

NOVEL COMPOUNDS FOR THE TREATMENT OF CANCER AND METABOLIC DISEASES

FIELD OF THE INVENTION

The present invention relates to novel compounds. The present invention also relates to said compounds for use as a medicine, more in particular for the prevention or treatment of diseases mediated by activity of PTPN2 and/or PTPN1, yet more in particular for the prevention or treatment of cancer. The present invention also relates to a method for the prevention or treatment of said diseases comprising the use of the novel compounds.

The present invention furthermore relates to pharmaceutical compositions or combination preparations of the novel compounds as well as to said compositions or preparations for use as a medicine, more preferably for the prevention or treatment of diseases mediated by activity of PTPN2 and/or PTPN1, yet more in particular for the prevention or treatment of cancer. The present invention also relates to processes for the preparation of said compounds. The invention also relates to combinations of the novel compounds with other therapeutic agents.

BACKGROUND OF THE INVENTION

Tyrosine-protein phosphatase non-receptor type 2 (PTPN2), also known as T cell protein tyrosine phosphatase (TC-PTP), is an enzyme that in humans is encoded by the *PTPN2* gene. It is a member of the PTP family of signaling proteins and regulates a variety of cellular processes by dephosphorylating either receptor protein tyrosine kinases, such as EGFR (epidermal growth factor receptor), CSF1R (Colony stimulating factor 1 receptor), PDGFR (Platelet-derived growth factor receptor), IR (insulin receptor) or non-receptor protein tyrosine kinases, such as JAK (janus family kinases), Src (src family kinases), or STAT (signal transducers and activators of transcription) family kinases, either in the cytoplasm or nucleus (J. Song et al, Int. J. Mol. Sci 2022, 23(17), 10025).

PTPN2 is associated with pathological processes, including inflammatory responses, immune disorders, and tumor development. The anti-inflammatory cytosolic protein tyrosine phosphatase, PTPN2, was identified as a cancer immunotherapy target after a CRISPR–Cas9-mediated genome editing study showed that deletion of PTPN2 in murine tumor cells promotes susceptibility of the tumor to checkpoint inhibitor therapy by enhancing IFN γ -mediated effects on antigen presentation and growth suppression. Enhanced anti-PD-1 response was accompanied by the recruitment of cytotoxic CD8⁺ T cells, increased antigen presentation, as reflected by the increased expression of MHC-I on tumor cells, and the increased activation of recruited T-cells. PTPN2-deficient tumor cells expressed higher levels of IFN- γ /STAT1 target genes, including those encoding T cell chemo-attractants as well as components of the antigen-processing and presentation pathway (Manguso, R.T. et al. *Nature* **2017**, 547, 413–418). More recently, PTPN2 deficiency has also been shown to enhance programmed T cell expansion and survival capacity of activated T cells (Flosbach, M. et al. *Cell Rep.* **2020**, 32, 107957). Hence, inhibitors of PTPN2

can be considered as a valuable approach as cancer immunotherapeutics.

Protein tyrosine phosphatase non-receptor type 1 (PTPN1), also known as protein tyrosine phosphatase-1B (PTP1B), has been shown to play a key role in insulin and leptin signaling and is a primary mechanism for down-regulating both the insulin and leptin receptor signaling pathways (Kenner K. A. et al., J Biol Chem 271: 19810-19816, 1996). Animals deficient in PTPN1 have improved glucose regulation and lipid profiles and are resistant to weight gain when treated with a high fat diet (Elchebly M. et al., Science 283: 1544-1548, 1999). Therefore, it is expected that PTPN1 inhibitors are useful for the treatment of metabolic diseases such as type 2 diabetes, obesity, and metabolic syndrome.

Protein tyrosine phosphatases (PTPs) have been traditionally considered challenging drug targets due to the positively charged and highly conserved nature of their catalytic site. For the former reason potent orthosteric PTP inhibitors are negatively charged and often characterized by poor cell-permeability/bioavailability. Recent patent applications from Calico/Abbvie describe inhibitors of PTPN2 and/or PTPN1: WO/2020/186199A1 and WO/2021/127499A1 describe small molecule inhibitors and WO/2021/127586 proposed protein degradation via PROTACs targeting PTPN2. Kumquat recently disclosed PTPN2 inhibitors in WO/2022/192598 and WO/2023/096928A1.

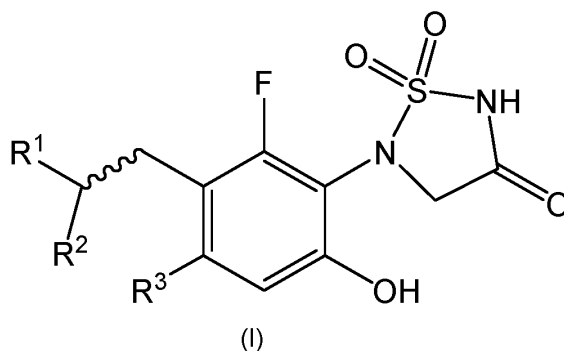
However, there is still a great need for novel, alternative or better therapeutics for the prevention or treatment of cancer and potentially other disease indications mediated by PTPN2 and/or PTPN1. Therapeutics with better target engagement, (cellular) potency, less side-effects, a higher activity, a lower toxicity, better pharmacokinetic or –dynamic properties, a better (oral) bioavailability, higher (hepatocyte) metabolic stability, varied volume of distribution, effective dosage or combinations thereof would be very welcome.

The present invention provides a class of novel compounds which can be used as inhibitors of PTPN2 and/or PTPN1 in cancer (immuno)therapy and potentially other disease indications mediated by PTPN2 and/or PTPN1.

SUMMARY OF THE INVENTION

The present invention is based on the unexpected finding that at least one of the above-mentioned problems can be solved by the below described compounds.

The present invention provides new compounds, especially a compound of formula (I), a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, hydrate, polymorph and/or prodrug thereof,



wherein:

- $\sim$ represents a double bond (=) or a triple bond (=);
- 5 - R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl;
- 10 whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with
- 15 one or more R^4 ;
- when $\sim$ is a triple bond, then R^2 is not present; when $\sim$ is a double bond, then R^2 is selected from hydrogen; alkyl and halogen; or R^2 can be taken together with R^1 to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle,
- 20 wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl, or a 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R^4 ;
- R^3 is selected from hydrogen and alkyl;
- each R^4 is independently selected from halogen; hydroxyl; sulfhydryl; =O ; =S ; -SCF_3 ; -SF_5 ; -CF_3 ;
- 25 -OCF_3 ; -CHF_2 ; -OCHF_2 ; cyano; nitro; -OZ^1 ; -SZ^1 ; -S(O)Z^1 ; $\text{-S(O)}_2\text{Z}^2$; $\text{-S(O)}_2\text{NZ}^3\text{Z}^4$; $\text{-S(O)(NZ}^3\text{)Z}^1$; $\text{-S(NZ}^3\text{)(NZ}^3\text{)Z}^1$; -C(O)H ; -C(O)Z^2 ; -C(O)OH ; -C(O)OZ^1 ; $\text{-C(O)NZ}^3\text{Z}^4$; $\text{-NZ}^3\text{Z}^4$; $\text{-NZ}^3\text{S(O)}_2\text{Z}^1$; $\text{-NZ}^3\text{S(O)}_2\text{NZ}^3\text{Z}^4$; $\text{-NZ}^3\text{C(O)OZ}^1$; $\text{-NZ}^3\text{C(O)Z}^1$; $\text{-NZ}^3\text{C(O)NZ}^3\text{Z}^4$; $\text{-P(O)Z}^3\text{Z}^4$; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl;
- 30 arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl;

heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl,

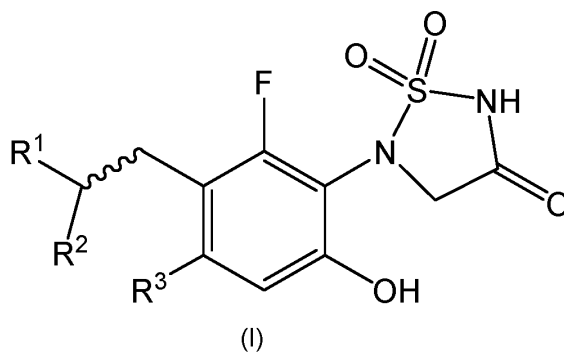
heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- 5 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclylheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

The present invention also encompasses preferably a compound of formula (I), and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), a solvate, a hydrate, a polymorph, an isotope, and/or a prodrug thereof,



wherein:

-  represents a double bond (====) or a triple bond (=====);

- R¹ is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl;

whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R⁴;

- when  is a triple bond, then R² is not present; when  is a double bond, then R² is selected from hydrogen; alkyl and halogen;

- R³ is selected from hydrogen and alkyl;

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; alkyl-oxy-alkyl; (mono or di)alkylamino; (mono or di)-alkyl-amino-alkyl; alkylthio; and alkyl-thio-alkyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, heterocyclheteroalkynyl, alkyl-oxy-alkyl, (mono or di)alkylamino, (mono or di)-alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;

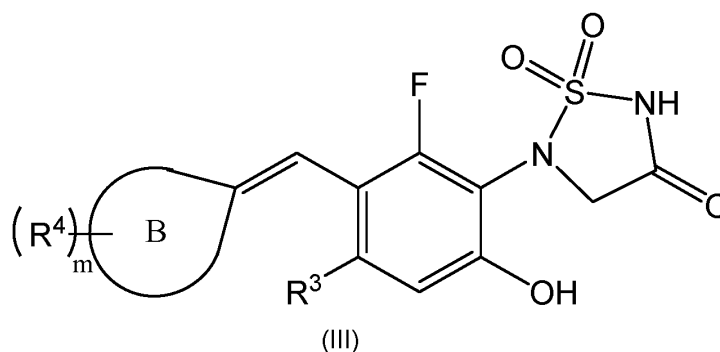
- or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;
- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle;

arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

The present invention also provides in a particular embodiment compounds of formula (III) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, polymorph and/or prodrug thereof,



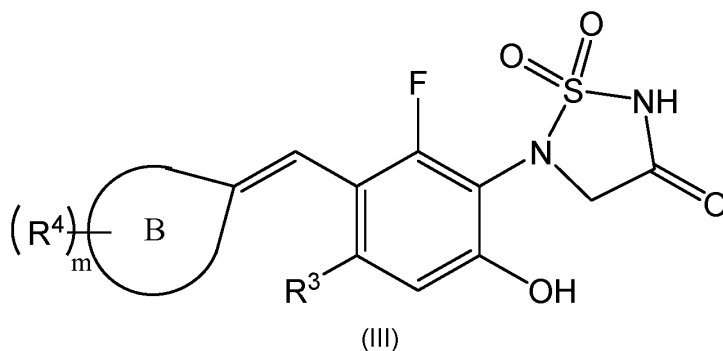
wherein:

- cycle B is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; and heterocycle;
- m is selected from 0; 1; 2; 3; 4; and 5;
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -

- NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 10 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;
- 15 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 20 and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.
- 25
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The present invention also provides in a particular embodiment compounds of formula (III) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, hydrate, polymorph, isotope, and/or prodrug thereof,



wherein:

- cycle B is selected from heterocycle; cycloalkyl; cycloalkenyl; and cycloalkynyl;
- 5 - m is selected from 0; 1; 2; 3; 4; and 5.
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 10 - wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, hydroxyl, cycloalkyl, alkenyl, alkynyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- 20 - or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, NH₂; and -NHalkyl, -N(alkyl)₂;
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- each Z^1 is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z^2 is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z^3 and Z^4 is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

The present invention provides new compounds which have been shown to possess inhibitory activity on PTPN2 and/or PTPN1. The present invention furthermore demonstrates that these compounds efficiently inhibit the activity of PTPN2 and/or PTPN1. Therefore, these compounds constitute a useful class of new potent compounds that can be used in the treatment and/or prevention of PTPN2 and/or PTPN1 mediated disorders in animals, mammals and humans, more specifically for the treatment and/or prevention of (i) cancer, more specifically lung cancer, breast cancer, head and neck cancer, oesophageal cancer, kidney cancer, bladder cancer, colon cancer, ovarian cancer, cervical cancer, endometrial cancer, liver cancer, skin cancer, pancreatic cancer, gastric cancer, brain cancer and prostate cancer, yet more specifically colon cancer, kidney cancer, pancreatic cancer, breast cancer, melanoma, head and neck squamous cell carcinoma and non-small cell lung cancer and (ii) metabolic diseases.

The present invention furthermore relates to the compounds of the invention for use as a medicine, to the use of such compounds as medicines and to their use for the manufacture of medicaments, more in particular for treating and/or preventing PTPN2 and/or PTPN1 mediated diseases, in particular (i) cancer and (ii) metabolic diseases in animals or mammals, more in particular in humans. The invention also relates to pharmaceutical compositions comprising the compounds of the invention in an effective amount, to said pharmaceutical compositions for use as a medicine, more in particular for use as a medicine for the prevention or treatment of PTPN2 and/or PTPN1 mediated disorders and to the method of preparation of manufacturing of said pharmaceutical compositions.

The present invention also relates to a method of treatment or prevention of PTPN2 and/or PTPN1 mediated disorders in humans by the administration of one or more such compounds, optionally in combination with one or more other medicines, to a patient in need thereof. Also

disclosed herein is a method of treating cancer in a patient in need thereof, comprising administering to the patient an effective amount of a compound disclosed herein in combination with an additional therapeutic agent. In some embodiments, the additional medicine is an immunotherapeutic agent. For example, in some embodiments, the immunotherapeutic agent is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody and an anti-CTLA-4 antibody.

When reference is made to the treatment or prevention of PTPN2 and/or PTPN1 mediated diseases, this in particular embodiment refers to (i) cancer, more in particular lung cancer, breast cancer, head and neck cancer, oesophageal cancer, kidney cancer, bladder cancer, colon cancer, ovarian cancer, cervical cancer, endometrial cancer, liver cancer, skin cancer, pancreatic cancer, gastric cancer, brain cancer and prostate cancer, yet more in particular colon cancer, kidney cancer, pancreatic cancer, breast cancer, melanoma, head and neck squamous cell carcinoma and non-small cell lung cancer and (ii) metabolic diseases, more specifically non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, type-2 diabetes, heart disease, atherosclerosis, arthritis, cystinosis, phenylketonuria, proliferative retinopathy, metabolic syndrome or Kearns-Sayre disease in animals or mammals, more in particular in humans.

More in particular in relation to the treatment or prevention of cancer, the invention comprises administering to the patient an effective amount of a compound disclosed herein, also in combination with an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an immunotherapeutic agent. For example, in some embodiments, the immunotherapeutic agent is selected from the group consisting of an anti-PD-1 antibody, an anti-PD-L1 antibody and an anti-CTLA-4 antibody. In particular related to the treatment or prevention of metabolic diseases comprises the treatment or prevention of type-2 diabetes in a patient in need thereof, comprising administering to the patient an effective amount of a compound disclosed herein, or comprises treating and/or controlling obesity in a patient in need thereof, comprising administering to the patient an effective amount of a compound disclosed herein. For example, disclosed herein is a method of inhibiting further weight gain in an overweight or obese patient in need thereof, comprising administering to the patient an effective amount of a compound disclosed herein.

The present invention also relates to a method of preparation of the compounds of the invention comprising the steps for synthesis of the compounds as described herein.

FIGURES

Figure 1: In vivo tumor growth inhibition with cpd008. Antitumor activity of cpd008 in the treatment of colon cancer in a syngeneic subcutaneous MC38 mouse tumor model performed in accordance with example 45.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further described and in some instances with respect to particular embodiments, but the invention is not limited thereto.

5 The term "PTPN2 and/or PTPN1 mediated diseases" or "PTPN2 and/or PTPN1 mediated disorders" refers to diseases, disorders or conditions in which PTPN2 and/or PTPN1 signaling is active or activated and whereby PTPN2 and/or PTPN1 activity or activation is contributing, driving, sustaining, enabling or the like such disease. PTPN2 and/or PTPN1 mediated diseases includes cancer, but also includes metabolic diseases or any other disease, disorder or ailment favorably responsive to PTPN2 or PTPN1 inhibitor treatment.

10 The term "cancer" as used herein refers to all types of animal, more specifically human cancers, neoplasm or (malignant) tumors including carcinomas, sarcomas, lymphomas, leukemias, germ cell tumors and blastomas and thus includes solid and lymphoid cancers. Exemplary cancers that may be treated with a compound, pharmaceutical composition, or method provided herein include lymphoma, sarcoma, bladder cancer, bone cancer, brain tumor,
15 cervical cancer, colon cancer, esophageal cancer, gastric cancer, head and neck cancer, kidney cancer, myeloma, thyroid cancer, leukemia, prostate cancer, breast cancer (e.g., ER positive, ER negative, chemotherapy resistant, herceptin resistant, HER2 positive, doxorubicin resistant, tamoxifen resistant, ductal carcinoma, lobular carcinoma, primary, metastatic), ovarian cancer, pancreatic cancer, liver cancer (e.g., hepatocellular carcinoma),
20 lung cancer (e.g., non-small cell lung carcinoma, squamous cell lung carcinoma, adenocarcinoma, large cell lung carcinoma, small cell lung carcinoma, carcinoid, sarcoma), glioblastoma multiforme, glioma, or melanoma. Additional examples include, cancer of the thyroid, endocrine system, brain, breast, cervix, colon, head & neck, liver, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus or Medulloblastoma,
25 Hodgkin's Disease, Non-Hodgkin's Lymphoma, multiple myeloma, neuroblastoma, glioma, glioblastoma multiforme, ovarian cancer, rhabdomyosarcoma, primary thrombocytosis, primary macroglobulinemia, primary brain tumors, cancer, malignant pancreatic insuloma, malignant carcinoid, urinary bladder cancer, premalignant skin lesions, testicular cancer, lymphomas, thyroid cancer, neuroblastoma, esophageal cancer, genitourinary tract cancer, malignant
30 hypercalcemia, endometrial cancer, adrenal cortical cancer, neoplasms of the endocrine or exocrine pancreas, medullary thyroid cancer, medullary thyroid carcinoma, melanoma, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, Paget's Disease of the Nipple, Phyllodes Tumors, Lobular Carcinoma, Ductal Carcinoma, cancer of the pancreatic stellate cells, cancer of the hepatic stellate cells, or prostate cancer.

35 The term "carcinoma" refers to a malignant new growth made up of epithelial cells tending to infiltrate the surrounding tissues and give rise to metastases. Exemplary carcinomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for

example, medullary thyroid carcinoma, familial medullary thyroid carcinoma, acinar carcinoma, acinous carcinoma, adenocystic carcinoma, adenoid cystic carcinoma, carcinoma adenomatosum, carcinoma of adrenal cortex, alveolar carcinoma, alveolar cell carcinoma, basal cell carcinoma, carcinoma basocellulare, basaloid carcinoma, basosquamous cell carcinoma, 5 bronchioalveolar carcinoma, bronchiolar carcinoma, bronchogenic carcinoma, cerebriform carcinoma, cholangiocellular carcinoma, chorionic carcinoma, colloid carcinoma, comedo carcinoma, corpus carcinoma, cribriform carcinoma, carcinoma en cuirasse, carcinoma cutaneum, cylindrical carcinoma, cylindrical cell carcinoma, duct carcinoma, ductal carcinoma, carcinoma durum, embryonal carcinoma, encephaloid carcinoma, epierrmoid carcinoma, 10 carcinoma epitheliale adenoides, exophytic carcinoma, carcinoma ex ulcere, carcinoma fibrosum, gelatiniformi carcinoma, gelatinous carcinoma, giant cell carcinoma, carcinoma gigantocellulare, glandular carcinoma, granulosa cell carcinoma, hair-matrix carcinoma, hematoid carcinoma, hepatocellular carcinoma, Hurthle cell carcinoma, hyaline carcinoma, hypernephroid carcinoma, infantile embryonal carcinoma, carcinoma in situ, intraepidermal carcinoma, intraepithelial 15 carcinoma, Krompecher's carcinoma, Kulchitzky-cell carcinoma, large-cell carcinoma, lenticular carcinoma, carcinoma lenticulare, lipomatous carcinoma, lobular carcinoma, lymphoepithelial carcinoma, carcinoma medullare, medullary carcinoma, melanotic carcinoma, carcinoma molle, mucinous carcinoma, carcinoma muciparum, carcinoma mucocellulare, mucoepidermoid carcinoma, carcinoma mucosum, mucous carcinoma, carcinoma myxomatodes, nasopharyngeal 20 carcinoma, oat cell carcinoma, carcinoma ossificans, osteoid carcinoma, papillary carcinoma, periportal carcinoma, preinvasive carcinoma, prickle cell carcinoma, pultaceous carcinoma, renal cell carcinoma of kidney, reserve cell carcinoma, carcinoma sarcomatodes, schneiderian carcinoma, scirrhus carcinoma, carcinoma scroti, signet- ring cell carcinoma, carcinoma simplex, small-cell carcinoma, solanoid carcinoma, spheroidal cell carcinoma, spindle cell 25 carcinoma, carcinoma spongiosum, squamous carcinoma, squamouscell carcinoma, string carcinoma, carcinoma telangiectaticum, carcinoma telangiectodes, transitional cell carcinoma, carcinoma tuberosum, tubular carcinoma, tuberos carcinoma, verrucous carcinoma, or carcinoma villosum.

The term "leukemia" refers broadly to progressive, malignant diseases of the blood- 30 forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number abnormal cells in the blood-leukemic or aleukemic 35 (subleukemic). Exemplary leukemias that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acute nonlymphocytic leukemia, chronic lymphocytic leukemia, acute granulocytic leukemia, chronic granulocytic leukemia, acute

promyelocytic leukemia, adult T-cell leukemia, aleukemic leukemia, a leukocythemic leukemia, basophylic leukemia, blast cell leukemia, bovine leukemia, chronic myelocytic leukemia, leukemia cutis, embryonal leukemia, eosinophilic leukemia, Gross' leukemia, hairy- cell leukemia, hemoblastic leukemia, hemocytoblastic leukemia, histiocytic leukemia, stem cell leukemia, acute

5 monocytic leukemia, leukopenic leukemia, lymphatic leukemia, lymphoblastic leukemia, lymphocytic leukemia, lymphogenous leukemia, lymphoid leukemia, lymphosarcoma cell leukemia, mast cell leukemia, megakaryocyte leukemia, micromyeloblastic leukemia, monocytic leukemia, myeloblasts leukemia, myelocytic leukemia, myeloid granulocytic leukemia, myelomonocytic leukemia, Naegeli leukemia, plasma cell leukemia, multiple myeloma,

10 plasmacytic leukemia, promyelocytic leukemia, Rieder cell leukemia, Schilling's leukemia, stem cell leukemia, subleukemic leukemia, or undifferentiated cell leukemia.

The term "sarcoma" generally refers to a tumor which is made up of a substance like the embryonic connective tissue and is generally composed of closely packed cells embedded in a fibrillar or homogeneous substance. Sarcomas that may be treated with a compound,

15 pharmaceutical composition, or method provided herein include a chondrosarcoma, fibrosarcoma, lymphosarcoma, melanosarcoma, myxosarcoma, osteosarcoma, Abemethy's sarcoma, adipose sarcoma, liposarcoma, alveolar soft part sarcoma, ameloblastic sarcoma, botryoid sarcoma, chloroma sarcoma, chorio carcinoma, embryonal sarcoma, Wilms' tumor sarcoma, endometrial sarcoma, stromal sarcoma, Ewing's sarcoma, fascial sarcoma, fibroblastic

20 sarcoma, giant cell sarcoma, granulocytic sarcoma, Hodgkin's sarcoma, idiopathic multiple pigmented hemorrhagic sarcoma, immunoblastic sarcoma of B cells, lymphoma, immunoblastic sarcoma of T-cells, Jensen's sarcoma, Kaposi's sarcoma, Kupffer cell sarcoma, angiosarcoma, leukosarcoma, malignant mesenchymoma sarcoma, parosteal sarcoma, reticulocytic sarcoma, Rous sarcoma, serocystic sarcoma, synovial sarcoma, or telangiectaltic sarcoma.

25 The term "melanoma" refers to a tumor arising from the melanocytic system of the skin and other organs. Melanomas that may be treated with a compound, pharmaceutical composition, or method provided herein include, for example, acral-lentiginous melanoma, amelanotic melanoma, benign juvenile melanoma, Cloudman's melanoma, S91 melanoma, Harding-Passey melanoma, juvenile melanoma, lentigo maligna melanoma, malignant melanoma, nodular

30 melanoma, subungal melanoma, or superficial spreading melanoma.

PTPN2 and/or PTPN1 mediated diseases also includes cancers that have developed resistance to prior treatments such as EGFR inhibitors, MEK inhibitors, AXL inhibitors, B-RAF inhibitors, RAS inhibitors, immunomodulatory agents and others.

The term "metabolic disease" as used herein refers to a disease or condition affecting a

35 metabolic process in a subject and includes non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes (e.g., Type I diabetes, Type II diabetes, or gestational diabetes),

metabolic syndrome, phenylketonuria, proliferative retinopathy, or Kearns- Sayre disease. In some embodiments, the treatment or prevention of a metabolic disease comprises decreasing or eliminating a symptom of such metabolic disease comprising elevated blood pressure, elevated blood sugar level, weight gain, fatigue, blurred vision, abdominal pain, flatulence, constipation, diarrhea, jaundice, and the like.

The term "treat" or "treating" as used herein is intended to refer to administration of a compound or composition of the invention to a subject for the purpose of effecting a therapeutic benefit or prophylactic benefit, here in particular through inhibition of PTPN2 and/or PTPN1. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity of, or preventing a disease, disorder, or condition, or one or more symptoms, complications or biochemical indicia of such disease, disorder or condition, here in particular mediated through PTPN2 and/or PTPN1. By "therapeutic benefit" is meant eradication, amelioration, reversing, alleviating, inhibiting the progress of or lessening the severity of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is afflicted with the underlying disorder in some embodiments. For prophylactic benefit, in some embodiments, the compositions are administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made. For example certain methods herein treat cancer by decreasing or reducing or preventing the occurrence, growth, metastasis, or progression of cancer or decreasing a symptom of cancer.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, a patient, who has been the object of treatment, observation or experiment or who is in need of such treatment.

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation or partial alleviation of the symptoms of the disease or disorder being treated.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the therapeutically effective amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "antagonist" or "inhibitor" as used herein in reference to inhibitors of the PTPN2 and/or PTPN1 activity or activation, refers to a compound capable of producing, depending on

the circumstance, a functional antagonism or inhibition of PTPN2 and/or PTPN1 activity or activation.

It is to be noticed that the term "comprising", used in the claims, should not be interpreted as being restricted to the means listed thereafter; it does not exclude other elements or steps.

5 Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all referring to the same embodiment, but may. Furthermore, the particular
10 features, structures or characteristics may be combined in any suitable manner, as would be apparent to one of ordinary skill in the art from this disclosure, in one or more embodiments. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

Similarly it should be appreciated that in the description of exemplary embodiments of the
15 invention, various features of the invention are sometimes grouped together in a single embodiment, figure, or description thereof for the purpose of streamlining the disclosure and aiding in the understanding of one or more of the various inventive aspects.

In each of the following definitions, the number of carbon atoms represents the maximum number of carbon atoms generally optimally present in the substituent or linker; it is understood
20 that where otherwise indicated in the present application, the number of carbon atoms represents the optimal maximum number of carbon atoms for that particular substituent or linker.

The term "leaving group" or "LG" as used herein means a chemical group which is susceptible to be displaced by a nucleophile or cleaved off or hydrolyzed in basic or acidic conditions. In a particular embodiment, a leaving group is selected from a halogen atom (e.g., Cl,
25 Br, I) or a sulfonate (e.g., mesylate, tosylate, triflate).

The term "protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. The chemical substructure of a protecting group varies widely. One function of a protecting group is to serve as intermediates in the synthesis of the parental drug substance. Chemical protecting groups and
30 strategies for protection/deprotection are well known in the art. See: "Protective Groups in Organic Chemistry", Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g. making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides
35 the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties in vitro and in vivo, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug in vivo. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency in vivo than the parental drug. Protecting groups are removed either in vitro, in the instance of chemical intermediates, or in vivo, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g. alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

The term "alkyl" or "C₁₋₁₈alkyl" as used herein means C₁-C₁₈ normal, secondary, or tertiary, linear, branched or straight hydrocarbon with no site of unsaturation. Examples are methyl, ethyl, 1-propyl (n-propyl), 2-propyl (iPr), 1-butyl, 2-methyl-1-propyl(i-Bu), 2-butyl (s-Bu), 2-dimethyl-2-propyl (t-Bu), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl, *n*-undecyl, *n*-dodecyl, *n*-tridecyl, *n*-tetradecyl, *n*-pentadecyl, *n*-hexadecyl, *n*-heptadecyl, *n*-octadecyl, *n*-nonadecyl, and *n*-icosyl. In particular embodiments, the term alkyl refers to C₁₋₁₂alkyl (C₁₋₁₂ hydrocarbons), yet more in particular to C₁₋₉alkyl (C₁₋₉ hydrocarbons), yet more in particular to C₁₋₆alkyl (C₁₋₆ hydrocarbons) as further defined herein above.

The term "haloalkyl" as a group or part of a group, refers to an alkyl group having the meaning as defined above wherein one, two, or three hydrogen atoms are each replaced with a halogen as defined herein. Non-limiting examples of such haloalkyl groups include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "alkoxy" or "alkyloxy", as a group or part of a group, refers to a group having the formula -OR^b wherein R^b is C₁₋₆alkyl as defined herein above. Non-limiting examples of suitable C₁₋₆alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy.

The term "haloalkoxy", as a group or part of a group, refers to a group of formula -O-R^c, wherein R^c is haloalkyl as defined herein. Non-limiting examples of suitable haloalkoxy include fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2-difluoroethoxy, 2,2,2-trichloroethoxy, trichloromethoxy, 2-bromoethoxy, pentafluoroethyl, 3,3,3-trichloropropoxy, 4,4,4-trichlorobutoxy.

The term "cycloalkyl" or "C₃₋₁₈ cycloalkyl" as used herein and unless otherwise stated means a saturated hydrocarbon monovalent group having from 3 to 18 carbon atoms consisting

of or comprising a C₃₋₁₀ monocyclic or C₇₋₁₈ polycyclic saturated hydrocarbon, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclopropylethylene, methylcyclopropylene, cyclohexyl, cycloheptyl, cyclooctyl, cyclooctylmethylene, norbornyl, fenchyl, trimethyltricycloheptyl, decalinyl, adamantyl and the like. In particular embodiments, the term cycloalkyl refers to C₃₋₁₂cycloalkyl (saturated cyclic C₃₋₁₂hydrocarbons), yet more in particular to C₃₋₉cycloalkyl (saturated cyclic C₃₋₉hydrocarbons), still more in particular to C₃₋₆cycloalkyl (saturated cyclic C₃₋₆hydrocarbons) as further defined herein above. For the avoidance of doubt, fused systems of a cycloalkyl ring with a heterocyclic ring are considered as heterocycle irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkyl ring with an aryl ring are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkyl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

The term "alkenyl" or "C₂₋₁₈alkenyl" as used herein is C₂-C₁₈ normal, secondary or tertiary, linear, branched or straight hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp² double bond. Examples include, but are not limited to: ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂). The double bond may be in the cis or trans configuration. In particular embodiments, the term alkenyl refers to C₂₋₁₂alkenyl (C₂₋₁₂hydrocarbons), yet more in particular to C₂₋₉ alkenyl (C₂₋₉hydrocarbons), still more in particular to C₂₋₆ alkenyl (C₂₋₆hydrocarbons) as further defined herein above with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp² double bond.

The term "alkenyloxy", as a group or part of a group, refers to a group having the formula -OR^d wherein R^d is alkenyl as defined herein above.

The term "cycloalkenyl" as used herein refers to a non-aromatic hydrocarbon group having from 5 to 18 carbon atoms with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp² double bond and consisting of or comprising a C₅₋₁₀ monocyclic or C₇₋₁₈ polycyclic hydrocarbon. Examples include, but are not limited to: cyclopentenyl (-C₅H₇), cyclopentenylpropylene, methylcyclohexenylene and cyclohexenyl (-C₆H₉). The double bond may be in the cis or trans configuration. In particular embodiments, the term cycloalkenyl refers to C₅₋₁₂ cycloalkenyl (cyclic C₅₋₁₂ hydrocarbons), yet more in particular to C₅₋₉ cycloalkenyl (cyclic C₅₋₉ hydrocarbons), still more in particular to C₅₋₆ cycloalkenyl (cyclic C₅₋₆ hydrocarbons) as further defined herein above with at least one site of unsaturation, namely a carbon-carbon, sp² double bond. For the avoidance of doubt, fused systems of a cycloalkenyl ring with a heterocyclic ring are considered as heterocycle irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkenyl ring with an aryl ring are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkenyl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

The term "alkynyl" or "C₂₋₁₈alkynyl" as used herein refers to C₂-C₁₈ normal, secondary,

tertiary, linear, branched or straight hydrocarbon with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond. Examples include, but are not limited to: ethynyl ($-\text{C}\equiv\text{CH}$), 3-ethyl-cyclohept-1-ynylene, and 1-propynyl (propargyl, $-\text{CH}_2\text{C}\equiv\text{CH}$). In particular embodiments, the term alkynyl refers to C_{2-12} alkynyl (C_{2-12} hydrocarbons), yet more in particular to C_{2-9} alkynyl (C_{2-9} hydrocarbons) yet more in particular to C_{2-6} alkynyl (C_{2-6} hydrocarbons) as further defined herein above with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond.

The term "alkynyloxy", as a group or part of a group, refers to a group having the formula $-\text{OR}^e$ wherein R^e is alkynyl as defined herein above.

The term "cycloalkynyl" as used herein refers to a non-aromatic hydrocarbon group having from 5 to 18 carbon atoms with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond and consisting of or comprising a C_{5-10} monocyclic or C_{7-18} polycyclic hydrocarbon. Examples include, but are not limited to: cyclohept-1-yne, 3-ethyl-cyclohept-1-ynylene, 4-cyclohept-1-yn-methylene and ethylene-cyclohept-1-yne. In particular embodiments, the term cycloalkynyl refers to C_{5-10} cycloalkynyl (cyclic C_{5-10} hydrocarbons), yet more in particular to C_{5-9} cycloalkynyl (cyclic C_{5-9} hydrocarbons), still more in particular to C_{5-6} cycloalkynyl (cyclic C_{5-6} hydrocarbons) as further defined herein above with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond. For the avoidance of doubt, fused systems of a cycloalkynyl ring with a heterocyclic ring are considered as heterocycle irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkynyl ring with an aryl ring are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of a cycloalkynyl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

The term "alkylene" as used herein each refer to a saturated, branched or straight chain hydrocarbon group of 1-18 carbon atoms (more in particular C_{1-12} , C_{1-9} or C_{1-6} carbon atoms), and having two monovalent group centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene include, but are not limited to: methylene ($-\text{CH}_2-$), 1,2-ethyl ($-\text{CH}_2\text{CH}_2-$), 1,3-propyl ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1,4-butyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), and the like.

The term "alkenylene" as used herein each refer to a branched or straight chain hydrocarbon of 2-18 carbon atoms (more in particular C_{2-12} , C_{2-9} or C_{2-6} carbon atoms) with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp² double bond, and having two monovalent centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene.

The term "alkynylene" as used herein each refer to a branched or straight chain hydrocarbon of 2-18 carbon atoms (more in particular C_{2-12} , C_{2-9} or C_{2-6} carbon atoms) with at least one site (usually 1 to 3, preferably 1) of unsaturation, namely a carbon-carbon, sp triple bond, and

having two monovalent centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne.

The term “heteroalkyl” as used herein refers to an alkyl wherein one or more carbon atoms are replaced by one or more atoms selected from the group comprising oxygen, nitrogen or sulphur atom. The term heteroalkyl thus comprises $-O-R^b$, $-NR^o-R^b$, $-R^a-O-R^b$, and $-S-R^b$, wherein R^a is alkylene, R^b is alkyl, and R^o is hydrogen or alky as defined herein. In particular embodiments, the term refers to C_{1-12} heteroalkyl, C_{1-9} heteroalkyl or C_{1-6} heteroalkyl. In some embodiments heteroalkyl is selected from the group comprising alkyloxy, alkyl-oxy-alkyl, (mono or di)alkylamino, (mono or di)alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl.

The term “heteroalkenyl” as used herein refers to an acyclic alkenyl wherein one or more carbon atoms are replaced by one or more atoms selected from oxygen, nitrogen or sulphur atom. The term heteroalkenyl thus comprises $-O-R^d$, $-NH-(R^d)$, $-N(R^d)_2$, $-N(R^b)(R^d)$, and $-S-R^d$ wherein R^b is alkyl and R^d is alkenyl as defined herein. In particular embodiments, the term refers to C_{2-12} heteroalkenyl, C_{2-9} heteroalkenyl or C_{2-6} heteroalkenyl. In some embodiments heteroalkenyl is selected from the group comprising alkenyloxy, alkenyl-oxy-alkenyl, (mono or di)alkenylamino, (mono or di)alkenyl-amino-alkenyl, alkenylthio, and alkenyl-thio-alkenyl,

The term “heteroalkynyl” as used herein refers to an acyclic alkynyl wherein one or more carbon atoms are replaced by an oxygen, nitrogen or sulphur atom. The term heteroalkynyl thus comprises but is not limited to $-O-R^d$, $-N(R^d)_2$, NHR^d , $-N(R^b)(R^e)$, $-N(R^d)(R^e)$, and $-S-R^d$ wherein R^b is alkyl, R^e is alkynyl and R^d is alkenyl as defined herein. In particular embodiments, the term refers to C_{2-12} heteroalkynyl, C_{2-9} heteroalkynyl or C_{2-6} heteroalkynyl. In some embodiments the term heteroalkynyl is selected from the group comprising alkynyloxy, alkynyl-oxy-alkynyl, (mono or di)alkynylamino, (mono or di)alkynyl-amino-alkynyl, alkynylthio, alkynyl-thio-alkynyl,

The term “heteroalkylene” as used herein refers to an alkylene wherein one or more carbon atoms are replaced by one or more oxygen, nitrogen or sulphur atoms.

The term “heteroalkenylene” as used herein refers to an alkenylene wherein one or more carbon atoms are replaced by one or more oxygen, nitrogen or sulphur atoms.

The term “heteroalkynylene” as used herein refers to an alkynylene wherein one or more carbon atoms are replaced by one or more oxygen, nitrogen or sulphur atom.

The term “aryl” as used herein means an aromatic hydrocarbon of 6-20 carbon atoms derived by the removal of hydrogen from a carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to 1 ring, or 2 or 3 rings fused together, derived from benzene, naphthalene, anthracene, biphenyl, and the like. In particular embodiments, the term aryl refers to a 6-14 carbon atoms membered aromatic cycle, yet more in particular refers to a 6-10 carbon atoms membered aromatic cycle. Fused systems of an aryl ring with a cycloalkyl ring, or a cycloalkenyl ring, or a cycloalkynyl ring, are considered as aryl irrespective of the ring that is bound to the core structure. Fused systems of an aryl ring with a heterocycle are considered as

heterocycle irrespective of the ring that is bound to the core structure. Thus, indoline, dihydrobenzofurane, dihydrobenzothiophene and the like are considered as heterocycle according to the invention. Fused systems of an aryl ring with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

5 The term “aryloxy”, as a group or part of a group, refers to a group having the formula –OR^g wherein R^g is aryl as defined herein above.

 The term “arylalkyl” or “arylalkyl-” as used herein refers to an alkyl in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom, is replaced with an aryl. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethyl, and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g. the alkyl moiety of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

 The term “arylalkyloxy”, as a group or part of a group, refers to a group having the formula -O-R^a-R^g wherein R^g is aryl, and R^a is alkylene as defined herein above.

15 The term “arylalkenyl” or “arylalkenyl-” as used herein refers to an alkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an aryl. The arylalkenyl group comprises 6 to 20 carbon atoms, e.g. the alkenyl moiety of the arylalkenyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

 The term “arylalkynyl” or “arylalkynyl-” as used herein refers to an alkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an aryl. The arylalkynyl group comprises 6 to 20 carbon atoms, e.g. the alkynyl moiety of the arylalkynyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

 The term “arylheteroalkyl” or “arylheteroalkyl-” as used herein refers to a heteroalkyl in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom, is replaced with an aryl. The arylheteroalkyl group comprises 6 to 20 carbon atoms, e.g. the heteroalkyl moiety of the arylheteroalkyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms. In some embodiments arylheteroalkyl is selected from the group comprising aryl-O-alkyl, arylalkyl-O-alkyl, aryl-NH-alkyl, aryl-N(alkyl)₂, arylalkyl-NH-alkyl, arylalkyl-N-(alkyl)₂, aryl-S-alkyl, and arylalkyl-S-alkyl.

30 The term “arylheteroalkenyl” or “arylheteroalkenyl-” as used herein refers to a heteroalkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an aryl. The arylheteroalkenyl group comprises 6 to 20 carbon atoms, e.g. the heteroalkenyl moiety of the arylheteroalkenyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms. In some embodiments arylheteroalkenyl is selected from the group comprising aryl-O-alkenyl, arylalkenyl-O-alkenyl, aryl-NH-alkenyl, aryl-N(alkenyl)₂, arylalkenyl-NH-alkenyl, arylalkenyl-N-(alkenyl)₂, aryl-S-alkenyl, and arylalkenyl-S-alkenyl.

 The term “arylheteroalkynyl” or “arylheteroalkynyl-” as used herein refers to a

heteroalkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an aryl. The arylheteroalkynyl group comprises 6 to 20 carbon atoms, e.g. the heteroalkynyl moiety of the arylheteroalkynyl group is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms. In some embodiments arylheteroalkynyl is selected from the group comprising aryl-O-alkynyl, arylalkynyl-O-alkynyl, aryl-NH-alkynyl, aryl-N(alkynyl)₂, arylalkynyl-NH-alkynyl, arylalkynyl-N-(alkynyl)₂, aryl-S-alkynyl, and arylalkynyl-S-alkynyl.

The term “heterocycle” or “heterocyclyl” as used herein refer to non-aromatic, fully saturated or partially unsaturated ring system of 3 to 18 atoms including at least one N, O, S, or P (for example, 3 to 7 member monocyclic, 7 to 11 member bicyclic, or comprising a total of 3 to 10 ring atoms). Each ring of the heterocycle or heterocyclyl may have 1, 2, 3 or 4 heteroatoms selected from N, O and/or S, where the N and S heteroatoms may optionally be oxidized and the N heteroatoms may optionally be quaternized; and wherein at least one carbon atom of heterocyclyl can be oxidized to form at least one C=O. The heterocycle may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocyclyls or heterocycles may be fused, bridged and/or joined through one or more spiro atoms. Fused systems of a heterocycle or heterocyclyl with an aryl ring are considered as heterocycle or heterocyclyl irrespective of the ring that is bound to the core structure. Fused systems of a heterocycle or heterocyclyl with a heteroaryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure.

Non limiting exemplary heterocycles or heterocyclic groups include piperidinyl, piperazinyl, homopiperazinyl, morpholinyl, tetrahydropyranyl, tetrahydrofuranyl, pyrrolidinyl, aziridinyl, oxiranyl, thiiranyl, azetidiny, oxetanyl, thietanyl, 2-imidazoliny, pyrazolidinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, succinimidyl, 3H-indolyl, indoliny, isoindoliny, chromanyl (also known as 3,4-dihydrobenzo[b]pyranyl), 2H-pyrrolyl, 1-pyrroliny, 2-pyrroliny, 3-pyrroliny, 4H-quinoliziny, 2-oxopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, tetrahydro-2H-pyranyl, 2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2-oxopiperidinyl, 2-oxopyrrolodiny, indoliny, tetrahydrothiophenyl, tetrahydroquinoliny, tetrahydroisoquinolin-1-yl, tetrahydroisoquinolin-2-yl, tetrahydroisoquinolin-3-yl, tetrahydroisoquinolin-4-yl, thiomorpholin-4-yl, thiomorpholin-4-ylsulfoxide, thiomorpholin-4-ylsulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 1H-pyrroliziny, tetrahydro-1,1-dioxothiophenyl, N-formylpiperazinyl, and morpholin-4-yl. The term “aziridinyl” as used herein includes aziridin-1-yl and aziridin-2-yl. The term “oxyranyl” as used herein includes oxyranyl-2-yl. The term “thiiranyl” as used herein includes thiiran-2-yl. The term “azetidiny” as used herein includes azetidin-1-yl, azetidin-2-yl and azetidin-3-yl. The term “oxetanyl” as used herein includes oxetan-2-yl and oxetan-3-yl. The term “thietanyl” as used herein includes thietan-2-yl and thietan-3-yl. The term “pyrrolidinyl” as used herein includes pyrrolidin-1-yl, pyrrolidin-2-yl and pyrrolidin-3-yl. The term “tetrahydrofuranyl” as used herein

includes tetrahydrofuran-2-yl and tetrahydrofuran-3-yl. The term "tetrahydrothiophenyl" as used herein includes tetrahydrothiophen-2-yl and tetrahydrothiophen-3-yl. The term "succinimidyl" as used herein includes succinimid-1-yl and succinimid-3-yl. The term "dihydropyrrolyl" as used herein includes 2,3-dihydropyrrol-1-yl, 2,3-dihydro-1H-pyrrol-2-yl, 2,3-dihydro-1H-pyrrol-3-yl, 2,5-dihydropyrrol-1-yl, 2,5-dihydro-1H-pyrrol-3-yl and 2,5-dihydropyrrol-5-yl. The term "2H-pyrrolyl" as used herein includes 2H-pyrrol-2-yl, 2H-pyrrol-3-yl, 2H-pyrrol-4-yl and 2H-pyrrol-5-yl. The term "3H-pyrrolyl" as used herein includes 3H-pyrrol-2-yl, 3H-pyrrol-3-yl, 3H-pyrrol-4-yl and 3H-pyrrol-5-yl. The term "dihydrofuranyl" as used herein includes 2,3-dihydrofuran-2-yl, 2,3-dihydrofuran-3-yl, 2,3-dihydrofuran-4-yl, 2,3-dihydrofuran-5-yl, 2,5-dihydrofuran-2-yl, 2,5-dihydrofuran-3-yl, 2,5-dihydrofuran-4-yl and 2,5-dihydrofuran-5-yl. The term "dihydrothiophenyl" as used herein includes 2,3-dihydrothiophen-2-yl, 2,3-dihydrothiophen-3-yl, 2,3-dihydrothiophen-4-yl, 2,3-dihydrothiophen-5-yl, 2,5-dihydrothiophen-2-yl, 2,5-dihydrothiophen-3-yl, 2,5-dihydrothiophen-4-yl and 2,5-dihydrothiophen-5-yl. The term "imidazolidinyl" as used herein includes imidazolidin-1-yl, imidazolidin-2-yl and imidazolidin-4-yl. The term "pyrazolidinyl" as used herein includes pyrazolidin-1-yl, pyrazolidin-3-yl and pyrazolidin-4-yl. The term "imidazoliny" as used herein includes imidazolin-1-yl, imidazolin-2-yl, imidazolin-4-yl and imidazolin-5-yl. The term "pyrazoliny" as used herein includes 1-pyrazolin-3-yl, 1-pyrazolin-4-yl, 2-pyrazolin-1-yl, 2-pyrazolin-3-yl, 2-pyrazolin-4-yl, 2-pyrazolin-5-yl, 3-pyrazolin-1-yl, 3-pyrazolin-2-yl, 3-pyrazolin-3-yl, 3-pyrazolin-4-yl and 3-pyrazolin-5-yl. The term "dioxolanyl" also known as "1,3-dioxolanyl" as used herein includes dioxolan-2-yl, dioxolan-4-yl and dioxolan-5-yl. The term "dioxolyl" also known as "1,3-dioxolyl" as used herein includes dioxol-2-yl, dioxol-4-yl and dioxol-5-yl. The term "oxazolidinyl" as used herein includes oxazolidin-2-yl, oxazolidin-3-yl, oxazolidin-4-yl and oxazolidin-5-yl. The term "isoxazolidinyl" as used herein includes isoxazolidin-2-yl, isoxazolidin-3-yl, isoxazolidin-4-yl and isoxazolidin-5-yl. The term "oxazoliny" as used herein includes 2-oxazoliny-2-yl, 2-oxazoliny-4-yl, 2-oxazoliny-5-yl, 3-oxazoliny-2-yl, 3-oxazoliny-4-yl, 3-oxazoliny-5-yl, 4-oxazoliny-2-yl, 4-oxazoliny-3-yl, 4-oxazoliny-4-yl and 4-oxazoliny-5-yl. The term "isoxazoliny" as used herein includes 2-isoxazoliny-3-yl, 2-isoxazoliny-4-yl, 2-isoxazoliny-5-yl, 3-isoxazoliny-3-yl, 3-isoxazoliny-4-yl, 3-isoxazoliny-5-yl, 4-isoxazoliny-2-yl, 4-isoxazoliny-3-yl, 4-isoxazoliny-4-yl and 4-isoxazoliny-5-yl. The term "thiazolidinyl" as used herein includes thiazolidin-2-yl, thiazolidin-3-yl, thiazolidin-4-yl and thiazolidin-5-yl. The term "isothiazolidinyl" as used herein includes isothiazolidin-2-yl, isothiazolidin-3-yl, isothiazolidin-4-yl and isothiazolidin-5-yl. The term "thiazoliny" as used herein includes 2-thiazoliny-2-yl, 2-thiazoliny-4-yl, 2-thiazoliny-5-yl, 3-thiazoliny-2-yl, 3-thiazoliny-4-yl, 3-thiazoliny-5-yl, 4-thiazoliny-2-yl, 4-thiazoliny-3-yl, 4-thiazoliny-4-yl and 4-thiazoliny-5-yl. The term "isothiazoliny" as used herein includes 2-isothiazoliny-3-yl, 2-isothiazoliny-4-yl, 2-isothiazoliny-5-yl, 3-isothiazoliny-3-yl, 3-isothiazoliny-4-yl, 3-isothiazoliny-5-yl, 4-isothiazoliny-2-yl, 4-isothiazoliny-3-yl, 4-isothiazoliny-4-yl and 4-isothiazoliny-5-yl. The term "piperidyl" also known as "piperidinyl" as used herein includes piperid-

1-yl, piperid-2-yl, piperid-3-yl and piperid-4-yl. The term “dihydropyridinyl” as used herein includes 1,2-dihydropyridin-1-yl, 1,2-dihydropyridin-2-yl, 1,2-dihydropyridin-3-yl, 1,2-dihydropyridin-4-yl, 1,2-dihydropyridin-5-yl, 1,2-dihydropyridin-6-yl, 1,4-dihydropyridin-1-yl, 1,4-dihydropyridin-2-yl, 1,4-dihydropyridin-3-yl, 1,4-dihydropyridin-4-yl, 2,3-dihydropyridin-2-yl, 2,3-dihydropyridin-3-yl, 2,3-dihydropyridin-4-yl, 2,3-dihydropyridin-5-yl, 2,3-dihydropyridin-6-yl, 2,5-dihydropyridin-2-yl, 2,5-dihydropyridin-3-yl, 2,5-dihydropyridin-4-yl, 2,5-dihydropyridin-5-yl, 2,5-dihydropyridin-6-yl, 3,4-dihydropyridin-2-yl, 3,4-dihydropyridin-3-yl, 3,4-dihydropyridin-4-yl, 3,4-dihydropyridin-5-yl and 3,4-dihydropyridin-6-yl. The term “tetrahydropyridinyl” as used herein includes 1,2,3,4-tetrahydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-2-yl, 1,2,3,4-tetrahydropyridin-3-yl, 1,2,3,4-tetrahydropyridin-4-yl, 1,2,3,4-tetrahydropyridin-5-yl, 1,2,3,4-tetrahydropyridin-6-yl, 1,2,3,6-tetrahydropyridin-1-yl, 1,2,3,6-tetrahydropyridin-2-yl, 1,2,3,6-tetrahydropyridin-3-yl, 1,2,3,6-tetrahydropyridin-4-yl, 1,2,3,6-tetrahydropyridin-5-yl, 1,2,3,6-tetrahydropyridin-6-yl, 2,3,4,5-tetrahydropyridin-2-yl, 2,3,4,5-tetrahydropyridin-3-yl, 2,3,4,5-tetrahydropyridin-4-yl, 2,3,4,5-tetrahydropyridin-5-yl and 2,3,4,5-tetrahydropyridin-6-yl. The term “tetrahydropyranyl” also known as “oxanyl” or “tetrahydro-2H-pyranyl”, as used herein includes tetrahydropyran-2-yl, tetrahydropyran-3-yl and tetrahydropyran-4-yl. The term “2H-pyranyl” as used herein includes 2H-pyran-2-yl, 2H-pyran-3-yl, 2H-pyran-4-yl, 2H-pyran-5-yl and 2H-pyran-6-yl. The term “4H-pyranyl” as used herein includes 4H-pyran-2-yl, 4H-pyran-3-yl and 4H-pyran-4-yl. The term “3,4-dihydro-2H-pyranyl” as used herein includes 3,4-dihydro-2H-pyran-2-yl, 3,4-dihydro-2H-pyran-3-yl, 3,4-dihydro-2H-pyran-4-yl, 3,4-dihydro-2H-pyran-5-yl and 3,4-dihydro-2H-pyran-6-yl. The term “3,6-dihydro-2H-pyranyl” as used herein includes 3,6-dihydro-2H-pyran-2-yl, 3,6-dihydro-2H-pyran-3-yl, 3,6-dihydro-2H-pyran-4-yl, 3,6-dihydro-2H-pyran-5-yl and 3,6-dihydro-2H-pyran-6-yl. The term “tetrahydrothiophenyl”, as used herein includes tetrahydrothiophen-2-yl, tetrahydrothiophenyl -3-yl and tetrahydrothiophenyl -4-yl. The term “2H-thiopyranyl” as used herein includes 2H-thiopyran-2-yl, 2H-thiopyran-3-yl, 2H-thiopyran-4-yl, 2H-thiopyran-5-yl and 2H-thiopyran-6-yl. The term “4H-thiopyranyl” as used herein includes 4H-thiopyran-2-yl, 4H-thiopyran-3-yl and 4H-thiopyran-4-yl. The term “3,4-dihydro-2H-thiopyranyl” as used herein includes 3,4-dihydro-2H-thiopyran-2-yl, 3,4-dihydro-2H-thiopyran-3-yl, 3,4-dihydro-2H-thiopyran-4-yl, 3,4-dihydro-2H-thiopyran-5-yl and 3,4-dihydro-2H-thiopyran-6-yl. The term “3,6-dihydro-2H-thiopyranyl” as used herein includes 3,6-dihydro-2H-thiopyran-2-yl, 3,6-dihydro-2H-thiopyran-3-yl, 3,6-dihydro-2H-thiopyran-4-yl, 3,6-dihydro-2H-thiopyran-5-yl and 3,6-dihydro-2H-thiopyran-6-yl. The term “piperazinyl” also known as “piperazidinyl” as used herein includes piperazin-1-yl and piperazin-2-yl. The term “morpholinyl” as used herein includes morpholin-2-yl, morpholin-3-yl and morpholin-4-yl. The term “thiomorpholinyl” as used herein includes thiomorpholin-2-yl, thiomorpholin-3-yl and thiomorpholin-4-yl. The term “dioxanyl” as used herein includes 1,2-dioxan-3-yl, 1,2-dioxan-4-yl, 1,3-dioxan-2-yl, 1,3-dioxan-4-yl, 1,3-dioxan-5-yl and 1,4-dioxan-2-yl. The term “dithianyl” as used herein includes 1,2-dithian-3-yl, 1,2-dithian-4-yl, 1,3-

dithian-2-yl, 1,3-dithian-4-yl, 1,3-dithian-5-yl and 1,4-dithian-2-yl. The term "oxathianyl" as used herein includes oxathian-2-yl and oxathian-3-yl. The term "trioxanyl" as used herein includes 1,2,3-trioxan-4-yl, 1,2,3-trioxan-5-yl, 1,2,4-trioxan-3-yl, 1,2,4-trioxan-5-yl, 1,2,4-trioxan-6-yl and 1,3,4-trioxan-2-yl. The term "azepanyl" as used herein includes azepan-1-yl, azepan-2-yl, 5 azepan-3-yl and azepan-4-yl. The term "homopiperaziny" as used herein includes homopiperazin-1-yl, homopiperazin-2-yl, homopiperazin-3-yl and homopiperazin-4-yl. The term "indolinyl" as used herein includes indolin-1-yl, indolin-2-yl, indolin-3-yl, indolin-4-yl, indolin-5-yl, indolin-6-yl, and indolin-7-yl. The term "quinoliziny" as used herein includes quinolizidin-1-yl, quinolizidin-2-yl, quinolizidin-3-yl and quinolizidin-4-yl. The term "isoindolinyl" as used herein 10 includes isoindolin-1-yl, isoindolin-2-yl, isoindolin-3-yl, isoindolin-4-yl, isoindolin-5-yl, isoindolin-6-yl, and isoindolin-7-yl. The term "3H-indolyl" as used herein includes 3H-indol-2-yl, 3H-indol-3-yl, 3H-indol-4-yl, 3H-indol-5-yl, 3H-indol-6-yl, and 3H-indol-7-yl. The term "quinoliziny" as used herein includes quinolizidin-1-yl, quinolizidin-2-yl, quinolizidin-3-yl and quinolizidin-4-yl. The term "quinoliziny" as used herein includes quinolizidin-1-yl, quinolizidin-2-yl, quinolizidin-3-yl and 15 quinolizidin-4-yl. The term "tetrahydroquinolinyl" as used herein includes tetrahydroquinolin-1-yl, tetrahydroquinolin-2-yl, tetrahydroquinolin-3-yl, tetrahydroquinolin-4-yl, tetrahydroquinolin-5-yl, tetrahydroquinolin-6-yl, tetrahydroquinolin-7-yl and tetrahydroquinolin-8-yl. The term "tetrahydroisoquinolinyl" as used herein includes tetrahydroisoquinolin-1-yl, tetrahydroisoquinolin-2-yl, tetrahydroisoquinolin-3-yl, tetrahydroisoquinolin-4-yl, 20 tetrahydroisoquinolin-5-yl, tetrahydroisoquinolin-6-yl, tetrahydroisoquinolin-7-yl and tetrahydroisoquinolin-8-yl. The term "chromanyl" as used herein includes chroman-2-yl, chroman-3-yl, chroman-4-yl, chroman-5-yl, chroman-6-yl, chroman-7-yl and chroman-8-yl. The term "1H-pyrrolizine" as used herein includes 1H-pyrrolizin-1-yl, 1H-pyrrolizin-2-yl, 1H-pyrrolizin-3-yl, 1H-pyrrolizin-5-yl, 1H-pyrrolizin-6-yl and 1H-pyrrolizin-7-yl. The term "3H-pyrrolizine" as used herein 25 includes 3H-pyrrolizin-1-yl, 3H-pyrrolizin-2-yl, 3H-pyrrolizin-3-yl, 3H-pyrrolizin-5-yl, 3H-pyrrolizin-6-yl and 3H-pyrrolizin-7-yl.

The term "heteroaryl" refers to an aromatic ring system of 5 to 18 atoms including at least one N, O, S, or P, containing 1 or 2 rings which can be fused together or linked covalently, each ring typically containing 5 to 6 atoms; at least one of said rings is aromatic, where the N and S 30 heteroatoms may optionally be oxidized and the N heteroatoms may optionally be quaternized, and wherein at least one carbon atom of said heteroaryl can be oxidized to form at least one C=O. Fused systems of a heteroaryl ring with a cycloalkyl ring, or a cycloalkenyl ring, or a cycloalkynyl ring, are considered as heteroaryl irrespective of the ring that is bound to the core structure. Fused systems of a heteroaryl ring with a heterocycle are considered as heteroaryl irrespective of the 35 ring that is bound to the core structure. Fused systems of a hetero aryl ring with an aryl ring are considered as heteroaryl irrespective of the ring that is bound to the core structure. Non-limiting examples of such heteroaryl, include: triazol-2-yl, pyridinyl, 1H-pyrazol-5-yl, pyrrolyl, furanyl,

thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3]thiazolyl, thieno[3,2-b]furanlyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, benzo[d]oxazol-2(3H)-one, 2,3-dihydro-benzofuranyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 6-oxo-pyridazin-1(6H)-yl, 2-oxopyridin-1(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl; preferably said heteroaryl group is selected from the group comprising pyridyl, pyrazinyl, pyrimidinyl, pyrazolyl, pyrrolyl, isoxazolyl, thiophenyl, imidazolyl, indolyl, benzimidazolyl, s-triazinyl, oxazolyl, isothiazolyl, furyl, thienyl, triazolyl and thiazolyl ; more preferably, said heteroaryl group is selected from the group comprising pyridyl, pyrazinyl, pyrimidinyl, indolyl and benzimidazolyl.

The term "pyrrolyl" (also called azolyl) as used herein includes pyrrol-1-yl, pyrrol-2-yl and pyrrol-3-yl. The term "furanlyl" (also called "furyl") as used herein includes furan-2-yl and furan-3-yl (also called furan-2-yl and furan-3-yl). The term "thiophenyl" (also called "thienyl") as used herein includes thiophen-2-yl and thiophen-3-yl (also called thien-2-yl and thien-3-yl). The term "pyrazolyl" (also called 1H-pyrazolyl and 1,2-diazolyl) as used herein includes pyrazol-1-yl, pyrazol-3-yl or 1H-pyrazol-5-yl, pyrazol-4-yl and pyrazol-5-yl. The term "imidazolyl" as used herein includes imidazol-1-yl, imidazol-2-yl, imidazol-4-yl and imidazol-5-yl. The term "oxazolyl" (also called 1,3-oxazolyl) as used herein includes oxazol-2-yl, oxazol-4-yl and oxazol-5-yl. The term "isoxazolyl" (also called 1,2-oxazolyl), as used herein includes isoxazol-3-yl, isoxazol-4-yl, and isoxazol-5-yl. The term "thiazolyl" (also called 1,3-thiazolyl), as used herein includes thiazol-2-yl, thiazol-4-yl and thiazol-5-yl (also called 2-thiazolyl, 4-thiazolyl and 5-thiazolyl). The term "isothiazolyl" (also called 1,2-thiazolyl) as used herein includes isothiazol-3-yl, isothiazol-4-yl, and isothiazol-5-yl. The term "triazolyl" as used herein includes triazol-2-yl, 1H-triazolyl and 4H-1,2,4-triazolyl, "1H-triazolyl" includes 1H-1,2,3-triazol-1-yl, 1H-1,2,3-triazol-4-yl, 1H-1,2,3-triazol-5-yl, 1H-1,2,4-triazol-1-yl, 1H-1,2,4-triazol-3-yl and 1H-1,2,4-triazol-5-yl. "4H-1,2,4-triazolyl" includes 4H-1,2,4-triazol-4-yl, and 4H-1,2,4-triazol-3-yl. The term "oxadiazolyl" as used herein includes 1,2,3-oxadiazol-4-yl, 1,2,3-oxadiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,5-oxadiazol-3-yl and 1,3,4-oxadiazol-2-yl. The term "thiadiazolyl" as used herein includes 1,2,3-thiadiazol-4-yl, 1,2,3-thiadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-thiadiazol-3-yl (also called furazan-3-yl) and 1,3,4-thiadiazol-2-yl. The term "tetrazolyl" as used herein includes 1H-tetrazol-1-yl, 1H-tetrazol-5-yl, 2H-tetrazol-2-yl, and 2H-tetrazol-5-yl. The term "oxatriazolyl" as

used herein includes 1,2,3,4-oxatriazol-5-yl and 1,2,3,5-oxatriazol-4-yl. The term "thiatriazolyl" as used herein includes 1,2,3,4-thiatriazol-5-yl and 1,2,3,5-thiatriazol-4-yl. The term "pyridinyl" (also called "pyridyl") as used herein includes pyridin-2-yl, pyridin-3-yl and pyridin-4-yl (also called 2-pyridyl, 3-pyridyl and 4-pyridyl). The term "pyrimidyl" as used herein includes pyrimid-2-yl, pyrimid-4-yl, pyrimid-5-yl and pyrimid-6-yl. The term "pyrazinyl" as used herein includes pyrazin-2-yl and pyrazin-3-yl. The term "pyridazinyl" as used herein includes pyridazin-3-yl and pyridazin-4-yl. The term "oxazinyl" (also called "1,4-oxazinyl") as used herein includes 1,4-oxazin-4-yl and 1,4-oxazin-5-yl. The term "dioxinyl" (also called "1,4-dioxinyl") as used herein includes 1,4-dioxin-2-yl and 1,4-dioxin-3-yl. The term "thiazinyl" (also called "1,4-thiazinyl") as used herein includes 1,4-thiazin-2-yl, 1,4-thiazin-3-yl, 1,4-thiazin-4-yl, 1,4-thiazin-5-yl and 1,4-thiazin-6-yl. The term "triazinyl" as used herein includes 1,3,5-triazin-2-yl, 1,2,4-triazin-3-yl, 1,2,4-triazin-5-yl, 1,2,4-triazin-6-yl, 1,2,3-triazin-4-yl and 1,2,3-triazin-5-yl. The term "imidazo[2,1-b][1,3]thiazolyl" as used herein includes imidazo[2,1-b][1,3]thiazol-2-yl, imidazo[2,1-b][1,3]thiazol-3-yl, imidazo[2,1-b][1,3]thiazol-5-yl and imidazo[2,1-b][1,3]thiazol-6-yl. The term "thieno[3,2-b]furanyl" as used herein includes thieno[3,2-b]furan-2-yl, thieno[3,2-b]furan-3-yl, thieno[3,2-b]furan-4-yl, and thieno[3,2-b]furan-5-yl. The term "thieno[3,2-b]thiophenyl" as used herein includes thieno[3,2-b]thien-2-yl, thieno[3,2-b]thien-3-yl, thieno[3,2-b]thien-5-yl and thieno[3,2-b]thien-6-yl. The term "thieno[2,3-d][1,3]thiazolyl" as used herein includes thieno[2,3-d][1,3]thiazol-2-yl, thieno[2,3-d][1,3]thiazol-5-yl and thieno[2,3-d][1,3]thiazol-6-yl. The term "thieno[2,3-d]imidazolyl" as used herein includes thieno[2,3-d]imidazol-2-yl, thieno[2,3-d]imidazol-4-yl and thieno[2,3-d]imidazol-5-yl. The term "tetrazolo[1,5-a]pyridinyl" as used herein includes tetrazolo[1,5-a]pyridine-5-yl, tetrazolo[1,5-a]pyridine-6-yl, tetrazolo[1,5-a]pyridine-7-yl, and tetrazolo[1,5-a]pyridine-8-yl. The term "indolyl" as used herein includes indol-1-yl, indol-2-yl, indol-3-yl, indol-4-yl, indol-5-yl, indol-6-yl and indol-7-yl. The term "indoliziny" as used herein includes indolizin-1-yl, indolizin-2-yl, indolizin-3-yl, indolizin-5-yl, indolizin-6-yl, indolizin-7-yl, and indolizin-8-yl. The term "isoindolyl" as used herein includes isoindol-1-yl, isoindol-2-yl, isoindol-3-yl, isoindol-4-yl, isoindol-5-yl, isoindol-6-yl and isoindol-7-yl. The term "benzofuranyl" (also called benzo[b]furanyl) as used herein includes benzofuran-2-yl, benzofuran-3-yl, benzofuran-4-yl, benzofuran-5-yl, benzofuran-6-yl and benzofuran-7-yl. The term "isobenzofuranyl" (also called benzo[c]furanyl) as used herein includes isobenzofuran-1-yl, isobenzofuran-3-yl, isobenzofuran-4-yl, isobenzofuran-5-yl, isobenzofuran-6-yl and isobenzofuran-7-yl. The term "benzothiophenyl" (also called benzo[b]thienyl) as used herein includes 2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl and 7-benzo[b]thiophenyl (also called benzothien-2-yl, benzothien-3-yl, benzothien-4-yl, benzothien-5-yl, benzothien-6-yl and benzothien-7-yl). The term "isobenzothiophenyl" (also called benzo[c]thienyl) as used herein includes isobenzothien-1-yl, isobenzothien-3-yl, isobenzothien-4-yl, isobenzothien-5-yl, isobenzothien-6-yl and isobenzothien-7-yl. The term "indazolyl" (also called 1H-indazolyl or 2-azaindolyl) as used herein includes 1H-

indazol-1-yl, 1H-indazol-3-yl, 1H-indazol-4-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1H-indazol-7-yl, 2H-indazol-2-yl, 2H-indazol-3-yl, 2H-indazol-4-yl, 2H-indazol-5-yl, 2H-indazol-6-yl, and 2H-indazol-7-yl. The term "benzimidazolyl" as used herein includes benzimidazol-1-yl, benzimidazol-2-yl, benzimidazol-4-yl, benzimidazol-5-yl, benzimidazol-6-yl and benzimidazol-7-yl. The term

5 "1,3-benzoxazolyl" as used herein includes 1,3-benzoxazol-2-yl, 1,3-benzoxazol-4-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl and 1,3-benzoxazol-7-yl. The term "1,2-benzisoxazolyl" as used herein includes 1,2-benzisoxazol-3-yl, 1,2-benzisoxazol-4-yl, 1,2-benzisoxazol-5-yl, 1,2-benzisoxazol-6-yl and 1,2-benzisoxazol-7-yl. The term "2,1-benzisoxazolyl" as used herein includes 2,1-benzisoxazol-3-yl, 2,1-benzisoxazol-4-yl, 2,1-benzisoxazol-5-yl, 2,1-benzisoxazol-6-

10 yl and 2,1-benzisoxazol-7-yl. The term "1,3-benzothiazolyl" as used herein includes 1,3-benzothiazol-2-yl, 1,3-benzothiazol-4-yl, 1,3-benzothiazol-5-yl, 1,3-benzothiazol-6-yl and 1,3-benzothiazol-7-yl. The term "1,2-benzisothiazolyl" as used herein includes 1,2-benzisothiazol-3-yl, 1,2-benzisothiazol-4-yl, 1,2-benzisothiazol-5-yl, 1,2-benzisothiazol-6-yl and 1,2-benzisothiazol-7-yl. The term "2,1-benzisothiazolyl" as used herein includes 2,1-benzisothiazol-

15 3-yl, 2,1-benzisothiazol-4-yl, 2,1-benzisothiazol-5-yl, 2,1-benzisothiazol-6-yl and 2,1-benzisothiazol-7-yl. The term "benzotriazolyl" as used herein includes benzotriazol-1-yl, benzotriazol-4-yl, benzotriazol-5-yl, benzotriazol-6-yl and benzotriazol-7-yl. The term "1,2,3-benzoxadiazolyl" as used herein includes 1,2,3-benzoxadiazol-4-yl, 1,2,3-benzoxadiazol-5-yl, 1,2,3-benzoxadiazol-6-yl and 1,2,3-benzoxadiazol-7-yl. The term "2,1,3-benzoxadiazolyl" as used

20 herein includes 2,1,3-benzoxadiazol-4-yl, 2,1,3-benzoxadiazol-5-yl, 2,1,3-benzoxadiazol-6-yl and 2,1,3-benzoxadiazol-7-yl. The term "1,2,3-benzothiadiazolyl" as used herein includes 1,2,3-benzothiadiazol-4-yl, 1,2,3-benzothiadiazol-5-yl, 1,2,3-benzothiadiazol-6-yl and 1,2,3-benzothiadiazol-7-yl. The term "2,1,3-benzothiadiazolyl" as used herein includes 2,1,3-benzothiadiazol-4-yl, 2,1,3-benzothiadiazol-5-yl, 2,1,3-benzothiadiazol-6-yl and 2,1,3-

25 benzothiadiazol-7-yl. The term "thienopyridinyl" as used herein includes thieno[2,3-b]pyridinyl, thieno[2,3-c]pyridinyl, thieno[3,2-c]pyridinyl and thieno[3,2-b]pyridinyl. The term "purinyl" as used herein includes purin-2-yl, purin-6-yl, purin-7-yl and purin-8-yl. The term "imidazo[1,2-a]pyridinyl", as used herein includes imidazo[1,2-a]pyridin-2-yl, imidazo[1,2-a]pyridin-3-yl, imidazo[1,2-a]pyridin-4-yl, imidazo[1,2-a]pyridin-5-yl, imidazo[1,2-a]pyridin-6-yl and imidazo[1,2-a]pyridin-7-

30 yl. The term "1,3-benzodioxolyl", as used herein includes 1,3-benzodioxol-4-yl, 1,3-benzodioxol-5-yl, 1,3-benzodioxol-6-yl, and 1,3-benzodioxol-7-yl. The term "quinolinyl" as used herein includes quinolin-2-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-7-yl and quinolin-8-yl. The term "isoquinolinyl" as used herein includes isoquinolin-1-yl, isoquinolin-3-yl, isoquinolin-4-yl, isoquinolin-5-yl, isoquinolin-6-yl, isoquinolin-7-yl and isoquinolin-8-yl. The term "cinnolinyl"

35 as used herein includes cinnolin-3-yl, cinnolin-4-yl, cinnolin-5-yl, cinnolin-6-yl, cinnolin-7-yl and cinnolin-8-yl. The term "quinazolinyl" as used herein includes quinazolin-2-yl, quinazolin-4-yl, quinazolin-5-yl, quinazolin-6-yl, quinazolin-7-yl and quinazolin-8-yl. The term "quinoxaliny" as

used herein includes quinoxalin-2-yl, quinoxalin-5-yl, and quinoxalin-6-yl.

Heteroaryl and heterocycle or heterocyclyl as used herein includes by way of example and not limitation these groups described in Paquette, Leo A. "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The
5 Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; Katritzky, Alan R., Rees, C.W. and Scriven, E. "Comprehensive Heterocyclic Chemistry" (Pergamon Press, 1996); and J. Am. Chem. Soc. (1960) 82:5566.

The term "heterocyclyoxy" or "heterocycleoxy", as a group or part of a group, refers to a
10 group having the formula $-O-R^i$ wherein R^i is heterocyclyl as defined herein above.

The term "heterocyclylalkyloxy" or "heterocycleoxy", as a group or part of a group, refers to a group having the formula $-O-R^a-R^i$ wherein R^i is heterocyclyl, and R^a is alkyl as defined herein above.

The term "heteroaryloxy", as a group or part of a group, refers to a group having the
15 formula $-O-R^k$ wherein R^k is heteroaryl as defined herein above.

The term "heteroarylalkyloxy", as a group or part of a group, refers to a group having the formula $-O-R^a-R^i$ wherein R^i is heteroaryl, and R^a is alkyl as defined herein above.

The term "heterocyclylalkyl" or "heterocycle-alkyl" as a group or part of a group, refers to an alkyl in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3
20 carbon atom, is replaced with a heterocyclyl. A non-limiting example of a heterocyclylalkyl or heterocycle-alkyl group is 2-piperidinyl-methylene. The heterocyclylalkyl or heterocycle-alkyl group can comprise 6 to 20 atoms, e.g. the alkyl moiety is 1 to 6 carbon atoms and the heterocyclyl moiety is 3 to 14 atoms.

The term "heterocyclylalkenyl" or "heterocycle-alkenyl" as a group or part of a group refers to an alkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an
25 heterocyclyl. The heterocyclylalkenyl or heterocycle-alkenyl group can comprise 6 to 20 atoms, e.g. the alkenyl moiety is 2 to 6 carbon atoms and the heterocyclyl moiety is 3 to 14 atoms.

The term "heterocyclylalkynyl" or "heterocycle-alkynyl" as a group or part of a group refers to an alkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a
30 heterocyclyl. The heterocyclylalkynyl or heterocycle-alkynyl group can comprise 6 to 20 atoms, e.g. the alkynyl moiety can comprise 2 to 6 carbon atoms and the heterocyclyl moiety can comprise 3 to 14 atoms.

The term "heterocyclylheteroalkyl" or "heterocycle-heteroalkyl" as a group or part of a group refers to a heteroalkyl in which one of the hydrogen atoms bonded to a carbon atom,
35 typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl. The heterocyclylheteroalkyl or heterocycle-heteroalkyl group can comprise 6 to 20 atoms, e.g. the heteroalkyl moiety can comprise 1 to 6 carbon atoms and the heterocyclyl moiety can comprise

3 to 14 atoms. In some embodiments heterocyclylheteroalkyl or heterocycle-heteroalkyl is selected from the group comprising heterocyclyl-O-alkyl, heterocyclylalkyl-O-alkyl, heterocyclyl-NH-alkyl, heterocyclyl-N(alkyl)₂, heterocyclylalkyl-NH-alkyl, heterocyclylalkyl-N-(alkyl)₂, heterocyclyl-S-alkyl, and heterocyclylalkyl-S-alkyl.

5 The term "heterocyclylheteroalkenyl" or "heterocycle-heteroalkenyl" as a group or part of a group refers to a heteroalkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heterocyclyl. The heterocyclylheteroalkenyl or heterocycle-heteroalkenyl group can comprise 6 to 20 atoms, e.g. the heteroalkenyl moiety can comprise 2 to 6 carbon atoms and the heterocyclyl moiety can comprise 3 to 14 atoms. In some embodiments heterocyclyl-
10 heteroalkenyl or heterocycle-heteroalkenyl is selected from the group comprising heterocyclyl-O-alkenyl, heterocyclylalkyl-O-alkenyl, heterocyclyl-NH-alkenyl, heterocyclyl-N(alkenyl)₂, heterocyclylalkyl-NH-alkenyl, heterocyclylalkyl-N-(alkenyl)₂, heterocyclyl-S-alkenyl, and heterocyclylalkenyl-S-alkenyl.

 The term "heterocyclylheteroalkynyl" or "heterocycle-heteroalkynyl" as a group or part of
15 a group refers to a heteroalkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heterocyclyl. The heterocyclylheteroalkynyl or heterocycle-heteroalkynyl group can comprise 6 to 20 atoms, e.g. the heteroalkynyl moiety can comprise 2 to 6 carbon atoms and the heterocyclyl moiety can comprise 3 to 14 atoms. In some embodiments heterocyclyl-heteroalkynyl is selected from the group comprising heterocyclyl-O-alkynyl, heterocyclylalkynyl-
20 O-alkynyl, heterocyclyl-NH-alkynyl, heterocyclyl-N(alkynyl)₂, heterocyclylalkynyl-NH-alkynyl, heterocyclylalkynyl-N-(alkynyl)₂, heterocyclyl-S-alkynyl, and heterocyclylalkynyl-S-alkynyl.

 The term "heteroarylalkyl" as a group or part of a group refers to an alkyl in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon atom, is replaced with a heteroaryl. An example of a heteroarylalkyl group is 2-pyridyl-methylene. The
25 heteroarylalkyl group can comprise 6 to 20 atoms, e.g. the alkyl moiety of the heteroarylalkyl group can comprise 1 to 6 carbon atoms and the heteroaryl moiety can comprise 5 to 14 atoms.

 The term "heteroarylalkenyl" as a group or part of a group refers to an alkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an heteroaryl. The heteroaryl-alkenyl group can comprise 6 to 20 atoms, e.g. the alkenyl moiety of the heteroaryl-
30 alkenyl group can comprise 2 to 6 carbon atoms and the heteroaryl moiety can comprise 5 to 14 atoms.

 The term "heteroarylalkynyl" as a group or part of a group as used herein refers to an alkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heteroaryl. The heteroarylalkynyl group comprises 6 to 20 atoms, e.g. the alkynyl moiety of the
35 heteroaryl-alkynyl group is 2 to 6 carbon atoms and the heteroaryl moiety is 5 to 14 atoms.

 The term "heteroarylheteroalkyl" as a group or part of a group as used herein refers to a heteroalkyl in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or

sp³ carbon atom, is replaced with a heteroaryl. The heteroarylheteroalkyl group comprises 7 to 20 atoms, e.g. the heteroalkyl moiety of the heteroaryl-heteroalkyl group is 2 to 6 carbon atoms and the heteroaryl moiety is 5 to 14 atoms. In some embodiments heteroaryl-heteroalkyl is selected from the group comprising heteroaryl-O-alkyl, heteroarylalkyl-O-alkyl, heteroaryl-NH-alkyl, heteroaryl-N(alkyl)₂, heteroarylalkyl-NH-alkyl, heteroarylalkyl-N-(alkyl)₂, heteroaryl-S-alkyl, and heteroarylalkyl-S-alkyl.

The term "heteroarylheteroalkenyl" as a group or part of a group as used herein refers to a heteroalkenyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with an heteroaryl. The heteroarylheteroalkenyl group comprises 8 to 20 atoms, e.g. the heteroalkenyl moiety of the heteroarylheteroalkenyl group is 3 to 6 carbon atoms and the heteroaryl moiety is 5 to 14 atoms. In some embodiments heteroarylheteroalkenyl is selected from the group comprising heteroaryl-O-alkenyl, heteroarylalkenyl-O-alkenyl, heteroaryl-NH-alkenyl, heteroaryl-N(alkenyl)₂, heteroarylalkenyl-NH-alkenyl, heteroarylalkenyl-N-(alkenyl)₂, heteroaryl-S-alkenyl, and heteroarylalkenyl-S-alkenyl.

The term "heteroarylheteroalkynyl" as a group or part of a group as used herein refers to a heteroalkynyl in which one of the hydrogen atoms bonded to a carbon atom, is replaced with a heteroaryl. The heteroarylheteroalkynyl group comprises 8 to 20 atoms, e.g. the heteroalkynyl moiety of the heteroarylheteroalkynyl group is 2 to 6 carbon atoms and the heteroaryl moiety is 5 to 14 atoms. In some embodiments heteroarylheteroalkynyl is selected from the group comprising heteroaryl-O-alkynyl, heteroarylalkynyl-O-alkynyl, heteroaryl-NH-alkynyl, heteroaryl-N(alkynyl)₂, heteroarylalkynyl-NH-alkynyl, heteroarylalkynyl-N-(alkynyl)₂, heteroaryl-S-alkynyl, and heteroarylalkynyl-S-alkynyl.

By way of example, carbon bonded heteroaryl or heterocyclic rings (or heterocycles) can be bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heteroaryls and heterocyclis include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl. By way of example, nitrogen bonded heterocyclic rings are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β -carboline. Still more typically, nitrogen bonded heteroaryls or

heterocyclyls include 1-aziridyl, 1-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

As used herein and unless otherwise stated, the terms "alkoxy", "cyclo-alkoxy", "aryloxy", "arylalkyloxy", "heteroaryloxy", "heterocyclyloxy", "alkylthio", "cycloalkylthio", "arylthio", "arylalkylthio", "heteroarylthio" and "heterocyclylthio" refer to substituents wherein an alkyl group, respectively a cycloalkyl, aryl, arylalkyl heteroaryl, or heterocyclyl (each of them such as defined herein), are attached to an oxygen atom or a sulfur atom through a single bond, such as but not limited to methoxy, ethoxy, propoxy, butoxy, thioethyl, thiomethyl, phenyloxy, benzyloxy, mercaptobenzyl and the like. The same definitions will apply for alkenyl and alkynyl instead of alkyl.

10 The term "alkylthio", as a group or part of a group, refers to a group having the formula $-S-R^b$ wherein R^b is alkyl as defined herein above. Non-limiting examples of alkylthio groups include methylthio ($-SCH_3$), ethylthio ($-SCH_2CH_3$), *n*-propylthio, isopropylthio, *n*-butylthio, isobutylthio, *sec*-butylthio, *tert*-butylthio and the like.

The term "alkenylthio", as a group or part of a group, refers to a group having the formula 15 $-S-R^d$ wherein R^d is alkenyl as defined herein above.

