

TYK2 PSEUDOKINASE LIGANDS

CROSS-REFERENCE

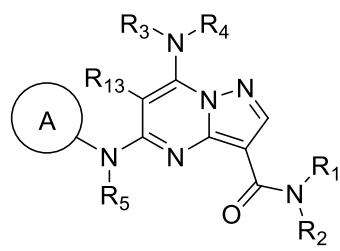
[0001] This application claims benefit of U.S. Provisional Application No. 62/802,642, filed on February 7, 2019, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. The four JAK family members are Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), Janus kinase 3 (JAK3), and Tyrosine kinase 2 (TYK2) and have been shown to be key components of cytokine-mediated effects. Unlike JAK1 deficient mice, TYK2 deficient mice are viable and the TYK2 deficiency has been shown to be protective in various models of autoimmunity.

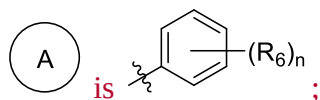
SUMMARY ~~OF THE INVENTION~~

[0002a] In an aspect of the present disclosure, there is provided a compound having the structure of Formula (I):



Formula (I):

wherein:



R₁ is hydrogen, C₁-C₆alkyl, or C₃-C₆cycloalkyl, wherein C₁-C₆alkyl or C₃-C₆cycloalkyl are optionally substituted with 1, 2, or 3 R₉;

R₂ is hydrogen or C₁-C₆alkyl;

R₃ and R₄ are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, and C₂-C₉heterocycloalkyl;

R₅ is hydrogen;

each R₆ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy and two R₆ are combined to form a heterocycloalkyl ring;

each R₉ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆heteroalkyl, oxo, -OR₁₁, -N(R₁₁)₂, -CN, -C(=O)R₁₂, -C(=O)OR₁₁, -C(=O)N(R₁₁)₂, -NR₁₁C(=O)R₁₂, -NR₁₁S(=O)₂R₁₂, -S(=O)₂R₁₂, and -S(=O)₂N(R₁₁)₂;

each R₁₁ is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, -OR₁₄, -N(R₁₄)₂, -C(=O)OR₁₄, and -C(=O)N(R₁₄)₂;

each R₁₂ is independently selected from C₁-C₆alkyl and C₁-C₆heteroalkyl;

R₁₃ is hydrogen, halogen, or -CN;

each R₁₄ is independently selected from hydrogen, C₁-C₆alkyl, and C₁-C₆haloalkyl; and
n is 2, 3, or 4;

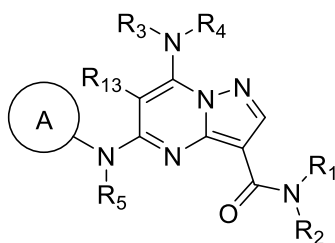
or a pharmaceutically acceptable salt or solvate thereof.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0002c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating an inflammatory or autoimmune disease in a patient in need thereof.

[0002d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

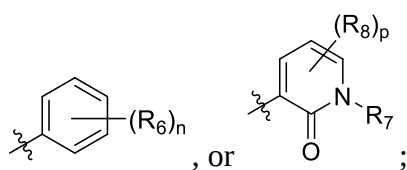
[0003] In one ~~aspect~~example, provided herein are compounds of Formula I:



Formula (I);

wherein:

 is a 5- or 6-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆,



R₁ is hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl, wherein C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl are optionally substituted with 1, 2, or 3 R₉;

R₂ is hydrogen or C₁-C₆alkyl;

R₃ and R₄ are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, and C₂-C₉heterocycloalkyl;

R₅ is hydrogen or C₁-C₆alkyl;

each R₆ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, -OR₁₁, -N(R₁₁)₂, -CN, -C(=O)R₁₂, -C(=O)OR₁₁, -C(=O)N(R₁₁)₂, -NR₁₁C(=O)R₁₂, -NR₁₁S(=O)₂R₁₂, -S(=O)₂R₁₂, and -S(=O)₂N(R₁₁)₂, wherein C₂-C₉heterocycloalkyl or C₂-C₉heteroaryl are optionally substituted with 1, 2, or 3 R₁₀; or two R₆ are combined to form a heterocycloalkyl ring optionally substituted with 1, 2, or 3 R₁₀;

R₇ is hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl, wherein C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl are optionally substituted with 1, 2, or 3 R₁₀;

each R₈ is independently selected from halogen, C₁-C₆alkyl, -C₁-C₆alkyl-OH, C₁-C₆haloalkyl, C₁-C₆alkoxy, -OR₁₁, -N(R₁₁)₂, -CN, -C(=O)R₁₂, -C(=O)OR₁₁, -C(=O)N(R₁₁)₂, -NR₁₁C(=O)R₁₂, -NR₁₁S(=O)₂R₁₂, -S(=O)₂R₁₂, and -S(=O)₂N(R₁₁)₂;

each R₉ and each R₁₀ is each independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆heteroalkyl, oxo, -OR₁₁, -N(R₁₁)₂, -CN, -C(=O)R₁₂, -C(=O)OR₁₁, -C(=O)N(R₁₁)₂, -NR₁₁C(=O)R₁₂, -NR₁₁S(=O)₂R₁₂, -S(=O)₂R₁₂, and -S(=O)₂N(R₁₁)₂;

each R₁₁ is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, -OR₁₄, -N(R₁₄)₂, -C(=O)OR₁₄, and -C(=O)N(R₁₄)₂;

each R₁₂ is independently selected from C₁-C₆alkyl and C₁-C₆heteroalkyl;

R₁₃ is hydrogen, halogen, or -CN;

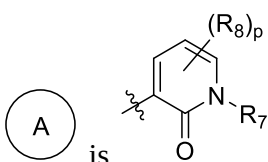
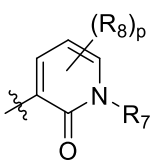
each R₁₄ is independently selected from hydrogen, C₁-C₆alkyl, and C₁-C₆haloalkyl;

n is 0, 1, 2, 3, 4, or 5; and

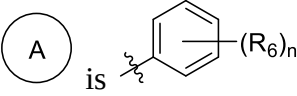
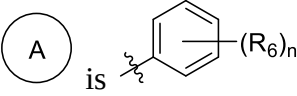
p is 0, 1, 2, or 3;

or a pharmaceutically acceptable salt or solvate thereof.

