroleum ether) to afford tert-butyl ((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)carbamate (9.0 g) as white solid. LCMS observed m/z = 382.2 $[M+H]^+$.

Step 3: Preparation of (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

Intermediate CU

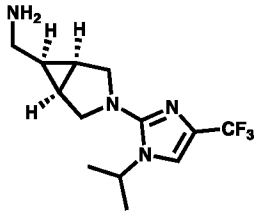


To a stirred solution of tert-butyl (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (8 g, 20.975 mmol) in dichloromethane (50 mL) was added Trifluoroacetic acid (6 mL, 209.754 mmol) at 0 °C and stirred the reaction mixture at rt for 5 h. The progress of the reaction was monitored by LCMS and TLC. The reaction mixture was concentrated under reduced pressure. The crude residue was triturated with diethyl ether and dried to afford (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) phenyl) methanamine (5 g) as off-white gum. LCMS observed *m/z* = 282.2 $[M+H]^+$.

Intermediate CV

Synthesis of ((1R,5S,6r)-3-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)methanamine

Intermediate CV

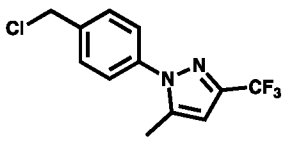


The title compound was prepared using a similar procedure as Intermediate BY, replacing tert-butyl (piperidin-4-ylmethyl)carbamate with tert-butyl (((1R,5S,6s)-3-azabicyclo[3.1.0]hexan-6-yl)methyl)carbamate. LCMS observed *m/z* = 289.2 $[M+H]^+$.

Intermediate CW

Synthesis of 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole

Intermediate CW

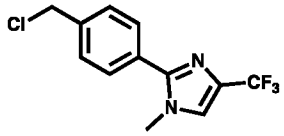


The title compound was prepared using a similar procedure as Intermediate D, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol (Intermediate BJ). LCMS observed *m/z* = 275.1 $[M+H]^+$.

Intermediate CX

Synthesis of 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole

Intermediate CX

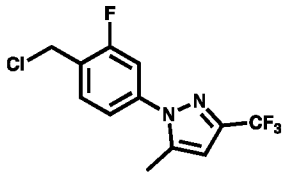


The title compound was prepared using a similar procedure as Intermediate D, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with (4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate AG). LCMS observed *m/z* = 275.1 $[M+H]^+$.

Intermediate CY

Synthesis of 1-(4-(chloromethyl)-3-fluorophenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole

Intermediate CY

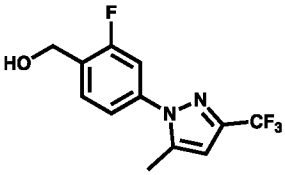


The title compound was prepared using a similar procedure as Intermediate CW, replacing (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol (Intermediate BJ) with (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol (Intermediate BK). LCMS observed *m/z* = 293.0 $[M+H]^+$.

Intermediate CZ

Synthesis of (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol

Intermediate CZ

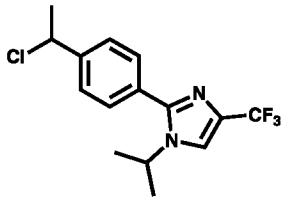


The title compound was prepared using a similar procedure as Intermediate BJ, replacing (4-(methoxycarbonyl)phenyl)boronic acid with (3-fluoro-4-(methoxycarbonyl)phenyl)boronic acid. LCMS observed *m/z* = 275.1 $[M+H]^+$.

Intermediate DA

Synthesis of 2-(4-(1-chloroethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole

Intermediate DA

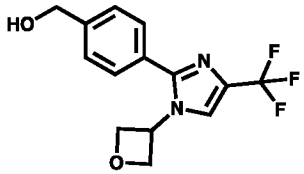


The title compound was prepared using a similar procedure as Intermediate D, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-ol (Intermediate Q). LCMS observed *m/z* = 317.1 $[M+H]^+$.

Intermediate DB

Synthesis of (4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol

Intermediate DB



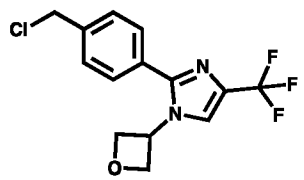
The title compound was prepared using a similar procedure as Intermediate A, replacing

4-formylbenzonitrile with methyl 4-formylbenzoate, replacing methyl iodide with 3-iodooxetane and using General Procedure C (diisobutyl aluminum hydride) to reduce the ester. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.46 (d, J = 1.2 Hz, 1H), 7.47 (q, J = 7.6 Hz, 4H), 5.56-5.49 (m, 1H), 5.32 (t, J = 5.6 Hz, 1H), 4.87 (t, J = 7.4 Hz, 2H), 4.79 (t, J = 6.6 Hz, 2H), 4.58 (d, J = 5.6 Hz, 2H). LCMS observed *m/z* = 299.3 $[M+H]^+$.

Intermediate DC

Synthesis of 2-(4-(chloromethyl)phenyl)-1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazole

Intermediate DC

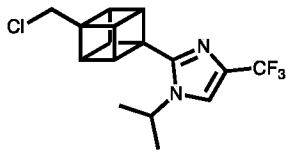


The title compound was prepared using a similar procedure as Intermediate D, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with (4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate DB). LCMS observed *m/z* = 317.0 $[M+H]^+$.

Intermediate DD

Synthesis of 2-(4-(chloromethyl)cuban-1-yl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole

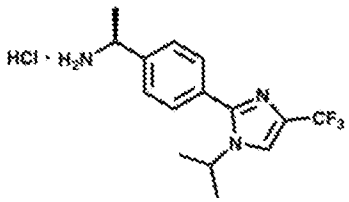
Intermediate DD



The title compound was prepared using a similar procedure as Intermediate D, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) with 4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol (Intermediate M). LCMS observed *m/z* = 329.1 $[M+H]^+$.

Intermediate DE

Synthesis of (*S*)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine.

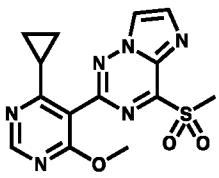


The title compound was prepared using a similar procedure as Intermediate CI, replacing *tert*-butyl (*R*)-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethyl)carbamate with *tert*-butyl (*S*)-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethyl)-carbamate. LCMS observed *m/z* = 298.4 $[M+H]^+$.

Intermediate DF

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-(methylsulfonyl)imidazo[2,1-f][1,2,4]triazine

Intermediate DF



The title compound was prepared using a similar procedure as Intermediate Z, replacing 2,6-dichloro-7-methyl-7H-purine with 2,4-dichloroimidazo[2,1-f][1,2,4]triazine. LCMS observed *m/z* = 347.0 $[M+H]^+$.

Intermediate DG

Synthesis of 2,4-dichloro-5-fluoro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine

Intermediate DG

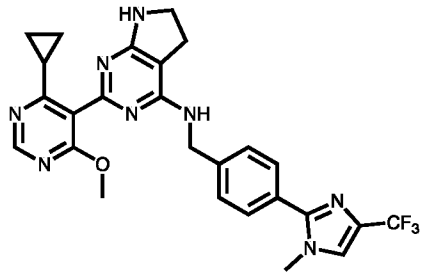
To a solution of 4,6-dichloro-3-fluoro-1H-1,5,7-triazaindene (400mg, 1.94mmol) in DMF (6.5mL) stirring at 0 °C was added NaH (85 mg, 2.14mmol, 60%w/w) and the reaction was stirred for 30 min. (2-chloromethoxyethyl)tris(methyl)silane (340mg, 2.04mmol) was added and the mixture was warmed to 23 °C and stirred for 3 h. The reaction was diluted with water (5 mL) and extracted with EtOAc in hexanes (1:1, 2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–10% EtOAc in hexanes) to afford 2,4-dichloro-5-fluoro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine as a white solid. LCMS observed *m/z* = 336.3 $[M+H]^+$.

Synthesis of Exemplified Compounds:

1.1 EXAMPLE 1

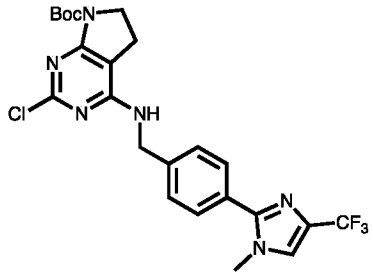
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

Compound 1



Step 1: Preparation of *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate.

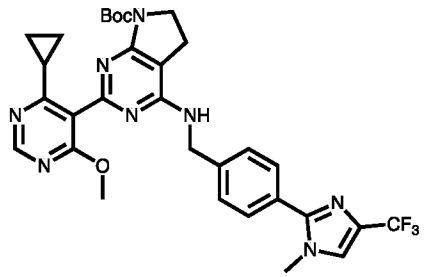
Compound 1.1



To a stirred solution of (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (0.176 g, 0.69 mmol, Intermediate A) dissolved in *N,N*-dimethylformamide (5 mL) was added *N,N*-diisopropylethylamine (0.37 mL, 2.07 mmol) followed by *tert*-butyl 2,4-dichloro-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (0.2 g, 0.69 mmol, Intermediate AE) at 23 °C. The reaction mixture was stirred at 100 °C for 16 h. After completion, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL x 2). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 25% EtOAc in petroleum ether) to afford *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (0.07 g). LCMS observed *m/z* = 509.63 $[M+H]^+$.

Step 2: Preparation of *tert*-butyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate.

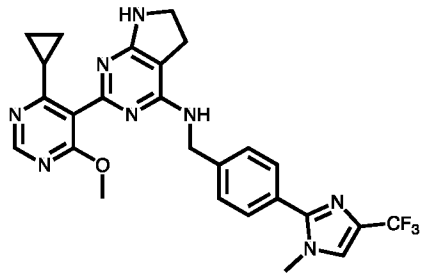
Compound 1.2



To a stirred solution of *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-d]pyrimidine-7-carboxylate (70.0 mg, 0.14 mmol) and (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid (53.3 mg, 0.28 mmol) in 1,2-dimethoxyethane (3.00 mL), milli-Q water (0.50 mL) was added potassium carbonate (47.4 mg, 0.34 mmol) at room temperature. The reaction mixture was degassed with nitrogen gas for 10 minutes before adding tetrakis(triphenylphosphine)palladium(0) (15.9 mg, 0.014 mmol). The reaction mixture was further degassed with nitrogen gas for additional 5 minutes and stirred under microwave at 100 °C for 1.5 h. After completion, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc (20 mL x 3). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 60% EtOAc in petroleum ether) to afford *tert*-butyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-d]pyrimidine-7-carboxylate (25.0 mg, 29 % yield) as an off-white solid. LCMS observed m/z = 623.59 $[M+H]^+$.

Step 3: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine.

Compound 1

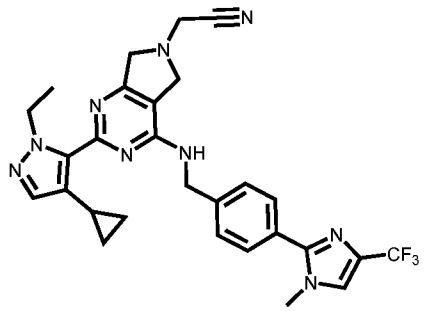


To a stirred solution of *tert*-butyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-d]pyrimidine-7-carboxylate (25.0 mg, 0.04 mmol) in dichloromethane (2.0 mL) was added trifluoroacetic acid (0.5 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h. After completion, the reaction mixture was concentrated under reduced pressure and the residue was triturated with pentane (5 mL x 2) and diethyl ether (5 mL x 2) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[2,3-d]pyrimidin-4-amine•TFA (7.5 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.16 (brs, 1H), 7.93 (s, 2H), 7.66 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.6 Hz, 2H), 4.66-4.65 (m, 2H), 3.88 (s, 3H), 3.76-3.71 (m, 5H), 2.96-2.95 (m, 2H), 1.83-1.82 (m, 1H), 0.99-0.98 (m, 2H), 0.83-0.82 (m, 2H). LCMS observed *m/z* = 523.44 $[M+H]^+$.

2.1 EXAMPLE 2

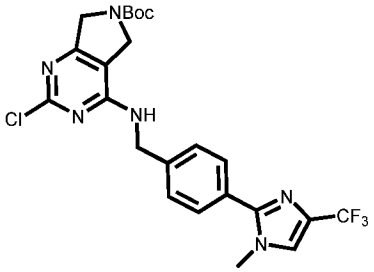
Synthesis of 2-(2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 2



Step 1: Preparation of *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate.

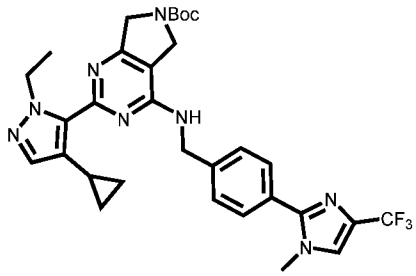
Compound 2.1



To a mixture of (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (600 mg, 2.35 mmol, Intermediate A) and triethylamine (1.94 mL, 11.75 mmol) in chloroform (6.00 mL) was added *tert*-butyl 2,4-dichloro-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (200 mg, 0.690 mmol) and stirred at 23 °C for 16 hours. The reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (3 X 30 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (600 mg) of *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate. LCMS observed *m/z* = 509.5 [M+H]+.

Step 2: Preparation of *tert*-butyl 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate.

Compound 2.2

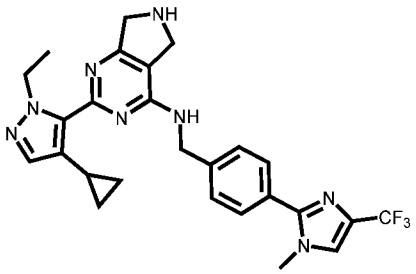


To a mixture of *tert*-butyl 2-chloro-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate (300 mg, 0.590 mmol) in DME (4.00 mL) was added water (2.00 mL), (4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)boronic acid (130 mg, 0.710 mmol), and potassium carbonate (200 mg, 1.47 mmol) and purged with N_2 for 15 minutes. To the mixture was added tetrakis(triphenylphosphine)-palladium(0) (70.0 mg, 0.0600 mmol) and the resulting mixture was stirred at 100 °C for 16 hours. The mixture was diluted with cold water (5 mL) and extracted with EtOAc (30 mL). The combined organic layer was washed with brine (5

mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–25% EtOAc in hexanes) to afford (150 mg) of *tert*-butyl 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate. LCMS observed *m/z* = 610.0 [M+H]+.

Step 3: Preparation of 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine.

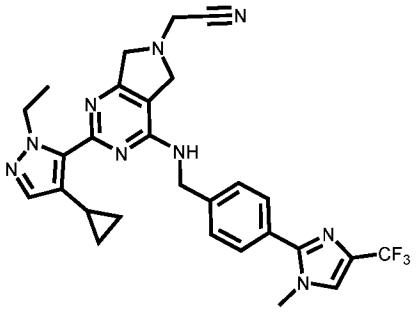
Compound 2.3



To a mixture of *tert*-butyl 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate (150 mg, 0.290 mmol) in dichloromethane (1.50 mL) was added dropwise trifluoroacetic acid (0.200 mL) at 0 °C under N_2. The resulting mixture was stirred at 23 °C for 6 hours. The mixture was concentrated under reduced pressure and the residue was triturated in diethyl ether (5 mL) to afford (120 mg) of *tert*-butyl 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carboxylate. LCMS observed *m/z* = 610.0 [M+H]+.

Step 4: Preparation of 2-(2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 2

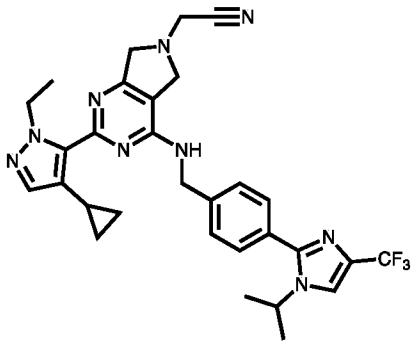


To a mixture of 2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine (180 mg, 0.250 mmol) in acetonitrile (1.80 mL) was added triethylamine (0.140 mL, 1.06 mmol) and the mixture was stirred at 0 °C for 15 minutes. To the mixture was added 2-bromoacetonitrile (50.0 mg, 0.430 mmol). The resulting mixture was stirred at 23 °C for 16 hours. The mixture was concentrated under reduced pressure, diluted with cold water (5 mL) and extracted with EtOAc (3 X 20 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–70% EtOAc in hexanes) to afford 2-(2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (t, J = 6.0 Hz 1H), 7.93 – 7.91 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 7.04 (s, 1H), 4.73 (d, J = 6.0 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 4.02 (s, 2H), 3.95 (s, 2H), 3.75 (s, 3H), 2.22 – 2.15 (m, 1H), 1.09 (t, J= 7.0 Hz, 3H), 0.63 – 0.60 (m, 2H), 0.43 – 0.39 (m, 2H). LCMS observed *m/z* = 548.5 $[M+H]^+$.

3.1 EXAMPLE 3

Synthesis of 2-(2-(4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)-4-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 3



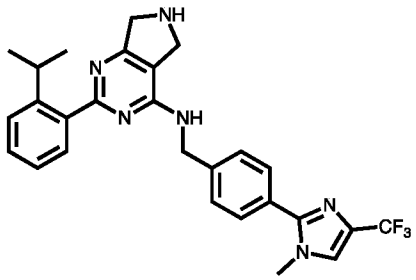
The title compound was prepared using a similar route as Compound 2, replacing (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (d, J = 0.8 Hz, 1H), 8.03 (t, J = 6.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 4.73 (d, J = 2.8 Hz, 2H), 4.47 – 4.40 (m, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.06 (s, 2H), 4.02 (s, 2H), 3.95 (s, 2H), 2.21 – 2.14 (m,

1H), 1.40 – 1.38 (m, 6H), 1.09 (t, J = 7.2 Hz, 3H), 0.61 – 0.56 (m, 2H), 0.44 – 0.39 (m, 2H). LCMS observed *m/z* = 576.4 $[M+H]^+$.

4.1 EXAMPLE 4

Synthesis of 2-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine.

Compound 4



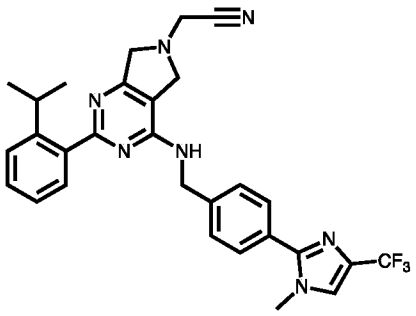
The title compound was prepared using a similar procedure as Compound 2, replacing (4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)boronic acid with (2-isopropylphenyl)boronic acid.

^{1}H NMR (400 MHz , DMSO-d_6) δ 9.39 (s, 2H), 8.20 (t, J = 6.0 Hz, 1H), 7.93 (s, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.45 – 7.38 (m, 5H), 7.23 – 7.19 (m, 1H), 4.76 (d, J = 5.6 Hz, 2H), 4.47 – 4.43 (m, 4H), 3.76 (s, 3H), 3.49 – 3.48 (m, 1H), 1.04 – 1.02 (m, 6H). LCMS observed *m/z* = 493.56 $[M+H]^+$.

5.1 EXAMPLE 5

Preparation of 2-(2-(2-isopropylphenyl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 5

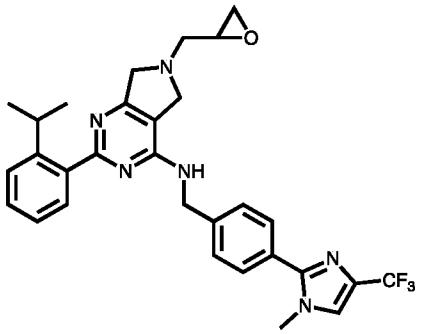


To a stirred solution of 2-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine (110 mg, 0.22 mmol, Compound 4) in acetonitrile (3.0 mL) was added triethylamine (0.15 mL, 1.12 mmol) at 0 °C and was stirred for 15 min before adding 2-bromoacetonitrile (40.2 mg, 0.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature for

20 h. Upon completion, the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the residue was triturated with a mixture of n-pentane in diethyl ether (1:1) and the resulting compound was further purified by preparative HPLC (mobile phase: 10–98% acetonitrile in water w/ 0.1% NH_4CO_3) to afford 2-(2-(2-isopropylphenyl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile (50 mg) as an off-white solid.. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 – 7.87 (m, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.43 – 7.41 (m, 3H), 7.35 – 7.31 (m, 2H), 7.20 – 7.16 (m, 1H), 4.72 (d, J = 5.6 Hz, 2H), 4.06 (s, 2H), 4.00 (s, 2H), 3.93 (s, 2H), 3.75 (s, 3H), 3.49 – 3.42 (m, 1H), 1.02 – 1.0 (m, 6H). LCMS observed *m/z* = 532.45 $[M+H]^+$.

6.1 EXAMPLE 6

Compound 6

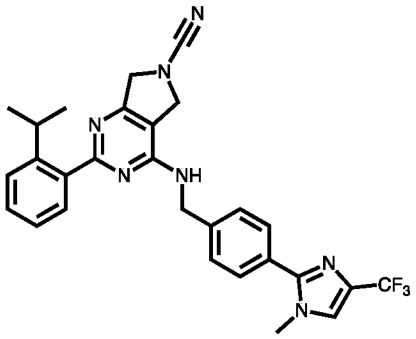


The title compound was prepared using a similar procedure as Compound 5, replacing 2-bromoacetonitrile with 2-(bromomethyl)oxirane. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 0.8 Hz, 1H), 7.81 (t, J = 6.0 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.42 – 7.40 (m, 3H), 7.35 – 7.31 (m, 2H), 7.20 – 7.16 (m, 1H), 4.70 (d, J = 6.0 Hz, 2H), 4.00 – 3.90 (m, 4H), 3.75 (s, 3H), 3.50 – 3.43 (m, 1H), 3.14 – 3.10 (m, 1H), 3.08 – 3.03 (m, 1H), 2.78 – 2.76 (m, 1H), 2.71 – 2.67 (m, 1H), 2.59 – 2.58 (m, 1H), 1.01 – 1.00 (m, 6H). LCMS observed *m/z* = 549.44 $[M+H]^+$.

7.1 EXAMPLE 7

Preparation of 2-(2-isopropylphenyl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carbonitrile.

Compound 7

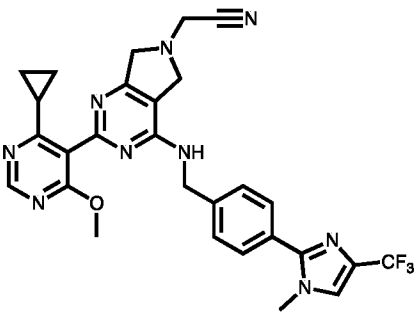


To a stirred solution of 2-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine (200 mg, 0.41 mmol, Compound 4) in THF (2 mL) was added sodium carbonate (129 mg, 1.22 mmol) at -20 °C and stirred at -20 °C for 15 min before adding cyanogen bromide (51.6 mg, 0.49 mmol) at -20 °C. The reaction mixture was stirred at 0 °C for 1 h. Upon completion, the reaction was diluted with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the residue was triturated with a mixture of n-pentane in diethyl ether (1:1) and the resulting compound was further purified by PREP-HPLC purification to afford 2-(2-isopropylphenyl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carbonitrile (29 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (t, J = 6.0 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.67 – 7.65 (m, 2H), 7.43 – 7.41 (m, 3H), 7.37 – 7.32 (m, 2H), 7.21 – 7.17 (m, 1H), 4.74 – 4.68 (m, 6H), 3.75 (s, 3H), 3.51 – 3.40 (m, 1H), 1.02 – 1.0 (m, 6H). LCMS observed *m/z* = 518.55 $[M+H]^+$.

8.1 EXAMPLE 8

Synthesis of 2-(2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 8

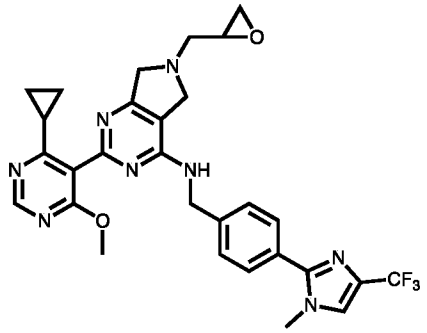


The title compound was prepared using a similar procedure as Compound 2, replacing (4-cyclopropyl-1-ethyl-1*H*-pyrazol-5-yl)boronic acid with (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.99 (t, J = 6.0 Hz, 1H), 7.92 (d, J = 1.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 4.05 (s, 2H), 3.98 (s, 2H), 3.93 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 1.70 – 1.64 (m, 1H), 0.97 – 0.94 (m, 2H), 0.80 – 0.79 (m, 2H). LCMS observed *m/z* = 562.55 $[M+H]^+$.

9.1 EXAMPLE 9

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6-(oxiran-2-ylmethyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine.

Compound 9

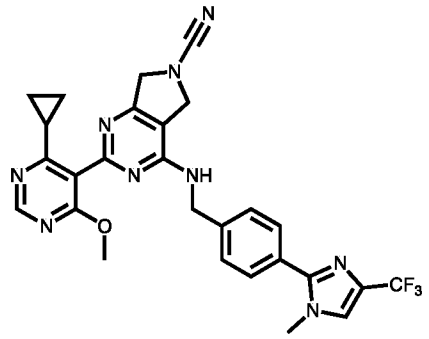


The title compound was prepared using a similar procedure as Compound 8, replacing 2-bromoacetonitrile with 2-(bromomethyl)oxirane. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.92 – 7.89 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.63 (d, J = 6.0 Hz, 2H), 3.98 – 3.89 (m, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 3.12 – 3.08 (m, 1H), 3.07 – 3.03 (m, 1H), 2.76 (t, J = 4.6 Hz, 1H), 2.70 – 2.67 (m, 1H), 2.58 – 2.50 (m, 1H), 1.68 – 1.64 (m, 1H), 0.95 – 0.94 (m, 2H), 0.78 – 0.75 (m, 2H). LCMS observed *m/z* = 579.43 $[M+H]^+$.

10.1 EXAMPLE 10

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidine-6-carbonitrile.

Compound 10

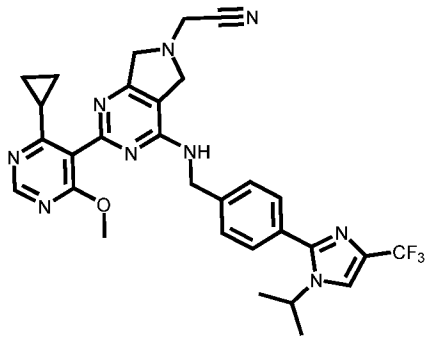


The title compound was prepared using a similar procedure as Compound 7, replacing 2-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine (Compound 8.3). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.60 (s, 1H), 8.15 (t, J = 6.0 Hz, 1H), 7.92 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 4.70 – 4.66 (m, 6H), 3.81 (s, 3H), 3.75 (s, 3H), 1.68-1.64 (m, 1H), 0.97 – 0.96 (m, 2H), 0.79 – 0.76 (m, 2H). LCMS observed *m/z* = 548.38 [M+H]$^+$.

11.1 EXAMPLE 11

Synthesis of 2-(2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,7-dihydro-6*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl)acetonitrile.

Compound 11

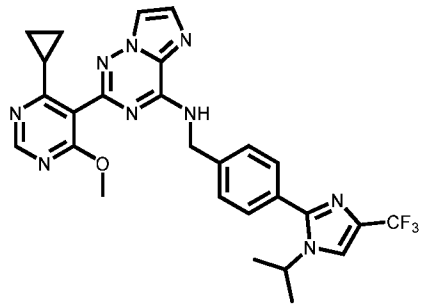


The title compound was prepared using a similar procedure as Compound 8, replacing (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate B). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.59 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.00 (t, J = 6.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 4.66 (d, J = 6.0 Hz, 2H), 4.47 – 4.40 (m, 1H), 4.06 (s, 2H), 3.98 (s, 2H), 3.93 (s, 2H), 3.81 (s, 3H), 1.70 – 1.63 (m, 1H), 1.40 – 1.38 (m, 6H), 0.94 – 0.93 (m, 2H), 0.80 – 0.70 (m, 2H). LCMS observed *m/z* = 590.5 [M+H]$^+$.

12.1 EXAMPLE 12

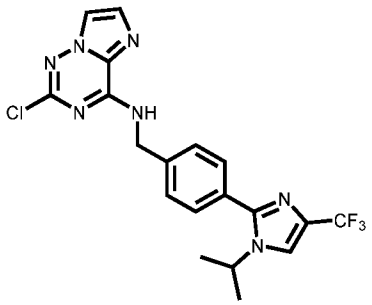
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 12



Step 1: Preparation of 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

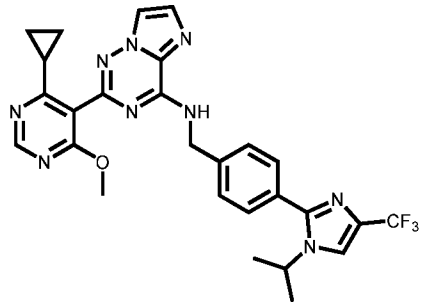
Compound 12.1



To a mixture of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (224 mg, 0.790 mmol) and *N,N*-diisopropylethylamine (1.10 mL, 6.34 mmol) in *N,N*-dimethylformamide (3.00 mL) was added 2,4-dichloroimidazo[2,1-*f*][1,2,4]triazine (150 mg, 0.790 mmol) and stirred at 23 °C for 16 hours. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 25–30% EtOAc in hexanes) to afford (100 mg) of methyl 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine. LCMS observed m/z = 436.6 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 12

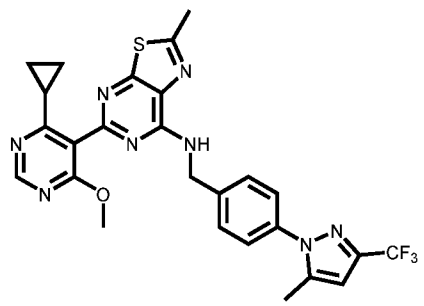


To a mixture of 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine (120 mg, 0.275 mmol) in 1,4-dioxane (4.00 mL) was added water (1.00 mL), (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid (267 mg, 1.37 mmol), and potassium carbonate (114 mg, 0.826 mmol) and purged with N_2 for 30 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (31.8 mg, 0.0280 mmol) and the resulting mixture was subjected to microwave heating under N_2 at 110 °C for 1 hour. The mixture was diluted with cold water (5 mL) and extracted with EtOAc (3 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by achiral SFC (mobile phase: 23% MeOH) to afford (17.0 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 9.59 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 2H), 7.68 (s, 1H), 7.50 (s, 4H), 4.77 (d, J = 6.4 Hz, 2H), 4.46-4.40 (m, 1H), 3.85 (s, 3H), 1.89-1.83 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10-0.98 (m, 2H), 0.83-0.80 (m, 2H). LCMS observed *m/z* = 550.4 $[M+H]^+$.

13.1 EXAMPLE 13

Synthesis of 5-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-2-methyl-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)thiazolo[5,4-*d*]pyrimidin-7-amine.

Compound 13

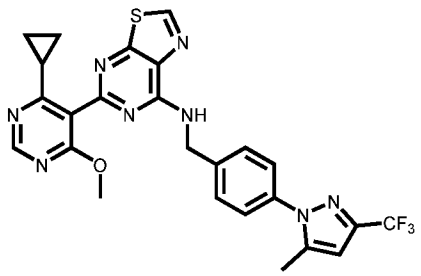


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine and 2,4-dichloroimidazo[2,1-*f*][1,2,4]triazine with (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine•HCl (Intermediate Y) and 5,7-dichloro-2-methylthiazolo[5,4-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.56 (s, 1H), 4.87 (s, 2H), 3.90 (s, 3H), 2.83 (s, 3H), 2.32 (s, 3H), 1.73 (tt, J = 8.6, 4.7 Hz, 1H), 1.12 – 1.03 (m, 2H), 0.90 – 0.74 (m, 2H). LCMS observed *m/z* = 553.6 $[M+H]^+$.

14.1 EXAMPLE 14

Synthesis of 5-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)thiazolo[5,4-*d*]pyrimidin-7-amine.

Compound 14

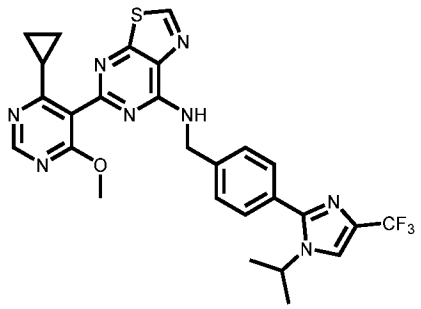


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine and 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine with (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)-methanamine•HCl (Intermediate Y) and 5,7-dichlorothiazolo[5,4-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.57 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 6.57 (s, 1H), 4.91 (s, 2H), 3.91 (s, 3H), 2.32 (s, 3H), 1.74 (tt, J = 8.5, 4.7 Hz, 1H), 1.12 – 1.05 (m, 2H), 0.88 – 0.80 (m, 2H). LCMS observed *m/z* = 539.6 $[M+H]^+$.

15.1 EXAMPLE 15

Synthesis of 5-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)thiazolo[5,4-*d*]pyrimidin-7-amine.

Compound 15

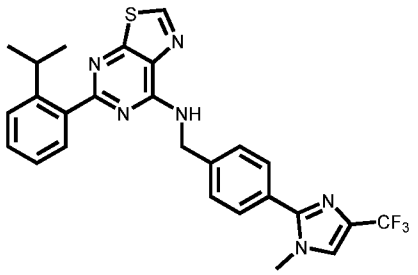


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine with 5,7-dichlorothiazolo[5,4-*d*]pyrimidine. ^{1}H NMR (400 MHz, CD_3OD) δ 9.12 (s, 1H), 8.57 (s, 1H), 7.94 – 7.88 (m, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.46 (m, 2H), 4.92 (s, 2H), 4.53 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.83 – 1.69 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.14 – 1.04 (m, 2H), 0.90 – 0.76 (m, 2H). LCMS observed *m/z* = 567.2 $[M+H]^+$.

16.1 EXAMPLE 16

Synthesis of 5-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)thiazolo[5,4-*d*]pyrimidin-7-amine.

Compound 16

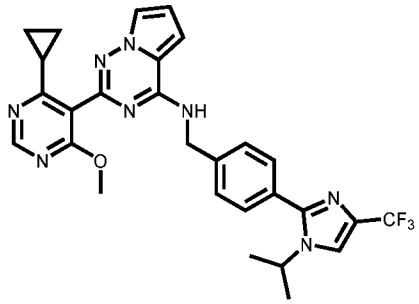


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine and (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with 5,7-dichlorothiazolo[5,4-*d*]pyrimidine and (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine in the S_NAr reaction (General Procedure F) and using (2-isopropylphenyl)boronic acid in the Suzuki coupling step (General Procedure F). ^{1}H NMR (400 MHz, CD_3OD) δ 9.08 (s, 1H), 7.67 (s, 1H), 7.60 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.26 – 7.20 (m, 1H), 4.95 (s, 2H), 3.75 (s, 3H), 3.42 (hept, J = 6.8 Hz, 1H), 1.10 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 509.2 $[M+H]^+$.

17.1 EXAMPLE 17

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 17

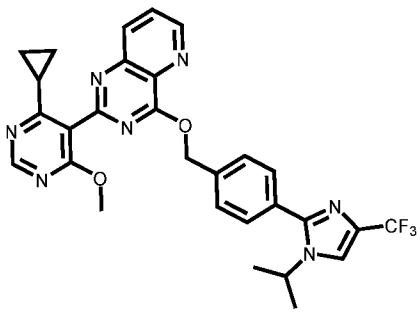


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine with 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 7.90 (s, 1H), 7.57 – 7.49 (m, 5H), 6.94 – 6.91 (m, 1H), 6.73 – 6.70 (m, 1H), 4.88 (s, 2H), 4.58 – 4.48 (m, 1H), 3.94 (s, 3H), 1.94 – 1.86 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H), 1.12 – 1.08 (m, 2H), 0.90 – 0.85 (m, 2H). LCMS observed *m/z* = 549.6 $[M+H]^+$.

18.1 EXAMPLE 18

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)pyrido[3,2-*d*]pyrimidine.

Compound 18

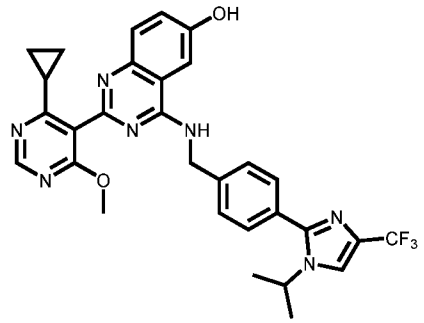


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine and (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with 2,4-dichloropyrido[3,4-*d*]pyrimidine and (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, J = 3.2 Hz, 1H), 8.72 (s, 1H), 8.44 (dd, J = 8.6, 1.2 Hz, 1H), 8.20 (s, 1H), 8.03 (dd, J = 8.6, 4.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 5.74 (s, 2H), 4.53-4.46 (m, 1H), 3.87 (s, 3H), 1.86-1.81 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.31-1.24 (m, 2H), 0.93-0.84 (m, 2H). LCMS observed *m/z* = 562.3 $[M+H]^+$.

19.1 EXAMPLE 19

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)quinazolin-6-ol.

Compound 19

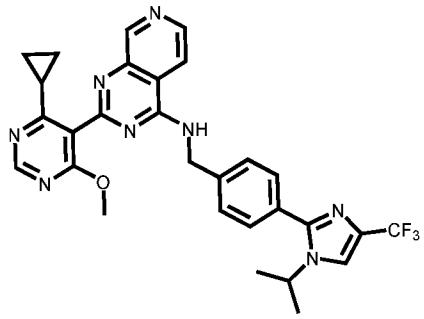


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine with 2,4-dichloroquinazolin-6-ol. ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 7.90 (s, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (dd, J = 5.6, 2.7 Hz, 3H), 7.39 (dd, J = 8.9, 2.6 Hz, 1H), 4.93 (s, 2H), 4.52 (h, J = 6.7 Hz, 1H), 3.90 (s, 3H), 1.75 (tt, J = 8.6, 4.7 Hz, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.07 (m, 2H), 0.79 (m, 2H). LCMS observed *m/z* = 576.6 $[M+H]^+$.

20.1 EXAMPLE 20

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)pyrido[3,4-*d*]pyrimidin-4-amine.

Compound 20

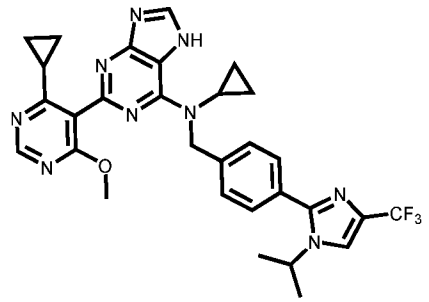


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-imidazo[2,1-*f*][1,2,4]triazine with 2,4-dichloropyrido[3,4-*d*]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (t, J = 5.8 Hz, 1H), 9.16 (s, 1H), 8.70 (d, J = 5.6 Hz, 1H), 8.64 (s, 1H), 8.24 (d, J = 5.6 Hz, 1H), 8.16 (s, 1H), 7.50 (s, 4H), 4.86 (d, J = 6.0 Hz, 2H), 4.45 – 4.41 (m, 1H), 3.82 (s, 3H), 1.78 – 1.72 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.78 – 0.75 (m, 2H). LCMS observed *m/z* = 561.4 $[M+H]^+$.

21.1 EXAMPLE 21

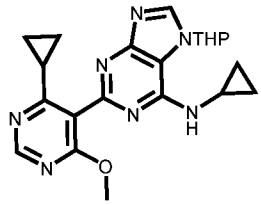
Synthesis of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine.

Compound 21



Step 1: Preparation of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

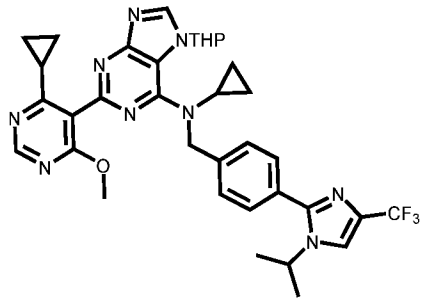
Compound 21.1



To a mixture of cyclopropanamine (100 mg, 1.74 mmol) in 1,4-dioxane (5.00 mL) was added *N,N*-diisopropylethylamine (1.00 mL, 5.81 mmol) and the mixture was stirred at 0 °C for 15 minutes. To the resulting mixture was added 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purine (500 mg, 1.29 mmol, Intermediate AB). The resulting mixture was stirred at 90 °C for 16 hours. The mixture was concentrated under reduced pressure and the residue was diluted with water (20 mL) and extracted with EtOAc (2 X 50 mL). The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–55% EtOAc in hexanes) to afford (250 mg) of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine as a white solid. LCMS observed *m/z* = 408.8 $[M+H]^+$.

Step 2: Preparation of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

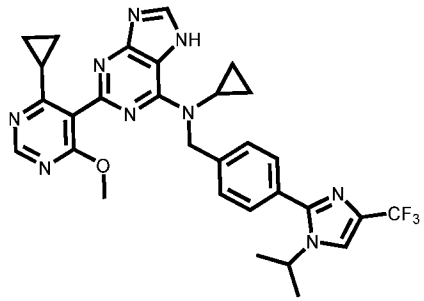
Compound 21.2



To a mixture of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (250 mg, 0.610 mmol) in *N,N*-dimethylformamide (3.00 mL) was added molecular sieves powder (200 mg), 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1*H*-imidazole (223 mg, 0.730 mmol, Intermediate D), and Cs_2CO_3 (600 mg, 1.84 mmol). The resulting mixture was stirred at 70 °C for 4 hours. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (5 mL) and extracted with EtOAc (2 X 5 mL). The combined organic layer was washed with brine (2 X 5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–55% EtOAc in hexanes) to afford (15.0 mg) of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine as a yellow solid. LCMS observed *m/z* = 674.3 $[M+H]^+$.

Step 3: Preparation of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine.

Compound 21



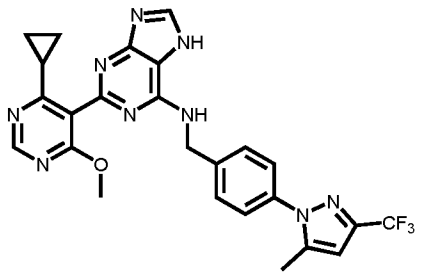
To *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (150 mg, 0.220 mmol) in dichloromethane (3.00 mL) was added dropwise trifluoroacetic acid (0.0510 mL, 0.660 mmol) at 0 °C under N_2. The resulting mixture was

stirred at 23 °C for 4 hours. The reaction mixture was diluted with a saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (2 X 5 mL). The combined organic layer was washed with brine (2 X 5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparatory HPLC (mobile phase: 25-100% acetonitrile in water) to afford (35.0 mg) of *N*-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.14 (s, 1H), 8.59 (s, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 5.35 (br s, 2H), 4.48 – 4.41 (m, 1H), 3.80 (s, 3H), 3.15 (br s, 1H), 1.83 (br s, 1H), 1.39 (d, J = 6.4 Hz, 6H), 0.98 – 0.80 (m, 8H). LCMS observed *m/z* = 590.5 [M+H]$^+$.

22.1 EXAMPLE 22

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)-7*H*-purin-6-amine.

Compound 22

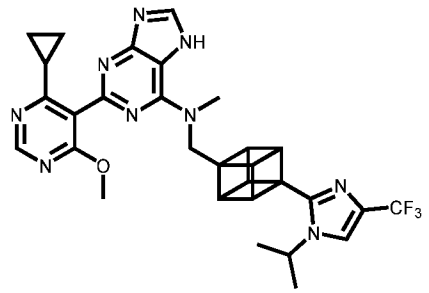


To 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine (100 mg, 0.289 mmol, Intermediate AC) was added a mixture of (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine (77.4 mg, 0.303 mmol) and *N,N*-diisopropylethylamine (0.126 mL, 0.722 mmol) in dimethyl sulfoxide (0.867 mL). The mixture was stirred at 50 °C for 1 hour. The mixture was concentrated under reduced pressure and The crude product was purified by preparatory HPLC (mobile phase: 10–90% acetonitrile in water w/ 0.1% formic acid) to afford (6.00 mg, 3.99% yield) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)-7*H*-purin-6-amine as a white solid. ^{1}H NMR (400 MHz, CD$_3$OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.58 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 6.57 (s, 1H), 4.87 (s, 2H), 3.90 (d, J = 1.0 Hz, 3H), 2.33 (s, 3H), 1.72 (tt, J = 8.5, 4.8 Hz, 1H), 1.08 (m, 2H), 0.84 (m, 2H). LCMS observed *m/z* = 522.5 [M+H]$^+$.

23.1 EXAMPLE 23

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methyl)-*N*-methyl-7*H*-purin-6-amine.

Compound 23

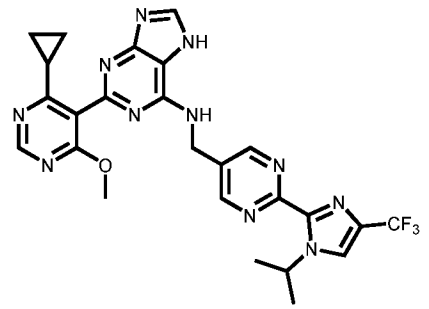


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with 1-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)-*N*-methylmethanamine•HCl (Intermediate N). ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.05 (s, 1H), 7.72 (s, 1H), 4.87 (s, 2H), 4.28 (t, J = 5.0 Hz, 3H), 4.23 – 4.13 (m, 1H), 4.02 (t, J = 5.0 Hz, 3H), 3.92 (s, 3H), 3.73 – 3.54 (m, 3H), 1.80 – 1.72 (m, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.16 – 1.10 (m, 2H), 0.95 – 0.88 (m, 2H). LCMS observed *m/z* = 590.6 $[M+H]^+$.

24.1 EXAMPLE 24

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrimidin-5-yl)methyl)-7*H*-purin-6-amine.

Compound 24

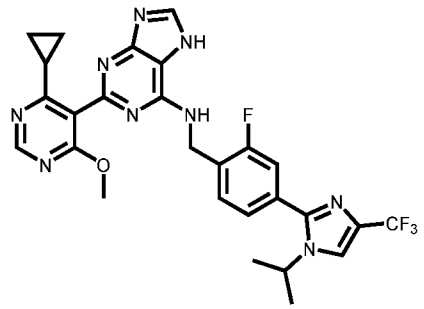


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrimidin-5-yl)methanamine•TFA (Intermediate U). ^{1}H NMR (400 MHz, CD_3OD) δ 8.96 (s, 2H), 8.56 (s, 1H), 8.15 (s, 1H), 8.01 (s, 1H), 5.72 (hept, J = 6.8 Hz, 1H), 4.90 (s, 2H), 3.89 (s, 3H), 1.74 – 1.62 (m, 1H), 1.51 (d, J = 6.7 Hz, 6H), 1.12 – 1.03 (m, 2H), 0.91 – 0.81 (m, 2H). LCMS observed *m/z* = 552.2 $[M+H]^+$.

25.1 EXAMPLE 25

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine.

Compound 25

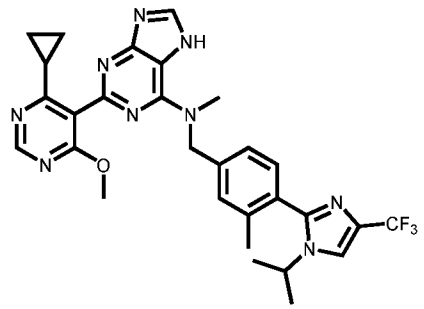


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-methanamine (Intermediate J). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.92 (s, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.32 (t, J = 10.7 Hz, 2H), 4.96 (s, 2H), 4.55 (hept, J = 6.6 Hz, 1H), 3.90 (s, 3H), 1.77 – 1.69 (m, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.13 – 1.05 (m, 2H), 0.90 – 0.74 (m, 2H). LCMS observed *m/z* = 568.3 $[M+H]^+$.

26.1 EXAMPLE 26

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)-*N*-methyl-7*H*-purin-6-amine.

Compound 26

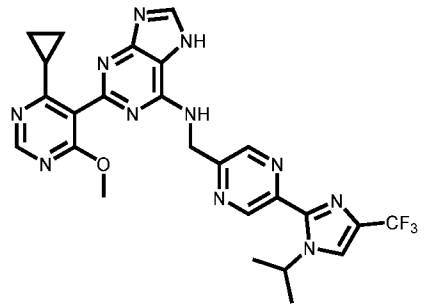


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-*N*-methylmethanamine•TFA (Intermediate H). ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.09 (s, 1H), 7.90 (s, 1H), 7.35 (s, 1H), 7.33 – 7.25 (m, 2H), 5.35 (s, 2H), 4.12 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 3.53 (s, 3H), 2.13 (s, 3H), 1.89 – 1.78 (m, 1H), 1.39 (d, J = 6.7 Hz, 6H), 1.16 – 1.08 (m, 2H), 0.93 – 0.81 (m, 2H). LCMS observed *m/z* = 578.3 $[M+H]^+$.

27.1 EXAMPLE 27

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((5-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)-7*H*-purin-6-amine.

Compound 27

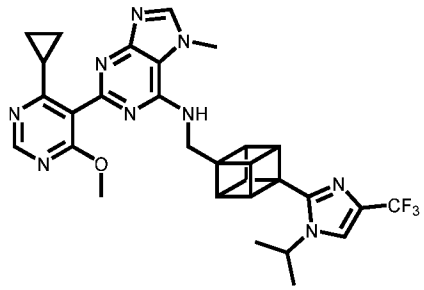


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methanamine•HCl (Intermediate V). ^{1}H NMR (400 MHz, CD_3OD) δ 9.16 (s, 1H), 8.74 (s, 1H), 8.55 (s, 1H), 8.17 (s, 1H), 8.01 (s, 1H), 5.62 (hept, J = 6.6 Hz, 1H), 5.01 (s, 2H), 4.58 (s, 1H), 3.87 (s, 3H), 1.72 – 1.62 (m, 1H), 1.50 (d, J = 6.7 Hz, 6H), 1.16 – 0.99 (m, 2H), 0.87 – 0.75 (m, 2H). LCMS observed *m/z* = 552.2 $[M+H]^+$.

28.1 EXAMPLE 28

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methyl)-7-methyl-7*H*-purin-6-amine.

Compound 28



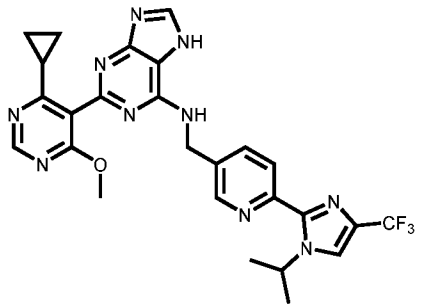
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine and 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanamine (Intermediate L) and 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylsulfonyl)-7*H*-purine (Intermediate Z). ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.15 (s, 1H), 7.72 (s, 1H), 4.26 – 4.20 (m, 3H), 4.20 – 4.13 (m, 4H), 4.06 – 3.99 (m, 3H), 3.93 (s, 2H), 3.90 (s, 3H),

1.78 – 1.69 (m, 1H), 1.46 (d, J = 6.7 Hz, 6H), 1.17 – 1.10 (m, 2H), 0.95 – 0.86 (m, 2H). LCMS observed *m/z* = 590.3 $[M+H]^+$.

29.1 EXAMPLE 29

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((6-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)-7*H*-purin-6-amine.

Compound 29

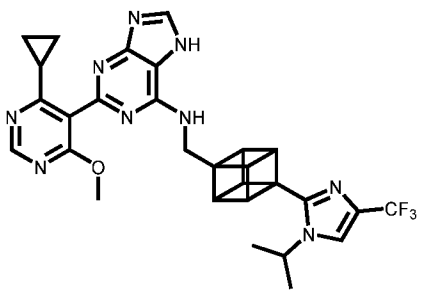


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanamine•HCl (Intermediate R). ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (s, 1H), 8.56 (s, 1H), 8.14 (s, 1H), 8.00 – 7.88 (m, 3H), 5.66 (hept, J = 6.8 Hz, 1H), 4.91 (s, 2H), 3.90 (s, 3H), 1.75 – 1.66 (m, 1H), 1.48 (d, J = 6.7 Hz, 6H), 1.15 – 1.03 (m, 2H), 0.89 – 0.79 (m, 2H). LCMS observed *m/z* = 551.2 $[M+H]^+$.

30.1 EXAMPLE 30

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methyl)-7*H*-purin-6-amine.

Compound 30



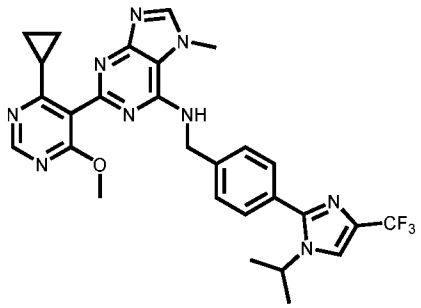
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanamine (Intermediate L). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.18 – 8.10 (m, 1H), 7.77 – 7.69 (m, 1H), 4.87 (s, 2H), 4.31 – 4.25 (m, 3H), 4.20 (hept, J = 6.6 Hz, 1H), 4.07 – 4.01 (m, 3H), 3.92 (s,

5H), 1.80 – 1.70 (m, 1H), 1.47 (d, J = 6.7 Hz, 6H), 1.18 – 1.10 (m, 2H), 0.96 – 0.88 (m, 2H). LCMS observed *m/z* = 576.3 $[M+H]^+$.

31.1 EXAMPLE 31

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)benzyl)-7-methyl-7*H*-purin-6-amine.

Compound 31



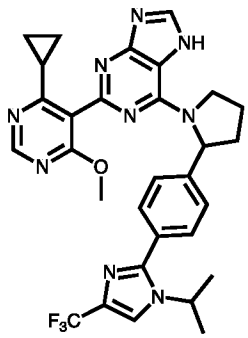
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine and 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate B) and 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7-methyl-6-(methylsulfonyl)-7*H*-purine (Intermediate Z).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.38 (s, 1H), 8.16 (s, 1H), 7.56 – 7.43 (m, 4H), 4.81 (d, J = 5.9 Hz, 2H), 4.41 (hept, J = 6.7 Hz, 1H), 4.15 (s, 3H), 3.80 (s, 3H), 1.73 – 1.64 (m, 1H), 1.39 (d, J = 6.6 Hz, 6H), 1.01 – 0.90 (m, 2H), 0.75 – 0.64 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

32.1 EXAMPLE 32

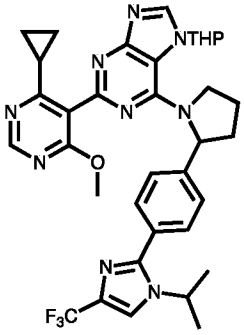
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine.

Compound 32



Step 1: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

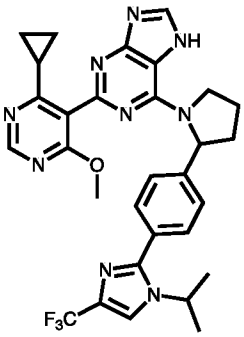
Compound 32.1



To a solution of 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole (510 mg, 1.57 mmol, Intermediate O) in *N,N*-dimethylformamide (10.0 mL) was added *N,N*-diisopropylethylamine (1.68 mL, 9.46 mmol) and 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purine (670 mg, 1.57 mmol, Intermediate AB) at 23 °C. The reaction mixture was heated at 65 °C for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 25–30% EtOAc in petroleum ether) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (400 mg) as a white powder. LCMS observed m/z = 674.3$[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine.

Compound 32



To a solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (400 mg, 0.594 mmol) in dichloromethane (10.0 mL) stirring at 0 °C was added trifluoroacetic acid (2.00 mL). The reaction mixture was warmed to 23 °C and stirred

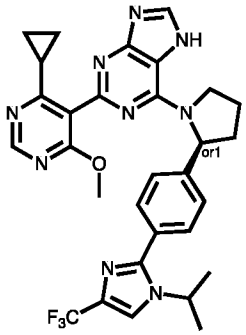
for 2 h. Upon completion, the reaction mixture was concentrated under reduced pressure. The resulting residue was purified by reverse phase chromatography (mobile phase: 20-100% acetonitrile in water w/ 0.1% formic acid) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine (250 mg) as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6) 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H). LCMS observed *m/z* = 590.37 $[M+H]^+$.

33.1 EXAMPLE 33

Preparation of *rel*-(*S*)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine.

Compound 33



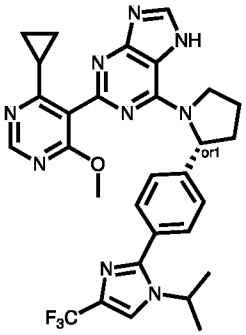
The racemic 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine (200 mg) was purified by chiral (SFC) separation to afford *rel*-(*S*)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine (38.2 mg).

^{1}H NMR (400 MHz, DMSO-d_6) 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H) ppm. LCMS observed *m/z* = 590.4 $[M+H]^+$.

34.1 EXAMPLE 34

Preparation of *rel*-(*R*)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine.

Compound 34



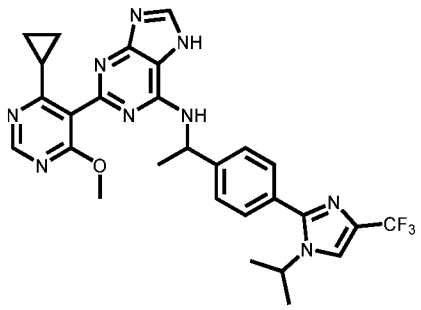
The racemic 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine (200 mg) was purified by chiral (SFC) separation to afford *rel*-(*R*)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(2-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)pyrrolidin-1-yl)-7*H*-purine (38.8 mg).

^{1}H NMR (400 MHz, DMSO-d_6) 13.00 (br s, 1H), 8.64 – 7.99 (m, 3H), 7.46 – 7.29 (m, 4H), 6.39 (br s, 0.4H), 5.59 (d, J = 7.2 Hz, 0.6H), 4.53 – 4.30 (m, 2H), 3.95 – 3.66 (m, 4H), 2.50 – 1.92 (m, 3H), 1.50 – 1.41 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.04 – 0.83 (m, 5H) ppm. LCMS observed *m/z* = 590.4 $[M+H]^+$.

35.1 EXAMPLE 35

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(1-(4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)phenyl)ethyl)-7*H*-purin-6-amine.

Compound 35

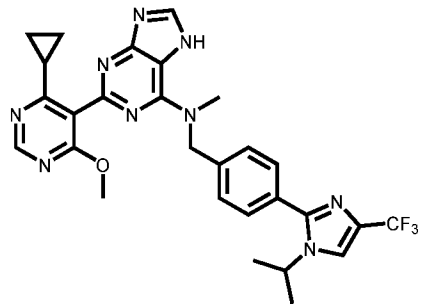


The title compound was prepared using a similar procedure as Compound 32, replacing 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine (Intermediate P). ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.15 (s, 1H), 7.89 (d, J = 1.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 2H), 7.55 – 7.47 (m, 2H), 5.62 (s, 1H), 4.54 (hept, J = 6.7 Hz, 1H), 3.87 (s, 3H), 1.67 (m, J = 7.0 Hz, 4H), 1.44 (dd, J = 6.7, 4.6 Hz, 6H), 1.04 (m, J = 4.5 Hz, 2H), 0.87 – 0.77 (m, 1H), 0.69 (m, 1H). LCMS observed *m/z* = 564.2 $[M+H]^+$.

36.1 EXAMPLE 36

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*-methyl-7*H*-purin-6-amine.