The term "alkynylthio", as a group or part of a group, refers to a group having the formula $-S-R^e$ wherein R^e is alkynyl as defined herein above.

The term "arylthio", as a group or part of a group, refers to a group having the formula $-S-R^g$ wherein R^g is aryl as defined herein above.

20 The term "arylalkylthio", as a group or part of a group, refers to a group having the formula $-S-R^a-R^g$ wherein R^a is alkylene and R^g is aryl as defined herein above.

The term "heterocyclylthio", as a group or part of a group, refers to a group having the formula $-S-R^i$ wherein R^i is heterocyclyl as defined herein above.

The term "heteroarylthio", as a group or part of a group, refers to a group having the 25 formula $-S-R^k$ wherein R^k is heteroaryl as defined herein above.

The term "heterocyclylalkylthio", as a group or part of a group, refers to a group having the formula $-S-R^a-R^i$ wherein R^a is alkylene and R^i is heterocyclyl as defined herein above.

The term "heteroarylalkylthio", as a group or part of a group, refers to a group having the formula $-S-R^a-R^k$ wherein R^a is alkylene and R^k is heteroaryl as defined herein above.

30 The term "mono- or di-alkylamino", as a group or part of a group, refers to a group of formula $-N(R^o)(R^b)$ wherein R^o is hydrogen, or alkyl, R^b is alkyl. Thus, alkylamino include mono-alkyl amino group (e.g. mono-alkylamino group such as methylamino and ethylamino), and di-alkylamino group (e.g. di-alkylamino group such as dimethylamino and diethylamino). Non-limiting examples of suitable mono- or di-alkylamino groups include *n*-propylamino, 35 isopropylamino, *n*-butylamino, *i*-butylamino, *sec*-butylamino, *t*-butylamino, pentylamino, *n*-hexylamino, di-*n*-propylamino, di-*i*-propylamino, ethylmethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, *n*-butylmethylamino, *i*-butylmethylamino, *t*-butylmethylamino, ethyl-*n*-

propylamino, ethyl-*i*-propylamino, *n*-butylethylamino, *i*-butylethylamino, *t*-butylethylamino, di-*n*-butylamino, di-*i*-butylamino, methylpentylamino, methylhexylamino, ethylpentylamino, ethylhexylamino, propylpentylamino, propylhexylamino, and the like.

The term “mono- or di-arylamino”, as a group or part of a group, refers to a group of
 5 formula $-N(R^q)(R^r)$ wherein R^q and R^r are each independently selected from hydrogen, aryl, or alkyl, wherein at least one of R^q or R^r is aryl.

The term “mono- or di-heteroarylamino”, as a group or part of a group, refers to a group of formula $-N(R^u)(R^v)$ wherein R^u and R^v are each independently selected from hydrogen, heteroaryl, or alkyl, wherein at least one of R^u or R^v is heteroaryl as defined herein.

10 The term “mono- or di-heterocyclylamino”, as a group or part of a group, refers to a group of formula $-N(R^w)(R^x)$ wherein R^w and R^x are each independently selected from hydrogen, heterocyclyl, or alkyl, wherein at least one of R^w or R^x is heterocyclyl as defined herein.

As used herein and unless otherwise stated, the term halogen means any atom selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

15 The terminology regarding a chemical group “which optionally includes one or more heteroatoms, said heteroatoms being selected from the atoms consisting of O, S, and N” as used herein, refers to a group where one or more carbon atoms are replaced by an oxygen, nitrogen or sulphur atom and thus includes, depending on the group to which is referred, heteroalkyl, heteroalkenyl, heteroalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloheteroalkyl,
 20 cycloheteroalkenyl, cycloheteroalkynyl, heteroaryl, arylheteroalkyl, heteroarylalkyl, heteroarylheteroalkyl, arylheteroalkenyl, heteroarylalkenyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, arylheteroalkynyl, heteroarylalkynyl, heteroarylheteroalkynyl, among others. This term therefore comprises, depending on the group to which is referred, as an example alkoxy, alkenyloxy, alkynyloxy, alkyl-O-alkylene, alkenyl-O-alkylene, arylalkoxy, benzyloxy,
 25 heteroarylheteroalkyl, heterocyclylheteroalkyl, heteroaryl-alkoxy, heterocyclyl-alkoxy, among others. As an example, the terminology “alkyl which optionally includes one or more heteroatoms, said heteroatoms being selected from the atoms consisting of O, S, and N” therefore refers to heteroalkyl, meaning an alkyl which comprises one or more heteroatoms in the hydrocarbon chain, whereas the heteroatoms may be positioned at the beginning of the hydrocarbon chain, in
 30 the hydrocarbon chain or at the end of the hydrocarbon chain. Examples of heteroalkyl include methoxy, methylthio, ethoxy, propoxy, $\text{CH}_3\text{-O-CH}_2\text{-}$, $\text{CH}_3\text{-S-CH}_2\text{-}$, $\text{CH}_3\text{-CH}_2\text{-O-CH}_2\text{-}$, $\text{CH}_3\text{-NH-}$, $(\text{CH}_3)_2\text{-N-}$, $(\text{CH}_3)_2\text{-CH}_2\text{-NH-CH}_2\text{-CH}_2\text{-}$, among many other examples. As an example, the terminology “arylalkylene which optionally includes one or more heteroatoms in the alkylene chain, said heteroatoms being selected from the atoms consisting of O, S, and N” therefore refers
 35 to arylheteroalkylene, meaning an arylalkylene which comprises one or more heteroatoms in the hydrocarbon chain, whereas the heteroatoms may be positioned at the beginning of the hydrocarbon chain, in the hydrocarbon chain or at the end of the hydrocarbon chain.

“Arylheteroalkylene” thus includes aryloxy, arylalkoxy, aryl-alkyl-NH- and the like and examples are phenyloxy, benzyloxy, aryl-CH₂-S-CH₂-, aryl-CH₂-O-CH₂-, aryl-NH-CH₂- among many other examples. The same counts for “heteroalkenylenes”, “heteroalkynylene”, and other terms used herein when referred to “which optionally includes one or more heteroatoms, said heteroatoms being selected from the atoms consisting of O, S, and N”.

The terminology regarding a chemical group “wherein optionally two or more hydrogen atoms on a carbon atom or heteroatom of said group can be taken together to form a =O or =S” as used herein, refers to a group where two or more hydrogen atoms on a carbon atom or heteroatom of said group are taken together to form =O or =S. As an example, the terminology refers to “an alkyl wherein optionally two or more hydrogen atoms on a carbon atom or heteroatom of said alkyl can be taken together to form a =O or =S”, includes among other examples CH₃-C(O)-CH₂-, CH₃-C(O)-, CH₃-C(S)-CH₂-, CH₃-S(O)₂-CH₂- and (CH₃)₂-CH₂-C(O)-CH₂-CH₂-.

The combination for a group “which optionally includes one or more heteroatoms, said heteroatoms being selected from the atoms consisting of O, S, and N” and “wherein optionally two or more hydrogen atoms on a carbon atom or heteroatom of said group can be taken together to form a =O or =S” can combine the two aspects described herein above and includes, if the group referred to is alkyl, among other examples CH₃-C(O)O-, CH₃-C(O)O-CH₂-, CH₃-NH-C(O)-, CH₃-C(O)-NH-, CH₃-NH-C(O)-CH₂-, CH₃-NH-C(S)-CH₂-, CH₃-NH-C(S)-NH-CH₂-, CH₃-NH-S(O)₂- and CH₃-NH-S(O)₂-NH-CH₂-.

The term “single bond” as used herein for a linking group i.e. in a way that a certain linking group is selected from a single bond, etc. in the formulas herein, refers to a molecule wherein the linking group is not present and therefore refers to compounds with a direct linkage via a single bond between the two moieties being linked by the linking group.

As used herein with respect to a substituting group, and unless otherwise stated, the terms “substituted” such as in “substituted alkyl”, “substituted alkenyl”, substituted alkynyl”, “substituted aryl”, “substituted heteroaryl”, “substituted heterocyclyl”, “substituted arylalkyl”, “substituted heteroaryl-alkyl”, “substituted heterocyclylalkyl” and the like refer to the chemical structures defined herein, and wherein the said alkyl, alkenyl, alkynyl, group and/or the said aryl, heteroaryl, or heterocyclyl may be optionally substituted with one or more substituents (preferable 1, 2, 3, 4, 5 or 6), meaning that one or more hydrogen atoms are each independently replaced with at least one substituent. Typical substituents include, but are not limited to and in a particular embodiment said substituents are being independently selected from the group consisting of halogen, amino, hydroxyl, sulfhydryl, alkyl, alkoxy, alkenyl, alkenyloxy, alkynyl, alkynyloxy, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocyclyl, arylalkyl, arylalkenyl, arylalkynyl, cycloalkylalkyl, cycloalkylalkenyl, cycloalkylalkynyl, heteroarylalkyl, heterocyclylalkyl, heteroarylalkenyl, heterocyclylalkenyl and heteroarylalkynyl, heterocyclylalkynyl, -X, -Z, -O⁻, -OZ, =O, -SZ, -S⁻, =S, -NZ₂, -N⁺Z₃, =NZ, =N-OZ, -CX₃ (e.g.

trifluoromethyl), -CN, -OCN, -SCN, -N=C=O, -N=C=S, -NO, -NO₂, =N₂, -N₃, -N₂C(O)Z, -N₂C(S)Z, -N₂C(O)O⁻, -N₂C(O)OZ, -N₂C(S)OZ, -N₂C(O)NZZ, N₂C(NZ)Z, N₂C(NZ)NZZ, -C(O)NZZ, -C(NZ)Z, -S(O)₂O⁻, -S(O)₂OZ, -S(O)₂Z, -OS(O)₂OZ, -OS(O)₂Z, -OS(O)₂O⁻, -S(O)₂NZZ, -S(O)(NZ)Z, -S(O)Z, -OP(O)(OZ)₂, -P(O)(OZ)₂, -P(O)(O⁻)₂, -P(O)(OZ)(O⁻), -P(O)(OH)₂, -C(O)Z, -C(O)X, -C(S)Z, -C(O)OZ, -C(O)O⁻, -C(S)OZ, -C(O)SZ, -C(S)SZ, -C(O)NZZ, -C(S)NZZ, -C(NZ)NZZ, -OC(O)Z, -OC(S)Z, -OC(O)O⁻, -OC(O)OZ, -OC(S)OZ, wherein each X is independently a halogen selected from F, Cl, Br, or I; and each Z is independently -H, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, protecting group or prodrug moiety, while two Z bonded to a nitrogen atom can be taken together with the nitrogen atom which they are bonded to form a heteroaryl, or heterocyclyl. Alkyl(ene), alkenyl(ene), and alkynyl(ene) groups may also be similarly substituted.

Any substituent designation that is found in more than one site in a compound of this invention shall be independently selected.

Substituents optionally are designated with or without bonds. Regardless of bond indications, if a substituent is polyvalent (based on its position in the structure referred to), then any and all possible orientations of the substituent are intended.

As used herein and unless otherwise stated, the term "solvate" includes any combination which may be formed by a derivative of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters, ethers, nitriles and the like.

The term "heteroatom(s)" as used herein means an atom selected from nitrogen, which can be quaternized; oxygen; and sulfur, including sulfoxide and sulfone.

The term "hydroxy" as used herein means -OH.

The term "carbonyl" as used herein means carbon atom bonded to oxygen with a double bond, i.e., C=O.

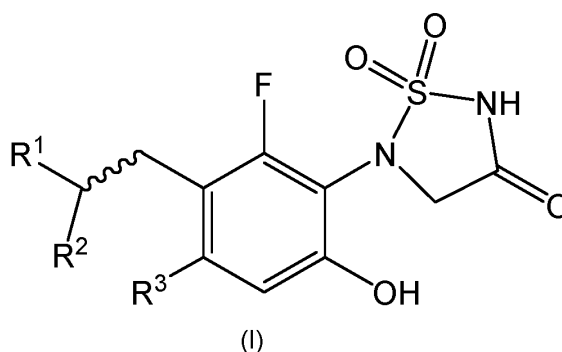
The term "amino" as used herein means the -NH₂ group.

The present invention provides novel compounds which have been shown to possess PTPN2 and/or PTPN1 inhibitory activity. Therefore, these compounds constitute a useful class of new potent compounds that can be used in the treatment and/or prevention of PTPN2 and/or PTPN1 mediated diseases in subjects, more specifically for the treatment and/or prevention of cancer and metabolic diseases, among other diseases.

The present invention furthermore relates to the compounds for use as medicines and to their use for the manufacture of medicaments for treating and/or preventing cancer or metabolic diseases. The present invention relates to the compounds for use as medicines for treating and/or preventing PTPN2 and/or PTPN1 mediated diseases such as cancer or metabolic diseases in animals, mammals, more in particular in humans. The invention also relates to methods for the preparation of all such compounds and to pharmaceutical compositions comprising them in an

effective amount. The present invention also relates to a method of treatment or prevention of cancer or metabolic diseases in humans by the administration of one or more such compounds, optionally in combination with one or more other medicines, to a patient in need thereof. The present invention also relates to the compounds for veterinary use and to their use as medicines
 5 for the prevention or treatment of diseases in a non-human mammal, such as cancer and metabolic diseases in non-human mammals.

More particularly, the compounds of the invention are compounds of formula (I) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, polymorph and/or prodrug thereof,



10

wherein:

- $\sim$ represents a double bond ($\equiv$) or a triple bond ($\equiv$);
- R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl;
- 15 where by each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R^4 ;
- 20 - when $\sim$ is a triple bond, then R^2 is not present; when $\sim$ is a double bond, then R^2 is selected from hydrogen; alkyl and halogen; or R^2 can be taken together with R^1 to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;
- R^3 is selected from hydrogen and alkyl;
- 25 - each R^4 is independently selected from halogen; hydroxyl; sulfhydryl; $=O$; $=S$; $-SCF_3$; $-SF_5$; $-CF_3$; $-OCF_3$; $-CHF_2$; $-OCHF_2$; cyano; nitro; $-OZ^1$; $-SZ^1$; $-S(O)Z^1$; $-S(O)_2Z^2$; $-S(O)_2NZ^3Z^4$; $-S(O)(NZ^3)Z^1$; -
- 30

- S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl;

heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

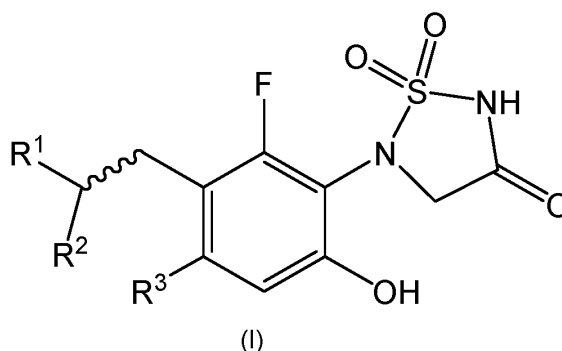
It is clear from the description of the invention that in formula (I) and other relevant formulas and embodiments herein, R¹ can be unsubstituted or substituted with one or more R⁴ and that in formula (I) and other relevant formulas and embodiments herein when  is a double bond, R² is selected from hydrogen; alkyl and halogen, or R² can be taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;

- wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl, or a 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R⁴, meaning that one or more hydrogen atoms on one or more carbon atoms or heteroatoms such as nitrogen atom, are each independently replaced with one or more R⁴ substituents;
- wherein
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;
- or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl.

Preferred or particular statements (features) and embodiments of the compounds of this invention are set herein below. Each statement, aspect and embodiment of the invention so defined may be combined with any other statement, aspect and/or embodiment, unless clearly indicated to the contrary. In particular, any feature indicated as being preferred, particular or advantageous may be combined with any other features or statements indicated as being preferred, particular or advantageous. Hereto, the present invention is in particular captured by any one or any combination of one or more of the below numbered statements and embodiments,

with any other statement, aspect and/or embodiment (which are not numbered).

A1. A compound of formula (I), a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), a solvate, a hydrate, a polymorph, an isotope, and/or a prodrug thereof,



wherein:

- $\sim$ represents a double bond ($=$) or a triple bond ($\equiv$);

- R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl;

whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R^4 ;

- when $\sim$ is a triple bond, then R^2 is not present; when $\sim$ is a double bond, then R^2 is selected from hydrogen; alkyl and halogen;

- R^3 is selected from hydrogen and alkyl;

- each R^4 is independently selected from halogen; hydroxyl; sulfhydryl; $=O$; $=S$; $-SCF_3$; $-SF_5$; $-CF_3$;

$-OCF_3$; $-CHF_2$; $-OCHF_2$; cyano; nitro; $-OZ^1$; $-SZ^1$; $-S(O)Z^1$; $-S(O)_2Z^2$; $-S(O)_2NZ^3Z^4$; $-S(O)(NZ^3)Z^1$; $-$

$S(NZ^3)(NZ^3)Z^1$; $-C(O)H$; $-C(O)Z^2$; $-C(O)OH$; $-C(O)OZ^1$; $-C(O)NZ^3Z^4$; $-NZ^3Z^4$; $-NZ^3S(O)_2Z^1$; $-$

$NZ^3S(O)_2NZ^3Z^4$; $-NZ^3C(O)OZ^1$; $-NZ^3C(O)Z^1$; $-NZ^3C(O)NZ^3Z^4$; $-P(O)Z^3Z^4$; alkyl; alkenyl; alkynyl;

heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl;

heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl;

arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl;

heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl;

heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl;
 heterocyclheteroalkynyl; alkyl-oxy-alkyl; (mono or di)alkylamino; (mono or di)alkyl-amino-alkyl;
 alkylthio; and alkyl-thio-alkyl;

5 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl,
 cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl,
 arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl,
 heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl,
 heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl,
 heterocyclheteroalkenyl, heterocyclheteroalkynyl, alkyl-oxy-alkyl, (mono or
 10 di)alkylamino, (mono or di)alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl is unsubstituted
 or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl,
 alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano,
 nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;

- or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-
 15 , 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or
 is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl,
 hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH;
 NH₂; -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl;
 20 cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl;
 arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl;
 heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl;
 heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl;
 heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

25 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl,
 heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl,
 arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl,
 heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl,
 heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl,
 30 heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is
 unsubstituted or is substituted with one or more substituents selected from alkyl,
 cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂,
 -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl;
 35 cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl;
 arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl;
 heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl;

heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

preferably wherein "heteroalkyl" as a group or part of a group is selected from the group comprising alkyloxy, alkyl-oxy-alkyl, (mono or di)alkylamino, (mono or di-)alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl;

preferably wherein "heteroalkenyl" as a group or part of a group is selected from the group comprising alkenyloxy, alkenyl-oxy-alkenyl, alkyl-oxy-alkenyl, alkenyl-oxy-alkyl, (mono or

di)alkenylamino, (alkyl)(alkenyl)amino, (mono or di-)alkenyl-amino-alkenyl, (mono or di-)alkyl-amino-alkenyl, (mono or di-)alkenyl-amino-alkyl, (alkyl)(alkenyl)amino-alkenyl, (alkyl)(alkenyl)amino-alkyl, alkenylthio, alkenyl-thio-alkyl, alkyl-thio-alkenyl, and alkenyl-thio-alkenyl;

- 5 preferably wherein "heteroalkynyl" as a group or part of a group is selected from the group comprising alkynyloxy, alkynyl-oxy-alkynyl, alkyl-oxy-alkynyl, alkynyl-oxy-alkyl, (mono or di)alkynylamino, (alkyl)(alkynyl)amino, (mono or di-)alkynyl-amino-alkynyl, (mono or di-)alkyl-amino-alkynyl, (mono or di-)alkynyl-amino-alkyl, (alkyl)(alkynyl)amino-alkynyl, (alkyl)(alkynyl)amino-alkyl, alkynylthio, alkynyl-thio-alkyl, alkyl-thio-alkynyl, and alkynyl-thio-alkynyl;

10 In some preferred embodiments:

- R¹ is selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₃₋₉cycloalkylC₁₋₆alkyl; C₅₋₁₀cycloalkenylC₁₋₆alkyl; C₇₋₁₀cycloalkynylC₁₋₆alkyl; C₃₋₉cycloalkylC₁₋₆heteroalkyl; C₅₋₁₀cycloalkenylC₁₋₆heteroalkyl; C₇₋₁₀cycloalkynylC₁₋₆heteroalkyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; heteroarylC₁₋₆alkyl; heterocyclylC₁₋₆alkyl; C₆₋₁₀arylC₁₋₆heteroalkyl; heteroarylC₁₋₆heteroalkyl; and heterocyclylC₁₋₆heteroalkyl;

- whereby each of said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₃₋₉cycloalkylC₁₋₆alkyl; C₅₋₁₀cycloalkenylC₁₋₆alkyl; C₇₋₁₀cycloalkynylC₁₋₆alkyl; C₃₋₉cycloalkylC₁₋₆heteroalkyl; C₅₋₁₀cycloalkenylC₁₋₆heteroalkyl; C₇₋₁₀cycloalkynylC₁₋₆heteroalkyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; heteroarylC₁₋₆alkyl; heterocyclylC₁₋₆alkyl; C₆₋₁₀arylC₁₋₆heteroalkyl; heteroarylC₁₋₆heteroalkyl; and heterocyclylC₁₋₆heteroalkyl is unsubstituted or is substituted with one or more R⁴;

- 25 - when  is a triple bond, then R² is not present; when  is a double bond, then R² is selected from hydrogen; C₁₋₉alkyl and halogen;

- R³ is selected from hydrogen and C₁₋₉alkyl;

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl;

heterocyclylC₂₋₆heteroalkynyl; C₁₋₆alkyl-oxy-C₁₋₆alkyl; (mono or di)C₁₋₆alkylamino; (mono or di-)C₁₋₆alkyl-amino-C₁₋₆alkyl; C₁₋₉alkylthio; and C₁₋₆alkyl-thio-C₁₋₆alkyl;

- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; heterocyclylC₂₋₆heteroalkynyl; C₁₋₆alkyl-oxy-C₁₋₆alkyl; (mono or di)C₁₋₆alkylamino; (mono or di-)C₁₋₆alkyl-amino-C₁₋₆alkyl; C₁₋₉alkylthio; and C₁₋₆alkyl-thio-C₁₋₆alkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -S(O)₂C₁₋₆alkyl, and -NHS(O)₂C₁₋₆alkyl;
- or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -S(O)₂C₁₋₆alkyl, and -NHS(O)₂C₁₋₆alkyl;
- each Z¹ is independently selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -

N(C₁₋₆alkyl)₂;

- each Z² is independently selected from hydroxyl; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;
- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;
- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S,

-CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from

- 5 C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

preferably wherein "C₁₋₁₂heteroalkyl" as a group or part of a group is selected from the group comprising C₁₋₁₂alkyloxy, C₁₋₆alkyl-oxy-C₁₋₆alkyl, (mono or di)C₁₋₆alkylamino, (mono or di-)C₁₋₆alkyl-amino-C₁₋₆alkyl, C₁₋₁₂alkylthio, and C₁₋₆alkyl-thio-C₁₋₆alkyl;

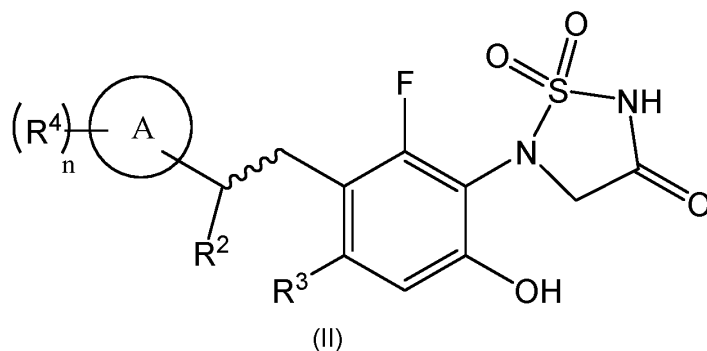
- 10 preferably wherein "C₂₋₁₂heteroalkenyl" as a group or part of a group is selected from the group comprising C₂₋₁₂alkenyloxy, C₂₋₆alkenyl-oxy-C₂₋₆alkenyl, C₁₋₆alkyl-oxy-C₂₋₆alkenyl, C₂₋₆alkenyl-oxy-C₁₋₆alkyl, (mono or di)C₂₋₆alkenylamino, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino, (mono or di-)C₂₋₆alkenyl-amino-C₂₋₆alkenyl, (mono or di-)C₁₋₆alkyl-amino-C₂₋₆alkenyl, (mono or di-)C₂₋₆alkenyl-amino-C₁₋₆alkyl, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino-C₂₋₆alkenyl, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino-C₁₋₆alkyl,
- 15 C₂₋₁₂alkenylthio, C₂₋₆alkenyl-thio-C₁₋₆alkyl, C₁₋₆alkyl-thio-C₂₋₆alkenyl, and C₂₋₆alkenyl-thio-C₂₋₆alkenyl;

preferably wherein "C₂₋₁₂heteroalkynyl" as a group or part of a group is selected from the group comprising C₂₋₁₂alkynyloxy, C₂₋₆alkynyl-oxy-C₂₋₆alkynyl, C₁₋₆alkyl-oxy-C₂₋₆alkynyl, C₂₋₆alkynyl-oxy-C₁₋₆alkyl, (mono or di)C₂₋₆alkynylamino, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino, (mono or di-)C₂₋₆alkynyl-amino-C₂₋₆alkynyl, (mono or di-)C₁₋₆alkyl-amino-C₂₋₆alkynyl, (mono or di-)C₂₋₆alkynyl-amino-C₁₋₆alkyl, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino-C₂₋₆alkynyl, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino-C₁₋₆alkyl, C₂₋₁₂alkynylthio, C₂₋₆alkynyl-thio-C₁₋₆alkyl, C₁₋₆alkyl-thio-C₂₋₆alkynyl, and C₂₋₆alkynyl-thio-C₂₋₆alkynyl;

- preferably each heteroaryl is 5 to 20 membered heteroaryl, more in particular is a 6 to 14 membered heteroaryl; yet more in particular is a 6 to 10 membered heteroaryl; including when
- 25 such heteroaryl is linked to alkyl, alkenyl or alkynyl such as in heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl;

- preferably each heterocycle is 5 to 20 membered heterocycle, more in particular is a 6 to 14 membered heterocycle; yet more in particular is a 6 to 10 membered heterocycle; including when such heterocycle is linked to alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl and heteroalkynyl
- 30 as in heterocyclealkyl, heterocyclealkenyl, heterocyclealkynyl, heterocycleheteroalkyl, heterocycleheteroalkenyl and heterocycleheteroalkynyl.

A2. In some embodiments of the compound according to statement A1, with a structure of formula (II)

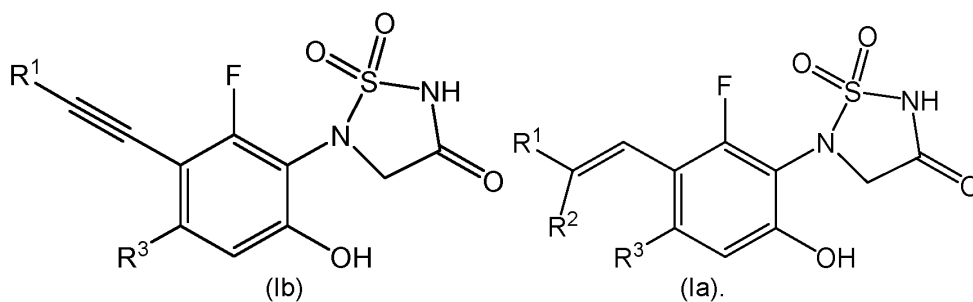


wherein:

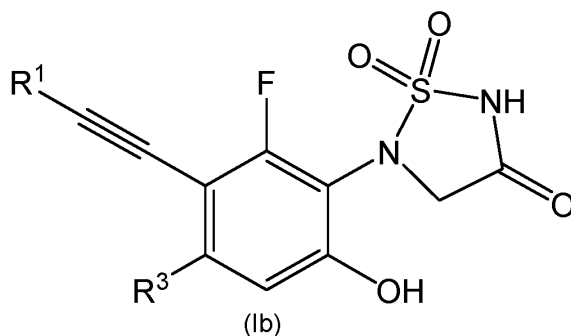
- cycle A is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;
- 5 preferably cycle A is selected from C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle; and

- n is selected from 0; 1; 2; 3; 4; and 5.

- A3. In some embodiments of the compound according to statement 2, n is selected from 1; 2; 3 and 4.
- 10 A4. In some embodiments of the compound according to any one of statements A1 to A3, represents a double bond (==).
- A5. In some embodiments of the compound according to any one of statements A1 to A3, represents a triple bond (≡).
- A6. In some embodiments of the compound according to statement A1, said compound has a
- 15 structure of formula (Ib) or (Ia)



- A7. In some embodiments of the compound according to any one of statements A1, A5, A6, said compound has a structure of formula (Ib)



wherein:

- R¹ is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl; preferably R¹ is selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₃₋₉cycloalkylC₁₋₆alkyl; C₅₋₁₀cycloalkenylC₁₋₆alkyl; C₇₋₁₀cycloalkynylC₁₋₆alkyl; C₃₋₉cycloalkylC₁₋₆heteroalkyl; C₅₋₁₀cycloalkenylC₁₋₆heteroalkyl; C₇₋₁₀cycloalkynylC₁₋₆heteroalkyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; heteroarylC₁₋₆alkyl; heterocyclC₁₋₆alkyl; C₆₋₁₀arylC₁₋₆heteroalkyl; heteroarylC₁₋₆heteroalkyl; and heterocyclC₁₋₆heteroalkyl;

- whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R⁴; preferably whereby each of said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₃₋₉cycloalkylC₁₋₆alkyl; C₅₋₁₀cycloalkenylC₁₋₆alkyl; C₇₋₁₀cycloalkynylC₁₋₆alkyl; C₃₋₉cycloalkylC₁₋₆heteroalkyl; C₅₋₁₀cycloalkenylC₁₋₆heteroalkyl; C₇₋₁₀cycloalkynylC₁₋₆heteroalkyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; heteroarylC₁₋₆alkyl; heterocyclC₁₋₆alkyl; C₆₋₁₀arylC₁₋₆heteroalkyl; heteroarylC₁₋₆heteroalkyl; and heterocyclC₁₋₆heteroalkyl is unsubstituted or is substituted with one or more R⁴;

- R³ is selected from hydrogen and alkyl; preferably R³ is selected from hydrogen and C₁₋₉alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl;

- heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and
- 5 heterocyclheteroalkynyl; preferably each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋
- 10 ₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 15 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl; preferably wherein said C₁₋₉alkyl;
- 20 C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 25 C₆₋₁₀heteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -S(O)₂C₁₋₆alkyl, and -NHS(O)₂C₁₋₆alkyl;
- 30 - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl;

arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclylheteroalkynyl; preferably

5 each Z¹ is independently selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl,

15 arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected alkyl, cycloalkyl,

20 alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected

30 from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl;

35 arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl;

- heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl; preferably - each Z² is independently selected from hydroxyl; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl; preferably each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

12heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl;

5 heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

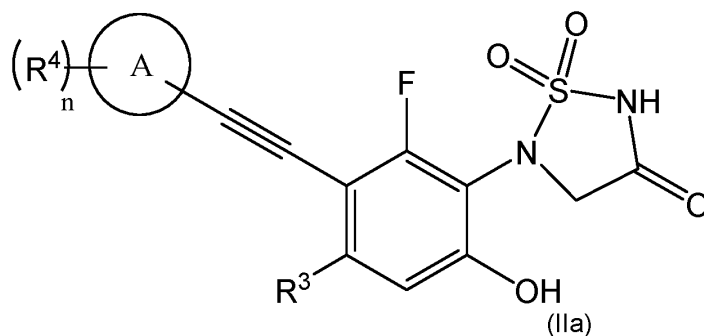
wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

15 20 25

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

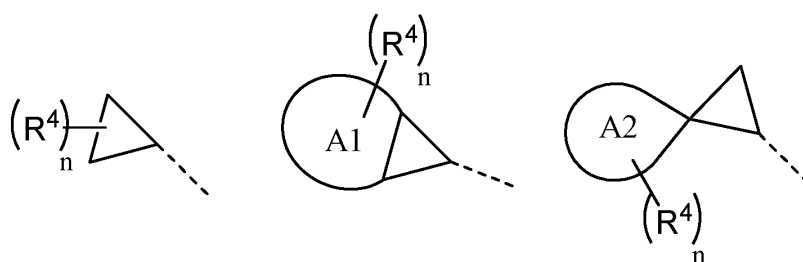
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35 A8. In some embodiments of the compound according to any one of statements A1-A3, A5-A7, said compound has a structure of formula (IIa):



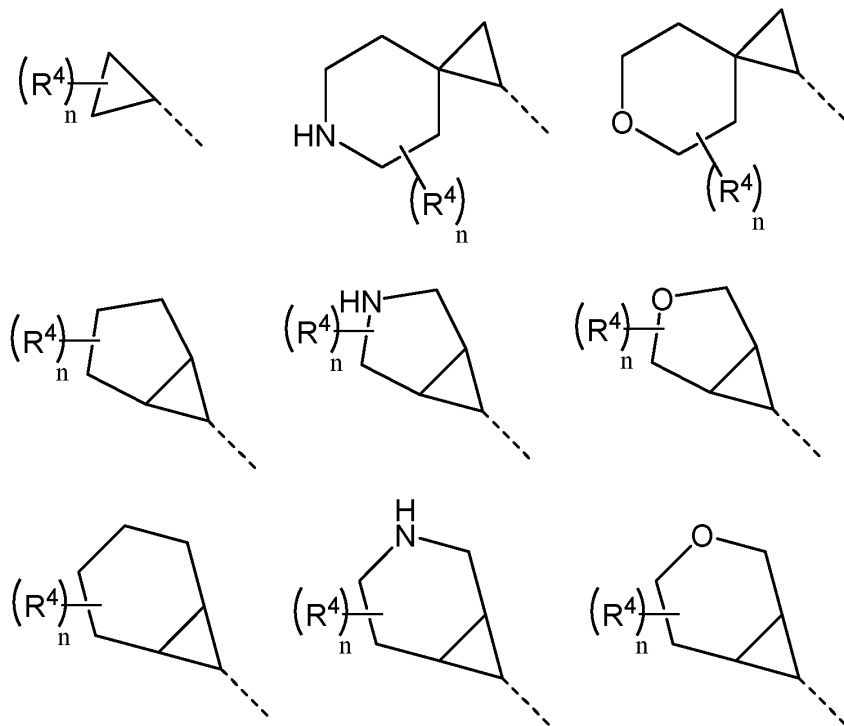
cycle A is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; and R^3 , n , each R^4 , have the same meaning as that defined in any one of statements A1-A3, A5-A7; preferably cycle A is selected from C_{3-9} cycloalkyl; C_{5-10} cycloalkenyl; C_{7-10} cycloalkynyl; C_{6-10} aryl; heteroaryl; and heterocycle; and R^3 , n , each R^4 , have the same meaning as that defined in any one of statements A1-A3, A5-A7.

A9. In some embodiments of the compound according to any one of statements A1-A8, R^1 or cycle A is selected from the group comprising

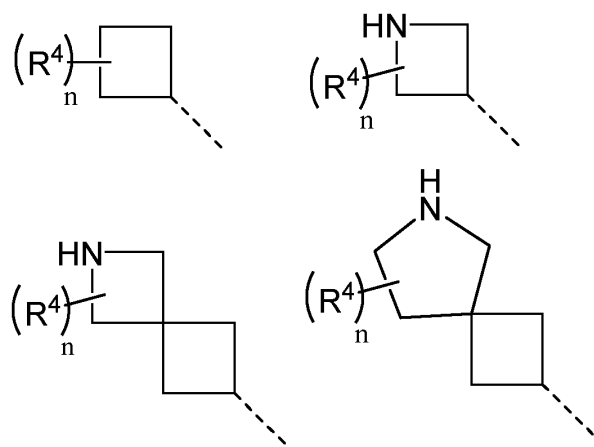


wherein each cycle A1 and cycle A2 is independently selected from 5-, 6-, or 7-membered heterocycle; 5-, 6-, or 7-membered cycloalkyl; and n , each R^4 , have the same meaning as that defined in any one of statements A1-A8.

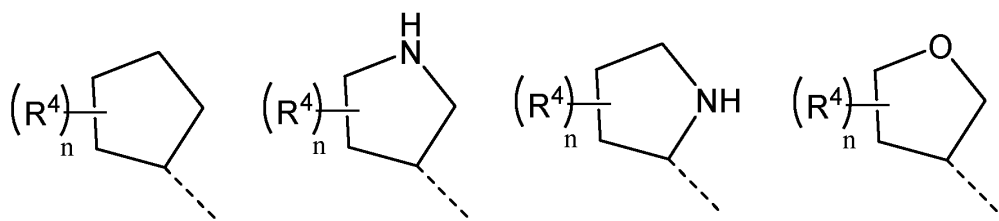
A10. In some embodiments of the compound according to any one of statements A1-A9, R^1 or cycle A is selected from the group comprising



A11. In some embodiments of the compound according to any one of statements A1-A9, R^1 or cycle A is selected from the group comprising



5 A12. In some embodiments of the compound according to any one of statements A1-A9, R^1 or cycle A is selected from the group comprising



- A13. In some embodiments of the compound according to any one of statements A1 to A12, R³ is hydrogen.
- A14. In some embodiments of the compound according to any one of statements A1 to A12, R³ is alkyl, preferably R³ is C₁₋₆alkyl,
- 5 A15. In some embodiments of the compound according to any one of statements A1-A14, each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl;
- 10 alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle, and heterocyclylalkyl; preferably each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; and heteroarylC₁₋₆alkyl;
- 15 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle and heterocyclylalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl; preferably wherein each of said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; and heteroarylC₁₋₆alkyl is unsubstituted or is substituted
- 20 with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, -N(C₁₋₆alkyl)₂, -S(O)₂C₁₋₆alkyl, and -NHS(O)₂C₁₋₆alkyl.
- 25
- 30
- A16. In some embodiments of the compound according to any one of statements A1 to A15,
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; alkyl;
- 35 alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; preferably each R⁴ is independently selected

from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; preferably wherein each of said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

A17. In some embodiments of the compound according to any one of statements A1 to A16, each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; heteroalkyl; aryl; heteroaryl; and heterocycle; preferably each R⁴ is independently selected from C₁₋₉alkyl; C₃₋₉cycloalkyl; halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₁₋₉heteroalkyl; C₆₋₁₀aryl; heteroaryl; and heterocycle;

wherein said alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; preferably wherein each of said C₁₋₉alkyl; C₁₋₁₂heteroalkyl; C₃₋₉cycloalkyl; C₆₋₁₀aryl; heteroaryl; and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

A18. In some embodiments of the compound according to any one of statements A1 to A17, - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl,

- alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z¹ is independently selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; and C₂₋₁₂heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl, heterocycle; and arylalkyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycle; and arylalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z² is independently selected from hydroxyl; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; heterocycle; and C₆₋₁₀arylC₁₋₆alkyl; wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; heterocycle; and C₆₋₁₀arylC₁₋₆alkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; and C₂₋₁₂heteroalkynyl is unsubstituted or

is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

A19. In some embodiments of the compound according to any one of statements A1 to A18,

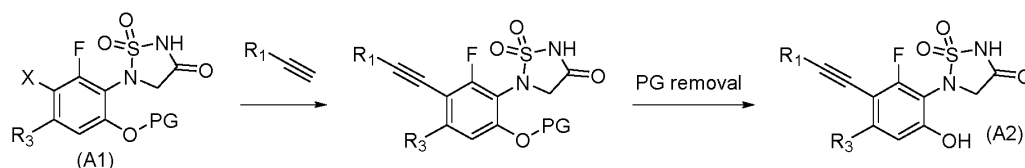
- each Z¹ is independently selected from alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z¹ is independently selected from C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl; and C₃₋₉cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z² is independently selected from hydroxyl; C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl; and C₃₋₉cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl; and C₃₋₉cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-

membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

- 5 A20. In some embodiments of the compound according to any one of statements A1-A19, said compound is selected from the group comprising Cpd001, Cpd002, Cpd003, Cpd004, Cpd005, Cpd006, Cpd007, Cpd008, Cpd009, Cpd010, Cpd011, Cpd012, Cpd013, Cpd014, Cpd015, Cpd016, Cpd017, Cpd018, Cpd019, Cpd020, Cpd021, Cpd022, Cpd023, Cpd024, Cpd025, Cpd026, Cpd027, Cpd028, Cpd029, Cpd030, Cpd031, Cpd032, Cpd033, Cpd034, Cpd035, Cpd036, Cpd040, Cpd041, Cpd042, Cpd043, Cpd044, Cpd045, Cpd049, Cpd050, Cpd051, Cpd052, Cpd053, Cpd054, Cpd055, Cpd056, Cpd057, Cpd058, Cpd059, Cpd060, Cpd061, Cpd062, Cpd063, Cpd064, Cpd065, Cpd066, Cpd067, Cpd068, Cpd069, Cpd070, Cpd071, Cpd072, Cpd073, Cpd074, Cpd075, Cpd076, Cpd077, Cpd078, Cpd079, Cpd080, Cpd081, Cpd082, Cpd083, Cpd084, Cpd085, Cpd086, Cpd087, Cpd088, Cpd089, Cpd090, Cpd091, Cpd092, Cpd093, Cpd094, Cpd097, Cpd098, Cpd099, Cpd100, Cpd101, Cpd102, Cpd103, Cpd104, Cpd105, Cpd106, Cpd107, Cpd108, Cpd109, Cpd110, Cpd111, Cpd112, Cpd113, Cpd080-en1, Cpd080-en2, Cpd116, Cpd117, Cpd118, Cpd119, Cpd120, Cpd121, Cpd122, Cpd123, Cpd124-en1, Cpd124-en2, Cpd125-en1, Cpd125-en2, Cpd126-en1, Cpd126-en2, Cpd127, Cpd128, Cpd129, Cpd134, Cpd135, Cpd136, Cpd137, Cpd138, Cpd140, Cpd141, Cpd142-en1, Cpd142-en2, Cpd148, Cpd149-en1, Cpd149-en2, Cpd150, Cpd151, Cpd152, Cpd153, Cpd154, Cpd155, Cpd161, and Cpd166.

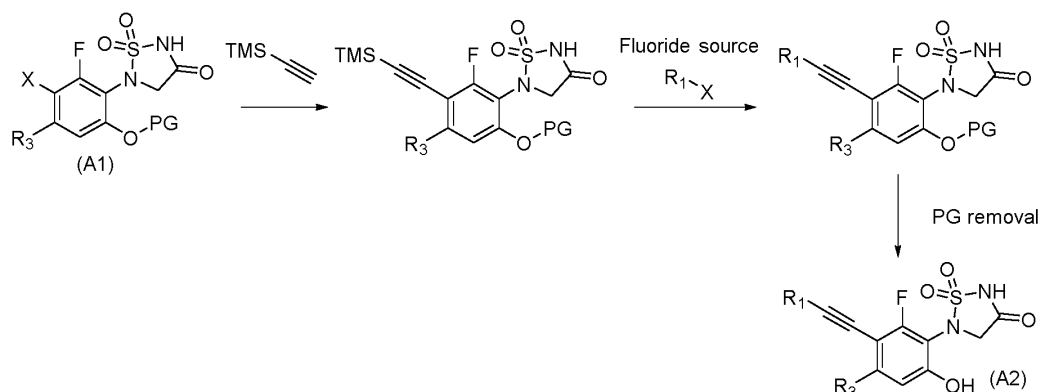
A21. A method for the preparation of compounds according to any one of statements A1-A20, comprising the steps of:

- coupling a halogen-containing compound of formula (A1) with an alkyne derivative and further removing PG (if different than H) thereby obtaining a compound of formula (A2), wherein R¹ and R³ have the same meaning as defined in any one of statements A1-A20, PG is a protecting group or a hydrogen and X is a halogen; or

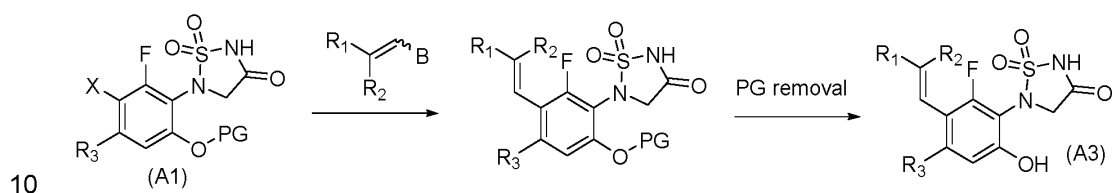


- coupling a halogen-containing compound of formula (A1) with a silylated-acetylene derivative; in a next step, performing concomitant in situ silyl deprotection with a fluoride source and coupling with a R¹-X halogen derivative, and further removing PG, if different than H, thereby obtaining a compound of formula (A2), wherein R¹ and R³ have the same meaning as defined

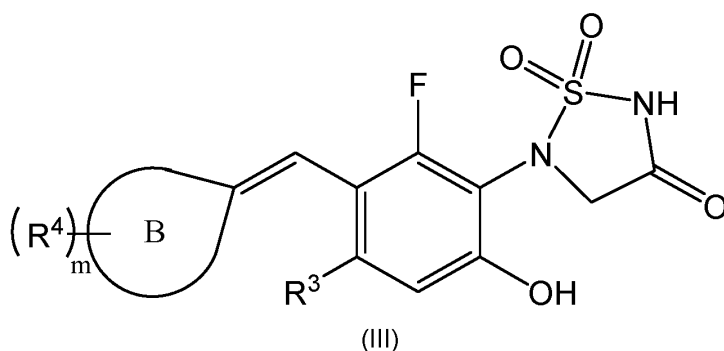
in any one of statements A1-A20, PG is a protecting group or a hydrogen and X is a halogen;
or



- 5 - coupling a halogen-containing compound of formula (A1) with an alkenyl boronic derivative and further removing PG, if different than H, thereby obtaining compound of formula (A3), wherein R^1 , R^2 and R^3 have the same meaning as defined in any one of statements A1-A20, PG is a protecting group or a hydrogen and X is a halogen, or alternatively, the alkenyl boronic derivative can be replaced by a terminal alkene, an alkenyl zinc reagent or an alkenyl stannane reagent



B1.A compound of formula (III), a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, hydrate, polymorph, isotope, and/or prodrug thereof,



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wherein:

- cycle B is selected from heterocycle; cycloalkyl; cycloalkenyl; and cycloalkynyl;
- m is selected from 0; 1; 2; 3; 4; and 5.
- R^3 is selected from hydrogen and alkyl;

- each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, hydroxyl, cycloalkyl, alkenyl, alkynyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;
- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is

unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclylheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclylheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents

selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

preferably wherein "heteroalkyl" as a group or part of a group is selected from the group comprising alkyloxy, alkyl-oxy-alkyl, (mono or di)alkylamino, (mono or di)-alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl;

preferably wherein "heteroalkenyl" as a group or part of a group is selected from the group comprising alkenyloxy, alkenyl-oxy-alkenyl, alkyl-oxy-alkenyl, alkenyl-oxy-alkyl, (mono or di)alkenylamino, (alkyl)(alkenyl)amino, (mono or di)-alkenyl-amino-alkenyl, (mono or di)-alkyl-amino-alkenyl, (mono or di)-alkenyl-amino-alkyl, (alkyl)(alkenyl)amino-alkenyl, (alkyl)(alkenyl)amino-alkyl, alkenylthio, alkenyl-thio-alkyl, alkyl-thio-alkenyl, and alkenyl-thio-alkenyl;

preferably wherein "heteroalkynyl" as a group or part of a group is selected from the group comprising alkynyloxy, alkynyl-oxy-alkynyl, alkyl-oxy-alkynyl, alkynyl-oxy-alkyl, (mono or di)alkynylamino, (alkyl)(alkynyl)amino, (mono or di)-alkynyl-amino-alkynyl, (mono or di)-alkyl-amino-alkynyl, (mono or di)-alkynyl-amino-alkyl, (alkyl)(alkynyl)amino-alkynyl, (alkyl)(alkynyl)amino-alkyl, alkynylthio, alkynyl-thio-alkyl, alkyl-thio-alkynyl, and alkynyl-thio-alkynyl;

In some preferred embodiments:

- R³ is selected from hydrogen and C₁₋₉alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; heterocyclylC₂₋₆heteroalkynyl;

wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₉alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; arylC₁₋₆heteroalkyl; arylC₂₋₆heteroalkenyl; arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and

heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

- 5 - or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- 10 - each Z¹ is independently selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

- each Z² is independently selected from hydroxyl; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;

wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋

- ₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₁₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl;
- wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₆₋₁₀aryl; heteroaryl; heterocycle; C₆₋₁₀arylC₁₋₆alkyl; C₆₋₁₀arylC₂₋₆alkenyl; C₆₋₁₀arylC₂₋₆alkynyl; C₆₋₁₀arylC₁₋₆heteroalkyl; C₆₋₁₀arylC₂₋₆heteroalkenyl; C₆₋₁₀arylC₂₋₆heteroalkynyl; heteroarylC₁₋₆alkyl; heteroarylC₂₋₆alkenyl; heteroarylC₂₋₆alkynyl; heteroarylC₁₋₆heteroalkyl; heteroarylC₂₋₆heteroalkenyl; heteroarylC₂₋₆heteroalkynyl; heterocyclylC₁₋₆alkyl; heterocyclylC₂₋₆alkenyl; heterocyclylC₂₋₆alkynyl; heterocyclylC₁₋₆heteroalkyl; heterocyclylC₂₋₆heteroalkenyl; and heterocyclylC₂₋₆heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- preferably wherein "C₁₋₁₂heteroalkyl" as a group or part of a group is selected from the group comprising C₁₋₁₂alkyloxy, C₁₋₆alkyl-oxy-C₁₋₆alkyl, (mono or di)C₁₋₆alkylamino, (mono or di)-C₁₋₆alkyl-amino-C₁₋₆alkyl, C₁₋₁₂alkylthio, and C₁₋₆alkyl-thio-C₁₋₆alkyl;

preferably wherein "C₂₋₁₂heteroalkenyl" as a group or part of a group is selected from the group comprising C₂₋₁₂alkenyloxy, C₂₋₆alkenyl-oxy-C₂₋₆alkenyl, C₁₋₆alkyl-oxy-C₂₋₆alkenyl, C₂₋₆alkenyl-oxy-C₁₋₆alkyl, (mono or di)C₂₋₆alkenylamino, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino, (mono or di-)C₂₋₆alkenyl-amino-C₂₋₆alkenyl, (mono or di-)C₁₋₆alkyl-amino-C₂₋₆alkenyl, (mono or di-)C₂₋₆alkenyl-amino-C₁₋₆alkyl, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino-C₂₋₆alkenyl, (C₁₋₆alkyl)(C₂₋₆alkenyl)amino-C₁₋₆alkyl, C₂₋₁₂alkenylthio, C₂₋₆alkenyl-thio-C₁₋₆alkyl, C₁₋₆alkyl-thio-C₂₋₆alkenyl, and C₂₋₆alkenyl-thio-C₂₋₆alkenyl;

preferably wherein "C₂₋₁₂heteroalkynyl" as a group or part of a group is selected from the group comprising C₂₋₁₂alkynyloxy, C₂₋₆alkynyl-oxy-C₂₋₆alkynyl, C₁₋₆alkyl-oxy-C₂₋₆alkynyl, C₂₋₆alkynyl-oxy-C₁₋₆alkyl, (mono or di)C₂₋₆alkynylamino, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino, (mono or di-)C₂₋₆alkynyl-amino-C₂₋₆alkynyl, (mono or di-)C₁₋₆alkyl-amino-C₂₋₆alkynyl, (mono or di-)C₂₋₆alkynyl-amino-C₁₋₆alkyl, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino-C₂₋₆alkynyl, (C₁₋₆alkyl)(C₂₋₆alkynyl)amino-C₁₋₆alkyl, C₂₋₁₂alkynylthio, C₂₋₆alkynyl-thio-C₁₋₆alkyl, C₁₋₆alkyl-thio-C₂₋₆alkynyl, and C₂₋₆alkynyl-thio-C₂₋₆alkynyl;

preferably each heteroaryl is 5 to 20 membered heteroaryl, more in particular is a 6 to 14 membered heteroaryl; yet more in particular is a 6 to 10 membered heteroaryl; including when such heteroaryl is linked to alkyl, alkenyl or alkynyl such as in heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl;

preferably each heterocycle is 5 to 20 membered heterocycle, more in particular is a 6 to 14 membered heterocycle; yet more in particular is a 6 to 10 membered heterocycle; including when such heterocycle is linked to alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl and heteroalkynyl as in heterocyclealkyl, heterocyclealkenyl, heterocyclealkynyl, heterocycleheteroalkyl, heterocycleheteroalkenyl and heterocycleheteroalkynyl.

B2. In some embodiments of the compound according to statement B1, wherein cycle B is selected from 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered heterocycle; 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered cycloalkyl; 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered cycloalkenyl; and 7-, 8-, 9-, 10-, or 11-membered cycloalkynyl.

B3. In some embodiments of the compound according to any one of statements B1-B2, wherein cycle B is selected from 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycle; 3-, 4-, 5-, 6-, or 7-, 8-, 9-, or 10-membered cycloalkyl; 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered cycloalkenyl; and 7-, 8-, 9-, or 10-membered cycloalkynyl.

B4. In some embodiments of the compound according to any one of statements B1-B3, cycle B is selected from the group comprising 4-, 5-, 6-, or 7-membered heterocycle; 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; 5-, 6-, or 7-membered cycloalkenyl; and 7-membered cycloalkynyl.

B5. In some embodiments of the compound according to any one of statements B1-B4, m is selected from 0; 1; 2; and 3, preferably m is 0, 1 or 2, for example m is 0, or m is 1 or m is 2.

B6. In some embodiments of the compound according to any one of statements B1-B5, R³ is hydrogen.

B7. In some embodiments of the compound according to any one of statements B1-B5, R³ is alkyl, for example R³ is C₁₋₆alkyl.

5 B8. In some embodiments of the compound according to any one of statements B1-B7, each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; preferably each R⁴ is independently selected from C₁₋₉alkyl; C₃₋₉cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle;

20 wherein said alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; preferably wherein each of said C₁₋₉alkyl; C₃₋₉cycloalkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

30 B9. In some embodiments of the compound according to any one of statements B1 to B8, - each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; preferably each R⁴ is independently selected from C₁₋₉alkyl; C₃₋₉cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋

₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle;

wherein said alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; preferably wherein each of said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₁₀cycloalkenyl; C₇₋₁₀cycloalkynyl; C₆₋₁₀aryl; heteroaryl; and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

B10. In some embodiments of the compound according to any one of statements B1 to B9, each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; heteroalkyl; aryl; heteroaryl; and heterocycle; preferably each R⁴ is independently selected from C₁₋₉alkyl; C₃₋₉cycloalkyl; halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₁₋₉heteroalkyl; C₆₋₁₀aryl; heteroaryl; and heterocycle;

wherein said alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; preferably wherein each of said C₁₋₉alkyl; C₁₋₁₂heteroalkyl; C₃₋₉cycloalkyl; C₆₋₁₀aryl; heteroaryl; and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

B11. In some embodiments of the compound according to any one of statements B1 to B10, - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z¹ is independently selected from C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; wherein said C₁₋₉alkyl;

C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; and C₂₋₁₂heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z² is independently selected from hydroxyl; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; heterocycle; and C₆₋₁₀arylC₁₋₆alkyl; wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl; heterocycle; and C₆₋₁₀arylC₁₋₆alkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; C₂₋₁₂heteroalkynyl wherein said C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₃₋₉cycloalkyl; C₃₋₁₀cycloalkenyl; C₃₋₁₀cycloalkynyl; C₁₋₁₂heteroalkyl; C₂₋₁₂heteroalkenyl; and C₂₋₁₂heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂, and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted

or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

B12. In some embodiments of the compound according to any one of statements B1 to B11,

- 5 - each Z¹ is independently selected from alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z¹ is independently selected from C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl; and C₃₋₉cycloalkyl is
- 10 unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- 15 - each Z² is independently selected from hydroxyl; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z² is independently selected from hydroxyl; C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl; and C₃₋₉cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂;
- 20 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³
- 25 and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; preferably each Z³ and Z⁴ is independently selected from hydrogen; C₁₋₉alkyl; and C₃₋₉cycloalkyl; wherein said C₁₋₉alkyl;
- 30 and C₃₋₉cycloalkyl is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-
- 35 membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-C₁₋₆alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHC₁₋₆alkyl, and -N(C₁₋₆alkyl)₂.

B13. In some embodiments of the compound according to any one of statements B1-B12,

- each R^4 is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; $-CF_3$; $-OCF_3$; $-CHF_2$; $-OCHF_2$; cyano; $-OZ^1$; $-C(O)Z^2$; $-C(O)OZ^1$; $-C(O)NZ^3Z^4$; $-NZ^3Z^4$; $-NZ^3S(O)_2Z^1$; $-NZ^3S(O)_2NZ^3Z^4$; $-NZ^3C(O)OZ^1$; $-NZ^3C(O)Z^1$; $-NZ^3C(O)NZ^3Z^4$; and aryl; preferably each R^4 is independently selected from C_{1-9} alkyl; C_{3-9} cycloalkyl; halogen; hydroxyl; $-CF_3$; $-OCF_3$; $-CHF_2$; $-OCHF_2$; cyano; $-OZ^1$; $-C(O)Z^2$; $-C(O)OZ^1$; $-C(O)NZ^3Z^4$; $-NZ^3Z^4$; $-NZ^3S(O)_2Z^1$; $-NZ^3S(O)_2NZ^3Z^4$; $-NZ^3C(O)OZ^1$; $-NZ^3C(O)Z^1$; $-NZ^3C(O)NZ^3Z^4$; and C_{6-10} aryl;

wherein said alkyl, cycloalkyl, and aryl is unsubstituted or is substituted with one or more substituents selected from alkyl, hydroxyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$; $-OCHF_2$, cyano, nitro, $-C(O)OH$, $-NH_2$, $-NH$ alkyl, and $-N(alkyl)_2$; preferably wherein each of said C_{1-9} alkyl; C_{3-9} cycloalkyl; and C_{6-10} aryl is unsubstituted or is substituted with one or more substituents selected from C_{1-9} alkyl, C_{3-9} cycloalkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ - C_{1-6} alkyl, $-OCF_3$, $-CHF_2$; $-OCHF_2$, cyano, nitro, $-C(O)OH$, $-NH_2$, $-NHC_{1-6}$ alkyl, and $-N(C_{1-6}alkyl)_2$

- each Z^1 is independently selected from alkyl; wherein said alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NH$ alkyl, and $-N(alkyl)_2$; preferably each Z^1 is independently selected from C_{1-9} alkyl; wherein said C_{1-9} alkyl is unsubstituted or is substituted with one or more substituents selected from C_{1-9} alkyl, C_{3-9} cycloalkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ - C_{1-6} alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NHC_{1-6}$ alkyl, and $-N(C_{1-6}alkyl)_2$;

- each Z^2 is independently selected from hydroxyl; and alkyl;

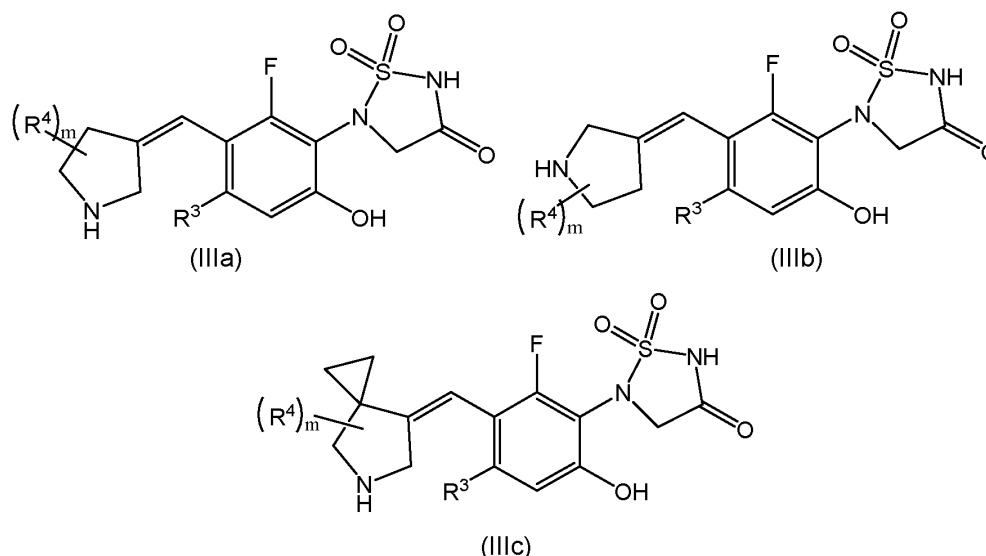
wherein said alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NH$ alkyl, and $-N(alkyl)_2$; preferably each Z^2 is independently selected from hydroxyl; and C_{1-9} alkyl; wherein said C_{1-9} alkyl is unsubstituted or is substituted with one or more substituents selected from C_{1-9} alkyl, C_{3-9} cycloalkyl, C_{2-9} alkenyl, C_{2-9} alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ - C_{1-6} alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NHC_{1-6}$ alkyl, and $-N(C_{1-6}alkyl)_2$;

- each Z^3 and Z^4 is hydrogen.

B14. In some embodiments of the compound according to any one of statements B1-B13, cycle B is selected from 4-, 5-, or 6-, or 7-membered heterocycle, preferably cycle B is selected from the group comprising pyrrolidinyl; azetidiny; oxetanyl; tetrahydrofuranyl; piperidinyl; tetrahydro-2H-pyranyl; and azepanyl; preferably cycle B is selected from the group comprising pyrrolidinyl; azetidiny; and piperidinyl.

B15. In some embodiments of the compound according to any one of statements B1-B13, cycle B is selected 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, preferably cycle B is selected from the group comprising cyclobutyl; cyclopentyl; cyclohexyl; and cycloheptyl.

B16. In some embodiments of the compound according to any one of statements B1-B14, said
5 compound is a compound of formula (IIIa), (IIIb) or (IIIc)



10 wherein R³, R⁴ and m have the same meaning as that defined in any one of statements B1-B14.

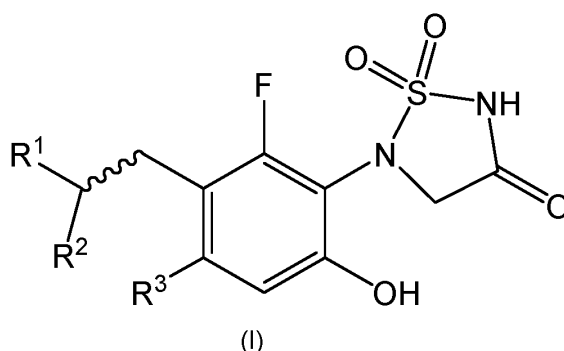
B17. In some embodiments of the compound according to any one of statements B1-B16, said compound is selected from the group comprising Cpd037, Cpd038, Cpd039, Cpd046, Cpd047, Cpd048, Cpd095, Cpd096, Cpd114, Cpd115, Cpd130, Cpd131, Cpd132, Cpd133, Cpd139, Cpd143, Cpd144, Cpd145, Cpd146, Cpd147, Cpd156, Cpd156-en1, Cpd156-en2, Cpd157, Cpd158, Cpd158-en1, Cpd158-en2, Cpd159, Cpd160, Cpd162, Cpd163, Cpd164, Cpd165, Cpd167 and Cpd168.

B18. The present invention also encompasses a pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient, an effective amount of a
20 compound according to any one of statements A1 to A20, B1 to B17.

B19. The present invention also encompasses a compound according to any one of statements A1 to A20, B1 to B17, or a pharmaceutical composition according to statement B18, for use as a medicine.

B20. The present invention also encompasses a compound according to any one of statements
25 A1 to A20, B1 to B17, or a pharmaceutical composition according to statement B18, for use in the prevention or treatment of a PTPN2 and/or PTPN1 mediated disorder in an animal, mammal or human.

- B21. In some embodiments of the compound for use according to statement B20, or the pharmaceutical composition for use according to statement B20, the PTPN2 and/or PTPN1 mediated disorders is selected from the group comprising cancer and metabolic diseases.
- B22. In some embodiments of the compound for use according to any one of statements B20, B21, or the pharmaceutical composition for use according to any of any one of statements B20, B21, the PTPN2 and/or PTPN1 mediated disorders is selected from lung cancer, breast cancer, head and neck cancer, oesophageal cancer, kidney cancer, bladder cancer, colon cancer, ovarian cancer, cervical cancer, endometrial cancer, liver cancer, skin cancer, pancreatic cancer, gastric cancer, brain cancer and prostate cancer.
- B23. The present invention also encompasses a method for the prevention or treatment of a PTPN2 and/or PTPN1 activation mediated disorders in an animal, mammal or human comprising administering to said animal, mammal or human in need for such prevention or treatment an effective dose of at least one compound according to any one of statements A1 to A20, B1 to B17.
- B24. In some embodiments of the method of treatment or prevention of PTPN2 and/or PTPN1 activation mediated disorder according to statement B23 comprising administering to a patient in need for such prevention or treatment an effective dose of at least one compound according to any one of statements A1 to A20, B1 to B17, in combination with one or more other anti-cancer agents, more specifically immunotherapeutic agents.
1. A compound of formula (I), or an isomer (preferably a stereo-isomer or a tautomer), a solvate, a salt (preferably a pharmaceutically acceptable salt) or a prodrug thereof, preferably a pharmaceutically acceptable salt, solvate, hydrate, polymorph, tautomer, stereoisomer, or prodrug thereof,



wherein:

- $\sim$ represents a double bond ($=$) or a triple bond ($\equiv$);
- R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle;

whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl,

cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R⁴;

- when  is a triple bond, then R² is not present; when  is a double bond, then R² is selected from hydrogen; alkyl and halogen; or R² can be taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; and heterocycle;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl;
- wherein said alkyl, alkenyl and alkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; and alkynyl;
- wherein said alkyl, alkenyl and alkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; and alkynyl;
- wherein said alkyl, alkenyl and alkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

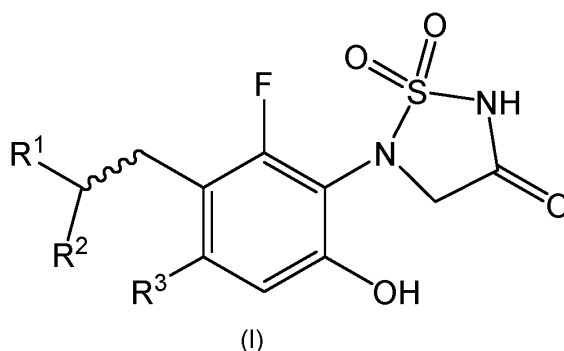
and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

In some embodiment, it is clear from the description of the invention that when  is

a double bond, R^2 is selected from hydrogen; alkyl and halogen, or R^2 can be taken together with R^1 to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;

wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl, or a 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R^4 .

2. A compound of formula (I), or an isomer (preferably a stereo-isomer or a tautomer), a solvate, a salt (preferably a pharmaceutically acceptable salt) or a prodrug thereof, preferably a pharmaceutically acceptable salt, solvate, hydrate, polymorph, tautomer, stereoisomer, or prodrug thereof,



wherein:

- $\sim$ represents a double bond ($\equiv$) or a triple bond ($\equiv$);
- R^1 is selected from alkyl; alkenyl; heteroalkyl; cycloalkyl; aryl; heteroaryl; heterocycle; whereby each of said alkyl, alkenyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R^4 ;
- when $\sim$ is a triple bond, then R^2 is not present; when $\sim$ is a double bond, then R^2 is selected from hydrogen; and alkyl, or R^2 can be taken together with R^1 to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; or a 4-, 5-, 6-, or 7-membered heterocycle;
- R^3 is selected from hydrogen and alkyl;
- each R^4 is independently selected from halogen; hydroxyl; sulfhydryl; $-\text{CF}_3$; $-\text{OCF}_3$; $-\text{CHF}_2$; $-\text{OCHF}_2$; cyano; $-\text{OZ}^1$; $-\text{C}(\text{O})\text{Z}^2$; $-\text{C}(\text{O})\text{OZ}^1$; $-\text{C}(\text{O})\text{NZ}^3\text{Z}^4$; $-\text{NZ}^3\text{Z}^4$; $-\text{NZ}^3\text{S}(\text{O})_2\text{Z}^1$; $-\text{NZ}^3\text{S}(\text{O})_2\text{NZ}^3\text{Z}^4$; $-\text{NZ}^3\text{C}(\text{O})\text{OZ}^1$; $-\text{NZ}^3\text{C}(\text{O})\text{Z}^1$; $-\text{NZ}^3\text{C}(\text{O})\text{NZ}^3\text{Z}^4$; alkyl; and aryl;
- wherein said alkyl and aryl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=\text{O}$, halogen, $-\text{SH}$, $=\text{S}$, $-\text{CF}_3$, $-\text{O-alkyl}$, $-\text{OCF}_3$, $-\text{CHF}_2$; $-\text{OCHF}_2$, cyano, nitro, $-\text{C}(\text{O})\text{OH}$, $-\text{NH}_2$, $-\text{NHalkyl}$, and $-\text{N}(\text{alkyl})_2$;
- each Z^1 is independently selected from alkyl; wherein said alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=\text{O}$, halogen, $-\text{SH}$, $=\text{S}$, $-\text{CF}_3$, $-\text{O-alkyl}$, $-\text{OCF}_3$, $-\text{CHF}_2$, $-\text{OCHF}_2$, cyano, nitro, $-\text{C}(\text{O})\text{OH}$; NH_2 ; $-\text{NHalkyl}$, and $-\text{N}(\text{alkyl})_2$;

- each Z^2 is independently selected from hydroxyl; and alkyl;
 wherein said alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

5 - each Z^3 and Z^4 is hydrogen.

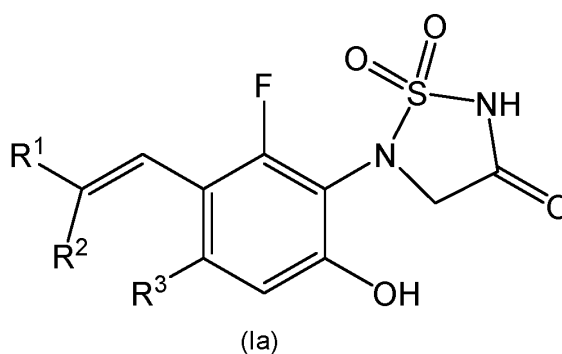
For further specification of this embodiment, when $\sim$ is a double bond, R^2 is selected from hydrogen; alkyl and halogen, or R^2 can be taken together with R^1 to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; or a 4-, 5-, 6-, or 7-membered heterocycle;

wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, or 4-, 5-, 6-, or 7-membered
 10 heterocycle is unsubstituted or substituted with one or more R^4 .

In a specific embodiment of the present invention, the compounds have a structure according to formula I described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to any one of statements A1, A2, 1, and 2 herein, whereby $\sim$ represents a double bond ($\equiv$).

15 In another specific embodiment of the present invention, the compounds have a structure according to formula I described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to any one of statements A1, A2, 1, and 2 herein, whereby $\sim$ represents a triple bond ($\equiv$).

3. A compound of formula (Ia), or an isomer (preferably a stereo-isomer or a tautomer), a
 20 solvate, a salt (preferably a pharmaceutically acceptable salt) or a prodrug thereof, preferably a pharmaceutically acceptable salt, solvate, hydrate, polymorph, tautomer, stereoisomer, or prodrug thereof,



25 wherein:

- R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl;
 30 and heterocyclheteroalkyl;

whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R⁴;

- R² is selected from hydrogen; alkyl and halogen, or R² can be taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; and heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; or heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl,

arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is

5 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

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wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is

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20 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

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wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is

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35 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂,

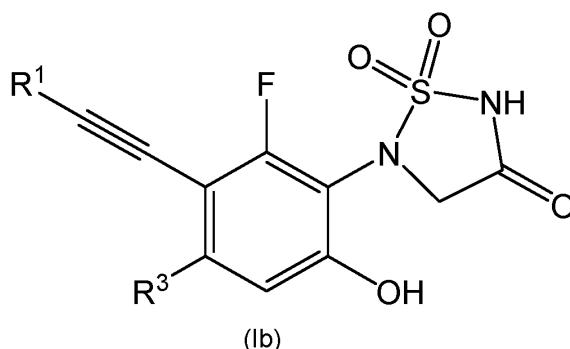
-OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

For further specification of this embodiment, R² is selected from hydrogen; alkyl and halogen, or R² can be taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl; or a 4-, 5-, 6-, or 7-membered heterocycle;

wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl, 3-, 4-, 5-, 6-, or 7-membered cycloalkynyl, or 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R⁴.

4. A compound of formula (Ib), or an isomer (preferably a stereo-isomer or a tautomer), a solvate, a salt (preferably a pharmaceutically acceptable salt) or a prodrug thereof, preferably a pharmaceutically acceptable salt, solvate, hydrate, polymorph, tautomer, stereoisomer, or prodrug thereof,



wherein:

- R¹ is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl;

and heterocyclheteroalkyl;

whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with

one or more R⁴;

- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -
- 5 S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; - -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl;
- 10 heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

- wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl,
- 15 arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl,
- 20 =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl;
- 25 heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl,
- 30 arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl,
- 35 cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl;

- cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl;
- 5 heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocycl heteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 10
- 15 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocycl heteroalkynyl;
- 20
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 25
- 30 and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.
- 35

In a specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc), described herein, more in

particular according to the other formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1-A20, B1-B17, 1, 2, 3, 4, 5, 6, and 7 herein, whereby:

- each alkyl is C₁-C₁₈ membered alkyl, more in particular is a C₁-C₁₂ membered alkyl; yet more in particular is a C₁-C₉ membered alkyl; still more in particular is a C₁-C₆ membered alkyl; including when such alkyl is linked for example to aryl, heteroaryl or heterocycle as for example in arylalkyl, heteroarylalkyl and heterocycle-alkyl;
- each alkenyl is C₂-C₁₈ membered alkenyl, more in particular is a C₂-C₁₂ membered alkenyl; yet more in particular is a C₂-C₉ membered alkenyl; still more in particular is a C₂-C₆ membered alkenyl; including when such alkenyl is linked to for example aryl, heteroaryl or heterocycle as for example in arylalkenyl, heteroarylalkenyl and heterocycle-alkenyl;
- each alkynyl is C₂-C₁₈ membered alkynyl, more in particular is a C₂-C₁₂ membered alkynyl; yet more in particular is a C₂-C₉ membered alkynyl; still more in particular is a C₂-C₆ membered alkynyl; including when such alkynyl is linked to for example aryl, heteroaryl or heterocycle as for example in arylalkynyl, heteroarylalkynyl and heterocycle-alkynyl;
- each heteroalkyl is C₁-C₁₈ membered heteroalkyl, more in particular is a C₁-C₁₂ membered heteroalkyl; yet more in particular is a C₁-C₉ membered heteroalkyl; still more in particular is a C₁-C₆ membered heteroalkyl; including when such heteroalkyl is linked for example to aryl, heteroaryl or heterocycle as for example in arylheteroalkyl, heteroarylheteroalkyl and heterocycle-heteroalkyl;
- each heteroalkenyl is C₂-C₁₈ membered heteroalkenyl, more in particular is a C₂-C₁₂ membered heteroalkenyl; yet more in particular is a C₂-C₉ membered heteroalkenyl; still more in particular is a C₂-C₆ membered heteroalkenyl; including when such heteroalkenyl is linked to for example aryl, heteroaryl or heterocycle as for example in arylheteroalkenyl, heteroarylheteroalkenyl and heterocycle-heteroalkenyl; and
- each heteroalkynyl is C₂-C₁₈ membered heteroalkynyl, more in particular is a C₂-C₁₂ membered heteroalkynyl; yet more in particular is a C₂-C₉ membered heteroalkynyl; still more in particular is a C₂-C₆ membered heteroalkynyl; including when such alkenyl is linked to for example aryl, heteroaryl or heterocycle as for example in arylheteroalkynyl, heteroarylheteroalkynyl and heterocycle-heteroalkynyl.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc), described herein, more in particular according to the other formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1-A20, B1-B17, 1, 2, 3, 4, 5, 6 and 7 herein, whereby:

- each cycloalkyl is C₃-C₁₈ membered cycloalkyl, more in particular is a C₃-C₁₂ membered cycloalkyl; yet more in particular is a C₃-C₉ membered cycloalkyl; still more in particular is a C₃-

C₆ membered cycloalkyl;

- each cycloalkenyl is C₅-C₁₈ membered cycloalkenyl, more in particular is a C₅-C₁₂ membered cycloalkenyl; yet more in particular is a C₅-C₉ membered cycloalkenyl; still more in particular is a C₅-C₆ membered cycloalkenyl;

- 5 - each cycloalkynyl is C₅-C₁₈ membered cycloalkynyl, more in particular is a C₅-C₁₂ membered cycloalkynyl; yet more in particular is a C₅-C₉ membered cycloalkynyl; still more in particular is a C₅-C₆ membered cycloalkynyl;

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc), described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet

- 10 more in particular according to statements A1-A20, B1-B17, 1, 2, 3, 4, 5, 6, and 7 herein, whereby:

- each aryl is C₆-C₂₀ membered aryl, more in particular is a C₆-C₁₄ membered aryl; yet more in particular is a C₆-C₁₀ membered aryl; including when such aryl is linked to alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl or heteroalkynyl, as in arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl;

- 15 - each heteroaryl is 5 to 20 membered heteroaryl, more in particular is a 6 to 14 membered heteroaryl; yet more in particular is a 6 to 10 membered heteroaryl; including when such heteroaryl is linked to alkyl, alkenyl or alkynyl such as in heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl;

- 20 - each heterocycle is 5 to 20 membered heterocycle, more in particular is a 6 to 14 membered heterocycle; yet more in particular is a 6 to 10 membered heterocycle; including when such heterocycle is linked to alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl and heteroalkynyl as in heterocyclealkyl, heterocyclealkenyl, heterocyclealkynyl, heterocycleheteroalkyl, heterocycleheteroalkenyl and heterocycleheteroalkynyl.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia) and (Ib) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1, A6, A7, 1, 2, 3 and 4 herein, whereby

- R¹ is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R⁴; or

- R¹ is selected from alkyl; alkenyl; heteroalkyl; heteroalkenyl; cycloalkyl; cycloalkenyl; aryl; heteroaryl; and heterocycle; whereby each of said alkyl, alkenyl, heteroalkyl, heteroalkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R⁴; or

- R¹ is selected from alkyl; alkenyl; heteroalkyl; cycloalkyl; aryl; heteroaryl; and heterocycle;

whereby each of said alkyl, alkenyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R⁴; or

- R¹ is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl and heteroalkynyl is unsubstituted

5 or is substituted with one or more R⁴; or

- R¹ is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle; whereby each of said cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more R⁴; or

- R¹ is selected from aryl; and heteroaryl; whereby each of said aryl and heteroaryl is unsubstituted
10 or is substituted with one or more R⁴.

In yet more particular embodiments of the present invention, the compounds have a structure according to formula (I), (Ia) and (Ib) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1, A6, A7, 1, 2, 3 and 4 herein, whereby:

15 - R¹ is selected from C₁-C₆ alkyl; yet more specifically whereby R¹ is selected from methyl, ethyl, propyl; butyl; pentyl and hexyl; or

- R¹ is selected from C₁-C₆ heteroalkyl; or

- R¹ is selected from C₃-C₆ cycloalkyl; yet more specifically whereby R¹ is selected from cyclopropyl; cyclobutyl; cyclopentyl and cyclohexyl; or

20 - R¹ is selected from C₁-C₆ alkyl; and C₃-C₆ cycloalkyl; yet more specifically whereby R¹ is selected from methyl, ethyl, propyl; butyl; pentyl; hexyl; cyclopropyl; cyclobutyl; cyclopentyl and cyclohexyl; or

- more in particular R¹ is selected from aryl; yet more specifically whereby R¹ is phenyl; or

- more in particular R¹ is selected from heteroaryl; yet more specifically whereby R¹ is selected
25 from pyrazolyl; isoxazolyl; pyridyl; and thiazolyl; or

- more in particular R¹ is selected from heterocycle; yet more specifically whereby R¹ is selected from azetidiny; oxetanyl; pyrrolidiny; tetrahydrofuranyl; piperidiny; tetrahydro-2H-pyranyl; and azepanyl.

In another specific embodiment of the present invention, the compounds have a structure
30 according to formula (I), (Ia) and (Ib) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1, A6, A7, 1, 2, 3 and 4 herein, whereby

- R¹ is selected from C₁-C₆ alkyl; yet more specifically whereby R¹ is selected from methyl, ethyl, propyl; butyl; pentyl and hexyl; and is unsubstituted or substituted with one or more R⁴; or

35 - R¹ is selected from C₁-C₆ heteroalkyl and is unsubstituted or is substituted with one or more R⁴; or

- R¹ is selected from C₃-C₄ cycloalkyl; yet more specifically whereby R¹ is selected from

cyclopropyl and cyclobutyl; or R¹ is selected from C₃ cycloalkyl; yet more specifically whereby R¹ is cyclopropyl; and for each of said R¹, R¹ is unsubstituted or is substituted with one or more R⁴.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I) and (Ia) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements 1, 2 and 3 herein, whereby

- R² is selected from hydrogen; and alkyl; yet more in particular R² is hydrogen; still more in particular R² is alkyl; or

- R² is taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 3-, 4-, 5-, 6-, or 7-membered cycloalkenyl; or a 4-, 5-, 6-, or 7-membered heterocycle;

- yet more in particular R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered cycloalkyl; or a 4-, 5-, 6-, or 7-membered heterocycle.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I) and (Ia) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements 1, 2 and 3 herein, whereby

- R² is selected from hydrogen; and alkyl; yet more in particular R² is hydrogen; still more in particular R² is alkyl; or

- R² is taken together with R¹ to form a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; a 5-, 6-, or 7-membered cycloalkenyl; or a 4-, 5-, 6-, or 7-membered heterocycle; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, 5-, 6-, or 7-membered cycloalkenyl, or 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R⁴;

- yet more in particular R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered cycloalkyl; or a 4-, 5-, 6-, or 7-membered heterocycle; wherein said 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, or a 4-, 5-, 6-, or 7-membered heterocycle is unsubstituted or substituted with one or more R⁴.

In yet more particular embodiments of the present invention, the compounds have a structure according to formula (I) and (Ia) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements 1, 2 and 3 herein, whereby:

- R² is selected from C₁-C₆ alkyl; yet more specifically whereby R² is selected from methyl; ethyl; propyl; butyl; pentyl and hexyl; or

- R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered cycloalkyl; yet more in particular to form cyclobutyl; cyclopentyl; cyclohexyl; or cycloheptyl; or

- R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered heterocycle; yet more in particular to form azetidiny; oxetanyl; pyrrolidinyl; tetrahydrofuranyl; piperidinyl; tetrahydro-2H-pyranyl; and azepanyl; still more in particular to form azetidiny; pyrrolidinyl; and piperidinyl.