[0004] In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable

salt or solvate thereof, wherein  is . In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is C₂-C₉heteroaryl optionally substituted with 1, 2, or 3 R₁₀. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl, wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl,

isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl are optionally substituted with 1, 2, or 3 R₁₀. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₇ is selected from pyrazolyl, pyridinyl, and pyridazinyl, wherein pyrazolyl, pyridinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R₁₀. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R₁₀ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R₈ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R₈ is halogen. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein p is 0. In some [embodimentexamples](#) is a compound of Formula (I), or a

pharmaceutically acceptable salt or solvate thereof, wherein  is . In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or

solvate thereof, wherein  is a 5- or 6-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically

acceptable salt or solvate thereof, wherein  is a 5-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a

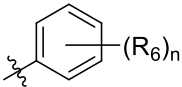
pharmaceutically acceptable salt or solvate thereof, wherein  is a 5-membered heteroaryl ring selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, and isothiazolyl, wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, and isothiazolyl are optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or

solvate thereof, wherein  is a 5-membered heteroaryl ring selected from pyrazolyl and isothiazolyl, wherein pyrazolyl and isothiazolyl are optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate

thereof, wherein  is a 6-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or

solvate thereof, wherein  is a 6-membered heteroaryl ring selected from pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a

pharmaceutically acceptable salt or solvate thereof, wherein  is pyridinyl optionally substituted with 1, 2, or 3 R₆. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically

acceptable salt or solvate thereof, wherein  is . In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1, 2, 3, or 4. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R₆ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein two R₆ are combined to form a heterocycloalkyl ring. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, C₁-C₆alkyl or C₃-C₆cycloalkyl, wherein C₁-C₆alkyl or C₃-C₆cycloalkyl are optionally substituted with 1, 2, or 3 R₉. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl optionally substituted with 1, 2, or 3 R₉. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl substituted with 1, 2, or 3 R₉ and each R₉ is independently selected from halogen, -OR₁₁, and -N(R₁₁)₂. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl substituted with 1, 2, or 3 R₉ and each R₉ is -OH. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is unsubstituted C₁-C₆alkyl. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is unsubstituted C₃-C₆cycloalkyl. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen. In some [embodimentexamples](#) is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is C₁-C₆alkyl. In some

embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ and R₄ are independently selected from hydrogen and C₁-C₆alkyl. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is C₁-C₆alkyl. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -CH₃. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen. In some embodimentexample is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is C₁-C₆alkyl. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is hydrogen. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is halogen. In some embodimentexamples is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is C₁-C₆alkyl.

[0005] In another aspectexample described herein is a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

[0006] In another aspectexample described herein is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodimentexamples is a method of treating an inflammatory or autoimmune disease in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein the disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, intestinal bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis, vitiligo, and atopic dermatitis.

INCORPORATION BY REFERENCE

[0007] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

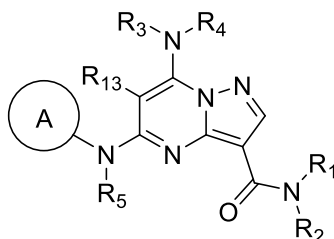
Definitions

[0008] In the context of this disclosure, a number of terms shall be utilized.

CLAIMS

WHAT IS CLAIMED IS:

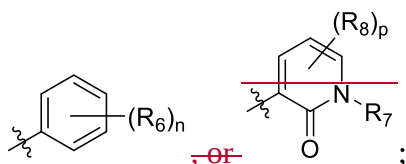
1. A compound having the structure of Formula (I):



Formula (I);

wherein:

 is ~~a 5- or 6- membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆,~~



R₁ is hydrogen, C₁-C₆alkyl, or C₃-C₆cycloalkyl, ~~C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl,~~ wherein C₁-C₆alkyl or, C₃-C₆cycloalkyl, ~~C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl~~ are optionally substituted with 1, 2, or 3 R₉;

R₂ is hydrogen or C₁-C₆alkyl;

R₃ and R₄ are independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, C₃-C₆cycloalkyl, and C₂-C₉heterocycloalkyl;

R₅ is hydrogen ~~or C₁-C₆alkyl~~;

each R₆ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy, ~~C₁-C₆haloalkoxy, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, OR₁₁, N(R₁₁)₂, CN, C(=O)R₁₂, C(=O)OR₁₁, C(=O)N(R₁₁)₂, NR₁₁C(=O)R₁₂, NR₁₁S(=O)₂R₁₂, S(=O)₂R₁₂, and S(=O)₂N(R₁₁)₂,~~ wherein ~~C₂-C₉heterocycloalkyl or C₂-C₉heteroaryl are optionally substituted with 1, 2, or 3 R₁₀; or~~ and two R₆ are combined to form a heterocycloalkyl ring ~~optionally substituted with 1, 2, or 3 R₁₀;~~

R₇ is ~~hydrogen, C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl,~~ wherein ~~C₁-C₆alkyl, C₃-C₆cycloalkyl, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, or C₆-C₁₀aryl~~ are optionally substituted with 1, 2, or 3 R₁₀;

each R₈ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆alkyl-OH, C₁-C₆haloalkyl, ~~C₁-C₆alkoxy, OR₁₁, N(R₁₁)₂, CN, C(=O)R₁₂, C(=O)OR₁₁, C(=O)N(R₁₁)₂, NR₁₁C(=O)R₁₂, NR₁₁S(=O)₂R₁₂, S(=O)₂R₁₂, and S(=O)₂N(R₁₁)₂;~~

each R₉ ~~is and each R₁₀ is each~~ independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆heteroalkyl, oxo, -OR₁₁, -N(R₁₁)₂, -CN, -C(=O)R₁₂, -C(=O)OR₁₁, -C(=O)N(R₁₁)₂, -NR₁₁C(=O)R₁₂, -NR₁₁S(=O)₂R₁₂, -S(=O)₂R₁₂, and -S(=O)₂N(R₁₁)₂;

each R₁₁ is independently selected from hydrogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, and phenyl, wherein phenyl is optionally substituted with 1, 2, or 3 groups selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, C₁-C₆alkoxy, C₁-C₆haloalkoxy, C₂-C₉heterocycloalkyl, C₂-C₉heteroaryl, -OR₁₄, -N(R₁₄)₂, -C(=O)OR₁₄, and -C(=O)N(R₁₄)₂;

each R₁₂ is independently selected from C₁-C₆alkyl and C₁-C₆heteroalkyl;

R₁₃ is hydrogen, halogen, or -CN;

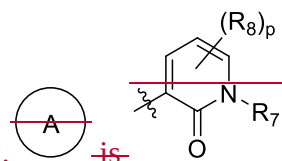
each R₁₄ is independently selected from hydrogen, C₁-C₆alkyl, and C₁-C₆haloalkyl; and

n is ~~0, 1,~~ 2, 3, or 4, ~~or 5;~~ and

~~p is 0, 1, 2, or 3;~~

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein n



is 2 and two R₆ are combined to form a heterocycloalkyl ring.

