

occurs.

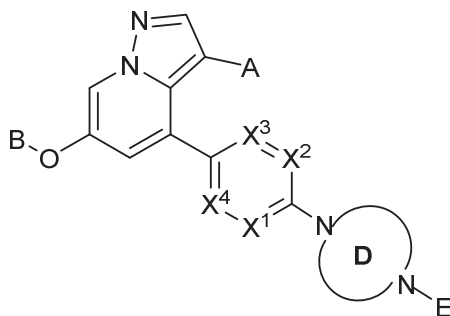
[0005] Upon binding of the ligand-co-receptor complex, RET dimerization and autophosphorylation on intracellular tyrosine residues recruits adaptor and signaling proteins to stimulate multiple downstream pathways. Adaptor protein binding to these docking sites leads to activation of Ras-MAPK and PI3K-Akt/mTOR signaling pathways or to recruitment of the CBL family of ubiquitin ligases that functions in RET downregulation of the RET-mediated functions.

[0006] Aberrant RET expression and/or activity have been demonstrated in different cancers and in gastrointestinal disorders such as irritable bowel syndrome (IBS).

SUMMARY

[0007] It has now been found that substituted pyrazolo[1,5-a]pyridine compounds are inhibitors of RET kinase, and are useful for treating diseases such as proliferative diseases including cancers.

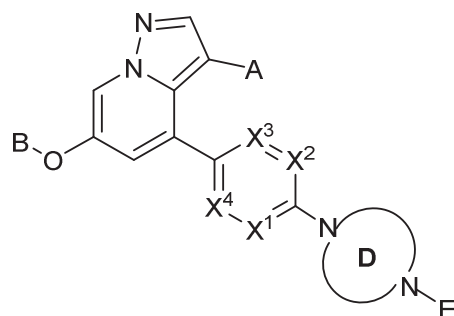
[0008] Accordingly, provided herein is a compound of the Formula **I**:



I

[0009] or pharmaceutically acceptable salt or solvate thereof, wherein A, B, X¹, X², X³, X⁴, and Ring D are as defined herein.

[0009a] In an aspect, there is provided a compound of the Formula **I**:



I

and pharmaceutically acceptable salts and solvates thereof, wherein:

X^1 , X^2 , X^3 and X^4 are independently CH, CF, CCH₃ or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

A is H, CN, Cl, CH₃-, CH₃CH₂-, cyclopropyl, -CH₂CN or -CH(CN)CH₃;

B is

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,
- (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
- (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (f) (R¹R²N)C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with OH and wherein R¹ and R² are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);
- (g) hetAr¹C1-C3 alkyl-, wherein hetAr¹ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;
- (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,
- (i) (hetCyc^a)C1-C3 alkyl-,
- (j) hetCyc^a-;
- (k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,
- (l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6

alkyl portions is optionally and independently substituted with 1-3 fluoros, or

(m) $(R^1R^2N)C(=O)C1-C6$ alkyl-, wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

hetCyc^a- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- and fluoro, or wherein hetCyc^a is substituted with oxo;

Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

E is

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (d) (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN - substituent wherein R^g and R^h are independently H or C1-C6 alkyl,
- (e) (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,
- (f) (C1-C6 alkoxy)C(=O)-,
- (g) (C3-C6 cycloalkyl)C(=O)-, wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O,
- (h) Ar^1C1-C6 alkyl-,
- (i) $Ar^1(C1-C6$ alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, R^mR^nN - or $R^mR^nN-CH_2$ - wherein each R^m and R^n is

independently H or C1-C6 alkyl,

(j) $\text{hetAr}^2\text{C1-C6 alkyl-}$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(k) $\text{hetAr}^2(\text{C1-C6 alkyl})\text{C(=O)-}$, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,

