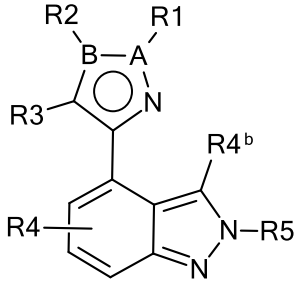
palmitoylation inhibitors. Compound 13 or 15 in this publication inhibits the HAQ STING variant (displacement assay) with a moderate IC50 of 84 or 41 nM and shows low cellular inhibitory activity of about 11 uM based on a cGAMP stimulated INFb production in THP1 cells.

- In International patent application WO2019069270, claims modulators of STING which either activate or inhibit STING accordingly.

Surprisingly it has now been found that the compounds described in the patent application are competitive inhibitors of STING.

SUMMARY

In one aspect, the present disclosure provides a compound of formula **1**;

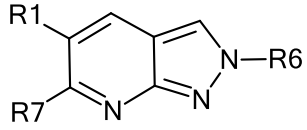


1

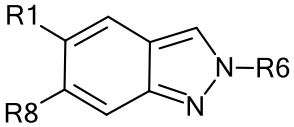
wherein

B-A is =C-N- or -N-C=;

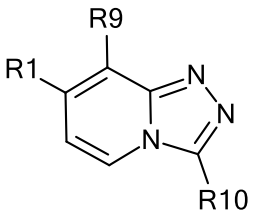
R1 is selected from



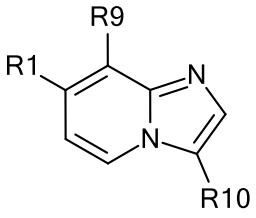
,



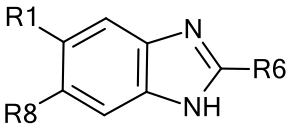
,



,



,



,

and R1 is the attaching point to the structure of formula **1**;

R2 for B-A is -N-C= has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-;

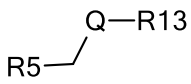
R2 for B-A is =C-N- has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-, C_{1-6}-alkyl-O-, HO-, H_2N-, C_{1-6}-alkyl-HN-, $(C_{1-6}\text{-alkyl})_2N$-;

R3 H- or C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl, C_{3-7}-heterocycloalkyl, each optionally substituted with a group selected from F-, HO-, Me-, EtO-, $NH_2(O)C$-;

R4 is H-, F- or HO-;

$R4^b$ is H-, F-, Cl-, Br-, NC- or HO-;

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

Q is -C(R11)(R12)-, -S(O)- or $-S(O)_2$-;

R6 is C_{2-6}-alkenyl,
or
C_{1-6}-alkyl, optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{3-6}-cycloalkyl-, halogen, HO-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}\text{-alkyl})_2N$-, NC-, $(C_{1-6}\text{-alkyl})_2(O)P$-, (4-Methoxyphenyl)methyl-,
or
a heterocycle selected from tetrahydrofuran-, 1, 4-dioxane-, pyrrolidine-, piperazine-, morpholine-, pyridine-, pyrazole-, triazole-, each optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{1-6}-alkyl-, halogen, O=;

R7, R8, R9 are C_{3-6}-cycloalkyl-, optionally substituted with C_{1-6}-alkyl- or one or two halogen atoms,
or
cyclopropylmethyl-, C_{1-6}-haloalkyl-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}\text{-alkyl})_2N$-, C_{1-6}-alkyl-S-,
or
C_{1-6}-alkyl, straight or branched, optionally substituted with HO-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}\text{-alkyl})_2N$- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-;
or
C_{1-6}-haloalkyl-O-;

R10 is C_{1-6}-alkyl- or C_{1-6}-haloalkyl-;

R11 is H, HO-, halogen-, or R14-O-, R14-NH-;

R12 is H- or F;

R13 is carbocyclyl, heterocyclyl, aryl, heteroaryl; each optionally substituted with one or two substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, HO-, NC-, halogen, R15-$(CH_2)_n$-O-, R15-$(CH_2)_n$-NH-, (R15-$(CH_2)_n)_2$-N-, R15-$(CH_2)_n$-S(O)-, R15-$(CH_2)_n$-$S(O)_2$-;

R14 is C_{1-6}-haloalkyl or C_{1-6}-alkyl, optionally substituted with C_{3-6}-cycloalkyl, C_{2-6}-alkenyl-, HO-, C_{1-6}-alkyl-O-, H_2N-C(O)-, C_{1-6}-alkyl-HN-C(O)-, (C_{1-6}-alkyl)$_2$N-C(O)-;

R15 is C_{1-4}-alkyl, C_{1-6}-haloalkyl, NC-, C_{1-6}-alkyl-HN-, (C_{1-6}-alkyl)$_2$N-, (C_{1-6}-alkyl)$_2$(HO)C-, aryl or heterocyclyl;

n is 0, 1, 2 or 3.

In another aspect, the present disclosure provides a salt of a compound of formula **1** as described herein.

In another aspect, the present disclosure provides a pharmaceutically acceptable salt of a compound of formula **1** as described herein.

In another aspect, the present disclosure provides the compound as described herein or the salt as described herein or the pharmaceutically acceptable salt as described herein for use in therapy.

In another aspect, the present disclosure provides use of the compound of formula **1, 1a**, **1b** or **1c**, as described herein, the salt as described herein or the pharmaceutically acceptable salt as described herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of systemic lupus erythematosus (SLE), (monogenic and digenic) interferonopathies (including STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières syndrome (AGS), COPA syndrome, and familial chilblain lupus), type 1 interferonopathies with mutations in DNASE2 or ATAD3A genes, age-related macular degeneration (AMD), retinopathy, glaucoma, amyotrophic lateral sclerosis (ALS), diabetes, obesity, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, Parkinson's disease, heart failure and cancer, systemic sclerosis (SSc), dermatomyositis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatotic hepatitis (NASH), acute on chronic liver failure (ACLF), interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), aging/muscle disorders, sepsis, heart failure, rheumatoid arthritis and osteoarthritis.

In another aspect, the present disclosure provides use of the compound of formula **1, 1a**, **1b** or **1c**, as described herein, the salt as described herein or the pharmaceutically acceptable salt as described herein in the manufacture of a medicament for the treatment of a fibrosing disease selected from the group consisting of systemic sclerosis (SSc), non-alcoholic steatohepatitis (NASH), acute on chronic liver failure (ACLF), (monogenic and digenic) interferonopathies (including STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières syndrome (AGS), COPA syndrome, and familial chilblain lupus), type 1 interferonopathies with mutations in DNASE2 or ATAD3A genes, and interstitial lung disease (ILD).

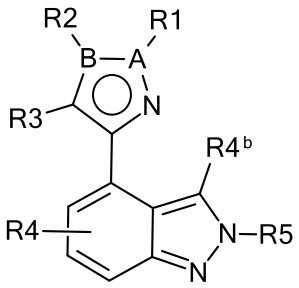
In another aspect, the present disclosure provides use of the compound of formula **1, 1a**, **1b** or **1c**, as described herein, the salt as described herein or the pharmaceutically acceptable salt as described herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of age-related macular degeneration (AMD), retinopathy, glaucoma, aging, muscle disorders, heart failure, COVID-19/SARS-CoV-2 infection, renal inflammation, renal fibrosis, dysmetabolism, vascular diseases, cardiovascular diseases, diabetes, obesity, and cancer.

In another aspect, the present disclosure provides pharmaceutical composition comprising a compound of formula **1, 1a**, **1b** or **1c** as described herein, the salt as described herein or the pharmaceutically acceptable salt as described herein and optionally one or more pharmaceutically acceptable carriers and/or excipients.

In another aspect, the present disclosure provides pharmaceutical composition comprising a compound of formula **1, 1a**, **1b** or **1c** as described herein, the salt as described herein or the pharmaceutically acceptable salt as described herein in combination with one or more active agents selected from the group consisting of PDE 4 inhibitors, anti-inflammatory agents, anti-fibrotic agents, anti-allergic agents/ anti-histamines, bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists, anticholinergic agents, methotrexate, mycophenolate mofetil, leukotriene modulators, JAK inhibitors, anti-interleukin antibodies, non-specific immunotherapeutics such as interferons or other cytokines/chemokines, cytokine/chemokine receptor modulators, toll-like receptor agonists, immune checkpoint regulators, an anti-TNF antibody, an anti-BAFF antibody.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a compound of formula **1**;

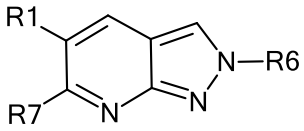
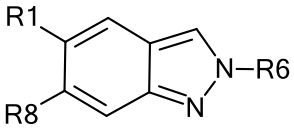
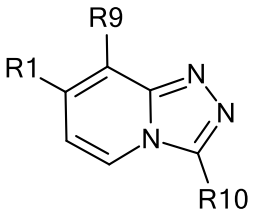
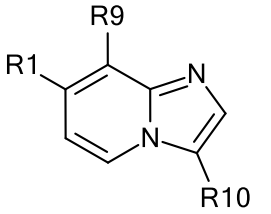
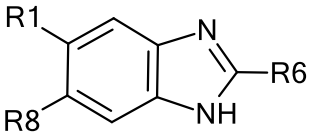


1;

wherein

B-A is =C-N- or -N-C=; this means A is C or N; B is C or N; but A and B are not N at the same time;

R1 is selected from


,

,

,

,


and R1 is the attaching point to the structure of formula **1**;

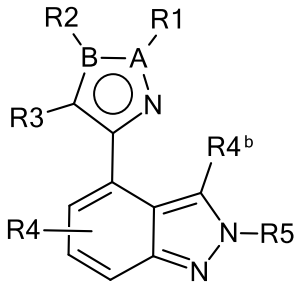
R2 for B-A is -N-C= has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-;

R2 for B-A is =C-N- has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-, C_{1-6}-alkyl-O-, HO-, H_2N-, C_{1-6}-alkyl-HN-, $(C_{1-6}\text{-alkyl})_2N$-;

R3 H- or C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl, C_{3-7}-heterocycloalkyl, each optionally substituted with a group selected from F-, HO-, Me-, EtO-, $NH_2(O)C$-;

CLAIMS

1. A compound of formula **1**;

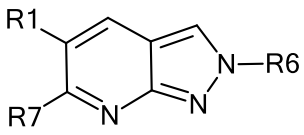
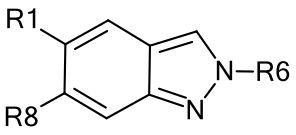
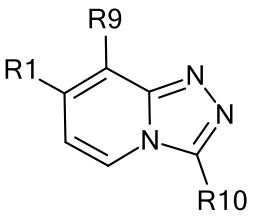
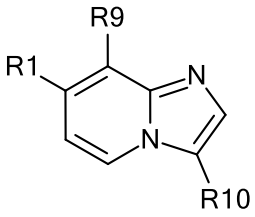
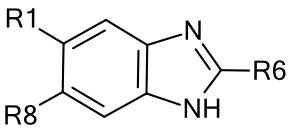


