

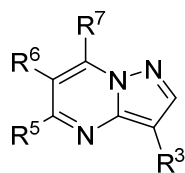
differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY

[0006] It has now been found that compounds of this present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of TYK2 kinase.

[0006a] In one aspect, the present disclosure refers to a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein: R³ is -C(O)NH₂; -C(O)NHR^{3A}; -C(O)N(R^{3A})₂; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with m instances of R^{3B}; R⁵ is hydrogen, or -L¹-R^{5A}; R⁶ is hydrogen, R^A, or R^B; or R⁵ and R⁶ are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by R^{5A} and n instances of R^C; R⁷ is hydrogen, halogen, -NH₂, -NHR^{7A}, or -NHC(O)R^{7A}; or R⁶ and R⁷ are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted by p instances of R^C; L¹ is a covalent bond or a C₁₋₄ bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(R^{5B})₂-, -CH(R^{5B})-, -N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)₂-,

$-\text{S}(\text{O})_2\text{N}(\text{R})-$, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{S}-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$; $\text{R}^{3\text{A}}$ and $\text{R}^{7\text{A}}$ are each independently R^{B} , and are each substituted by q instances of R^{C} ; $\text{R}^{5\text{A}}$ and each instance of $\text{R}^{5\text{B}}$ are each independently R^{A} or R^{B} , and are each substituted by r instances of R^{C} ; each instance of R^{A} is independently oxo, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{NR})\text{NR}_2$, $-\text{N}(\text{R})\text{S}(\text{O})_2\text{NR}_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$; each instance of R^{B} is independently C_{1-6} aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each instance of R^{C} is independently oxo, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}$, $-\text{SR}$, $-\text{NR}_2$, $-\text{S}(\text{O})_2\text{R}$, $-\text{S}(\text{O})_2\text{NR}_2$, $-\text{S}(\text{O})\text{R}$, $-\text{S}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})\text{OR}$, $-\text{C}(\text{O})\text{NR}_2$, $-\text{C}(\text{O})\text{N}(\text{R})\text{OR}$, $-\text{OC}(\text{O})\text{R}$, $-\text{OC}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{O})\text{OR}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{R}$, $-\text{N}(\text{R})\text{C}(\text{O})\text{NR}_2$, $-\text{N}(\text{R})\text{C}(\text{NR})\text{NR}_2$, $-\text{N}(\text{R})\text{S}(\text{O})_2\text{NR}_2$, or $-\text{N}(\text{R})\text{S}(\text{O})_2\text{R}$ or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each R is independently hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or: two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur; wherein each hydrogen bound to carbon can be optionally and independently replaced by deuterium; and each instance of m , n , p , q , and r is independently 0, 1, 2, 3, or 4.

[0006b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0006c] In yet another aspect, the present disclosure refers to the compound disclosed herein, or the pharmaceutical composition disclosed herein for use as a medicament.

[0006d] In a further aspect, the present disclosure refers to a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for inhibiting TYK2 in a biological sample.

[0006e] In another aspect, the present disclosure refers to a use of a pharmaceutical composition disclosed herein, or the compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an TYK2-mediated disorder, disease, or condition in a patient.

[0006f] In yet another aspect, the present disclosure refers to a pharmaceutical composition disclosed herein, or the compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in inhibiting TYK2 in a biological sample, or treating an TYK2-mediated disorder, disease, or condition.

[0007] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with regulation of signaling pathways implicating TYK2 kinases. Such diseases, disorders, or conditions include those described herein.

[0008] Compounds provided by this disclosure are also useful for the study of TYK2 enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new TYK2 inhibitors or other regulators of kinases, signaling pathways, and cytokine levels *in vitro* or *in vivo*.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

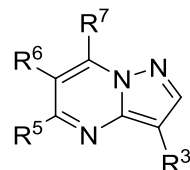
[0009] Compounds of the present invention, and compositions thereof, are useful as inhibitors of TYK2 protein kinase.