~~3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein~~

~~R₇ is C₂-C₉heteroaryl optionally substituted with 1, 2, or 3 R₁₀;~~

~~4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt or solvate~~

~~thereof, wherein R₇ is selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl, wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, and triazinyl are optionally substituted with 1, 2, or 3 R₁₀;~~

~~5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt or solvate~~

~~thereof, wherein R₇ is selected from pyrazolyl, pyridinyl, and pyridazinyl, wherein pyrazolyl, pyridinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R₁₀;~~

~~6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt or solvate~~

~~thereof, wherein each R₁₀ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy.~~

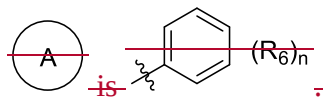
7. ~~The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein each R₈ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy.~~
8. ~~The compound of any one of claims 1-7, or a pharmaceutically acceptable salt or solvate thereof, wherein each R₈ is halogen.~~
9. ~~The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 1.~~
10. ~~The compound of any one of claims 1-6, or a pharmaceutically acceptable salt or solvate thereof, wherein p is 0.~~
11. ~~The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 5- or 6-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆.~~
12. ~~The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 5-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆.~~
13. ~~The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 5-membered heteroaryl ring selected from oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, and isothiazolyl, wherein oxazolyl, thiazolyl, pyrazolyl, furanyl, thienyl, pyrrolyl, imidazolyl, triazolyl, isoxazolyl, and isothiazolyl are optionally substituted with 1, 2, or 3 R₆.~~
14. ~~The compound of claim 12, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 5-membered heteroaryl ring selected from pyrazolyl and isothiazolyl, wherein pyrazolyl and isothiazolyl are optionally substituted with 1, 2, or 3 R₆.~~
15. ~~The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 6-membered heteroaryl ring optionally substituted with 1, 2, or 3 R₆.~~
16. ~~The compound of claim 15, or a pharmaceutically acceptable salt or solvate thereof, wherein~~
 ~~is a 6-membered heteroaryl ring selected from pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl, wherein pyridinyl, pyrimidinyl, pyrazinyl, and pyridazinyl are optionally substituted with 1, 2, or 3 R₆.~~

~~17. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, wherein~~



~~is pyridinyl optionally substituted with 1, 2, or 3 R₆.~~

~~18. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein~~



~~19. The compound of claim 18, or a pharmaceutically acceptable salt or solvate thereof, wherein
n is 1, 2, 3, or 4.~~

~~20. The compound of any one of claims 11-19, or a pharmaceutically acceptable salt or solvate thereof, wherein each R₆ is independently selected from halogen, C₁-C₆alkyl, C₁-C₆haloalkyl, and C₁-C₆alkoxy.~~

~~21. The compound of any one of claims 11-19, or a pharmaceutically acceptable salt or solvate thereof, wherein two R₆ are combined to form a heterocycloalkyl ring.~~

~~22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen, C₁-C₆alkyl, or C₃-C₆cycloalkyl, wherein C₁-C₆alkyl or C₃-C₆cycloalkyl are optionally substituted with 1, 2, or 3 R₉.~~

~~23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl optionally substituted with 1, 2, or 3 R₉.~~

~~24.3.~~ The compound of ~~any one of claims 1-23~~claim 1 or claim 2, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl substituted with 1, 2, or 3 R₉ and each R₉ is independently selected from halogen, -OR₁₁, and -N(R₁₁)₂.

~~25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is C₁-C₆alkyl substituted with 1, 2, or 3 R₉ and each R₉ is -OH.~~

~~26.4.~~ The compound of any one of claims 1-~~233~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is unsubstituted C₁-C₆alkyl.

~~27.5.~~ The compound of any one of claims 1-~~224~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is unsubstituted C₃-C₆cycloalkyl.

~~28. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁ is hydrogen.~~

~~29.6.~~ The compound of any one of claims 1-~~285~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is hydrogen.

~~30. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, wherein R₂ is C₁-C₆alkyl.~~

~~31.7.~~ The compound of any one of claims 1-~~306~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ and R₄ are independently selected from hydrogen and C₁-C₆alkyl.

~~32.8.~~ The compound of any one of claims 1-~~317~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₃ is hydrogen.

~~33.9.~~ The compound of any one of claims 1-~~328~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is C₁-C₆alkyl.

~~34.~~ The compound of any one of claims 1-33, or a pharmaceutically acceptable salt or solvate thereof, wherein R₄ is -CH₃.

~~35.~~ The compound of any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is hydrogen.