In yet more particular embodiments of the present invention, the compounds have a structure according to formula (I) and (Ia) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements 1, 2 and 3 herein, whereby:

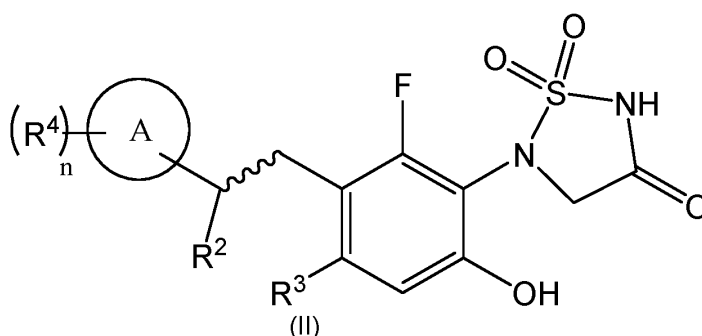
- 5 - R² is selected from C₁-C₆ alkyl; yet more specifically whereby R² is selected from methyl; ethyl; propyl; butyl; pentyl and hexyl; or
- R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered cycloalkyl unsubstituted or substituted with one or more R⁴; yet more in particular to form cyclobutyl; cyclopentyl; cyclohexyl; or cycloheptyl; wherein said cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl is unsubstituted or
- 10 substituted with one or more R⁴; or
- R² is taken together with R¹ to form a 4-, 5-, 6-, or 7-membered heterocycle unsubstituted or substituted with one or more R⁴; yet more in particular to form azetidiny; oxetanyl; pyrrolidiny; tetrahydrofuranyl; piperidiny; tetrahydro-2H-pyranyl; and azepanyl; wherein said azetidiny, oxetanyl, pyrrolidiny, tetrahydrofuranyl, piperidiny, tetrahydro-2H-pyranyl, and azepanyl is
- 15 unsubstituted or substituted with one or more R⁴; still more in particular to form azetidiny; pyrrolidiny; and piperidiny; wherein said azetidiny, pyrrolidiny, and piperidiny is unsubstituted or substituted with one or more R⁴.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia) and (Ib) described herein, more in particular according to the

20 formulas, statements, embodiments and aspects described herein, yet more in particular according to any one of statements A1-A20, B1-B17, 1, 2, 3 and 4 herein, whereby

- R³ is hydrogen; or
- R³ is C₁-C₆ alkyl; yet more specifically R³ is selected from methyl; ethyl; propyl; butyl; pentyl and hexyl; still more in particular R³ is selected from methyl, ethyl, and propyl;

- 25 5. More particularly, the compounds of the invention are compounds of formula (II) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, polymorph and/or prodrug thereof,



30 wherein:

-  represents a double bond () or a triple bond ();
 - cycle A is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;
 - when  is a triple bond, then R² is not present; when  is a double bond, then R² is selected from hydrogen; alkyl and halogen;
- 5 - R³ is selected from hydrogen and alkyl;
- n is selected from 0, 1, 2, 3, 4 and 5;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; and heterocyclheteroalkynyl;
- 10 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- 15 - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; or heterocyclheteroalkynyl;
- 20 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is
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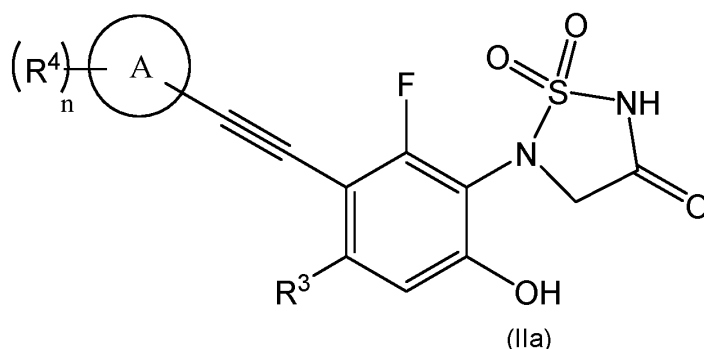
unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocycl heteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocycl heteroalkynyl;

- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH,

=S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

In another specific embodiment of the present invention, the compounds have a structure according to formula (IIa) described herein, more in particular according to the statements, 5 embodiments and aspects described herein:



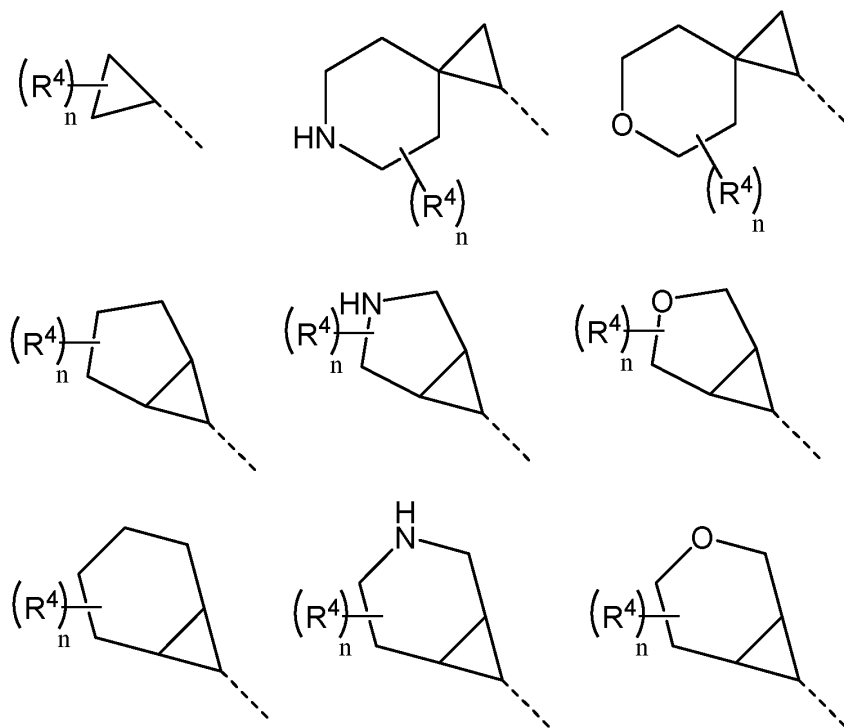
wherein cycle A, R³, n, each R⁴, each Z¹, each Z², each Z³ and each Z⁴ are independently according to the formulas, statements, aspects and embodiments described herein, such as for 10 formula (II).

In another specific embodiment of the present invention, the compounds have a structure according to formulas, statements, embodiments and aspects described herein whereby:

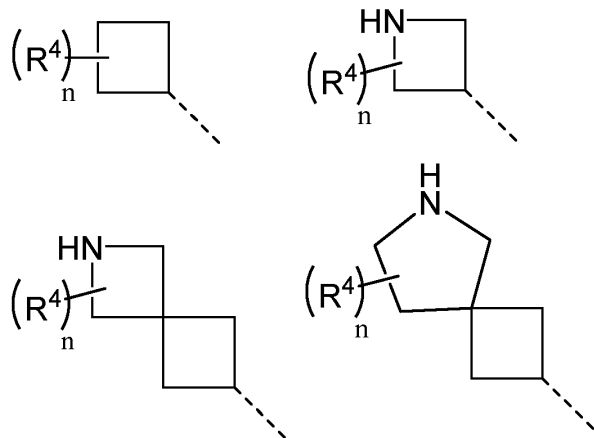
R¹ is cycle A selected from cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;

- at least one R⁴ substituent is present on cycle A, more in particular such substituent is 15 positioned in the meta-position.

In a more particular embodiment, the compounds have a structure according to formulas, statements, embodiments and aspects described herein whereby R¹ or cycle A is unsubstituted or substituted with one or more R⁴, and is selected from the following structures:

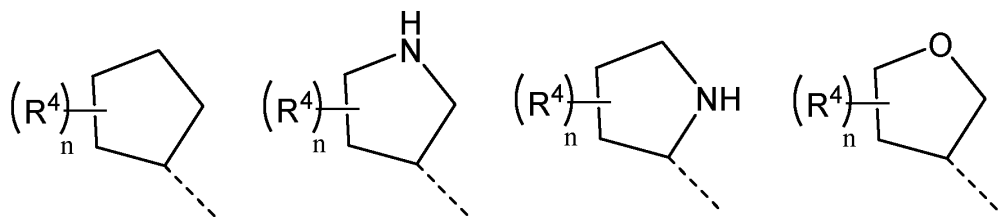


In another more particular embodiment, the compounds have a structure according to formulas, statements, embodiments and aspects described herein whereby R^1 or cycle A unsubstituted or substituted with one or more R^4 and is selected from the following structures:

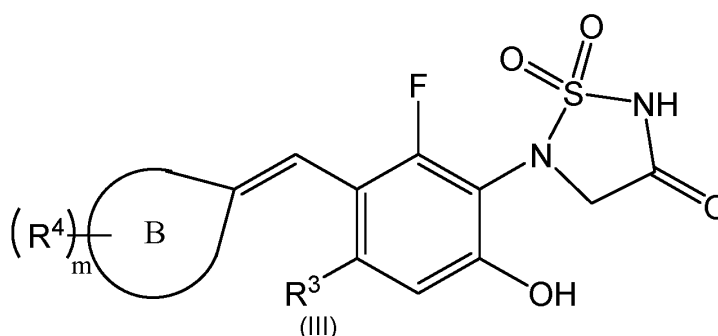


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In yet another more particular embodiment, the compounds have a structure according to formulas, statements, embodiments and aspects described herein whereby R^1 or cycle A unsubstituted or substituted with one or more R^4 and is selected from the following structures:



6. More particularly, the compounds of the invention are compounds of formula (III) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, polymorph and/or prodrug thereof,



5

wherein:

- cycle B is selected from cycloalkyl; cycloalkenyl; cycloalkynyl; and heterocycle;
- m is selected from 0; 1; 2; 3; 4; and 5;
- 10 - each R^4 is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 15
- 20 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted
- 25 with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl,

=O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocycl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

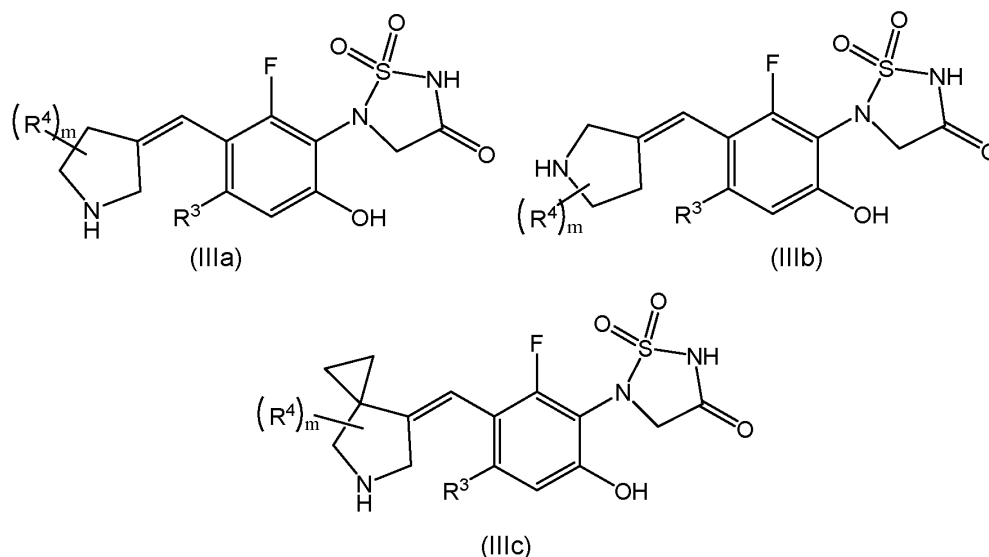
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl;

heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

7. More particularly, the compounds of the invention are compounds of formula (IIIa), (IIIb) and (IIIc) and any subgroup thereof as described herein, a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, polymorph and/or prodrug thereof,



25 wherein:

- m is selected from 0; 1; 2; 3; 4 and 5;
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃;

- OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 10 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted
- 15 with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; or heterocyclheteroalkynyl;
- 20 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 25 - each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 30 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- 35 - each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl;

heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; or heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements A1, A3-A7, 1, 2, 3, 4, 5, 6 and 7 herein, whereby R¹ is substituted with 1, 2, 3, 4, 5 or 6 R⁴; or more specifically, R¹ is substituted with 1, 2, 3, 4 or 5 R⁴;

or more specifically, R^1 is substituted with 1, 2, 3 or 4 R^4 ; still more in particular, R^1 is substituted with 1, 2 or 3 R^4 ; yet more in particular, R^1 is substituted with 1 or 2 R^4 ; still more in particular, R^1 is substituted with 1 R^4 ; or in another embodiment, R^1 is unsubstituted.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements 1, 2, 3, 4, 5, 6 and 7 herein, whereby R^1 taken together with R^2 is substituted with 1, 2, 3, 4, 5 or 6 R^4 ; or more specifically, R^1 taken together with R^2 is substituted with 1, 2, 3, 4 or 5 R^4 ; or more specifically, R^1 taken together with R^2 is substituted with 1, 2, 3 or 4 R^4 ; still more in particular, R^1 taken together with R^2 is substituted with 1, 2 or 3 R^4 ; yet more in particular, R^1 taken together with R^2 is substituted with 1 or 2 R^4 ; still more in particular, R^1 taken together with R^2 is substituted with 1 R^4 ; or in another embodiment, R^1 taken together with R^2 is unsubstituted.

In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is selected from 1, 2, 3, 4, 5 and 6. In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is selected from 1, 2, 3, 4 and 5. In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is selected from 1, 2, 3 and 4. In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is selected from 1, 2 and 3. In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is selected from 1 and 2. In another embodiment, the compounds are according to any one of statements A2, A8-A12, 5, wherein n is not 0.

In yet another embodiment, the compounds are according to any one of statements B1-B17, 6, wherein m is selected from 1, 2, 3, 4, 5 and 6. In another embodiment, the compounds are according to any one of statements B1-B17, 6, wherein m is selected from 1, 2, 3, 4 and 5. In another embodiment, the compounds are according to any one of statements B1-B17, 6, wherein m is selected from 1, 2, 3 and 4. In another embodiment, the compounds are according to any one of statements B1-B17, 6 and 7, wherein m is selected from 1, 2 and 3. In another embodiment, the compounds are according to any one of statements B1-B17, 6 and 7, wherein m is selected from 1 and 2. In another embodiment, the compounds are according to any one of statements B1-B17, 6 and 7, wherein m is not 0.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to any one of statements A1-A20, B1-B17, 1, 2, 3, 4, 5 and 6 and 7 herein, whereby:

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;

wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or

- each R⁴ is independently selected from halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; alkyl; heteroalkyl; cycloalkyl; aryl; heteroaryl; and heterocycle;

wherein said alkyl, heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to any one of statements A1-A20, B1-B17, 1, 2, 3, 4, 5 and 6 and 7 herein, whereby:

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋

alkynyl; C₁₋₉heteroalkyl; C₂₋₉heteroalkenyl; C₂₋₉heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₉cycloalkenyl; C₅₋₉cycloalkynyl; aryl; heteroaryl; and heterocycle;

wherein said C₁₋₉alkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, C₁₋₉heteroalkyl, C₂₋₉heteroalkenyl, C₂₋₉heteroalkynyl, C₃₋₉cycloalkyl, C₅₋₉cycloalkenyl, C₅₋₉cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₁₋₉alkyl; C₂₋₉alkenyl; C₂₋₉alkynyl; C₁₋₉heteroalkyl; C₂₋₉heteroalkenyl; C₂₋₉heteroalkynyl; C₃₋₉cycloalkyl; C₅₋₉cycloalkenyl; C₅₋₉cycloalkynyl; aryl; heteroaryl; and heterocycle;

wherein said C₁₋₉alkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, C₁₋₉heteroalkyl, C₂₋₉heteroalkenyl, C₂₋₉heteroalkynyl, C₃₋₉cycloalkyl, C₅₋₉cycloalkenyl, C₅₋₉cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from C₁₋₉alkyl, C₃₋₉cycloalkyl, C₂₋₉alkenyl, C₂₋₉alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or

- each R⁴ is independently selected from halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; C₁₋₉alkyl; C₁₋₉heteroalkyl; C₃₋₉cycloalkyl; aryl; heteroaryl; and heterocycle;

wherein said C₁₋₉alkyl, C₁₋₉heteroalkyl, C₃₋₉cycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet more in particular according to statements any one of A1-A20, B1-B17, 1, 2, 3, 4, 5 and 6 and 7 herein, whereby:

- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; alkoxy; and alkyl; wherein said alkoxy and alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or more specifically

- each R⁴ is independently selected from halogen; hydroxyl; CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; alkoxy; and alkyl; wherein said alkoxy and alkyl is unsubstituted or is substituted with one or more

substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂; or more specifically

- each R⁴ is independently selected from halogen; hydroxyl; CF₃; -OCF₃; alkoxy; and alkyl; or

5 more specifically

- each R⁴ is independently selected from F; Cl; hydroxyl; CF₃; -OCF₃; alkoxy; and alkyl.

In another specific embodiment of the present invention, the compounds have a structure according to formula (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) described herein, more in particular according to the formulas, statements, embodiments and aspects described herein, yet

10 more in particular according to any one of statements A1-A20, B1-B17, 1, 2, 3, 4, 5 and 6 and 7 herein, whereby:

- each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is

15 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is

20 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be

25 cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be

30 taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

In another more particular embodiment,

35 - each Z¹ is independently selected from alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano,

- nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z² is independently selected from hydroxyl; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

In a particular embodiment, the compounds of the invention are selected from the compounds listed in Table 1 and as described with their chemical name below.

- Cpd001: 5-(3-(cyclopentylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd002: 5-(3-(3,3-dimethylbut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd003: 5-(3-((3-chlorophenyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd004: 5-(2-fluoro-3-((3-fluorophenyl)ethynyl)-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd005: 5-(2-fluoro-6-hydroxy-3-(pyridin-2-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd006: 5-(2-fluoro-6-hydroxy-3-(pyridin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd007: 5-(2-fluoro-6-hydroxy-3-(3-(methylamino)prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd008: 5-(2-fluoro-6-hydroxy-3-(phenylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd009: 5-(3-(cyclopropylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd010: 5-(2-fluoro-6-hydroxy-3-((1-(methylsulfonyl)pyrrolidin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd011: 5-(2-fluoro-6-hydroxy-3-(4-methylpent-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd012: 5-(3-((2,5-difluorophenyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one

- 1,1-dioxide;
Cpd013: 5-(2-fluoro-6-hydroxy-3-((2-methylthiazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd014: 5-(2-fluoro-6-hydroxy-3-((5-methylisoxazol-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
5 Cpd015: 5-(2-fluoro-6-hydroxy-3-((5-methylthiazol-2-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd016: 5-(2-fluoro-6-hydroxy-3-((3-(trifluoromethyl)phenyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
10 Cpd017: 5-(3-((3,4-dichlorophenyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd018: 5-(3-((1H-pyrazol-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd019: 5-(3-(azetidin-3-ylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
15 Cpd020: 5-(2-fluoro-6-hydroxy-3-(pyrrolidin-2-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd021: 5-(3-((1-acetylazetidin-3-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
20 Cpd022: 5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd023: 5-(3-(cyclohexylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd024: 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
25 Cpd025: 5-(3-(but-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd026: 5-(2-fluoro-6-hydroxy-3-(3-methoxy-3-methylbut-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd027: 5-(2-fluoro-6-hydroxy-3-(3-methylbut-3-en-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
30 Cpd028: N-(4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)-2-methylenebut-3-yn-1-yl)methanesulfonamide;
Cpd029: 5-(2-fluoro-6-hydroxy-3-((3-methoxyphenyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
35 Cpd030: 5-(2-fluoro-6-hydroxy-3-((3-hydroxyoxetan-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
Cpd031: 5-(2-fluoro-6-hydroxy-3-((3-methoxyoxetan-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-

- one 1,1-dioxide;
- Cpd032: 5-(2-fluoro-6-hydroxy-3-((1-phenylcyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd033: 5-(2-fluoro-6-hydroxy-3-((4-methoxyphenyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 5 Cpd034: 5-(3-((3-chloro-4-methoxyphenyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd035: 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd036: 5-(2-fluoro-6-hydroxy-4-methyl-3-(phenylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 10 Cpd037: (E)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd038: (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 15 Cpd039: 5-(3-(azetidin-3-ylidenemethyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd040: (E)-5-(2-fluoro-3-(3-fluorostyryl)-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd041: (E)-5-(3-(2-cyclopropylvinyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 20 Cpd042: (E)-5-(3-(3,3-dimethylbut-1-en-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd043: 5-(2-fluoro-6-hydroxy-3-(2-methylprop-1-en-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 25 Cpd044: (E)-5-(3-(2-cyclohexylvinyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd045: (E)-5-(2-fluoro-6-hydroxy-3-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd046: 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 30 Cpd047: 5-(3-(cyclopentylidenemethyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd048: 5-(2-fluoro-6-hydroxy-3-((1-propylpiperidin-4-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd049: N-(4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)-2-methylbut-3-yn-2-yl)methanesulfonamide;
- 35 Cpd050: 5-(2-fluoro-6-hydroxy-3-(pyrimidin-5-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;

- Cpd051: 5-(3-((2,3-difluorophenyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd052: 5-(2-fluoro-6-hydroxy-3-(imidazo[1,2-b]pyridazin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 5 Cpd053: 5-(2-fluoro-6-hydroxy-3-((1-(methylsulfonyl)piperidin-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd054: 5-(2-fluoro-6-hydroxy-3-((1-(methylsulfonyl)piperidin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd055: 5-(2-fluoro-6-hydroxy-3-(3-methoxyprop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 10 Cpd056: 5-(3-((1H-pyrazol-4-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd057: 5-(2-fluoro-6-hydroxy-3-(3-methylbut-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 15 Cpd058: 5-(2-fluoro-6-hydroxy-3-((5-methoxypyridin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd059: 5-(2-fluoro-6-hydroxy-3-((6-methylpyridin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd060: 5-(2-fluoro-6-hydroxy-3-((1-(hydroxymethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 20 Cpd061: 5-(2-fluoro-6-hydroxy-3-((1-methyl-1H-pyrazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd062: 5-(2-fluoro-6-hydroxy-3-((tetrahydrofuran-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 25 Cpd063: 5-(3-(cyclopropylethynyl)-2-fluoro-6-hydroxy-4-methylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd064: 5-(3-((1H-imidazol-2-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd065: 5-(3-((1H-imidazol-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 30 Cpd066: 5-(3-((1H-pyrrolo[2,3-b]pyridin-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd067: 5-(2-fluoro-6-hydroxy-3-(pyrazin-2-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- 35 Cpd068: 5-(3-((5-chloropyridin-3-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd069: 5-(2-fluoro-6-hydroxy-3-((5-methylpyridin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-

- one 1,1-dioxide;
- Cpd070: 5-(2-fluoro-6-hydroxy-3-(3,3,3-trifluoroprop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide;
- Cpd071: N-(3-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)prop-2-yn-1-yl)methanesulfonamide;
- 5 Cpd072: 5-(2-fluoro-6-hydroxy-3-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd073: 5-(2-fluoro-6-hydroxy-3-(3-methylpent-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 10 Cpd074: 5-(3-((3,3-difluorocyclobutyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd075: 5-(3-((1H-pyrazolo[3,4-b]pyridin-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd076: N-(4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)but-3-yn-15 2-yl)methanesulfonamide
- Cpd077: 5-(3-(((1R,5S,6S)-3-oxabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd078: 5-(3-((2,2-dimethylcyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 20 Cpd079: 5-(3-(((1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd080: 5-(3-(4-amino-3-methylbut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd080-en1: 5-(3-(4-amino-3-methylbut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-25 thiadiazolidin-3-one 1,1-dioxide
- Cpd080-en2: 5-(3-(4-amino-3-methylbut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd081: 5-(3-((1H-1,2,4-triazol-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 30 Cpd082: 5-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)nicotinonitrile
- Cpd083: 5-(2-fluoro-6-hydroxy-3-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd084: 5-(2-fluoro-6-hydroxy-3-(pyridazin-4-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-35 dioxide
- Cpd085: 5-(2-fluoro-6-hydroxy-3-(pyridazin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

- Cpd086: 5-(3-(((1R,5S,6S)-3-(ethylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd087: 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-(methylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 5 Cpd088: methyl (1R,5S,6S)-6-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate
- Cpd089: 5-(3-(((1R,5S,6S)-3-(cyclopropylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd090: 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-(morpholinosulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 10 Cpd091: 5-(3-(((1R,5S,6S)-3-(benzylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd092: 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-((4-methylpiperazin-1-yl)sulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 15 Cpd093: (1R,5S,6S)-6-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)-3-azabicyclo[3.1.0]hexane-3-sulfonamide
- Cpd094: 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl-d3)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd095: (Z)-5-(2-fluoro-6-hydroxy-3-(piperidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 20 Cpd096: (E)-5-(2-fluoro-6-hydroxy-3-(piperidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd097: 5-(3-(4-aminobut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 25 Cpd098: 5-(3-((6-oxaspiro[2.5]octan-1-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd099: rel-5-(2-fluoro-6-hydroxy-3-(((1R,6R,7R)-3-(methylsulfonyl)-3-azabicyclo[4.1.0]heptan-7-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd100: rel-N-((1R,5R,6R)-6-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)bicyclo[3.1.0]hexan-2-yl)methanesulfonamide
- 30 Cpd101: 5-(3-(((1R,5S,6R)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd102: 5-(3-((2-azaspiro[3.3]heptan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 35 Cpd103: 5-(3-(((1S,3S)-3-aminocyclobutyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

- Cpd104: 5-(3-(((1R,3R)-3-aminocyclobutyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd105: rel-5-(2-fluoro-6-hydroxy-3-(((1R,2R)-2-(hydroxymethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 5 Cpd106: rel-5-(2-fluoro-6-hydroxy-3-(((1R,2R)-2-(methoxymethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd107: rel-(1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)-N-methylcyclopropane-1-carboxamide
- Cpd108: 5-(3-((5-(2-(dimethylamino)ethyl)pyridin-3-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-
10 thiadiazolidin-3-one 1,1-dioxide
- Cpd109: 5-(2-fluoro-6-hydroxy-3-((1-(2-hydroxyethyl)-1H-imidazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd110: 5-(2-fluoro-6-hydroxy-3-((1-(2-(methylamino)ethyl)-1H-pyrazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 15 Cpd111: 5-(3-((1-(2-(dimethylamino)ethyl)-1H-imidazol-4-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd112: 5-(3-((E)-2-((1R,5S,6S)-3-azabicyclo[3.1.0]hexan-6-yl)vinyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd113: 5-(3-((1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-
20 1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd114: (E)-5-(2-fluoro-6-hydroxy-3-((1-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd115: (Z)-5-(2-fluoro-6-hydroxy-3-((1-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 25 Cpd116: 5-(2-fluoro-6-hydroxy-3-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd117: rel-5-(2-fluoro-6-hydroxy-3-(((1R,5S,6R)-3-hydroxybicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd118: (R)-5-(3-(3-aminobut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one
30 1,1-dioxide
- Cpd119: (S)-5-(3-(3-aminobut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd120: 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-(piperidin-4-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 35 Cpd121: (1R,5S,6S)-N-(2-aminoethyl)-6-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)-N-methyl-3-azabicyclo[3.1.0]hexane-3-sulfonamide

- Cpd122: 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd123: 5-(3-((6-azaspiro[3.4]octan-2-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 5 Cpd124-en1: 5-(2-fluoro-6-hydroxy-3-(3-methyl-4-(methylamino)but-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd124-en2: 5-(2-fluoro-6-hydroxy-3-(3-methyl-4-(methylamino)but-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd125-en1: 5-(3-(3-(aminomethyl)pent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-
- 10 thiadiazolidin-3-one 1,1-dioxide
- Cpd125-en2: 5-(3-(3-(aminomethyl)pent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd126-en1: 5-(3-(5-amino-3-methylpent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 15 Cpd126-en2: 5-(3-(5-amino-3-methylpent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd127: 5-(3-(((1R,5S,6S)-3-((2-(dimethylamino)ethyl)sulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd128: rel-5-(3-(((1R,2R)-2-(aminomethyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-
- 20 1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd129: rel-N-(((1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)cyclopropyl)methyl)methanesulfonamide
- Cpd130: (R,Z)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 25 Cpd131: (R,E)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd132: (S,Z)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd133: (S,E)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-
- 30 thiadiazolidin-3-one 1,1-dioxide
- Cpd134: 5-(3-((6-azaspiro[2.5]octan-1-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd135: 5-(2-fluoro-6-hydroxy-3-((6-(methylsulfonyl)-6-azaspiro[2.5]octan-1-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 35 Cpd136: (R)-5-(3-(4-aminopent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

- Cpd137: (S)-5-(3-(4-aminopent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd138: 5-[3-(4-aminopent-4-en-1-ynyl)-2-fluoro-6-hydroxy-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one
- 5 Cpd139: (Z)-5-(3-((5-azaspiro[2.4]heptan-7-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd140: *rel*-5-(2-fluoro-6-hydroxy-3-(((1S,2S)-2-((methylamino)methyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd141: *rel*-5-(3-(((1S,2S)-2-((dimethylamino)methyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.
- 10 Cpd142-en1: *rel*-5-(3-(((1R,6R,7R)-3-azabicyclo[4.1.0]heptan-7-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd142-en2: *rel*-5-(3-(((1R,6R,7R)-3-azabicyclo[4.1.0]heptan-7-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 15 Cpd143: (S,Z)-5-(2-fluoro-6-hydroxy-3-((4-(hydroxymethyl)pyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd144: (S,E)-5-(2-fluoro-6-hydroxy-3-((4-(hydroxymethyl)pyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd145: (Z)-5-(2-fluoro-6-hydroxy-3-((4-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 20 Cpd146: (Z)-5-(4-ethyl-2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd147: (E)-5-(4-ethyl-2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 25 Cpd148: 5-(2-fluoro-6-hydroxy-3-(4-(methylamino)but-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd149-en1: (E)-5-(3-(4-amino-3-methylbut-1-en-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd149-en2: (E)-5-(3-(4-amino-3-methylbut-1-en-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 30 Cpd150: *rel*-5-(3-(((1R,2R)-2-((2-(dimethylamino)ethoxy)methyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd151: *rel*-5-(3-(((1R,2R)-2-(chloromethyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 35 Cpd152: *rel*-5-(2-fluoro-6-hydroxy-3-(((1R,2R)-2-(morpholinomethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

- Cpd153: *rel*-5-(2-fluoro-6-hydroxy-3-(((1*R*,2*R*)-2-(pyrrolidin-1-ylmethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd154: *rel*-5-(3-(((1*S*,2*S*)-2-((3,3-difluoropyrrolidin-1-yl)methyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 5 Cpd155: *rel*-5-(2-fluoro-6-hydroxy-3-(((1*R*,2*R*)-2-((4-methylpiperazin-1-yl)methyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd156: (*Z*)-5-(3-((4-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd157: (*E*)-5-(3-((4-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-
- 10 thiadiazolidin-3-one 1,1-dioxide
- Cpd158: (*Z*)-5-(3-((4-cyclopropylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd159: (*E*)-5-(3-((4-cyclopropylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 15 Cpd160: (*Z*)-5-(2-fluoro-6-hydroxy-3-((4-isobutylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd161: 5-(3-(azetidin-2-ylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd162: (*Z*)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-
- 20 thiadiazolidin-3-one 1,1-dioxide
- Cpd163: (*E*)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd156-en1: (*Z*)-5-(3-((4-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 25 Cpd156-en2: (*Z*)-5-(3-((4-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd158-en1: (*Z*)-5-(3-((4-cyclopropylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd158-en2: (*Z*)-5-(3-((4-cyclopropylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-
- 30 1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd164: (*Z*)-5-(3-((2,2-dimethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- Cpd165: (*E*)-5-(3-((2,2-dimethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide
- 35 Cpd166: 5-(2-fluoro-6-hydroxy-3-(((1*R*,5*S*,6*S*)-3-((1-methylpiperidin-4-yl)sulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Cpd167: (Z)-5-(3-((1-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

Cpd168: (Z)-5-(3-((8-oxa-2-azaspiro[4.5]decan-4-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

5 In particular embodiment of the present invention, the compounds have a structure according to the formulas provided herein selected from (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) or other formulas, aspects, statements or embodiments described herein provided that:

- R¹ is not alkyl; or
- R¹ is not cycloalkyl; or
- 10 - R¹ is not aryl; more in particular R¹ is not phenyl; or
- R¹ is not heteroaryl; more in particular R¹ is not pyridyl; or
- R¹ is not heterocycle; more in particular R¹ is not pyrazolyl;

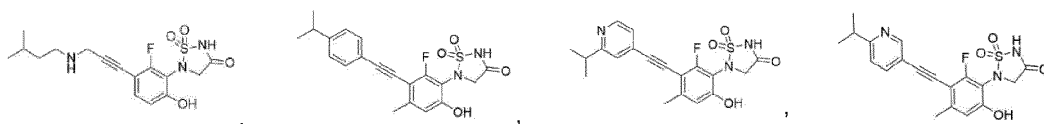
In a particular embodiment of the present invention, the compounds have a structure according to the formulas provided herein selected from (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) or other formulas, aspects, statements or embodiments described herein provided that
15 R² is not hydrogen.

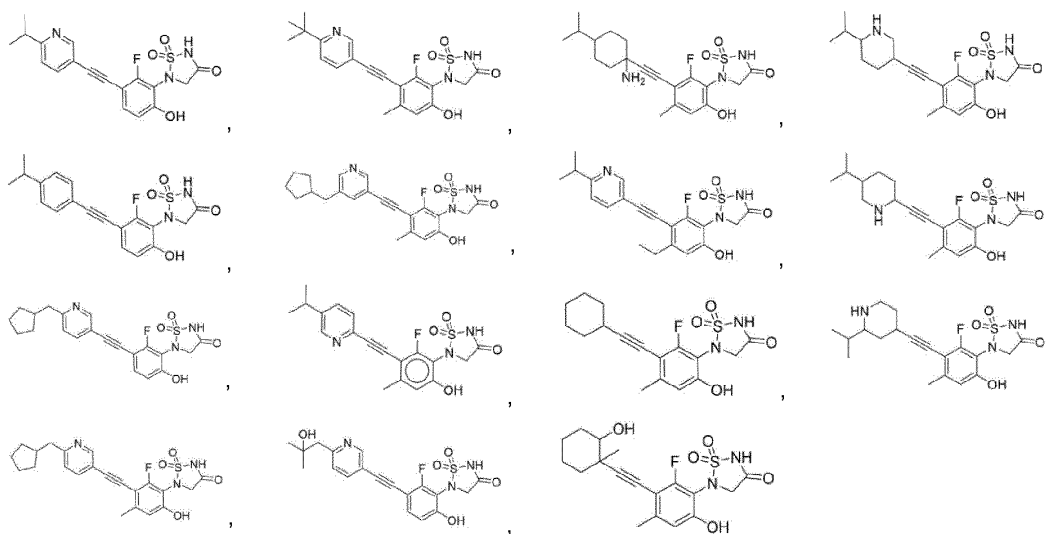
In a particular embodiment of the present invention, the compounds have a structure according to the formulas provided herein selected from (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) or other formulas, aspects, statements or embodiments described herein provided that
20 R³ is not hydrogen.

In a particular embodiment of the present invention, the compounds have a structure according to the formulas provided herein selected from (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) or other formulas, aspects, statements or embodiments described herein provided that
n is not 0; or n is not 1; or n is not 2; or n is not 1 and 2; or n is not 0 and 2.

25 In a particular embodiment of the present invention, the compounds have a structure according to the formulas provided herein selected from (I), (Ia), (Ib), (II), (IIa), (III), (IIIa), (IIIb) and (IIIc) or other formulas, aspects, statements or embodiments described herein provided that
m is not 0; or m is not 1; or m is not 2; or m is not 1 and 2; or m is not 0 and 2.

In a particular embodiment of the present invention, said compound is not a compound
30 listed below:





The present compounds used in the current invention may also exist in their stereochemically isomeric form, defining all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures, which are not interchangeable. Unless otherwise mentioned or indicated, the chemical designation of compounds encompasses the mixture of all possible stereochemically isomeric forms, which said compounds might possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds used in the present invention either in pure form or in admixture with each other are intended to be embraced within the scope of the present invention including any racemic mixtures or racemates.

More generally, the invention relates to the compounds of the formulae described herein and embodiments, statements and aspects thereof being useful as agents having biological activity or as diagnostic agents. Any of the uses mentioned with respect to the present invention may be restricted to a non-medical use, a non-therapeutic use, a non-diagnostic use, or exclusively an in vitro use, or a use related to cells remote from an animal.

Compounds of the present disclosure are small molecule PTPN2 and/or PTPN1 inhibitors. Small molecule PTPN2 and/or PTPN1 inhibitors are useful, e.g., for the treatment of cancer, including with no limitations, lung cancer, breast cancer, head and neck cancer, oesophageal cancer, kidney cancer, bladder cancer, colon cancer, ovarian cancer, cervical cancer, endometrial cancer, liver cancer, skin cancer, pancreatic cancer, gastric cancer, brain cancer and prostate cancer, mesotheliomas, and/or sarcomas. In other embodiments, small molecule PTPN2 and/or PTPN1 inhibitors are useful for the treatment of cancers selected from colon cancer, kidney cancer, pancreatic cancer, breast cancer, multiple myeloma or cancers of secretory cells. In more particular embodiments, the compounds of the invention are useful for the treatment of cancers

selected from colon cancer, kidney cancer, pancreatic cancer, breast cancer, melanoma, head and neck squamous cell carcinoma and non-small cell lung cancer. Still in more particular embodiments, the compounds of the invention are useful for the treatment of colon cancer, melanoma and lung cancer. In some embodiments, solid cancers are characterized by the overexpression of PTPN2 and/or PTPN1.

Small molecule PTPN2 and/or PTPN1 inhibitors may also be useful to treat cancers that have developed resistance to prior treatments. This may include, for instance, the treatment of cancers that have developed resistance to chemotherapy, or to targeted therapy or to immunotherapy.

Small molecule PTPN2 and/or PTPN1 inhibitors may also be useful to treat a metastasized cancer. In some instances, the metastasized cancer is selected from metastasized uveal melanoma, esophageal cancer, liver cancer, breast cancer, hepatocellular carcinoma, lung adenocarcinoma, glioma, colon cancer, gastric cancer, medulloblastoma, ovarian cancer, esophageal squamous cell carcinoma, sarcoma, Ewing sarcoma, head and neck cancer, prostate cancer and meningioma.

In some embodiments, small molecule PTPN2 and/or PTPN1 inhibitors are useful, e.g., for the treatment of metabolic disorders, such as non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, obesity, heart disease, atherosclerosis, arthritis, cystinosis, diabetes (e.g., Type I diabetes, Type II diabetes, or gestational diabetes) and metabolic syndrome. In some embodiments, the treatment or prevention of a metabolic disease comprises decreasing or eliminating a symptom of such metabolic disease comprising elevated blood pressure, elevated blood sugar level, weight gain, fatigue, blurred vision, abdominal pain, flatulence, constipation, diarrhea, jaundice, and the like.

Small molecule PTPN2 and/or PTPN1 inhibitors and pharmaceutical compositions comprising them may also be useful when combined, upon simultaneous administration, or subsequent administration, with other agents used for the treatment of diseases such as cancer and metabolic diseases. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another.

In certain embodiments, the second agent is an anti-cancer agent. In certain embodiments, the second agent is a chemotherapeutic. In other embodiments, the second agent is a (cancer) immunotherapy or (cancer) immunotherapeutic agent. In again other embodiments,

the second agent is an agent for treating a metabolic disease. In particular embodiments, the second agent is an anti-diabetic agent. In some embodiments, the second agent is an anti-obesity agent.

"Anti-cancer agent" refers to a composition (e.g. compound, drug, antagonist, inhibitor, modulator, vaccine, cells) having antineoplastic properties or the ability to inhibit the growth or proliferation of cells or in general an agent having utility in treating or preventing cancer and comprises chemotherapeutic agents, immunotherapeutic agents, radiotherapeutic agents, cancer vaccines and the like. In some embodiments, an anticancer agent is an agent approved by the FDA or EMA or similar regulatory agency of a country other than the USA or Europe, for treating cancer.

Cancer immunotherapy refers to the use of the immune system to treat cancer. Types of immunotherapy used to treat cancer include compound-based, cell-based, antibody-based, and cytokine therapies. Exemplary immunotherapies or immunotherapeutic agent that may be useful when combined with the compounds of the invention include, but are not limited to a compounds (e.g., a ligand, an antibody) that inhibits the immune checkpoint blockade pathway. In some embodiments, the immunotherapeutic agent is a compound that inhibits the indoleamine 2,3-dioxygenase (IDO) pathway. In some embodiments, the immunotherapeutic agent is a compound that agonizes the STING pathway. Cancer immunotherapy (e.g., anti-tumor immunotherapy or anti-tumor immunotherapeutics) includes but is not limited to, immune checkpoint antibodies (e.g., PD-1 antibodies, PD-L1 antibodies, PD-L2 antibodies, CTLA-4 antibodies, TIM3 antibodies, LAG3 antibodies, TIGIT antibodies); and cancer vaccines (e.g., anti-tumor vaccines or vaccines based on neoantigens such as a peptide or RNA vaccine). Cell-based therapies (e.g., cancer vaccines), usually involve the removal of immune cells from a subject suffering from cancer, either from the blood or from a tumor. Immune cells specific for the tumor will be activated, grown, and returned to a subject suffering from cancer where the immune cells provide an immune response against the cancer. Cell types that can be used in this way are e.g., natural killer cells, lymphokine-activated killer cells, cytotoxic T-cells, dendritic cells, CAR-T therapies (e.g., chimeric antigen receptor T-cells which are T-cells engineered to target specific antigens), TIL therapy (e.g., administration of tumor-infiltrating lymphocytes), TCR gene therapy, protein vaccines, and nucleic acid vaccines. An exemplary cell-based therapy is Provenge. In some embodiments, the cell-based therapy is a CAR-T therapy. Interleukin-2 and interferon-alpha are examples of cytokines, proteins that regulate and coordinate the behavior of the immune system. Cancer vaccines with neoantigens might also be combined with the compounds of the invention. Neoantigens are antigens encoded by tumor-specific mutated genes.

The invention described herein comprises, in some embodiments, administering in combination with a compound of the invention a cancer immunotherapy. In some embodiments, the immunotherapeutic agent is a compound (e.g., an inhibitor or antibody) that inhibits the

immune checkpoint blockade pathway. Immune checkpoint proteins, under normal physiological conditions, maintain self-tolerance (e.g., prevent autoimmunity) and protect tissues from damage when the immune system is responding to e.g., pathogenic infection. Immune checkpoint proteins can be dysregulated by tumors as an important immune resistance mechanism (Pardoll, Nature Rev. Cancer, 2012, 12, 252-264). Agonists of co- stimulatory receptors or antagonists of inhibitory signals (e.g., immune checkpoint proteins), provide an amplification of antigen-specific T-cell responses. Antibodies that block immune checkpoints do not target tumor cells directly but typically target lymphocyte receptors or their ligands to enhance endogenous antitumor activity. [00241] Exemplary checkpoint blocking antibodies include but are not limited to, anti-CTLA-4, anti-PD-1, anti-LAG3 (e.g., antibodies against lymphocyte activation gene 3), and anti-TIM3 (e.g., antibodies against T-cell membrane protein 3). Exemplary anti-CTLA-4 antibodies include but are not limited to, ipilimumab and tremelimumab. Exemplary anti-PD-1 ligands include but are not limited to, PD-L1 (e.g., B7-H1 and CD274) and PD-L2 (e.g., B7-DC and CD273). Exemplary anti-PD-1 antibodies include but are not limited to, nivolumab (e.g., MDX- 1106, BMS-936558, or ONO-4538), CT-011, AMP-224, pembrolizumab (trade name Keytruda), and MK-3475. Exemplary PD-L1-specific antibodies include but are not limited to, BMS936559 (e.g., MDX-1105), MEDI4736 and MPDL-3280A. Exemplary checkpoint blocking antibodies also include but are not limited to, IMP321 and MGA271. [00242] T-regulatory cells (e.g., CD4+, CD25+, or T-reg) are also involved in policing the distinction between self and non-self (e.g., foreign) antigens, and may represent an important mechanism in suppression of immune response in many cancers. T-reg cells can either emerge from the thymus (e.g., "natural T-reg") or can differentiate from mature T-cells under circumstances of peripheral tolerance induction (e.g., "induced T-reg"). Strategies that minimize the action of T-reg cells would therefore be expected to facilitate the immune response to tumors.

IDO pathway inhibitors. The IDO pathway regulates immune response by suppressing T cell function and enabling local tumor immune escape. IDO expression by antigen-presenting cells (APCs) can lead to tryptophan depletion, and resulting antigen-specific T cell energy and regulatory T cell recruitment. Some tumors even express IDO to shield themselves from the immune system. A compound that inhibits IDO or the IDO pathway activates the immune system to attack the cancer (e.g., tumor in a subject). Exemplary IDO pathway inhibitors include indoximod, epacadostat and EOS200271.

STING pathway agonists. Stimulator of interferon genes (STING) is an adaptor protein that plays an important role in the activation of type I interferons in response to cytosolic nucleic acid ligands. Evidence indicates involvement of the STING pathway in the induction of antitumor immune response. For example, activation of the STING-dependent pathway in cancer cells can result in tumor infiltration with immune cells and modulation of the anticancer immune response. STING agonists are being developed as a class of cancer therapeutics. Exemplary STING

agonists include MK-1454 and ADU-S100.

In some embodiments, the immunotherapeutic agent is a co-stimulatory inhibitor or antibody, e.g. by depleting or activating anti-4-1BB, anti-OX40, anti-GITR, anti-CD27 and anti-CD40, and variants thereof. Also immunostimulants (e.g., Bacillus Calmette- Guerin (BCG),
5 levamisole, interleukin-2, alpha-interferon, etc.) are considered to be covered by immunotherapeutic agents.

Other examples of anti-cancer agents include, but are not limited to MEK inhibitors, EGFR inhibitors, RAS inhibitors, inhibitors of B-RAF, alkylating agents, nitrogen mustards, ethylenimine and methylmelamines, alkyl sulfonates, nitrosoureas, triazenes, anti-metabolites, pyrimidine
10 analogs, purine analogs, plant alkaloids, topoisomerase inhibitors, antitumor antibiotics, platinum-based compounds, anthracenedione, substituted urea, methyl hydrazine derivative, adrenocortical suppressant, epipodophyllotoxins, inhibitors of mitogen-activated protein kinase signaling, mTOR inhibitors, agents that arrest cells in the G2-M phases and/or modulate the formation or stability of microtubules, antiestrogen, antiandrogen, monoclonal antibodies (e.g.,
15 anti-CD20, anti-HER2, anti-CD52, anti-HLA-DR, and anti-VEGF monoclonal antibodies such as Alemtuzumab, Bevacizumab, Bretuximab vedotin, Cetuximab, Gemtuzumab ozogamicin, Ibritumomab tiuxetan, Ipilimumab, Ofatumumab, Panitumumab, Rituximab, Tositumomab, Trastuzumab, Nivolumab, Pembrolizumab, Avelumab, durvalumab and pidilizumab), immunotoxins (e.g., anti-CD33 monoclonal antibody-calicheamicin conjugate, anti-CD22
20 monoclonal antibody-pseudomonas exotoxin conjugate, etc.), radioimmunotherapy (e.g., anti-CD20 monoclonal antibody conjugated to ^{111}In , ^{90}Y , or ^{131}I , etc.) and the like. Within the group of anti-cancer agents, "Chemotherapeutic" or "chemotherapeutic agent" refers to a chemical composition or compound having antineoplastic properties or the ability to inhibit the growth or proliferation of cells.

25 In a further embodiment, the compounds described herein can be co-administered with conventional radiotherapeutic agents including, but not limited to, radionuclides such as ^{47}Sc , ^{64}Cu , ^{67}Cu , ^{89}Sr , ^{86}Y , ^{87}Y , ^{90}Y , ^{105}Rh , ^mAg , ^mIn , ^{117m}Sn , ^{149}Pm , ^{153}Sm , ^{166}Ho , ^{177}Lu , ^{186}Re , ^{188}Re , ^{211}At , and ^{212}Bi , optionally conjugated to antibodies directed against tumor antigens.

The compounds of the invention can inhibit PTPN2 and/or PTPN1 activity. The
30 compounds have been shown to inhibit PTPN2 and/or PTPN1 activity in cellular models and in an animal model. The compounds have also been shown to have an inhibitory effect on cancer cell lines and on the growth of cancer in an animal cancer model.

The compounds of the invention can optionally be bound covalently to an insoluble matrix and used for affinity chromatography (separations, depending on the nature of the groups of the
35 compounds, for example compounds with pendant aryl are useful in hydrophobic affinity separations).

When using one or more derivatives of the formulae as defined herein:

- the active ingredients of the compound(s) may be administered to the animal or mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.
- the therapeutically effective amount of the preparation of the compound(s), especially for the treatment of diseases mediated by activity of PTPN2 and/or PTPN1 in humans and other mammals (such as cancer, metabolic diseases and certain congenital disorders), preferably is a PTPN2 and/or PTPN1 inhibiting amount of the compounds of the formulae, statements, aspects and embodiments as defined herein and corresponds to an amount which ensures a plasma level that is able to inhibit the PTPN2 and/or PTPN1 activity and is in a particular embodiment between 1ng/ml and 100 mg/ml, more in particular between 1ng/ml and 1mg/ml, still more in particular between 1ng/ml and 1µg/ml.

Suitable dosages of the compounds or compositions of the invention should be used to treat or prevent the targeted diseases in a subject. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

According to a particular embodiment of the invention, the compounds of the invention may be employed in combination with other therapeutic agents for the treatment or prophylaxis of diseases mediated by activity of PTPN2 and/or PTPN1 in humans and other mammals (such as cancer and metabolic disorders). The invention therefore relates to the use of a composition comprising:

- (a) one or more compounds of the formulae and aspects, statements and embodiments herein, and
- (b) one or more further therapeutic or preventive agents that are used for the prevention or treatment of cancer or metabolic diseases as biologically active agents in the form of a combined preparation for simultaneous, separate or sequential use.

The compound or composition can be administered concurrently with, prior to, or subsequent to the one or more additional therapeutic agents, which are different from the compound described herein and may be useful as, e.g., combination therapies. Examples of such further therapeutic agents for use in combinations include anti-cancer agents as described herein.

The pharmaceutical composition or combined preparation according to this invention may contain the compounds of the present invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the derivatives of the present invention of the combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

Those of skill in the art will also recognize that the compounds of the invention may exist

in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any particular protonation state - any and all protonated
5 forms of the compounds are intended to fall within the scope of the invention.

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms which the compounds of formulae herein are able to form. Therefore, the compounds of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+ , Li^+ , K^+ , Ca^{2+} and Mg^{2+} .
10 Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by
15 which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention
20 is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in association with counter ions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a
25 more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalogen acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-
30 hydroxypropanoic, 2-oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the solvates which the compounds of formulae herein as well as their salts are able to form, such as for example
35 hydrates, alcoholates and the like. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1 - C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X typically is independently selected from H or a C_1 - C_4 alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

As used herein and unless otherwise stated, the term "enantiomer" means each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (e.g. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms, including tautomeric and stereochemical forms, which the compounds of formulae herein may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of formulae herein may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either *cis*- or *trans*-configuration.

Pure isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular,

the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (e.g. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood
5 in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question.

Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active
10 resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2)
15 formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α -methyl-
b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced
20 to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S.
25 (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched compound. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, α -methoxy-
30 α -(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is
35 separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD,

OF, OG, OJ and OK, and Chiralpak™ AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like. ("Chiral Liquid Chromatography" (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990)

5 "Optical resolution of dihydropyridine enantiomers by High-performance liquid chromatography using phenylcarbamates of polysaccharides as a chiral stationary phase", J. of Chromatogr. 513:375-378).

The terms *cis* and *trans* are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents on a ring moiety. The

10 absolute stereochemical configuration of the compounds of the formulae described herein may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

The present invention also includes isotopically labelled compounds, which are identical to those recited in the formulas recited herein, but for the fact that one or more atoms are replaced

15 by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that may be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹¹C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³¹P, ³²P, ³⁵S, ¹⁸F, and ³⁶Cl, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said

20 compounds or which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ³H and ¹⁴C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³H, and carbon-14, i.e., ¹⁴C, isotopes are particularly preferred for their ease of preparation and detectability. Further,

25 substitution with heavier isotopes such as deuterium, i.e., ²H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of the formulas of this invention may generally be prepared by carrying out the procedures disclosed in the examples and preparations described herein, by substituting a

30 readily available isotopically labelled reagent for a non-isotopically labelled reagent.

Also encompassed within the invention are modifications of the compounds of the formula (I) or other formulas, embodiments, aspects or parts thereof or metabolites thereof using PROTAC technology (Schapira M. et al, *Nat. Rev. Drug Discov.* 2019, 18(12), 949-963). Specifically, the PROTAC technology designs a bifunctional small molecule, one end of which is

35 a compound of the general formula (I) or other formulas, embodiments, aspects or parts thereof or metabolites thereof, and the other end of which is connected with a ligand of E3 ubiquitin ligase through a connecting chain, to form a target-induced protein degradation complex. Because this

degradation has a catalytic effect, a lower dosage can achieve efficient degradation. The compound of the general formula (I) or other formulas, embodiments, aspects or parts thereof or metabolites thereof can be connected via a linker arm (e.g. long-chain ethylene glycol with the length of 2-10, long-chain propylene glycol with the length of 2-10 and long-chain fatty alkane with the length of 2-10) to a ligand of E3 ubiquitin ligase such as e.g. thalidomide analogs.

The compounds of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, e.g. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention. They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or sodium chloride) and the like, provided the same are consistent with pharmaceutical practice, e.g. carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the selected carrier material and, where appropriate, the other additives such as surface-active agents. may also be prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of about 1 to 10 µm, namely for the manufacture of microcapsules for controlled or sustained release of the active ingredients.

Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the pharmaceutical compositions of the present invention are non-ionic, cationic and/or anionic

materials having good emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C_{10} - C_{22}), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl group having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcoholamine salts of dodecylbenzene sulphonic acid or dibutyl-naphthalenesulphonic acid or a naphthalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl -choline and their mixtures.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediaminopolypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100 propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxy polyethoxyethanol, polyethyleneglycol and octylphenoxy polyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon groups optionally substituted with halo, phenyl, substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C₈₋₂₂alkyl (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl.

A more detailed description of surface-active agents suitable for this purpose may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Corp., Ridgewood, New Jersey, 1981), "Tensid-Taschenbuch", 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants, (Chemical Publishing Co., New York, 1981).

Compounds of the invention and their pharmaceutically acceptable salts (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a

binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, e.g. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as diisoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein

the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc.), which is administered in the manner in which snuff is taken, e.g. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

Compounds of the invention can be used to provide controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled

release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers, methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polymethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

Another embodiment of this invention relates to various precursor or "pro-drug" forms of the compounds of the present invention. It may be desirable to formulate the compounds of the present invention in the form of a chemical species which itself is not significantly biologically-active, but which when delivered to the animal, mammal or human will undergo a chemical reaction catalyzed by the normal function of the body of the fish, *inter alia*, enzymes present in the stomach or in blood serum, said chemical reaction having the effect of releasing a compound as defined herein. The term "pro-drug" thus relates to these species which are converted *in vivo* into the active pharmaceutical ingredient.

The pro-drugs of the compounds of the present invention can have any form suitable to the formulator, for example, esters are non-limiting common pro-drug forms. In the present case,

however, the pro-drug may necessarily exist in a form wherein a covalent bond is cleaved by the action of an enzyme present at the target *locus*. For example, a C-C covalent bond may be selectively cleaved by one or more enzymes at said target *locus* and, therefore, a pro-drug in a form other than an easily hydrolysable precursor, *inter alia* an ester, an amide, and the like, may be used. The counterpart of the active pharmaceutical ingredient in the pro-drug can have different structures such as an amino acid or peptide structure, alkyl chains, sugar moieties and others as known in the art.

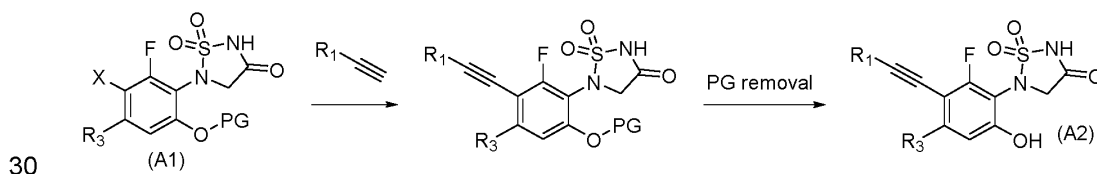
For the purpose of the present invention the term “therapeutically suitable pro-drug” is defined herein as “a compound modified in such a way as to be transformed *in vivo* to the therapeutically active form, whether by way of a single or by multiple biological transformations, when in contact with the tissues of the animal, mammal or human to which the pro-drug has been administered, and without undue toxicity, irritation, or allergic response, and achieving the intended therapeutic outcome”.

More specifically the term “prodrug”, as used herein, relates to an inactive or significantly less active derivative of a compound such as represented by the structural formulae herein described, which undergoes spontaneous or enzymatic transformation within the body in order to release the pharmacologically active form of the compound. For a comprehensive review, reference is made to Rautio J. et al. (“Prodrugs: design and clinical applications” Nature Reviews Drug Discovery, 2008, doi: 10.1038/nrd2468).

The compounds of the invention can be prepared while using a series of chemical reactions well known to those skilled in the art, altogether making up the process for preparing said compounds and exemplified further. The processes described further are only meant as examples and by no means are meant to limit the scope of the present invention.

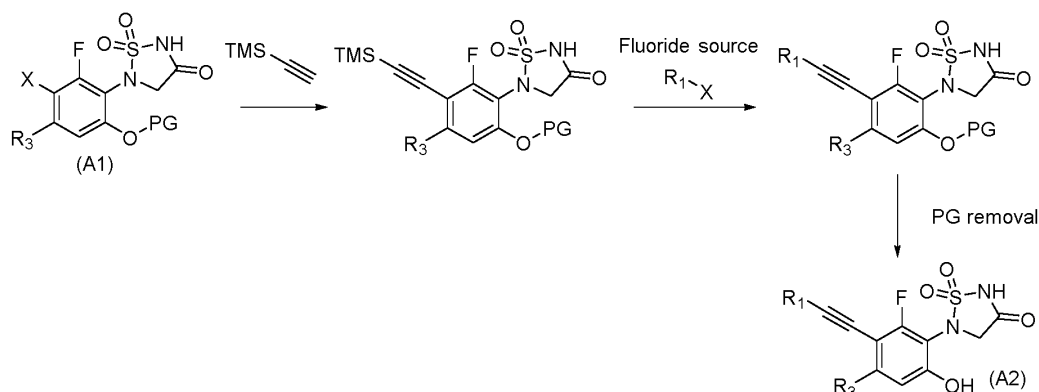
The present invention relates to methods for the preparation of the compounds, comprising the steps of:

- coupling a halogen-containing compound of formula (A1) with an alkyne derivative and further removing PG (if different than H) thereby obtaining a compound of formula (A2), wherein R¹ and R³ have the meaning according to any one of the formula or embodiments presented herein, PG is a protecting group or a hydrogen and X is a halogen; or

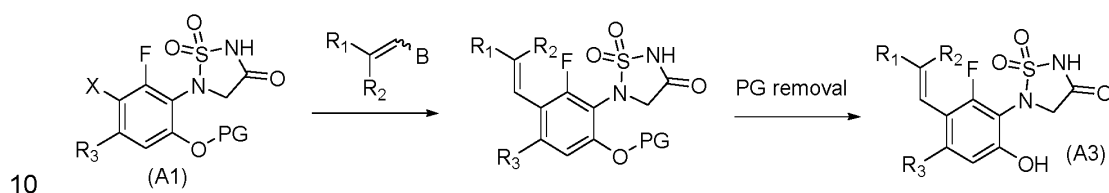


- coupling a halogen-containing compound of formula (A1) with a silylated-acetylene derivative; in a next step, performing concomitant in situ silyl deprotection with a fluoride source and coupling with a R¹-X halogen derivative, and further removing PG (if different than H) thereby obtaining a compound of formula (A2), wherein R¹ and R³ have the meaning according to

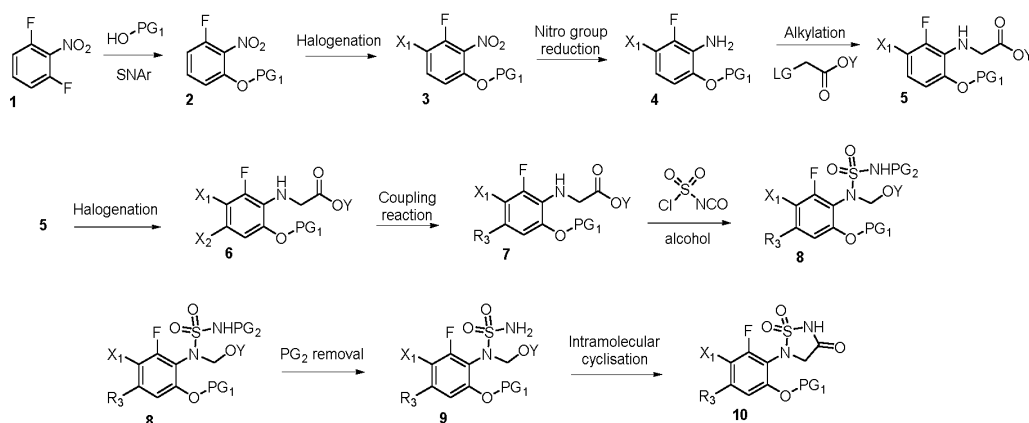
any one of the formula or embodiments presented herein, PG is a protecting group or a hydrogen and X is a halogen; or



- 5 - coupling a halogen-containing compound of formula (A1) with an alkenyl boronic derivative and further removing PG (if different than H) thereby obtaining compound of formula (A3), wherein R^1 , R^2 and R^3 have the meaning according to any one of the formula or embodiments presented herein, PG is a protecting group or a hydrogen and X is a halogen. Alternatively, the alkenyl boronic derivative can be replaced by a terminal alkene, an alkenyl zinc reagent or an alkenyl stannane reagent



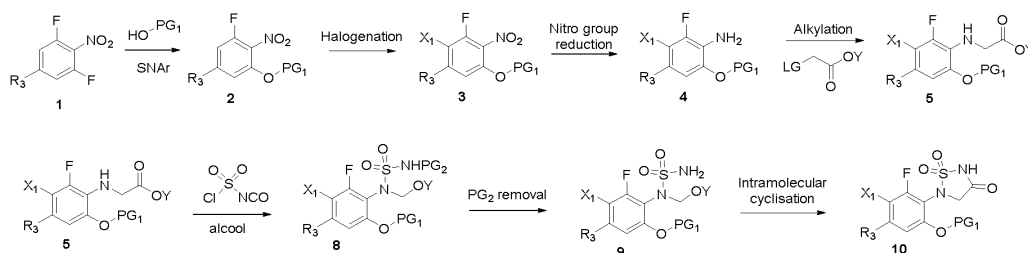
The compounds of the present invention may be prepared according to the general procedures outlined in below Schemes.



- 15 *Scheme A: all R^3 (different than H) are as described for the compounds of the present invention and its embodiments and formulae. X_1 , X_2 are halogen (Br, I, Cl). PG is protecting group. LG is leaving group. Y is an ester protecting group (like methyl, ethyl, t-Bu and the like).*

2,6-difluoronitrobenzene **1** may be reacted with a primary alcohol of general formula PG_1OH (like benzylalcohol, MeOH, 4-methoxybenzylalcohol and the like) in the presence of a base (like NaH, K_2CO_3 , Cs_2CO_3 , DBU and the like) in a suitable solvent (e.g., DCM, THF, toluene and the like) at a temperature ranging from -78°C to 100°C to provide intermediates of formula **2**. Intermediates of formula **2** may be halogenated with a suitable halogenating agent (e.g. Bromine, N-bromosuccinimide, N-chlorosuccinimide, N-iodosuccinimide and the like) in a polar aprotic solvent (e.g. dichloromethane, tetrahydrofuran and the like) at a temperature ranging from 0 to 100°C to provide the intermediates of formula **3**. Reduction of intermediates of formula **3** with a reducing agent (e.g., hydrogen gas, ammonium formate, cyclohexadiene and the like) using a catalyst (more preferably Pd or Pt) in a protic or aprotic solvent (e.g., THF, EtOH, EtOAc, dioxane and the like) may provide anilines of formula **4**. Anilines of formula **4** may be reacted with ester derivatives having a leaving group LG (like Br, Cl, OM and the like) and where Y is an ester protecting group (like methyl, ethyl, t-Bu and the like) in the presence of a base (e.g. DIPEA, K_2CO_3 , Cs_2CO_3 , DBU and the like) in a polar aprotic solvent (e.g., CH_3CN , THF, DCM and the like) at a temperature ranging from 0°C to 100°C to provide intermediates of formula **5**. Anilines of formula **5** may be halogenated with a suitable halogenating agent (e.g. Bromine, N-bromosuccinimide, N-chlorosuccinimide, N-iodosuccinimide and the like) in a polar aprotic solvent (e.g. dichloromethane, tetrahydrofuran and the like) at a temperature ranging from 0 to 100°C to provide intermediates of formula **6**. Intermediates of general formula **6** may be reacted further with appropriate coupling agents selected from, but not limited, to boronic acids, boronic esters, boroxines, organozinc reagents, organotin reagents, amines and alcohols in combination with suitable Pd or Cu based catalysts to afford intermediates of general formula **7**. Anilines of formula **7** may react with chlorosulfonyl isocyanate in the presence of a suitable alcohol derivative (tBuOH, benzylalcohol and the like) to provide sulfonylureas of formula **8**. Removal of the N-protecting group PG_2 may be performed following procedures known to the skilled in the art (e.g. treatment in presence of an acid such as HCl or TFA if $\text{PG}_2 = \text{Boc}$, hydrogenolysis if $\text{PG}_2 = \text{cBz}$) to provide sulfonylureas intermediates of formula **9**. Intermediates of formula **9** can themselves undergo an intermolecular cyclisation in the presence of a base (like NaOMe, NaOEt, NaH and the like) in a aprotic or protic polar solvent (e.g. THF, MeOH, EtOH and the like) at a temperature ranging from -78°C to 100°C to provide intermediates of formula **10**.

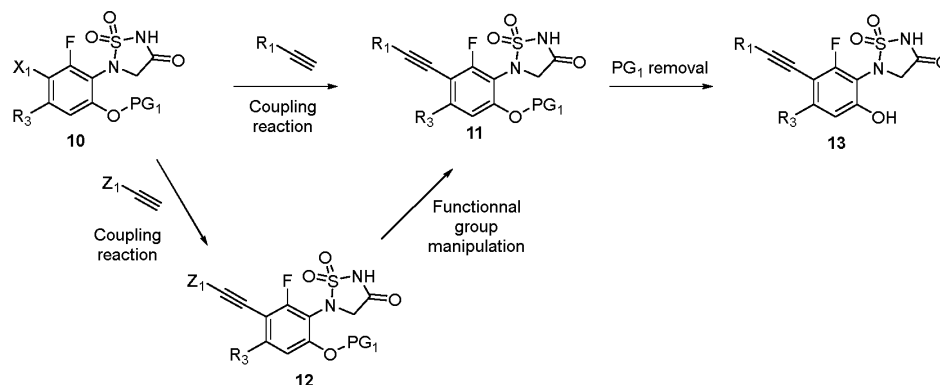
In another embodiment, compounds of the present invention may also be synthesized according to the general procedure outlined in Scheme B.



Scheme B: all R₃ are H as described for the compounds of the present invention and its embodiments, statements and formulae. X₁ are halogen (Br, I, Cl). PG is protecting group. LG is leaving group. Y is an ester protecting group (like methyl, ethyl, t-Bu and the like).

- 5 2,6-difluoronitrobenzene **1** may be reacted with a primary alcohol of general formula PG₁OH (like benzylalcohol, MeOH, 4-methoxybenzylalcohol and the like) in the presence of a base (like NaH, K₂CO₃, Cs₂CO₃, DBU and the like) in a suitable solvent (e.g., DCM, THF, toluene and the like) at a temperature ranging from -78°C to 100°C to provide intermediates of formula **2**. Intermediates of formula **2** may be halogenated with a suitable halogenating agent (e.g. Bromine, N-bromosuccinimide, N-chlorosuccinimide, N-iodosuccinimide and the like) in a polar aprotic solvent (e.g. dichloromethane, tetrahydrofuran and the like) at a temperature ranging from 0 to 100°C to provide the intermediates of formula **3**. Reduction of intermediates of formula **3** with a reducing agent (e.g., hydrogen gas, ammonium formate, cyclohexadiene and the like) using a catalyst (more preferably Pd or Pt) in a protic or aprotic solvent (e.g., THF, EtOH, EtOAc, dioxane and the like) may provide anilines of formula **4**. Anilines of formula **4** may be reacted with ester derivatives having a leaving group LG (like Br, Cl, OMes and the like) and where Y is an ester protecting group (like methyl, ethyl, t-Bu and the like) in the presence of a base (e.g. DIPEA, K₂CO₃, Cs₂CO₃, DBU and the like) in a polar aprotic solvent (e.g., CH₃CN, THF, DCM and the like) at a temperature ranging from 0°C to 100°C to provide intermediates of formula **5**. Anilines of formula **5** may react with chlorosulfonyl isocyanate in the presence of a suitable alcohol derivative (tBuOH, benzylalcohol and the like) to provide sulfonamide intermediates of formula **8**. Removal of the N-protecting group PG₂ may be performed following procedures known to the skilled in the art (e.g. treatment in presence of an acid such as HCl or TFA if PG₂ = Boc, hydrogenolysis if PG₂ = cBz) to provide sulfonamide intermediates of formula **9**. Intermediates of formula **9** can themselves undergo an intermolecular cyclisation in the presence of a base (like NaOMe, NaOEt, NaH and the like) in a aprotic or protic polar solvent (e.g. THF, MeOH, EtOH and the like) at a temperature ranging from -78°C to 100°C to provide intermediates of formula **10**.

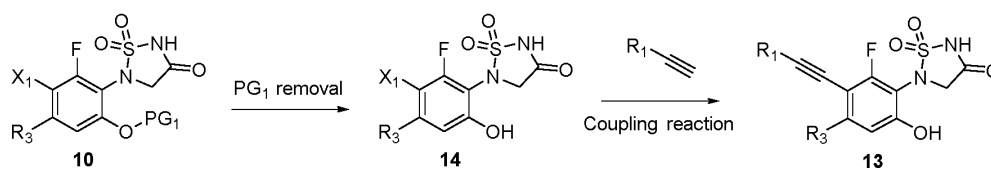
In another embodiment, compounds of the present invention may also be synthesized according to the general procedure outlined in Scheme C.



Scheme C: all R_1 , R_3 , are as described for the compounds of the present invention and its embodiments, statements and formulae. X_1 are halogen (Br, I, Cl). PG = protecting group.

Alkyne derivatives of formulae **11** or **12** may be obtained by reaction of an halogenated compound of formula **10** and a suitable terminal alkyne (either commercially available or synthesized by procedures known to the skilled in the art or as set forth in the examples below or also generated *in situ* from an appropriated terminally silylated alkyne in the presence of a fluoride source in the reaction medium (CsF, TBAF and the like)) in the presence of a Pd catalyst (e.g. $PdCl_2(PPh_3)_2$, $Pd(dppf)Cl_2$, $Pd(dtbpf)Cl_2$, $PdCl_2(CH_3CN)_2$ and the like), optionally a Cu catalyst (Cul and the like) and a base (e.g. Et_3N , K_2CO_3 , Cs_2CO_3 and the like) in a polar aprotic solvent (e.g. CH_3CN , DMF, DMSO and the like) at a temperature ranging from $0^\circ C$ to $100^\circ C$. Alkyne derivatives of formula **12** may themselves undergo functional group manipulation (using a series of chemical reactions well known to those skilled in the art or as set forth in the examples below) to provide alkyne intermediates of formula **11** which are converted in compounds of formula **13** after removal of the O-protecting group following procedures known to the skilled in the art (e.g. treatment with BBr_3 or BCl_3 , hydrogenation with H_2 in the presence of Pd/C and the like) as described in Scheme C.

In another embodiment, compounds of the present invention may also be synthesized according to the general procedure outlined in Scheme D.

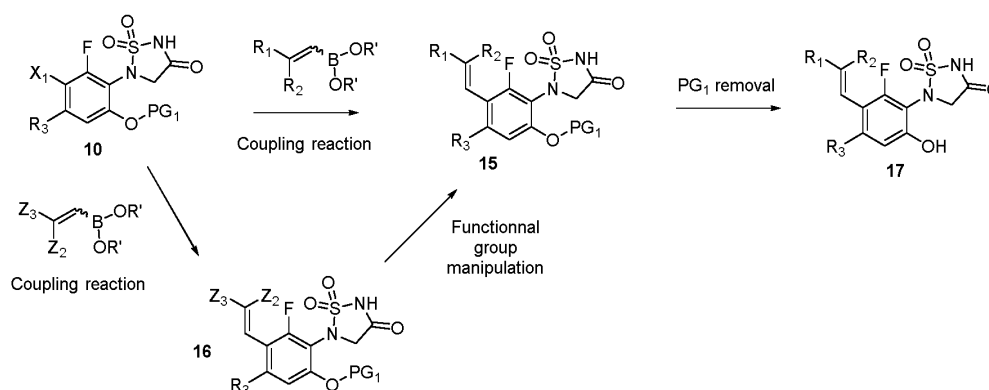


Scheme D: all R_1 , R_3 , are as described for the compounds of the present invention and its embodiments, statements and formulae. X_1 are halogen (Br, I, Cl), PG = protecting group.

Phenols derivatives of formula **14** may be obtained by removal of the O-protecting group from intermediates of general **10** following procedures known to the skilled in the art (e.g. treatment with BBr_3 or BCl_3 , hydrogenation with H_2 in the presence of Pd/C and the like). Alkynes

compounds of formula **13** may be obtained by reaction of an halogenated compound of formula **14** and a suitable terminal alkyne (either commercially available or synthesized by procedures known to the skilled in the art or as set forth in the examples below or also generated *in situ* from an appropriated terminally silylated alkyne in the presence of a fluoride source in the reaction medium (CsF, TBAF and the like)) in the presence of a Pd catalyst (e.g. PdCl₂(PPh₃)₂, Pd(dppf)Cl₂, Pd(dtbpf)Cl₂, PdCl₂(CH₃CN)₂ and the like), optionally a Cu catalyst (CuI and the like) and a base (e.g. Et₃N, K₂CO₃, Cs₂CO₃ and the like) in a polar aprotic solvent (e.g. CH₃CN, DMF, DMSO and the like) and at a temperature ranging from 0°C to 100°C.

In another embodiment, compounds of the present invention may also be synthesized according to the general procedure outlined in Scheme E.



Scheme E: all R₁, R₂, R₃, are as described for the compounds of the present invention and its embodiments, statements and formulae. X₁ are halogen (Br, I, Cl). PG = protecting group.

Alkenes derivatives of formulae **15** or **16** may be obtained by reaction of an halogenated intermediate of formula **10** and boronic derivatives (such as boronic acids or boronic esters, either commercially available or synthesized by procedures known to the skilled in the art or as set forth in the examples below) in the presence of a Pd catalyst (e.g. Pd(PPh₃)₄, PdCl₂(PPh₃)₂, Pd(dppf)Cl₂, Pd(dtbpf)Cl₂ and the like) and a base (e.g. K₃PO₄, K₂CO₃, Cs₂CO₃ and the like) in a suitable solvent (e.g. dioxane, water, toluene, DMF, DMSO and the like) at a temperature ranging from 0°C to 150°C. Alkenes derivatives of formula **16** may themselves undergo functional group transformation (using a series of chemical reactions well known to those skilled in the art or as set forth in the examples) to deliver alkenes derivatives of formula **15**. Compounds of interest having a formula **17** may be obtained after removal of the O-protecting group following procedures known to the skilled in the art (e.g. treatment with BBr₃ or BCl₃, hydrogenation with H₂ in the presence of Pd/C and the like) as described in Scheme E.

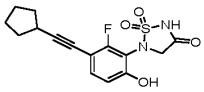
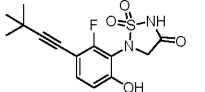
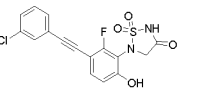
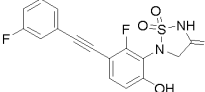
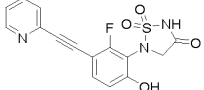
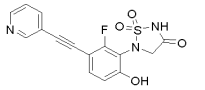
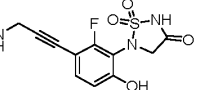
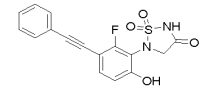
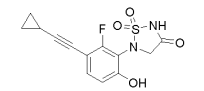
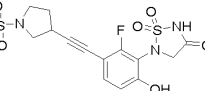
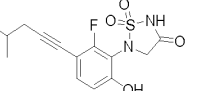
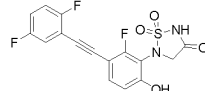
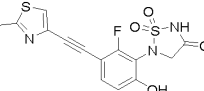
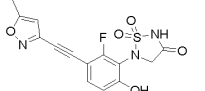
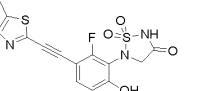
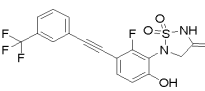
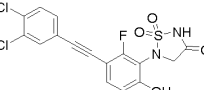
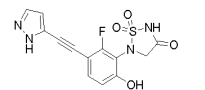
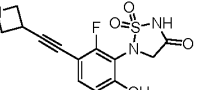
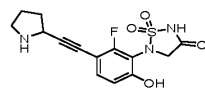
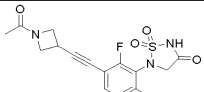
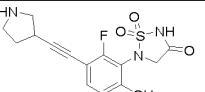
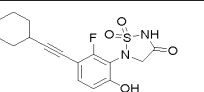
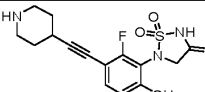
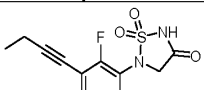
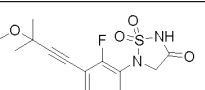
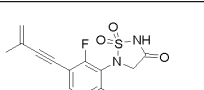
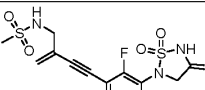
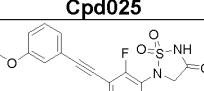
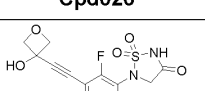
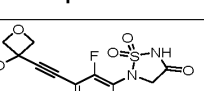
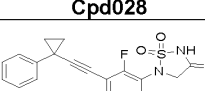
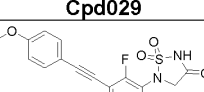
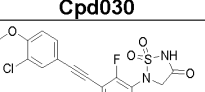
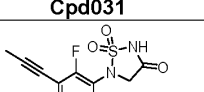
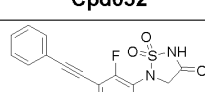
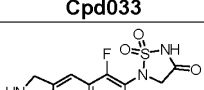
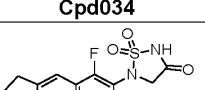
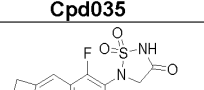
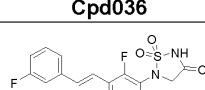
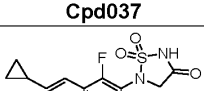
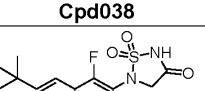
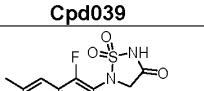
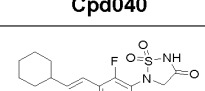
The general schemes depicted above should be considered as non-limiting examples. It will be understood that compounds of the invention may be obtained through other methods, which are known to people skilled in the art.

