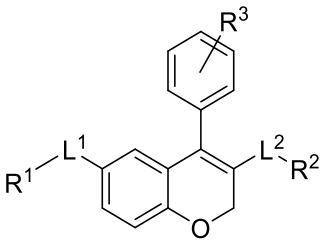
compounds should exhibit good activity on in vivo pharmacological trial, good oral absorption when administered orally, as well as being metabolically stable and having a favorable pharmacokinetic profile. Moreover, the compounds should not be toxic and present minimal side effects.

SUMMARY ~~OF THE INVENTION~~

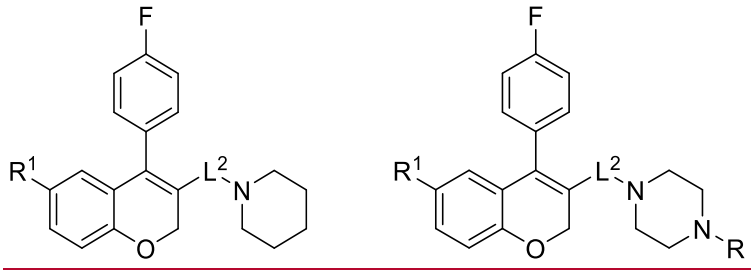
[0010] It has now been found that compounds of this ~~invention~~present disclosure, and pharmaceutically acceptable compositions thereof, are effective at modulators of the interaction of TRC with Nck. Such compounds have a general **Formula I**:



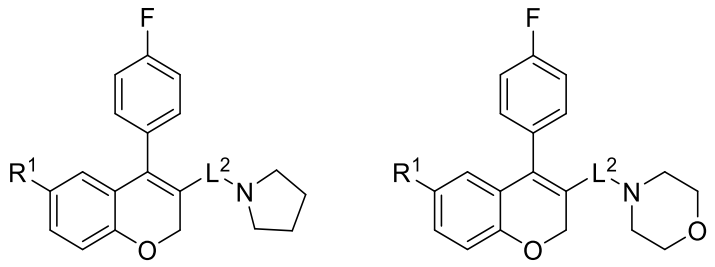
I

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

[0010a] In an aspect of the present disclosure, there is provided a compound selected from any 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, wherein:

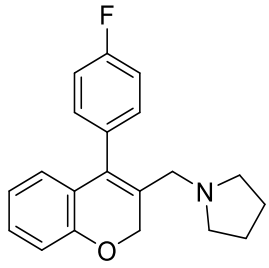
R^1 is R, halogen, -CN, -OR, -NHR, or $-N(R)_2$;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 member saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

or two R on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 5-6 membered heterocyclic ring having 0-1 heteroatoms in addition to the nitrogen attached thereto wherein such heteroatom is oxygen, nitrogen, or sulfur;

L^2 is a covalent bond or a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, or -N(R)C(O)N(R)-; and

wherein said compound is other than a compound selected from: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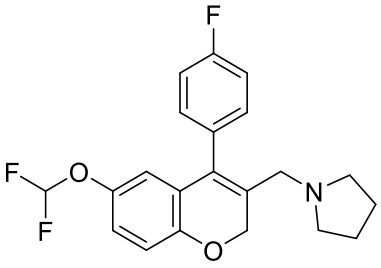
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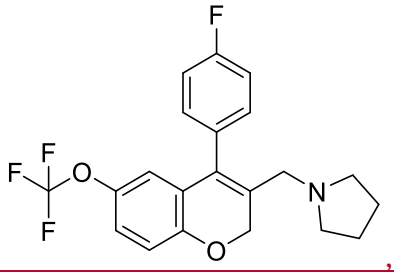
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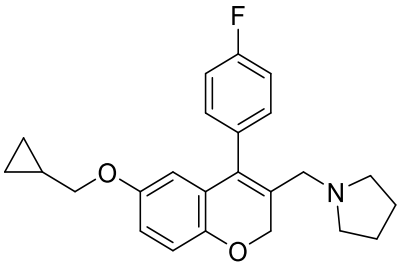
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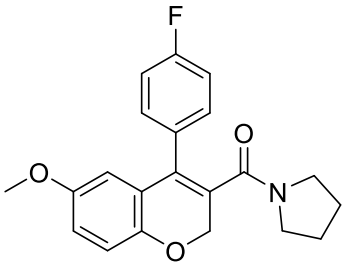
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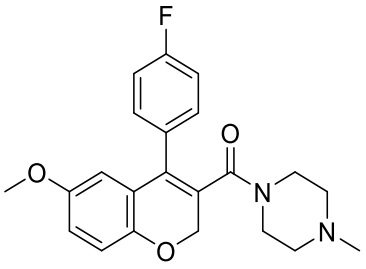
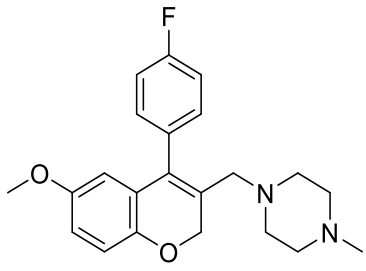


4 *5* *7*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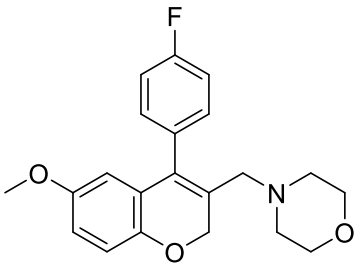
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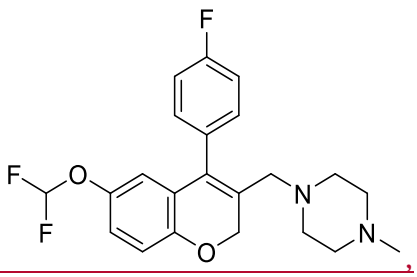
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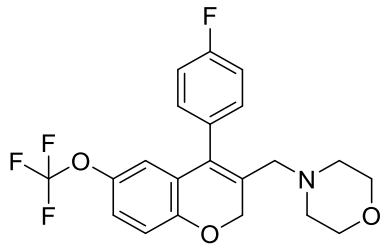
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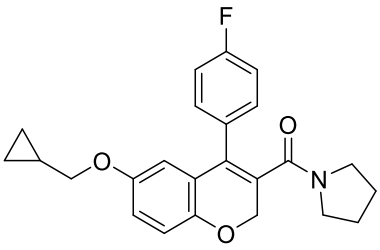
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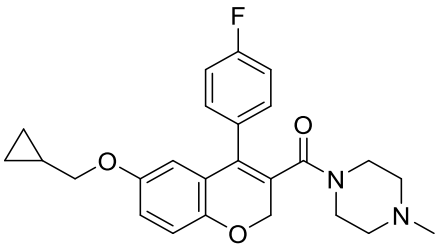

