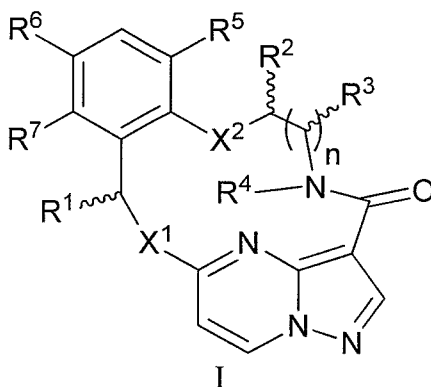


Discovery, **2014**, 4, 1022–1035) patients due to mutation of C481S required for covalent binding of ibrutinib to the kinase active site. Ibrutinib inhibited the recombinant BTK C481S 25-fold less potently than WT. (Woyach JA, et al. *New England Journal of Medicine*, **2014**, 370, 2286–2294) The loss of covalent binding cysteine leads to ineffective BTK inhibition and ultimately results in ibrutinib resistance. Therefore, the development of reversible ATP competitive BTK inhibitors with comparable activity towards wild type BTK and mutated C481S BTK is necessary to provide an alternative treatment option for patients with acquired resistance to ibrutinib. It was reported that BTK regulates B-cell and macrophage-mediated T-cell suppression in pancreas adenocarcinomas. (Gunderson AJ, et al. *Cancer Discov.* **2016**, 6, 270-285) The BTK inhibitor ibrutinib restored T cell-dependent antitumor immune responses to inhibit PDAC growth and improved responsiveness to chemotherapy. In addition to its critical roles in B cell development, Btk also contributes to the activation of the FcγR and FcεR signalling pathways in macrophages, neutrophils and mast cells. Btk is a promising target for therapeutic intervention in autoimmune and inflammatory disease, e. g. rheumatoid arthritis (RA) (Di Paolo JA, et al. *Nature Chemical Biology* **2011**, 7, 41–50) and systemic lupus erythematosus (SLE). (Bender AT, et al. *Clinical Immunology* **2016**, 164, 65–77) The development of reversible and highly selective BTK inhibitors is highly desired for chronic disease treatment.

SUMMARY

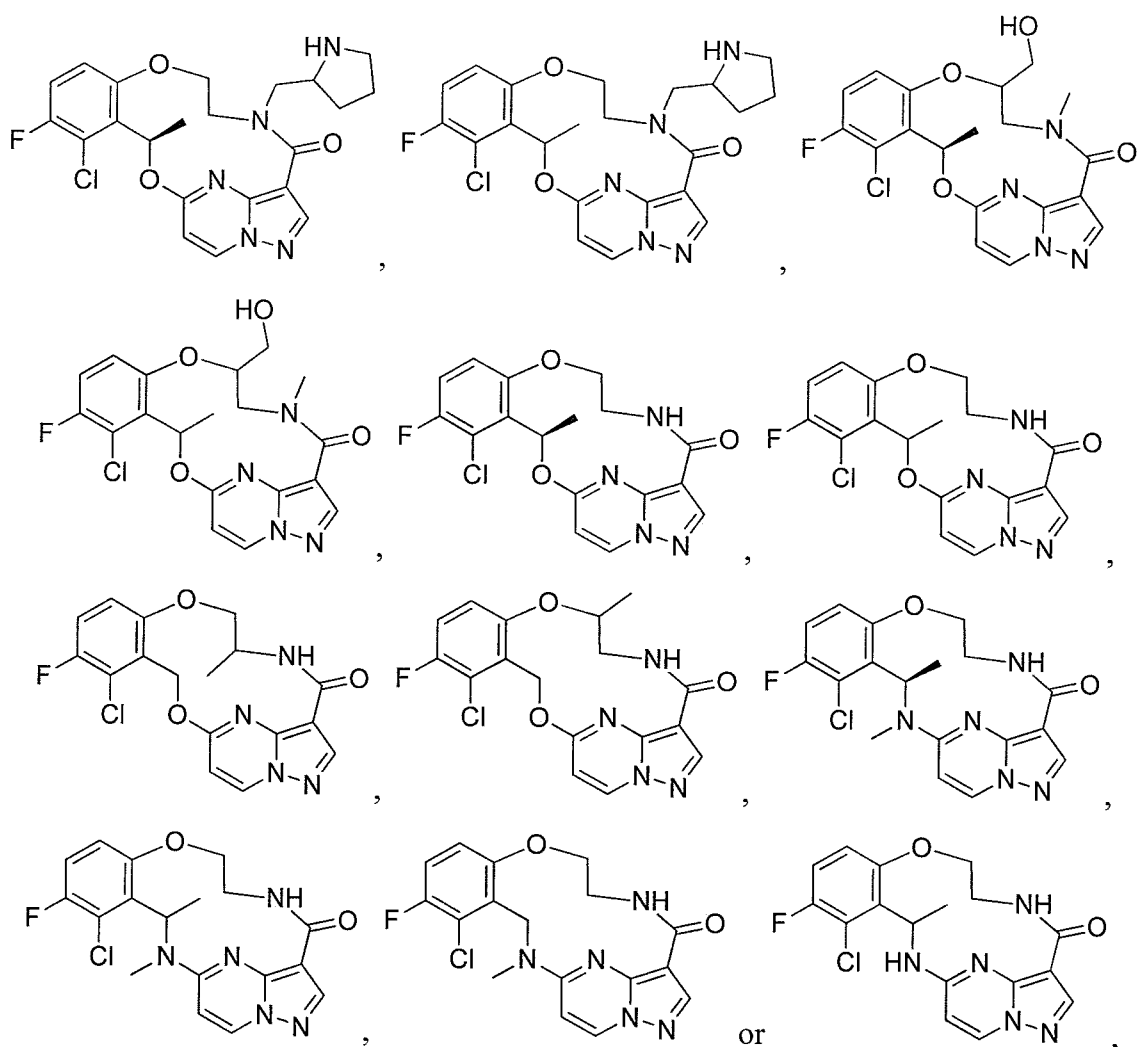
[0005] The disclosure relates to of the formula I



[0006] or a pharmaceutically acceptable salt thereof, wherein

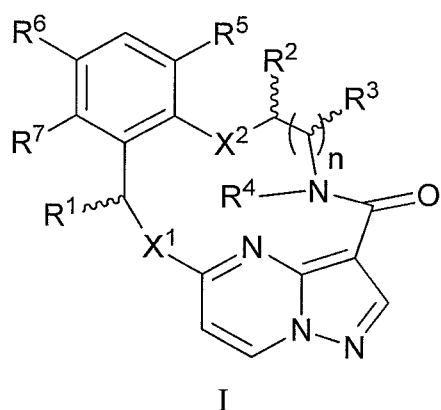
[0007] X¹ and X² are independently S, S(O), S(O)₂, O or N(R¹⁰);

[0008] R¹ is H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₀ aryl, -C(O)OR⁸ or -C(O)NR⁸R⁹; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₆-C₁₀ aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂,



or a pharmaceutically acceptable salt thereof.

