

agonists in normal lung fibroblasts, pro-fibrotic responses were observed via activation of S1PR2 and S1PR3, which suggests that antagonists of the specific S1P receptors S1P2R and S1P3R may be particularly beneficial in reducing fibrosis (Sobel et al., 2013).

[0008] Fibrosis is a process that can be triggered by chronic tissue damage because of toxic substances, viral infection, inflammation, or mechanical stress (Nanthakumar et al., 2015); and may be defined as the abnormal or excessive production and accumulation of extracellular matrix (ECM).

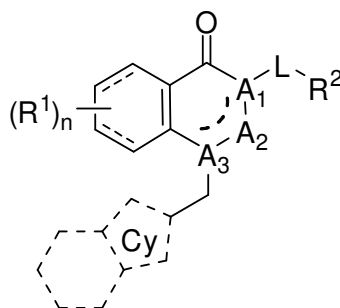
[0009] In particular, fibrosis is a key driver of progressive organ dysfunction in many inflammatory and metabolic diseases, including idiopathic pulmonary fibrosis, advanced liver disease (e.g. non-alcoholic steatohepatitis (NASH)) and advanced kidney disease. These conditions remain poorly treated despite advances in the understanding of the disease mechanism and, more recently, an increase in the number of clinical trials reflecting the need to identify new treatments, particularly in IPF (Nanthakumar et al., 2015). In the case of IPF for example, only two drugs have been approved despite their undesirable side effects (Brunnemer et al., 2018; Lancaster et al., 2017; Richeldi et al., 2014), and therefore there is clear need for improved therapies (Raghu, 2015).

[0010] Therefore current therapies are not satisfactory, and in developing an effective therapeutic arsenal, novel modulators of S1PR, in particular selective S1PR2 would be particularly beneficial for the prevention and or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.

SUMMARY

[0011] The present disclosure relates to compounds of the disclosure useful in the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases. The present disclosure also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods for the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases by administering the compounds of the disclosure.

[0012] Accordingly, in a first aspect of the disclosure, the compounds of the disclosure are provided having a Formula I:



I

- N-linked spirocyclic 7-9 membered heterocycloalkyl comprising at least one N atom, and optionally one or two heteroatoms selected from N, O, and S, optionally substituted with one or more halo;

each R^{7a} , R^{7b} , R^{8a} , R^{8b} , R^{9a} and R^{9b} is independently selected from H, and C_{1-4} alkyl;

provided that:

- when A_1 and A_2 are C, A_3 is N, L is absent, R^3 is unsubstituted C_{1-6} alkoxy or C_{1-6} alkoxy substituted with halogen, then R^2 is not COOH; and
- when A_1 and A_2 are N, A_3 is C, and R^{4a} is $-CH_3$ then R^3 is not unsubstituted C_{1-4} alkoxy.

[0013] In a particular example, the compounds of the disclosure are provided for use in the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.

[0014] In a particular example the compounds of the disclosure are sphingosine 1-phosphate receptor (S1PR) modulators. In a more particular example, the compounds of the disclosure are sphingosine 1-phosphate receptor 2 (S1PR2) antagonists. In a most particular example, the compounds of the disclosure may show selectivity towards S1PR2, which may be advantageous in reducing undesirable effect associated with non-selective modulation of S1PR.

[0015] In yet another example, the compounds of the disclosure may surprisingly show good ADME properties.

[0016] In a further example, a compound of the disclosure according to one or more of the examples described above may show a good ADME profile, in metabolic stability, bioavailability, and/or low plasma protein binding (PPB), which may result in a lower dose regimen and/or good compliance with dose regimen.

[0017] In one aspect, the present disclosure provides a pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof as disclosed herein, and a pharmaceutically acceptable carrier. In a further example, the present disclosure provides pharmaceutical compositions comprising a compound of the disclosure, and a pharmaceutical carrier, excipient or diluent. In a particular example, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the disclosure. In a more particular example, the further therapeutically active ingredient is an agent for the treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.

[0018] Moreover, the compounds of the disclosure, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

[0019] In a further example of the disclosure, this disclosure provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases, which method

comprises administering an effective amount of the pharmaceutical composition or compounds of the disclosure as described herein.

[0020] In another aspect, the present disclosure provides a compound or a pharmaceutically acceptable salt thereof, as disclosed herein, or a pharmaceutical composition as disclosed herein for use in medicine. In another aspect, the present disclosure provides a use of a compound or a pharmaceutically acceptable salt thereof, as disclosed herein, or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases. The present disclosure also provides pharmaceutical compositions comprising a compound of the disclosure, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular

example, the pharmaceutical composition is for use in the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.

[0021] In additional examples, this disclosure provides methods for synthesizing the compounds of the disclosure, with representative synthetic protocols and pathways disclosed later on herein.