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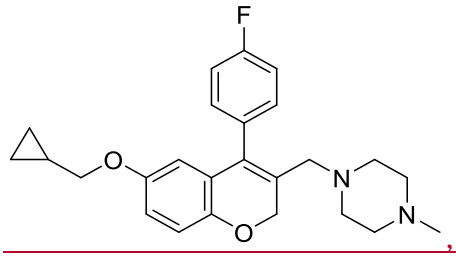
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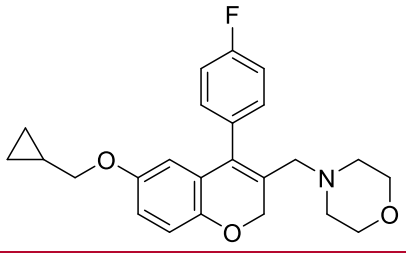
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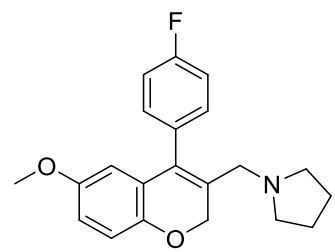
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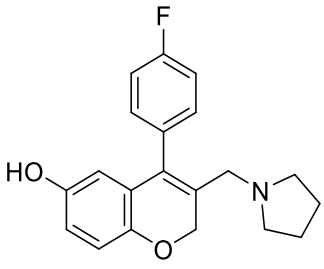
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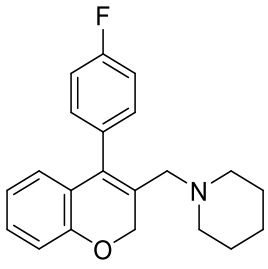
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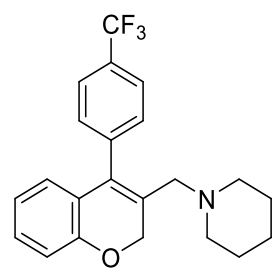
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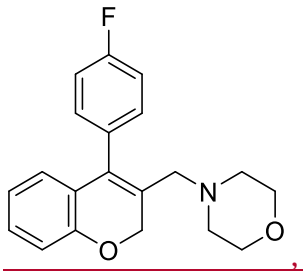

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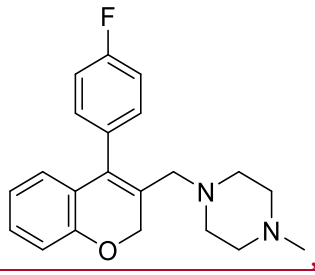

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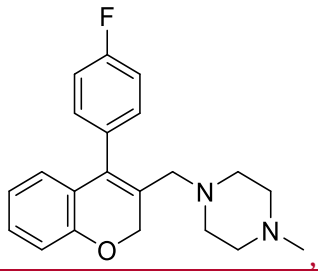

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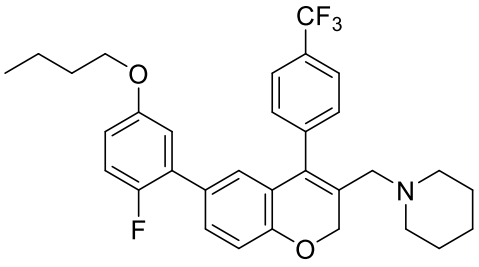

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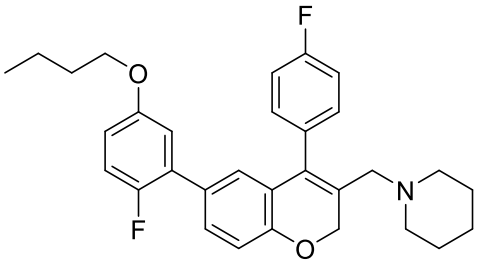

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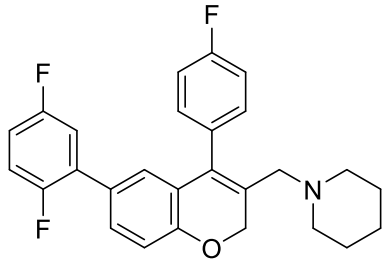
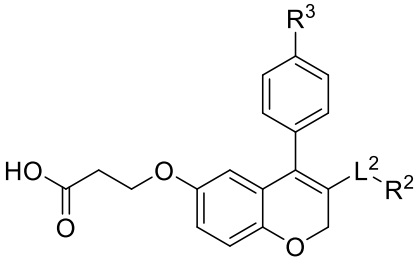


51.

[0010b] In another aspect of the present disclosure, there is provided a compound of formula **IX:**



IX

or a pharmaceutically acceptable salt thereof, wherein:

R^2 is R, halogen, -C(O)N(R)$_2$, or -N(R)$_2$;

R^3 is hydrogen or an electron withdrawing group;

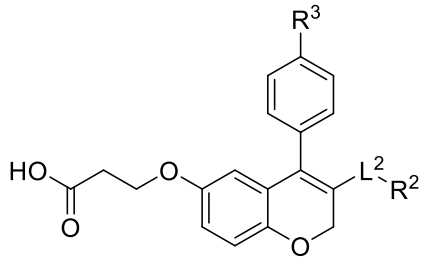
each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 member saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-8

membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

or two R on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 5-6 membered heterocyclic ring having 0-1 heteroatoms in addition to the nitrogen attached thereto wherein such heteroatom is oxygen, nitrogen, or sulfur; and

L^2 is a covalent bond or a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, $-C(F)_2-$, -N(R)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, or -N(R)C(O)N(R)-.

[0010c] In a further aspect of the present disclosure, there is provided a compound of formula **IX**:



IX

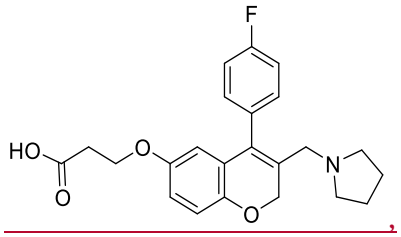
or a pharmaceutically acceptable salt thereof, wherein:

R^2 is $-N(R)_2$ wherein the two R groups on the nitrogen are taken together with their intervening atoms to form a 5-6 membered heterocyclic ring having no heteroatom in addition to the nitrogen attached thereto, and wherein such 5-6 membered heterocyclic ring is optionally substituted 1-6 times by C_{1-3} aliphatic or halogen;

R^3 is halogen;

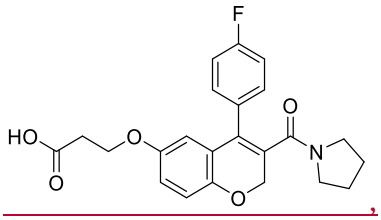
L^2 is a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1 methylene unit of the chain is optionally replaced with -C(O)-.