[017] In one aspect, there is provided a compound of the formula I



or a pharmaceutically acceptable salt thereof, wherein

X^1 and X^2 are independently S, S(O), S(O)₂, O or N(R¹⁰);

R^1 is H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₀ aryl, -C(O)OR⁸ or -C(O)NR⁸R⁹; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₆-C₁₀ aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂,

-NHC(O)C₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)C₁-C₆ alkyl, -NHC(O)NH₂, -NHC(O)NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NHC₁-C₆ alkyl, -NHC(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)₂, -NHC(O)OC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)OC₁-C₆ alkyl, -NHS(O)(C₁-C₆ alkyl), -NHS(O)₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -NHS(O)NH₂, -NHS(O)₂NH₂, -N(C₁-C₆ alkyl)S(O)NH₂, -N(C₁-C₆ alkyl)S(O)₂NH₂, -NHS(O)NH(C₁-C₆ alkyl), -NHS(O)₂NH(C₁-C₆ alkyl), -NHS(O)N(C₁-C₆ alkyl)₂, -NHS(O)₂N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)₂N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -SC₁-C₆ alkyl, -S(O)C₁-C₆ alkyl, -S(O)₂C₁-C₆ alkyl, -S(O)NH(C₁-C₆ alkyl), -S(O)₂NH(C₁-C₆ alkyl), -S(O)N(C₁-C₆ alkyl)₂, -S(O)₂N(C₁-C₆ alkyl)₂, -P(C₁-C₆ alkyl)₂, -P(O)(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or 3- to 7-membered heterocycloalkyl;

each R² and R³ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₀ aryl, -C(O)OR⁸ or -C(O)NR⁸R⁹; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₆-C₁₀ aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NHC(O)C₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)C₁-C₆ alkyl, -NHC(O)NH₂, -NHC(O)NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NHC₁-C₆ alkyl, -NHC(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)₂, -NHC(O)OC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)OC₁-C₆ alkyl, -NHS(O)(C₁-C₆ alkyl), -NHS(O)₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -NHS(O)NH₂, -NHS(O)₂NH₂, -N(C₁-C₆ alkyl)S(O)NH₂, -N(C₁-C₆ alkyl)S(O)₂NH₂, -NHS(O)NH(C₁-C₆ alkyl), -NHS(O)₂NH(C₁-C₆ alkyl), -NHS(O)N(C₁-C₆ alkyl)₂, -NHS(O)₂N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)₂N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -SC₁-C₆ alkyl, -S(O)C₁-C₆ alkyl, -S(O)₂C₁-C₆ alkyl, -S(O)NH(C₁-C₆ alkyl), -S(O)₂NH(C₁-C₆ alkyl), -S(O)N(C₁-C₆ alkyl)₂, -S(O)₂N(C₁-C₆ alkyl)₂, -P(C₁-C₆ alkyl)₂, -P(O)(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or 3- to 7-membered heterocycloalkyl; or R² and R³ taken together with the carbon atoms to which they are attached optionally form a C₅-C₇ cycloalkyl or a 5- to 7-membered heterocycloalkyl; or R² and R⁶ taken together with the atoms to which they are attached optionally form a 5- to 7-membered heterocycloalkyl;

R⁴ is H, C₁-C₆ alkyl or 3- to 7-membered heterocycloalkyl, wherein each hydrogen atom in C₁-C₆ alkyl or 3- to 7-membered heterocycloalkyl is independently optionally substituted by halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H,

-C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

R⁵, R⁶ and R⁷ are each independently selected from the group consisting of H, fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆-C₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁-C₆ alkyl, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₇ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂;

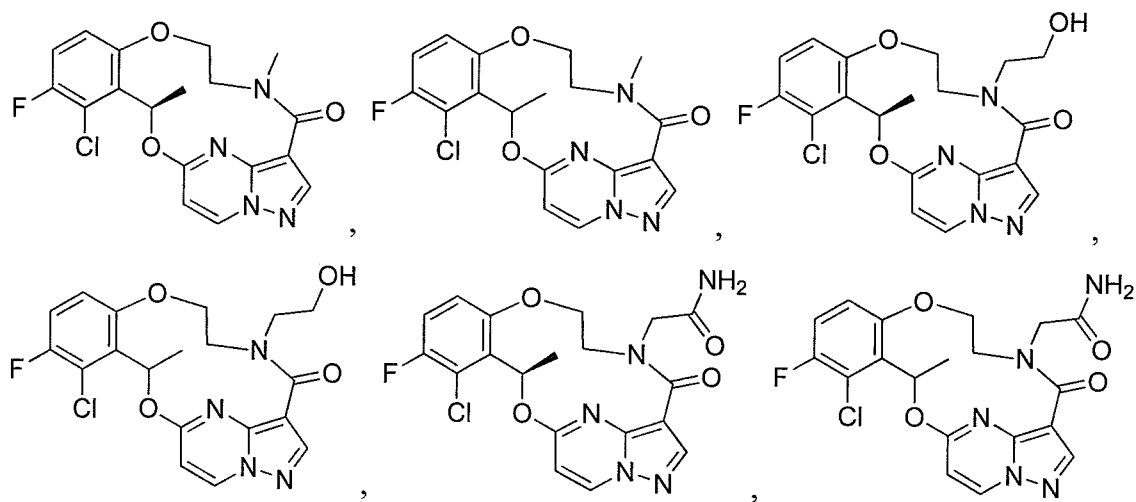
each R⁸ and R⁹ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl or heteroaryl;

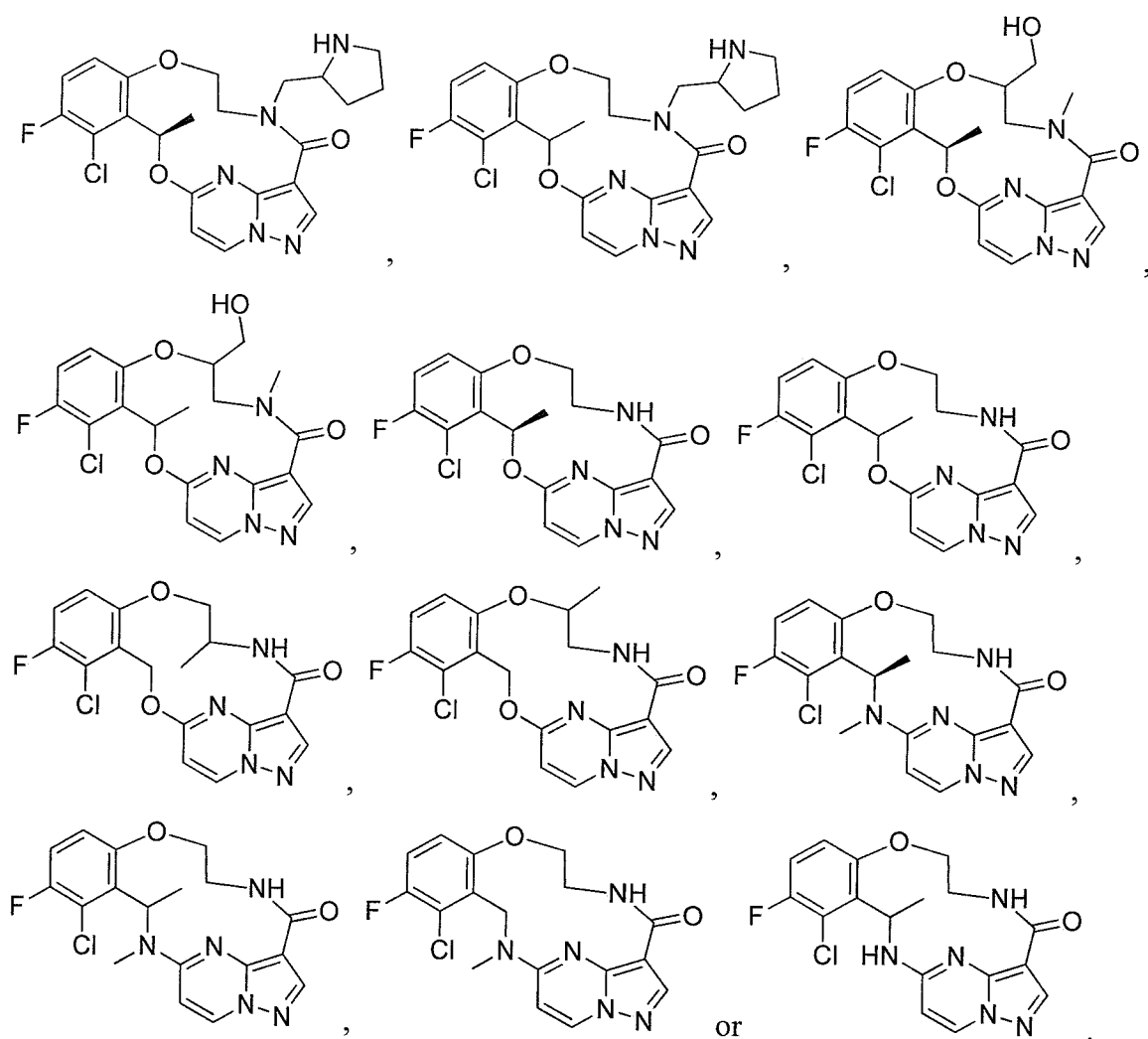
each R¹⁰ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl or -OR⁸;