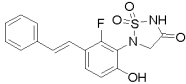
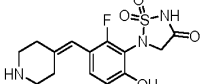
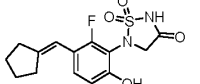
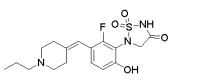
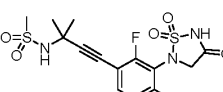
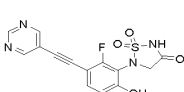
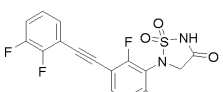
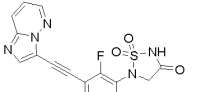
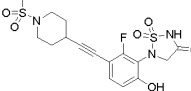
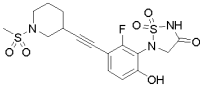
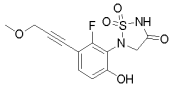
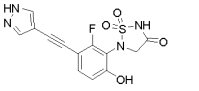
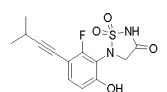
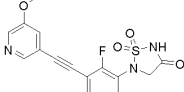
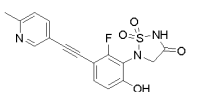
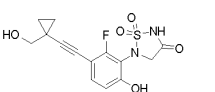
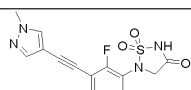
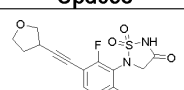
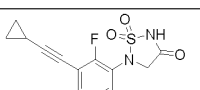
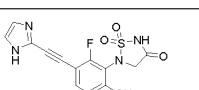
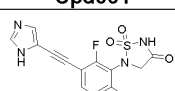
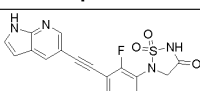
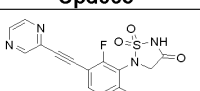
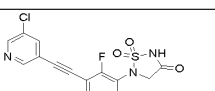
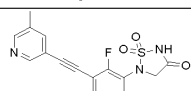
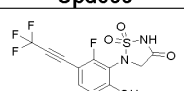
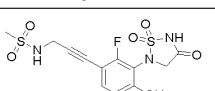
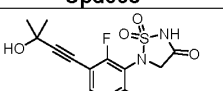
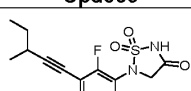
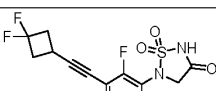
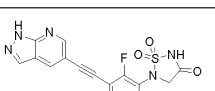
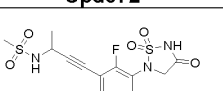
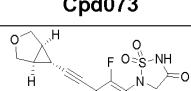
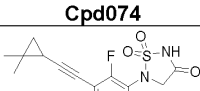
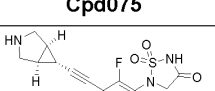
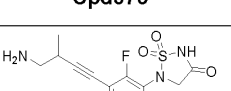
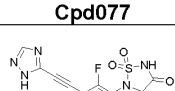
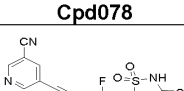
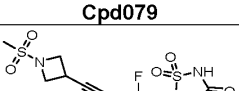
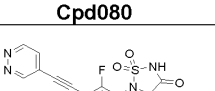
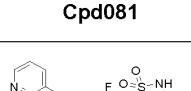
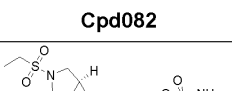
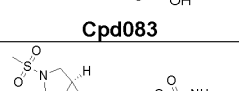
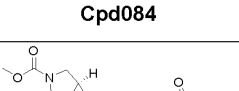
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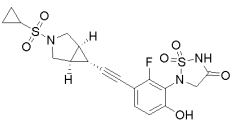
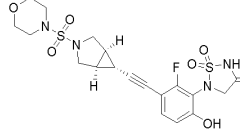
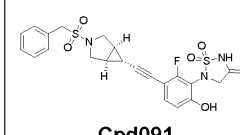
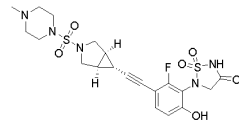
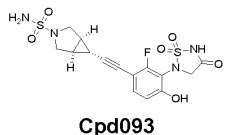
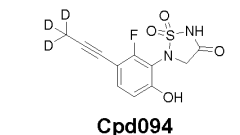
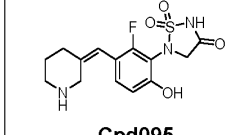
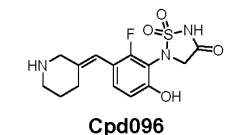
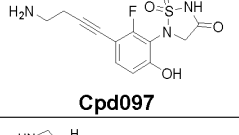
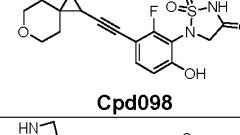
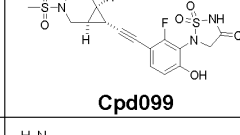
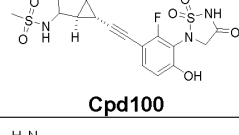
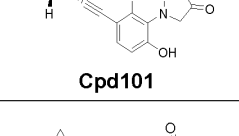
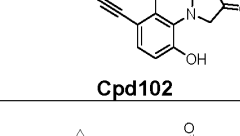
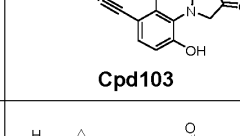
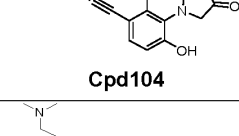
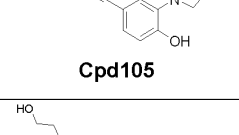
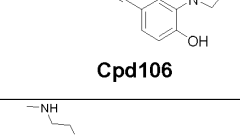
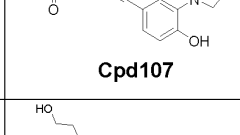
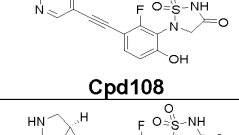
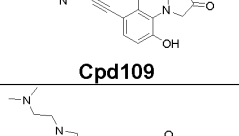
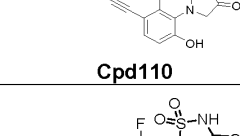
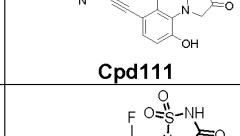
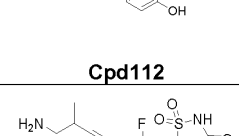
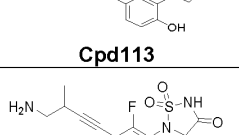
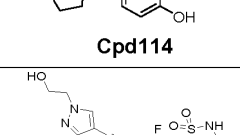
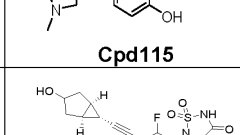
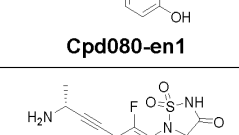
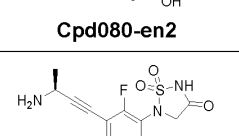
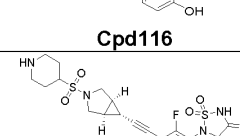
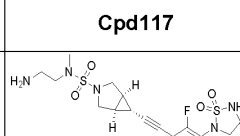
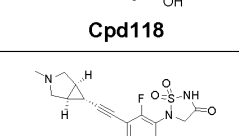
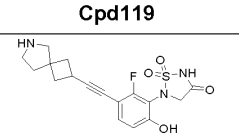
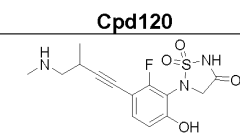
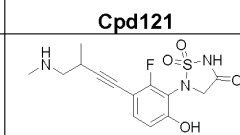
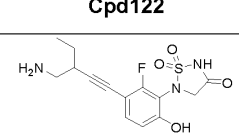
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aq.	aqueous	Me	methyl
BnOH	benzyl alcohol	MeOH	methanol
Boc	<i>tert</i> -butoxycarbonyl	min	minute
brs	broad singulet	MsCl	mesyl chloride
cBz	carboxybenzyl	m/z	mass-to-charge ratio
conc.	concentrated	<i>n</i> -BuLi	<i>n</i> -butyllithium
DAST	(diethylamino)sulfur trifluoride	NEt ₃	triethylamine
DCM	dichloromethane	NIS	<i>N</i> -iodosuccinimide
DHP	3,4-Dihydropyran	NMP	<i>N</i> -methyl-2-pyrrolidone
DIPEA	diisopropylethylamine	Pd/C	palladium on carbon
DMAP	4-dimethylaminopyridine	PE	Petroleum ether
DME	1,2-dimethoxyethane	PG	protecting group
DMF	<i>N,N</i> -dimethylformamide	PMB	<i>para</i> -methoxy benzyl
DMSO	dimethyl sulfoxide	<i>p</i> -TsCl	<i>para</i> -toluenesulfonyl chloride
dppf	1,1'-bis(diphenylphosphino)ferrocene	PTSA	<i>para</i> -toluenesulfonic acid
dtbpf	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene	r.t.	retention time
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide	RT	room temperature
en	enantiomer	sat	saturated
Et	ethyl	SPhos	dicyclohexyl(2',6'-dimethoxy biphenyl-2-yl)phosphine
EtMgBr	ethylmagnesium bromide	T3P	propylphosphonic anhydride
Et ₂ O	diethyl ether	TBAF	tetrabutylammonium fluoride
EtOAc	ethyl acetate	TBS	<i>tert</i> -butyldimethylsilyl
EtOH	ethanol	Temp	temperature
eq	equivalent	<i>t</i> Bu	<i>tert</i> -butyl
FA	formic acid	<i>t</i> BuOH	<i>tert</i> -butanol
h	hour	Tf	trifluoromethanesulfonyl
HPLC	high performance liquid chromatography	TFA	trifluoroacetic acid
<i>i</i> Pr	<i>iso</i> -propyl	THF	tetrahydrofuran
<i>i</i> PrOH	propan-2-ol	TLC	thin layer chromatography
KOtBu	potassium <i>tert</i> -butoxide	Tos	toluenesulfonyl
LDA	lithium diisopropylamide	Tr	triphenylmethyl
LG	leaving group	Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
		XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

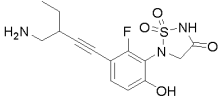
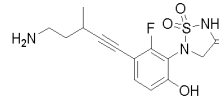
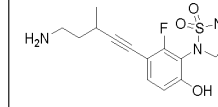
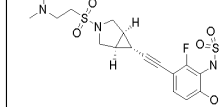
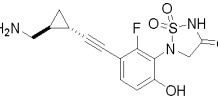
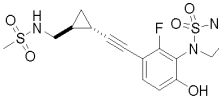
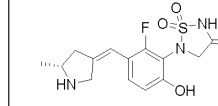
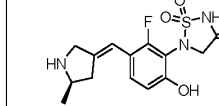
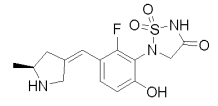
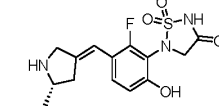
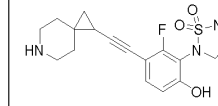
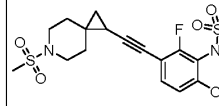
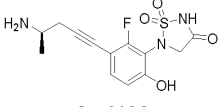
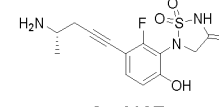
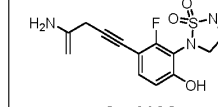
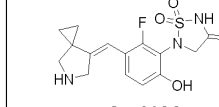
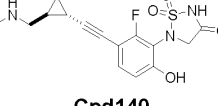
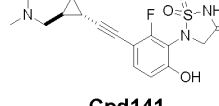
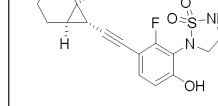
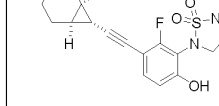
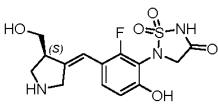
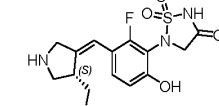
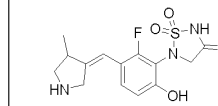
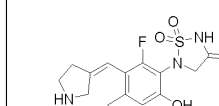
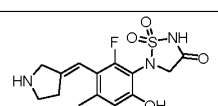
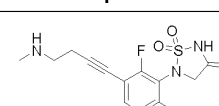
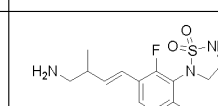
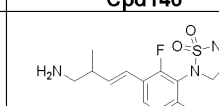
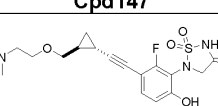
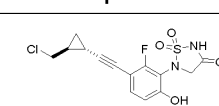
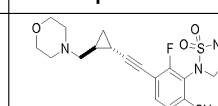
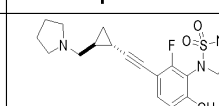
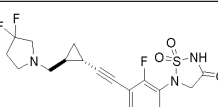
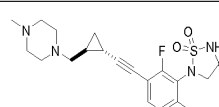
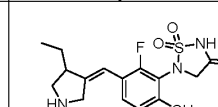
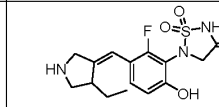
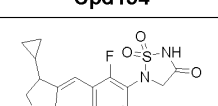
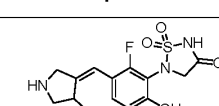
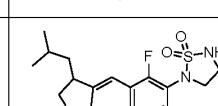
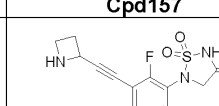
The following examples are provided for the purpose of illustrating the present invention and by no means should be interpreted to limit the scope of the present invention.

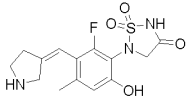
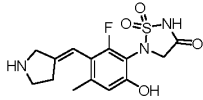
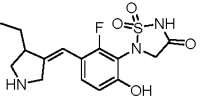
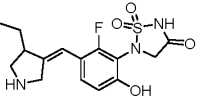
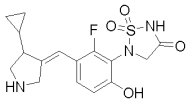
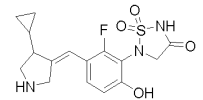
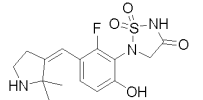
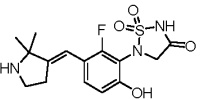
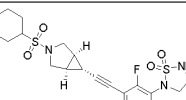
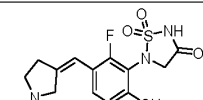
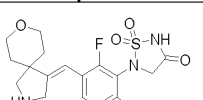
Table 1: Structures of example compounds of the invention and their respective codes

Structure and Compound Code	Structure and Compound Code	Structure and Compound Code	Structure and Compound Code
 Cpd001	 Cpd002	 Cpd003	 Cpd004
 Cpd005	 Cpd006	 Cpd007	 Cpd008
 Cpd009	 Cpd010	 Cpd011	 Cpd012
 Cpd013	 Cpd014	 Cpd015	 Cpd016
 Cpd017	 Cpd018	 Cpd019	 Cpd020
 Cpd021	 Cpd022	 Cpd023	 Cpd024
 Cpd025	 Cpd026	 Cpd027	 Cpd028
 Cpd029	 Cpd030	 Cpd031	 Cpd032
 Cpd033	 Cpd034	 Cpd035	 Cpd036
 Cpd037	 Cpd038	 Cpd039	 Cpd040
 Cpd041	 Cpd042	 Cpd043	 Cpd044

 Cpd045	 Cpd046	 Cpd047	 Cpd048
 Cpd049	 Cpd050	 Cpd051	 Cpd052
 Cpd053	 Cpd054	 Cpd055	 Cpd056
 Cpd057	 Cpd058	 Cpd059	 Cpd060
 Cpd061	 Cpd062	 Cpd063	 Cpd064
 Cpd065	 Cpd066	 Cpd067	 Cpd068
 Cpd069	 Cpd070	 Cpd071	 Cpd072
 Cpd073	 Cpd074	 Cpd075	 Cpd076
 Cpd077	 Cpd078	 Cpd079	 Cpd080
 Cpd081	 Cpd082	 Cpd083	 Cpd084
 Cpd085	 Cpd086	 Cpd087	 Cpd088

			
Cpd089	Cpd090	Cpd091	Cpd092
			
Cpd093	Cpd094	Cpd095	Cpd096
			
Cpd097	Cpd098	Cpd099	Cpd100
			
Cpd101	Cpd102	Cpd103	Cpd104
			
Cpd105	Cpd106	Cpd107	Cpd108
			
Cpd109	Cpd110	Cpd111	Cpd112
			
Cpd113	Cpd114	Cpd115	Cpd080-en1
			
Cpd080-en2	Cpd116	Cpd117	Cpd118
			
Cpd119	Cpd120	Cpd121	Cpd122
			
Cpd123	Cpd124-en1	Cpd124-en2	Cpd125-en1

 Cpd125-en2	 Cpd126-en1	 Cpd126-en2	 Cpd127
 Cpd128	 Cpd129	 Cpd130	 Cpd131
 Cpd132	 Cpd133	 Cpd134	 Cpd135
 Cpd136	 Cpd137	 Cpd138	 Cpd139
 Cpd140	 Cpd141	 Cpd142-en1	 Cpd142-en2
 Cpd143	 Cpd144	 Cpd145	 Cpd146
 Cpd147	 Cpd148	 Cpd149-en1	 Cpd149-en2
 Cpd150	 Cpd151	 Cpd152	 Cpd153
 Cpd154	 Cpd155	 Cpd156	 Cpd157
 Cpd158	 Cpd159	 Cpd160	 Cpd161

 Cpd162	 Cpd163	 Cpd156-en1	 Cpd156-en2
 Cpd158-en1	 Cpd158-en2	 Cpd164	 Cpd165
 Cpd166	 Cpd167	 Cpd168	

Structures of example compounds that contain stereocentres are drawn and named with absolute stereochemistry, if known. In case of unknown absolute stereochemistry the compounds can be either racemic, a mixture of diastereomers, a pure diastereomer of unknown stereochemistry, or a pure enantiomer of unknown stereochemistry.

5 EXAMPLES

Part A represent the preparation of the compounds of the invention whereas Part B represents the pharmacological examples.

Part A: Experimental chemistry procedures

The compounds of the invention can be prepared while using a series of chemical reactions well known to those skilled in the art, altogether making up the process for preparing said compounds and exemplified further. The processes described further are only meant as examples and by no means are meant to limit the scope of the present invention.

All reagents which are not explicitly described were either commercially available (the details of suppliers such as for example ABCR, Apollo Scientific, BLD, Combi-Blocks, Enamine, FluoroChem-DougDiscovery, MatrixScientific, Maybridge, Merck, TCI etc. can be found in the SciFinder® Database for example) and used as received without further purification, unless otherwise stated or the synthesis thereof has already been described precisely in the specialist literature (experimental guidelines can be found in the Reaxys® Database or the SciFinder® Database respectively, for example) or can be prepared using the conventional methods known to the person skilled in the art.

The reactions were, if necessary, carried out under an inert atmosphere (mostly argon and N₂). Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. The number of equivalents of reagents and the amounts of solvents employed as well as the reaction temperatures and times can vary slightly between different reactions carried out by

analogous methods. The work-up and purification methods were adapted according to the characteristic properties of each compound and can vary slightly for analogous methods. The yields of the compounds prepared are not optimized. The indication "equivalents" ("eq." or "eq" or "equiv.") means molar equivalents, "RT" or "rt" means room temperature T (23 +/- 7 °C), "M" are indications of concentration in mol/l, "sol." means solution, "conc." means concentrated, "sat." means saturated. The mixing ratios of solvents are usually stated in the volume / volume ratio.

Key analytical characterization was carried out by means of ¹H-NMR spectroscopy and/or mass spectrometry (MS, m/z for [M+H]⁺ and/or [M-H]⁻) for all the exemplary compounds and selected intermediate products. In certain cases, where e.g. regioisomers and/or diastereomers could be/were formed during the reaction, additional analytics, such as, e.g. ¹³C NMR and NOE (nuclear overhauser effect) NMR experiments were performed. NMR data were recorded using Bruker Advance 400MHz or 600MHz NMR spectrometers (TopSpin-software). ¹H data were calibrated using tetramethylsilane as an internal calibration reference. The chemical shifts δ-values are expressed in parts per million (ppm). The following acronyms were used: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), brs (broadened singlet).

The LC/MS analyses mentioned in the experimental part were performed on Waters systems combining either a Waters Acquity UPLC H-Class Plus system (instrument 1), a Waters Acquity UPLC I-Class Plus system (instrument 2), a Waters Acquity Premier system (instrument 3), a Waters Alliance e2695 system (instrument 4) or a Waters 2545 system (instrument 5) or a Waters 1290 Infinity (instrument 6) equipped with the below described detectors and with columns and chromatographic conditions outlined in the table below.

Table 2: Description of LC/MS analysis methods used in the preparation and analysis of compounds of the invention.

Method Code	Instrument	Column	Mobile Phase	Gradient Time (min)/%B	Flow; Column Temp.
LC-A	2 equipped with SQ Detector 2	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μm)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.4/3, 2/98, 3.4/98, 3.5/3, 4/3	0.6 mL/min; 35°C
LC-B	4 equipped with SQ Detector 2	Waters ; X Bridge C18 (4.6*150 mm, 3.5 μm)	A: 10 mM NH ₄ HCO ₃ in H ₂ O B: CH ₃ CN	0/5, 1/5, 3/15, 7/55, 11/98, 16/98, 16.01/5, 20/5	1.0 mL/min; ambient
LC-C	1 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity HSS C18 (2.1*50 mm, 1.8 μm)	A: 0.1% FA in H ₂ O B: CH ₃ CN	0/5, 3.18/50, 4/90, 5/90	0.5 mL/min; 40°C
LC-D	2 equipped with SQ Detector 2	Waters ; Acquity BEH C18 (2.1*100 mm, 1.7 μm)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 8.5/100, 9.0/100, 9.5/3, 10/3	0.55 mL/min; 50°C
LC-E	4 equipped with SQ Detector 2	Waters ; X bridge C18 (4.6*75 mm, 3.5 μm)	A: 10 mM NH ₄ HCO ₃ in H ₂ O B: CH ₃ CN	0/5, 0.5/5, 1.0/15, 4.0/98, 7.0/98, 7.5/5, 8.0/5	1.3 mL/min; 35°C

LC-F	2 equipped with SQ Detector 2	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.4/3, 7.5/98, 9.5/98, 9.6/3, 10/3	0.6 mL/min; 35°C
LC-G	1 equipped with SQ Detector 2	Waters ; Acquity BEH C8 (2.1*50 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN: H ₂ O (90:10)	0/5, 0.75/5, 1.5/25, 3/95, 4/95, 4.5/5, 5/5	0.8 mL/min; 50°C
LC-H	1 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 10 mM NH ₄ OAc in H ₂ O (pH 7) + 5% CH ₃ CN B: CH ₃ CN	0/0, 3.18/48, 4/90, 5/90	0.5 mL/min; 40°C
LC-I	1 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 10 mM NH ₄ OAc in H ₂ O (pH7) + 5% CH ₃ CN B: CH ₃ CN	0/16, 3.4/58, 4/90, 5/90	0.5 mL/min; 40°C
LC-J	2 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 0.05% TFA in H ₂ O B: 0.05% TFA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.5/98, 3.6/3, 4/3	0.6 mL/min; 35°C
LC-K	1 equipped with a DAD Detector and SQ Detector 2	Agilent ; ZORBAX RRHD Eclipse Plus C18 (3.0*50 mm, 1.8 μ m)	A: 0.05% TFA in H ₂ O B: 0.05% TFA in CH ₃ CN: H ₂ O (90:10)	0/5, 0.75/5, 1.5/25, 3.0/95, 4.0/95, 4.5/5, 5/5	0.8 mL/min; 50°C
LC-L	1 equipped with a SQ Detector 2	Waters ; Acquity BEH C18 (2.1*30 mm, 1.7 μ m)	A: 10 mM NH ₄ OAc in H ₂ O B: 10 mM NH ₄ OAc in CH ₃ CN: H ₂ O (90:10)	0/2, 0.75/2, 3.5/98, 4.5/98, 4.75/2, 5/2	0.5 mL/min; ambient
LC-M	3 equipped with a SQ Detector 2	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.5/98, 3.6/3, 4/3	0.6 mL/min; 35°C
LC-N	1 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity HSS C18 (2.1*30 mm, 1.8 μ m)	A: 0.1% FA in H ₂ O B: CH ₃ CN	0/5, 1.5/90, 2.5/90	0.8 mL/min; 40°C
LC-O	1 equipped with PDA Detector, ELS Detector and TQ Detector	Waters ; Acquity BEH C18 (2.1*30 mm, 1.7 μ m)	A: 10 mM NH ₄ OAc in H ₂ O (pH 7) + 5% CH ₃ CN B: CH ₃ CN	0/0, 1.5/90, 2.5/90	0.8 mL/min; 40°C
LC-P	5 equipped with a 2489 UV/Vis Detector and a MS3100 Mass detector (SQ)	Waters ; X-Bridge C18 (3*50 mm, 3.5 μ m)	A: 10 mM NH ₄ OAc in H ₂ O B: CH ₃ CN	0/5, 0.5/5, 1.0/50, 2.5/100, 3.5/100, 3.6/5, 5/5	1 mL/min; ambient
LC-Q	1 equipped with SQ Detector 2	YMC ; YMC-Triart-C18 (2.1*50 mm, 1.9 μ m)	A: 0.05% TFA in H ₂ O B: 0.05% TFA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.5/98, 3.6/3, 4/3	0.6 mL/min; 35°C
LC-R	2 equipped with a PDA detector and a TQ-S detector	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.6/98, 3.7/3	0.6 mL/min; 35°C
LC-S	3 equipped with SQ Detector 2	YMC ; YMC-Triart-C18 (2.1*50 mm, 1.9 μ m)	A: 0.05% TFA in H ₂ O B: 0.05% TFA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.5/98, 3.6/3, 4/3	0.6 mL/min; 35°C
LC-T	3 equipped with SQ Detector 2	Waters ; CORTECS C18 (3.0*30 mm, 1.6 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.05/3, 1.2/98, 1.6/98, 1.65/3, 2/3	0.85 mL/min; 45°C

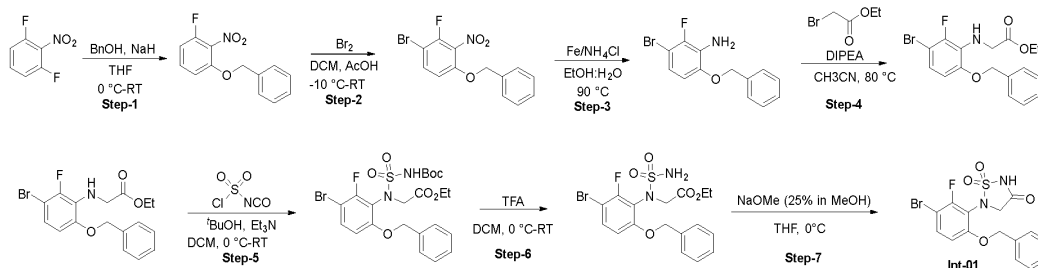
LC-U	3 equipped with SQ Detector 2	Waters ; Acquity BEH C18 (3.0*30 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.05/3, 0.9/98, 1.65/98, 1.70/3, 2/3	0.85 mL/min; 45°C
LC-V	2 equipped with SQ Detector 2	Waters ; Acquity UPLC BEH SHIELD RP 18 (2.1*100mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 8.5/100, 9.0/100, 9.5/3, 10/3	0.55 mL/min; 50°C
LC-W	1 equipped with SQ Detector 2	Waters ; Acquity BEH C18 (2.1*50 mm, 1.7 μ m)	A: 0.05% FA in H ₂ O B: 0.05% FA in CH ₃ CN	0/3, 0.4/3, 2.5/98, 3.5/98, 3.6/3	0.6 mL/min 35°C
LC-X	6 equipped with 6130 Quadrupole & 385 ELSD Detector	Waters ; X-Bridge C18 (4.6*75 mm, 3.5 μ m)	A: 10 mM NH ₄ OAc in H ₂ O B: CH ₃ CN	0/5, 0.5/5, 2/10, 4/95, 8/95, 8.1/5, 10/5	1.0 mL/min 45°C

All the preparative HPLC purifications mentioned in this experimental part were carried out either with a

- Waters system combining a Waters 2545 Binary Gradient Module, a Waters 2489 UV/Visible Detector ((dual wavelength detection at 210 nm and 254 nm), a System Fluidics Organizer, a 515 HPLC Pump, a Waters 2767 Sample Manager and a Waters MS3100 Mass detector
 - Shimadzu (LC-20AP, LC solution software) with SPD-20AV UV/VIS detector (dual wavelength detection at 215 nm and 254 nm)
 - Waters system (2707 autosampler, Empower software) with a 2996 PDA detector (PDA Max plot detection)
 - Gilson (GX-271, Trilution software) system with a 171 PDA detector (dual wavelength detection at 215 nm and 254 nm)
 - a Knauer (Azura P 2.1L, Purity chrom software) system with a Azura MWD 2.1 L detector (dual wavelength detection at 215 nm and 254 nm)
- The chiral SFC purifications methods mentioned in this experimental part were carried out with a Waters Acquity UPC2 system. The SFC method used in the preparation and analysis of compounds of the invention referred to as "SFC-Method A") is as following: Column: CHIRALCEL OX-H (4.6*250 mm, 5 μ m), Co-Solvent: 0.5% diethylamine in MeOH, Total Flow: 3mL/min, % of CO₂: 65; % of Co-Solvent: 35, ABPR: 1500 psi, Column Temp: 30 °C. The SFC method used in the preparation and analysis of compounds of the invention referred to as "SFC-Method B" is as following: Column: CHIRALPAK IK (4.6*250 mm, 5 μ m), 0.5% isopropylamine in IPA:CH₃CN (1:1), Total Flow: 4 mL/min, % of CO₂: 60; % of Co-Solvent: 40, ABPR: 1500 psi, Column Temp: 30 °C.

Examples of intermediates for the synthesis of the compounds of the invention and their preparation.

- Synthesis of **Int-01**: synthesis of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Int-01**)



Step-1: To a stirred solution of benzyl alcohol (7.19 mL, 69 mmol) in THF (250 mL), was added NaH (60% in mineral oil, 3.04 g, 76 mmol) at 0 °C. After 15 min, 1,3-difluoro-2-nitrobenzene (1.10 g, 63 mmol) dissolved in dry THF (50 mL) was added dropwise to the above reaction mixture at 0 °C. The resulting reaction mixture was slowly allowed to RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice cold water (300 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get the crude product. Similarly, two more batches were performed following the exact procedure. The crude product of the three batches were combined and purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (4-5%) to yield 1-(benzyloxy)-3-fluoro-2-nitrobenzene as a brown liquid (49.5 g from three batches).

¹H NMR (400 MHz, CDCl₃) δ ppm 7.40-7.32 (m, 6H), 6.87-6.81 (m, 2H), 5.20 (s, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -122.4 (t)

Step-2: To a stirred solution of 1-(benzyloxy)-3-fluoro-2-nitrobenzene (25 g, 101 mmol) in AcOH (600 mL) and DCM (600 mL), was added Br₂ (104.3 mL, 2.02 mol) at -10 °C. The reaction mixture was slowly allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0 °C, quenched with ice-water (200 mL) and extracted with EtOAc (2 x 500 mL). The combined organic layers were washed with a saturated solution of NaHSO₃, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. Similarly, 1 more batch was performed on same scale following the exact same procedure.

The crude material of the 2 batches were combined, pentane (300 mL) was added to the resulting residue and stirred for 30 min. The solid obtained was filtered and further stirred with a mixture of pentane (100 mL) and diethyl ether (100 mL) for 30 min. The solid was again filtered and dried under vacuum to afford 1-(benzyloxy)-4-bromo-3-fluoro-2-nitrobenzene (33 g from 2 batches), which was used as such in the next step without further purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.98-7.94 (t, 1H), 7.44-7.31 (m, 6H), 5.35 (s, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -117.5 (d)

Step-3: To a stirred solution of 1-(benzyloxy)-4-bromo-3-fluoro-2-nitrobenzene (25 g, 76.7 mmol) in ethanol (250 mL) and H₂O (100 mL), were added iron powder (12.8 g, 229.9 mmol) and NH₄Cl (42 g, 383.3 mmol) at RT. The resulting reaction mixture was heated at 90 °C. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through a celite bed and the bed

was washed thoroughly with EtOH. The filtrate was concentrated under reduced pressure, diluted with water (200 mL) and extracted with EtOAc (2 x 250 mL). The combined organic layers were concentrated under reduced pressure and the residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-30%) to yield 22 g of 6-(benzyloxy)-3-bromo-2-fluoroaniline as a pale yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.48 (d, 2H), 7.38 (t, 2H), 7.32 (t, 1H), 6.77-6.73 (m, 2H), 5.14 (s, 2H), 4.99 (brs, 2H).

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -128.1 (d).

Step-4: To a stirred solution of 6-(benzyloxy)-3-bromo-2-fluoroaniline (40 g, 135.1 mmol), in acetonitrile (400 mL), were added DIPEA (95.6 mL, 540 mmol) followed by ethyl 2-bromoacetate (29.8 mL, 270 mmol) at RT. The reaction mixture was then stirred at 80°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a saturated NaHCO₃ solution at 0°C and then concentrated under reduced pressure. The obtained crude product was diluted with water (150 mL) and extracted with EtOAc (2x300 mL). The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-5%). The obtained compound was again purified by reverse phase C18 column chromatography eluting with a gradient of CH₃CN in H₂O containing 0.1% FA (0-50%). The pure fractions were concentrated and extracted with EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to provide 22 g of ethyl (6-(benzyloxy)-3-bromo-2-fluorophenyl)glycinate.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.47-7.45 (m, 2H), 7.42-7.38 (m, 2H), 7.35-7.32 (m, 1H), 6.87 (t, 1H), 6.78 (dd, 1H), 5.37-5.33 (m, 1H), 5.14 (s, 2H), 4.09-4.04 (m, 4H), 1.14 (t, 3H).

¹⁹F NMR (376 MHz, CDCl₃) δ ppm -126.8 (d)

Step-5: To a stirred solution of chlorosulfonyl isocyanate (9.54 g, 109.8 mmol) in DCM (150 mL) was added tBuOH (10.42 mL, 109.9 mmol) dropwise at 0°C. The reaction mixture was stirred for 30 min at the same temperature under N₂ atmosphere. This pre-reagent mixture was added to a stirred solution of ethyl (6-(benzyloxy)-3-bromo-2-fluorophenyl)glycinate (21 g, 54.94 mmol) and triethylamine (23 mL, 164.8 mmol) in DCM (150 mL) at 0°C. The resulting reaction mixture was allowed to RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water (150 mL) and extracted with DCM (2 x 200 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (8-50%) to yield 22 g of ethyl N-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-N-(N-(tert-butoxycarbonyl)sulfamoyl) glycinate as a white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 11.40 (s, 1H), 7.62-7.66 (m, 1H), 7.45-7.46 (m, 2H), 7.35-7.41 (m, 2H), 7.31-7.33 (m, 1H), 6.91-6.94 (m, 1H), 5.19-5.29 (q, 2H), 4.68-4.73 (d, 1H), 4.34-4.38 (d, 1H), 3.97-4.07 (m, 2H), 1.32 (s, 9H), 1.09-1.17 (m, 3H)

Step-6: To a stirred solution of ethyl N-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-N-(N-(tert-butoxycarbonyl)sulfamoyl)glycinate (21 g, 37.4 mmol, 1.0 eq) in DCM (200 mL), was added TFA (42.4 mL, 561 mmol, 15 eq) at 0°C. The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure, quenched with a saturated NaHCO₃ aqueous solution and extracted with DCM (3 x 100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-50%). The pure fractions were combined and concentrated under reduced pressure. The obtained residue was dissolved in DCM (40 mL) and PE (80 mL) was slowly added. The white precipitated solid was filtered and dried under vacuum to provide 12 g of ethyl N-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-N-sulfamoylglycinate as a white solid.

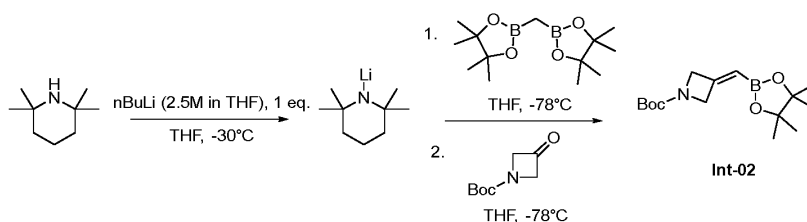
¹H NMR (400 MHz, CDCl₃) δ ppm 7.57-7.61 (q, 1H), 7.49 (d, 2H), 7.41 (t, 2H), 7.31-7.34 (m, 1H), 7.08 (bs, 2H), 6.95-6.97 (dd, 1H), 5.18 (s, 2H), 4.19-4.42 (dd, 2H), 3.98-4.04 (m, 2H), 1.10 (t, 3H)

Step-7: To a stirred solution of ethyl N-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-N-sulfamoylglycinate (12 g, 26.0 mmol, 1.0 eq) in THF (120 mL), was added sodium methoxide (25% solution in methanol, 8.43 mL, 39.0 mmol, 1.5 eq) at 0°C. The resulting reaction mixture was stirred at 0°C. After completion of the reaction (TLC monitoring), the reaction mixture was acidified with AcOH (0.5 mL) and evaporated under reduced pressure to obtain a crude residue, which was triturated with n-pentane followed by diethyl ether to afford 11 g of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.55 (t, 1H), 7.49 (d, 2H), 7.38-7.28 (m, 3H), 6.93 (dd, 1H), 5.18 (s, 2H), 3.99 (s, 2H)

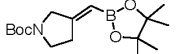
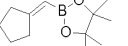
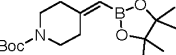
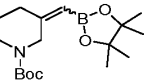
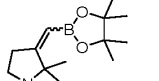
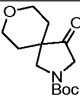
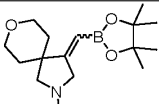
¹⁹F NMR (376 MHz, CDCl₃) δ ppm -109.8 (d).

Synthesis of **Int-02**: synthesis of tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidine-1-carboxylate (**Int-02**)

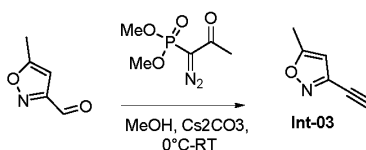


A stirred solution of 2,2,6,6-tetramethylpiperidine (2.15 mL, 12.62 mmol, 1.2 eq) in THF (30 mL), cooled to -30°C, was treated with a 2.5M THF solution of n-BuLi (5.1 mL, 12.6 mmol, 1.2 eq) and then stirred for 30 min. The reaction mixture was further cooled to -78°C, treated with a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (3.10 g, 11.6 mmol, 1.1 eq) in THF (30 mL) and stirred for another 30 min at -78°C. A solution of tert-butyl 3-oxoazetidine-1-carboxylate (1.8 g, 10.5 mmol) in THF (30 mL) was then added at the same temperature. The resulting

- reaction mixture was then allowed to warm to RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0°C, quenched with a sat. NH₄Cl solution (6 mL) and stirred for 1 h. The solids were filtered off and the filtrate was evaporated under reduced pressure. The crude product was diluted with water (250 mL) and extracted with EtOAc (2 x 150 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-4%) to yield 1.4 g of tert-butyl 3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)azetidine-1-carboxylate as a colorless liquid. LC-MS (LC-R): r.t. = 2.32 min ; m/z 239 [M-isobutene+H]⁺
- 10 The following vinyl boronic esters were prepared in a manner similar to **Int-02** (by use of appropriate starting ketones, reagents and purification methods known to the person skilled in the art):

Ketone reagent	Product	¹ H NMR (400 MHz, CDCl ₃) δ ppm
		5.24 (s, 1H), 4.04-4.00 (m, 1H), 3.92 (d, 1H), 3.40-3.32 (m, 2H), 2.74 (s, 1H), 2.63 (s, 1H), 1.40 (s, 9H), 1.20 (s, 12H)
		5.28-5.26 (m, 1H), 2.54-2.50 (m, 2H), 2.38-2.35 (m, 2H), 1.73-1.63 (m, 4H), 1.25 (s, 12H)
		5.13 (s, 1H), 3.44-3.40 (m, 4H), 2.58 (t, 2H), 2.25-2.22 (m, 2H), 1.45 (s, 9H), 1.24 (s, 12H)
		LC-MS (LC-U): r.t. = 1.10 min ; m/z 324 [M+H] ⁺
		5.21 (s, 1H), 3.46 (brs, 2H), 2.83-2.59 (m, 2H), 1.56 (s, 9H), 1.40 (s, 6H), 1.23 (s, 12H)
		LC-MS (LC-M): r.t. = 2.32 min ; m/z 324 [M-isobutene+H] ⁺

Synthesis of **Int-03**: synthesis of 3-ethynyl-5-methylisoxazole (**Int-03**)

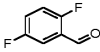
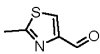
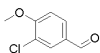
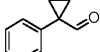
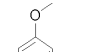
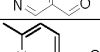
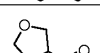
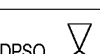
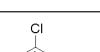
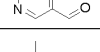
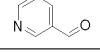
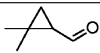
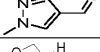
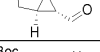
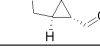
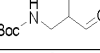
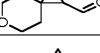


- 15 To a stirred solution of 5-methylisoxazole-3-carbaldehyde (2 g, 18.0 mmol, 1 eq) in MeOH (20 mL) at 0°C was added Cs₂CO₃ (11.7 g, 36.0 mmol, 2 eq) followed by dimethyl(1-diazo-2-oxopropyl)phosphonate (5.19 g, 27.0 mmol, 1.5 eq) and the reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water (50 mL) and extracted with DCM (2 x 25 mL). The combined organic layers were dried over

anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of DCM in PE (0-10%) to yield 2.1 g of 3-ethynyl-5-methylisoxazole as a pale-yellow liquid.

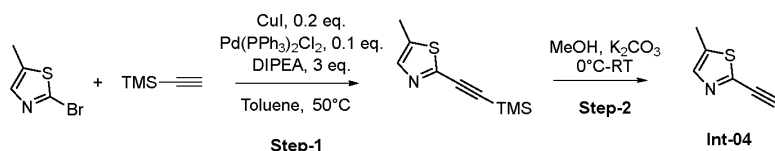
¹H NMR (400 MHz, CDCl₃) δ ppm 6.09 (s, 1H), 3.31 (s, 1H), 2.44 (s, 3H)

- 5 The following compounds were prepared in a manner similar to **Int-03** (by use of appropriate aldehyde reagents, solvent, inorganic base (like K₂CO₃, etc...), reaction temperature and purification methods known to the skilled in the art):

Aldehyde reagent	Product	¹ H NMR (400 MHz, CDCl ₃) (unless otherwise stated) δ ppm
		7.19-7.15 (m, 1H), 7.06-7.02 (m, 2H), 3.33 (s, 1H)
		7.37 (s, 1H), 3.09 (s, 1H), 2.71 (s, 3H)
		7.50 (d, 1H), 7.37 (dd, 1H), 6.86 (d, 1H), 3.91 (s, 3H), 3.02 (s, 1H)
		7.37-7.29 (m, 5H), 2.10 (s, 1H), 1.47-1.42 (m, 2H), 1.14-1.07 (m, 2H)
		8.33 (d, 1H), 8.28 (d, 1H), 7.27 (t, 1H), 3.86 (s, 3H), 3.20 (s, 1H)
		8.61 (d, 1H), 7.66 (dd, 1H), 7.12 (d, 1H), 3.16 (s, 1H), 2.57 (s, 3H)
		4.01 (t, 1H), 3.92 (m, 1H), 3.85 (m, 1H), 3.65 (m, 1H), 2.98 (m, 1H), 2.21 (m, 1H), 2.11 (d, 1H), 2.02 (m, 1H)
		7.69-7.66 (m, 4H), 7.44-7.36 (m, 6H), 3.66 (s, 2H), 1.88 (s, 1H), 1.07-1.03 (m, 9H), 0.88-0.85 (m, 2H), 0.82-0.81 (m, 2H)
		8.59 (d, 1H), 8.54 (d, 1H), 7.77 (t, 1H), 3.26 (s, 1H)
		8.53 (d, 1H), 8.40 (d, 1H), 7.59 (s, 1H), 3.18 (s, 1H), 2.33 (s, 3H)
		2.98-2.82 (m, 2H), 2.64-2.56 (m, 2H), 2.36-2.32 (m, 1H), 2.05 (s, 1H)
		crude used as such in the next step
		7.60 (s, 1H), 7.52 (s, 1H), 3.89 (s, 3H), 3.00 (s, 1H)
		crude used as such in the next step
		(600MHz) 3.68 (d, 1 H), 3.59 (d, 1 H), 3.41-3.32 (m, 2 H), 1.90 (d, 1 H), 1.88-1.79 (m, 2 H), 1.45 (s, 9 H), 1.13 (d, 1 H)
		4.87 (brs, 1H), 3.32-3.26 (m, 1H), 3.09-3.02 (m, 1H), 2.66-2.60 (m, 1H), 2.08 (s, 1H), 1.47 (s, 9H), 1.18 (d, 3H)
		crude used as such in the next step
		crude used as such in the next step

		(DMSO-d6) 3.28 (dd, 1 H), 3.23 (s, 3 H), 3.11 (dd, 1 H), 2.65 (d, 1 H), 1.27-1.19 (m, 2 H), 0.77 (m, 1 H)
		crude used as such in the next step
		6.94 (brs, 1 H), 2.94-2.75 (m, 2 H), 2.61 (d, 1 H), 1.38 (s, 9 H), 1.24-1.08 (m, 2 H), 0.76-0.63 (m, 2 H)
		3.67-3.51 (m, 2 H), 3.40 (dt, 1 H), 3.32 (ddd, 1 H), 1.87 (d, 1 H), 1.62 (t, 2 H), 1.53-1.41 (m, 10 H), 1.26-1.16 (m, 2 H), 0.83 (dd, 1 H), 0.66 (t, 1 H)
		7.95 (s, 1H), 7.37-7.31 (m, 9H), 7.14-7.11 (m, 6H), 3.07 (s, 1H)
		3.63 (dd, 2H), 3.52-3.47 (m, 2H), 1.95 (d, 1H), 1.81-1.77 (m, 2H), 1.63-1.60 (m, 1H), 1.43 (s, 9H)
		3.77 (d, 1H), 3.30-3.25 (m, 2H), 2.75 (s, 3H), 2.74-2.65 (m, 1H), 2.12-2.07 (m, 1H), 1.99-1.94 (m, 1H), 1.87 (d, 1H), 1.54-1.44 (m, 2H), 1.35-1.32 (m, 1H)
		(DMSO-d6) 7.10 (d, 1H), 3.95-3.87 (m, 1H), 2.93 (s, 3H), 2.65 (d, 1H), 1.83-1.67 (m, 4H), 1.58-1.54 (m, 1H), 1.43-1.41 (m, 1H), 1.02-0.90 (m, 1H)
		(DMSO-d6) 3.82 (brs, 2 H), 3.77 (brs, 2 H), 2.99 (d, 1 H), 2.87 (m, 1 H), 2.48-2.40 (m, 2 H), 2.19-2.10 (m, 2 H), 1.35 (s, 9 H)
		crude used as such in the next step
		4.70 (brs, 1 H), 4.40 (brs, 1 H), 2.93 (td, 1 H), 2.76-2.55 (m, 1 H), 2.53-2.36 (m, 1 H), 2.26-2.04 (m, 2 H), 2.04-1.83 (m, 1 H), 1.61 (d, 1 H), 1.47-1.35 (m, 9 H)
		4.63 (brs, 1H), 3.84 (brs, 1H), 2.46-2.36 (m, 1H), 2.34-2.32 (m, 1H), 2.01 (t, 1H), 1.44 (s, 9H), 1.23 (d, 3H)
		4.64 (brs, 1H), 3.86 (brs, 1H), 2.48-2.44 (m, 1H), 2.38-2.36 (m, 1H), 2.02 (t, 1H), 1.45 (s, 9H), 1.23 (d, 3H)
		4.23 (t, 1H), 2.02-1.97 (m, 2H), 1.81-1.78 (m, 3H), 1.70-1.66 (m, 1H), 1.63-1.58 (m, 2H), 0.88 (s, 9H), 0.00 (s, 6H)
		3.92 (d, 1H), 3.48-3.22 (m, 2H), 2.89 (brs, 1H), 1.98-1.90 (m, 1H), 1.85 (d, 1H), 1.79 (brs, 1H), 1.44 (s, 9H), 1.42-1.38 (m, 2H), 1.06-1.03 (m, 1H)
		3.30-3.19 (m, 2H), 2.94 (s, 3H), 2.80-2.74 (m, 1H), 2.05 (d, 1H), 1.46 (s, 9H), 1.15 (d, 3H)
		4.86 (brs, 1H), 3.37-3.31 (m, 1H), 3.10-3.04 (m, 1H), 2.49-2.46 (m, 1H), 2.10 (d, 1H), 1.62-1.53 (m, 2H), 1.45 (s, 9H), 1.05 (t, 3H)
		3.51-3.41 (m, 2 H), 3.33 (dd, 1H), 3.17 (dd, 1 H), 2.64 (d, 1 H), 2.42 (t, 2 H), 2.17 (s, 6 H), 1.34-1.25 (m, 1 H), 1.24-1.17 (m, 1 H), 0.82-0.76 (m, 1 H), 0.70 (ddd, 1 H)
		(DMSO-d6) 4.70 (ddd, 1 H), 3.83-3.68 (m, 2 H), 3.48 (d, 1 H), 2.48-2.40 (m, 1 H), 2.18-2.01 (m, 1 H), 1.42-1.32 (m, 9 H), 0.92-0.75 (m, 1 H)

Synthesis of Int-04: synthesis of 2-ethynyl-5-methylthiazole (Int-04)



Step-1: A stirred solution of 2-bromo-5-methylthiazole (4 g, 22.47 mmol, 1.0 eq) and DIPEA (11.98 mL, 67.4 mmol, 3.0 eq) in toluene (40 mL) was degassed with Ar for 10 min. Then, ethynyltrimethylsilane (6.62 g, 67.4 mmol, 3.0 eq), followed by PdCl₂(PPh₃)₂ (1.6 mg, 2.24 mmol, 0.1 eq) and CuI (0.86 g, 4.49 mmol, 0.2 eq) were added at RT. The resulting reaction mixture was then stirred at 50°C in a sealed tube. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through celite bed and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in hexane (0-5%) to yield 1.0 g of 5-methyl-2-((trimethylsilyl)ethynyl) thiazole as a brown liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (s, 1H), 2.48 (s, 3H), 0.26 (s, 9H)

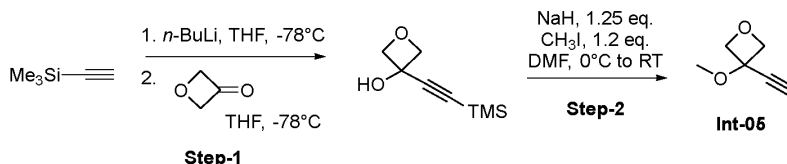
Step-2: A stirred solution of 5-methyl-2-((trimethylsilyl)ethynyl) thiazole (1.0 g, 5.12 mmol, 1.0 eq) in MeOH (10 mL) at RT, was treated portionwise with K₂CO₃ (1.41 g, 10.24 mmol, 2.0 eq) at 0°C. The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water (100 mL) and extracted with DCM (2 x 20 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to get 500 mg of 2-ethynyl-5-methylthiazole as a pale-brown liquid, which was used in the next step without purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 (s, 1H), 3.41 (s, 1H), 2.48 (s, 3H)

The following compounds were prepared in a manner similar to **Int-04** (by use of appropriate halogen reagents, solvent, reaction temperature and purification methods known to the person skilled in the art):

Reagent step-1	Product	Solvent, temperature step 1	¹ H NMR (400 MHz, CDCl ₃) δ ppm
		CH ₃ CN, 100°C	10.59 (brs, 1H), 8.47 (s, 1H), 8.09 (d, 1H), 7.39 (d, 1H), 6.51 (d, 1H), 3.12 (s, 1H)
		CH ₃ CN, 100°C	11.07 (brs, 1H), 8.68 (d, 1H), 8.25 (d, 1H), 8.10 (s, 1H), 3.17 (s, 1H)

Synthesis of Int-05: synthesis of 3-ethynyl-3-methoxyoxetane (Int-05)



Step-1: To a stirred solution of trimethylsilylacetylene (5.14 mL, 36.08 mmol, 1.3 eq) in THF (20 mL) under N₂ atmosphere and cooled at -78°C, was added n-BuLi (1.6 M in hexane, 21.7 mL,

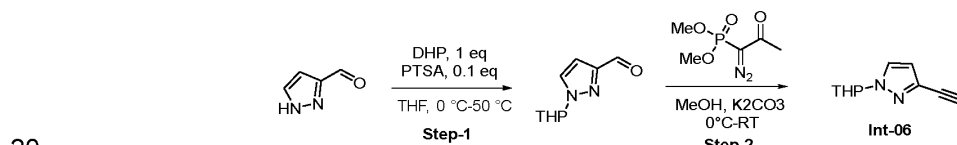
34.7 mmol, 1.25 eq). The reaction mixture was stirred at -78°C for 20 min and a solution of oxetane-3-one (2 g, 27.75 mmol, 1 eq) in THF (5 mL) was then added at the same temperature. The reaction mixture was stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure to yield 4.5 g of crude 3-((trimethylsilyl)ethynyl)oxetane as a pale-yellow solid, which is used in the next step without any further purification.

¹H NMR (400 MHz, CDCl₃) δ ppm 4.84 (d, 2H), 4.70 (d, 2H), 2.54 (s, 1H), 0.21 (s, 9H)

Step-2: To a stirred solution of 3-((trimethylsilyl)ethynyl)oxetan-3-ol (4.50 g, 26.4 mmol, 1 eq) in DMF (50 mL), was added sodium hydride (60% in mineral oil, 1.32 g, 33.0 mmol, 1.25 eq) at 0°C. After 15 min, CH₃I (1.97 mL, 31.7 mmol, 1.2 eq) was added at 0°C. The resulting reaction mixture was then allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0°C, quenched with ice cold water (30 mL) and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (3-5%). Combined pure fractions were then concentrated under reduced pressure at low temperature (20°C) to yield 550 mg of 3-ethynyl-3-methoxyoxetane as a pale-yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 4.71 (d, 2H), 4.67 (d, 2H), 3.36 (s, 1H), 3.32 (s, 3H)

Synthesis of **Int-06**: synthesis of 3-ethynyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (**Int-06**)



25 Step-1: To a stirred solution of 1H-pyrazole-5-carbaldehyde (500 mg, 5.2 mmol, 1 eq) in THF (10 mL) at 0°C, was added 3,4-dihydro-2H-pyran (0.41 mL, 5.20 mmol, 1 eq) followed by PTSA (99 mg, 0.52 mmol, 0.1 eq). The reaction mixture was then heated at 50°C. After completion of the reaction (TLC monitoring), the reaction mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-18%) to yield 600 mg of 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbaldehyde as a pale-yellow gum, which was used in the next step.

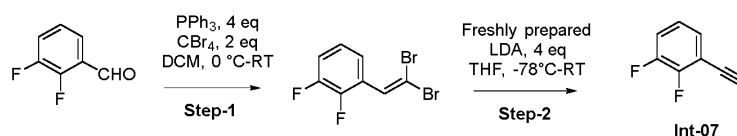
30 Step-2: To a stirred solution of 1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole-3-carbaldehyde (600 mg, 1.04 mmol, 1 eq) in MeOH (5 mL) at 0°C, were added K₂CO₃ (918 mg, 6.66 mmol, 2 eq) followed by dimethyl(1-diazo-2-oxopropyl)phosphonate (960 mg, 4.99 mmol, 1.5 eq). The reaction mixture was slowly allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water (50 mL) and extracted with DCM (2x100 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on

silica gel eluting with a gradient of EtOAc in PE (0-30%) to yield 500 mg of 3-ethynyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole as a white solid. LC-MS (LC-M): r.t. = 0.80 min ; m/z 177 [M+H]⁺

The following compounds were prepared in a manner similar to **Int-06** (by use of appropriate aldehyde reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Solvent/Acid step-1	Product
	THF / PTSA	
	THF / PTSA	
	Toluene / TFA	

Synthesis of **Int-07**: synthesis of 1-ethynyl-2,3-difluorobenzene (**Int-07**)

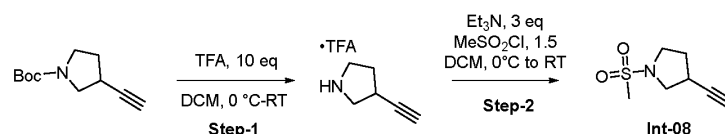


Step-1: To a stirred solution of 2,3-difluorobenzaldehyde (5 g, 35.2 mmol, 1 eq) in DCM (100 mL) at 0°C, were added PPh₃ (36.9 g, 140.8 mmol, 4 eq) followed by CBr₄ (23.3 g, 70.4 mmol, 2 eq) under N₂ atmosphere. The resulting reaction mixture was allowed to be stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water (200 mL) and extracted with DCM (2 x 150 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in hexane (0-30%) to yield 8 g of 1-(2,2-dibromovinyl)-2,3-difluorobenzene as a pale-yellow liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.52-7.47 (m, 2H), 7.19-7.06 (m, 2H)

Step-2: To a stirred solution of diisopropylamine (5.67 mL, 40.3 mmol, 4.0 eq) in THF (10 mL) at 0°C, was added n-BuLi (2.5 M in hexane, 16.11 mL, 40.3 mmol, 4.0 eq) dropwise under an N₂ atmosphere. The reaction was stirred at 0°C for 1 h. This freshly prepared lithium diisopropylamide (LDA) solution was added dropwise to a stirred solution of 1-(2,2-dibromovinyl)-2,3-difluorobenzene (10.1 mmol, 1 eq) in THF (10 mL) at -78°C. The reaction mixture was then allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with saturated NH₄Cl solution (50 mL) and extracted with diethyl ether (2 x 50 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with diethylether to yield 500 mg of 1-ethynyl-2,3-difluorobenzene as a brown liquid.

¹H NMR (400 MHz, CDCl₃) δ ppm 7.25-7.22 (m, 1H), 7.20-7.14 (m, 1H), 7.06-7.01 (m, 1H), 3.35 (s, 1H)

Synthesis of **Int-08**: synthesis of 3-ethynyl-1-(methylsulfonyl) pyrrolidine (**Int-08**)

Step-1: To a stirred solution of t-butyl 3-ethynylpyrrolidine-1-carboxylate (2 g, 10.24 mmol, 1.0 eq) in DCM (25mL), was added TFA (7.84 mL, 102.4 mmol, 10 eq) at 0°C. The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure to yield 1.8 g of crude 3-ethynylpyrrolidine-TFA salt as a yellow oil, which is used in the next step without any further purification.

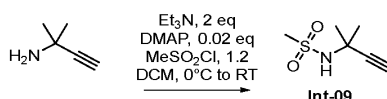
¹H NMR (400 MHz, CDCl₃) δ ppm 8.40 (brs, 2H), 3.61-3.54 (m, 2H), 3.50-3.45 (m, 1H), 3.39-3.34 (m, 1H), 3.26-3.22 (m, 1H), 2.37-2.32 (m, 1H), 2.25 (s, 1H), 2.22-2.15 (m, 1H)

Step-2: To a stirred solution of 3-ethynylpyrrolidine-TFA salt (1.8 g, 8.61 mmol, 1.0 eq) in DCM (20 mL), was added triethylamine (3.27 mL, 25.8 mmol, 3.0 eq) at 0°C. After 10 min, methane sulfonyl chloride (1.0 mL, 12.91 mmol, 1.5 eq) was added dropwise at 0°C. The resulting reaction mixture was then allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water (20 mL) and extracted with DCM (3x25 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (30-35%) to yield 650 mg of 3-ethynyl-1-(methylsulfonyl) pyrrolidine as a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ ppm 3.64-3.60 (m, 1H), 3.49-3.45 (m, 2H), 3.37-3.33 (m, 1H), 3.08-3.05 (m, 1H), 2.87 (s, 3H), 2.27-2.19 (m, 1H), 2.18 (s, 1H), 2.11-2.05 (m, 1H)

The following compound was prepared in a manner similar to **Int-08** (by use of appropriate alkyne reagents, solvent, reaction temperature and purification methods known to the skilled in the art).

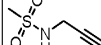
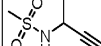
Reagent Step-1	Product
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<chem>COC(=O)N1CCCC(C#C)C1</chem>	<chem>COC(=O)N1CCCC(C#C)C1</chem>
<chem>COC(=O)N1CCC(C#C)C1</chem>	<chem>COC(=O)N1CCC(C#C)C1</chem>

Synthesis of **Int-09**: synthesis of N-(1,1-dimethylprop-2-ynyl)methanesulfonamide (**Int-09** ; CAS = 1279876-13-9)

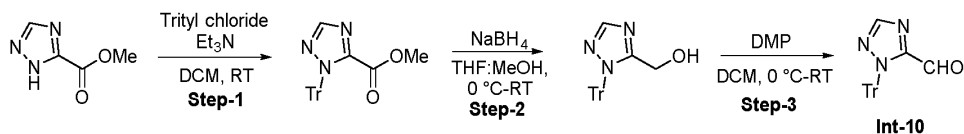
A mixture of 1,1-dimethylpropargylamine (0.32 mL, 2.86 mmol, 1 eq), triethylamine (0.796 mL,

5.71 mmol, 2 eq.), DMAP (7 mg, 0.06 mmol, 0.02 eq.) in dry DCM (9.5 mL) was slowly treated dropwise at 0 °C and under an N₂ atmosphere with mesylchloride (0.27 mL, 3.43 mmol, 1.2 eq) and the resulting mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the crude reaction mixture was diluted with DCM and partitioned with water. Aqueous layer was back extracted again twice with DCM. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated under vacuo to give the crude compound as a colorless oil. Recovered oil was taken up in a minimum volume of EtOAc and layered with PE. Obtained solid was filtered and dried to afford 342 mg of N-(1,1-dimethylprop-2-ynyl)methanesulfonamide as a thin white powder, which was used in the next step without purification. ¹H NMR (600 MHz, CDCl₃) δ ppm 4.59 (brs, 1 H), 3.19 (s, 3 H), 2.53 (s, 1 H), 1.66 (s, 6 H).

The following compound was prepared in a manner similar to **Int-09** (by use of appropriate alkyne reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Product
	
	

Synthesis of **Int-10**: synthesis of 1-trityl-1H-1,2,4-triazole-5-carbaldehyde (**Int-10**)



Step-1: To a stirred solution of methyl 1H-1,2,4-triazole-3-carboxylate (5.0 g, 39.4 mmol, 1.0 eq) in DCM (50 mL), were added triphenylmethyl chloride (10.94 g, 39.4 mmol, 1 eq) followed by Et₃N (16.42 mL, 118.2 mmol, 3 eq) dropwise at 0 °C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with ice cold water (500 mL) and extracted with DCM (2 x 250 mL). The combined organic layers were washed with a brine solution (2 x 300 mL) and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-10%) to yield 7.0 g of methyl 1-trityl-1H-1,2,4-triazole-5-carboxylate as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm. 8.38 (s, 1H), 7.43-7.40 (m, 9H), 7.08-7.06 (m, 6H), 3.84 (s, 3H)

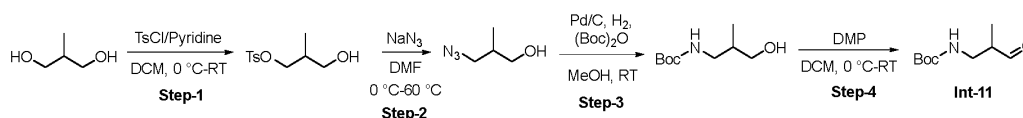
Step-2: To a stirred solution of methyl 1-trityl-1H-1,2,4-triazole-3-carboxylate (5.0 g, 13.54 mmol, 1 eq) in THF:MeOH (1:1, 200 mL), was added NaBH₄ (1.54 g, 40.60 mmol, 3 eq) at 0 °C portion-wise. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice-cold water (25 mL) at 0 °C and extracted with DCM (2 x 50 mL). The combined organic layers were washed with a brine solution (2 x 30 mL) and concentrated. The residue was purified by

column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-10%) to yield 4.0 g of 1-trityl-1H-1,2,4-triazol-5-yl) methanol as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm. 7.96 (s, 1H), 7.37-7.30 (m, 9H), 7.15-7.11 (m, 6H), 4.75 (brs, 2H)

- 5 Step-3: To a stirred solution of 1-trityl-1H-1,2,4-triazol-5-yl) methanol (2 g, 5.86 mmol, 1 eq) in DCM (20 mL) at 0 °C, was added Dess–Martin periodinane (3.74 g, 8.79 mmol, 1.5 eq) portion-wise. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0 °C and quenched with a saturated Na₂SO₃ solution (100 mL), extracted with DCM (2 X 100 mL) and washed with a NaHCO₃ solution (100 mL). The organic layer was separated and concentrated to get 900 mg of 1-trityl-1H-1,2,4-triazole-5-carbaldehyde as a white solid. The crude compound was used as such in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm: 10.04 (s, 1H), 8.13 (s, 1H), 7.41-7.30 (m, 9H), 7.16-7.09 (m, 6H)

Synthesis of Int-11: synthesis of tert-butyl (2-methyl-3-oxopropyl) carbamate



- 15 Step-1: To a stirred solution of 2-methylpropane-1,3-diol (100 g, 1110 mmol, 1 eq) in DCM (1 L), were added pyridine (43.9 g, 555 mmol, 0.5 eq) followed by 4-toluenesulfonyl chloride (212 g, 1110 mmol, 1 eq) portion-wise at 0 °C and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was washed with 1N HCl (200 mL), then by a saturated NaHCO₃ solution (2 mL) and then concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-20%) to yield 80 g of 3-hydroxy-2-methylpropyl 4-methylbenzenesulfonate. ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.80 (dd, 2H), 7.35 (dd, 2H), 4.03-4.00 (m, 2H), 3.61-3.49 (m, 2H), 2.45 (s, 3H), 2.03-1.97 (m, 1H), 0.91 (d, 3H)

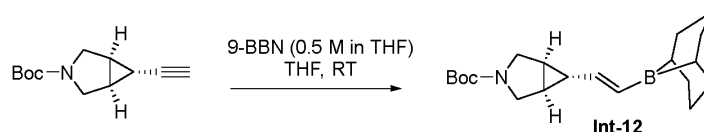
- Step-2: A stirred solution of 3-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (50 g, 204.6 mmol, 1 eq) in DMF (500 mL) was treated portionwise with NaN₃ (66.5 g, 1023.3 mmol, 5 eq) at 0 °C and the resulting reaction mixture was then stirred at 60 °C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated, the residue was dissolved in EtOAc (200 mL) and stirred for 5 min, filtered through celite bed and concentrated to yield 20 gr of 3-azido-2-methylpropan-1-ol as a pale-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm. 3.61-3.53 (m, 2H), 3.39-3.31 (m, 2H), 1.89-1.83 (m, 2H), 0.98 (d, 3H)

- Step-3: To a stirred solution of 3-azido-2-methylpropan-1-ol (18 g, 156.4 mmol, 1 eq) in MeOH (200 mL) were added 10% Pd/C (800 mg) and Boc₂O (51.2 g, 234.6 mmol, 1.5 eq) at RT under a N₂ atmosphere. The resulting reaction mixture was then stirred at RT under an hydrogen balloon atmosphere. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through a celite bed and the bed was washed with MeOH (20 mL). The filtrate was concentrated

and the residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (30-35%) to yield 12 g of tert-butyl (3-hydroxy-2-methylpropyl) carbamate as a pale-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm. 4.84 (brs, 1H), 3.58-3.52 (m, 1H), 3.36-3.25 (m, 3H), 3.07-3.00 (m, 1H), 1.77-1.75 (m, 1H), 1.47 (s, 9H), 0.88 (d, 3H).

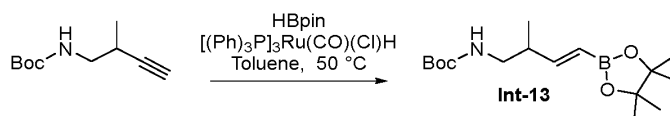
- 5 Step-4: A solution of tert-butyl (3-hydroxy-2-methylpropyl) carbamate (10 g, 48.93 mmol, 1 eq) in DCM (100 mL) was treated portion-wise with Dess-Martin periodinane (31.1 g, 73.4 mmol, 1.5 eq) at 0°C and stirred 30 minutes at 0°C. The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a saturated NaHCO₃ solution (50 mL) at 0 °C. The reaction mixture was filtered through a celite
- 10 bed, which was further washed with DCM (500 mL). The organic layer was separated, washed with brine (10 mL), dried over anhydrous Na₂SO₄ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (4-6%) to yield 6 g of tert-butyl (2-methyl-3-oxopropyl) carbamate as a colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm. 9.68 (s, 1H), 4.86 (brs, 1H), 3.37-3.26 (m, 2H), 2.65-2.60 (m, 1H),
- 15 1.45 (s, 9H), 1.24 (d, 3H)

Synthesis of **Int-12**: synthesis of tert-butyl (1S,5R,6S)-6-[(E)-2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]vinyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate



- To a stirred mixture of tert-butyl (1S,5R,6S)-6-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate
- 20 (300 mg, 1.45 mmol) in dry THF (2.9 mL) was slowly added dropwise under inert atmosphere a 0.5M 9-borabicyclo[3.3.1]nonane solution in THF (2.9 mL, 1.45 mmol, 1Eq.) and the reaction mixture was further stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was used as such in the next step as a 0.25M solution of tert-butyl(1S,5R,6S)-6-[(E)-2-(9-borabicyclo[3.3.1]nonan-9-yl)vinyl]-3-azabicyclo[3.1.0] hexane-3-carboxylate in THF.

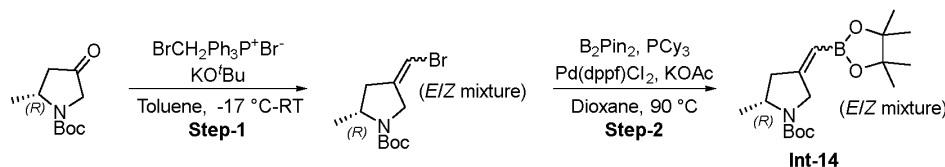
- 25 Synthesis of **Int-13**: synthesis of (E)-tert-butyl (2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) but-3-en-1-yl) carbamate (**Int-13**)



- To a stirred solution of tert-butyl (2-methylbut-3-yn-1-yl) carbamate (2.5 g, 13.64 mmol, 1 eq) in toluene (20 mL) were added pinacolborane (8.73 mL, 68.2 mmol, 5 eq) and carbonylchlorohydridotris(triphenylphosphine)ruthenium (II) (1299 mg, 1.36 mmol, 0.1 eq) at RT. The resulting reaction mixture was degassed, put under a N₂ atmosphere and then stirred at 50 °C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and

the crude residue was by column chromatography on silica gel eluting with a gradient of EtOAc in PE (4-8%) to yield 2.30 g of (*E*)-*tert*-butyl (2-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) but-3-en-1-yl) carbamate as a pale-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm. 6.47 (dd, 1H), 5.47 (dd, 1H), 4.54 (brs, 1H), 3.20-3.16 (m, 1H), 3.03-2.97 (m, 1H), 2.42-2.38 (m, 1H),
 5 1.47 (s, 9H), 1.25 (s, 12H), 1.02 (d, 3H)

Synthesis of **Int-14**: synthesis of *tert*-butyl (*R*-2-methyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)pyrrolidine-1-carboxylate (*E/Z* mixture)



Step-1: A stirred solution of (bromomethyl)triphenylphosphonium bromide (3.50 g, 8.03 mmol, 8.0
 10 eq) in toluene (20 mL), cooled to -17°C, was treated dropwise with KOtBu (1M solution in THF, 8.03 mL, 8.03 mmol, 8.0 eq) and the reaction mixture was then stirred at RT for 1.5 h. The reaction mixture was cooled again to -17 °C, treated dropwise with a solution of *tert*-butyl (*R*)-2-methyl-4-oxopyrrolidine-1-carboxylate (0.20 g, 1.00 mmol, 1.0 eq) in toluene (10 mL), stirred for 1.5 h at -17°C and then allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction
 15 mixture was quenched with a sat. NH₄Cl solution. The medium was filtered through a celite bed, the filtrate was dried over Na₂SO₄ and concentrated. Similarly, four more batches were conducted on the same scale (4 x 0.20 g) following the same procedure. All the crude compounds were combined and purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (4-5%) to yield 0.50 g of *tert*-butyl (*R*)-4-(bromomethylene)-2-methylpyrrolidine-1-
 20 carboxylate (as a *E/Z* mixture) as a pale-yellow liquid.

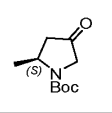
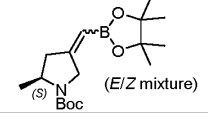
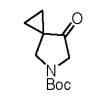
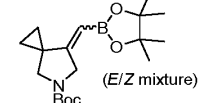
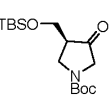
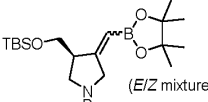
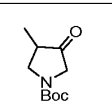
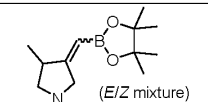
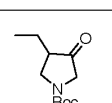
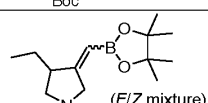
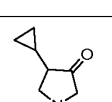
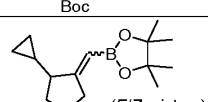
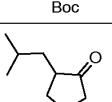
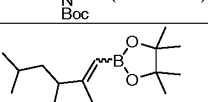
¹H NMR (400 MHz, CDCl₃) δ ppm. 6.12-6.00 (m, 1H), 4.23-3.88 (m, 3H), 2.79-2.68 (m, 1H), 2.40-2.19 (m, 1H), 1.50-1.46 (m, 9H), 1.17-1.14 (m, 3H)

Step-2: A stirred solution of *tert*-butyl (*R*)-4-(bromomethylene)-2-methylpyrrolidine-1-carboxylate (as a *E/Z* mixture) (500 mg, 1.81 mmol, 1 eq), bis(pinacolato)diboron (1.15 g, 4.53 mmol, 2.5 eq) and KOAc (444 mg, 4.53 mmol, 2.5 eq) in dioxane (30 mL) was degassed with Ar for 10 min. Later, Pd(dppf)Cl₂ (74 mg, 0.091 mmol, 0.05 eq) and PCy₃ (51 mg, 0.181 mmol, 0.1 eq) were added at RT, the mixture was further degassed with Ar for 5 min and stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled down, filtered through a celite bed and the bed was washed with EtOAc (30 mL). The filtrate was concentrated
 25 and the residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (3-5%) to yield 700 mg of *tert*-butyl (*R*)-2-methyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)pyrrolidine-1-carboxylate (as a *E/Z* mixture) as a pale-yellow gummy.
 30

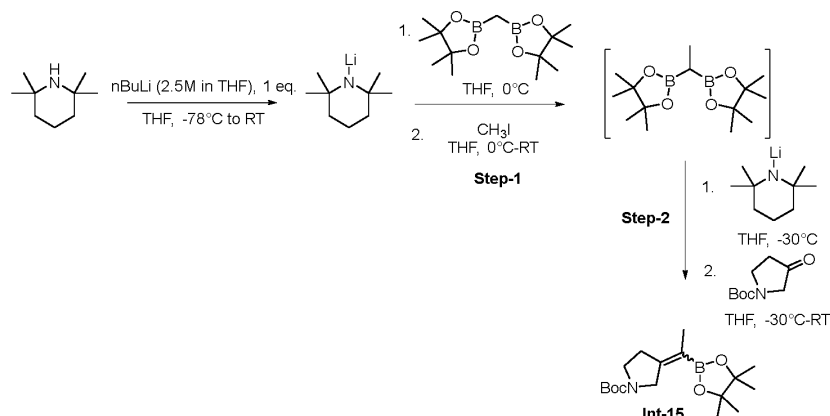
¹H NMR (400 MHz, CDCl₃) δ ppm. 5.34-5.30 (m, 1H), 4.19-3.94 (m, 3H), 2.94-2.81 (m, 1H), 2.68-2.21 (m, 1H), 1.51-1.46 (m, 9H), 1.26-1.24 (m, 12H), 1.18-1.10 (m, 3H)

The following compounds were prepared in a manner similar to **Int-14** (by use of appropriate ketone reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

5

Reagent step-1	Product	¹ H NMR (400 MHz, CDCl ₃) δ ppm
		5.34-5.30 (m, 1H), 4.19-3.94 (m, 3H), 2.94-2.81 (m, 1H), 2.68-2.21 (m, 1H), 1.51-1.46 (m, 9H), 1.26-1.24 (m, 12H), 1.18-1.10 (m, 3H)
		4.68 (t, 1H), 4.45-4.38 (m, 2H), 3.45-3.42 (m, 2H), 1.48 (s, 9H), 1.26 (s, 12H), 0.96-0.91 (m, 4H)
		5.36-5.32 (m, 1H), 4.23-3.80 (m, 3H), 3.48-3.34 (m, 4H), 1.48 (s, 9H), 1.26 (s, 12H), 0.89 (s, 9H), 0.04 (s, 6H)
		4.96-4.94 (m, 1H), 4.06-3.91 (m, 2H), 3.77-3.69 (m, 1H), 2.95-2.88 (m, 1H), 2.72 (brs, 1H), 1.47 (s, 9H), 1.26 (s, 12H), 1.14 (d, 3H)
		5.30-5.27 (m, 1H), 4.25-3.80 (m, 2H), 3.70-3.40 (m, 1H), 3.20-3.04 (m, 1H), 2.60 (brs, 1H), 1.70-1.62 (m, 1H), 1.46 (s, 9H), 1.40-1.30 (m, 1H), 1.26 (s, 12H), 0.93 (t, 3H)
		5.62 (m, 1H), 4.23-4.10 (m, 2H), 4.09-3.60 (m, 2H), 1.99-1.96 (m, 1H), 1.48 (s, 9H), 1.26 (s, 12H), 0.72-0.62 (m, 2H), 0.58-0.41 (m, 2H), 0.28-0.19 (m, 1H)
		5.28-5.27 (m, 1H), 4.25-4.19 (m, 2H), 3.70-3.60 (m, 1H), 2.99 (brs, 1H), 2.73 (brs, 1H), 1.69-1.52 (m, 3H), 1.48 (s, 9H), 1.24 (s, 12H), 0.96-0.89 (m, 6H)

Synthesis of **Int-15**: synthesis of *tert*-butyl 3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)pyrrolidine-1-carboxylate ((*E/Z* mixture))

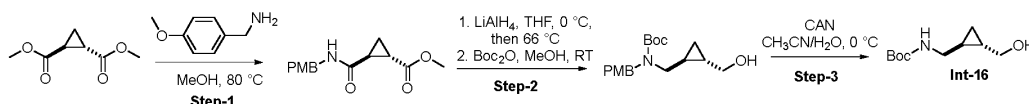


Step-1: A stirred solution of 2,2,6,6-tetramethylpiperidine (4.00 g, 28.37 mmol, 1 eq) in THF (80 mL), at -78°C, was treated with n-BuLi (2.5M solution in hexane, 13.62 mL, 34.04 mmol, 1.2 eq) and then allowed to room temperature over 30 min. The reaction medium, at 0°C, was then treated with a solution of bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (8.0 g, 28.37 mmol, 1 eq) in THF (50 mL) and stirred for 10 min. Then, iodomethane (1.77 mL, 28.37 mmol, 1 eq) was added dropwise at 0 °C and the resulting reaction mixture was allowed to RT and stirred for 1 h, then used as such in the next step.

Step-2: A stirred solution of 2,2,6,6-tetramethylpiperidine (4.41 g, 31.21 mmol, 1 eq) in THF (50 mL) was cooled down to -78°C, treated with n-BuLi (2.5M solution in hexane, 13.00 mL, 34.04 mmol, 1.2 eq) and allowed to room temperature over 30 min. The reaction mixture was cooled to -30°C, treated with above reaction mixture from step 1 (i.e. crude 2,2'-(ethane-1,1-diyl) bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane), stirred for 30 minutes and then treated with a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (5.26 g, 28.37 mmol, 1 eq) in THF (30 mL), still at -30 °C. Reaction mixture was then allowed to RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0 °C and quenched with a sat. NH₄Cl solution. The solids were filtered off and the filtrate was concentrated. The crude material was diluted with water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated. The crude residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in ether (6-7%) to yield 1.3 g of *tert*-butyl 3-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) ethylidene) pyrrolidine-1-carboxylate (as a *E/Z* mixture) as an off-white gummy residue.

¹H NMR (400 MHz, CDCl₃) δ ppm. 4.21-3.94 (m, 2H), 3.47 (brs, 2H), 2.85-2.56 (m, 2H), 1.70 (s, 3H), 1.48 (s, 9H), 1.23 (s, 12H)

Synthesis of **Int-16**: synthesis of *tert*-butyl *N*-[[*rel*-(1*S*,2*S*)-2-(hydroxymethyl) cyclopropyl] methyl]carbamate

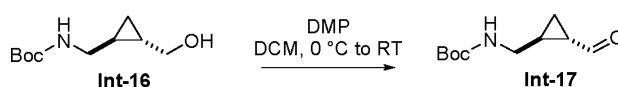


Step-1: A mixture of dimethyl trans-1,2-cyclopropanedicarboxylate (2.88 g, 17.45 mmol, 1 eq) and (4-methoxyphenyl)methanamine (4.18 g, 29.85 mmol, 1.7 eq) in MeOH (10 mL) was stirred at 80°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled down and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of Et₂O in DCM (10-100%) to yield 2.21 g of methyl rel-(1S,2S)-2-[(4-methoxyphenyl)methylcarbamoyl]cyclopropanecarboxylate (2.21 g, 48 %) as a white solid.

Step-2: A solution of methyl rel-(1S,2S)-2-[(4-methoxyphenyl)methylcarbamoyl]cyclopropane carboxylate (735 mg, 2.79 mmol) in THF (12 mL) was cooled to 0°C and treated dropwise with a 2.4 M LiAlH₄ solution in THF (3.5 mL, 8.40 mmol, 3 eq). The mixture was stirred at 0 °C for 30 min and then at 66°C. In total, 3 batches were run following the same conditions and amounts. After completion of the reaction (TLC monitoring), the reaction mixture of the three vials were cooled down and diluted with 100 mL of THF. The reaction mixture was then quenched by addition of NaSO₄·10H₂O (33 g), stirred overnight at RT and then was filtered. The filtrate was dried over MgSO₄ and concentrated. The residue was dissolved in MeOH (25 mL) and Boc₂O (2.10 g, 9.21 mmol, 1.1 eq) was added. The reaction mixture was stirred at RT for 30 min and then concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of DCM in Et₂O (10-100%) to yield 2.38 g of tert-butyl N-[(4-methoxyphenyl)methyl]-N-[[rel-(1S,2S)-2-(hydroxymethyl)cyclopropyl]methyl]carbamate as an oily residue. LC-MS (LC-N): r.t. = 1.44 min ; m/z 344 [M+H+Na]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 7.15 (d, 2 H), 6.89 (d, 2 H), 4.48-4.31 (m, 3 H), 3.73 (s, 3 H), 3.20 (brs, 2 H), 3.13-3.02 (m, 1 H), 1.41 (brs, 9 H), 0.90-0.67 (m, 2 H), 0.33- 0.22 (m, 2 H)

Step-3: A solution of tert-butyl N-[(4-methoxyphenyl)methyl]-N-[[rel-(1S,2S)-2-(hydroxymethyl)cyclopropyl]methyl]carbamate (2.36 g, 7.35 mmol) in MeCN (70 mL), cooled to 0°C, was treated dropwise with a solution of ammonium cerium (IV) nitrate (12.33 g, 22.04 mmol, 3 eq) in H₂O (34 mL). After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted 3 times with DCM. The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of Et₂O in DCM (10-100%) to yield 1.35 g of tert-butyl N-[[rel-(1S,2S)-2-(hydroxymethyl)cyclopropyl]methyl]carbamate as an oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 6.80 (brs, 1 H), 4.39 (t, 1 H), 3.22 (t, 2 H), 2.88-2.73 (m, 2 H), 1.43-1.32 (m, 8 H), 0.83-0.67 (m, 2 H), 0.34-0.23 (m, 2 H)

Synthesis of Int-17: synthesis of tert-butyl N-[[rel-(1S,2S)-2-formylcyclopropyl]methyl]carbamate



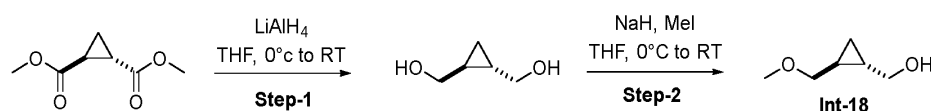
A solution of *tert*-butyl *N*-[[*rel*-(1*S*,2*S*)-2-(hydroxymethyl)cyclopropyl] methyl]carbamate (1.35 g, 6.55 mmol) in DCM (50.0 mL), cooled to 0 °C, was treated portionwise with Dess-martin periodinane (3.22 g, 7.20 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 10 minutes and then allowed to RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM and washed with an aq. saturated solution of NaHCO₃. The organic layer was then dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in heptane (10-100%) to yield 1.23 g of *tert*-butyl *N*-[[*rel*-(1*S*,2*S*)-2-formylcyclopropyl]methyl]carbamate as an oily residue.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm. 8.86 (d, 1 H), 7.00 (brs, 1 H), 3.03 (dt, 1 H), 2.93-2.76 (m, 1 H), 1.74-1.66 (m, 1 H), 1.66-1.58 (m, 1 H), 1.38 (s, 9 H), 1.21 (dt, 1 H), 1.00 (ddd, 1 H).

The following compounds were prepared in a manner similar to **Int-17** (by use of appropriate starting alcohol reagent, solvent, reaction temperature and purification methods known to the person skilled in the art).