[0010d] In another aspect of the present disclosure, there is provided a compound:



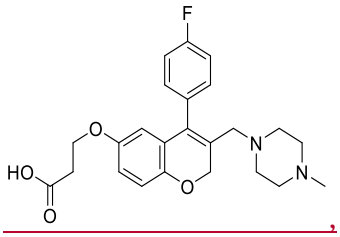
or a pharmaceutically acceptable salt thereof.

[0010e] In a further aspect of the present disclosure, there is provided a compound:



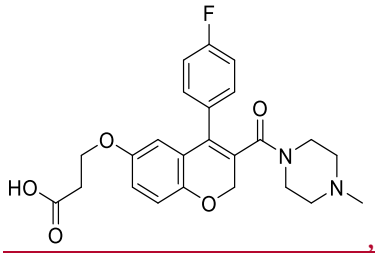
or a pharmaceutically acceptable salt thereof.

[0010f] In another aspect of the present disclosure, there is provided a compound:



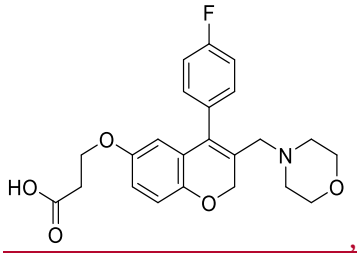
or a pharmaceutically acceptable salt thereof.

[0010g] In a further aspect of the present disclosure, there is provided a compound:



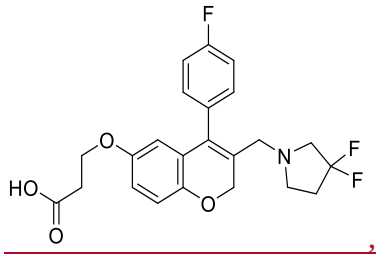
or a pharmaceutically acceptable salt thereof.

[0010h] In another aspect of the present disclosure, there is provided a compound:



or a pharmaceutically acceptable salt thereof.

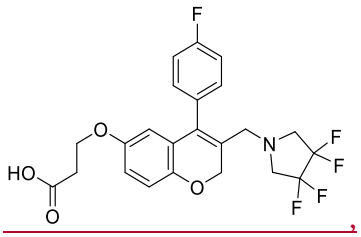
[0010i] In a further aspect of the present disclosure, there is provided a compound:



,

or a pharmaceutically acceptable salt thereof.

[0010j] In another aspect of the present disclosure, there is provided a compound:



,

or a pharmaceutically acceptable salt thereof.

[0010k] In a further aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, adjuvant, or vehicle.

[0010l] In another aspect of the present disclosure, there is provided an *in vitro* method of modulating a protein-protein interaction in a cell comprising contacting the cell with a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[0010m] In a further aspect of the present disclosure, there is provided an *in vitro* method of modulating the protein-protein interaction between TCR-Nck in a biological sample comprising contacting the biological sample with a compound disclosed herein, or a pharmaceutically acceptable salt thereof.

[0010n] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0010o] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating the protein-protein interaction between TCR-Nck in a patient.

[0010p] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a TCR-Nck mediated disease, disorder, or condition in a patient in need thereof.

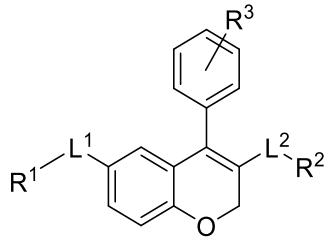
[0010q] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder, or condition in a patient in need thereof, wherein the disease, disorder, or condition is selected from rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, cutaneous lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, autoimmune hepatitis, myasthenia gravis, ankylosing spondylitis, Crohn's disease, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

[0011] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders, or conditions, associated with T-cell activation. Such diseases, disorders, or conditions include those described herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

General Description of Certain Embodiments of the Invention:

[0012] In certain embodiments, the present invention provides a compound of **Formula I**:



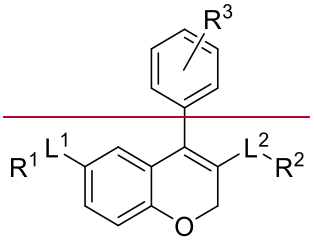
I

or a pharmaceutically acceptable salt thereof, wherein:

CLAIMS

We claim:

1. A compound selected from any of formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**~~of Formula I~~:



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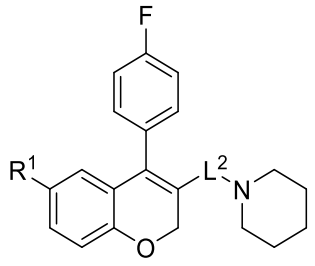
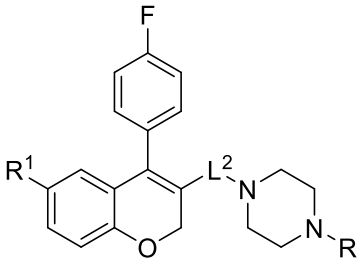
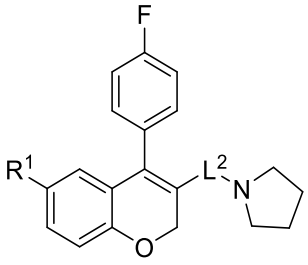


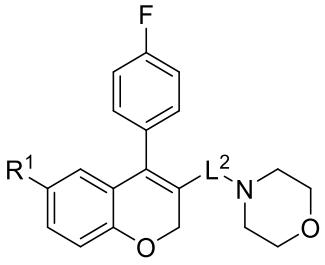
IV-a



IV-b



IV-c



IV-d

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is R, halogen, -CN, -OR, -NHR, or $-N(R)_2$;

~~R^2 is R, halogen, $-C(O)N(R)_2$, or $-N(R)_2$;~~

~~R^3 is hydrogen or an electron withdrawing group;~~

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 member saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

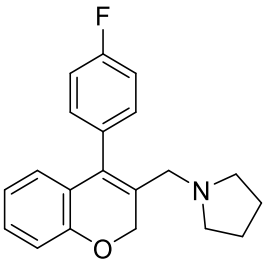
or two R on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 5-6 membered heterocyclic ring having 0-1 heteroatoms in addition to the nitrogen attached thereto wherein such heteroatom is oxygen, nitrogen, or sulfur;

~~L^1 is a covalent bond or a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -C(R)$_2$-, -CH(R)-, -C(F)$_2$-, -N(R)-, -C(O)N(R)-, -RNC(O)-, -OC(O)N(R)-, -N(R)C(O)N(R)-, or -Cy-;~~

L^2 is a covalent bond or a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -C(R)$_2$-, -CH(R)-, -C(F)$_2$-, -N(R)-, -C(O)N(R)-, -~~R~~N(R)C(O)-, -OC(O)N(R)-, or -N(R)C(O)N(R)-; and

~~each Cy is independently a bivalent optionally substituted 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, optionally substituted phenylene, an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;~~

wherein said compound is other than a compound selected from:



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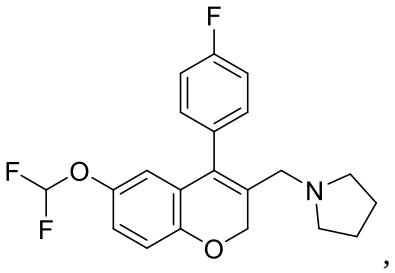

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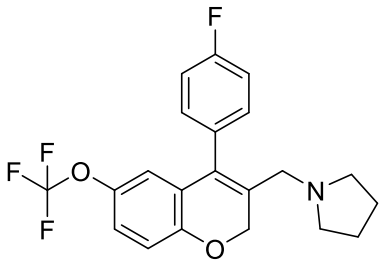

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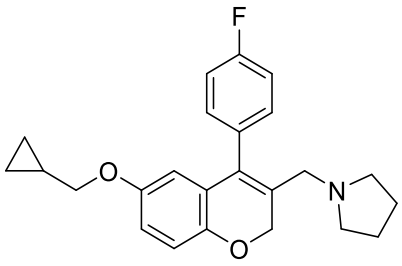

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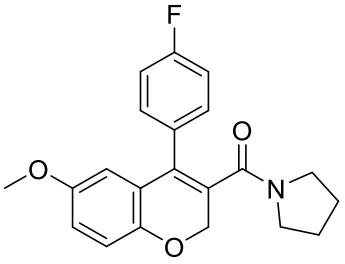

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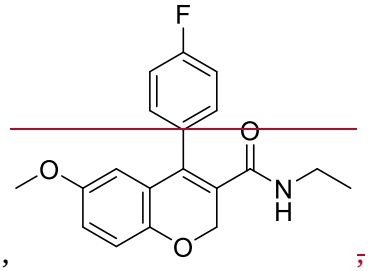

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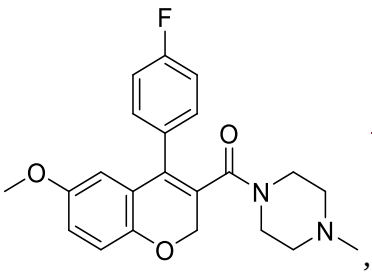

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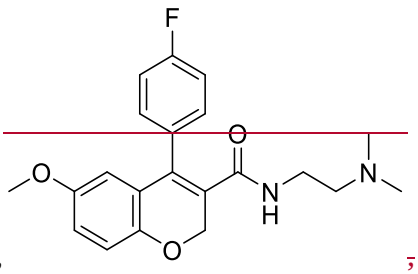

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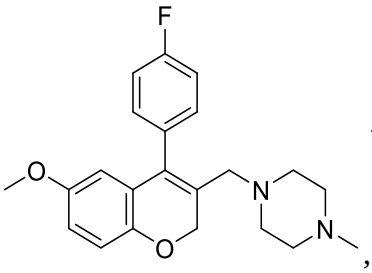

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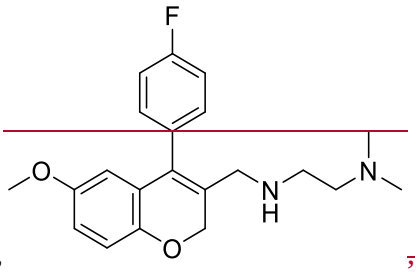

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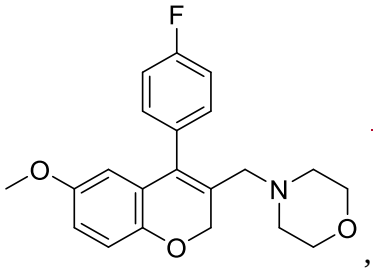

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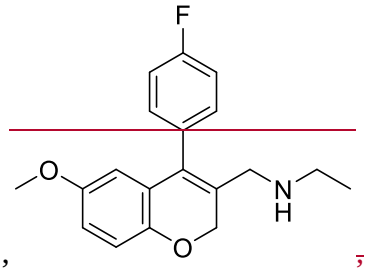

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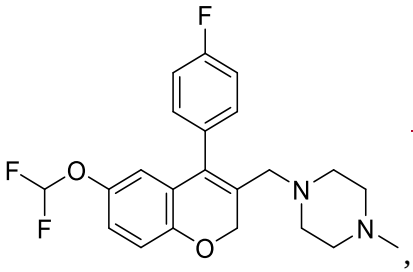

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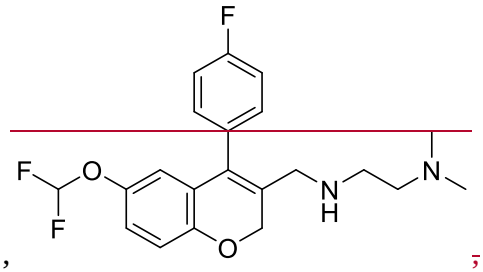

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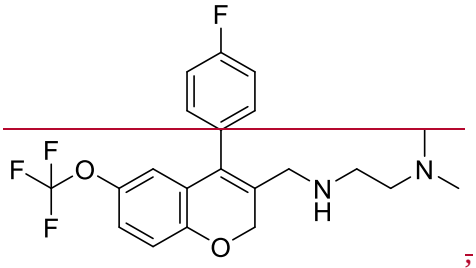

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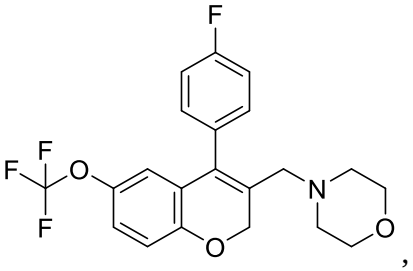

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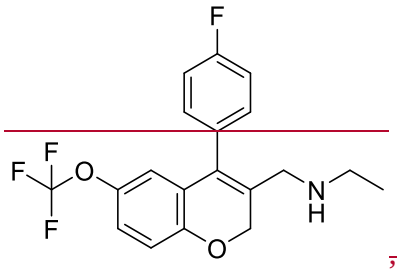

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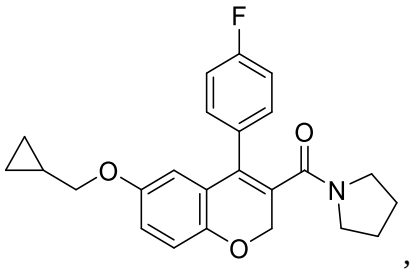

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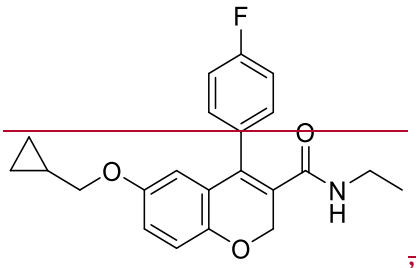