n is 1 or 2; and

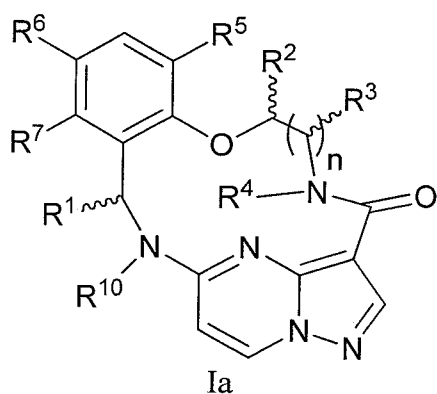
provided that at least one of R⁵ or R⁷ is not H, and

provided that the compound of the formula I is not of the formula





[018] In another aspect, there is provided a compound of the formula Ia



[019] or a pharmaceutically acceptable salt thereof, wherein

[020] R^1 is H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{10} aryl, $-C(O)OR^8$ or $-C(O)NR^8R^9$; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and C_6 - C_{10} aryl is independently optionally substituted by deuterium, halogen, $-OH$, $-CN$, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $_2$,

-C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or monocyclic 5- to 7-membered heterocycloalkyl;

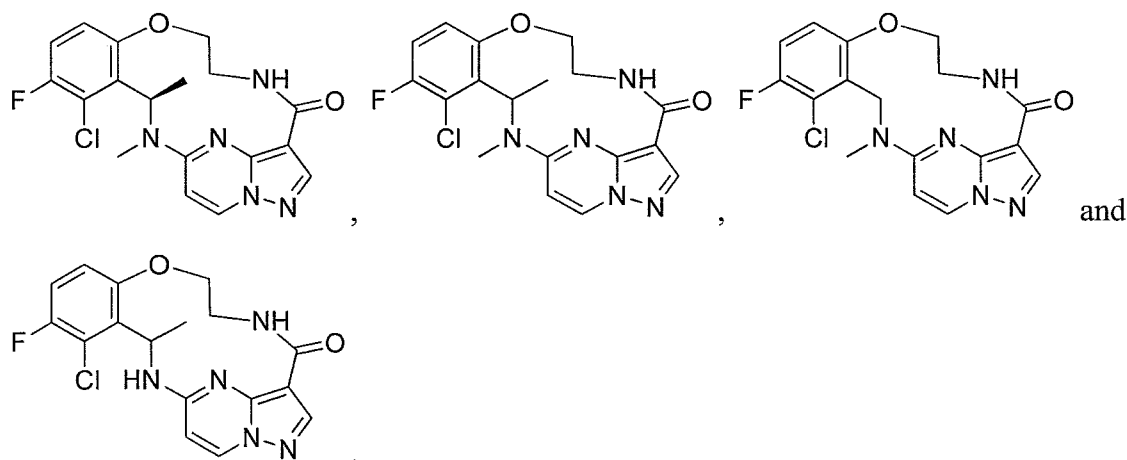
[023] R⁵, R⁶ and R⁷ are each independently selected from the group consisting of H, fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆-C₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁-C₆ alkyl, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₇ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂;

[024] each R⁸ and R⁹ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl or heteroaryl;

[025] each R¹⁰ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl or -OR⁸;

[026] n is 1 or 2;

[027] provided that at least one of R⁵ or R⁷ is not H; and provided that the compound is not of the formula

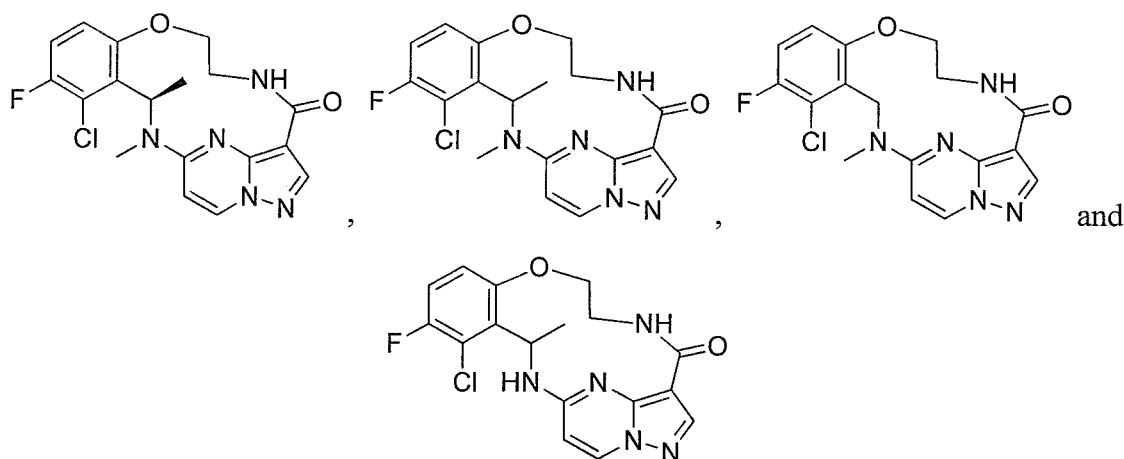


[028] In another aspect, there is provided a compound of the formula Ib

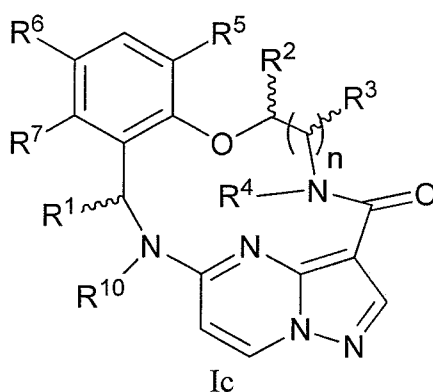
[036] each R^{10} is independently H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or $-OR^8$;