[0022] Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

[0023] It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0024] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

[0025] When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein.

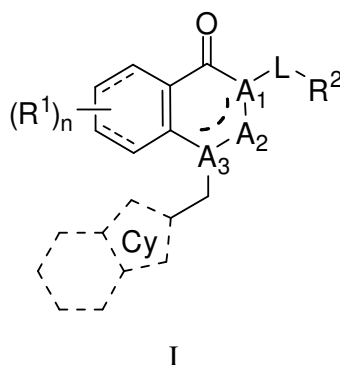
[0026] The articles ‘a’ and ‘an’ may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example ‘an analogue’ means one analogue or more than one analogue.

[0027] ‘Alkyl’ means straight or branched aliphatic hydrocarbon having the specified number of carbon atoms. Particular alkyl groups have 1 to 6 carbon atoms or 1 to 4 carbon atoms. Branched means that one or more alkyl groups such as methyl, ethyl or propyl is attached to a linear alkyl chain. Particular alkyl groups are methyl ($-\text{CH}_3$), ethyl ($-\text{CH}_2\text{CH}_3$), n-propyl ($-\text{CH}_2\text{CH}_2\text{CH}_3$), isopropyl ($-\text{CH}(\text{CH}_3)_2$), n-butyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), tert-butyl ($-\text{CH}_2\text{C}(\text{CH}_3)_3$), sec-butyl ($-\text{CH}_2\text{CH}(\text{CH}_3)_2$), n-pentyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), n-hexyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), and 1,2-dimethylbutyl ($-\text{CH}(\text{CH}_3)\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$). Particular alkyl groups have between 1 and 4 carbon atoms.

[0028] ‘Alkoxy’ refers to the group O-alkyl, where the alkyl group has the number of carbon atoms specified. In particular the term refers to the group $-\text{O}-\text{C}_{1-6}$ alkyl. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

WHAT IS CLAIMED:

- 1) A compound, or a pharmaceutically acceptable salt, or a solvate or the pharmaceutically acceptable salt of a solvate thereof, according to Formula I:



wherein

each A₁, A₂ and A₃ is independently selected from C and N provided that A₁, A₂ and A₃ are not simultaneously C or N;

each R¹ is independently selected from

- C₁₋₄ alkyl,
- C₁₋₄ alkoxy,
- C₃₋₆ cycloalkyl,
- 4-7 membered monocyclic heteroaryl comprising 1, 2, or 3 hteroatoms independently selected from N, O, or S, optionally substituted with one or two =O groups,
- -S(O)₂C₁₋₄ alkyl,
- -CN,
- -C(=O)NH₂, and
- halo;

the subscript n is 0, 1 or 2;

Cy is a 5-membered ring linked 9-membered fused 5-6 bicyclic heteroaryl, comprising 1, 2 or 3 N atoms, which heteroaryl is substituted with one R³ group and one R^{4a} group, and optionally further substituted with one halo, or OH;

R³ is C₁₋₆ alkoxy optionally substituted with one or more independently selected

- halo,
- C₁₋₄ alkoxy, or
- C₃₋₇ cycloalkyl optionally substituted with one C₁₋₄ alkyl, halo, or -CN;

R^{4a} is

- C₁₋₄ alkyl optionally substituted with one or more halo,
- halo, or
- -CN;

L is absent or is -CR^{5a}R^{5b}-;

R^2 is

- $-C(=O)OH$,
- $-C(=O)NR^{6a}R^{6b}$,
- $-C(O)NHS(O)_2-C_{1-4}$ alkyl,
- $-C(O)NHS(O)_2-C_{3-7}$ cycloalkyl,
- $-Cy_1$, or
- $-C(=O)Cy_2$;

each R^{5a} and R^{5b} is independently selected from

- H,
- C_{1-4} alkyl optionally substituted with one, two or three halo or $-NR^{8a}R^{8b}$, and
- C_{1-4} alkoxy;

each R^{6a} and R^{6b} is independently selected from

- H,
- C_{1-6} alkyl optionally substituted from one more independently selected
 - o OH,
 - o $-CN$,
 - o halo,
 - o C_{1-4} alkoxy,
 - o monocyclic 4-6 membered heterocycloalkyl comprising one or two heteroatoms selected from N, O, and S, optionally substituted with one $-CH_2-OH$
 - o $-S(O)_2C_{1-4}$ alkyl,
 - o $-S(O)_2NH_2$,
 - o $-C(O)NR^{9a}R^{9b}$, or
 - o C_{3-7} cycloalkyl optionally substituted with OH, or halo;
- C_{1-4} alkoxy,
- C_{3-7} cycloalkyl optionally substituted with one or more OH, and
- monocyclic 4-6 membered heterocycloalkyl comprising one or two heteroatoms selected from N, O, and S, optionally substituted with one or two oxo;