[0010] The pseudokinase binding pocket of TYK2 contains a plurality of hydration sites, each of which is occupied by a single molecule of water. Each of these water molecules has a stability rating associated with it. As used herein, the term “stability rating” refers to a numerical calculation which incorporates the enthalpy, entropy, and free energy values associated with each

CLAIMS

We claim:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R³ is -C(O)NH₂; -C(O)NHR^{3A}; -C(O)N(R^{3A})₂; or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with m instances of R^{3B};

R⁵ is hydrogen, or -L¹-R^{5A};

R⁶ is hydrogen, R^A, or R^B;

or R⁵ and R⁶ are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by R^{5A} and n instances of R^C;

R⁷ is hydrogen, halogen, -NH₂, -NHR^{7A}, or -NHC(O)R^{7A};

or R⁶ and R⁷ are taken together with their intervening atoms to form a 4-7 membered partially unsaturated, or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur; wherein said ring is substituted by p instances of R^C;

L¹ is a covalent bond or a C₁₋₄ bivalent saturated or unsaturated, straight or branched hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -C(R^{5B})₂-, -CH(R^{5B})-, -N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)₂-, -S(O)₂N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)-, or -S(O)₂-;

R^{3A} and R^{7A} are each independently R^B, and are each substituted by q instances of R^C;

R^{5A} and each instance of R^{5B} are each independently R^A or R^B, and are each substituted by r instances of R^C;

each instance of R^A is independently oxo, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR,

-OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂,
-N(R)S(O)₂NR₂, or -N(R)S(O)₂R;

each instance of R^B is independently C₁₋₆ aliphatic; phenyl; a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; a 3-7 membered saturated or partially unsaturated carbocyclic ring; a 3-7 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur; or a 7-12 membered saturated or partially unsaturated bicyclic heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each instance of R^C is independently oxo, halogen, -CN, -NO₂, -OR, -SR, -NR₂, -S(O)₂R, -S(O)₂NR₂, -S(O)R, -S(O)NR₂, -C(O)R, -C(O)OR, -C(O)NR₂, -C(O)N(R)OR, -OC(O)R, -OC(O)NR₂, -N(R)C(O)OR, -N(R)C(O)R, -N(R)C(O)NR₂, -N(R)C(NR)NR₂, -N(R)S(O)₂NR₂, or -N(R)S(O)₂R or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

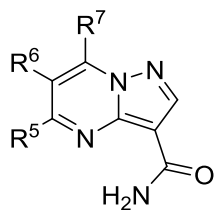
each R is independently hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

two R groups on the same nitrogen are taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen, and sulfur;

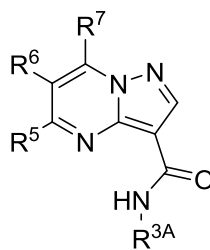
wherein each hydrogen bound to carbon can be optionally and independently replaced by deuterium; and

each instance of m, n, p, q, and r is independently 0, 1, 2, 3, or 4.

2. The compound of claim 1 of one of formulas **II** or **III**:



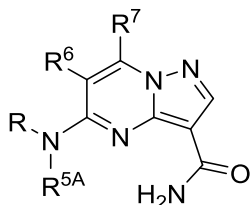
II



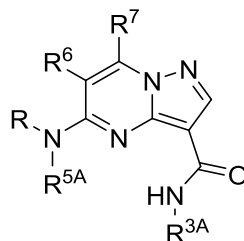
III

or a pharmaceutically acceptable salt thereof.

3. The compound of any one of claims 1 or 2 of formula **V** or **VI**:



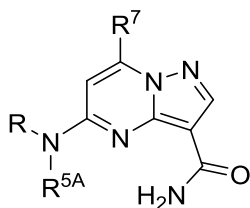
V



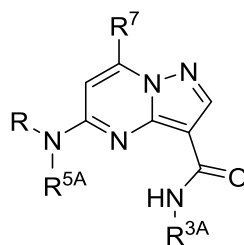
VI

or a pharmaceutically acceptable salt thereof.