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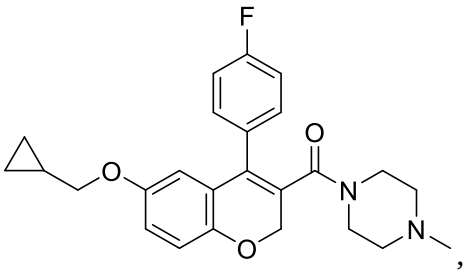

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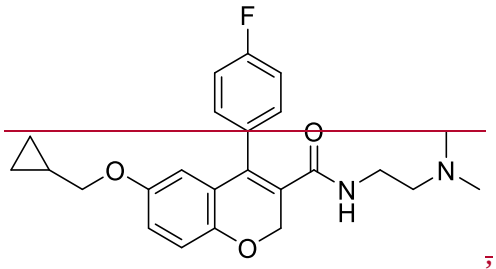

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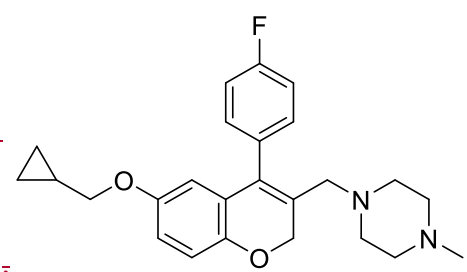

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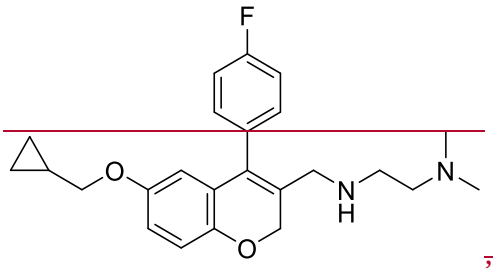

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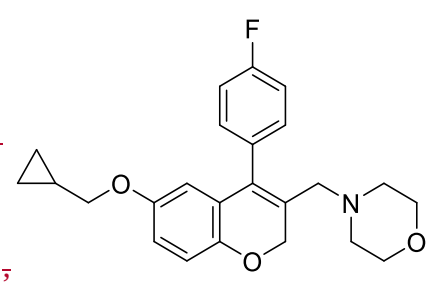

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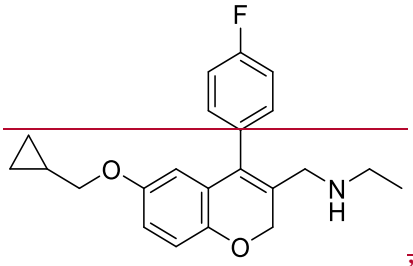

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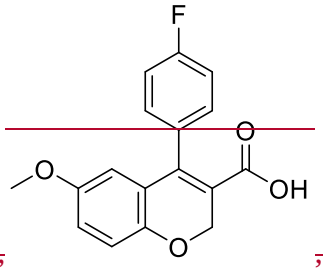

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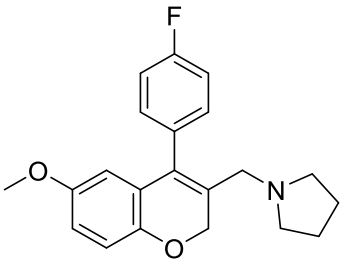

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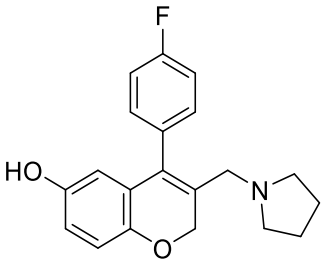

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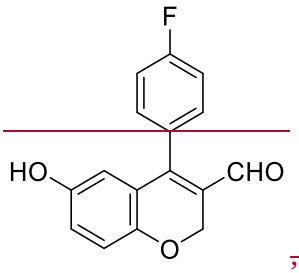

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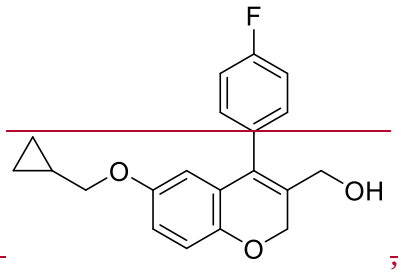

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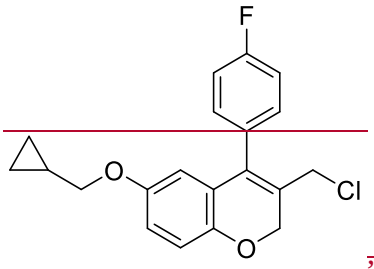

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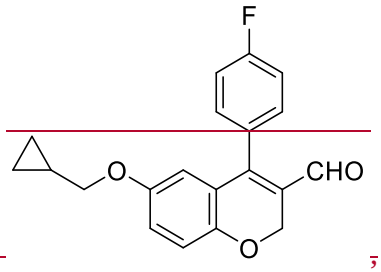

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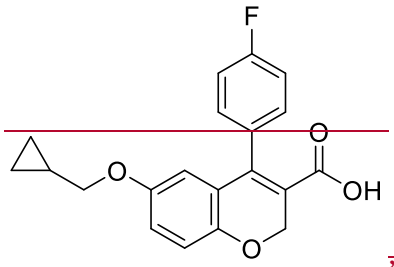

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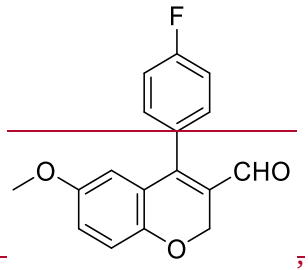

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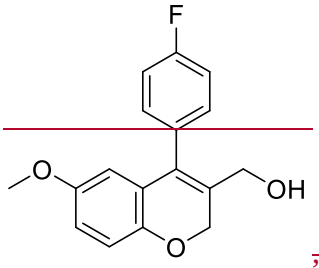

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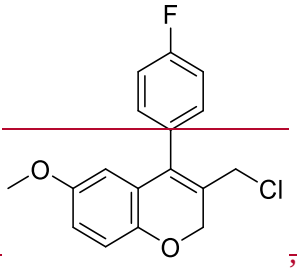

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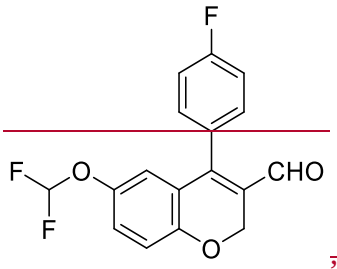

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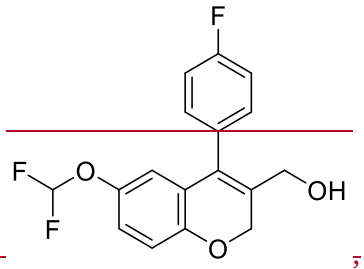