Cy_1 is

- C_{3-7} monocyclic cycloalkyl, optionally substituted with one $-C(=O)OH$,
- monocyclic 4-6 membered heterocycloalkyl comprising one or two heteroatoms selected from N, O, and S, optionally substituted with one or two
 - o C_{1-4} alkyl optionally substituted with one $-C(=O)OH$,

Cy_2 is

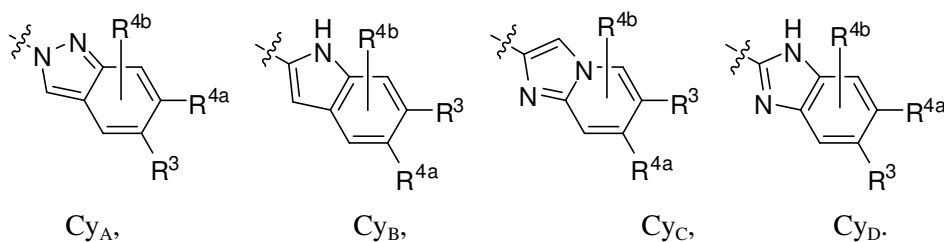
- N-linked monocyclic 4-7 membered heterocycloalkyl comprising at least one N atom, and optionally one or two heteroatoms selected from N, O, and S, optionally substituted with one or more
 - o OH,

- Oxo,
 - -CN,
 - halo,
 - C₁₋₄ alkoxy,
 - C₁₋₄ alkyl optionally substituted with one or more independently selected
 - halo,
 - OH,
 - C₃₋₇ cycloalkyl,
 - -S(O)₂C₁₋₄ alkyl, or
 - -NR^{7a}R^{7b}; or
- N-linked spirocyclic 7-9 membered heterocycloalkyl comprising at least one N atom, and optionally one or two heteroatoms selected from N, O, and S, optionally substituted with one or more halo;

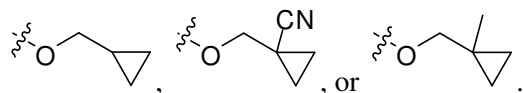
each R^{7a}, R^{7b}, R^{8a}, R^{8b}, R^{9a} and R^{9b} is independently selected from H, and C₁₋₄ alkyl;

provided that

- when L is absent, A₁ and A₂ are C, A₃ is N, and R² is COOH, R³ is unsubstituted C₁₋₆ alkoxy or C₁₋₆ alkoxy substituted with halogen, then not COOH; and
 - when A₁ and A₂ are N, A₃ is C, and R^{4a} is -CH₃ then R³ is not unsubstituted C₁₋₄ alkoxy.
- 2) The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the subscript n is 0.
- 3) The compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein Cy is selected from Cy_A, Cy_B, Cy_C, and Cy_D:

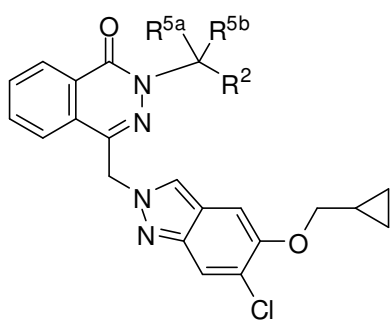


- 4) The compound or pharmaceutically acceptable salt thereof according to claim 3, wherein R³ is -OCH₃, -OCH₂CH₃, -OCF₃, -OCH₂CF₃, -OCH₂CHF₂, -OCH₂CH₂OCH₃,

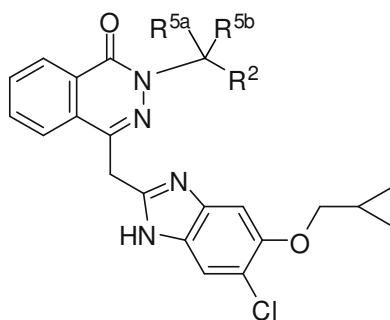


- 5) The compound or pharmaceutically acceptable salt thereof according to claim 3 or 4, wherein R^{4b} is H, F, Cl or OH.
- 6) The compound or pharmaceutically acceptable salt thereof according to claim 3 or 4, wherein R^{4a} is F, Cl, -CN, or -CF₃.