[037] n is 1 or 2; and

[038] provided that the compound is not of the formula



[039] In another aspect, there is provided a compound of the formula Ic



[040] or a pharmaceutically acceptable salt thereof, wherein

[041] R^1 is H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{10} aryl, $-C(O)OR^8$ or $-C(O)NR^8R^9$; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and C_6 - C_{10} aryl is independently optionally substituted by deuterium, halogen, $-OH$, $-CN$, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)C_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)C_1$ - C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)NH_2$, $-N(C_1$ - C_6 alkyl) $C(O)NHC_1$ - C_6 alkyl, $-NHC(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $C(O)N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)OC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)OC_1$ - C_6 alkyl, $-NHS(O)(C_1$ - C_6 alkyl), $-NHS(O)_2(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)(C_1$ - C_6 alkyl),

[044] R^5 is selected from the group consisting of fluoro, chloro, bromo, C_1 - C_6 alkyl, -OH, -CN, -OC $_1$ - C_6 alkyl, -NHC $_1$ - C_6 alkyl, -N(C_1 - C_6 alkyl) $_2$, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C_3 - C_6 cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C_6 - C_{10} aryl, and -CF $_3$; wherein each hydrogen atom in C_1 - C_6 alkyl, -OC $_1$ - C_6 alkyl, -NHC $_1$ - C_6 alkyl, -N(C_1 - C_6 alkyl) $_2$, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C_3 - C_6 cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C_6 - C_{10} aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC $_1$ - C_6 alkyl, -NH $_2$, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl) $_2$, C_3 - C_7 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl, 5- to 7-membered heteroaryl, -CO $_2$ H, -C(O)OC $_1$ - C_6 alkyl, -C(O)NH $_2$, -C(O)NH(C_1 - C_6 alkyl) and -C(O)N(C_1 - C_6 alkyl) $_2$;

[045] R^6 and R^7 are each independently selected from the group consisting of H, fluoro, chloro, bromo, C_1 - C_6 alkyl, -OH, -CN, -OC $_1$ - C_6 alkyl, -NHC $_1$ - C_6 alkyl, -N(C_1 - C_6 alkyl) $_2$, 5- to 7-membered heteroaryl, C_6 - C_{10} aryl, and -CF $_3$; wherein each hydrogen atom in C_1 - C_6 alkyl, 5- to 7-membered heteroaryl and C_6 - C_{10} aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC $_1$ - C_6 alkyl, -NH $_2$, -NH(C_1 - C_6 alkyl), -N(C_1 - C_6 alkyl) $_2$, -CO $_2$ H, -C(O)OC $_1$ - C_6 alkyl, -C(O)NH $_2$, -C(O)NH(C_1 - C_6 alkyl) and -C(O)N(C_1 - C_6 alkyl) $_2$;

[046] each R^8 and R^9 is independently H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl or heteroaryl;

[047] each R^{10} is independently H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, 3- to 7-membered heterocycloalkyl, C_6 - C_{10} aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl or -OR ^{8} ; and

[048] n is 1 or 2.

[049] In another aspect, there is provided a pharmaceutical composition comprising a compound of the formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, and optionally at least one diluent, carrier or excipient.

[050] The disclosure is directed to a method of treating cancer, pain, neurological diseases, autoimmune diseases, or inflammation comprising administering to a subject in need of such treatment an effective amount of at least one compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof. cancer, pain, neurological diseases, autoimmune diseases, or inflammation.

[051] In another aspect, there is provided use of a compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cancer, pain, neurological diseases, autoimmune diseases, or inflammation. In some embodiments, the disease is a cancer. In some embodiments, the disease is an autoimmune disease. In some embodiments, the disease is inflammation.

[052] The disclosure is directed to use of a compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, for treating cancer, pain, neurological diseases, autoimmune diseases, or inflammation. In some embodiments, the disease is a cancer. In some embodiments, the disease is an autoimmune disease. In some embodiments, the disease is inflammation.

[053] The disclosure is directed to use of a compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cancer, pain, neurological diseases, autoimmune diseases, or inflammation, and the use of such compounds and salts for treatment of cancer, pain, neurological diseases, autoimmune diseases, or inflammation. In some embodiments, the disease is a cancer. In some embodiments, the disease is an autoimmune disease. In some embodiments, the disease is inflammation.

[054] The disclosure relates to a method of inhibiting non-receptor tyrosine kinases, including one or more of JAK2 or BTK, comprising contacting a cell comprising one or more of such kinases with an effective amount of at least one compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, and/or with at least one pharmaceutical composition of the disclosure, wherein the contacting is *in vitro*, *ex vivo*, or *in vivo*.

[054a] In another aspect, there is provided a method of inhibiting non-receptor tyrosine kinases selected from the group consisting of JAK2 and BTK, comprising contacting a cell comprising one or more of such kinases with an effective amount of at least one compound of formula I, Ia, Ib or Ic, or a pharmaceutically acceptable salt thereof, and/or with at least one pharmaceutical composition as described herein, wherein the contacting is *in vitro* or *ex vivo*.

[054b] In another aspect, there is provided a compound as described herein for use in treating cancer, inflammation or an autoimmune disease in a patient.

[055] Additional embodiments, features, and advantages of the disclosure will be apparent from the following detailed description and through practice of the disclosure. The compounds of the present disclosure can be described as embodiments in any of the following enumerated clauses. It will be understood that any of the embodiments described herein can be used in connection with any other embodiments described herein to the extent that the embodiments do not contradict one another.