(l) $\text{hetAr}^2\text{C(=O)-}$,

(m) $\text{hetCyc}^1\text{C(=O)-}$,

(n) $\text{hetCyc}^1\text{C1-C6 alkyl-}$,

(o) $\text{R}^3\text{R}^4\text{NC(=O)-}$,

(p) $\text{Ar}^1\text{N(R}^3)\text{C(=O)-}$,

(q) $\text{hetAr}^2\text{N(R}^3)\text{C(=O)-}$,

(r) $(\text{C1-C6 alkyl})\text{SO}_2-$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(s) Ar^1SO_2- ,

(t) $\text{hetAr}^2\text{SO}_2-$,

(u) $\text{N-(C1-C6 alkyl)pyridinonyl}$,

(v) $\text{Ar}^1\text{C(=O)-}$,

(w) $\text{Ar}^1\text{O-C(=O)-}$,

(x) $(\text{C3-C6 cycloalkyl})(\text{C1-C6 alkyl})\text{C(=O)-}$,

(y) $(\text{C3-C6 cycloalkyl})(\text{C1-C6 alkyl})\text{SO}_2-$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,

(z) $\text{Ar}^1(\text{C1-C6 alkyl})\text{SO}_2-$,

(aa) $\text{hetCyc}^1\text{-O-C(=O)-}$,

(bb) $\text{hetCyc}^1\text{CH}_2\text{C(=O)-}$,

(cc) hetAr^2 , or

(dd) C3-C6 cycloalkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), $\text{R}^e\text{R}^f\text{N-}$ wherein R^e and R^f are independently H or C1-C6 alkyl,, $(\text{R}^p\text{R}^q\text{N})\text{C1-C6 alkoxy-}$ wherein R^p and R^q are independently H or C1-C6 alkyl, and $(\text{hetAr}^a)\text{C1-C6 alkyl-}$ wherein hetAr^a is a 5-6 membered heteroaryl ring

having 1-2 ring nitrogen atoms, or Ar¹ is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

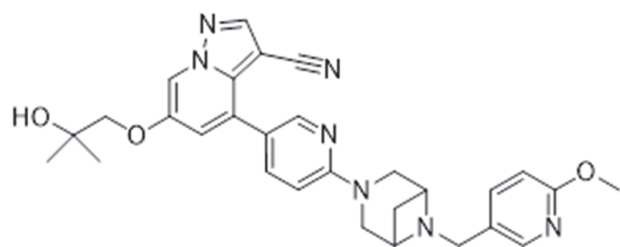
hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr² is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl;

hetCyc¹ is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and halogen;

R³ is H or C1-C6 alkyl; and

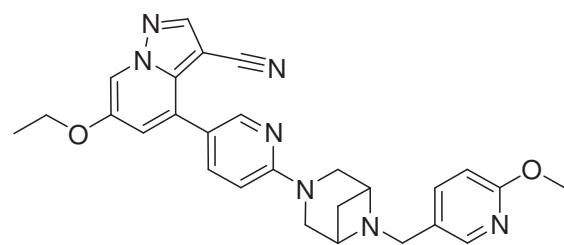
R⁴ is C1-C6 alkyl.

[0009b] In another aspect, there is provided a compound which is



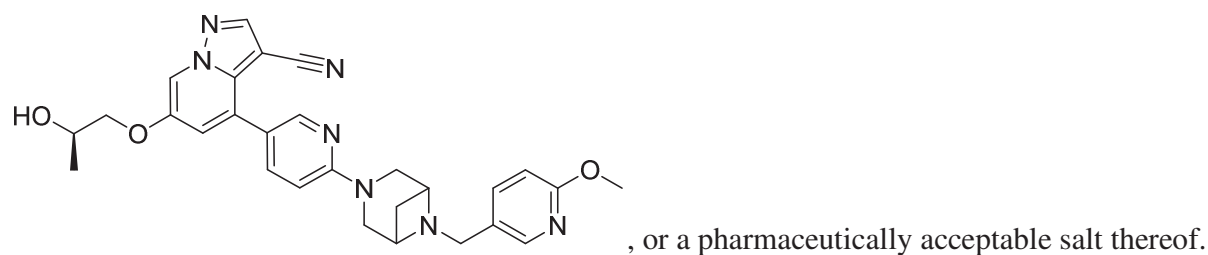
, or a pharmaceutically acceptable salt thereof.