Compound 36

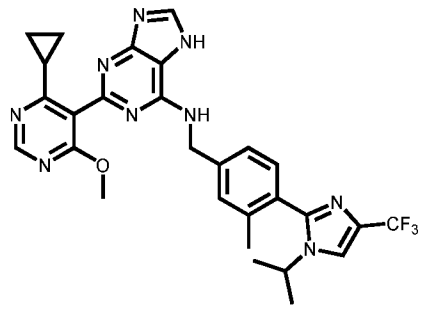


The title compound was prepared using a similar procedure as Compound 32, replacing 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methyl-methanamine•HCl (Intermediate E). ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.06 (s, 1H), 7.90 (s, 1H), 7.51 (s, 4H), 5.37 (s, 2H), 4.54 (hept, J = 6.7 Hz, 1H), 3.91 (s, 3H), 3.63 (s, 3H), 1.88 – 1.75 (m, 1H), 1.44 (d, J = 6.7 Hz, 6H), 1.16 – 1.02 (m, 2H), 0.95 – 0.75 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

37.1 EXAMPLE 37

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)-7*H*-purin-6-amine.

Compound 37



The title compound was prepared using a similar procedure as Compound 32, replacing 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)-methanamine•HCl (Intermediate G).

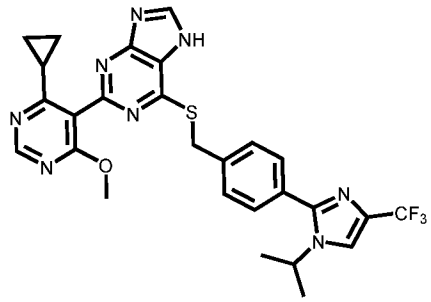
^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.47 – 7.34 (m, 2H), 7.31 – 7.23 (m, 1H), 4.93 – 4.87 (m, 2H), 4.10 (hept, J = 6.8 Hz, 1H), 3.92 (s, 3H),

2.13 (s, 3H), 1.81 – 1.71 (m, 1H), 1.38 (d, J = 6.7 Hz, 6H), 1.13 – 1.07 (m, 2H), 0.90 – 0.81 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

38.1 EXAMPLE 38

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)thio)-7*H*-purine.

Compound 38

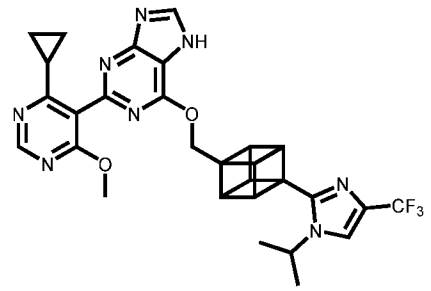


The title compound was prepared using a similar procedure as Compound 32, replacing 1-isopropyl-2-(4-(pyrrolidin-2-yl)phenyl)-4-(trifluoromethyl)-1*H*-imidazole with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanethiol (Intermediate K). ^{1}H NMR (400 MHz, DMSO-d_6) 13.80 (br s, 1H), 8.69 (s, 1H), 8.52 (s, 1H), 8.16 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.69 (s, 2H), 4.47 – 4.41 (m, 1H), 3.87 (s, 3H), 1.74 – 1.70 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.19 – 1.15 (m, 2H), 1.07 – 1.06 (m, 2H). LCMS observed *m/z* = 567.3 $[M+H]^+$.

39.1 EXAMPLE 39

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methoxy)-7*H*-purine.

Compound 39



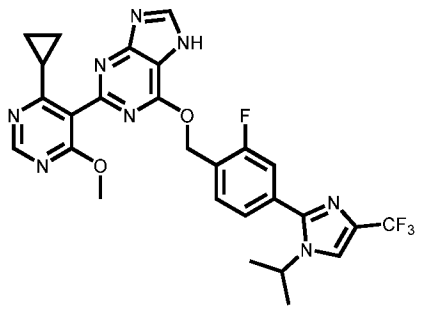
To a mixture of (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol (67.2 mg, 0.217 mmol) in *N,N*-dimethylformamide (0.619 mL) was added sodium hydride (13.0 mg, 60% dispersion in mineral oil, 0.325 mmol). The mixture was stirred at 23 °C for 30 minutes. To the mixture was added 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine (75.0 mg, 0.217 mmol). The

resulting mixture was stirred at 80 °C for 5 hours. The mixture was concentrated under reduced pressure and The crude product was purified by preparatory HPLC (mobile phase: 10–70% acetonitrile in water) to afford (60.0 mg, 48.1% yield) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methoxy)-7*H*-purine as a tan oil. ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.38 (s, 1H), 7.74 (s, 1H), 4.87 (s, 2H), 4.38 – 4.27 (m, 3H), 4.21 (hept, J = 6.7 Hz, 1H), 4.14 – 4.03 (m, 3H), 3.91 (s, 3H), 1.78 – 1.67 (m, 1H), 1.48 (d, J = 6.7 Hz, 6H), 1.21 – 1.09 (m, 2H), 0.97 – 0.82 (m, 2H). LCMS observed *m/z* = 577.3 $[M+H]^+$.

40.1 EXAMPLE 40

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7*H*-purine.

Compound 40

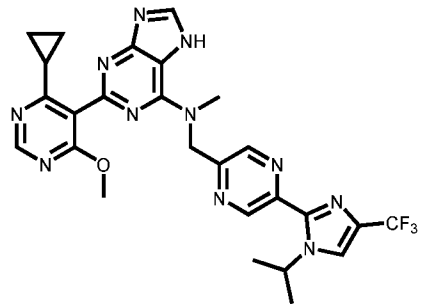


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with (2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate I). ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.39 (s, 1H), 7.95 (s, 1H), 7.81 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 10.1 Hz, 2H), 5.82 (s, 2H), 4.57 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.79 – 1.68 (m, 1H), 1.47 (d, J = 6.6 Hz, 6H), 1.19 – 1.10 (m, 2H), 0.94 – 0.85 (m, 2H). LCMS observed *m/z* = 569.2 $[M+H]^+$.

41.1 EXAMPLE 41

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((5-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)methyl)-*N*-methyl-7*H*-purin-6-amine.

Compound 41

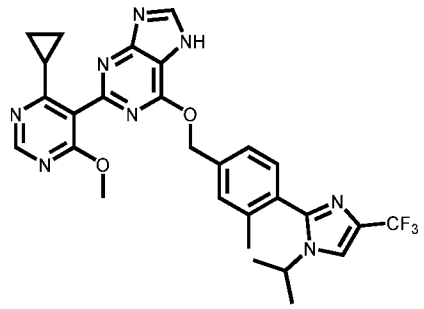


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with 1-(5-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyrazin-2-yl)-*N*-methylmethanamine•HCl (Intermediate W). ^{1}H NMR (400 MHz, CD_3OD) δ 9.15 (s, 1H), 8.72 (s, 1H), 8.57 (s, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 5.62 (hept, J = 6.2 Hz, 1H), 5.39 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 1.83 – 1.70 (m, 1H), 1.51 (d, J = 6.7 Hz, 6H), 1.13 – 1.03 (m, 2H), 0.92 – 0.77 (m, 2H). LCMS observed *m/z* = 566.3 $[M+H]^+$.

42.1 EXAMPLE 42

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)-3-methylbenzyl)oxy)-7*H*-purine.

Compound 42

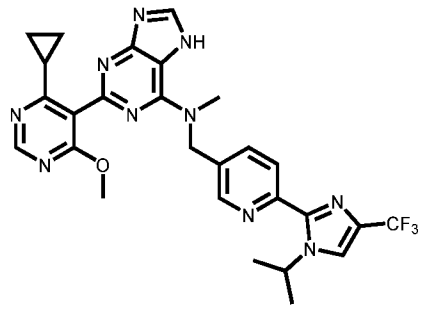


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)-3-methylphenyl)methanol (Intermediate F). ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.39 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 5.73 (s, 2H), 4.11 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 2.17 (s, 3H), 1.77 – 1.70 (m, 1H), 1.40 (d, J = 6.7 Hz, 6H), 1.18 – 1.11 (m, 2H), 0.93 – 0.86 (m, 2H). LCMS observed *m/z* = 565.3 $[M+H]^+$.

43.1 EXAMPLE 43

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-((6-(1-isopropyl-4-(trifluoro-methyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methyl)-*N*-methyl-7*H*-purin-6-amine.

Compound 43

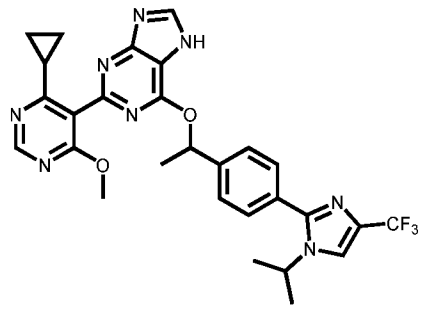


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with 1-(6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)-*N*-methyl-methanamine•HCl (Intermediate S). ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 8.56 (s, 1H), 8.08 (s, 1H), 7.98 – 7.89 (m, 3H), 5.67 (hept, J = 6.7 Hz, 1H), 5.33 (s, 2H), 3.92 (s, 3H), 3.61 (s, 3H), 1.84 – 1.74 (m, 1H), 1.49 (d, J = 6.7 Hz, 6H), 1.16 – 1.06 (m, 2H), 0.93 – 0.84 (m, 2H). LCMS observed *m/z* = 565.3 $[M+H]^+$.

44.1 EXAMPLE 44

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethoxy)-7*H*-purine.

Compound 44

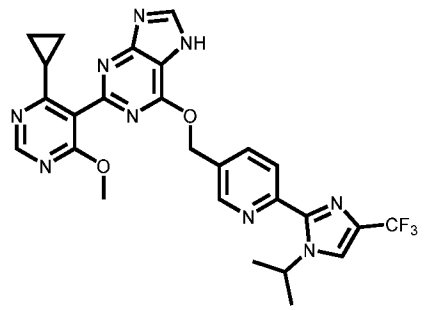


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-ol (Intermediate Q). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.40 (s, 1H), 7.91 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.54 (d, 2H), 6.64 (q, J = 6.5 Hz, 1H), 4.53 (hept, J = 6.8 Hz, 1H), 3.86 (s, 3H), 1.79 (d, J = 6.5 Hz, 3H), 1.66 – 1.55 (m, 1H), 1.44 (dd, J = 9.8, 6.7 Hz, 6H), 1.12 – 1.03 (m, 2H), 0.91 – 0.64 (m, 2H). LCMS observed *m/z* = 565.3 $[M+H]^+$.

45.1 EXAMPLE 45

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methoxy)-7*H*-purine.

Compound 45

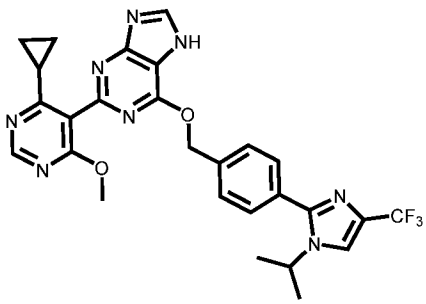


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with (6-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)pyridin-3-yl)methanol (Intermediate T). ^{1}H NMR (400 MHz, CD_3OD) δ 8.84 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.10 (dd, J = 8.2, 2.2 Hz, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.95 (s, 1H), 5.78 (s, 2H), 5.71 (hept, J = 6.7 Hz, 1H), 3.90 (s, 3H), 1.76 – 1.65 (m, 1H), 1.49 (d, J = 6.7 Hz, 6H), 1.20 – 1.07 (m, 2H), 0.95 – 0.81 (m, 2H). LCMS observed *m/z* = 552.2 $[M+H]^+$.

46.1 EXAMPLE 46

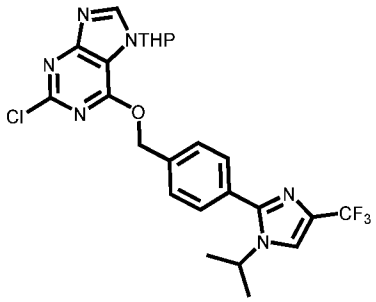
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7*H*-purine.

Compound 46



Step 1: Preparation of 2-chloro-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

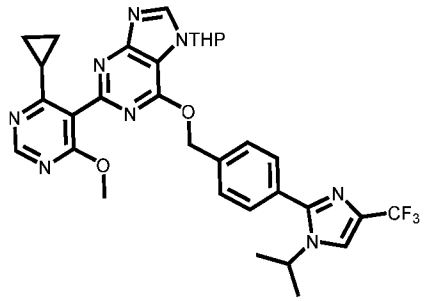
Compound 46.1



To a mixture of 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (500 mg, 1.83 mmol) and (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanol (Intermediate C) (520 mg, 1.83 mmol) in acetonitrile (10.0 mL) was added potassium carbonate (760 mg, 5.49 mmol) and stirred at 60 °C for 16 hours. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 X 30 mL). The combined organic layer was washed with water (40 mL), brine (40 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–35% EtOAc in hexanes) to afford (100 mg) of 2-chloro-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine as a white solid. LCMS observed *m/z* = 521.5 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

Compound 46.2

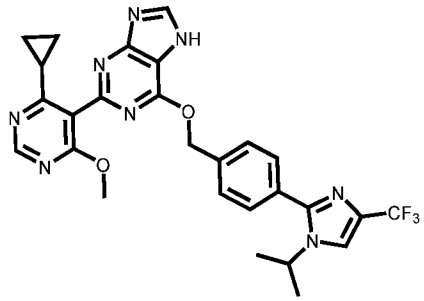


To a mixture of 2-chloro-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (100 mg, 0.190 mmol) in DME (5.00 mL) was added water (1.00 mL), (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid (70.0 mg, 0.380 mmol), and potassium carbonate (70.0 mg, 0.480 mmol) and purged with N_2 for 15 minutes. To the mixture was added tetrakis(triphenylphosphine)palladium(0) (20.0 mg, 0.0200 mmol) and the resulting mixture was subjected to microwave heating under N_2 at 100 °C for 2 hours. The mixture was filtered through celite and extracted with

EtOAc (50 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–70% EtOAc in hexanes) to afford (50.0 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine as a white solid. LCMS observed *m/z* = 635.6 $[M+H]^+$.

Step 3: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7*H*-purine.

Compound 46

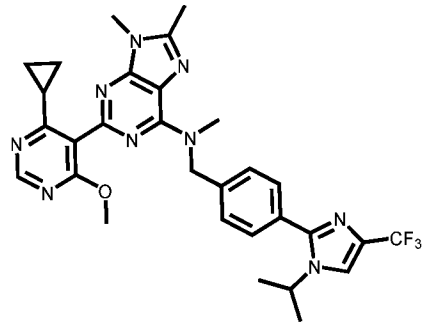


To 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (50.0 mg, 0.0800 mmol) in dichloromethane (5.00 mL) was added dropwise trifluoroacetic acid (0.0600 mL, 0.790 mmol) at 0 °C. The resulting mixture was stirred at 23 °C for 45 minutes. The reaction mixture was concentrated under reduced pressure and The crude product was purified by preparatory HPLC (mobile phase: 10–70% acetonitrile in water with 0.1% formic acid) to afford (18.0 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)oxy)-7*H*-purine as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (br s, 1H), 8.68 (s, 1H), 8.47 (br s, 1H), 8.19 (s, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 5.69 (s, 2H), 4.51 – 4.45 (m, 1H), 3.85 (s, 3H), 1.76 – 1.70 (m, 1H), 1.42 – 1.40 (d, J = 6.8 Hz, 6H), 1.05 – 1.03 (m, 2H), 0.90-0.80 (m, 2H). LCMS observed *m/z* = 551.4 $[M+H]^+$.

47.1 EXAMPLE 47

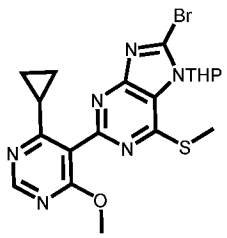
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,7,8-trimethyl-9*H*-purin-6-amine.

Compound 47



Step 1: Preparation of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

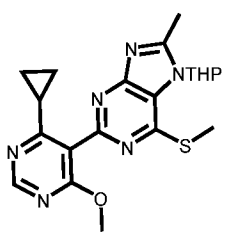
Compound 47.1



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (1.60 g, 4.01 mmol) in THF (20.0 mL) was added *n*-butyllithium (0.386 g, 6.02 mmol) at -78 °C and stirred for 15 minutes. To the mixture was added cyanogen bromide (468 mg, 4.42 mmol). The resulting mixture was stirred at 23 °C for 15 minutes. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–20% EtOAc in hexanes) to afford (1.50 g) of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine as a white solid. LCMS observed *m/z* = 477.1 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

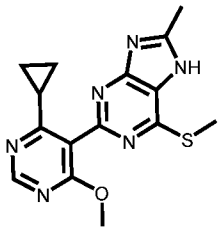
Compound 47.2



To a mixture of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (600 mg, 1.25 mmol) and trimethylboroxine (610 mg, 5.02 mmol) in 1,4-dioxane (8.00 mL) was added water (2.00 mL) and potassium carbonate (520 mg, 3.77 mmol) and purged with N_2 for 20 minutes. To the mixture was added bis(triphenylphosphine)palladium(II) dichloride (88.0 mg, 0.126 mmol) and the resulting mixture was stirred at 100 °C for 16 hours in a sealed tube. The mixture was diluted with cold water (20 mL) and extracted with EtOAc (3 X 25 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–30% EtOAc in hexanes) to afford (400 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine as a white solid. LCMS observed *m/z* = 413.3 $[M+H]^+$.

Step 3: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7*H*-purine.

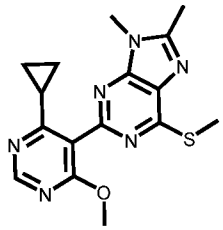
Compound 47.3



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (200 mg, 0.450 mmol) in dichloromethane (3.00 mL) was added dropwise trifluoroacetic acid (1.00 mL) at 0 °C. The resulting mixture was stirred at 23 °C for 2 hours. The mixture was concentrated under reduced pressure and the residue was triturated in pentane (5 mL) to afford (50.0 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7*H*-purine as a white solid. LCMS observed *m/z* = 329.0 $[M+H]^+$.

Step 4: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-(methylthio)-9*H*-purine.

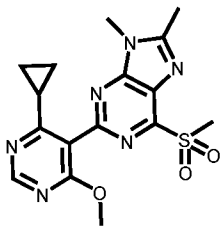
Compound 47.4



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7*H*-purine (250 mg, 0.761 mmol) in *N,N*-dimethylformamide (2.00 mL) was added potassium carbonate (210 mg, 1.52 mmol) at 0 °C and stirred for 10 minutes. To the mixture was added dropwise iodomethane (130 mg, 0.914 mmol) and the resulting mixture was stirred at 23 °C for 16 hours. The mixture was cooled to 0 °C, diluted with cold water (10 mL) and extracted with EtOAc (2 X 25 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 5-7% MeOH in dichloromethane) to afford (144 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-(methylthio)-9*H*-purine as a white solid. The material was carried forward as a mix of regioisomers. LCMS observed *m/z* = 343.1 $[M+H]^+$.

Step 5: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-(methylsulfonyl)-9*H*-purine.

Compound 47.5

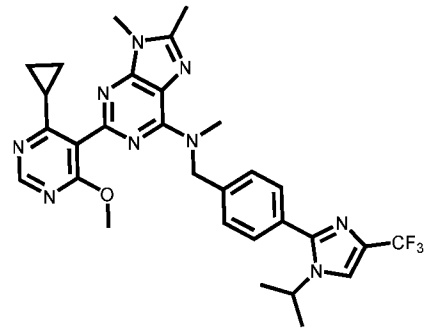


To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-(methylthio)-9*H*-purine (144 mg, 0.421 mmol) in dichloromethane (5.00 mL) was added 3-chloroperoxybenzoic acid (181 mg, 1.05 mmol) at 0°C and the resulting mixture was stirred at 0 °C for 4 hours. The mixture was diluted with a saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (2 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50–70% EtOAc in hexanes) to afford (114 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-

(methylsulfonyl)-9*H*-purine. The material was carried forward as a mix of regioisomers. LCMS observed *m/z* = 375.0 $[M+H]^+$.

Step 6: Preparation 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8,9-trimethyl-9*H*-purin-6-amine.

Compound 47

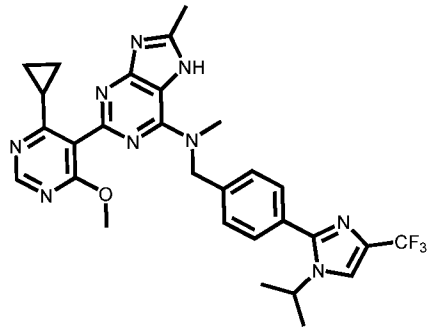


To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8,9-dimethyl-6-(methylthio)-9*H*-purine (115 mg, 0.307 mmol) in *N,N*-dimethylformamide (1.00 mL) was added 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methylmethanamine (91.0 mg, 0.307 mmol, Intermediate E) and *N,N*-diisopropylethylamine (198 mg, 1.53 mmol). The mixture was stirred at 90 °C for 48 hours. The mixture was diluted with water (10 mL) and extracted with dichloromethane (2 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparatory HPLC (mobile phase: 10–98% acetonitrile in water) to afford (3.00 mg, 2% yield) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8,9-trimethyl-9*H*-purin-6-amine as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 8.61 (s, 1H), 8.16 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 5.50 (br s, 2H), 4.47 – 4.43 (m, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.57 (br s, 3H), 2.53 (s, 3H), 1.73 – 1.72 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10 – 0.98 (m, 2H), 0.96 – 0.70 (m, 2H). LCMS observed *m/z* = 592.5 $[M+H]^+$.

48.1 EXAMPLE 48

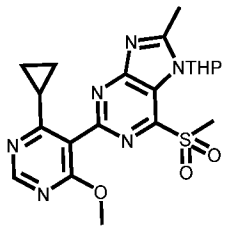
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7*H*-purin-6-amine.

Compound 48



Step 1: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylsulfonyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

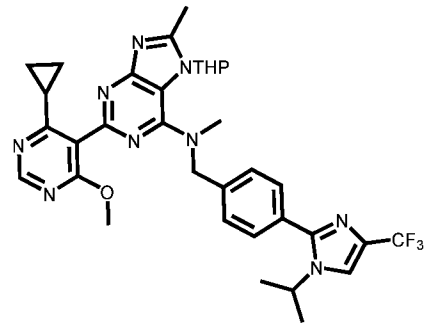
Compound 48.1



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (150 mg, 0.364 mmol, Compound 47.2) in dichloromethane (3.00 mL) was added 3-chloroperoxybenzoic acid (157 mg, 0.909 mmol) at 0°C and the resulting mixture was stirred at 0 °C for 16 hours. The mixture was diluted with a saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (2 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (100 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylsulfonyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine. LCMS observed *m/z* = 445.5 $[M+H]^+$.

Step 2: Preparation 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

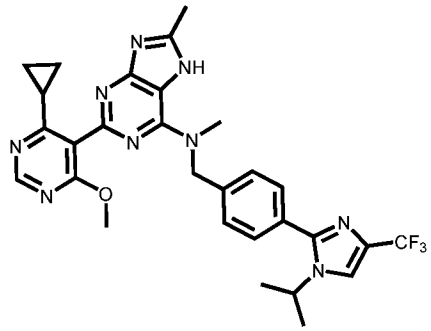
Compound 48.2



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-6-(methylsulfonyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (100 mg, 0.225 mmol) in *N*,*N*-dimethylformamide (1.00 mL) was added 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methylmethanamine (67.0 mg, 0.225 mmol, Intermediate E) and *N*,*N*-diisopropylethylamine (0.108 mL, 0.627 mmol). The mixture was stirred at 65 °C for 16 hours. The mixture was diluted with water (10 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford (100 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

Step 3: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7*H*-purin-6-amine.

Compound 48

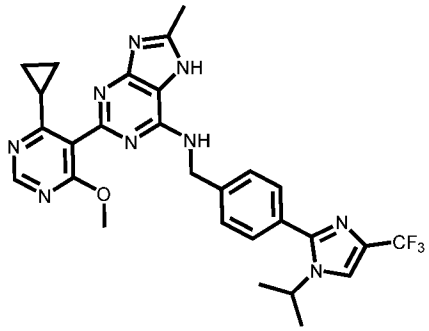


To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (115 mg, 0.174 mmol) in dichloromethane (3.00 mL) was added dropwise trifluoroacetic acid (1.00 mL) at 0 °C. The resulting mixture was stirred at 23 °C for 2 hours. The mixture was concentrated under reduced pressure and The crude product was purified by preparatory HPLC (mobile phase: 10-100% acetonitrile in water) to afford (24.0 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-*N*,8-dimethyl-7*H*-purin-6-amine as a white solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) 12.84 (s, 1H), 8.60 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 5.16 (br s, 2H), 4.49 – 4.43 (m, 1H), 3.83 (s, 3H), 3.46 (br s, 3H), 2.47 (s, 3H), 1.80 – 1.82 (m, 1H), 1.35 (d, J = 7.2 Hz, 6H), 0.98 – 0.89 (m, 2H), 0.84 – 0.81 (m, 2H). LCMS observed *m/z* = 578.5 $[M+H]^+$.

49.1 EXAMPLE 49

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-8-methyl-7*H*-purin-6-amine.

Compound 49

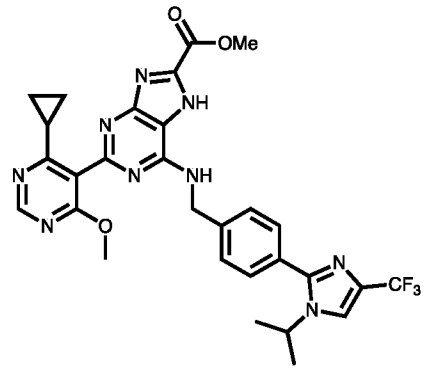


The title compound was prepared using a similar procedure as Compound 48, replacing 1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)-*N*-methylmethanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate B). ^{1}H NMR (400 MHz, DMSO-d$_6$) 12.81 (br s, 1H), 8.60 (s, 1H), 8.30 (br s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.47 (br s, 4H), 4.73 (br s, 2H), 4.46 – 4.40 (m, 1H), 3.81 (s, 3H), 2.49 (s, 3H), 1.73 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.96 (m, 2H), 0.82 – 0.75 (m, 2H). LCMS observed *m/z* = 564.5 [M+H]$^+$.

50.1 EXAMPLE 50

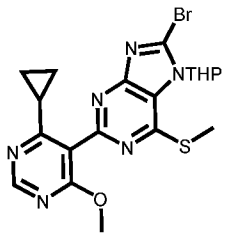
Synthesis of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine-8-carboxylate.

Compound 50



Step 1: Preparation of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine.

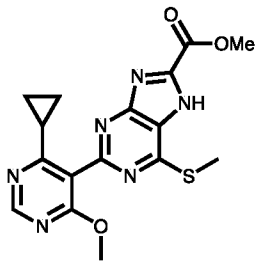
Compound 50.1



To a mixture of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (1.60 g, 4.01 mmol) in THF (20.0 mL) was added *n*-butyllithium (0.386 g, 6.02 mmol) at -78 °C and stirred for 15 minutes. To the mixture was added cyanogen bromide (468 mg, 4.42 mmol). The resulting mixture was stirred at 23 °C for 15 minutes. The reaction mixture was quenched with saturated ammonium chloride (20 mL) and extracted with EtOAc (3 X 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 0–20% EtOAc in hexanes) to afford (1.50 g) of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine as a white solid. LCMS observed *m/z* = 477.1 [M+H]+.

Step 2: Preparation of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7*H*-purine-8-carboxylate.

Compound 50.2

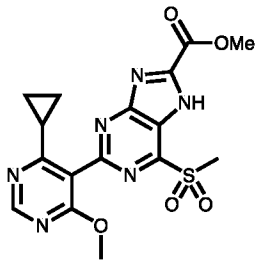


To a mixture of 8-bromo-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (500 mg, 1.04 mmol) in MeOH (1.00 mL) and 1,4-dioxane (5.00 mL) in a steel bomb was added *N,N*-diisopropylethylamine (0.720 mL, 4.19 mmol) and purged with N_2 for 20 minutes. To the mixture was added [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II) (70.0 mg, 0.100 mmol) and CO gas (150 psi) was added and the resulting mixture was stirred at 70 °C for 16 hours. The mixture was diluted with cold water (20 mL) and extracted with EtOAc (2 X 20 mL). The combined organic layer was washed with water (20 mL), brine (20 mL), dried over

anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 20–30% EtOAc in hexanes) to afford (200 mg) of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7*H*-purine-8-carboxylate as a yellow solid. LCMS observed *m/z* = 373.1 $[M+H]^+$.

Step 3: Preparation of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine-8-carboxylate.

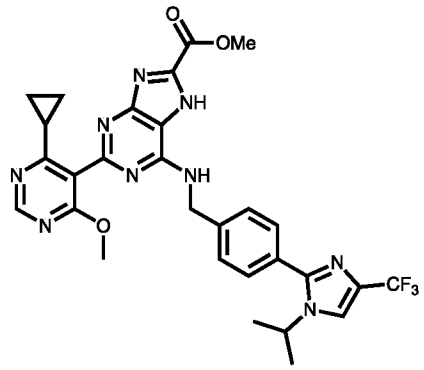
Compound 50.3



To a mixture of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylthio)-7*H*-purine-8-carboxylate (340 mg, 0.910 mmol) in dichloromethane (5.00 mL) was added 3-chloroperoxybenzoic acid (315 mg, 1.82 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 4 hours. The mixture was diluted with a saturated sodium bicarbonate solution (5 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50–70% EtOAc in hexanes) to afford (300 mg) of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine-8-carboxylate. LCMS observed *m/z* = 405.2 $[M+H]^+$.

Step 4: Preparation of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7*H*-purine-8-carboxylate.

Compound 50



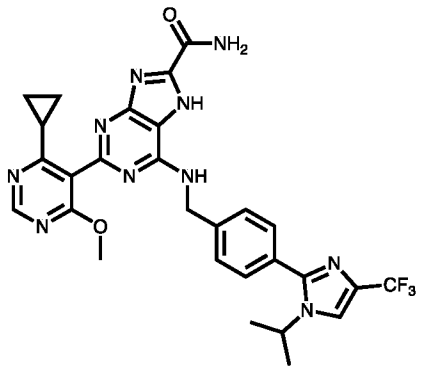
To a mixture of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine-8-carboxylate (110 mg, 0.272 mmol) and (4-(1-isopropyl-4-

(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (92.0 mg, 0.326 mmol, Intermediate B) in *N,N*-dimethylformamide (2.00 mL) was added *N,N*-diisopropylethylamine (176 mg, 1.36 mmol) and stirred at 23 °C for 16 hours. To the mixture was added and the resulting mixture was stirred at 70 °C for 16 hours. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (2 X 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by preparatory HPLC (mobile phase: 10–65% acetonitrile in water) to afford (91.0 mg) of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7*H*-purine-8-carboxylate as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) 14.06 (br s, 1H), 9.06 (br s, 1H), 8.61 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.47 (s, 4H), 4.74 (d, J = 4.8 Hz, 2H), 4.46 – 4.40 (m, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 1.73 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96 – 0.95 (m, 2H), 0.26 – 0.24 (m, 2H). LCMS observed *m/z* = 608.4 $[M+H]^+$.

51.1 EXAMPLE 51

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7*H*-purine-8-carboxamide.

Compound 51



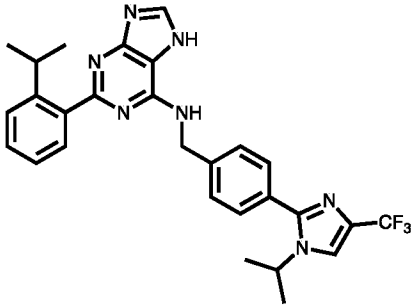
To a mixture of methyl 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7*H*-purine-8-carboxylate (67.0 mg, 0.110 mmol, Compound 50) in MeOH (2.00 mL) was added 25% aqueous ammonia solution (1.00 mL) at 0 °C. The resulting mixture was stirred at 23 °C for 48 hours. The reaction mixture was concentrated under reduced pressure and The crude product was purified by preparatory HPLC (mobile phase: 15–95% acetonitrile in water) to afford (9.40 mg) of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-7*H*-purine-8-carboxamide as a white solid. ^{1}H NMR (400

MHz, DMSO-d_6) 13.63 (br s, 1H), 8.61 (s, 1H), 8.38 (br s, 1H), 8.15 (s, 1H), 7.92 (br s, 2H), 7.49 (s, 4H), 4.77 (br s, 2H), 4.47 – 4.42 (m, 1H), 3.82 (s, 3H), 1.72 – 1.70 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 0.90 – 0.88 (m, 2H), 0.41 – 0.21 (m, 2H). LCMS observed *m/z* = 593.4 $[M+H]^+$.

52.1 EXAMPLE 52

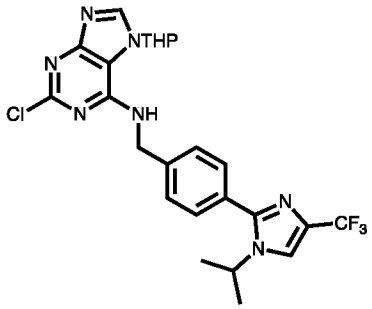
Synthesis of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7*H*-purin-6-amine.

Compound 52



Step 1: Preparation of 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

Compound 52.1

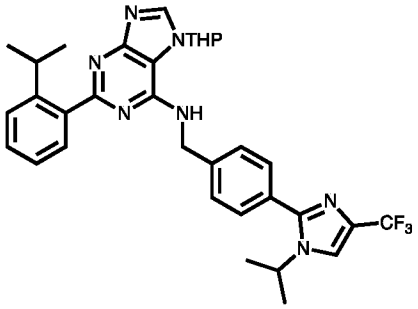


To a stirred solution of 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine (0.7 g, 2.57 mmol, Intermediate AA) in ethanol (10 mL) was added *N,N*-diisopropylethylamine (1.34 mL, 7.71 mmol) at 0 °C and the reaction mixture was stirred at 0 °C for 15 min. (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (0.81 g, 2.83 mmol, Intermediate B) was added and the reaction mixture was stirred at 70 °C for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layer was washed with brine (10 mL) dried over anhydrous sodium sulfate, filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by flash chromatography (silica gel, 80% EtOAc in petroleum ether) to afford 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-

yl)-7*H*-purin-6-amine (1.00 g, 75%) as white solid. LCMS observed *m/z* = 520.44 $[M+H]^+$.

Step 2: Preparation of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine.

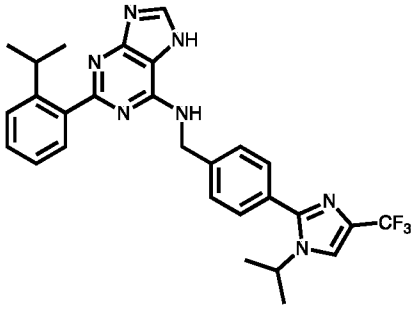
Compound 52.2



To a solution of 2-chloro-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (350 mg, 0.66 mmol) and (2-isopropylphenyl)boronic acid (165 mg, 1.0 mmol) in 1,2-dimethoxyethane (2 mL), Milli-Q Water (0.2 mL) was added potassium carbonate (464 mg, 3.36 mmol) at room temperature. The reaction mixture was degassed with nitrogen gas for 10 minutes before adding tetrakis(triphenylphosphine)palladium(0) (78 mg, 0.07 mmol). The reaction mixture was degassed with nitrogen gas for additional 5 minutes and then stirred at 100 °C for 2 h under microwave irradiation. The reaction mixture was filtered through celite bed and the bed was thoroughly washed with EtOAc (50 mL). The combined organic layer was washed with water (5 mL), brine (5 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 50% EtOAc in petroleum ether) to afford *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (260 mg) as a brown gum. LCMS observed *m/z* = 604.63 $[M+H]^+$.

Step 3: Preparation of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7*H*-purin-6-amine.

Compound 52

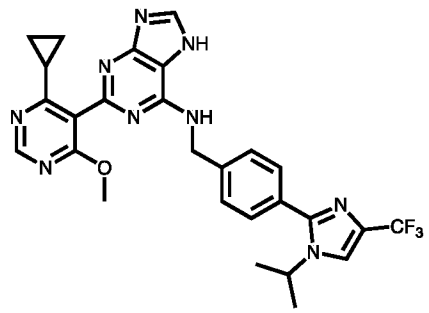


To a stirred solution of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purin-6-amine (200 mg, 0.33 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (0.07 mL, 0.99 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion, the reaction mixture was concentrated and the residue was basified with sat. sodium bicarbonate solution and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by SFC purification method to afford *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-isopropylphenyl)-7*H*-purin-6-amine (58 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.36 (br s, 1H), 8.16-8.15 (m, 2H), 7.50-7.44 (m, 5H), 7.36-7.30 (m, 2H), 7.21-7.17 (m, 1H), 4.81 (s, 2H), 4.48-4.41 (m, 1H), 3.58-3.51 (m, 1H), 1.38-1.37 (m, 6H), 1.01-1.0 (m, 6H). LCMS observed *m/z* = $[M+H]^+$ = 520.43.

53.1 EXAMPLE 53

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine.

Compound 53



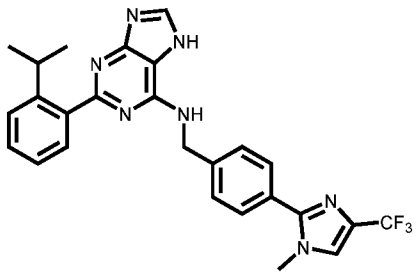
The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 8.60 (s, 1H), 8.41 (s, 1H), 8.19 (s, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.48 (s, 4H), 5.16-4.74 (m, 2H), 4.47-4.40 (m, 1H), 3.81 (s, 3H), 1.76-1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96-0.94 (m, 2H), 0.75-0.73 (m, 2H). LC LCMS observed *m/z* = 550.42 $[M+H]^+$.

54.1 EXAMPLE 54

Preparation of 2-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-7*H*-purin-6-amine.

Compound 54

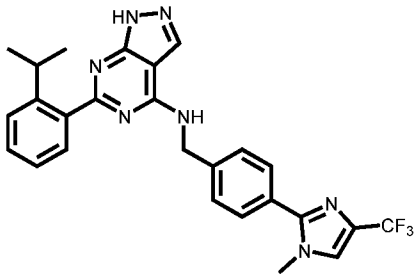


The title compound was prepared using a similar procedure as Compound 52, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate A). ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.67 (s, 1H), 7.61 (d, J = 7.8 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H), 7.46 – 7.33 (m, 3H), 7.21 (t, J = 7.0 Hz, 1H), 4.95 (s, 2H), 3.75 (s, 3H), 3.39 (hept, J = 6.9 Hz, 1H), 1.11 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 492.2 $[M+H]^+$.

55.1 EXAMPLE 55

Synthesis of 6-(2-isopropylphenyl)-*N*-(4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine.

Compound 55



The title compound was prepared using a similar procedure as Compound 52, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine and 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)-7*H*-purine with (4-(1-methyl-4-

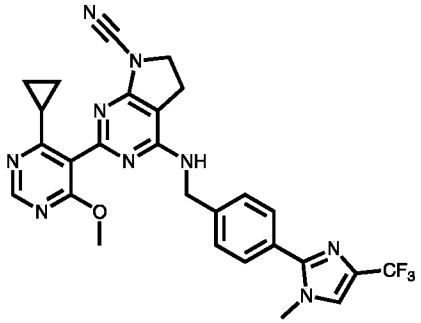
(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (Intermediate A) and 4,6-dichloro-1*H*-pyrazolo[3,4-*d*]pyrimidine.

^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, J = 11.1 Hz, 2H), 7.69 (s, 1H), 7.63 (d, J = 7.9 Hz, 2H), 7.55 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.7 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.24 (t, J = 6.9 Hz, 1H), 4.95 (s, 2H), 3.78 (s, 3H), 3.43 (hept, J = 6.9 Hz, 1H), 1.22 – 1.11 (m, 6H). LCMS observed *m/z* = 492.2 $[M+H]^+$.

56.1 EXAMPLE 56

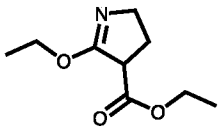
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile.

Compound 56



Step 1: Preparation of ethyl 5-ethoxy-3,4-dihydro-2*H*-pyrrole-4-carboxylate.

Compound 56.1

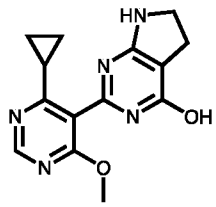


To a stirred solution of ethyl 2-oxopyrrolidine-3-carboxylate (5.00 g, 31.8 mmol) in dichloromethane (10.0 mL) was added triethyloxonium tetrafluoroborate (12.1 g, 63.6 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 16 h. After completion, the reaction mixture was basified with saturated potassium carbonate solution (90 mL) to pH 8 and subsequently, the product was extracted with dichloromethane (2 x 80 mL). The combined organic layers were washed with water (70 mL), brine (70 mL), dried over anhydrous sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash chromatography (silica gel, 20% EtOAc in petroleum ether) to afford ethyl 5-ethoxy-3,4-dihydro-2*H*-pyrrole-4-carboxylate (4.00 g) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$,) δ 4.26 – 4.17 (m, 4H), 3.80 – 3.78 (m, 1H), 3.67 – 3.56 (m, 1H), 3.56 (t, J = 4.2 Hz, 1H), 2.36 – 2.30 (m, 2H), 1.32 – 1.26 (m, 6H).

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol.

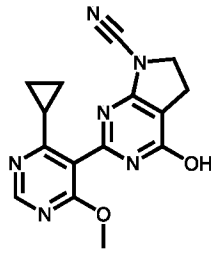
Compound 56.2



To a stirred solution of 4-cyclopropyl-6-methoxypyrimidine-5-carboximidamide (1.00 g, 5.20 mmol) and ethyl 5-ethoxy-3,4-dihydro-2*H*-pyrrole-4-carboxylate (2.89 g, 15.6 mmol) in MeOH (10 mL) was added sodium hydride (0.15 g, 6.24 mmol) at 0 °C and the reaction mixture was stirred for 10 min. Then, the reaction mixture was heated to 50 °C and stirred for 16 h. Upon completion, the reaction mixture was concentrated under reduced pressure, and The crude product was purified by preparative HPLC (mobile phase: 20-100% acetonitrile in water w/ 0.1% formic acid) afford the desired product 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (0.3 g) as an off-white solid. LCMS observed *m/z* = 285.97 $[M+H]^+$.

Step 3: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-hydroxy-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile.

Compound 56.3

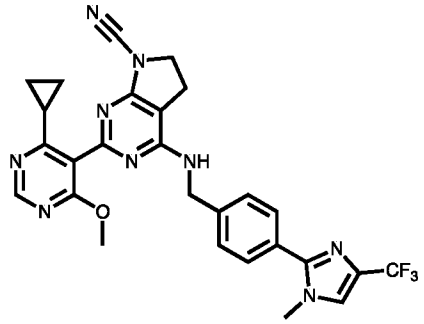


To a stirred solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6,7-dihydro-5*H*-pyrrolo[2,3-*d*]pyrimidin-4-ol (0.300 g, 1.05 mmol) in *N*,*N*-dimethylformamide (3.0 mL) and tetrahydrofuran (3.0 mL) was added sodium hydride (0.130 g, 5.26 mmol) at 0 °C, and the suspension was stirred for 30 min before adding cyanogen bromide (0.220 g, 2.10 mmol). The resulting reaction mixture was stirred at 23 °C for 2 h. Upon completion, the mixture was diluted with ice-cold water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the crude product was purified by preparative HPLC (mobile phase: 20-100% acetonitrile in water w/ 0.1% formic acid) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-

5-yl)-4-hydroxy-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile (90.0 mg) as an off-white solid. LCMS observed *m/z* = 311.02 $[M+H]^+$.

Step 4: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile.

Compound 56

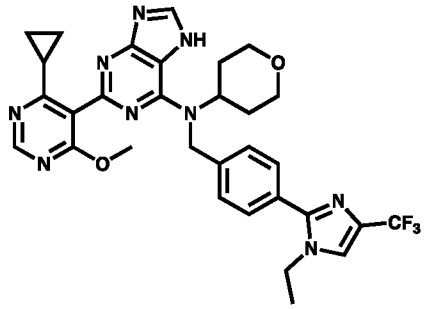


To a stirred solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-hydroxy-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile (85.0 mg, 0.27 mmol) in dichloromethane (5.0 mL) were added *N,N*-diisopropylethylamine (0.15 mL, 0.82 mmol) and trifluoromethanesulfonic anhydride (0.06 mL) at 0 °C. The mixture was stirred for 2 h then (4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine (70.0 mg, 0.280 mmol) was added, and the resulting reaction mixture was stirred at 0 °C for 16 h. Upon completion, the mixture was diluted with ice-cold water (30 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure and The crude product was purified by preparative HPLC (mobile phase: 10–76% acetonitrile in water w/ 0.1% NH_4CO_3) to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-methyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)amino)-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carbonitrile (14.0 mg, 9% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.94 – 7.90 (m, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.65 (d, J = 6.0 Hz, 2H), 4.14 (t, J = 8.6 Hz, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 3.05 (t, J = 8.4 Hz, 2H), 1.70 – 1.64 (m, 1H), 0.97 – 0.86 (m, 2H), 0.81 – 0.79 (m, 2H). LCMS observed *m/z* = 548.43 $[M+H]^+$.

57.1 EXAMPLE 57

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-7H-purin-6-amine.

Compound 57

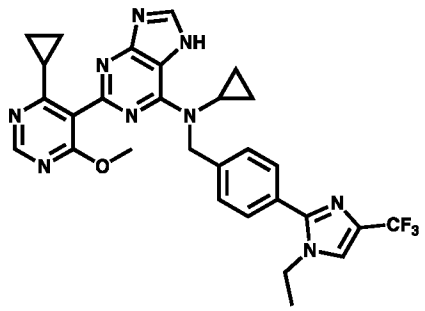


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)tetrahydro-2H-pyran-4-amine (Intermediate AJ). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (br s, 1H), 8.58 (s, 1H), 8.24 (br s, 1H), 8.00 (s, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 5.05 (br s, 3H), 4.06 (q, J = 7.2 Hz, 2H), 3.91 – 3.80 (m, 5H), 3.40 – 3.40 (m, 2H), 1.90 – 1.78 (m, 3H), 1.78 – 1.67 (m, 2H), 1.33 (t, J = 5.6 Hz, 3H), 1.29 – 1.23 (m, 4H). LCMS observed *m/z* = 620.5 [M+H]$^+$.

58.1 EXAMPLE 58

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 58

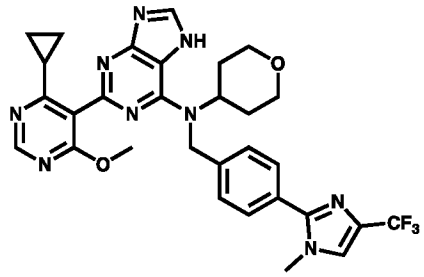


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)cyclopropanamine (Intermediate AN). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (br s, 1H), 8.61 (s, 1H), 8.22 (br s, 1H), 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.34 (br s, 2H), 4.05 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.16 – 3.16 (m, 1H), 1.83 – 1.83 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.98 – 0.80 (m, 8H). LCMS observed *m/z* = 576.4 [M+H]$^+$.

59.1 EXAMPLE 59

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-7H-purin-6-amine.

Compound 59

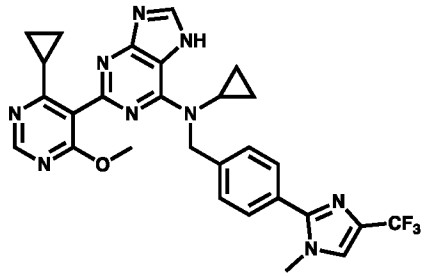


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)tetrahydro-2H-pyran-4-amine (Intermediate AH). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.18 (s, 1H), 8.58 (br s, 1H), 8.24 (br s, 1H), 7.91 (s, 1H), 7.61 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.01 – 5.06 (m, 3H), 3.91 – 3.89 (m, 2H), 3.80 – 3.75 (m, 6H), 3.42 – 3.40 (m, 2H), 1.84 – 1.64 (m, 5H), 0.93 – 0.75 (m, 4H). LCMS observed *m/z* = 606.4 [M+H]$^+$.

60.1 EXAMPLE 60

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 60

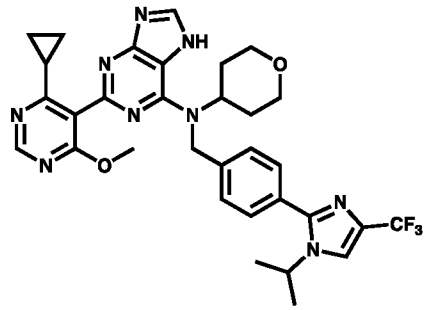


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)cyclopropanamine (Intermediate AL). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.19 (br s, 1H), 8.62 (s, 1H), 8.30 (br s, 1H), 7.91 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 5.30 (br s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.17 – 3.17 (m, 1H), 1.83 – 1.83 (m, 1H), 0.99 – 0.92 (m, 4H), 0.82 – 0.82 (m, 4H). LCMS observed *m/z* = 562.4 [M+H]$^+$.

61.1 EXAMPLE 61

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-7H-purin-6-amine.

Compound 61

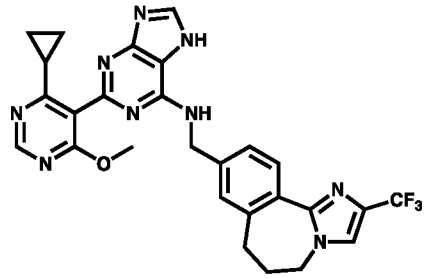


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)tetrahydro-2H-pyran-4-amine (Intermediate AF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.58 (s, 1H), 8.25 – 8.16 (m, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 6.02 – 5.06 (m, 3H), 4.45 – 4.42 (m, 1H), 3.92 – 3.90 (m, 2H), 3.80 (s, 3H), 3.40 (br s, 2H), 1.84 – 1.82 (m, 5H), 1.39 (d, J = 6.4 Hz, 6H), 0.93 – 0.73 (m, 4H). LCMS observed m/z = 634.4 $[M+H]^+$.

62.1 EXAMPLE 62

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)-7H-purin-6-amine.

Compound 62



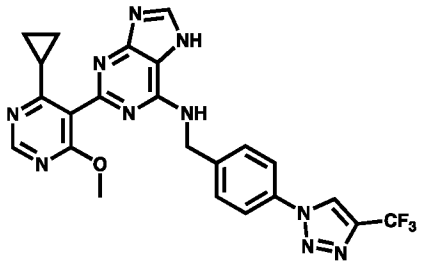
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2-(trifluoromethyl)-6,7-dihydro-5*H*-benzo[*c*]imidazo[1,2-*a*]azepin-9-yl)methanamine (Intermediate BH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.54 (s, 1 H), 8.14 (s, 1H), 7.73 (s, 1H), 7.63 – 7.59 (m, 1H), 7.47 – 7.41 (m 1H), 7.40 (m. 1H), 3.99 (t, J = 6.9 Hz, 2H),

3.91 (s, 3H), 2.70 (t, J = 7.1 Hz, 2H), 2.34 (pent., J = 7.0 Hz, 2H), 1.78 – 1.66 (m, 1H), 1.11 – 1.05 (m, 2H), 0.85 – 0.77 (m, 2H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

63.1 EXAMPLE 63

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(4-(trifluoromethyl)-1*H*-1,2,3-triazol-1-yl)benzyl)-7*H*-purin-6-amine.

Compound 63

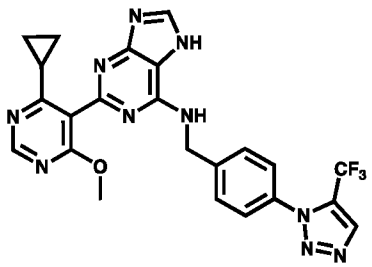


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(4-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 9.55 (s, 1H), 8.60 (s, 1H), 8.49 (br s, 1H), 8.19 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.58 – 7.58 (m, 2H), 4.74 (br s, 2H), 3.81 (s, 3H), 1.74 – 1.68 (m, 1H), 0.85 – 0.96 (m, 2H), 0.65 – 0.76 (m, 2H). LCMS observed *m/z* = 509.3 $[M+H]^+$.

64.1 EXAMPLE 64

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 64



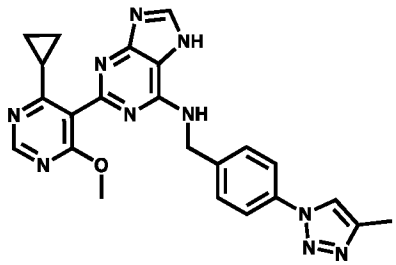
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(5-(trifluoromethyl)-1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AP). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.74 (s, 1H), 8.60 (s, 1H), 8.47 (br s, 1H), 8.20 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.56 – 7.56 (m, 2H), 4.74 (s, 2H), 3.80 (s, 3H), 1.71

– 1.68 (m, 1H), 0.94 – 0.83 (m, 2H), 0.73 – 0.65 (m, 2H). LCMS observed *m/z* = 509.3 $[M+H]^+$.

65.1 EXAMPLE 65

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(4-methyl-1H-1,2,3-triazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 65

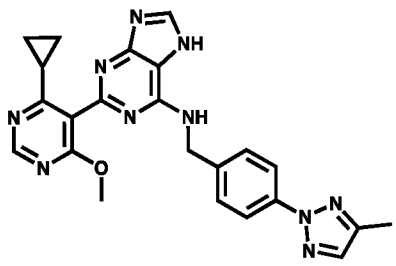


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(4-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (s, 1H), 8.60 (s, 1H), 8.47 (s, 2H), 8.19 (s, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.51 – 7.51 (m, 2H), 4.71 (br s, 2H), 3.81 (s, 3H), 2.31 (s, 3H), 1.73 – 1.69 (m, 1H), 0.95 – 0.95 (m, 2H), 0.74 – 0.74 (m, 2H). LCMS observed *m/z* = 455.3 $[M+H]^+$.

66.1 EXAMPLE 66

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(4-methyl-2H-1,2,3-triazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 66

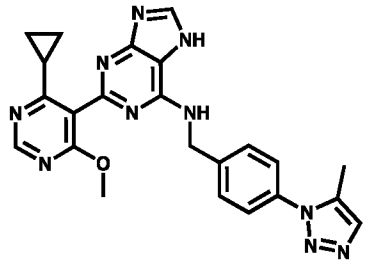


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(4-methyl-2H-1,2,3-triazol-2-yl)phenyl)methanamine (Intermediate AS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 8.60 (s, 1H), 8.42 (br s, 1H), 8.19 (s, 1H), 7.88 – 7.84 (m, 3H), 7.48 – 7.48 (m, 2H), 4.70 (br s, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 1.73 – 1.69 (m, 1H), 0.95 – 0.95 (m, 2H), 0.74 – 0.74 (m, 2H). LCMS observed *m/z* = 455.3 $[M+H]^+$.

67.1 EXAMPLE 67

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-1H-1,2,3-triazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 67

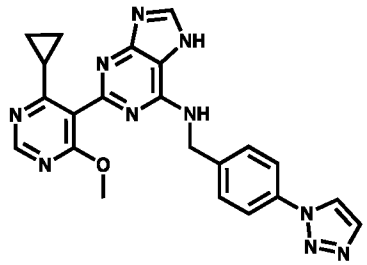


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(5-methyl-1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AQ). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.03 (s, 1H), 8.60 (s, 1H), 8.49 (brs, 1H), 8.20 (s, 1H), 7.67 (s, 1H), 7.52 – 7.52 (m, 4H), 4.76 (s, 2H), 3.81 (s, 3H), 2.29 (s, 3H), 1.74 – 1.69 (m, 1H), 0.96 – 0.96 (m, 2H), 0.75 – 0.75 (m, 2H). LCMS observed *m/z* = 455.3 $[M+H]^+$.

68.1 EXAMPLE 68

Preparation of N-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7H-purin-6-amine.

Compound 68

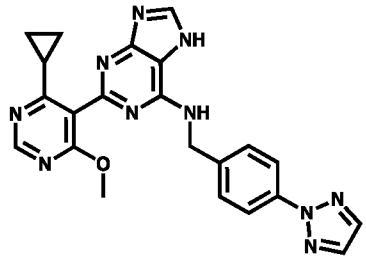


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AU). ^{1}H NMR (400 MHz, DMSO-d$_6$) 8.79 – 8.77 (m, 2H), 8.61 (d, J = 12.0 Hz, 2H), 8.29 (s, 1H), 7.96 (d, J = 0.8 Hz, 1H), 7.83 (d, J = 12.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 4.75 (br s, 2H), 3.82 (s, 3H), 1.71 (s, 1H), 0.97 (br s, 2H), 0.76 (br s, 2H). LCMS observed *m/z* = 441.3 $[M+H]^+$.

69.1 EXAMPLE 69

Preparation of N-(4-(2H-1,2,3-triazol-2-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7H-purin-6-amine.

Compound 69

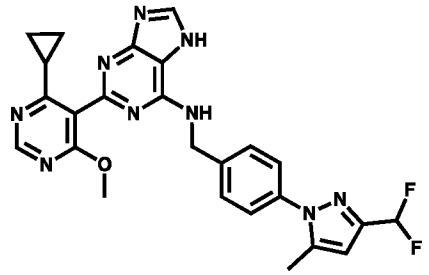


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(2H-1,2,3-triazol-2-yl)phenyl)methanamine (Intermediate AT). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (br s, 1H), 8.60 (s, 1H), 8.39 (br s, 1H), 8.19 (s, 1H), 8.09 (s, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 7.6 Hz, 2H), 4.72 (br s, 2H), 3.80 (s, 3H), 1.74 – 1.67 (m, 1H), 1.00 – 0.90 (m, 2H), 0.85 – 0.60 (m, 2H). LCMS observed *m/z* = 441.3 $[M+H]^+$.

70.1 EXAMPLE 70

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 70

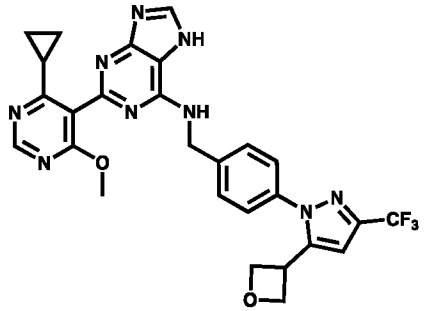


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(3-(difluoromethyl)-5-methyl-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BG). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.61 – 7.53 (m, 2H), 7.46 – 7.37 (m, 2H), 6.89 – 6.40 (m, 2H), 4.91 (s, 2H), 3.90 (s, 3H), 2.32 (s, 3H), 1.78 – 1.67 (m, 1H), 1.13 – 1.03 (m, 2H), 0.90 – 0.76 (m, 2H). LCMS observed *m/z* = 504.2 $[M+H]^+$.

71.1 EXAMPLE 71

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 71

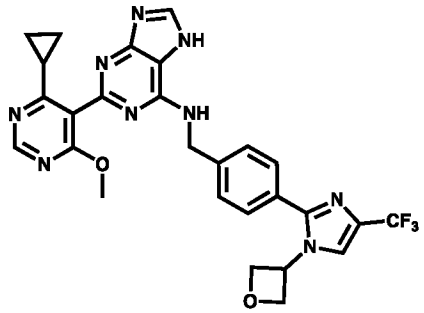


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(5-(oxetan-3-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate AZ). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.61 (s, 1H), 8.45 (br s, 1H), 8.21 (s, 1H), 7.49 (d, J = 5.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 4.74 – 4.62 (m, 5H), 4.31 – 4.27 (m, 1H), 3.82 (s, 3H), 1.75 – 1.71 (m, 1H), 0.97 – 0.97 (m, 2H), 0.87 – 0.87 (m, 3H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

72.1 EXAMPLE 72

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 72

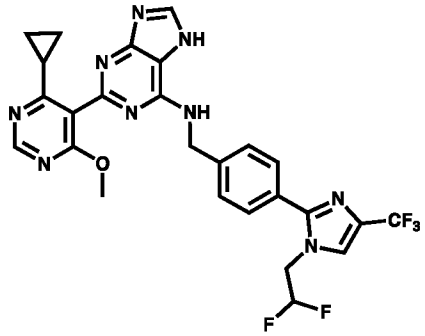


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate BC). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.29 – 8.24 (m, 1H), 8.14 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.48 – 7.41 (m, 2H), 5.52 (tt, J = 7.3, 6.0 Hz, 1H), 4.96 (t, J = 7.4 Hz, 2H), 4.91 (s, 2H), 4.84 – 4.80 (m, 2H), 3.91 (s, 3H), 1.77 – 1.68 (m, 1H), 1.12 – 1.05 (m, 2H), 0.91 – 0.78 (m, 2H). LCMS observed *m/z* = 564.2 $[M+H]^+$.