Alcohol reagent	Product	¹ H NMR (400 MHz, CDCl ₃) δ ppm
		9.11 (s, 1H), 7.65-7.64 (m, 5H), 7.45-7.36 (m, 5H), 3.95 (s, 2H), 1.14 (t, 2H), 1.10 (t, 2H), 1.06 (s, 9H)
		8.88 (d, 1 H), 4.72 (t, 1 H), 3.53-3.43 (m, 1 H), 3.33-3.25 (m, 1 H), 1.77-1.64 (m, 2 H), 1.29-1.17 (m, 1 H), 1.03 (td, 1 H)
		8.89 (d, 1 H), 3.41-3.33 (m, 2 H), 3.25-3.19 (m, 4 H), 1.80-1.69 (m, 2 H), 1.27 (dt, 1 H), 1.04 (ddd, 1 H)
		3.74 (brs, 1H), 3.49-3.44 (m, 2H), 3.34-3.32 (m, 1H), 2.94-2.93 (m, 1H), 2.86 (s, 3H), 1.82 (brs, 1H), 1.46 (s, 9H), 0.96 (d, 3H)
		9.69 (d, 1H), 4.83 (brs, 1H), 3.38-3.28 (m, 2H), 2.47-2.46 (m, 1H), 1.80-1.69 (m, 1H), 1.54-1.52 (m, 1H), 1.46 (s, 9H), 1.01 (t, 3H)
		9.28 (s, 1H), 3.96 (d, 1H), 3.54-3.49 (m, 2H), 3.02-2.92 (m, 1H), 2.10-1.98 (m, 1H), 1.91-1.76 (m, 4H), 1.45 (s, 9H)
		9.47 (d, 1H), 3.79 (d, 1H), 3.42-3.31 (m, 2H), 2.78 (s, 3H), 2.78-2.73 (m, 1H), 2.19-2.09 (m, 2H), 2.05-1.88 (m, 3H)
		9.20 (d, 1H), 4.97 (d, 1H), 4.28-4.23 (m, 1H), 3.00 (s, 3H), 2.33-2.30 (m, 1H), 2.08-2.02 (m, 3H), 1.97-1.93 (m, 2H), 1.12-1.06 (m, 1H)
		9.22 (d, 1H), 4.30 (t, 1H), 2.34-2.31 (m, 1H), 2.15-2.08 (m, 2H), 2.00 (t, 2H), 1.85-1.81 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H)
		(DMSO- <i>d</i> ₆): 8.88 (d, 1 H), 3.46 (t, 2 H), 3.42 (dd, 1 H), 3.28 (dd, 1 H), 2.38 (t, 2 H), 2.14 (s, 6 H), 1.80-1.68 (m, 2 H), 1.27 (dt, 1 H), 1.04 (ddd, 1 H)

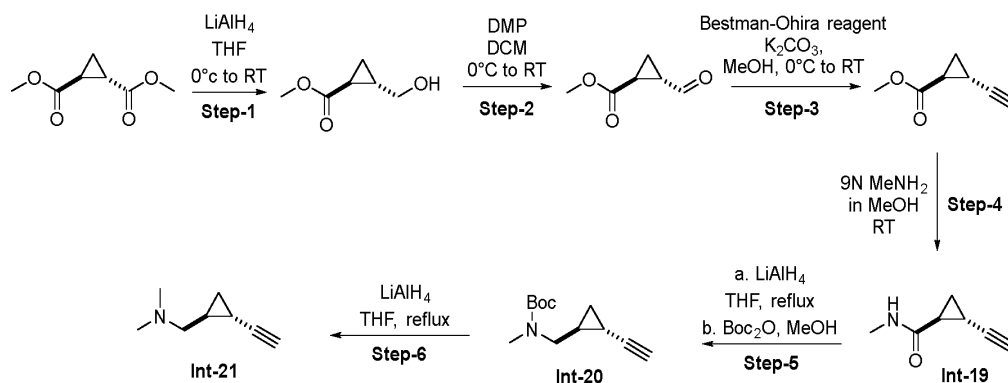
Synthesis of **Int-18**: synthesis of [*rel*-(1*S*,2*S*)-2-(methoxymethyl)cyclopropyl]methanol



Step-1: A solution of dimethyl *rel*-(1*S*,2*S*)-cyclopropane-1,2-dicarboxylate (3.12 g, 18.94 mmol, 1 eq) in THF (35 mL) was cooled to 0 °C and treated dropwise over 10 minutes with a 2.4M solution of LiAlH₄ in THF (11.0 mL, 26.40 mmol, 1.4). The mixture was stirred at 0 °C for 30 min and then allowed to RT. After completion of the reaction (TLC monitoring), the mixture was diluted with 100 mL of THF and quenched by addition of Na₂SO₄·10H₂O sodium (30.82 g, 94.69 mmol, 5 eq). The mixture was stirred for 2 hours at RT, solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in EtOAc (1-8%) to yield 1.86 g of [*rel*-(1*S*,2*S*)-2-(hydroxymethyl)cyclopropyl]methanol as an yellowish oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 4.38 (t, 2 H), 3.29 (dt, 2 H), 3.20 (dt, 2 H), 0.85-0.73 (m, 2 H), 0.29 (t, 2 H).

Step-2: To a solution of [*rel*-(1*S*,2*S*)-2-(hydroxymethyl)cyclopropyl]methanol (0.93 g, 9.11 mmol, 1 eq) in THF (9 mL), cooled in an ice bath, was added NaH (60% w/w in mineral oil, 437 mg, 10.93 mmol, 1.2 eq). The mixture was stirred at 0 °C for 30 min then treated dropwise with CH₃I (1.1 mL, 18.21 mmol, 2 eq). The mixture was stirred at 0 °C for 30 min and then overnight at RT. The reaction mixture was then diluted with water and extracted three times with EtOAc. The combined organic extracts were dried over MgSO₄, solids were filtered off and filtrate was concentrated (caution : volatile compound). The residue was purified by column chromatography on silica gel eluting with a gradient of Et₂O in pentane (50-100%) to yield 487 mg of [*rel*-(1*S*,2*S*)-2-(methoxymethyl)cyclopropyl]methanol as an oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 4.45 (t, 1 H), 3.26 (t, 2 H), 3.22 (s, 3 H), 3.17 (dd, 2 H), 0.90-0.77 (m, 2 H), 0.40-0.34 (m, 1 H), 0.33-0.27 (m, 1 H).

Synthesis of **Int-19** *rel*-(1*S*,2*S*)-2-ethynyl-*N*-methyl-cyclopropanecarboxamide, **Int-20** *rel*-(*tert*-butyl *N*-methyl-*N*-[[(1*S*,2*S*)-2-ethynylcyclopropyl]methyl]carbamate) and **Int-21** *rel*-(*N,N*-dimethyl-1-[(1*S*,2*S*)-2-ethynylcyclopropyl]methanamine):



Step-1: A solution of dimethyl *rel*-(1*S*,2*S*)-cyclopropane-1,2-dicarboxylate (3.17 g, 19.42 mmol, 1 eq) in THF (12 mL), cooled in an ice bath, was treated dropwise over 10 minutes with a 2.4 M solution of LiAlH₄ in THF (4.0 mL, 9.71 mmol, 0.5 eq). The mixture was stirred at 0 °C for 30 min and then allowed to RT. After completion of the reaction (TLC monitoring), the mixture was diluted

with 100 mL of THF and quenched by addition of Na₂SO₄·10H₂O (31.60 g, 97.09 mmol, 5 eq). The mixture was stirred for 2 hours at RT, solids were filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in EtOAc (1-8%) to yield 1.39 g of methyl *rel*-(1*S*,2*S*)-2-(hydroxymethyl)cyclopropanecarboxylate as a yellowish oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 4.67 (t, 1 H), 3.59 (s, 3 H), 3.45 (dt, 1 H), 3.24 (dt, 1 H), 1.55 (dt, 1 H), 1.51-1.42 (m, 1 H), 0.98 (dt, 1 H), 0.87 (ddd, 1 H)

Step-2: A solution of methyl *rel*-(1*S*,2*S*)-2-(hydroxymethyl)cyclopropanecarboxylate (1.23 g, 9.41 mmol, 1 eq) in DCM (50 mL), cooled to 0°C, was treated portionwise with Dess-martin periodinane (4.62 g, 10.35 mmol, 1.1 eq). The reaction mixture was stirred at 0 °C for 10 minutes and then allowed to RT. After completion of the reaction (TLC monitoring), the reaction mixture was filtered on celite. The filtrate was washed with a 1M aq. solution of Na₂CO₃ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in heptane (7-75%) to yield 0.72 g of methyl *rel*-(1*S*,2*S*)-2-formylcyclopropanecarboxylate as an oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 9.01 (d, 1 H), 3.64 (s, 3 H), 2.36 (td, 1 H), 2.21 (dtd, 1 H), 1.59-1.54 (m, 1 H), 1.48 (ddd, 1 H).

Step-3: To a stirred solution methyl *rel*-(1*S*,2*S*)-2-formylcyclopropanecarboxylate (703 mg, 5.49 mmol, 1 eq) and dimethyl(1-diazo-2-oxopropyl)phosphonate (0.953 mL, 6.22 mmol, 1.13 eq) in MeOH (20 mL), cooled to 0°C, was added K₂CO₃ (1.53 g, 11.04 mmol, 2 eq). The mixture was stirred at 0°C for 1 hour and then allowed to warm to RT. After completion of the reaction (TLC monitoring), the solids were filtered off, the filtrate was diluted with water (10 mL) and the mixture was extracted with n-pentane. The combined organic extracts were dried over MgSO₄, solids were filtered off and filtrate was concentrated (caution : volatile compound). The residue was purified by column chromatography on silica gel eluting with a gradient of Et₂O in pentane (5-60%) to yield 591 mg of methyl *rel*-(1*S*,2*S*)-2-ethynylcyclopropanecarboxylate as a colorless oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 3.63 (s, 3 H), 2.89 (d, 1 H), 1.95 (ddd, 1 H), 1.84-1.77 (m, 1 H), 1.30-1.19 (m, 2 H).

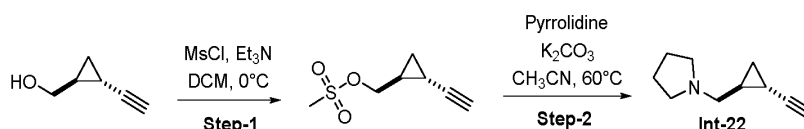
Step-4: A solution of methyl *rel*-(1*S*,2*S*)-2-ethynylcyclopropanecarboxylate (271 mg, 2.18 mmol, 1 eq) and a 9 M methanolic solution of methylamine (10.0 mL, 20.00 mmol, 9.2 eq) was stirred at RT for 24 hours and then was concentrated under reduced pressure to afford 196 mg of crude *rel*-(1*S*,2*S*)-2-ethynyl-*N*-methyl-cyclopropanecarboxamide as a brown solid, which was used as such in the next step. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 8.18 (m, 1 H), 2.76 (d, 1 H), 2.60 (d, 3 H), 1.84 (ddd, 1 H), 1.59-1.52 (m, 1 H), 1.10 (m, 1 H), 0.98 (m, 1 H).

Step-5: A solution of *rel*-(1*S*,2*S*)-2-ethynyl-*N*-methyl-cyclopropanecarboxamide (190 mg, 1.54 mmol, 1 eq) in THF (8 mL) was cooled to 0°C and treated dropwise with a 2.4M solution of LiAlH₄ in THF (1.0 mL, 2.40 mmol, 1.55 eq). The mixture was stirred at 0 °C for 30 min and then stirred at 66°C. After completion of the reaction (TLC monitoring), the mixture was cooled down

to RT, diluted with 30 mL of THF and quenched by addition of Na₂SO₄·10H₂O sodium (7.00 g, 21.51 mmol, 14 eq). The mixture was stirred overnight at RT and solids were filtered off. The filtrate was dried over MgSO₄ and concentrated under reduced pressure. The residue was resuspended in MeOH (5 mL), treated with Boc₂O (370 mg, 1.70 mmol, 1.1 eq) and the reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with a gradient of Et₂O in n-pentane (5-100%) to yield 212 mg of *rel-tert-butyl N-methyl-N-[(1S,2S)-2-ethynylcyclopropyl]methyl]carbamate* as an oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 3.12 (dd, 1 H), 3.01 (dd, 1 H), 2.82 (s, 3 H), 2.65 (s, 1 H), 1.40 (s, 9 H), 1.31-1.18 (m, 2 H), 0.83-0.76 (m, 1 H), 0.72 (td, 1 H).

Step-6: A solution of *rel-tert-butyl N-methyl-N-[(1S,2S)-2-ethynylcyclopropyl] methyl]carbamate* (270 mg, 1.29 mmol) in THF (8 mL) was cooled to 0 °C and treated dropwise with a 2.4M solution of LiAlH₄ in THF (1.5 mL, 3.60 mmol, 2.8 eq). The mixture was stirred at 0 °C for 30 min and then stirred at 66 °C. After completion of the reaction (TLC monitoring), the mixture was cooled down to RT, diluted with 30 mL of THF and quenched by addition of Na₂SO₄·10H₂O sodium (5.85 g, 17.99 mmol, 14 eq). The mixture was stirred overnight at RT and solids were filtered off. The filtrate was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (2-16%) to yield 101 mg of *rel-N,N-dimethyl-1-[(1S,2S)-2-ethynylcyclopropyl]methanamine* as an oily residue. ¹H NMR (400 MHz, DMSO-d₆) δ ppm. 2.62 (d, 1 H), 2.23 (dd, 1 H), 2.16 (s, 6 H), 2.00 (dd, 1 H), 1.12-1.04 (m, 2 H), 0.83-0.76 (m, 1 H), 0.64-0.57 (m, 1 H).

Synthesis of **Int-22** *rel-1-(((1S,2S)-2-ethynylcyclopropyl)methyl)pyrrolidine*:

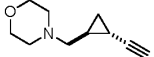
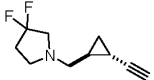
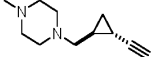


Step-1: To a solution of *rel-(1S,2S)-2-ethynylcyclopropyl]methanol* (440 mg, 4.58 mmol, 1 eq) in DCM (12 mL), cooled at 0 °C, were added sequentially Et₃N (0.96 mL, 6.87 mmol, 1.5 eq) and mesyl chloride (0.375 mL, 4.81 mmol, 1.05 eq). The mixture was stirred at 0 °C for 2 hours and then was diluted in DCM. The mixture was washed with a 1N aq. Na₂CO₃ solution, dried over MgSO₄ and concentrated to afford 708 mg of *rel-(1S,2S)-2-ethynylcyclopropyl]methyl methanesulfonate* as an oily residue, which was used as such in the next step.

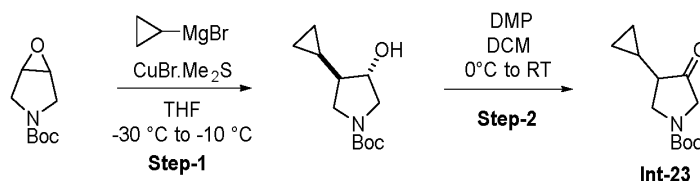
Step-2: A mixture of *rel-(1S,2S)-2-ethynylcyclopropyl]methyl methanesulfonate* (236 mg, 1.35 mmol), pyrrolidine (0.337 mL, 4.06 mmol, 3 eq) and K₂CO₃ (187 mg, 1.35 mmol, 1 eq) in CH₃CN (8 mL) was stirred at 60 °C. After completion of the reaction (TLC monitoring), the mixture was cooled down to RT, partitioned between DCM and water. The organic layer was dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel

eluting with a gradient of 3N methanolic NH₃ solution in DCM (1-8%) to yield 175 mg of *rel*-1-(((1*S*,2*S*)-2-ethynylcyclopropyl)methyl)pyrrolidine as an oily residue. ¹H NMR (400 MHz, CDCl₃) δ ppm. 2.62-2.49 (m, 4 H), 2.44 (dd, 1 H), 2.26 (dd, 1 H), 1.86-1.75 (m, 5 H), 1.38-1.27 (m, 1 H), 1.10-1.03 (m, 1 H), 0.97-0.89 (m, 1 H), 0.66 (ddd, 1 H).

- 5 The following compounds were prepared in a manner similar to **Int-22** (by use of appropriate reagents, solvent, reaction temperature and purification methods known to the person skilled in the art):

Reagent step-2	Solvent, base, and temperature step-2	Product step-2	¹ H NMR (400 MHz) δ ppm
	CH ₃ CN, K ₂ CO ₃ , 50°C		DMSO-d ₆ , δ ppm: 3.57 (t, 4 H), 2.63 (d, 1 H), 2.39 (q, 4 H), 2.31 (dd, 1 H), 2.08 (dd, 1 H), 1.15-1.08 (m, 2 H), 0.83-0.77 (m, 1 H), 0.66-0.58 (m, 1 H)
	CH ₃ CN, K ₂ CO ₃ , 85°C		ND
	CH ₃ CN, K ₂ CO ₃ , 60°C		CDCl ₃ , δ ppm: 2.85-2.36 (m, 8 H), 2.39 (dd, 1 H), 2.30 (s, 3 H), 2.20 (dd, 1 H), 1.80 (d, 1 H), 1.31-1.21 (m, 1 H), 1.08-1.00 (m, 1 H), 0.97-0.99 (m, 1 H), 0.64 (ddd, 1 H)

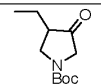
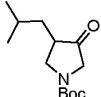
Synthesis of **Int-23**: synthesis of *tert*-butyl-3-cyclopropyl-4-oxopyrrolidine-1-carboxylate



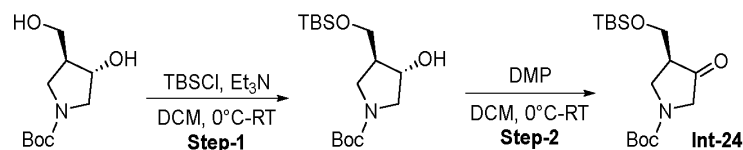
- 10 Step-1: To a stirred solution of *tert*-butyl 6-oxa-3-azabicyclo[3.1.0]hexane-3-carboxylate (5.0 g, 27.00 mmol, 1.0 eq) in THF (200 mL), cooled to -30°C, was added CuBr.Me₂S (1.11 g, 5.40 mmol, 0.2 eq). Then, a 0.5 M solution of cyclopropyl magnesium bromide in THF (205 mL, 102.5 mmol, 3.8 eq) was added dropwise to the reaction mixture at -30 °C. The resulting reaction mixture was allowed to warm to -10°C and stirred at this temperature. After completion of the reaction (TLC
- 15 monitoring), the mixture was quenched with a sat. aq. NH₄Cl solution (100 mL) and extracted twice with EtOAc. The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient EtOAc in PE (25-35%) to yield 6.0 g of *tert*-butyl-3-cyclopropyl-4-hydroxypyrrolidine-1-carboxylate as a pale-yellow gummy residue.
- 20 ¹H NMR (400 MHz, CDCl₃) δ ppm. 4.24-4.19 (m, 1H), 3.70-3.54 (m, 2H), 3.31-3.17 (m, 2H), 1.80 (s, 1H), 1.48 (s, 9H), 1.47-1.43 (m, 1H), 0.63-0.46 (m, 3H), 0.29-0.26 (m, 1H), 0.16-0.12 (m, 1H). Step-2: To a stirred solution of *tert*-butyl-3-cyclopropyl-4-hydroxypyrrolidine-1-carboxylate (6.0 g, 26.40 mmol, 1.0 eq) in DCM (90 mL) was added Dess-Martin periodinane (16.80 g, 39.60 mmol, 1.5 eq) portion-wise at 0°C. The resulting reaction mixture was then stirred at RT. After completion

of the reaction (TLC monitoring), the reaction mixture was filtered through a celite be and the bed was washed with DCM (100 mL). The filtrate was washed with a sat. aq. NaHCO₃ solution (2x150 mL) and extracted with DCM. The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient EtOAc in PE (15-25%) to yield 5 g of *tert*-butyl-3-cyclopropyl-4-oxopyrrolidine-1-carboxylate as a pale-yellow oily residue. ¹H NMR (400 MHz, CDCl₃) δ ppm. 3.95-3.72 (m, 3H), 3.41-3.37 (m, 1H), 2.13-2.11 (m, 1H), 1.48 (s, 9H), 0.92-0.86 (m, 1H), 0.66-0.64 (m, 1H), 0.53-0.48 (m, 1H), 0.42-0.38 (m, 1H), 0.24-0.21 (m, 1H).

The following compounds were prepared in a manner similar to **Int-23** (by use of appropriate reagents, solvent, reaction temperature and purification methods known to the person skilled in the art):

Reagents step-1	Product	¹ H NMR (400 MHz, CDCl ₃) δ ppm
CuI, EtMgBr		4.05 (brs, 1H), 3.90-3.85 (m, 1H), 3.70-3.65 (m, 1H), 3.32-3.27 (m, 1H), 2.52-2.49 (m, 1H), 1.86-1.80 (m, 1H), 1.49 (s, 9H), 1.47-1.43 (m, 1H), 0.98 (t, 3H)
CuBr.Me ₂ S, ⁱ BuMgCl		4.05 (brs, 1H), 3.94-3.87 (m, 1H), 3.69-3.64 (m, 1H), 3.24-3.19 (m, 1H), 2.61-2.59 (m, 1H), 1.74-1.63 (m, 2H), 1.49 (s, 9H), 1.30-1.23 (m, 1H), 0.94-0.88 (m, 6H)

Synthesis of **Int-24**: synthesis of *tert*-butyl (3*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-oxopyrrolidine-1-carboxylate.



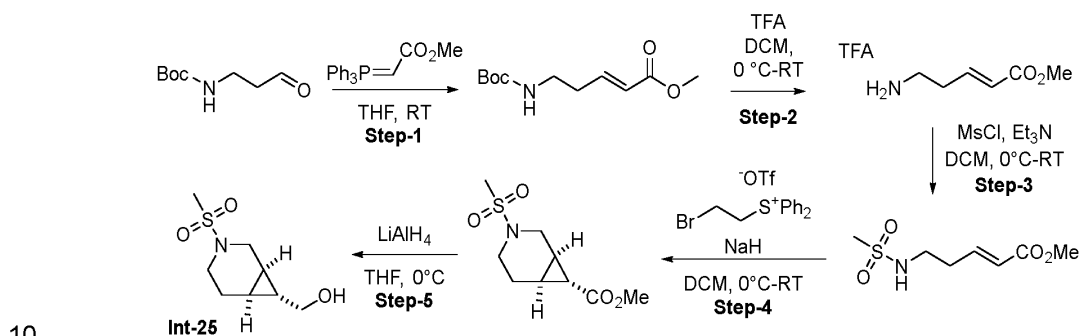
Step-1: To a stirred solution of *tert*-butyl (3*S*,4*S*)-3-hydroxy-4-(hydroxymethyl) pyrrolidine-1-carboxylate (2.0 g, 9.21mmol, 1.0 eq) and Et₃N (5.12 mL, 36.82 mmol, 4.0 eq) in DCM (30 mL), cooled at 0°C, was added *tert*-butylchlorodimethylsilane (2.78 g, 18.41 mmol, 2.0 eq). After addition, the resulting reaction mixture was allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude product was purified by column chromatography eluting with a gradient of EtOAc (10-20%) in PE to afford 2.1 g *tert*-butyl (3*S*,4*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxypyrrolidine-1-carboxylate. LC-MS (LC-W): r.t. = 2.53 min; m/z = 332 [M⁺H]⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.21 (brs, 1H), 4.49-3.76 (m, 4H), 3.25-3.16 (m, 1H), 3.09-3.02 (m, 1H), 2.58-2.52 (m, 1H), 2.28-2.25 (m, 1H), 1.44 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H).

Step-2: To a stirred solution of *tert*-butyl (3*S*,4*S*)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxypyrrolidine-1-carboxylate (2.1 g, 6.33 mmol, 1.0 eq) in DCM (30 mL), cooled at 0 °C, was added Dess-Martin periodinane (6.72 g, 15.84 mmol, 2.5 eq) portionwise. After addition, the resulting reaction mixture was allowed to stir at RT. After completion (TLC monitoring), the

reaction mixture was diluted with an aq. sat. NaHCO₃ solution and extracted with DCM (3x30 mL). The combined organic extracts were washed with water, brine, then dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column on silica gel eluting with a gradient of EtOAc (5-10%) in PE to afford 1.8 g of tert-butyl (S)-3-(((tert-butyl

5 dimethyldimethylsilyl)oxy)methyl)-4-oxopyrrolidine-1-carboxylate.
 1H NMR (400 MHz, CDCl₃) δ ppm 4.01-3.94 (m, 2H), 3.84-3.66 (m, 4H), 2.69-2.65 (m, 1H), 1.48 (s, 9H), 0.85 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H).

Synthesis of **Int-25**: synthesis of *rel*-((1*R*,6*S*,7*R*)-3-(methylsulfonyl)-3-azabicyclo[4.1.0]heptan-7-yl)methanol.



Step-1: To a stirred solution of *tert*-butyl (3-oxopropyl)carbamate (10 g, 57.7 mmol, 1.0 eq) in THF (150 mL) was added methyl (triphenylphosphoranylidene)acetate (23.17 g, 69.3 mmol, 1.2 eq) and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was filtered and the filtrate was concentrated. The crude product

was purified by column chromatography on silica gel eluting with a gradient of EtOAc (15-20%) in PE to yield 7.0 g of methyl (*E*)-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate as a pale yellow gummy. 1H NMR (400 MHz, CDCl₃) δ ppm: 6.90 (dt, 1H), 5.89 (dt, 1H), 4.58 (brs, 1H), 3.73 (s, 3H), 3.27 (q, 2H), 2.41 (q, 2H), 1.44 (s, 9H).

Step-2: To a stirred solution of methyl (*E*)-5-((*tert*-butoxycarbonyl)amino)pent-2-enoate (4.0 g, 17.45 mmol, 1.0 eq) in DCM (60 mL) was added trifluoroacetic acid (13.35 mL, 174.46 mmol, 10.0 eq) at 0°C. The resulting reaction mixture was then left stirring at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure and the residue was triturated with PE. The solid material was collected by filtration and dried to afford 4.30 g of methyl (*E*)-5-aminopent-2-enoate 2,2,2-trifluoroacetate.

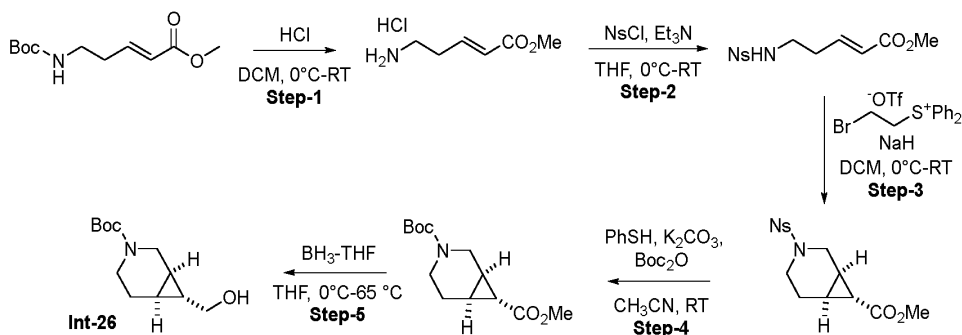
Step-3: A stirred solution of methyl (*E*)-5-aminopent-2-enoate 2,2,2-trifluoroacetate (4.30 g, 17.68 mmol, 1.0 eq) and Et₃N (12.3 mL, 88.41 mmol, 5.0 eq) in DCM (60 mL) at 0°C were treated with methanesulfonyl chloride (2.74 mL, 35.34 mmol, 2.0 eq). After addition, the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture

was diluted with water (30 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (40-50%) in PE to afford 1.90 g of methyl (*E*)-5-(methylsulfonamido)pent-2-enoate as a pale-brown gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.88 (dt, 1H), 5.94 (dt, 1H), 4.31 (brs, 1H), 3.75 (s, 3H), 3.30 (q, 2H), 2.97 (s, 3H), 2.54-2.48 (qd, 2H).

Step-4: To a stirred solution of (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (5.08 g, 11.46 mmol, 1.25 eq) in DCM (30 mL), cooled to 0 °C, was added NaH (60% w/w in mineral oil, 770 mg, 32.09 mmol, 3.5 eq). The resulting reaction mixture was stirred at 0 °C for 15 min and then treated dropwise with a solution of methyl (*E*)-5-(methylsulfonamido)pent-2-enoate (1.90 g, 9.17 mmol, 1.0 eq) in DCM (8 mL). After addition, the reaction mixture was allowed to warm up and stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0 °C, quenched with AcOH (5 mL), diluted with water (30 mL) and extracted with DCM (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (40-70%) in PE to yield 700 mg of *rel*-methyl (1*R*,6*S*,7*R*)-3-(methylsulfonyl)-3-azabicyclo[4.1.0]heptane-7-carboxylate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.76 (d, 1H), 3.68 (s, 3H), 3.37-3.27 (m, 2H), 2.77 (s, 3H), 2.76-2.70 (m, 1H), 2.14-2.10 (m, 1H), 1.98-1.92 (m, 1H), 1.80-1.74 (m, 3H).

Step-5: To a stirred solution of *rel*-methyl (1*R*,6*S*,7*R*)-3-(methylsulfonyl)-3-azabicyclo[4.1.0]heptane-7-carboxylate (6, 700 mg, 3.0 mmol, 1.0 eq) in THF (15 mL), was added dropwise at 0 °C a 2M THF solution of LiAlH₄ (3 mL, 6.0 mmol, 2.0 eq) and the resulting reaction mixture was stirred at 0 °C. After completion of the reaction, the reaction mixture was quenched by dropwise addition of a sat. NH₄Cl aq. solution, stirred for 30 min at RT, and then filtered on celite. The celite pad was washed with EtOAc. The filtrate was washed with water, then brine, dried over anhydrous Na₂SO₄ and concentrated to afford 450 mg of *rel*-((1*R*,6*S*,7*R*)-3-(methylsulfonyl)-3-azabicyclo[4.1.0]heptan-7-yl)methanol as a pale brown liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.64 (d, 1H), 3.54-3.48 (m, 2H), 3.35 (dd, 1H), 3.24-3.19 (m, 1H), 2.82-2.76 (m, 1H), 2.75 (s, 3H), 2.13-2.07 (m, 1H), 1.90-1.84 (m, 1H), 1.36 (brs, 1H), 1.18-1.11 (m, 1H), 1.09-1.01 (m, 2H).

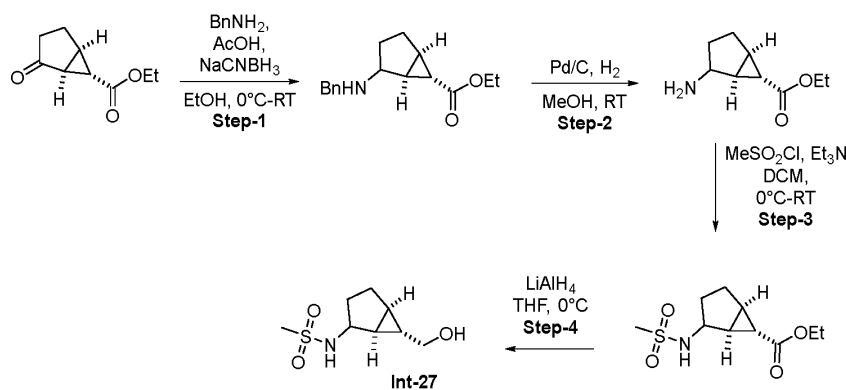
Synthesis of Int-26: synthesis of *rel*-tert-butyl (1*R*,6*S*,7*R*)-7-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate.



- Step-1: A stirred solution of methyl (*E*)-5-((tert-butoxycarbonyl)amino)pent-2-enoate (15 g, 65.42 mmol, 1.0 eq) in DCM (150 mL), cooled to 0°C, was treated with a 4M HCl solution in dioxane (164 mL, 656 mmol, 10.0 eq). The resulting reaction mixture was allowed to warm up and was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The residue was triturated with Et₂O to yield 10.0 g of methyl (*E*)-5-aminopent-2-enoate hydrochloride as a pale yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.15 (brs, 2H), 6.88 (dt, 1H), 5.98 (dt, 1H), 3.66 (s, 3H), 2.96-2.91 (m, 2H), 2.57-2.53 (m, 2H).
- Step-2: To a stirred solution of methyl (*E*)-5-aminopent-2-enoate hydrochloride (10.0 g, 60.38 mmol, 1.0 eq.) in THF (200 mL), cooled at 0°C, were added sequentially Et₃N (42.2 mL, 301.9 mmol, 5.0 eq) and 4-nitrobenzenesulfonyl chloride (14.72 g, 66.42 mmol, 1.10 eq). The resulting mixture was then warm up and stirred at RT. After completion of the reaction (TLC monitoring), the resulting reaction mixture was diluted with water and extracted with EtOAc (2x200 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was triturated with Et₂O and dried to yield 15.0 g of methyl (*E*)-5-((4-nitrophenyl)sulfonamido)pent-2-enoate as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 8.39-8.36 (m, 2H), 8.07-8.03 (m, 2H), 6.75 (dt, 1H), 5.83 (dt, 1H), 4.71 (t, 1H), 3.72 (s, 3H), 3.20 (q, 2H), 2.46-2.40 (qd, 2H).
- Step-3: To a stirred solution of (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (17.63 g, 39.77 mmol, 1.25 eq) in DCM (100 mL), cooled to 0°C, was added NaH (60% in mineral oil, 4.45 g, 111.35 mmol, 3.5 eq). After 15 min, a solution of methyl (*E*)-5-((4-nitrophenyl)sulfonamido)pent-2-enoate (10.0 g, 31.82 mmol, 1.0 eq) in DCM (50 mL) was added dropwise at 0°C. The resulting reaction mixture was allowed to warm up and stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched at 0°C by addition of AcOH (down to pH = 5), diluted with water and extracted with DCM (2x150 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (20-25%) in PE to afford 7.0 g of *rel*-methyl (1*R*,6*S*,7*R*)-3-((4-nitrophenyl)sulfonyl)-3-azabicyclo[4.1.0]heptane-7-carboxylate as an off-white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm:

8.40-8.38 (m, 2H), 7.94-7.92 (m, 2H), 3.76-3.72 (m, 1H), 3.67 (s, 3H), 3.36-3.28 (m, 1H), 3.07 (dd, 1H), 2.57-2.50 (m, 1H), 2.14-2.08 (m, 1H), 1.98-1.91 (m, 1H), 1.74-1.67 (m, 3H).

- Step-4: To a stirred solution of *rel*-methyl (1*R*,6*S*,7*R*)-3-((4-nitrophenyl)sulfonyl)-3-azabicyclo[4.1.0]heptane-7-carboxylate (7.0 g, 20.57 mmol, 1.0 eq) in CH₃CN (105 mL), were added K₂CO₃ (11.37 g, 82.27 mmol, 4.0 eq) and thiophenol (4.20 mL, 41.13 mmol, 2.0 eq). The resulting mixture was stirred at RT for 16 h and then Boc₂O (6.73 g, 30.85 mmol, 1.5 eq) was added. The resulting mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted twice with EtOAc. The combined organic layers were washed with an aq. sat. sodium thiosulfate solution, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (10-12%) in PE to provide 4.0 g of *rel*-3-(*tert*-butyl) 7-methyl (1*R*,6*S*,7*R*)-3-azabicyclo[4.1.0]heptane-3,7-dicarboxylate as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.91 (d, 1H), 3.67 (s, 3H), 3.51-3.46 (m, 2H), 2.97-2.90 (m, 1H), 2.01-1.93 (m, 1H), 1.79-1.68 (m, 3H), 1.48-1.46 (m, 1H), 1.45 (s, 9H).
- Step-5: A stirred solution of *rel*-3-(*tert*-butyl) 7-methyl (1*R*,6*S*,7*R*)-3-azabicyclo[4.1.0]heptane-3,7-dicarboxylate (4.0 g, 15.67 mmol, 1.0 eq) in THF (60 mL) was treated dropwise with a 1M THF solution of BH₃-THF complex (47.0 mL, 47.0 mmol, 3 eq). After addition, the resulting reaction mixture was stirred at 65°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0°C and quenched with EtOH (10 mL). The resulting mixture was refluxed for 2 h and then was concentrated under reduced pressure to afford 3.50 g of *rel*-*tert*-butyl (1*R*,6*S*,7*R*)-7-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate as a pale yellow liquid which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.82-3.76 (m, 1H), 3.67-3.63 (m, 1H), 3.56-3.50 (m, 1H), 3.48-3.32 (brs, 1H), 3.00-2.93 (m, 1H), 1.97-1.90 (m, 1H), 1.57-1.50 (m, 1H), 1.44 (s, 9H), 1.43-1.40 (m, 1H), 0.99-0.85 (m, 4H).
- Synthesis of **Int-27**: synthesis of *rel*-*N*-((1*S*,5*R*,6*R*)-6-(hydroxymethyl)bicyclo[3.1.0]hexan-2-yl)methanesulfonamide.



Step-1: To a stirred solution of *rel*-ethyl (1*S*,5*R*,6*S*)-2-oxobicyclo[3.1.0]hexane-6-carboxylate (10 g, 59.46 mmol, 1.0 eq) and benzylamine (7.14 mL, 65.40 mmol, 1.1 eq) in EtOH (100 mL), cooled

- at 0°C, was added AcOH (14.28 mL, 249.72 mmol, 4.2 eq). After 30 min stirring at 0°C, NaCNBH₃ (3.74 g, 59.46 mmol, 1.0 eq) was added. The resulting reaction mixture was allowed to warm up and stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (15-20% MeOH) in DCM to afford 2.7 g of *rel*-ethyl (1*S*,5*R*,6*S*)-2-(benzylamino)bicyclo[3.1.0]hexane-6-carboxylate as a colorless gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.45-7.43 (dd, 2H), 7.34-7.32 (m, 3H), 4.14-4.04 (m, 2H), 3.99 (s, 2H), 3.68-3.62 (m, 1H), 2.06-2.04 (m, 1H), 1.98-1.94 (m, 3H), 1.92-1.82 (m, 3H), 1.26 (t, 3H), 1.24-1.19 (m, 1H).
- Step-2: To a stirred solution of *rel*-ethyl (1*S*,5*R*,6*S*)-2-(benzylamino)bicyclo[3.1.0]hexane-6-carboxylate (6.0 g, 23.14 mmol, 1.0 eq) in MeOH (100 mL) was added 10% Pd/C (6.03 g, 50.9 mmol, 2.2 eq) at RT and under an inert atmosphere. The resulting reaction mixture was degassed and then was stirred under H₂ atmosphere at RT. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through celite and the celite pad was washed with MeOH. The filtrate was concentrated under reduced pressure to afford 3.6 g of *rel*-ethyl (1*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-6-carboxylate as a brown gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 5.70 (brs, 2H), 4.15-4.07 (m, 2H), 2.08-1.91 (m, 7H), 1.25 (t, 3H), 1.14-1.13 (m, 1H).
- Step-3: A stirred solution of *rel*-ethyl (1*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-6-carboxylate (3.6 g, 21.27 mmol, 1.0 eq) and Et₃N (9 mL, 63.82 mmol, 3.0 eq) in DCM (40 mL), cooled at 0°C, was treated dropwise with mesylchloride (2.47 mL, 31.91 mmol, 1.5 eq). The resulting reaction mixture was then allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted with dichloromethane (3x50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (1-5%) in DCM to yield 2.5 g of *rel*-ethyl (1*S*,5*R*,6*S*)-2-(methylsulfonamido)bicyclo[3.1.0]hexane-6-carboxylate as a brown gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 4.68 (d, 1H), 4.18-4.15 (m, 1H), 4.12 (q, 2H), 3.01 (s, 3H), 2.16-2.06 (m, 1H), 2.07-2.02 (m, 1H), 1.95-1.89 (m, 3H), 1.71-1.66 (m, 1H), 1.26 (t, 3H), 1.28-1.24 (m, 1H).
- Step-4: To a stirred solution of *rel*-ethyl (1*S*,5*R*,6*S*)-2-(methylsulfonamido) bicyclo[3.1.0] hexane-6-carboxylate (2.5 g, 10.11 mmol, 1.0 eq) in THF (50 mL) was added a 1M THF solution of LiAlH₄ (20.22 mL, 20.22 mmol, 2.0 eq) at 0°C. The resulting reaction mixture was stirred at 0°C for 2 h, then quenched with a sat. NH₄Cl aq. solution and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography eluting with a gradient of MeOH (1-5%) in DCM to afford 1.5 g of *rel*-N-((1*S*,5*R*,6*R*)-6-(hydroxymethyl)bicyclo[3.1.0]hexan-2-yl)methanesulfonamide as a brown gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 5.42 (d, 1H),

4.07-4.05 (m, 1H), 3.82-3.78 (m, 1H), 3.09-3.05 (m, 1H), 3.01 (s, 3H), 2.80 (brs, 1H), 1.99-1.82 (m, 1H), 1.82-1.79 (m, 2H), 1.52-1.49 (m, 1H), 1.27-1.22 (m, 2H), 1.09 (s, 1H).

Synthesis of **Int-28**: synthesis of *rel*-((1*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-yl)methanol.



5

Step-1: To a stirred solution of cyclopent-3-en-1-ol (12 g, 142.66 mmol, 1.0 eq) in THF (300 mL), cooled at 0°C, were added imidazole (19.45 g, 285.31 mmol, 2.0 eq) and then a solution of tert-butylchlorodimethylsilane (27.95 g, 185.45 mmol, 1.3 eq) in THF (50 mL). The resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted with EtOAc (2x150 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with PE to yield 25 g of tert-butyl(cyclopent-3-en-1-yloxy)dimethylsilane as a colorless liquid.

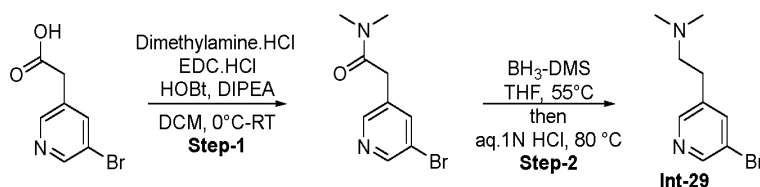
1H NMR (400 MHz, CDCl₃) δ ppm: 5.65 (s, 2H), 4.55-4.51 (m, 1H), 2.56 (dd, 2H), 2.27 (dd, 2H), 0.88 (s, 9H), 0.05 (s, 6H).

Step-2: To a stirred mixture of tert-butyl(cyclopent-3-en-1-yloxy)dimethylsilane (35.0 g, 176.4 mmol, 1.0 eq) and copper powder (1.12 g, 17.6 mmol, 0.1 eq.), heated to 100°C, was added ethyl diazoacetate (37.28 mL, 352.86 mmol, 2.0 eq) via a syringe pump over a period of 4 h and stirring was then continued at 100 °C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT and concentrated. The crude product was purified by column chromatography on silica eluting with a gradient of EtOAc (0-2%) in PE to afford 35 g of *rel*-ethyl (1*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexane-6-carboxylate as a colorless liquid. 1H NMR (400 MHz, CDCl₃) δ ppm: 4.13-4.06 (m, 2H), 3.92-3.86 (m, 1H), 2.17-2.01 (m, 4H), 1.85-1.78 (m, 3H), 1.24 (t, 3H), 0.87 (s, 9H), 0.02 (s, 6H) (Note: mixture of diastereoisomers).

Step-3: A stirred solution of *rel*-ethyl (1*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexane-6-carboxylate (35 g, 123.04 mmol, 1.0 eq) in THF (700 mL), cooled at 0°C, was treated dropwise with a 2M THF solution of LiAlH₄ (123 mL, 246.0 mmol, 2.0 eq) and stirring was continued at 0°C. After completion of the reaction (TLC monitoring), the reaction mixture was carefully quenched with a sat. NH₄Cl aq. solution. After 30 minutes, mixture was filtered on celite and the celite pad was further washed with EtOAc (250 mL). The filtrate was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (8-12%) in PE to provide 8.5 g of *rel*-((1*R*,5*S*,6*R*)-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[3.1.0]hexan-6-yl)methanol as a pale yellow liquid. 1H NMR (400 MHz, CDCl₃) δ ppm: 4.27 (t, 1H), 3.39-3.37 (m, 2H), 2.03-1.97 (m, 2H), 1.72-1.68 (m, 2H), 1.47-1.43 (m, 1H), 1.25-1.23 (m, 1H), 1.15 (t, 2H), 0.85

(s, 9H), 0.00 (s, 6H).

Synthesis of **Int-29**: synthesis of 2-(5-bromopyridin-3-yl)-*N,N*-dimethylethan-1-amine.



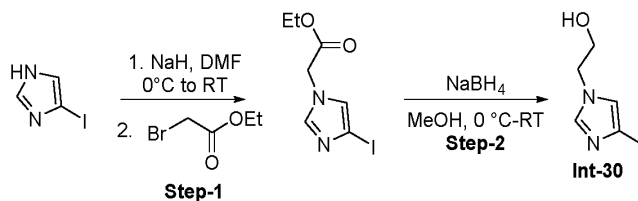
Step-1: To a stirred solution of 2-(5-bromopyridin-3-yl)acetic acid (3.0 g, 13.89 mmol, 1.0 eq) and dimethylamine hydrochloride (3.40 g, 41.66 mmol, 3.0 eq) in DCM (40 mL), cooled at 0°C, were sequentially added *N,N*-diisopropylethylamine (4.89 mL, 27.77 mmol, 2.0 eq), 1-hydroxybenzotriazole monohydrate (4.25 g, 27.77 mmol, 2.0 eq) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.32 g, 27.77 mmol, 2.0 eq). The resulting reaction mixture was allowed to warm up and was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM and a 1N aq. solution of HCl (10 mL) was added. The organic layer was separated and the aqueous solution was neutralized with an aq. sat. NaHCO₃ solution and extracted with DCM (3x50 mL). The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated to afford 2.1 g of the crude 2-(5-bromopyridin-3-yl)-*N,N*-dimethylacetamide which was used as such in the next step.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.57 (d, 1H), 8.39 (d, 1H), 7.81 (t, 1H), 3.68 (s, 2H), 3.07 (s, 3H), 2.99 (s, 3H).

Step-2: A stirred solution of 2-(5-bromopyridin-3-yl)-*N,N*-dimethylacetamide (1.8 g, 7.40 mmol, 1.0 eq) in THF (30 mL) was treated dropwise with a 2M solution of BH₃-S(CH₃)₂ in THF (19.51 mL, 39.02 mmol, 5.27 eq) at RT. The resulting reaction mixture was then stirred at 55°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was redissolved in a 1N HCl solution (30 mL) at room temperature. The resulting reaction mixture was stirred at 80°C overnight and then was quenched with a sat. aq. NaHCO₃ solution (20 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 700 mg of crude 2-(5-bromopyridin-3-yl)-*N,N*-dimethylethan-1-amine which was used as such in the next step.

¹H NMR (400 MHz, CDCl₃) δ ppm 8.52 (d, 1H), 8.38 (d, 1H), 7.69 (t, 1H), 2.76 (t, 2H), 2.54 (t, 2H), 2.29 (s, 6H).

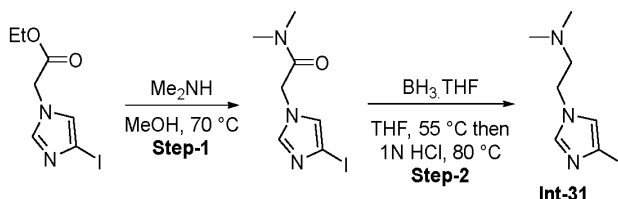
Synthesis of **Int-30**: synthesis of 2-(4-iodo-1*H*-imidazol-1-yl)ethan-1-ol.



Step-1: To a stirred solution of 4-iodo-1*H*-imidazole (5 g, 25.78 mmol, 1.0 eq) in DMF (50 mL), cooled at 0°C, was added NaH (60% dispersion in mineral oil, 1.54 g, 38.66 mmol, 1.5 eq), followed by ethyl bromoacetate (3.13 mL, 28.35 mmol, 1.1 eq). The resulting reaction mixture was allowed to warm up and was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice cold water and extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na₂SO₄ and the filtrate was concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (10-15%) in hexanes to provide 4.5 g of ethyl 2-(4-iodo-1*H*-imidazol-1-yl)acetate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.41 (d, 1H), 7.05 (d, 1H), 4.67 (s, 2H), 4.25 (q, 2H), 1.30 (t, 3 H).

Step-2: To a stirred solution of ethyl 2-(4-iodo-1*H*-imidazol-1-yl)acetate (2.5 g, 8.93 mmol, 1 eq) in MeOH (50 mL), cooled at 0°C, was added NaBH₄ (1.35 g, 35.71 mmol, 4 eq). The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice cold water (10 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (10-15%) in hexanes to afford 2 g of 2-(4-iodo-1*H*-imidazol-1-yl) ethan-1-ol as an off- white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.30 (d, 1H), 7.02 (d, 1H), 4.02 (t, 2H), 3.93 (t, 2H).

Synthesis of **Int-31**: synthesis of 2-(4-iodo-1*H*-imidazol-1-yl)-*N,N*-dimethylethan-1-amine.

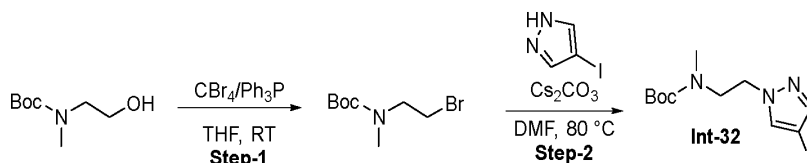


Step-1: To a stirred solution of ethyl 2-(4-iodo-1*H*-imidazol-1-yl)acetate (2 g, 7.14 mmol, 1.0 eq) in MeOH (30 mL) was added a 2N methanolic solution of Me₂NH (7.85 mL, 35.7 mmol, 5.0 eq) at RT and the resulting reaction mixture was then stirred at reflux. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated to yield 1.5 g of 2-(4-iodo-1*H*-imidazol-1-yl)-*N,N*-dimethylacetamide as a brown solid which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (d, 1H), 7.04 (d, 1H), 4.74 (s, 2H), 3.06 (s, 3H), 3.00 (s, 3H).

Step-2: To a stirred solution of 2-(4-iodo-1*H*-imidazol-1-yl)-*N,N*-dimethylacetamide (1.5 g, 5.38 mmol, 1.0 eq) in THF (20 mL) was added a 1M THF solution of BH₃-THF complex (28.33 mL,

28.33 mmol, 5.27 eq) at RT. The resulting reaction mixture was then stirred at 55°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was resuspended in a 1N HCl aq. solution (60 mL) at RT. The resulting reaction mixture was stirred at 80°C overnight and then was quenched with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford 750 mg of 2-(4-iodo-1*H*-imidazol-1-yl)-*N,N*-dimethylethan-1-amine which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.41 (d, 1H), 7.07 (d, 1H), 3.98 (t, 2H), 2.61 (t, 2H), 2.26 (s, 6H).

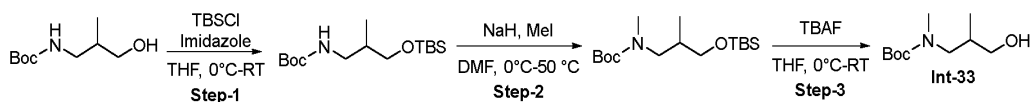
10 Synthesis of **Int-32**: synthesis of *tert*-butyl (2-(4-iodo-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate.



Step-1: To a stirred solution of *tert*-butyl (2-hydroxyethyl)(methyl)carbamate (15 g, 85.6 mmol, 1.0 eq) in THF (200 mL) were added sequentially PPh₃ (33.68 g, 128.40 mmol, 1.5 eq) and CBr₄ (42.58 g, 128.40 mmol, 1.5 eq) at RT. The resulting reaction mixture was stirred at RT for 1 h, solids were filtered off and the filtrate was concentrated. The crude compound was purified by column chromatography on silica gel eluting with a gradient of EtOAc (5-8%) in PE to afford 8 g of *tert*-butyl (2-bromoethyl)(methyl)carbamate as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.58 (t, 2H), 3.44 (t, 2H), 2.93 (s, 3H), 1.47 (s, 9H)

Step-2: To a stirred solution of 4-iodo-1*H*-pyrazole (4.0 g, 20.62 mmol, 1.0 eq) and Cs₂CO₃ (16.79 g, 51.55 mmol, 2.5 eq) in DMF (60 mL) was added *tert*-butyl(2-bromoethyl) (methyl)carbamate (5.40 g, 22.68 mmol, 1.1 eq) at RT and the resulting reaction mixture was then stirred at 80°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, quenched with ice cold water and the mixture was then extracted twice with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (15-20%) in PE to afford 5 g of *tert*-butyl (2-(4-iodo-1*H*-pyrazol-1-yl)ethyl)(methyl)carbamate as a pale yellow gummy. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.52 (s, 1H), 7.38 (s, 1H), 4.26 (brs, 2H), 3.59 (t, 2H), 2.65 (s, 3H), 1.43 (s, 9H).

Synthesis of **Int-33**: synthesis of *tert*-butyl (3-hydroxy-2-methylpropyl)(methyl)carbamate.

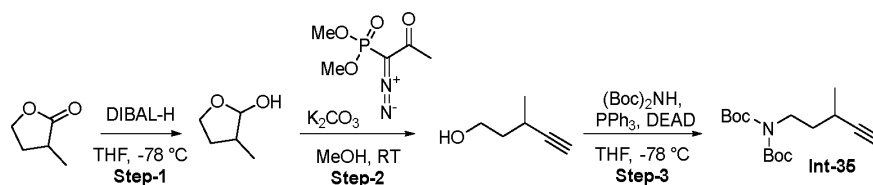


Step-3: To a stirred solution of *tert*-butyl (3-((*tert*-butyldimethylsilyloxy)-2-methylpropyl) (methyl)carbamate (6.0 g, 18.90 mmol, 1 eq) in THF (100 mL) cooled at 0 °C was added a 1M THF solution of TBAF (56.70 mL, 56.69 mmol, 3 eq). After addition, the reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM (100 mL), washed with water, brine and the organic layer was concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (10-15%) in PE to provide 3.8 g of *tert*-butyl (3-hydroxy-2-methylpropyl) (methyl)carbamate as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.74 (br.s, 1H), 3.49-3.44 (m, 2H), 3.34-3.32 (m, 1H), 2.94-2.93 (m, 1H), 2.86 (s, 3H), 1.82 (brs, 1H), 1.46 (s, 9H), 0.96 (d, 3H).

177

- mmol, 1.0 eq). After addition, the reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was washed with a 1N aq. solution of HCl (2x300 mL) and then a sat. aq. solution of NaHCO₃ (2x300 mL). The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. Another batch of the crude product was
- 5 obtained starting from 10 g of 2-ethylpropane-1,3-diol (same protocol). The crude product from two batches was purified by column chromatography on silica gel eluting with a gradient EtOAc (10-15%) in PE to afford 26.0 g of 2-(hydroxymethyl) butyl 4-methylbenzenesulfonate as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.79 (d, 2H), 7.35 (d, 2H), 4.13-4.04 (m, 2H), 3.62-3.55 (m, 2H), 2.45 (s, 3H), 1.75-1.72 (m, 1H), 1.36-1.24 (m, 2H), 0.87 (t, 3H).
- 10 Step-2: To a stirred solution of 2-(hydroxymethyl)butyl 4-methylbenzenesulfonate (26 g, 100.65 mmol, 1.0 eq) in DMF (300 mL) was added NaN₃ (65.43 g, 1.00 mol, 10 eq) at 0 °C. After addition, the resulting reaction mixture was stirred at 60°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted twice with EtOAc. The organic layer was washed with water and brine, dried over anhydrous Na₂SO₄ and concentrated
- 15 to yield 14 g of crude 2-(azidomethyl) butan-1-ol as a brown gummy which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.69-3.57 (m, 2H), 3.46-3.31 (m, 2H), 1.72-1.64 (m, 1H), 1.43-1.33 (m, 2H), 0.97 (t, 3H).
- Step-3: To a stirred solution of 2-(azidomethyl) butan-1-ol (14 g, 108.39 mmol, 1.0 eq) in MeOH (140 mL) were added 10% Pd/C (9.23 g, 86.71 mmol, 0.8 eq) and Boc₂O (37.35 g, 162.59 mmol, 1.5 eq) at RT. The resulting reaction mixture was stirred at RT under a H₂ atmosphere. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through celite and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (14-20%) in PE to afford 9 g of *tert*-butyl (2-(hydroxymethyl) butyl) carbamate as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm 4.82 (br.s, 1H), 3.59-3.58 (m, 1H), 3.42-
- 20 3.29 (m, 3H), 3.13-3.06 (m, 1H), 1.50 (s, 9H), 1.36-1.21 (m, 2H), 0.93 (t, 3H).

Synthesis of **Int-35**: synthesis of *tert*-butyl (*tert*-butoxycarbonyl) (3-methylpent-4-yn-1-yl) carbamate.



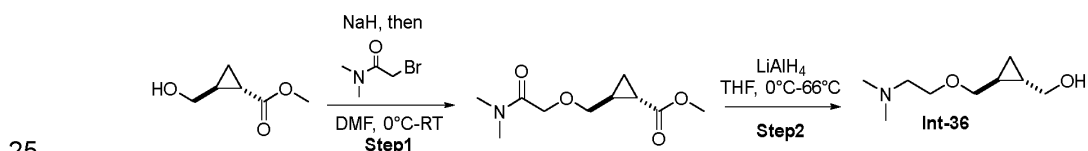
- Step-1: To a stirred solution of 3-methyldihydrofuran-2(3*H*)-one (25 g, 249.71 mmol, 1.0 eq) in DCM (250 mL), cooled at -78°C, was added a 1M toluene solution of DIBAL-H (216.42 mL, 324.62 mmol, 1.3 eq) under nitrogen atmosphere. The resulting reaction mixture was stirred at -78°C for 1 h and then was quenched with a sat. aq. solution of Rochelle salt (500 mL) at -78°C. After quenching, the reaction mixture was stirred at RT for 12 h and then extracted twice with Et₂O.
- 30

The organic extracts were concentrated to yield 15 g of crude 3-methyltetrahydrofuran-2-ol as a pale yellow liquid, which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 5.10 (d, 1H), 4.11-3.93 (m, 2H), 2.24-2.19 (m, 2H), 1.55-1.50 (m, 1H), 1.03 (d, 3H).

Step-2: To a stirred solution of 3-methyltetrahydrofuran-2-ol (6 g, 58.75 mmol, 1 eq) in MeOH (50 mL) were added K₂CO₃ (16.21 g, 117.50 mmol, 2.0 eq) and dimethyl diazo-2-oxopropylphosphonate (13.47 g, 70.50 mmol, 1.2 eq). The resulting reaction mixture was stirred at RT. After completion of the reaction, the reaction mixture was quenched with water and extracted twice with Et₂O and the combined organic extracts were concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (4-10%) in PE to provide 3.0 g of 3-methylpent-4-yn-1-ol as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm 3.84-3.79 (m, 2H), 2.67-2.61 (m, 1H), 2.07 (d, 1H), 1.76-1.66 (m, 2H), 1.53 (t, 1H), 1.23 (d, 3H).

Step-3: To a stirred solution of 3-methylpent-4-yn-1-ol (4 g, 40.76 mmol, 1.0 eq) and (Boc)₂NH (10.61 g, 48.91 mmol, 1.2 eq) in THF (40 mL) were added PPh₃ (16.03 g, 61.13 mmol, 1.5 eq) and diethylazodicarboxylate (26.62 mL, 61.13 mmol, 1.5 eq) at 0 °C. The resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted twice with EtOAc. Combined organic extracts were concentrated and the crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (4-8) in PE to afford 2.8 g of *tert*-butyl (*tert*-butoxycarbonyl) (3-methylpent-4-yn-1-yl) carbamate as a pale-yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 3.80-3.72 (m, 1H), 3.68-3.60 (m, 1H), 2.48-2.43 (m, 1H), 2.05 (d, 1H), 1.75-1.69 (m, 2H), 1.51 (s, 18H), 1.21 (d, 3H).

Synthesis of Int-36: synthesis of *rel*-[(1*S*,2*S*)-2-[2-(dimethylamino)ethoxymethyl]cyclopropyl]methanol.

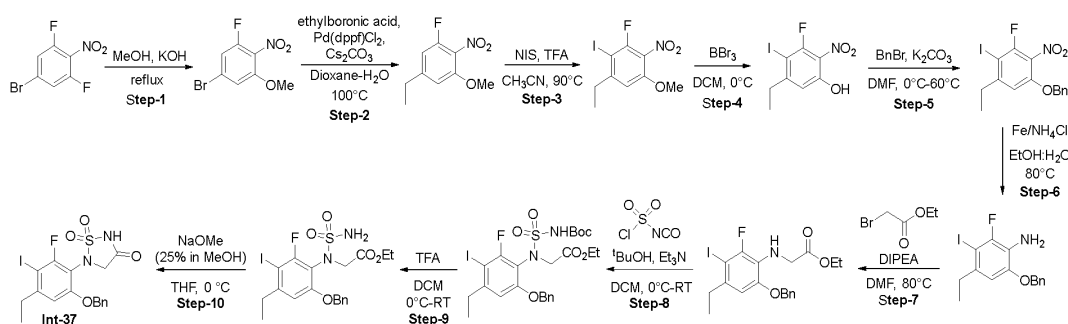


Step-1: To a stirred solution of *rel*-methyl (1*S*,2*S*)-2-(hydroxymethyl)cyclopropane-1-carboxylate (531 mg, 4.08 mmol) in DMF (6 mL), cooled to 0°C, was added NaH (60% w/w in mineral oil, 180 mg, 4.49 mmol). The mixture was stirred at 0°C for 30 min and 2-bromo-*N,N*-dimethyl-acetamide (0.520 mL, 4.28 mmol, 1.05 eq) was added. The mixture was stirred at 0°C for 30 min and then overnight at RT. After completion of the reaction, the reaction mixture was quenched with water and extracted twice with EtOAc. The combined organic extracts were dried over MgSO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (1-8%) in EtOAc to afford 574 mg of *rel*-methyl (1*S*,2*S*)-2-((2-(dimethylamino)-2-oxoethoxy)methyl)cyclopropane-1-carboxylate as an oily residue. ¹H NMR

(400 MHz, DMSO- d_6) δ ppm: 4.11 (s, 2 H), 3.60 (s, 3 H), 3.47 (dd, 1 H), 3.24 (dd, 1 H), 2.89 (s, 3 H), 2.80 (s, 3 H), 1.66-1.59 (m, 1 H), 1.58-1.50 (m, 1 H), 1.03 (dt, 1 H), 0.90 (ddd, 1 H).

Step-2: A stirred solution of *rel*-methyl (1*S*,2*S*)-2-((2-(dimethylamino)-2-oxoethoxy)methyl)cyclopropane-1-carboxylate (565 mg, 2.62 mmol) in THF (12 mL), cooled to 0°C, was treated dropwise with a 2.4M THF solution of LiAlH₄ (3.5 mL, 8.40 mmol, 3.2 eq). The mixture was stirred at 0°C for 30 min and then refluxed. After completion of the reaction, the reaction mixture was cooled down to RT, diluted with THF and quenched by addition of Na₂SO₄·10H₂O (8.0 g). The mixture was stirred at RT overnight and then was filtered. The filtrate was dried over MgSO₄, concentrated and the crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (1-12%) in DCM to afford 421 mg of *rel*-((1*S*,2*S*)-2-((2-(dimethylamino)ethoxy)methyl)cyclopropyl)methanol as an oily residue. ¹H NMR (400 MHz, DMSO- d_6) δ ppm: 4.45 (brs, 1 H), 3.51-3.38 (m, 2 H), 3.28-3.17 (m, 4 H), 2.37 (t, 2 H), 2.14 (s, 6 H), 0.89-0.74 (m, 2 H), 0.39-0.26 (m, 2 H).

Synthesis of Int-37: synthesis of 5-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.



Step-1: To a stirred solution of 5-bromo-1,3-difluoro-2-nitrobenzene (25 g, 105.05 mmol, 1.0 eq) in MeOH (250 mL) was added KOH (6.47 g, 115.55 mmol, 1.1 eq) portionwise at RT and the resulting reaction mixture was then stirred at reflux. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM (500 mL), washed with water and the organic layer was concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (4-10%) in PE to yield 20 g of 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.04 (dd, 1H), 7.00 (t, 1H), 3.94 (s, 3H).

Step-2: A stirred mixture of 5-bromo-1-fluoro-3-methoxy-2-nitrobenzene (25 g, 99.99 mmol, 1 eq), ethylboronic acid (9.24 g, 124.99 mmol, 1.25 eq), Cs₂CO₃ (120.54 g, 369.97 mmol, 3.7 eq) and Pd(dppf)Cl₂ (4.08 g, 5.00 mmol, 0.05 eq) in dioxane (200 mL) and water (20 mL), at RT, was degassed and put under an inert atmosphere, then stirred at 100 °C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with 10% of EtOAc in

PE to provide 11 g of 5-ethyl-1-fluoro-3-methoxy-2-nitrobenzene as a pale yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ ppm: 6.67-6.64 (m, 2H), 3.92 (s, 3H), 2.67 (q, 2H), 1.25 (t, 3H).

Step-3: To a stirred solution of 5-ethyl-1-fluoro-3-methoxy-2-nitrobenzene (10 g, 50.21 mmol, 1 eq) in CH₃CN (100 mL), were added sequentially at RT *N*-iodosuccinimide (45.18 g, 200.8 mmol, 4 eq) and TFA (0.77 mL, 10.05 mmol, 0.2 eq). The resulting reaction mixture was stirred at 90 °C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM and washed with a sat. aq. solution of Na₂S₂O₃. The organic layer was concentrated and the crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (4-8%) in PE to afford 11 g of 1-ethyl-3-fluoro-2-iodo-5-methoxy-4-nitrobenzene as a

white solid. ¹H NMR (400 MHz, CDCl₃) δ ppm 6.78 (d, 1H), 3.93 (s, 3H), 2.82 (q, 2H), 1.23 (t, 3H).

Step-4: To a stirred solution of 1-ethyl-3-fluoro-2-iodo-5-methoxy-4-nitrobenzene (11 g, 33.84 mmol, 1 eq) in DCM (100 mL) was added a 1M DCM solution of BBr₃ (102 mL, 102 mmol, 3 eq) dropwise at 0 °C. The resulting reaction mixture was stirred at 0 °C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water and extracted twice with

DCM. Combined organic extracts were concentrated under reduced pressure to afford 8 g of 5-ethyl-3-fluoro-4-iodo-2-nitrophenol as a pale yellow solid, which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.46 (br. s, 1H), 6.95 (d, 1H), 2.78 (q, 2H), 1.26 (t, 3H).

Step-5: To a stirred solution of 5-ethyl-3-fluoro-4-iodo-2-nitrophenol (8 g, 25.72 mmol, 1 eq) in DMF (80 mL) were added K₂CO₃ (4.26 g, 30.86 mmol, 1.2 eq.) and (bromomethyl)benzene (3.1 mL, 25.72 mmol, 1.0 eq.) dropwise at 0 °C and the resulting reaction mixture was stirred at 60 °C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with water.

The precipitated solid was collected by filtration, washed with cold water followed by PE and dried to yield 10 g of 1-(benzyloxy)-5-ethyl-3-fluoro-4-iodo-2-nitrobenzene as a brown solid, which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39-7.34 (m, 5H), 6.80 (d, 1H),

5.19 (s, 2H), 2.77 (q, 2H), 1.18 (t, 3H).

Step-6: To a stirred solution of 1-(benzyloxy)-5-ethyl-3-fluoro-4-iodo-2-nitrobenzene (10 g, 24.93 mmol, 1 eq) in EtOH (100 mL) and water (50 mL) were added at RT NH₄Cl (13.33 g, 249.27 mmol, 10 eq) followed by iron powder (6.96 g, 124.63 mmol, 5 eq). The resulting reaction mixture was stirred at 80 °C. After completion of the reaction (TLC monitoring), the reaction mixture was filtered

through celite. The filtrate was diluted with water and extracted twice with EtOAc and the combined organic extracts were concentrated. The crude compound was purified by column chromatography on silica gel eluting with a gradient of EtOAc (4-8%) in PE to provide 8 g of 6-(benzyloxy)-4-ethyl-2-fluoro-3-iodoaniline as a brown liquid, which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44-7.34 (m, 5H), 6.62 (d, 1H), 5.08 (s, 2H), 3.75 (br. s,

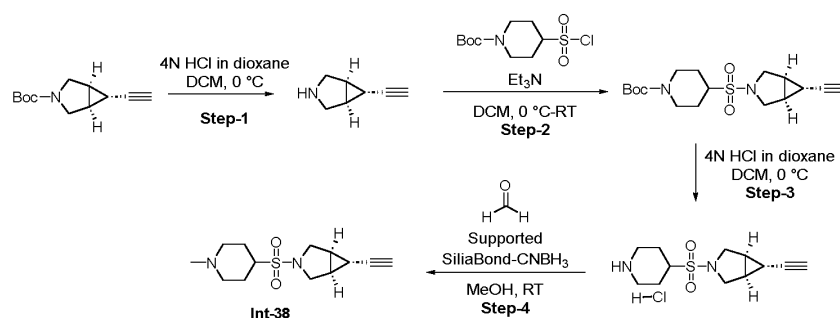
2H), 2.67 (q, 2H), 1.14 (t, 3H).

Step-7: To a stirred solution of 6-(benzyloxy)-4-ethyl-2-fluoro-3-iodoaniline (8 g, 21.55 mmol, 1 eq) in DMF (80 mL) were added sequentially DIPEA (15.30 mL, 86.21 mmol, 4.0 eq) and ethyl 2-

- bromoacetate (4.77 mL, 43.10 mmol, 2.0 eq) and the resulting reaction mixture was stirred at 80 °C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a sat. aq. solution of NaHCO₃ at 0 °C and extracted with EtOAc (3x100 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (2-4%) in PE to yield 7 g of ethyl (6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)glycinate as a brown wax, which was used as such in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45-7.34 (m, 5H), 6.62 (d, 1H), 5.10 (s, 2H), 4.50 (br. s, 1H), 4.18 (q, 2H), 4.05 (dd, 2H), 2.65 (q, 2H), 1.25 (t, 3H), 1.13 (t, 3H).
- Step-8: To a stirred solution of chlorosulfonyl isocyanate (2.96 mL, 34.12 mmol, 2.0 eq) in DCM (60 mL), cooled at 0 °C, was added dropwise *tert*-butanol (3.24 mL, 34.12 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 30 min and then was added to a stirred solution of ethyl (6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)glycinate (7 g, 15.31 mmol, 1.0 eq) and Et₃N (7.14 mL, 51.18 mmol, 3.0 eq) in DCM (60 mL) at 0 °C. The resulting reaction mixture was allowed to warm up and was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted with DCM (3x200 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (15-20%) in PE to afford 9 g of ethyl *N*-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-*N*-(*N*-(*tert*-butoxycarbonyl)sulfamoyl)glycinate as a brown gummy liquid, which was used as such in the next step. LC-MS (LC-M): r.t. = 2.69 min; m/z = 635 [M-H].
- Step-9: To a stirred solution of ethyl *N*-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-*N*-(*N*-(*tert*-butoxycarbonyl)sulfamoyl)glycinate (9 g, 14.14 mmol, 1.0 eq) in DCM (90 mL), cooled at 0 °C, was added TFA (5.41 mL, 70.70 mmol, 5 eq) and the resulting reaction mixture was allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated. The residue was suspended in a sat. aq. solution of NaHCO₃ (50 mL), diluted with water and extracted with DCM (3x100 mL). Combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (15-20%) in PE to yield 6 g of ethyl *N*-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-*N*-sulfamoylglycinate as a white solid, which was used as such in the next step. LC-MS (LC-M): r.t. = 2.31 min; m/z = 535 [M-H].
- Step-10: To a stirred solution of ethyl *N*-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-*N*-sulfamoylglycinate (5 g, 9.32 mmol, 1.0 eq) in THF (40 mL), cooled at 0 °C, was added NaOMe (25% in MeOH, 4.02 mL, 18.64 mmol, 2.0 eq). The resulting reaction mixture was stirred at 0 °C and after completion of the reaction (TLC monitoring) was acidified with AcOH (4 mL) at 0 °C and was concentrated. The crude product was triturated with *n*-pentane (200 mL), Et₂O (3x200 mL) and dried. The obtained solid was dissolved in a 1:1 mixture of THF and EtOAc (1.0 L) and

washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 4 g of 5-(6-(benzyloxy)-4-ethyl-2-fluoro-3-iodophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid, which was used as such in the next step. LC-MS (LC-R): r.t. = 1.69 min; m/z = 489 $[\text{M}-\text{H}]^-$.

- 5 Synthesis of **Int-38**: synthesis of (1*R*,5*S*,6*S*)-6-ethynyl-3-((1-methylpiperidin-4-yl)sulfonyl)-3-azabicyclo[3.1.0]hexane.



- Step-1: A stirred solution of *tert*-butyl (1*S*,5*R*)-6-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (0.50 g, 2.41 mmol, 1 eq) in DCM (10 mL), cooled at 0 °C, was treated dropwise with a 4N HCl solution in dioxane (6.0 mL, 24.0 mmol, 9.95 eq) and the reaction mixture was stirred at 0 °C. After completion of the reaction (TLC monitoring), the reaction mixture was partitioned between DCM and a 1N aq. solution of Na_2CO_3 . After separation, the aqueous layer was extracted twice with DCM. Combined organic extracts were dried over MgSO_4 and concentrated to afford 219 mg of (1*S*,5*R*)-6-ethynyl-3-azabicyclo[3.1.0]hexane which was used as such in the next step.

- 15 Step2: A stirred solution of (1*S*,5*R*)-6-ethynyl-3-azabicyclo[3.1.0]hexane (219 mg, 2.04 mmol, 1 eq) in DCM (6 mL), cooled at 0 °C, was treated sequentially with Et_3N (0.43 mL, 3.07 mmol, 1.5 eq) and 1-Boc-4-chlorosulfonylpiperidine (651 mg, 2.25 mmol, 1.1 eq) and the reaction mixture was then allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel eluting with a gradient of EtOAc (5-80%) in heptane to afford 510 mg of *tert*-butyl 4-[[[(1*S*,5*R*)-6-ethynyl-3-azabicyclo[3.1.0]hexan-3-yl]sulfonyl] piperidine-1-carboxylate as a white solid.

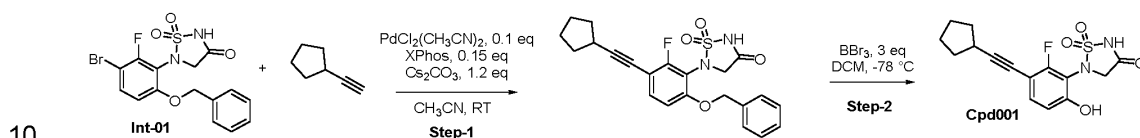
- Step3: A stirred solution of *tert*-butyl 4-[[[(1*S*,5*R*)-6-ethynyl-3-azabicyclo[3.1.0]hexan-3-yl]sulfonyl] piperidine-1-carboxylate (458 mg, 1.29 mmol, 1 eq) in DCM (6 mL), cooled at 0 °C, was treated dropwise with a 4N HCl solution in dioxane (3.0 mL, 12.0 mmol, 9.3 eq) and the reaction mixture was stirred at 0 °C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated to yield 371 mg of (1*S*,5*R*)-6-ethynyl-3-(4-piperidylsulfonyl)-3-azabicyclo[3.1.0]hexane as hydrochloride salt as a white solid, which was used as such in the next step. LC-MS (infusion): m/z 255 $[\text{M}+\text{H}-\text{HCl}]^+$

- Step4: To a stirred suspension of (1*S*,5*R*)-6-ethynyl-3-(4-piperidylsulfonyl)-3-azabicyclo[3.1.0]hexane (hydrochloride salt) (184 mg, 0.63 mmol, 1 eq) and a 0.89 mmol/g

Supported SiliaBond-CNBH₃ (1.42 g, 1.27 mmol, 2 eq) in MeOH (10 mL) was added formaldehyde (0.095 mL, 1.27 mmol, 2 eq) and the reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was filtered, the filtrate was concentrated and the crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (1-12%) in DCM to yield 145 mg of rac-(1S,5R)-6-ethynyl-3-[(1-methyl-4-piperidyl)sulfonyl]-3-azabicyclo[3.1.0]hexane as a white solid. LC-MS (infusion): m/z 269 [M+H]⁺

Examples of compounds of the invention and their preparation

Example 1: Synthesis of 5-(3-(cyclopentylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd001)



Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (600 mg, 1.46 mmol, 1 eq), ethynylcyclopentane (408 mg, 4.33 mmol, 3 eq) and Cs₂CO₃ (565 mg, 1.73 mmol, 1.2 eq) in CH₃CN (20 mL) was degassed for 20 min with N₂. Then, Pd(CH₃CN)₂Cl₂ (37.5 mg, 0.144 mmol, 0.1 eq) followed by XPhos (103 mg, 0.21 mmol, 0.15 eq) were added at RT and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture filtered through a celite bed and the bed was washed with 10% MeOH in DCM (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (8-20%) to yield 450 mg of 5-(6-(benzyloxy)-3-(cyclopentylethynyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown gum.

LC-MS (LC-M): r.t. = 1.86 min ; m/z 427 [M-H]⁻

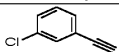
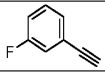
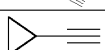
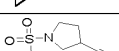
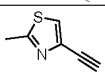
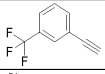
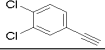
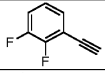
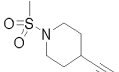
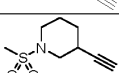
Step-2: To a stirred solution of 5-(6-(benzyloxy)-3-(cyclopentylethynyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (400 mg, 0.93 mmol, 1 eq) in DCM (15 mL) was added BBr₃ (1M in DCM, 2.8 mL, 2.80 mmol, 3 eq) dropwise at -78°C and the resulting solution was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and then evaporated under reduced pressure to get a crude residue, which was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (0-30%). Obtained compound was further purified by Prep-HPLC (Column: X-SELECT CSH C18 (25*150 mm, 8μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B): 0/10, 2/10, 10/45, 13.5/45, 13.7/98, 17/98, 17.2/10, 20/10. Flow: 20 mL/min. Temperature: ambient.) to yield 75 mg of 5-(3-(cyclopentylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd001) as an off-white solid. LC-MS (LC-A): r.t. = 1.65 min (98.6%) ; m/z 337 [M-H]⁻

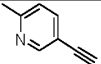
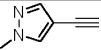
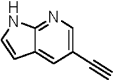
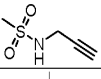
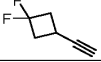
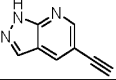
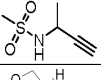
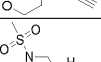
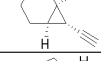
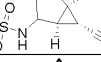
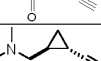
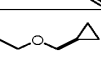
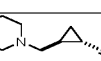
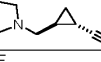
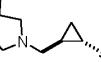
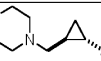
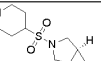
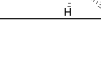
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.15 (t, 1H), 6.62 (dd, 1H), 3.94 (s, 2H) 2.87-2.83 (m, 1H),

1.99-1.93 (m, 2H), 1.72-1.63 (m, 6H).

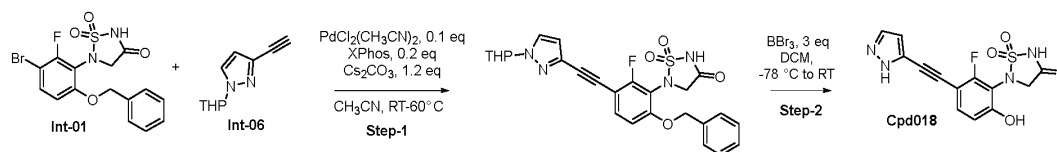
^{19}F NMR (376 MHz, DMSO- d_6) δ ppm: -114.1 (d).

- The following compounds were prepared in a manner similar to compound **Cpd001** (by use of appropriate alkyne reagent in step-1 and purification methods known to the skilled in the art). The
- 5 final debenzylation (phenol deprotection) can be performed by any suitable reagent known to the person skilled in the art (e.g. BBr_3 (neat or as solution in an appropriate solvent), BCl_3 , ...). The reagents are commercially available or synthesized as described in the section "Examples of intermediates and their preparation".

Reagent Step-1	Solvent Step-1	Temp. Step-1	Reagent Step-2	Compound
	CH_3CN	RT	BBr_3	Cpd002
	CH_3CN	90°C	BBr_3	Cpd003
	CH_3CN	RT	BBr_3	Cpd004
	CH_3CN	80°C	BBr_3	Cpd005
	DMF	90°C	BBr_3	Cpd006
	CH_3CN	60°C	BBr_3	Cpd007
	CH_3CN	90°C	BBr_3	Cpd008
	CH_3CN	90°C	BBr_3	Cpd009
	CH_3CN	60°C	BBr_3	Cpd010
	CH_3CN	RT	BBr_3	Cpd011
	CH_3CN	RT	BBr_3	Cpd012
	CH_3CN	60°C	BBr_3	Cpd013
	CH_3CN	60°C	BBr_3	Cpd014
	CH_3CN	70°C	BBr_3	Cpd015
	CH_3CN	RT	BBr_3	Cpd016
	CH_3CN	60°C	BBr_3	Cpd017
	CH_3CN	80°C	BBr_3	Cpd051
	CH_3CN	90°C	BBr_3	Cpd053
	CH_3CN	90°C	BBr_3	Cpd054
	CH_3CN	60°C	BBr_3	Cpd055
	CH_3CN	60°C	BBr_3	Cpd057

	CH ₃ CN	60°C	BBr ₃	Cpd059
	CH ₃ CN	60°C	BBr ₃	Cpd061
	CH ₃ CN	60°C	BBr ₃	Cpd066
	CH ₃ CN	60°C	BBr ₃	Cpd068
	CH ₃ CN	60°C	BBr ₃	Cpd069
	CH ₃ CN	60°C	BBr ₃	Cpd071
	CH ₃ CN	70°C	BBr ₃	Cpd073
	CH ₃ CN	60°C	BBr ₃	Cpd074
	CH ₃ CN	90°C	BBr ₃	Cpd075
	CH ₃ CN	60°C	BBr ₃	Cpd076
	CH ₃ CN	50°C	BBr ₃	Cpd077
	CH ₃ CN	65°C	BBr ₃	Cpd078
	CH ₃ CN	90°C	BBr ₃	Cpd098
	CH ₃ CN	60°C	BBr ₃	Cpd099
	CH ₃ CN	60°C	BBr ₃	Cpd100
	CH ₃ CN	RT	BCl ₃	Cpd106
	CH ₃ CN	50°C	BBr ₃	Cpd107
	CH ₃ CN	90°C	BCl ₃	Cpd141
	CH ₃ CN	80°C	BCl ₃	Cpd150, Cpd151
	CH ₃ CN	80°C	BCl ₃	Cpd152
	CH ₃ CN	50°C	BCl ₃	Cpd153
	CH ₃ CN	40°C	BCl ₃	Cpd154
	CH ₃ CN	50°C	BCl ₃	Cpd155
	CH ₃ CN	90°C	BCl ₃	Cpd166

Example 2: Synthesis of 5-(3-((1H-pyrazol-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd018**)



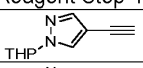
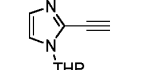
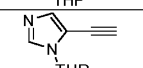
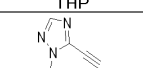
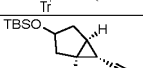
Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (250 mg, 0.60 mmol, 1 eq), 3-ethynyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazole (159 mg, 0.90 mmol, 1.5 eq) and Cs_2CO_3 (235 mg, 0.72 mmol, 1.2 eq) in CH_3CN (10 mL) was degassed for 10 min with Ar. Then $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (15.6 mg, 0.06 mmol, 0.1 eq) followed by XPhos (57.4 mg, 0.12 mmol, 0.2 eq) were added at RT. The resulting reaction mixture was then stirred at 60°C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (5-10%) to yield 200 mg of 5-(6-(benzyloxy)-2-fluoro-3-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown gum. LC-MS (LC-M): r.t. = 0.79 min ; m/z 509 $[\text{M}-\text{H}]^-$

Step-2: To a stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-3-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (400 mg, 0.78 mmol, 1 eq) in DCM (30 mL) was added BBr_3 (1M solution in DCM, 2.35 mL, 2.35 mmol, 3 eq) dropwise at -78°C. The resulting reaction mixture was allowed to reach RT and stirred at this temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and concentrated under reduced pressure. The crude material was purified by Prep-HPLC (Column: UniHybrid C18 (25*150mm, 8 μm). Mobile phase A: 10 mM NH_4HCO_3 in H_2O ; Mobile phase B: CH_3CN . Gradient (Time(min)/%B): 0/10, 2/10, 10/35, 10.1/98, 16/98, 16.1/10, 20/10. Flow: 20 mL/min. Temperature: ambient.) to yield 35 mg of 5-(3-((1H-pyrazol-5-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid. LC-MS (LC-A): r.t. = 1.26 min (98.7%); m/z 337 $[\text{M}+\text{H}]^+$

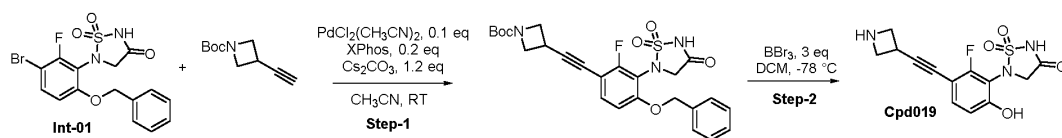
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 13.23 (brs, 1H), 7.75 (brs, 1H), 7.33 (t, 1H), 6.72 (d, 1H), 6.54 (s, 1H), 3.97 (s, 2H)

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm: -112.9 (s)

The following compounds were prepared in a manner similar to compound **Cpd018** (by use of appropriate alkyne reagent in step-1, reagents and purification methods known to the skilled in the art). The final debenzoylation (phenol deprotection) and cleavage of labile protecting group when applicable (e.g. THP, Trityl, TBS group, ...) can be performed by any suitable reagent known to the person skilled in the art (e.g. BBr_3 (neat or as solution in an appropriate solvent), BCl_3 , ...). The reagents are commercially available or synthesized as described in the section "Examples of intermediates and their preparation".