[0009c] In another aspect, there is provided a compound which is

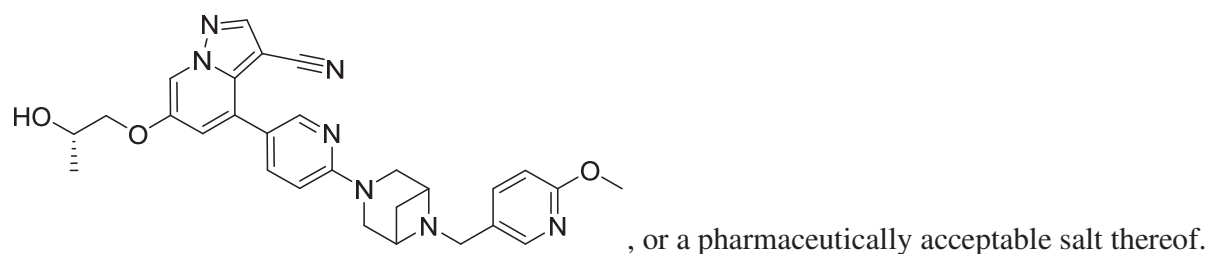


, or a pharmaceutically acceptable salt thereof.

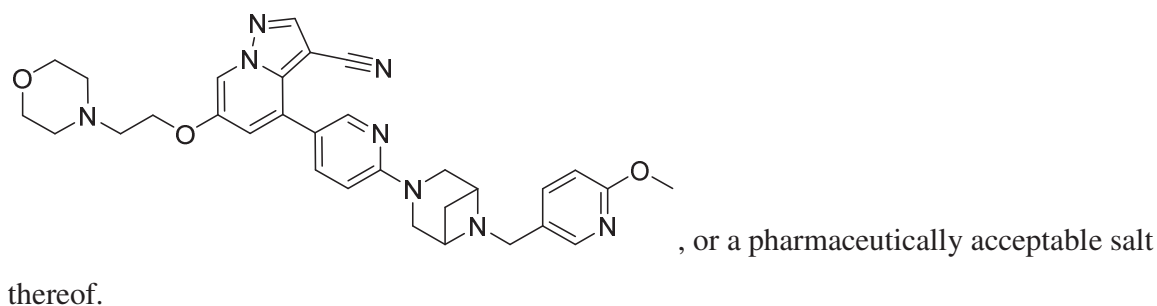
[0009d] In another aspect, there is provided a compound which is



[0009e] In another aspect, there is provided a compound which is



[0009f] In another aspect, a compound which is



[0010] Also provided herein is a pharmaceutical composition comprising a compound of Formula **I** or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable diluent or carrier.

[0010a] In another aspect, there is provided a pharmaceutical composition, comprising a

compound, or a pharmaceutically acceptable salt thereof disclosed herein, in admixture with a pharmaceutically acceptable diluent or carrier.

[0011] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0012] Also provided herein is a method of treating a RET-associated disease or disorder

in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0013] Also provided herein is a method of treating cancer and/or inhibiting metastasis associated with a particular cancer in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0013a] In another aspect, there is provided use of a compound disclosed herein or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

[0014] Also provided herein is a method of treating irritable bowel syndrome (IBS) and/or pain associated with IBS in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0015] Also provided is a method of providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein.

[0016] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein for use in therapy.

[0017] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of cancer and/or inhibiting metastasis associated with a particular cancer.

[0018] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use in the treatment of irritable bowel syndrome (IBS) or pain associated with IBS.

[0019] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof as defined herein for use providing supportive care to a cancer patient, including preventing or minimizing gastrointestinal disorders, such as diarrhea, associated with treatment, including chemotherapeutic treatment.