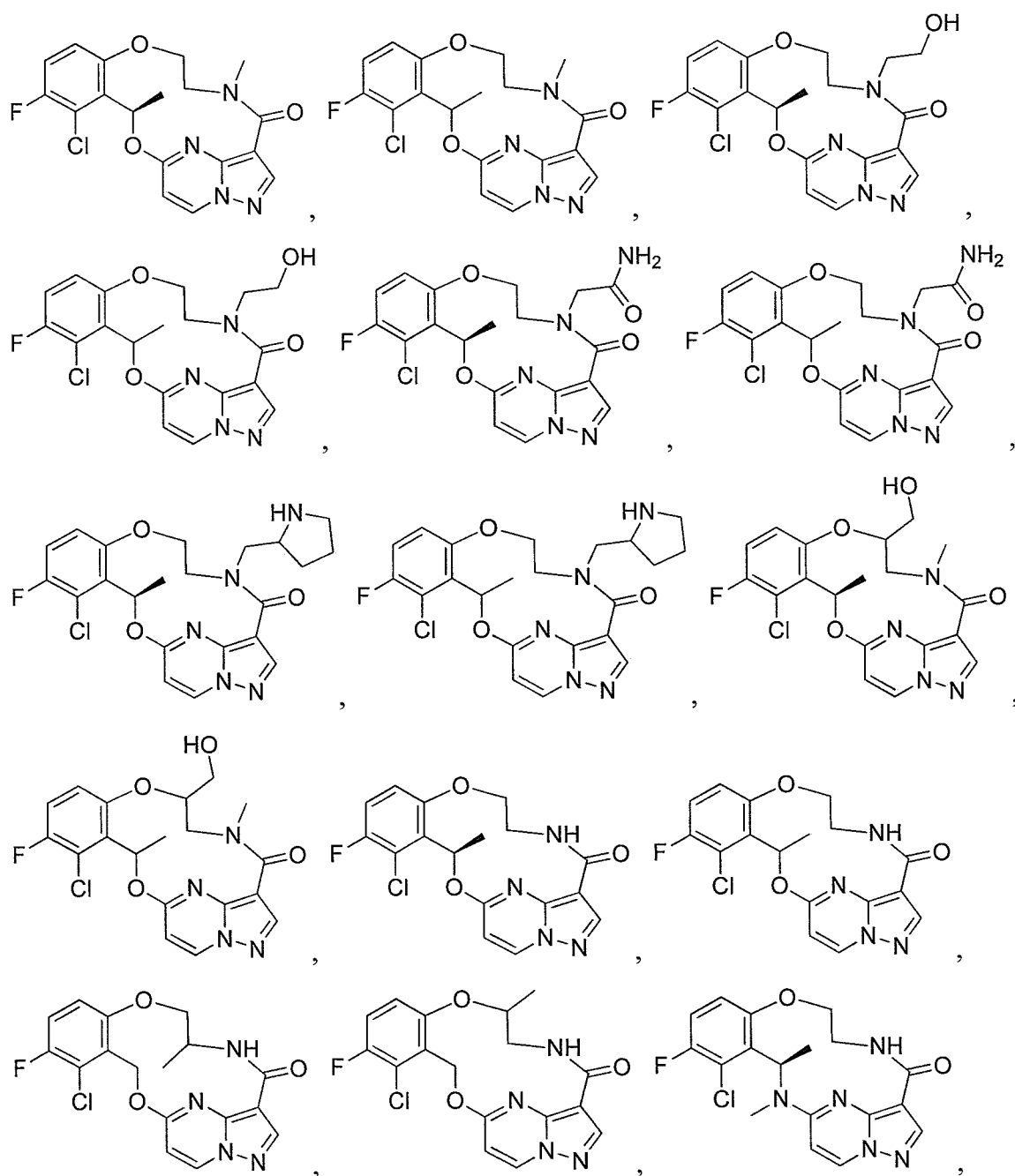
[056] 1. A compound of the formula I

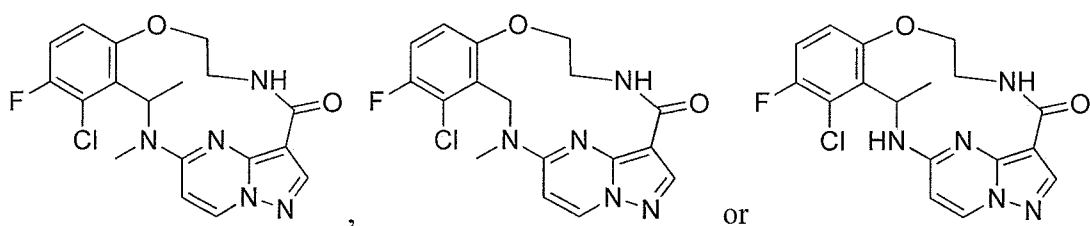
heteroaryl; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl or -OR⁸;

n is 1 or 2; and

provided that at least one of R⁵ or R⁷ is not H, and

provided that the compound of the formula I is not of the formula

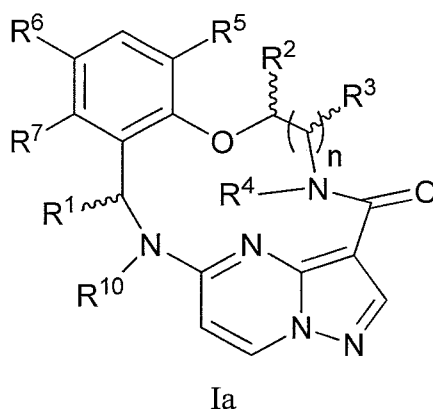




2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein X^1 is $N(R^{10})$.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein X^2 is O.

4. A compound of the formula Ia



or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{10} aryl, $-C(O)OR^8$ or $-C(O)NR^8R^9$; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and C_6 - C_{10} aryl is independently optionally substituted by deuterium, halogen, $-OH$, $-CN$, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)C_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)C_1$ - C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)NH_2$, $-N(C_1$ - C_6 alkyl) $C(O)NHC_1$ - C_6 alkyl, $-NHC(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $C(O)N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)OC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)OC_1$ - C_6 alkyl, $-NHS(O)(C_1$ - C_6 alkyl), $-NHS(O)_2(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)_2(C_1$ - C_6 alkyl), $-NHS(O)NH_2$, $-NHS(O)_2NH_2$, $-N(C_1$ - C_6 alkyl) $S(O)NH_2$, $-N(C_1$ - C_6 alkyl) $S(O)_2NH_2$, $-NHS(O)NH(C_1$ - C_6 alkyl), $-NHS(O)_2NH(C_1$ - C_6 alkyl), $-NHS(O)N(C_1$ - C_6 alkyl) $_2$, $-NHS(O)_2N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $S(O)NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)_2NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6

6. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from the group consisting of fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, 5- to 7-membered heteroaryl, and -CF₃.

7. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R⁷ is fluoro, chloro, -CN, or -CF₃.

8. The compound of any one claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆-C₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁-C₆ alkyl, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₇ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

9. The compound of any one claims 1 to 4 or 8, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆-C₁₀ aryl

and -CF₃, wherein each hydrogen atom in C₁-C₆ alkyl, -OC₁-C₆ alkyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₇ cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

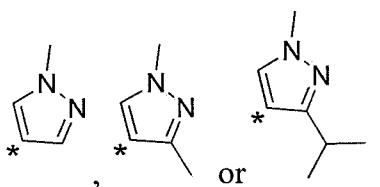
10. The compound of any one claims 1 to 4, 8 or 9, or a pharmaceutically acceptable salt thereof, wherein R⁵ is fluoro, chloro, bromo, -OH, -CN, -CF₃, methoxy, ethoxy, iso-propoxy, or n-propoxy.

11. The compound of any one claims 1 to 4, 8 or 9, or a pharmaceutically acceptable salt thereof, wherein R⁵ is 5- to 7-membered heteroaryl; wherein each hydrogen atom in 5- to 7-membered heteroaryl is independently optionally substituted by fluoro, chloro, bromo, -OH,

-CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

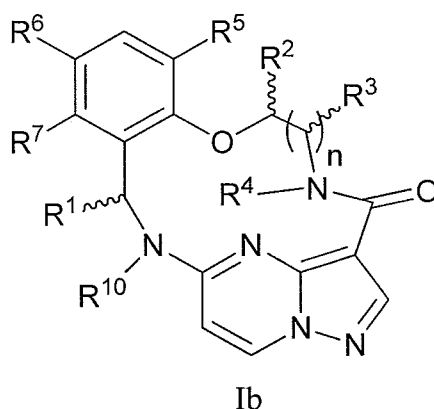
12. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein 5- to 7-membered heteroaryl is pyrazolyl substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

13. The compound of claim 11, or a pharmaceutically acceptable salt thereof, wherein 5- to 7-membered heteroaryl is



14. The compound of any one claims 1 to 4, 8 or 9, or a pharmaceutically acceptable salt thereof, wherein R⁵ is C₆-C₁₀ aryl, wherein each hydrogen atom in C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