73.1 EXAMPLE 73

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(2,2-difluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 73

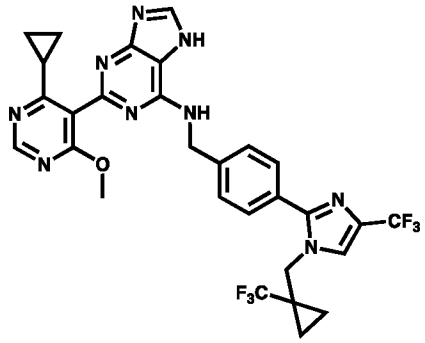


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-(2,2-difluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate AW). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.13 (s, 1H), 7.79 (s, 1H), 7.56 (q, J = 8.4 Hz, 4H), 6.14 (tt, J = 54.5, 3.2 Hz, 1H), 4.92 (s, 2H), 4.50 (td, J = 15.1, 3.2 Hz, 2H), 3.91 (s, 3H), 1.78 – 1.69 (m, 1H), 1.13 – 1.05 (m, 2H), 0.89 – 0.79 (m, 2H). LCMS observed *m/z* = 572.2 $[M+H]^+$.

74.1 EXAMPLE 74

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(4-(trifluoromethyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 74



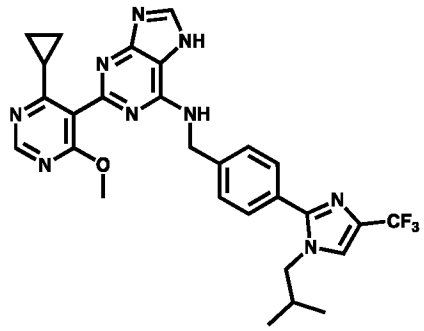
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(4-(trifluoromethyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate AX). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.83 – 7.80 (m, 1H), 7.59 (d, J = 8.3 Hz, 2H), 7.53 – 7.49 (m, 2H), 4.95 (s,

2H), 4.35 (s, 2H), 3.91 (s, 3H), 1.79 – 1.70 (m, 1H), 1.13 – 1.07 (m, 2H), 1.04 – 1.00 (m, 2H), 0.89 – 0.83 (m, 2H), 0.82 – 0.78 (m, 2H). LCMS observed *m/z* = 630.2 $[M+H]^+$.

75.1 EXAMPLE 75

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 75

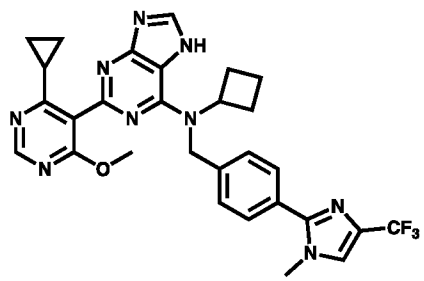


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-isobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate AV). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.75 – 7.73 (m, 1H), 7.58 – 7.51 (m, 4H), 4.92 (s, 2H), 3.93 – 3.89 (m, 5H), 1.99 – 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.12 – 1.03 (m, 2H), 0.88 – 0.81 (m, 2H), 0.76 (d, J = 6.7 Hz, 6H). LCMS observed *m/z* = 564.2 $[M+H]^+$.

76.1 EXAMPLE 76

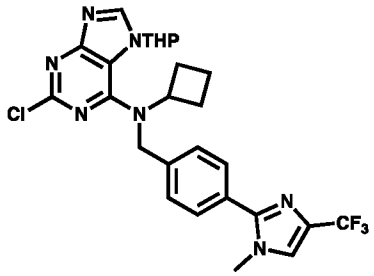
Preparation of N-cyclobutyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 76



Step 1: Preparation of 2-chloro-N-cyclobutyl-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-6-amine.

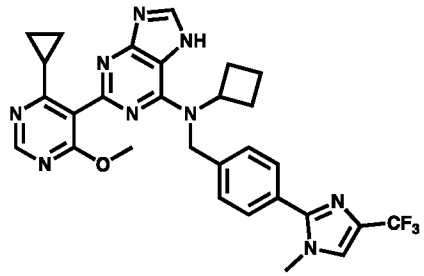
Compound 76.1



To a solution of 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)purine (95.1 mg, 348 µmol) in acetonitrile (1.39 mL, 26.7 mmol) was added N-ethyldiisopropylamine (91 µL, 1.5 eq., 522 µmol) followed by cyclobutylamine (35.8 µL, 1.2 eq., 418 µmol) and the mixture was stirred at 23 °C for 3d. The reaction was cooled to 0 °C and hydridosodium 60%w/w (41.8 mg, 3 eq., 1.04 mmol) was added. The mixture was warmed to 23 °C and stirred for 30 min. 2-[p-(chloromethyl)phenyl]-1-methyl-4-(trifluoromethyl)imidazole (Intermediate CX) (95.7 mg, 348 µmol) was added and the reaction was stirred for 16 h. The reaction was quenched with water (1 mL) poured into EtOAc (10 mL) and washed with sat. NaHCO3 (5 mL), brine (5 mL), dried over MgSO4, filtered and concentrated under reduced pressure. The residue was used crude assuming 100% conversion. LCMS observed *m/z* = 546.1 $[M+H]^+$.

Step 2: Preparation of N-cyclobutyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 76



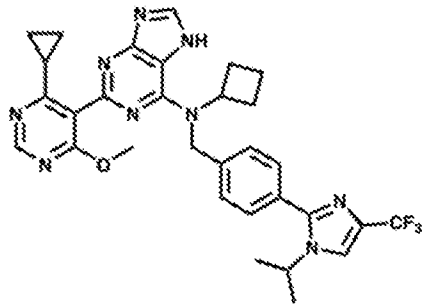
To a solution of 2-chloro-9a-cyclobutyl-9a-({p-[1-methyl-4-(trifluoromethyl)-2-imidazolyl]phenyl}methyl)-7-(tetrahydro-2H-pyran-2-yl)adenine (190 mg, 348 µmol) in 1,4-dioxane (1.74 mL, 20.4 mmol) and water (348 µL, 19.3 mmol) was added (4-cyclopropyl-6-methoxy-5-pyrimidinyl)boranediol (122 mg, 1.8 eq., 626 µmol), dicaesium carbonate (340 mg, 3 eq., 1.04 mmol), and palladium—triphenylphosphine (1/4) (40.2 mg, 0.1 eq., 34.8 µmol). The vial was degassed via vacuum/N2 backfill (5x), sealed, and heated in the uW at 100 °C for 4 h. The reaction was complete by LCMS. The mixture was diluted with water (5 mL) and extracted with dichloromethane (2 x 5 mL). The combined organics

were dried over MgSO4, filtered and concentrated to afford the crude product as a brown solid. The solid was dissolved in trifluoroacetic acid (2 mL) and stirred for 2h at which time the reaction was complete by LCMS. The reaction was concentrated and The crude product was purified via preparatory HPLC (10–75% MeCN/H2O w/ 0.1% FA) to afford the product as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.67 (s, 1H), 7.59 – 7.55 (m, 2H), 7.42 – 7.38 (m, 2H), 5.83 (br s, 1H), 5.45 (s, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 2.34 – 2.22 (m, 4H), 1.77 – 1.67 (m, 3H), 1.07 – 1.01 (m, 2H), 0.81 – 0.76 (m, 2H). LCMS observed *m/z* = 576.3 $[M+H]^+$.

77.1 EXAMPLE 77

Preparation of N-cyclobutyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 77

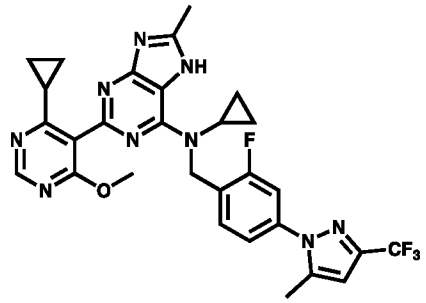


The title compound was prepared using a similar procedure as Compound 76, replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (Intermediate D). ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 8.07 (s, 1H), 7.89 (s, 1H), 7.49 – 7.45 (m, 2H), 7.43 – 7.39 (m, 2H), 5.84 (br s, 1H), 5.47 (s, 2H), 4.54 (sept., J = 6.8 Hz, 1H), 3.88 (s, 3H), 2.34 – 2.22 (m, 4H), 1.77 – 1.67 (m, 3H), 1.44 (d, J = 6.7 Hz, 6H), 1.07 – 1.01 (m, 2H), 0.81 – 0.76 (m, 2H). LCMS observed *m/z* = 604.4 $[M+H]^+$.

78.1 EXAMPLE 78

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-8-methyl-7H-purin-6-amine.

Compound 78

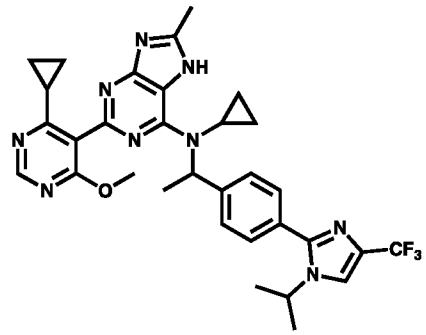


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine and 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 1-(4-(chloromethyl)-3-fluorophenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole (Intermediate CY) and replacing cyclobutylamine with cyclopropylamine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.35 (dd, J = 10.5, 2.2 Hz, 1H), 7.26 (dd, J = 8.1, 2.2 Hz, 1H), 6.58 (s, 1H), 5.29 (br s, 2H), 3.89 (s, 3H), 3.21 (br s, 1H), 2.61 (s, 3H), 2.36 (s, 3H), 1.76 – 1.68 (m, 1H), 1.10 – 1.00 (m, 4H), 0.93 – 0.85 (m, 2H), 0.85 – 0.79 (m 2H). LCMS observed *m/z* = 594.3 $[M+H]^+$.

79.1 EXAMPLE 79

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)-8-methyl-7H-purin-6-amine.

Compound 79



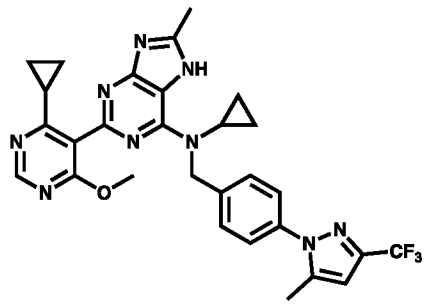
The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine and 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(1-chloroethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (Intermediate DA). ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 7.90 (s, 1H), 7.59 – 7.54 (m, 2H), 7.51 – 7.46 (m, 2H), 6.37 (br s, 1H), 4.54 (sept, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.08 (m, 1H), 2.61 (m, 3H), 1.92 (d, J = 7.2 Hz, 3H), 1.85 –

1.78 (m, 1H), 1.45 (dd, J = 6.6, 2.5 Hz, 6H), 1.13 – 1.04 (m, 2H), 1.01 – 0.91 (m, 1H), 0.91 – 0.84 (m, 2H), 0.83 – 0.68 (m, 2H), 0.59 – 0.42 (m, 1H). LCMS observed *m/z* = 618.3 $[M+H]^+$.

80.1 EXAMPLE 80

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 80

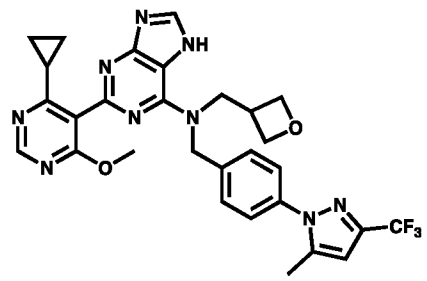


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine and 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole (Intermediate CW). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.51 – 7.45 (m, 2H), 7.44 – 7.39 (m, 2H), 6.57 (s, 1H), 5.42 – 5.06 (m, 2H), 3.90 (s, 3H), 3.19 (br s, 1H), 2.59 (br s, 3H), 2.32 (s, 3H), 1.75 (m, 1H), 1.12 – 1.04 (m, 3H), 1.04 – 0.92 (m, 2H), 0.90 – 0.78 (m 3H). LCMS observed *m/z* = 576.3 $[M+H]^+$.

81.1 EXAMPLE 81

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-N-(oxetan-3-ylmethyl)-7H-purin-6-amine.

Compound 81



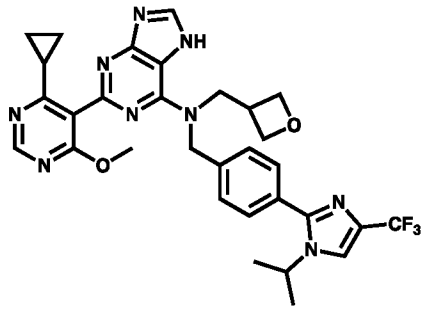
The title compound was prepared using a similar procedure as Compound 21, replacing 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole (Intermediate CW)

and replacing cyclopropylamine with oxetan-3-ylmethanamine. ^{1}H NMR (400 MHz, CD_3OD) δ8.66 (s, 1H), 8.55 (s, 1H), 7.59 – 7.54 (m, 2H), 7.52 – 7.48 (m, 2H), 6.60 (s, 1H), 5.31 (br s, 2H), 4.72 (m, 1H), 4.40 (dd, J = 13.4, 9.4 Hz, 1H), 4.03 – 3.99 (m, 1H), 3.98 (m, 3H), 3.95 – 3.88 (m, 1H), 3.67 – 3.58 (m, 2H), 2.69 – 2.60 (m, 1H), 2.35 (s, 3H), 1.98 – 1.91 (m, 1H), 1.19 – 1.14 (m, 2H), 0.91 – 0.86 (m 2H). LCMS observed *m/z* = 592.3 $[M+H]^+$.

82.1 EXAMPLE 82

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-N-(oxetan-3-ylmethyl)-7H-purin-6-amine.

Compound 82

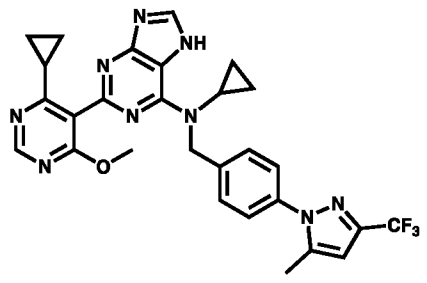


The title compound was prepared using a similar procedure as Compound 21, replacing cyclopropylamine with oxetan-3-ylmethanamine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.35 (s, 1H), 7.92 (s, 1H), 7.57 – 7.49 (m, 4H), 5.25 – 5.16 (m, 2H), 4.63 – 4.56 (m, 1H), 4.54 (hept, J = 6.8 Hz, 1H), 4.28 (dd, J = 13.1, 9 Hz, 1H), 3.91 (s, 3H), 3.88 – 3.84 (m, 1H), 3.75 – 3.70 (m, 1H), 3.61 – 3.56 (m, 2H), 2.59 – 2.51 (m, 1H), 1.85 – 1.79 (m, 1H), 1.46 (d, J = 6.8 Hz, 6H), 1.11 – 1.07 (m, 2H), 0.85 – 0.80 (m, 2H). LCMS observed *m/z* = 620.3 $[M+H]^+$.

83.1 EXAMPLE 83

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 83

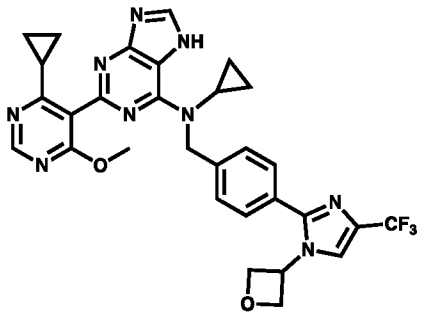


The title compound was prepared using a similar procedure as Compound 21, replacing 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 1-(4-(chloromethyl)phenyl)-5-methyl-3-(trifluoromethyl)-1H-pyrazole (Intermediate CW). ^{1}H NMR (400 MHz, DMSO-d_6) δ13.15 (s, 1H), 8.61 (s, 1H), 8.23 (s, 1H), 7.52 – 7.48 (m, 2H), 7.44 – 7.38 (m, 2H), 6.73 (s, 1H), 5.35 (br s, 2H), 3.83 (s, 3H), 3.25 – 3.08 (s, 1H), 2.31 (s, 3H), 1.88 – 1.77 (m, 1H), 1.02 – 0.95 (m, 2H), 0.93 – 0.86 (m, 2H), 0.84 – 0.76 (m 4H). LCMS observed *m/z* = 562.3 $[M+H]^+$.

84.1 EXAMPLE 84

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 84

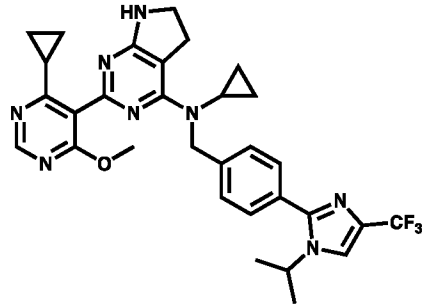


The title compound was prepared using a similar procedure as Compound 21, replacing 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazole (Intermediate DC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.40 (s, 1H), 8.22 (s, 1H), 7.39 – 7.36 (m, 2H), 7.34 – 7.30 (m, 2H), 5.42 (p, J = 6.9 Hz, 1H), 5.25 (s, 2H), 4.78 (t, J = 7.3 Hz, 2H), 4.71 (t, J = 6.8 Hz, 2H), 3.77 (s, 3H), 3.08 (s, 1H), 1.77 (s, 1H), 0.93 (s, 2H), 0.88 – 0.83 (m, 2H), 0.75 (s, 4H). LCMS observed *m/z* = 604.3 $[M+H]^+$.

85.1 EXAMPLE 85

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 85

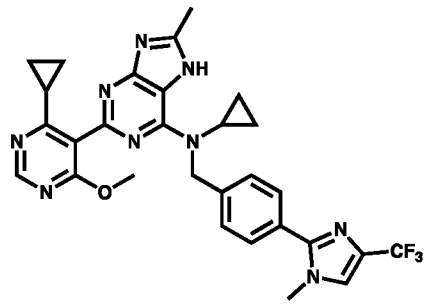


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with *tert*-butyl 2,4-dichloro-5,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidine-7-carboxylate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.16 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 6.87 (s, 1H), 6.66 (s, 1H), 4.84 (s, 2H), 4.57 – 4.40 (m, 2H), 3.81 (s, 3H), 3.48 – 3.46 (m, 4H), 2.88 (t, J = 5.0 Hz, 1H), 2.1 – 2.04 (m, 2H), 2.0 – 1.97 (m, 1H), 1.75 – 1.72 (m, 1H), 1.59 – 1.39 (m, 6H), 1.23 (s, 1H), 0.99 – 0.96 (m, 2H), 0.90 – 0.86 (m, 2H). LCMS observed *m/z* = 591.4 $[M+H]^+$.

86.1 EXAMPLE 86

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-8-methyl-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 86

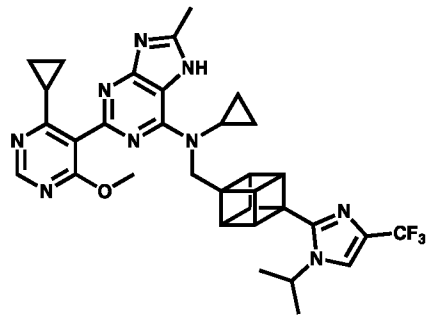


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine and 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole (Intermediate D). ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.68 (s, 1H), 7.62 – 7.58 (m, 2H), 7.48 – 7.43 (m, 2H), 5.28 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.19 (s, 1H), 2.61 (s, 3H), 1.80 – 1.71 (m, 1H), 1.10 – 1.06 (m, 2H), 1.05 – 0.96 (m, 2H), 0.94 – 0.80 (m 4H). LCMS observed *m/z* = 576.3 $[M+H]^+$.

87.1 EXAMPLE 87

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(((1s,2R,3s,4r,5S,6r,7R,8S)-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)cuban-1-yl)methyl)-8-methyl-7H-purin-6-amine.

Compound 87

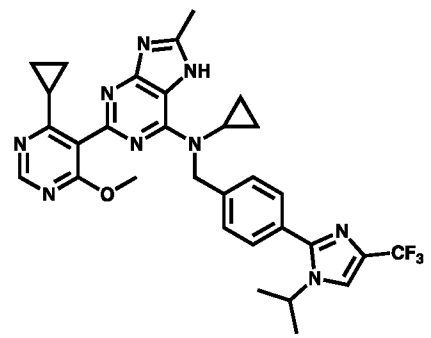


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine and 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with 2-(3-(chloromethyl)cuban-1-yl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole (Intermediate DD) and replacing cyclobutylamine with cyclopropylamine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 7.72 (s, 1H), 4.33 (br s, 2H), 4.28 – 4.23 (m, 3H), 4.16 (sept., J = 6.7 Hz, 1H), 3.99 – 3.92 (m, 3H), 3.92 (s, 3H), 3.24 (br s, 1H), 2.61 (s, 3H), 1.78 (m, 1H), 1.45 (d, J = 6.7 Hz, 6H), 1.16 – 1.10 (m, 2H), 1.11 – 1.03 (m 2H), 0.95 – 0.87 (m 2H), 0.86 – 0.72 (m, 2H). LCMS observed *m/z* = 630.5 $[M+H]^+$.

88.1 EXAMPLE 88

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-8-methyl-7H-purin-6-amine.

Compound 88



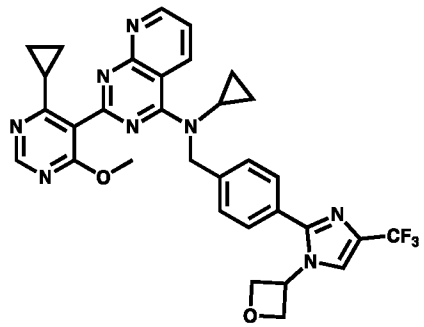
The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,6-dichloro-8-

methyl-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1H), 7.90 (s, 1H), 7.47 (m, 4H), 5.36 – 5.13 (m, 2H), 4.52 (sept., J = 6.6 Hz, 1H), 3.90 (s, 3H), 3.18 (s, 1H), 2.59 (m, 3H), 1.75 (s, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.20 – 1.05 (m, 3H), 1.05 – 0.92 (m, 2H), 0.91 – 0.78 (m, 3H). LCMS observed *m/z* = 604.3 $[M+H]^+$.

89.1 EXAMPLE 89

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrido[2,3-d]pyrimidin-4-amine.

Compound 89

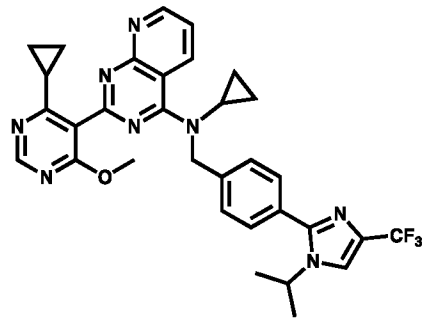


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,4-dichloropyrido[2,3-*d*]pyrimidine and 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazole (Intermediate DC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (dd, J = 8.6, 1.8 Hz, 1H), 9.03 (dd, J = 4.4, 1.6 Hz, 1H), 8.63 (s, 1H), 8.47 (d, J = 0.8 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.48 – 7.43 (m, 4H), 5.53 – 5.46 (m, 1H), 5.18 (s, 2H), 4.86 – 4.77 (m, 4H), 3.80 (s, 3H), 3.56 – 3.52 (m, 1H), 1.80 – 1.75 (m, 1H), 1.00 – 0.98 (m, 4H), 0.81 – 0.77 (m, 4H). LCMS observed *m/z* = 615.3 $[M+H]^+$.

90.1 EXAMPLE 90

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrido[2,3-d]pyrimidin-4-amine.

Compound 90

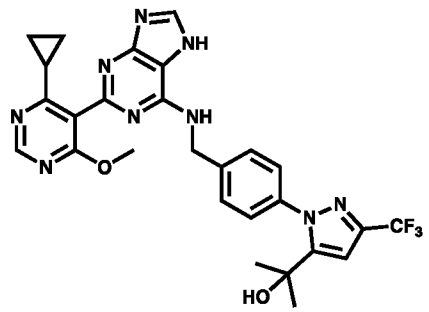


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2*H*-pyran-2-yl)-7*H*-purine with 2,4-dichloropyrido[2,3-*d*]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.57 (dd, J = 4.8, 1.6 Hz, 1H), 8.31 (dd, J = 7.8, 1.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.03 (d, J = 8.0 Hz, 2H), 5.36 – 5.23 (m, 2H), 4.44 – 4.41 (m, 1H), 3.80 – 3.73 (m, 4H), 1.93 – 1.89 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.11 – 1.07 (m, 1H), 0.98 – 0.95 (m, 1H), 0.79 – 0.73 (m, 4H), 0.67 – 0.66 (m, 2H). LCMS observed *m/z* = 601.4 $[M+H]^+$.

91.1 EXAMPLE 91

Synthesis of 2-(1-(4-(((2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7H-purin-6-yl)amino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)propan-2-ol.

Compound 91

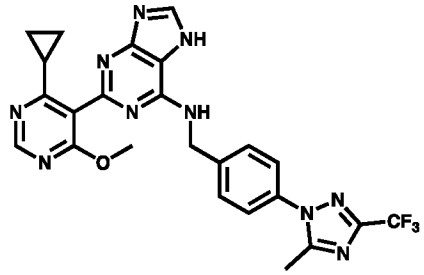


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with 2-(1-(4-(aminomethyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)propan-2-ol (Intermediate CB). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.57 – 7.51 (m, 2H), 7.50 – 7.44 (m, 2H), 6.69 (s, 1H), 4.92 (s, 2H), 3.91 (s, 3H), 1.78 – 1.70 (m, 1H), 1.41 (s, 6H), 1.13 – 1.06 (m, 2H), 0.92 – 0.85 (m, 2H). LCMS observed *m/z* = 566.3 $[M+H]^+$.

92.1 EXAMPLE 92

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 92

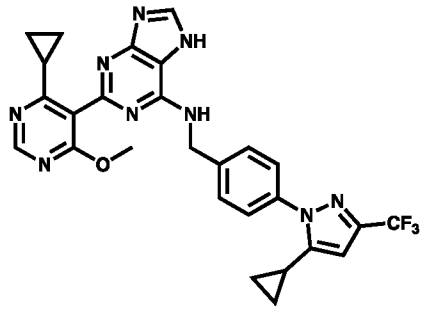


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with 2(4-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)phenyl)methanamine (Intermediate AY). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.65 – 7.59 (m, 2H), 7.55 – 7.49 (m, 2H), 4.93 (s, 2H), 3.90 (s, 3H), 2.52 (s, 3H), 1.76 – 1.65 (m, 1H), 1.12 – 1.03 (m, 2H), 0.89 – 0.76 (m, 2H). LCMS observed *m/z* = 523.3 $[M+H]^+$.

93.1 EXAMPLE 93

Synthesis of N-(4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-7H-purin-6-amine.

Compound 93

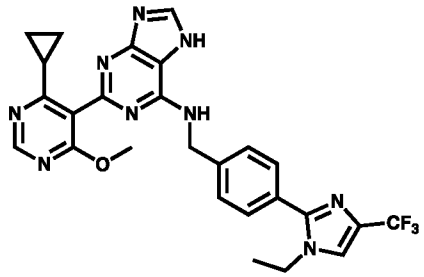


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BU). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (bs, 1H), 8.61 – 8.56 (m, 2H), 8.26 (s, 1H), 7.58 – 7.54 (m, 4H), 6.60 (s, 1H), 4.77 (brs, 2H), 3.82 (s, 3H), 1.81 – 1.72 (m, 2H), 0.97 – 0.94 (m, 4H), 0.93 – 0.92 (m, 4H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

94.1 EXAMPLE 94

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 94

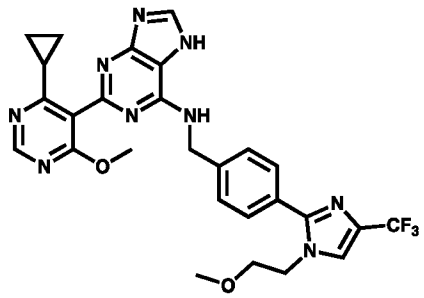


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate BB). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.16 (s, 1H), 7.82 – 7.76 (m, 1H), 7.63 – 7.53 (m, 4H), 4.94 (s, 2H), 4.12 (q, J = 7.3 Hz, 2H), 3.93 (s, 3H), 1.80 – 1.70 (m, 1H), 1.38 (t, J = 7.3 Hz, 3H), 1.17 – 1.05 (m, 2H), 0.91 – 0.78 (m, 2H). LCMS observed *m/z* = 536.2 $[M+H]^+$.

95.1 EXAMPLE 95

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(2-methoxyethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 95

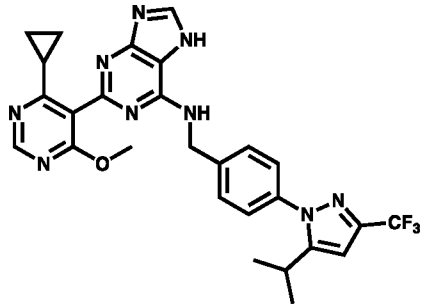


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-(2-methoxyethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CC). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.79 – 7.73 (m, 1H), 7.62 – 7.53 (m, 4H), 4.91 (s, 2H), 4.20 (t, 2H), 3.91 (s, 3H), 3.64 (t, J = 4.6 Hz, 2H), 3.28 (s, 3H), 1.82 – 1.68 (m, 1H), 1.12 – 1.04 (m, 2H), 0.90 – 0.78 (m, 2H). LCMS observed *m/z* = 566.2 $[M+H]^+$.

96.1 EXAMPLE 96

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 96

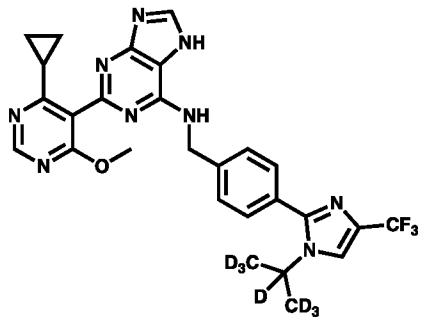


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with ((4-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (s, 1H), 8.60 (s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.48 (s, 4H), 4.74 – 5.30 (m, 2H), 4.45 – 4.40 (m, 1H), 3.81 (s, 3H), 1.74 – 1.70 (m, 1H), 1.34 – 1.29 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.90 (m, 2H), 0.89 – 0.70 (m, 2H). LCMS observed *m/z* = 550.3 $[M+H]^+$.

97.1 EXAMPLE 97

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(propan-2-yl-d7)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 97

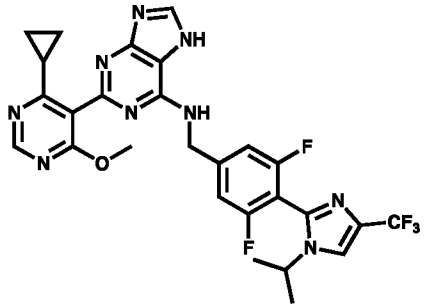


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-(propan-2-yl-d7)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CD). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.50 (s, 2H), 8.19 (s, 1H), 8.14 (d, J = 0.8 Hz, 1H), 7.48 (s, 4H), 4.73 (br s, 2H), 3.81 (s, 3H), 1.74 – 1.70 (m, 1H), 0.99 – 0.94 (m, 2H), 0.78 – 0.73 (m, 2H). LCMS observed *m/z* = 557.5 $[M+H]^+$.

98.1 EXAMPLE 98

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(3,5-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 98

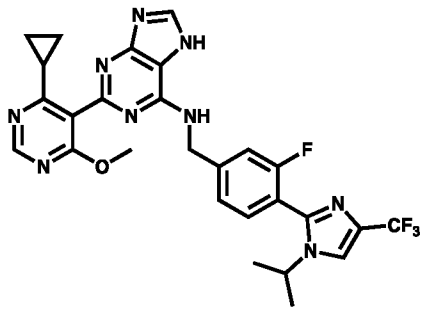


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (3,5-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CE). ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.15 (s, 1H), 8.02 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 4.91 (s, 2H), 4.25 – 4.10 (m, 1H), 3.90 (s, 3H), 1.79 – 1.66 (m, 1H), 1.41 (d, J = 1.8 Hz, 6H), 1.16 – 1.05 (m, 2H), 0.93 – 0.79 (m, 2H). LCMS observed *m/z* = 586.2 $[M+H]^+$.

99.1 EXAMPLE 99

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(3-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 99

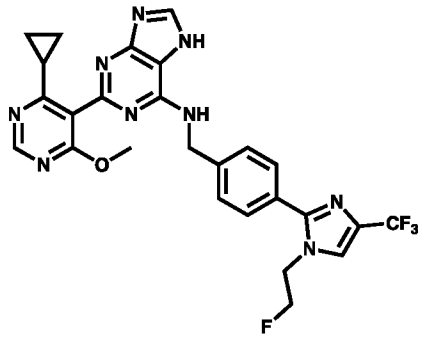


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (3-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate BE). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.31 (m, 2H), 4.92 (s, 2H), 4.25 (p, J = 6.8 Hz, 1H), 3.91 (s, 3H), 1.81 – 1.67 (m, 1H), 1.41 (d, J = 6.7 Hz, 6H), 1.15 – 1.00 (m, 2H), 0.91 – 0.78 (m, 2H). LCMS observed *m/z* = 568.2 $[M+H]^+$.

100.1 EXAMPLE 100

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(2-fluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 100

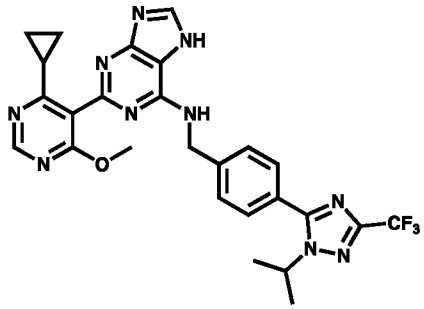


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-(2-fluoroethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CF). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.81 (s, 1H), 7.56 (t, J = 2.2 Hz, 4H), 4.91 (s, 2H), 4.73 (t, J = 4.8 Hz, 1H), 4.61 (t, J = 4.8 Hz, 1H), 4.40 (t, J = 4.9 Hz, 1H), 4.33 (t, J = 5.0 Hz, 1H), 3.91 (s, 3H), 1.79 – 1.66 (m, 1H), 1.15 – 1.05 (m, 2H), 0.94 – 0.77 (m, 2H). LCMS observed *m/z* = 554.2 $[M+H]^+$.

101.1 EXAMPLE 101

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)benzyl)-7H-purin-6-amine.

Compound 101

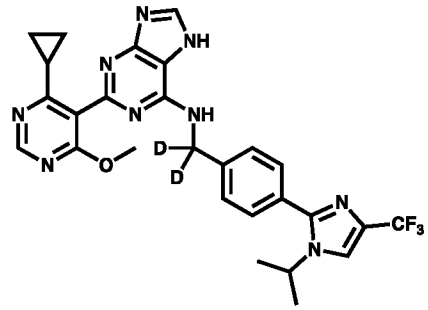


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-isopropyl-3-(trifluoromethyl)-1H-1,2,4-triazol-5-yl)phenyl)methanamine (Intermediate BA). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (br s, 1H), 8.60 (s, 1H), 8.45 (br s, 1H), 8.20 (s, 1H), 7.63 – 7.55 (m, 4H), 4.76 – 4.68 (m, 3H), 3.81 (s, 3H), 1.75 – 1.68 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 0.95 – 0.95 (m, 2H), 0.73 – 0.73 (m, 2H). LCMS observed *m/z* = 551.3 $[M+H]^+$.

102.1 EXAMPLE 102

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methyl-d2)-7H-purin-6-amine.

Compound 102

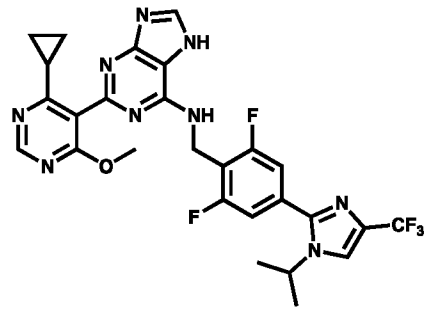


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methan-d2-amine (Intermediate CL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02 (br s, 1H), 8.60 (s, 1H), 8.44 (br s, 1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.48 (s, 4H), 4.45 – 4.40 (m, 1H), 3.81 (s, 3H), 1.76 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.96 – 0.94 (m, 2H), 0.75 – 0.72 (m, 2H). LCMS observed *m/z* = 552.3 $[M+H]^+$.

103.1 EXAMPLE 103

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2,6-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 103



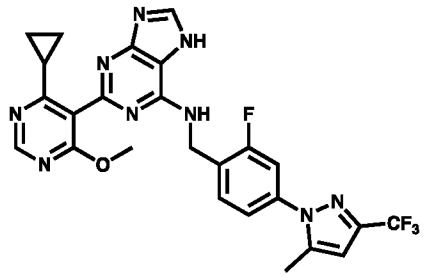
The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2,6-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CG). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.23 (d, J = 7.3 Hz, 2H), 4.98 (s, 2H), 4.57 (p, J = 6.6 Hz, 1H), 3.91 (d, J = 1.7 Hz, 3H), 1.74

(d, J = 8.3 Hz, 1H), 1.47 (d, J = 6.6 Hz, 6H), 1.15 – 1.09 (m, 2H), 0.89 (d, J = 7.6 Hz, 2H). LCMS observed *m/z* = 586.5 $[M+H]^+$.

104.1 EXAMPLE 104

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 104

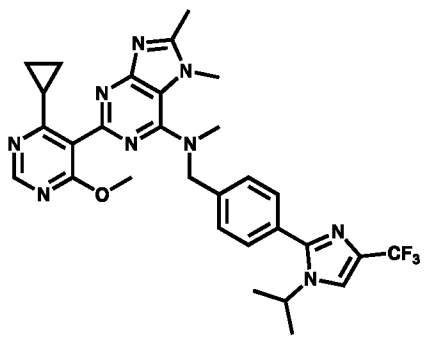


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BD). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.15 (s, 1H), 7.60 (t, J = 8.2 Hz, 1H), 7.32 (dd, J = 26.0, 9.4 Hz, 2H), 6.58 (s, 1H), 4.94 (s, 2H), 3.89 (s, 3H), 2.37 (s, 3H), 1.74 – 1.67 (m, 1H), 1.08 (q, J = 3.9 Hz, 2H), 0.88 – 0.79 (m, 2H). LCMS observed *m/z* = 540.5 $[M+H]^+$.

105.1 EXAMPLE 105

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-N,7,8-trimethyl-7H-purin-6-amine.

Compound 105



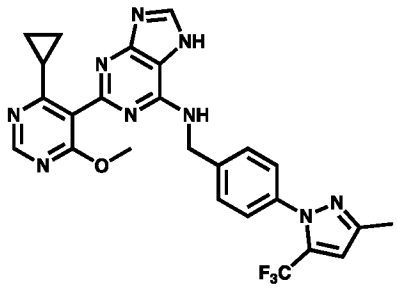
The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloro-4a,5-dihydroimidazo[2,1-*f*][1,2,4]triazine with 2,6-dichloro-8,9-dimethyl-9*H*-purine and (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with 1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-

yl)phenyl)-N-methylmethanamine (Intermediate E). ^{1}H NMR (400 MHz, DMSO-d_6) 8.62 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.73 (s, 2H), 4.49 – 4.42 (m, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.00 (s, 3H), 2.58 (s, 3H), 1.65 – 1.61 (m, 1H), 1.40 (d, J = 6.4 Hz, 6H), 1.00 – 0.96 (m, 2H), 0.80 – 0.79 (m, 2H). LCMS observed *m/z* = 592.4 $[M+H]^+$.

106.1 EXAMPLE 106

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-purin-6-amine.

Compound 106

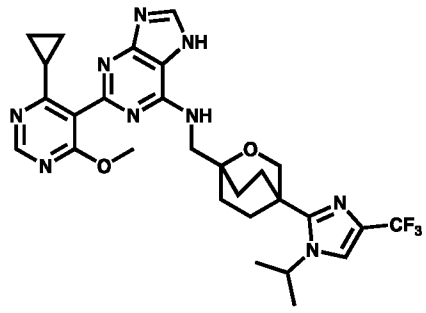


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(3-methyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate CM). ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.14 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 6.75 (s, 1H), 5.00 – 4.90 (m, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.72 (tt, J = 8.5, 4.6 Hz, 1H), 1.08 (p, J = 4.0 Hz, 2H), 0.84 (dq, J = 7.2, 3.9 Hz, 2H). LCMS observed *m/z* = 522.3 $[M+H]^+$.

107.1 EXAMPLE 107

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)methyl)-7H-purin-6-amine.

Compound 107

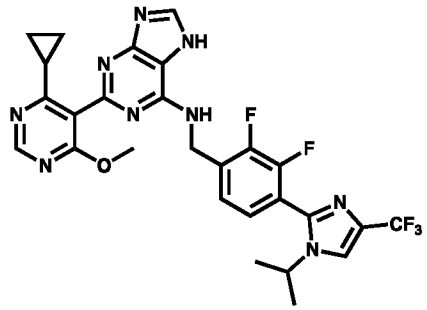


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2-oxabicyclo[2.2.2]octan-1-yl)methanamine (Intermediate BI). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 8.15 (s, 1H), 7.70 (s, 1H), 4.96 – 4.90 (m, 1H), 4.26 (s, 2H), 3.92 (s, 3H), 3.65 (s, 2H), 2.34 – 2.23 (m, 2H), 2.10 – 2.00 (m, 4H), 1.89 – 1.79 (m, 2H), 1.79 – 1.70 (m, 1H), 1.46 (d, J = 6.5 Hz, 6H), 1.16 – 1.10 (m, 2H), 0.95 – 0.89 (m, 2H). LCMS observed *m/z* = 584.4 $[M+H]^+$.

108.1 EXAMPLE 108

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2,3-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 108

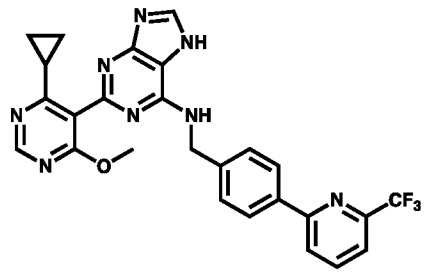


The title compound was prepared using a similar procedure as Compound 22, replacing (4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)methanamine with (2,3-difluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CK). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H), 8.60 (s, 1H), 8.41 (br s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.29 (s, 2H), 4.84 (br s, 2H), 4.21 – 4.14 (m, 1H), 3.79 (s, 3H), 1.74 – 1.68 (m, 1H), 1.36 (d, J = 6.4 Hz, 6H), 1.02 – 0.96 (m, 2H), 0.87 – 0.75 (m, 2H). LCMS observed *m/z* = 586.3 $[M+H]^+$.

109.1 EXAMPLE 109

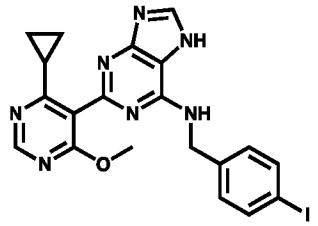
Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(6-(trifluoromethyl)pyridin-2-yl)benzyl)-7H-purin-6-amine.

Compound 109



Step 1: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-iodobenzyl)-7H-purin-6-amine.

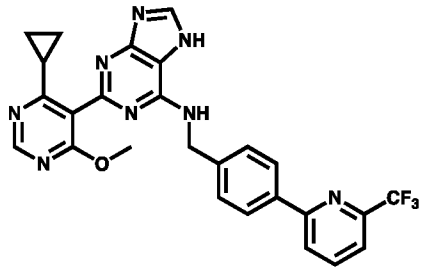
Compound 109.1



The title compound was prepared using general procedure E using 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7H-purine (Intermediate AC) and (4-iodophenyl)methanamine in DMF. LCMS observed *m/z* = 500.0 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(6-(trifluoromethyl)pyridin-2-yl)benzyl)-7H-purin-6-amine.

Compound 109

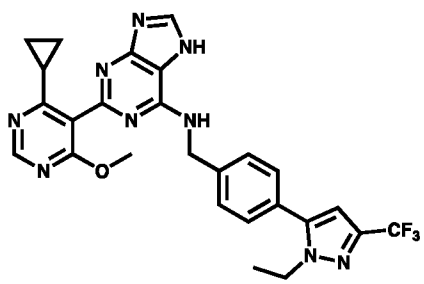


The title compound was prepared using general procedure F using 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine and in dioxanes. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 8.12 – 8.02 (m, 4H), 7.69 (dd, J = 7.4, 1.0 Hz, 1H), 7.56 – 7.50 (m, 3H), 4.88 (s, 2H), 3.90 (s, 3H), 1.75 – 1.64 (m, 1H), 1.09 – 1.01 (m, 2H), 0.85 – 0.73 (m, 2H). LCMS observed *m/z* = 519.2 $[M+H]^+$.

110.1 EXAMPLE 110

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-ethyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl)-7H-purin-6-amine.

Compound 110

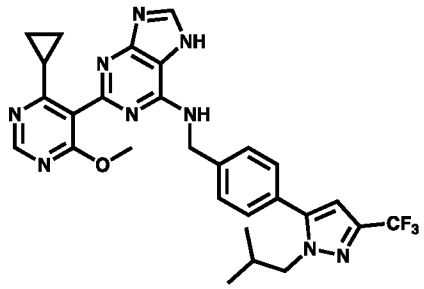


The title compound was prepared using a similar procedure as Compound 109, replacing 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine with 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole. ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1H), 8.13 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 6.60 (s, 1H), 4.90 (s, 2H), 4.20 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 1.78 – 1.65 (m, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.12 – 1.03 (m, 2H), 0.81 (m, 2H). LCMS observed *m/z* = 536.3 $[M+H]^+$.

111.1 EXAMPLE 111

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isobutyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)benzyl)-7H-purin-6-amine.

Compound 111

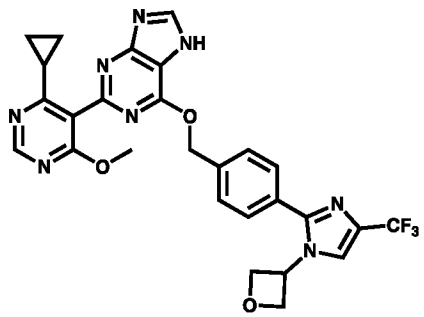


The title compound was prepared using a similar procedure as Compound 109, replacing 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine with 1-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole. ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1H), 8.18 (s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.43 (d, 2H), 6.60 (s, 1H), 4.93 (s, 2H), 4.01 (d, J = 7.5 Hz, 2H), 3.91 (s, 3H), 2.09 (hept, J = 6.9 Hz, 1H), 1.82 – 1.68 (m, 1H), 1.14 – 1.04 (m, 2H), 0.86 – 0.78 (m, 2H), 0.74 (d, J = 6.7 Hz, 6H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

112.1 EXAMPLE 112

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)oxy)-7H-purine.

Compound 112

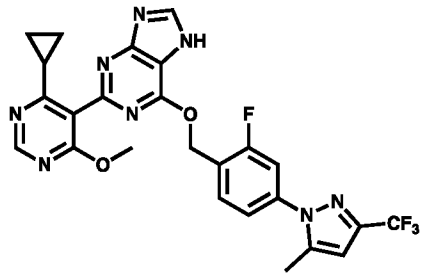


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with (4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate BL). ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.39 (s, 1H), 8.29 (d, J = 1.4 Hz, 1H), 7.71 (d, J = 8.1 Hz, 2H), 7.57 – 7.48 (m, 2H), 5.77 (s, 2H), 5.61 – 5.47 (m, 1H), 4.98 (t, J = 7.3 Hz, 2H), 4.86 (s, 2H), 3.91 (s, 3H), 1.77 – 1.66 (m, 1H), 1.18 – 1.10 (m, 2H), 0.92 – 0.83 (m, 2H). LCMS observed *m/z* = 565.2 $[M+H]^+$.

113.1 EXAMPLE 113

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)oxy)-7H-purine.

Compound 113

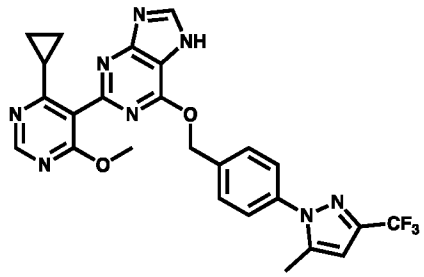


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with ((2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol (Intermediate BK). ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1H), 8.37 (s, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.48 – 7.35 (m, 2H), 6.60 (s, 1H), 5.81 (s, 2H), 4.86 (s, 2H), 3.92 (s, 3H), 2.40 (s, 3H), 1.77 – 1.67 (m, 1H), 1.18 – 1.10 (m, 2H), 0.95 – 0.81 (m, 2H). LCMS observed *m/z* = 541.2 $[M+H]^+$.

114.1 EXAMPLE 114

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)oxy)-7H-purine.

Compound 114

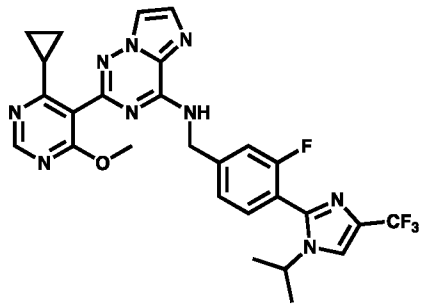


The title compound was prepared using a similar procedure as Compound 39, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanol (Intermediate BJ). ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1H), 8.39 (s, 1H), 7.78 – 7.68 (m, 2H), 7.57 – 7.49 (m, 2H), 6.59 (s, 1H), 5.77 (s, 2H), 4.85 (s, 2H), 3.91 (s, 3H), 2.35 (s, 3H), 1.75 – 1.65 (m, 1H), 1.17 – 1.09 (m, 2H), 0.94 – 0.81 (m, 2H). LCMS observed *m/z* = 523.2 $[M+H]^+$.

115.1 EXAMPLE 115

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(3-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 115

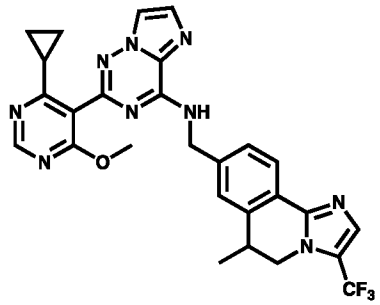


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (3-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate BE). ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.95 (m, 2H), 7.65 (s, 1H), 7.51 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H), 4.91 (s, 2H), 4.24 (sept, J = 6.6 Hz, 1H), 3.93 (s, 3H), 1.94 – 1.85 (m, 1H), 1.41 (d, J = 6.6 Hz, 6H), 1.16 – 1.08 (m, 2H), 0.95 – 0.85 (m, 2H). LCMS observed *m/z* = 568.3 $[M+H]^+$.

116.1 EXAMPLE 116

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 116

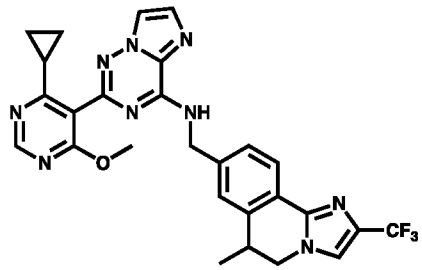


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine (Intermediate CO). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.55 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.66 (m, 2H), 7.38 – 7.40 (m, 2H), 4.74 (m, 2H), 4.29 – 4.25 (m, 1H), 4.04 – 3.99 (m, 1H), 3.81 (s, 3H), 3.37 – 3.32 (m, 1H), 1.91 – 1.59 (m, 1H), 1.23 (d, J = 6.4 Hz, 3H), 0.99 – 0.81 (m, 4H). LCMS observed *m/z* = 548.5 [M+H]$^+$.

117.1 EXAMPLE 117

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 117

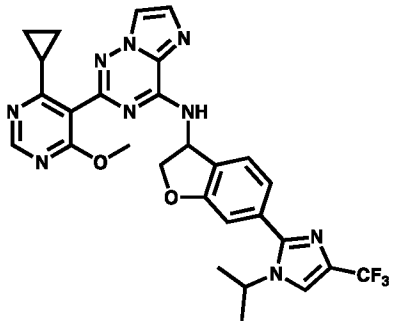


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (6-methyl-2-(trifluoromethyl)-5,6-dihydroimidazo[2,1-a]isoquinolin-8-yl)methanamine (Intermediate CN). ^{1}H NMR ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.55 – 9.54 (m, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.88 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.67 (s, 1H), 7.33 (s, 1H), 7.36 (d, J = 10.4 Hz, 1H), 4.75 – 4.72 (m, 2H), 4.27 – 4.22 (m, 1H), 4.04 – 4.00 (m, 1H), 3.77 (s, 3H), 3.31 – 3.26 (m, 1H), 1.69 (m, 1H), 1.15 (d, J = 7.2 Hz, 3H), 1.00 – 1.00 (m, 2H), 0.83 – 0.82 (m, 2H). LCMS observed *m/z* = 548.3 [M+H]$^+$.

118.1 EXAMPLE 118

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 118

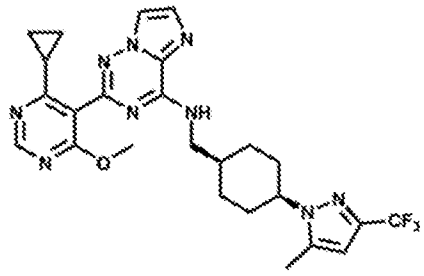


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with 6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-2,3-dihydrobenzofuran-3-amine (Intermediate CP). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, J = 7.2 Hz, 1H), 8.70 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.03 – 7.01 (m, 2H), 6.17 – 6.14 (m, 1H), 4.85 – 4.76 (m, 2H), 4.48 – 4.42 (m, 1H), 3.94 (s, 3H), 2.07 – 2.01 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.10 – 1.06 (m, 4H). LCMS observed *m/z* = 578.3 $[M+H]^+$.

119.1 EXAMPLE 119

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-cis-((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 119



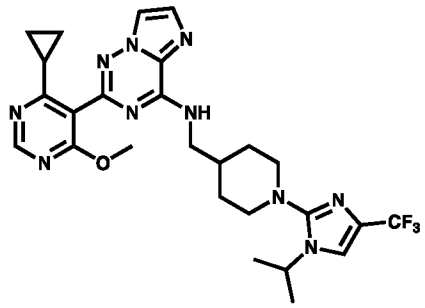
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanamine (Intermediate BX). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (t, J = 5.8 Hz, 1H), 8.64 (s, 1H), 8.11 (d, J =

1.2 Hz, 1H), 7.63 (s, 1H), 6.44 (s, 1H), 4.25 – 4.19 (m, 1H), 3.85 (s, 3H), 3.62 (t, J = 6.8 Hz, 2H), 2.50 (s, 3H), 2.29 – 2.00 (m, 3H), 1.95 (t, J = 7.4 Hz, 1H), 1.88 – 1.82 (m, 6H), 1.00 – 1.00 (m, 2H), 0.99 – 0.86 (m, 2H). LCMS observed *m/z* = 528.9 $[M+H]^+$.

120.1 EXAMPLE 120

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 120

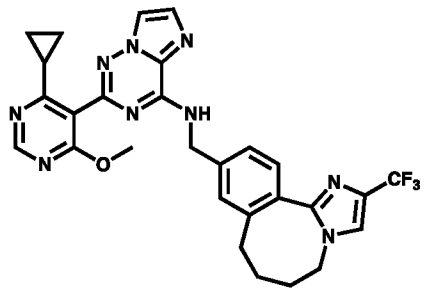


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (1-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)piperidin-4-yl)methanamine (Intermediate BY). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.2 Hz, 1H), 8.67 (s, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 4.38 – 4.31 (m, 1H), 3.87 (s, 3H), 3.46 (t, J = 6.6 Hz, 2H), 3.09 (d, J = 12.0 Hz, 2H), 2.73 – 2.68 (m, 2H), 1.93 – 1.88 (m, 2H), 1.74 – 1.71 (m, 2H), 1.41 – 1.38 (m, 2H), 1.33 (d, J = 6.4 Hz, 6H), 1.05 – 1.04 (m, 2H), 0.90 – 0.99 (m, 2H). LCMS observed *m/z* = 557.5 $[M+H]^+$.

121.1 EXAMPLE 121

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 121

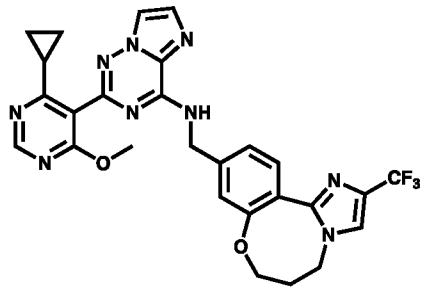


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[c]imidazo[1,2-a]azocin-10-yl)methanamine (Intermediate BQ). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.2 Hz, 1H), 8.67 (s, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 4.38 – 4.31 (m, 1H), 3.87 (s, 3H), 3.46 (t, J = 6.6 Hz, 2H), 3.09 (d, J = 12.0 Hz, 2H), 2.73 – 2.68 (m, 2H), 1.93 – 1.88 (m, 2H), 1.74 – 1.71 (m, 2H), 1.41 – 1.38 (m, 2H), 1.33 (d, J = 6.4 Hz, 6H), 1.05 – 1.04 (m, 2H), 0.90 – 0.99 (m, 2H). LCMS observed *m/z* = 562.3 $[M+H]^+$.

122.1 EXAMPLE 122

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 122

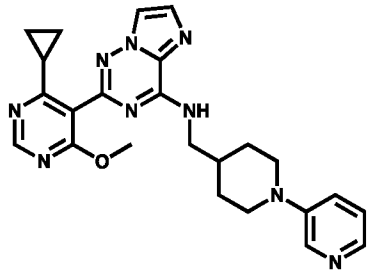


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[b]imidazo[2,1-d][1,5]oxazocin-10-yl)methanamine (Intermediate BN). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.17 (s, 1H), 7.94 (s, 1H), 7.68 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.21 – 7.09 (m, 2H), 4.72 (d, J = 6.0 Hz, 2H), 4.05 (t, J = 4.8 Hz, 4H), 3.85 (s, 3H), 1.93 – 1.84 (m, 3H), 1.01 – 1.01 (m, 2H), 0.86 – 0.83 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

123.1 EXAMPLE 123

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((1-(pyridin-3-yl)piperidin-4-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 123

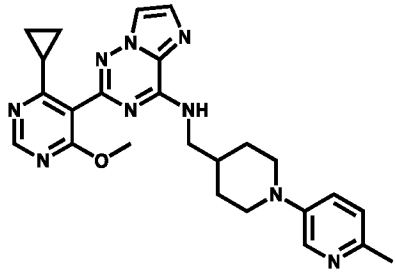


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (1-(pyridin-3-yl)piperidin-4-yl)methanamine (Intermediate BZ). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.26 (d, J = 2.8 Hz, 1H), 8.11 (d, J = 0.8 Hz, 1H), 7.94 (d, J = 4.0 Hz, 1H), 7.64 (d, J = 0.8 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.19 – 7.15 (m, 1H), 3.87 (s, 3H), 3.74 – 3.71 (m, 2H), 3.44 (t, J = 8.0 Hz, 2H), 2.67 (t, J = 11.4 Hz, 2H), 1.93 – 1.88 (m, 2H), 1.76 – 1.73 (m, 2H), 1.35 – 1.25 (m, 2H), 1.06 – 1.03 (m, 2H), 1.06 – 1.03 (m, 2H). LCMS observed *m/z* = 458.4 $[M+H]^+$.