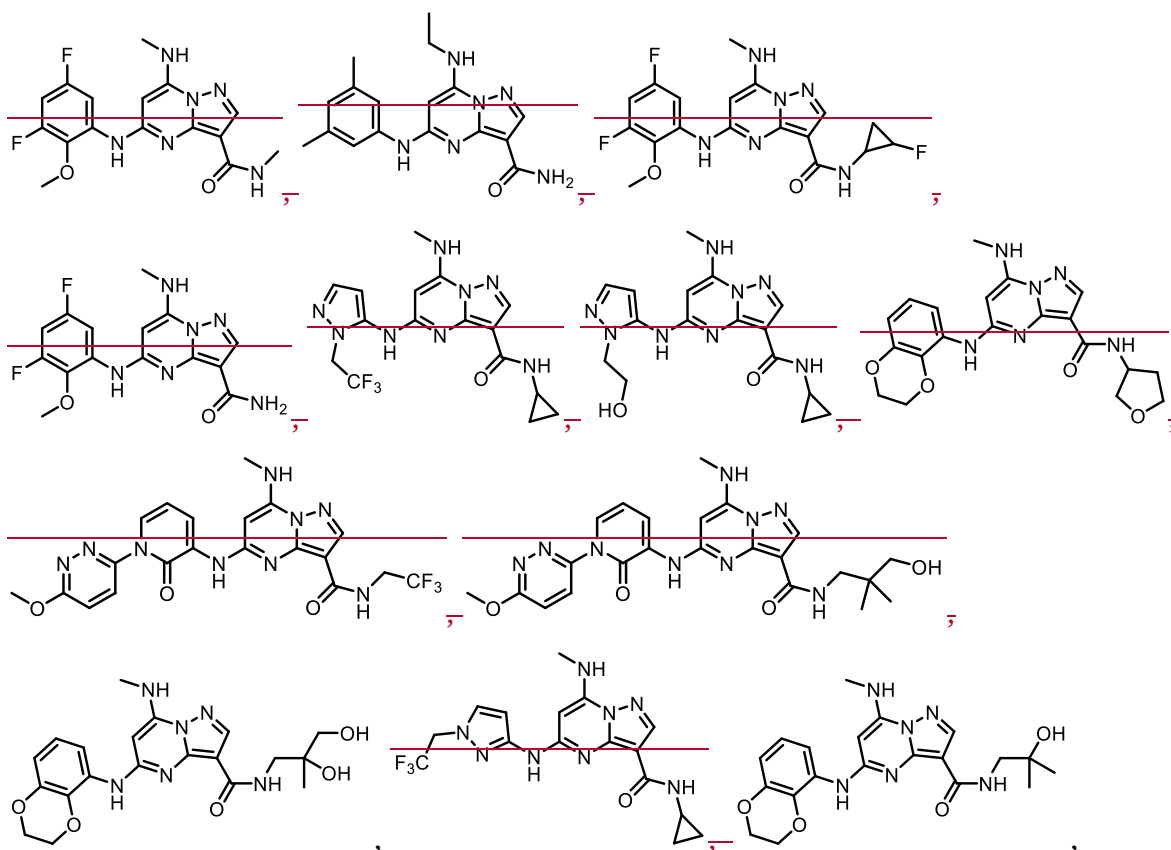
~~36.~~ The compound of any one of claims 1-34, or a pharmaceutically acceptable salt or solvate thereof, wherein R₅ is C₁-C₆alkyl.

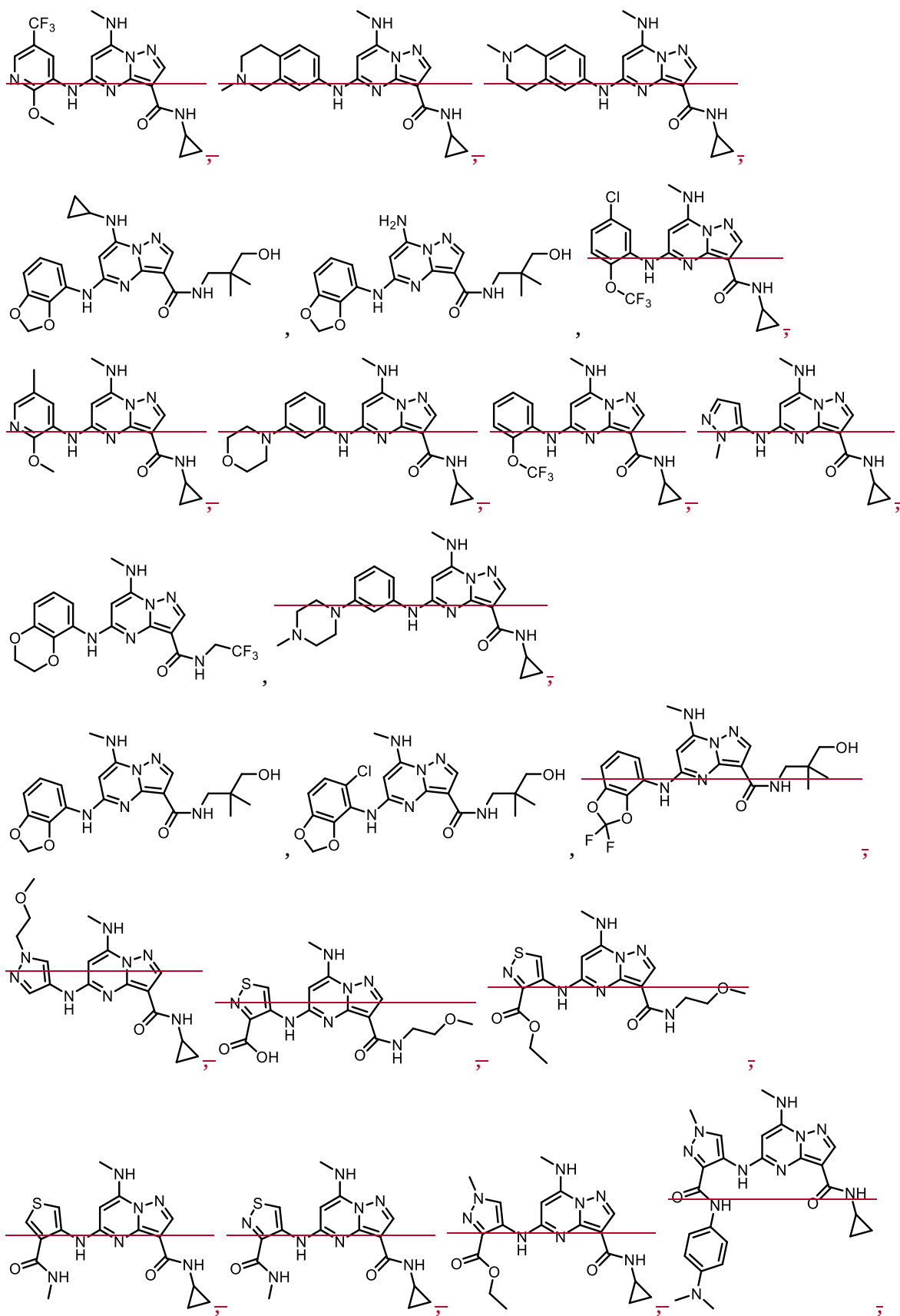
~~37.10.~~ The compound of any one of claims 1-~~369~~, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is hydrogen.