15. A compound of the formula Ib



or a pharmaceutically acceptable salt thereof, wherein

R^1 is H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{10} aryl, $-C(O)OR^8$ or $-C(O)NR^8R^9$; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and C_6 - C_{10} aryl is independently optionally substituted by deuterium, halogen, $-OH$, $-CN$, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)C_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)C_1$ - C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)NH_2$, $-N(C_1$ - C_6 alkyl) $C(O)NHC_1$ - C_6 alkyl, $-NHC(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $C(O)N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)OC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)OC_1$ - C_6 alkyl, $-NHS(O)(C_1$ - C_6 alkyl), $-NHS(O)_2(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)_2(C_1$ - C_6 alkyl), $-NHS(O)NH_2$, $-NHS(O)_2NH_2$, $-N(C_1$ - C_6 alkyl) $S(O)NH_2$, $-N(C_1$ - C_6 alkyl) $S(O)_2NH_2$, $-NHS(O)NH(C_1$ - C_6 alkyl), $-NHS(O)_2NH(C_1$ - C_6 alkyl), $-NHS(O)N(C_1$ - C_6 alkyl) $_2$, $-NHS(O)_2N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $S(O)NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)_2NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $S(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $S(O)_2N(C_1$ - C_6 alkyl) $_2$, $-CO_2H$, $-C(O)OC_1$ - C_6 alkyl, $-C(O)NH_2$, $-C(O)NH(C_1$ - C_6 alkyl), $-C(O)N(C_1$ - C_6 alkyl) $_2$, $-SC_1$ - C_6 alkyl, $-S(O)C_1$ - C_6 alkyl, $-S(O)_2C_1$ - C_6 alkyl, $-S(O)NH(C_1$ - C_6 alkyl), $-S(O)_2NH(C_1$ - C_6 alkyl), $-S(O)N(C_1$ - C_6 alkyl) $_2$, $-S(O)_2N(C_1$ - C_6 alkyl) $_2$, $-P(C_1$ - C_6 alkyl) $_2$, $-P(O)(C_1$ - C_6 alkyl) $_2$, C_3 - C_6 cycloalkyl, or 3- to 7-membered heterocycloalkyl;

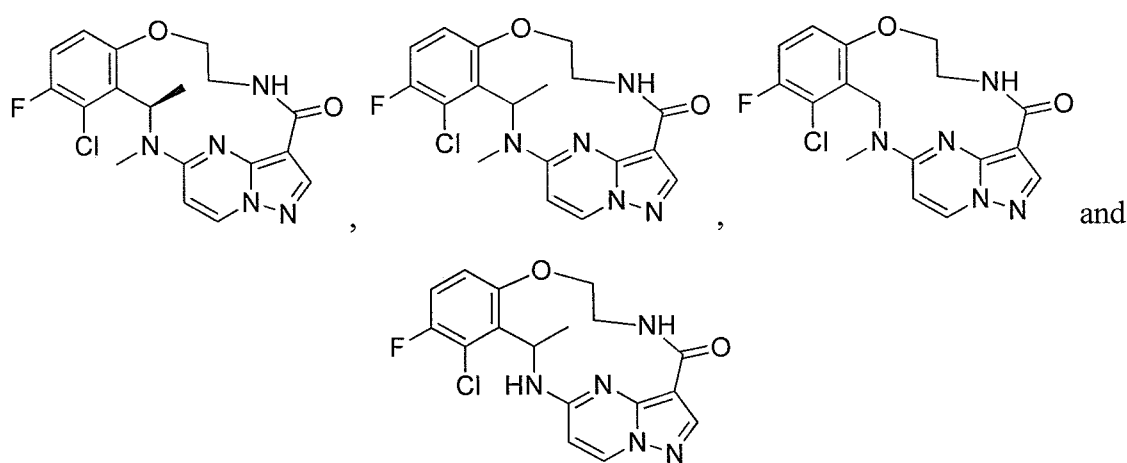
each R^2 and R^3 is independently H, deuterium, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_6 - C_{10} aryl, $-C(O)OR^8$ or $-C(O)NR^8R^9$; wherein each hydrogen atom in C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and C_6 - C_{10} aryl is independently optionally substituted by deuterium, halogen, $-OH$, $-CN$, $-OC_1$ - C_6 alkyl, $-NH_2$, $-NH(C_1$ - C_6 alkyl), $-N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)C_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)C_1$ - C_6 alkyl, $-NHC(O)NH_2$, $-NHC(O)NHC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)NH_2$, $-N(C_1$ - C_6 alkyl) $C(O)NHC_1$ - C_6 alkyl, $-NHC(O)N(C_1$ - C_6 alkyl) $_2$, $-N(C_1$ - C_6 alkyl) $C(O)N(C_1$ - C_6 alkyl) $_2$, $-NHC(O)OC_1$ - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $C(O)OC_1$ - C_6 alkyl, $-NHS(O)(C_1$ - C_6 alkyl), $-NHS(O)_2(C_1$ - C_6 alkyl), $-N(C_1$ - C_6

each R⁸ and R⁹ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl or heteroaryl;

each R¹⁰ is independently H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl or -OR⁸;

n is 1 or 2; and

provided that the compound is not of the formula

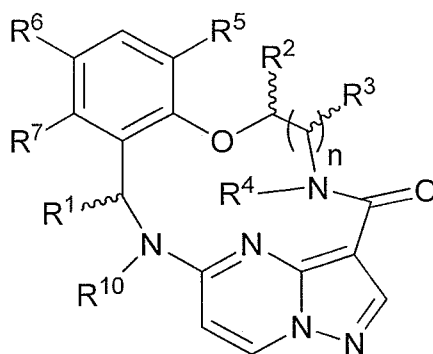


16. The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from the group consisting of fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, -NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)₂, 5- to 7-membered heteroaryl, C₆-C₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁-C₆ alkyl, 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

17. The compound of claim 15 or 16, or a pharmaceutically acceptable salt thereof, wherein R⁷ is selected from the group consisting of fluoro, chloro, bromo, C₁-C₆ alkyl, -OH, -CN, -OC₁-C₆ alkyl, 5- to 7-membered heteroaryl, and -CF₃.

18. The compound of any one of claims 15 to 17, or a pharmaceutically acceptable salt thereof, wherein R⁷ is fluoro, chloro, -CN or -CF₃.