1

wherein

B-A is =C-N- or -N-C=;

R1 is selected from


,

,

,

,


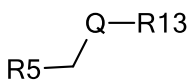
and R1 is the attaching point to the structure of formula **1**;

R2 for B-A is -N-C= has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-;
R2 for B-A is =C-N- has the meaning of C_{1-6}-alkyl-, C_{3-6}-cycloalkyl-, C_{1-6}-haloalkyl-, C_{1-6}-alkyl-O-, HO-, H_2N-, C_{1-6}-alkyl-HN-, $(C_{1-6}$-alkyl$)_2N$-;

R3 H- or C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl, C_{3-7}-heterocycloalkyl, each optionally substituted with a group selected from F-, HO-, Me-, EtO-, $NH_2(O)C$-;

R4 is H-, F- or HO-;
$R4^b$ is H-, F-, Cl-, Br-, NC- or HO-;

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

Q is -C(R11)(R12)-, -S(O)- or -$S(O)_2$-;

R6 is C_{2-6}-alkenyl,
or

C_{1-6}-alkyl, optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{3-6}-cycloalkyl-, halogen, HO-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}$-alkyl$)_2$N-, NC-, $(C_{1-6}$-alkyl$)_2$(O)P-, (4-Methoxyphenyl)methyl-,
or
a heterocycle selected from tetrahydrofuran-, 1, 4-dioxane-, pyrrolidine-, piperazine-, morpholine-, pyridine-, pyrazole-, triazole-, each optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{1-6}-alkyl-, halogen, O=;

R7, R8, R9 are C_{3-6}-cycloalkyl-, optionally substituted with C_{1-6}-alkyl- or one or two halogen atoms,
or
cyclopropylmethyl-, C_{1-6}-haloalkyl-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}$-alkyl$)_2$N-, C_{1-6}-alkyl-S-,
or
C_{1-6}-alkyl, straight or branched, optionally substituted with HO-, C_{1-6}-alkyl-O-, C_{1-6}-alkyl-HN-, $(C_{1-6}$-alkyl$)_2$N- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-;
or
C_{1-6}-haloalkyl-O-;

R10 is C_{1-6}-alkyl- or C_{1-6}-haloalkyl-;

R11 is H, HO-, halogen-, or R14-O-, R14-NH-;

R12 is H- or F;

R13 is carbocyclyl, heterocyclyl, aryl, heteroaryl; each optionally substituted with one or two substituents selected from the group consisting of C_{1-6}-alkyl, C_{1-6}-haloalkyl, HO-, NC-, halogen, R15-$(CH_2)_n$-O-, R15-$(CH_2)_n$-NH-, (R15-$(CH_2)_n)_2$-N-, R15-$(CH_2)_n$-S(O)-, R15-$(CH_2)_n$-$S(O)_2$-;

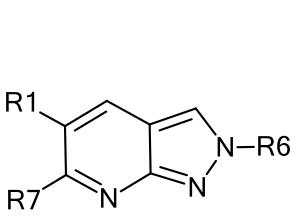
R14 is C_{1-6}-haloalkyl or C_{1-6}-alkyl, optionally substituted with C_{3-6}-cycloalkyl, C_{2-6}-alkenyl-, HO-, C_{1-6}-alkyl-O-, H_2N-C(O)-, C_{1-6}-alkyl-HN-C(O)-, $(C_{1-6}$-alkyl$)_2$N-C(O)-;

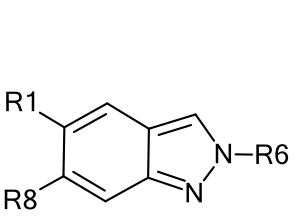
R15 is C_{1-4}-alkyl, C_{1-6}-haloalkyl, NC-, C_{1-6}-alkyl-HN-, $(C_{1-6}$-alkyl$)_2$N-, $(C_{1-6}$-alkyl$)_2$(HO)C-, aryl or heterocyclyl;

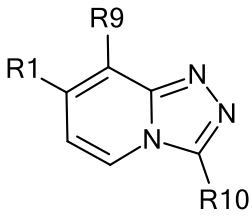
n is 0, 1, 2 or 3.

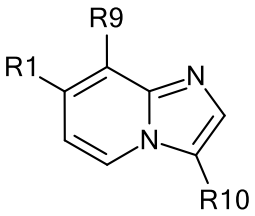
2. A compound according to claim 1, wherein

R1 is selected from



,


,


,


.

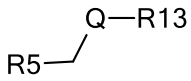
3. A compound according to claim 1 or 2, wherein

R3 H- or C_{1-6}-alkyl, C_{3-7}-cycloalkyl, C_{2-5}-alkenyl, C_{3-7}-heterocycloalkyl, each optionally substituted with a group selected from F-, HO-, Me-, EtO-, $NH_2(O)C$-;

R4 is H-, F- or HO-;

$R4^b$ is H- or F-, Cl-, Br-, NC-, HO-;

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

Q is -C(R11)(R12)-, -S(O)- or $-S(O)_2$-;

R6 is C_{2-4}-alkenyl,
or
C_{1-4}-alkyl, optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{3-4}-cycloalkyl-, halogen, HO-, C_{1-4}-alkyl-O-, C_{1-4}-alkyl-HN- $(C_{1-4}$-alkyl$)_2$N-, NC-, $(C_{1-4}$-alkyl$)_2(O)$P-, (4-Methoxyphenyl)methyl-,
or
a heterocycle selected from tetrahydrofuran-, 1, 4-dioxane-, pyrrolidine-, piperazine-, morpholine-, pyridine-, pyrazole-, triazole-, each optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{1-4}-alkyl-, halogen, O=;

R7, R8, R9 are C_{3-4}-cycloalkyl-, optionally substituted with C_{1-4}-alkyl- or one or two halogen atoms,
or
cyclopropylmethyl-, C_{1-4}-haloalkyl-, C_{1-4}-alkyl-O-, C_{1-4}-alkyl-HN-, $(C_{1-4}$-alkyl$)_2$N-, C_{1-4}-alkyl-S-,
or
C_{1-4}-alkyl, straight or branched, optionally substituted with HO-, C_{1-4}-alkyl-O-, C_{1-4}-alkyl-HN-, $(C_{1-4}$-alkyl$)_2$N- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-,
or
C_{1-4}-haloalkyl-O-;

R10 is C_{1-4}-alkyl- or C_{1-4}-haloalkyl-;

R11 is H, HO-, halogen-, or R14-O-, R14-NH-;

R12 is H- or F;

R13 is carbocyclyl, heterocyclyl, aryl, heteroaryl; each optionally substituted with one or two substituents selected from the group consisting of C_{1-4}-alkyl, C_{1-4}-haloalkyl, HO-, NC-, halogen, R15-$(CH_2)_n$-O-, R15-$(CH_2)_n$-NH-, (R15-$(CH_2)_n)_2$-N-, R15-$(CH_2)_n$-S(O)-, R15-$(CH_2)_n$-$S(O)_2$-;

R14 is C_{1-4}-haloalkyl-, or C_{1-5}-alkyl, optionally substituted with C_{3-4}-cycloalkyl, C_{2-4}-alkenyl-, HO-, C_{1-4}-alkyl-O-, H_2N-C(O)-, C_{1-4}-alkyl-HN-C(O)-, (C_{1-4}-alkyl)$_2$N-C(O)-;

R15 is C_{1-4}-alkyl, C_{1-4}-haloalkyl, NC-, C_{1-6}-alkyl-HN-, (C_{1-4}-alkyl)$_2$N-, (C_{1-4}-alkyl)$_2$(HO)C-, aryl or heterocyclyl;

n is 0, 1, 2 or 3.

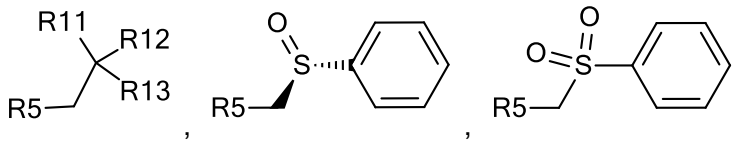
4. A compound according to one of the claims 1 to 3, wherein

R2 is C_{1-4}-alkyl-;

R3 is C_{1-4}-alkyl- optionally substituted with HO-,
or
C_{3-4}-cycloalkyl-, optionally substituted with methyl-;

R4 is H- or F-;

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

R6 is C_{2-4}-alkenyl,
or
C_{1-4}-alkyl, optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{3-4}-cycloalkyl-, halogen, HO-, C_{1-4}-alkyl-O-, (C_{1-4}-alkyl)$_2$N-, NC-, (C_{1-4}-alkyl)$_2$(O)P-, (4-Methoxyphenyl)methyl-,
or
a heterocycle selected from tetrahydrofuran-, 1, 4-dioxane-, pyrrolidine-, piperazine-, morpholine-, pyridine-, pyrazole-, triazole-, each optionally substituted independently of one another by one or two substituents selected from the group consisting of C_{1-4}-alkyl-, halogen, O=;

R7 is C_{3-4}-cycloalkyl-, optionally substituted with C_{1-4}-alkyl- or one or two halogen atoms,
or
cyclopropylmethyl-, C_{1-4}-haloalkyl-, C_{1-4}-alkyl-O-, C_{1-4}-alkyl-HN-, (C_{1-4}-alkyl)$_2$N-, C_{1-4}-alkyl-S-,

or
C_{1-4}-alkyl, straight or branched, optionally substituted with HO-, C_{1-4}-alkyl-O-, C_{1-4}-alkyl-HN-, $(C_{1-4}\text{-alkyl})_2N$- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-;

R8 is C_{1-4}-haloalkyl-O-;

R9 is C_{1-4}-alkyl- or C_{3-4}-cycloalkyl-;

R10 is C_{1-4}-alkyl- or C_{1-4}-haloalkyl-;

R11 is H, HO-, halogen-, or R14-O-;

R12 is H- or F;

R13 is cyclohexyl-, 3, 4-difluorphenyl-, 3-methyl-4N-pyridinyl-, or phenyl-, optionally substituted in 4-position with methyl, HO-, F-, Cl-, Br-, R15-$(CH_2)_n$-O-;

R14 is C_{1-4}-haloalkyl-, or C_{1-5}-alkyl, optionally substituted with C_{3-4}-cycloalkyl, C_{2-4}-alkenyl-, HO-, C_{1-4}-alkyl-O-, H_2N-C(O)-, $(C_{1-4}\text{-alkyl})$NH-C(O)-, $(C_{1-4}\text{-alkyl})_2$N-C(O)-;

R15 is NC-, $(C_{1-4}\text{-alkyl})_2N$-, $(C_{1-4}\text{-alkyl})_2(HO)C$-, phenyl, or a heterocycle selected from oxetane-, tetrahydropyran-, morpholine-;

n is 0, 1 or 2.