Reagent Step-1	Solvent Step-1	Temp. Step-1	Reagent Step-2	Compound
	CH ₃ CN	60°C	BBr ₃	Cpd056
	CH ₃ CN	60°C	BBr ₃	Cpd064
	CH ₃ CN	60°C	BBr ₃	Cpd065
	CH ₃ CN	90°C	BBr ₃	Cpd081
	CH ₃ CN	60°C	BBr ₃	Cpd117

Example 3: Synthesis of 5-(3-(azetidin-3-ylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd019)



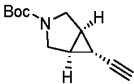
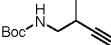
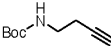
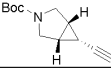
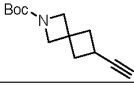
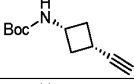
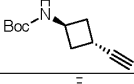
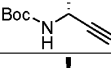
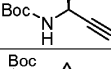
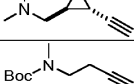
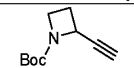
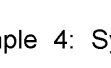
- Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (800 mg, 1.93 mmol, 1 eq), tert-butyl 3-ethynylazetidine-1-carboxylate (1.04 g, 5.78 mmol, 3 eq) and Cs₂CO₃ (753 mg, 2.31 mmol, 1.2 eq) in CH₃CN (20 mL) was degassed for 10 min with N₂. Then, Pd(CH₃CN)₂Cl₂ (50 mg, 0.193 mmol, 0.1 eq) followed by XPhos (184 mg, 0.385 mmol, 0.2 eq) were added and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was filtered through a celite bed and the bed was washed with 10% MeOH in DCM (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (8-20%) to yield 600 mg of tert-butyl 3-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl) azetidine-1-carboxylate as a light brown gum. LC-MS (LC-M): r.t. = 1.75 min ; m/z 514 [M-H]⁻
- Step-2: To a stirred solution of tert-butyl 3-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)azetidine-1-carboxylate (300 mg, 0.582 mmol, 1 eq) in DCM (15 mL) was added dropwise BBr₃ (1M in DCM, 1.74 mL, 1.74 mmol, 3 eq) dropwise at -78°C and the resulting reaction mixture was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and concentrated under reduced pressure to get a crude residue, which was purified by reverse phase column chromatography eluting with a gradient of CH₃CN in H₂O (0-30%). Obtained compound was further purified by Prep-HPLC (Column: Phenomenex LUNA C18 (25*150mm, 5 μm). Mobile phase A: 0.1% FA in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B) : 0/7, 2/7, 10/20, 10.1/98, 14.5/98, 14.6/7, 19/7. Flow: 18 mL/min. Temperature: ambient.) to yield 10 mg of 5-(3-(azetidin-3-ylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-E): r.t. = 1.40 min (99.1%)

; m/z 326 [M+H]⁺

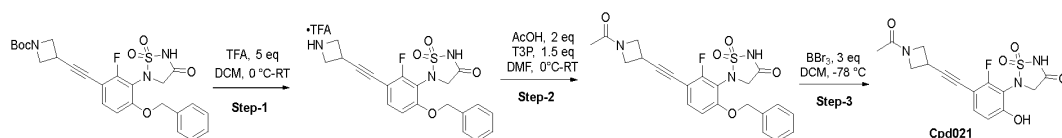
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.16 (brs, 3H), 7.23 (t, 1H), 6.69 (d, 1H), 4.19 (t, 2H), 4.00-3.93 (m, 5H).

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.2 (d).

- 5 The following compounds were prepared in a manner similar to compound **Cpd019** (by use of appropriate alkyne reagent and purification method known to the person skilled in the art). The final debenzoylation (phenol deprotection) and cleavage of labile protecting group when applicable (e.g. Boc group, silylated group, etc...) can be performed by any suitable reagent known to the person skilled in the art (e.g. BBr₃ (neat or as solution in an appropriate solvent), BCl₃, ...). The
- 10 reagents are commercially available or synthesized as described in the section "Examples of intermediates and their preparation".

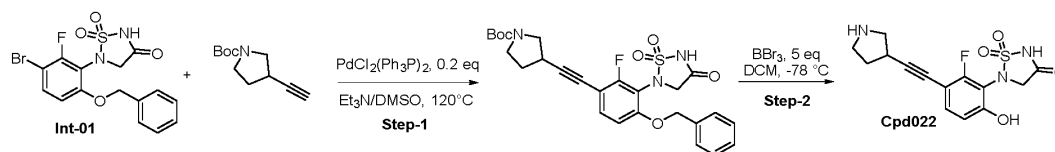
Reagent Step-1	Solvent Step-1	Temp. Step-1	Reagent Step-2	Compound
	CH ₃ CN	RT	BBr ₃	Cpd020
	CH ₃ CN	90°C	BBr ₃	Cpd079
	CH ₃ CN	60°C	BBr ₃	Cpd080
	CH ₃ CN	60°C	BBr ₃	Cpd097
	CH ₃ CN	60°C	BBr ₃	Cpd101
	CH ₃ CN	90°C	BCl ₃	Cpd102
	CH ₃ CN	60°C	BCl ₃	Cpd103
	CH ₃ CN	60°C	BCl ₃	Cpd104
	CH ₃ CN	90°C	BCl ₃	Cpd118
	CH ₃ CN	90°C	BCl ₃	Cpd119
	CH ₃ CN	90°C	BCl ₃	Cpd140
	CH ₃ CN	85°C	BCl ₃	Cpd148
	CH ₃ CN	65°C	BCl ₃	Cpd161

Example 4: Synthesis of 5-(3-((1-acetylazetidin-3-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd021**)



- Step-1: To a stirred solution of tert-butyl 3-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)azetidine-1-carboxylate (Intermediate from Cpd019 synthesis, 300 mg, 0.582 mmol, 1 eq) in DCM (10 mL) was added TFA (331 mg, 2.91 mmol, 5.0 eq) dropwise at 0°C and the resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and co-distilled with DCM to obtain 300 mg of 5-(3-(azetidin-3-ylethynyl)-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (as TFA salt), which was used in the next step without purification. LC-MS (LC-M): r.t. = 1.27 min ; m/z 414 [M-H]⁻
- Step-2: To a stirred solution of 5-(3-(azetidin-3-ylethynyl)-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (as TFA salt, 250 mg, 0.602 mmol, 1 eq) and AcOH (72 mg, 1.20 mmol, 2.0 eq) in DMF (5 mL) were added DIPEA (0.32 mL, 1.81 mmol, 3.0 eq), followed by T3P (50% in EtOAc, 0.287 mL, 0.90 mmol, 1.5 eq) at 0°C. The resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to 0°C, quenched with ice-water (1 mL) and concentrated under reduced pressure to get a crude residue, which was purified by reverse phase column chromatography eluting with a gradient of CH₃CN in H₂O (10-30%) to yield 250 mg of 5-(3-((1-acetylazetidin-3-yl)ethynyl)-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown solid. LC-MS (LC-U): r.t. = 0.68 min ; m/z 456 [M-H]⁻
- Step-3: To a stirred solution of 5-(3-((1-acetylazetidin-3-yl)ethynyl)-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (180 mg, 0.393 mmol, 1.0 eq) in DCM (15 mL) was added BBr₃ (1M in DCM, 1.18 mL, 1.18 mmol, 3 eq) dropwise at -78°C and the resulting reaction mixture was then stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and concentrated under reduced pressure to get a crude residue, which was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (0-30%). Obtained compound was further purified by Prep-HPLC (Column: X-Bridge C18 (19*150 mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B): 0/10, 2/10, 10/35, 12/35, 12.1/100, 15/100, 15.1/10, 20/10. Flow: 15 mL/min. Temperature: ambient.) to yield 30 mg of 5-(3-((1-acetylazetidin-3-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-E): r.t. = 2.60 min (99.9%); m/z 368 [M+H]⁺
- ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.23 (t, 1H), 6.66 (d, 1H), 4.39 (t, 1H), 4.15-4.13 (m, 2H), 3.94 (s, 2H), 3.79-3.70 (m, 2H), 1.76 (s, 3H)
- ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.6 (d).

Example 5: Synthesis of 5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd022)



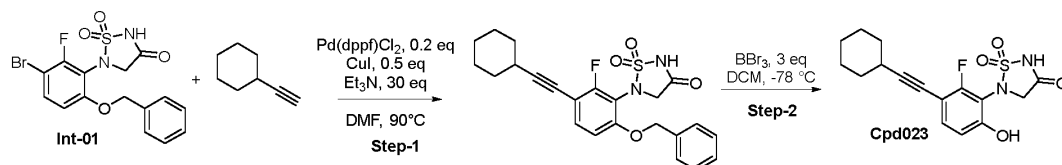
Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (1 g, 2.41 mmol), tert-butyl 3-ethynylpyrrolidine-1-carboxylate (1.4 g, 7.23 mmol, 1 eq) in triethylamine (5 mL) and DMSO (5 mL) was degassed for 10 min with Ar. Then $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (338 mg, 0.482 mmol, 0.2 eq) was added at RT and the resulting reaction mixture was heated and stirred at 120°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by reverse phase column chromatography eluting with a gradient of CH_3CN in H_2O (0-30%) to yield 350 mg of tert-butyl 3-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl) ethynyl) pyrrolidine-1-carboxylate as a pale-yellow solid. LC-MS (LC-M): r.t. = 1.82 min ; m/z 528 $[\text{M}-\text{H}]^-$

Step-2: To a stirred solution of tert-butyl 3-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl) ethynyl) pyrrolidine-1-carboxylate (330 mg, 0.623 mmol, 1 eq) in DCM (15 mL) was added BBr_3 (1M in DCM, 3.11 mL, 3.11 mmol, 5 eq) dropwise at -78°C and the resulting reaction mixture was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and concentrated under reduced pressure to get a crude residue, which was purified by reverse phase column chromatography eluting with a gradient of CH_3CN in H_2O (0-30%). Obtained compound was further purified by Prep-HPLC (Column: UniHybrid C18 (150*25 mm, 8 μm). Mobile phase A: 10 mM NH_4HCO_3 in H_2O ; Mobile phase B: CH_3CN . Gradient (Time(min)/%B) : 0/5, 2/5, 10/30, 12.8/30, 13/100, 17/100, 17.02/5, 20/5. Flow: 18 mL/min. Temperature: ambient.) to yield 18 mg of 5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off- white solid. LC-MS (LC-A): r.t. = 1.02 min (99.4%); m/z 340 $[\text{M}+\text{H}]^+$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 7.19 (t, 1H), 6.66 (d, 1H), 3.94 (s, 2H) 3.25-2.93 (m, 5H), 2.22-2.15 (m, 1H), 1.90-1.84 (m, 1H)

^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ ppm: -113.6 (d).

Example 6: Synthesis of 5-(3-(cyclohexylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd023)



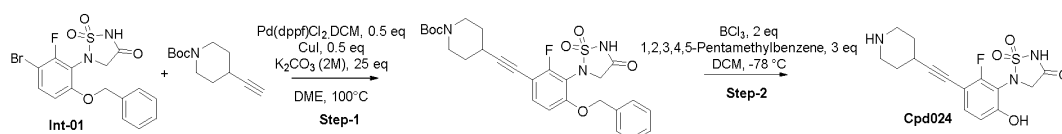
Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.72 mmol), ethynylcyclohexane (313 mg, 2.89 mmol, 4 eq) and triethylamine (3.02 mL, 21.68 mmol, 30 eq) in DMF (6 mL) was degassed for 20 min with Ar. Then
 5 Pd(dppf)Cl₂ (106 mg, 0.144 mmol, 0.2 eq) followed by CuI (69 mg, 0.361 mmol, 0.5 eq) were added at RT and the resulting reaction mixture was then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was evaporated and the residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (10-12%) to yield
 10 231 mg of 5-(6-(benzyloxy)-3-(cyclohexylethynyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown gummy. LC-MS (LC-R): r.t. = 2.04 min ; m/z 441 [M-H]⁻

Step-2: To a stirred solution of 5-(6-(benzyloxy)-3-(cyclohexylethynyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (230 mg, 0.520 mmol, 1 eq) in DCM (7 mL) was added BBr₃ (1M in DCM, 1.56 mL, 1.56 mmol, 3 eq) dropwise at -78°C and the reaction mixture was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture
 15 was quenched with aq. NaHCO₃ solution at -78°C, then allowed to warm to RT. Volatiles were evaporated and remaining aqueous solution was lyophilized. The obtained residue was purified by reverse phase column chromatography eluting with a gradient of CH₃CN in H₂O (0-35%) to yield 72 mg of 5-(3-(cyclohexylethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-E): r.t. = 3.54 min (97.2%); m/z 351 [M-H]⁻

20 ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.84 (s, 1H), 7.15 (t, 1H), 6.63 (d, 1H), 3.94 (s, 2H), 2.67-2.62 (m, 1H), 1.80-1.66 (m, 4H), 1.50-1.33 (m, 6H).

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -114.0 (s).

Example 7 : Synthesis of 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd024)



25

Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (200 mg, 0.482 mmol, 1 eq) and K₂CO₃ (6 mL, 2M aq. solution, 25 eq) in DME (6 mL) was degassed for 10 minutes with Ar. Phenylacetylene (0.26 g, 2.41 mmol, 5 eq), CuI (46 mg, 0.240 mmol, 0.5 eq) and Pd(dppf)Cl₂-DCM complex (197 mg, 0.241 mmol, 0.5 eq) were then
 30 added and the reaction mixture was heated at 100°C. After completion of the reaction (monitored by LCMS), the reaction mixture was diluted with DCM and the organic layer was separated. The

aqueous layer was extracted with 30% MeOH-DCM. The combined organic layers were dried over Na₂SO₄ and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%) to yield 150 mg of 5-(2-(Benzyloxy)-6-fluoro-4-(phenylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown solid.

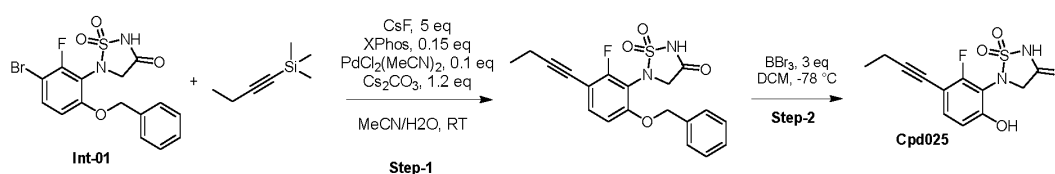
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.48 (d, 2 H), 7.35-7.29 (m, 4 H), 6.91-6.88 (m, 1 H), 5.19 (s, 2H), 4.09 (bs, 1 H), 3.96 (s, 2 H), 3.58 (bs, 2 H), 3.16 (s, 3 H), 2.9 (s, 1 H), 1.79 (s, 2 H), 1.55-1.49 (m, 1 H), 1.40 (s, 9 H).

Step-2: To a stirred solution of tert-butyl 4-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)piperidine-1-carboxylate (85 mg, 0.194 mmol, 1 eq) in DCM (1 mL) at -78°C was added 1,2,3,4,5-pentamethylbenzene (86 mg, 0.58 mmol, 3 eq) and BCl₃ (0.39 mL, 0.39 mmol, 1M solution in DCM, 2 eq) and the reaction mixture was stirred at -78°C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water, allowed to reach RT and volatiles were removed. Residue was purified by Prep-HPLC (Column: YMC-Actus C18 (20*250 mm, 5 μm). Mobile phase A: 20 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B) : 0/5, 8/5, 30/55, 31/95, 33/95, 34/5, 36/5. Flow: 16 mL/min. Temperature: ambient.) to yield 18 mg of 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white gum.

LC-MS (LC-G): r.t. = 1.53 min (97.7%) ; m/z 354 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.60 (bs, 2 H), 7.20 (t, 1 H), 6.66 (d, 2 H), 3.94 (s, 2H), 3.16-3.15 (m, 2 H), 3.02-2.96 (m, 3 H), 2.02-1.96 (m, 2 H), 1.76-1.71 (m, 2 H).

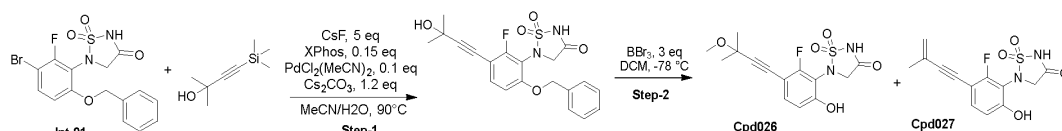
Example 8 : Synthesis of 5-(3-(but-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd025)



Step-1: A solution of 5-(6-benzyloxy-3-bromo-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (203 mg, 0.49 mmol, 1 eq), CsF (383 mg, 2.44 mmol, 5 eq), Pd(CH₃CN)₂Cl₂ (13 mg, 0.049 mmol, 0.1 eq), Cs₂CO₃ (193 mg, 0.59 mmol, 1.2 eq), XPhos (35 mg, 0.073 mmol, 0.15 eq) in CH₃CN (6.1 mL) and H₂O (0.050 mL) was degassed with Ar. 1-(trimethylsilyl)-1-butyne (0.35 mL, 2.44 mmol) was then added and the resulting mixture was stirred at RT. After completion of the reaction (TLC monitoring), the mixture was diluted with DCM, washed with a 1M aq. NaHSO₄ solution. The organic layer was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (2-12%) to yield 139 mg of 5-(6-benzyloxy-3-but-1-ynyl-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a beige solid. LC-MS (LC-N): r.t. = 1.22 min ; m/z 389 [M+H]⁺, 387 [M-H]⁻

Step-2: A solution of 5-(6-benzyloxy-3-but-1-ynyl-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (131 mg, 0.34 mmol, 1 eq) in DCM (5 mL), cooled at -78°C, was treated with BBr₃ (0.097 mL, 1.01 mmol, 3 eq) and the reaction mixture was stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a 8:2 mixture of DCM/3N ammonia solution in MeOH at -78°C. The reaction mixture was partitioned between water and DCM and the pH of the aq. layer was adjusted to 2 by addition of a 1M solution of NaHSO₄. The organic phase was separated and the aqueous layer was reextracted 3 times with EtOAc. Combined organic layers were concentrated and the residue was purified by column chromatography on silica gel eluting with MeOH in DCM (2-16%). Obtained compound was further purified by Prep-HPLC (Column: XBridge C18 (19*100 mm, 5 μm). Mobile phase A: 25 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN:MeOH (50:50). Gradient (Time(min)/%B): 0/25, 1/25, 7/95, 9.8/95, 10/25, 12/25. Flow: 20 mL/min. Temperature: ambient.) to yield 17 mg of 5-(3-(but-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid. LC-MS (LC-H): r.t. = 2.38 min (99.0%); m/z 299 [M+H-NH₃]⁺, 297 [M-H-NH₃]⁻.
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.89 (s, 1H), 6.88 - 7.31 (m, 5H), 6.64 (d, 1H), 3.95 (s, 2H), 2.42 (q, 2H), 1.16 (t, 3H)
 Column: XBridge C18 (19*100 mm, 5 μm). Mobile phase A: 25 mM NH₄HCO₃ in H₂O; Mobile

Example 9: Synthesis of 5-(2-fluoro-6-hydroxy-3-(3-methoxy-3-methylbut-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd026) and 5-(2-fluoro-6-hydroxy-3-(3-methylbut-3-en-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd027)



Step-1: A solution of 5-(6-benzyloxy-3-bromo-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (250 mg, 0.60 mmol, 1 eq), 2-methyl-4-(trimethylsilyl)but-3-yn-2-ol (495 mg, 3.0 mmol, 3 eq), Pd(CH₃CN)₂Cl₂ (16 mg, 0.060 mmol, 0.1 eq), Cs₂CO₃ (238 mg, 0.72 mmol, 1.2 eq), XPhos (43 mg, 0.090 mmol, 0.15 eq) in a mix of CH₃CN (6.0 mL) and H₂O (0.020 mL) was degassed and backfilled with Ar. CsF (471 mg, 3.01 mmol, 5 eq) was then added and the mixture was stirred at RT. After completion of the reaction (LC-MS monitoring), the mixture was diluted with DCM, washed with a 1M aq. NaHSO₄ solution. The organic layer was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (1-16%) to yield 173 mg of 5-[6-benzyloxy-2-fluoro-3-(3-hydroxy-3-methyl-but-1-ynyl)phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a beige solid. LC-MS (LC-O): r.t. = 1.12 min ; m/z 401 [M+H- H₂O]⁺, 417 [M-H]⁻

Step-2: A solution of 5-[6-benzyloxy-2-fluoro-3-(3-hydroxy-3-methyl-but-1-ynyl)phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (173 mg, 0.41 mmol, 1 eq) in dry DCM (8.0 mL) was cooled at -78°C,

treated with BBr_3 (0.119 mL, 1.24 mmol, 3 eq.) and then stirred at -78°C . After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a 8:2 mixture of DCM/3N ammonia solution in MeOH at -78°C . The reaction mixture was partitioned between water and DCM and the pH of the aq. layer was adjusted to 2 by addition of a 1M solution of NaHSO_4 . The organic phase was separated and the aqueous layer was reextracted 3 times with EtOAc. Combined organic layers were concentrated and the residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (2-16%) to afford a mixture of the 2 title compounds. This mixture was further purified by Prep-HPLC (Column: XBridge C18 (19*100 mm, 5 μm). Mobile phase A: 25 mM NH_4HCO_3 in H_2O ; Mobile phase B: $\text{CH}_3\text{CN}:\text{MeOH}$ (50:50). Gradient (Time(min)/%B): 0/25, 1/25, 7/95, 9.8/95, 10/25, 12/25. Flow: 20 mL/min. Temperature: ambient.) to yield 8 mg of 5-[2-fluoro-6-hydroxy-3-(3-methoxy-3-methylbut-1-yn-1-yl)phenyl]-1 λ^6 ,2,5-thiadiazolidine-1,1,3-trione as a white solid and 6 m of 5-[2-fluoro-6-hydroxy-3-(3-methylbut-3-en-1-yn-1-yl)phenyl]-1 λ^6 ,2,5-thiadiazolidine-1,1,3-trione as a white solid.

15 Analytically of 5-(2-fluoro-6-hydroxy-3-(3-methoxy-3-methylbut-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd026**).

LC-MS (LC-C): r.t. = 2.82 min (98.7%); m/z 311 $[\text{M}+\text{H}-\text{CH}_3\text{OH}]^+$, 341 $[\text{M}-\text{H}]^-$

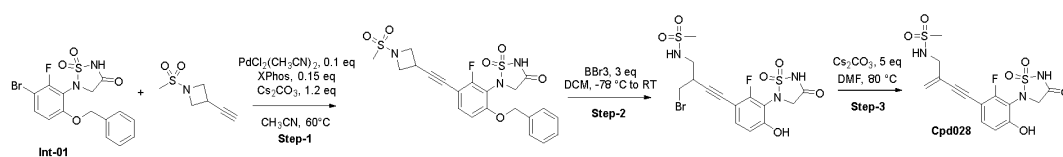
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 7.22 (t, 1H), 7.09 (brs., 2H), 6.67 (d, 1H), 3.95 (s, 2H), 3.30 (brs, 3H), 1.46 (s, 6H)

20 Analytically of 5-(2-fluoro-6-hydroxy-3-(3-methylbut-3-en-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd027**).

LC-MS (LC-C): r.t. = 3.16 min (98.0%); m/z 311 $[\text{M}+\text{H}]^+$, 309 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 7.25 (t, 1H), 7.10 (brs., 1H), 6.69 (d, 1H), 5.37 (brs., 2H), 3.96 (s, 2H), 1.94 (s, 3 H)

25 Example 10: Synthesis of N-(4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)-2-methylenebut-3-yn-1-yl)methanesulfonamide (**Cpd028**)



30 Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (500 mg, 1.20 mmol, 1 eq), 3-ethynyl-1-(methyl sulfonyl)azetidine (575 mg, 3.61 mmol, 3 eq) and Cs_2CO_3 (471 mg, 1.44 mmol, 1.2 eq) in CH_3CN (15 mL) was degassed for 10 min with Ar. $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (15.6 mg, 0.060 mmol, 0.05 eq) followed by XPhos (86 mg, 0.18 mmol, 0.15 eq) were added at RT and the resulting reaction mixture was then stirred at 60°C . After completion of the reaction (TLC monitoring), the reaction mixture was diluted with water (30 mL) and extracted with DCM (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by

reverse phase C18 column chromatography eluting with a gradient of CH₃CN in H₂O (22-25%) to yield 400 mg of 5-(6-(benzyloxy)-2-fluoro-3-((1-(methylsulfonyl) azetidin-3-yl) ethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-Q): r.t. = 1.93 min ; m/z 494 [M+H]⁺

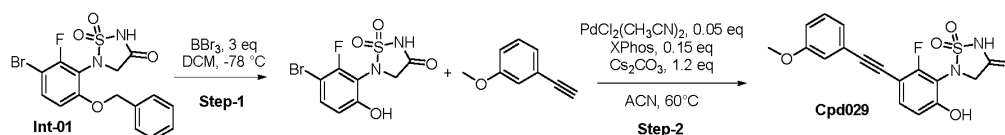
- 5 Step-2: A stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-((1-(methylsulfonyl) azetidin-3-yl) ethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.60 mmol, 1.0 eq) in DCM (10 mL), cooled to -78°C, was treated dropwise with a BBr₃ solution (1M in DCM, 3.64 mL, 3.64 mmol, 6 eq). The resulting reaction mixture was then allowed to warm to RT and stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with sat. NaHCO₃
- 10 solution (6 mL) and concentrated under reduced pressure to get the crude compound N-(2-(bromomethyl)-4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl) but-3-yn-1-yl) methanesulfonamide (300 mg) as a brown solid, which was used in the next step without purification. LC-MS (LC-M): r.t. = 1.31 min ; m/z 484 [M-H]⁻

- Step-3: To a stirred solution of N-(2-(bromomethyl)-4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl) but-3-yn-1-yl) methanesulfonamide (300 mg, 0.61 mmol, 1 eq) in DMF (7 mL) was added Cs₂CO₃ (1 g, 3.09 mmol, 5 eq) at 0°C. The resulting reaction mixture was then stirred at 80°C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the residue was purified by reverse phase column chromatography (C18) eluting with a gradient of CH₃CN in H₂O (22-25%). Obtained compound was further purified by
- 20 reverse phase Prep-HPLC (Column: LUNA C18 (250*21.2 mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B): 0/15, 2/15, 10/35, 12.2/35, 12.3/98, 17/98, 17.1/15, 20/15. Flow: 16 mL/min. Temperature: ambient.) to yield 20 mg of N-(4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)-2-methylenebut-3-yn-1-yl)methanesulfonamide as an off-white solid. LC-MS (LC-A): r.t. = 1.31 min (96.7%); m/z 402
- 25 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.28 (t, 1H), 6.70 (d, 1H), 5.61-5.55 (m, 2H), 3.95 (s, 2H), 3.72 (s, 2H), 2.94 (s, 3H)

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -112.7 (d).

- Example 11: Synthesis of 5-(2-fluoro-6-hydroxy-3-((3-methoxyphenyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd029**)
- 30



- Step-1: To a stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (3 g, 7.23 mmol, 1 eq) in DCM (50 mL) was added BBr₃ (1M in DCM, 21.7 mL, 21.7 mmol, 3 eq) dropwise at -78°C and the resulting reaction mixture was stirred at -78°C. After
- 35 completion of the reaction (TLC monitoring), the reaction mixture was quenched with a 7M NH₃

solution in MeOH at -78°C and then concentrated under reduced pressure. The residue was purified by reverse phase column chromatography eluting with a gradient of CH₃CN in H₂O (10-20%) to yield 2.2 g of 5-(2-fluoro-6-hydroxy-3-(4-methylpent-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid.

5 ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.79 (brs, 2H), 7.39 (t, 1H), 6.69 (dd, 1H), 3.98 (s, 2H)

Step-2: A stirred solution of 5-(3-bromo-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (250 mg, 0.77 mmol, 1.0 eq), 1-ethynyl-3-methoxybenzene (305 mg, 2.31 mmol, 3.0 eq) and Cs₂CO₃ (300 mg, 0.92 mmol, 1.2 eq) in CH₃CN (10 mL) was degassed with Ar for 10 min.

Then Pd(CH₃CN)₂Cl₂ (9.9 mg, 0.038 mmol, 0.05 equiv.) and XPhos (55 mg, 0.115 mmol, 0.15

10 equiv.) were added and the resulting mixture was stirred at 60°C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The residue

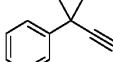
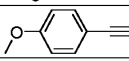
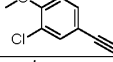
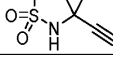
was purified by reverse phase column chromatography eluting with a gradient of CH₃CN in H₂O (40-45%). The obtained compound was further purified by Prep-HPLC (Column: X-SELECT CSH C18 (19*150mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN.

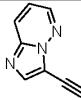
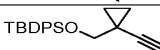
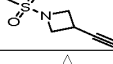
15 Gradient (Time (min)/%B): 0/20, 2/20, 10/50, 12/50, 12.1/98, 15/98, 15.1/20, 18/20. Flow: 15 mL/min. Temperature: ambient.) to yield 21 mg of 5-(2-fluoro-6-hydroxy-3-((3-methoxyphenyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-F): r.t. = 4.63 min (98.8%); m/z 375 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.37-7.30 (m, 2H), 7.11-7.06 (m, 2H), 6.98 (dd, 1H), 6.72 (d, 1H), 3.98 (s, 2H), 3.79 (s, 3H).

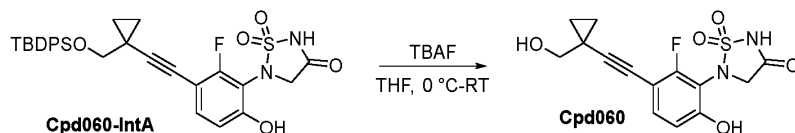
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -112.8 (d).

The following compounds were prepared in a manner similar to compound **Cpd029** (by use of appropriate alkyne reagent in step-2 and purification methods known to the person skilled in the art). The reagents are commercially available or synthesized as described in the section "examples of intermediates and their preparation".

Reagent Step-2	Solvent Step-2	Temp. Step-2	Compound
	CH ₃ CN	60°C	Cpd030
	CH ₃ CN	60°C	Cpd031
	CH ₃ CN	60°C	Cpd032
	DMA	80°C	Cpd033
	CH ₃ CN	60°C	Cpd034
	CH ₃ CN	60°C	Cpd049

	CH ₃ CN	60°C	Cpd050
	CH ₃ CN	90°C	Cpd052
	CH ₃ CN	60°C	Cpd058
	CH ₃ CN	60°C	Cpd060-IntA
	CH ₃ CN	60°C	Cpd062
	CH ₃ CN	60°C	Cpd072
	CH ₃ CN	90°C	Cpd083
	CH ₃ CN	50°C	Cpd105

Cpd060 can be obtained from Cpd060-IntA following the below procedure :

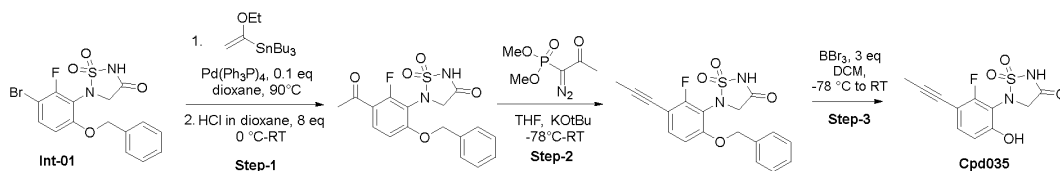


A stirred solution of Cpd060-IntA (225 mg, 0.389 mmol, 1.0 eq) in THF (5 mL), at 0°C, was treated with a 1M TBAF solution in THF (0.583 mL, 0.583 mmol, 1.5 eq). The reaction mixture was then allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was evaporated and the crude compound was purified by Prep-HPLC (Column: LUNA C18 (21.2*250mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B): 0/5,2/5,10/40,12/40,12.1/98,17/98,17.1/5,19/5. Flow: 15 mL/min. Temperature: ambient.) to yield 6 mg of 5-(2-fluoro-6-hydroxy-3-((1-(hydroxymethyl)cyclopropyl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

LC-MS (LC-A): r.t. = 1.23 min (97.6%); m/z 339 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.16 (t, 1H), 6.63 (d, 1H), 4.90 (t, 1H), 3.93 (s, 2H), 3.42 (d, 2H), 0.85 (brs, 4H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.7 (d).

Example 12: Synthesis of 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd035)



Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (800 mg, 1.83 mmol, 1 eq) and tributyl(1-ethoxyvinyl)stannane (1.30 mL, 3.85 mmol,

2 eq) in 1,4-dioxane (10 mL) was degassed with Ar for 10 min. Pd(PPh₃)₄ (223 mg, 0.193 mmol, 0.1 eq) was added at RT and the resulting reaction mixture was then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was treated with 4M HCl in dioxane (4 mL) at 0°C and then stirred at RT for 2 h. The reaction mixture was filtered through a celite bed and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (30-36%) to yield 450 mg of 5-(3-acetyl-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-U): Rt = 0.65 min ; m/z 377 [M-H]⁻

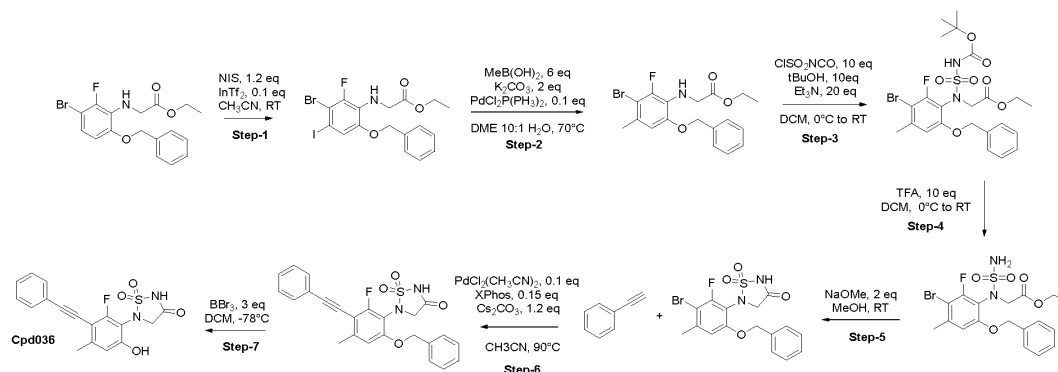
Step-2: To a stirred solution of dimethyl (1-diazo-2-oxopropyl)phosphonate (203 mg, 1.06 mol, 2 eq) in THF (5 mL) was added potassium tert-butoxide (1M in THF, 3.17 mL, 3.17 mol, 6 eq) at -78°C. The reaction mixture was stirred at the same temperature for 10 min and then treated dropwise with a solution of 5-(3-acetyl-6-(benzyloxy)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (200 mg, 0.529 mol, 1 eq) in THF (5 mL). The resulting reaction mixture was then allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice water (2 mL) and concentrated under reduced pressure. The residue was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (25%) to yield 100 mg of 5-(6-(benzyloxy)-2-fluoro-3-(prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a brown solid. LC-MS (LC-U): r.t. = 0.77 min ; m/z 373 [M-H]⁻

Step-3: To a stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-(prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (200 mg, 0.534 mmol, 1 eq) in DCM (20 mL) was added BBr₃ (1M in DCM, 1.60 mL, 1.60 mmol, 3 eq) at -78°C. The resulting reaction mixture was then stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M NH₃ solution in MeOH at -78°C and concentrated under reduced pressure. The residue was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (0-12%). The obtained crude compound (70 mg) was further purified by Prep-HPLC (Column: XBridge C18 (19*150 mm, 5 µm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B): 0/15, 2/15, 10/55, 13/55, 13.1/100, 16/100, 16.02/15, 19/15. Flow: 15 mL/min. Temperature: ambient.) to yield 5 mg of 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a pale-brown solid. LC-MS (LC-D): r.t. = 2.45 min (95.1%); m/z 283 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.17 (t, 1H), 6.64 (dd, 1H), 3.94 (s, 2H), 2.04 (s, 3H).

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -114.4 (d).

Example 13: Synthesis of 5-(2-fluoro-6-hydroxy-4-methyl-3-(phenylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd036)



Step-1: In a light-protected flask (alumina foil), a stirred mixture of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-anilino)acetate (221 mg, 0.58 mmol, 1 eq) and Indium(III) trifluoromethanesulfonate (33 mg, 0.058 mmol, 0.1 eq) in CH₃CN (4.4 mL) was treated portionwise with N-Iodosuccinimide (159 mg, 0.69 mmol, 1.2 eq) and the resulting mixture was stirred at RT. After completion of the reaction (TLC monitoring), the crude reaction mixture was poured onto iced water. 5 mL of a sat. Na₂S₂O₃ aq. solution were added and the mixture was partitioned with EtOAc. Aqueous layer was back extracted again twice with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-10%) to yield 200 mg of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-iodo-anilino)acetate as a colorless oil.

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.51-7.45 (m, 2H), 7.45-7.39 (m, 2H), 7.39-7.32 (m, 1H), 7.31 (d, 1H), 5.47 (td, 1H), 5.16 (s, 2H), 4.10-3.99 (m, 4H), 1.14 (t, 3H).

Step-2: To a stirred suspension of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-iodo-anilino)acetate (670 mg, 1.32 mmol, 1 eq), methylboronic acid (488 mg, 7.91 mmol, 6 eq) and K₂CO₃ (364 mg, 2.64 mmol, 2 eq) in a previously degassed 5:1 mixture of monoglyme (13.2 mL) and H₂O (2.7 mL) was added (under Ar atmosphere) PdCl₂(PPh₃)₂ (94 mg, 0.13 mmol, 0.1 eq) and the resulting mixture was heated up to 70°C. After completion of the reaction (TLC monitoring), the crude reaction mixture was diluted with EtOAc and filtered through a pad of celite. The liquor was then partitioned with a sat. NaHCO₃ aq. solution and the aqueous layer was back extracted twice with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of EtOAc in PE (0-10%) to yield 332 mg of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-anilino)acetate as a colorless oil. LC-MS (LC-O): r.t. = 1.82 min; m/z 396 [M+H]⁺

Step-3: A stirred solution of 2-methylpropan-2-ol (0.790 mL, 8.33 mmol, 10 eq) in dry DCM (8.3 mL) was slowly treated at 0°C and under an Ar atmosphere with chlorosulfonyl isocyanate (0.740 mL, 8.33 mmol, 10 eq) and the resulting mixture was left under stirring for 30min at 0°C. A previously made solution of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-anilino)acetate (330 mg, 0.83 mmol, 1 eq) and triethylamine (2.3 mL, 16.66 mmol, 20 eq) in 5 mL of dry DCM was then added dropwise at 0°C and the resulting mixture was stirred at RT. After completion of the

reaction (TLC monitoring), the crude reaction mixture was diluted with DCM and partitioned with iced water. Aqueous layer was back extracted again twice with DCM. Combined organic extracts were successively washed with a 1M NaHSO₄ aq. solution, with brine, dried over MgSO₄, filtered and concentrated under vacuo to give the 480 mg of ethyl 2-[6-benzyloxy-3-bromo-N-(tert-butoxycarbonylsulfamoyl)-2-fluoro-4-methyl-anilino]acetate as a colorless oil which crystallized upon standing. LC-MS (LC-O): r.t. = 1.64 min ; m/z 573, 575 [M-H]⁻

Step-4: A stirred solution of ethyl 2-[6-benzyloxy-3-bromo-N-(tert-butoxycarbonylsulfamoyl)-2-fluoro-4-methyl-anilino]acetate (480 mg, 0.83 mmol, 1 eq) in dry DCM (8.3 mL) was cooled to 0°C and treated with TFA (0.638 mL, 8.34 mmol, 10 eq) and the resulting mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the crude mixture was concentrated to dryness. The residue was diluted with DCM, partitioned with a sat. NaHCO₃ aq. solution and the aqueous layer was back extracted twice with DCM. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated under vacuo to yield 395 mg of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-N-sulfamoyl-anilino)acetate as a ginger oil which was used in the next step without purification. LC-MS (LC-O): r.t. = 1.57 min; m/z 475, 477 [M-H]⁻

Step-5: A stirred mixture of ethyl 2-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-N-sulfamoyl-anilino)acetate (400 mg, 0.84 mmol, 1 eq) in dry MeOH (5.6 mL) was treated with a 25% wt. NaOMe solution (0.385 mL, 1.68 mmol, 2 eq) and the resulting mixture was stirred at RT. After completion of the reaction (TLC monitoring), the crude mixture was poured onto crushed ice. The pH was then adjusted to ~2 with a 1N HCl aq. solution and the resulting aqueous layer was extracted three times with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%). Pure fractions were combined, evaporated and residue was triturated in Et₂O to yield 180 mg of 5-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a light grey powder. LC-MS (LC-N): r.t. = 1.16 min; m/z 427, 429 [M-H]⁻

Step-6: To a stirred mixture of 5-(6-benzyloxy-3-bromo-2-fluoro-4-methyl-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (120 mg, 0.28 mmol, 1 eq), phenylacetylene (0.094 mL, 0.84 mmol, 3 eq) and Cs₂CO₃ (110 mg, 0.34 mmol, 1.2 eq) in degassed CH₃CN (2.8 mL) were added under inert atmosphere XPhos (20 mg, 0.042 mmol, 0.15 eq) and Pd(CH₃CN)₂Cl₂ (7.3 mg, 0.028 mmol, 0.1 eq) and the resulting mixture was heated up to 90°C. After completion of the reaction (TLC monitoring), the crude mixture was diluted with DCM and filtered through a pad of celite. The liquor was then partitioned with water. Aqueous layer was acidified to a pH value of ~4 adding a 1M NaHSO₄ aq. solution and was extracted three times with DCM. Combined chlorinated extracts were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-10%) to yield 40 mg of 5-[6-benzyloxy-2-fluoro-4-methyl-3-(2-phenylethynyl)phenyl]-1,1-dioxo-1,2,5-

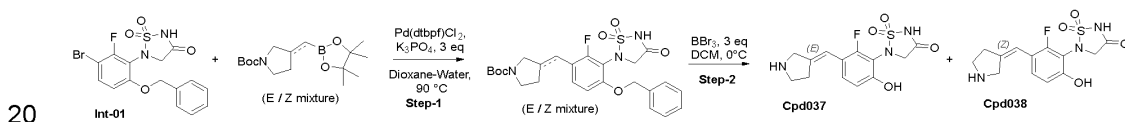
thiadiazolidin-3-one as a pale yellowish solid. LC-MS (LC-N): r.t. = 1.37 min ; m/z 451 [M+H]⁺, 449 [M-H]⁻

- Step-7: A stirred solution of 5-[6-benzyloxy-2-fluoro-4-methyl-3-(2-phenylethynyl)phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (40 mg, 0.089 mmol, 1 eq) in dry DCM (8.9 mL) was treated with BBr₃ (0.026 mL, 0.27 mmol, 3 eq) dropwise at -78°C and then stirred at the same temperature. After completion of the reaction (TLC monitoring), the crude mixture was quenched by 10 mL of a 10:1 DCM/MeOH solution and the resulting solution was concentrated to dryness. The residue was purified by reversed phase column chromatography (C18) eluting with a gradient of CH₃CN in H₂O (0-50%) to yield 22 mg of 5-(2-fluoro-6-hydroxy-4-methyl-3-(phenylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a thin white powder. LC-MS (LC-I): r.t. = 2.27 min (92.2%) ; m/z 359 [M-H]⁻
- ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.94 (s, 1H), 7.60-7.48 (m, 2H), 7.48-7.33 (m, 3H), 6.66 (s, 1H), 3.96 (s, 2H), 2.39 (s, 3H).

- The following compounds were prepared in a manner similar to compound **Cpd036** (by use of appropriate alkyne reagent in step-6 and purification methods known to the person skilled in the art).

Reagent Step-6	Solvent Step-6	Temp. Step-6	Compound
	CH ₃ CN	90°C	Cpd063

Example 14: Synthesis of (E)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd037**) and (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd038**)



- Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (400 mg, 0.963 mmol, 1 eq), tert-butyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)pyrrolidine-1-carboxylate ((E-Z) mixture, 447 mg, 1.45 mmol, 2.4 eq) and K₃PO₄ (613 mg, 2.89 mmol, 3 eq) in a pre-degassed mix of 1,4-dioxane (10 mL) and water (2 mL) was degassed with Ar for 15 min. Pd(dtbpf)Cl₂ (63 mg, 0.096 mmol, 0.1 eq) was added at RT and solution was again degassed for another 5 min. The resulting reaction mixture was then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, quenched with ice cold water (40 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na₂SO₄ and concentrated.
- 30 The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-10%) to yield 430 mg of tert-butyl-3-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorobenzylidene)pyrrolidine-1-carboxylate as a E/Z mixture. LC-MS

(LC-A): r.t. = 2.28 min ; m/z 516 [M+H]⁺

- Step-2: A stirred solution of a E/Z mixture of tert-butyl-3-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorobenzylidene) pyrrolidine-1-carboxylate from step-1 (400 mg, 0.77 mmol, 1 eq) in DCM (20 mL) was treated with BBr₃ (1M in DCM, 2.32 mL, 2.33 mmol, 3 eq) dropwise at 0°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a 7M NH₃ in MeOH solution at 0°C and evaporated under reduced pressure. The residue was purified by Prep-HPLC (run 1 - Column: YMC Triart C18 (19*250 mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B): 0/5, 2/5, 8/25, 12/25, 12.1/100, 14/100, 14.1/5, 20/5. Flow: 17 mL/min. Temperature: ambient.) to yield 43 mg of (E)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide and a second mixed fraction (67 mg, yellow solid) which was again purified by Prep-HPLC (run 2 - Column: YMC Hydrosphere C18 (20*250 mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN:MeOH (50:50). Gradient (Time (min)/%B): 0/10, 2/10, 10/20, 15/90, 17/90, 17.2/10, 20/10. Flow: 17 mL/min. Temperature: ambient.) to yield 25 mg of (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid.

Analysis of (E)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd037**)

LC-MS (LC-J): r.t. = 2.01 min (98.3%) ; m/z 328 [M+H]⁺

- ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.68-8.60 (m, 2H), 7.21 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.05 (s, 2H), 3.86 (brs, 2H), 3.26 (t, 2H), 2.69-2.65 (m, 2H)

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -120.2 (d)

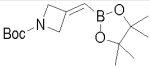
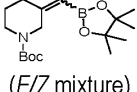
Analysis of (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd038**)

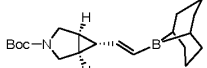
- LC-MS (LC-J): r.t. = 2.07 min (98.5%) ; m/z 328 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.98 (brs, 3H), 7.06 (t, 1H), 6.72 (d, 1H), 6.52 (s, 1H), 3.96 (s, 2H), 3.91 (s, 2H), 3.28 (t, 2H), 2.77 (t, 2H)

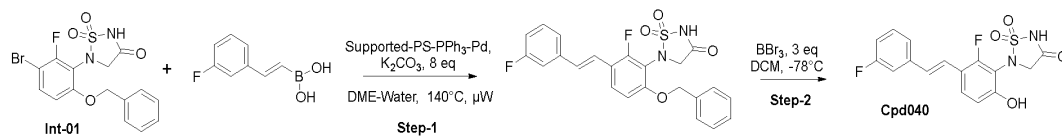
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.5 (d).

- The following compound were prepared in a manner similar to compound **Cpd037** (by use of appropriate reagent, catalyst, base, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Catalyst/Base/Solvent/Temp. Step-1	Compound
	Pd(dppf)Cl ₂ /K ₃ PO ₄ /dioxane-H ₂ O/90°C	Cpd039
 (E/Z mixture)	Pd(dtbpf)Cl ₂ /K ₃ PO ₄ /dioxane-H ₂ O/90°C	Cpd095, Cpd096

	Pd(dtbpf)Cl ₂ /K ₃ PO ₄ /dioxane-H ₂ O/80°C	Cpd112
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Example 15: Synthesis of (E)-5-(2-fluoro-3-(3-fluorostyryl)-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd040**)



Step 1: In a vial, a mixture of [(E)-2-(3-fluorophenyl)vinyl]boronic acid (179 mg, 1.06 mmol, 2 eq),
 5 5-(6-benzyloxy-3-bromo-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (220 mg, 0.53 mmol, 1 eq), K₂CO₃ (575 mg, 4.16 mmol, 8 eq), Supported PS-PPh₃-Pd (Biotage 0.12 mmol/g) (200 mg, 0.024 mmol, 0.05 eq) in a mix of DME (11 mL) and H₂O (3 mL) was degassed and back filled with Ar. This process was repeated 3 times and the vial was capped. The resulting mixture was then stirred in a microwave oven at 140°C for 30 min. The pH of the reaction mixture was
 10 adjusted to ~2 by addition of a 1M solution of NaHSO₄ and solids were filtered off. The filtrate was then partitioned between H₂O and EtOAc. After separation, the aqueous layer was extracted 3 times with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (2-20%) to yield 132 mg of 5-[6-benzyloxy-
 15 2-fluoro-3-[(E)-2-(3-fluorophenyl)vinyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a white solid. LC-MS (LC-P): r.t. = 1.86 min ; m/z 457 [M-H]⁻

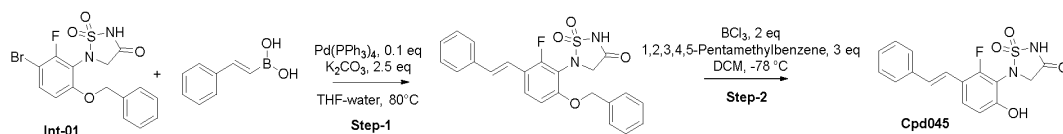
Step 2: A solution of 5-[6-benzyloxy-2-fluoro-3-[(E)-2-(3-fluorophenyl)vinyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (132 mg, 0.29 mmol, 1 eq) in DCM (5 mL) was treated with BBr₃ (0.083 mL, 0.87 mmol, 3 eq) dropwise at -78°C and resulting mixture was stirred at -78°C. After
 20 completion of the reaction (TLC monitoring), the mixture was quenched by addition of a 8:2 mixture of DCM and 3N solution of NH₃ in MeOH. The reaction mixture was partitioned between water and DCM. After separation, the organic layer was extracted twice with DCM. Combined organic extracts were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a gradient of MeOH in DCM (2-18%) to yield 69 mg of (E)-5-
 25 (2-fluoro-3-(3-fluorostyryl)-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid. LC-MS (LC-H): r.t. = 3.08 min (98.9%) ; m/z 367 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.80 (s, 1H), 7.53 (t, 1H), 7.49-7.33 (m, 3H), 7.30-7.20 (m, 1H), 7.18-7.11 (m, 1H), 7.11-7.03 (m, 1H), 6.75 (d, 1H), 4.02 (s, 2H).

The following compounds were prepared in a manner similar to compound **Cpd040** (by use of
 30 appropriate reagent, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Catalyst/Base/Solvent/Temp. Step-1	Purification method	Compound
	Supported PS-Pd-PPh ₃ /K ₂ CO ₃ /DME-H ₂ O/140°C (μW)	silica gel column chromatography	Cpd041
	Supported PS-Pd-PPh ₃ /K ₂ CO ₃ /DME-H ₂ O/140°C (μW)	silica gel column chromatography	Cpd042
	Supported PS-Pd-PPh ₃ /K ₂ CO ₃ /DME-H ₂ O/140°C (μW)	Prep-HPLC	Cpd043
	Pd(dtbpf)Cl ₂ /Cs ₂ CO ₃ /dioxane-H ₂ O/90°C	Prep-HPLC	Cpd044

Example 16: Synthesis of (E)-5-(2-fluoro-6-hydroxy-3-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd045**).



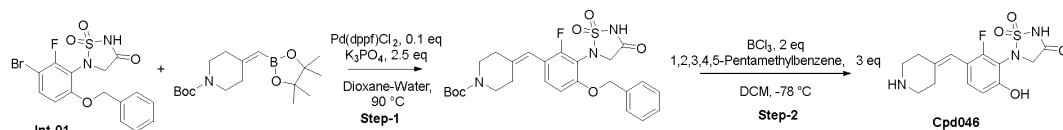
Step 1: To a degassed solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.72 mmol, 1 eq) in a mixture of THF (2 mL) and H₂O (0.5 mL) was added (E)-styrylboronic acid (160 mg, 1.08 mmol, 1.5 eq), K₂CO₃ (250 mg, 1.80 mmol, 2.5 eq) and Pd(PPh₃)₄ (84 mg, 0.072 mmol, 0.1 eq) and the mixture was heated at 80°C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with H₂O and extracted three times with 30% MeOH-DCM. The combined organic layers were dried over Na₂SO₄, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%) to yield 140 mg of (E)-5-(6-(benzyloxy)-2-fluoro-3-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as white solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.67-7.50 (m, 5H), 7.39-7.25 (m, 5H), 7.20 (s, 2H), 6.99 (d, 1H), 5.21 (s, 2H), 4.01 (s, 2H).

Step 2: To a stirred solution of (E)-5-(6-(benzyloxy)-2-fluoro-3-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (100 mg, 0.228 mmol, 1 eq) in DCM (2 mL) at -78°C was added 1,2,3,4,5-pentamethylbenzene (101 mg, 0.684 mmol, 3 eq) and BCl₃ (1M solution in DCM, 0.5 mL, 0.456 mmol, 2 eq). After completion of the reaction (TLC monitoring), the reaction mixture quenched with water and volatiles were evaporated. The residue was purified by Prep-HPLC (Column: YMC Actus Triart C18 (20*250 mm, 5 μm). Mobile phase A: 20 mM NH₄HCO₃ in H₂O; Mobile phase B: MeOH. Gradient (Time (min)/%B): 0/20, 3/50, 22/80, 23/95, 25/95, 26/20, 30/20. Flow: 16 mL/min. Temperature: ambient.) to yield 27 mg of (E)-5-(2-fluoro-6-hydroxy-3-styrylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as white solid. LC-MS (LC-K): r.t. = 2.85 min; m/z 347 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.66 (bs, 1H), 7.58-7.51 (m, 3H), 7.37 (t, 2H), 7.25 (t, 1H), 7.15 (d, 2H), 6.73 (d, 1H), 3.99 (s, 2H)

Example 17: Synthesis of 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd046**)



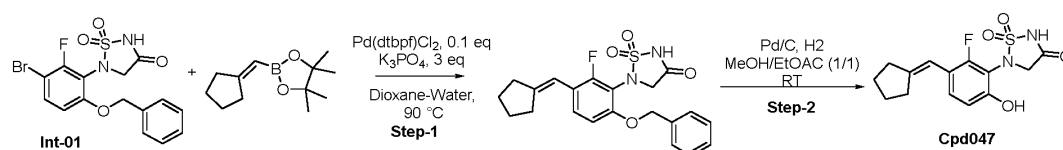
Step-1: A stirred solution of tert-butyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)piperidine-1-carboxylate (300 mg, 0.722 mmol, 1 eq), K₃PO₄ (246 mg, 1.81 mmol, 2.5 eq) and 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (351 mg, 1.08 mmol, 1.5 eq) in a mixture of 1,4-dioxane (4 mL) and H₂O (1 mL) was degassed for 15 min under Ar atmosphere and then treated with PdCl₂(dppf) (53 mg, 0.072 mmol, 0.1 eq). The resulting reaction mixture was then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with H₂O and EtOAc. The aqueous layer was back-extracted three times with EtOAc. The combined organic fractions were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%) to yield 350 mg of tert-butyl 4-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorobenzylidene)piperidine-1-carboxylate as brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.48 (d, 1H), 7.36-7.27 (m, 3H), 7.12 (t, 1H), 6.88 (d, 1H), 6.19 (s, 1H), 5.16 (s, 2H), 3.40 (s, 2H), 3.16 (d, 1H), 2.29-2.25 (m, 4H), 1.40 (s, 9H)

Step-2: To a stirred solution of tert-butyl 4-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorobenzylidene)piperidine-1-carboxylate (200 mg, 0.376 mmol, 1 eq) in DCM (5 mL), cooled to -78°C, was added 1,2,3,4,5-pentamethylbenzene (167 mg, 1.13 mmol, 3 eq) and BCl₃ (1 M solution in DCM, 0.75 mL, 0.75 mmol, 2 eq) and the reaction mixture was stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction was quenched with water and volatiles were evaporated. The residue was purified by Prep-HPLC (Column: YMC Actus Triart C18 (20*250 mm, 5 μm). Mobile phase A: 20 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B): 0/5, 3/5, 20/35, 21/95, 22/95, 23/5, 25/5. Flow: 16 mL/min. Temperature: ambient.) to yield 5-(2-fluoro-6-hydroxy-3-(piperidin-4-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide. LC-MS (LC-L): r.t. = 1.03 min ; m/z 342 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.5 (bs, 1H), 8.6 (bs, 2H), 7.03 (t, 1H), 6.68 (d, 1H), 6.26 (s, 1H), 3.95 (s, 2H), 3.16-3.14 (m, 2H), 3.09-3.06 (m, 2H), 2.49-2.45 (m, 4H)

Example 18: Synthesis of 5-(3-(cyclopentylidenemethyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd047**).



Step 1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.72 mmol, 1 eq), 2-(cyclopentylidenemethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (301 mg, 1.45 mmol, 2 eq) and K_3PO_4 (461 mg, 2.17 mmol, 3.0 eq) in a mix of 1,4-dioxane (10 mL) and water (4 mL) was degassed with Ar for 15 min. $PdCl_2(dtbpf)$ (47 mg, 0.072 mmol, 0.1 eq) was added at RT and the resulting reaction mixture was then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (2x10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%) to yield 200 mg of 5-(6-(benzyloxy)-3-(cyclopentylidenemethyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a pale brown solid. LC-MS (LC-T): r.t. = 0.91 min ; m/z 415 $[M+H]^+$

Step 2: To a stirred solution of 5-(6-(benzyloxy)-3-(cyclopentylidenemethyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (170 mg, 0.4 mmol, 1 eq) in a mixture of MeOH (5 mL) and EtOAc (5 mL) was added 10% Pd/C (125 mg) at RT, under inert atmosphere. The resulting reaction mixture was stirred under 1 atm of H_2 (balloon). After completion of the reaction (TLC monitoring), the reaction mixture was filtered through Whatman filter paper and concentrated under reduced pressure. The residue was purified by Prep-HPLC (Column: X-BRIDGE C18 (19*150mm, 5 μ m). Mobile phase A: H_2O ; Mobile phase B: CH_3CN . Gradient (Time (min)/%B): 0/20, 2/20, 10/65, 10.1/98, 13/98, 13.1/20, 17/20. Flow: 14 mL/min. Temperature: ambient.) to yield 23 mg of 5-(3-(cyclopentylidenemethyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

LC-MS (LC-E): r.t. = 3.40 min (99.9%) ; m/z 325 $[M-H]^-$

1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.29 (brs, 1H), 7.18 (t, 1H), 6.66 (d, 1H), 6.27 (s, 1H), 3.95 (s, 2H), 2.44-2.32 (m, 4H), 1.73-1.58 (m, 4H)

^{19}F NMR (376 MHz, DMSO- d_6) δ ppm: -121.1 (d)

Example 19: Synthesis of 5-(2-fluoro-6-hydroxy-3-((1-propylpiperidin-4-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd048).



Step-1: A stirred solution of tert-butyl 4-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorobenzylidene)piperidine-1-carboxylate (Intermediate in Cpd046 synthesis, 600 mg, 1.13 mmol, 1 eq) in DCM (15 mL), cooled to 0°C, was treated with 4M HCl in dioxane (3.39 mL, 13.5 mmol, 12 eq) and the resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was evaporated under reduced pressure. The residue was triturated with Et_2O and obtained solid was dried under vacuum to provide 550 mg of 5-(6-(benzyloxy)-2-fluoro-3-(piperidin-4-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide hydrochloride as a brown solid. LC-MS (LC-S): r.t. = 1.50 min ; m/z 432 $[M-H]^-$

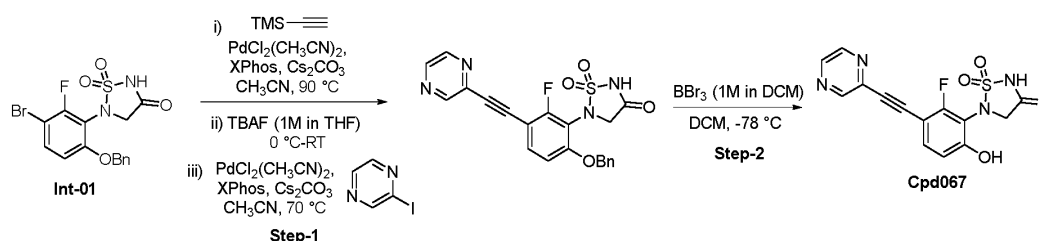
Step-2: To a stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-(piperidin-4-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide hydrochloride (320 mg, 0.68 mmol, 1 eq) in 15 mL of a 1:1 THF:MeOH mixture, were added propionaldehyde (397 mg, 6.84 mmol, 10 eq) followed by AcOH (102 mg, 1.71 mmol, 2.5 eq) at 0°C and the reaction mixture was stirred at 65°C for 16 h. The reaction mixture was cooled to 0°C, treated with NaBH₃(CN) (129 mg, 2.05 mmol, 3 eq) and then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (10-30%) to yield 300 mg of 5-(6-(benzyloxy)-2-fluoro-3-((1-propylpiperidin-4-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide. LC-MS (LC-A): r.t. = 1.77 min ; m/z 474 [M+H]⁺

Step-3: A stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-((1-propylpiperidin-4-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (275 mg, 0.74 mmol, 1 eq) in DCM (15 mL) was treated with BBr₃ (1M in DCM, 1.47 mL, 1.47 mmol, 3 eq) dropwise at 0°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with a 7M NH₃ solution in MeOH and volatiles were evaporated. The residue was purified by Prep-HPLC (Column: LUNA C18 (25*150 mm, 5 μm). Mobile phase A: 0.1% FA in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/5, 2/5, 10/40, 13/40, 13.1/98, 17/98, 17.1/5, 20/5. Flow: 16 mL/min. Temperature: ambient.) to yield 17 mg of 5-(2-fluoro-6-hydroxy-3-((1-propylpiperidin-4-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-A): r.t. = 1.15 min (96.8%) ; m/z 384 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.59 (s, 1H), 9.28 (brs, 1H), 7.21-6.95 (m, 1H), 6.69 (d, 1H), 6.30 (s, 1H), 3.98 (s, 2H), 3.58-3.48 (m, 2H), 3.06-2.90 (m, 4H), 2.70-2.57 (m, 3H), 2.42-2.39 (m, 1H), 1.70-1.64 (m, 2H), 0.91 (t, 3H)

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -118.3 (d).

Example 20: Synthesis of 5-(2-fluoro-6-hydroxy-3-(pyrazin-2-ylethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (Cpd067)



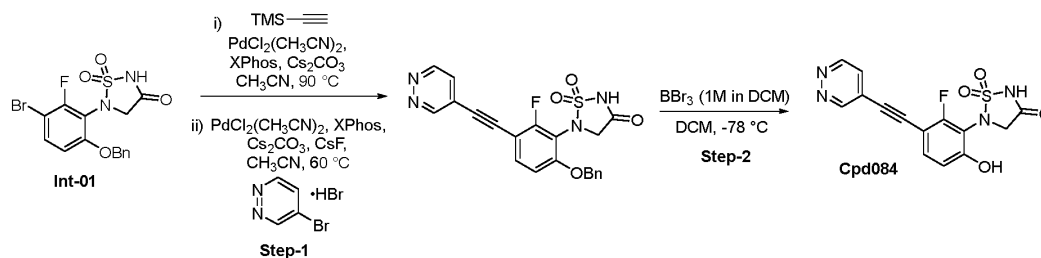
Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (500 mg, 1.20 mmol, 1 eq), Cs₂CO₃ (470 mg, 1.45 mmol, 1.2 eq) in CH₃CN (20 mL) was degassed for 10 min with Ar. Then, Pd(CH₃CN)₂Cl₂ (31.2 mg, 0.12 mmol, 0.1 eq) followed by XPhos (115 mg, 0.24 mmol, 0.2 eq) and trimethylsilyl acetylene (0.343 mL, 2.41 mmol, 2 eq) were added at RT and the resulting reaction mixture was then stirred at 90°C.

- After completion of the reaction (TLC and LC-MS monitoring: LC-MS (LC-U): r.t. = 0.92 min ; m/z 433 [M+H]⁺), the crude reaction mixture containing 5-(6-(benzyloxy)-2-fluoro-3-((trimethylsilyl)ethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide was cooled to 0 °C and treated with TBAF (1M in THF, 2.31 mL, 2.31 mmol, 2 eq) and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC and LC-MS monitoring: LC-MS (LC-U): r.t. = 0.84 min ; m/z 359 [M-H]⁻), the crude was again degassed for 10 min with Ar and treated with Pd(CH₃CN)₂Cl₂ (36.0 mg, 0.139 mmol, 0.1 eq), XPhos (133 mg, 0.278 mmol, 0.2 eq) and 2-iodopyrazine (572 mg, 2.77 mmol, 2 eq). The resulting reaction mixture was then stirred at 70 °C in a sealed tube. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced and the residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (2-10%). Fractions containing product were further purified by reverse phase column eluting with a gradient of CH₃CN in water (0-45%) to yield 350 mg of 5-(6-(benzyloxy)-2-fluoro-3-(pyrazin-2-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a pale-yellow solid. LC-MS (LC-M): r.t. = 1.88 min ; m/z 437 [M-H]⁻
- Step-2: To a stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-(pyrazin-2-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.684 mmol, 1.0 eq) in DCM (10 mL) was added BBr₃ (1M in DCM, 3.42 mL, 3.42 mmol, 5.0 eq) dropwise at -78°C and the resulting solution was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78°C and then evaporated under reduced pressure to get a crude residue, which was purified by reverse phase column eluting with a gradient of CH₃CN in H₂O (0-30%). Obtained compound was further purified by Prep-HPLC (Column: X-bridge C18 (19*150mm, 5 µm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B): 0/10, 2/10, 10/30, 14/30, 14.2/98, 17/98, 17.2/10, 20/10. Flow: 14 mL/min. Temperature: ambient.) to yield 21 mg of 5-(2-fluoro-6-hydroxy-3-(pyrazin-2-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide. LC-MS (LC-A): r.t. = 1.27 min (99.1%); m/z 349 [M+H]⁺
- ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.84 (d, 1H), 8.68 (t, 1H), 8.62 (d, 1H), 7.45 (t, 1H), 6.78 (d, 1H), 3.98 (s, 2H).
- ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -111.9 (d).

- The following compounds were prepared in a manner similar to compound **Cpd067** (by use of appropriate reagent in step-1 and purification methods known to the person skilled in the art).

Reagent Step-1	Compound
	Cpd082

Example 21: Synthesis of 5-(2-fluoro-6-hydroxy-3-(pyridazin-4-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd084**)



Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (500 mg, 1.20 mmol, 1 eq), Cs_2CO_3 (588 mg, 1.81 mmol, 1.5 eq) in CH_3CN (10 mL) was degassed for 10 min with Ar. Then, $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (31.2 mg, 0.12 mmol, 0.1 eq) followed by XPhos (115 mg, 0.24 mmol, 0.2 eq) and trimethylsilyl acetylene (0.51 mL, 3.61 mmol, 3 eq) were added at RT and the resulting reaction mixture was then stirred at 90 °C.

After completion of the reaction (TLC and LC-MS monitoring: LC-MS (LC-M): r.t. = 1.56 min ; m/z 431 $[\text{M-H}]^-$), the crude reaction mixture containing 5-(6-(benzyloxy)-2-fluoro-3-((trimethylsilyl)ethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide was treated with 4-bromopyridazine hydrobromide (555 mg, 2.31 mmol, 2.0 eq), Cs_2CO_3 (377 mg, 1.16 mmol, 1.0 eq) and CsF (527 mg, 3.47 mmol, 3.0 eq.). The reaction mixture was again degassed for 10 min with Ar and then treated with $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (30 mg, 0.116 mmol, 0.1 eq) followed by XPhos (110 mg, 0.23 mmol, 0.2 eq). The resulting reaction mixture was then stirred at 60 °C in a sealed tube. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced and the residue was purified by reverse phase column eluting with a gradient of CH_3CN in water (25-30%) to yield 350 mg of 5-(6-(benzyloxy)-2-fluoro-3-(pyridazin-4-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a pale-yellow solid.

LC-MS (LC-O): r.t. = 1.76 min ; m/z 437 $[\text{M-H}]^-$

^1H NMR (400 MHz, DMSO-d_6) δ ppm: 9.34 (dd, 1H), 9.28 (dd, 1H), 7.85 (dd, 1H), 7.61 (t, 1H), 7.51 (d, 2H), 7.39-7.29 (m, 3H), 7.07 (d, 1H), 5.26 (s, 2H), 4.01 (s, 2H).

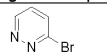
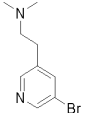
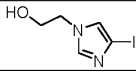
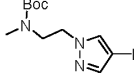
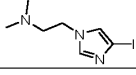
Step-2: To a stirred solution of 5-(6-(benzyloxy)-2-fluoro-3-(pyridazin-4-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 1.02 mmol, 1.0 eq) in DCM (10 mL) was added BBr_3 (1M in DCM, 6.15 mL, 6.15 mmol, 6.0 eq) dropwise at -78 °C and the resulting solution was then stirred at the same temperature. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with 7M ammonia solution in MeOH at -78 °C and then evaporated under reduced pressure to get a crude residue, which was purified by reverse phase column chromatography eluting with a gradient of CH_3CN in H_2O (30-35%). Obtained compound was further purified by Prep HPLC (Column: Luna C18 (21.2*250mm, 5 μm). Mobile phase A: 10 mM NH_4HCO_3 in H_2O ; Mobile phase B: CH_3CN . Gradient (Time (min)/%B): 0/10, 2/10, 10/35, 10.5/35, 10.7/98, 16/98, 16.2/10, 20/10. Flow: 14 mL/min. Temperature: ambient.) to yield 79 mg of 5-(2-fluoro-6-hydroxy-3-(pyridazin-4-ylethynyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

LC-MS (LC-A): r.t. = 1.21 min (98.7%); m/z 349 $[\text{M+H}]^+$

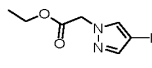
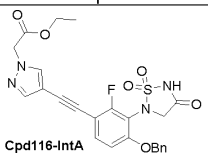
^1H NMR (400 MHz, DMSO- d_6) δ ppm: 9.31 (dd, 1H), 9.26 (dd, 1H), 7.82 (dd, 1H), 7.44 (t, 1H), 6.78 (d, 1H), 3.98 (s, 2H).

^{19}F NMR (376 MHz, DMSO- d_6) δ ppm: -111.5 (d).

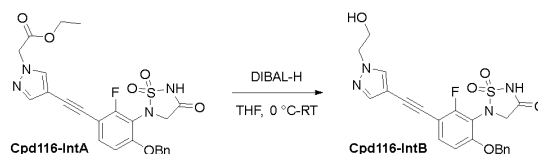
- The following compounds were prepared in a manner similar to compound **Cpd084** (by use of appropriate reagent in step-1 and purification methods known to the person skilled in the art).
 5 The final debenzylation (phenol deprotection) and cleavage of labile protecting group when applicable can be performed by any suitable reagent known to the skilled in the art (e.g. BBr_3 (neat or as solution in an appropriate solvent), BCl_3 , ...). The reagents are commercially available or synthesized as described in the section "Examples of intermediates and their preparation".

Reagent Step-1	Compound
	Cpd085
	Cpd108
	Cpd109
	Cpd110
	Cpd111

- 10 **Cpd116-IntA** was obtained following procedure described in step 1 of above Example 21.

Reagent Step-1	Compound
	 Cpd116-IntA LC-MS (LC-M): r.t. = 1.84 min; m/z 513 $[\text{M}+\text{H}]^+$

Cpd116-IntA was then converted into **Cpd116-IntB** according to below procedure.



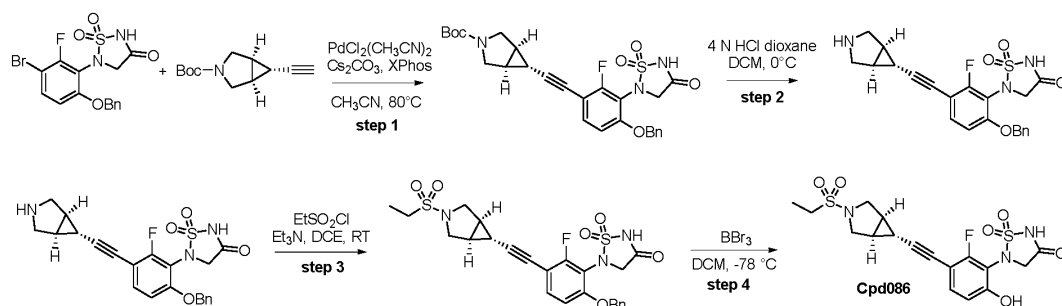
- A stirred solution of ethyl 2-(4-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl) ethynyl)-1H-pyrazol-1-yl) acetate (350 mg, 0.68 mmol, 1.0 eq) in THF (25 mL), was
 15 treated, at -78°C , with a 1M solution of diisobutylaluminum hydride in toluene (1.37 mL, 1.37 mmol, 2.0 eq). After completion of the reaction (TLC monitoring), the reaction mixture was quenched with NH_4Cl solution (5 mL) and extracted with EtOAc (2 X 20 mL). The combined

organic layers were washed with water (2 x 20 mL), brine (20 mL), then dried over anhydrous Na_2SO_4 . Solids were filtered off and filtrate was evaporated to get crude **Cpd116-IntB** which was used as such in the next step. LC-MS (LC-W): r.t. = 1.59 min; m/z 471 $[\text{M}+\text{H}]^+$.

Deprotection of **Cpd116-IntB** according to procedure described in step 2 of Example 21 above

5 afforded final compound **Cpd116**.

Example 22: Synthesis of 5-(3-(((1R,5S,6S)-3-(ethylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd086**)



Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one

10 1,1-dioxide (400 mg, 0.96 mmol, 1 eq), tert-butyl (1S,5R,6S)-6-ethynyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (598 mg, 2.89 mmol, 3 eq) and Cs_2CO_3 (380 mg, 1.16 mmol, 1.2 eq) in CH_3CN (10 mL) was degassed for 20 min with N_2 . Then, $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (25 mg, 0.096 mmol, 0.1 eq) followed by XPhos (69 mg, 0.14 mmol, 0.15 eq) were added at RT and the resulting reaction mixture was heated at 90°C. After completion of the reaction (TLC monitoring),

15 the reaction mixture was diluted with EtOAc, filtered through a celite bed and the bed was washed with EtOAc. The filtrate was then partitioned with water, the aqueous layer was acidified to a pH value of ~4 (via addition of a 1M NaHSO_4 aq. solution) and was then extracted with EtOAc. Combined organic extracts were washed with brine, dried over MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-10%) to yield 320 mg of tert-butyl (1S,5R,6S)-6-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate as a light grey solid.

LC-MS (LC-O): r.t. = 1.37 min ; m/z 442 $[\text{M}-\text{Boc}+\text{H}]^+$, 540 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 7.48 (d, 2 H), 7.43-7.23 (m, 4 H), 6.93 (d, 1 H), 5.18 (s, 2 H), 4.04 (s, 2 H), 3.52 (d, 2 H), 3.40-3.23 (m, 2 H), 1.98 (br. s., 2 H), 1.38 (s, 9 H), 1.34-1.28 (m, 2 H).

Step-2: A stirred mixture of tert-butyl (1S,5R,6S)-6-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-3-azabicyclo[3.1.0]hexane-3-carboxylate (500 mg, 0.92 mmol) in DCM (6.2 mL) was treated dropwise at 0°C with a 4N HCl solution in dioxane (1.4 mL, 5.54 mmol, 6 eq) and the resulting mixture was then stirred at RT. After completion of the reaction

30

(TLC monitoring), the reaction mixture was concentrated, the residue was taken up in MeOH and purified by catch-release exchange chromatography over Propylsulfonic acid modified silica gel (3g Biotage SCX-2 sorbent) using an isocratic elution of DCM 1:1 MeOH (release was achieved after addition of a 2N NH₃.MeOH solution) to yield 400 mg of 5-[3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a thin off-white powder.

LC-MS (LC-O): r.t. = 0.99 min ; m/z 442 [M+H]⁺, 440 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.49 (d, 2 H), 7.42-7.21 (m, 4 H), 6.93 (d, 1 H), 5.19 (s, 2 H), 4.10-3.94 (m, 2 H), 3.44 (d, 2 H), 3.36 (d, 2 H), 2.19 (s., 2 H), 1.73 (t, 1 H).

10 Step-3: A stirred mixture of 5-[3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (240 mg, 0.54 mmol, 1 eq) and Et₃N (0.23 mL, 1.63 mmol, 3 eq) in DCE (5 mL) was cooled down to 0°C and then treated dropwise under inert atmosphere with ethanesulfonyl chloride (0.158 mL, 1.63 mmol, 3 eq) and allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched
15 with ice and diluted with DCM. The aqueous layer was back extracted again twice with DCM. The combined organic layers were washed with a 1N NaHSO₄ aq. solution, then with brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (0-15%) to yield 175 mg of 5-[6-benzyloxy-3-[2-[(1S,5R,6S)-3-ethylsulfonyl-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-2-fluoro-phenyl]-1,1-dioxo-
20 1,2,5-thiadiazolidin-3-one as an off white solid.

LC-MS (LC-O): r.t. = 1.17 min ; m/z 532 [M-H]⁻

Step-4: A stirred solution of 5-[6-benzyloxy-3-[2-[(1S,5R,6S)-3-ethylsulfonyl-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (170 mg, 0.32 mmol) in DCM (12 mL) was cooled down to -78°C and then treated dropwise under inert
25 atmosphere with neat BBr₃ (0.091 mL, 0.96 mmol, 3 eq) and stirring was continued at -78°C. After completion of the reaction (TLC monitoring), the mixture was quenched with of a 10/1 mixture of DCM/3N NH₃ in MeOH and evaporated under reduced pressure. The residue was purified by Prep-HPLC (Column: X-Bridge Prep C18 (100*19mm, 5 μm). Mobile phase A: 25 mM NH₄HCO₃ in H₂O, pH 8.5; Mobile phase B: MeOH-MeCN (50:50). Gradient (Time(min)/%B): 0/5, 0.5/5,
30 6.5/65, 6.6/95, 9.0/95, 9.2/5, 12/5. Flow : 20 mL/min. Temperature: ambient.) to yield 32 mg of 5-(3-(((1R,5S,6S)-3-(ethylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

LC-MS (LC-H): r.t. = 2.46 min (96.8%); m/z 444 [M+H]⁺, 442 [M-H]⁻

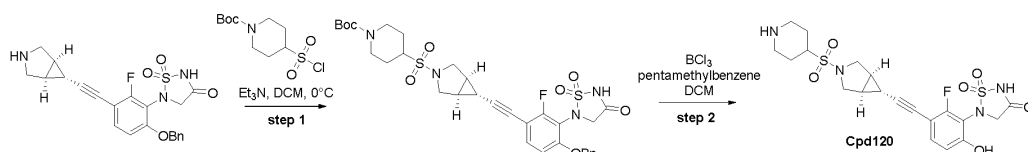
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.18 (t, 1 H), 6.65 (dd, 1 H), 3.96 (s, 2 H), 3.53-3.45 (m, 2 H), 3.44- 3.37 (m, 2 H), 3.11 (q, 2 H), 2.06-1.98 (m, 2 H), 1.53 (t, 1 H), 1.19 (t, 3 H).

The following compounds were prepared in a manner similar to compound **Cpd086** (by use of appropriate sulfonyl chloride or chloroformate reagent in step-3 and purification methods known

to the person skilled in the art). The final debenzoylation (phenol deprotection) can be performed by any suitable reagent known to the skilled in the art (e.g. BBr_3 (neat or as solution in an appropriate solvent), BCl_3 , ...). The reagents are commercially available or synthesized as described in the section "Examples of intermediates and their preparation".

Reagent Step-3	Reagent Step-4	Compound
	BBr_3	Cpd087
	BBr_3	Cpd088
	BBr_3	Cdp089
	BCl_3	Cpd090
	BCl_3	Cpd091
	BCl_3	Cpd092

5 Example 23: Synthesis of 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-(piperidin-4-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd120**)



Step-1: To a solution of 5-[6-benzyloxy-2-fluoro-3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (150 mg, 0.34 mmol) and 1-Boc-4-chlorosulfonylpiperidine (101 mg, 0.36 mmol, 1.05 eq) in DCM (12 mL), cooled in an ice bath, was added Et_3N (0.060 mL, 0.41 mmol, 1.2 eq). After completion of the reaction (TLC monitoring), the mixture was concentrated and the residue was purified by flash chromatography on silica gel using a gradient of MeOH (1-12%) in DCM to afford 155 mg of tert-butyl 4-[[[(1S,5R,6S)-6-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-3-azabicyclo[3.1.0]hexan-3-yl]sulfonyl]piperidine-1-carboxylate.

LC-MS (LC-O): r.t. = 1.39 min (100%) ; m/z 589 $[\text{M}+\text{H}-\text{Boc}]^+$, 687 $[\text{M}-\text{H}]^-$

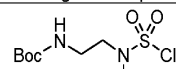
Step-2: A solution of tert-butyl 4-[[[(1S,5R,6S)-6-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-3-azabicyclo[3.1.0]hexan-3-yl]sulfonyl]piperidine-1-carboxylate (150 mg, 0.22 mmol) and pentamethylbenzene (261 mg, 1.74 mmol, 8 eq) in DCM (10 mL), cooled at -78°C , was treated dropwise with a 1M BCl_3 solution in DCM (1.5 mL, 1.5 mmol, 6.8 eq). After completion of the reaction (TLC monitoring), the reaction mixture was quenched by addition of a 7N solution of NH_3 in MeOH. The resulting mixture was then concentrated under reduced pressure and the residue was purified by Prep-HPLC (Column: X-Bridge Prep C18 (100*19mm, 5 μm). Mobile phase A: 25 mM NH_4HCO_3 in H_2O , pH 8.5; Mobile phase B: $\text{CH}_3\text{CN}:\text{MeOH}$ (50:50). Gradient (Time(min)/%B): 0/5, 0.5/5, 6.5/65, 6.6/95,

9.0/95,9.2/5, 12/5. Flow : 20 mL/min. Temperature: ambient) to yield 6 mg of 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-(piperidin-4-ylsulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd120**).