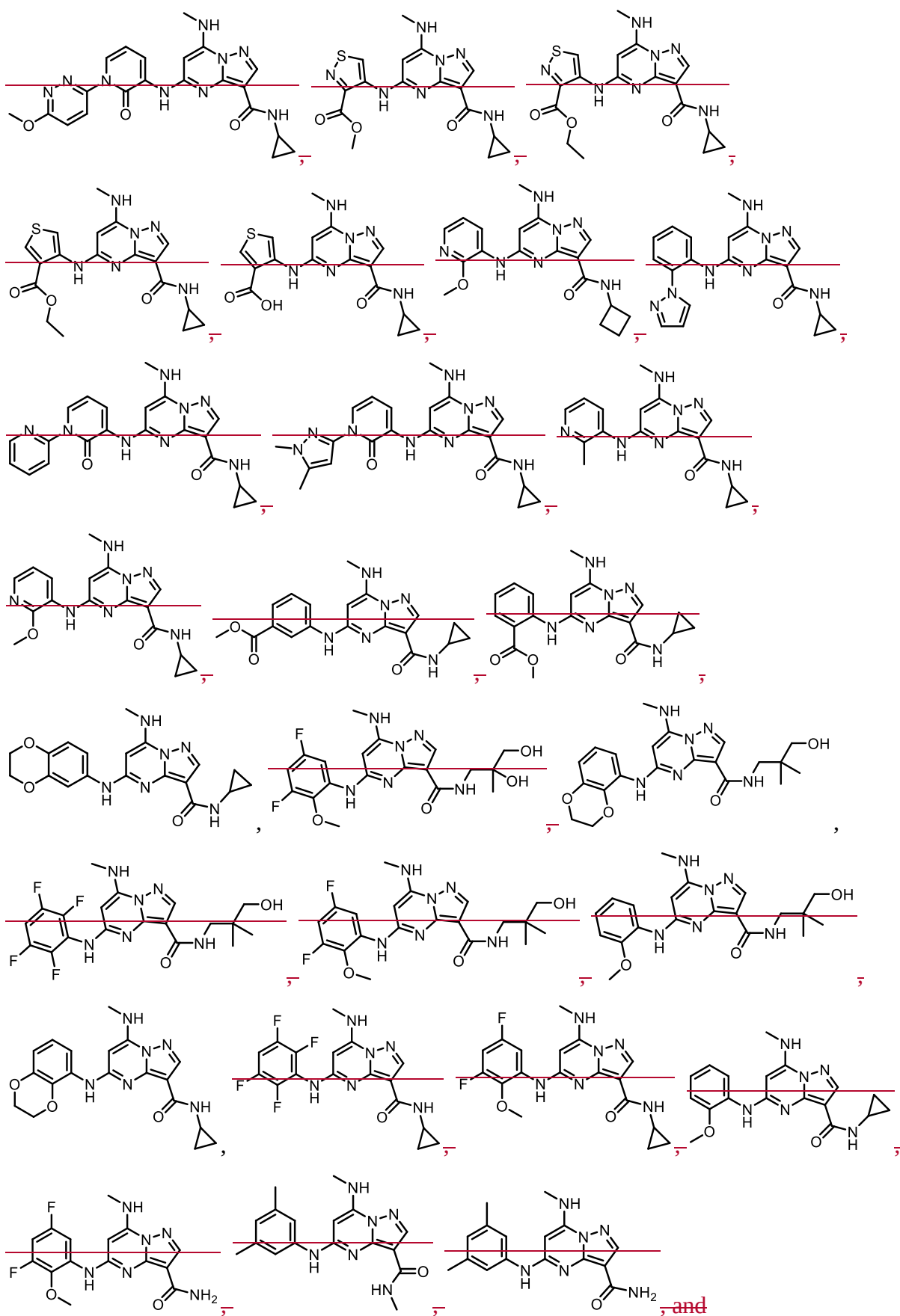
~~38.~~ The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is halogen.

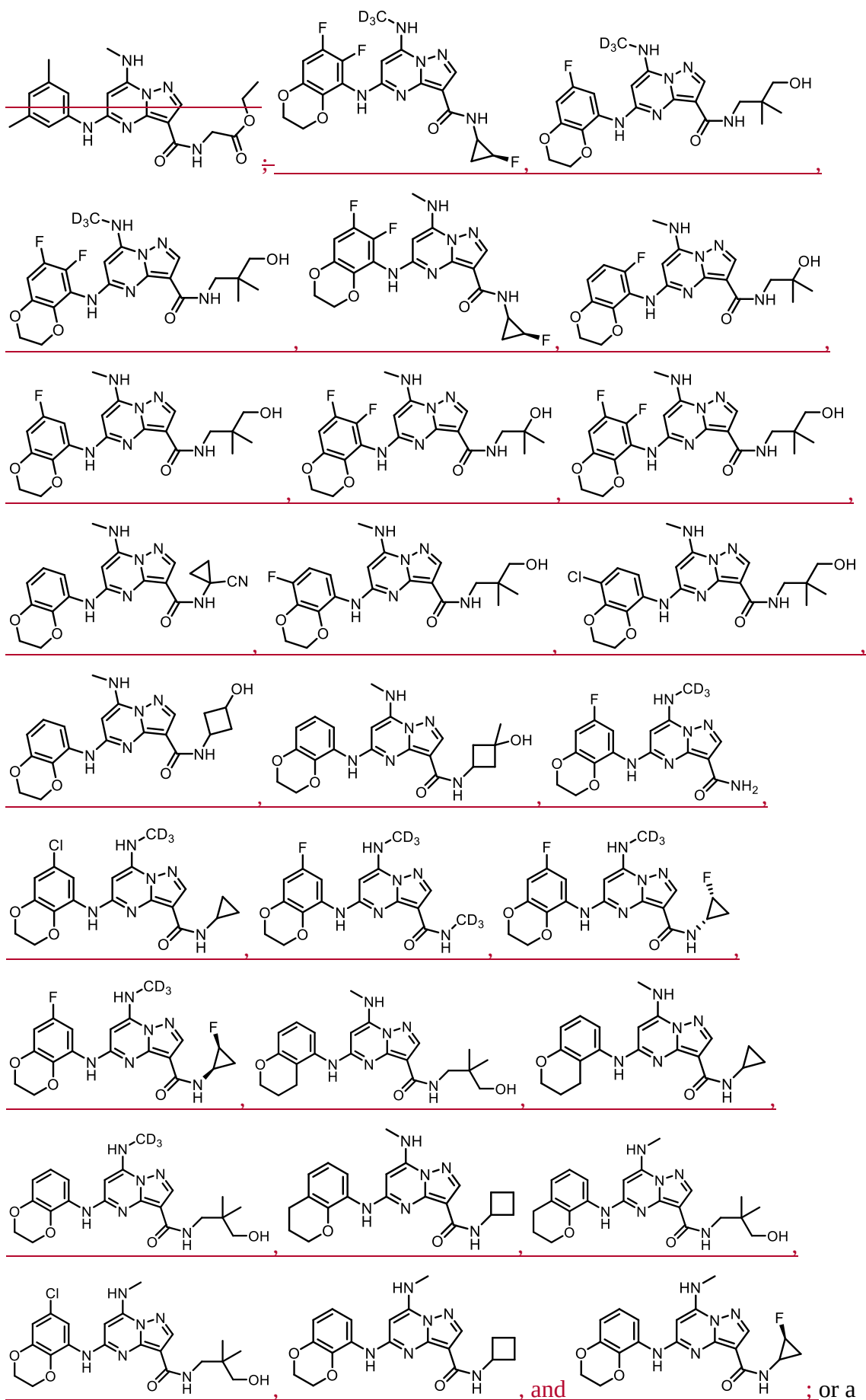
~~39.~~ The compound of any one of claims 1-36, or a pharmaceutically acceptable salt or solvate thereof, wherein R₁₃ is C₁-C₆alkyl.