19. A compound of the formula Ic



Ic

or a pharmaceutically acceptable salt thereof, wherein

R¹ is H, deuterium, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₆-C₁₀ aryl, -C(O)OR⁸ or -C(O)NR⁸R⁹; wherein each hydrogen atom in C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl and C₆-C₁₀ aryl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NHC(O)C₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)C₁-C₆ alkyl, -NHC(O)NH₂, -NHC(O)NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NHC₁-C₆ alkyl, -NHC(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)₂, -NHC(O)OC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)OC₁-C₆ alkyl, -NHS(O)(C₁-C₆ alkyl), -NHS(O)₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -NHS(O)NH₂, -NHS(O)₂NH₂, -N(C₁-C₆ alkyl)S(O)NH₂, -N(C₁-C₆ alkyl)S(O)₂NH₂, -NHS(O)NH(C₁-C₆ alkyl), -NHS(O)₂NH(C₁-C₆ alkyl), -NHS(O)N(C₁-C₆ alkyl)₂, -NHS(O)₂N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)₂N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -SC₁-C₆ alkyl, -S(O)C₁-C₆ alkyl, -S(O)₂C₁-C₆ alkyl, -S(O)NH(C₁-C₆ alkyl), -S(O)₂NH(C₁-C₆ alkyl), -S(O)N(C₁-C₆ alkyl)₂, -S(O)₂N(C₁-C₆ alkyl)₂, -P(C₁-C₆ alkyl)₂, -P(O)(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or 3- to 7-membered heterocycloalkyl;

heteroaryl, -CO₂H, -C(O)OC₁₋₆ alkyl, -C(O)NH₂, -C(O)NH(C₁₋₆ alkyl) and -C(O)N(C₁₋₆ alkyl)₂;

R⁶ and R⁷ are each independently selected from the group consisting of H, fluoro, chloro, bromo, C₁₋₆ alkyl, -OH, -CN, -OC₁₋₆ alkyl, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, 5- to 7-membered heteroaryl, C₆₋₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁₋₆ alkyl, 5- to 7-membered heteroaryl and C₆₋₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁₋₆ alkyl, -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, -CO₂H, -C(O)OC₁₋₆ alkyl, -C(O)NH₂, -C(O)NH(C₁₋₆ alkyl) and -C(O)N(C₁₋₆ alkyl)₂;

each R⁸ and R⁹ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl or heteroaryl;

each R¹⁰ is independently H, deuterium, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl; wherein each hydrogen atom in C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, or mono- or bicyclic heteroaryl is independently optionally substituted by deuterium, halogen, C₁₋₆ alkyl, C₁₋₆ haloalkyl or -OR⁸; and

n is 1 or 2.

20. The compound of claims 19, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of fluoro, chloro, bromo, C₁₋₆ alkyl, -OH, -CN, -OC₁₋₆ alkyl, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃₋₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆₋₁₀ aryl, and -CF₃; wherein each hydrogen atom in C₁₋₆ alkyl, -OC₁₋₆ alkyl, -NHC₁₋₆ alkyl, -N(C₁₋₆ alkyl)₂, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃₋₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆₋₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁₋₆ alkyl, -NH₂, -NH(C₁₋₆ alkyl), -N(C₁₋₆ alkyl)₂, C₃₋₇ cycloalkyl, 3- to 7-membered heterocycloalkyl, C₆₋₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁₋₆ alkyl, -C(O)NH₂, -C(O)NH(C₁₋₆ alkyl) and -C(O)N(C₁₋₆ alkyl)₂.

21. The compound of claim 19 or 20, or a pharmaceutically acceptable salt thereof, wherein R⁵ is selected from the group consisting of fluoro, chloro, bromo, C₁₋₆ alkyl, -OH, -CN, -OC₁₋₆ alkyl, C₃₋₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃₋₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl, C₆₋₁₀ aryl and -CF₃, wherein

each hydrogen atom in C₁-C₆ alkyl, -OC₁-C₆ alkyl, C₃-C₆ cycloalkyl, 3- to 7-membered heterocycloalkyl, -O-(C₃-C₆ cycloalkyl), -O-(3- to 7-membered heterocycloalkyl), 5- to 7-membered heteroaryl and C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, C₃-C₇ cycloalkyl, 3-to 7-membered heterocycloalkyl, C₆-C₁₀ aryl, 5- to 7-membered heteroaryl, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

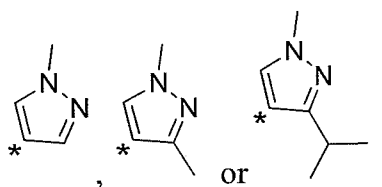
22. The compound of any one claims 19 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁵ is fluoro, chloro, bromo, -OH, -CN, -CF₃, methoxy, ethoxy, iso-propoxy, or n-propoxy.

23. The compound of any one claims 19 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁵ is 5- to 7-membered heteroaryl; wherein each hydrogen atom in 5- to 7-membered heteroaryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆

alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

24. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein 5- to 7-membered heteroaryl is pyrazolyl substituted with one or more substituents selected from the group consisting of fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

25. The compound of claim 23, or a pharmaceutically acceptable salt thereof, wherein 5- to 7-membered heteroaryl is



26. The compound of any one claims 19 to 21, or a pharmaceutically acceptable salt thereof, wherein R⁵ is C₆-C₁₀ aryl, wherein each hydrogen atom in C₆-C₁₀ aryl is independently optionally substituted by fluoro, chloro, bromo, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl) and -C(O)N(C₁-C₆ alkyl)₂.

27. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is H or C₁-C₆ alkyl.

28. The compound of claim 27, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is methyl, ethyl or isopropyl.

29. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R² is H or C₁-C₆ alkyl; wherein each hydrogen atom in C₁-C₆ alkyl is independently optionally substituted by deuterium, halogen, -OH, -CN, -OC₁-C₆ alkyl, -NH₂, -NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)₂, -NHC(O)C₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)C₁-C₆ alkyl, -NHC(O)NH₂, -NHC(O)NHC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)NH₂, -N(C₁-C₆ alkyl)C(O)NHC₁-C₆ alkyl, -NHC(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)C(O)N(C₁-C₆ alkyl)₂, -NHC(O)OC₁-C₆ alkyl, -N(C₁-C₆ alkyl)C(O)OC₁-C₆ alkyl, -NHS(O)(C₁-C₆ alkyl), -NHS(O)₂(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂(C₁-C₆ alkyl), -NHS(O)NH₂, -NHS(O)₂NH₂, -N(C₁-C₆ alkyl)S(O)NH₂, -N(C₁-C₆ alkyl)S(O)₂NH₂, -NHS(O)NH(C₁-C₆ alkyl), -NHS(O)₂NH(C₁-C₆ alkyl), -NHS(O)N(C₁-C₆ alkyl)₂, -NHS(O)₂N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)₂NH(C₁-C₆ alkyl), -N(C₁-C₆ alkyl)S(O)N(C₁-C₆ alkyl)₂, -N(C₁-C₆ alkyl)S(O)₂N(C₁-C₆ alkyl)₂, -CO₂H, -C(O)OC₁-C₆ alkyl, -C(O)NH₂, -C(O)NH(C₁-C₆ alkyl), -C(O)N(C₁-C₆ alkyl)₂, -SC₁-C₆ alkyl, -S(O)C₁-C₆ alkyl, -S(O)₂C₁-C₆ alkyl, -S(O)NH(C₁-C₆ alkyl), -S(O)₂NH(C₁-C₆ alkyl), -S(O)N(C₁-C₆ alkyl)₂, -S(O)₂N(C₁-C₆ alkyl)₂, -P(C₁-C₆ alkyl)₂, -P(O)(C₁-C₆ alkyl)₂, C₃-C₆ cycloalkyl, or 3- to 7-membered heterocycloalkyl.

30. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R² is C₁-C₆ alkyl, wherein one hydrogen atom in C₁-C₆ alkyl substituted by -OH.