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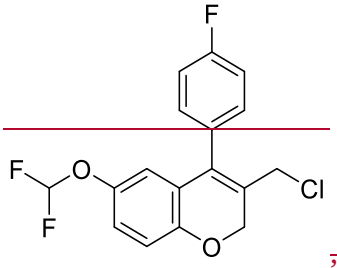

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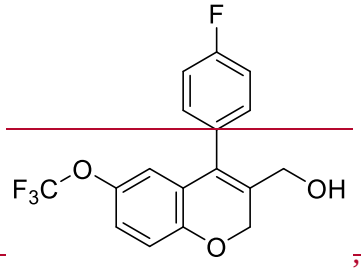

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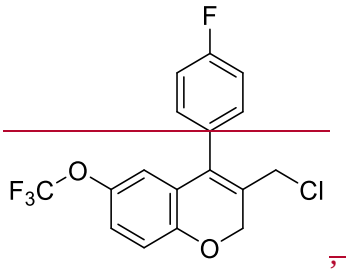

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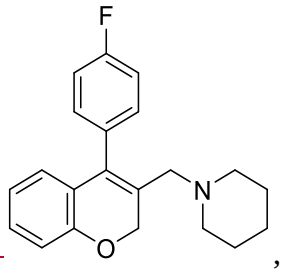

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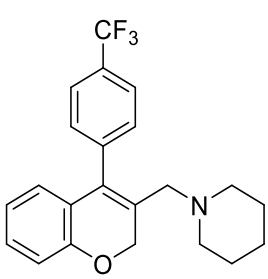

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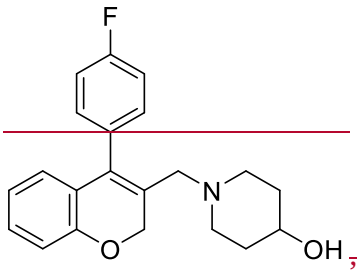

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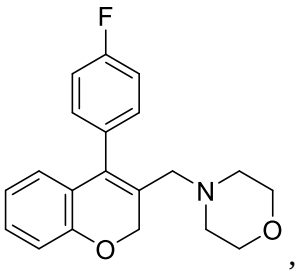

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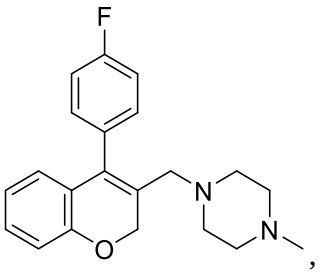

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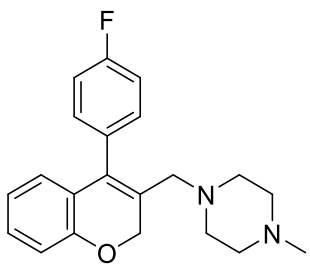

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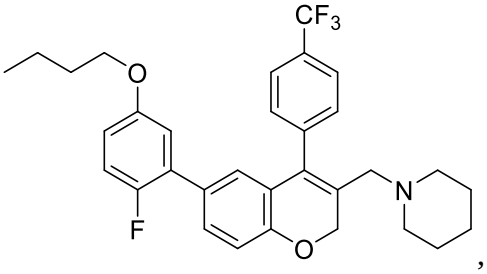

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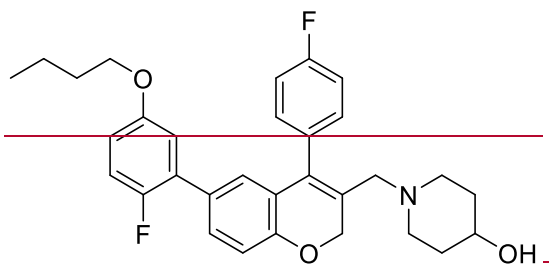

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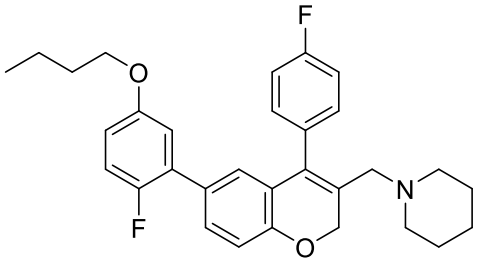

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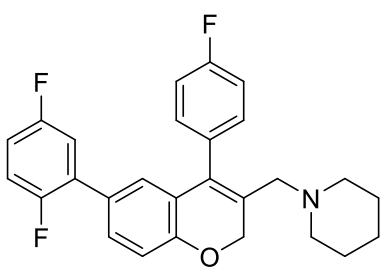

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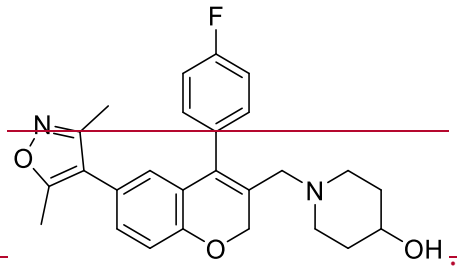

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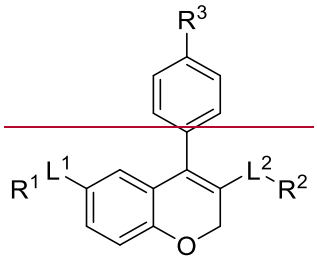
~~52~~

~~2. The compound of claim 1, wherein the compound formula is:~~



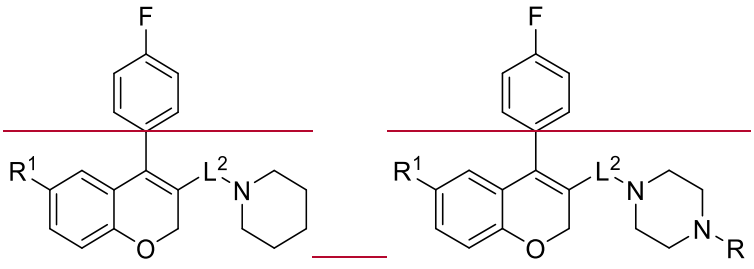
II

or a pharmaceutically acceptable salt thereof.

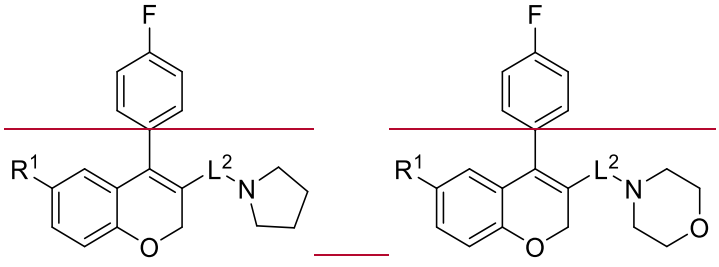
3. The compound according to claim 2, wherein R^3 is F, or a pharmaceutically acceptable salt thereof.