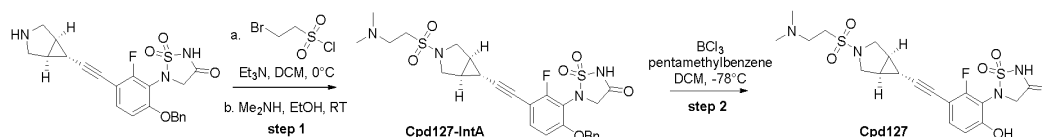
LC-MS (LC-H): r.t. = 2.31 min (98.9%); m/z 499 [M+H]⁺, 497 [M-H]⁻

- 5 ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.54-3.42 (m, 6 H), 2.86 (t, 2 H), 2.14-1.99 (m, 4 H), 1.79-1.67 (m, 2 H), 1.58 (brs, 1 H).

The following compounds were prepared in a manner similar to compound **Cpd120** (by use of appropriate sulfonyl chloride in step-1 and purification methods known to the person skilled in the art).

Reagent Step-1	Compound
	Cpd121

- 10 Example 24: Synthesis of 5-(3-(((1R,5S,6S)-3-((2-(dimethylamino)ethyl)sulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd127**)



Step-1: A stirred solution of 5-[3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (225 mg, 0.42 mmol) in DCM (10 mL) was cooled to 0°C and then treated with 2-bromoethanesulfonyl chloride (0.068 mL, 0.63 mmol, 1.5 eq) and Et₃N (0.296 mL, 2.10 mmol, 5 eq). The reaction mixture was stirred at 0°C for 30 minutes and was then concentrated under reduced pressure. The residue was dissolved in EtOH (6 mL), treated with a 2M solution of dimethylamine in THF (4.0 mL, 8.0 mmol, 20 eq) and the mixture was then stirred at RT. After completion of the reaction (LC-MS monitoring), the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (1-20%) in DCM to yield 69 mg of 5-(6-(benzyloxy)-3-(((1R,5S,6S)-3-((2-(dimethylamino)ethyl)sulfonyl)-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

- 25 LC-MS (LC-O): r.t. = 1.14 min (93.0%); m/z 577 [M+H]⁺, 575 [M-H]⁻

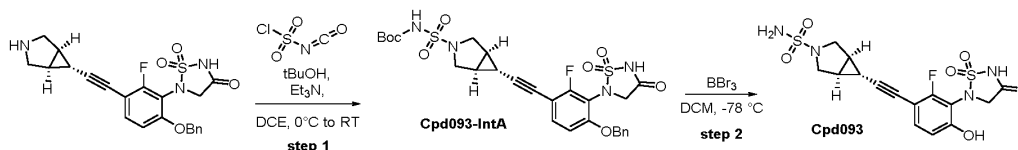
Step-2: Deprotection of **Cpd127-IntA** according to procedure described in step 2 of Example 23 above afforded 5 mg of final compound **Cpd127**.

LC-MS (LC-H): r.t. = 2.47 min (95.0%); m/z 487 [M+H]⁺, 485 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.96 (s, 1 H), 7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.59-3.45 (m, 6 H), 3.40-3.35 (m, 2 H), 2.81-2.74 (m, 6 H), 2.12-2.05 (m, 2 H), 1.61 (t, 1 H).

- 30

Example 25: Synthesis of (1R,5S,6S)-6-(((1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)-3-azabicyclo[3.1.0]hexane-3-sulfonamide (**Cpd093**)



Step-1: A stirred mixture of 2-methylpropan-2-ol (0.091 mL, 1.63 mmol) in DCE (5.4 mL) was cooled down to 0°C before being treated dropwise with chlorosulfonyl isocyanate (0.145 mL, 1.63 mmol). After 30 minutes, this solution was added dropwise at 0°C over a previously made suspension of 5-[3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (240 mg, 0.54 mmol) and Et₃N (0.460 mL, 3.26 mmol) in DCE (5 mL) and the resulting mixture was left under stirring warming up to RT. After completion of the reaction (TLC monitoring), the crude reaction mixture was quenched over crushed ice and partitioned with DCM. Aqueous layer was back extracted twice with DCM. Combined organic extracts were successively washed with a 1N NaHSO₄ aq. solution, then with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography over silica gel using a gradient elution of MeOH (0-10%) in DCM to yield 130 mg of tert-butyl N-[[[(1S,5R,6S)-6-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-3-azabicyclo[3.1.0]hexan-3-yl]sulfonyl]carbamate as an off white solid.

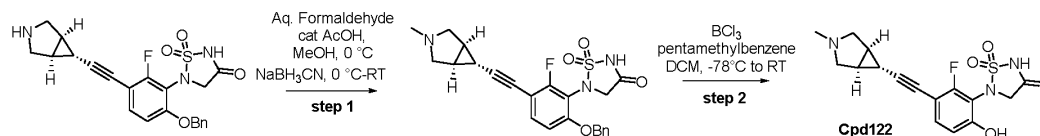
LC-MS (LC-O): r.t. = 1.15 min; m/z 619 [M-H]⁻

Step-2: Deprotection of **Cpd093-IntA** according to procedure described in step 4 of Example 22 above afforded final compound **Cpd093**.

LC-MS (LC-C): r.t. = 2.49 min (98.3%); m/z 431 [M+H]⁺, 429 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.17 (t, 1 H), 6.83 (brs, 2 H), 6.64 (d, 1 H), 3.95 (s, 2 H), 3.32 (brs, 2 H), 3.26-3.20 (m, 2 H), 2.02 (brs, 2 H), 1.61 (t, 1 H).

Example 26: Synthesis of 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd122**)



Step-1: To a stirred suspension of 5-[3-[2-[(1S,5R,6S)-3-azabicyclo[3.1.0]hexan-6-yl]ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (67 mg, 0.15 mmol) and 37% aq. Formaldehyde (0.094 mL, 1.25 mmol, 8 eq) in dry MeOH (1.7 mL) was added a cat. Amount of AcOH and the resulting mixture was heated at 60°C for 20 min. The mixture was then cooled down to 0°C and treated portionwise with NaBH₃CN (79 mg, 1.25 mmol, 8 eq). The ice bath was removed and the reaction mixture was left under stirring at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the residue was diluted with EtOAc

before being partitioned with water. Aqueous layer was back extracted twice with EtOAc. Combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was purified by catch-release exchange chromatography over Propylsulfonic-modified silica gel (3g Biotage SCX-2 sorbent) using an isocratic elution of DCM 1:1 MeOH (release was achieved adding a 2N NH_3 in MeOH solution) to yield 67 mg of 5-(6-(benzyloxy)-2-fluoro-3-(((1R,5S,6S)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide.

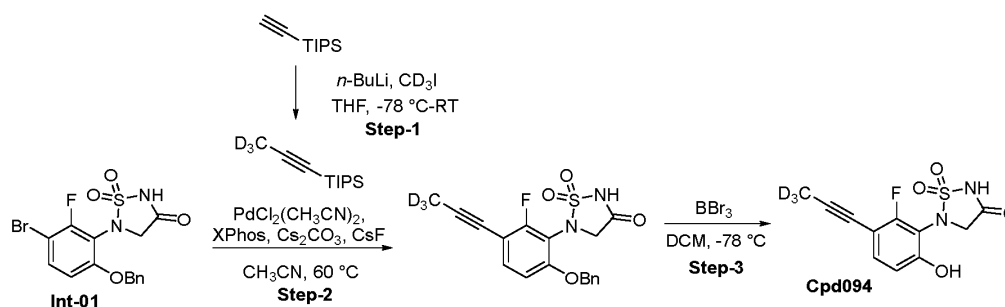
LC-MS (LC-O): r.t. = 1.07 min (94%); m/z 456 $[\text{M}+\text{H}]^+$, 454 $[\text{M}-\text{H}]^-$

Step-2: A solution of 5-(6-(benzyloxy)-2-fluoro-3-(((1R,5S,6S)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (67 mg, 0.15 mmol) and pentamethylbenzene (110 mg, 0.74 mmol, 5 eq) in DCM (6 mL), cooled at -78°C , was treated dropwise with a 1M BCl_3 solution in DCM (0.44 mL, 0.44 mmol, 3 eq) and mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched by addition of a 7N solution of NH_3 in MeOH. The resulting mixture was then concentrated under reduced pressure and the residue was purified by reverse-phase column chromatography over C18 modified silica gel using a gradient elution of MeCN (0-30%) in water to yield 27 mg of 5-(2-fluoro-6-hydroxy-3-(((1R,5S,6S)-3-methyl-3-azabicyclo[3.1.0]hexan-6-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd122**).

LC-MS (LC-H): r.t. = 1.99 min (93.2%); m/z 366 $[\text{M}+\text{H}]^+$, 364 $[\text{M}-\text{H}]^-$

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 6.93 (t, 1 H), 6.33 (d, 1 H), 3.95 (s, 2 H), 2.97 (d, 2 H), 2.26-2.22 (m, 2 H), 2.20 (s, 3 H), 1.76-1.72 (m, 3 H), 1.64 (s, 2 H).

Example 27: Synthesis of 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl- d_3)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd094**)



Step-1: To a stirred solution of ethynyltriisopropylsilane (4.0 g, 21.9 mmol, 1.0 eq) in THF (50 mL), under argon atmosphere, was added $n\text{-BuLi}$ (2.5M in hexane, 10.53 mL, 26.32 mmol, 1.2 eq) dropwise at -78°C . The mixture was stirred for 30 min at the same temperature and then treated dropwise with Iodomethane- d_3 (4.77 g, 32.90 mmol, 1.5 eq.) at -78°C . After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice cold water (50 mL) and extracted with Et_2O (2 x 75 mL). The combined organic layers were washed with brine (50 mL),

dried over anhydrous Na₂SO₄ and evaporated (below 20 °C). The residue was purified by column chromatography on silica gel eluting with PE to yield 800 mg of triisopropyl(prop-1-yn-1-yl-d₃)silane as a pale-yellow liquid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm. 1.05-1.03 (m, 21H).

- 5 Step-2: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (400 mg, 0.963 mmol, 1.0 eq), Cs₂CO₃ (470.8 mg, 1.45 mmol, 1.5 eq) and CsF (439 mg, 2.89 mmol, 3.0 eq) in CH₃CN (15 mL) was degassed for 10 min with Ar. Then, Pd(CH₃CN)₂Cl₂ (12.5 mg, 0.048 mmol, 0.05 eq) and X-Phos (45.9 mg, 0.096 mmol, 0.1 eq) were added followed by triisopropyl(prop-1-yn-1-yl-d₃)silane (769 mg, 3.85 mmol, 4.0 eq) at RT and the resulting
- 10 reaction mixture was stirred to 60 °C. After completion of the reaction (TLC monitoring), the reaction mixture filtered through a celite bed and the bed was washed with EtOAc (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (4-6%) to yield 250 mg of 5-(6-(benzyloxy)-2-fluoro-3-(prop-1-yn-1-yl-d₃)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a
- 15 pale-brown solid.

LC-MS (LC-M): r.t. = 1.95 min ; m/z 376 [M-H]⁻

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.48 (d, 2H), 7.37-7.29 (m, 5H), 6.89 (d, 1H), 5.18 (s, 2H), 3.97 (s, 2H)

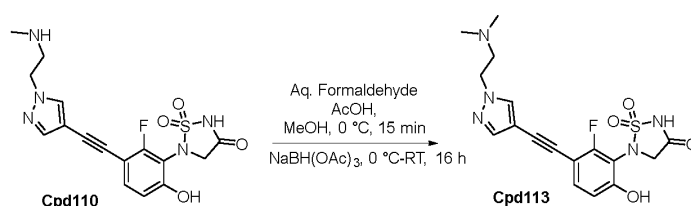
- Step-3: 5-(6-(benzyloxy)-2-fluoro-3-(prop-1-yn-1-yl-d₃)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide was then treated with BBr₃ according to procedure described in step 2 of Example 1 (phenol deprotection) to yield 5-(2-fluoro-6-hydroxy-3-(prop-1-yn-1-yl-d₃)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd094**).
- 20

LC-MS (LC-A): r.t. = 1.30 min (98.0)% ; m/z 286 [M+H]⁺

¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.17 (t, 1H), 6.64 (dd, 1H), 3.94 (s, 2H)

- 25 ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -114.4 (s).

Example 28: Synthesis of 5-(3-((1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd113**).



- A stirred solution of 5-(2-fluoro-6-hydroxy-3-((1-(2-(methylamino)ethyl)-1H-pyrazol-4-yl)ethynyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (400 mg, 1.02 mmol, 1 eq) in MeOH (20 mL), at 0 °C, was treated with AcOH (1.50 mL) then by 37% aq. Formaldehyde (0.85 mL, 10.2 mmol, 10 eq) and was then stirred for 15 min. Sodium cyanoborohydride (192 mg, 3.05 mmol, 3 eq) was added portionwise at 0 °C and resulting reaction mixture was the allowed to reach RT.
- 30

After completion of the reaction (TLC monitoring), the reaction mixture was filtered through a celite bed and the bed was washed with MeOH (10 mL). The filtrate was concentrated and the crude residue was purified by Prep-HPLC (Column: YMC TRIART C18 (25*150 mm, 10 μ m). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/5, 2/5, 10/25, 13.6/25, 13.8/98, 16.8/98, 17/5, 20/5. Flow: 18 mL/min. Temperature: ambient) to yield 23 mg of 5-(3-((1-(2-(dimethylamino)ethyl)-1H-pyrazol-4-yl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid.

LC-MS (LC-A): r.t. = 1.14 min (99.3%) ; m/z 408 [M+H]⁺.

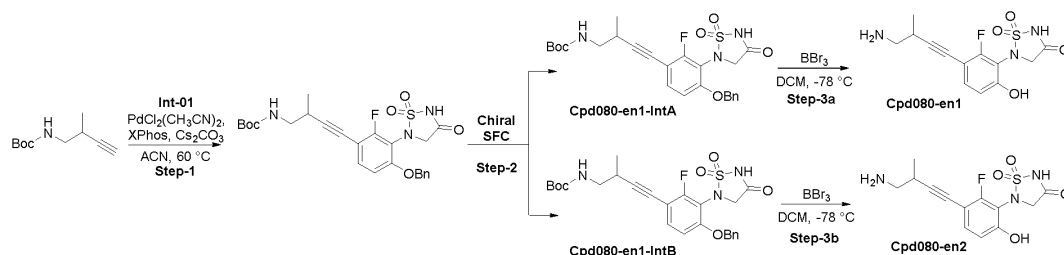
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 10.07 (s, 1H), 9.27 (brs, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.28 (t, 1H), 6.70 (dd, 1H), 4.52 (t, 2H), 3.96 (s, 2H), 3.54 (brs, 2H), 2.78 (s, 6H)

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.3 (d).

The following compounds were prepared in a manner similar to compound **Cpd113** (by use of appropriate reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Compound
Cpd037	Cpd114
Cpd038	Cpd115

Example 29: Synthesis of 5-(3-(4-amino-3-methylbut-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd080-en1** and **Cpd080-en2**).



Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (2.0 g, 4.82 mmol, 1 eq) and Cs₂CO₃ (1.88 g, 5.78 mmol, 1.2 eq) in CH₃CN (40 mL) was degassed with Ar for 10 min. Then, Pd(CH₃CN)₂Cl₂ (125 mg, 0.482 mmol, 0.1 eq), Xphos (459 mg, 0.963 mmol, 0.2 eq) and tert-butyl (2-methylbut-3-yn-1-yl) carbamate (1.765 g, 9.64 mmol, 2 eq) were added at RT and the mixture was then stirred at 60°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, evaporated under reduced pressure and the crude compound was purified by reverse phase column eluting with a gradient of CH₃CN (10-30%) in water (10-30%) to yield 1.5 g of tert-butyl (4-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)-2-methylbut-3-yn-1-yl) carbamate as an off-white solid. LC-MS (LC-X): r.t. = 4.06 min ; m/z 516 [M-H]⁻. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.49 (d, 2H), 7.37-7.29 (m, 4H), 7.03 (t, 1H), 6.91 (d, 1H), 5.18 (s, 2H), 3.95 (s, 2H), 3.17-3.08 (m, 1H),

3.00-2.94 (m, 1H), 2.81-2.75 (m, 1H), 1.38 (s, 9H), 1.14 (d, 3H).

Step-2: 1.5 g of tert-butyl -(4-(4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)-2-methylbut-3-yn-1-yl) carbamate were further subjected to chiral SFC purification (Preparative SFC Conditions: Column: Lux Cellulose-4 (30*250 mm, 5 μ m). CO₂: 60% -
 5 Cosolvent: 40% (0.5% Methanolic ammonia in Methanol). Total Flow: 100 g/min. Back-pressure: 100 bar. Temperature: 30 °C. Wavelength detection: 215 nm. Stack time: 12.3 mins.) to yield 600 mg of **Cpd080-en1-IntA** as an off-white solid (first eluting, SFC-Method A : r.t. = 8.75 min (97.8%)) and 700 mg of **Cpd080-en2-IntA** as an off-white solid (second eluting, SFC-Method A : r.t. = 18.08 min (95.4%)).

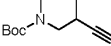
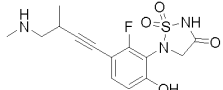
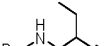
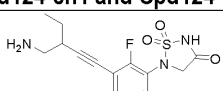
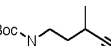
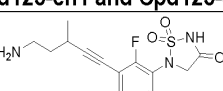
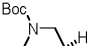
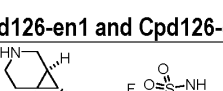
- 10 Step-3a: Deprotection of 600 mg of **Cpd080-en1-IntA** according to procedure described in step 2 of Example 3 above afforded 64 mg of final compound **Cpd080-en1**.

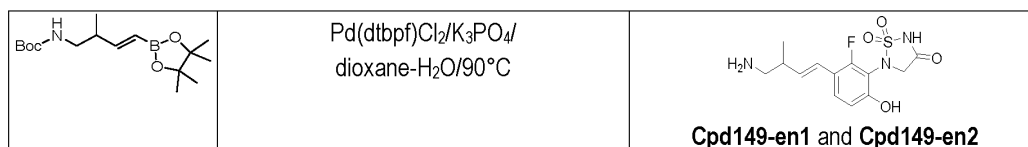
LC-MS (LC-B): r.t. = 5.41 min (95.0%); m/z 328 [M+H]⁺. SFC-Method A : r.t. = 11.69 min (99.8%).
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.86 (brs, 3H), 7.23 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 2.98-2.84 (m, 3H), 1.24 (d, 3H).
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.31 (d).

- 15 Step-3b: Deprotection of 700 mg of **Cpd080-en2-IntA** according to procedure described in step 2 of Example 3 above yielded 80 mg of final compound **Cpd080-en2**.

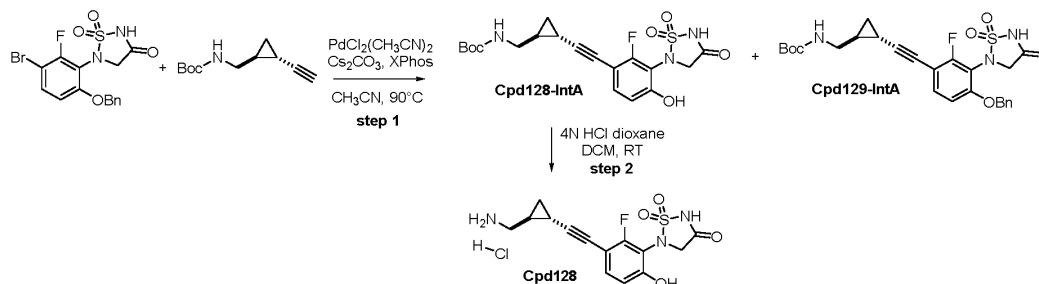
LC-MS (LC-A): r.t. = 1.11 min (99.7%); m/z 328 [M+H]⁺. SFC-Method A : r.t. = 12.19 min (99.9%).
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.08 (brs, 3H), 7.24 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 3.03-2.91 (m, 3H), 1.25 (d, 3H).
¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.21 (d).

- 20 The following compounds were prepared in a manner similar to compounds **Cpd080-en1** and **Cpd080-en2** (by use of appropriate reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

Alkyn reagent Step-1	Conditions Step-1	Compounds
	PdCl ₂ (CH ₃ CN) ₂ /XPhos/ Cs ₂ CO ₃ /CH ₃ CN/60°C	 Cpd124-en1 and Cpd124-en2
	PdCl ₂ (CH ₃ CN) ₂ /XPhos/ Cs ₂ CO ₃ /CH ₃ CN/RT	 Cpd125-en1 and Cpd125-en2
	PdCl ₂ (CH ₃ CN) ₂ /XPhos/ Cs ₂ CO ₃ /CH ₃ CN/60°C	 Cpd126-en1 and Cpd126-en2
	PdCl ₂ (CH ₃ CN) ₂ /XPhos/ Cs ₂ CO ₃ /CH ₃ CN/60°C	 Cpd142-en1 and Cpd142-en2



Example 30: Synthesis of rel-5-(3-(((1R,2R)-2-(aminomethyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd128**).

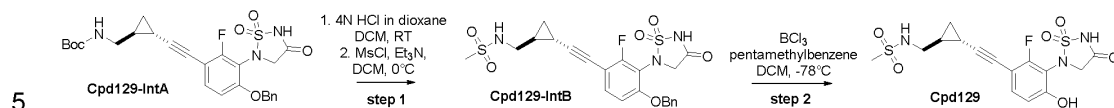


- Step-1: A solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (250 mg, 0.60 mmol, 1 eq), rel-tert-butyl (((1R,2R)-2-ethynylcyclopropyl)methyl)carbamate (176 mg, 0.90 mmol, 1.5 eq), Cs_2CO_3 (238 mg, 0.72 mmol, 1.2 eq), $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$ (16 mg, 0.060 mmol, 0.1 eq), XPhos (43 mg, 0.090 mmol, 0.15 eq) in CH_3CN (10 mL) was degassed and back filled with Ar (three cycles). The resulting reaction mixture was heated at 90°C . After completion of the reaction (TLC monitoring), the reaction mixture was partitioned between EtOAc and water and the aqueous layer was acidified to a pH value of 2 (via addition of a 1M NaHSO_4 aq. solution). After separation, the aqueous layer was extracted twice with EtOAc, combined organic extracts were dried over MgSO_4 and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH in DCM (1-16%) to yield 63 mg of rel-tert-butyl (((1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)cyclopropyl) methyl) carbamate **Cpd 128-IntA** (LC-MS (LC-N): r.t. = 1.13 min ; m/z 340 $[\text{M}+\text{H}-\text{Boc}]^+$, 438 $[\text{M}-\text{H}]^-$) and 201 mg of rel-tert-butyl (((1R,2R)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)cyclopropyl)methyl) carbamate **Cpd129-IntA** (LC-MS (LC-N): r.t. = 1.27 min ; m/z 430 $[\text{M}+\text{H}-\text{Boc}]^+$, 528 $[\text{M}-\text{H}]^-$).
- Step-2: A solution of rel-tert-butyl (((1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)cyclopropyl) methyl) carbamate **Cpd 128-IntA** (63 mg, 0.14 mmol) in DCM (5 mL), cooled at 0°C , was treated with a 4N HCl solution in dioxane (4 mL, 16 mmol). The reaction mixture was then stirred at RT for 2 h and then concentrated. The residue was suspended in Et_2O , sonicated, filtered and thoroughly dried to yield 44 mg of rel-5-(3-(((1R,2R)-2-(aminomethyl)cyclopropyl)ethynyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (as hydrochloride salt) **Cpd128**. LC-MS (LC-C): r.t. = 1.73 min ; m/z 340 $[\text{M}+\text{H}-\text{HCl}]^+$, 338 $[\text{M}-\text{H}-\text{HCl}]^-$.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 8.04 (brs, 2 H), 7.23 (t, 1 H), 6.74 (d, 1 H), 4.34-4.15 (m,

2 H), 2.93-2.79 (m, 1 H), 2.78-2.62 (m, 1 H), 1.73-1.63 (m, 1 H), 1.51-1.37 (m, 1 H), 1.05-0.91 (m, 2 H)

Example 31: Synthesis of rel-N-(((1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)ethynyl)cyclopropyl)methyl)methanesulfonamide **Cpd129**.



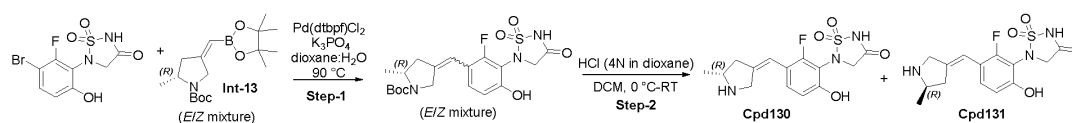
Step-1: A stirred solution of rel-tert-butyl (((1R,2R)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)cyclopropyl)methyl) carbamate **Cpd129-IntA** (95 mg, 0.18 mmol) in DCM (7 mL), cooled at 0°C, was treated with a 4N HCl solution in dioxane (4 mL, 16 mmol). The reaction mixture was stirred at RT for 1 h and concentrated. The residue was resuspended in DCM (12 mL), the resulting suspension was cooled at 0°C and treated sequentially with Et₃N (0.080 mL, 0.57 mmol, 3 eq) and mesyl chloride (0.022 mL, 0.28 mmol, 1.55 eq). After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel using a gradient of MeOH (1-16%) in DCM to yield 53 mg of rel-N-(((1R,2R)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl) cyclopropyl)methyl)methane sulfonamide **Cpd129-IntB**. LC-MS (LC-H): r.t. = 3.17 min (90%) ; m/z 525 [M+NH₄]⁺, 506 [M-H]⁻

Step-2: A solution of rel-N-(((1R,2R)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thia diazolidin-2-yl)-2-fluorophenyl)ethynyl)cyclopropyl)methyl)methanesulfonamide **Cpd129-IntB** (90 mg, 0.18 mmol) and pentamethylbenzene (133 mg, 0.89 mmol, 5 eq) in DCM (8 mL), cooled at -78 °C, was treated dropwise with a 1M BCl₃ solution in DCM (0.180 mL, 0.18 mmol, 1 eq). After completion of the reaction (TLC monitoring), the reaction mixture was quenched by addition of a 7N solution of NH₃ in MeOH. The reaction mixture was partitioned between DCM and water and the aqueous layer was acidified to a pH value of 2 (via addition of a 1M NaHSO₄ aq. solution). After separation, the aqueous layer was extracted twice with EtOAc, combined organic extracts were dried over MgSO₄ and concentrated. The residue was purified by flash chromatography on silica gel using a gradient of MeOH (10-20%) in DCM to yield 19 mg of rel-N-(((1R,2R)-2-((3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxy phenyl)ethynyl)cyclopropyl)methyl) methanesulfonamide **Cpd129**.

LC-MS (LC-C): r.t. = 2.52 min (95.2%); m/z 418 [M+H]⁺, 416 [M-H]⁻
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 7.21 (t, 1 H), 7.16 (t, 1 H), 6.63 (d, 1 H), 3.94 (s, 2 H), 3.03-2.83 (m, 5 H), 1.53-1.43 (m, 1 H), 1.43-1.29 (m, 1 H), 0.96-0.81 (m, 2 H).

Example 32: Synthesis of (R,Z)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd130**) and (R,E)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide

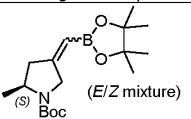
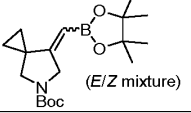
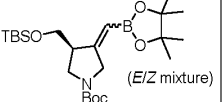
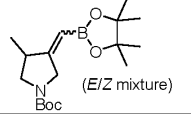
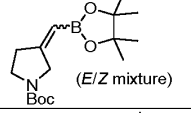
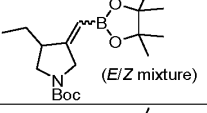
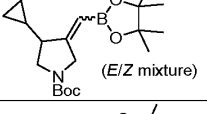
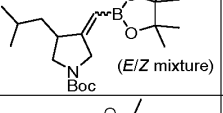
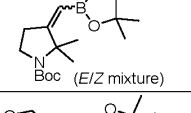
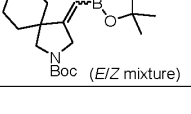
(Cpd131).



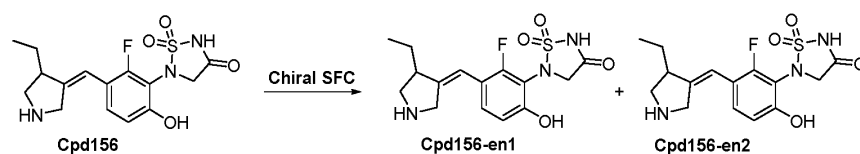
- Step-1: A stirred solution of 5-(3-bromo-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (0.40 g, 1.23 mmol, 1.0 eq), *tert*-butyl (*R*)-2-methyl-4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)pyrrolidine-1-carboxylate (as a *E/Z* mixture, 0.60 g, 1.85 mmol, 1.5 eq) and K₃PO₄ (0.78 g, 3.69 mmol, 3.0 eq) in a 9:1 dioxane:water mix (20 mL) was degassed with Ar for 10 min. Later, Pd(dtbpf)Cl₂ (80 mg, 0.123 mmol, 0.1 eq) was added, the mixture was further degassed with Ar for another 5 min and then stirred at 90 °C in a sealed tube. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, filtered over a celite bed and the filtrate was concentrated. The crude residue was purified by reverse phase column eluting with a gradient of CH₃CN in water (15-30%) to yield 150 mg of *tert*-butyl (*R*)-4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxybenzylidene)-2-methylpyrrolidine-1-carboxylate (as a *E/Z* mixture) as a pale-brown solid. LC-MS (LC-F): r.t. = 4.60 min (95.4%); m/z 386 [M-isobutene+H]⁺
- Step-2: A stirred solution of *tert*-butyl (*R*)-4-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxybenzylidene)-2-methylpyrrolidine-1-carboxylate (as a *E/Z* mixture) (150 mg, 0.34 mmol, 1.0 eq) in DCM (10 mL) was treated with a 4N HCl solution in dioxane (0.85 mL, 3.40 mmol, 10 eq) at 0 °C and the resulting reaction mixture was then allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure.
- The crude product was dissolved in a sat. NaHCO₃ solution (3 mL), stirred for 15 min and this aqueous layer was directly purified by Prep-HPLC (Column: HI Crome C18 (30*150 mm, 10 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/0.5, 2/0.5, 10/20, 12/20, 12.1/98, 18.2/0.5, 23/0.5. Flow: 14 mL/min. Temperature: ambient) to yield 14 mg of (*R,E*)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide **Cpd131**. LC-MS (LC-A): r.t. = 0.98 min (97.8%); m/z 342 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.73 (brs, 2H), 7.20 (t, 1H), 6.71 (d, 1H), 6.48 (s, 1H), 4.05-3.91 (m, 4H), 3.71-3.65 (m, 1H), 2.91 (dd, 1H), 2.41-2.33 (m, 1H), 1.30 (d, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -120.08 (d).
- and 25 mg of (*R,Z*)-5-(2-fluoro-6-hydroxy-3-((5-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide **Cpd130**. LC-MS (LC-A): r.t. = 1.08 min (96.9%); m/z 342 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.96 (brs, 2H), 7.08 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.03-3.91 (m, 4H), 3.70-3.65 (m, 1H), 2.94 (dd, 1H), 2.49-2.43 (m, 1H), 1.30 (d, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.56 (d).

The following compound were prepared in a manner similar to compound **Cpd130** and **Cpd131**

(by use of appropriate reagent, catalyst, base, solvent, reaction temperature and purification methods known to the person skilled in the art).

Reagent Step-1	Compounds
 (E/Z mixture)	Cpd132, Cpd133
 (E/Z mixture)	Cpd139
 (E/Z mixture)	Cpd143, Cpd144
 (E/Z mixture)	Cpd145
 (E/Z mixture)	Cpd037, Cpd038
 (E/Z mixture)	Cpd156, Cpd157
 (E/Z mixture)	Cpd158, Cpd159
 (E/Z mixture)	Cpd160
 (E/Z mixture)	Cpd164, Cpd165
 (E/Z mixture)	Cpd168

Example 33: Synthesis of (Z)-5-((4-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide **Cpd156-en1** and **Cpd156-en2** via SFC-separation.

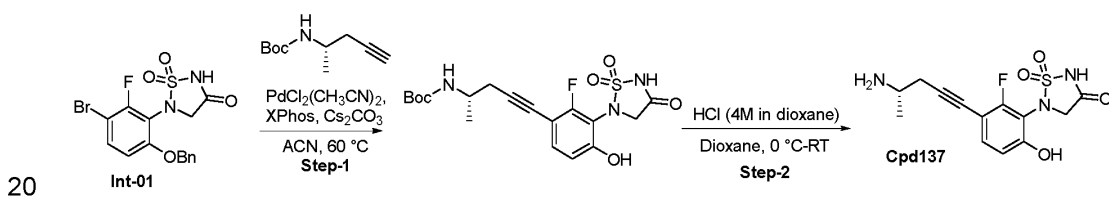


- 210 mg of **Cpd156** were subjected to Chiral-SFC purification (Preparative SFC Conditions: Column: Chiralpak IK (30*250 mm, 5 μ m). CO₂: 60% - Cosolvent: 40% (0.5% isopropylamine in IPA:CH₃CN (1:1)). Total Flow: 90 g/min. Back-pressure: 100 bar. Temperature: 30 °C. Wavelength detection: 257 nm. Stack time: 14.5 mins). The separated pure fractions were
- 5 concentrated under reduced pressure to afford
- 80 mg of **Cpd156-en1** (first eluting from SFC) as an off-white solid. LC-MS (LC-F): r.t. = 3.57 min (98.7%); m/z 356 [M+H]⁺. SFC-Method B : r.t. = 5.90 min (99.2%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.99 (brs, 3H), 7.06 (t, 1H), 6.71 (d, 1H), 6.43 (s, 1H), 3.96-3.93 (m, 4H), 3.45-3.40 (m, 1H), 2.95-2.91 (m, 1H), 2.82-2.79 (m, 1H), 1.77-1.68 (m, 1H), 1.52-1.44 (m, 1H), 0.95 (t, 3H).
- 10 ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.31 (d).
- and 75 mg of **Cpd156-en2** (second eluting from SFC) as a pale-brown solid. LC-MS (LC-F): r.t. = 3.57 min (98.2%); m/z 356 [M+H]⁺. SFC-Method B : r.t. = 8.84 min (97.5%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.01 (brs, 3H), 7.06 (t, 1H), 6.71 (d, 1H), 6.43 (s, 1H), 3.96-3.93 (m, 4H), 3.45-3.42 (m, 1H), 2.95-2.91 (m, 1H), 2.82-2.79 (m, 1H), 1.75-1.72 (m, 1H), 1.50-1.46 (m, 1H),
- 15 0.95 (t, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.32 (d).

The following compounds were prepared in a manner similar to compounds **Cpd156-en1** and **Cpd156-en2** (by use of appropriate purification methods known to the person skilled in the art).

Starting racemic compound	Preparative SFC conditions	Compounds
Cpd158	Column: Cellulose-SZ (10*250 mm, 5 μ m). CO ₂ : 65% - Cosolvent: 35% (0.5% isopropylamine in IPA:CH ₃ CN (1:1)). Total Flow: 20 g/min. Back-pressure: 120 bar. Temperature: 30 °C. Wavelength detection: 257 nm. Stack time: 10.5 mins	Cpd158-en1 , Cpd158-en2

Example 34: Synthesis of (S)-5-(3-(4-aminopent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd137**).



- Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluorophenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (500 mg, 1.20 mmol, 1.0 eq), *tert*-butyl (S)-pent-4-yn-2-ylcarbamate (662 mg, 3.61 mmol, 3.0 eq) and Cs₂CO₃ (0.785 g, 2.41 mmol, 2.0 eq) in CH₃CN (10 mL) was degassed with Ar for 10 min. Later, Pd(CH₃CN)₂Cl₂ (31.2 mg, 0.120 mmol, 0.1 eq) and XPhos (115 mg, 0.241 mmol,
- 25 0.2 eq) were added at RT and the resulting reaction mixture was stirred at 60 °C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT and concentrated. The crude residue was purified by reverse phase column chromatography eluting with a gradient of

CH₃CN in water (10-30%) to yield 250 mg of *tert*-butyl (S)-(5-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)pent-4-yn-2-yl) carbamate as an off-white solid. LC-MS (LC-M): r.t. = 1.66 min (86.1%); m/z 426 [M-H].

Step-2: A stirred solution of *tert*-butyl (S)-(5-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxyphenyl)pent-4-yn-2-yl)carbamate (250 mg, 0.585 mmol, 1.0 eq) in dioxane (10 mL) was treated dropwise with a 4N HCl solution in dioxane (5.00 mL, 10.0 mmol, 17.1 eq) at 0 °C and the resulting reaction mixture was stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude residue was purified by Prep-HPLC (Column: HI Crome C18 (30*150 mm, 10 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/8,2/8,10/20,12/20,12.1/98,16/98,16.2/8,20.2/8. Flow: 17 mL/min. Temperature: ambient) to yield 26.5 mg of (S)-5-(3-(4-aminopent-1-yn-1-yl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid.

LC-MS (LC-A): r.t. = 1.05 min (98.0%) ; m/z 328 [M+H]⁺.

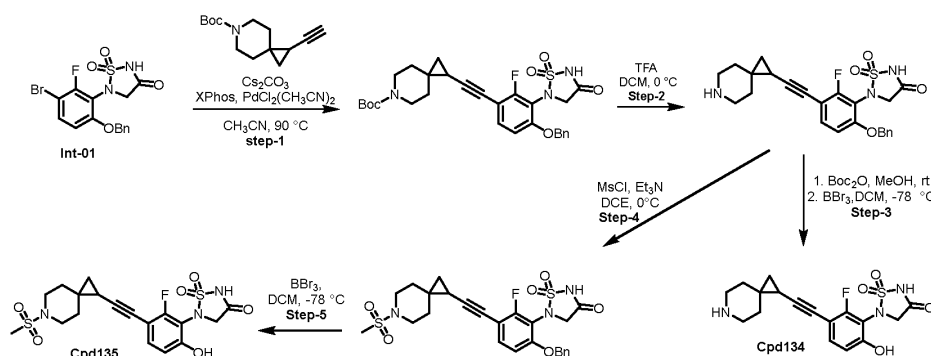
¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.16 (brs, 3H), 7.24 (t, 1H), 6.67 (dd, 1H), 3.95 (s, 2H), 3.43-3.38 (m, 1H), 2.79-2.65 (m, 2H), 1.29 (d, 3H)

¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -113.6 (d).

The following compounds were prepared in a manner similar to compounds **Cpd137** (by use of appropriate reagents, solvent, reaction temperature and purification methods known to the person skilled in the art).

Alkyne reagent Step-1	Compound
	Cpd136

Example 35: Synthesis of 5-[3-[2-(6-azaspiro[2.5]octan-2-yl)ethynyl]-2-fluoro-6-hydroxy-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (**Cpd134**) and 5-[2-fluoro-6-hydroxy-3-[2-(6-methylsulfonyl)-6-azaspiro[2.5]octan-2-yl)ethynyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (**Cpd135**).



Step-1: A stirred suspension of 5-(6-benzyloxy-3-bromo-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (340 mg, 0.82 mmol, 1 eq), *tert*-butyl 2-ethynyl-6-azaspiro[2.5]octane-6-carboxylate (231 mg, 0.98 mmol, 1.2 eq), PdCl₂(MeCN)₂ (21 mg, 0.082 mmol, 0.1 eq), Cs₂CO₃ (404 mg, 1.23 mmol, 1.5 eq) and Xphos (59 mg, 0.12 mmol, 0.15 eq) in CH₃CN (10 mL) was
5 degassed and put under an Ar atmosphere and then stirred at 90 °C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to room temperature, quenched with water (pH adjusted to 2 by addition of a 1M aq. NaHSO₄ solution). The reaction mixture was then extracted three times with EtOAc. Combined organic extracts were dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with
10 a gradient of methanol (1-16%) in DCM to yield 250 mg of *tert*-butyl 2-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-6-azaspiro [2.5]octane-6-carboxylate as a beige solid. LCMS (LC-A): r.t. = 1.39 min; m/z 570 [M+H]⁺

Step-2: A stirred solution of *tert*-butyl 2-[2-[4-benzyloxy-2-fluoro-3-(1,1,4-trioxo-1,2,5-thiadiazolidin-2-yl)phenyl]ethynyl]-6-azaspiro[2.5]octane-6-carboxylate (250 mg, 0.36 mmol,
15 1 eq) in DCM, cooled to 0 °C, was treated with 2,2,2-trifluoroacetic acid (6.0 mL, 78.4 mmol, 218 eq) and the reaction mixture was stirred at 0°C. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The crude product was purified by catch and release procedure using Supported SiliaBond-propylsulfonic acid (release step via addition of a 3N solution of NH₃ in MeOH) to yield 162 mg of 5-[3-[2-(6-azaspiro[2.5]octan-2-yl)ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a beige solid.
20 LCMS (LC-O): r.t. = 1.07 min; m/z 470 [M+H]⁺, 468 [M-H]⁻

Step-3: To a stirred solution of 5-[3-[2-(6-azaspiro[2.5]octan-2-yl)ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (75 mg, 0.15 mmol, 1 eq) in MeOH (5 mL) was added *tert*-butoxycarbonyl *tert*-butyl carbonate (66 mg, 0.30 mmol, 2 eq) and the mixture was stirred at
25 RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated under reduced pressure. The residue was redissolved in dry DCM (6 mL), the solution was cooled to -78°C, treated with BBr₃ (0.291 mL, 3.03 mmol, 20 eq) and then stirred at -78°C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched by addition of 30 mL of a 8:2 mix of DCM and a 7N solution of NH₃ in MeOH. Ice cold water was added to the
30 reaction mixture and the pH of the mixture was adjusted to 2 by addition of a 1M aq. NaHSO₄ solution. After separation, the aqueous layer was extracted three times with EtOAc and the combined organic extracts were concentrated. The crude product was purified by column chromatography on silica gel eluting with a gradient of MeOH (2-16%) in DCM followed by Prep-HPLC (Column: X-Bridge Prep C18 (100*19mm, 5 µm). Mobile phase A: 25 mM NH₄HCO₃ in
35 H₂O, pH 8.5; Mobile phase B: MeOH-MeCN (50:50). Gradient (Time(min)/%B): 0/5, 0.5/5, 6.5/65, 6.6/95, 9.0/95, 9.2/5, 12/5. Flow : 20 mL/min. Temperature: ambient) to yield 8.3 mg of 5-[3-[2-(6-

azaspiro[2.5]octan-2-yl)ethynyl]-2-fluoro-6-hydroxy-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (**Cpd134**) as a white solid.

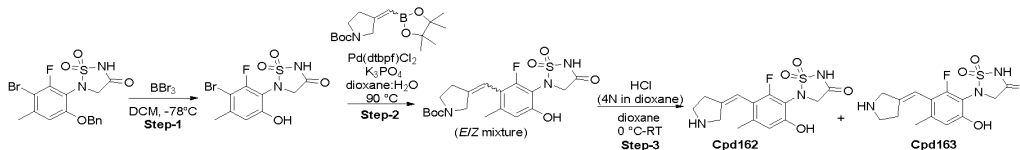
¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.18 (t, 1H), 6.64 (d, 1H), 3.94 (s, 2H), 3.25-2.98 (m, 4H), 1.89-1.78 (m, 1H), 1.77-1.64 (m, 3H), 1.55-1.42 (m, 1H), 1.04 (dd, 1H), 0.77 (t, 1H). LCMS (LC-C): r.t. = 2.05 min; m/z 380 [M+H]⁺, 378 [M-H]⁻.

Step-4: A mixture of 5-[3-[2-(6-azaspiro[2.5]octan-2-yl)ethynyl]-6-benzyloxy-2-fluoro-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (60 mg, 0.13 mmol, 1 eq) and Et₃N (0.036 mL, 0.26 mmol, 2 eq) in DCE (3 mL) was sonicated for 15 min and then cooled to 0 °C. To this cooled mixture was added mesyl chloride (0.020 mL, 0.26 mmol, 2 eq). The reaction mixture was stirred at 0 °C for 25 minutes and an excess of mesyl chloride (0.020 μ L, 0.26 mmol, 2 eq) and Et₃N (0.036 mL, 0.26 mmol, 2 eq) was added. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with DCM and washed with a sat. aq. NaHCO₃ solution of NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to yield 50.5 mg of crude 5-[6-benzyloxy-2-fluoro-3-[2-(6-methylsulfonyl-6-azaspiro[2.5]octan-2-yl)ethynyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a beige solid which was used in the next step without purification. LCMS (LC-N): r.t. = 1.22 min; m/z 548 [M+H]⁺, 546 [M-H]⁻.

Step-5: To a stirred solution of 5-[6-benzyloxy-2-fluoro-3-[2-(6-methylsulfonyl-6-azaspiro[2.5]octan-2-yl)ethynyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (51 mg, 0.088 mmol, 1 eq) in DCM (3 mL), cooled to -78 °C, was added BBr₃ (0.027 μ L, 0.29 mmol, 3.25 eq). The reaction mixture was stirred at -78 °C. After completion of the reaction (TLC monitoring), the reaction mixture was quenched by addition of 15 mL of a 8:2 mixture of DCM and a 3N solution of NH₃ in MeOH. Ice cold water was added to the reaction mixture and the pH of the mixture was adjusted to 2 by addition of a 1M aq. NaHSO₄ solution. After separation, the aqueous layer was extracted three times with EtOAc. Combined organic extracts were concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a gradient of MeOH (2-16%) in DCM to yield 18 mg of 5-[2-fluoro-6-hydroxy-3-[2-(6-methylsulfonyl-6-azaspiro[2.5]octan-2-yl)ethynyl]phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (**Cpd135**) as a beige solid.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.18 (brs., 1H), 6.64 (d, 1H), 3.95 (brs, 2H), 3.12 (brs, 2H), 2.89 (brs, 3H), 1.70 (brs, 2H), 1.60 (brs, 2H), 1.43 (brs, 1H), 0.99 (brs, 1H), 0.70 (brs, 1H). LCMS (LC-C): r.t. = 2.95 min; m/z 458 [M+H]⁺, 456 [M-H]⁻.

Example 36: Synthesis of (Z)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd162**) and (E)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd163**).



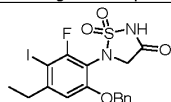
Step-1: A stirred solution of 5-(6-(benzyloxy)-3-bromo-2-fluoro-4-methylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (3.5 g, 8.154 mmol, 1.0 eq) in DCM (40 mL), at -78°C, was treated dropwise with a 1M solution of BBr₃ in DCM (40.77 mL, 40.77 mmol, 5 eq). After completion of the reaction, the reaction mixture was quenched with a 7N NH₃ solution in MeOH (40 mL) at -78°C and stirred for 30 min. The reaction mixture was then concentrated and the residue was purified by reverse phase column chromatography eluting with a gradient of CH₃CN (10-30%) in H₂O to yield 2.5 g of 5-(3-bromo-2-fluoro-6-hydroxy-4-methylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as a white solid. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 6.72 (d, 1H), 3.94 (s, 2H), 2.29 (s, 3H).

Step-2: A stirred solution of 5-(3-bromo-2-fluoro-6-hydroxy-4-methylphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (0.50 g, 1.475 mmol, 1.0 eq), *tert*-butyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)pyrrolidine-1-carboxylate (as an *E/Z* mixture, 0.684 g, 2.21 mmol, 1.5 eq) and K₃PO₄ (0.939 g, 4.425 mmol, 3.0 eq) in a mix of dioxane (60 mL) and water (10 mL) was degassed with Ar for 15 min. Later, Pd(dtbpf)Cl₂ (96.0 mg, 0.147 mmol, 0.1 eq) was added at RT and the mixture was again degassed for another 5 min, then stirred at 90°C. After completion of the reaction (TLC monitoring), the reaction mixture was cooled to RT, filtered and the filtrate was concentrated. The residue was purified by reverse phase column chromatography eluting with a gradient of CH₃CN (10-30%) in H₂O to yield 500 mg of *tert*-butyl-3-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxy-6-methylbenzylidene)pyrrolidine-1-carboxylate (as an *E/Z* mixture) as a brown solid. LCMS (LC-F): r.t. = 2.95 min; m/z 458 [M+H]⁺, 456 [M-H]⁻.

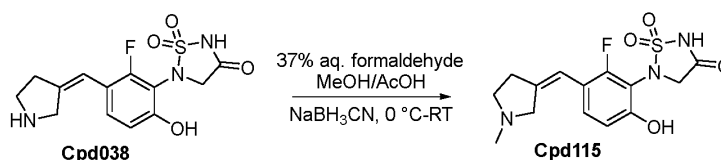
Step-3: A stirred solution of *tert*-butyl-3-(3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluoro-4-hydroxy-6-methylbenzylidene)pyrrolidine-1-carboxylate (as an *E/Z* mixture, 450 mg, 1.019 mmol, 1.0 eq) in dioxane (10 mL) was treated with a 4N HCl solution in dioxane (1.274 mL, 5.097 mmol, 5.0 eq) at 0°C and the resulting reaction mixture was then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude was purified by Prep-HPLC (Column: X-Bridge Prep C18 (250*19mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time(min)/%B): 0/5,4/5,10/25,14/25,14.1/98,17/98,17.1/5, 21/5. Flow : 12 mL/min. Temperature: ambient) to yield 74 mg of (*E*)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide **Cpd163**. LC-MS (LC-Q): r.t. = 1.06 min (98.4%); m/z 342 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.91 (brs, 3H), 6.57 (s, 1H), 6.32 (s, 1H), 3.96 (brs, 2H), 3.92 (s, 2H), 3.29 (t, 2H), 2.37 (t, 2H), 2.14 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -116.50 (s).

and 130 mg of (Z)-5-(2-fluoro-6-hydroxy-4-methyl-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide **Cpd162**. LC-MS (LC-Q): r.t. = 1.15 min (99.5%); m/z 342 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 8.78 (brs, 3H), 6.58 (s, 1H), 6.32 (s, 1H), 3.93 (s, 2H), 3.56 (brs, 2H), 3.32 (t, 2H), 2.77 (t, 2H), 2.15 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -117.11 (s).

The following compounds were prepared in a manner similar to compound **Cpd162** and **Cpd163** (by use of appropriate reagent, catalyst, base, solvent, reaction temperature and purification methods known to the person skilled in the art).

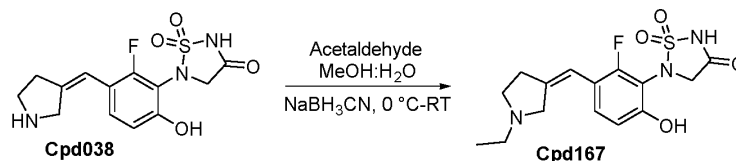
Reagent Step-1	Compounds
	Cpd146 , Cpd147

Example 37: Synthesis of (Z)-5-(2-fluoro-6-hydroxy-3-((1-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd115**).



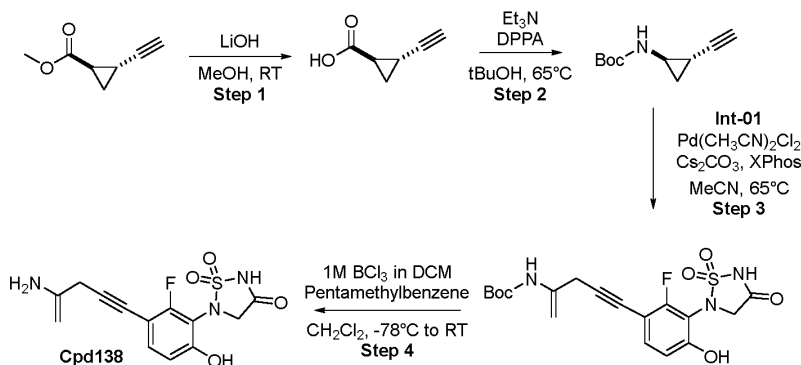
A stirred solution of (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (300 mg, 0.92 mmol, 1 eq) in MeOH (10 mL), at 0°C, was treated with AcOH (0.20 mL) then by 37% aq. Formaldehyde (0.76 mL, 9.2 mmol, 10 eq) and was then stirred for 15 min. NaBH₃CN (173 mg, 2.75 mmol, 3 eq) was added portionwise at 0°C and resulting reaction mixture was the allowed to reach RT. After completion of the reaction (TLC monitoring), the reaction mixture was quenched with ice water and then concentrated. The crude residue was purified by Prep-HPLC (Column: X-SELECT CSH C18 (19*250 mm, 5 μm). Mobile phase A: 10 mM NH₄HCO₃ in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/10,2/10,10/30,12.1/30,12.3/98,17.8/98,18/10,21/10. Flow: 12 mL/min. Temperature: ambient) to yield 100 mg of (Z)-5-(2-fluoro-6-hydroxy-3-((1-methylpyrrolidin-3-ylidene)methyl)phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-A): r.t. = 1.01 min (98.1%); m/z 342 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.83 (brs, 1H), 9.69 (s, 1H), 7.02 (t, 1H), 6.72 (d, 1H), 6.50 (s, 1H), 4.09 (brs, 2H), 3.96 (s, 2H), 3.42 (brs, 2H), 2.86 (brs, 5H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.4 (d).

Example 38: Synthesis of (Z)-5-(3-((1-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (**Cpd167**).



To a stirred solution of (Z)-5-(2-fluoro-6-hydroxy-3-(pyrrolidin-3-ylidenemethyl) phenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide (200 mg, 0.61 mmol, 1 eq) in MeOH (6 mL) and H₂O (0.5 mL) was added acetaldehyde (0.509 mL, 6.11 mmol, 10 eq) and the reaction mixture was then stirred at RT for 2 hours. The resulting reaction mixture was then cooled to 0°C, treated with NaBH₃CN (115 mg, 1.833 mmol, 3 eq) and then stirred at RT. After completion of the reaction (TLC monitoring), the reaction mixture was concentrated and the crude residue was purified by Prep-HPLC (Column: XBridge C18 Prep OBD (19*150 mm, 5 μm). Mobile phase A: 0.1% formic acid in H₂O; Mobile phase B: CH₃CN. Gradient (Time (min)/%B) : 0/5,2/5,10/15,11/15,11.2/98,13.9/98,14/5,17/5. Flow: 13 mL/min. Temperature: ambient) to yield 80 mg of (Z)-5-(3-((1-ethylpyrrolidin-3-ylidene)methyl)-2-fluoro-6-hydroxyphenyl)-1,2,5-thiadiazolidin-3-one 1,1-dioxide as an off-white solid. LC-MS (LC-A): r.t. = 1.00 min (99.6%) ; m/z 356 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 9.68 (s, 2H), 7.06 (t, 1H), 6.72 (d, 1H), 6.50 (s, 1H), 4.07 (brs, 2H), 3.96 (s, 2H), 3.43 (brs, 2H), 3.19-3.16 (m, 2H), 2.83 (brs, 2H), 1.22 (t, 3H). ¹⁹F NMR (376 MHz, DMSO-d₆) δ ppm: -119.5 (s).

Example 39: Synthesis of 5-[3-(4-aminopent-4-en-1-ynyl)-2-fluoro-6-hydroxy-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one (**Cpd138**)



Step-1: A stirred mixture of *rel*-methyl (1*R*,2*R*)-2-ethynylcyclopropanecarboxylate (1.50 g, 12.08 mmol, 1 eq) and LiOH monohydrate (1.55 g, 36.25 mmol, 3 eq) in MeOH (50 mL) was stirred at RT. After completion of the reaction (TLC monitoring), the crude reaction mixture was quenched with crushed ice and the pH was adjusted to an acidic value by adding a 1N aq. NaHSO₄ solution. Aqueous layer was extracted with Et₂O, combined organic extracts were washed with brine, dried over MgSO₄ and concentrated to give 1.33 g of *rel*-(1*R*,2*R*)-2-ethynylcyclopropanecarboxylic acid as a colorless oil, which was used as such in the next step. ¹H NMR (400 MHz, DMSO-d₆) δ ppm: 12.54 (brs, 1 H), 2.84 (d, 1 H), 1.86-1.62 (m, 2 H), 1.30-1.11 (m, 2 H).

Step-2: A stirred mixture of *rel*-(1*R*,2*R*)-2-ethynylcyclopropanecarboxylic acid (800 mg, 7.27 mmol, 1 eq) and Et₃N (1.1 mL, 7.63 mmol, 1.05 eq) in tBuOH (7 mL) was treated with diphenyl phosphoryl azide (1.8 mL, 7.99 mmol, 1.1 eq) and the resulting mixture was heated at 65°C. After completion of the reaction (TLC monitoring), the crude reaction mixture was diluted with iced water. The pH was adjusted to ~7 by adding a 1N NaHSO₄ aq. solution and the resulting aqueous layer was extracted several times with Et₂O. Combined organic extracts were washed with brine, dried over MgSO₄ and concentrated. The crude residue was purified by column chromatography over silica gel eluting with a gradient of Et₂O (0-20%) in pentane to give 720 mg of *rel-tert*-butyl *N*-[(1*R*,2*S*)-2-ethynylcyclopropyl]carbamate as a colorless solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 7.18 (brs, 1 H), 2.69 (d, 1 H), 2.64 (brs, 1 H), 1.38 (s, 9 H), 1.30-1.16 (m, 1 H), 1.00-0.82 (m, 2 H).

Step-3: To a stirred mixture of *rel-tert*-butyl *N*-[(1*R*,2*S*)-2-ethynylcyclopropyl]carbamate (655 mg, 3.61 mmol, 3 eq), XPhos (57 mg, 0.12 mmol, 0.1 eq) and PdCl₂(MeCN)₂ (16 mg, 0.060 mmol, 0.05 eq) in carefully degassed dry CH₃CN (72.2 mL) were added under inert atmosphere Cs₂CO₃ (1.18 g, 3.61 mmol, 3 eq) and 5-(6-benzyloxy-3-bromo-2-fluoro-phenyl)-1,1-dioxo-1,2,5-thiadiazolidin-3-one (Int-01, 0.50 g, 1.20 mmol, 1 eq) and the resulting mixture was then stirred at 65°C. After completion of the reaction (TLC monitoring), the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. Filtering cake was rinsed twice with EtOAc and combined filtrates were partitioned with water. The pH was adjusted to an acidic value adding an aq. 1N NaHSO₄ solution. The aqueous layer was extracted twice with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄ and concentrated. Residue was purified by column chromatography over silica gel eluting with a gradient of MeOH (0-10%) in EtOAc to give 335 mg of *rel-tert*-butyl ((1*S*,2*R*)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)cyclopropyl)carbamate. LC-MS (LC-O): r.t. = 1.38 min ; m/z 416 [M+H-Boc]⁺ ; -m/z 514 [M-H]⁻

Step-4: A stirred mixture of *rel-tert*-butyl ((1*S*,2*R*)-2-((4-(benzyloxy)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-2-fluorophenyl)ethynyl)cyclopropyl)carbamate (165 mg, 0.32 mmol, 1 eq) and pentamethylbenzene (240 mg, 1.60 mmol, 5 eq) in DCM (2 mL), cooled down to -78°C, was treated dropwise with a 1M BCl₃ solution in DCM (0.96 mL, 0.96 mmol, 3 eq). After a 15min stirring at -78°C, the mixture was allowed to stir at RT. After completion of the reaction (TLC monitoring), the reaction mixture was cooled down back to -78°C and carefully quenched with a 8/2 mix of DCM/3N NH₃ MeOH solution. The mixture was then diluted with MeOH and concentrated. Co-evaporation with MeOH was performed twice. Residue was purified by reverse-phase column chromatography over C18 modified silica gel using a stepwise gradient of MeCN (0-40%) in H₂O to give 53 mg of 5-[3-(4-aminopent-4-en-1-ynyl)-2-fluoro-6-hydroxy-phenyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one as a thin white powder. LC-MS (LC-H): r.t. = 2.32 min (99.2%) ; m/z 326 [M+H]⁺ ; -m/z 324 [M-H]⁻. ¹H NMR (400 MHz, acetonitrile-*d*₃) δ ppm: 9.02 (brs, 1 H), 7.04 (t, 1 H),

6.73 (dd, 1 H), 6.66- 6.56 (m, 1 H), 6.00 (q, 1 H), 5.85 (brs, 1 H), 4.17 (s, 2 H), 3.88 (s, 2 H).

Table 3: Analytical LC-MS and NMR data for example compounds of the invention

Code	LC-MS Method	r.t (min.)	LC-MS purity (%)	[M+H] ⁺ (m/z)	[M-H] ⁻ (m/z)	¹ H NMR 400 MHz δ ppm (DMSO-d ₆)
Cpd001	A	1.65	98.6	-	337	7.15 (t, 1H), 6.62 (dd, 1H), 3.94 (s, 2H) 2.87-2.83 (m, 1H), 1.99- (m, 2H), 1.72-1.63 (m, 6H)
Cpd002	B	8.42	99.2	-	325	9.85 (brs, 1H), 7.16 (t, 1H), 6.63 (dd, 1H), 3.94 (s, 2H), 1.27 (s, 9H)
Cpd003	C	3.78	99.2	-	379	7.60 (s, 1 H), 7.42 - 7.54 (m, 3 H), 7.37 (t, 1 H), 6.74 (d, 1 H), 3.98 (s, 2 H)
Cpd004	A	1.78	96.1	-	363	10.59 (s, 1H), 7.50-7.37 (m, 4H), 7.30-7.25 (m, 1H), 6.77 (d, 1H), 4.18 (s, 2H)
Cpd005	A	1.28	99.5	348	-	10.86 (brs, 1H), 8.61 (d, 1H), 7.86 (m, 1H), 7.63 (d, 1H), 7.48 (t, 1H), 7.44-7.40 (m, 1H), 6.80 (d, 1H), 4.29 (s, 2H)
Cpd006	A	1.24	98.8	348	-	10.84 (brs, 1H), 8.75 (s, 1H), 8.60 (m, 1H), 8.00 (m, 1H), 7.51-7.45 (m 2H), 6.80 (m, 1H), 4.29 (s, 2H)
Cpd007	B	4.08	98.2	314	-	9.03 (brs, 2H), 7.29 (m, 1H), 6.72 (m, 1H), 4.13 (s, 2H), 3.95 (s, 2H), 2.63 (s, 3H)
Cpd008	A	1.65	99.6	-	345	7.54-7.51 (m, 2H), 7.43-7.40 (m, 3H) 7.35 (m, 1H), 6.73 (m, 1H), 3.98 (s, 2H)
Cpd009	A	1.52	97.7	-	309	7.15 (t, 1H), 6.62 (dd, 1H), 3.93 (s, 2H) 1.56-1.50 (m, 1H), 0.89-0.84 (m, 2H), 0.72-0.71 (m, 2H)
Cpd010	D	2.47	99.7	-	416	7.21 (t, 1H), 6.66 (dd, 1H), 3.94 (s, 2H), 3.62-3.58 (m, 1H), 3.43-3.37 (m, 2H), 3.29-3.19 (m, 2H), 2.93 (s, 3H), 2.28-2.23 (m, 1H), 2.00-1.95 (m, 1H)
Cpd011	A	1.74	98.9	-	325	7.17 (t, 1H), 6.64 (dd, 1H), 3.94 (s, 2H), 2.32 (d, 2H), 1.91-1.79 (m, 1H), 0.98 (d, 6H)
Cpd012	A	1.66	99.2	-	381	10.31 (s, 1H), 7.52-7.48 (m, 1H), 7.42-7.30 (m, 3H), 6.75 (d, 1H), 3.98 (s, 2H)
Cpd013	E	3.00	98.4	368	-	7.88 (s, 1H), 7.35 (t, 1H), 6.73 (d, 1H), 3.97 (s, 2H), 2.67 (s, 3H)
Cpd014	A	1.44	99.3	352	-	7.41 (t, 1H), 6.75 (d, 1H), 6.54 (s, 1H), 3.97 (s, 2H), 2.45 (s, 3H)
Cpd015	F	4.28	96.6	368	-	7.64 (s, 1H), 7.42 (t, 1H), 6.75 (d, 1H), 3.97 (s, 2H), 2.49 (s, 3H)
Cpd016	A	1.87	95.4	-	413	7.87-7.83 (m, 2H), 7.77 (d, 1H), 7.67 (t, 1H), 7.40 (t, 1H), 6.75 (d, 1H), 3.98 (s, 2H)
Cpd017	A	1.81	96.6	-	413	10.22 (brs, 1H), 7.81 (d, 1H), 7.68 (d, 1H), 7.51 (dd, 1H), 7.36 (t, 1H), 6.72 (d, 1H), 3.97 (s, 2H)
Cpd018	A	1.26	98.7	337	-	13.23 (brs, 1H), 7.75 (brs, 1H), 7.33 (t, 1H), 6.72 (d, 1H), 6.54 (s, 1H), 3.97 (s, 2H)
Cpd019	E	1.40	99.2	326	-	9.16 (brs, 3H), 7.23 (t, 1H), 6.69 (d, 1H), 4.19 (t, 2H), 4.00-3.93 (m, 5H)
Cpd020	D	1.29	97.6	340	-	9.29 (brs, 1H), 7.25 (t, 1H), 6.70 (d, 1H), 4.42 (brs, 1H), 3.95 (s, 2H), 3.18-3.15 (m, 1H), 3.09 (brs, 1H), 2.28-2.23 (m, 1H), 1.98-1.86 (m, 3H)

Cpd021	E	2.6	99.9	368	-	7.23 (t, 1H), 6.66 (d, 1H), 4.39 (t, 1H), 4.15-4.13 (m, 2H), 3.94 (s, 2H), 3.79-3.70 (m, 2H), 1.76 (s, 3H)
Cpd022	A	1.2	99.4	340	-	7.19 (t, 1H), 6.66 (d, 1H), 3.94 (s, 2H) 3.25-2.93 (m, 5H), 2.22-2.15 (m, 1H), 1.90-1.84 (m, 1H)
Cpd023	E	3.54	97.2	-	351	9.84 (s, 1H), 7.15 (t, 1H), 6.63 (d, 1H), 3.94 (s, 2H), 2.67-2.62 (m, 1H), 1.80-1.66 (m, 4H), 1.50-1.33 (m, 6H)
Cpd024	G	1.53	97.7	-	354	8.60 (bs, 2H), 7.20 (t, 1H), 6.66 (d, 2H), 3.94 (s, 2H), 3.16-3.15 (m, 2H), 3.02-2.96 (m, 3H), 2.02-1.96 (m, 2H), 1.76-1.71 (m, 2H)
Cpd025	H	2.38	99.0	-	297	9.89 (s, 1H), 6.88 - 7.31 (m, 5H), 6.64 (d, 1H), 3.95 (s, 2H), 2.42 (q, 2H), 1.16 (t, 3H)
Cpd026	C	2.82	99.0	-	341	7.22 (t, 1H), 7.09 (brs, 2H), 6.67 (d, 1H), 3.95 (s, 2H), 3.30 (brs., 3H), 1.46 (s, 6H)
Cpd027	C	3.16	98.0	-	309	7.25 (t, 1H), 7.10 (brs, 1H), 6.69 (d, 1H), 5.37 (brs, 2H), 3.96 (s, 2H), 1.94 (s, 3H)
Cpd028	A	1.31	96.7	-	402	7.28 (t, 1H), 6.70 (d, 1H), 5.61-5.55 (m, 2H), 3.95 (s, 2H), 3.72 (s, 2H), 2.94 (s, 3H)
Cpd029	F	4.63	98.8	-	375	7.37-7.30 (m, 2H), 7.11-7.06 (m, 2H), 6.98 (dd, 1H), 6.72 (d, 1H), 3.98 (s, 2H), 3.79 (s, 3H)
Cpd030	D	1.46	90.2	-	341	7.26 (t, 1H), 6.69 (d, 1H), 6.59 (s, 1H), 4.73 (d, 2H), 4.58 (d, 2H), 3.95 (s, 2H)
Cpd031	A	1.28	99.8	-	355	7.31 (t, 1H), 6.70 (d, 1H), 4.71 (d, 2H), 4.63 (d, 2H), 3.95 (s, 2H), 3.32 (s, 3H)
Cpd032	A	1.71	99.2	-	385	7.38 (d, 2H), 7.33 (t, 2H), 7.26-7.19 (m, 2H), 6.66 (d, 1H), 3.95 (s, 2H), 1.51-1.48 (m, 2H), 1.40-1.37 (m, 2H)
Cpd033	F	4.68	98.7	-	375	7.48-7.29 (m, 3H), 6.97 (d, 2H), 6.71 (d, 1H), 3.97 (s, 2H), 3.79 (s, 3H)
Cpd034	E	3.49	99.7	-	409	7.48 (s, 1H), 7.39 (dd, 1H), 7.15 (d, 1H), 7.01 (t, 1H), 6.25 (d, 1H), 4.01 (s, 2H), 3.88 (s, 3H)
Cpd035	D	2.45	95.1	-	283	7.17 (t, 1H), 6.64 (dd, 1H), 3.94 (s, 2H), 2.04 (s, 3H)
Cpd036	I	2.27	92.2	-	359	9.94 (s, 1H), 7.48 - 7.60 (m, 2H), 7.33 - 7.48 (m, 3H), 6.66 (s, 1H), 3.96 (s, 2H), 2.39 (s, 3H)
Cpd037	J	2.01	98.3	328	-	8.68-8.60 (m, 2H), 7.21 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.05 (s, 2H), 3.86 (brs, 2H), 3.26 (t, 2H), 2.69-2.65 (m, 2H)
Cpd038	J	2.07	98.5	328	-	8.98 (brs, 3H), 7.06 (t, 1H), 6.72 (d, 1H), 6.52 (s, 1H), 3.96 (s, 2H), 3.91 (s, 2H), 3.28 (t, 2H), 2.77 (t, 2H)
Cpd039	A	2.00	96.1	314	-	8.60 (brs, 1H), 6.92 (t, 1H), 6.68 (d, 1H), 6.24 (s, 1H), 4.57 (s, 2H), 4.44 (s, 2H), 3.95 (s, 2H)
Cpd040	H	3.08	98.9	-	365	9.80 (s, 1H), 7.53 (t, 1H), 7.33 - 7.49 (m, 3H), 7.20 - 7.30 (m, 1H), 7.11 - 7.18 (m, 1H), 7.03 - 7.11 (m, 1H), 6.75 (d, 1H), 4.02 (s, 2H)
Cpd041	C	3.06	92.0	-	311	9.39 (s, 1H), 7.24 (t, 1H), 6.63 (d, 1H), 6.42 (d, 1H), 5.70 (dd, 1H), 3.96 (s, 2H), 1.48-1.65 (m, 1H), 0.71-0.83 (m, 2H), 0.42-0.56 (m, 2H)
Cpd042	C	3.62	98.0	-	327	9.42 (s, 1H), 7.31 (t, 1H), 6.65 (d, 1H), 6.25 (m, 2H), 3.96 (s, 2H), 1.09 (s, 9H)

Cpd043	C	2.91	98.0	-	299	9.34 (brs, 1H), 6.86-7.31 (m, 5H), 6.66 (d, 1H), 6.07 (brs, 1H), 3.96 (s, 2H), 1.86 (s, 3H), 1.72 (s, 3H)
Cpd044	J	1.92	97.5	353	-	7.43 (t, 1H), 6.64 (d, 1H), 6.30 (d, 1H), 6.11 (dd, 1H), 3.95 (s, 2H), 2.12-2.07 (m, 1H), 1.75-1.61 (m, 5H), 1.30-1.12 (m, 5H)
Cpd045	K	2.85	96.7	347	-	9.66 (bs, 1H), 7.58-7.51 (m, 3H), 7.37 (t, 2H), 7.25 (t, 1H), 7.15 (d, 2H), 6.73 (d, 1H), 3.99 (s, 2H)
Cpd046	L	1.03	99.3	342	-	9.5 (bs, 1H), 8.6 (bs, 2H), 7.03 (t, 1H), 6.68 (d, 1H), 6.26 (s, 1H), 3.95 (s, 2H), 3.16-3.14 (m, 2H), 3.09-3.06 (m, 2H), 2.49-2.45 (m, 4H)
Cpd047	E	3.40	99.9	-	325	9.29 (brs, 1H), 7.18 (t, 1H), 6.66 (d, 1H), 6.27 (s, 1H), 3.95 (s, 2H), 2.44-2.32 (m, 4H), 1.73-1.58 (m, 4H)
Cpd048	A	1.15	96.8	-	381	9.59 (s, 1H), 9.28 (brs, 1H), 7.21-6.95 (m, 1H), 6.69 (d, 1H), 6.30 (s, 1H), 3.98 (s, 2H), 3.58-3.48 (m, 2H), 3.06-2.90 (m, 4H), 2.70-2.57 (m, 3H), 2.42-2.39 (m, 1H), 1.70-1.64 (m, 2H), 0.91 (t, 3H)
Cpd049	H	1.93	95.1	-	404	10.09 (brs, 1H), 7.50 (s, 1H), 7.21 (t, 1H), 6.69 (d, 1H), 3.95 (s, 2H), 3.01-3.12 (m, 3H), 1.58 (s, 6H)
Cpd050	H	1.65	99.9	349	347	9.19 (s, 1H), 8.99 (s, 2H), 7.37-7.43 (m, 1H), 6.76 (dd, 1H), 3.99 (s, 2H)
Cpd051	A	1.63	97.2	-	381	10.32 (s, 1H), 7.53-7.36 (m, 3H), 7.29-7.24 (m, 1H), 6.75 (d, 1H), 3.98 (s, 2H)
Cpd052	A	1.21	99.4	388	-	8.69 (dd, 1H), 8.23 (dd, 1H), 8.16 (s, 1H), 7.42-7.35 (m, 2H), 6.76 (dd, 1H), 3.99 (s, 2H)
Cpd053	C	2.67	98.0	432	430	9.96 (brs, 1H), 7.20 (t, 1H), 6.65 (d, 1H), 3.95 (s, 2H), 3.42-3.35 (m, 2H), 3.10-2.99 (m, 2H), 2.92-2.80 (m, 4H), 1.93 (ddd, 2H), 1.74-1.59 (m, 2H)
Cpd054	C	2.68	99.0	432	430	9.98 (brs, 1H), 7.18 (t, 1H), 6.65 (d, 1H), 3.95 (s, 2H), 3.60-3.50 (m, 1H), 3.43-3.38 (m, 1H), 2.99-2.79 (m, 6H), 2.04-1.89 (m, 1H), 1.83-1.70 (m, 1H), 1.61-1.44 (m, 2H)
Cpd055	D	2.14	95.0	-	313	7.25 (t, 1H), 6.68 (d, 1H), 4.32 (s, 2H), 3.95 (s, 2H), 3.31 (s, 3H)
Cpd056	E	2.63	98.8	337	-	13.16 (brs, 1H), 8.05-7.77 (2H), 7.27 (t, 1H), 6.69 (d, 1H), 3.96 (s, 2H)
Cpd057	A	1.58	97.6	-	311	7.15 (t, 1H), 6.63 (d, 1H), 3.94 (s, 2H), 2.79 (m, 1H), 1.20 (d, 6H)
Cpd058	A	1.34	98.2	378	-	8.15-8.14 (m, 2H), 7.35 (s, 1H), 6.88 (t, 1H), 5.98 (d, 1H), 4.08 (s, 2H), 3.84 (s, 3H)
Cpd059	A	1.16	99.4	362	-	8.59 (d, 1H), 7.82 (dd, 1H), 7.36 (t, 1H), 7.31 (d, 1H), 6.73 (d, 1H), 3.97 (s, 2H), 2.50 (s, 3H)
Cpd060	A	1.23	97.6	-	339	7.16 (t, 1H), 6.63 (d, 1H), 4.90 (t, 1H), 3.93 (s, 2H), 3.42 (d, 2H), 0.85 (brs, 4H)
Cpd061	A	1.25	98.8	351	-	8.05 (s, 1H), 7.66 (s, 1H), 7.27 (t, 1H), 6.69 (d, 1H), 3.96 (s, 2H), 3.84 (s, 3H)
Cpd062	F	3.95	95.5	-	339	6.86 (t, 1H), 6.17 (d, 1H), 4.01 (s, 2H), 3.94 (t, 1H), 3.84-3.78 (m, 1H), 3.75-3.70 (m, 1H), 3.50 (t, 1H), 3.23-3.15 (m, 1H), 2.25-2.17 (m, 1H), 1.92-1.83 (m, 1H)
Cpd063	C	3.17	97.8	-	323	600 MHz : 6.56 (s, 1H), 3.91 (s, 2H), 2.24 (s, 3H), 1.63-1.51 (m, 1H), 0.93-0.85 (m, 2H), 0.75-0.67 (m, 2H)

Cpd064	A	1.57	97.3	337	-	12.92 (brs, 1H), 7.36 (t, 1H), 7.29-7.04 (m, 2H), 6.74 (d, 1H), 3.98 (s, 2H)
Cpd065	B	5.50	96.7	337	-	12.62 (brs, 1H), 10.07 (s, 1H), 7.77 (s, 1H), 7.49 (s, 1H), 7.30 (t, 1H), 6.71 (d, 1H), 3.97 (s, 2H)
Cpd066	F	4.22	97.4	387	-	11.89 (brs, 1H), 8.36 (d, 1H), 8.14 (d, 1H), 7.55 (d, 1H), 7.36 (t, 1H), 6.73 (d, 1H), 6.49 (d, 1H), 3.99 (s, 2H)
Cpd067	A	1.27	99.1	349	-	8.84 (d, 1H), 8.68 (t, 1H), 8.62 (d, 1H), 7.45 (t, 1H), 6.78 (d, 1H), 3.98 (s, 2H)
Cpd068	E	3.21	97.9	382	-	8.68 (d, 1H), 8.64 (d, 1H), 8.16 (t, 1H), 7.39 (t, 1H), 6.76 (d, 1H), 3.98 (s, 2H)
Cpd069	A	1.23	98.7	362	-	10.61 (brs, 1H), 8.55 (s, 1H), 8.45 (s, 1H), 7.84 (s, 1H), 7.42 (t, 1H), 6.78 (d, 1H), 4.17 (s, 2H), 2.33 (s, 3H)
Cpd071	A	1.13	94.1	-	376	7.24 (t, 1H), 6.68 (d, 1H), 4.06 (s, 2H), 3.94 (s, 2H), 3.01 (s, 3H)
Cpd072	F	3.68	91.3	-	327	7.17 (t, 1H), 6.65 (dd, 1H), 5.44 (s, 1H), 3.94 (s, 2H), 1.44 (s, 6H)
Cpd073	A	1.66	96.7	-	325	7.16 (t, 1H), 6.63 (dd, 1H), 3.94 (s, 2H), 2.64-2.59 (m, 1H), 1.55-1.41 (m, 2H), 1.18 (d, 3H), 1.00 (t, 3H)
Cpd074	A	1.62	99.0	-	359	7.21 (t, 1H), 6.66 (dd, 1H), 3.94 (s, 2H), 3.27-3.21 (m, 1H), 3.17-2.97 (m, 2H), 2.75-2.65 (m, 2H)
Cpd075	A	1.27	98.2	388	-	13.68 (brs, 1H), 8.65 (d, 1H), 8.45 (d, 1H), 8.19 (s, 1H), 7.39 (t, 1H), 6.74 (d, 1H), 3.99 (s, 2H)
Cpd076	A	1.27	97.8	-	390	7.22 (t, 1H), 6.67 (d, 1H), 4.37 (q, 1H), 3.94 (s, 2H), 3.02 (s, 3H), 1.43 (d, 3H)
Cpd077	C	2.63	99.0	353	351	7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.83 (d, 2 H), 3.60 (d, 2 H), 2.08-2.03 (m, 2 H), 1.38 (t, 1 H)
Cpd078	I	2.19	98.0	-	337	7.34 (brs, 1 H), 7.16 (t, 1 H), 6.63 (d, 1 H), 3.94 (s, 2 H), 1.43 (dd, 1 H), 1.22 (s, 3 H), 1.11 (s, 3 H), 0.88 (dd, 1 H), 0.57 (t, 1 H)
Cpd079	H	1.31	91.9	352	351	7.16 (t, 1 H), 6.64 (dd, 1 H), 3.94 (s, 2 H), 3.14-3.06 (m, 2 H), 2.96-2.86 (m, 2 H), 1.93-1.86 (m, 2 H), 1.61-1.55 (m, 1 H)
Cpd080	A	1.06	95.3	328	-	7.23 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 3.01-2.88 (m, 3H), 1.24 (d, 3H)
Cpd080-en1	B	5.41	95.0	328	-	7.86 (brs, 3H), 7.23 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 2.98-2.84 (m, 3H), 1.24 (d, 3H)
Cpd080-en2	A	1.11	99.7	328	-	8.08 (brs, 3H), 7.24 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 3.03-2.91 (m, 3H), 1.25 (d, 3H)
Cpd081	A	1.03	98.5	338	-	8.54 (s, 1H), 7.41 (t, 1H), 6.75 (d, 1H), 3.98 (s, 2H)
Cpd082	A	1.38	99.0	373	-	8.99 (dd, 2H), 8.53 (t, 1H), 7.39 (t, 1H), 6.75 (d, 1H), 3.98 (s, 2H)
Cpd083	A	1.25	98.6	404	-	7.24 (t, 1H), 6.70 (d, 1H), 4.13 (t, 2H), 3.94 (s, 2H), 3.90 (t, 2H), 3.78-3.72 (m, 1H), 3.05 (s, 3H)
Cpd084	A	1.21	98.7	349	-	9.31 (dd, 1H), 9.26 (dd, 1H), 7.82 (dd, 1H), 7.44 (t, 1H), 6.78 (d, 1H), 3.98 (s, 2H)
Cpd085	V	3.10	96.9	349	-	10.96 (brs, 1H), 9.22 (dd, 1H), 7.92 (dd, 1H), 7.78-7.74 (m, 1H), 7.55 (t, 1H), 6.83 (d, 1H), 4.29 (s, 2H)
Cpd086	H	2.46	96.8	444	442	7.18 (t, 1 H), 6.65 (dd, 1 H), 3.96 (s, 2 H), 3.53-3.45 (m, 2 H), 3.44-3.37 (m, 2 H), 3.11 (q, 2 H), 2.06-1.98 (m, 2 H), 1.53 (t, 1 H), 1.19 (t, 3 H)