124.1 EXAMPLE 124

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((1-(6-methylpyridin-3-yl)piperidin-4-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 124

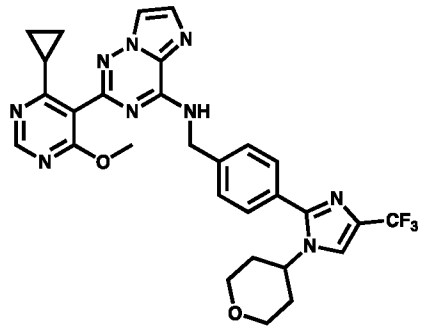


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (1-(6-methylpyridin-3-yl)piperidin-4-yl)methanamine (Intermediate CA). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (t, J = 6.0 Hz, 1H), 8.67 (s, 1H), 8.11 (s, 2H), 7.63 (s, 1H), 7.20 (dd, J = 8.6, 3.0 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 3.87 (s, 3H), 3.63 (d, J = 12.4 Hz, 2H), 3.44 – 3.42 (m, 2H), 2.63 – 2.57 (m, 2H), 2.33 (s, 3H), 1.92 – 1.87 (m, 2H), 1.73 (d, J = 11.6 Hz, 2H), 1.35 – 1.25 (m, 2H), 1.06 – 1.04 (m, 2H), 0.94 – 0.93 (m, 2H). LCMS observed *m/z* = 472.4$[M+H]^+$.

125.1 EXAMPLE 125

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 125

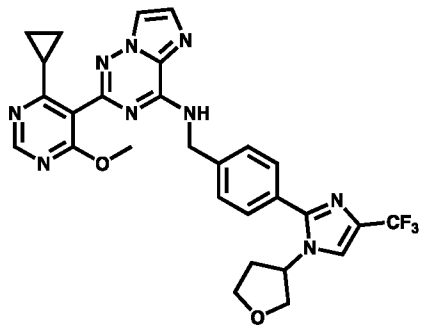


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-(tetrahydro-2H-pyran-4-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.23 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.54 – 7.48 (m, 4H), 4.78 (d, J = 6.0 Hz, 2H), 4.33 – 4.27 (m, 1H), 3.92 – 3.86 (m, 5H), 3.28 (s, 1H), 2.07 – 1.97 (m, 2H), 1.91 – 1.86 (m, 3H), 1.28 – 1.24 (m, 1H), 1.00 – 0.99 (m, 2H), 0.88 – 0.88 (m, 3H). LCMS observed *m/z* = 592.3 $[M+H]^+$.

126.1 EXAMPLE 126

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(tetrahydrofuran-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 126



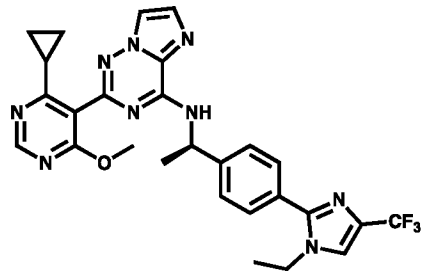
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-(tetrahydrofuran-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine

(Intermediate CS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 – 9.55 (m, 1H), 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.87 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.55 – 7.49 (m, 4H), 4.89 – 4.87 (m, 1H), 4.77 (d, J = 6.0 Hz, 2H), 4.10 (q, J = 3.5 Hz, 1H), 3.90 – 3.86 (m, 5H), 3.72 (q, J = 3.6 Hz, 1H), 2.46 – 2.44 (m, 1H), 2.19 – 2.08 (m, 1H), 1.88 – 1.85 (m, 1H), 1.01 – 0.99 (m, 2H), 0.85 – 0.82 (m, 2H). LCMS observed *m/z* = 578.3 $[M+H]^+$.

127.1 EXAMPLE 127

Synthesis of (R)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)imidazo[2,1-f][1,2,4]triazin-4-amine

Compound 127

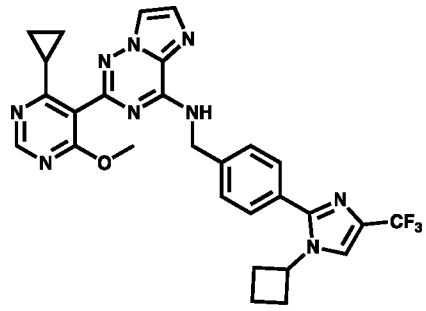


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (R)-1-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethan-1-amine (Intermediate CT). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.52 (d, J = 8.4 Hz, 1H), 8.66 (s, 1H), 8.14 (d, J = 0.8 Hz, 1H), 8.01 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 – 7.57 (m, 4H), 5.60 – 5.53 (m, 1H), 4.09 – 4.07 (m, 2H), 3.82 (s, 3H), 1.81 – 1.75 (m, 1H), 1.63 (d, J = 6.8 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 0.99 – 0.98 (m, 2H), 0.87 – 0.87 (m, 1H), 0.84 – 0.84 (m, 1H). LCMS observed *m/z* = 550.3 $[M+H]^+$.

128.1 EXAMPLE 128

Synthesis of N-(4-(1-cyclobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 128

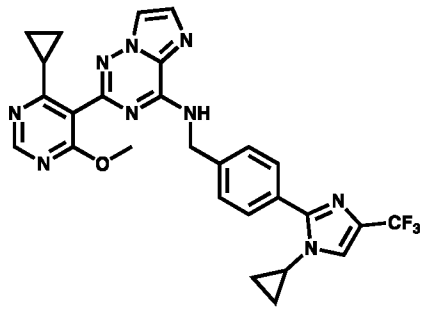


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-cyclobutyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.27 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.49 (t, J = 9.4 Hz, 4H), 4.78 – 4.73 (m, 3H), 3.86 (s, 3H), 2.38 – 2.33 (m, 4H), 1.89 – 1.87 (m, 1H), 1.78 – 1.63 (m, 2H), 1.01 – 1.00 (m, 2H), 0.85 – 0.82 (m, 2H). LCMS observed *m/z* = 562.4 $[M+H]^+$.

129.1 EXAMPLE 129

Synthesis of N-(4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 129

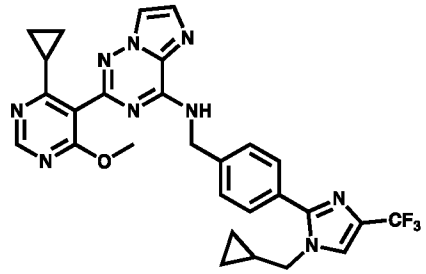


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CU). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.91 (d, J = 0.8 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 0.8 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.74 – 3.68 (m, 1H), 1.91 – 1.85 (m, 1H), 1.01 – 0.93 (m, 8H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

130.1 EXAMPLE 130

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(cyclopropylmethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 130

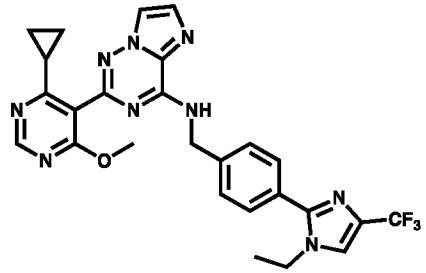


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-(cyclopropylmethyl)-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate CJ). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.02 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 3.91 – 3.86 (m, 5H), 1.89 – 1.89 (m, 1H), 1.13 – 1.13 (m, 1H), 1.00 – 1.00 (m, 2H), 0.84 – 0.84 (m, 2H), 0.50 – 0.50 (m, 2H), 0.29 – 0.29 (m, 2H). LCMS observed *m/z* = 562.3 $[M+H]^+$.

131.1 EXAMPLE 131

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 131

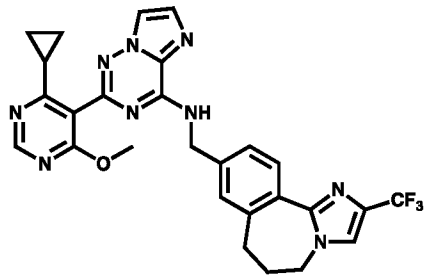


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-ethyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate BB). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.67 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 4.77 (d, J = 6.0 Hz, 2H), 4.06 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 1.88 – 1.85 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.02 – 0.99 (m, 2H), 0.85 – 0.84 (m, 2H). LCMS observed *m/z* = 536.3 $[M+H]^+$.

132.1 EXAMPLE 132

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 132

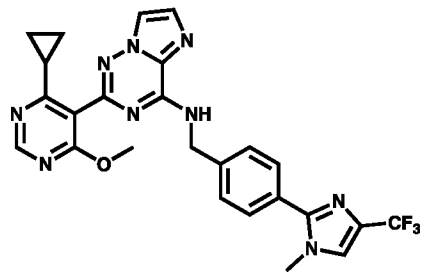


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-9-yl)methanamine (Intermediate BH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.94 (s, 1H), 7.75 (s, 1H), 7.67 – 7.61 (m, 2H), 7.47 – 7.43 (m, 1H), 7.41 (s, 1H), 3.99 (t, J = 6.9 Hz, 2H), 3.93 (s, 3H), 2.71 (t, J = 7.1 Hz, 2H), 2.35 (pent, J = 7.00 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.14 – 1.08 (m, 2H), 0.91 – 0.84 (m, 2H). LCMS observed *m/z* = 548.2 $[M+H]^+$.

133.1 EXAMPLE 133

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 133

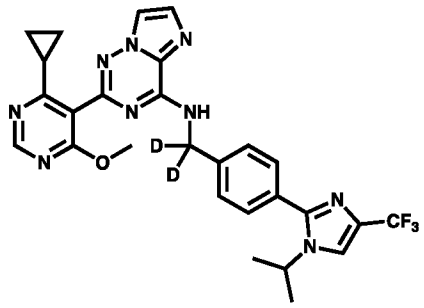


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate A). ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.93 (s, 1H), 7.68 (s, 1H), 7.62 (d, J = 6.7 Hz, 3H), 7.59 – 7.56 (m, 2H), 4.90 (s, 2H), 3.93 (s, 3H), 3.77 (s, 3H), 1.92 – 1.85 (m, 1H), 1.14 – 1.09 (m, 2H), 0.92 – 0.87 (m, 2H). LCMS observed *m/z* = 522.5 $[M+H]^+$.

134.1 EXAMPLE 134

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methyl-d2)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 134

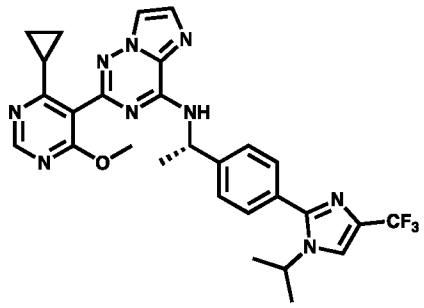


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methan-d2-amine (Intermediate CL). ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 7.93 (s, 1H), 7.91 (s, 1H), 7.63 (s, 1H), 7.61 – 7.57 (m, 2H), 7.54 – 7.50 (m, 2H), 4.53 (sept, J = 6.6 Hz, 1H), 3.93 (s, 3H), 1.92 – 1.86 (m, 1H), 1.44 (d, J = 6.6 Hz, 6H), 1.14 – 1.10 (m, 2H), 0.91 – 0.87 (m, 2H). LCMS observed *m/z* = 552.3 $[M+H]^+$.

135.1 EXAMPLE 135

Synthesis of (S)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 135



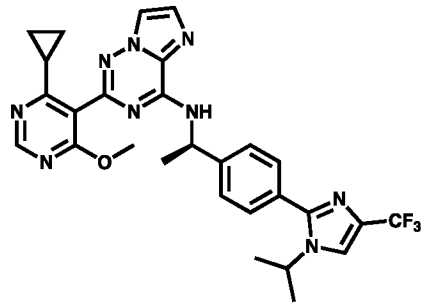
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (*S*)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine (Intermediate DE). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.60 – 5.53 (m, 1H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H),

1.79 – 1.75 (m, 1H), 1.63 (d, J = 7.2 Hz, 3H), 0.70 (d, J = 7.2 Hz, 6H), 1.10 – 0.99 (m, 2H), 0.98 – 0.98 (m, 1H), 0.97 – 0.96 (m, 1H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

136.1 EXAMPLE 136

Synthesis of (R)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(1-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)ethyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 136

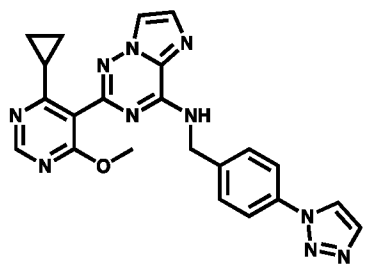


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (*R*)-1-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)ethan-1-amine (Intermediate CI). ^{1}H NMR (400 MHz, DMSO-d_6) 9.53 (d, J = 8.4 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 5.60 – 5.53 (m, 1H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H), 1.79 – 1.75 (m, 1H), 1.63 (d, J = 7.2 Hz, 3H), 0.70 (d, J = 7.2 Hz, 6H), 1.10 – 0.99 (m, 2H), 0.98 – 0.98 (m, 1H), 0.97 – 0.96 (m, 1H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

137.1 EXAMPLE 137

Synthesis of N-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 137



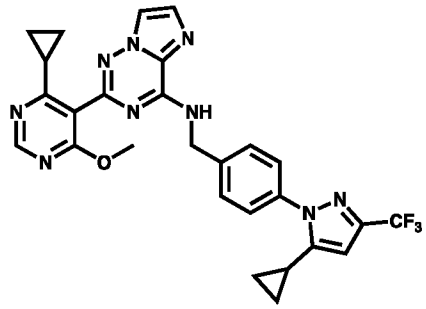
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(1H-1,2,3-triazol-1-yl)phenyl)methanamine (Intermediate AU). ^{1}H NMR (400 MHz,

DMSO-d_6) δ 9.58 (s, 1H), 8.78 (d, J = 0.8 Hz, 1H), 8.65 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 9.54 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 0.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 4.76 (d, J = 5.6 Hz, 2H), 3.84 (s, 3H), 1.88 – 1.82 (m, 1H), 1.01 – 0.99 (m, 2H), 0.84 – 0.81 (m, 2H). LCMS observed *m/z* = 441.3 $[M+H]^+$.

138.1 EXAMPLE 138

Synthesis of N-(4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 138

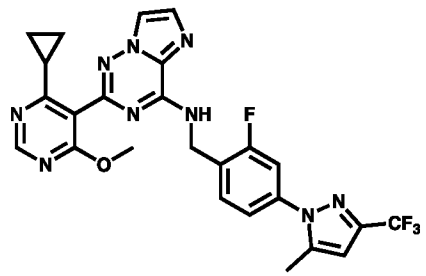


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BU). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 1.2 Hz, 1H), 7.61 – 7.56 (m, 4H), 6.38 (s, 1H), 4.91 (s, 2H), 3.93 (s, 3H), 1.88 (tt, J = 8.4, 4.7 Hz, 1H), 1.80 (ddd, J = 13.4, 8.4, 5.1 Hz, 1H), 1.14 – 1.09 (m, 2H), 1.04 – 0.97 (m, 2H), 0.93 – 0.86 (m, 2H), 0.83 – 0.77 (m, 2H). LCMS observed *m/z* = 548.4 $[M+H]^+$.

139.1 EXAMPLE 139

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 139



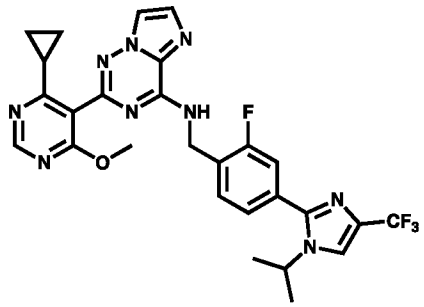
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (2-fluoro-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine

(Intermediate BD). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (s, 1H), 7.66 – 7.58 (m, 2H), 7.34 (ddd, J = 20.6, 9.2, 2.1 Hz, 2H), 6.58 (s, 1H), 4.94 (s, 2H), 3.91 (s, 3H), 2.37 (s, 3H), 1.86 (tt, J = 8.3, 4.6 Hz, 1H), 1.15 – 1.06 (m, 2H), 0.93 – 0.84 (m, 2H). LCMS observed *m/z* = 540.4 $[M+H]^+$.

140.1 EXAMPLE 140

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 140

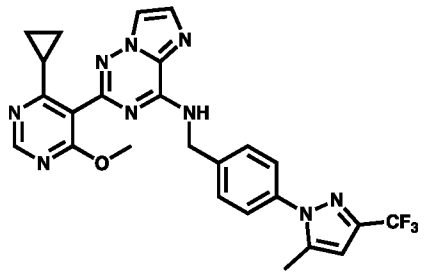


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with (2-fluoro-4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate J). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.98 – 7.90 (m, 2H), 7.67 – 7.58 (m, 2H), 7.40 – 7.29 (m, 2H), 4.95 (s, 2H), 4.55 (hept, J = 6.7 Hz, 1H), 3.92 (s, 3H), 1.88 (tt, J = 8.3, 4.6 Hz, 1H), 1.45 (d, J = 6.6 Hz, 6H), 1.15 – 1.07 (m, 2H), 0.92 – 0.84 (m, 2H). LCMS observed *m/z* = 568.4 $[M+H]^+$.

141.1 EXAMPLE 141

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 141



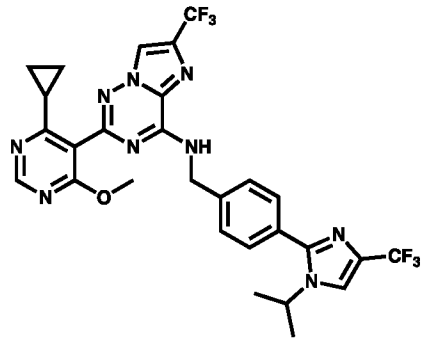
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)phenyl)methanamine with

(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate Y). ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.93 (s, 1H), 7.63 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.57 (s, 1H), 4.91 (s, 2H), 3.93 (s, 3H), 2.33 (s, 3H), 1.91 – 1.84 (m, 1H), 1.14 – 1.09 (m, 2H), 0.92 – 0.87 (m, 2H). LCMS observed *m/z* = 522.5 [M+H]$^+$.

142.1 EXAMPLE 142

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-6-(trifluoromethyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 142

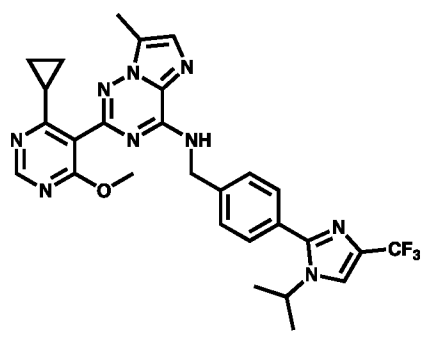


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-6-(trifluoromethyl)imidazo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (br s, 1H), 8.88 (s, 1H), 8.67 (s, 1H), 8.16 (s, 1H), 7.50 (s, 4H), 4.78 (s, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 2.01 – 1.94 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 (s, 2H), 0.83 – 0.82 (m, 2H). LCMS observed *m/z* = 618.2 [M+H]$^+$.

143.1 EXAMPLE 143

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-methylimidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 143

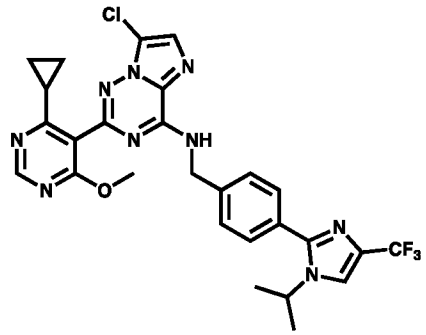


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-7-methylimidazo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 7.54 – 7.46 (m, 5H), 4.76 (d, J = 6.4 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.85 (s, 3H), 2.42 (s, 3H), 1.88 – 1.81 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.00 – 0.94 (m, 2H), 0.84 – 0.82 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

144.1 EXAMPLE 144

Synthesis of 7-chloro-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 144

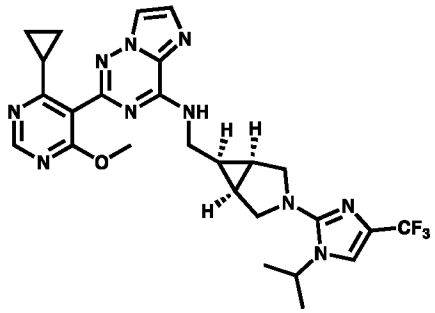


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4,7-trichloroimidazo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 8.67 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.81 (s, 1H), 7.49 (s, 4H), 4.78 (d, J = 4.8 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 1.93 – 1.86 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.03 – 1.00 (m, 2H), 0.83 – 0.83 (m, 2H). LCMS observed *m/z* = 584.3 $[M+H]^+$.

145.1 EXAMPLE 145

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(((1R,5S,6r)-3-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 145

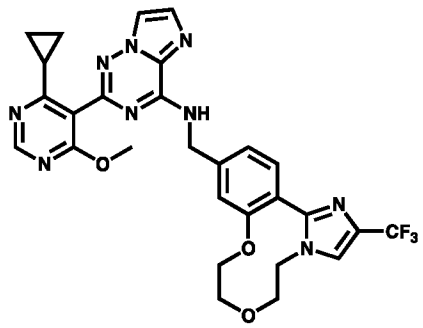


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with ((1R,5S,6r)-3-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)methanamine (Intermediate CV). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (br s, 1H), 8.67 (s, 1H), 8.11 (s, 1H), 7.64 (s, 1H), 7.61 (s, 1H), 7.32 – 7.31 (m, 1H), 4.33 – 4.26 (m, 1H), 3.86 (s, 3H), 3.42 – 3.33 (m, 6H), 1.92 – 1.88 (m, 1H), 1.64 (d, J = 8.4 Hz, 2H), 1.36 – 1.34 (m, 6H), 1.04 – 1.11 (m, 2H), 0.91 – 0.90 (m, 2H). LCMS observed *m/z* = 555.4 $[M+H]^+$.

146.1 EXAMPLE 146

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 146

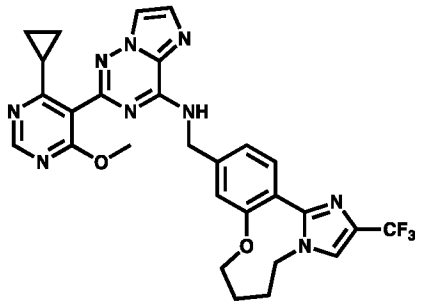


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-5,6,8,9-tetrahydrobenzo[i]imidazo[1,2-g][1,4,7]dioxazecin-12-yl)methanamine (Intermediate BW). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.54 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.98 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.31 (s, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.12 (d, J = 1.2 Hz, 1H), 4.76 (d, J = 6.4 Hz, 2H), 4.18 – 4.11 (m, 2H), 3.94 (s, 3H), 3.87 (d, J = 5.2 Hz, 4H), 3.56 – 3.54 (m, 2H), 1.91 – 1.87 (m, 1H), 1.03 – 1.00 (m, 2H), 0.88 – 0.85 (m, 2H). LCMS observed *m/z* = 594.3 $[M+H]^+$.

147.1 EXAMPLE 147

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[b]imidazo[2,1-d][1,5]oxazonin-11-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 147

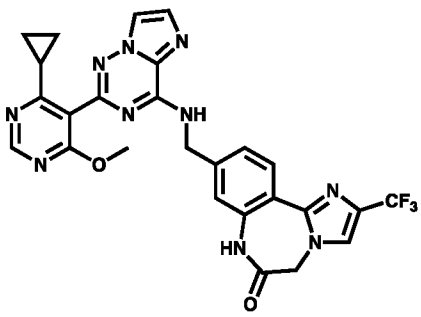


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-5,6,7,8-tetrahydrobenzo[b]imidazo[2,1-d][1,5]oxazonin-11-yl)methanamine (Intermediate BO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.97 (d, J = 1.2 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.13 (dd, J = 7.6, 1.2 Hz, 1H), 4.75 (d, J = 6.4 Hz, 2H), 4.16 (t, J = 5.0 Hz, 2H), 3.85 (s, 3H), 3.70 – 3.67 (m, 2H), 1.91 – 1.89 (m, 4H), 1.72 – 1.68 (m, 3H), 1.03 – 0.99 (m, 2H). LCMS observed *m/z* = 578.3 $[M+H]^+$.

148.1 EXAMPLE 148

Synthesis of 9-(((2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)amino)methyl)-2-(trifluoromethyl)-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-6(7H)-one.

Compound 148



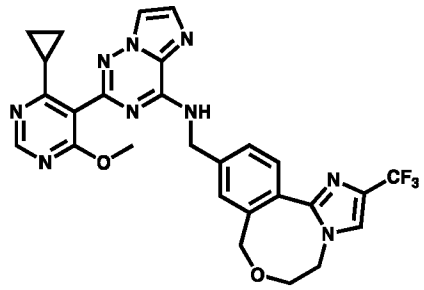
The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with 9-(aminomethyl)-2-(trifluoromethyl)-5H-benzo[f]imidazo[1,2-d][1,4]diazepin-6(7H)-one

(Intermediate BS). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 9.58 (t, J = 6.2 Hz, 1H), 8.65 (s, 1H), 8.18 (s, 1H), 8.10 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.18 (s, 1H), 4.75 (d, J = 10.4 Hz, 4H), 3.84 (s, 3H), 1.91 – 1.87 (m, 1H), 1.02 – 0.97 (m, 2H), 0.77 – 0.75 (m, 2H). LCMS observed *m/z* = 563.3 $[M+H]^+$.

149.1 EXAMPLE 149

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 149

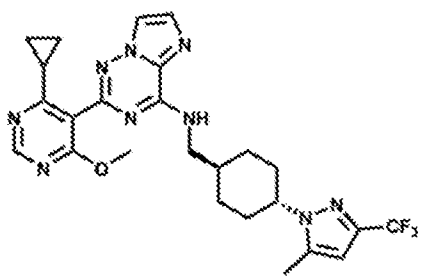


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-5,6-dihydro-8H-benzo[f]imidazo[1,2-d][1,4]oxazocin-10-yl)methanamine (Intermediate BR). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.68 – 7.51 (m, 1H), 7.43 – 7.42 (m, 2H), 4.78 (d, J = 6.0 Hz, 2H), 4.34 – 4.34 (m, 2H), 3.99 – 3.99 (m, 2H), 3.85 (s, 3H), 3.82 – 3.76 (m, 2H), 1.91 – 1.84 (m, 1H), 1.00 – 0.98 (m, 2H), 0.88 – 0.80 (m, 2H). LCMS observed *m/z* = 564.4 $[M+H]^+$.

150.1 EXAMPLE 150

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(((1r,4r)-4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 150

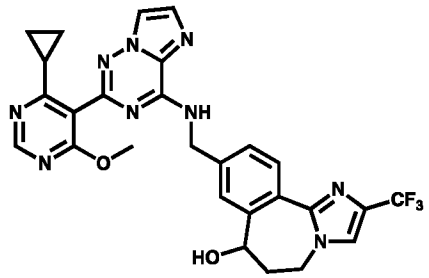


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)cyclohexyl)methanamine (Intermediate BX). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (t, J = 5.8 Hz, 1H), 8.68 (s, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 6.43 (s, 1H), 4.22 – 4.16 (m, 1H), 3.88 (s, 3H), 3.41 (t, J = 6.0 Hz, 2H), 2.30 (s, 3H), 1.92 – 1.68 (m, 8H), 1.26 – 1.18 (m, 2H), 1.08 – 1.05 (m, 4H). LCMS observed *m/z* = 528.3 $[M+H]^+$.

151.1 EXAMPLE 151

Synthesis of 9-(((2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)amino)methyl)-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-7-ol.

Compound 151

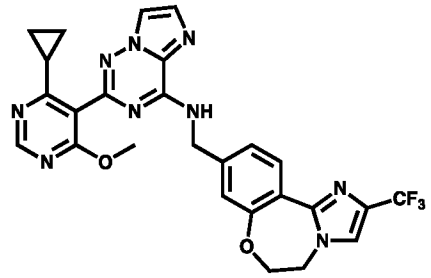


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with 9-(aminomethyl)-2-(trifluoromethyl)-6,7-dihydro-5H-benzo[c]imidazo[1,2-a]azepin-7-ol (Intermediate BT). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.4 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.94 (s, 1H), 7.68 – 7.61 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 5.45 (d, J = 4.4 Hz, 1H), 4.78 (d, J = 6.4 Hz, 2H), 4.59 – 4.57 (m, 1H), 4.17 – 4.12 (m, 1H), 3.85 (s, 3H), 3.81 – 3.77 (m, 1H), 2.61 – 2.57 (m, 1H), 2.09 – 2.04 (m, 1H), 1.89 – 1.85 (m, 1H), 1.01 – 0.99 (m, 2H), 0.85 – 0.83 (m, 2H). LCMS observed *m/z* = 564.3 $[M+H]^+$.

152.1 EXAMPLE 152

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 152

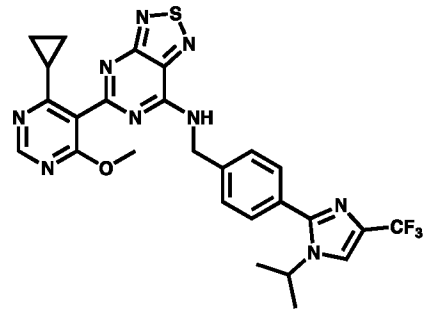


The title compound was prepared using a similar procedure as Compound 12, replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (2-(trifluoromethyl)-5,6-dihydrobenzo[f]imidazo[1,2-d][1,4]oxazepin-9-yl)methanamine (Intermediate BP). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.54 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 0.8 Hz, 1H), 7.10 (dd, J = 8.4, 1.6 Hz, 1H), 7.00 (d, J = 1.2 Hz, 1H), 4.68 (d, J = 6.4 Hz, 2H), 4.44 (s, 4H), 3.85 (s, 3H), 1.89 – 1.83 (m, 1H), 1.02 – 0.99 (m, 2H), 0.87 – 0.86 (m, 2H). LCMS observed *m/z* = 550.3 [M+H]$^+$.

153.1 EXAMPLE 153

Synthesis of 5-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-[1,2,5]thiadiazolo[3,4-d]pyrimidin-7-amine.

Compound 153

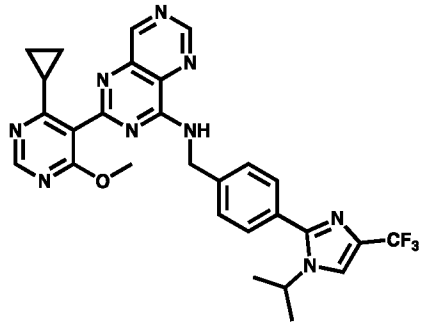


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 5,7-dichloro-[1,2,5]thiadiazolo[3,4-d]pyrimidine. ^{1}H NMR ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.99 (s, 1H), 8.65 (s, 1H), 8.16 (s, 1H), 7.64 – 7.51 (m, 4H), 4.85 (d, J = 4.8 Hz, 2H), 4.44 – 4.41 (m, 1H), 3.84 (s, 3H), 1.91 – 1.86 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.00 – 0.99 (m, 2H), 0.80 – 0.77 (m, 2H). LCMS observed *m/z* = 568.3 [M+H]$^+$.

154.1 EXAMPLE 154

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrimido[5,4-d]pyrimidin-4-amine.

Compound 154

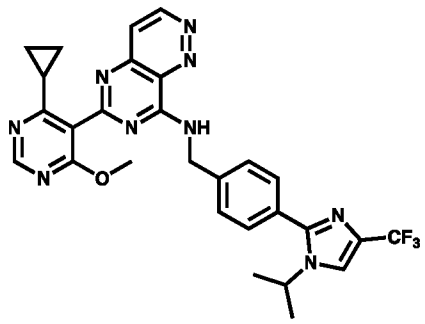


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloropyrimido[5,4-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (t, J = 6.4 Hz, 1H), 9.44 (s, 1H), 9.41 (s, 1H), 8.65 (s, 1H), 8.15 (s, 1H), 7.52 – 7.47 (m, 4H), 4.83 (d, J = 6.0 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.83 (s, 3H), 1.84 – 1.78 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.80 – 0.75 (m, 2H). LCMS observed *m/z* = 562.4 $[M+H]^+$.

155.1 EXAMPLE 155

Synthesis of 6-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrimido[5,4-c]pyridazin-8-amine.

Compound 155

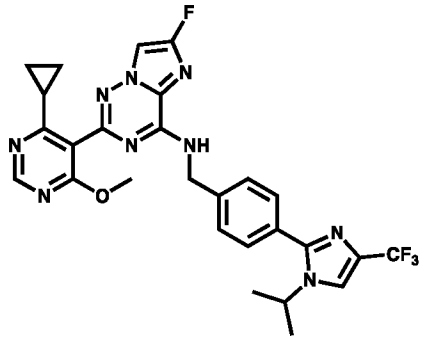


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 6,8-dichloropyrimido[5,4-c]pyridazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (t, J = 6.2 Hz, 1H), 9.57 (d, J = 6.0 Hz, 1H), 8.65 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.98 (d, J = 6.0 Hz, 1H), 7.52 (q, J = 8.5 Hz, 4H), 4.88 (d, J = 6.0 Hz, 2H), 4.46 – 4.40 (m, 1H), 3.84 (s, 3H), 1.88 – 1.82 (m, 1H), 1.40 (d, J = 7.6 Hz, 6H), 1.01 – 0.99 (m, 2H), 0.79 – 0.78 (m, 2H). LCMS observed *m/z* = 562.3 $[M+H]^+$.

156.1 EXAMPLE 156

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-fluoro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 156

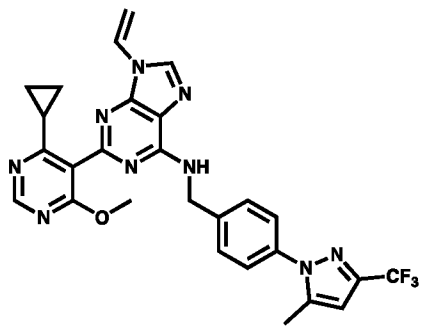


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-6-fluoroimidazo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.57 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.51 – 7.46 (m, 4H), 4.75 (d, J = 6.0 Hz, 2H), 4.46 – 4.39 (m, 1H), 3.85 (s, 3H), 1.90 – 1.85 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.03 – 0.97 (m, 2H), 0.84 – 0.82 (m, 2H). LCMS observed *m/z* = 568.3 $[M+H]^+$.

157.1 EXAMPLE 157

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-9-vinyl-9H-purin-6-amine.

Compound 157



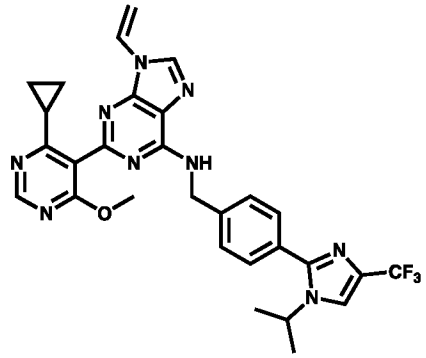
To a solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)-9*H*-purin-6-amine (208 mg, 0.400 mmol, Compound 22) in DMF (3.0 mL, 0.13 M) was added 1,2-dibromoethane (0.5 mL, 1.81 mmol) followed by Cs_2CO_3 (1.0 g, 1.82 mmol) and the reaction mixture was stirred at 50 °C for 5 hours. The reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue purified by achiral SFC (80% CO_2, 20% MeCN/isopropanol, 100 mL/min, 100 bar) affording 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-

1H-pyrazol-1-yl)benzyl)-9-vinyl-9H-purin-6-amine (2.5 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (br s, 1H), 8.61 (s, 2H), 7.49 (s, 4H), 7.32 (dd, J = 16.0, 9.2 Hz, 1H), 6.74 (s, 1H), 6.02 (d, J = 16.0 Hz, 1H), 5.13 (d, J = 8.8 Hz, 1H), 4.76 (s, 2H), 3.82 (s, 3H), 2.31 (s, 3H), 1.72 – 1.70 (m, 1H), 0.85 – 0.77 (m, 2H), 0.79 – 0.75 (m, 2H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

158.1 EXAMPLE 158

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-9-vinyl-9H-purin-6-amine.

Compound 158

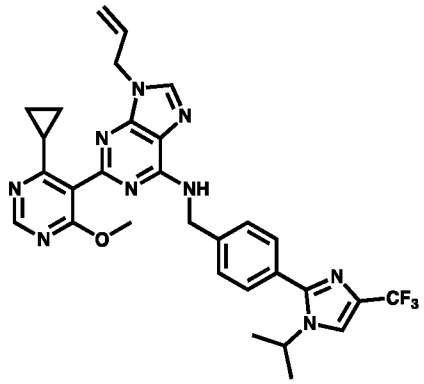


The title compound was prepared using a similar procedure as Compound 157, replacing 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)-9*H*-purin-6-amine with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-9*H*-purin-6-amine (Compound 53). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (br s, 1H), 8.62 (s, 2H), 8.15 (d, J = 1.2 Hz, 1H), 7.50 – 7.44 (m, 4H), 7.32 (dd, J = 16.0 Hz, J = 9.2 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.12 (d, J = 8.4 Hz, 1H), 4.75 (d, J = 4.4 Hz, 2H), 4.43 (t, J = 6.4 Hz, 1H), 3.82 (s, 3H), 1.74 – 1.68 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.99 – 0.93 (m, 2H), 0.78 – 0.73 (m, 2H). LCMS observed *m/z* = 576.3 $[M+H]^+$.

159.1 EXAMPLE 159

Synthesis of 9-allyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-9H-purin-6-amine.

Compound 159

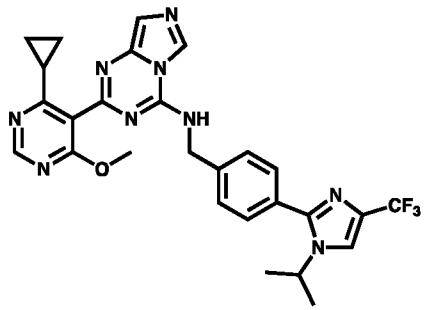


The title compound was prepared using a similar procedure as Compound 157, replacing 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-methyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)benzyl)-9*H*-purin-6-amine with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-9*H*-purin-6-amine (Compound 53) and 1,2-dibromoethane with 1,3-dibromopropane. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.61 – 8.56 (m, 2H), 8.21 (s, 1H), 8.15 (s, 1H), 7.48 – 7.48 (m, 4H), 6.12 – 6.03 (m, 1H), 5.21 (d, J = 10.4 Hz, 1H), 5.13 – 5.13 (m, 1H), 4.81 – 4.74 (m, 4H), 4.45 – 4.41 (m, 1H), 3.81 (s, 3H), 1.71 – 1.67 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.85 – 0.84 (m, 2H), 0.74 – 0.74 (m, 2H). LCMS observed *m/z* = 590.4 [M+H]$^+$.

160.1 EXAMPLE 160

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[1,5-a][1,3,5]triazin-4-amine.

Compound 160

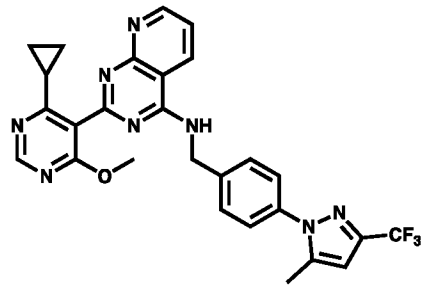


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloroimidazo[1,5-a][1,3,5]triazine. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.12 (br s, 1H), 8.58 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 6.99 (s, 1H), 4.74 (s, 2H), 4.49 – 4.43 (m, 1H), 3.84 (s, 3H), 1.98 – 1.98 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.98 – 0.97 (m, 2H), 0.85 – 0.83 (m, 2H). LCMS observed *m/z* = 550.2 [M+H]$^+$.

161.1 EXAMPLE 161

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)pyrido[2,3-d]pyrimidin-4-amine.

Compound 161

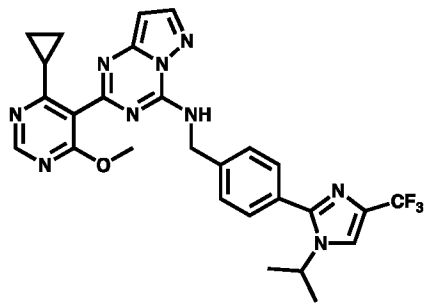


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloropyrido[2,3-d]pyrimidine and replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate Y). ^{1}H NMR (400 MHz, CD_3OD) δ 9.02 (dd, J = 4.4, 1.8 Hz, 1H), 8.71 (dd, J = 8.3, 1.9 Hz, 1H), 8.57 (s, 1H), 7.63 – 7.60 (m, 1H), 7.60 – 7.56 (m, 2H), 7.47 – 7.42 (m, 2H), 6.57 (s, 1H), 4.96 (s, 2H), 3.90 (s, 3H), 2.32 (s, 3H), 1.87 – 1.78 (m, 1H), 1.13 – 1.07 (m, 2H), 0.87 – 0.81 (m, 2H). LCMS observed *m/z* = 533.5 $[M+H]^+$.

162.1 EXAMPLE 162

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrazolo[1,5-a][1,3,5]triazin-4-amine.

Compound 162



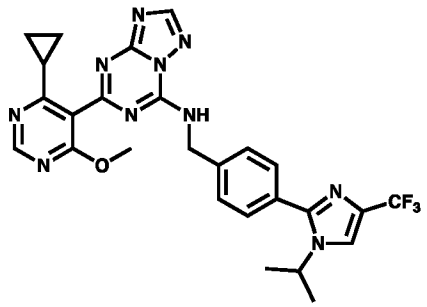
The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloropyrazolo[1,5-a][1,3,5]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (br s, 1H), 8.64 (s, 1H), 8.26 (d, J = 2.0 Hz, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.51 (s, 4H), 6.56 (d, J = 2.0 Hz, 1H), 4.79 (s, 2H),

4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.92 – 1.88 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.90 – 0.86 (m, 2H). LCMS observed *m/z* = 550.4 $[M+H]^+$.

163.1 EXAMPLE 163

Synthesis of 5-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-[1,2,4]triazolo[1,5-a][1,3,5]triazin-7-amine.

Compound 163

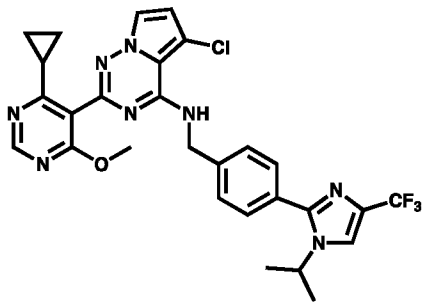


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 5,7-dichloro-[1,2,4]triazolo[1,5-a][1,3,5]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.98 (br s, 1H), 8.66 (s, 1H), 8.63 (s, 1H), 8.17 (d, J = 0.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.80 (s, 2H), 4.46 – 4.39 (m, 1H), 3.86 (s, 3H), 2.04 – 1.99 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 1.02 – 1.01 (m, 2H), 0.82 – 0.81 (m, 2H). LCMS observed *m/z* = 551.3$[M+H]^+$.

164.1 EXAMPLE 164

Synthesis of 5-chloro-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.

Compound 164



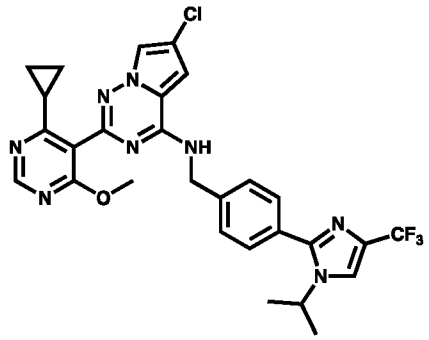
The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4,5-trichloropyrrolo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.16 (t, J = 6.0 Hz, 2H), 7.81 (d, J = 3.2 Hz, 1H), 7.49 (t, J = 5.2 Hz, 4H), 6.82 (d, J = 3.2 Hz, 1H), 4.83 (d, J = 6.0

Hz, 2H), 4.47 – 4.41 (m, 1H), 3.84 (s, 3H), 1.86 – 1.82 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.98 – 0.98 (m, 2H), 0.97 – 0.97 (m, 2H). LCMS observed *m/z* = 583.3[M+H]$^+$.

165.1 EXAMPLE 165

Synthesis of 6-chloro-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine.

Compound 165

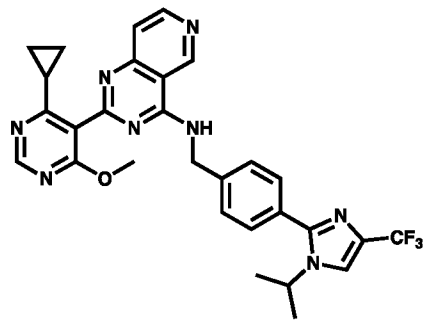


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4,6-trichloropyrrolo[2,1-f][1,2,4]triazine. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.12 (t, J = 6.0 Hz, 1H), 8.64 (s, 1H), 8.17 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 1.6 Hz, 1H), 7.53 – 7.47 (m, 4H), 7.06 (s, 1H), 4.79 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.87 – 1.80 (m, 1H), 1.81 (d, J = 4.4 Hz, 6H), 1.40 – 1.40 (m, 2H), 1.38 – 1.38 (m, 2H). LCMS observed *m/z* = 583.3[M+H]$^+$.

166.1 EXAMPLE 166

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)pyrido[4,3-d]pyrimidin-4-amine.

Compound 166



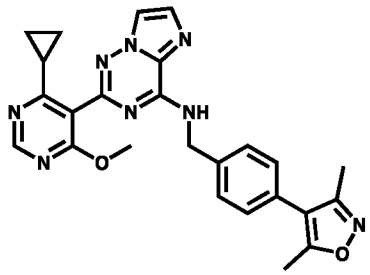
The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloropyrido[4,3-d]pyrimidine. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.75 (br s, 1H), 9.61 (t, J = 5.6 Hz, 1H),

8.89 (br s, 1H), 8.64 (s, 1H), 8.16 (d, J = 1.2 Hz, 1H), 7.65 (s, 1H), 7.51 (s, 4H), 4.88 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.82 (s, 3H), 1.78 – 1.71 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.78 – 0.75 (m, 2H). LCMS observed *m/z* = 561.3[M+H]$^+$.

167.1 EXAMPLE 167

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(3,5-dimethylisoxazol-4-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 167

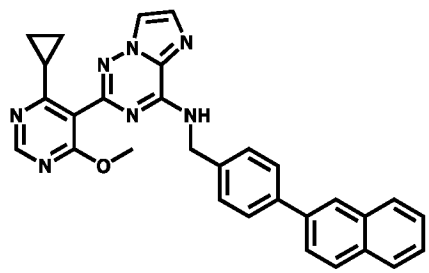


The title compound was prepared using a similar procedure as Compound 109, replacing 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7H-purine (Intermediate AC) with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-(methylsulfonyl)imidazo[2,1-f][1,2,4]triazine (Intermediate DF) and replacing 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine with (3,5-dimethylisoxazol-4-yl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1H), 7.91 (s, 1H), 7.61 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 4.85 (s, 2H), 3.92 (s, 3H), 2.37 (s, 3H), 2.21 (s, 3H), 1.87 (tt, J = 8.3, 4.7 Hz, 1H), 1.10 (dq, J = 6.5, 3.9 Hz, 2H), 0.85 (dq, J = 7.0, 3.7 Hz, 2H). LCMS observed *m/z* = 469.4 [M+H]$^+$.

168.1 EXAMPLE 168

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(naphthalen-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 168



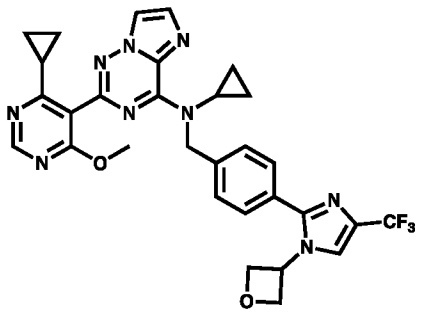
The title compound was prepared using a similar procedure as Compound 109, replacing 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7H-purine (Intermediate AC) with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-

(methylsulfonyl)imidazo[2,1-f][1,2,4]triazine (Intermediate DF) and replacing 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)pyridine with naphthalen-2-ylboronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1H), 8.55 (s, 1H), 8.08 (s, 1H), 7.98 – 7.84 (m, 5H), 7.80 – 7.71 (m, 3H), 7.63 (s, 1H), 7.54 – 7.47 (m, 4H), 3.93 (s, 3H), 1.91 – 1.84 (m, 1H), 1.13 – 1.09 (m, 2H), 0.88 (dd, J = 7.9, 3.2 Hz, 2H). LCMS observed *m/z* = 500.1 $[M+H]^+$.

169.1 EXAMPLE 169

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 169

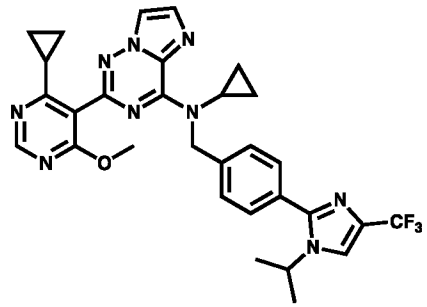


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)-7H-purine with 2,4-dichloroimidazo[2,1-f][1,2,4]triazine and replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-(oxetan-3-yl)-4-(trifluoromethyl)-1H-imidazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (s, 1H), 8.23 (d, J = 0.8 Hz, 1H), 7.73 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 5.89 – 5.86 (m, 1H), 5.10 – 5.05 (m, 1H), 5.54 – 5.47 (m, 1H), 4.85 (t, J = 7.2 Hz, 2H), 4.79 (t, J = 6.6 Hz, 2H), 3.88 (s, 3H), 3.28 – 3.35 (m, 1H), 2.10 (s, 1H), 1.04 – 0.75 (m, 8H). LCMS observed *m/z* = 604.3 $[M+H]^+$.

170.1 EXAMPLE 170

Preparation of N-cyclopropyl-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 170

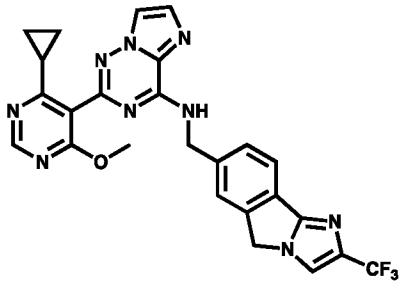


The title compound was prepared using a similar procedure as Compound 21, replacing 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)-7H-purine with 2,4-dichloroimidazo[2,1-f][1,2,4]triazine and replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with 2-(4-(chloromethyl)phenyl)-1-isopropyl-4-(trifluoromethyl)-1H-imidazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.24 (d, J = 0.8 Hz, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.74 (br s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 5.90 (br s, 1H), 5.07 (br s, 1H), 4.47 – 4.44 (m, 1H), 3.87 (s, 3H), 3.00 – 2.91 (m, 1H), 2.07 – 1.99 (m, 1H), 1.39 (d, J = 6.8 Hz, 6H), 1.04 – 0.89 (m, 8H). LCMS observed *m/z* = 590.3 $[M+H]^+$.

171.1 EXAMPLE 171

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((2-(trifluoromethyl)-5H-imidazo[2,1-a]isoindol-7-yl)methyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 171

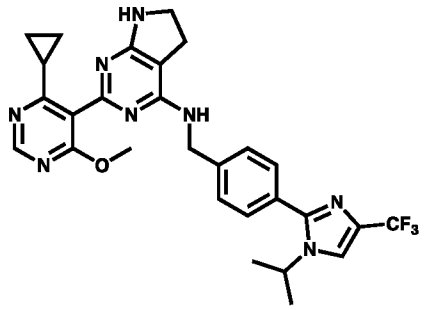


The title compound was isolated as a side product during the isolation of Compound 149. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (t, J = 6.0 Hz, 1H), 8.66 (s, 1H), 8.16 (s, 1H), 8.10 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.61 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H), 4.79 (d, J = 6.4 Hz, 2H), 3.85 (s, 3H), 1.88-1.86 (m, 1H), 0.99-0.99 (m, 2H), 0.81-0.78 (m, 2H). LCMS observed *m/z* = 520.3 $[M+H]^+$.

172.1 EXAMPLE 172

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 172

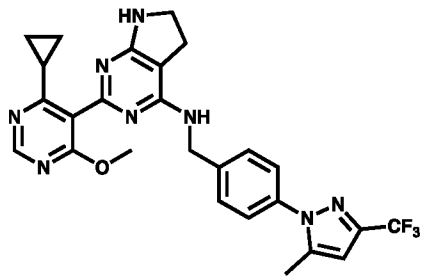


The title compound was prepared using a similar procedure as Compound 1, replacing (4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate B). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.06 (t, J = 6.4 Hz, 1H), 6.57 (s, 1H), 4.57 (d, J = 5.6 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.81 (s, 3H), 3.50 (t, J = 9.0 Hz, 2H), 2.84 (t, J = 8.8 Hz, 2H), 1.77 – 1.71 (m, 1H), 1.39 (d, J = 6.4 Hz, 6H), 0.91 – 0.90 (m, 2H), 0.75 (m, 2H). LCMS observed *m/z* = 551.3 $[M+H]^+$.

173.1 EXAMPLE 173

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 173

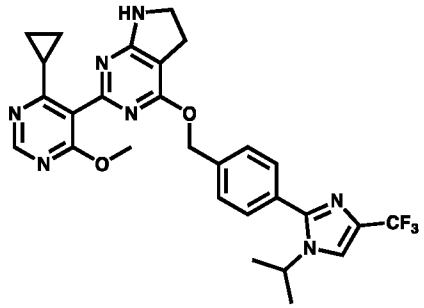


The title compound was prepared using a similar procedure as Compound 1, replacing (4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with ((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate Y). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.49 – 7.43 (m, 4H), 7.07 (t, J = 6.2 Hz, 1H), 6.74 (s, 1H), 6.58 (s, 1H), 4.59 (d, J = 6.4 Hz, 2H), 3.81 (s, 3H), 3.50 (t, J = 8.8 Hz, 2H), 2.84 (t, J = 8.8 Hz, 2H), 2.31 (s, 3H), 1.24 (s, 1H), 0.92 – 0.92 (m, 2H), 0.78 – 0.77 (m, 2H). LCMS observed *m/z* = 523.3 $[M+H]^+$.

174.1 EXAMPLE 174

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)oxy)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidine.

Compound 174

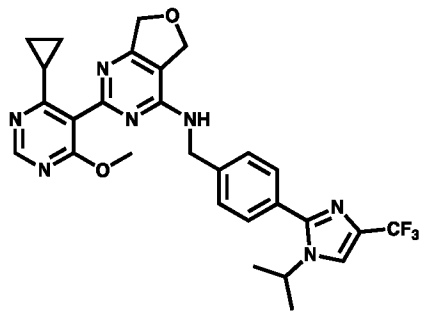


The title compound was prepared using a similar procedure as Compound 1, replacing (4-(1-methyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate C) and using NaH for the SNAr step as described by general procedure E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.18 (s, 1H), 7.55 (s, 4H), 7.28 (s, 1H), 5.44 (s, 2H) 4.50 – 4.45 (m, 1H), 3.84 (s, 3H), 3.59 (t, J = 9.0 Hz, 2H), 2.97 (t, J = 8.8 Hz, 2H), 1.75 – 1.69 (m, 1H), 1.41 (d, J = 6.4 Hz, 6H), 0.99 – 0.97 (m, 2H), 0.85 – 0.85 (m, 2H). LCMS observed *m/z* = 552.4 $[M+H]^+$.

175.1 EXAMPLE 175

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine.

Compound 175



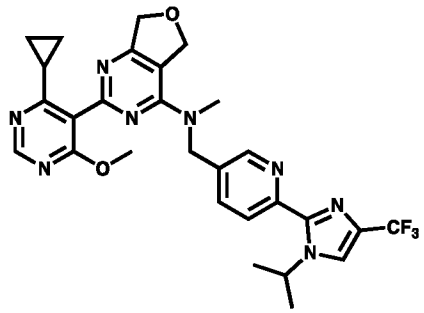
The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-5,7-dihydrofuro[3,4-d]pyrimidine. ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1H), 7.90 (s, 1H), 7.53 – 7.46 (m, 4H), 5.08 (s, 2H), 4.95 (s, 2H), 4.79 (s, 2H), 4.57 – 4.48 (m, 1H), 3.91 (s, 3H), 1.77 – 1.67

(m, 1H), 1.44 (d, J = 1.6 Hz, 6H), 1.11 – 1.03 (m, 2H), 0.87 – 0.78 (m, 2H). LCMS observed *m/z* = 552.3[M+H]$^+$.

176.1 EXAMPLE 176

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-((6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-3-yl)methyl)-N-methyl-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine.

Compound 176

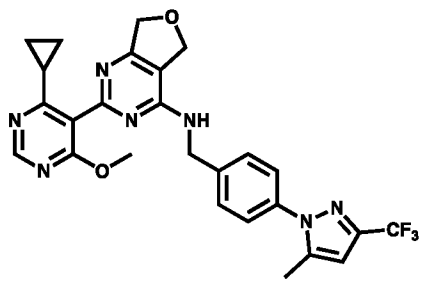


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-5,7-dihydrofuro[3,4-d]pyrimidine and replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with 1-(6-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-3-yl)-N-methyl-methanamine•HCl (Intermediate S). ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1H), 8.55 (s, 1H), 7.97 – 7.93 (comp m, 2H), 7.88 – 7.83 (comp m, 1H), 5.67 (h, J = 6.8 Hz, 1H), 5.45 (s, 2H), 4.96 (s, 2H), 4.92 (s, 2H), 3.91 (s, 3H), 3.24 (s, 3H), 1.78 – 1.72 (m, 1H), 1.48 (d, J = 6.8 Hz, 6H), 1.11 – 1.05 (comp m, 2H), 0.90 – 0.84 (comp m, 2H). LCMS observed *m/z* = 567.3[M+H]$^+$.

177.1 EXAMPLE 177

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-5,7-dihydrofuro[3,4-d]pyrimidin-4-amine.

Compound 177

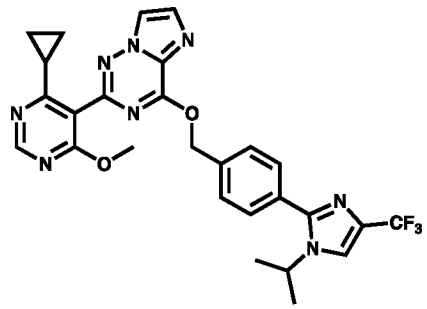


The title compound was prepared using a similar procedure as Compound 12, replacing 2,4-dichloroimidazo[2,1-f][1,2,4]triazine with 2,4-dichloro-5,7-dihydrofuro[3,4-d]pyrimidine and replacing (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine with (4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate Y). ^{1}H NMR (400 MHz, CD_3OD) 8.54 (s, 1H), 7.53 – 7.49 (comp m, 2H), 7.45 – 7.40 (comp m, 2H), 6.56 (s, 1H), 5.09 – 5.04 (m, 2H), 4.95 – 4.91 (m, 2H), 4.78 (s, 2H), 3.89 (s, 3H), 2.32 (s, 3H), 1.74 – 1.66 (m, 1H), 1.09 – 1.02 (m, 2H), 0.87 – 0.78 (m, 2H). LCMS observed *m/z* = 524.2[M+H]$^+$.