4. The compound according to claim 3, wherein L^1 is a covalent bond, or a pharmaceutically acceptable salt thereof.

5. The compound according to claim 4, wherein the compound is selected from any of formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



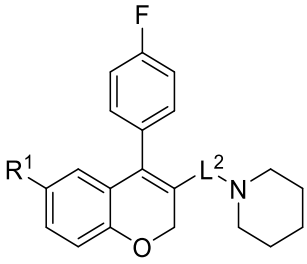
IV-a **IV-b**



IV-c **IV-d**

or a pharmaceutically acceptable salt thereof.

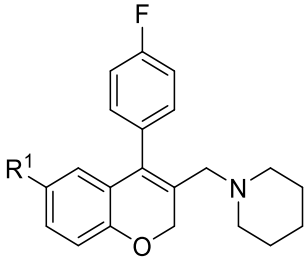
6.2. The compound according to claim 51, wherein the compound formula is:



IV-a

or a pharmaceutically acceptable salt thereof.

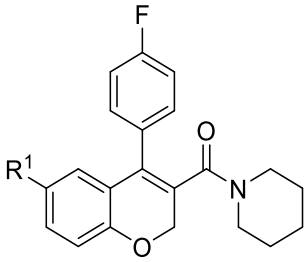
~~7.~~3. The compound according to claim ~~6~~2, wherein the compound formula is:



V-a

or a pharmaceutically acceptable salt thereof.

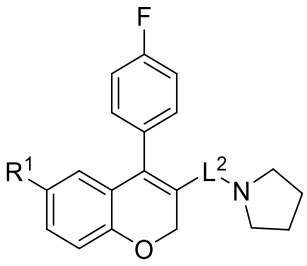
~~8.~~4. The compound according to claim ~~6~~2, wherein the compound formula is:



VI-a

or a pharmaceutically acceptable salt thereof.

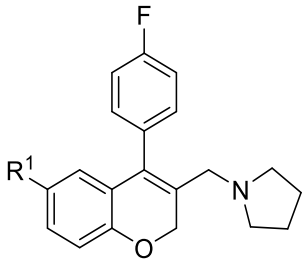
~~9.~~5. The compound according to claim ~~5~~1, wherein the compound formula is:



IV-c

or a pharmaceutically acceptable salt thereof.

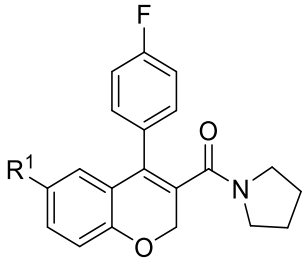
~~10.~~6. The compound according to claim ~~9~~5, wherein the compound formula is:



V-c

or a pharmaceutically acceptable salt thereof.

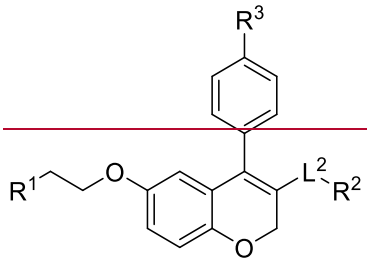
~~11.~~7. The compound according to claim ~~9~~5, wherein the compound formula is:



VI-c

or a pharmaceutically acceptable salt thereof.

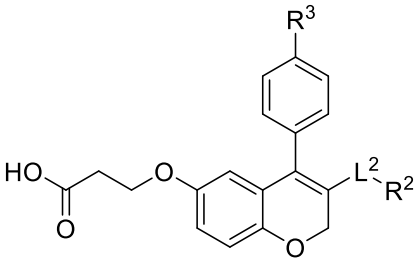
~~12. The compound of claim 2, wherein the compound formula is~~



~~VII~~

~~or a pharmaceutically acceptable salt thereof.~~

~~13.~~8. ~~The~~ A compound of formula **IX:**~~claim 12, wherein the compound formula is~~



IX

or a pharmaceutically acceptable salt thereof, wherein:

R^2 is R, halogen, -C(O)N(R)$_2$, or -N(R)$_2$;

R^3 is hydrogen or an electron withdrawing group;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 member saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur,

or two R on the same nitrogen are taken together with their intervening atoms to form an optionally substituted 5-6 membered heterocyclic ring having 0-1 heteroatoms in addition to the nitrogen attached thereto wherein such heteroatom is oxygen, nitrogen, or sulfur; and

L^2 is a covalent bond or a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-2 methylene units of the chain are independently and optionally replaced with -

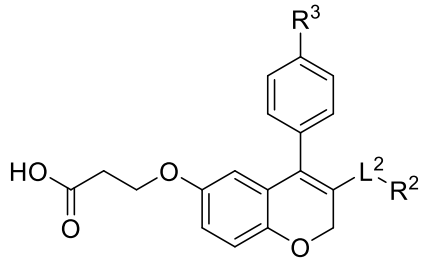
O-, -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -$C(F)_2$-, -N(R)-, -C(O)N(R)-, -N(R)C(O)-, -OC(O)N(R)-, or -N(R)C(O)N(R)-.

9. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^2 is -$N(R)_2$ wherein the two R groups on the nitrogen are taken together with their intervening atoms to form a 5-6 membered heterocyclic ring having no heteroatom in addition to the nitrogen attached thereto, and wherein such 5-6 membered heterocyclic ring is optionally substituted 1-6 times by C_{1-3} aliphatic or halogen.

10. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein R^3 is halogen, -CN, -NO_2, or C_{1-4} aliphatic substituted with 1-9 halogens.

11. The compound of claim 8, or a pharmaceutically acceptable salt thereof, wherein L^2 is C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1 methylene unit of the chain is optionally replaced with -C(O)-.

12. A compound of formula **IX**:



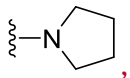
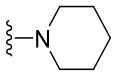
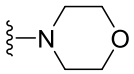
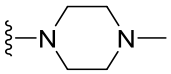
IX

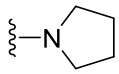
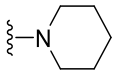
or a pharmaceutically acceptable salt thereof, wherein:

R^2 is -$N(R)_2$ wherein the two R groups on the nitrogen are taken together with their intervening atoms to form a 5-6 membered heterocyclic ring having no heteroatom in addition to the nitrogen attached thereto, and wherein such 5-6 membered heterocyclic ring is optionally substituted 1-6 times by C_{1-3} aliphatic or halogen;

R^3 is halogen;

L^2 is a C_{1-4} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1 methylene unit of the chain is optionally replaced with -C(O)-.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^2 is  ,  ,  or  .

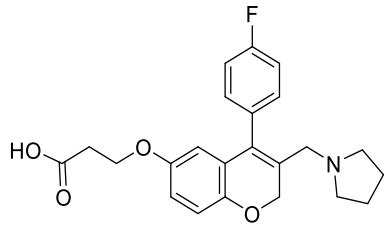
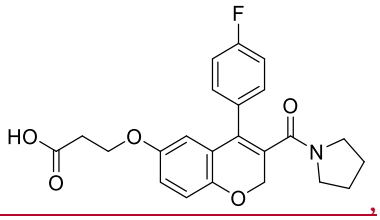
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein R^2 is  or  .