[0020] Also provided herein is a compound of Formula I or a pharmaceutically acceptable

inhibitor).

[0033] Also provided are methods of treating an individual with a RET-associated cancer that include administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, before, during, or after administration of another anticancer drug (e.g., a first RET kinase inhibitor).

[0034] Also provided herein is a method for treating irritable bowel syndrome (IBS) in a patient in need thereof, the method comprising (a) determining if the IBS is associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same; and (b) if the IBS is determined to be associated with a dysregulation of a RET gene, a RET kinase, or expression or activity or level of any of the same, administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof.

[0035] Also provided herein is a pharmaceutical combination for treating irritable bowel syndrome (IBS) in a patient in need thereof, which comprises administering (a) a compound of General Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier, for simultaneous, separate or sequential use for the treatment of IBS, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the IBS. Also provided herein is a pharmaceutical composition comprising such a combination. Also provided herein is the use of such a combination for the preparation of a medicament for the treatment of the IBS. Also provided herein is a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of the IBS a patient in need thereof.

[0036] Also provided herein is a process for preparing a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0037] Also provided herein is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof obtained by a process of preparing the compound as defined herein.

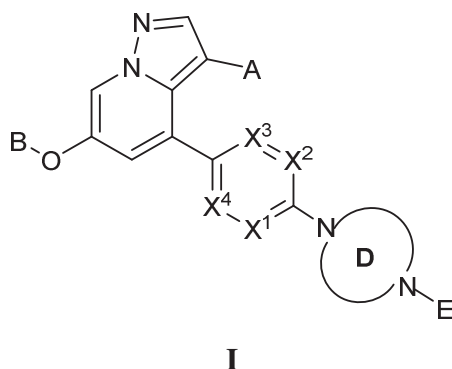
[0038] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Methods and materials are described herein for use in the present disclosure; other,

suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0039] Other features and advantages of the disclosure will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0040] Provided herein is a compound of the Formula I:



[0041] and pharmaceutically acceptable salts and solvates thereof, wherein:

[0042] X^1 , X^2 , X^3 and X^4 are independently CH, CF, CCH₃ or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

[0043] A is H, CN, Cl, CH₃-, CH₃CH₂-, cyclopropyl, -CH₂CN or -CH(CN)CH₃;

[0044] B is

[0045] (a) hydrogen,

[0046] (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,

[0047] (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,

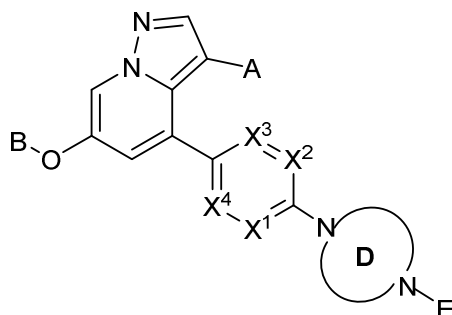
[0048] (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,

[0049] (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,

[0050] (f) (R¹R²N)C1-C6 alkyl- wherein said alkyl portion is optionally substituted with OH and wherein R¹ and R² are independently H or C1-C6 alkyl (optionally substituted with 1-3

What is claimed is:

1. A compound of the Formula I:



I

and pharmaceutically acceptable salts and solvates thereof, wherein:

X^1 , X^2 , X^3 and X^4 are independently CH, CF, CCH_3 or N, wherein zero, one or two of X^1 , X^2 , X^3 and X^4 is N;

A is H, CN, Cl, CH_3 -, CH_3CH_2 -, cyclopropyl, $-CH_2CN$ or $-CH(CN)CH_3$;