~~40.11.~~ A compound of claim 1 selected from:



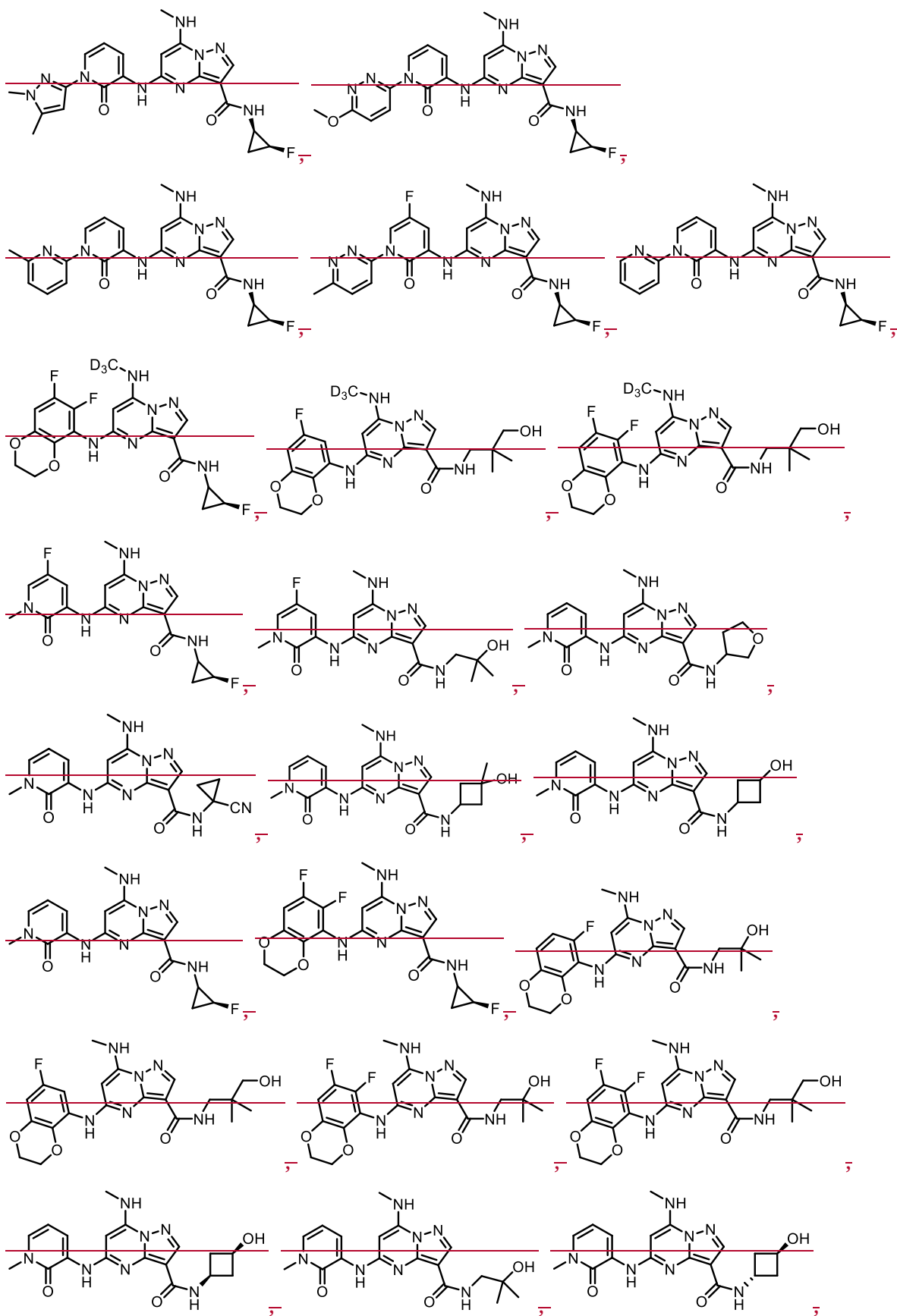


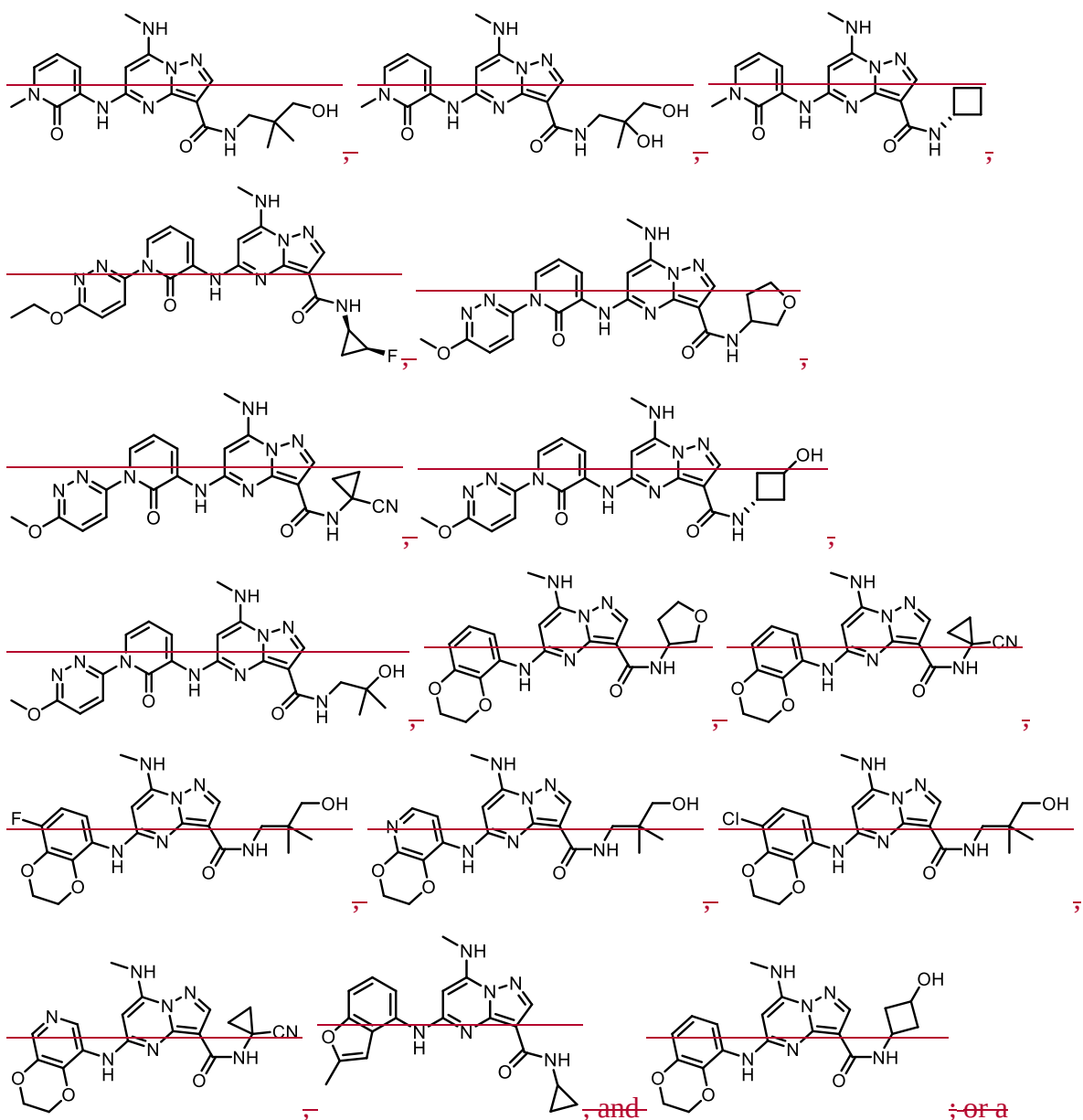




pharmaceutically acceptable salt or solvate thereof.

