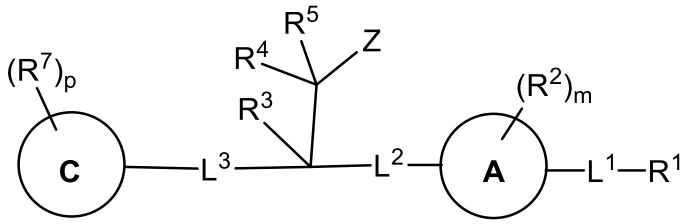
models of PD in multiple species (Bingol et al., The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. Nature 2014, 510:370-375; Bian et al., Overexpression of parkin ameliorates dopaminergic neurodegeneration induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in mice. PLoS One 2012, 7:e39953. PMC3390003; Hou et al., Parkin represses 6-hydroxydopamine-induced apoptosis via stabilizing scaffold protein p62 in PC12 cells. Acta Pharmacol Sin 2015, 36:1300-1307. PMC4635325; Lo Bianco et al., Lentiviral vector delivery of parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. Proc Natl Acad Sci USA 2004, 101:17510-17515. PMC536019; Paterna et al., DJ-1 and Parkin modulate dopamine-dependent behavior and inhibit MPTP-induced nigral dopamine neuron loss in mice. Mol Ther 2007, 15:698-704; Vercammen et al., Parkin protects against neurotoxicity in the 6-hydroxydopamine rat model for Parkinson's disease. Mol Ther 2006, 14:716-723; Yasuda et al., Parkin-mediated protection of dopaminergic neurons in a chronic MPTP-minipump mouse model of Parkinson disease. J Neuropathol Exp Neurol 2011, 70:686-697; Yasuda et al., Neuronal specificity of alpha-synuclein toxicity and effect of Parkin co-expression in primates. Neuroscience 2007, 144:743-753; Liang et al., USP30 deubiquitylates mitochondrial Parkin substrates and restricts apoptotic cell death. EMBO Rep 2015, 16:618-627. PMC4428036.). PINK1/Parkin-dependent linear ubiquitination of proteins on the outer mitochondrial membrane (OMM) leads to removal of damaged protein and mitochondria through fission of mitochondrial derived vesicles (MDVs) or recruitment of phagophores to begin the mitophagy process. The deubiquitinating (DUB) enzyme, USP30, is present specifically on the OMM (unlike other DUBs such as USP8,15 and 35 implicated in mitochondrial quality control), and acts as a counterbalance to this process by specifically removing ubiquitin chains on parkin substrates. Involvement of USP30 in regulating mitophagy has been well established through functional genomic studies in mammalian, including human, cells and flies, further validating it as a promising target (Bingol et al., 2014). Without wishing to be bound by any particular theory, it is believed that USP30 inhibitors will promote the clearance of damaged mitochondria to restore mitochondrial homeostasis, attenuating the pathogenic cascade associated with PD pathogenesis.

## SUMMARY

**[0006a]** In an aspect of the present disclosure, there is provided a compound of formula **I**:




**I**

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$L^1$ is a covalent bond or a $C_{1-3}$ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by –C($CF_3$)H–, –N(R)–, –O–, –C(O)–, –OC(O)–, –C(O)O–, –C(O)N(R)–, –N(R)C(O)–, –S(O)–, –$S(O)_2$–, –S(O)N(R)–, –$S(O)_2$N(R)–, or –S(O)(R)=N–;

each R is independently hydrogen or an optionally substituted $C_{1-3}$ aliphatic group; or:

two R groups on the same nitrogen are optionally 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, or sulfur; or

an R group and $R^1$ on the same nitrogen are optionally 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, or sulfur;

$R^1$ is hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected

from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^2$ is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or an optionally substituted $C_{1-6}$ aliphatic group; or

two $R^2$ on the same carbon are optionally taken together to form =O;

$L^2$ is selected from the group consisting of $–C(O)N(R')–$, $–CH_2O–$, $–CH_2N(R')–$, $–C(OH)(H)CH_2N(R')–$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a $C_{1-3}$ aliphatic group;

$L^3$ is selected from the group consisting of $–C(O)N(R")–$, $–OC(O)N(R")–$, $–CH_2O–$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R" is hydrogen or a $C_{1-3}$ aliphatic group;

$R^3$ is hydrogen or $C_{1-3}$ aliphatic; or:

$R^3$ and $R^4$ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

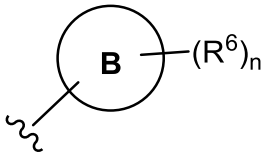
$R^3$ and $R^5$ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

$R^4$ is hydrogen or $C_{1-3}$ aliphatic;

$R^5$ is hydrogen or $C_{1-3}$ aliphatic;

Z is:

(a) selected from an optionally substituted $C_{1-6}$ aliphatic group, and –OR;

(b) 

;

(c) taken together with $R^4$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$;

(d) taken together with $R^5$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$; or

(e) taken together with R" and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of $L^3$, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$;

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^6$ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, –C(O)R, –C(O)OR, or an optionally substituted $C_{1-6}$ aliphatic group; or:

two $R^6$ on the same carbon are optionally taken together to form =O;

an $R^6$ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an $R^6$ group and $R^3$ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an $R^6$ group and R" group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^7$ is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted $C_{1-6}$ aliphatic group; or

two $R^7$ on the same carbon are optionally taken together to form =O;

each of m, n, and p is independently 0, 1, 2, 3 or 4; and

the compound is other than one depicted in **Table 1-X**.

**[0006b]** In another aspect of the present disclosure, there is provided a compound depicted in **Table 12** of the specification, or a pharmaceutically acceptable salt thereof.

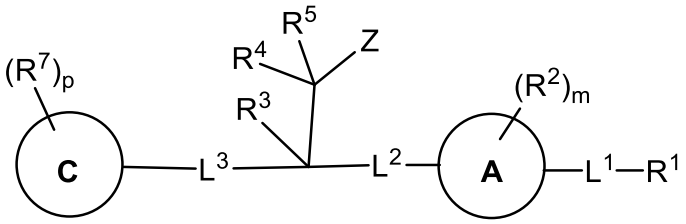
**[0006c]** In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

**[0006d]** In another aspect of the present disclosure, there is provided a method of inhibiting USP30 in a biological sample comprising contacting the sample with the compound disclosed herein, or a pharmaceutically acceptable salt thereof.

**[0006e]** In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating an USP30-mediated disorder, disease, or condition in a patient.

**[0006f]** In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in therapy.

**[0007]** It has now been found that compounds of this disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of USP30. Such compounds have the general formula **I**:




**I**

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

**[0008]** Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with mitochondrial homeostasis implicating USP30. Such diseases, disorders, or conditions include those described herein.

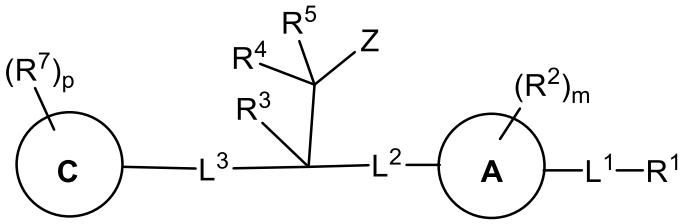
**[0009]** Compounds provided by this disclosure are also useful for the study of USP30 in biological and pathological phenomena; the study of mitochondrial homeostasis occurring in bodily tissues; and the comparative evaluation of new USP30 inhibitors or other regulators of mitochondrial homeostasis *in vitro* or *in vivo*.

## DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

### *1. General Description of Certain Embodiments of the Invention:*

**[0010]** Compounds of the present invention, and compositions thereof, are useful as inhibitors of USP30.

**[0011]** In certain embodiments, the present invention provides a compound of formula **I**:




**I**

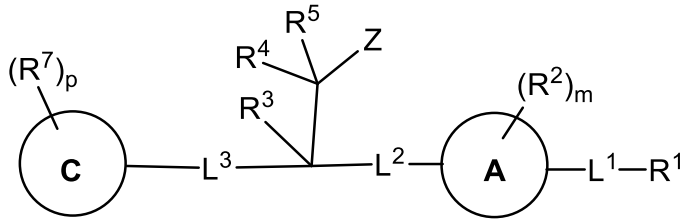
or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered

## CLAIMS

**We claim:**

1. A compound of formula **I**:




**I**

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an 8-10 membered bicyclic aryl or heteroaryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

$L^1$ is a covalent bond or a $C_{1-3}$ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by $–C(CF_3)H–$, $–N(R)–$, $–O–$, $–C(O)–$, $–OC(O)–$, $–C(O)O–$, $–C(O)N(R)–$, $–N(R)C(O)–$, $–S(O)–$, $–S(O)_2–$, $–S(O)N(R)–$, $–S(O)_2N(R)–$, or $–S(O)(R)=N–$;

each R is independently hydrogen or an optionally substituted $C_{1-3}$ aliphatic group; or:

two R groups on the same nitrogen are optionally 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, or sulfur; or

an R group and $R^1$ on the same nitrogen are optionally 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, or sulfur;

$R^1$ is hydrogen or an optionally substituted group selected from $C_{1-6}$ aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 5-8 membered

saturated or partially unsaturated bridged bicyclic carbocyclic ring, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^2$ is independently halogen, $–CF_3$, –CN, –C(O)NHR, $–NO_2$, –NHR, –NHC(O)R, $–NHS(O)_2R$, $–N(R)_2$, or –OR, or an optionally substituted $C_{1-6}$ aliphatic group; or

two $R^2$ on the same carbon are optionally taken together to form =O;

$L^2$ is selected from the group consisting of $–C(O)N(R')–$, $–CH_2O–$, $–CH_2N(R')–$, $–C(OH)(H)CH_2N(R')–$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R' is hydrogen or a $C_{1-3}$ aliphatic group;

$L^3$ is selected from the group consisting of $–C(O)N(R")–$, $–OC(O)N(R")–$, $–CH_2O–$, and a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R" is hydrogen or a $C_{1-3}$ aliphatic group;

$R^3$ is hydrogen or $C_{1-3}$ aliphatic; or:

$R^3$ and $R^4$ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring; or

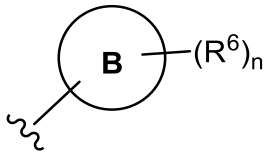
$R^3$ and $R^5$ are optionally taken together with their intervening atoms to form a 3-5 membered saturated carbocyclic ring;

$R^4$ is hydrogen or $C_{1-3}$ aliphatic;

$R^5$ is hydrogen or $C_{1-3}$ aliphatic;

Z is:

(a) selected from an optionally substituted $C_{1-6}$ aliphatic group, and –OR;

(b) 

;

(c) taken together with $R^4$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$;

(d) taken together with $R^5$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$; or

(e) taken together with R" and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of $L^3$, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$;

Ring B is phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each $R^6$ is independently halogen, phenyl, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, –C(O)R, –C(O)OR, or an optionally substituted $C_{1-6}$ aliphatic group; or:

two $R^6$ on the same carbon are optionally taken together to form =O;

an $R^6$ group and R' group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

an $R^6$ group and $R^3$ group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen or sulfur; or

an $R^6$ group and R" group are optionally taken together with their intervening atoms to form a 5-8 membered partially unsaturated fused ring having 0-2 heteroatoms, in addition to the nitrogen, independently selected from nitrogen, oxygen or sulfur;

Ring C is phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

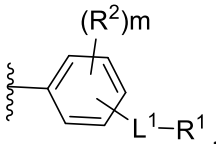
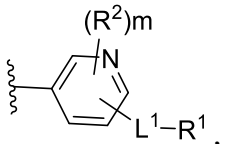
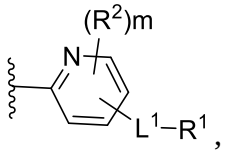
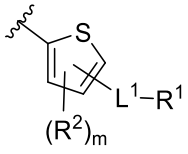
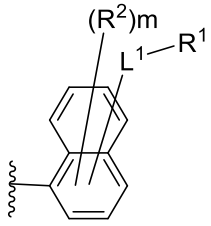
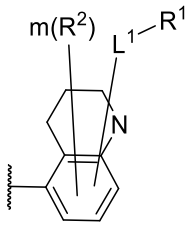
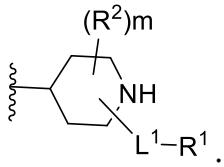
independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

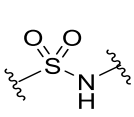
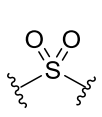
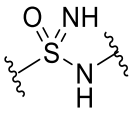
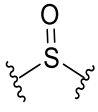
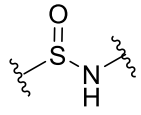
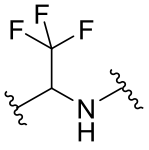
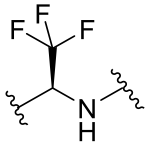
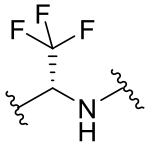
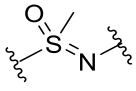
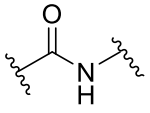
each $R^7$ is independently halogen, –CN, $–NO_2$, –NHR, $–N(R)_2$, –OR, or an optionally substituted $C_{1-6}$ aliphatic group; or

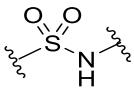
two $R^7$ on the same carbon are optionally taken together to form =O;