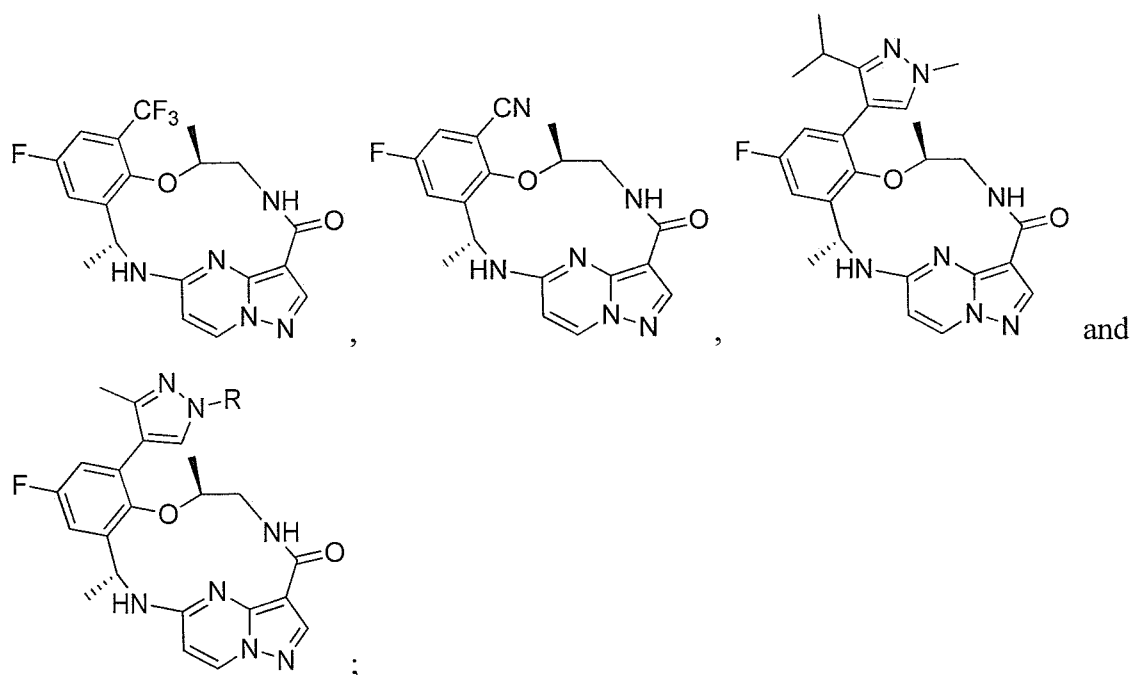
31. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^2 is $-CH_2OH$.

32. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein each R^3 is H.

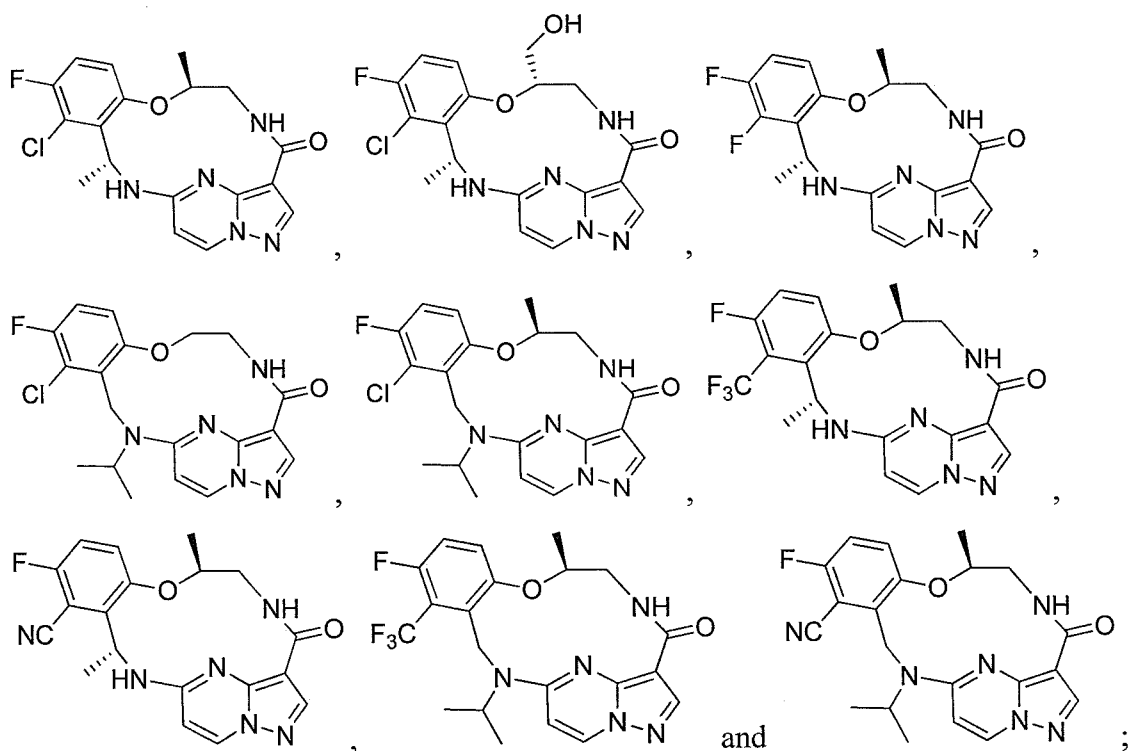
33. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^4 is H.

34. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro.

35. The compound of claim 1, selected from the group consisting of



36. The compound of claim 1, selected from the group consisting of



37. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof, and optionally at least one diluent, carrier or excipient.

38. Use of a compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cancer, pain, neurological diseases, autoimmune diseases, or inflammation.

39. A method of inhibiting a non-receptor tyrosine kinases selected from the group consisting of JAK2 and BTK, comprising contacting a cell comprising one or more of such kinases with an effective amount of at least one compound of any one of claims 1 to 36, or a pharmaceutically acceptable salt thereof, and/or with at least one pharmaceutical composition, wherein the contacting is *in vitro* or *ex vivo*.

40. A compound of any one of claims 1 to 36 for use in treating cancer, inflammation or an autoimmune disease in a patient.

41. The use of claim 38 or compound of claim 40, wherein the cancer is mediated by BTK or JAK2.

42. The use of claim 38 or compound of claim 40, wherein the cancer is mediated by a genetically altered BTK or genetically altered JAK2.

43. The use or compound of claim 42, wherein the genetically altered BTK comprises at least one resistance mutation.

44. The use or compound of claim 43, wherein the at least one resistance mutation is C481S.
45. The use or compound of claim 42, wherein the cancer is mediated by a fusion protein comprising a fragment of a protein encoded by an JAK2 gene and a fragment of a protein encoded by a TEL or PCM1 gene.
46. The use or compound of claim 42, wherein the genetically altered JAK2 is a TEL-JAK2 fusion protein.
47. The use or compound of claim 42, wherein the genetically altered JAK2 is a PCM1-JAK2 fusion protein.
48. The use or compound of claim 42, wherein the genetically altered JAK2 comprises a V617F point mutation.
49. The use of claim 38 or compound of claim 40, wherein the autoimmune disease is rheumatoid arthritis or systemic lupus erythematosus.
50. The use of claim 38 or compound of claim 40, wherein the cancer is selected from the group consisting of NSCLC, triple negative breast cancer, leukemia, myeloproliferative neoplasms, chronic lymphocytic leukemia, mantle cell leukemia and pancreas adenocarcinoma.