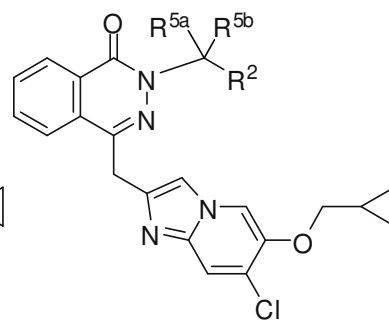
- 7) The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula Va, Vb, Vc, VIa, VIb, or VIc:



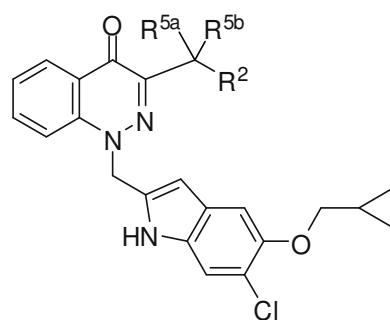
Va,



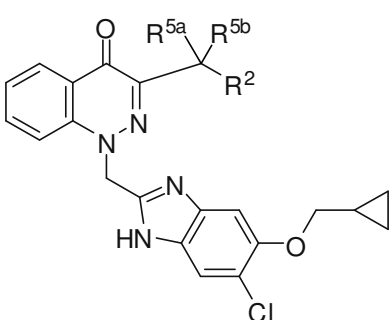
Vb,



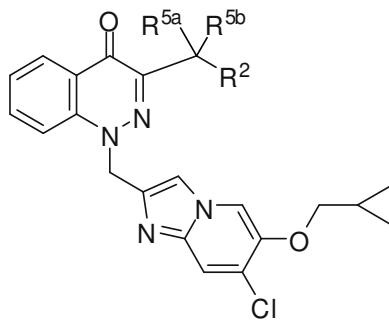
Vc



VIa,

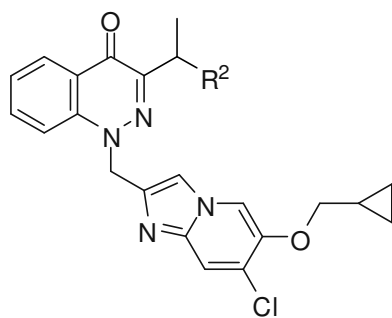


VIb, or

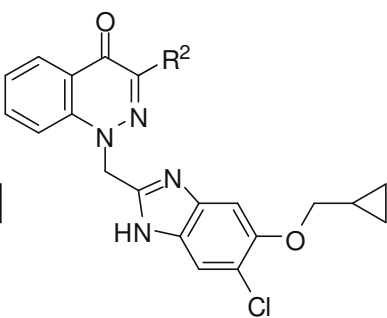


VIc.

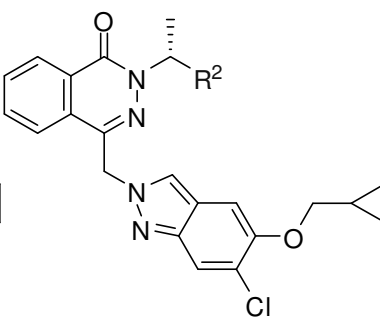
- 8) The compound or pharmaceutically acceptable salt thereof according to claim 3 or 4, wherein wherein each R^{5a} and R^{5b} is independently selected from H, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CH_2CH_3$, $-CH_3$, $-CH_2CHF_2$, $-CH_2CF_3$, and $-CH_2CH_2-N(CH_3)_2$.
- 9) The compound or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound is according to Formula VIIa, VIIb, or VIIc:



VIIa,

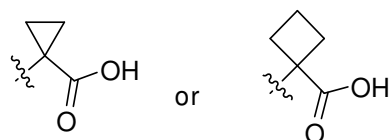


VIIb, or



VIIc

- 10) The compound or pharmaceutically acceptable salt thereof according to anyone of claims 1-9, wherein R^2 is $-C(=O)OH$, $-C(O)NHS(O)_2-CH_3$, $-C(O)NHS(O)_2-C_{3-7}$ cycloalkyl,



11) The compound or pharmaceutically acceptable salt thereof, wherein the compound according to claim 1 is selected from:

6-(2,2-difluoroethoxy)-2-[[4-oxo-3-(pyrrolidin-2-ylmethyl)phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,
 2-(azetidin-3-yl)-4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]phthalazin-1-one,
 2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,
 2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]propanoic acid,
 1-[[6-chloro-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-cinnoline-3-carboxylic acid,
 2-[4-[(5-chloro-6-ethoxy-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[6-cyano-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[6-cyano-5-(2,2-difluoroethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-indol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 6-(cyclopropylmethoxy)-2-[[3-[2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-cinnolin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,
 4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-indol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)-1-oxo-phthalazine-6-carboxamide,
 6-(2,2-difluoroethoxy)-2-[[3-[2-[(3S)-3-hydroxypyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,
 2-[(1-acetylpyrrolidin-2-yl)methyl]-4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]phthalazin-1-one,
 2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]-N-methylsulfonyl-propanamide,
 2-[1-[[5-chloro-6-(cyclopropylmethoxy)-1H-indol-2-yl]methyl]-4-oxo-cinnolin-3-yl]acetic acid,
 ((2R)-2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid),
 (2S)-2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,
 (2S)-2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxocinnolin-3-yl]propanoic acid,
 (2R)-2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxocinnolin-3-yl]propanoic acid,
 (2-[1-[[5-cyano-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxocinnolin-3-yl]-3-(dimethylamino)propanoic acid),
 2-[4-[(7-chloro-6-ethoxy-indazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-6-cyano-1-oxo-phthalazin-2-yl]acetic acid,