178.1 EXAMPLE 178

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)oxy)imidazo[2,1-f][1,2,4]triazine.

Compound 178

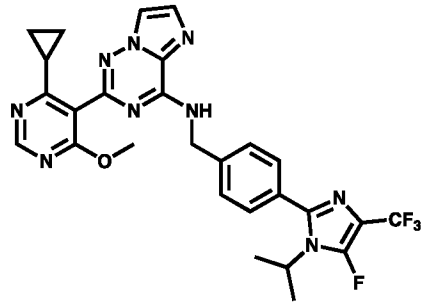


The title compound was prepared using a similar procedure as Compound 12, replacing 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-6-(methylsulfonyl)-7*H*-purine with 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-4-(methylsulfonyl)imidazo[2,1-f][1,2,4]triazine (Intermediate DF) and replacing (4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)cuban-1-yl)methanol with ((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanol (Intermediate C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.46 (d, J = 0.8 Hz, 1H), 8.19 (s, 1H), 7.88 (d, J = 0.8 Hz, 1H), 7.69 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 5.74 (s, 2H), 4.52 – 4.46 (m, 1H), 3.89 (s, 3H), 2.02 – 1.97 (m, 1H), 1.41 (d, J = 6.4 Hz, 6H), 1.10 – 1.08 (m, 2H), 0.95 – 0.94 (m, 2H). LCMS observed *m/z* = 551.3 [M+H]$^+$.

179.1 EXAMPLE 179

Synthesis of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(5-fluoro-1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 179

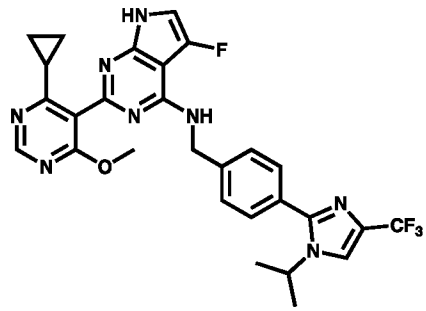


To a stirred solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.1 g, 0.18 mmol. Compound 12) in MeCN (5 mL), was added selectfluor (0.07 g, 0.22 mmol) and the reaction was stirred at 25 °C for 12 h in a sealed tube. The reaction mixture was concentrated under reduced pressure and The crude product was purified by SFC-Prep to afford 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-*N*-(4-(5-fluoro-1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (9 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.2 Hz, 1H), 8.66 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.68 (d, J = 0.8 Hz, 1H), 7.50 (s, 4H), 4.77 (d, J = 6.0 Hz, 2H), 4.47 – 4.40 (m, 1H), 3.85 (s, 3H), 1.87 – 1.84 (m, 1H), 1.45 (d, J = 6.0 Hz, 6H), 1.02 – 0.98 (m, 2H), 0.83-0.80 (m, 2H). LCMS observed *m/z* = 568.3 $[M+H]^+$.

180.1 EXAMPLE 180

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-5-fluoro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 180



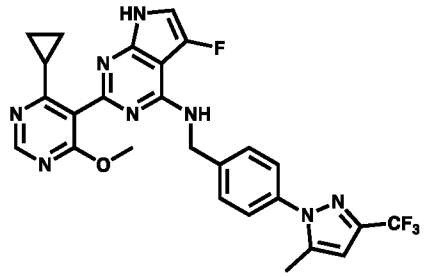
The title compound was prepared using a similar procedure as Compound 102, replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (Intermediate B) and replacing 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)purine with 2,4-dichloro-5-fluoro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (Intermediate DF). ^{1}H

NMR (400 MHz, CD_3OD) δ 8.53 (s, 1H), 7.89 (s, 1H), 7.56 – 7.51 (m, 2H), 7.50 – 7.43 (m, 2H), 6.93 (s, 1H), 4.52 (hept, J = 6.5 Hz, 1H), 3.88 (s, 3H), 1.75 – 1.69 (m, 1H), 1.43 (d, J = 6.5 Hz, 6H), 1.06 – 1.02 (m, 2H), 0.79 – 0.75 (m, 2H). LCMS observed *m/z* = 567.3 $[M+H]^+$.

181.1 EXAMPLE 181

Preparation of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-5-fluoro-N-(4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-7H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 181

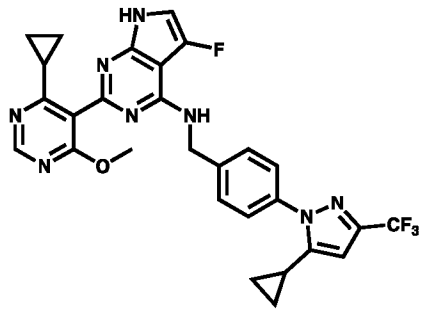


The title compound was prepared using a similar procedure as Compound 102, replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with ((4-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate Y) and replace 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)purine with 2,4-dichloro-5-fluoro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (Intermediate DF). ^1H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.59 (s, 1H), 7.85 (t, J = 6.3 Hz, 1H), 7.51 – 7.46 (m, 4H), 7.17 – 7.13 (m, 1H), 6.73 (s, 1H), 4.75 (d, J = 6.3 Hz, 2H), 3.80 (s, 3H), 2.30 (s, 3H), 1.75 – 1.69 (m, 2H), 0.97 – 0.92 (m, 2H), 0.77 – 0.72 (m, 2H). LCMS observed *m/z* = 539.2 $[M+H]^+$.

182.1 EXAMPLE 182

Preparation of N-(4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzyl)-2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-4-amine.

Compound 182

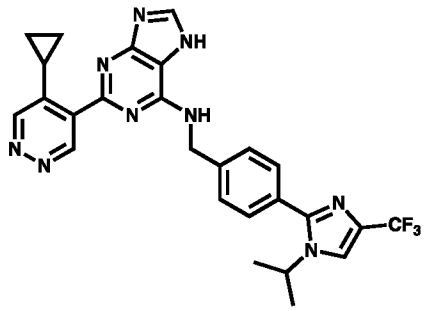


The title compound was prepared using a similar procedure as Compound 102, replacing 2-(4-(chloromethyl)phenyl)-1-methyl-4-(trifluoromethyl)-1H-imidazole with (4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl)methanamine (Intermediate BU) and replacing 2,6-dichloro-7-(tetrahydro-2H-pyran-2-yl)purine with 2,4-dichloro-5-fluoro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (Intermediate DF). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (d, J = 2.9 Hz, 1H), 8.58 (s, 1H), 7.89 – 7.80 (m, 1H), 7.57 – 7.48 (m, 4H), 7.15 (t, J = 2.6 Hz, 1H), 6.61 (s, 1H), 4.75 (d, J = 6.3 Hz, 2H), 3.80 (s, 3H), 1.83 – 1.68 (m, 2H), 0.97 – 0.90 (m, 4H), 0.84 – 0.78 (m, 2H), 0.76 – 0.70 (m, 2H). LCMS observed *m/z* = 565.3 $[M+H]^+$.

183.1 EXAMPLE 183

Preparation of 2-(5-cyclopropylpyridazin-4-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 183

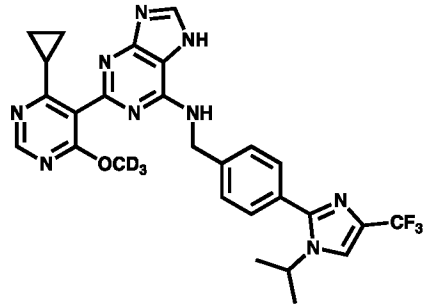


The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with 4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 9.29 (s, 1H), 8.74 (s, 1H), 8.63 (br s, 1H), 8.28 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.49 (m, J = 7.2 Hz, 4H), 4.82 (s, 2H), 4.48 – 4.42 (m, 1H), 2.89 (s, 1H), 1.37 (d, J = 6.8 Hz, 6H), 0.94 – 0.94 (m, 2H), 0.84 – 0.84 (m, 2H). LCMS observed *m/z* = 520.4 $[M+H]^+$.

184.1 EXAMPLE 184

Preparation of 2-(4-cyclopropyl-6-(methoxy-d3)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 184

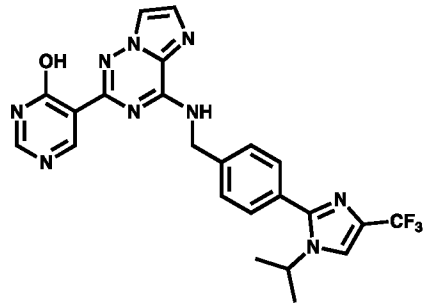


The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with 4-cyclopropyl-6-(methoxy-*d*3)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 13.03 (br s, 1H), 8.60 (s, 1H), 8.45 (br s, 1H), 8.20 – 8.15 (m, 2H), 7.48 (s, 4H), 4.74 (s, 2H), 4.45 – 4.42 (m, 1H), 1.74 – 1.69 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H), 0.98 – 0.92 (m, 2H), 0.76 – 0.71 (m, 2H). LCMS observed *m/z* = 553.3 $[M+H]^+$.

185.1 EXAMPLE 185

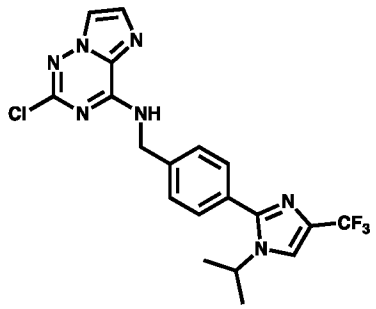
Preparation of 5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol.

Compound 185



Step 1: Preparation of 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 185.1

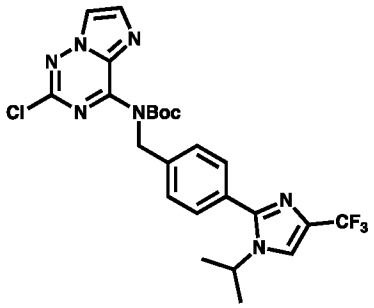


To a stirred solution of (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)phenyl)methanamine (2.923 g, 10.318 mmol) in Acetonitrile (15 mL) were added DIPEA

(7.123 mL, 39.683 mmol) followed by 2,4-dichloroimidazo[2,1-f][1,2,4]triazine (1.5 g, 7.937 mmol) and heated the reaction mixture at 60 °C for 16 h. The progress of the reaction was monitored by LCMS and TLC. On completion, the reaction mixture was directly concentrated under reduced pressure to get the crude. The crude product was purified by normal phase flash chromatography (silica gel, 25–30% EtOAc in hexanes) to afford 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (2 g) as a yellow gum.. LCMS observed *m/z* = 436.4 $[M+H]^+$.

Step 2: Preparation of tert-butyl (2-chloroimidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate.

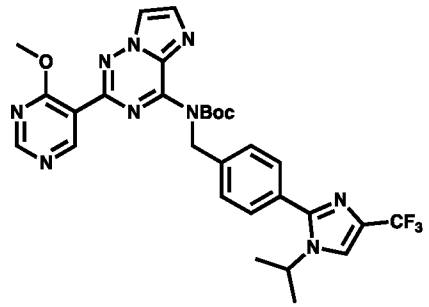
Compound 185.2



To a stirred solution of 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (2 g, 4.589 mmol) in dichloromethane (20 mL) were added triethyl amine (1.908 mL, 13.767 mmol), di-tert-butyl dicarbonate (1.581 mL, 6.883 mmol) followed by 4-(Dimethylamino)pyridine (0.056 g, 0.459 mmol) and reaction mixture was stirred at rt for 16 h. The progress of the reaction was monitored by LCMS and TLC. Upon completion, the reaction mixture was quenched with cold water (20 mL), extracted with dichloromethane (50 mL x 2). The combined organic layer was washed with brine solution (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (davisil silica gel, 15–20% EtOAc in petroleum ether) to afford tert-butyl (2-chloroimidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (2.4 g) as a yellow gum. LCMS observed *m/z* = 536.2 $[M+H]^+$.

Step 3: Preparation of tert-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)(2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)carbamate.

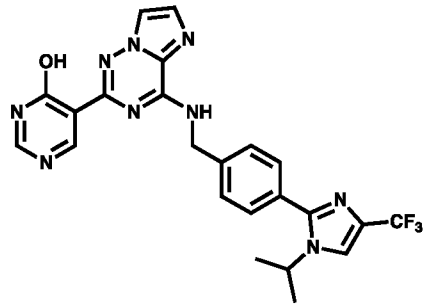
Compound 185.3



To a stirred reaction mixture of tert-butyl (2-chloroimidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (2 g, 3.732 mmol) and 4-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (1.321 g, 5.597 mmol) in 1,4-dioxane (20 mL) and Water (4 mL), was added K_3PO_4 (2.376 g, 11.195 mmol) and reaction mixture was degassed with nitrogen for 10 min. Then XPhosPdG3 (0.316 g, 0.373 mmol) was added and reaction mixture was heated at 110 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. On completion (monitored by TLC, R_f: 0.20, mobile phase: 70% EtOAc in hexanes), the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (2 x 10 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by normal phase flash chromatography (silica gel, 65–70% EtOAc in hexanes) to afford tert-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)(2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)carbamate (1.1 g) as a yellow gum. LCMS observed m/z = 610.6 $[M+H]^+$.

Step 4: Preparation of 5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol.

Compound 185



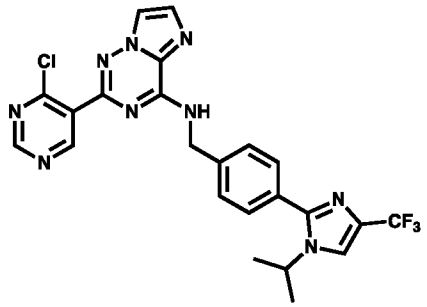
To a stirred reaction mixture of tert-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)(2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)carbamate (1.1 g, 1.804 mmol) in Methanol (55.000 mL), were added Hydrogen chloride, 4M in 1,4-dioxane (55.000 mL, 1.804 mmol) in 0 °C and heated the reaction mixture at 80 °C for 16 h. Progress of the reaction was monitored by TLC and LCMS. On completion, the

reaction mixture was directly evaporated and the crude was quenched with saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 10 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude 5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol (0.85 g, 95%) as pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 9.42 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 8.15 (d, J = 0.8 Hz, 1H), 8.11 (d, J = 1.2 Hz, 1H), 7.63 (d, J = 0.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 4.82 (s, 2H), 4.49 – 4.43 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 496.3 $[M+H]^+$.

186.1 EXAMPLE 186

Preparation of 2-(4-chloropyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 186



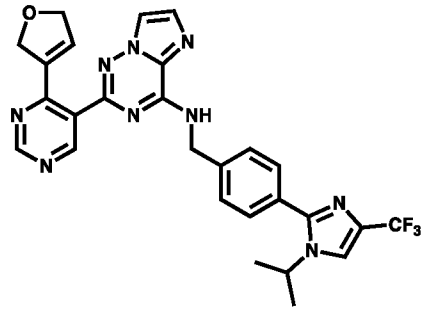
To a stirred solution of 5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol (0.350 g, 0.706 mmol, Compound 185) in $POCl_3$ (4 mL) was added N,N-Diisopropylethylamine (0.326 mL, 1.766 mmol) at 0 °C and the reaction mixture was stirred at 100 °C for 3 h. The progress of reaction was monitored by TLC and LCMS. On completion, the reaction mixture was concentrated to dryness and the resulted crude was diluted with EtOAc (30 mL), suspended and poured into saturated sodium bicarbonate solution (30 mL). The reaction mixture was stirred at room temperature for 10 minutes. The combined organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, 15–20% EtOAc in petroleum ether) to afford 2-(4-chloropyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.36 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 – 9.76 (m, 1H), 9.15 – 9.11 (m, 2H), 8.23 (d, *J* = 0.8 Hz, 1H), 8.15 (d, *J* = 1.2 Hz, 1H), 7.72 (d, *J* = 0.8 Hz, 1H), 7.52 (s, 4H),

4.84 (d, J = 5.6 Hz, 2H), 4.48 – 4.41 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H). LCMS observed m/z = 514.3 $[M+H]^+$.

187.1 EXAMPLE 187

Preparation of 2-(4-(2,5-dihydrofuran-3-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 187

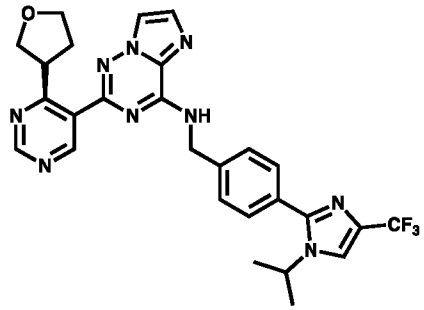


To a stirred solution of 2-(4-chloropyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.35 g, 0.681 mmol, Compound 186) and 2-(2,5-dihydrofuran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.160 g, 0.817 mmol) in dioxane (3.0 mL) and water (0.5 mL), and was added Potassium phosphate (0.392 g, 1.703 mmol) and purged with nitrogen gas for 10 min. XPhosPdG3 (0.058 g, 0.068 mmol) was added. The reaction mixture was stirred at 100 °C for 16 h. On completion (monitored by TLC, R_f: 0.30, mobile phase: 100% EtOAc in hexanes), reaction mixture was diluted with water (10.0 mL) and extracted with EtOAc (2 X 10 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by normal phase flash chromatography (silica gel, 75–80% EtOAc in hexanes) to afford 2-(4-(2,5-dihydrofuran-3-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.210 g) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (t, J = 6.4 Hz, 1H), 9.23 (s, 1H), 8.90 (s, 1H), 8.18 (dd, J = 12.8, 1.2 Hz, 2H), 7.70 – 7.68 (m, 1H), 7.54 – 7.47 (m, 4H), 6.32 – 6.31 (m, 1H), 4.83 – 4.76 (m, 4H), 4.52 – 4.43 (m, 3H), 1.39 (d, J = 6.8 Hz, 6H). LCMS observed m/z = 548.3 $[M+H]^+$.

188.1 EXAMPLE 188

Preparation of ("R")-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-(tetrahydrofuran-3-yl)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 188

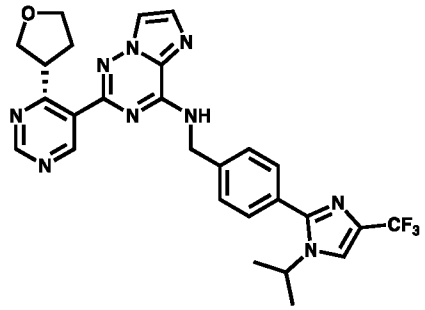


To a stirred solution of 2-(4-(2,5-dihydrofuran-3-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.15 g, 0.274 mmol, Compound 187) in EtOAc (50 mL) was added Palladium 10% on Carbon (wet with ca. 55% Water) (0.087 g, 0.822 mmol) and stirred the reaction mixture at room temperature in par shaker under hydrogen atmosphere (80 psi) for 16 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion, the reaction mixture was filtered through celite pad washed with EtOAc (100 mL). The filtrated was concentrated under reduced pressure. The crude product was purified by flash chromatography (davisil silica, 60–70% EtOAc in petroleum ether) to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-(tetrahydrofuran-3-yl)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.110 g, 73.06%) as a pale yellow gum. The purified product of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-(tetrahydrofuran-3-yl)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.120 g, 0.218 mmol) was submitted for chiral separation. Analytical SFC Conditions, Chiralcel OJ-H (30x250)mm,5µ, % CO2: 78%, % Co solvent: 22% (0.1% IPAmine in IPA), Flow: 100mL/min, Back Pressure: 100 bar, Temperature: 300 C, UV: 248 nm, the stereochemistry was arbitrarily defined. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (bs, 1H), 9.20 (s, 1H), 8.96 (s, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.13 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.52 (s, 4H), 4.86 (s, 2H), 4.48 – 4.45 (m, 1H), 4.14 – 4.10 (m, 1H), 3.91 – 3.87 (m, 2H), 3.73 (t, J = 7.4 Hz, 1H), 3.59 (q, J = 7.3 Hz, 1H), 2.14 – 2.11 (m, 1H), 2.07 – 2.01 (m, 1H), 1.38 (d, J = 6.8 Hz, 6H). LCMS observed m/z = 550.3 $[M+H]^+$.

189.1 EXAMPLE 189

Preparation of ("*S*")-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(4-(tetrahydrofuran-3-yl)pyrimidin-5-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 189.1

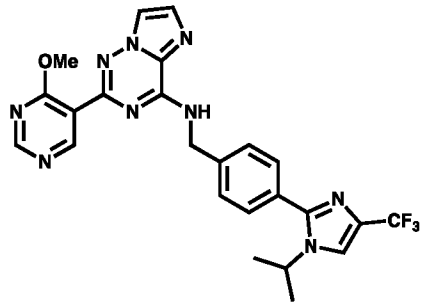


The title compound was isolated during the preparation of Compound 188, the stereochemistry was arbitrarily defined. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.20 (s, 1H), 9.02-8.96 (m, 1H), 8.21 (d, J = 1.2 Hz, 1H), 8.15 (s, 1H), 7.70-7.68 (m, 1H), 7.54-7.50 (m, 4H), 4.86-4.77 (m, 2H), 4.49-4.43 (m, 1H), 4.15-4.11 (m, 1H), 3.92-3.84 (m, 2H), 3.72 (t, J = 7.6 Hz, 1H), 3.60 (q, J = 7.3 Hz, 1H), 2.18-2.01 (m, 2H), 1.38 (d, J = 6.4 Hz, 6H). LCMS observed m/z = 550.4 $[M+H]^+$.

190.1 EXAMPLE 190

Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 190



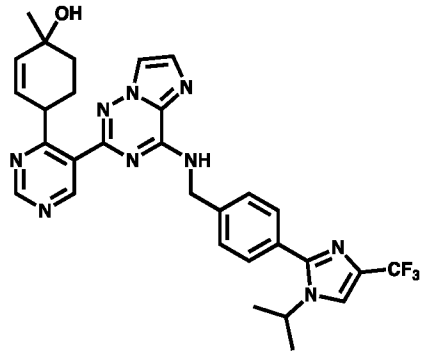
To a stirred solution of tert-butyl (4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)(2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)carbamate (0.1 g, 0.164 mmol, Compound 185.3) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL, 0.820 mmol) at 0° C and reaction was allowed to stir at rt for 1 h. Progress of the reaction was monitored by TLC and LCMS. On completion, reaction mixture was directly evaporated and triturated with diethyl ether to get the crude. The crude product was purified by flash chromatography (devisal silica, 60–70% EtOAc in petroleum ether) to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-methoxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.013 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (t, J = 6.2 Hz, 1H), 8.86 (d, J = 13.6 Hz, 2H), 8.17 – 8.15 (m, 2H), 7.67 (d, J = 1.2 Hz, 1H), 7.57 – 7.52 (m, 4H), 4.82 (d, J = 6.0 Hz, 2H),

4.49 – 4.42 (m, 1H), 3.97 (s, 3H), 1.38 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 510.3 $[M+H]^+$.

191.1 EXAMPLE 191

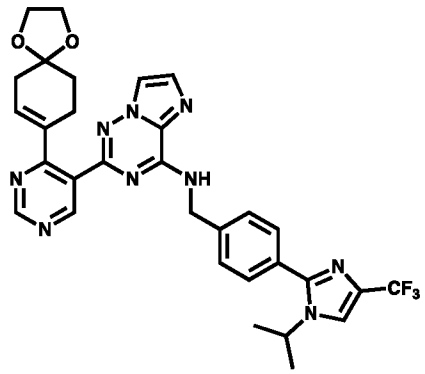
Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)-1-methylcyclohex-2-en-1-ol.

Compound 191



Step 1: Preparation of 2-(4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 191.1

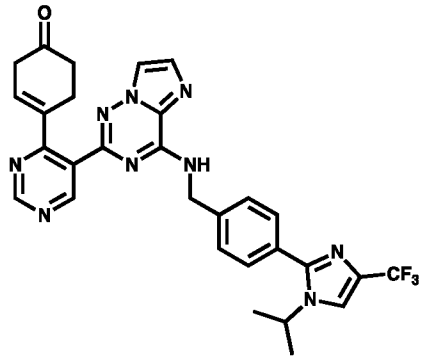


To a stirred solution of 2-(4-chloropyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) imidazo[2,1-f] [1,2,4] triazin-4-amine (Compound 212.5) (0.5 g, 0.97 mmol) in dioxane (5.0 mL) and water (1.0 mL), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (0.31 g, 1.16 mmol) was added, followed by potassium phosphate (0.56 g, 2.43 mmol). The reaction mixture was purged with nitrogen gas for 30 minutes. XPhos Pd G3 (0.082 g, 0.09 mmol) was then added, and the reaction was stirred at 110 °C for 3 hours. Upon completion, the mixture was diluted with water (10 mL), and extracted with EtOAc (2 × 50 mL). The combined organic layers

were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (40% EtOAc/petroleum ether eluent) to afford 2-(4-(1,4-dioxaspiro [4.5] dec-7-en-8-yl) pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) imidazo[2,1-f] [1,2,4] triazin-4-amine (0.4 g) as a pale brown gum. LCMS observed *m/z* = 619.2 $[M+H]^+$.

Step 2: Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)cyclohex-3-en-1-one.

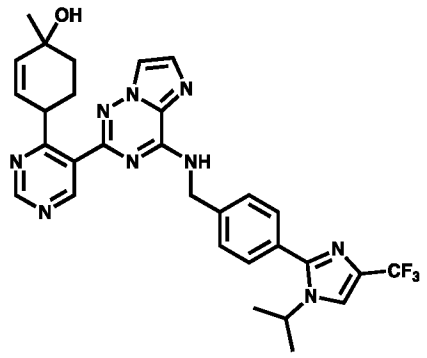
Compound 191.2



To a stirred solution of 2-(4-(1,4-dioxaspiro [4.5] dec-7-en-8-yl) pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) imidazo[2,1-f] [1,2,4] triazin-4-amine (0.4 g, 0.64 mmol) in dichloromethane (5 mL), trifluoroacetic acid (2.5 mL) was added at 0 °C. The reaction mixture was then stirred at 40 °C for 30 minutes. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude product was dissolved in EtOAc (5 mL) and neutralized with saturated $NaHCO_3$ solution (1 mL) to adjust the pH to 6–8. The organic layer was concentrated under reduced pressure to afford 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl) cyclohex-3-en-1-one (0.37 g) as a pale brown gum. LCMS observed *m/z* = 574.1 $[M+H]^+$.

Step 3: Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)-1-methylcyclohex-2-en-1-ol.

Compound 191

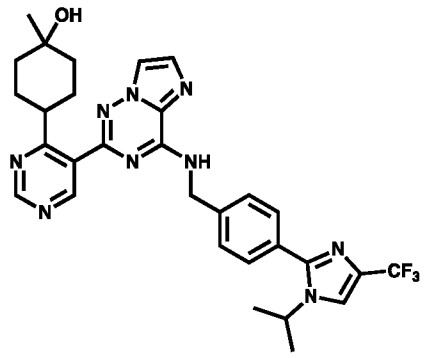


To a stirred solution of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazo-2-yl) benzyl) amino) imidazole[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl) cyclohex-3-en-1-one (0.12 g, 0.20 mmol, Compound 191.2) in THF (3 mL) was added Cerium(III) chloride (0.026 g, 0.10 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was cooled to -78 °C. After that methyl magnesium bromide 3M in diethyl ether (0.13 mL, 0.41 mmol) was added at -78 °C and stirred at -78 °C for 0.5 h. The reaction progress was monitored by TLC and LCMS. Upon completion of reaction, the reaction mixture was quenched with aqueous ammonium chloride solution (2 mL) and extracted with EtOAc (10 x 3 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified using by HPLC preparative method to afford 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl)-1-methylcyclohex-2-en-1-ol (0.009 g, 7.3 %) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (t, J = 6.2 Hz, 1H), 9.18 (s, 1H), 8.95 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.15 (s, 1H), 7.70 (d, J = 1.2 Hz, 1H), 7.52 – 7.52 (m, 4H), 5.61 – 5.59 (m, 1H), 5.49 – 5.46 (m, 1H), 4.84 (d, J = 6.0 Hz, 2H), 4.49 – 4.42 (m, 2H), 4.29 – 4.25 (m, 1H), 2.07 – 2.01 (m, 1H), 1.88 – 1.70 (m, 2H), 1.61 – 1.55 (m, 1H), 1.38 (d, J = 5.6 Hz, 6H), 1.19 (s, 3H). LCMS observed *m/z* = 590.3 $[M+H]^+$.

192.1 EXAMPLE 192

Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)-1-methylcyclohexan-1-ol.

Compound 192

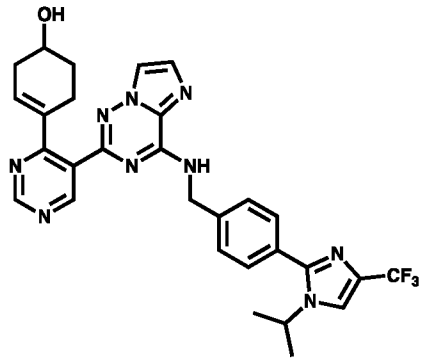


To a stirred solution of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl)-1-methylcyclohex-3-en-1-ol (0.08 g, 0.13 mmol, Compound 191.2) in EtOAc (5 mL) was added palladium 10% on carbon (0.087 g, 0.81 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred under H_2 gas (80 psi) in parr shaker at room temperature for 16 h . The reaction progress was monitored by TLC and LCMS. Upon completion of reaction, the reaction mixture was filtered through by celite and washed with EtOAc (25 mL) and the filtrate was concentrated under reduced pressure to afford crude product. The crude product was purified using by SFC preparative method to afford 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl)-1-methylcyclohexan-1-ol (0.005 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.18 (s, 1H), 8.90 (s, 1H), 8.19 (d, J = 0.8 Hz, 1H), 8.15 (s, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.53 – 7.48 (m, 4H), 4.85 (d, J = 4.8 Hz, 2H), 4.47 – 4.44 (m, 1H), 4.26 (s, 1H), 3.39 – 3.36 (m, 1H), 1.74 – 1.74 (m, 4H), 1.59 – 1.56 (m, 2H), 1.38 – 1.34 (m, 6H), 1.24 – 1.23 (m, 2H), 1.17 – 1.14 (m, 3H). LCMS observed m/z = 592.4 $[M+H]^+$.

193.1 EXAMPLE 193

Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)cyclohex-3-en-1-ol.

Compound 193

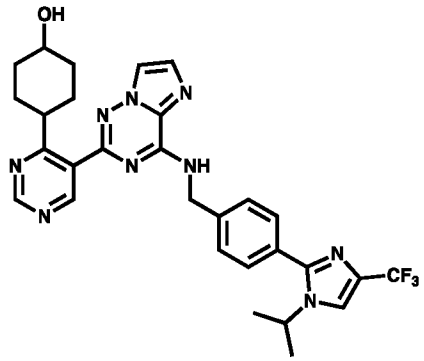


To a stirred solution of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl) cyclohex-3-en-1-one (0.18 g, 0.31 mmol, Compound 191.2) in MeOH (5 mL) and THF (5 mL), $NaBH_4$ (0.024 g, 0.62 mmol) was added at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 25 °C for 10 minutes. Upon completion, the reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and extracted with EtOAc (25 mL). The crude product was purified by preparative HPLC to afford 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) amino) imidazo[2,1-f] [1,2,4] triazin-2-yl) pyrimidin-4-yl) cyclohex-3-en-1-ol (0.008 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 – 9.57 (m, 1H), 9.17 – 9.16 (m, 1H), 8.89 (s, 1H), 8.17 – 8.15 (m, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.52 – 7.46 (m, 4H), 5.80 (s, 1H), 4.85 – 4.80 (m, 2H), 4.66 – 4.65 (m, 1H), 4.46 – 4.41 (m, 1H), 3.61 (br s, 1H), 2.24 – 2.19 (m, 2H), 1.91 – 1.84 (m, 1H), 1.72 – 1.69 (m, 1H), 1.48 – 1.42 (m, 6H), 1.39 – 1.23 (m, 2H). LCMS observed m/z = 576.4 $[M+H]^+$.

194.1 EXAMPLE 194

Preparation of 4-(5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-yl)cyclohexan-1-ol.

Compound 194

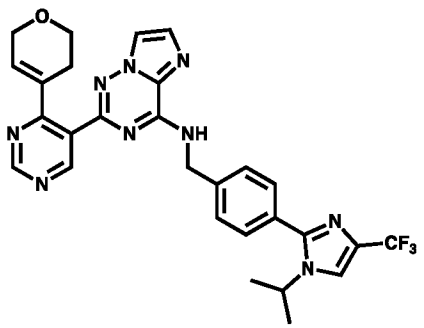


The title compound was prepared using a similar procedure as Compound 192. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (s, 1H), 9.16 (s, 1H), 8.91 (s, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.15 (d, J = 0.8 Hz, 1H), 7.70 (d, J = 0.8 Hz, 1H), 7.55 – 7.48 (m, 4H), 5.76 (s, 1H), 4.86 (s, 2H), 4.49 – 4.43 (m, 1H), 3.33 (s, 2H), 1.85 – 1.64 (m, 6H), 1.38 (d, J = 6.4 Hz, 6H), 1.17 – 1.10 (m, 2H). LCMS observed m/z = 578.4 $[M+H]^+$.

195.1 EXAMPLE 195

Preparation of 2-(4-(3,6-dihydro-2H-pyran-4-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 195

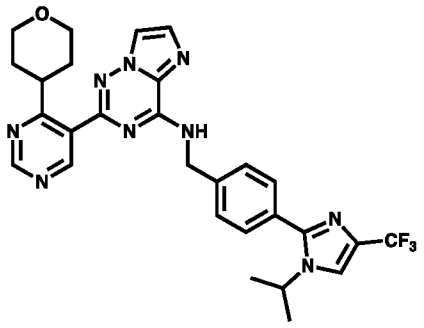


To a stirred solution of 2-(4-chloropyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (Compound 212.5) (3 mg, 0.006 mmol) in dioxane (0.3 mL) and water (0.1 mL) were added 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.47 mg, 0.007 mmol) followed by potassium phosphate (3.36 mg, 0.04 mmol) and purged with nitrogen gas for 30 min. Subsequently XPhos Pd G3 (0.46 mg, 0.001 mmol) was added and the reaction mixture was stirred at 110 °C for 3 h. Upon completion, the reaction mixture was diluted with ice cold water (10 mL), extracted with EtOAc (25 mL x 2). The combined organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by preparative HPLC to afford 2-(4-(3,6-dihydro-2H-pyran-4-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.009 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (t, J = 6.4 Hz, 1H), 9.21 (s, 1H), 8.91 (s, 1H), 8.19 – 8.15 (m, 2H), 7.68 – 7.67 (m, 1H), 7.55 – 7.47 (m, 4H), 6.11 (s, 1H), 4.81 (d, J = 6.4 Hz, 2H), 4.48 – 4.42 (m, 1H), 4.07 – 4.02 (m, 2H), 3.62 (t, J = 5.4 Hz, 2H), 2.33 – 2.33 (m, 2H), 1.38 (d, J = 6.8 Hz, 6H). LCMS observed m/z = 562.3 $[M+H]^+$.

196.1 EXAMPLE 196

Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-(tetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 196

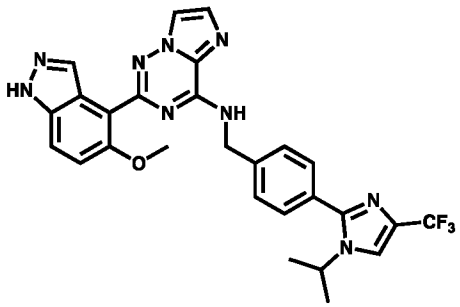


To a stirred solution of 2-(4-(3,6-dihydro-2H-pyran-4-yl)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.09 g, 0.016 mmol, Compound 195) in EtOAc (5 mL) was added palladium 10% on carbon (0.051 mg) and the reaction mixture was stirred under hydrogen gas (80 psi) in parr shaker at room temperature for 16 h. Upon completion of reaction, the reaction mixture was filtered thru celite bed and washed with EtOAc (25 mL). The combined filtrate was concentrated under reduced pressure to afford crude product. The crude product was purified using by preparative SFC to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-(tetrahydro-2H-pyran-4-yl)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.011 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (br s, 1H), 9.21 (s, 1H), 8.94 (s, 1H), 8.20 (s, 1H), 8.16 (d, J = 0.8 Hz, 1H), 7.71 (s, 1H), 7.54 – 7.49 (m, 4H), 4.86 (s, 2H), 4.47 – 4.40 (m, 1H), 3.79 – 3.75 (m, 2H), 3.67 – 3.61 (m, 1H), 3.11 – 3.05 (m, 2H), 1.90 – 1.79 (m, 2H), 1.61 – 1.59 (m, 2H), 1.39 – 1.37 (m, 6H). LCMS observed m/z = 564.4 $[M+H]^+$.

197.1 EXAMPLE 197

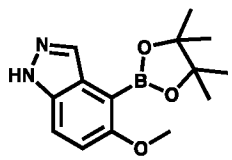
Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(5-methoxy-1H-indazol-4-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 197



Step 1: Preparation of 5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole.

Compound 197.1

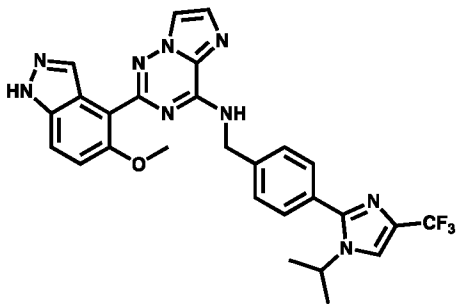


To a stirred solution of 4-bromo-5-methoxy-1H-indazole (250 mg, 1.101 mmol) in 1,4-dioxane (10.00 mL) were added bis(pinacolato)diboron (419 mg, 1.65 mmol) followed by potassium acetate (324 mg, 3.30 mmol) and purged with nitrogen for 20 min. To the

reaction mixture was added (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloride (90 mg, 0.110 mmol) and reaction was stirred at 90 °C for 16 h. Reaction mixture was quenched with water (40.0 mL), extracted with EtOAc (2 x 30.0 mL). The combined organic layer was washed with brine (30.0 mL), dried over Anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to offord 5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (300 mg) as a red liquid. LCMS observed *m/z* = 274.8 $[M+H]^+$.

Step 2: Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(5-methoxy-1H-indazol-4-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 197

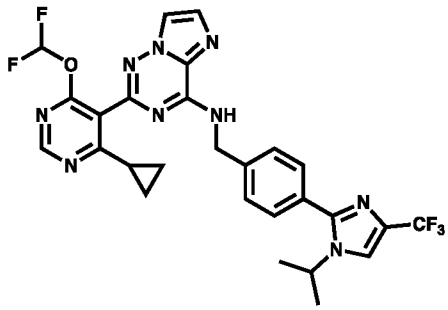


To the stirred solution of 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.13 g, 0.298 mmol) in dioxane (8.00 mL) and water (2.00 mL) were added 5-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indazole (0.30 g, 1.10 mmol) followed by tripotassium phosphate (0.21 g, 1.49 mmol) and purged with nitrogen for 20 min. To the reaction mixture was added XPhos Pd G_3 (0.025 g, 0.030 mmol) and stirred at 100 °C for 1 h under micro wave. Reaction mixture was quenched with water (30.0 mL), extracted with EtOAc (2 x 20.0 mL). The combined organic layer was washed with brine (2 x 30.0 mL), dried over Anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by SFC-prep to afford *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(5-methoxy-1H-indazol-4-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.025 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 9.45 – 9.44 (m, 1H), 8.15 (s, 2H), 7.70 (s, 1H), 7.68 (d, *J* = 1.2 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.53 – 7.48 (m, 4H), 7.30 (d, *J* = 9.2 Hz, 1H), 4.80 (d, *J* = 5.2 Hz, 2H), 4.54 – 4.47 (m, 1H), 3.76 (s, 3H), 1.39 (d, *J* = 6.8 Hz, 6H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

198.1 EXAMPLE 198

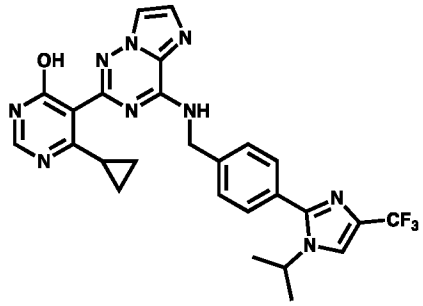
Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 198



Step 1: Preparation of 6-cyclopropyl-5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol.

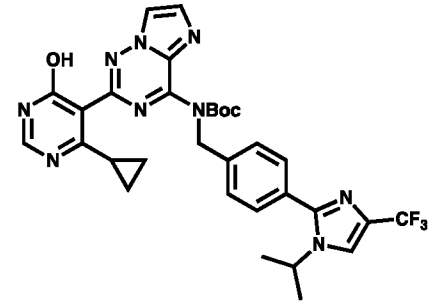
Compound 198.1



To a stirred solution of 2-(4-cyclopropyl-6-methoxypyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl) imidazo[2,1-f][1,2,4]triazin-4-amine (250 mg, 0.45 mmol) in MeOH (25 mL) was added hydrogen chloride 4.0 M in dioxane (25 mL) at 0 °C. The reaction mixture was stirred for 16 h at 80 °C. After completion, the reaction mixture was concentrated under reduced pressure. The crude was quenched with cold-water (25 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to get 6-cyclopropyl-5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl) benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol (220 mg) as a pale brown solid. LCMS observed m/z = 536.9 $[M+H]^+$.

Step 2: Preparation of tert-butyl (2-(4-cyclopropyl-6-hydroxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate.

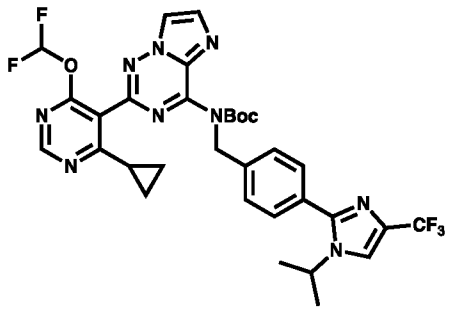
Compound 198.2



To a stirred solution of 6-cyclopropyl-5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol (0.1 g, 0.19 mmol) in dichloromethane (10 mL) were added triethylamine (0.08 mL, 0.56 mmol), 4-Dimethylaminopyridine (2.28 mg, 0.02 mmol) followed by Boc anhydride (0.06 mL, 0.28 mmol) at 0 °C and stirred at 25°C for 16 h. After completion, the reaction mixture was quenched with cold-water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (70% EtOAc/petroleum ether eluent) to afford tert-butyl (2-(4-cyclopropyl-6-hydroxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (90 mg) as an off-white gum. LCMS observed *m/z* = 636.8 $[M+H]^+$.

Step 3: Preparation of tert-butyl (2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate.

Compound 198.3

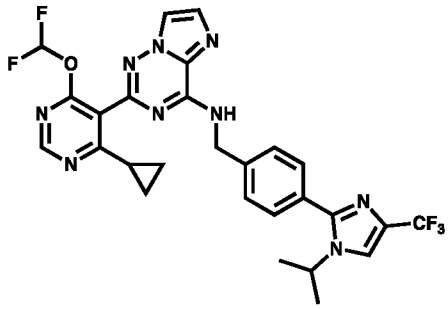


To a stirred suspension of tert-butyl (2-(4-cyclopropyl-6-hydroxypyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (0.08 g, 0.13 mmol) in MeCN (5.0 mL) was added Cs_2CO_3 (410 mg, 1.26 mmol) at 0 °C and the reaction mixture was stirred for 10 mins. 2,2-difluoro-2-(methylsulfonyl)acetic acid (26 mg, 0.15 mmol) was added and the reaction mixture was

stirred at 0 °C for 1 h. After completion, the reaction mixture was quenched with cold-water (25 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (90% EtOAc/ petroleum ether eluent) to afford tert-butyl (2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (50 mg) as a pale brown solid. LCMS observed *m/z* = 686.9 $[M+H]^+$.

Step 4: Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 198

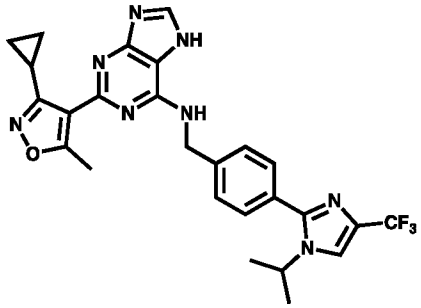


To a stirred solution of tert-butyl (2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)imidazo[2,1-f][1,2,4]triazin-4-yl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)carbamate (50 mg, 0.07 mmol) in dichloromethane (5. 0 mL) at 0 °C, Trifluoroacetic Acid (1.0 mL) was added at 0 °C. The reaction mixture was stirred at 25 °C for 4 h. After completion, the reaction mixture was quenched with cold-water (10 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure to get 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (5.4 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.71 (t, *J* = 6.0 Hz, 1H), 8.79 (s, 1H), 8.21 (s, 1H), 8.16 (s, 1H), 7.99 – 7.64 (m, 2H), 7.49 – 7.49 (m, 4H), 4.78 (d, *J* = 5.6 Hz, 2H), 4.46 – 4.40 (m, 1H), 2.05 – 1.99 (m, 1H), 1.38 (d, *J* = 6.8 Hz, 6H), 1.07 – 1.01 (m, 2H), 0.93 – 0.91 (m, 2H). LCMS observed *m/z* = 586.3 $[M+H]^+$.

199.1 EXAMPLE 199

Preparation of 2-(3-cyclopropyl-5-methylisoxazol-4-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 199

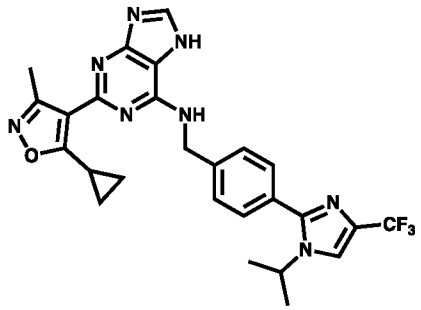


The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with 3-cyclopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.41 (s, 1H), 8.15 (s, 2H), 7.51 – 7.44 (m, 4H), 4.82 (s, 1H), 4.47 – 4.40 (m, 1H), 2.60 (s, 3H), 2.03 – 1.97 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 0.87 – 0.75 (m, 5H). LCMS observed *m/z* = 523.3 $[M+H]^+$.

200.1 EXAMPLE 200

Preparation of 2-(5-cyclopropyl-3-methylisoxazol-4-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 200

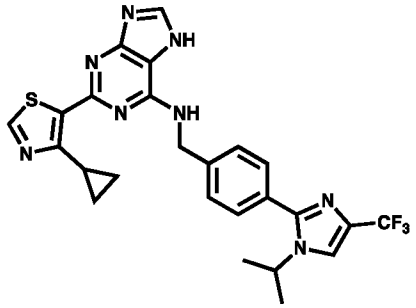


The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with 5-cyclopropyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.36 (s, 1H), 8.13 (d, J = 8.8 Hz, 2H), 7.51 – 7.44 (m, 4H), 4.81 (s, 2H), 4.47 – 4.40 (m, 1H), 3.06 (s, 1H), 2.40 (s, 3H), 1.38 (d, J = 6.4 Hz, 6H), 1.05 – 0.92 (m, 4H). LCMS observed *m/z* = 523.3 $[M+H]^+$.

201.1 EXAMPLE 201

Preparation of 2-(4-cyclopropylthiazol-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 201

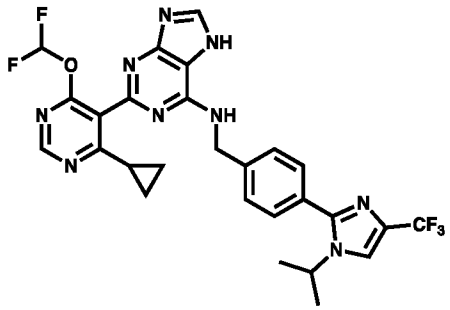


The title compound was prepared using a similar procedure as Compound 52, replacing (2-isopropylphenyl)boronic acid with 4-cyclopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.83 (s, 1H), 8.54 (s, 1H), 8.15 (d, J = 6.8 Hz, 2H), 7.50 (s, 4H), 4.78 (s, 2H), 4.48-4.41 (m, 2H), 1.38 (d, J = 6.8 Hz, 6H), 1.32-1.24 (m, 1H), 1.18-1.14 (m, 4H). One extra proton observed due to the presence of TFA. LCMS observed *m/z* = 525.3 $[M+H]^+$.

202.1 EXAMPLE 202

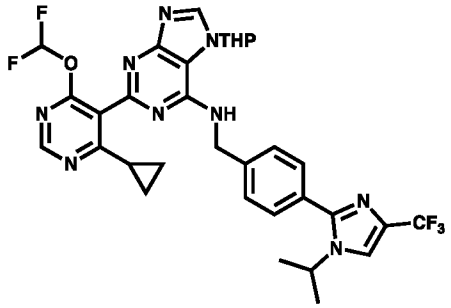
Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 202



Step 1: Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-6-amine.

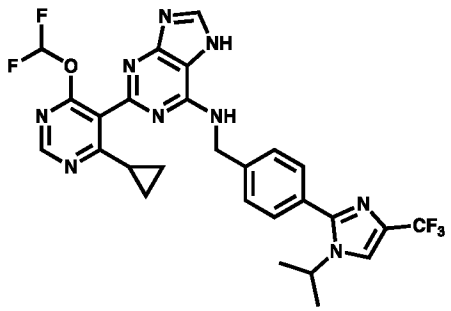
Compound 202.1



To a stirred solution of 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-6-amine (0.4 g, 0.76 mmol) in Dioxane (4 mL) water (1mL) were added (4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)boronic acid (0.354 g, 1.53 mmol) followed by Potassium phosphate (0.408 g, 1.92 mmol) and purged with argon gas for 15 minute before adding XPhos Pd G3 (0.073 g, 0.07 mmol). The resulting reaction mixture was stirred at 100 °C for 8 h. The progress of the reaction was monitored by TLC and LCMS. Upon completion of reaction, the reaction mixture was quenched with water (100 mL) and extracted with EtOAc (2 x 50 mL). Combined organic layer was washed with ice cold water (100 mL), brine (100 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by silica gel (Devisil, 70% EtOAc in petroleum ether) to afford a 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-6-amine (0.250 g) as a white solid. LCMS observed m/z = 670.9 $[M+H]^+$.

Step 2: Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine.

Compound 202



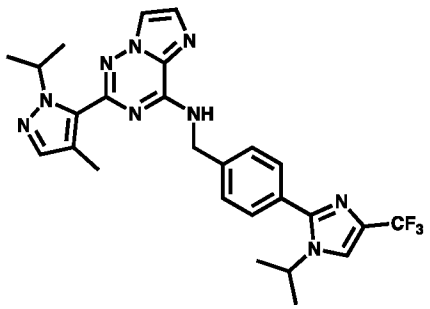
To a stirred solution of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-6-amine (0.250 g, 0.37 mmol) in dichloromethane (4 mL) was added Trifluoroacetic acid (2 mL) at 0 °C and reaction mixture was allowed to stir at room temperature for 2 h. The progress of the reaction was monitored by TLC and LCMS. Upon

completion, the reaction mixture was concentrated under reduced pressure to afford crude residue. The crude product was purified by Prep HPLC to afford 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-7H-purin-6-amine (0.083 g,) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.73 (s, 1H), 8.54 (s, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.79 (s, 1H), 7.61 – 7.47 (m, 4H), 5.32 (s, 2H), 4.47 – 4.40 (m, 1H), 1.89 – 1.83 (m, 1H), 1.38 (d, J = 6.4 Hz, 6H), 1.03 (s, 2H), 0.83 (s, 2H). LCMS observed m/z = 586.3 $[M+H]^+$.

203.1 EXAMPLE 203

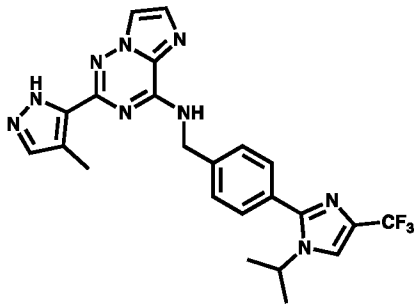
Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 203



Step 1: Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 203.1

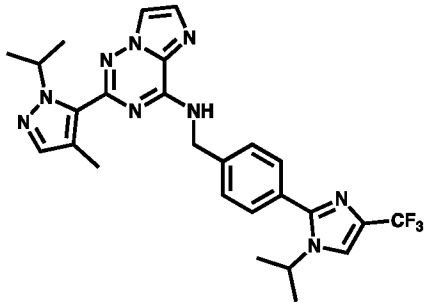


To the stirred solution of 2-chloro-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.15 g, 0.344 mmol) in 1,4-dioxane (8 mL) and water (2 mL) were added 4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.29 g, 1.38 mmol) followed by tripotassium phosphate (0.22 g, 1.03 mmol) and purged with nitrogen for 20 min. To the reaction mixture was added XPhos Pd G_3 (0.03 g, 0.034 mmol) and stirred at 110 °C for 2 h under micro wave. Reaction mixture was quenched with water (30.0 mL), extracted with EtOAc (2 x 20.0 mL). The

combined organic layer was washed with brine (2 x 30.0 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (70% EtOAc/ petroleum ether eluent) to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (150 mg) as an off-white solid. LCMS observed *m/z* = 482.9 $[M+H]^+$.

Step 2: Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 203

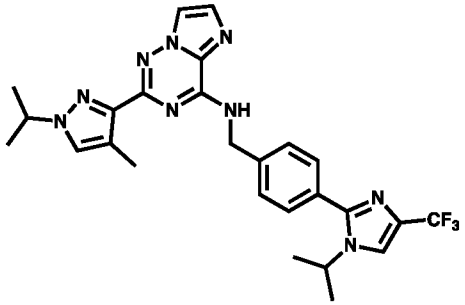


To a stirred solution of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.150 g, 0.31 mmol) in dimethylformamide (5.0 mL), was added Cs_2CO_3 (0.31 g, 0.94 mmol) and 2-iodopropane (0.16 g, 0.94 mmol) at 25 °C. The reaction mixture was stirred for 16 h at 25 °C. Upon completion (monitored by TLC, R_f: 0.50, mobile phase: 70% EtOAc in hexanes), the reaction mixture was diluted with water (50.0 mL) and extracted with EtOAc (2X30 mL). Combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford crude product. The crude product was purified by prep-HPLC (0 to 100% MeCN/H_2O eluent w/ 0.1% formic acid) to afford N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(1-isopropyl-4-methyl-1H-pyrazol-5-yl)imidazo[2,1-f][1,2,4]triazin-4-amine (0.025 g) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (t, J = 6.2 Hz, 1H), 8.15 (d, J = 0.8 Hz, 2H), 7.68 (d, J = 1.2 Hz, 1H), 7.54 – 7.46 (m, 4H), 7.33 (s, 1H), 5.09 – 5.03 (m, 1H), 4.84 (d, J = 6.0 Hz, 2H), 4.47 – 4.41 (m, 1H), 2.09 (s, 3H), 1.38 (d, J = 6.4 Hz, 6H), 1.21 (d, J = 6.8 Hz, 6H). LCMS observed *m/z* = 524.4 $[M+H]^+$.

204.1 EXAMPLE 204

Preparation of N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)-2-(1-isopropyl-4-methyl-1H-pyrazol-3-yl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 204

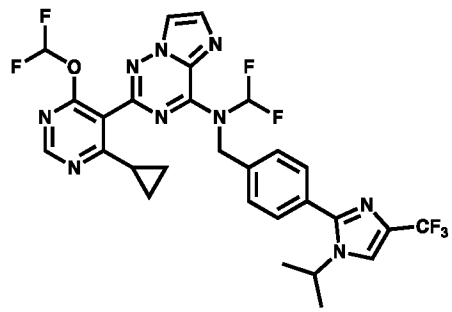


The title compound was prepared using a similar procedure as Compound 203. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (t, J = 6.2 Hz, 1H), 8.14 (d, J = 1.2 Hz, 1H), 8.12 (d, J = 1.2 Hz, 1H), 7.61 (s, 2H), 7.53 (q, J = 8.3 Hz, 4H), 4.86 (d, J = 6.0 Hz, 2H), 4.51-4.39 (m, 2H), 2.16 (s, 3H), 1.37 (d, J = 6.4 Hz, 6H), 1.42 (d, J = 6.4 Hz, 6H). LCMS observed *m/z* = 524.2 $[M+H]^+$.

205.1 EXAMPLE 205

Preparation of 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(difluoromethyl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine.

Compound 205



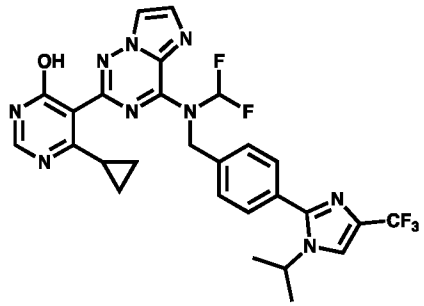
To a stirred suspension of 6-cyclopropyl-5-(4-((4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol (90 mg, 0.17 mmol) in ACN (10 mL), Cs_2CO_3 (274 mg, 0.84 mmol) was added at 0 °C, stirred the reaction mixture for 10 mins and 2,2-difluoro-2-(methylsulfonyl)acetic acid (53 mg, 0.30 mmol) was added and the reaction mixture was stirred at 0 °C for 1 h. After completion, the reaction mixture was quenched with cold-water (25 mL) and extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The filtrate was concentrated under reduced pressure and The crude product was purified by Preparative-HPLC purification method, second eluent peak 2-(4-cyclopropyl-6-

(difluoromethoxy)pyrimidin-5-yl)-N-(difluoromethyl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (19.89 mg) as an off-white solid. ^{1}H- NMR (400 MHz, DMSO-d_6) δ 9.41 – 9.14 (m, 1H), 8.81 (s, 1H), 8.53 (d, *J* = 1.2 Hz, 1H), 8.16 (s, 1H), 7.97 – 7.62 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 5.26 (s, 2H), 4.45 – 4.39 (m, 1H), 2.04 – 2.03 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 6H), 1.00 – 1.04 (m, 2H), 0.86 – 0.84 (m, 2H). LCMS observed *m/z* = 636.3 $[M+H]^+$.

206.1 EXAMPLE 206

Preparation of 6-cyclopropyl-5-(4-((difluoromethyl)(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)amino)imidazo[2,1-f][1,2,4]triazin-2-yl)pyrimidin-4-ol.

Compound 206

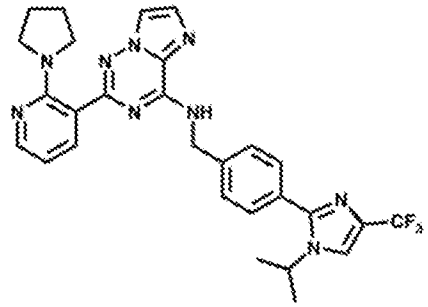


The title compound was prepared using a similar procedure as Compound 205, the product was the first eluent peak from the Prep-HPLC purification affording 2-(4-cyclopropyl-6-(difluoromethoxy)pyrimidin-5-yl)-N-(4-(1-isopropyl-4-(trifluoromethyl)-1H-imidazol-2-yl)benzyl)imidazo[2,1-f][1,2,4]triazin-4-amine (20 mg) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.61 (br s, 1H), 9.40 – 9.12 (m, 1H), 8.45 – 8.41 (m, 1H), 8.16 (d, J = 1.2 Hz, 1H), 8.13 (s, 1H), 7.91 (d, *J* = 0.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H), 5.25 (s, 2H), 4.47 – 4.40 (m, 1H), 1.69 (t, *J* = 4.0 Hz, 1H), 1.39 (d, *J* = 6.4 Hz, 6H), 0.91 – 0.85 (m, 2H), 0.66 – 0.65 (m, 2H). LCMS observed *m/z* = 586.3 $[M+H]^+$.