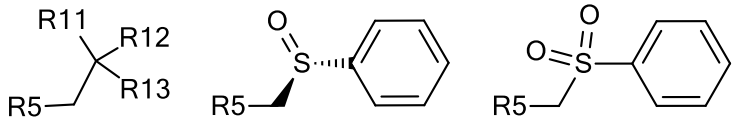
5. A compound according to one of the claims 1 to 4, wherein

R2 is methyl- or ethyl-;

R3 is ethyl-, iso-propyl-, cyclopropyl-, 1-methyl-cyclopropyl-, 1-hydroxy-iso-propyl-;

R4 is H- or F-:

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

R6 is C_{2-4}-alkenyl,
or
C_{1-4}-alkyl, optionally substituted independently of one another by one or two substituents selected from the group consisting of cyclopropyl-, F-, HO-, H_3C-O-, $(H_3C)_2N$-, NC-, $(H_3C)_2(O)P$-, (4-methoxyphenyl)methyl-,
or

a heterocycle selected from tetrahydrofuran-, 1, 4-dioxane-, pyrrolidine-, piperazine-, morpholine-, pyridine-, pyrazole-, triazole-, each optionally substituted independently of one another by one or two substituents selected from the group consisting of H_3C-, F-, O=;

R7 is cyclopropyl-, 1-flourocyclopropyl-, 2, 2-diflourocyclopropyl-, 1-methyl-cyclopropyl-, cyclobutanyl-, cyclopropylmethyl-, F_2HC-, F_3C-, (iPr)-O-, $(H_3C)NH$-, $(H_3C)_2N$-, H_3C-S-,
or
C_{1-4}-alkyl, straight or branched, optionally substituted with HO-, H_3C-O-, H_3C-CH_2-O-, $(H_3C)NH$-, $(H_3C)_2N$- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-;

R8 is F_2HC-O-, F_3C-O-;

R9 is methyl or cyclopropyl;

R10 is methyl or F_2C-;

R11 is H, HO-, F-, or R14-O-;

R12 is H- or F;

R13 is cyclohexyl-, 3, 4-difluorphenyl-, 3-methyl-4N-pyridinyl-, or phenyl-, optionally substituted in 4-position with methyl, HO-, F-, Cl-, Br-, R15-$(CH_2)_n$-O-;

R14 is FH_2C-, FH_2C-CH_2-, or C_{1-5}-alkyl, optionally substituted with cyclopropyl, H_2C=CH-, HO-, H_3C-O-, H_2N-C(O)-, $(H_3C)NH$-C(O)-;

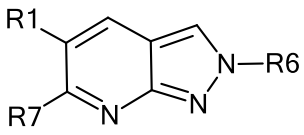
R15 is NC-, $(H_3C)_2N$-, $(H_3C)_2(HO)C$-, phenyl, or a heterocycle selected from oxetane-, tetrahydropyran-, morpholine-;

n is 0, 1 or 2.

6. A compound according to one of the claims 1 to 5, wherein

B-A is =C-N- or -N-C=;

R1 is selected from



;

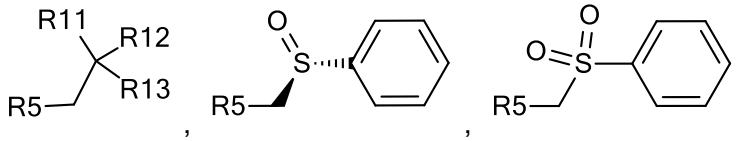
and R1 is the attaching point to the structure of formula **1**;

R2 is methyl-;

R3 is ethyl-, iso-propyl-, cyclopropyl-, 1-methyl-cyclopropyl-, 1-hydroxy-iso-propyl-;

R4 is H- or F-;

R5 is selected from



and R5 is the attaching point to the structure of formula **1**;

R6 is methyl-, ethyl-, iso-propyl-, cyclopropyl-;

R7 is cyclopropyl-, 1-fluorocyclopropyl-, 2, 2-difluorocyclopropyl-, 1-methyl-cyclopropyl-, cyclobutanyl-, cyclopropylmethyl-, F_2HC-, F_3C-, (iPr)-O-, $(H_3C)NH$-, $(H_3C)_2N$-, H_3C-S-,
or
C_{1-4}-alkyl, straight or branched, optionally substituted with HO-, H_3C-O-, H_3C-CH_2-O-, $(H_3C)NH$-, $(H_3C)_2N$- or morpholine-,
or
a heterocycle selected from pyrrolidine-, tetrahydrofuran-, tetrahydropyran-;

R11 is H, HO-, F-, or R14-O-;

R12 is H-;

R13 is cyclohexyl-, 3, 4-difluorphenyl-, 3-methyl-4N-pyridinyl-, or phenyl-, optionally substituted in 4-position with methyl, HO-, F-, Cl-, Br-, R15-$(CH_2)_n$-O-;

R14 is FH_2C-, FH_2C-CH_2-, or C_{1-5}-alkyl, optionally substituted with cyclopropyl, H_2C=CH-, HO-, H_3C-O-, H_2N-C(O)-, $(H_3C)NH$-C(O)-;

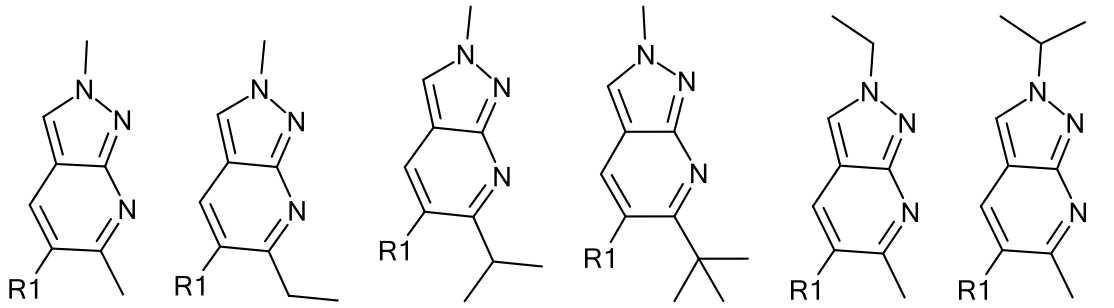
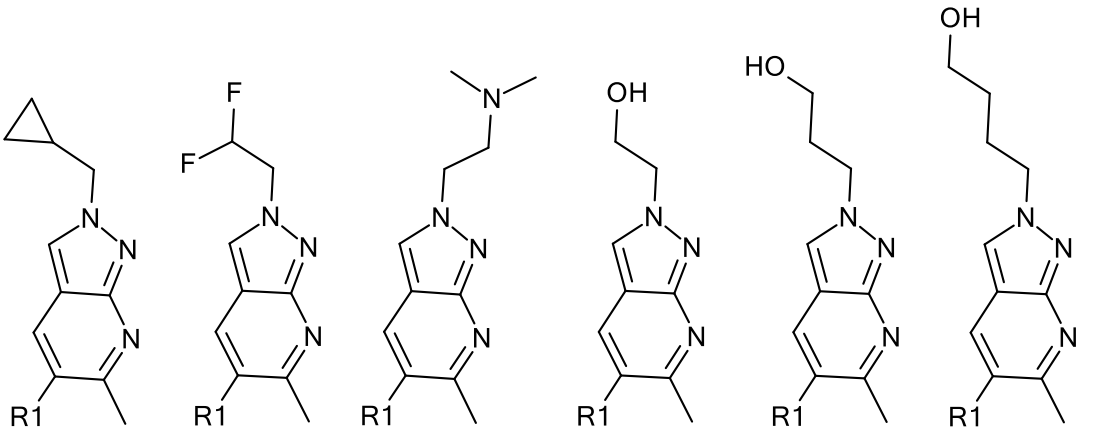
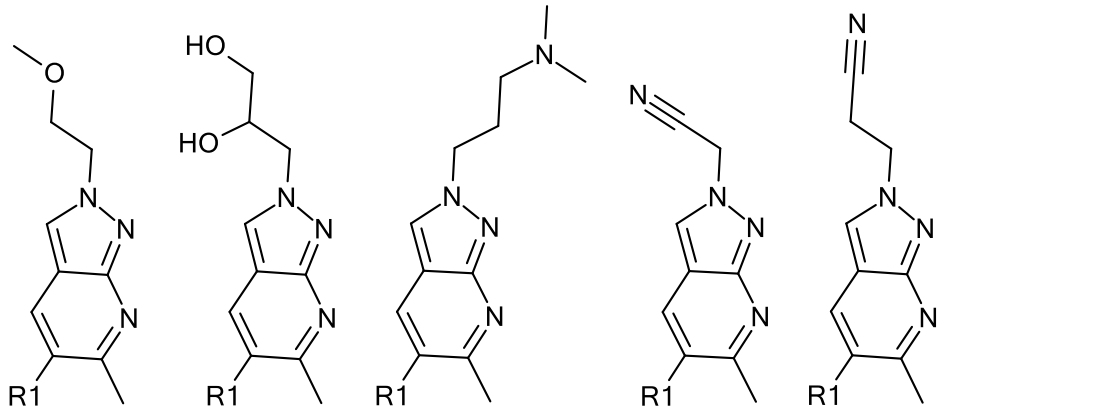
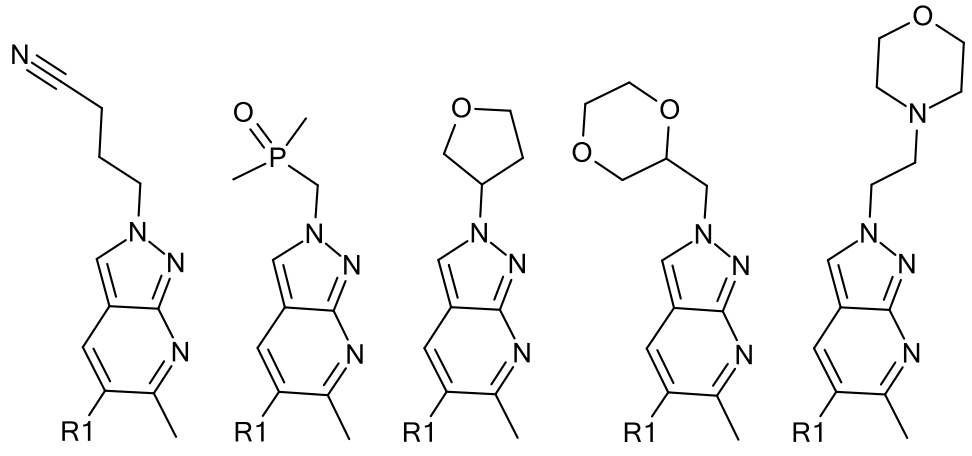
R15 is NC-, $(H_3C)_2N$-, $(H_3C)_2(HO)C$-, phenyl, or a heterocycle selected from oxetane-, tetrahydropyran-, morpholine-;