4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-cyclopentyl-phthalazin-1-one,

4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-cyclopropyl-phthalazin-1-one,

4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-cyclobutyl-phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(cyclopropylmethyl)phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(cyclobutylmethyl)phthalazin-1-one,

4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-6-methoxy-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-7-methoxy-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-2-cyclopropyl-phthalazin-1-one,

4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-7-morpholino-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(THF-2-ylmethyl)phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(tetrahydropyran-2-ylmethyl)phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-[(3-methyloxetan-3-yl)methyl]phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-[(1-methyl-3-piperidyl)methyl]phthalazin-1-one,

1-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazine-6-carbonitrile,

4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-6-methylsulfonyl-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

6-(cyclopropylmethoxy)-2-[(3-cyclopropyl-4-oxo-phthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-[(2,2-difluorocyclopropyl)methyl]phthalazin-1-one,

4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(3,3-dimethyl-2-oxo-butyl)phthalazin-1-one,

1-[4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]methyl]cyclopropanecarboxylic acid,

4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-5-cyclopropyl-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

6-(2,2-Difluoro-ethoxy)-2-[3-(2-morpholin-4-yl-2-oxo-ethyl)-4-oxo-4H-cinnolin-1-ylmethyl]-3H-
 enzoimidazole-5-carbonitrile,
 1-[5-(2,2-Difluoro-ethoxy)-6-fluoro,
 -1H-benzimidazol-2-ylmethyl]-3-(2-morpholin-4-yl-2-oxo-ethyl)-1H-cinnolin-4-one,
 6-(2-methoxyethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-
 benzimidazole-5-carbonitrile,
 6-(2,2-difluoropropoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-
 benzimidazole-5-carbonitrile,
 7-chloro-6-(2,2-difluoroethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-
 benzimidazole-5-carbonitrile,
 2-[[8-cyclopropyl-3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-
 3H-benzimidazole-5-carbonitrile,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(pyrrolidin-2-ylmethyl)phthalazin-1-
 one,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(4-piperidylmethyl)phthalazin-1-one,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(pyrrolidin-3-ylmethyl)phthalazin-1-
 one,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(3-piperidylmethyl)phthalazin-1-one,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-pyrrolidin-3-yl-phthalazin-1-one,
 2-(azetidin-3-ylmethyl)-4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]phthalazin-1-
 one,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(4-piperidyl)phthalazin-1-one,
 4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(morpholin-2-ylmethyl)phthalazin-1-
 one,
 6-(2,2-difluoroethoxy)-2-[(4-oxo-3-pyrrolidin-3-yl-phthalazin-1-yl)methyl]-3H-benzimidazole-5-
 carbonitrile,
 6-(2-methoxyethoxy)-2-[(4-oxo-3-pyrrolidin-3-yl-phthalazin-1-yl)methyl]-3H-benzimidazole-5-
 carbonitrile,
 6-(2,2-difluoroethoxy)-2-[[8-methyl-3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-
 benzimidazole-5-carbonitrile,
 4-[[6-chloro-5-(2-methoxyethoxy)-1H-benzimidazol-2-yl]methyl]-2-pyrrolidin-3-yl-phthalazin-1-one,
 2-[[3-(azetidin-3-yl)-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-
 carbonitrile,
 2-[3-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]azetidin-
 1-yl]acetic acid,
 2-[2-[[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-
 yl]methyl]pyrrolidin-1-yl]acetic acid,

2-[3-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]pyrrolidin-1-yl]acetic acid,

6-(2,2-difluoroethoxy)-2-[[3-(1-methylpyrrolidin-3-yl)-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[3-[4-[[7-cyano-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]azetidin-1-yl]acetic acid,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-3-(dimethylamino)propanoic acid,

3-(azetidin-1-yl)-2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,

2-[4-[[6-chloro-5-(2,2-difluoroethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,

2-[4-[(6-chloro-5-ethoxy-1H-benzimidazol-2-yl)methyl]-8-methyl-1-oxo-phthalazin-2-yl]acetic acid,

{1-[6-Chloro-5-(2,2-difluoro-ethoxy)-1H-benzoimidazol-2-ylmethyl]-4-oxo-1,4-dihydro-cinnolin-3-yl}-acetic acid,

2-[4-[[7-cyano-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

1-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-quinoline-3-carboxylic acid,

2-[4-[[7-cyano-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,

2-[4-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]propanoic acid,

1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-quinoline-3-carboxylic acid,