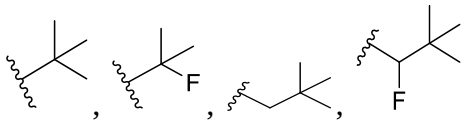
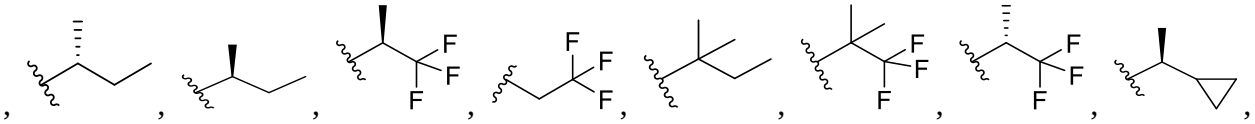
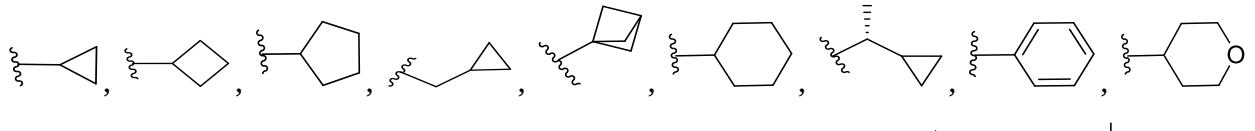
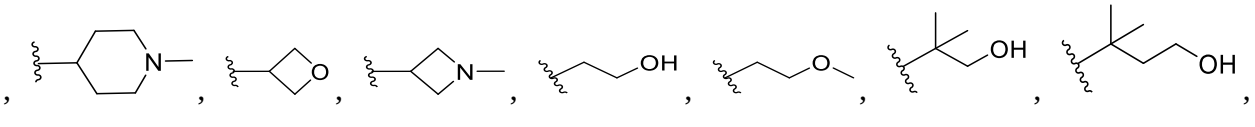
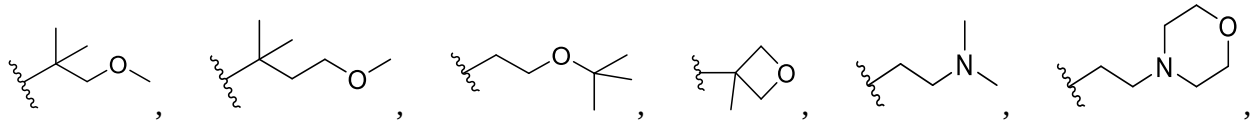
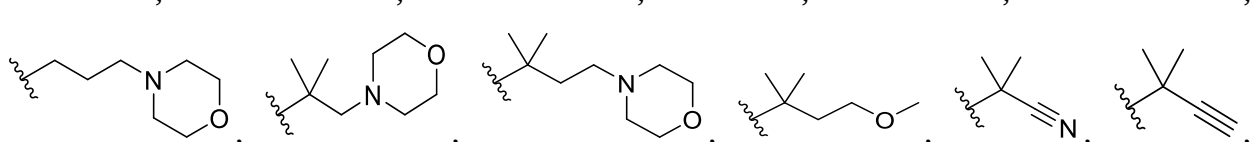
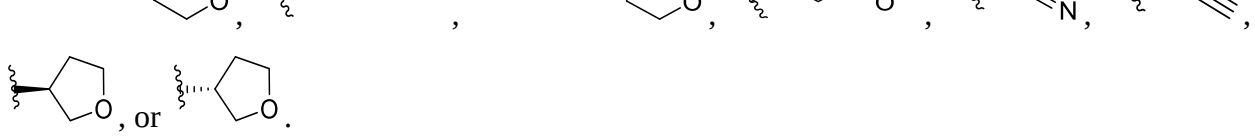
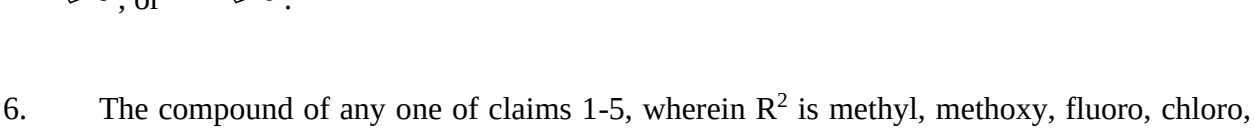
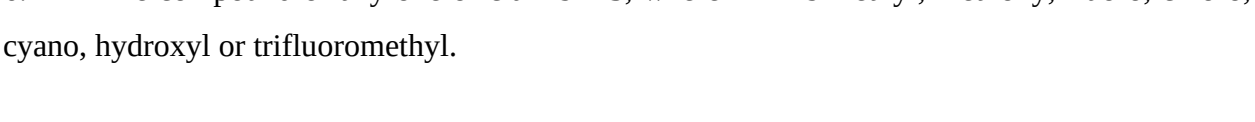
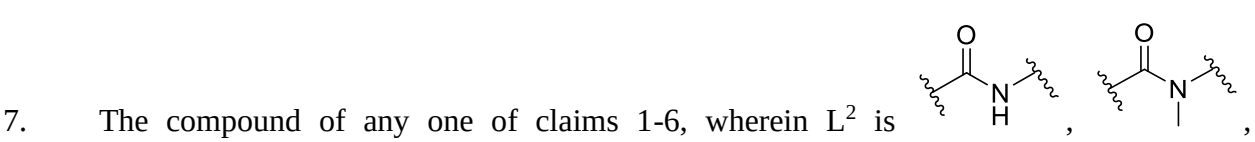
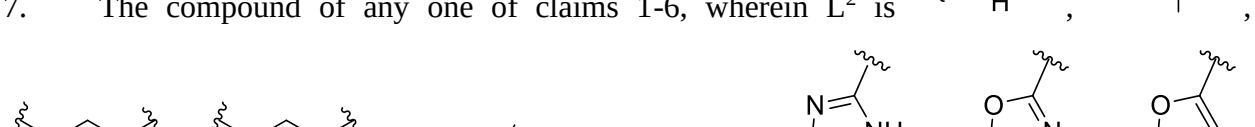
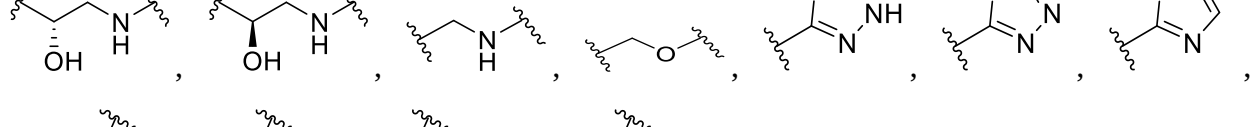
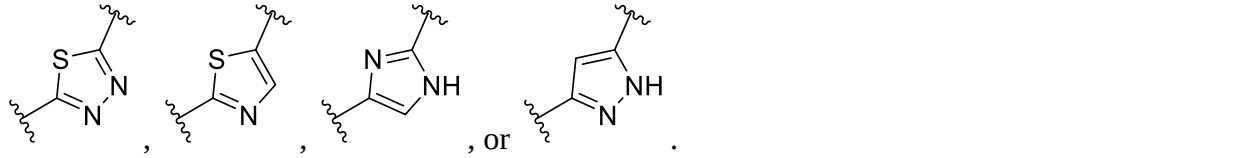
each of m, n, and p is independently 0, 1, 2, 3 or 4; and

the compound is other than one depicted in **Table 1-X**.

2. The compound of claim 1, wherein Ring A is , , , , , , or .

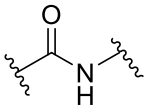
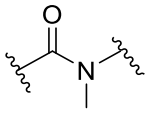
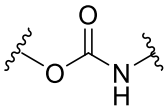
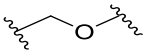
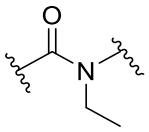
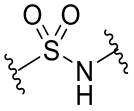
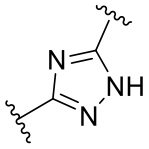
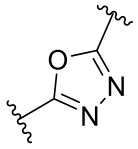
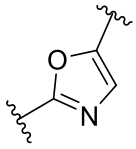
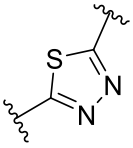
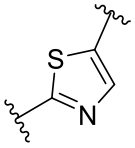
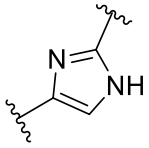
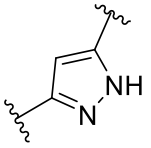
3. The compound of any one of claims 1-2, wherein $L^1$ is , , , , , , , , , or .