207.1 EXAMPLE 207

Preparation of *N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)-2-(2-(pyrrolidin-1-yl)pyridin-3-yl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 207

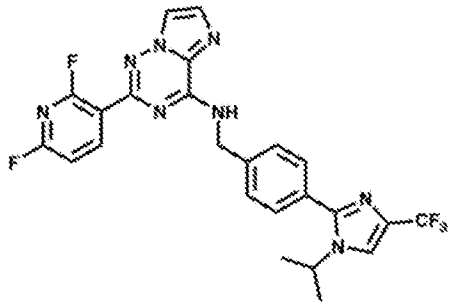


The title compound was prepared using a similar procedure as Compound 12, replacing (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid with (2-(pyrrolidin-1-yl)pyridin-3-yl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.10 (d, J = 5.1 Hz, 1H), 7.90 (s, 2H), 7.76 (d, J = 7.4 Hz, 1H), 7.63 – 7.49 (m, 5H), 6.73 (dd, J = 7.1, 5.1 Hz, 1H), 4.92 (s, 2H), 4.54 (p, J = 6.9 Hz, 1H), 3.28 – 3.17 (m, 4H), 1.76 (d, J = 6.3 Hz, 4H), 1.44 (d, J = 6.6 Hz, 6H). LCMS observed *m/z* = 548.3 $[M+H]^+$.

208.1 EXAMPLE 208

Preparation of 2-(2,6-difluoropyridin-3-yl)-*N*-(4-(1-isopropyl-4-(trifluoromethyl)-1*H*-imidazol-2-yl)benzyl)imidazo[2,1-*f*][1,2,4]triazin-4-amine.

Compound 208



The title compound was prepared using a similar procedure as Compound 12, replacing (4-cyclopropyl-6-methoxypyrimidin-5-yl)boronic acid with (2,6-difluoropyridin-3-yl)boronic acid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (q, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.69 – 7.58 (m, 3H), 7.53 (d, J = 7.8 Hz, 2H), 7.10 (dd, J = 8.2, 2.7 Hz, 1H), 4.98 (s, 2H), 4.52 (p, J = 6.8 Hz, 1H), 1.42 (d, J = 6.6 Hz, 6H). LCMS observed *m/z* = 515.2 $[M+H]^+$.

Test EXAMPLES

The compounds' activities that target USP-1 protein complex and the compounds' physiochemical and pharmacological properties can be assessed by the following *in vitro* and *in vivo* methods.

USP1 and USP30 Ubiquitin-Rhodamine Activity Assay

To measure USP1 activity, purified recombinant USP1-UAF1 heterodimer (R&D Systems, Cat# E-568) was diluted into assay buffer containing 50mM HEPES pH 8.0, 100nM NaCl, 1 mM EDTA, 1 mM TCEP, 0.01% Tween-20, and 0.5 mg/mL Bovine Serum Albumin. Compounds were dispensed into black, round bottom, low binding, 384-well assay plates (Corning, Cat# 4514) in a 10-pt 3.16 step serial dilution and backfilled with dimethyl sulfoxide to a final concentration of 1% using an Echo acoustic liquid dispenser (Labcyte/Beckman Coulter). 1 μM KSQ-4279 (C_{pos}) and dimethyl sulfoxide (C_{neg}) were used as reference compounds for USP1. Enzymes were dispensed into compound-containing plates using a Multidrop™ Combi liquid dispenser (ThermoFisher). Enzymes were incubated with compounds for 45 minutes at room temperature before adding Ubiquitin-Rhodamine110 substrate (R&D systems, Cat# U-555) for a final concentration of 0.1 nM USP1-UAF1. Reaction proceeded for 45 minutes at room temperature before adding an acetic acid stop solution to a final concentration of 100 mM acetic acid. Assay was read on an Envision 2105 multimode plate reader (Perkin Elmer) with filters and mirrors for 485 nm excitation and 535 nm emission wavelengths.

Percent inhibition was calculated using the following equation: % Inhibition = (FI – C_{pos})/(C_{pos}-C_{neg}) * 100, where FI is the fluorescence intensity of wells treated with test compound. The compound concentration of compound leading to 50% inhibition of enzyme activity (IC_{50}) was carried out by fitting a 4-parameter non-linear regression using GraphPad Prism. IC_{50}s were measured in at least 3 independent experiments for each compound.

Ubiquityl-PCNA Immunofluorescence Assay

All cell lines used were obtained from ATCC. To measure ubiquityl-PCNA (Ub-PCNA) levels, the human colorectal cancer cell lines HCT-116 (CVCL_1724) were used.

Cells were cultured in McCoy 5A media (ThermoFisher Cat# 16600082) supplemented with 10% fetal bovine serum (Cytiva Cat# SH30071.03IH25), 1x penicillin/streptomycin (ThermoFisher Cat# 15140122), 1x non-essential ammino acids (ThermoFisher Cat# 11140050), 2 mM GlutaMAX (ThermoFisher Cat# 35050079). Cells were cultured at 37 ºC in a humidified 5% CO_2 incubator. To seed cells for the assay, cells were trypsinized and resuspended in complete culture media to the desired concentration (60,000 cells/mL). Cell suspensions were seeded in 50 μL of complete culture media and onto 384-well black clear-bottom optical plastic plates (Greiner Bio-One Cat# 781097) using a Multidrop™ Combi liquid dispenser in the slowest setting in triplicate. After 24 h,

cells were treated with compounds in a 10-pt, 3.16 step serial dilution using an Echo acoustic liquid dispenser and incubated at 37 °C in a humidified 5% CO_2 incubator. 10 μM KSQ-4279 (C_{pos}) and dimethyl sulfoxide (C_{neg}) were used as reference compounds.

6 h after compound treatments, cells were fixed in ice cold 100% MeOH for 10 min, washed three times with PBS, with extreme care taken to prevent sample dehydration. Samples were blocked and further permeabilized in 1x PBS containing 10% goat serum and 0.1% triton X-100 for at least 30 min. After blocking and permeabilization, plates were evacuated to decant all media. Recombinant rabbit primary antibody against Ub-PCNA (Lys 164) (Cell Signaling Technology, Cat# #13439, clone D5C7P) in blocking/permeabilization solution was added to plates and incubated for 16 h at 4 °C. After 1° antibody incubation, plates were evacuated and decanted to remove all media. Blocking/permeabilization solution containing the DNA counterstain Hoechst, and a secondary antibody against rabbit (raised in goats) conjugated to a AlexaFluor 647 fluorophore (ThermoFisher Cat# A32728), were added to empty plates, and incubated for 30 min at 25 °C, in the dark. After 2° antibody incubation, plates were washed 5 times in PBS, and sealed with thermal foil seals.

Sealed plates were imaged using an ImageXpress Micro slit confocal microscope (Molecular Devices) using a 40x water immersion objective, and 6 fields of views per well. Exposure parameters were optimized to prevent pixel saturation for each channel. Images were analyzed using MetaXpress Custom Module Editor, by using a Hoechst mask to identify nuclei, then measuring the average AlexaFluor 648 intensity across all nuclei in the FOV, background corrected, then averaged.

Percent Ub-PCNA signal was calculated by using the following equation: $\%S = (T - C_{pos})/(C_{pos} - C_{neg}) * 100$, where %S is percent Ub-PCNA signal and T is the measured Ub-PCNA fluorescence of the wells treated with test compound, C_{pos} and C_{neg} are reference compounds defined above. The effective compound concentration leading to a 50% induction of Ub-PCNA signal (EC_{50}), and the resulting cell Ub-PCNA signal measured at the highest tested compound tested (c_{max}) was carried out by fitting a 4-parameter non-linear regression using GraphPad Prism. At least three biological replicates were done per compound tested.

MDA-MB-436 Cell Viability Assay:

The human breast cancer cell line MDA-MB-436 (ATCC cat. no. HTB-130) was used to assess the effect of compound treatment on cellular viability. The complete media for the cells was prepared by supplementing RPMI 1640 + GlutaMAX (Gibco cat. no. 61870-036) with 10% fetal bovine serum (Corning cat. no. 35-015-CV), and 1x

penicillin/streptomycin (Gibco cat. no. 15140-122). The cells were maintained at 37°C / 5% CO_2 (similar incubation conditions were used throughout the experiment).

For the Viability Assay, cells were resuspended in complete media at 6,250 cells/mL and seeded into 384-well, white, clear-bottom plates (ThermoFisher cat. no. 142762) at 40 mL/well (250 cells/well). Following overnight incubation, cells were compound treated (10-pt 3.16 step serial dilution) and backfilled with dimethyl sulfoxide to a final concentration of 1% using an Echo acoustic liquid dispenser (Labcyte/Beckman Coulter). 10 mM KSQ-4279 (C_{pos}) and dimethyl sulfoxide (C_{neg}) were used as reference compounds. Eleven days post compound addition, viability was assessed by measuring cellular ATP concentrations. Briefly, an equivalent volume (40 mL/well) of CellTiter-Glo 2.0 reagent (Promega cat. no. G9241) was added and plates were mixed on a plate shaker (700rpm) for 2 minutes. Plates were then allowed to equilibrate for 10 minutes at room temperature before taking luminescence readings using an EnVision Multimode Plate Reader (Perkin Elmer).

Percent inhibition of cell growth (%INH) was calculated by the following equation: $\%INH = 100 - ((RLU_{TC} - RLU_{Cpos}) / (RLU_{Cpos} - RLU_{Cneg}) * 100)$, where RLU_{TC} is the measured luminescence of the wells treated with test compound, and RLU_{Cpos} and RLU_{Cneg} the measured luminescence of the positive and negative controls, respectively. The effective compound concentration leading to a 50% inhibition of cell growth (IC_{50}) was determined by fitting %INH and compound concentration values to a 4-parameter non-linear regression equation (using GraphPad Prism or CDD). At least three biological replicates were done per compound tested.

Table 3: Exemplary Compounds and Biological Data.

Example	USP1-UbRho IC50 (μM)	HCT116 Ub-PCNA EC50 (μM)	MDA-MB-436 IC50 (μM)
1	0.064	0.019	0.055
2	3.270	3.03	> 9.99
3	2.200	1.55	> 9.99
4	0.063	0.277	1.52
5	0.072	0.030	0.166
6	0.229	0.910	3.34
7	1.330	0.406	0.952
8	0.190	0.094	1.34
9	3.460	6.230	> 9.99
10	1.020	0.604	8.77
11	0.201	0.080	0.765
12	0.053	0.022	0.044
13	0.293	0.042	0.066
14	0.089	0.001	0.032
15	0.052	0.104	0.035

16	0.038	0.044	0.072
17	0.106	0.038	0.069
18	0.043	0.013	0.025
19	0.186	0.192	0.190
20	0.608	0.446	0.505
21	0.083	0.005	0.077
22	0.113	0.017	0.092
23	0.072	0.003	0.050
24	1.220	1.820	> 9.99
25	0.080	0.035	0.077
26	0.102	0.023	0.053
27	5.730	4.240	> 9.99
28	0.148	0.431	1.64
29	0.304	0.371	0.341
30	0.036	0.011	0.028
31	0.111	0.759	3.21
32	2.470	0.504	1.7
33	1.170	0.217	0.775
34	5.330	0.942	3.63
35	0.137	0.041	0.153
36	0.042	0.042	0.043
37	0.106	0.017	0.065
38	0.101	0.034	0.164
39	0.048	0.018	0.058
40	0.101	0.079	0.184
41	1.420	0.436	> 4.65
42	0.092	0.035	0.079
43	0.196	0.032	0.128
44	0.098	0.056	0.212
45	0.268	0.123	0.509
46	0.054	0.033	0.109
47	0.341	0.492	0.636
48	0.110	0.407	0.085
49	0.062	0.249	0.069
50	1.720	0.624	> 9.99
51	1.420	2.470	> 9.99
52	0.032	0.028	0.097
53	0.040	0.019	0.076
54	0.027	0.026	0.074
55	0.148	0.046	0.164
56	0.092	0.102	0.425
57	0.387	0.030	0.207
58	0.087	0.011	0.1
59	0.969	0.160	0.603
60	0.114	0.018	0.075
61	0.457	0.029	0.158
62	0.063	0.022	0.054
63	3.390	3.110	> 9.99
64	3.210	> 9.99	3.842
65	2.410	> 9.99	> 9.99
66	2.830	5.160	7.669
67	6.610	> 9.99	> 9.99
68	> 18.2	> 9.99	
69	6.020	5.250	> 9.99
70	0.154	0.055	0.106
71	0.079	0.039	0.142
72	0.136	0.072	0.16
73	0.154	0.062	0.083

74	0.228	0.132	0.222
75	0.064	0.013	0.024
76	0.549	0.057	0.26
77	0.477	0.029	0.111
78	0.437	0.053	
79	0.228	0.096	
80	0.156	0.027	
81	0.112		
82	0.102		
83	0.166	0.022	0.019
84	0.178	0.085	0.096
85	0.709	0.980	
86	0.085	0.039	
87	0.085	0.025	
88	0.078	0.080	
89	0.132	0.044	0.779
90	> 20.6	> 9.99	
91	0.334	0.116	
92	1.870	1.380	
93	0.112	0.021	0.05
94	0.048	0.020	
95	0.148	0.047	
96	0.056	0.017	
97	0.084	0.029	
98	0.056	0.012	
99	0.073	0.019	
100	0.082	0.041	0.292
101	0.766	0.127	0.628
102	0.067	0.022	0.107
103	0.254	0.061	0.28
104	0.229	0.066	0.253
105	0.080		0.499
106	1.270	0.269	0.725
107	4.380	2.490	> 9.99
108	0.084	0.015	
109	0.162	0.062	0.134
110	2.470	0.722	
111	> 20.6	> 9.99	
112	0.095	0.054	
113	0.235	0.045	
114	0.075	0.020	
115	0.055	0.014	0.028
116	1.120	0.393	
117	0.250	0.043	0.132
118	0.181	0.024	0.067
119	> 14.7	5.360	
120	0.136	0.020	0.087
121	0.061	0.008	0.018
122	0.157	0.019	0.058
123	1.260	0.546	
124	1.620	0.717	
125	0.096	0.009	0.037
126	0.117	0.024	0.061
127	1.890	0.124	0.551
128	0.068	0.006	0.02
129	0.059	0.005	0.013
130	0.079	0.003	0.012
131	0.052	0.010	0.013

132	0.063	0.006	0.027
133	0.053	0.009	0.026
134	0.079	0.007	0.026
135	2.610	0.332	0.736
136	0.089	0.011	0.028
137	4.720	3.450	> 9.99
138	0.194	0.016	0.048
139	0.221	0.021	0.062
140	0.087	0.011	0.053
141	0.129	0.011	0.008
142	2.640	0.110	
143	0.696	0.337	1.166
144	0.721	0.194	0.709
145	0.736	0.080	
146	0.287	0.038	0.184
147	0.045	0.004	0.039
148	2.080	0.394	
149	0.141	0.036	0.117
150	0.193	0.019	0.043
151	0.212	0.031	0.099
152	0.631	0.066	
153	0.065	0.010	0.041
154	0.214	0.224	
155	0.069	0.011	0.025
156	0.479	0.056	0.066
157	1.000	0.384	
158	0.451	0.307	
159	0.205	0.481	
160	0.385		
161	0.048	0.015	0.006
162	0.080	0.013	0.022
163	0.159	0.037	
164	0.118	0.016	0.063
165	1.640	0.068	
166	0.087	0.018	0.095
167	2.740	3.270	
168	> 20.6	> 9.99	
169	0.156	0.047	0.168
170	0.211	0.032	0.046
171	0.809	0.109	0.589
172	0.094	0.025	
173	0.079	0.024	0.073
174	0.059	0.027	0.075
175	0.138	0.061	0.199
176	0.531	0.349	0.307
177	0.121	0.035	0.128
178	0.093	0.016	0.082
179	0.190	0.018	0.092
180	0.057	0.010	0.011
181	0.124	0.011	0.005
182	0.206	0.012	
183	> 20.6	> 9.99	
184	0.068	0.019	0.158
185	> 20.6	> 9.99	> 9.990
186	6.840	> 9.99	0.935
187	> 20.6	> 9.99	> 9.990
188	2.240	0.868	> 9.990
189	4.400	> 9.99	> 9.990

190	3.140	1.760	2.126
191	> 20.6	4.660	
192	> 20.6	> 9.99	> 9.990
193	6.080	3.710	> 9.990
194	6.490	3.140	> 9.990
195	1.400	0.412	
196	2.560	1.820	2.963
197	> 20.6	> 9.99	5.069
198	0.088	0.032	0.036
199	0.813	0.263	
200	0.969	0.298	
201	6.110	1.160	
202	0.057	0.012	
203	0.101	0.032	
204	> 20.6	> 9.99	
205	0.806	0.017	
206	> 20.6	> 9.99	
207	0.118	0.042	
208	> 20.6	> 9.99	

Caco-2 Permeability Assay:

Preparation of stock solutions: 10 mM stock solutions of test compounds were prepared in DMSO. The stock solutions of positive controls were prepared in DMSO at the concentration of 10 mM. Digoxin, minoxidil and propranolol were used as control compounds in this assay.

Preparation of Caco-2 cells: 50 μL and 25 mL of cell culture medium were added to each well of the Transwell insert and reservoir, respectively. And then the HTS transwell plates were incubated at 37 °C, 5% CO_2 for 1 hour before cell seeding. Caco-2 cells were diluted to $6.86x10^5$ cells/mL with culture medium and 50 μL of cell suspension were dispensed into the filter well of the 96-well HTS Transwell plate. Cells were cultivated for 14-18 days in a cell culture incubator at 37 °C, 5% CO_2, 95% relative humidity. Cell culture medium was replaced every other day, beginning no later than 24 hours after initial plating.

Assessment of cell monolayer integrity: Medium was removed from the reservoir and each Transwell insert and replaced with prewarmed fresh culture medium. Transepithelial electrical resistance (TEER) across the monolayer was measured using Millicell Epithelial Volt-Ohm measuring system (Millipore, USA). The plate was returned to the incubator once the measurement was done. The TEER value was calculated according to the following equation:

TEER measurement (ohms) x Area of membrane (cm2) = TEER value (ohm•cm2)

TEER value should be greater than 230 ohm•cm2 , which indicates the well-qualified Caco-2 monolayer.

Assay procedure: The Caco-2 plate was removed from the incubator and washed twice with pre-warmed HBSS (10 mM HEPES, pH 7.4), and then incubated at 37 °C for 30 minutes. The stock solutions of control compounds and test compounds were diluted in DMSO to get 1 mM solutions and then diluted with HBSS (10 mM HEPES, pH 7.4) get 5 μM working solutions. The final concentration of DMSO in the incubation system was 0.5%. To determine the rate of drug transport in the apical to basolateral direction. 125 μL of 5 μM working solution of control compounds and test compounds were added to the Transwell insert (apical compartment) and transfer 50 μL sample (D_0 sample) immediately from the apical compartment to a new 96-well plate. Fill the wells in the receiver plate (basolateral compartment) with 235 μL of HBSS (10 mM HEPES, pH 7.4). To determine the rate of drug transport in the basolateral to apical direction. 285 μL of 5 μM working solution of control compounds and test compounds were to the receiver plate wells (basolateral compartment), and transfer 50 μL sample (D_0 sample) immediately from the basolateral compartment to a new 96-well plate. Fill the wells in the Transwell insert (apical compartment) with 75 μL of HBSS (10 mM HEPES, pH 7.4). The assay was performed in duplicate. The plates were incubated at 37 °C for 2 hours. At the end of the incubation, 50 μL samples from donor sides (apical compartment for Ap→Bl flux, and basolateral compartment for Bl→Ap) and receiver sides (basolateral compartment for Ap→Bl flux, and apical compartment for Bl→Ap) were transferred to wells of a new 96-well plate, followed by the addition of 4 volume of cold MeCN containing appropriate internal standards (IS). Samples were Vortexed for 5 minutes and then centrifuged at 3,220 g for 40 minutes. An aliquot of 100 μL of the supernatant was mixed with an appropriate volume of ultra-pure water before LCMS/MS analysis. To determine the Lucifer Yellow leakage after 2 hour transport period, stock solution of Lucifer yellow was prepared in water and diluted with HBSS (10 mM HEPES, pH 7.4) to reach the final concentration of 100 μM. 100 μL of the Lucifer yellow solution was added to each Transwell insert (apical compartment), followed by filling the wells in the receiver plate (basolateral compartment) with 300 μL of HBSS (10 mM HEPES, pH 7.4). The plates were Incubated at 37 °C for 30 mins. 80 μL samples were removed directly from the apical and basolateral wells (using the basolateral access holes) and transferred to wells of new 96 wells plates. The Lucifer Yellow fluorescence (to monitor monolayer integrity) signal was measured in a fluorescence plate reader at 485 nM excitation and 530 nM emission. The apparent permeability coefficient (Papp), in units of centimeter per second, can be calculated for Caco-2 drug transport assays using the following equation: Papp = (VA×[drug]acceptor)/(Area×Time×[drug]initial,donor). Where

VA is the volume (in mL) in the acceptor well, Area is the surface area of the membrane (0.143 cm^2 for Transwell-96 Well Permeable Supports), and time is the total transport time in seconds. The efflux ratio will be determined using the following equation: Efflux Ratio=Papp(B-A)/Papp(A-B).

Table 4: Permeability of Exemplary Compounds

Example	Caco-2 Papp (a–b) 10^{-6} cm/s	Caco-2 Efflux Ratio
1	2.73	14
3	0.39	25
11	0.24	70
12	3.93	1.5
13	0.51	1.4
14	1.07	1.3
15	3.89	2.6
17	1.89	1.9
18	5.07	1.8
19	0.11	180
20	2.7	7.4
21	2.89	4.4
22	1.37	8.2
23	1.77	5.3
24	0.06	170
25	0.44	33
26	1.36	3.2
27	1.09	20
28	0.31	76
29	0.75	24
30	0.26	68
31	0.03	330
33	2.7	3.6
34	2.33	4.9
35	0.22	59
36	1.15	5.7
37	0.39	29
38	0.96	4.8
39	0.76	19
40	0.93	13
41	3.27	2.6
42	2.42	6.8
43	3.09	2
44	3.09	2
45	0.7	22
46	0.33	42
47	2.51	1.8
48	1.82	2.9
49	0.44	26
50	0.56	40
53	0.12	120
56	0.59	36
57	1.16	13
58	0.91	20
62	0.7	42

63	1.07	22
64	1.16	2.4
65	1.76	22
66	5.55	3.7
67	0.4	78
68	0.93	37
69	4.71	6.3
70	2.39	10
71	0.42	67
72	0.12	170
73	0.38	61
74	0.19	80
75	0.63	27
76	0.76	7.5
77	0.25	6
78	0.39	5.1
79	0.71	11
80	0.49	7.9
81	0.09	140
82	0.1	53
83	1.14	4.4
84	0.33	67
86	1.27	20
87	1.11	15
88	1.36	9.7
90	3.75	5.2
91	0.24	110
92	1.17	24
93	0.86	3.8
94	0.49	37
95	0.27	71
96	0.49	67
97	0.41	83
98	0.13	160
99	0.15	140
100	0.21	58
101	0.64	30
102	0.55	35
103	0.74	23
104	1.45	6.9
105	0.85	37
106	1.82	6.4
107	0.48	57
108	0.36	55
109	0.62	3.7
110	1.34	5.9
111	0.11	18
112	0.47	59
113	1.38	2.8
114	4.02	1.9
115	2.53	4.1
117	2.2	1.4
118	1.43	1.4
120	8.96	1.3
121	5.7	1.8
122	3.96	3.4
123	11.53	1.6
124	11.68	1.6

125	3.37	5.3
126	5.67	
128	2.25	
129	6.21	2.5
130	3.28	3.1
131	3.11	2.6
132	8.12	1.2
133	5.92	2
134	5.33	2.2
135	2.99	2.4
136	3.04	2.2
137	18.78	1.1
138	0.11	4.4
139	0.69	2.6
140	4.15	2.2
141	1.43	2.5
142	0.06	4.3
143	1.39	3.6
144	1.33	1.9
146	6.22	4.4
147	13.38	2.4
148	0.8	29
149	9.94	2.3
150	1.64	3.1
151	1.52	13
152	4.84	1.3
153	2.91	5
154	3.8	3.2
155	6.9	2.6
160	0.27	64
161	1.17	21
162	4	2.8
163	1.93	15
164	0.07	4
165	0.05	7.3
166	1.39	16
169	7.35	1.7
170	1.1	2.4
171	6.4	2.4
172	1.59	17
173	3.61	3.2
174	2.99	3
175	5.29	6.2
177	3.69	2.8
178	2.36	2.2
179	0.48	4
180	0.73	6.2
183	0.18	160
184	0.13	150
187	4.3	3.2
188	6.32	3
189	5.42	3.1
194	2.45	8
195	7.6	2.5
196	4.48	3.1
197	1.59	8.8
198	0.49	3.6
202	0.34	26

203	1.6	1.6
204	2.17	2.6

Hepatocyte Stability Assay:

Prepare 10 mM stock solutions of test compound(s) and positive control in appropriate solvent (DMSO). In separate conical tubes, dilute the 10 mM test compound and the positive control to 100 µM by combining 495 µL of 50% MeCN/50% water and 5 µL of 10 mM stock. Preparation of hepatocytes: Place incubation medium (William's E Medium supplemented with GlutaMAX) and hepatocyte thawing medium in a 37°C water bath and allow warming for at least 15 minutes prior to use. Remove a vial of cryopreserved hepatocytes from storage, ensuring that vials remain at cryogenic temperatures until thawing process ensues. Thaw the cells by placing the vial in a 37°C water bath and gently shaking the vials for 2 minutes. After thawing is completed, spray vial with 70% ethanol, transfer the vial to a biosafety cabinet. Use wide-bore pipette tip to transfer hepatocytes into 50 mL conical tube containing thawing medium. Place the 50 mL conical tube into a centrifuge and spin at 100 g for 10 minutes. Upon completion of spin, aspirate thawing medium and resuspend hepatocytes in enough incubation medium to yield ~1.5 × 106 cells/mL. Using an AOPI staining solution, count cells and determine the viable cell density. Cells with poor viability (<75% viability) are not acceptable for use. Dilute cells with incubation medium to a working cell density of 0.5×10^6 viable cells/mL. A portion of the hepatocytes at 0.5×10^6 viable cells/mL should be boiled for 5 min prior to adding to the plate as representative of a negative control. This will eliminate the enzymatic activity so that little or no substrate turnover should be observed.

Procedure for Stability Determination: Pipette 198 µL of hepatocytes into each wells of a 96-well non-coated plate. Place the plate in the incubator on an orbital shaker to allow the hepatocytes to warm for 10 minutes. Pipette 2 µL of the 100 µM test compound or positive control into respective wells of the 96-well non-coated plate to start the reaction. The final concentration of test compound or control compounds was 1 µM. Return the plate to the incubator and place on an orbital shaker. Remove well contents in 25 µL aliquots at time points of 0 and 60 minutes. The aliquots are then mixed with 6 volumes (150 µL) of MeCN containing internal standards (IS: 100 nM alprazolam, 200 nM labetalol, 200 nM caffeine and 2 µM ketoprofen) to terminate the reaction. Centrifuge the plate for 20 minutes at 3,220 g. Aliquot of 100 µL of the supernatant was mixed with 100 µL of ultra-pure H_2O and then used for LCMS/MS analysis. All incubations will be performed in duplicate.

Table 5: Hepatocyte Stability of Exemplary Compounds

Example	Mouse %Remaining 1 h	Human %Remaining 1 h
12	41	97
13	2	
14	0	
15	2	
17	9	
18	74	98
21	77	85
22	8	
25	67	
28	>99	
30	40	97
35	61	
36	26	
37	9	
38	4	
40	88	
42	57	
49	49	97
53	47	89
56	12	
57	49	82
58	56	90
60	58	97
62	4	92
63		76
64		96
70		65
71		45
72		88
73		109
74		104
75		49
76	72	107
77	51	90
78		101
79		91
80		100
81		97
82		81
83		97
84		96
86		87
87		95
88	65	97
90		58
91		101
92		101
93		99
94	58	106
95		55
96		25
97		27
98		82

99	21	106
100		93
101		101
102	32	113
103		101
104		80
108		112
109		99
110		96
111		69
112		93
113		86
114	6	91
115	67	98
117	22	48
118	62	96
120	21	88
121	38	8
122	39	92
123	1	40
124	21	59
125	2	91
126	1	
128	25	78
129	64	96
130	63	
131	60	88
132	41	63
133	70	88
134	54	89
136	79	98
138		97
139		88
140	45	92
141		96
142		112
143		76
144		97
146	39	73
147	69	71
148	54	98
149	47	92
150	56	87
151	68	
152	30	
153	0	39
154	58	22
155	42	
160		77
161		20
162		28
163		64
164		78
165		91
166		92
170		92
171	41	77
172		15

175		45
178		94
179		88
180		98
181		94
182		98
184		93
187	0	5
188	0	46
189	0	36
194	31	91
195	0	
196	3	86
197		78
198	36	
202	28	
203		8
204		65

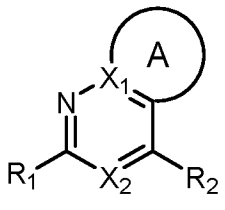
MDA-MB-436 Efficacy Model:

Evaluation of In Vivo Efficacy in a Subcutaneous MDA-MB-436 Xenograft Model

All mice studies were performed at the Mispro Vivarium facility in New York, NY, and were conducted according to the guidelines of the Mispro Institutional Animal Care and Use Committee and Eikon Therapeutics protocol. MDA-MB-436 cells ($2.5x10^6$ cells/mouse in 50% Matrigel:50% HBSS) were injected subcutaneously into the right hind flank of female NOD/SCID mice at 7-9 weeks of age. Body weight was measured twice weekly. Tumor length (L) and width (W) were measured twice weekly using digital calipers to calculate tumor volumes using the following formula: 0.5*L*W^2. Once tumor volumes reached an average of approximately 100 mm^3, mice were randomly assigned (n=8) into treatment groups. Mice were treated daily by oral gavage (10 mL/kg). Animals were euthanized if body weight loss >20% was observed, tumor volume achieved >1500 mm^3, or a humane endpoint was reached. Means with error bars representing s.e.m. were plotted. The treatment groups were as follows: (1) Vehicle (0.5% HPMC, 0.1% Tween 80); (2) Example 12 30 mg/kg (FIG. 1); (3) Example 12 100 mg/kg (FIG. 1); (4) Example 21 30 mg/kg (FIG. 2); (5) Example 21 100 mg/kg (FIG. 2); (6) Example 129 30 mg/kg (FIG. 3); (7) Example 129 100 mg/kg (FIG. 3); (8) Example 133 30 mg/kg (FIG. 4); (9) Example 133 100 mg/kg (FIG. 4).

CLAIMS

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



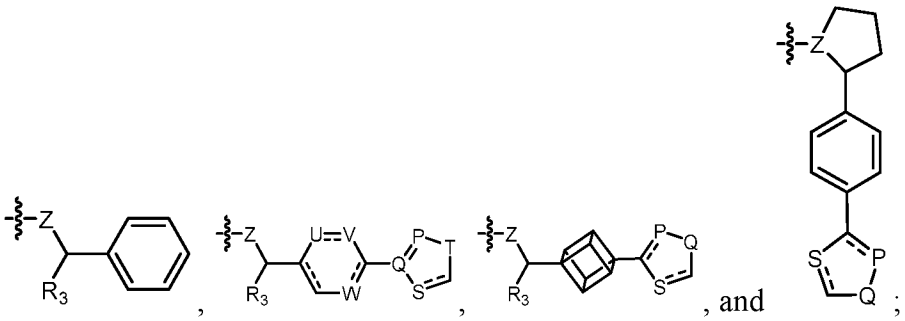
(I)

wherein:

R_1 is selected from C_3-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, $-OCD_3$, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, - COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

R_2 is selected from:

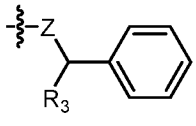


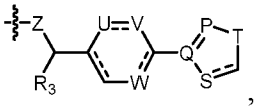
;

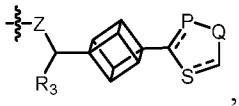
R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

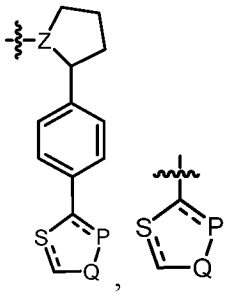
Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S;

wherein Z, U, V, W, P, Q, S, and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is  , the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is  , the 5- or 6-membered ring is saturated or unsaturated;

wherein when R_2 is  , the 5-membered ring is saturated or unsaturated;

wherein when R_2 is  , , is saturated or unsaturated;

X_1 is selected from C and N;

X_2 is selected from C and N;

wherein when X_2 is C, the said C is optionally substituted with hydrogen, halogen, -CN, $-OR_4$, $-SR_4$, $-N(R_5)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, wherein R_4 and R_5 are independently selected from C_1-C_6 alkyl; and

Ring A is a C_6-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring;

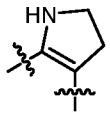
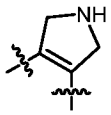
wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

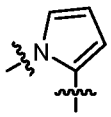
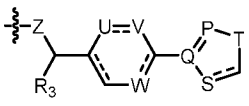
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

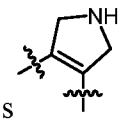
wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S;

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ;

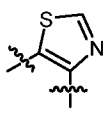
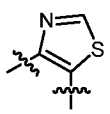
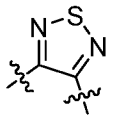
wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

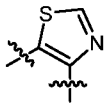
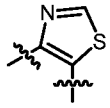
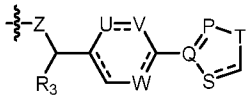
wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

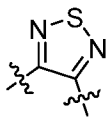
wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N;

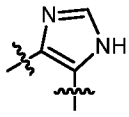
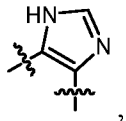
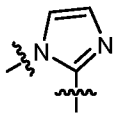
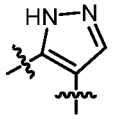
wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

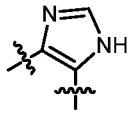
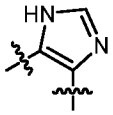
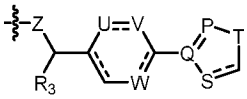
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

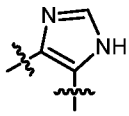
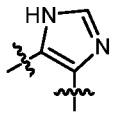
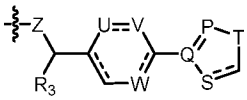
(ii) S or P are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

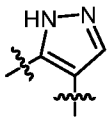
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

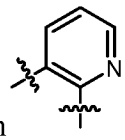
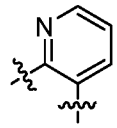
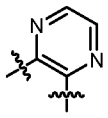
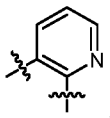
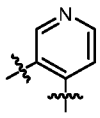
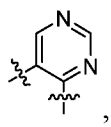
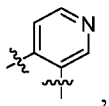
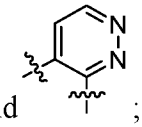
wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring, 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

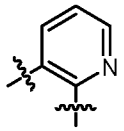
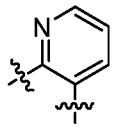
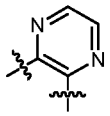
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  , and  ;

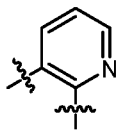
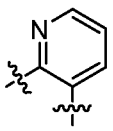
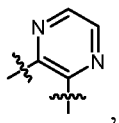
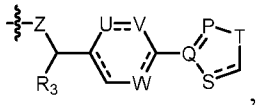
wherein when ring A is  or  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

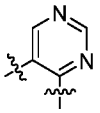
wherein when ring A is  or  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ,  ,  ,  ,  ,  ,  , and  ;

wherein when ring A is  ,  or  , Z is O;

wherein when ring A is  ,  , or  , Z is O and R_2 is  , P and S are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is  , Z is N and ring A is optionally substituted with one or more groups selected from -COOH, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

2. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1, wherein R_1 is selected from C_3-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

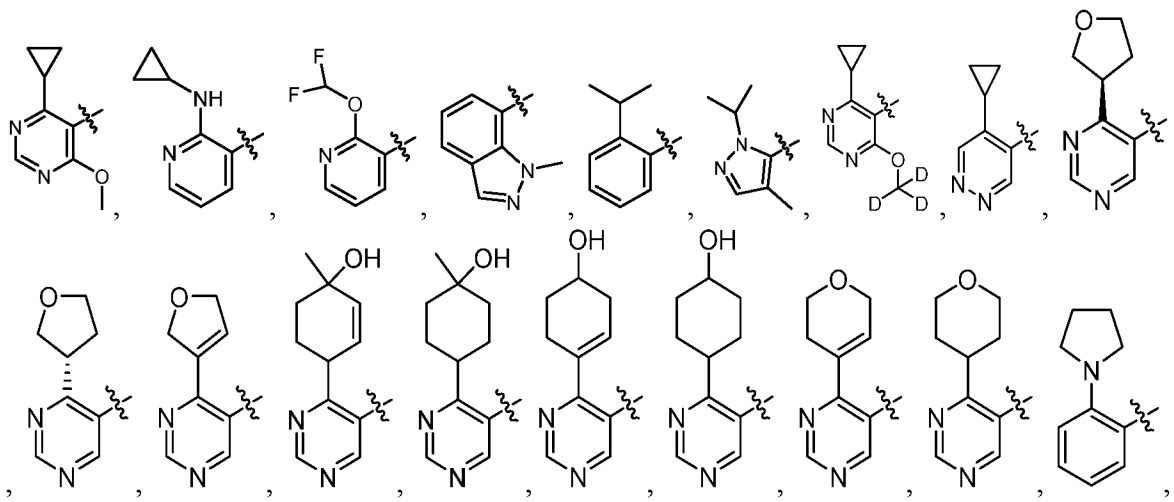
wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -OCD_3, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl,

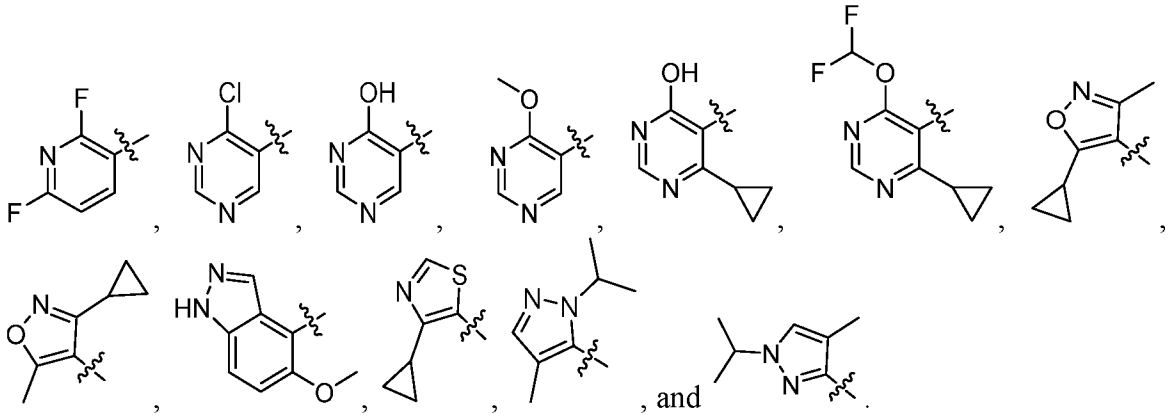
and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl.

3. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 1 or 2, wherein R_1 is selected from C_6 aryl, 5- or 6-memered heterocyclic ring and C_6 aryl fused with 5-membered heterocyclic group;

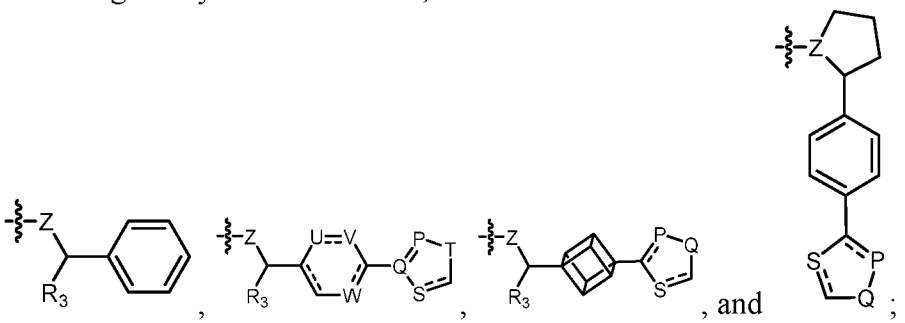
wherein R_1 is optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, -OCD_3, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, 3-8 membered heterocyclyl, -O-C_{1-6} alkyl, -O-C_{1-6} alkylene, -O-C_{1-6} haloalkyl, -NH-C_{1-6} alkyl, and -NH-C_{3-8} cycloalkyl, wherein the C_{6-10} aryl, 5-8 membered heteroaryl, C_{3-8} cycloalkyl, and 3-8 membered heterocyclyl are each independently optionally substituted with one or more substituents selected from the group consisting of -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl.

4. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 3, wherein R_1 is selected from:





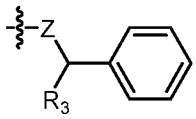
5. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 4, wherein R_2 is selected from:

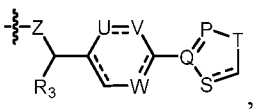


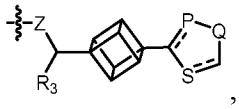
R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

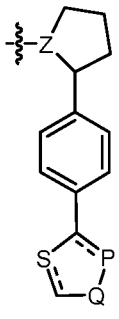
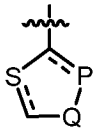
Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S,

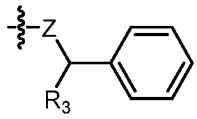
wherein Z, U, V, W, P, Q, S, and T are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is  , the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when R_2 is  , the 5- or 6-membered ring is saturated or unsaturated;

wherein when R_2 is  , the 5-membered ring is saturated or unsaturated;

wherein when R_2 is  , wherein  is saturated or unsaturated;

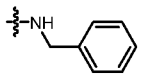
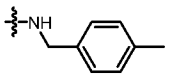
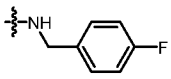
6. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 5, wherein R_2 is  ,

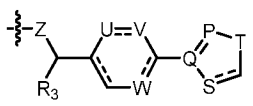
Z is selected from C, O, N, and S; and

R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl;

wherein the phenyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

7. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 6, wherein R_2 is selected from:

 ,  , and  .

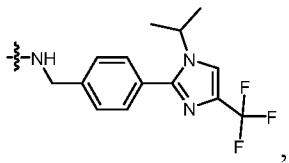
8. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5, wherein R_2 is  and the 5 or 6 membered ring is saturated or unsaturated;

R_3 is selected from H, D, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and

Z, U, V, W, P, Q, S, and T are independently selected from C, O, N, and S,

wherein Z, U, V, W, P, Q, S and T are optionally substituted with one or more groups selected from -OH, -COOH, -NH$_2$, -CN, -CD(CD$_3$)$_2$, halogen, C$_{1-6}$ alkyl, C$_{2-6}$ alkynyl, C$_{1-6}$ haloalkyl, C$_{1-6}$ alkoxy, C$_{1-6}$ haloalkoxy, C$_{1-6}$ hydroxyalkyl, and C$_3$-C$_8$ cycloalkyl ring.

9. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 8, wherein R$_2$ is selected from: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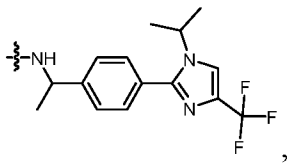
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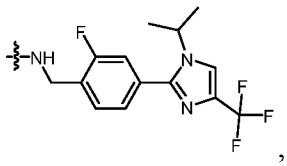
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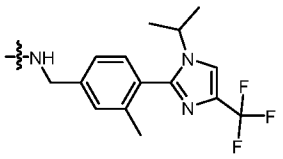
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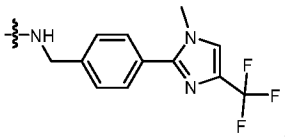
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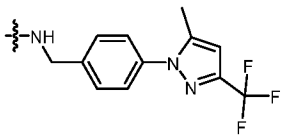
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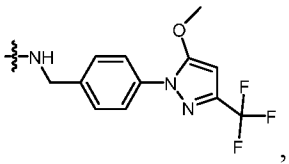
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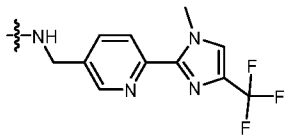
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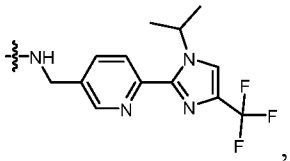
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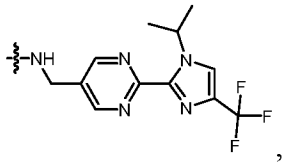
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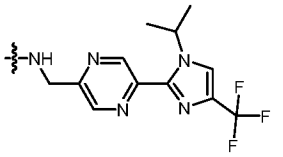
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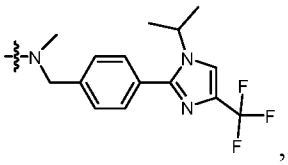
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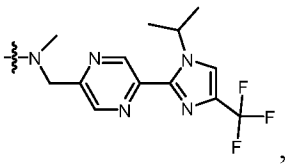
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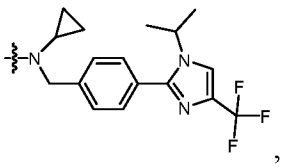
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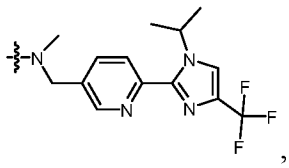
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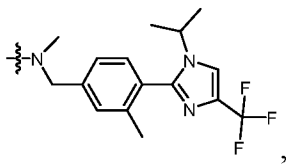
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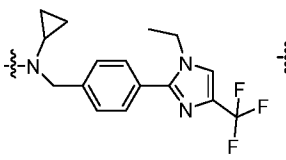
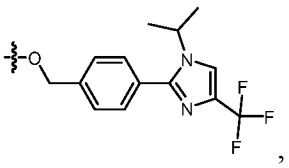
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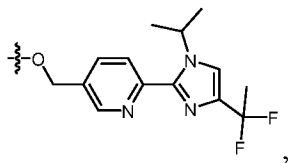
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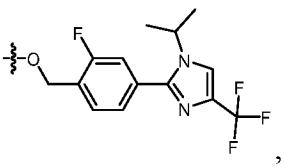
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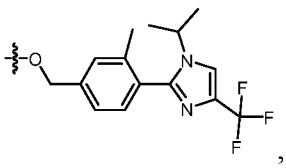
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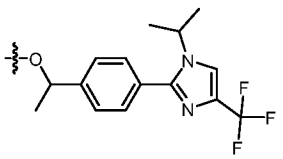
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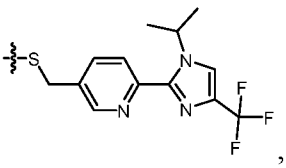
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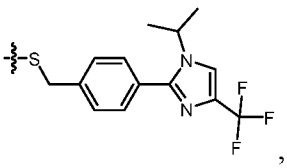
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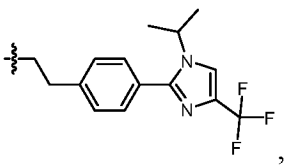
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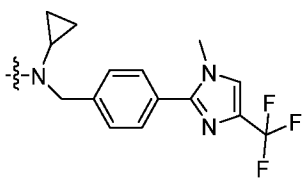
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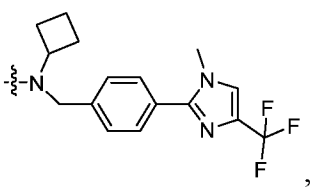
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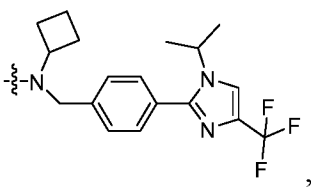
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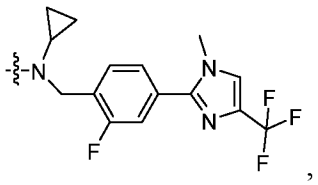
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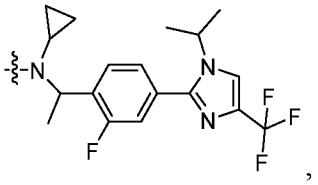
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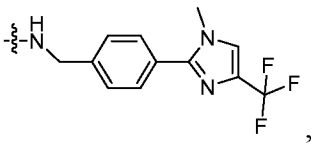
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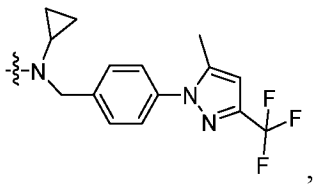
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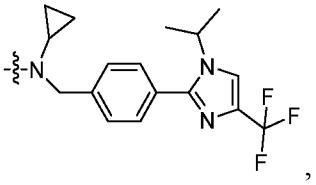
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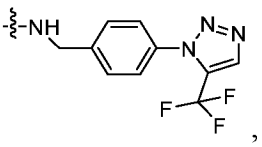
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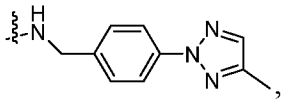
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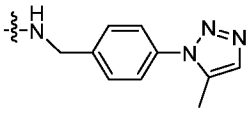
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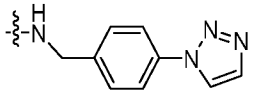
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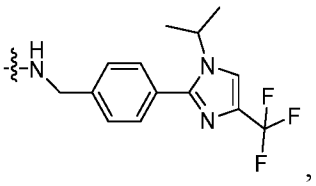
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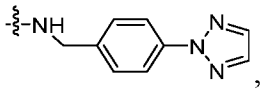
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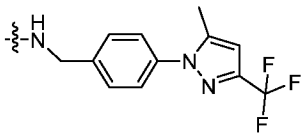
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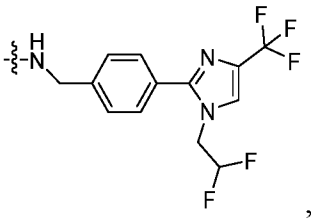
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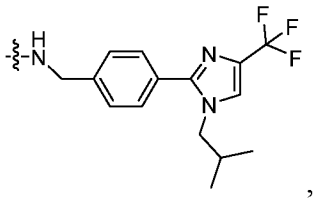
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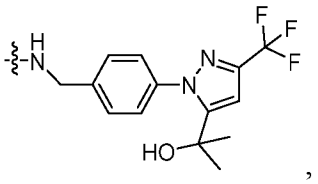
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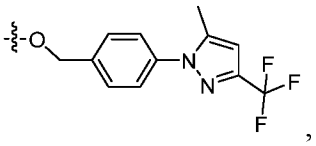
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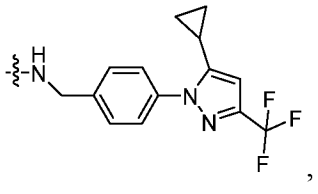
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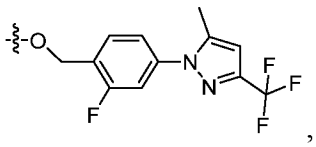
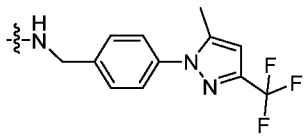
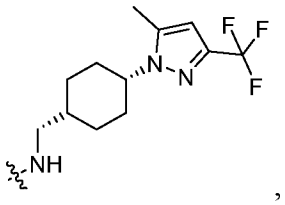
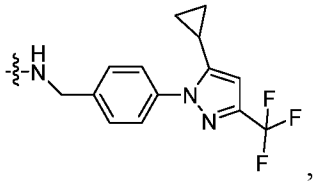
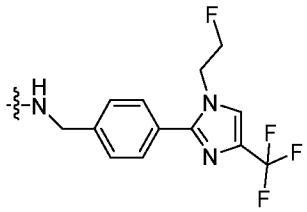
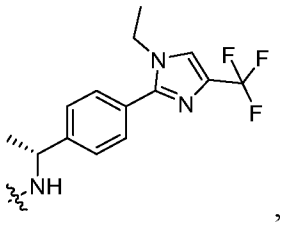
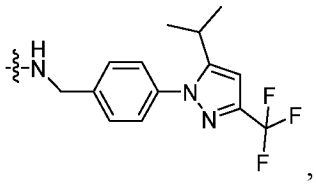
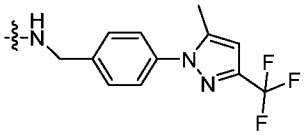
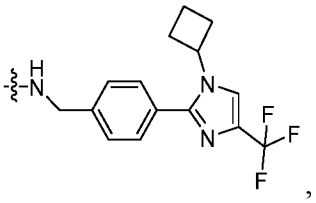
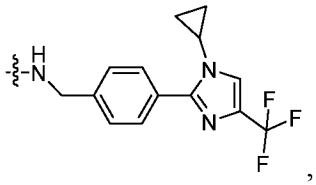
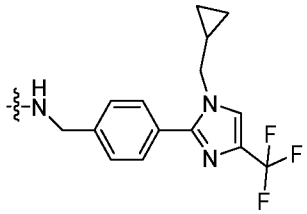
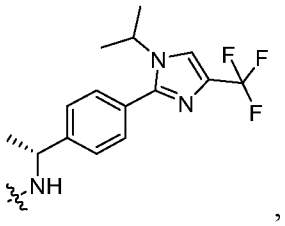
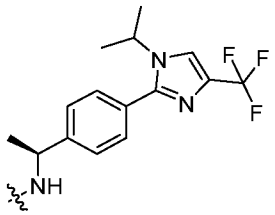
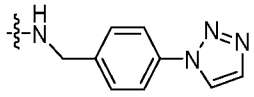
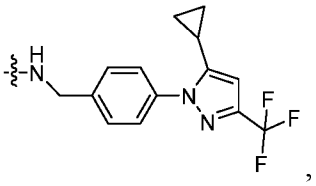
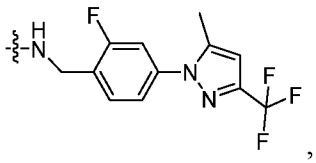
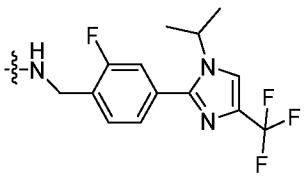
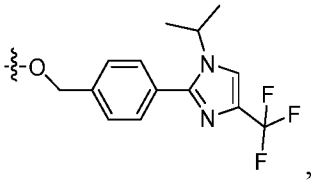
 ,
 ,
 ,

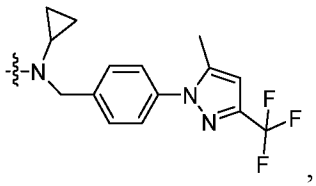
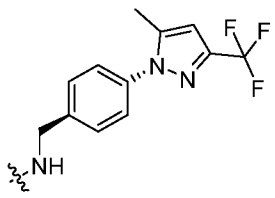
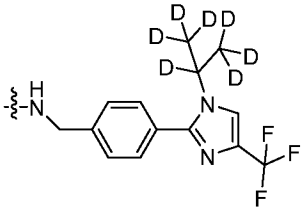
 ,
 ,
 ,

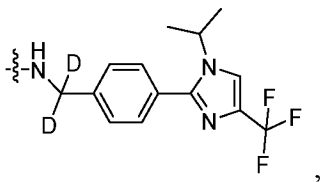
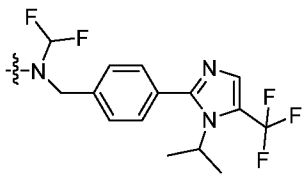
 ,
 ,
 ,

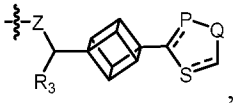
 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 ,
 ,
 ,

 , and  .

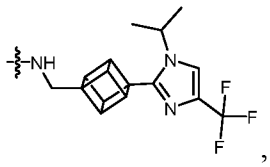
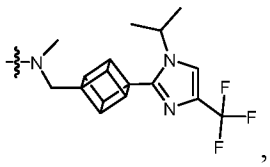
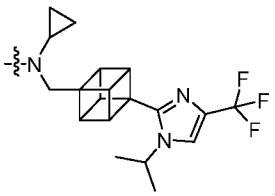
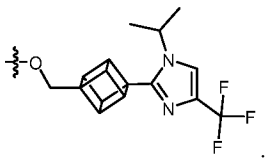
10. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any of claims 1 to 5, wherein R_2 is  , and the 5-membered ring is saturated or unsaturated;

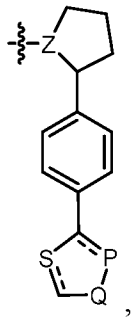
R_3 is selected from H, D, -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, and C_{1-6} hydroxyalkyl; and

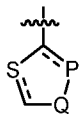
Z, P, Q, and S are independently selected from C, O, N, and S,

wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

11. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 10, wherein R_2 is selected from:

 ,  ,  , and  .

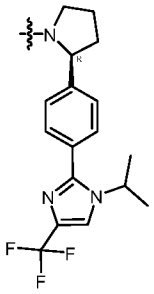
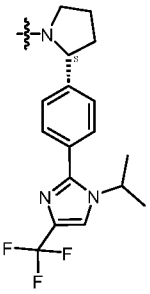
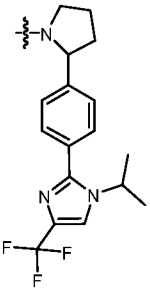
12. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 5, wherein R_2 is  ,

 is saturated or unsaturated;

Z, P, Q, and S are independently selected from C, O, N, and S,

wherein Z, P, Q, and S are optionally substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring.

13. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 12, wherein R_2 is selected from:


, 
, and 
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14. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 13, wherein X_1 is selected from C and N.

15. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 14, wherein X_2 is selected from C and N;

wherein when X_2 is C, the said C is optionally substituted with hydrogen, halogen, -CN, $-OR_4$, $-SR_4$, $-N(R_5)_2$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, wherein R_4 and R_5 are independently selected from C_1-C_6 alkyl.