1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnoline-3-carboxylic acid,

2-[4-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-6-fluoro-1-oxo-phthalazin-2-yl]propanoic acid,

2-[3-[4-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-1-oxo-phthalazin-2-yl]pyrrolidin-1-yl]acetic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]-2-methyl-propanoic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]acetic acid,

1-[[6-chloro-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-quinoline-3-carboxylic acid,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]cyclobutanecarboxylic acid,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-6-cyano-1-oxo-phthalazin-2-yl]propanoic acid,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]propanoic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]-2-methoxy-acetic acid,

1-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]cyclopropanecarboxylic acid,

1-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]cyclopropanecarboxylic acid,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-7-methoxy-1-oxo-phthalazin-2-yl]propanoic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]butanoic acid,

2-[1-[[6-(cyclopropylmethoxy)-7-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]acetic acid,

2-[1-[[6-(cyclopropylmethoxy)-7-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]propanoic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-7-fluoro-4-oxo-cinnolin-3-yl]acetic acid,

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-5-methyl-4-oxo-cinnolin-3-yl]acetic acid,

2-[1-[[6-(cyclopropylmethoxy)-7-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-cinnolin-3-yl]butanoic acid,

(1-[[5-(cyclopropylmethoxy)-6-(trifluoromethyl)-1H-benzimidazol-2-yl]methyl]-4-oxocinnoline-3-carboxylic acid),

2-[1-[[7-chloro-6-(cyclopropylmethoxy)imidazo[1,2-a]pyridin-2-yl]methyl]-4-oxo-5,6,7,8-tetrahydrocinnolin-3-yl]acetic acid,

(1-[[5-(cyclopropylmethoxy)-6-(trifluoromethyl)-1H-benzimidazol-2-yl]methyl]-4-oxoquinoline-3-carboxylic acid),

2-[1-[[6-cyano-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-cinnolin-3-yl]propanoic acid,

2-[1-[[6-cyano-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-cinnolin-3-yl]acetic acid,

2-[1-[[6-bromo-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-cinnolin-3-yl]acetic acid,

1-[[5-cyano-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-4-oxo-cinnoline-3-carboxylic acid,

2-[4-[[6-bromo-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetic acid,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(cyclopropylmethoxy)-7-fluoro-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetic acid,

2-[4-[(5-chloro-6-methoxy-1H-benzimidazol-2-yl)methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetic acid,

2-[4-[(5-chloro-6-ethoxy-1H-benzimidazol-2-yl)methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetic acid,

2-[4-(6-Chloro-5-cyclopropylmethoxy-1H-benzimidazol-2-ylmethyl)-1-oxo-1H-phthalazin-2-yl]-propionic acid,

2-[4-[[5-(cyclopropylmethoxy)-6-(trifluoromethyl)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-(cyclopropylmethoxy)-6-fluoro-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

{4-[5-Chloro-6-(2,2-difluoro-ethoxy)-1H-benzimidazol-2-ylmethyl]-1-oxo-1H-isoquinolin-2-yl}-acetic acid,

2-[4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-5,8-difluoro-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-ethoxy-6-(trifluoromethyl)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[(5-chloro-6-ethoxy-3-oxo-1H-indazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[(5-ethoxy-6-fluoro-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-(2,2-difluoroethoxy)-6-fluoro-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-[(1-methylcyclopropyl)methoxy]-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(2,2-dimethylpropoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-[(1-cyanocyclopropyl)methoxy]-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[5-chloro-6-(cyclopropylmethoxy)-3-oxo-1H-indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[6-cyano-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[6-chloro-5-methoxy-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[6-bromo-5-ethoxy-indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[5-cyano-6-ethoxy-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,
 2-[4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-[(1S,2R)-2-hydroxycyclopentyl]acetamide,
 2-[4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(1,1-dioxothian-4-yl)acetamide,
 4-[[6-chloro-5-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-[(1S,2S)-2-hydroxycyclopentyl]acetamide,
 N-tert-butyl-2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetamide,
 4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)-5,6,7,8-tetrahydrophthalazin-1-one,
 2-[4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]-N-[(1S,2S)-2-hydroxycyclopentyl]acetamide,
 2-[4-[[5-chloro-6-(trifluoromethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]-N-[(1S,2S)-2-hydroxycyclopentyl]acetamide,
 4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[5-chloro-6-(cyclopropylmethoxy)-7-fluoro-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 2-[4-[[5-chloro-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-cyclopentyl-acetamide,
 4-[[5-chloro-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-5,8-difluoro-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)-1-oxo-phthalazine-6-carbonitrile,
 4-[(5-chloro-6-ethoxy-3-oxo-1H-indazol-2-yl)methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-(6-Chloro-5-cyclopropylmethoxy-1H-benzimidazol-2-yl)methyl]-2-(1-methyl-2-morpholin-4-yl-2-oxo-ethyl)-2H-phthalazin-1-one,
 4-[[5-(2,2-difluoroethoxy)-6-fluoro-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,