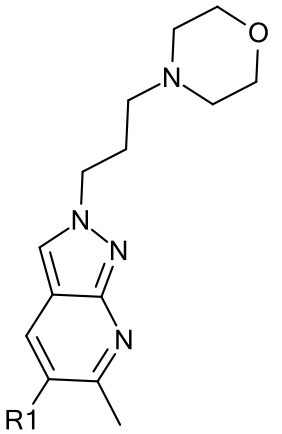
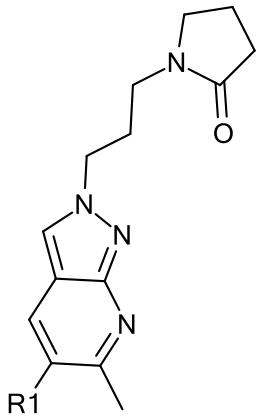
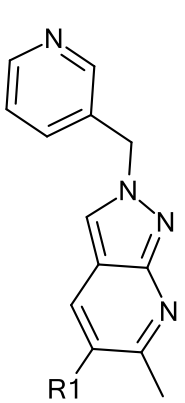
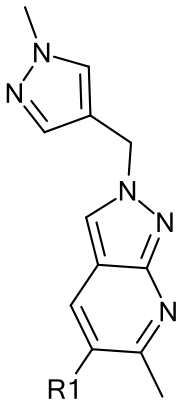
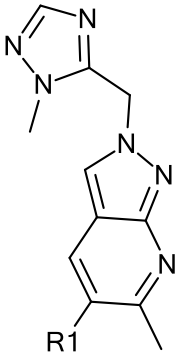
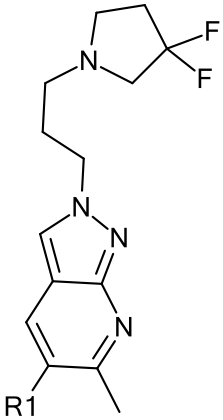
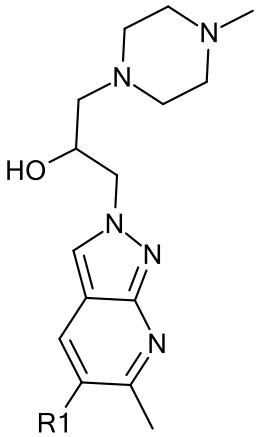
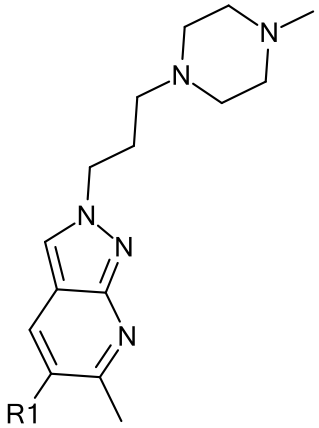
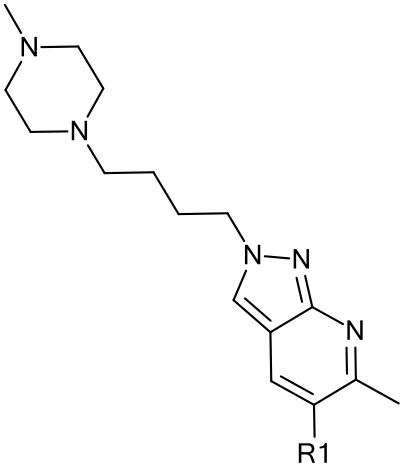
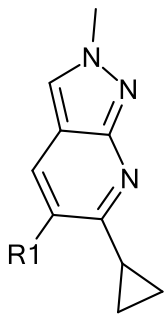
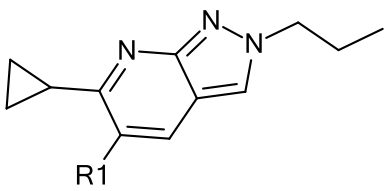
n is 0, 1 or 2.

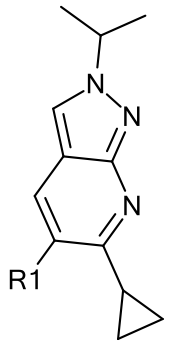
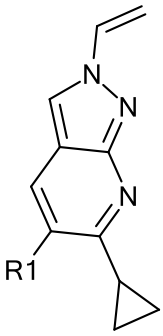
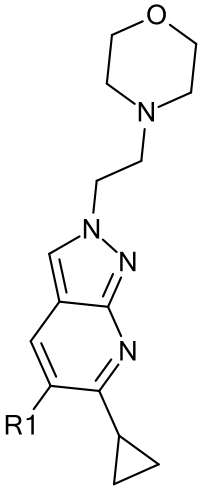
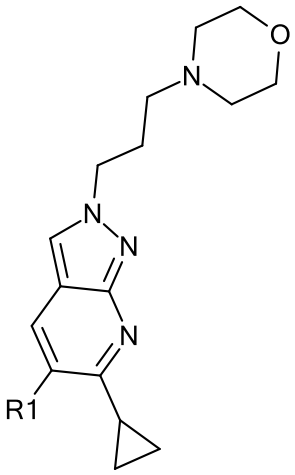
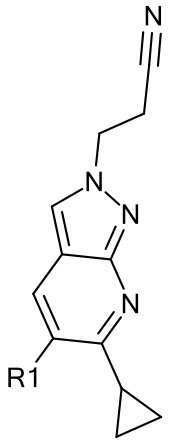
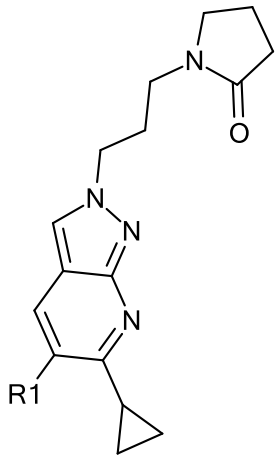
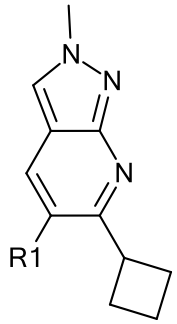
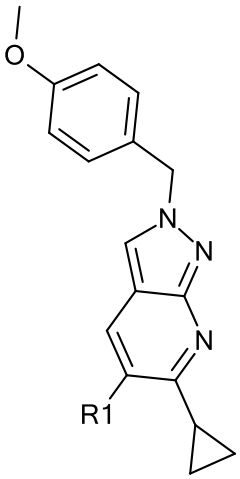
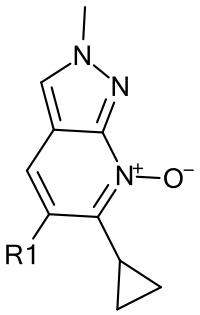
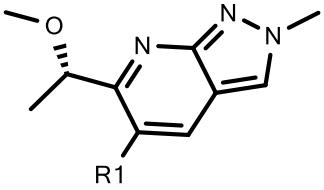
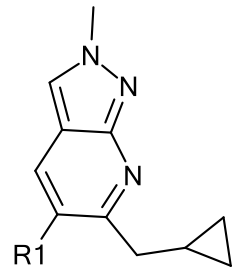
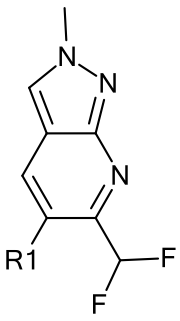
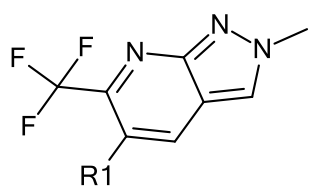
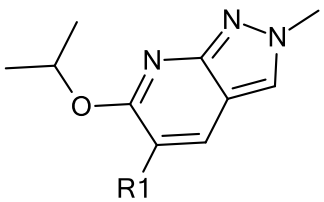
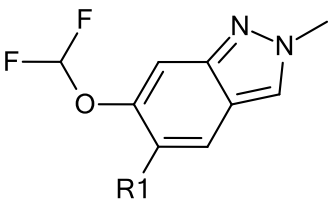
7. A compound according to one of the claims 1 to 6, wherein

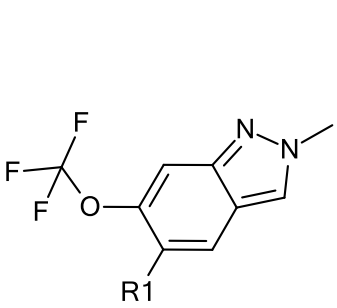
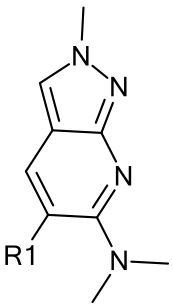
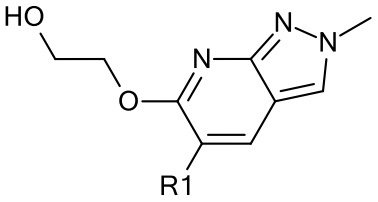
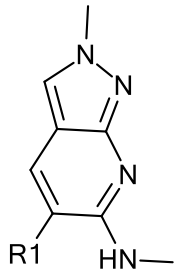
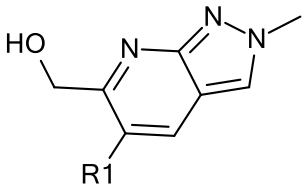
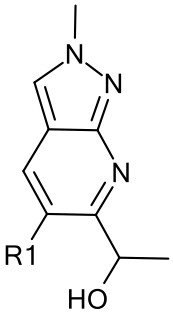
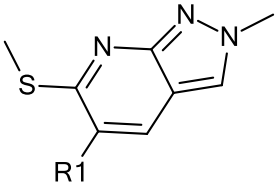
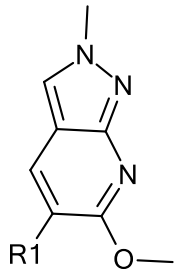
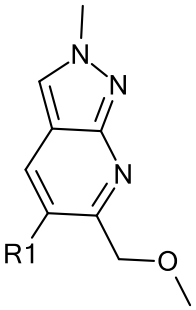
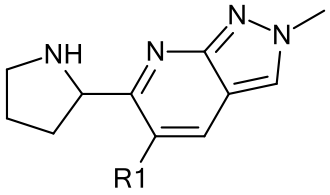
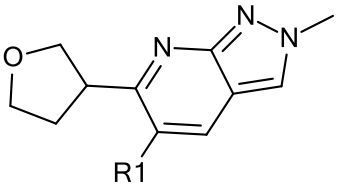
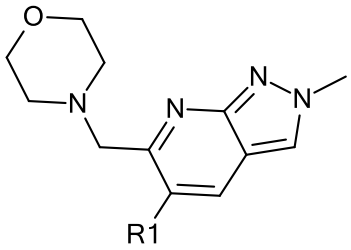
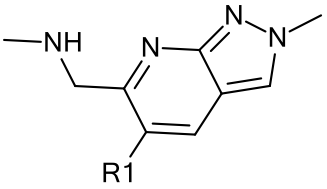
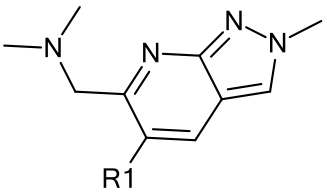
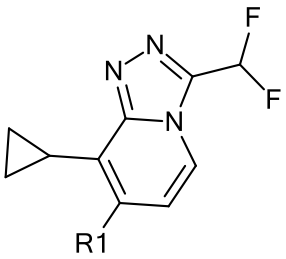
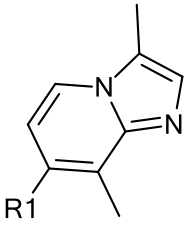
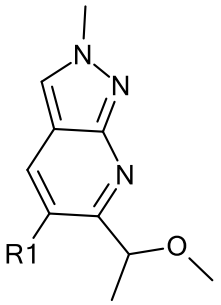
B-A is =C-N- or -N-C=;