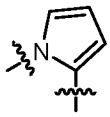
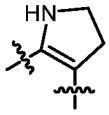
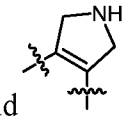
16. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 15, wherein ring A is a C_6-C_8 cycloalkyl ring, C_6-C_{10} aryl, or 4-, 5-, 6-, or 7- membered heterocyclyl ring

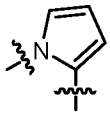
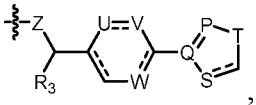
wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide;

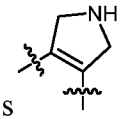
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ;

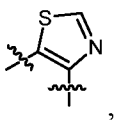
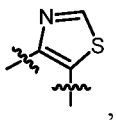
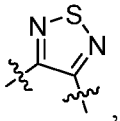
wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

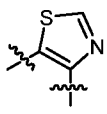
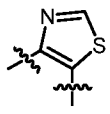
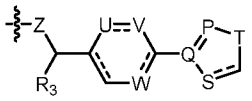
wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

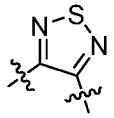
wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N;

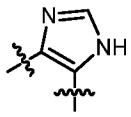
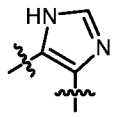
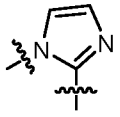
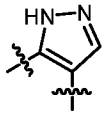
wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

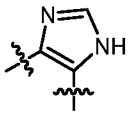
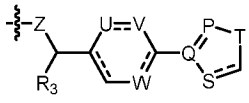
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

(ii) S or P are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

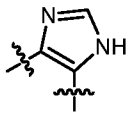
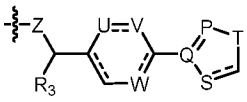
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

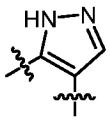
wherein when ring A is  and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

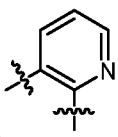
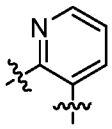
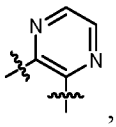
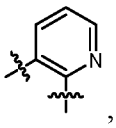
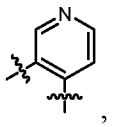
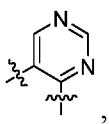
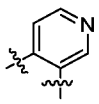
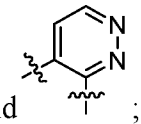
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  , and  ;

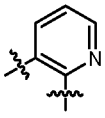
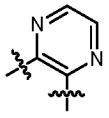
wherein when ring A is  , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, -

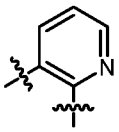
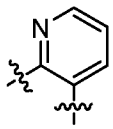
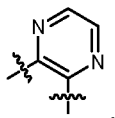
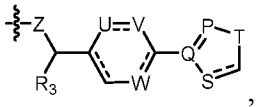
NH_2, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

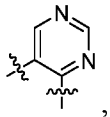
wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ,  ,  ,  ,  ,  ,  , and  ;

wherein when ring A is  or  , Z is O;

wherein when ring A is  ,  or  , Z is O and R_2 is  , P and S are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN,

-$CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is  , Z is N and ring A is optionally substituted with one or more groups selected from -COOH, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

17. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 16, wherein ring A is a 5-membered heterocyclyl ring;

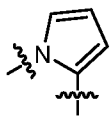
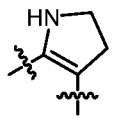
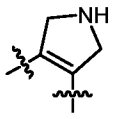
wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide;

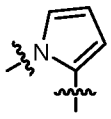
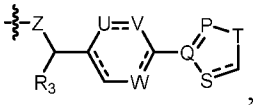
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

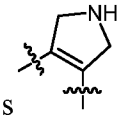
wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom selected from N, ring A is selected from  ,  , and  ;

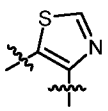
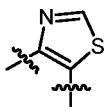
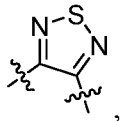
wherein when ring A is  and R_2 is  , V and W are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

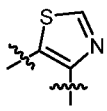
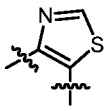
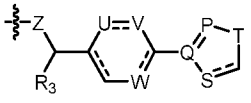
wherein when ring A is  and Z is O, ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, $-NH_2$, -(NH)-, =O, =NH, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide;

wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl;

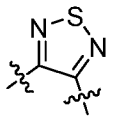
wherein when ring A is a 5-membered heterocyclyl ring and at least one heteroatom is S, ring A is selected from  ,  , or  , where Z is N;

wherein when ring A is selected from  or  , Z is N, and R_2 is  where S and P are N, wherein:

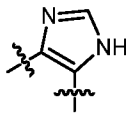
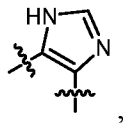
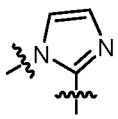
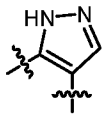
(i) when S or P are substituted with C_1 alkyl then R_1 is C_6-C_{10} aryl;

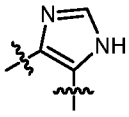
(ii) S or P are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl; or

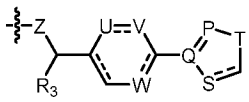
(iii) V or W are substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

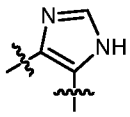
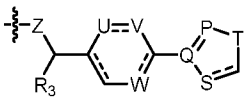


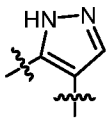
wherein when ring A is and Z is N, R_1 is selected from C_3-C_8 cycloalkyl ring or 4-, 5-, 6-, or 7- membered heterocyclyl ring, and C_6-C_{10} aryl fused with 3-8 membered heterocyclic group;

wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms selected from N, ring A is selected from  ,  ,  , and  ;

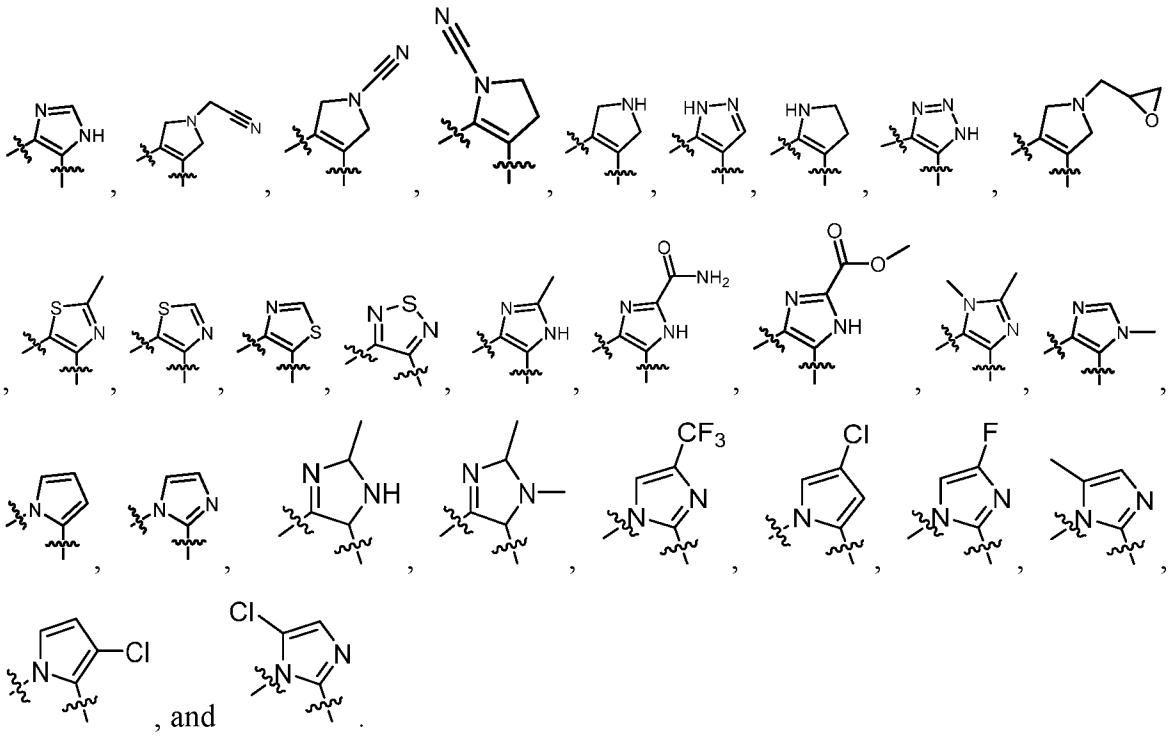


wherein when ring A is , Z is O, and R_2 is  where S and P are N, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  , Z is O, and R_2 is  where Q and P are N, S is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_3-C_8 cycloalkyl ring;

wherein when ring A is  and Z is O, S and P are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, $-CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring.

18. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 17, wherein ring A is selected from:



, and .

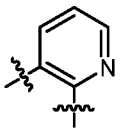
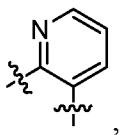
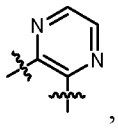
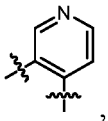
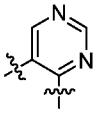
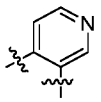
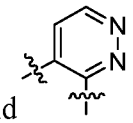
19. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 16, wherein ring A is a 6-membered heterocyclyl ring,

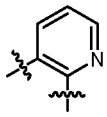
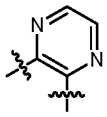
wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6}alkyl-epoxide;

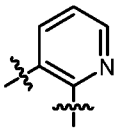
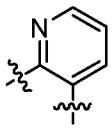
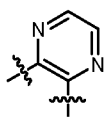
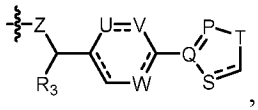
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

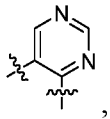
wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl

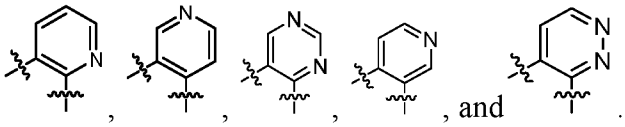
wherein when ring A contains ring carbon atoms and one or more heteroatoms, the heteroatoms are selected from N and S wherein when ring A is a 6-membered heterocyclyl ring and contains one or two heteroatoms selected from N, ring A is selected from  ,  ,  ,  ,  ,  , and  ;

wherein when ring A is  or  , Z is O;

wherein when ring A is  ,  or  , Z is O and R_2 is  , P and S are substituted with one or more groups selected from -OH, -COOH, -NH_2, -CN, -$CD(CD_3)_2$, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, and C_4-C_8 cycloalkyl ring;

wherein when ring A is  , Z is N and ring A is optionally substituted with one or more groups selected from -COOH, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and -C_{1-6} alkyl-epoxide.

20. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 19, wherein ring A is selected from:

 , and .

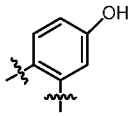
21. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 16, wherein ring A is a C_6-C_{10} aryl

wherein the said ring A is optionally substituted with one or more groups selected from -OH, -COOH, -C(O)-, -NH_2, -(NH)-, =O, =NH, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_{1-6} nitrile, and C_{1-6} alkyl-epoxide;

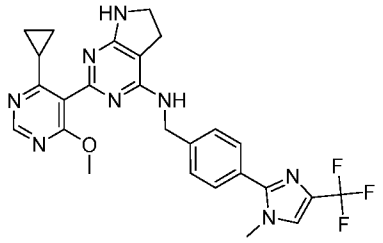
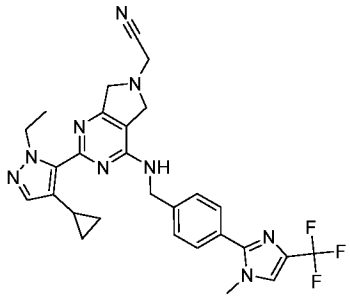
wherein the said -C(O)- is optionally substituted with H, -OH, NH_2, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl;

wherein the said –(NH)- is optionally substituted with one or more groups selected from H, C_{1-6} alkyl, C_{1-6} nitrile, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, or C_{1-6} hydroxyalkyl, and C_{1-6} alkyl-epoxide;

wherein the said C_{1-6} alkyl-epoxide is optionally substituted with one or more C_{1-6} alkyl.

22. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to claim 21, wherein ring A is  .

23. The compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-22, wherein the compound is selected from:


,

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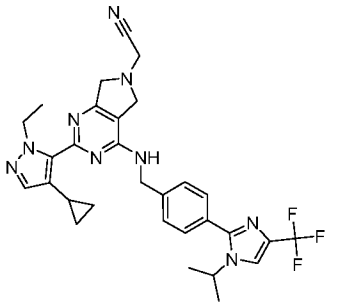
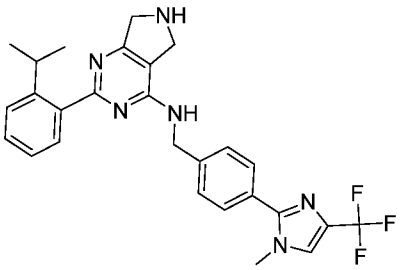

,

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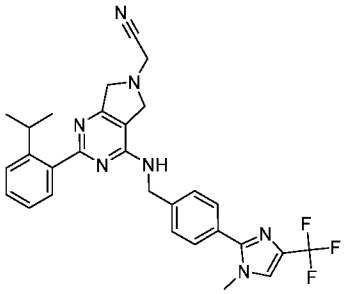
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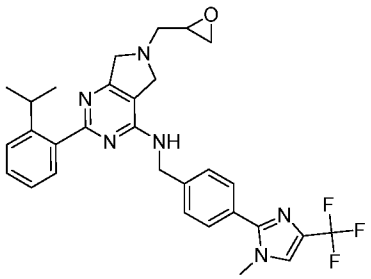
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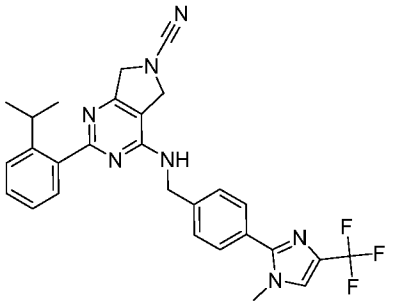
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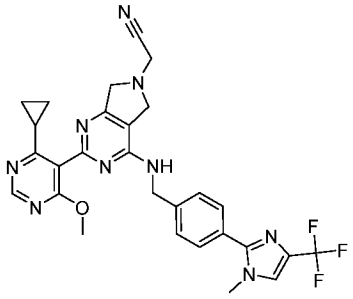
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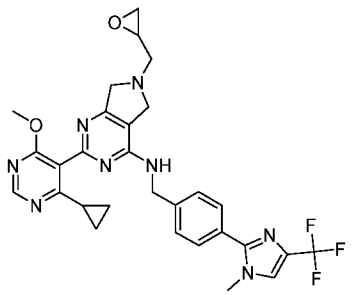
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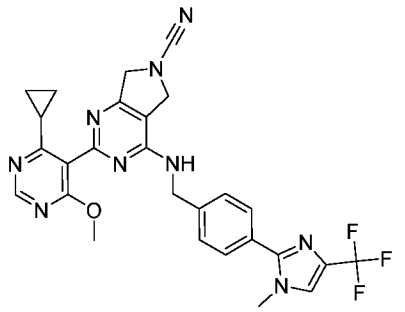
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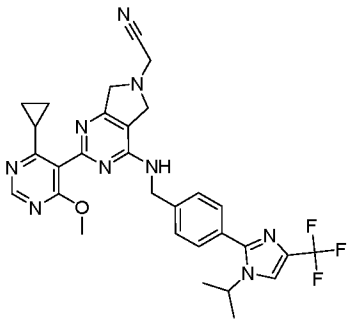
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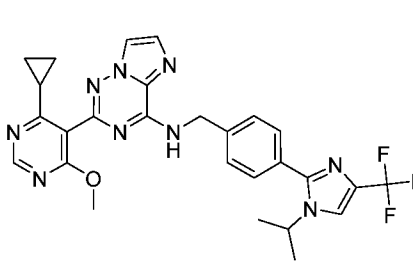
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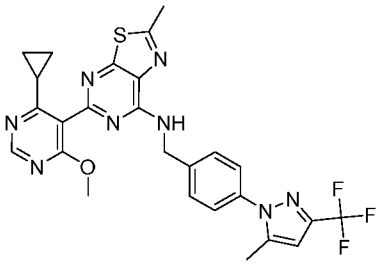
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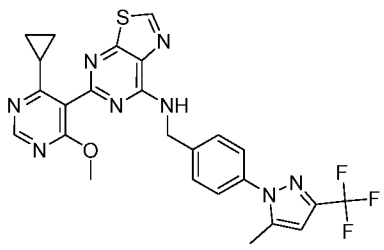
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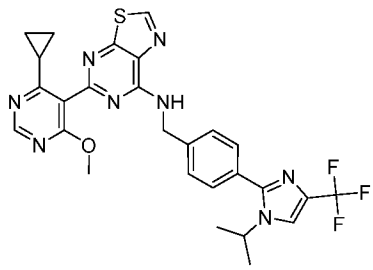
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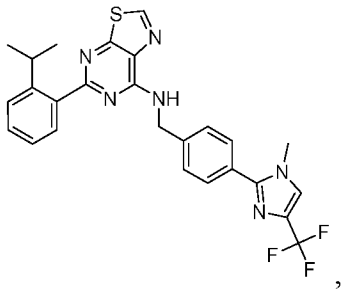
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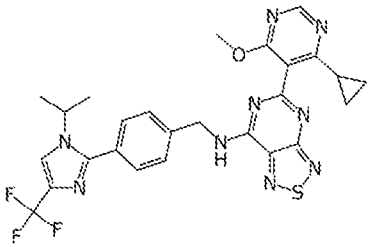
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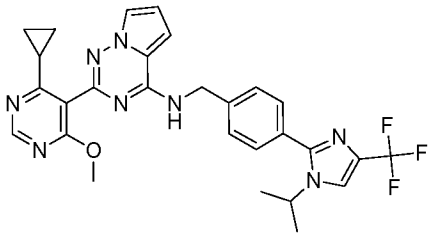
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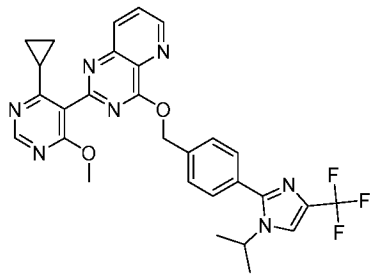
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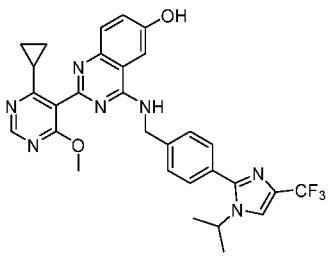
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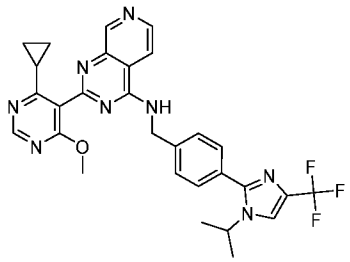
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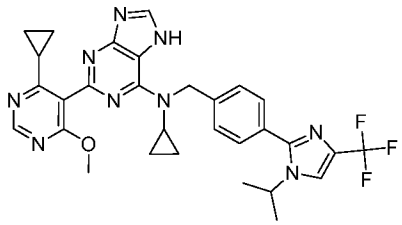
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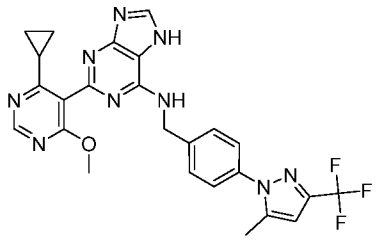
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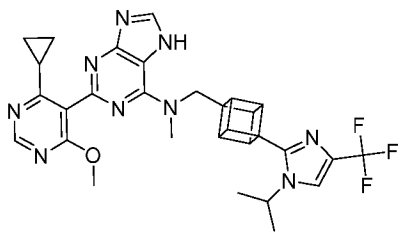
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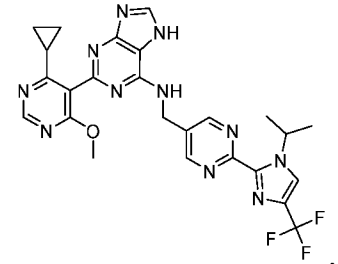
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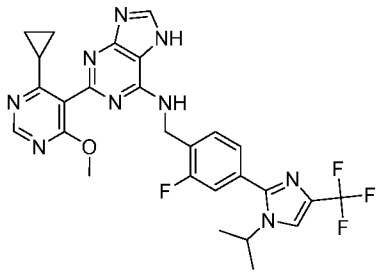
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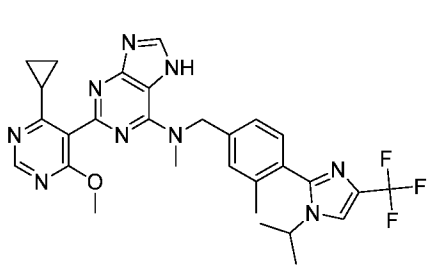
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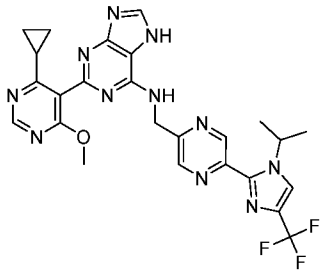
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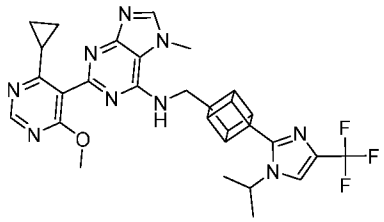
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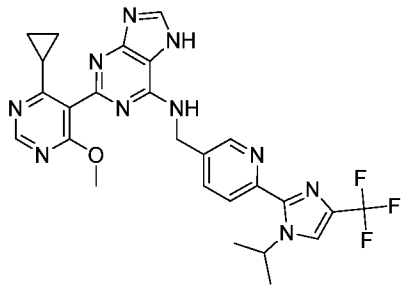
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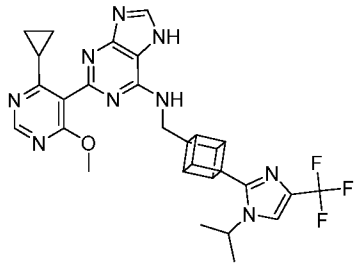
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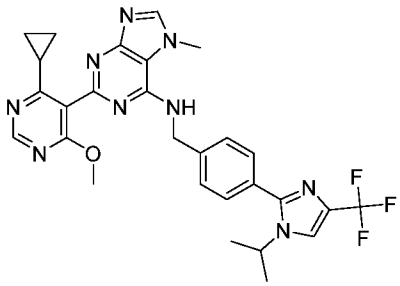
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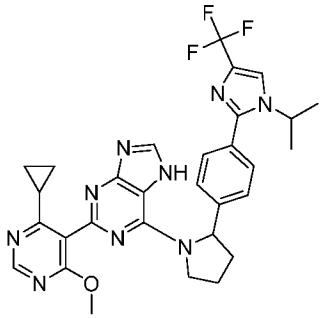
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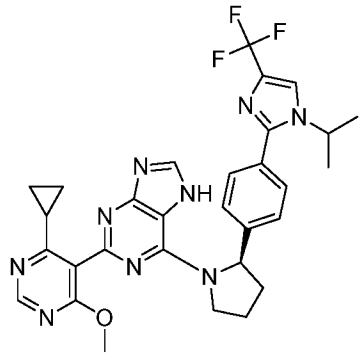
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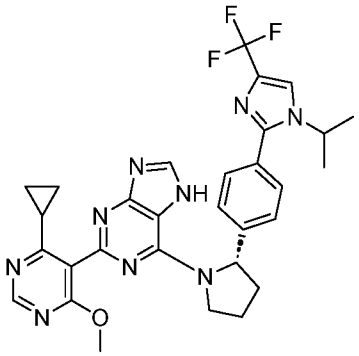
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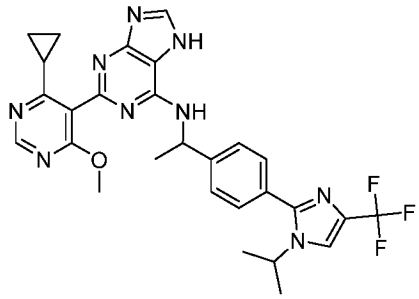
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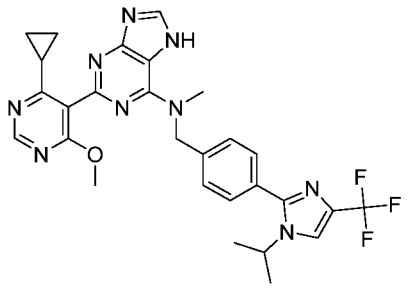
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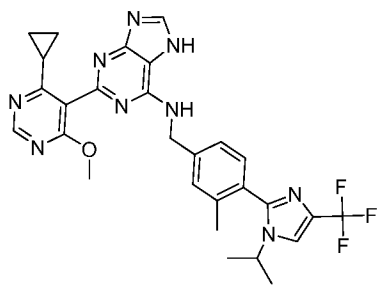
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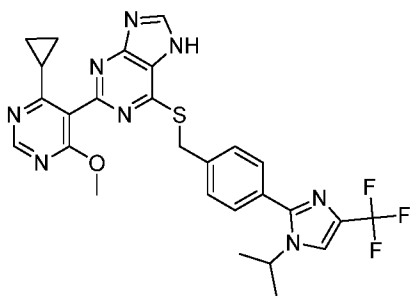
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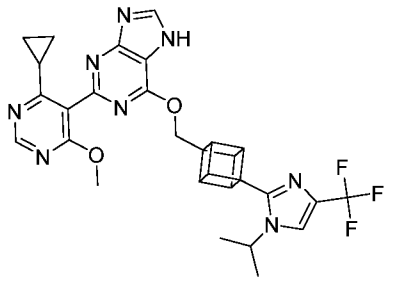
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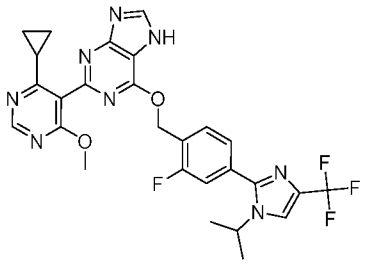
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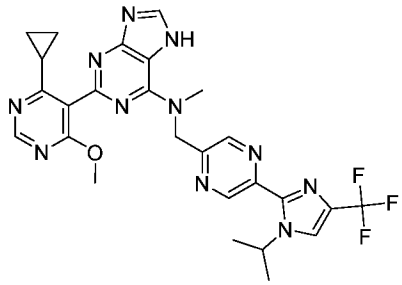
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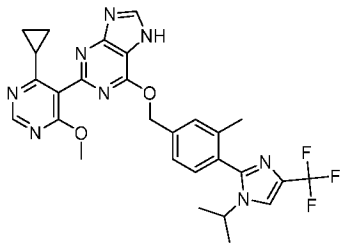
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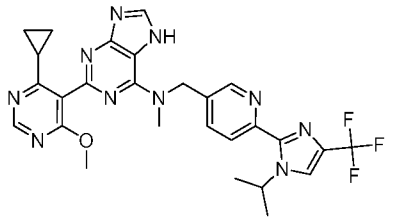
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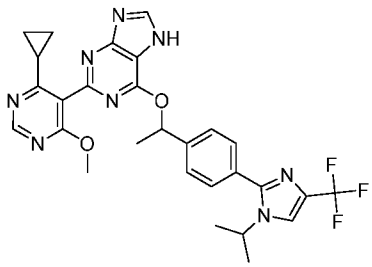
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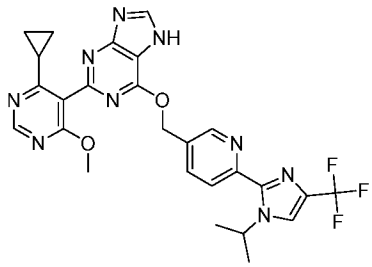
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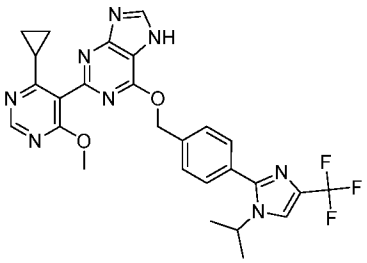
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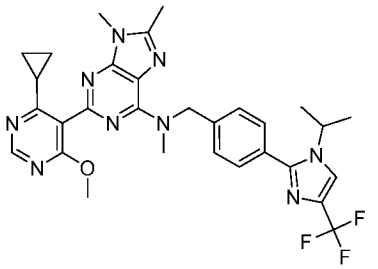
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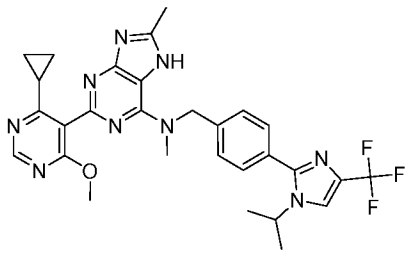
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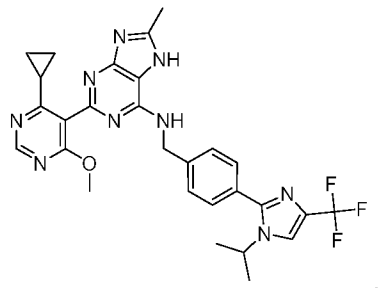
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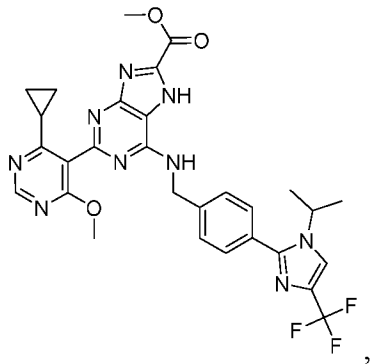
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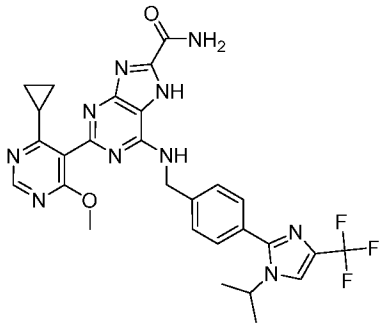
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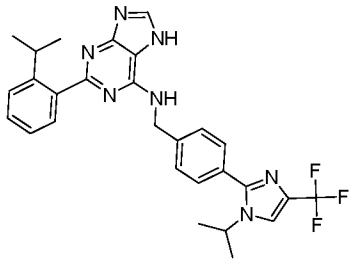
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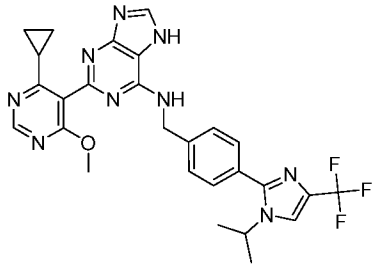
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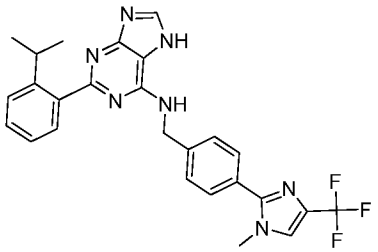
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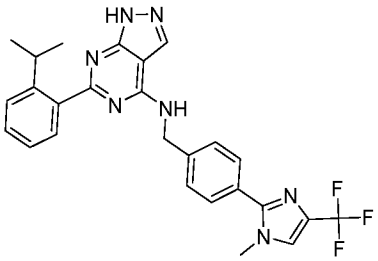
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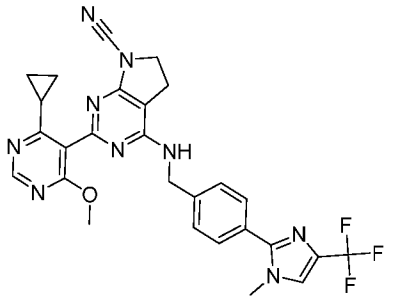
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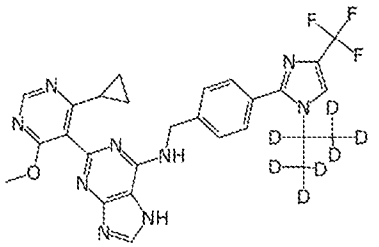
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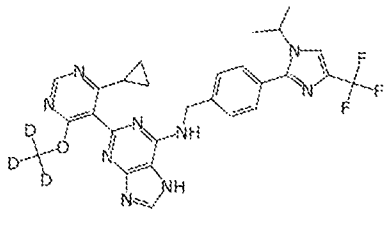
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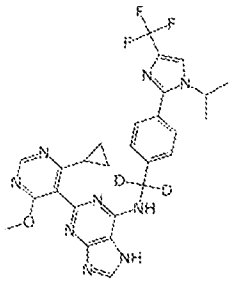
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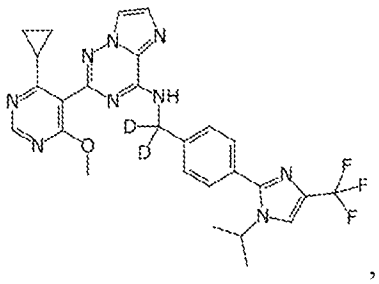
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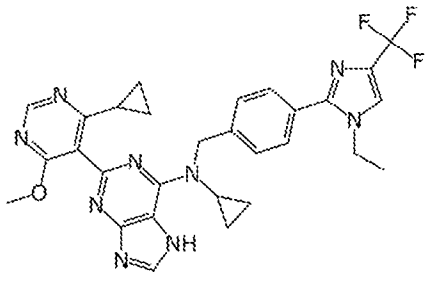
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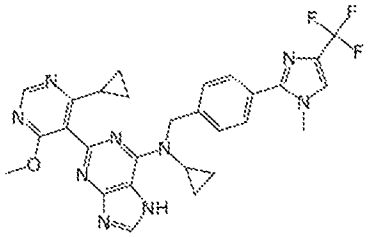
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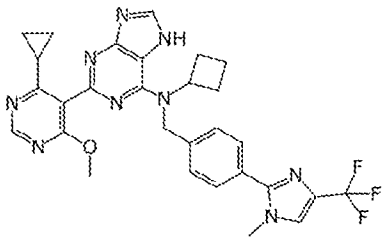
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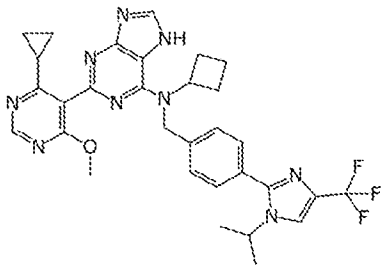
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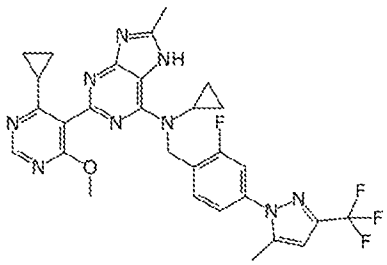
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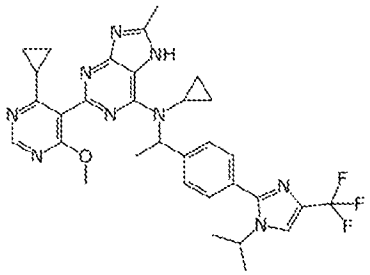
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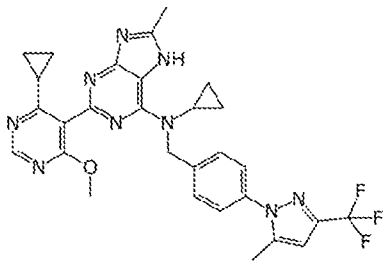
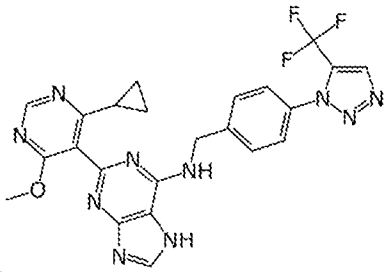
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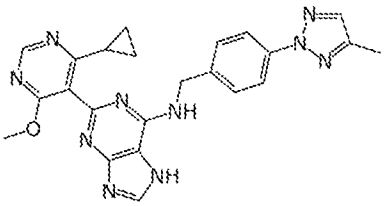
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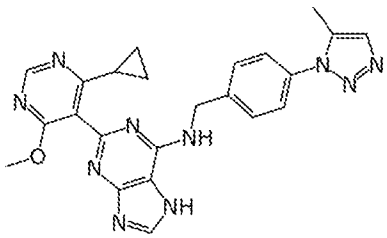
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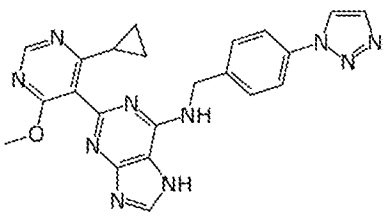
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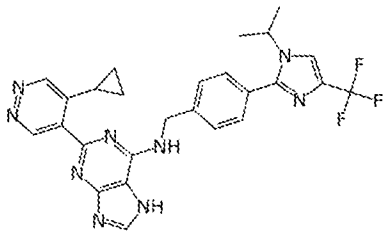
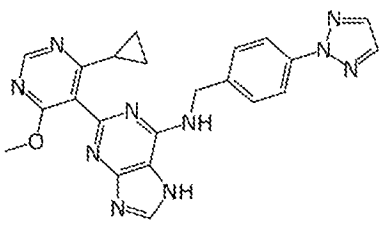
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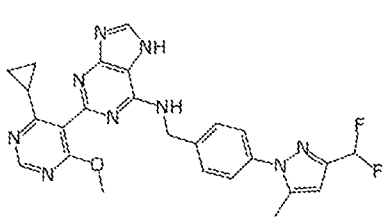
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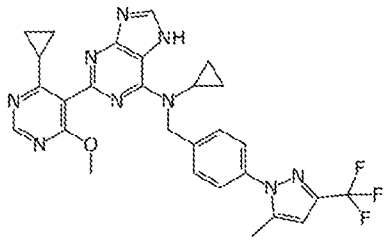
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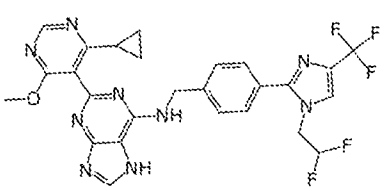
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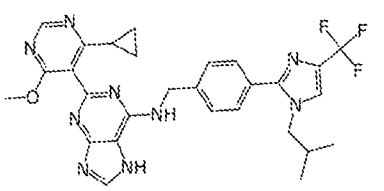
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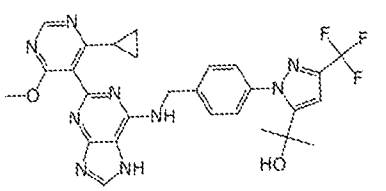
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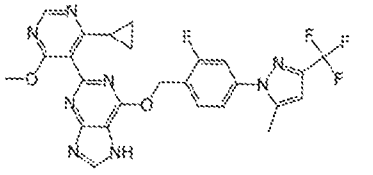
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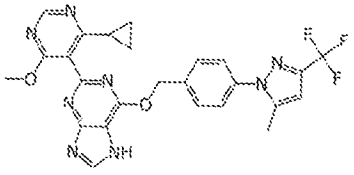
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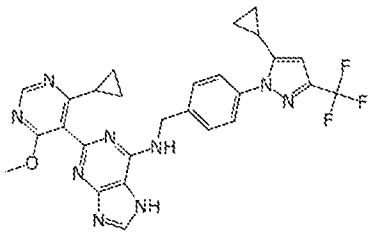
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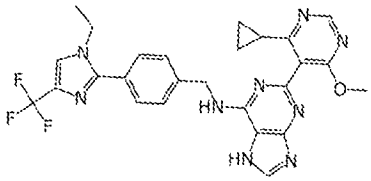
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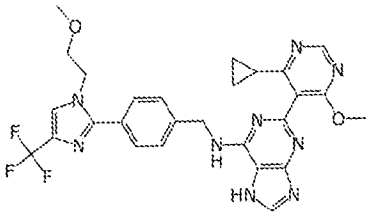
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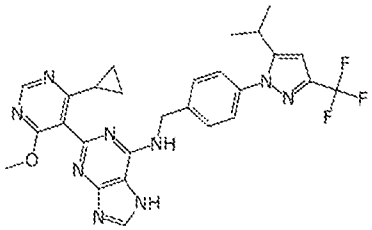
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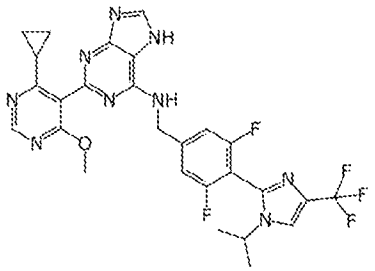
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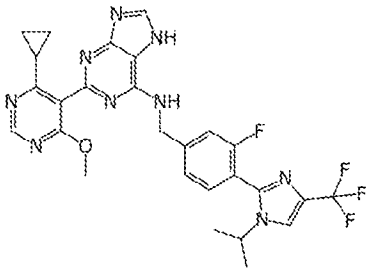
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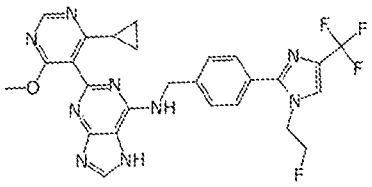
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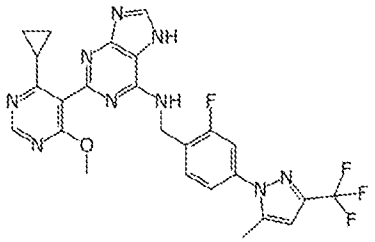
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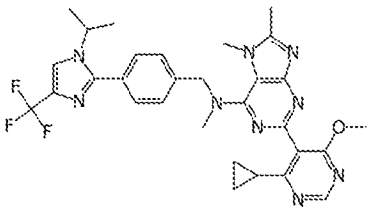
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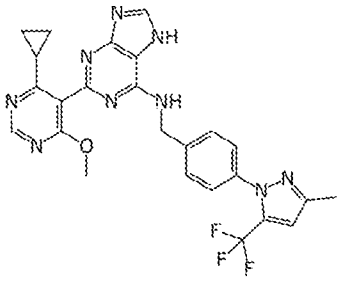
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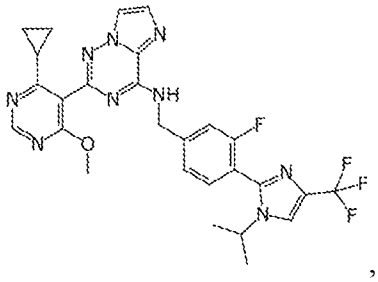
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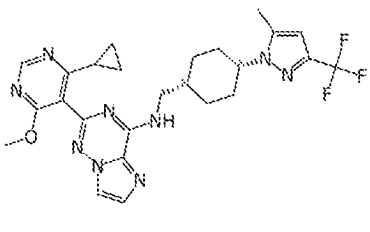
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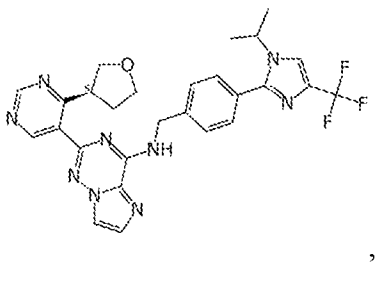
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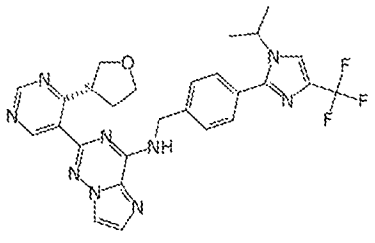
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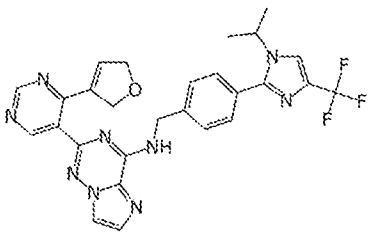
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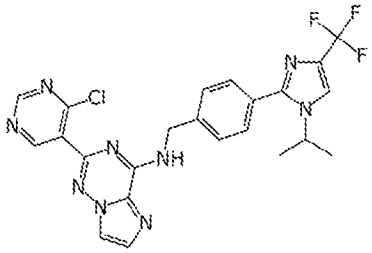
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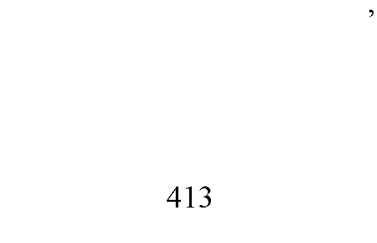
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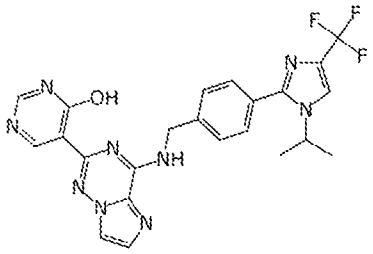
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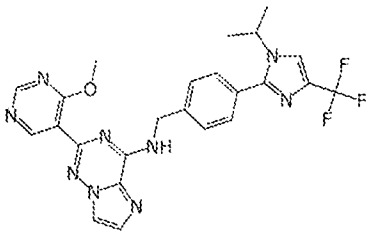
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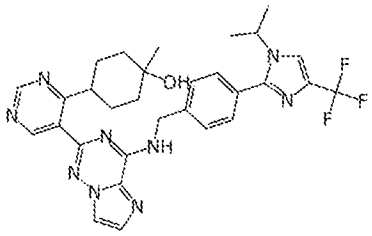
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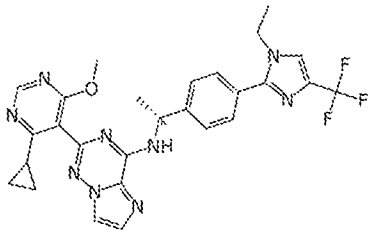
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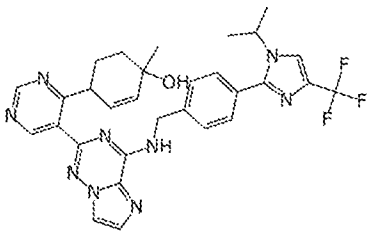
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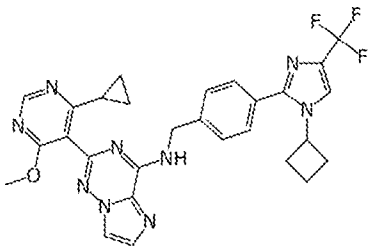
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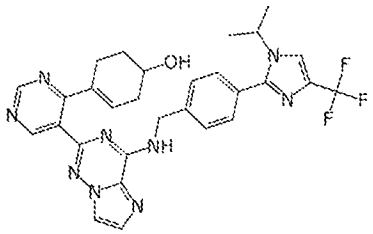
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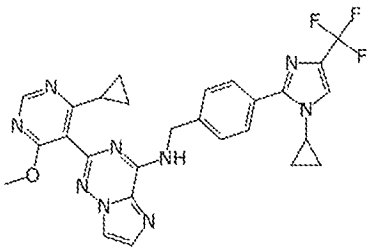
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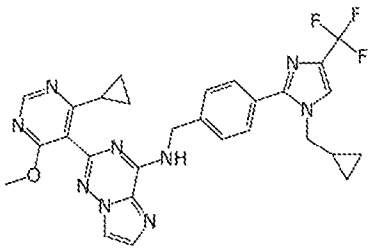
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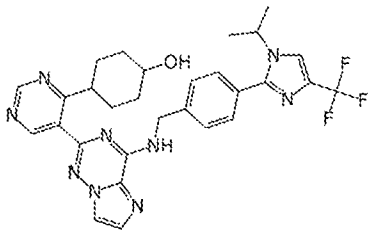
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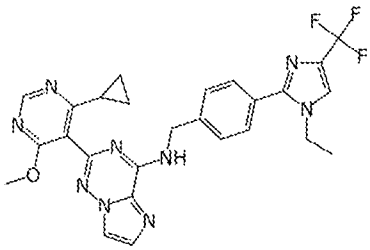
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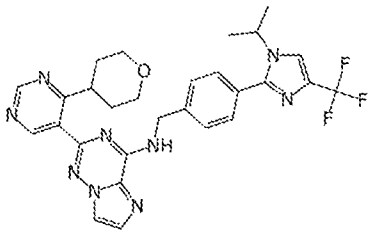
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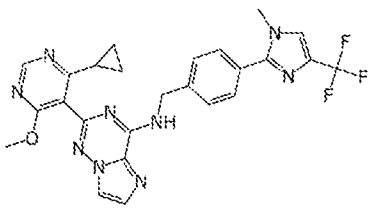
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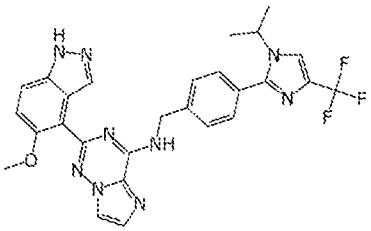
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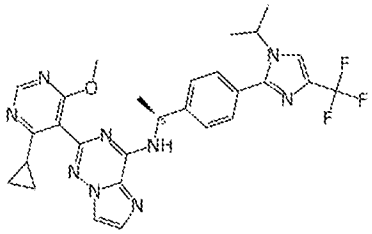
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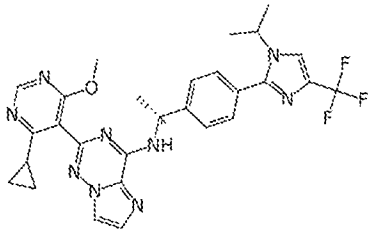
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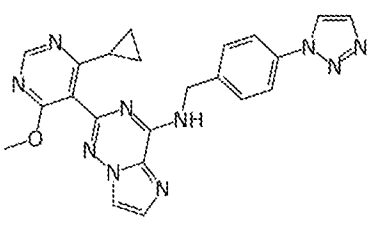
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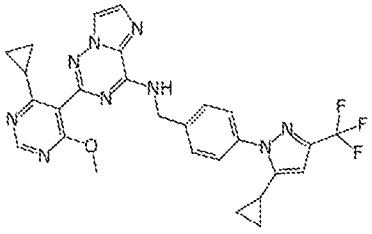
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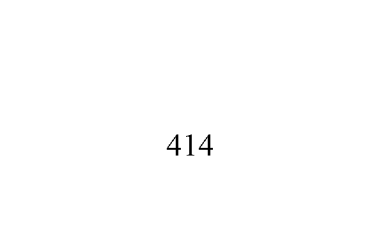
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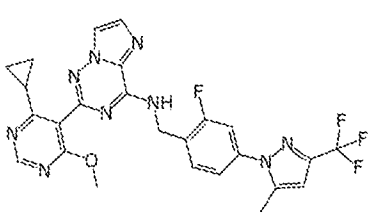
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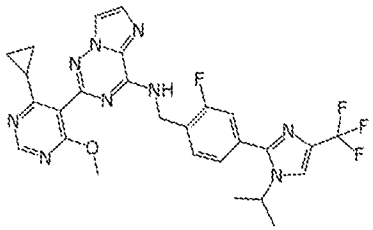
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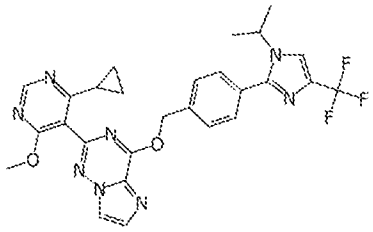
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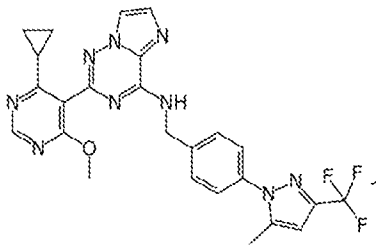
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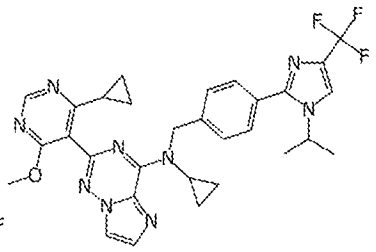
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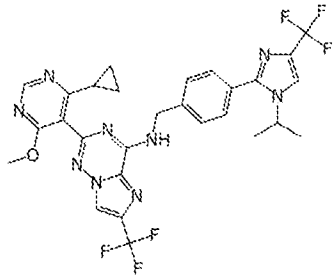
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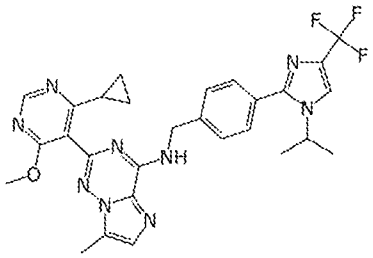
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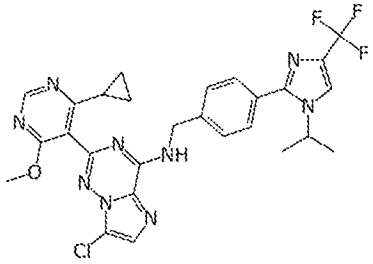
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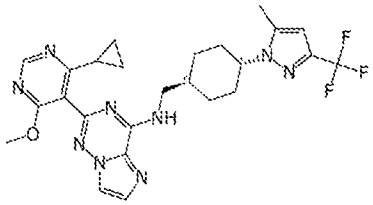
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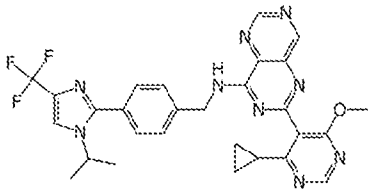
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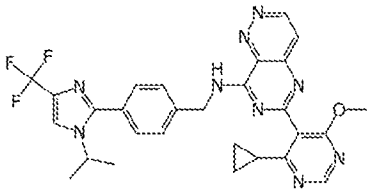
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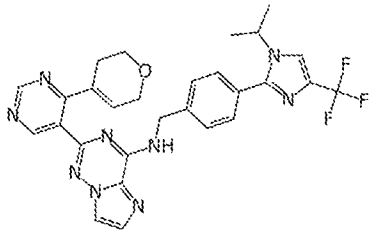
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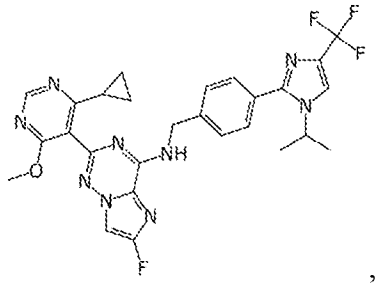
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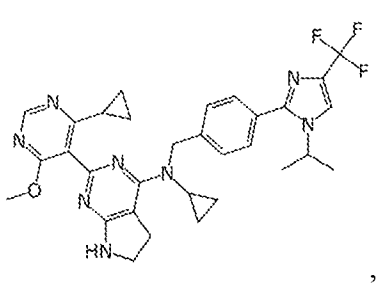
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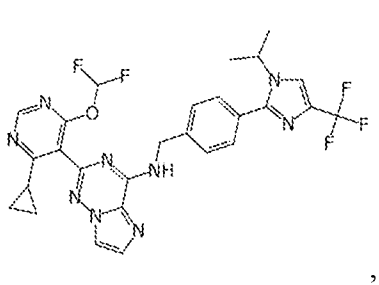
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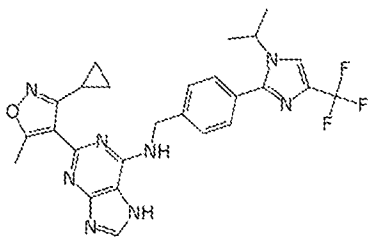
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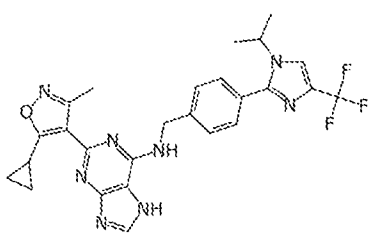
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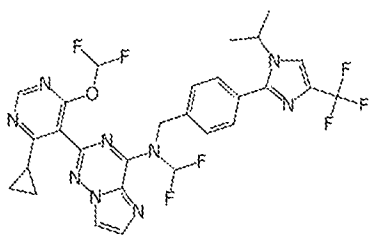
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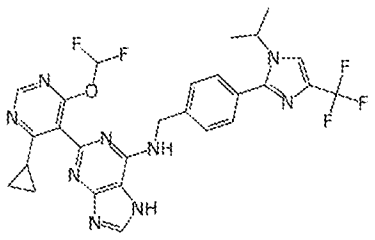
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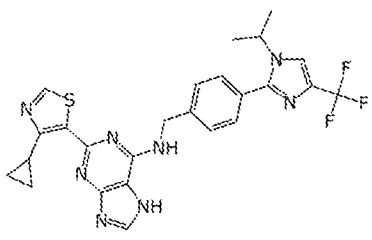
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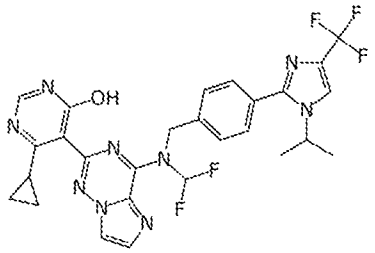
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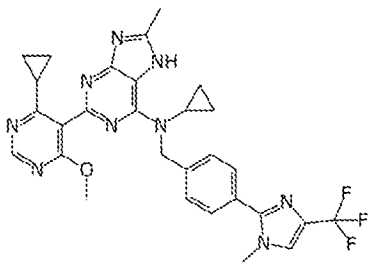
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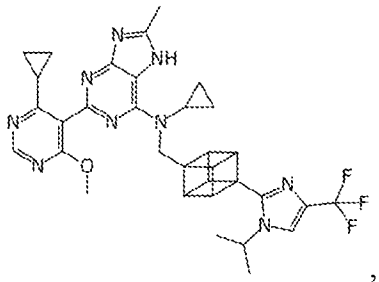
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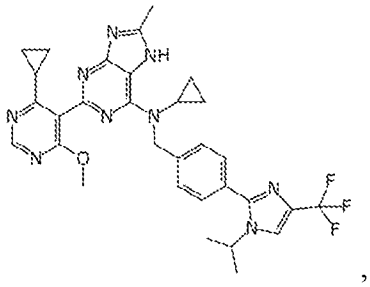
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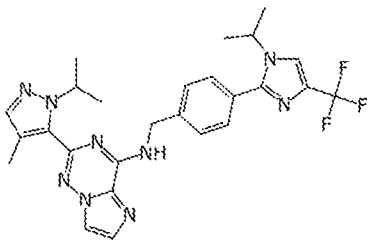
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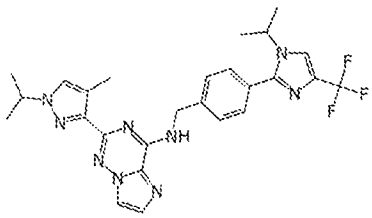
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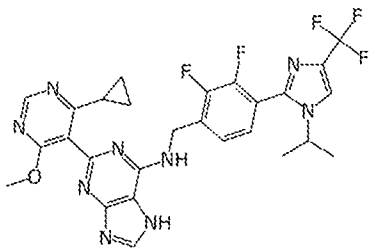
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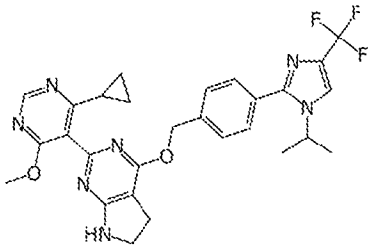
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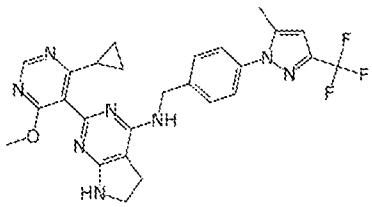
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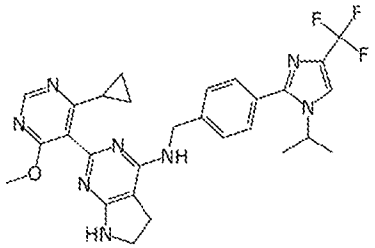
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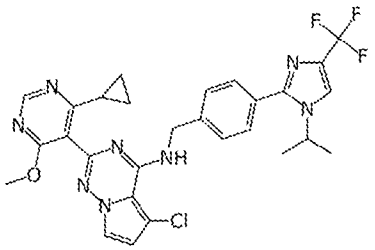
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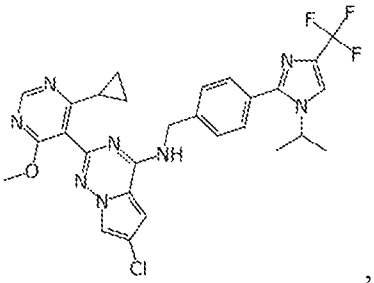
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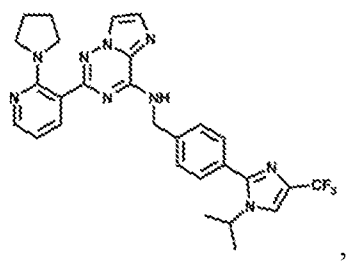
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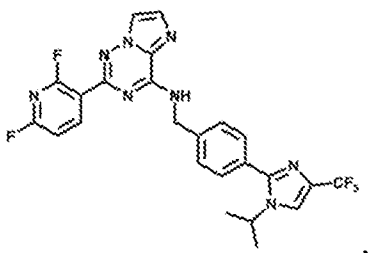
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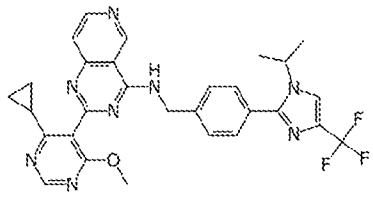
, and
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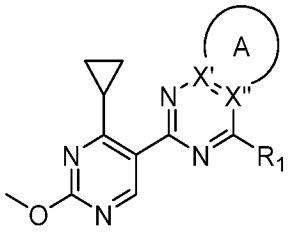
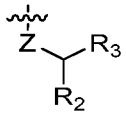
24. A compound of formula (II), or a pharmaceutically acceptable salt thereof:



(II)

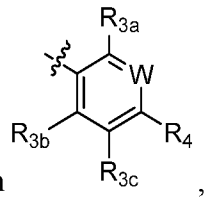
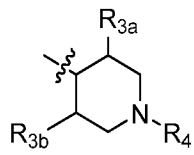
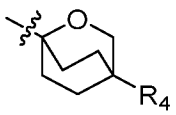
wherein:

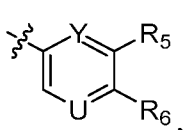
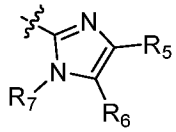
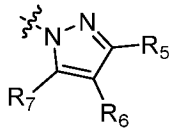
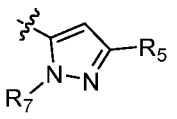
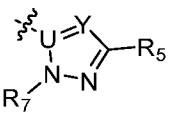
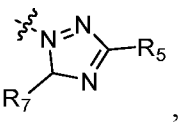
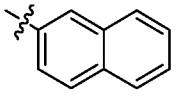
X' and X" are independently selected from N or C;

R_1 is 

wherein Z is selected from O or N optionally substituted with R_{1a} or $-CH_2R_{1a}$, wherein R_{1a} is C_3-C_6 cycloalkyl or 4-, 5-, or 6- membered heterocyclyl;

wherein R_2 is selected from H or deuterium;

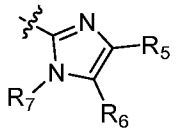
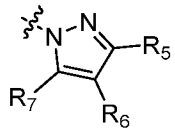
R_3 is selected from  ,  , and  , wherein W is selected from C or N, and wherein R_{3a}, R_{3b}, and R_{3c} are independently selected from -H or halogen, R_{3a} and R_2 optionally form a bond to form a 5- or 6-membered heterocyclyl, or R_{3a} and R_{3b} optionally combine to form a bridge;

R_4 is selected from  ,  ,  ,  ,  ,  ,  , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C;

wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl,

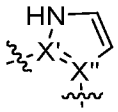
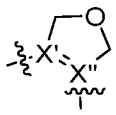
C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

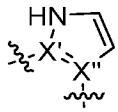
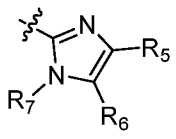
wherein the said C_{1-6} haloalkyl ring is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  ;and

wherein R_{3c} optionally forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen;

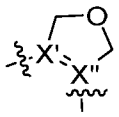
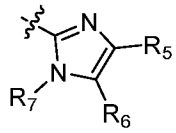
Ring A is a 5- or 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S;

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C;

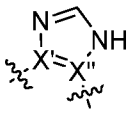
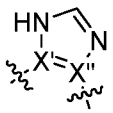
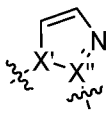
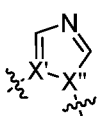
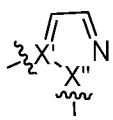
wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6}

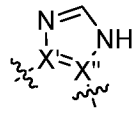
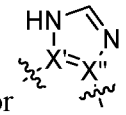
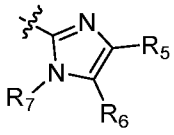
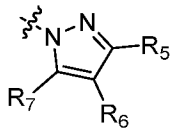
alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

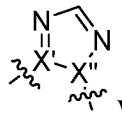
wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring;

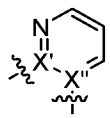
wherein the said C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

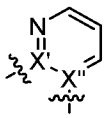
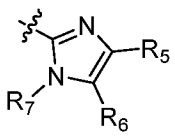
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N;

wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

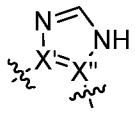
wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N;

wherein when ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N;

wherein when ring A is  where X' and X" are C, Z is N, and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

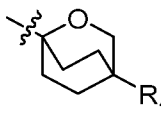
wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl;

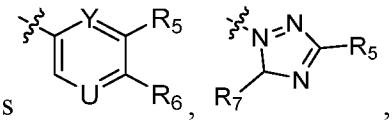
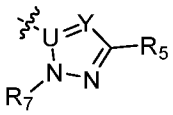
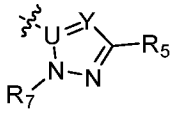
wherein when ring A is  where X' and X" are C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of:

Z is substituted with R_{1a} or $-CH_2R_{1a}$,

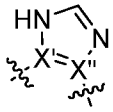
R_{3a} and R_{3b} are halogen,

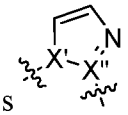
R_5, R_6, or R_7 is a 4-, 5-, or 6- membered heterocyclyl ring,

R_3 is  ,

R_4 is  , where U and Y are C,  where U is C and Y is N, or R_3 is  where U is N and Y is C,

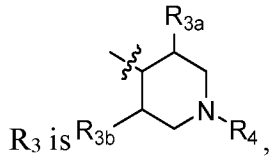
or a combination thereof;

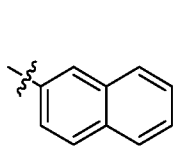
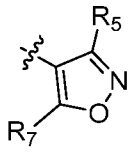
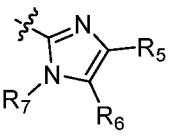
wherein when ring A is  where X' and X" are C , the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises a ring A substituted with a C2-C6 alkenyl;

wherein when ring A is  where X' is N and X" is C, the compound of formula (II) or a pharmaceutically acceptable salt thereof comprises one or more of:

R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl,

R_{3a} and R_{3b} combine to form a bridge,

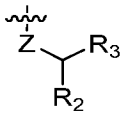
R_3 is  ,

R_4 is  ,  , or  ,

R_5, R_6, or R_7 a 4-, 5-, or 6- membered heterocyclyl ring,

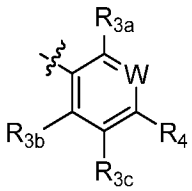
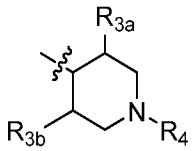
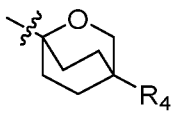
R_{3c} forms a bond with R_5 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl,

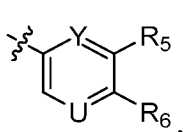
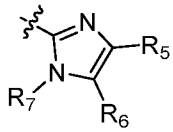
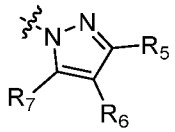
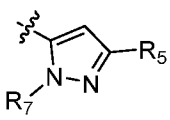
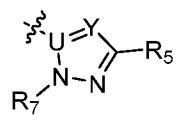
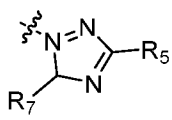
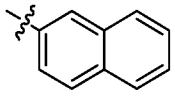
or a combination thereof.

25. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 24, wherein R_1 is  ;

wherein Z is selected from O or N optionally substituted with R_{1a} or -CH_2R_{1a}, wherein R_{1a} is C_3-C_6 cycloalkyl or 4-, 5-, or 6- membered heterocyclyl

wherein R_2 is selected from H or deuterium;

R_3 is selected from  ,  , and  , wherein W is selected from C or N, and wherein R_{3a}, R_{3b}, and R_{3c} are independently selected from -H or halogen, R_{3a} and R_2 optionally form a bond to form a 5- or 6-membered heterocyclyl, or R_{3a} and R_{3b} optionally combine to form a bridge;

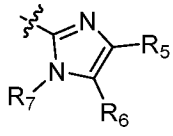
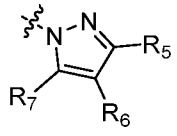
R_4 is selected from  ,  ,  ,  ,  ,  ,  , or  ,

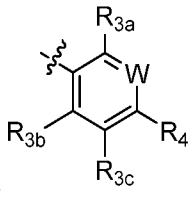
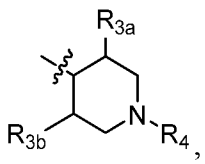
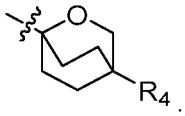
wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C;

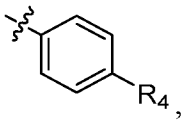
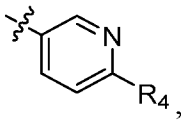
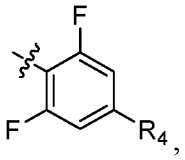
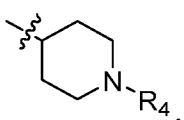
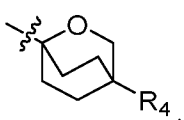
wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

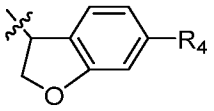
wherein the said C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

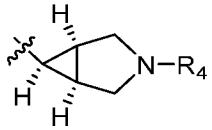
wherein R_{3c} optionally forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen;

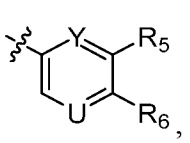
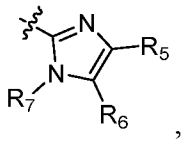
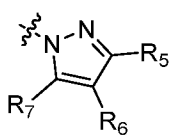
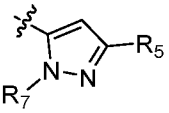
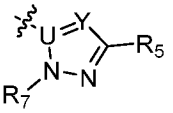
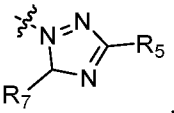
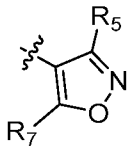
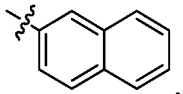
wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  .

26. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 24-25, wherein R_3 is selected from  ,  , and  .

27. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claims 24-26, wherein R_3 is selected from  ,  ,  ,  , and  .

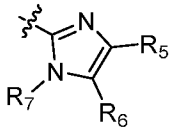
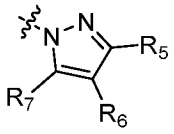
28. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 24-25, wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_3 is  .

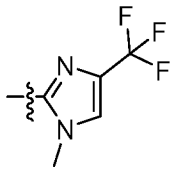
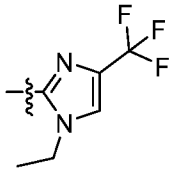
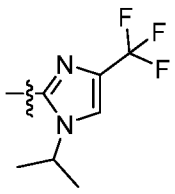
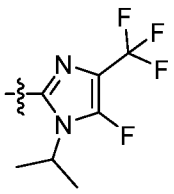
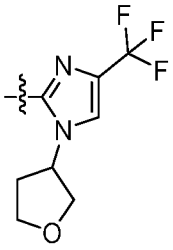
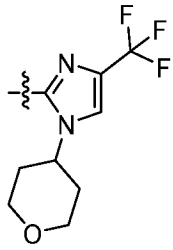
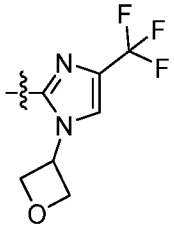
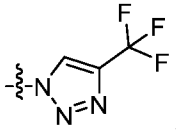
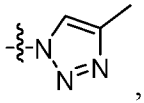
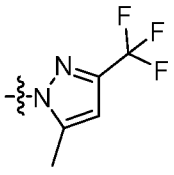
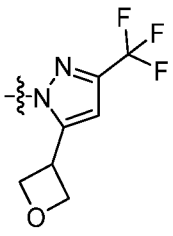
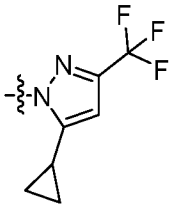
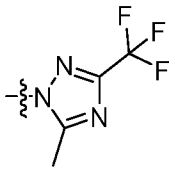
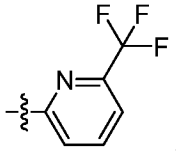
29. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 24-25, wherein when R_{3a} and R_{3b} combine to form a bridge, R_3 is  .

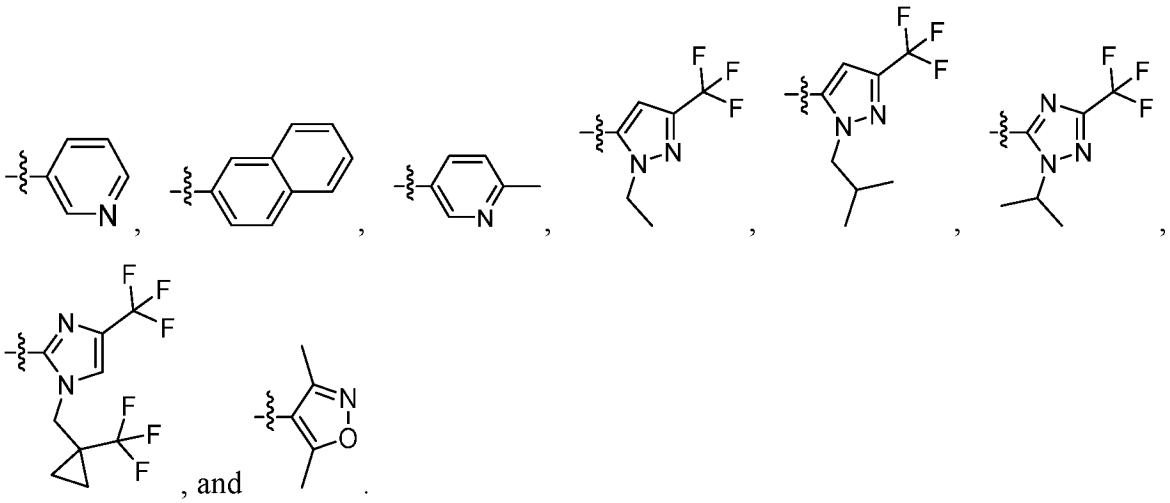
30. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claims 24-29, wherein R_4 is selected from  ,  ,  ,  ,  ,  ,  , and  , wherein U and Y are independently selected from C or N, and wherein when U is N, Y is C, and when U is C, Y is N or C;

wherein R_5, R_6, and R_7 are independently selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

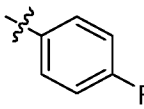
wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

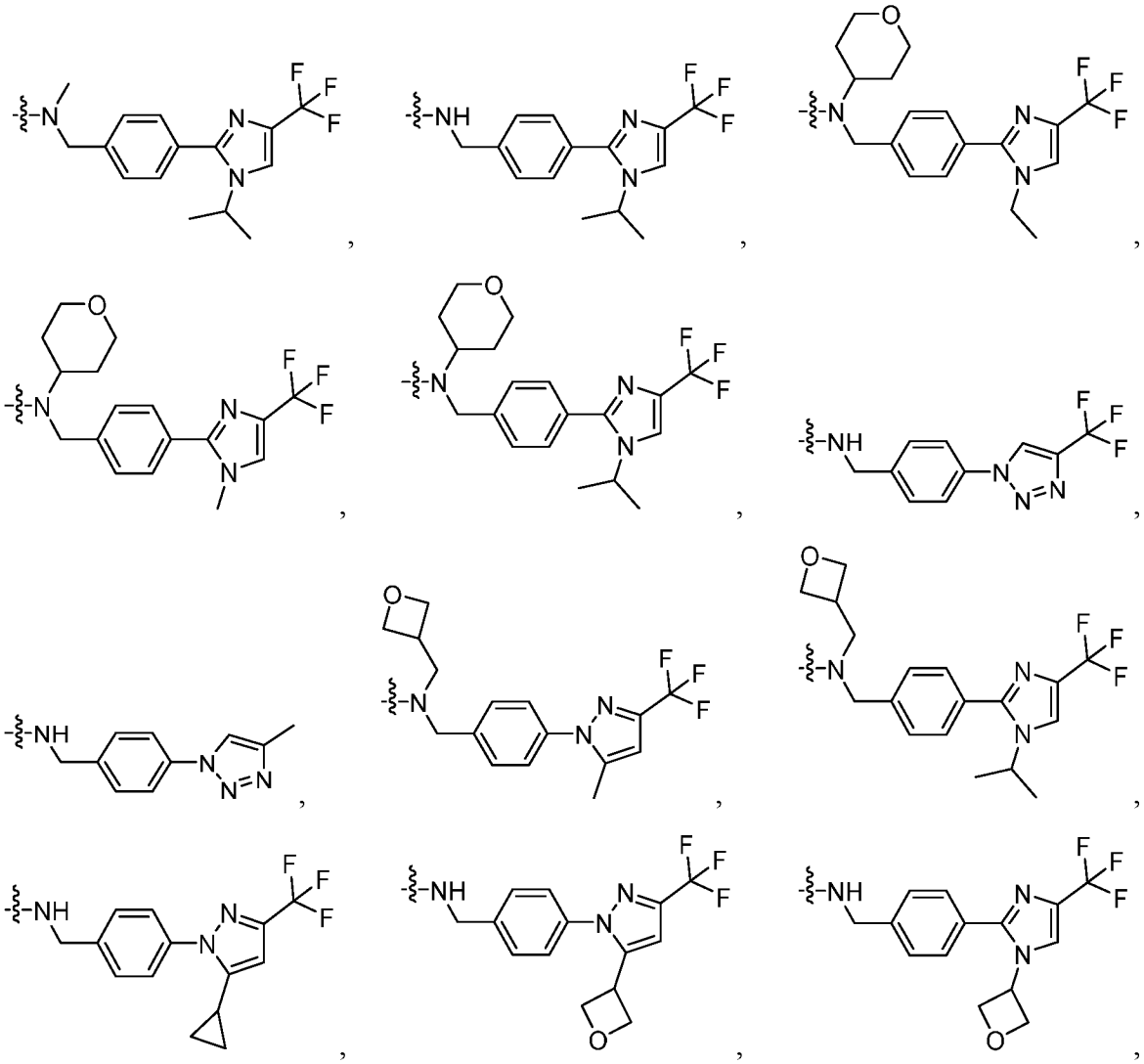
wherein when R_7 is a 4-, 5-, or 6- membered heterocyclyl ring, R_4 is  or  .

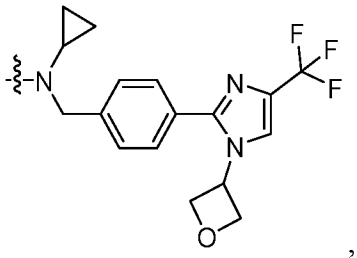
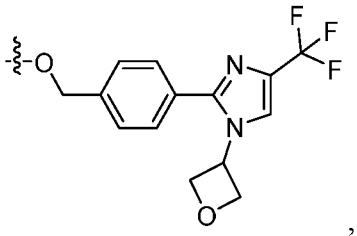
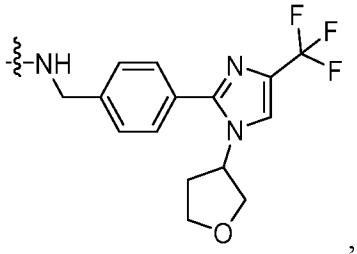
31. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 30, wherein R_4 is selected from:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , 

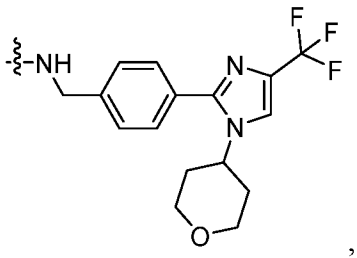
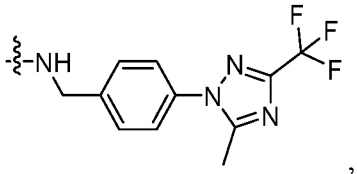
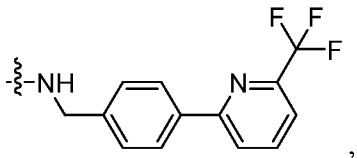


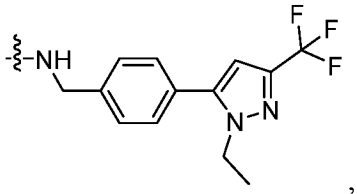
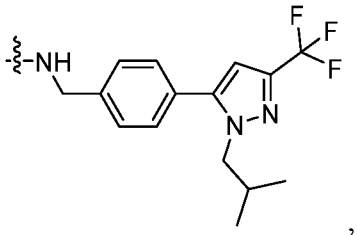
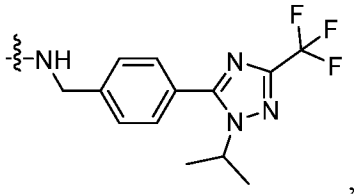
, and .

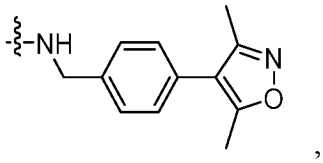
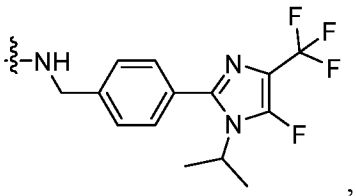
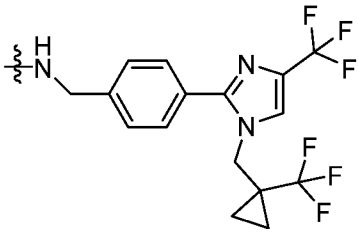
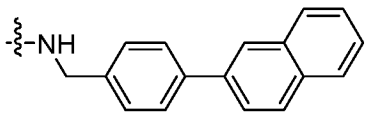
32. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any of claims 25-31, wherein when R_3 is  , R_1 is selected from:

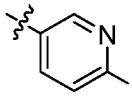
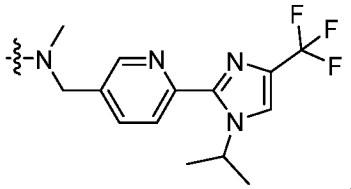


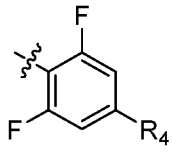
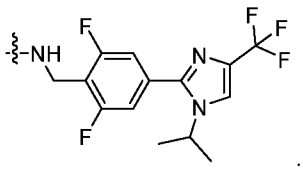
 ,  ,  ,

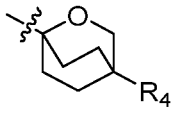
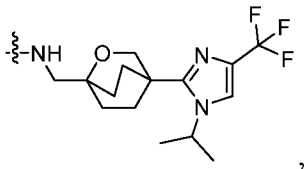
 ,  ,  ,

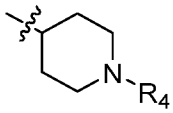
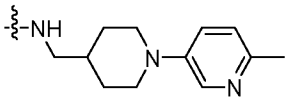
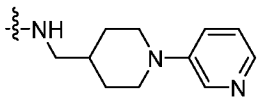
 ,  ,  ,

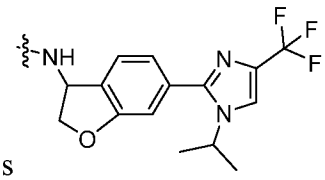
 ,  ,  , and  .

33. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any of claims 24-27 and 31, wherein when R_3 is  , R_1 is  .

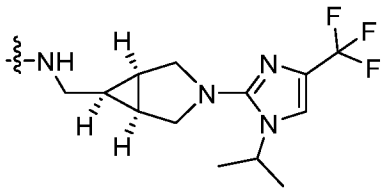
34. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any of claims 24-27 and 31, wherein when R_3 is  , R_1 is  .

35. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any of claims 24-27 and 31, wherein when R_3 is  , R_1 is  ,

36. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any of claims 24-37 and 31, wherein when R_3 is  , R_1 is selected from  and  .

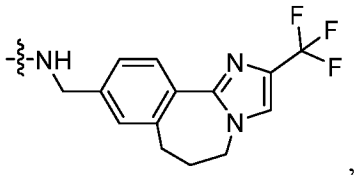
37. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claims 28 and 31, wherein when R_{3a} and R_2 form a bond to form a 5- or 6-membered heterocyclyl, R_1 is  .

38. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claims 29 and 31, wherein when R_{3a} and R_{3b} combine to form a bridge, R_1 is



.

39. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claims 24-30, wherein when R_{3c} forms a bond with R_5 or R_7 to form a 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl, wherein the 5-, 6-, 7-, 8-, 9-, 10-, 11-, or 12- membered heterocyclyl or C_5-C_{12} cycloalkyl is optionally substituted with one or more groups selected from C_1-C_6 alkyl, -OH, =O, C_1-C_6 alkoxy, and halogen, R_1 is selected from: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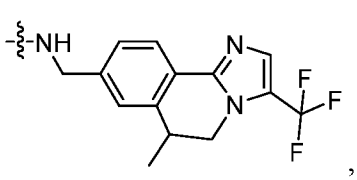
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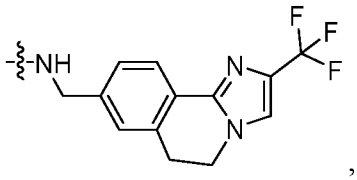
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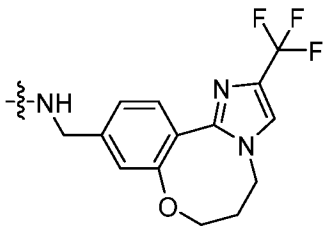
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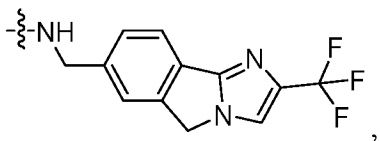
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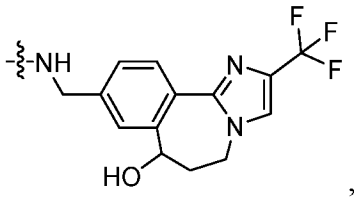
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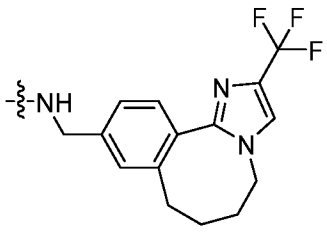
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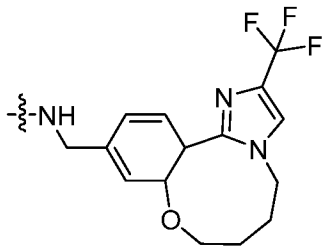
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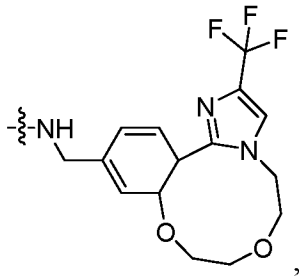
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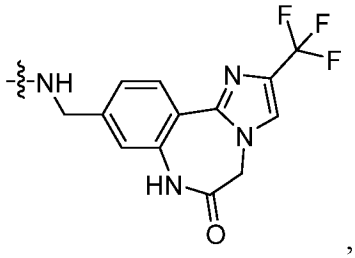
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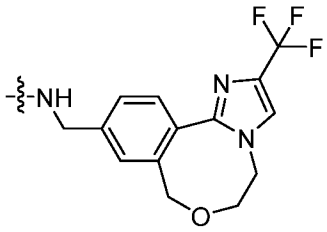
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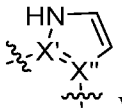
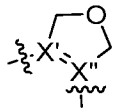
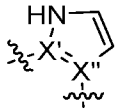
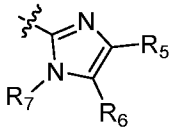
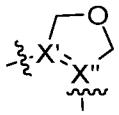
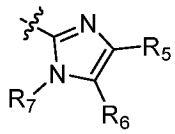
40. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any one of claim 24, wherein ring A is a 5- or 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S;

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C;

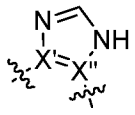
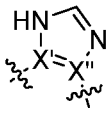
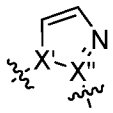
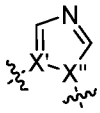
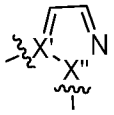
wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

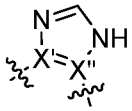
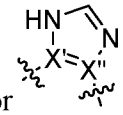
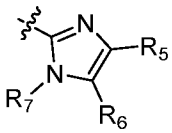
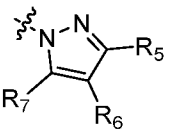
wherein the said C_{1-6} haloalkyl or C_4-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

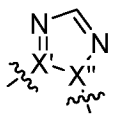
wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6}

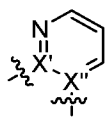
hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

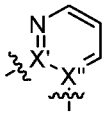
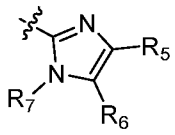
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N;

wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{2-6} alkyl, C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N;

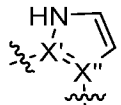
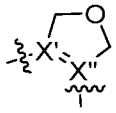
wherein when R ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N;

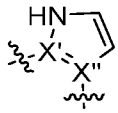
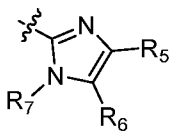
wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{2-6} alkyl, C_{1-6} haloalkyl or C_3-C_8 cycloalkyl ring are optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

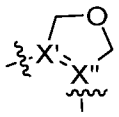
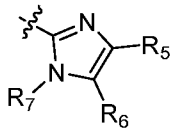
41. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 40, wherein Ring A is a 5- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S;

wherein when ring A is a 5-membered heterocyclyl ring and contains one heteroatom, ring A is selected from  where X' and X" are C and  where X' and X" are C;

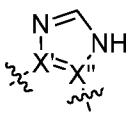
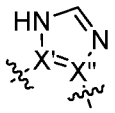
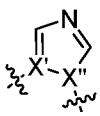
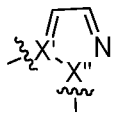
wherein when ring A is  where X' and X" are C, R_4 is  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{3-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6}

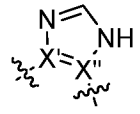
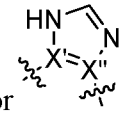
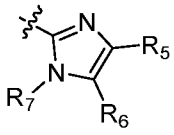
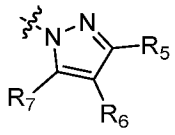
alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_4-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

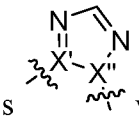
wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6-membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

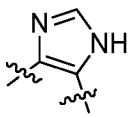
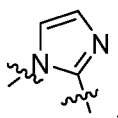
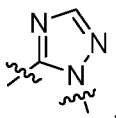
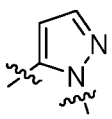
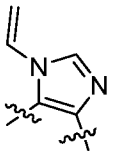
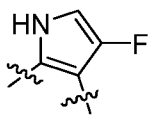
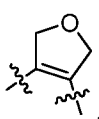
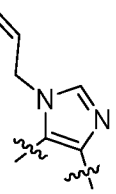
wherein when ring A is a 5-membered heterocyclyl ring and contains two heteroatoms, ring A is selected from  where X' and X" are C,  where X' and X" are C,  where X' is N and X" is C,  where X' is C and X" is N, and  where X' is C and X" is N;

wherein when  where X' and X" are C or  where X' and X" are C, R_4 is  or  , and Z is O, R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

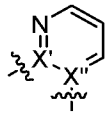
wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

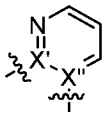
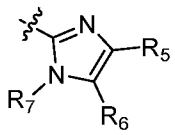
wherein when ring A is a 5-membered heterocyclyl ring and contains three heteroatoms, ring A is  where X' is C and X" is N;

wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

42. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 41, wherein ring A is selected from:  ,  ,  ,  ,  ,  ,  , and  .

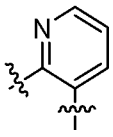
43. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 40, wherein Ring A is a 6- membered heterocyclyl ring comprising one to three heteroatoms selected from N, O, or S;

wherein when R ring A is 6-membered heterocyclyl ring, ring A is  where X' and X" are C and Z is N;

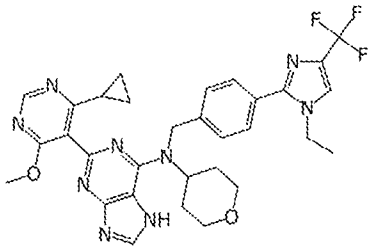
wherein when ring A is  where X' and X" are C and R_4 is  , R_7 is selected from -H, -OH, -COOH, $-NH_2$, -CN, halogen, C_{2-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said C_{1-6} haloalkyl is optionally substituted with one or more groups selected from -OH, -COOH, $-NH_2$, -CN, halogen, C_{1-6} alkyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{1-6} hydroxyalkyl, C_3-C_8 cycloalkyl ring, C_3-C_8 spiro-cycloalkyl, and 4-, 5-, or 6- membered heterocyclyl ring;

wherein the said ring A is optionally substituted with one or more groups selected from =O, C_{1-6} alkyl, C_2-C_6 alkenyl, and C_{2-6} alkynyl.

44. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to claim 42, wherein ring A is  .

45. The compound of formula (II), or a pharmaceutically acceptable salt thereof, according to any one of claims 24-44 wherein the compound is selected from: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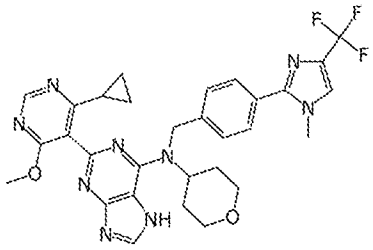
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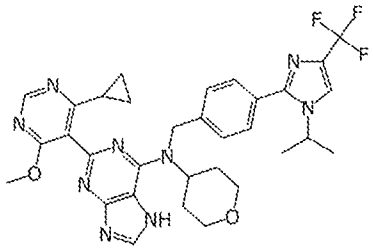
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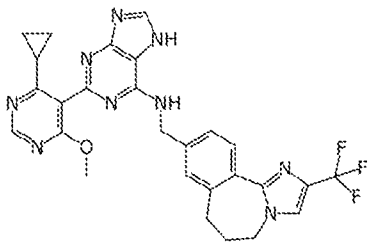
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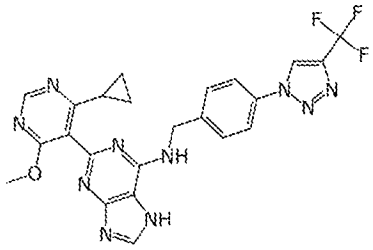
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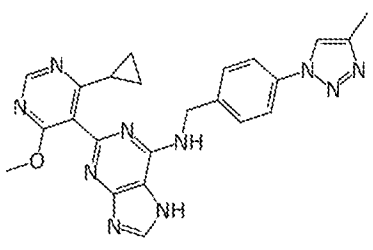
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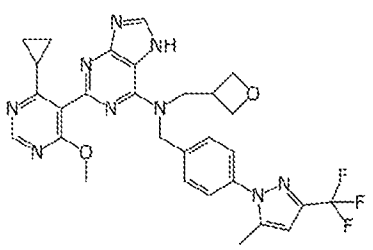
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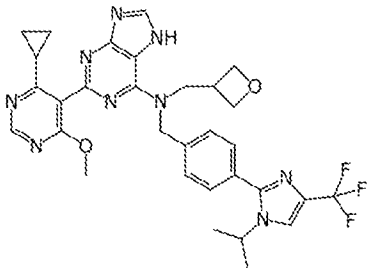
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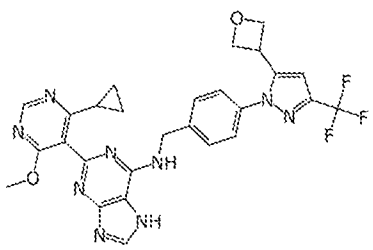
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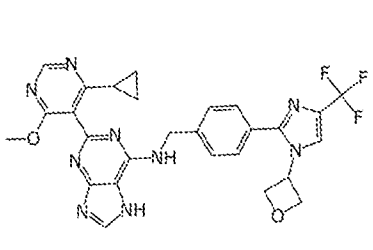
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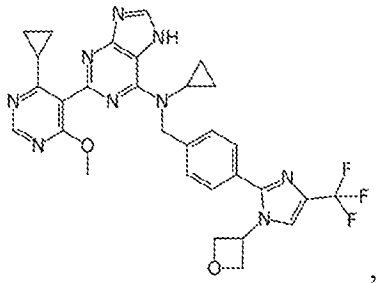
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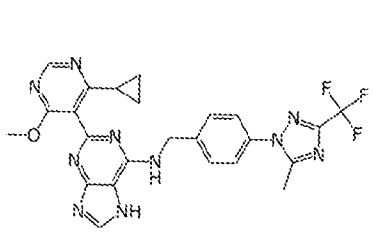
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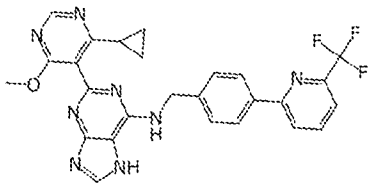
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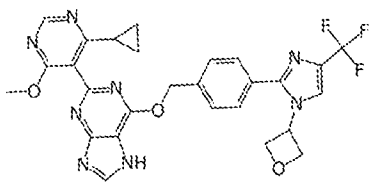
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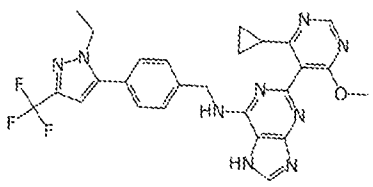
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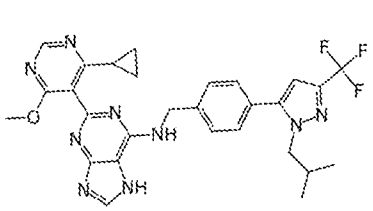
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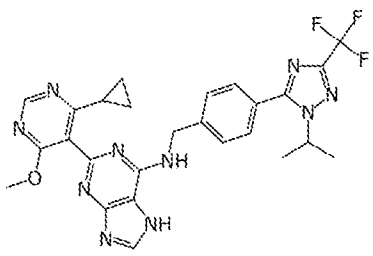
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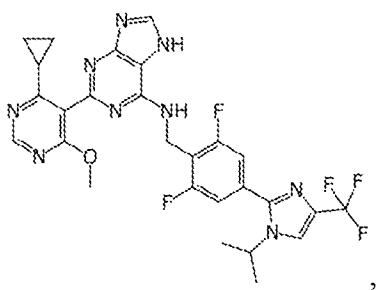
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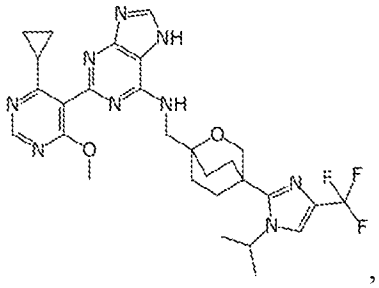
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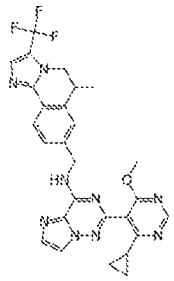
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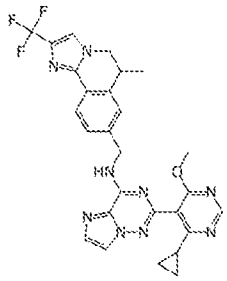
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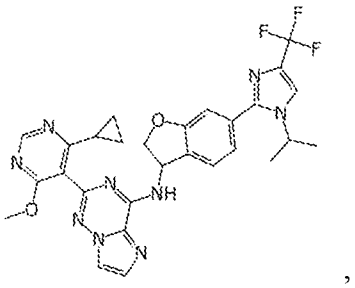
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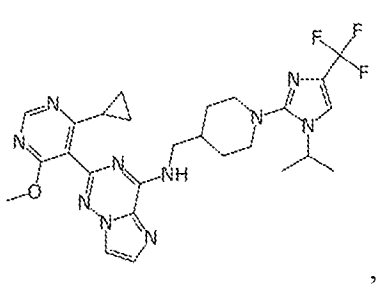
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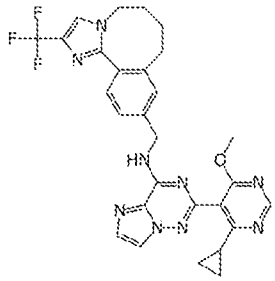
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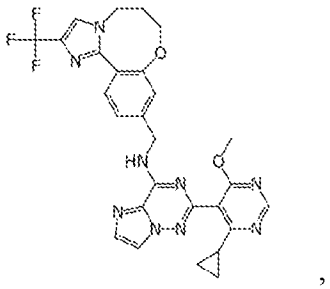
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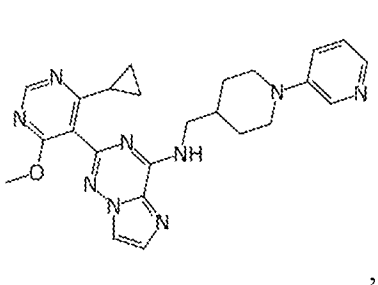
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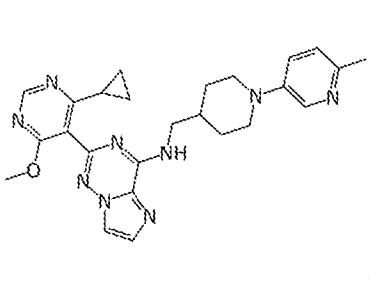
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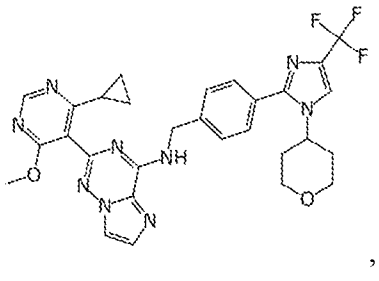
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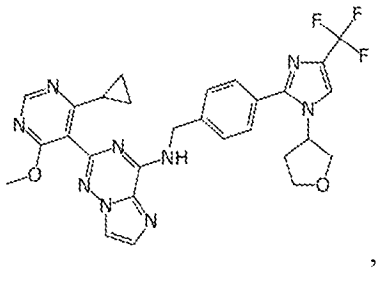
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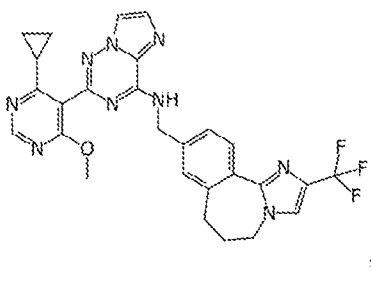
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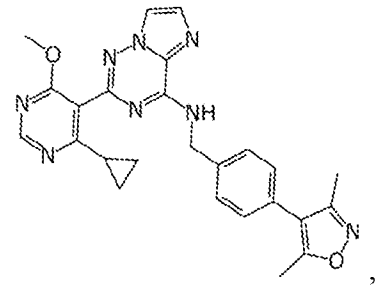
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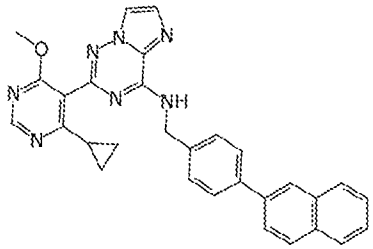
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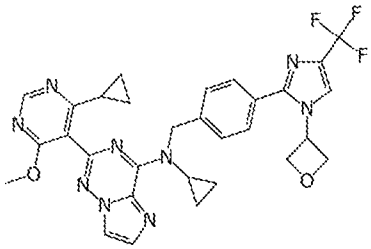
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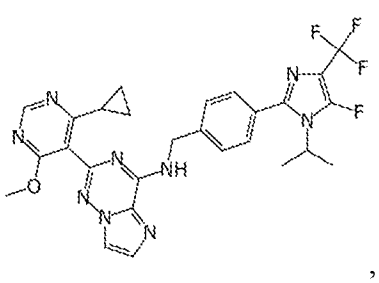
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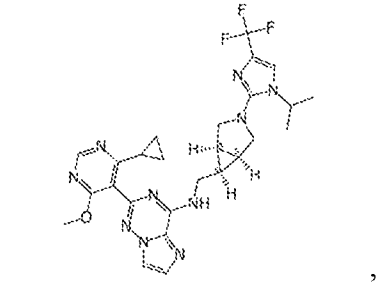
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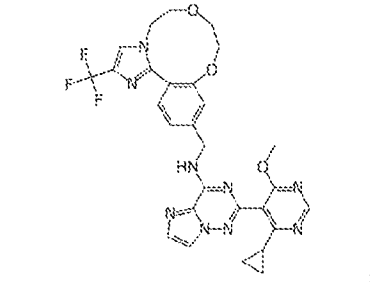
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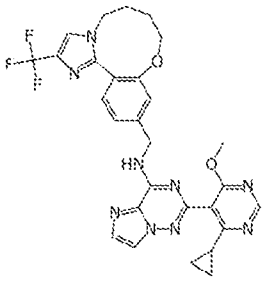
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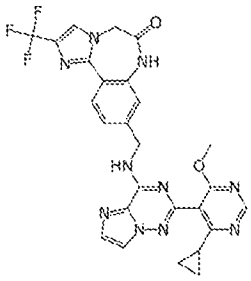
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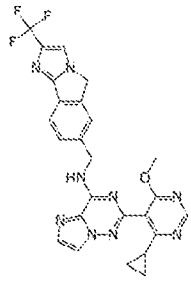
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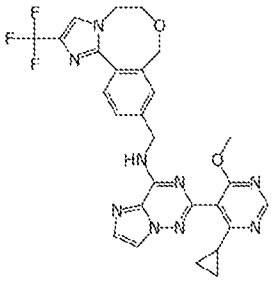
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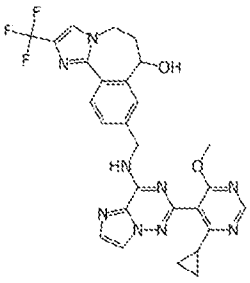
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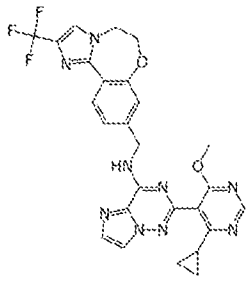
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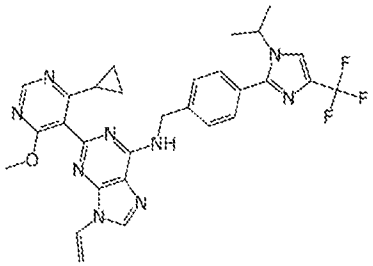
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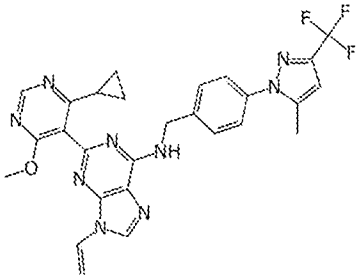
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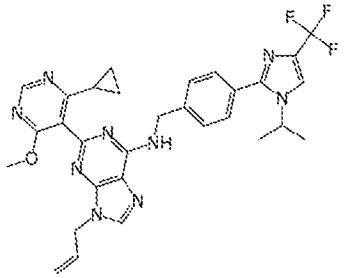
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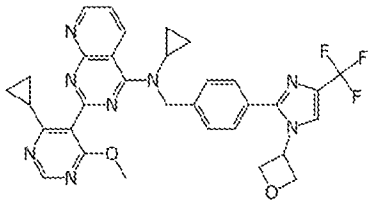
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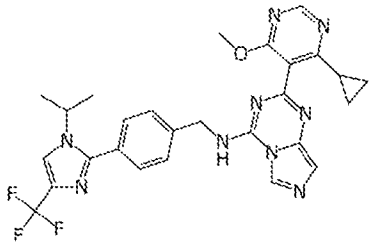
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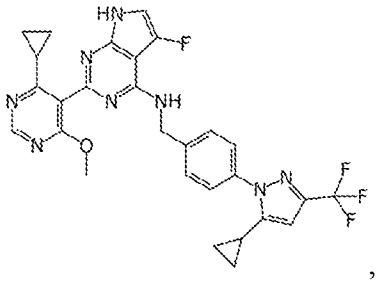
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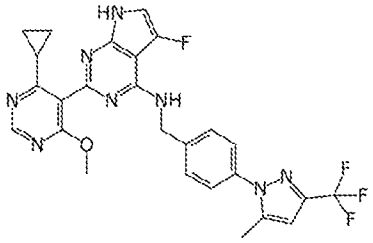
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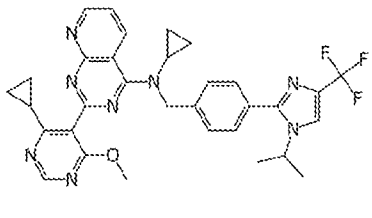
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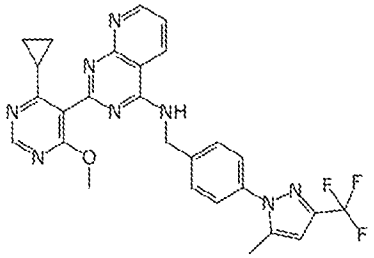
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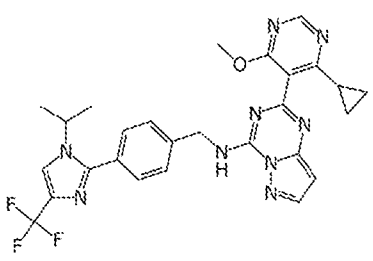
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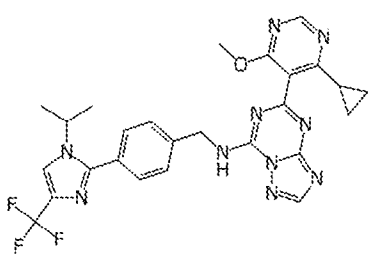
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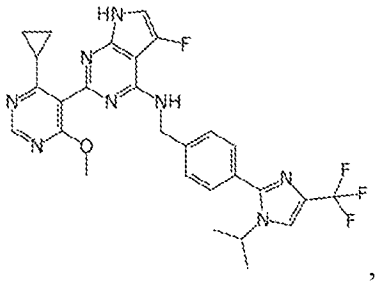
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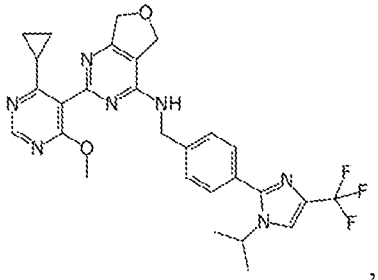
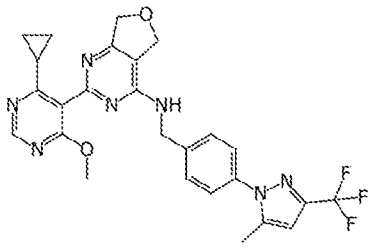
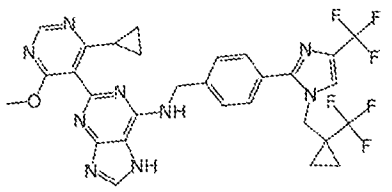
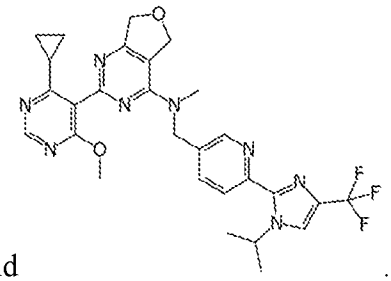
 ,  ,  , 

and .

46. A method of modulating USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-45.

47. A method of inhibiting USP1 activity in a subject, wherein the method comprises administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-45.

48. A method of treating a disorder or disease with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-45.

49. A method of treating cancer with a USP1 inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-45.

50. A method of treating cancer with a USP1 inhibitor in a subject, comprising administering a compound of formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1-45, wherein the cancer is characterized by over expression of USP1.

51. The method according to claim 50, wherein the cancer characterized by overexpression of USP1 is selected from prostate, breast, ovarian, non-small cell lung

cancer, mesothelioma, Merkel cell carcinoma, synovial sarcoma, renal cell carcinoma, and osteosarcoma.

52. The use of a compound, or pharmaceutically acceptable salt thereof, according to any one of claims 1-45, in the manufacture of a medicament for the treatment of cancer.

53. The use according to claim 52, of a compound or pharmaceutically acceptable salt thereof according to any one of claims 1-45, wherein the cancer is characterized by overexpression of USP1.

54. A process to manufacture a compound according to any one of claims 1-45, or a pharmaceutically acceptable salt thereof.

FIG. 1

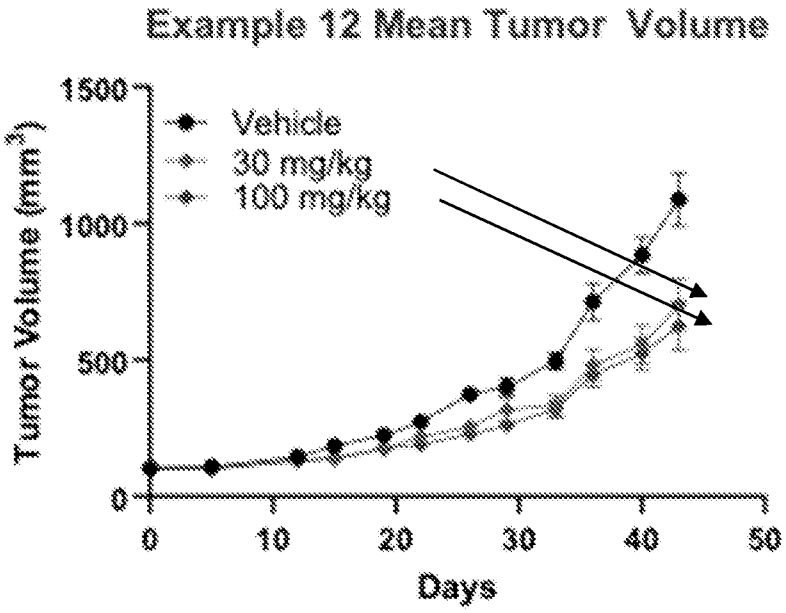

Example 12 Mean Tumor Volume
Tumor Volume (mm3)
1500
1000
500
0
Vehicle
30 mg/kg
100 mg/kg
0
10
20
30
40
50
Days

FIG. 2

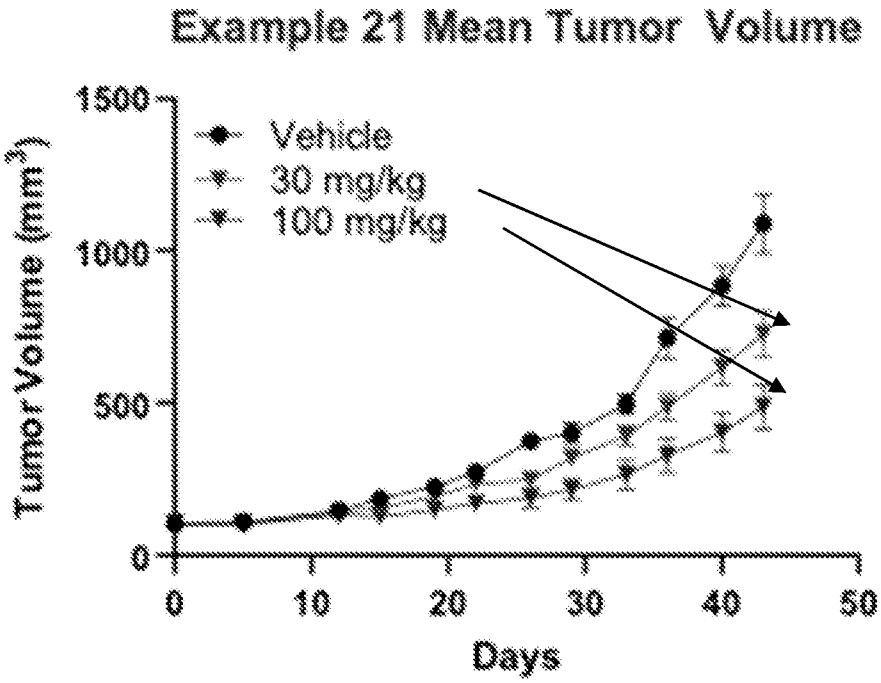

Example 21 Mean Tumor Volume
Tumor Volume (mm3)
1500
1000
500
0
Vehicle
30 mg/kg
100 mg/kg
0
10
20
30
40
50
Days

FIG. 3

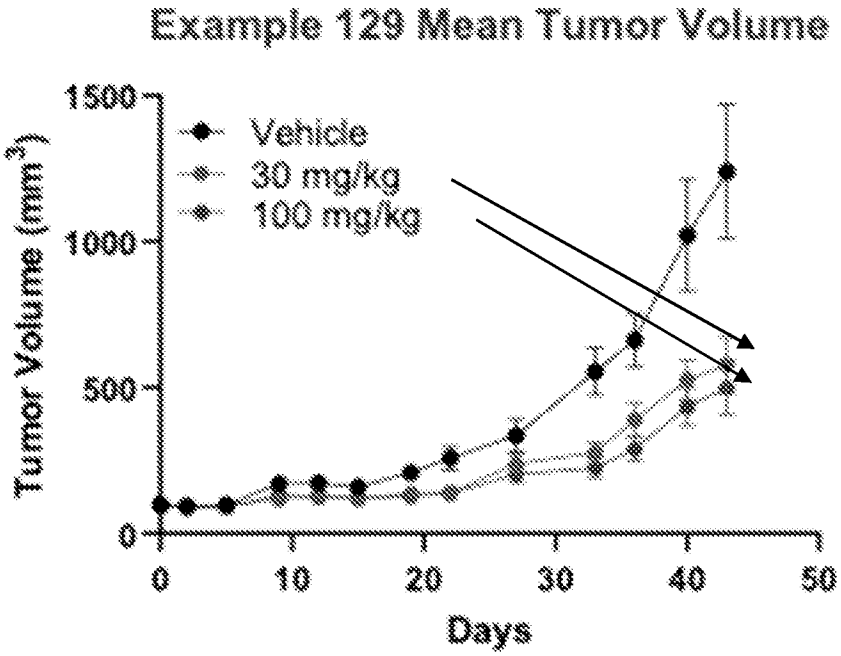
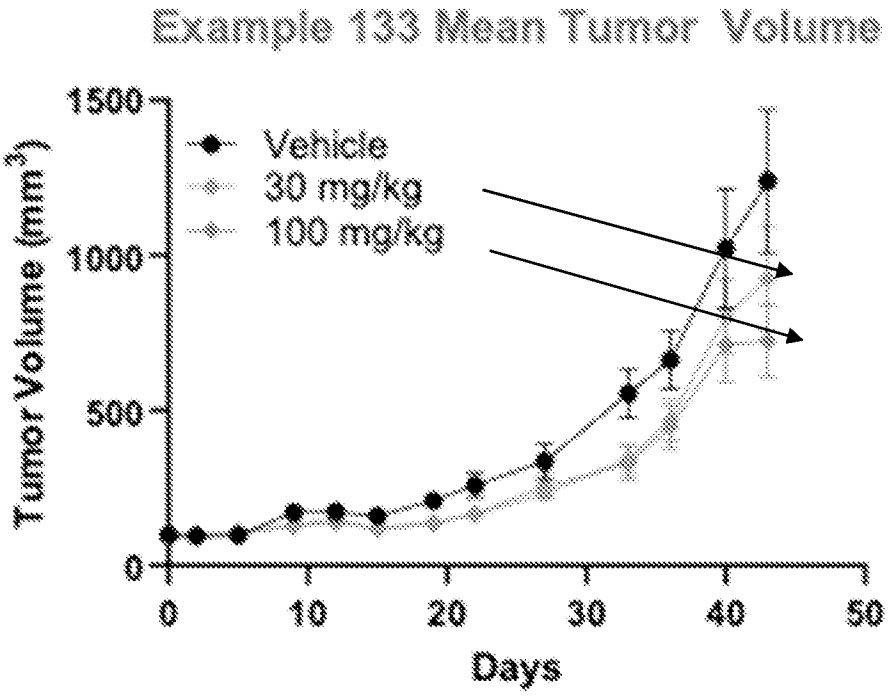

Example 129 Mean Tumor Volume
Tumor Volume (mm3)
1500
1000
500
0
Vehicle
30 mg/kg
100 mg/kg
0
10
20
30
40
50
Days

FIG. 4


Example 133 Mean Tumor Volume
Tumor Volume (mm3)
1500
1000
500
0
Vehicle
30 mg/kg
100 mg/kg
0
10
20
30
40
50
Days