B is

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) hydroxyC2-C6 alkyl-, wherein the alkyl portion is optionally substituted with 1-3 fluoros or a C3-C6 cycloalkylidene ring,
- (d) dihydroxyC3-C6 alkyl-, wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring,
- (e) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (f) (R^1R^2N)C1-C6 alkyl-, wherein said alkyl portion is optionally substituted with OH and wherein R^1 and R^2 are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);
- (g) $hetAr^1$ C1-C3 alkyl-, wherein $hetAr^1$ is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S and is optionally substituted with one or more independently selected C1-C6 alkyl substituents;
- (h) (C3-C6 cycloalkyl)C1-C3 alkyl-, wherein said cycloalkyl is optionally substituted with OH,
- (i) ($hetCyc^a$)C1-C3 alkyl-,

- (j) hetCyc^a-;
- (k) C3-C6 cycloalkyl-, wherein said cycloalkyl is optionally substituted with OH,
- (l) (C1-C4 alkyl)C(=O)O-C1-C6 alkyl-, wherein each of the C1-C4 alkyl and C1-C6 alkyl portions is optionally and independently substituted with 1-3 fluoros, or
- (m) (R¹R²N)C(=O)C1-C6 alkyl-, wherein R¹ and R² are independently H or C1-C6 alkyl (optionally substituted with 1-3 fluoros);

hetCyc^a- is a 4-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O and optionally substituted with one or more substituents independently selected from OH, C1-C6 alkyl (optionally substituted with 1-3 fluoros), hydroxyC1-C6 alkyl-, C1-C6 alkoxy, (C1-C6 alkyl)C(=O)-, (C1-C6 alkoxy)C1-C6 alkyl- and fluoro, or wherein hetCyc^a is substituted with oxo;

Ring D is (i) a saturated 4-7 membered heterocyclic ring having two ring nitrogen atoms, (ii) a saturated 7-9 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, (iii) a saturated 7-11 membered heterospirocyclic ring having two ring nitrogen atoms, or (iv) a saturated 9-10 membered bicyclic fused heterocyclic ring having two ring nitrogen atoms, wherein each of said rings is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group;

E is

- (a) hydrogen,
- (b) C1-C6 alkyl optionally substituted with 1-3 fluoros,
- (c) (C1-C6 alkoxy)C1-C6 alkyl- optionally substituted with 1-3 fluoros,
- (d) (C1-C6 alkyl)C(=O)-, wherein said alkyl portion is optionally substituted with 1-3 fluoros or with a R^gR^hN- substituent wherein R^g and R^h are independently H or C1-C6 alkyl,
- (e) (hydroxyC2-C6 alkyl)C(=O)- optionally substituted with 1-3 fluoros,
- (f) (C1-C6 alkoxy)C(=O)-,
- (g) (C3-C6 cycloalkyl)C(=O)-, wherein said cycloalkyl is optionally substituted with one or more substituents independently selected from C1-C6 alkyl, C1-C6 alkoxy, OH, and (C1-C6 alkoxy)C1-C6 alkyl-, or said cycloalkyl is substituted with a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N and O,