4. The compound of any one of claims 1-2, wherein $L^1$ is .

5. The compound of any one of claims 1-4, wherein $R^1$ is , , , , , , , , , , , , , , , , or .

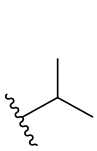
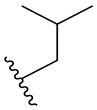
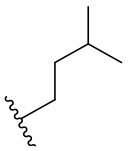
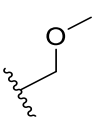
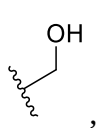
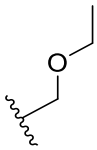
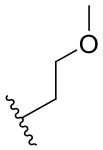
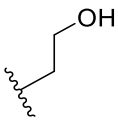
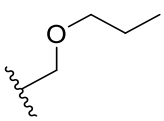
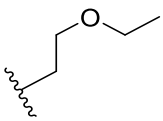
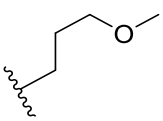
6. The compound of any one of claims 1-5, wherein $R^2$ is methyl, methoxy, fluoro, chloro, cyano, hydroxyl or trifluoromethyl.

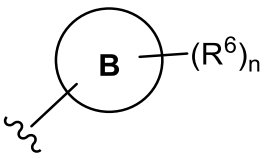
7. The compound of any one of claims 1-6, wherein $L^2$ is , , , , , or .

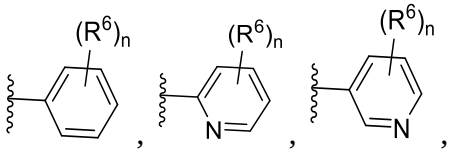
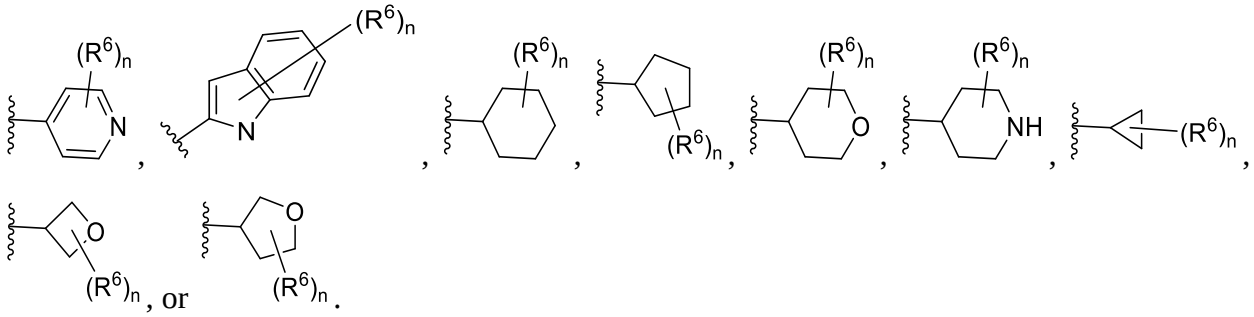
8. The compound of any one of claims 1-7, wherein $L^3$ is , , , , , , , , , , , , or .

9. The compound of any one of claims 1-8, wherein at least one of $L^2$ and $L^3$ is a bivalent 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

10. The compound of any one of claims 1-9, wherein Z is selected from an optionally substituted $C_{1-6}$ aliphatic group, and –OR.

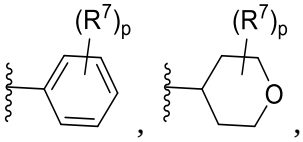
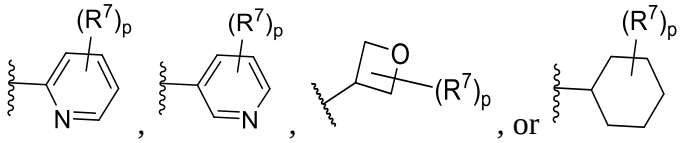
11. The compound of any one of claims 1-10, wherein Z is , , , , , , , , , , , , or , or an optionally substituted group selected from ethyl, n-propyl, n-butyl, and n-pentyl.

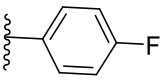
12. The compound of any one of claims 1-9, wherein Z is .

13. The compound of any one of claims 1-9, wherein Z is , , or .

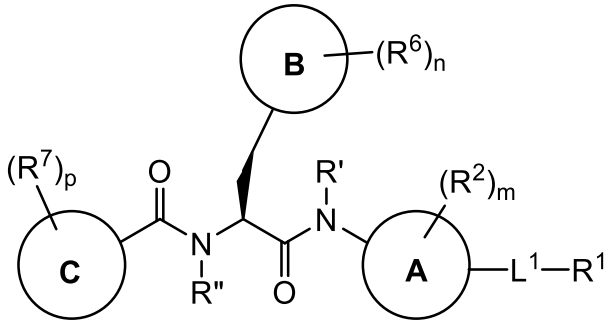
14. The compound of any one of claims 1-9, wherein Z is taken together with $R^4$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$; or Z is taken together with $R^5$ and the intervening carbon atom to form a 3-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$.

15. The compound of any one of claims 1-9, wherein Z is taken together with R" and their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring having 0-3 heteroatoms, in addition to the nitrogen of $L^3$, independently selected from nitrogen, oxygen, or sulfur, optionally substituted with n instances of $R^6$.

16. The compound of any one of claims 1-15, wherein Ring C is , , or .

17. The compound of any one of claims 1-16, wherein Ring C is .

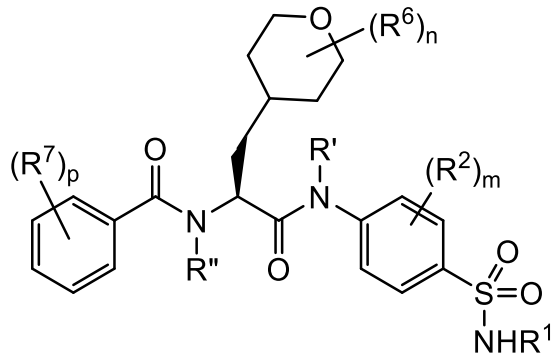
18. The compound of claim 1, of formula **II**:



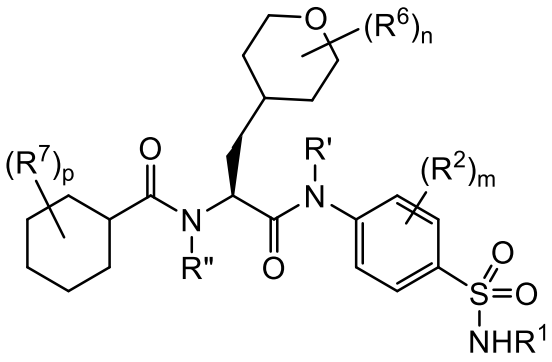
**II**

or a pharmaceutically acceptable salt thereof.