4-[(5-ethoxy-6-fluoro-1H-benzimidazol-2-yl)methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 6-(cyclopropylmethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,
 1-[6-Chloro-5-(2,2-difluoro-ethoxy)-1H-benzimidazol-2-ylmethyl]-3-(2-morpholin-4-yl-2-oxo-ethyl)-1H-cinnolin-4-one,
 4-[[5-chloro-6-(2,2-dimethylpropoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 1-[[6-chloro-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazol-5-yl]oxymethyl]cyclopropanecarbonitrile,
 1-[[6-chloro-2-[[3-[2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazol-5-yl]oxymethyl]cyclopropanecarbonitrile,
 4-[[5-chloro-6-[(1-methylcyclopropyl)methoxy]-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 6-(2,2-difluoroethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-5,6,7,8-tetrahydrophthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,
 4-[(5-chloro-6-ethoxy-1H-benzimidazol-2-yl)methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[5-chloro-6-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 6-ethoxy-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-5,6,7,8-tetrahydrophthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,
 4-[[6-ethoxy-5-(trifluoromethyl)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[6-Chloro-5-(2,2-difluoro-ethoxy)-1H-benzimidazol-2-ylmethyl]-2-(2-morpholin-4-yl-2-oxo-ethyl)-2H-isoquinolin-1-one,
 6-ethoxy-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,
 6-(2,2-difluoroethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,
 4-[[5-chloro-6-(2,2-difluoropropoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[(5-chloro-6-isobutoxy-1H-benzimidazol-2-yl)methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 4-[[5-chloro-6-(2-methoxyethoxy)-1H-benzimidazol-2-yl]methyl]-2-(2-morpholino-2-oxo-ethyl)phthalazin-1-one,
 2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]-6-(2,2,2-trifluoroethoxy)-3H-benzimidazole-5-carbonitrile,
 6-(2,2-difluoroethoxy)-2-[[3-[2-[3-(dimethylamino)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-[(2S,6R)-2,6-dimethylmorpholin-4-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl)methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-THF-3-yl-acetamide,

4-[[5-(2,2-difluoroethoxy)-6-fluoro-1H-benzimidazol-2-yl)methyl]-2-(2-morpholino-2-oxo-ethyl)-5,6,7,8-tetrahydrophthalazin-1-one,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-methyl-N-(THF-2-ylmethyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-cyanoethyl)-N-cyclopropyl-acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-methoxy-2-methyl-propyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-methoxyethyl)-N-methyl-acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-tetrahydropyran-3-yl-acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4,4-difluoro-1-piperidyl)-2-oxo-ethyl]-4-oxo-5,6,7,8-tetrahydrophthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3-methoxypyrrolidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-methoxyethyl)acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4,4-difluoro-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(6-oxa-9-azaspiro[3.5]nonan-9-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(3,3,3-trifluoro-2-hydroxy-2-methyl-propyl)acetamide,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-[(2S)-3,3,3-trifluoro-2-hydroxy-propyl]acetamide,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-hydroxy-3-methoxy-propyl)acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4-hydroxy-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl)methyl]-1H-benzimidazole-5-carbonitrile,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2,2-difluoroethyl)-N-(2-hydroxyethyl)acetamide,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-(2-cyanopropyl)-N-methyl-acetamide,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(cyclopropylmethyl)-N-methyl-acetamide,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2,2-difluoroethyl)-N-methyl-acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,

2-[4-[[5-cyano-6-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-[[3-(hydroxymethyl)oxetan-3-yl]methyl]acetamide,

2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-5,6,7,8-tetrahydrophthalazin-1-yl]methyl]-6-(2,2,2-trifluoroethoxy)-1H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3-hydroxy-3-methyl-pyrrolidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2,2-dimethylpropyl)acetamide,

N-tert-butyl-2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-5,6,7,8-tetrahydrophthalazin-2-yl]acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-[3-(dimethylamino)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-5,6,7,8-tetrahydrophthalazin-1-yl]methyl]-1H-benzimidazole-5-carbonitrile,

5-(2,2-difluoroethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]indazole-6-carbonitrile,

5-(2,2-difluoroethoxy)-2-[[3-[2-[(3R)-3-(dimethylamino)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]indazole-6-carbonitrile,

5-(2,2-difluoroethoxy)-2-[[3-[2-[(3S)-3-(dimethylamino)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]indazole-6-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-cyclopentyl-acetamide,

5-(cyclopropylmethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl]methyl]indazole-6-carbonitrile,