- (h) $\text{Ar}^1\text{C1-C6 alkyl-}$,
- (i) $\text{Ar}^1(\text{C1-C6 alkyl})\text{C(=O)-}$, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl-, C1-C6 alkoxy, $\text{R}^m\text{R}^n\text{N-}$ or $\text{R}^m\text{R}^n\text{N-CH}_2\text{-}$ wherein each R^m and R^n is independently H or C1-C6 alkyl,
- (j) $\text{hetAr}^2\text{C1-C6 alkyl-}$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,
- (k) $\text{hetAr}^2(\text{C1-C6 alkyl})\text{C(=O)-}$, wherein said alkyl portion is optionally substituted with OH, hydroxyC1-C6 alkyl- or C1-C6 alkoxy,
- (l) $\text{hetAr}^2\text{C(=O)-}$,
- (m) $\text{hetCyc}^1\text{C(=O)-}$,
- (n) $\text{hetCyc}^1\text{C1-C6 alkyl-}$,
- (o) $\text{R}^3\text{R}^4\text{NC(=O)-}$,
- (p) $\text{Ar}^1\text{N(R}^3\text{)C(=O)-}$,
- (q) $\text{hetAr}^2\text{N(R}^3\text{)C(=O)-}$,
- (r) $(\text{C1-C6 alkyl})\text{SO}_2\text{-}$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,
- (s) $\text{Ar}^1\text{SO}_2\text{-}$,
- (t) $\text{hetAr}^2\text{SO}_2\text{-}$,
- (u) $\text{N-(C1-C6 alkyl)pyridinonyl}$,
- (v) $\text{Ar}^1\text{C(=O)-}$,
- (w) $\text{Ar}^1\text{O-C(=O)-}$,
- (x) $(\text{C3-C6 cycloalkyl})(\text{C1-C6 alkyl})\text{C(=O)-}$,
- (y) $(\text{C3-C6 cycloalkyl})(\text{C1-C6 alkyl})\text{SO}_2\text{-}$, wherein the alkyl portion is optionally substituted with 1-3 fluoros,
- (z) $\text{Ar}^1(\text{C1-C6 alkyl})\text{SO}_2\text{-}$,
- (aa) $\text{hetCyc}^1\text{-O-C(=O)-}$,
- (bb) $\text{hetCyc}^1\text{CH}_2\text{C(=O)-}$,
- (cc) hetAr^2 , or
- (dd) C3-C6 cycloalkyl;

Ar^1 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), $\text{R}^e\text{R}^f\text{N-}$ wherein R^e and R^f are independently H or C1-C6 alkyl,, $(\text{R}^p\text{R}^q\text{N})\text{C1-C6 alkoxy-}$ wherein R^p and R^q are independently H

or C1-C6 alkyl, and (hetAr^a)C1-C6 alkyl- wherein hetAr^a is a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms, or Ar¹ is a phenyl ring fused to a 5-6 membered heterocyclic ring having 1-2 ring heteroatoms independently selected from N and O;

hetAr² is a 5-6 membered heteroaryl ring having 1-3 ring heteroatoms independently selected from N, O and S or a 9-10 membered bicyclic heteroaryl ring having 1-3 ring nitrogen atoms, wherein hetAr² is optionally substituted with one or more substituents independently selected from the group consisting of halogen, CN, C1-C6 alkyl (optionally substituted with 1-3 fluoros), C1-C6 alkoxy (optionally substituted with 1-3 fluoros), (C1-C6 alkoxy)C1-C6 alkyl- (optionally substituted with 1-3 fluoros), R^eR^fN- wherein R^e and R^f are independently H or C1-C6 alkyl, OH, (C1-C6 alkoxy)C1-C6 alkoxy- and C3-C6 cycloalkyl;

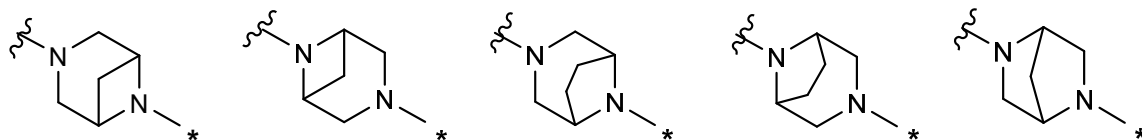
hetCyc¹ is a 4-6 membered saturated heterocyclic ring having 1-2 ring heteroatoms independently selected from N, O and S wherein said heterocyclic ring is optionally substituted with one or more substituents independently selected from C1-C6 alkoxy and halogen;

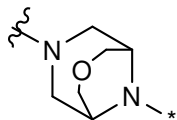
R³ is H or C1-C6 alkyl; and

R⁴ is C1-C6 alkyl.

2. A compound according to claim 1, wherein Ring D is a saturated 7-8 membered bridged heterocyclic ring having two ring nitrogen atoms and optionally having a third ring heteroatom which is oxygen, wherein said ring is optionally substituted with (a) one to four groups independently selected from halogen, OH, C1-C3 alkyl which is optionally substituted with 1-3 fluoros, or C1-C3 alkoxy which is optionally substituted with 1-3 fluoros, (b) a C3-C6 cycloalkylidene ring, or (c) an oxo group.