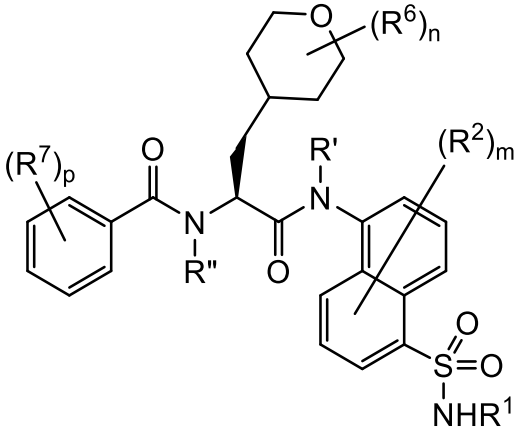
19. The compound of claim 1, of formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



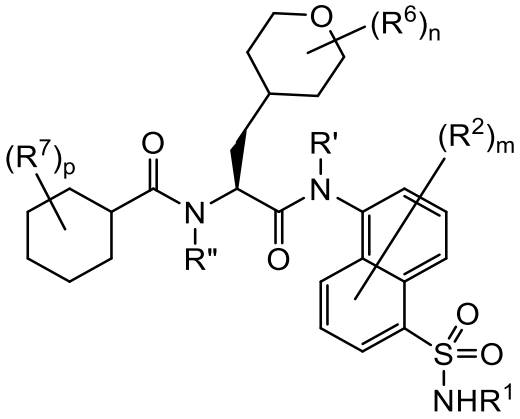
**IV-a**



**IV-b**



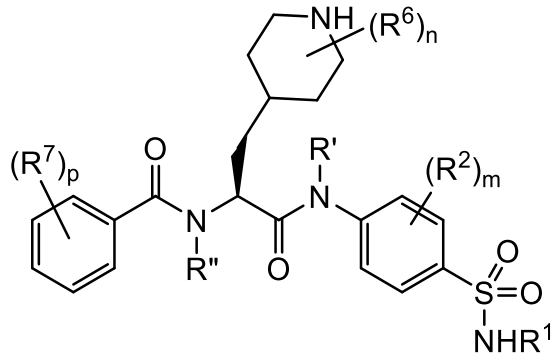
**IV-c**



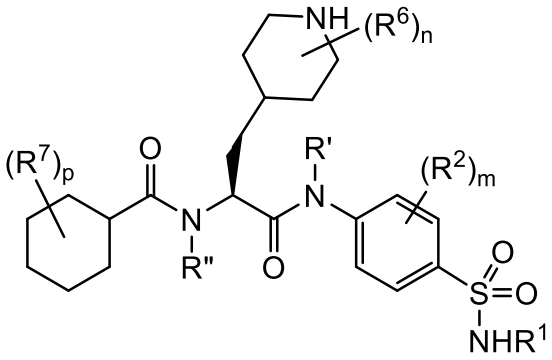
**IV-d**

or a pharmaceutically acceptable salt thereof.

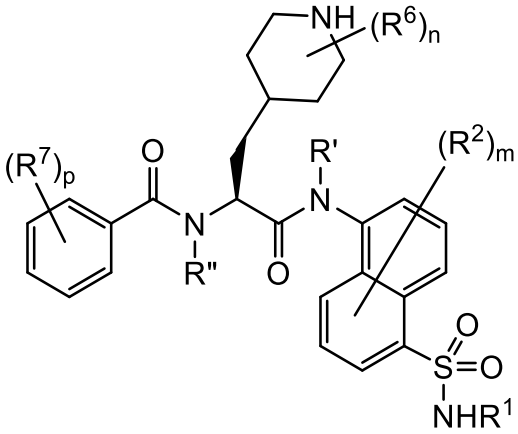
20. The compound of claim 1, of formulae **VI-a**, **VI-b**, **VI-c**, or **VI-d**:



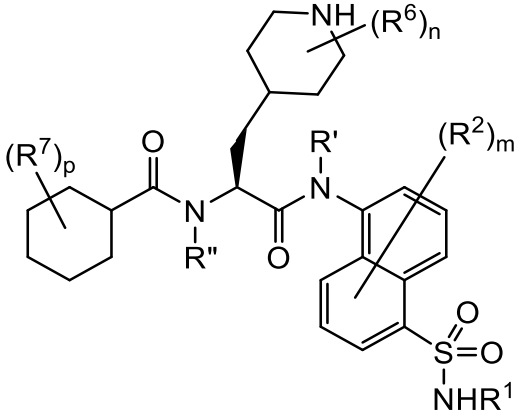
**VI-a**



**VI-b**



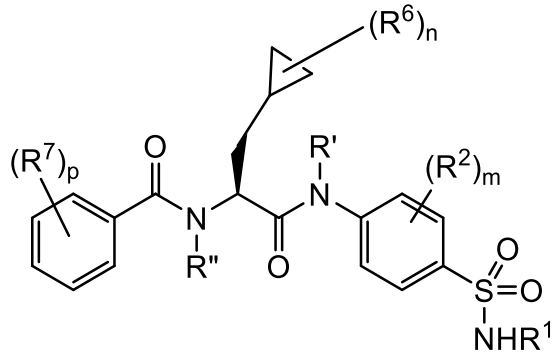
**VI-c**



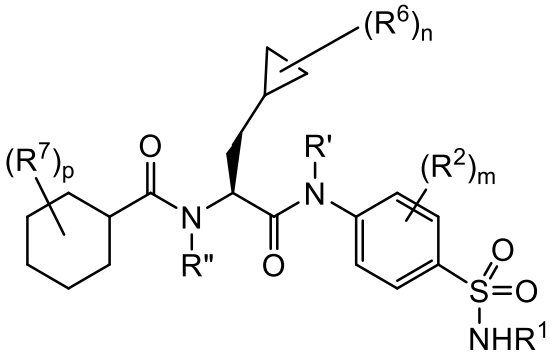
**VI-d**

or a pharmaceutically acceptable salt thereof.

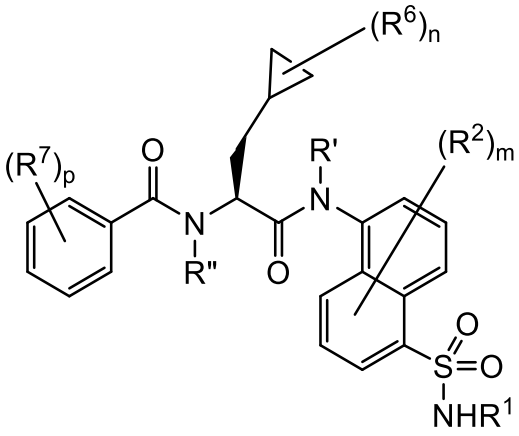
21. The compound of claim 1, of formulae **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d**:



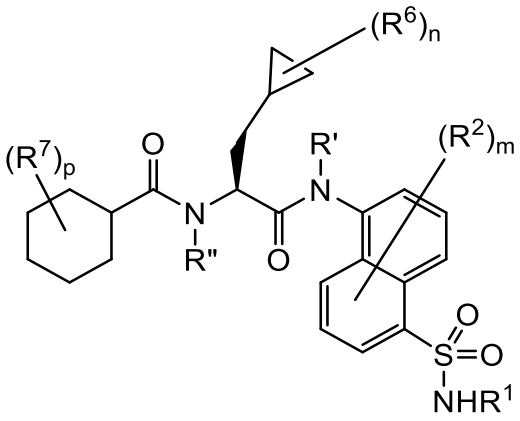
**VIII-a**



**VIII-b**



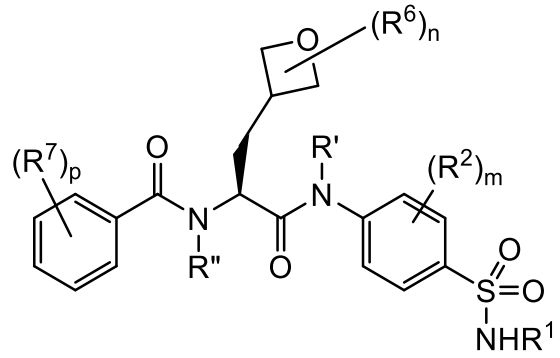
**VIII-c**



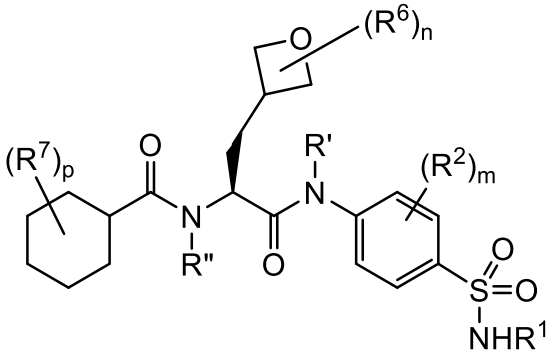
**VIII-d**

or a pharmaceutically acceptable salt thereof.