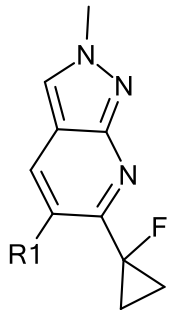
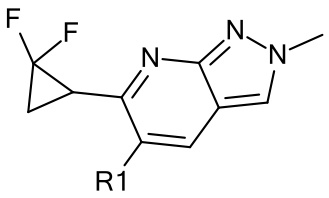
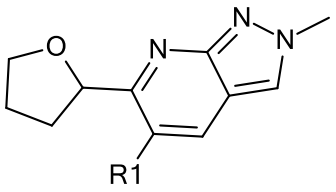
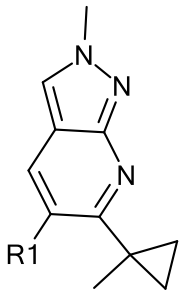
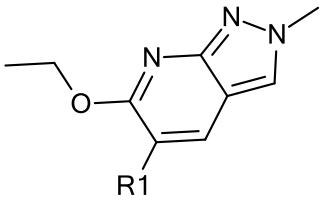
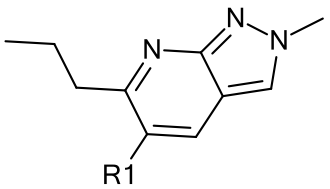
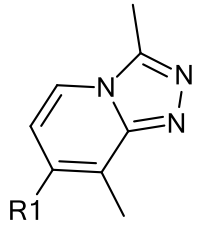
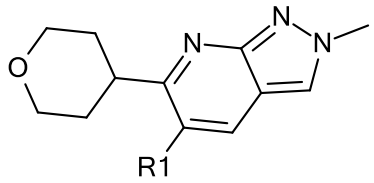
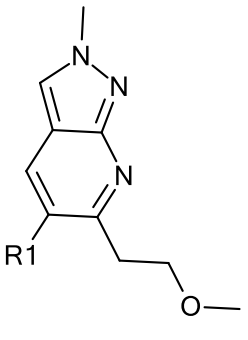
R1 is selected from


,

,

,

,

,

,

,

,

,

,

,


,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

,

5

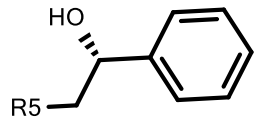
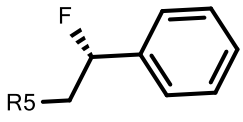
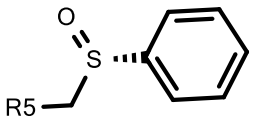
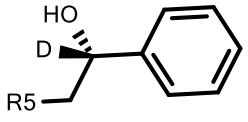
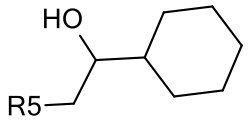
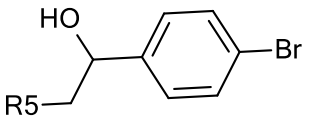
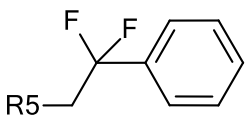
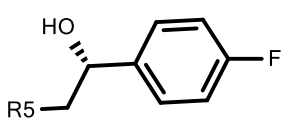
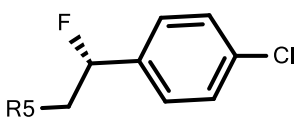
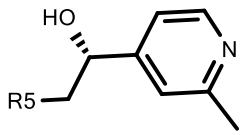
and R1 is the attaching point to the structure of formula **1**;

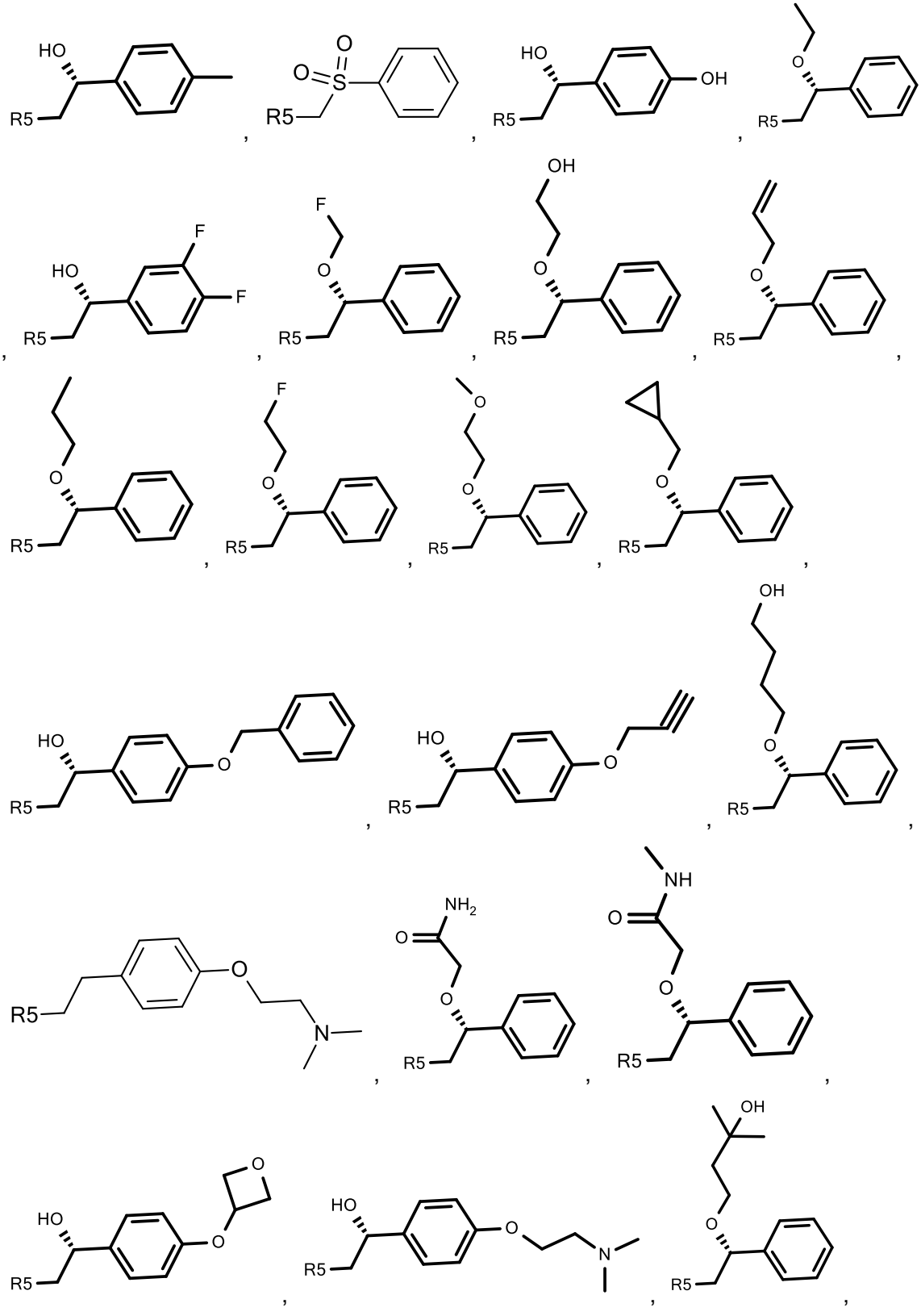
R2 is methyl- or ethyl-;

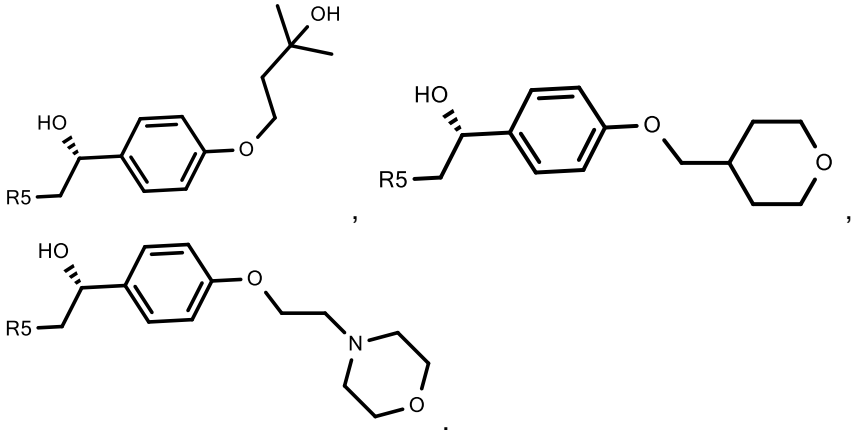
R3 is ethyl-, iso-propyl-, cyclopropyl-, 1-methyl-cyclopropyl-, ((HO)H_2C)(H_3C)HC-;

R4 is H- or F-;

R5 is selected from

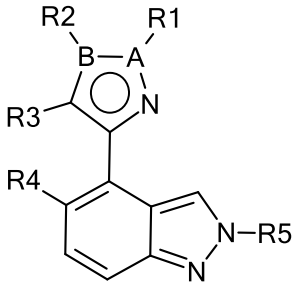















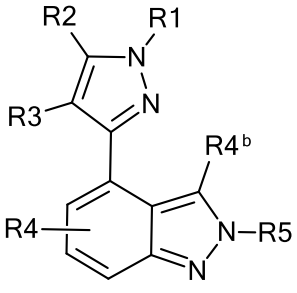
and R5 is the attaching point to the structure of formula **1**.