6-(cyclopropylmethoxy)-2-[[3-[2-(3-hydroxy-3-methyl-pyrrolidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]imidazo[1,2-a]pyridine-7-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3,3-difluoro-4-hydroxy-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[[3-[2-(4-cyclopropyl-4-hydroxy-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

2-[[3-[2-(3-cyclopropyl-3-hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl],

-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

2-[[3-[2-(3-cyclopropyl-3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-[3-hydroxy-3-(trifluoromethyl)pyrrolidin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

1-[[6-bromo-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-3-[2-[(3S,4S)-3,4-dihydroxypyrrolidin-1-yl]-2-oxo-ethyl]cinnolin-4-one,

2-[[3-[2-[4-(cyclopropylmethyl)piperazin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

2-[[3-[2-(4-cyano-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methyl-N-(2-methylsulfonyl)acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3-methylsulfonylpyrrolidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2-hydroxy-3,3-dimethyl-butyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2,2-difluoroethyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(3,3,3-trifluoropropyl)acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-[4-(2-hydroxyethyl)piperazin-1-yl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

N-[cyano(cyclopropyl)methyl]-2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(2,2-dimethylmorpholin-4-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2,2-difluoro-3-hydroxy-propyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2-sulfamoyl)acetamide,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(2,2,2-trifluoroethyl)acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3-hydroxy-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-[(3,3-difluorocyclobutyl)methyl]acetamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-(3,3-dimethylpyrrolidin-1-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4,4-dimethyl-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[[3-[2-(2,2-difluoro-5-azaspiro[2.4]heptan-5-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-6-(2,2-difluoroethoxy)-3H-benzimidazole-5-carbonitrile,

1-[2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetyl]-N,N-dimethyl-piperidine-4-carboxamide,

6-(2,2-difluoroethoxy)-2-[[3-[2-[3-(1-hydroxy-1-methyl-ethyl)-1-piperidyl]-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4-morpholino-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(7-oxa-2-azaspiro[3.5]nonan-2-yl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

6-(2,2-difluoroethoxy)-2-[[3-[2-(4-ethylsulfonyl-1-piperidyl)-2-oxo-ethyl]-4-oxo-phthalazin-1-yl]methyl]-3H-benzimidazole-5-carbonitrile,

2-[4-[[6-cyano-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-(dimethylamino)-2-oxo-ethyl]-N-methyl-acetamide,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[[6-chloro-5-(cyclopropylmethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-cyclopropylsulfonyl-acetamide,

2-[4-[[6-chloro-5-(2,2-difluoroethoxy)-1H-benzimidazol-2-yl]methyl]-6-cyano-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

N-{2-[4-(6-Chloro-5-cyclopropylmethoxy-1H-benzimidazol-2-yl)methyl]-1-oxo-1H-phthalazin-2-yl]-propionyl}-methanesulfonamide,

2-[4-[(5-ethoxy-6-fluoro-1H-benzimidazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[[5-(2,2-difluoroethoxy)-6-fluoro-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[[6-chloro-5-[(1-cyanocyclopropyl)methoxy]-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[[6-chloro-5-[(1-methylcyclopropyl)methoxy]-1H-benzimidazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]-N-methylsulfonyl-acetamide,

2-[4-[(6-chloro-5-ethoxy-indazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[6-chloro-5-(2,2,2-trifluoroethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[[6-chloro-5-(2,2-difluoroethoxy)indazol-2-yl]methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[(4-chloro-5-ethoxy-indazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,

2-[4-[(5-chloro-6-ethoxy-indazol-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid,
6-(2,2-difluoroethoxy)-2-[[3-(2-morpholino-2-oxo-ethyl)-4-oxo-phthalazin-1-yl)methyl]imidazo[1,2-a]pyridine-7-carbonitrile, and
2-[4-[[6-chloro-5-(cyclopropylmethoxy)-1H-imidazo[4,5-b]pyridin-2-yl)methyl]-1-oxo-phthalazin-2-yl]acetic acid.

- 12) A pharmaceutical composition comprising a compound or a pharmaceutically acceptable salt thereof according to any one of claims 1-11, and a pharmaceutically acceptable carrier.
- 13) A pharmaceutical composition according to claim 12 comprising a further therapeutic agent.
- 14) A compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or a pharmaceutical composition according to claim 12 or 13 for use in medicine.
- 15) Use of a compound or a pharmaceutically acceptable salt thereof, according to any one of claims 1-11, or a pharmaceutical composition according to claim 12 or 13 in the manufacture of a medicament for the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.
- 16) A pharmaceutical composition according to claim 13, wherein the further therapeutic agent is an agent for the prophylaxis and/or treatment of fibrotic diseases, inflammatory diseases, respiratory diseases, autoimmune diseases, metabolic diseases, cardiovascular diseases, and/or proliferative diseases.