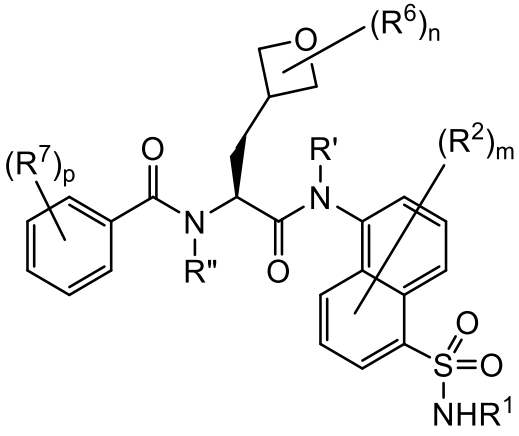
22. The compound of claim 1, of formulae **X-a**, **X-b**, **X-c**, or **X-d**:



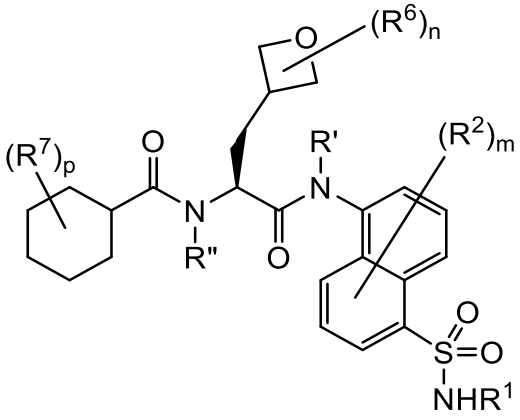
**X-a**



**X-b**



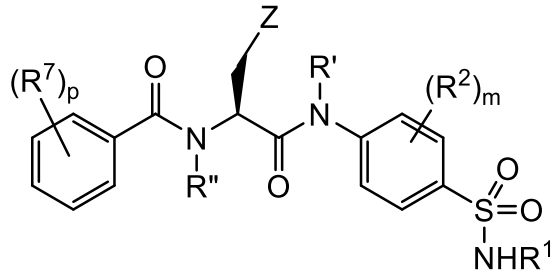
**X-c**



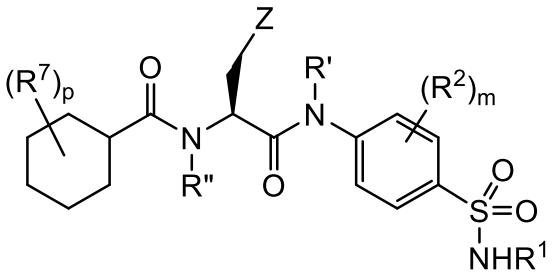
**X-d**

or a pharmaceutically acceptable salt thereof.

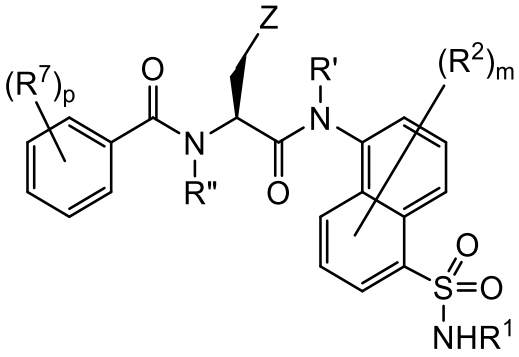
23. The compound of claim 1, of formulae **XII-a**, **XII-b**, **XII-c**, or **XII-d**:



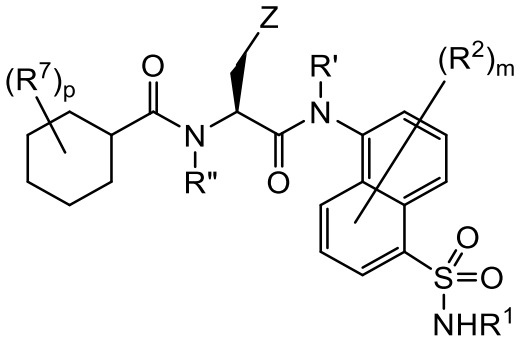
**XII-a**



**XII-b**



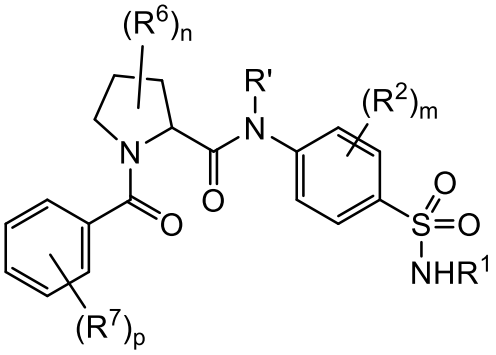
**XII-c**



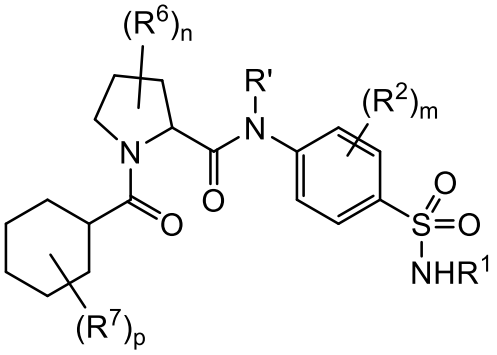
**XII-d**

or a pharmaceutically acceptable salt thereof.