4. The compound of any one of claims 1-3 of formula **V-a** or **VI-a**:



V-a

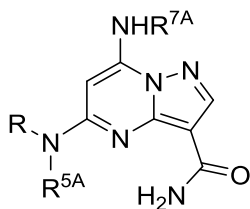


VI-a

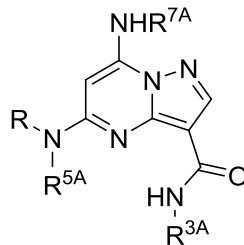
or a pharmaceutically acceptable salt thereof.

5. The compound of any one of claims 1-4 wherein R^7 is $-NH_2$ or $-NHR^{7A}$, or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-5 of one of formulas V-c or VI-c:



V-c



VI-c

or a pharmaceutically acceptable salt thereof.

7. The compound of any one of claims 1-6 wherein each of R^{3A} and R^{7A} is independently R^B, and is substituted by q instances of R^C, provided that neither of R^{3A} or R^{7A} is phenyl.
8. The compound of any one of claims 1-7 wherein R^{7A} is C₁₋₆ aliphatic.
9. The compound of any one of claims 1-8 wherein R^{7A} is methyl.
10. The compound of any one of claims 1-9, selected from those depicted in Table 1 of the specification, or a pharmaceutically acceptable salt thereof.
11. A pharmaceutical composition comprising a compound according to any one of claims 1-10, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
12. The compound of claims 1 to 10, or the pharmaceutical composition of claim 11 for use as a medicament.
13. Use of a compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 11, in the manufacture of a medicament for inhibiting TYK2 in a biological sample.

14. Use of a pharmaceutical composition of claim 11, or the compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating an TYK2-mediated disorder, disease, or condition in a patient.
15. The use of claim 14 wherein the disorder is selected from an autoimmune disorder, an inflammatory disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation.
16. The use of claim 15 wherein the disorder is an autoimmune disorder.
17. The use of claim 16 wherein the autoimmune disorder is selected from type 1 diabetes, ankylosing spondylitis, cutaneous lupus erythematosus, systemic lupus erythematosus, multiple sclerosis, systemic sclerosis, psoriasis, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.
18. The use of claim 15 wherein the disorder is an inflammatory disorder.
19. The use of claim 18 wherein the inflammatory disorder is selected from rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, psoriasis, Crohn's disease, ulcerative colitis, and inflammatory bowel disease.
20. The use of claim 15 wherein the disorder is a proliferative disorder.
21. The use of claim 20 wherein the proliferative disorder is a hematological cancer.
22. The use of claim 20 wherein the proliferative disorder is a leukemia.
23. The use of claim 22 wherein the leukemia is a T-cell leukemia.

24. The use of claim 23 wherein the T-cell leukemia is T-cell acute lymphoblastic leukemia (T-ALL).
25. The use of claim 20 wherein the proliferative disorder is associated with one or more activating mutations in TYK2.
26. The use of claim 15 wherein the disorder is associated with transplantation.
27. The use of claim 26 wherein the disorder is transplant rejection or graft versus host disease.
28. The use of claim 15 wherein the disorder is an endocrine disorder.
29. The use of claim 28 wherein the endocrine disorder is polycystic ovary syndrome, Crouzon's syndrome, or type 1 diabetes.
30. The use of claim 15 wherein the disorder is a neurological disorder.
31. The use of claim 30 wherein the neurological disorder is Alzheimer's disease.
32. The use of claim 14 wherein the disorder is associated with type I interferon, IL-10, IL-12, or IL-23 signaling.
33. A pharmaceutical composition of claim 11, or the compound of any one of claims 1-10, or a pharmaceutically acceptable salt thereof, for use in inhibiting TYK2 in a biological sample, or treating an TYK2-mediated disorder, disease, or condition.