3. A compound according to claim 2, wherein Ring D is

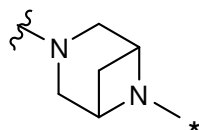




or

wherein the wavy line indicates the point of attachment of Ring D to the ring comprising X^1 , X^2 , X^3 and X^4 , and the asterisk indicates the point of attachment to E.

4. A compound according to claim 3, wherein Ring D is



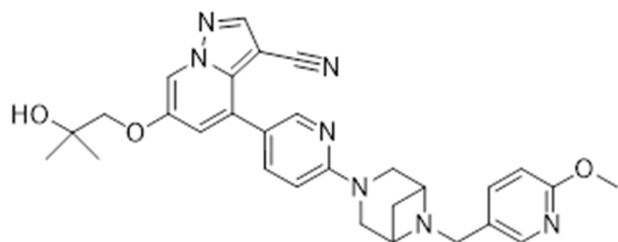
5. A compound according to any one of claims 1-4, wherein B is hydroxyC2-C6 alkyl- wherein the alkyl portion is optionally substituted with a C3-C6 cycloalkylidene ring.

6. A compound according to any one of claims 1-4, wherein B is (hetCyc^a)C1-C3 alkyl-.

7. A compound according to any one of claims 1-6, wherein X^1 is N, and X^2 , X^3 and X^4 are CH.

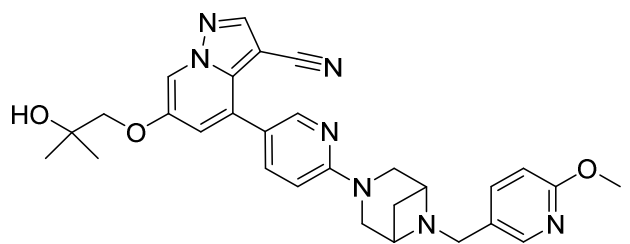
8. A compound according to any one of claims 1-7, wherein A is CN.

9. A compound which is

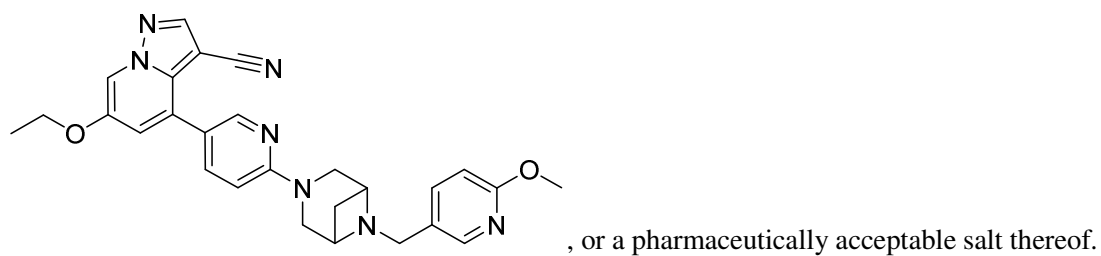


, or a pharmaceutically acceptable salt thereof.