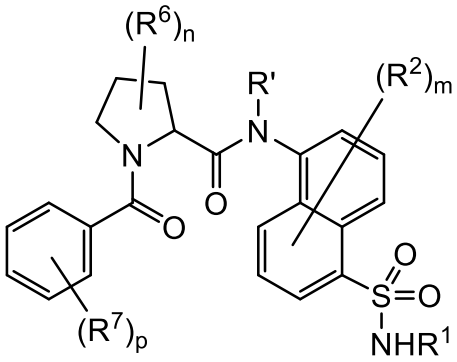
24. The compound of claim 1, of formulae **XIV-a**, **XIV-b**, **XIV-c**, or **XIV-d**:



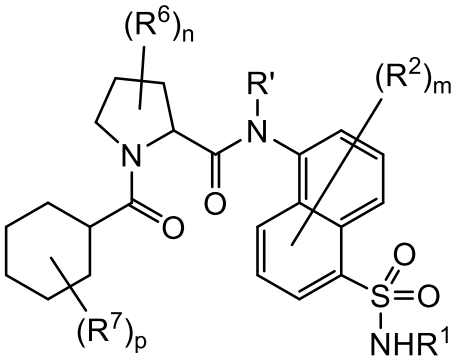
**XIV-a**



**XIV-b**



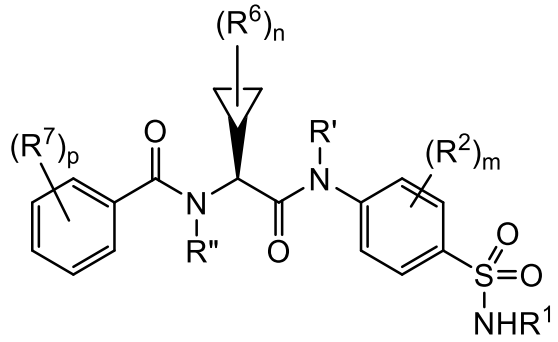
**XIV-c**



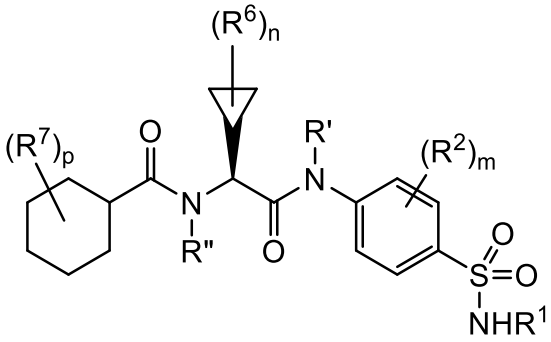
**XIV-d**

or a pharmaceutically acceptable salt thereof.

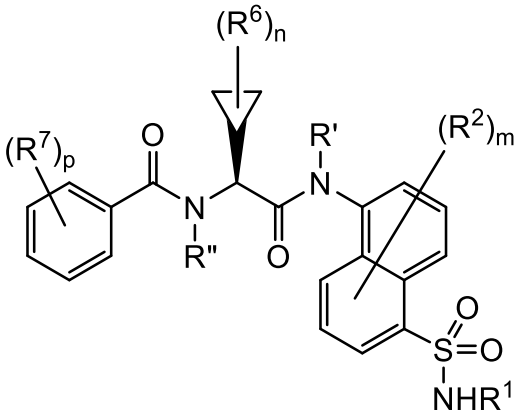
25. The compound of claim 1, of formulae **XVI-a**, **XVI-b**, **XVI-c**, and **XVI-d** respectively:



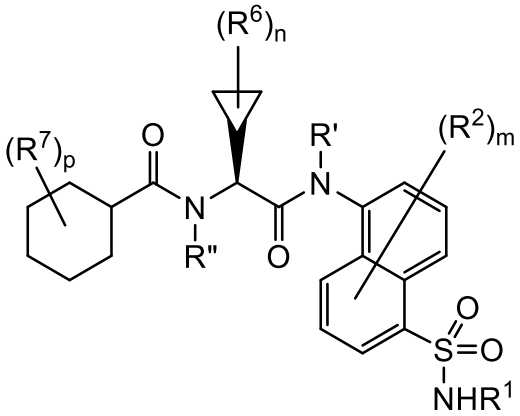
**XVI-a**



**XVI-b**



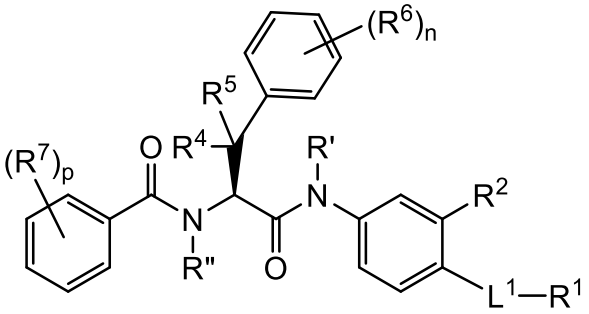
**XVI-c**



**XVI-d**

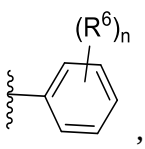
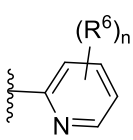
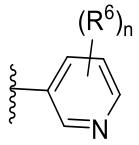
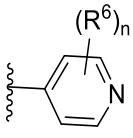
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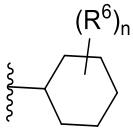
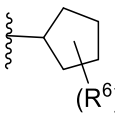
26. The compound of claim 1, of formula **XVII**:

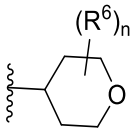
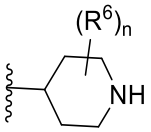


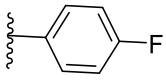
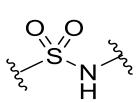
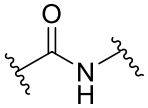
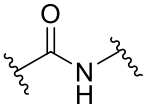
**XVII**

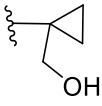
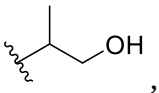
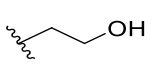
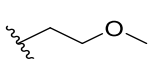
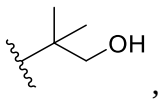
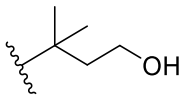
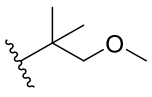
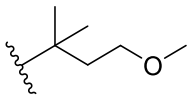
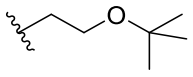
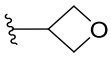
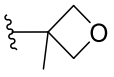
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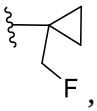
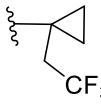
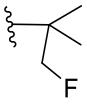
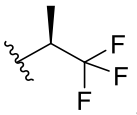
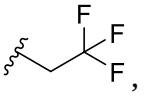
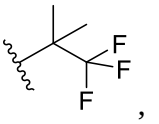
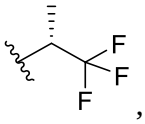
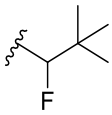
27. The compound of any one of claims 1-4, wherein Z is , , , or .

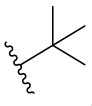
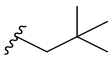
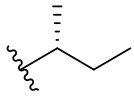
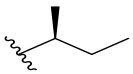
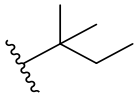
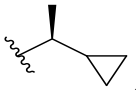
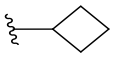
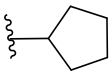
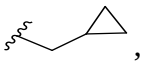
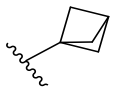
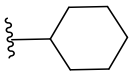
28. The compound of any one of claims 1-4, wherein Z is  or .

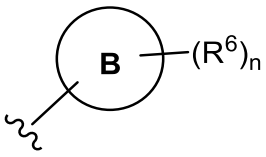
29. The compound of any one of claims 1-4, wherein Z is  or .

30. The compound of any one of claims 27-29, wherein Ring C is , $L^1$ is , $L^2$ is , and $L^3$ is .

31. The compound of any one of claims 1-4 or 18-30, wherein $R^1$ is , , , , , , , , , , or .

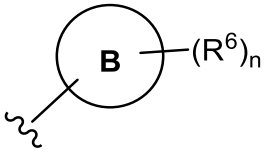
32. The compound of any one of claims 1-4 or 18-30, wherein $R^1$ is , , , , , , , , or .