8. A compound according to one of the claims 1 to 7, wherein the compound of formula **1** is a compound of formula **1a**



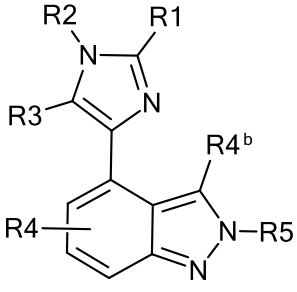
1a.

9. A compound according to one of the claims 1 to 7, wherein the compound of formula **1** is a compound of formula **1b**



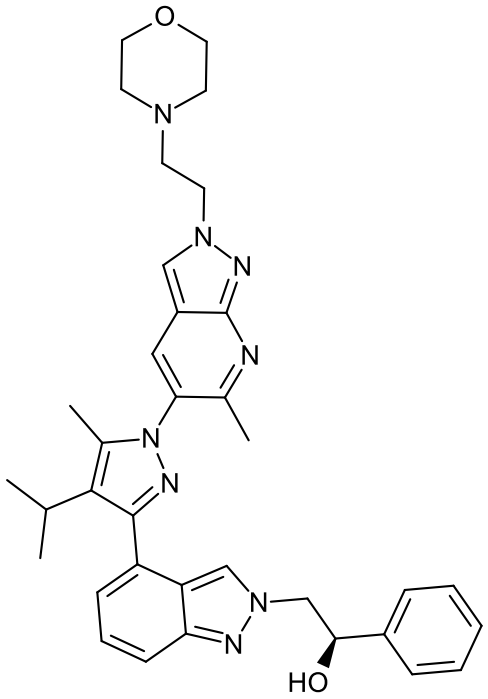
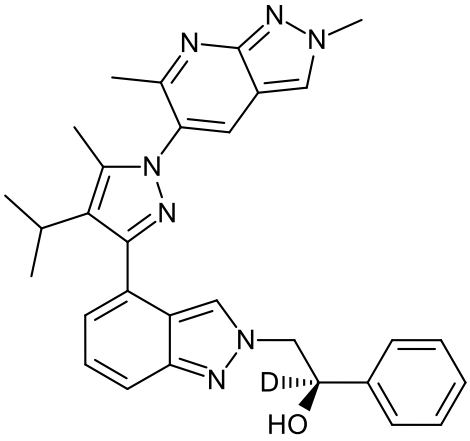
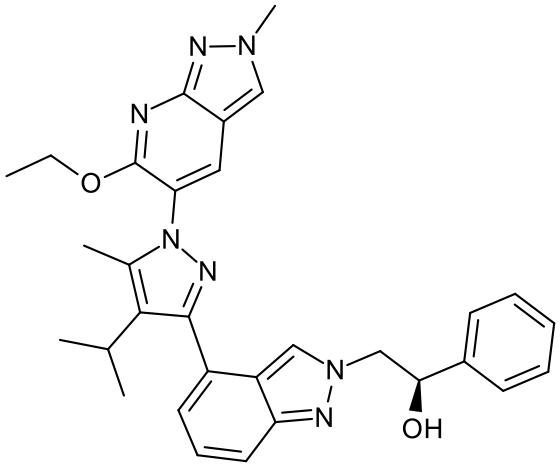
1b.

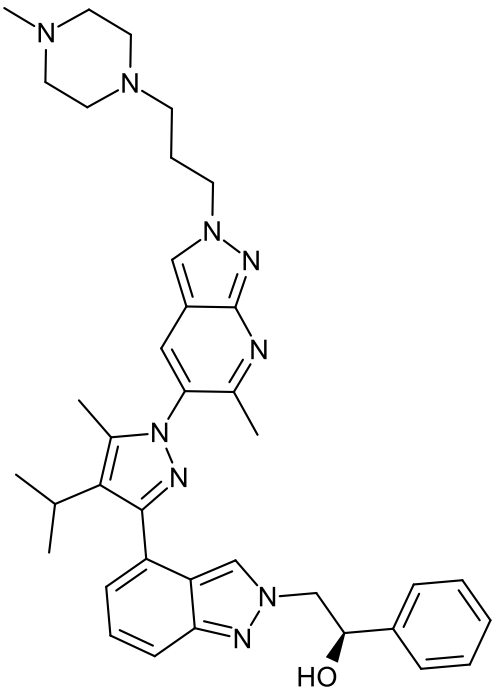
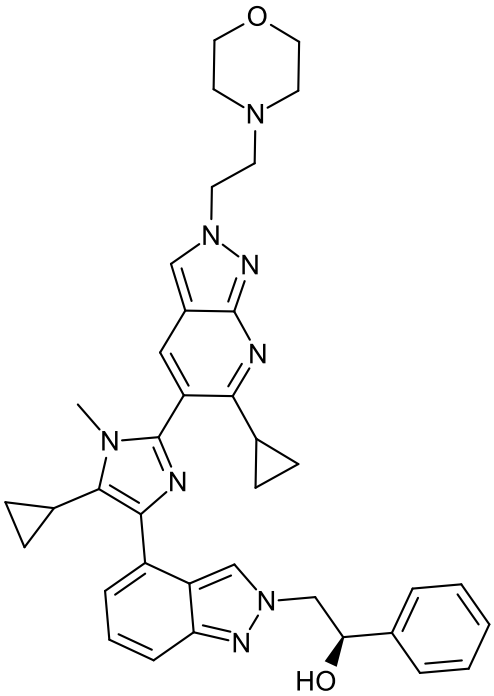
10. A compound according to one of the claims 1 to 7, wherein the compound of formula **1** is a compound of formula **1c**

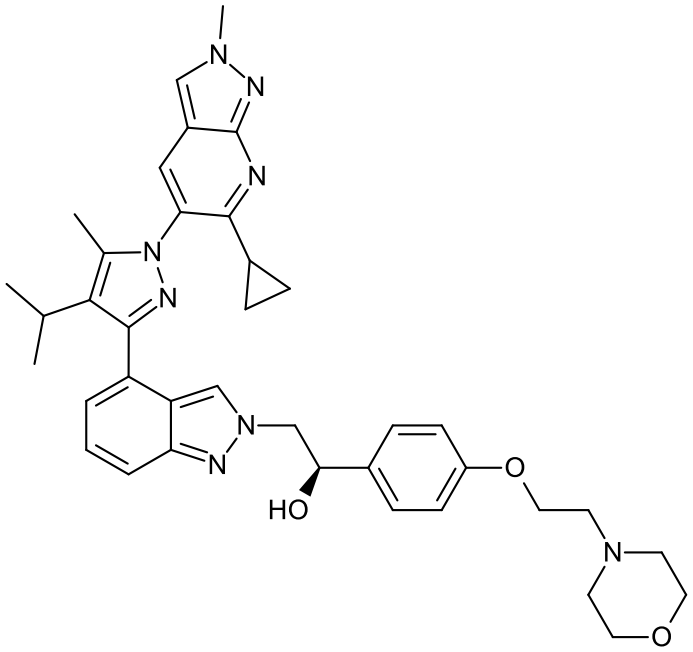
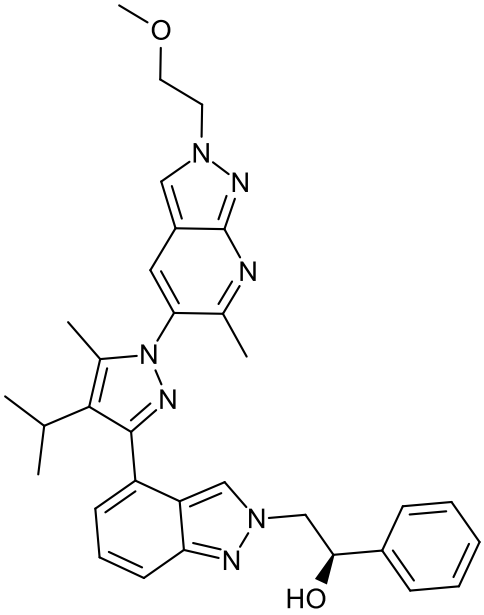
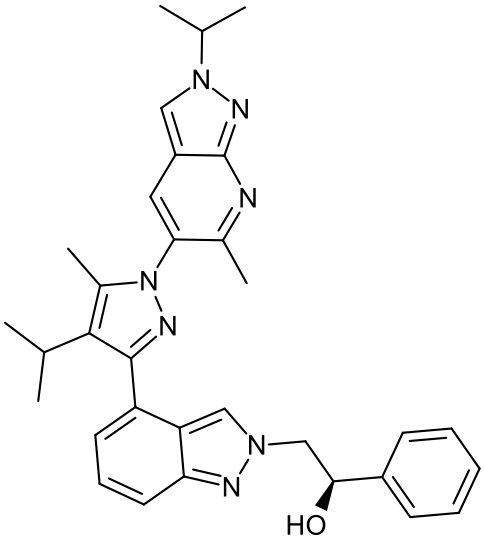


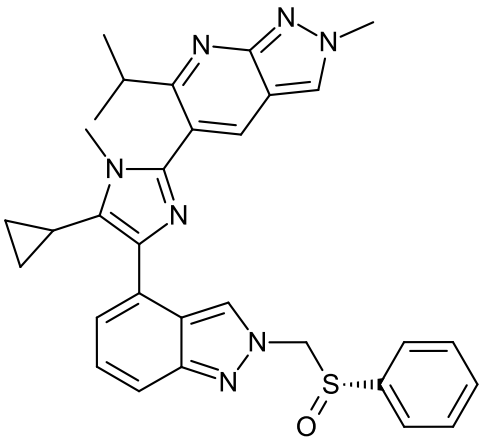
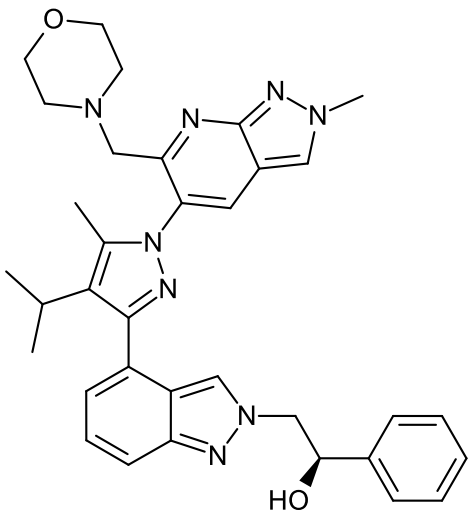
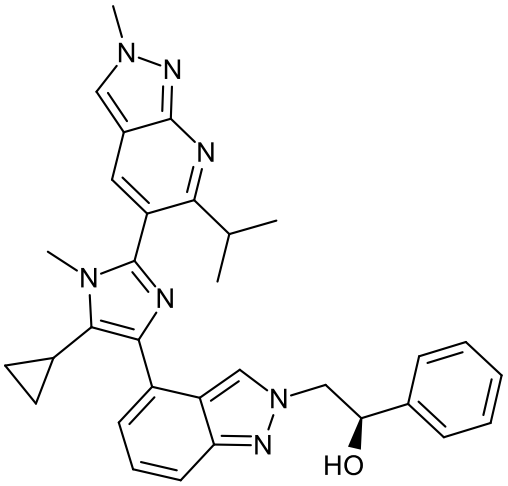
1c.