Cpd087	C	2.55	99.5	430	428	7.49 (b.s, 1 H), 7.24-7.11 (m, 1 H), 6.64 (dd, 1 H), 3.94 (s, 2 H), 3.49-3.42 (m, 3 H), 3.40-3.38 (m, 2 H), 2.93 (s, 2 H), 2.09-1.99 (m, 2 H), 1.57 (t, 1 H)
Cpd088	C	2.74	96.3	410	408	7.16 (t, 1 H), 6.62 (d, 1 H), 3.94 (s, 2 H), 3.60-3.55 (m, 4 H), 3.55 (s, 1 H), 1.98 (d, 2 H), 1.84 (s, 1 H), 1.40 (t, 1 H)
Cpd089	H	2.83	98.7	456	454	7.65 (brs, 2 H), 7.18 (t, 1 H), 6.65 (d, 1 H), 3.96 (s, 2 H), 3.51-3.47 (m, 4 H), 2.81-2.66 (m, 1 H), 2.11-1.97 (m, 2 H), 1.68-1.50 (m, 1 H), 1.04-0.94 (m, 2 H), 0.94-0.82 (m, 2 H)
Cpd090	H	2.94	99.0	501	499	7.55 (brs, 1 H), 7.18 (t, 1 H), 6.65 (dd, 1 H), 3.96 (s, 2 H), 3.66-3.56 (m, 4 H), 3.48 (d, 2 H), 3.38 (dt, 3 H), 3.12-3.03 (m, 4 H), 2.06-1.96 (m, 2 H), 1.56 (t, 1 H)
Cpd091	H	3.36	97.3	-	504	7.45-7.32 (m, 5 H), 7.17 (t, 1 H), 6.63 (d, 1 H), 4.51-4.43 (m, 2 H), 3.94 (s, 2 H), 3.46-3.38 (m, 2 H), 2.03-1.94 (m, 2 H), 1.46 (t, 1 H), 1.32-1.17 (m, 2 H)
Cpd092	H	2.77	99.9	514	512	7.17 (t, 1 H), 6.66 (d, 1 H), 3.96 (s, 2 H), 3.85-3.58 (brs, 1 H), 3.52-3.44 (m, 3 H), 3.41 (brs, 2 H), 3.28-2.90 (brs, 4 H), 2.83 (s, 3 H), 2.06 (brs, 2 H), 1.62 (t, 1 H)
Cpd093	C	2.49	98.3	431	429	7.17 (t, 1 H), 6.83 (brs, 2 H), 6.64 (d, 1 H), 3.95 (s, 2 H), 3.32 (brs, 2 H), 3.26-3.20 (m, 2 H), 2.02 (brs, 2 H), 1.61 (t, 1 H)
Cpd094	A	1.3	97.9	286	-	7.17 (t, 1H), 6.64 (dd, 1H), 3.94 (s, 2H)
Cpd095	V	1.48	92.0	342	-	7.02 (t, 1H), 6.71 (d, 1H), 6.40 (s, 1H), 3.96 (s, 2H), 3.70 (brs, 2H), 3.12 (t, 2H), 2.45 (t, 2H), 1.78 (brs, 2H)
Cpd096	V	1.15	95.3	342	-	7.02 (t, 1H), 6.69 (d, 1H), 6.29 (s, 1H), 3.96 (s, 2H), 3.58 (s, 2H), 3.01 (brs, 2H), 2.39 (t, 2H), 1.65 (brs, 2H)
Cpd097	B	3.61	90.2	314	-	7.22 (t, 1H), 6.66 (d, 1H), 3.94 (s, 2H), 2.91 (t, 2H), 2.65 (t, 2H)
Cpd098	H	2.62	97.5	-	379	9.92 (br. s., 1 H), 7.16 (t, 1 H), 6.63 (d, 1 H), 3.95 (s, 2 H), 3.76-3.52 (m, 4 H), 1.61 (t, 2 H), 1.58-1.51 (m, 1 H), 1.51-1.43 (m, 1 H), 1.39-1.28 (m, 1 H), 0.96 (dd, 1 H), 0.67 (t, 1 H)
Cpd099	A	1.45	98.1	444	-	7.40 (brs, 2H), 7.16 (t, 1H), 6.63 (d, 1H), 3.93 (s, 2H), 3.49-3.39 (m, 2H), 3.05-2.98 (m, 1H), 2.85 (s, 3H), 2.84-2.77 (m, 1H), 2.09-2.03 (m, 1H), 1.87-1.80 (m, 1H), 1.66-1.60 (m, 1H), 1.52-1.47 (m, 2H)
Cpd100	A	1.42	93.6	-	442	7.17 (d, 1H), 7.15 (t, 1H), 6.62 (d, 1H), 3.96-3.93 (m, 3H), 2.96 (s, 3H), 1.89-1.80 (m, 4H), 1.23-1.20 (m, 2H), 1.06-1.04 (m, 1H)
Cpd101	A	1.13	95.0	352	-	10.04-8.65 (brs, 2H), 7.32 (t, 1H), 6.68 (dd, 1H), 3.96 (s, 2H), 3.59 (dd, 2H), 3.12 (d, 2H), 2.28-2.22 (m, 3H)
Cpd102	H	1.92	93.0	366	364	7.16 (t, 1 H), 6.64 (d, 1 H), 3.98 (s, 2 H), 3.94 (d, 4 H), 3.20-3.10 (m, 1 H), 2.65-2.57 (m, 2 H), 2.36-2.28 (m, 2 H)
Cpd103	H	1.65	96.3	340	338	7.20 (t, 1 H), 6.69 (dd, 1 H), 4.03-3.96 (m, 2 H), 3.60-3.50 (m, 1 H), 3.14-3.01 (m, 1 H), 2.68-2.57 (m, 2 H), 2.20 (qd, 2 H)
Cpd104	H	1.42	97.7	340	338	7.29-7.11 (m, 1 H), 6.69 (dd, 1 H), 3.99 (s, 2 H), 3.96-3.83 (m, 1 H), 3.49-3.37 (m, 1 H), 2.72-2.59 (m, 1 H), 2.49-2.36 (m, 3 H), 2.31-2.16 (m, 1 H)
Cpd105	C	2.14	95.6	341	339	7.15 (t, 1 H), 6.62 (d, 1 H), 4.67 (t, 1 H), 3.94 (s, 2 H), 3.48-3.39 (m, 1 H), 3.30-3.23 (m, 1 H), 1.46-1.38 (m, 1 H), 1.38-1.29 (m, 1 H), 0.88-0.77 (m, 2 H)

Cpd106	H	2.69	98.2	355	353	9.89 (brs, 1 H), 7.28-7.11 (m, 2 H), 7.08 (brs, 1 H), 6.95 (brs, 1 H), 6.63 (d, 1 H), 3.94 (s, 2 H), 3.25 (s, 2 H), 3.21-3.12 (m, 1 H), 1.53-1.34 (m, 2 H), 0.98-0.88 (m, 1 H), 0.87-0.76 (m, 1 H)
Cpd107	C	2.08	96.5	368	366	9.96 (br. s, 1 H), 8.22 (q, 1 H), 7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 2.61 (d, 3 H), 1.99-1.90 (m, 1 H), 1.82-1.76 (m, 1 H), 1.26-1.19 (m, 1 H), 1.10 (ddd, 1 H)
Cpd108	A	1.17	95.3	419	-	10.27 (s, 1H), 9.36 (s, 1H), 8.62 (d, 1H), 8.52 (d, 1H), 7.94 (s, 1H), 7.37 (t, 1H), 6.75 (d, 1H), 3.98 (s, 2H), 3.31 (s, 2H), 2.99 (t, 2H), 2.77 (s, 6H)
Cpd109	E	2.31	95.9	381	-	10.19 (s, 1H), 7.97 (brs, 1H), 7.68 (s, 1H), 7.32 (t, 1H), 6.72 (d, 1H), 4.99 (brs, 1H), 4.05 (t, 2H), 4.01 (s, 2H), 3.67 (t, 2H)
Cpd110	A	1.09	95.7	394	-	8.66 (brs, 2H), 8.15 (s, 1H), 7.78 (s, 1H), 7.27 (t, 1H), 6.70 (dd, 1H), 4.38 (t, 2H), 3.96 (s, 2H), 3.31 (t, 2H), 2.53 (d, 3H)
Cpd111	E	2.61	99.3	408	-	10.07 (s, 1H), 9.43 (s, 1H), 7.78 (s, 1H), 7.66 (s, 1H), 7.29 (t, 1H), 6.71 (d, 1H), 4.32 (brs, 2H), 3.97 (s, 2H), 3.33 (brs, 2H), 2.67 (brs, 6H)
Cpd112	H	1.39	96.0	354	352	7.28 (t, 1 H), 6.67 (d, 1 H), 6.39 (d, 1 H), 5.79 (dd, 1 H), 4.04-3.94 (m, 2 H), 3.42-3.26 (m, 4 H), 1.98-1.86 (m, 3 H), 1.71-1.60 (m, 1 H)
Cpd113	A	1.14	99.3	408	-	10.07 (s, 1H), 9.27 (brs, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.28 (t, 1H), 6.70 (dd, 1H), 4.52 (t, 2H), 3.96 (s, 2H), 3.54 (brs, 2H), 2.78 (s, 6H)
Cpd114	B	5.61	95.9	342	-	9.82 (brs, 1H), 9.67 (s, 1H), 7.23 (t, 1H), 6.72 (d, 1H), 6.53 (s, 1H), 4.04 (brs, 2H), 3.96 (s, 2H), 3.42 (brs, 2H), 2.83 (s, 3H)
Cpd115	A	1.01	98.9	342	-	9.83 (brs, 1H), 9.69 (s, 1H), 7.02 (t, 1H), 6.72 (d, 1H), 6.50 (s, 1H), 4.09 (brs, 2H), 3.96 (s, 2H), 3.42 (brs, 2H), 2.86 (brs, 5H)
Cpd116	F	3.67	95.1	381	-	8.05 (s, 1H), 7.67 (s, 1H), 7.27 (t, 1H), 6.69 (d, 1H), 4.92 (t, 1H), 4.14 (t, 2H), 3.96 (s, 1H), 3.72 (q, 2H)
Cpd117	E	3.09	96.2	367	-	7.14 (t, 1H), 6.61 (d, 1H), 4.57 (bs, 1H), 4.15 (t, 1H), 3.93 (s, 2H), 2.01-1.95 (m, 2H), 1.78-1.72 (m, 3H), 1.63 (t, 2H)
Cpd118	H	0.97	94.9	-	312	7.24 (t, 1 H), 6.73 (d, 1 H), 4.37 (q, 1 H), 3.96 (s, 2 H), 1.48 (d, 3 H)
Cpd119	H	1.01	98.2	-	312	7.24 (t, 1 H), 6.71 (d, 1 H), 4.40 (q, 1 H), 3.95 (s, 2 H), 1.47 (d, 3 H)
Cpd120	H	2.31	98.9	499	497	7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.54-3.42 (m, 6 H), 2.86 (t, 2 H), 2.14-1.99 (m, 4 H), 1.79-1.67 (m, 2 H), 1.58 (brs, 1 H)
Cpd121	H	2.36	99.4	488	486	7.16 (t, 1 H), 6.64 (d, 1 H), 3.93 (s, 2 H), 3.45 (d, 2 H), 3.38-3.34 (m, 2 H), 3.28 (t, 2 H), 2.94 (t, 2 H), 2.78 (s, 3 H), 2.05 (brs, 2 H), 1.59 (t, 1 H)
Cpd122	H	1.99	93.2	366	364	6.93 (t, 1 H), 6.33 (d, 1 H), 3.95 (s, 2 H), 2.97 (d, 2 H), 2.26-2.22 (m, 2 H), 2.20 (s, 3 H), 1.76-1.72 (m, 3 H), 1.64 (s, 2 H)
Cpd123	C	2.05 2.16	95.2	380	378	7.20 (t, 1 H), 6.74-6.63 (m, 1 H), 3.98 (s, 2 H), 3.34-3.22 (m, 1 H), 3.22-3.09 (m, 4 H), 2.50-2.43 (m, 1 H), 2.43-2.32 (m, 1 H), 2.26-2.09 (m, 2 H), 2.09-1.94 (m, 2 H)
Cpd124-en1	A	1.05	96.2	342	-	8.63 (brs, 2H), 7.23 (t, 1H), 6.68 (d, 1H), 3.94 (s, 2H), 3.14-3.04 (m, 3H), 2.61 (s, 3H), 1.26 (d, 3H)

Cpd124-en2	A	1.06	95.4	342	-	8.52 (brs, 2H), 7.23 (t, 1H), 6.68 (d, 1H), 3.94 (s, 2H), 3.13-3.03 (m, 3H), 2.61 (s, 3H), 1.26 (d, 3H)
Cpd125-en1	A	1.13	96.9	342	-	7.99 (brs, 4H), 7.25 (t, 1H), 6.68 (d, 1H), 3.95 (s, 2H), 2.99-2.81 (m, 3H), 1.68-1.44 (m, 2H), 1.03 (t, 3H)
Cpd125-en2	A	1.13	97.7	342	-	8.09 (brs, 3H), 7.25 (t, 1H), 6.68 (d, 1H), 3.95 (s, 2H), 2.97-2.88 (m, 3H), 1.69-1.43 (m, 2H), 1.05 (t, 3H)
Cpd126-en1	A	1.12	98.9	342	-	8.06 (brs, 3H), 7.18 (t, 1H), 6.65 (d, 1H), 3.94 (s, 2H), 3.01-2.91 (m, 2H), 2.87-2.82 (s, 1H), 1.78-1.68 (m, 2H), 1.23 (d, 3H)
Cpd126-en2	A	1.13	95.1	342	-	7.57 (brs, 3H), 7.17 (t, 1H), 6.65 (d, 1H), 3.94 (s, 2H), 3.17-2.83 (m, 3H), 1.77-1.65 (m, 2H), 1.22 (d, 3H)
Cpd127	H	2.47	95.0	487	485	9.96 (s, 1 H), 7.17 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.59-3.45 (m, 6 H), 3.40-3.35 (m, 2 H), 2.81-2.74 (m, 6 H), 2.12-2.05 (m, 2 H), 1.61 (t, 1 H)
Cpd128	C	1.73	92.7	340	338	8.04 (brs, 2 H), 7.23 (t, 1 H), 6.74 (d, 1 H), 4.34-4.15 (m, 2 H), 2.93-2.79 (m, 1 H), 2.78-2.62 (m, 1 H), 1.73-1.63 (m, 1 H), 1.51-1.37 (m, 1 H), 1.05-0.91 (m, 2 H)
Cpd129	C	2.52	95.2	418	416	7.21 (t, 1 H), 7.16 (t, 1 H), 6.63 (d, 1 H), 3.94 (s, 2 H), 3.03-2.83 (m, 5 H), 1.53-1.43 (m, 1 H), 1.43-1.29 (m, 1 H), 0.96-0.81 (m, 2 H)
Cpd130	A	1.08	96.9	342	-	8.96 (brs, 2H), 7.08 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.03-3.91 (m, 4H), 3.70-3.65 (m, 1H), 2.94 (dd, 1H), 2.49-2.43 (m, 1H), 1.30 (d, 3H)
Cpd131	A	0.98	97.8	342	-	8.73 (brs, 2H), 7.20 (t, 1H), 6.71 (d, 1H), 6.48 (s, 1H), 4.05-3.91 (m, 4H), 3.71-3.65 (m, 1H), 2.91 (dd, 1H), 2.41-2.33 (m, 1H), 1.30 (d, 3H)
Cpd132	A	1.10	97.7	342	-	8.97 (brs, 3H), 7.08 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.03-3.91 (m, 4H), 3.70-3.64 (m, 1H), 2.94 (dd, 1H), 2.49-2.41 (m, 1H), 1.30 (d, 3H)
Cpd133	A	1.00	97.9	342	-	9.01 (brs, 3H), 7.20 (t, 1H), 6.71 (d, 1H), 6.49 (s, 1H), 4.06-3.92 (m, 4H), 3.73-3.67 (m, 1H), 2.92 (dd, 1H), 2.41-2.33 (m, 1H), 1.31 (d, 3H)
Cpd134	C	2.05	99.5	380	378	7.18 (t, 1 H), 6.64 (d, 1 H), 3.94 (s, 2 H), 3.25-2.98 (m, 4 H), 1.89-1.78 (m, 1 H), 1.77-1.64 (m, 3 H), 1.55-1.42 (m, 1 H), 1.04 (dd, 1 H), 0.77 (t, 1 H)
Cpd135	C	2.95	97.4	458	456	7.18 (brs, 1 H), 6.64 (d, 1 H), 3.95 (brs, 2 H), 3.12 (brs, 2 H), 2.89 (brs, 3 H), 1.70 (brs, 2 H), 1.60 (brs, 2 H), 1.43 (brs, 1 H), 0.99 (brs, 1 H), 0.70 (brs, 1 H)
Cpd136	A	1.05	99.2	328	-	7.86 (brs, 3H), 7.24 (t, 1H), 6.67 (d, 1H), 3.94 (s, 2H), 3.37-3.32 (m, 1H), 2.75-2.62 (m, 2H), 1.26 (d, 3H)
Cpd137	A	1.05	98.0	328	-	8.16 (brs, 3H), 7.24 (t, 1H), 6.67 (dd, 1H), 3.95 (s, 2H), 3.43-3.38 (m, 1H), 2.79-2.65 (m, 2H), 1.29 (d, 3H)
Cpd138	H	2.32	99.2	326	324	(acetonitrile-d3) 9.02 (brs, 1 H), 7.04 (t, 1 H), 6.73 (dd, 1 H), 6.66- 6.56 (m, 1 H), 6.00 (q, 1 H), 5.85 (brs, 1 H), 4.17 (s, 2 H), 3.88 (s, 2 H).

Cpd139	A	1.08	99.9	354	-	9.06 (brs, 3H), 7.04 (t, 1H), 6.70 (d, 1H), 5.91 (s, 1H), 4.14 (brs, 2H), 3.95 (s, 2H), 3.31 (s, 2H), 1.13-1.08 (m, 2H), 1.04-1.01 (m, 2H)
Cpd140	H	1.66	98.6	354	352	7.09 (t, 1H), 6.58 (d, 1H), 3.88 (s, 2H), 2.90 (dd, 1H), 2.82-2.69 (m, 1H), 2.44 (brs, 3H), 1.62 (brs., 1H), 1.37 (brs, 1H), 0.98 (brs, 1H), 0.91 (brs, 1H)
Cpd141	H	1.82	99.2	368	366	7.17 (t, 1H), 6.65 (d, 1H), 3.95 (s, 2H), 3.08-2.93 (m, 2H), 2.78 (s, 6H), 1.75-1.65 (m, 1H), 1.56-1.44 (m, 1H), 1.14-1.05 (m, 1H), 1.04-0.94 (m, 1H)
Cpd142-en1	X	2.47	98.5	-	364	7.86 (brs, 2H), 7.15 (t, 1H), 6.63 (d, 1H), 3.93 (s, 2H), 3.43-3.38 (m, 1H), 3.12 (d, 1H), 2.81-2.75 (m, 1H), 2.68-2.61 (m, 1H), 2.08-2.02 (m, 1H), 1.91-1.84 (m, 1H), 1.78-1.76 (m, 1H), 1.52-1.48 (m, 2H)
Cpd142-en2	X	2.47	97.1	-	364	8.15 (brs, 2H), 7.15 (t, 1H), 6.63 (d, 1H), 3.93 (s, 2H), 3.43-3.38 (m, 1H), 3.12 (d, 1H), 2.87-2.79 (m, 1H), 2.69-2.62 (m, 1H), 2.11-2.03 (m, 1H), 1.93-1.85 (m, 1H), 1.79-1.76 (m, 1H), 1.52-1.49 (m, 2H)
Cpd143	E	2.03	99.9	358	-	8.89 (brs, 2H), 7.05 (t, 1H), 6.71 (d, 1H), 6.50 (s, 1H), 5.01 (brs, 1H), 3.96 (s, 2H), 3.91-3.85 (m, 2H), 3.65-3.61 (m, 1H), 3.53-3.49 (m, 1H), 3.39-3.36 (m, 1H), 3.16-3.13 (m, 1H), 3.03-3.01 (m, 1H)
Cpd144	E	1.96	99.7	358	-	8.87 (brs, 3H), 7.33 (t, 1H), 6.72 (d, 1H), 6.53 (s, 1H), 5.01 (brs, 1H), 3.96 (s, 2H), 3.92-3.91 (m, 2H), 3.48-3.35 (m, 5H)
Cpd145	A	1.04	95.2	342	-	8.27 (brs, 1H), 7.06 (t, 1H), 6.70 (d, 1H), 6.33 (brs, 1H), 3.96 (s, 2H), 3.92-3.81 (m, 2H), 3.34-3.31 (m, 1H), 2.85-2.81 (m, 1H), 2.67-2.60 (m, 1H), 1.19 (d, 3H)
Cpd146	E	2.69	95.0	356	-	8.85 (brs, 3H), 6.57 (s, 1H), 6.35 (s, 1H), 3.93 (s, 2H), 3.54 (brs, 2H), 3.31 (t, 2H), 2.76 (t, 2H), 2.48 (t, 2H), 1.08 (t, 3H)
Cpd147	E	2.56	96.4	356	-	9.05 (brs, 2H), 6.57 (s, 1H), 6.28 (s, 1H), 3.93 (s, 2H), 3.85 (brs, 2H), 3.19 (t, 2H), 2.48 (t, 2H), 2.30 (t, 2H), 1.08 (t, 3H)
Cpd148	H	0.95	97.9	328	326	7.25 (t, 1H), 6.70 (d, 1H), 3.98 (s, 2H), 3.04 (t, 2H), 2.77 (t, 2H), 2.55 (s, 3H)
Cpd149-en1	A	1.07	99.8	330	-	7.95 (brs, 3H), 7.33 (t, 1H), 6.68 (d, 1H), 6.47 (d, 1H), 6.02 (dd, 1H), 3.95 (s, 2H), 2.88-2.75 (m, 2H), 2.62-2.59 (m, 1H), 1.09 (d, 3H)
Cpd149-en2	A	1.07	99.6	330	-	7.94 (brs, 3H), 7.33 (t, 1H), 6.68 (d, 1H), 6.47 (d, 1H), 6.02 (dd, 1H), 3.95 (s, 2H), 2.87-2.75 (m, 2H), 2.60-2.55 (m, 1H), 1.09 (d, 3H)
Cpd150	H	1.84	93.6	412	-	9.87 (brs, 1H), 7.08 (t, 1H), 6.57 (d, 1H), 3.87 (s, 2H), 3.64 (t, 2H), 3.45 (dd, 2H), 3.25-3.15 (m, 2H), 2.71 (s, 6H), 1.55-1.35 (m, 2H), 0.95-0.75 (m, 2H)
Cpd151	H	3.04	95.8	-	357	9.93 (s, 1H), 7.21 (s, 1H), 7.17 (t, 1H), 7.08 (s, 1H), 6.95 (s, 1H), 6.63 (dd, 1H), 3.94 (s, 1H), 3.70-3.57 (m, 2H), 1.70-1.56 (m, 2H), 1.07 (dt, 1H), 0.98 (dt, 1H)

Cpd152	A	2.37	98.0	410	408	(recorded in D2O): 7.21 (t, 1 H), 6.63 (d, 1 H), 4.29 (s, 2 H), 3.80 (brs, 4 H), 2.92 (brs, 4 H), 2.74 (dd, 1 H), 2.59 (dd, 1 H), 1.49-1.42 (m, 1 H), 1.42-1.34 (m, 1 H), 1.11-1.03 (m, 1 H), 0.89-0.80 (m, 1 H)
Cpd153	H	1.94	98.0	394	392	9.96 (s, 1 H), 7.17 (t, 1 H), 6.64 (d, 1 H), 3.93 (s, 2 H), 3.21-3.14 (m, 1 H), 3.13-3.04 (m, 1 H), 2.55-2.51 (m, 2H), 2.01 (brs, 2 H), 1.90 (brs, 2 H), 1.79-1.69 (m, 1 H), 1.59-1.46 (m, 1 H), 1.15-1.05 (m, 1 H), 1.04-0.97 (m, 1 H)
Cpd154	H	3.03	99.0	430	428	(D2O) 7.31-7.22 (m, 1H), 6.70 (d, 1H), 4.30 (s, 2H), 3.48 (t, 2H), 3.37-3.25 (m, 2H), 2.98-2.86 (m, 1H), 2.79 (dd, 1H), 2.47 (tt, 2H), 1.54-1.47 (m, 1H), 1.46-1.37 (m, 1H), 1.10 (dt, 1H), 0.89 (dt, 1H)
Cpd155	H	2.03	96.0	423	421	9.92 (brs, 1 H), 7.15 (t, 1 H), 6.63 (d, 1 H), 3.93 (s, 2 H), 1.50-1.27 (m, 2 H), 0.97 (brs, 1 H), 0.79 (brs, 1 H). Piperazine protons under DMSO signal
Cpd156	A	1.12	99.7	356	-	9.03 (brs, 3H), 7.06 (t, 1H), 6.71 (d, 1H), 6.44 (s, 1H), 3.99-3.91 (m, 4H), 3.46-3.42 (m, 1H), 2.97-2.93 (m, 1H), 2.84-2.80 (m, 1H), 1.77-1.70 (m, 1H), 1.52-1.45 (m, 1H), 0.95 (t, 3H)
Cpd157	A	1.01	99.5	356	-	8.95 (brs, 3H), 7.20 (t, 1H), 6.72 (d, 1H), 6.47 (s, 1H), 3.99-3.89 (m, 4H), 3.39-3.37 (m, 1H), 3.21-3.16 (m, 1H), 3.14-3.09 (m, 1H), 1.49-1.44 (m, 1H), 1.34-1.29 (m, 1H), 0.83 (t, 3H)
Cpd158	A	1.16	98.6	368	-	9.01 (brs, 3H), 7.08 (t, 1H), 6.72 (d, 1H), 6.68 (s, 1H), 4.01 (s, 2H), 3.96 (s, 2H), 3.48 (q, 1H), 3.01 (q, 1H), 2.24 (q, 1H), 0.90-0.87 (m, 1H), 0.69-0.66 (m, 1H), 0.50-0.40 (m, 2H), 0.26-0.22 (m, 1H)
Cpd159	A	1.04	98.0	368	-	8.90 (brs, 3H), 7.23 (t, 1H), 6.70 (d, 1H), 6.51 (s, 1H), 4.07-4.03 (m, 1H), 3.99-3.91 (m, 3H), 3.43-3.38 (m, 1H), 3.21-3.16 (m, 1H), 2.80 (brs, 1H), 0.89-0.84 (m, 1H), 0.32-0.30 (m, 2H), 0.87-0.11 (m, 1H), 0.04-0.00 (m, 1H)
Cpd160	A	1.32	96.9	384	-	8.33 (brs, 1H), 7.04 (t, 1H), 6.69 (d, 1H), 6.29 (s, 1H), 3.95 (s, 2H), 3.74 (brs, 2H), 3.21-3.17 (m, 1H), 2.75 (brs, 1H), 2.67-2.60 (m, 1H), 1.63-1.60 (m, 1H), 1.51-1.44 (m, 1H), 1.38-1.31 (m, 1H), 0.94-0.85 (m, 6H)
Cpd161	H	1.70	99.5	326	-	7.30 (t, 1 H), 6.78-6.63 (m, 1 H), 5.41 (dd, 1 H), 4.04 (s, 2 H), 3.48-3.34 (m, 1 H), 3.27 (dt, 1 H), 2.24-2.06 (m, 1 H), 2.06-1.91 (m, 1 H)
Cpd162	Q	1.15	99.5	342	-	8.78 (brs, 3H), 6.58 (s, 1H), 6.32 (s, 1H), 3.93 (s, 2H), 3.56 (brs, 2H), 3.32 (t, 2H), 2.77 (t, 2H), 2.15 (s, 3H)
Cpd163	Q	1.06	98.4	342	-	8.91 (brs, 3H), 6.57 (s, 1H), 6.32 (s, 1H), 3.96 (brs, 2H), 3.92 (s, 2H), 3.29 (t, 2H), 2.37 (t, 2H), 2.14 (s, 3H)
Cpd156-en1	F	3.57	98.7	356	-	8.99 (brs, 3H), 7.06 (t, 1H), 6.71 (d, 1H), 6.43 (s, 1H), 3.96-3.93 (m, 4H), 3.45-3.40 (m, 1H), 2.95-2.91 (m, 1H), 2.82-2.79 (m, 1H), 1.77-1.68 (m, 1H), 1.52-1.44 (m, 1H), 0.95 (t, 3H)
Cpd156-en2	F	3.57	98.2	356	-	9.01 (brs, 3H), 7.06 (t, 1H), 6.71 (d, 1H), 6.43 (s, 1H), 3.96-3.93 (m, 4H), 3.45-3.42 (m, 1H), 2.95-2.91 (m, 1H), 2.82-2.79 (m, 1H), 1.75-1.72 (m, 1H), 1.50-1.46 (m, 1H), 0.95 (t, 3H)

Cpd158-en1	A	1.17	99.4	368	-	8.72 (brs, 2H), 7.08 (t, 1H), 6.71 (d, 1H), 6.65 (s, 1H), 3.96-3.94 (m, 4H), 3.42-3.38 (m, 1H), 2.93 (t, 1H), 2.21-2.10 (m, 1H), 0.91-0.83 (m, 1H), 0.69-0.62 (m, 1H), 0.49-0.44 (m, 2H), 0.24-0.19 (m, 1H)
Cpd158-en2	A	1.16	98.0	368	-	8.54 (brs, 2H), 7.08 (t, 1H), 6.71 (d, 1H), 6.63 (s, 1H), 3.96-3.91 (m, 4H), 3.42-3.38 (m, 1H), 2.89 (t, 1H), 2.17-2.10 (m, 1H), 0.89-0.82 (m, 1H), 0.67-0.64 (m, 1H), 0.47-0.38 (m, 2H), 0.24-0.21 (m, 1H)
Cpd164	A	1.04	99.1	356	-	9.32 (brs, 3H), 6.93 (t, 1H), 6.68 (d, 1H), 6.37 (s, 1H), 3.94 (s, 2H), 3.30 (t, 2H), 2.85 (td, 2H), 1.27 (s, 6H)
Cpd165	A	1.02	99.7	356	-	8.88 (brs, 3H), 7.19 (t, 1H), 6.72 (d, 1H), 6.41 (s, 1H), 3.96 (s, 2H), 3.37 (t, 2H), 2.84 (td, 2H), 1.50 (s, 6H)
Cpd166	H	2.42	99.2	513	-	9.90 (s, 1 H), 7.10 (t, 1 H), 6.57 (d, 1 H), 3.87 (s, 2 H), 3.50-3.34 (m, 8 H), 2.80 (brs, 1 H), 2.67 (brs, 3 H), 2.15-2.03 (m, 2 H), 1.99 (brs, 2 H), 1.80-1.62 (m, 2 H), 1.52 (brs, 1 H)
Cpd167	A	1.00	99.6	356	-	9.68 (s, 2H), 7.06 (t, 1H), 6.72 (d, 1H), 6.50 (s, 1H), 4.07 (brs, 2H), 3.96 (s, 2H), 3.43 (brs, 2H), 3.19-3.16 (m, 2H), 2.83 (brs, 2H), 1.22 (t, 3H)
Cpd168	A	1.03	99.5	398	-	9.17 (brs, 3H), 7.06 (t, 1H), 6.72 (t, 1H), 6.44 (s, 1H), 4.03 (s, 2H), 3.96 (s, 2H), 3.84 (dd, 2H), 3.43 (t, 2H), 3.39 (s, 2H), 1.78 (td, 2H), 1.63 (d, 2H)

Part B: Experimental pharmacology procedures / procedures for determining biological activity of the compounds of the invention

Example 40: Activity of the compounds of the invention as PTPN2 and/or PTPN1 inhibitors
Phosphatase activity assay to determine potency against PTPN2.

- 5 Compound activity was determined using a GST-tagged PTPN2 protein (TC45, accession # NP_002819.2) (Active motif, Cat# 31592) in an in vitro enzymatic reaction. The enzymatic assay used to determine potency was the phosphatase (PTP) activity inhibition assay. The assay is performed using a buffer comprising 50mM HEPES pH7.5, 2mM EDTA, 3mM DTT and 100mM NaCl and as phosphorylated substrate 10 μ M 6,8-Difluoro-4-Methylumbelliferyl Phosphate (DiFMUP) (ThermoFisher, Cat# D6567) was used.

- 10 The assay is carried out at room temperature in 384-well plate. The compounds were dispensed on a white 384-well plate at varying concentrations (10 point, 1: 5 dilution). Next, PTPN2 enzyme was added at final concentration of 4 nM and incubated with compound for 10 minutes at room temperature. Then, the reaction is initiated by adding the substrate (DiFMUP) mix to each well of reaction plate to the final concentration of 10 μ M, followed by incubation at room temperature for 30 minutes. Finally, a quench solution was added to the reaction plates and the phosphatase activity of the PTPN2 enzyme is assessed by monitoring the appearance of the fluorescent product 6,8-difluoro-7-hydroxyl-4-coumarin (DiFMU) from DiFMUP using the EnVision® multimode plate reader (PerkinElmer, Cat# 2105-0010) with excitation of 360 nm and

emission at 450 nm for DiFMU. The % of DiFMU conversion (the amount of phosphorylated substrate which was de-phosphorylated by PTPN2) was plotted against the concentration of the small molecule PTPN2 inhibitor, and the data were fitted using a four-parameter equation. Each plate had a positive control (no PTPN2 enzyme) and a negative control (DMSO + PTPN2 enzyme), which were used to calculate % of inhibition. The % inhibition was then used to determine the IC₅₀ values of the compounds disclosed here for the specific PTPN2 enzyme.

Phosphatase activity assay to determine potency against PTPN1.

Compound activity was determined using a GST-tagged PTPN1 protein (PTPN1B, accession # NP_002818.1) (Active motif, Cat# 81034) in an in vitro enzymatic reaction. The enzymatic assay used to determine potency was the phosphatase (PTP) activity inhibition assay. The assay is performed using a buffer comprising 50mM HEPES pH7.5, 2mM EDTA, 3mM DTT and 100mM NaCl and as phosphated substrate 10 µM 6,8-Difluoro-4-Methylumbelliferyl Phosphate (DiFMUP) (ThermoFisher, Cat# D6567) was used.

The assay is carried out at room temperature in 384-well plate. The compounds were dispensed on a white 384-well plate at varying concentrations (10 point, 1: 5 dilution). Next, PTPN1 enzyme was added at final concentration of 2 nM and incubated with compound for 10 minutes at room temperature. Then, the reaction is initiated by adding the substrate (DiFMUP) mix to each well of reaction plate to the final concentration of 10 µM, followed by incubation at room temperature for 30 minutes. Finally, a quench solution was added to the reaction plates and the phosphatase activity of the PTPN1 enzyme is assessed by monitoring the appearance of the fluorescent product 6,8-difluoro-7-hydroxyl-4-coumarin (DiFMU) from DiFMUP using the EnVision® multimode plate reader (PerkinElmer, Cat# 2105-0010) with excitation of 360 nm and emission at 450 nm for DiFMU. The % of DiFMU conversion (the amount of phosphorylated substrate which was de-phosphorylated by PTPN2) was plotted against the concentration of the small molecule PTPN1 inhibitor, and the data were fitted using a four-parameter equation. Each plate had a positive control (no PTPN1 enzyme) and a negative control (DMSO + PTPN1 enzyme), which were used to calculate % of inhibition. The % inhibition was then used to determine the IC₅₀ values of the compounds disclosed here for the specific PTPN1 enzyme. Activities of example compounds of the invention in the PTPN2 and PTPN1 inhibition assays are depicted in the table below.

Table 4: PTPN2 and PTPN1 inhibitory activity of compounds of the invention. “A” represents IC₅₀ <20 nM; “B” represents an IC₅₀ of 20nM ≤ IC₅₀ ≤ 100 nM and “C” represents IC₅₀ 100nM < IC₅₀ ≤ 1 µM.

PTPN2 IC ₅₀ value	Compounds	PTPN1 IC ₅₀ value	Compounds
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A	Cpd001, Cpd003, Cpd004, Cpd006, Cpd008, Cpd033, Cpd034, Cpd036, Cpd040, Cpd053, Cpd063, Cpd066, Cpd068, Cpd075, Cpd086, Cpd087, Cpd089, Cpd090, Cpd091, Cpd092, Cpd093, Cpd099, Cpd100, Cpd103, Cpd106, Cpd108, Cpd110, Cpd112, Cpd113, Cpd115, Cpd117, Cpd120, Cpd121, Cpd123, Cpd124-en2, Cpd125-en2, Cpd127, Cpd128, Cpd129, Cpd139, Cpd140, Cpd141, Cpd142-en1, Cpd142-en2, Cpd145, Cpd149-en2, Cpd151, Cpd152, Cpd153, Cpd154, Cpd156, Cpd156-en1, Cpd156-en2, Cpd158, Cpd158-en1, Cpd158-en2, Cpd160, Cpd166, Cpd168	A	Cpd001, Cpd003, Cpd004, Cpd006, Cpd008, Cpd009, Cpd010, Cpd012, Cpd014, Cpd015, Cpd016, Cpd017, Cpd018, Cpd021, Cpd028, Cpd029, Cpd033, Cpd034, Cpd036, Cpd040, Cpd041, Cpd045, Cpd051, Cpd052, Cpd053, Cpd054, Cpd056, Cpd059, Cpd061, Cpd063, Cpd065, Cpd066, Cpd068, Cpd069, Cpd075, Cpd077, Cpd082, Cpd083, Cpd084, Cpd086, Cpd087, Cpd088, Cpd089, Cpd090, Cpd091, Cpd092, Cpd093, Cpd099, Cpd100, Cpd105, Cpd106, Cpd107, Cpd110, Cpd112, Cpd113, Cpd116, Cpd117, Cpd120, Cpd121, Cpd123, Cpd124-en2, Cpd127, Cpd129, Cpd139, Cpd142-en1, Cpd142-en2, Cpd143, Cpd145, Cpd149-en2, Cpd151, Cpd152, Cpd153, Cpd154, Cpd156, Cpd156-en1, Cpd156-en2, Cpd158, Cpd158-en1, Cpd158-en2, Cpd160, Cpd166, Cpd168
B	Cpd005, Cpd007, Cpd009, Cpd010, Cpd011, Cpd012, Cpd013, Cpd014, Cpd015, Cpd016, Cpd017, Cpd018, Cpd019, Cpd020, Cpd021, Cpd022, Cpd023, Cpd024, Cpd025, Cpd027, Cpd028, Cpd029, Cpd035, Cpd038, Cpd039, Cpd041, Cpd042, Cpd044, Cpd045, Cpd046, Cpd048, Cpd050, Cpd051, Cpd052, Cpd054, Cpd056, Cpd057, Cpd058, Cpd059, Cpd061, Cpd065, Cpd067, Cpd069, Cpd071, Cpd073, Cpd074, Cpd077, Cpd079, Cpd080, Cpd080-en1, Cpd080-en2, Cpd082, Cpd083, Cpd084, Cpd088, Cpd094, Cpd096, Cpd097, Cpd102, Cpd104, Cpd105, Cpd107, Cpd109, Cpd116, Cpd118, Cpd119, Cpd122, Cpd124-en1, Cpd125-en1, Cpd126-en1, Cpd126-en2, Cpd130, Cpd131, Cpd132, Cpd133, Cpd134, Cpd135, Cpd136, Cpd137, Cpd143, Cpd144, Cpd148, Cpd149-en1, Cpd150, Cpd155, Cpd157, Cpd159, Cpd161, Cpd163, Cpd165, Cpd167	B	Cpd002, Cpd005, Cpd007, Cpd011, Cpd013, Cpd019, Cpd020, Cpd022, Cpd023, Cpd024, Cpd025, Cpd027, Cpd032, Cpd035, Cpd037, Cpd038, Cpd039, Cpd042, Cpd043, Cpd044, Cpd046, Cpd047, Cpd048, Cpd049, Cpd050, Cpd057, Cpd058, Cpd060, Cpd062, Cpd067, Cpd071, Cpd073, Cpd074, Cpd076, Cpd078, Cpd079, Cpd080, Cpd080-en1, Cpd080-en2, Cpd085, Cpd094, Cpd096, Cpd097, Cpd098, Cpd102, Cpd103, Cpd104, Cpd108, Cpd109, Cpd111, Cpd115, Cpd119, Cpd122, Cpd124-en1, Cpd125-en1, Cpd125-en2, Cpd126-en1, Cpd126-en2, Cpd128, Cpd134, Cpd135, Cpd136, Cpd137, Cpd140, Cpd141, Cpd144, Cpd148, Cpd149-en1, Cpd150, Cpd155, Cpd157, Cpd161, Cpd165, Cpd167
C	Cpd002, Cpd026, Cpd030, Cpd031, Cpd032, Cpd037, Cpd043, Cpd047, Cpd049, Cpd055, Cpd060, Cpd062, Cpd064, Cpd072, Cpd076, Cpd078, Cpd081, Cpd085, Cpd095, Cpd098, Cpd101, Cpd111, Cpd114, Cpd138, Cpd146, Cpd147, Cpd162, Cpd164	C	Cpd026, Cpd030, Cpd031, Cpd055, Cpd064, Cpd072, Cpd081, Cpd095, Cpd101, Cpd114, Cpd118, Cpd138, Cpd146, Cpd147, Cpd159, Cpd162, Cpd163, Cpd164

Example 41: Activity of the compounds of the invention to potentiate/enhance IFN γ -induced/mediated tumor growth inhibition

IFN γ is a cytokine that is produced by immune cells, like T cells or NK cells. It plays a crucial role in regulating anti-tumor immune responses and it has been shown to have anti-proliferative and anti-tumor effects in various cancer types, including melanoma and colorectal cancer. Notably, tumor growth is promoted when IFN γ signaling is impaired, whereas enhancing IFN γ signaling leads to greater inhibition of tumor growth. Since PTPN2 and PTPN1 act as negative regulators of cytokine signaling, including IFN γ signaling, by dephosphorylating JAK and STAT proteins, the compounds of the invention facilitate tumor growth arrest in the presence of IFN γ . Compounds of the present invention amplify mouse B16F10 melanoma and human T84 colorectal cancer cells growth inhibition in the presence of IFN γ .

10 Mouse B16F10 cells IFN γ -Induced Growth Inhibition Assay

B16F10 mouse melanoma cells (ATCC Cat# CRL-6475) were seeded at density of 1500 cells per well in two 96-well white bottom plates (Greiner, Cat# 655083) in 100 μ L total volume of RPMI 1640 + 10% FBS. Cells were allowed to adhere for 3 hours at 37°C + 5% CO $_2$. Next, compounds resuspended in DMSO at 10 mM were diluted in 1: 3 dilutions in DMSO ranging from 10 mM to 0.0002 mM and DMSO only controls were included. The compound/DMSO dilutions were further diluted 1: 25 in RPMI 1640 + 10% FBS, and 50 μ L of these dilutions were added in duplicates to cells of both plates. Final compound concentration ranged from 100 μ M to 0.002 μ M with a final DMSO concentration of 1%. Compounds were only dosed in the inner 60-wells avoiding the outer 1-well perimeter of the plate to minimize edge effects. Next, 50 μ L of mouse IFN γ (Roche, Cat# 11276905001) was added to the first plate at a concentration of 2 ng/mL for a final assay concentration of 0.5 ng/mL of IFN γ . Media only (50 μ L of RPMI 1640 + 10% FBS) was added to the second plate and both IFN γ treated and non- IFN γ control plates were maintained in a 37°C + 5% CO $_2$ incubator. After 5 days of incubation, plates were leveled up to 50 μ L and 50 μ L of ATPlite (PerkinElmer, Cat# 6016949) was added to determine cell growth. After incubation for 10 minutes at room temperature under shaking, luminescence signal was measured using the EnVision® multimode plate reader (PerkinElmer, Cat# 2105-0010). For each compound, the percent growth inhibition at every compound dose level was calculated relative to the "DMSO/with IFN γ " control and used to determine the IC $_{50}$.

Human T84 cells IFN γ -Induced Growth Inhibition Assay

30 T84 human colorectal carcinoma cells (ATCC Cat# CCL-248) were seeded in a 96-well format. Before cell seeding, plates were coated with 40 μ L of 40 μ g/mL rat tail collagen type I (Gibco, Cat# A10483-01) in 20 mM acetic acid and allowed for 1 hour in room temperature for achieving a thin collagen layer. Next, plates were washed 3 times with PBS and T84 cells were seeded at density of 3500 cells per well in two 96-well white bottom plates (Greiner, Cat# 655083) in 100 μ L total volume of DMEM/F12 + 10% FBS. Cells were allowed to adhere for 3 hours at 37°C + 5% CO $_2$. Next, compounds resuspended in DMSO at 10 mM were diluted in 1: 3 dilutions in DMSO ranging

from 10 mM to 0.0002 mM and DMSO only controls were included. The compound/DMSO dilutions were further diluted 1: 25 in DMEM/F12 + 10% FBS, and 50 μ L of these dilutions were added in triplicates to cells of both plates. Final compound concentration ranged from 100 μ M to 0.002 μ M with a final DMSO concentration of 1%. Compounds were only dosed in the inner 60-

5 wells avoiding the outer 1-well perimeter of the plate to minimize edge effects. After, 50 μ L of human IFN γ (Roche, Cat# 1104596001) was added to the first plate at a concentration of 20 ng/mL for a final assay concentration of 5 ng/mL of IFN γ . Media only (50 μ L of RPMI 1640 + 10% FBS) was added to the second plate and both IFN γ treated and non- IFN γ control plates were maintained in a 37°C + 5% CO₂ incubator. After 4 days of incubation, plates were leveled up to

10 50 μ L and 50 μ L of ATPlite (PerkinElmer, Cat# 6016949) was added to determine cell growth. After incubation for 10 minutes at room temperature under shaking, luminescence signal was measured using the EnVision® multimode plate reader (PerkinElmer, Cat# 2105-0010). For each compound, the percent growth inhibition at every compound dose level was calculated relative to the "DMSO/with IFN γ " control and used to determine the IC₅₀. Table 5 below shows the IC₅₀

15 values of examples of the compounds of the invention in the mouse B16F10 and human T84 IFN γ -induced growth inhibition assays.

Table 5: Activity of the compounds of the invention in the B16F10 cell and T84 cell assays. "A" represents an IC₅₀ < 10 μ M; "B" represents IC₅₀ of 10 μ M $\leq$ IC₅₀ $\leq$ 100 μ M and "C" represents IC₅₀ values > 100 μ M.

B16F10 GI assay IC ₅₀ value	Compounds	T84 GI assay IC ₅₀ value	Compounds
A	Cpd001, Cpd003, Cpd004, Cpd005, Cpd006, Cpd007, Cpd008, Cpd009, Cpd016, Cpd018, Cpd019, Cpd020, Cpd021, Cpd022, Cpd033, Cpd036, Cpd037, Cpd038, Cpd040, Cpd041, Cpd047, Cpd048	A	Cpd009, Cpd025, Cpd035, Cpd041, Cpd057, Cpd063, Cpd086, Cpd087, Cpd089, Cpd092, Cpd094, Cpd099,
B	Cpd002, Cpd023, Cpd024, Cpd039, Cpd042, Cpd044, Cpd045, Cpd046	B	Cpd001, Cpd002, Cpd003, Cpd004, Cpd005, Cpd006, Cpd007, Cpd010, Cpd011, Cpd012, Cpd013, Cpd014, Cpd015, Cpd016, Cpd017, Cpd018, Cpd019, Cpd020, Cpd022, Cpd024, Cpd026, Cpd027, Cpd029, Cpd031, Cpd032, Cpd033, Cpd034, Cpd036, Cpd040, Cpd043, Cpd045, Cpd046, Cpd047, Cpd054, Cpd055, Cpd056, Cpd059, Cpd060, Cpd061, Cpd062, Cpd064, Cpd065, Cpd066, Cpd067, Cpd068, Cpd069, Cpd071, Cpd072, Cpd073, Cpd074, Cpd075, Cpd077, Cpd078, Cpd079, Cpd080, Cpd080-en1, Cpd080-en2, Cpd081, Cpd082,

			Cpd083, Cpd084, Cpd085, Cpd090, Cpd091, Cpd093, Cpd095, Cpd097, Cpd100, Cpd102, Cpd105, Cpd106, Cpd107, Cpd110, Cpd113, Cpd115, Cpd116, Cpd117, Cpd122, Cpd127, Cpd128, Cpd129, Cpd136, Cpd137, Cpd140, Cpd141, Cpd148
C		C	Cpd021, Cpd023, Cpd042, Cpd044, Cpd049, Cpd050, Cpd051, Cpd052, Cpd053, Cpd058, Cpd076, Cpd088, Cpd096, Cpd098, Cpd101, Cpd108, Cpd111, Cpd114, Cpd134, Cpd135

Example 42: T cell activation activity of the compounds of the invention as antitumor response evidenced by enhanced phosphorylation of STAT1 in human Jurkat T cells stimulated with IFN γ

IFN γ in T cells promotes activation of multiple signaling pathways associated with T cell activation and antitumor responses. A key target of this signaling is phosphorylation of the transcriptional factor STAT1. STAT1 is also a direct target of PTPN2 and PTPN1 which serve as negative regulators of IFN γ signaling. A PTPN2/N1 inhibitor is expected to increase the phosphorylation of STAT1 upon stimulation with IFN γ .

To assess the ability of compounds of the invention to stimulate T cell activation as evidenced by increase in pSTAT1 signaling, human Jurkat T cells (DSMZ, Cat# ACC282) were seeded at a density of 150.000 cells per well in a 96-well U-bottom plate in 25 μ L total volume of RPMI + 1% FCS. Next, compounds resuspended in DMSO at 10 mM were diluted in 1:3 dilutions in DMSO ranking from 10 mM to 0.005 mM and DMSO only controls were included. The compound/DMSO dilutions were further diluted in 1:74 in RPMI + 1% FCS, and 10 μ L of these increasing concentrations of the compound dilutions were added in duplicates to cells and incubated for 2.5 hours at 37°C. Final compound concentration ranged from 30 μ M to 0.014 μ M with a final DMSO concentration of 0.3%.

To induce STAT1 phosphorylation, 10 μ L of human IFN γ (Roche Cat# 1104096001) was added at a concentration of 22.5 ng/ml for a final assay concentration of 5 ng/ml IFN γ . After 30 minutes incubation, 15 μ L/well of 4x supplemented lysis buffer (PerkinElmer, Cat# 64KL2FDF) was added and samples were incubated for 1 hour at room temperature under shaking. After homogenization by pipetting up and down, 16 μ L of cell lysates were subsequently transferred from the 96-well cell-assay plate to a 384-small volume (SV) white detection plate for the detection of Phospho-STAT1 by HTRF Phospho-STAT1 (Tyr701) cellular kit (PerkinElmer Cat# 63ADK026PEH) ending with quadruples per cpd dilution.

In particular, 4 μ L of premixed Phospho-STAT1 (Tyr701) antibody solutions (vol/vol), using 2 different specific antibodies, one labelled with Eu3+-Cryptate (donor) and the second with d2 (acceptor), prepared in the detection buffer and added in the detection plates. After overnight incubation at room temperature, the fluorescence emission at two different wavelengths (665nm

and 620nm) was measured using the EnVision® multimode plate reader (PerkinElmer, Cat# 2105-0010). The amount of STAT1 phosphorylation was assessed by calculating the ratio of the acceptor and donor emission signals for each individual well. For each compound the percentage of STAT1 phosphorylation enhancement at every compound dose level was calculated relative to the "DMSO/with IFN γ " control. Compound dose-response curves were determined using a four-parameter logistic non-linear regression model from which half maximal effective concentrations (EC₅₀) were calculated. The table below summarizes the EC₅₀ of STAT1 phosphorylation in Jurkat T cells treated with the compounds.

Protein tyrosine phosphatases PTPN2 and PTPN1 serve as negative regulators for various cellular pathways, including JAK/STAT-mediated cytokine signaling involving IFN γ , IFN α , and IL2. Inhibition of PTPN2/N1 is anticipated to enhance STAT phosphorylation by delaying the dephosphorylation of STAT proteins. To assess the impact of compounds on IFN γ signaling, the phosphorylation of the direct target of PTPN2/N1, STAT1, was measured as proximal translational marker in human Jurkat T cells. The Jurkat T cell line facilitates high-throughput assessment of PTPN2/N1 inhibitors in potentiating the activation of human T cells in a dose dependent manner with determination of half maximal effective concentrations. In human Jurkat T cells treated with active compounds, a dose dependent enhancement of STAT1 phosphorylation after stimulation with IFN γ was observed. The results demonstrate that the exemplified compounds disclosed herein (e.g. PTPN2/N1 inhibitors) are capable of enhancing T cell activation associated with IFN γ -induced STAT1 phosphorylation. The activities of the example compounds of the invention are shown in the table below.

Table 6: Activity of the compounds of the invention in the pSTAT1 assay. "A" represents an IC₅₀ < 5 μ M; "B" represents an IC₅₀ of 5 μ M $\leq$ IC₅₀ $\leq$ 30 μ M and "C" represents an IC₅₀ > 30 μ M.

Jurkat-pStat IC ₅₀ value	Compounds
A	Cpd001, Cpd002, Cpd003, Cpd004, Cpd005, Cpd006, Cpd008, Cpd009, Cpd012, Cpd013, Cpd014, Cpd016, Cpd017, Cpd018, Cpd025, Cpd027, Cpd029, Cpd033, Cpd034, Cpd035, Cpd036, Cpd038, Cpd040, Cpd041, Cpd045, Cpd051, Cpd055, Cpd056, Cpd057, Cpd058, Cpd059, Cpd060, Cpd061, Cpd063, Cpd065, Cpd066, Cpd067, Cpd068, Cpd073, Cpd074, Cpd075, Cpd077, Cpd082, Cpd086, Cpd087, Cpd089, Cpd090, Cpd092, Cpd093, Cpd094, Cpd099, Cpd105, Cpd106, Cpd110, Cpd117, Cpd120, Cpd121, Cpd127, Cpd139, Cpd145, Cpd156-en1, Cpd156-en2, Cpd158
B	Cpd007, Cpd011, Cpd015, Cpd019, Cpd021, Cpd023, Cpd032, Cpd043, Cpd044, Cpd047, Cpd048, Cpd050, Cpd052, Cpd062, Cpd064, Cpd069, Cpd071, Cpd072, Cpd078, Cpd079, Cpd080, Cpd080-en1, Cpd080-en2, Cpd081, Cpd083, Cpd084, Cpd085, Cpd088, Cpd091, Cpd097, Cpd100, Cpd103, Cpd104, Cpd107, Cpd111, Cpd112, Cpd113, Cpd115, Cpd116, Cpd118, Cpd119, Cpd122, Cpd124-en1, Cpd124-en2, Cpd125-en1, Cpd125-en2, Cpd126-en1, Cpd128, Cpd129, Cpd132, Cpd140, Cpd141, Cpd142-en1, Cpd142-en2, Cpd149-en1, Cpd150, Cpd154, Cpd156

C	Cpd010, Cpd020, Cpd022, Cpd024, Cpd031, Cpd037, Cpd039, Cpd042, Cpd046, Cpd049, Cpd053, Cpd054, Cpd076, Cpd095, Cpd096, Cpd098, Cpd101, Cpd102, Cpd108, Cpd114, Cpd126-en2, Cpd130, Cpd134, Cpd135, Cpd136, Cpd137, Cpd143, Cpd144, Cpd146, Cpd147, Cpd148, Cpd149-en2, Cpd152, Cpd153, Cpd155, Cpd157, Cpd159, Cpd160, Cpd161, Cpd162, Cpd163
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Example 43: Activation of primary human T cells by compounds of the invention as evidenced by enhanced expression of activation markers and increased production of cytotoxic effector molecules and antitumor cytokines

Enhancing T cell activation and function is a main strategy in novel immune oncology approaches aimed at promoting effective tumor immunity. In vitro assays utilizing primary T cells are frequently employed to evaluate the effects of compounds on T cell activation and function.

Primary human CD3⁺ T cells were isolated from PBMCs using a StemCell T cell isolation kit (StemCell technologies, Grenoble, France) according to manufacturer's instructions. Isolated T cells (150.00 cell/well) were re-suspended in RPMI 1640 supplemented with 10% FBS and seeded into antiCD28/antiCD3 coated 96-well flat-bottom cell culture wells. Directly after seeding, the compounds were added at 10 and 30 μ M. The same amount of DMSO only was added to controls. After 24 hours of stimulation, cells were re-stimulated with PMA (50 ng/mL) and Ionomycin (1 μ M) in the presence of Brefeldin A (3 ug/mL) to stain for cytokines (TNF α ⁺ and IFN γ ⁺) and Granzyme B levels in T cells. After 3 hours incubation, the cells were stained with Zombie NIR Fixable Viability Kit (Biolegend, San Diego, CA) diluted in Dulbecco's PBS for 10 minutes on ice to exclude dead cells followed by staining for surface markers for 15 minutes on ice using the following flow cytometry antibodies in FACS buffer (PBS, 2% FCS, 2mM EDTA): Brilliant Violet (BV) 450-labeled anti-CD45, Brilliant Ultraviolet (BUV) 661-labeled anti-CD3, Brilliant Violet (BV) 570-labeled anti-CD4, PE-TexasRed-labeled anti-CD8, Brilliant Blue 630-labelled anti-CD69. Cells were washed in FACS buffer, permeabilized with Fixation/Permeabilization Buffer (PoxP3/transcriptional Factor Staining Buffer Set, eBioscience) and stained intracellularly with PE-labeled anti-pSTAT1, PerCP-Cy5.5-labeled anti-Granzyme B, PE-Cy7-labelled anti-IFN γ and BV781-labelled anti-TNF α diluted in Permeabilization buffer for 15 minutes on ice. After staining, cells were washed with Permeabilization buffer, and the samples were acquired on a BD Symphony flow cytometer (BD Biosciences, San Jose, CA) and analyzed with FlowJo V10 software (FlowJo, Ashland, OR). The frequency of CD69⁺, Granzyme B⁺, IFN γ ⁺ and TNF α ⁺ cells within CD8⁺ T cell population in vehicle or Cpd008 treated CD3⁺ T cells are reported.

Cpd008 was tested at 10 μ M and 30 μ M in the primary human T cell activation assay and significantly enhances T cell activation and antitumor function as reflected by the increased CD8⁺ T cell cytotoxic activity. In particular, upon Cpd008 treatment of T cells, elevated levels of the T cell activation marker CD69 as well as increased production of the cytotoxic effector molecule Granzyme B and the antitumor cytokines IFN γ and TNF α were measured. The activity of Cpd008

is shown in the table below.

Table 7: summary of T cell activation effect of Cpd008 (at 10 μ M and 30 μ M). Data for CD69+, Granzyme B+, IFN γ + and TNF α + cells within CD8+ T cell population in vehicle or compound treated primary, human CD3+ T cells are shown. Data represent the mean $\pm$ SD.

Compound	% CD69+ cells within the CD8+ T cells	% GzB+ cells within the CD8+ T cells	% IFN γ + cells within the CD8+ T cells	% TNF α + cells within the CD8+ T cells
Vehicle Control	31.9 $\pm$ 3.5	1.9 $\pm$ 0.6	15.3 $\pm$ 3.0	14.6 $\pm$ 3.7
Cpd008 at 10 μ M	61.3 $\pm$ 2.8	4.0 $\pm$ 0.8	35.5 $\pm$ 7.6	33.1 $\pm$ 9.1
Cpd008 at 30 μ M	57.8 $\pm$ 6.3	7.4 $\pm$ 0.5	37.3 $\pm$ 8.2	45.2 $\pm$ 6.2

5 Example 44: *In vivo* immune cell activation by compounds of the invention upon systemic dosing in mice

Animals: All experiments were conducted in compliance with Swiss animal welfare legislation and the Animal Welfare Commission of the Canton of Zürich approved all procedures (License ZH179/2019). C57Bl/6 female mice were obtained from Janvier Elevages Ltd. (St. Ile, France).

- 10 The mice were group-housed 5 per cage. Food and water were available ad libitum. Animals were acclimated to the animal facilities for a period of at least two weeks prior to start of the experiments.

In vivo compound treatment and assessment of target engagement and T cell activation:

- Mice were sacrificed on day 1, after a single oral dose with either Cpd008 (10/mg/kg) or vehicle control (n = 5 mice/group). Cpd008 was formulated in 40% PEG-400, 30% PG and 30% water, and was dosed at 10 mL /Kg. After 6 hours post Cpd008 or vehicle administration, spleens were excised and dissociated over 100 μ m strainers, red blood cells lysed, and single cell suspensions were prepared. The cells were re-stimulated with PMA (50ng/mL) and Ionomycin (1 μ M) in the presence of Brefeldin A (3 μ g/mL) to stain for cytokines (TNF α + and IFN γ +), Granzyme B and
- 20 Perforin levels in T cells. After 3.5 hours incubation, the cells were stained with Zombie NIR Fixable Viability Kit (Biolegend, San Diego, CA) diluted in Dulbecco's PBS for 10 minutes on ice to exclude dead cells followed by staining for surface markers for 15 minutes on ice using the following flow cytometry antibodies in FACS buffer (PBS, 2% FCS, 2mM EDTA): Brilliant Violet(BV)450-labeled anti-CD45, Brilliant Ultraviolet (BUV)661-labeled anti-CD3, BV570-labeled
- 25 anti CD4 and PE-TexasRed-labeled anti-CD8. Cells were washed in FACS buffer, permeabilized with Fixation/Permeabilization Buffer (PoxP3/transcriptional Factor Staining Buffer Set; eBioscience) and stained intracellularly with PE-labeled anti-pSTAT1, AlexaFluor488-labelled-pSTAT5, PerCP-Cy5.5-labeled anti-Granzyme B, PE-Cy7-labelled anti-IFN γ , APC-labelled anti-Perforin, and BV781-labelled anti-TNF α diluted in Permeabilization buffer for 15 minutes on ice.

After staining, cells were washed with Permeabilization buffer, and the samples were acquired on a BD Symphony flow cytometer (BD Biosciences, San Jose, CA) and analyzed with FlowJo V10 software (FlowJo, Ashland, OR). The frequency of pSTAT1+, pSTAT5+, Granzyme B+, Perforin+, TNFα+ and IFNγ+ cells within splenic CD8+ T cell population in vehicle or compound treated animals are reported

Cpd008 of the invention was tested in the model described and exhibited significant in vivo immune activation in splenic CD8+ T cells as assessed by measuring elevated levels of STAT1 and STAT5 phosphorylation upon in vivo administration. This was accompanied by enhanced CD8+ T cell cytotoxic activity, as reflected by the increased expression of Granzyme B, IFNγ and TNFα that mediate cytotoxic CD8+ T cell responses. The activity of Cpd008 is shown in the table below.

Table 8: summary of in vivo target engagement of Cpd008 (oral 10/mg/kg/dose dosed at 10 mL/Kg formulated in 40% PEG-400, 30% PG and 30% water). Data for pSTAT1+ cells within splenic CD8+ T cell population in vehicle or compound treated animals are shown. Data represent the mean ± SD.

Compound	pSTAT1 levels [MFI] in the splenic CD8+ T cells	pSTAT5 levels [MFI] in the splenic CD8+ T cells
Vehicle	1018 ± 99	2262 ± 376
Cpd008	1868 ± 224	4108 ± 499

Table 9: summary of in vivo T cell activation effect of Cpd008 (oral 10/mg/kg/dose dosed at 10 mL/Kg formulated in 40% PEG-400, 30% PG and 30% water). Data for Granzyme B+, Perforin+, IFNγ+ and TNFα+ cells within splenic CD8+ T cell population in vehicle or compound treated animals are shown. Data represent the mean ± SD.

Compound	% GzB+ cells within the splenic CD8+ T cells	% Perforin+ cells within the splenic CD8+ T cells	% IFNγ+ cells within the splenic CD8+ T cells	% TNFα+ cells within the splenic CD8+ T cells
Vehicle	5.9 ± 0.9	5.6 ± 2.3	3.7 ± 1.2	2 ± 0.5
Cpd008	18.5 ± 5.7	17.4 ± 6.5	21.3 ± 5.7	16.5 ± 6.4

20 **Example 45: In vivo efficacy of compounds of the invention in syngeneic subcutaneous MC38 mouse tumor model and impact on pharmacodynamic markers.**

Animals: All experiments were conducted in compliance with Swiss animal welfare legislation and the Animal Welfare Commission of the Canton of Zürich approved all procedures (License ZH179/2019). C57Bl/6 female mice were obtained from Janvier Elevages Ltd. (St. Ile, France).

25 The mice were group-housed 5 per cage. Food and water were available ad libitum. Animals were acclimated to the animal facilities for a period of at least two weeks prior to start of the experiments.

Tumor Cell Inoculation and Treatments: Cells were grown to passage 3 in vitro. A total of 5×10^5

viable MC-38 cells (100ul, re-suspended in cell culture medium) were injected subcutaneously into the left and right flanks of 9-12 week old female C57Bl/6 mice on day 0. Treatments were initiated on day 6. Dosing of mice was conducted orally, twice a day (BID) at 6 a.m and 6 p.m for 8 days. Mice were dosed (10/mg/kg/dose) with either Cpd008 or vehicle controls (n = 5 mice/group). Cpd008 was formulated in 40% PEG-400, 30% PG and 30% water and was dosed at 5 mL/Kg.

Assessment of inhibition of tumor growth inhibition: Tumor volume was calculated every 2nd day. Measurements of the length (L) and width (W) of the tumor were taken via electronic caliper and the volume was calculated according to the ellipsoid equation: $V = \frac{3}{4} \times \pi \times L/2 \times (W/2)^2$. Mice were euthanized on day 13 post tumor inoculation. Tumor growth inhibition (TGI) was calculated as $TGI = 1 - (\text{Mean TV}_{\text{Timepoint (Treatment)}} / \text{Mean TV}_{\text{Timepoint (vehicle)}})$ for each time point that tumor volumes were measured. Reported TGI_{MAX} is the largest TGI value for any timepoint that tumor volumes were measured for that treated group and depicted in table 10.

Assessment of tumor infiltrating CD8+ T cell activation: Mice were sacrificed on day 13 of dosing with Cpd008 (2 hours after the 8th dose) and tumors were excised. Tumors were digested in digestion solution (0.5 mg/mL collagenase type IV (Sigma Aldrich) and 0.05 mg/mL DNase I) to obtain single cell suspensions. Next, tumor single cell suspensions were re-stimulated with PMA (50ng/mL) and Ionomycin (1uM) in the presence of Brefeldin A (3 ug/mL) to stain for cytokines (TNFα+ and IFNγ+), Granzyme B and Perforin levels in T cells. After 3.5 hours incubation, tumor cells were stained with Zombie NIR Fixable Viability Kit (Biolegend, San Diego, CA) diluted in Dulbecco's PBS for 10 minutes on ice to exclude dead cells followed by staining for surface markers for 15 minutes on ice using the following flow cytometry antibodies in FACS buffer (PBS, 2% FCS, 2mM EDTA): Brilliant Violet(BV)450-labeled anti-CD45, Brilliant Ultraviolet (BUV)661-labeled anti-CD3, BV570-labeled anti CD4 and PE-TexasRed-labeled anti-CD8. Cells were washed in FACS buffer, permeabilized with Fixation/Permeabilization Buffer (PoxP3/transcriptional Factor Staining Buffer Set; eBioscience) and stained intracellularly with PE-labeled anti-pSTAT1, PerCP-Cy5.5-labeled anti-Granzyme B and PE-Cy7-labelled anti-IFNγ diluted in Permeabilization buffer for 15 minutes on ice. After staining, cells were washed with Permeabilization buffer, and the samples were acquired on a BD Symphony flow cytometer (BD Biosciences, San Jose, CA) and analyzed with FlowJo V10 software (FlowJo, Ashland, OR). The frequency of pSTAT1+, Granzyme B+ and IFNγ+ cells within intratumor CD8+ T cell population in vehicle or compound treated animals are reported.

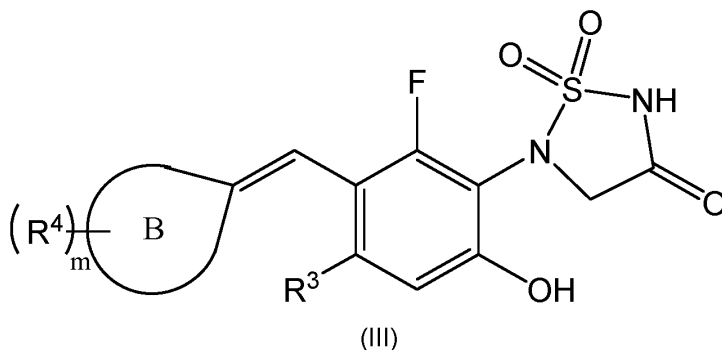
Cpd008 exhibited clear anti-tumor efficacy in this MC38 mouse model as assessed by significant tumor growth inhibition as shown in figure 1 and table 10. Notably, infiltrating CD8+ T cells exhibited increased activation, evident by elevated levels of STAT1 phosphorylation. There was also a marked increase in the cytotoxic activity of intratumor CD8+ T cells, as indicated by a higher proportion of cells expressing intracellular Granzyme B and IFNγ.

Table 10: summary of the anti-tumor effect of Cpd008 (oral 10/mg/kg/dose dosed BID at 5 mL/Kg formulated in 40% PEG-400, 30% PG and 30% water) in the MC38-syngenic tumor model. Maximum tumor growth inhibition was determined over the entire study. Data for pSTAT1+, Granzyme B+ and IFN γ + cells within intratumor CD8+ T cell population on day 13 post tumor inoculation in vehicle or compound treated animals are shown. Data represent the mean $\pm$ SD.

Compound	Tumor Growth Inhibition (MAX) compared to vehicle [%]	% pSTAT1+ cells within the intratumor CD8+ T cells	% GzB+ cells within the intratumor CD8+ T cells	% IFN γ + cells within the intratumor CD8+ T cells
Vehicle		14.8 $\pm$ 5.7	22.1 $\pm$ 5.4	36.9 $\pm$ 19
Cpd008	66.4	47.8 $\pm$ 9.3	36.1 $\pm$ 7.6	69.5 $\pm$ 15.6

CLAIMS

1. A compound of formula (III), a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), solvate, hydrate, polymorph, isotope, and/or prodrug thereof,



wherein:

- cycle B is selected from heterocycle; cycloalkyl; cycloalkenyl; and cycloalkynyl;
- m is selected from 0; 1; 2; 3; 4; and 5.
- 10 - R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- 15 - wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, hydroxyl, cycloalkyl, alkenyl, alkynyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂;
- 20 - or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or

a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; and -NHalkyl, -N(alkyl)₂;

- 5 - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

10 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- 20 - each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;

25 wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, and heterocyclheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- 30 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl;

- heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclyl heteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;
- and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.
2. The compound according to claim 1, wherein cycle B is selected from 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered heterocycle; 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered cycloalkyl; 4-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-membered cycloalkenyl; and 7-, 8-, 9-, 10-, or 11-membered cycloalkynyl.
 3. The compound according to any one of claims 1-2, wherein cycle B is selected from 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycle; 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10 membered cycloalkyl; 4-, 5-, 6-, 7-, 8-, 9- or 10-membered cycloalkenyl; and 7-, 8-, 9- or 10-membered cycloalkynyl.
 4. The compound according to any one of claims 1-3, wherein cycle B is selected from 4-, 5-, 6-, or 7-membered heterocycle; 3-, 4-, 5-, 6-, or 7-membered cycloalkyl; 5-, 6-, or 7-membered cycloalkenyl; and 7-membered cycloalkynyl.
 5. The compound according to any one of claims 1-4, wherein m is selected from 0; 1; 2; and 3, preferably m is 0, 1 or 2.
 6. The compound according to any one of claims 1-5, wherein R³ is hydrogen.
 7. The compound according to any one of claims 1-5, wherein R³ is alkyl.
 8. The compound according to any one of claims 1-7, wherein each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -

S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;

5 wherein said alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂.

10 9. The compound according to any one of claims 1 to 8, wherein

- each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; and heterocycle;

15 wherein said alkyl, cycloalkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂.

20 10. The compound according to any one of claims 1 to 9, wherein each R⁴ is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; =O; -CF₃; -OCF₃; -CHF₂; -OCHF₂; cyano; -OZ¹; -S(O)Z¹; -S(O)₂Z²; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -NZ³S(O)₂Z¹; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; heteroalkyl; aryl; heteroaryl; and heterocycle;

25 wherein said alkyl, heteroalkylcycloalkyl, aryl, heteroaryl and heterocycle is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂; -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, and -N(alkyl)₂.

30 11. The compound according to any one of claims 1 to 7, wherein two R⁴ can be taken together in order to form a 4-, 5-, or 6-membered heterocycle or a 3-, 4-, 5-, or 6-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

12. The compound according to any one of claims 1 to 11, wherein

35 - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl,

alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

5 - each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

10 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; and heteroalkynyl; wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

13. The compound according to any one of claims 1 to 12, wherein

- each Z¹ is independently selected from alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

30 - each Z³ and Z⁴ is independently selected from hydrogen; alkyl; and cycloalkyl; wherein said alkyl and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂; and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

14. The compound according to any one of claims 1-13, wherein

- each R^4 is independently selected from alkyl; cycloalkyl; halogen; hydroxyl; sulfhydryl; $-CF_3$; $-OCF_3$; $-CHF_2$; $-OCHF_2$; cyano; $-OZ^1$; $-C(O)Z^2$; $-C(O)OZ^1$; $-C(O)NZ^3Z^4$; $-NZ^3Z^4$; $-NZ^3S(O)_2Z^1$; $-NZ^3S(O)_2NZ^3Z^4$; $-NZ^3C(O)OZ^1$; $-NZ^3C(O)Z^1$; $-NZ^3C(O)NZ^3Z^4$; and aryl;

5 wherein said alkyl, cycloalkyl, and aryl is unsubstituted or is substituted with one or more substituents selected from alkyl, hydroxyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$; $-OCHF_2$, cyano, nitro, $-C(O)OH$, $-NH_2$, $-NHalkyl$, and $-N(alkyl)_2$;

10 - each Z^1 is independently selected from alkyl; wherein said alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NHalkyl$, and $-N(alkyl)_2$;

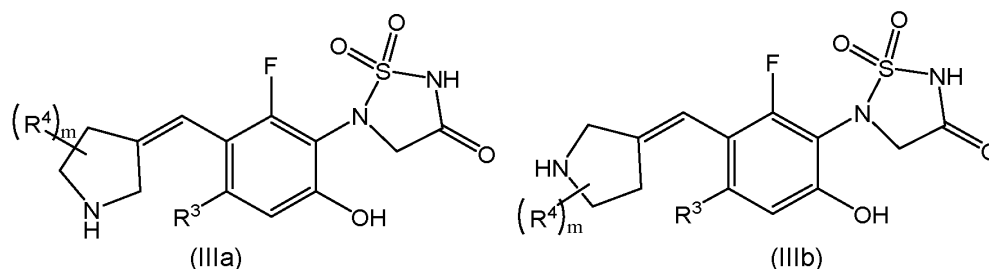
- each Z^2 is independently selected from hydroxyl; and alkyl;
wherein said alkyl is unsubstituted or is substituted with one or more substituents selected
15 from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, $=O$, halogen, $-SH$, $=S$, $-CF_3$, $-O$ -alkyl, $-OCF_3$, $-CHF_2$, $-OCHF_2$, cyano, nitro, $-C(O)OH$; NH_2 ; $-NHalkyl$, and $-N(alkyl)_2$;

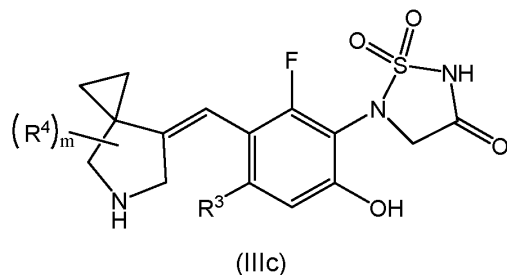
- each Z^3 and Z^4 is hydrogen.

15. The compound according to any one of claims 1-14, wherein cycle B is selected from 4-, 5-, 6-, or 7-membered heterocycle, preferably cycle B is selected from the group comprising
20 pyrrolidinyl; azetidiny; oxetanyl; tetrahydrofuranyl; piperidinyl; tetrahydro-2H-pyranyl; and azepanyl; preferably cycle B is selected from the group comprising pyrrolidinyl; azetidiny; and piperidinyl.

16. The compound according to any one of claims 1-14, wherein cycle B is selected 4-, 5-, 6-, or 7-membered cycloalkyl, preferably cycle B is selected from the group comprising cyclobutyl;
25 cyclopentyl; cyclohexyl; and cycloheptyl.

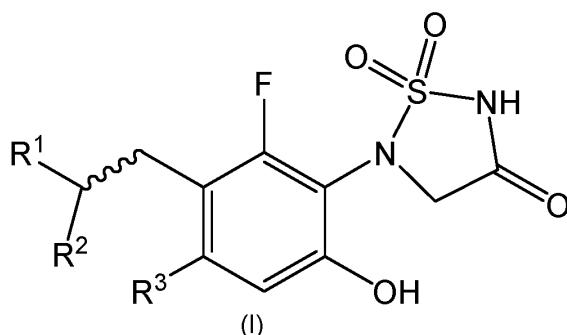
17. The compound according to any one of claims 1-16, wherein said compound is a compound of formula (IIIa), (IIIb), or (IIIc)





wherein R^3 , R^4 and m have the same meaning as that defined in any one of claims 1-16.

18. A compound selected from the group comprising Cpd037, Cpd038, Cpd039, Cpd046, Cpd047, Cpd048, Cpd095, Cpd096, Cpd114, Cpd115, Cpd130, Cpd131, Cpd132, Cpd133, Cpd139, Cpd143, Cpd144, Cpd145, Cpd146, Cpd147, Cpd156, Cpd156-en1, Cpd156-en2, Cpd157, Cpd158, Cpd158-en1, Cpd158-en2, Cpd159, Cpd160, Cpd162, Cpd163, Cpd164, Cpd165, Cpd167 and Cpd168.
19. A compound of formula (I), a stereo-isomeric form, a tautomer, a salt (in particular a pharmaceutically acceptable salt), a solvate, a hydrate, a polymorph, an isotope, and/or a prodrug thereof,



wherein:

- $\sim$ represents a double bond ($\equiv$) or a triple bond ($\equiv$);
- R^1 is selected from alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; cycloalkylalkyl; cycloalkenylalkyl; cycloalkynylalkyl; cycloalkylheteroalkyl; cycloalkenylheteroalkyl; cycloalkynylheteroalkyl; aryl; heteroaryl; heterocycle; arylalkyl; heteroarylalkyl; heterocyclalkyl; arylheteroalkyl; heteroarylheteroalkyl; and heterocyclheteroalkyl;
- whereby each of said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, cycloalkylalkyl, cycloalkenylalkyl, cycloalkynylalkyl, cycloalkylheteroalkyl, cycloalkenylheteroalkyl, cycloalkynylheteroalkyl, aryl, heteroaryl, heterocycle, arylalkyl, heteroarylalkyl, heterocyclalkyl, arylheteroalkyl, heteroarylheteroalkyl, and heterocyclheteroalkyl is unsubstituted or is substituted with one or more R^4 ;

- when  is a triple bond, then R² is not present; when  is a double bond, then R² is selected from hydrogen; alkyl and halogen;
- R³ is selected from hydrogen and alkyl;
- each R⁴ is independently selected from halogen; hydroxyl; sulfhydryl; =O; =S; -SCF₃; -SF₅; -CF₃;
- 5 -OCF₃; -CHF₂; -OCHF₂; cyano; nitro; -OZ¹; -SZ¹; -S(O)Z¹; -S(O)₂Z²; -S(O)₂NZ³Z⁴; -S(O)(NZ³)Z¹; -S(NZ³)(NZ³)Z¹; -C(O)H; -C(O)Z²; -C(O)OH; -C(O)OZ¹; -C(O)NZ³Z⁴; -NZ³Z⁴; -NZ³S(O)₂Z¹; -NZ³S(O)₂NZ³Z⁴; -NZ³C(O)OZ¹; -NZ³C(O)Z¹; -NZ³C(O)NZ³Z⁴; -P(O)Z³Z⁴; alkyl; alkenyl; alkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl;
- 10 arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl; heterocyclheteroalkyl; heterocyclheteroalkenyl; heterocyclheteroalkynyl; alkyl-oxy-alkyl; (mono or di)alkylamino; (mono or di)-alkyl-amino-alkyl; alkylthio; and alkyl-thio-alkyl;
- 15 wherein said alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclalkyl, heterocyclalkenyl, heterocyclalkynyl, heterocyclheteroalkyl, heterocyclheteroalkenyl, heterocyclheteroalkynyl, alkyl-oxy-alkyl, (mono or di)alkylamino, (mono or di)-alkyl-amino-alkyl, alkylthio, and alkyl-thio-alkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH, -NH₂, -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;
- 20
- 25 - or two R⁴ can be taken together in order to form a 4-, 5-, 6-, or 7-membered heterocycle or a 3-, 4-, 5-, 6-, or 7-membered cycloalkyl, wherein said heterocycle and cycloalkyl is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, -N(alkyl)₂, -S(O)₂alkyl, and -NHS(O)₂alkyl;
- 30 - each Z¹ is independently selected from alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclalkyl; heterocyclalkenyl; heterocyclalkynyl;
- 35 heterocyclheteroalkyl; heterocyclheteroalkenyl; and heterocyclheteroalkynyl;
- wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl,

arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is
 5 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z² is independently selected from hydroxyl; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is
 15 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

- each Z³ and Z⁴ is independently selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; heteroalkyl; heteroalkenyl; heteroalkynyl; aryl; heteroaryl; heterocycle; arylalkyl; arylalkenyl; arylalkynyl; arylheteroalkyl; arylheteroalkenyl; arylheteroalkynyl; heteroarylalkyl; heteroarylalkenyl; heteroarylalkynyl; heteroarylheteroalkyl; heteroarylheteroalkenyl; heteroarylheteroalkynyl; heterocyclylalkyl; heterocyclylalkenyl; heterocyclylalkynyl; heterocyclylheteroalkyl; heterocyclylheteroalkenyl; and heterocyclyl heteroalkynyl;

wherein said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, aryl, heteroaryl, heterocycle, arylalkyl, arylalkenyl, arylalkynyl, arylheteroalkyl, arylheteroalkenyl, arylheteroalkynyl, heteroarylalkyl, heteroarylalkenyl, heteroarylalkynyl, heteroarylheteroalkyl, heteroarylheteroalkenyl, heteroarylheteroalkynyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, heterocyclylheteroalkyl, heterocyclylheteroalkenyl, and heterocyclylheteroalkynyl is
 20 unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

-OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂;

and wherein each Z³ and Z⁴ can be taken together in order to form a (4-, 5-, 6-, or 7-membered) heterocycle which is unsubstituted or is substituted with one or more substituents selected from alkyl, cycloalkyl, alkenyl, alkynyl, hydroxyl, =O, halogen, -SH, =S, -CF₃, -O-alkyl, -OCF₃, -CHF₂, -OCHF₂, cyano, nitro, -C(O)OH; NH₂; -NHalkyl, and -N(alkyl)₂.

20. A pharmaceutical composition comprising a pharmaceutically acceptable carrier, and as active ingredient, an effective amount of a compound according to any one of claims 1-19.
21. The compound according to any one of claims 1-19, or a pharmaceutical composition according to claim 20, for use as a medicine.
22. The compound according to any one of claims 1-19, or a pharmaceutical composition according to claim 20, for use in the prevention or treatment of a PTPN2 and/or PTPN1 mediated disorder in an animal, mammal or human.
23. The compound for use according to claim 22, or a pharmaceutical composition for use according to claim 22, wherein the PTPN2 and/or PTPN1 mediated disorders is selected from the group comprising cancer and metabolic diseases.
24. The compound for use according to any of claims 22, 23 or a pharmaceutical composition for use according to any of claims 22, 23 wherein the PTPN2 and/or PTPN1 mediated disorders is selected from the group comprising lung cancer, breast cancer, head and neck cancer, oesophageal cancer, kidney cancer, bladder cancer, colon cancer, ovarian cancer, cervical cancer, endometrial cancer, liver cancer, skin cancer, pancreatic cancer, gastric cancer, brain cancer and prostate cancer.
25. A method for the prevention or treatment of a PTPN2 and/or PTPN1 activation mediated disorders in an animal, mammal or human comprising administering to said animal, mammal or human in need for such prevention or treatment an effective dose of a compound according to any one of claims 1-19.
26. A method of treatment or prevention of PTPN2 and/or PTPN1 activation mediated disorder according to claim 25 comprising administering to a patient in need thereof an effective dose of a compound according to any one of claims 1-19, in combination with one or more other anti-cancer agents, more specifically immunotherapeutic agents.