33. The compound of any one of claims 1-4 or 18-30, wherein $R^1$ is , , , , , , , , , , , , , or .

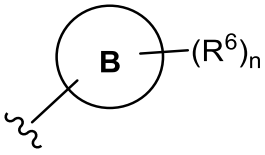
34. The compound of claim 1, wherein Ring A is phenyl; $L^1$ is $–S(O)_2N(H)–$; R is a $C_1$ aliphatic group; $R^1$ is $C_4$ aliphatic or a 4-membered saturated heterocyclic ring having 1 oxygen atom; $R^2$ is –OR; $L^2$ is –C(O)N(H)–; $L^3$ is –C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is ; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl; $R^7$ is halogen; m is 1; p is 1; and n is 0.

35. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $L^1$ is $–S(O)_2N(H)–$; $R^1$ is $C_4$ aliphatic; $L^2$ is –C(O)N(H)–; $L^3$ is –

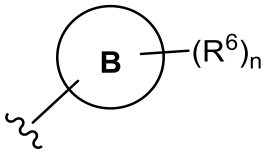
C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is a $C_3$ aliphatic group; Ring C is phenyl; $R^7$ is halogen; m is 0; and p is 1.

36. The compound of claim 1, wherein Ring A is phenyl; $L^1$ is $–S(O)_2N(H)–$; R is a $C_1$ aliphatic group; $R^1$ is a optionally substituted 3-membered saturated monocyclic carbocyclic ring; $R^2$ is –OR; $L^2$ is –C(O)N(H)–; $L^3$ is –C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is 

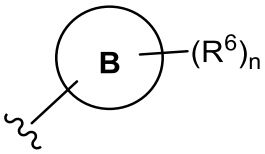
; Ring B is phenyl; Ring C is phenyl; $R^7$ is halogen; m is 0 or 1; p is 1; and n is 0.

37. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $L^1$ is $–S(O)_2N(H)–$; R is a $C_1$ aliphatic group; $R^1$ is a $C_4$ aliphatic or 4-membered heterocyclic ring with 1 oxygen atom; $R^2$ is –OR; $L^2$ is –C(O)N(H)–; $L^3$ –C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is 

; Ring B is a 6-membered saturated heterocyclic ring having 1 nitrogen atom; $R^6$ is a $C_1$ aliphatic group; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $R^7$ is halogen; m is 0 or 1; p is 1; and n is 0 or 1.

38. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $L^1$ is $–S(O)_2N(H)–$; R is a $C_1$ aliphatic group; $R^1$ is an optionally substituted group selected from 3-membered saturated monocyclic carbocyclic ring or $C_{3-4}$ aliphatic; $R^2$ is –OR; $L^2$ is –C(O)N(H)–; $L^3$ is –C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is 

; Ring B is phenyl; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $R^7$ is halogen; m is 0 or 1; p is 1; and n is 0.

39. The compound of claim 1, wherein Ring A is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $L^1$ is $–S(O)_2N(H)–$; R is a $C_1$ aliphatic group; $R^1$ is an optionally substituted $C_4$ aliphatic or a 4-5 membered saturated monocyclic carbocyclic ring; $R^2$ is –OR; $L^2$ is –C(O)N(H)–; $L^3$ is –C(O)N(H)–; $R^3$ is hydrogen; $R^4$ is hydrogen; $R^5$ is hydrogen; Z is 

; Ring B is a 6-membered saturated heterocyclic ring having 1 oxygen atom; Ring C is phenyl or a 6-membered heteroaryl ring having 1 nitrogen atom; $R^7$ is halogen; m is 0 or 1; p is 1; and n is 0.

40. The compound of claim 1, wherein said compound is selected from those depicted in **Table 1** of the specification, or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1, wherein said compound is selected from those depicted in **Table 11** of the specification, or a pharmaceutically acceptable salt thereof.

42. A compound depicted in **Table 12** of the specification, or a pharmaceutically acceptable salt thereof.

43. A pharmaceutical composition comprising a compound according to any one of claims 1-42, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

44. A method of inhibiting USP30 in a biological sample comprising contacting the sample with the compound of any one of claims 1-42, or a pharmaceutically acceptable salt thereof.

45. Use of a pharmaceutical composition of claim 43, in the manufacture of a medicament for treating an USP30-mediated disorder, disease, or condition in a patient.

46. The use of claim 45, wherein the disorder, disease, or condition is selected from the group consisting of a neurodegenerative disease; mitochondrial myopathy, encephalopathy,

lactic acidosis, and stroke-like episodes (MELAS) syndrome; Leber's hereditary optic neuropathy (LHON); neuropathy, ataxia, retinitis pigmentosa- maternally inherited Leigh syndrome (NARP-MILS); Danon disease; ischemic heart disease leading to myocardial infarction; multiple sulfatase deficiency (MSD); mucolipidosis II (ML II); mucolipidosis III (ML III); mucolipidosis IV (ML IV); GM1 -gangliosidosis (GM1); neuronal ceroid- lipofuscinoses (NCL1); Alpers disease; Barth syndrome; Beta-oxidation defects; carnitine- acyl-carnitine deficiency; carnitine deficiency; creatine deficiency syndromes; coenzyme Q10 deficiency; complex I deficiency; complex II deficiency; complex III deficiency; complex IV deficiency; complex V deficiency; COX deficiency; chronic progressive external ophthalmoplegia syndrome (CPEO); CPT I deficiency; CPT II deficiency; glutaric aciduria type II; Kearns-Sayre syndrome; lactic acidosis; long-chain acyl-CoA dehydrogenase deficiency (LCHAD); Leigh disease or syndrome; lethal infantile cardiomyopathy (LIC); Luft disease; glutaric aciduria type II; medium-chain acyl-CoA dehydrogenase deficiency (MCAD); myoclonic epilepsy and ragged-red fiber (MERRF) syndrome; mitochondrial recessive ataxia syndrome; mitochondrial cytopathy; mitochondrial DNA depletion syndrome; myoneurogastointestinal disorder and encephalopathy; Pearson syndrome; pyruvate carboxylase deficiency; pyruvate dehydrogenase deficiency; POLG mutations; medium/short-chain 3-hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency; and very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency.

47. The use of claim 45, wherein the disorder, disease, or condition is a neurodegenerative disease selected from the group consisting of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, ischemia, stroke, dementia with Lewy bodies, and frontotemporal dementia.

48. The use of claim 47, wherein the neurodegenerative disease is Alzheimer's disease or Parkinson's disease.

49. The use of claim 45, wherein the disorder, disease, or condition is a neoplastic disease selected from the group consisting of metastatic carcinoma, multiple myeloma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, nasopharyngeal carcinoma, and leukemia.

50. The use of claim 45, wherein the disorder, disease, or condition is cardiovascular disease, kidney disease, pulmonary fibrosis, ophthalmic conditions, cancer, cognitive disease, peroxisome related disease, natural aging, or an age-related disease.

51. The use of claim 45, wherein the disorder, disease, or condition is a peroxisome related disease selected from the group consisting of Ataxia-telangiectasia mutated, Heimler syndrome, Infantile refsum disease, Neonatal adrenoleukodystrophy, Rhizomelic chondrodysplasia punctate, White matter dementia, Zellweger syndrome, and Zellweger spectrum disorder.

52. A pharmaceutical composition of claim 43, for use in therapy.