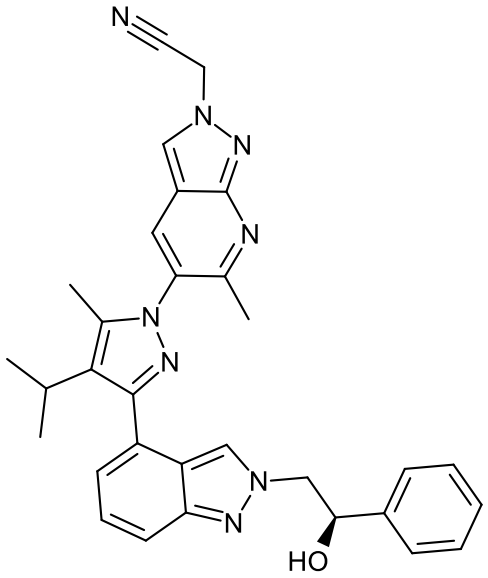
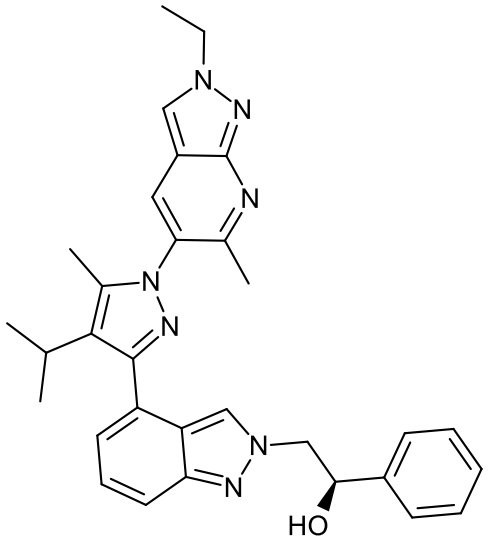
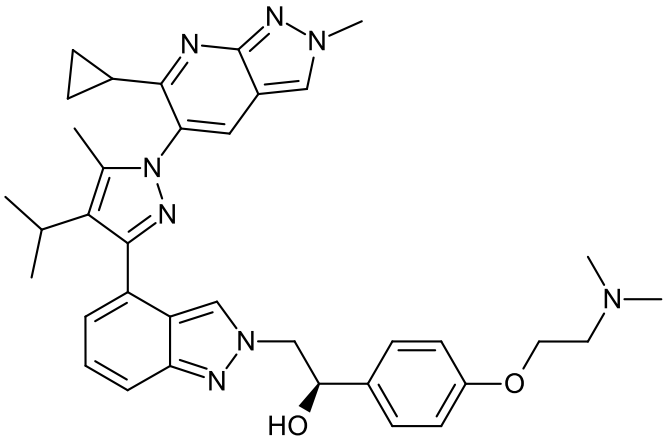
11. A compound according to one of the claims 1 to 7, selected from the following examples

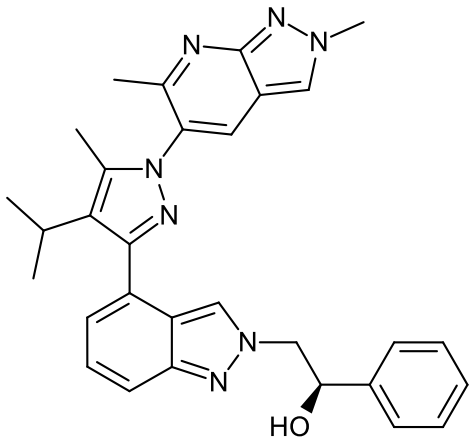
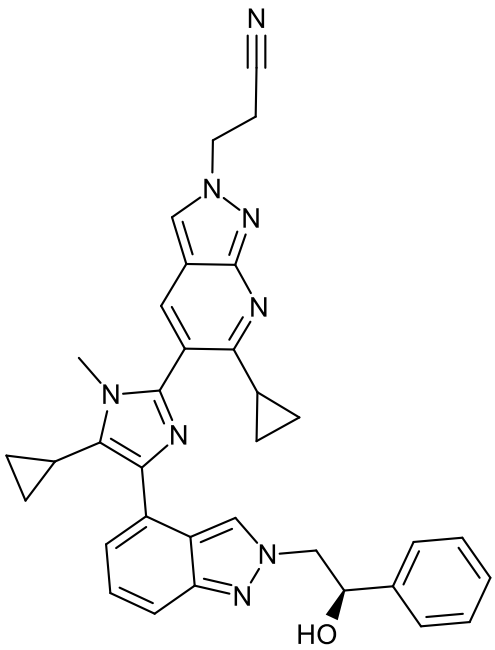
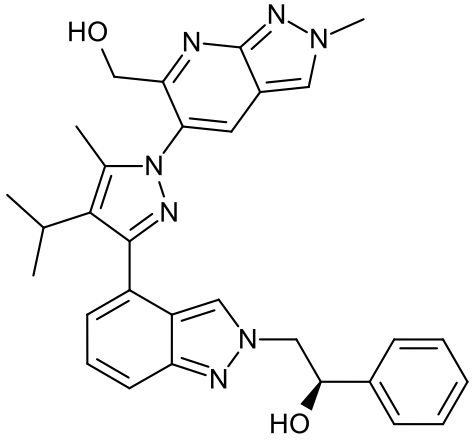
1	
3	
5	

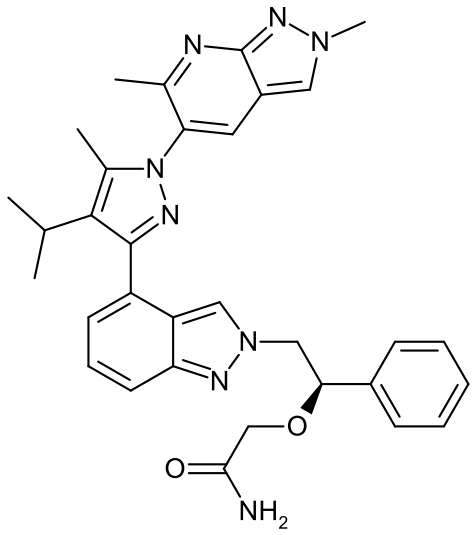
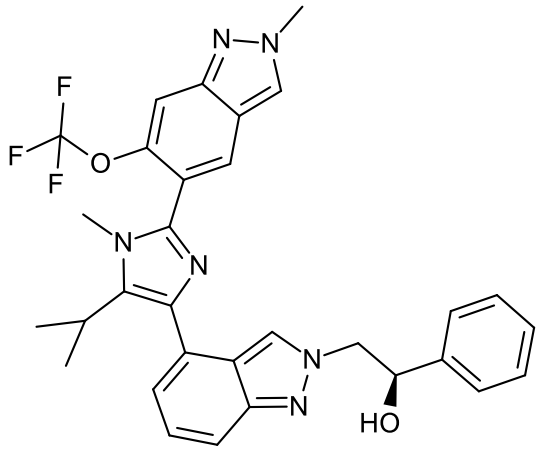
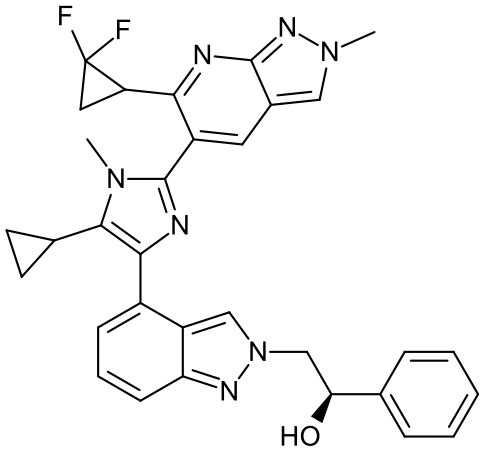
7	
10	

15	
16	
18	

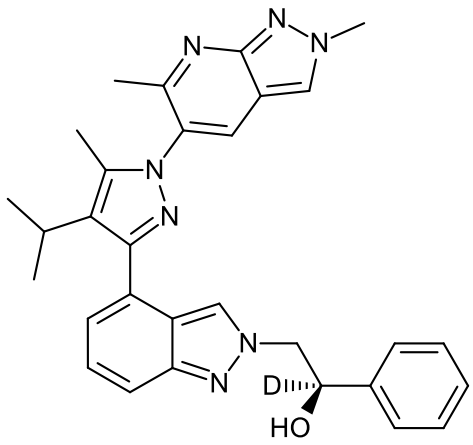
22	
26	
97	

98	
100	
101	

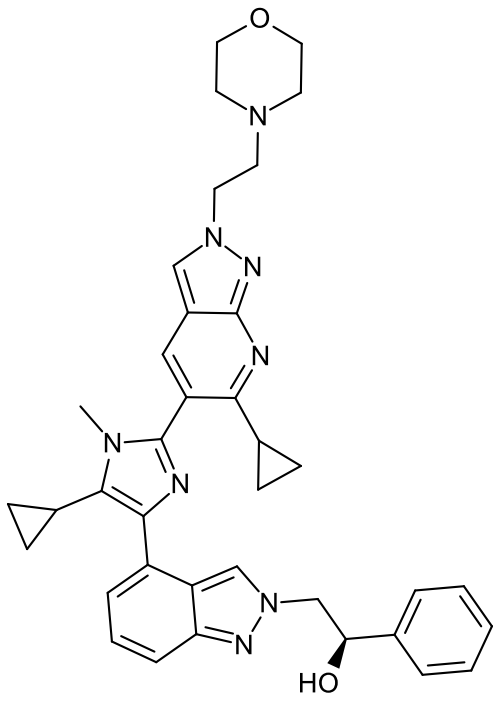
102	
104	
106	

108	
109	
110	 .