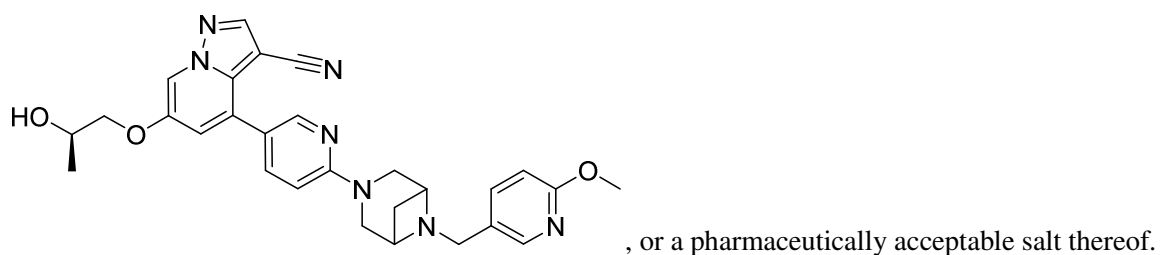
10. The compound of claim 9, which is



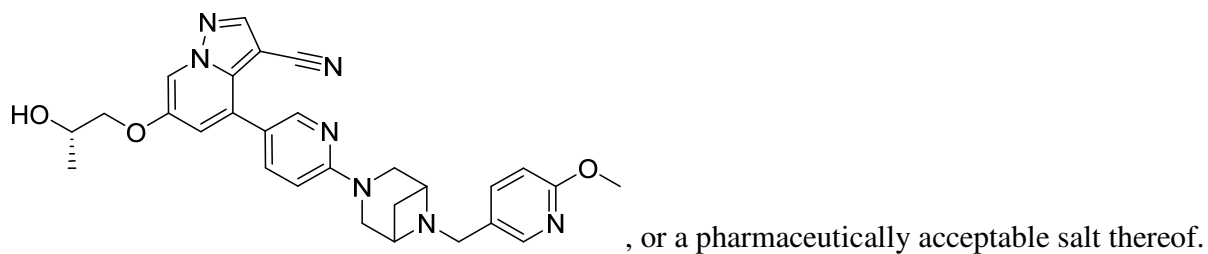
11. A compound which is



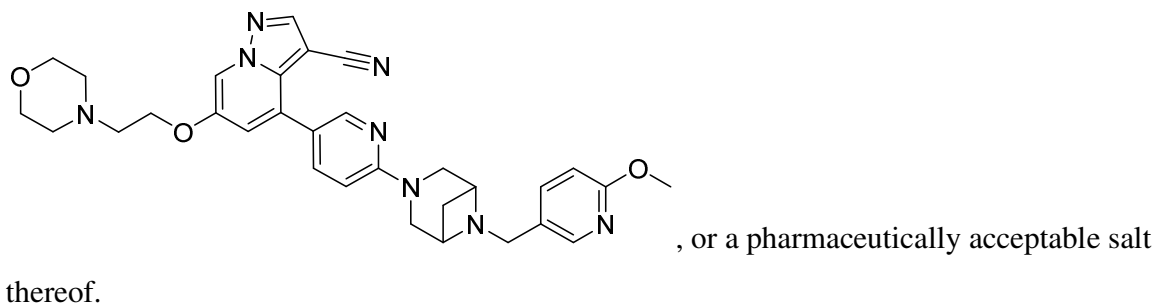
12. A compound which is



13. A compound which is



14. A compound which is



15. A pharmaceutical composition, comprising a compound, or a pharmaceutically acceptable salt thereof, according to any one of claims 1-14, in admixture with a pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition, comprising a compound, or pharmaceutically acceptable salt thereof, according to any one of claim 8 to 14 in admixture with a pharmaceutically acceptable diluent or carrier.

17. Use of a compound of any one of claims 1-14 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

18. The use according to claim 17, for the manufacture of a medicament for treating a RET-associated cancer in a patient.

19. The use of claim 18, wherein the RET-associated cancer is a cancer having a dysregulation in a RET gene, a RET kinase protein, or expression or activity or level of any of the same.

20. The use of any one of claims 18-19, wherein the RET-associated cancer is selected from the group consisting of: lung cancer, papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer, papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, and cervical cancer.

21. The use of claim 20, wherein the lung cancer is RET fusion lung cancer or the cancer is medullary thyroid cancer.

22. The use of claim 20, wherein the lung cancer is small cell lung carcinoma, non-small cell lung cancer, bronchioles lung cell carcinoma, or lung adenocarcinoma.

23. The use of any one of claims 17-22, wherein the medicament is formulated for oral administration.