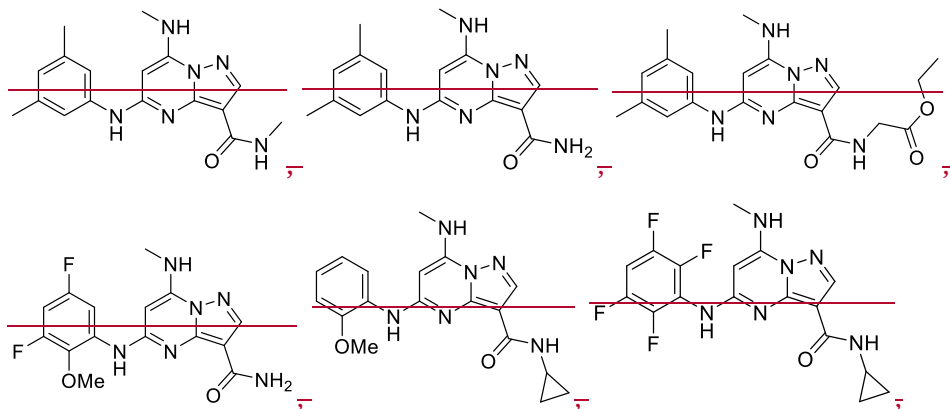
~~41. A compound selected from:~~

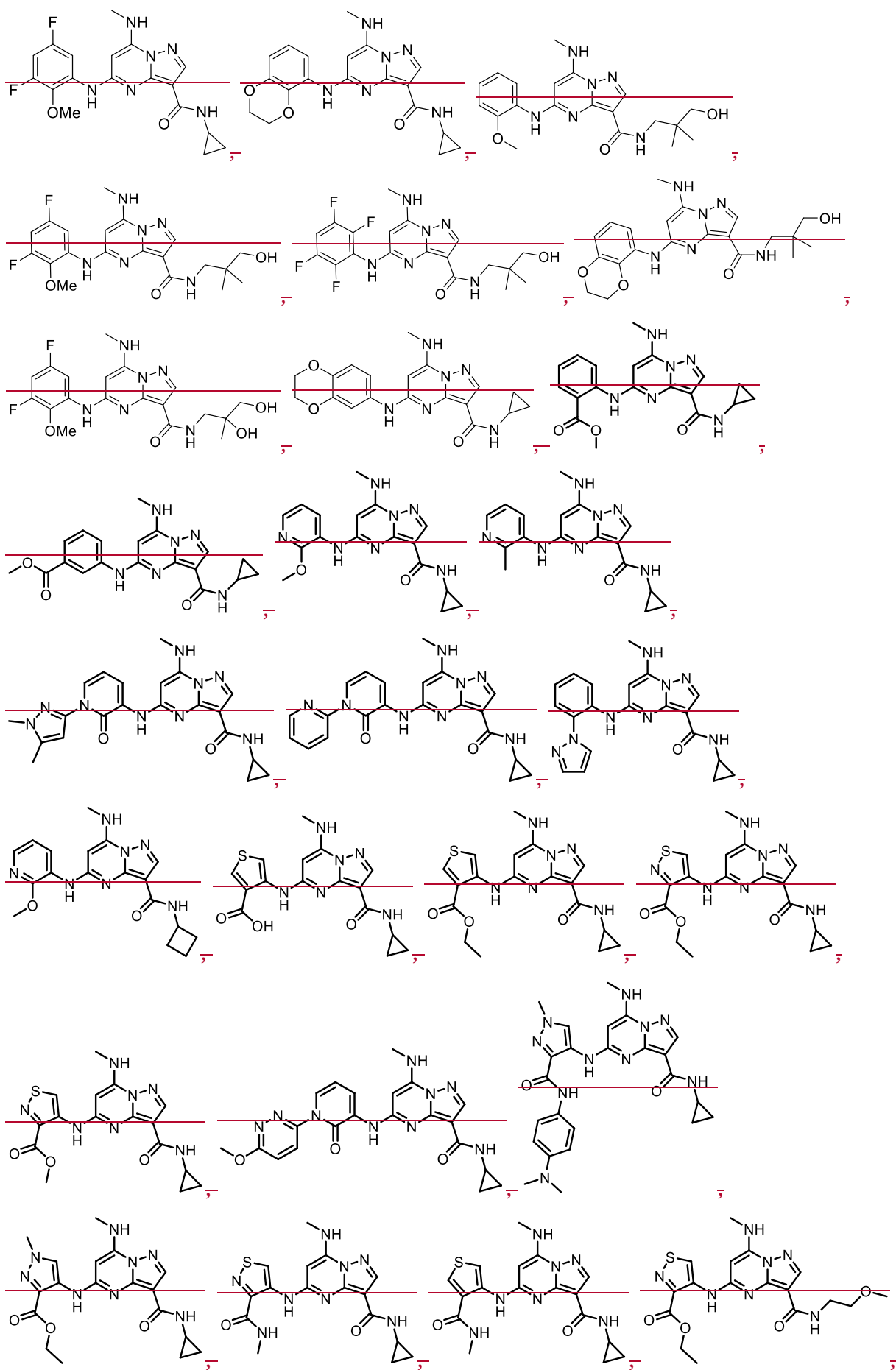


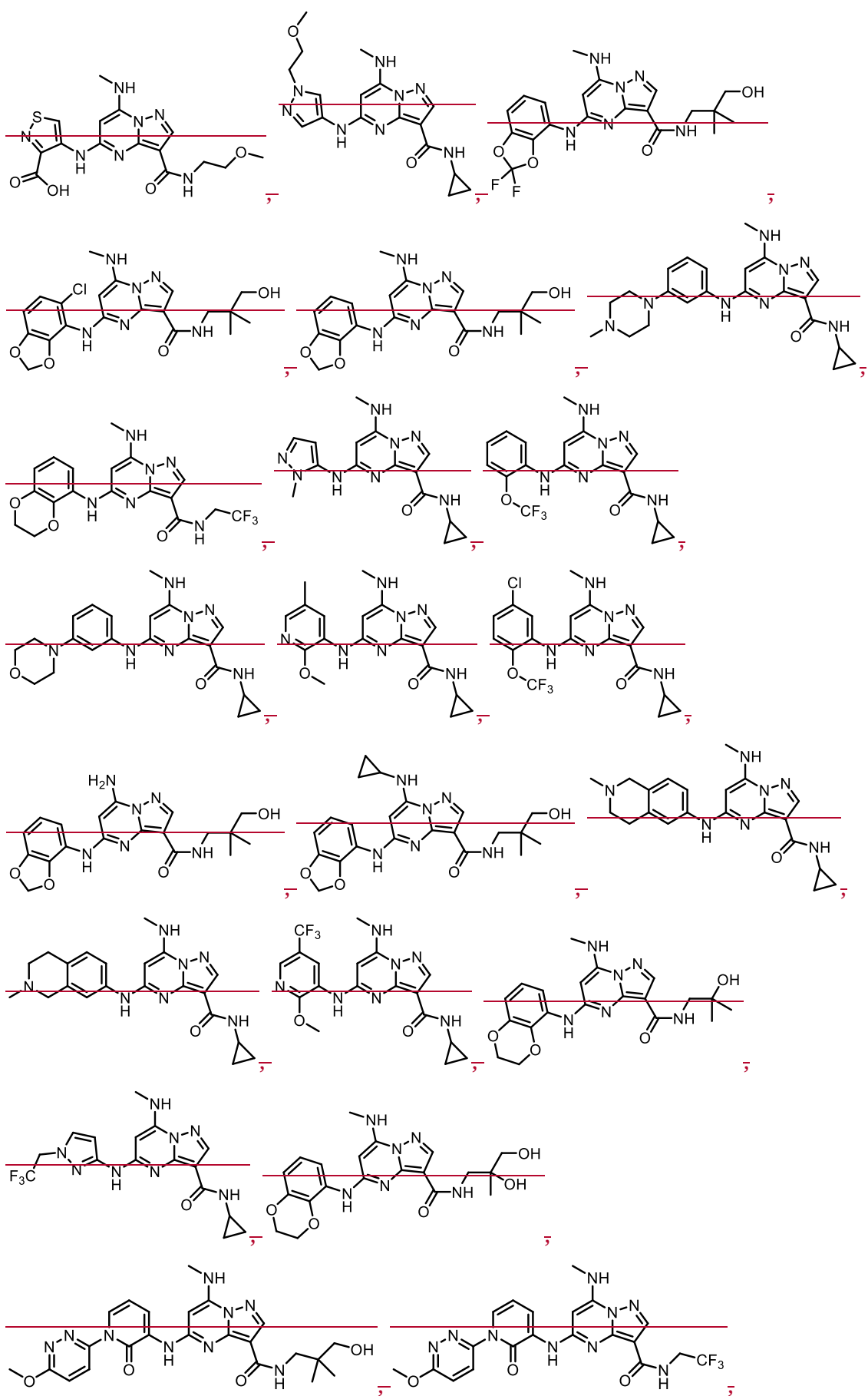


pharmaceutically acceptable salt or solvate thereof.

42. A compound selected from:











~~; or a pharmaceutically acceptable salt or~~

~~43.12.~~ A pharmaceutical composition comprising a compound of any one of claims 1-~~11~~⁴², or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

~~44.13.~~ Use of a compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for ~~A method of~~ treating an inflammatory or autoimmune disease in a patient in need thereof, ~~comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-42, or a pharmaceutically acceptable salt or solvate thereof.~~

~~45.14.~~ The ~~use~~^{method} of claim ~~13~~⁴⁴, wherein the disease is selected from rheumatoid arthritis, multiple sclerosis, psoriasis, lupus, intestinal bowel disease, Crohn's disease, ulcerative colitis, ankylosing spondylitis, vitiligo, and atopic dermatitis.

15. A compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.