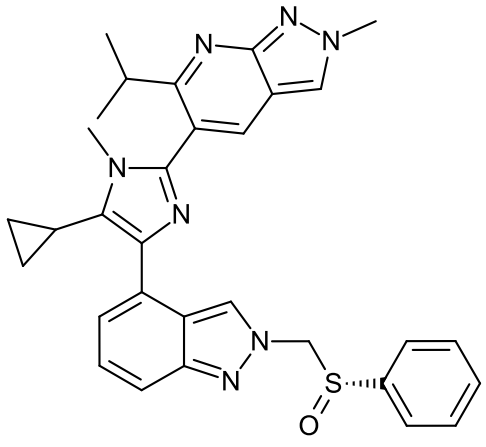
12. A compound according to one of the claims 1 to 7, wherein the compound is

3	

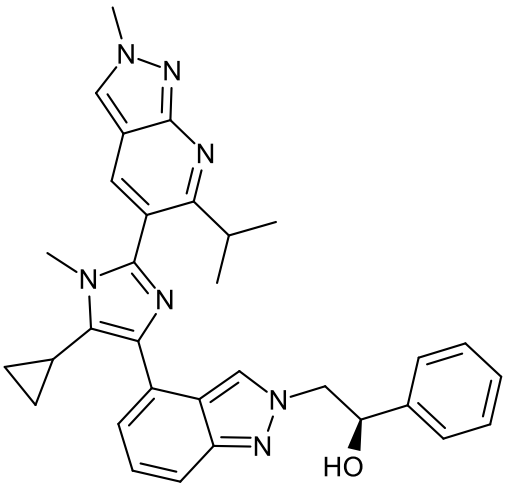
13. A compound according to one of the claims 1 to 7, wherein the compound is

10	

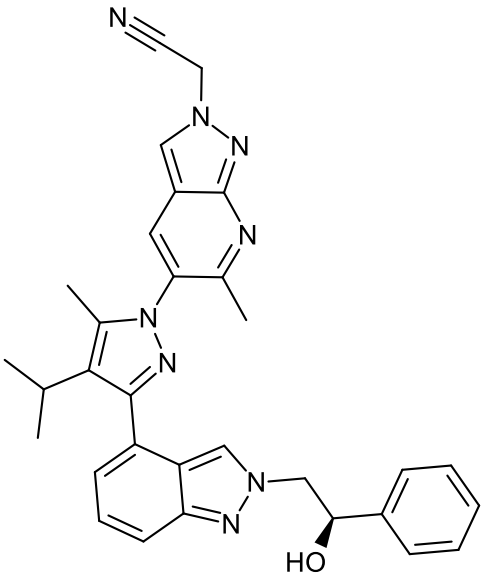
14. A compound according to one of the claims 1 to 7, wherein the compound is

22	

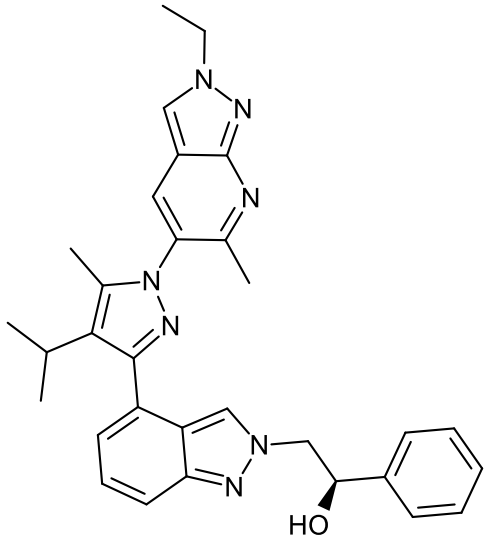
15. A compound according to one of the claims 1 to 7, wherein the compound is

97	

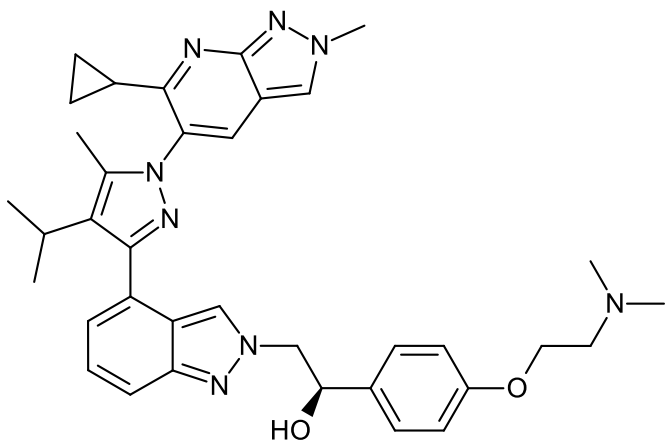
16. A compound according to one of the claims 1 to 7, wherein the compound is

98	

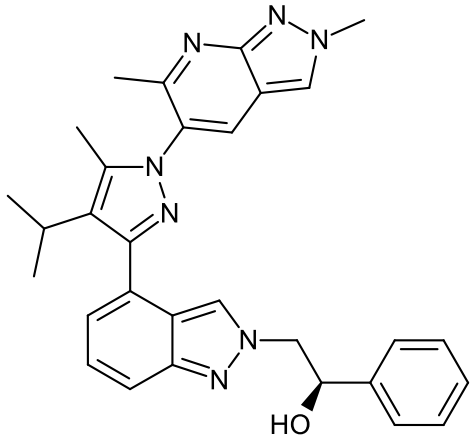
17. A compound according to one of the claims 1 to 7, wherein the compound is

100	

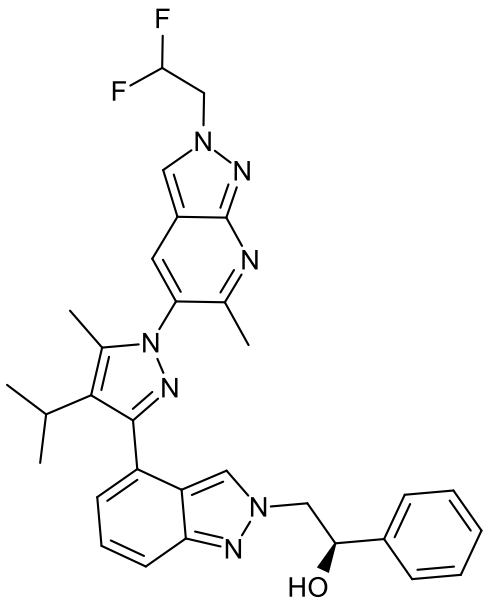
18. A compound according to one of the claims 1 to 7, wherein the compound is

101	

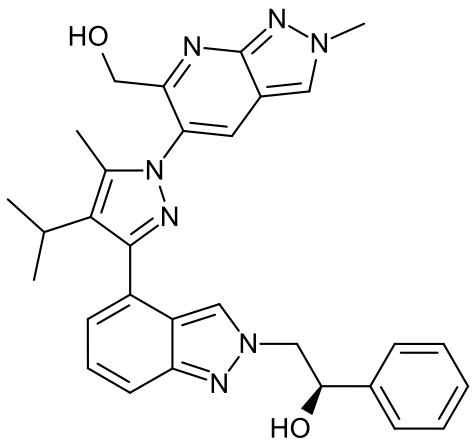
19. A compound according to one of the claims 1 to 7, wherein the compound is

102	

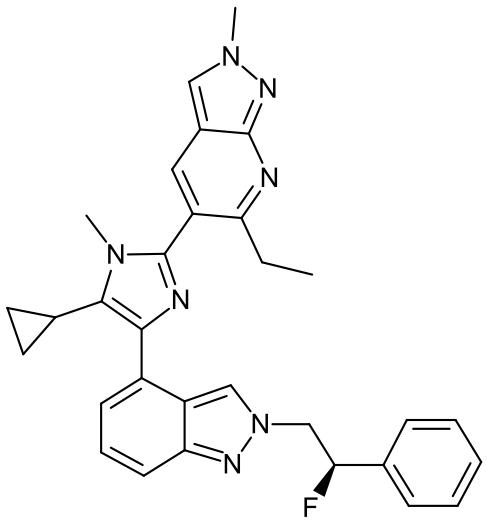
20. A compound according to one of the claims 1 to 7, wherein the compound is

103	

21. A compound according to one of the claims 1 to 7, wherein the compound is

106	

22. A compound according to one of the claims 1 to 7, wherein the compound is

107	

23. A salt of a compound of formula **1** according to any of claims 1 to 22.

24. A pharmaceutically acceptable salt of a compound of formula **1** according to any of claims 1 to 22.

25. The compound of formula **1, 1a**, **1b** or **1c** according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 for use in therapy.

26. Use of the compound of formula **1, 1a**, **1b** or **1c**, according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of systemic lupus erythematosus (SLE), (monogenic and digenic) interferonopathies (including STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières syndrome (AGS), COPA syndrome, and familial chilblain lupus), type 1 interferonopathies with mutations in DNASE2 or ATAD3A genes, age-related macular degeneration (AMD), retinopathy, glaucoma, amyotrophic lateral sclerosis (ALS), diabetes, obesity, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), Bloom's syndrome, Sjogren's syndrome, Parkinson's disease, heart failure and cancer, systemic sclerosis (SSc), dermatomyositis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatotic hepatitis (NASH), acute on chronic liver failure (ACLF), interstitial lung disease (ILD), idiopathic pulmonary fibrosis (IPF), aging/muscle disorders, sepsis, heart failure, rheumatoid arthritis and osteoarthritis.

27. Use of the compound of formula **1, 1a**, **1b** or **1c**, according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 in the manufacture of a medicament for the treatment of a fibrosing disease selected from the group consisting of systemic sclerosis (SSc), non-alcoholic steatohepatitis (NASH), acute on chronic liver failure (ACLF), (monogenic and digenic) interferonopathies (including STING-associated vasculopathy with onset in infancy (SAVI), Aicardi-Goutières syndrome (AGS), COPA syndrome, and familial chilblain lupus), type 1 interferonopathies with mutations in DNASE2 or ATAD3A genes, and interstitial lung disease (ILD).

28. Use of the compound of formula **1, 1a**, **1b** or **1c**, according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of age-related macular degeneration (AMD), retinopathy, glaucoma, aging, muscle disorders, heart failure, COVID-19/SARS-CoV-2 infection, renal inflammation, renal fibrosis, dysmetabolism, vascular diseases, cardiovascular diseases, diabetes, obesity, and cancer.

29. Pharmaceutical composition comprising a compound of formula **1, 1a**, **1b** or **1c** according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 and optionally one or more pharmaceutically acceptable carriers and/or excipients.

30. Pharmaceutical composition comprising a compound of formula **1, 1a**, **1b** or **1c** according to any of claims 1 to 22, the salt according to claim 23 or the pharmaceutically acceptable salt according to claim 24 in combination with one or more active agents selected from the group consisting of PDE 4 inhibitors, anti-inflammatory agents, anti-fibrotic agents, anti-allergic agents/ anti-histamines, bronchodilators, beta 2 agonists /betamimetics, adrenergic agonists, anticholinergic agents, methotrexate, mycophenolate mofetil, leukotriene modulators, JAK inhibitors, anti-interleukin antibodies, non-specific immunotherapeutics such as interferons or other cytokines/chemokines, cytokine/chemokine receptor modulators, toll-like receptor agonists, immune checkpoint regulators, an anti-TNF antibody, an anti-BAFF antibody.