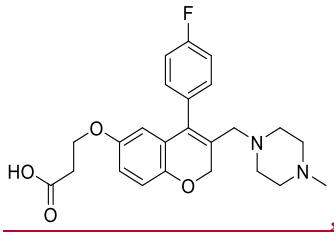
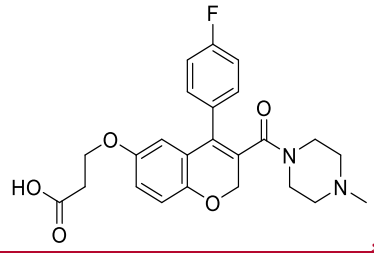
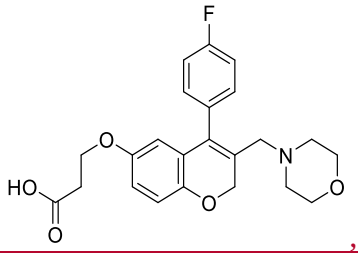
15. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein R^3 is fluorine.

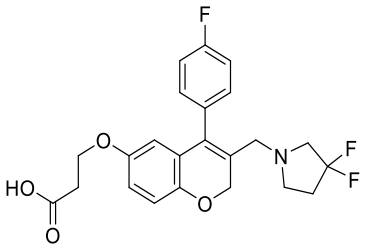
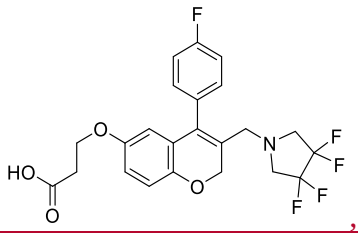
16. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein L^2 is -C(O)-.

17. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein L^2 is $-CH_2-$ or $-(CH_2)_2-$.

18. The compound of claim 12, selected from the group consisting of:

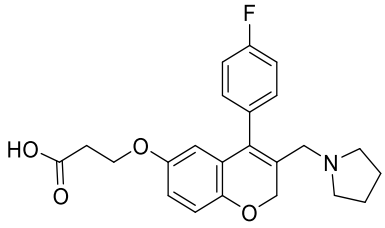
 ,  ,

 ,  ,  ,

 , and  ,

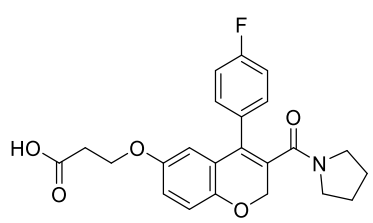
or a pharmaceutically acceptable salt thereof.

19. A compound:

 ,

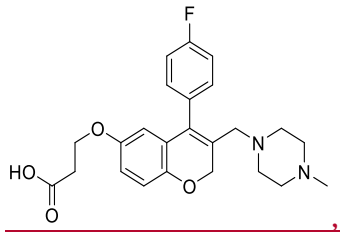
or a pharmaceutically acceptable salt thereof.

20. A compound:

 ,

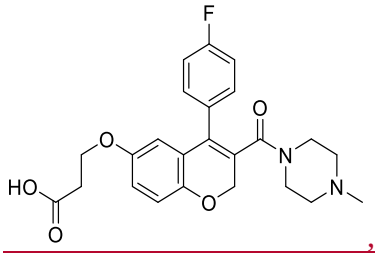
or a pharmaceutically acceptable salt thereof.

21. A compound:



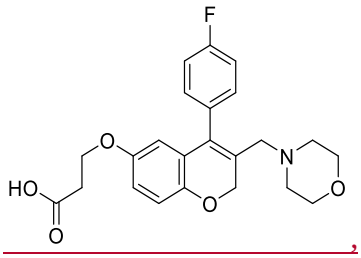
or a pharmaceutically acceptable salt thereof.

22. A compound:



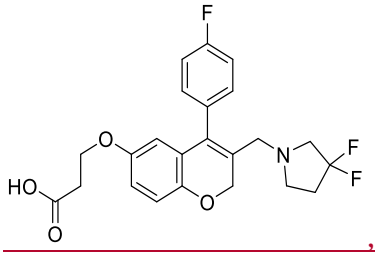
or a pharmaceutically acceptable salt thereof.

23. A compound:



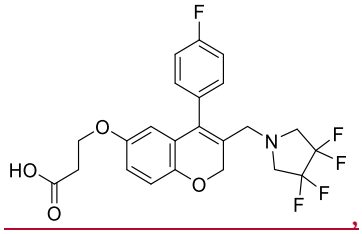
or a pharmaceutically acceptable salt thereof.

24. A compound:



or a pharmaceutically acceptable salt thereof.

25. A compound:



or a pharmaceutically acceptable salt thereof.

~~14.~~26. A pharmaceutically acceptable composition comprising a compound according to any one of claims 1-25 ~~through 13~~, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient, adjuvant, or vehicle.

~~15.~~27. An *in vitro* method of modulating a protein-protein interaction in a cell comprising contacting the cell with a compound according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof ~~through 13~~.

~~16.~~28. The method of claim 27~~15~~, wherein said cell is a T lymphocyte.

~~17.~~29. The method of claim 28~~16~~, wherein said protein-protein interaction modulated comprises TCR and at least one additional protein.

~~18.~~30. The method of claim 28~~16~~, wherein said protein-protein interaction modulated comprises Nck and at least one additional protein.

~~19.~~31. The method of claim 28~~16~~, where said protein-protein interaction modulated comprises TCR and Nck.

~~20.~~32. An *in vitro* method of modulating the protein-protein interaction between TCR-Nck in a biological sample comprising contacting the biological sample with a compound according to any one of claims 1-25, or a pharmaceutically acceptable salt thereof ~~through 13~~.

33. A compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~21.~~34. ~~A method of~~ Use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating the protein-protein interaction between TCR-Nck in a patient ~~comprising administering to the patient a compound according to any one of claims 1 through 13 or a pharmaceutically acceptable composition thereof~~.

~~22.~~35. ~~A method of~~ Use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a TCR-Nck mediated disease, disorder, or condition in a patient in need thereof~~, comprising administering to the patient a compound according to any one of claims 1 through 13 or a pharmaceutically acceptable composition thereof~~.

~~23.~~36. ~~A method of~~ Use of a compound of any one of claims 1-25, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder, or condition in a patient in need thereof, ~~comprising administering to the patient a compound according to any one of claims 1 through 13 or a pharmaceutically acceptable composition thereof,~~ wherein the disease, disorder, or condition is selected from rheumatoid arthritis, psoriatic arthritis, psoriasis, type I diabetes, complications from diabetes, multiple sclerosis, systemic lupus erythematosus, cutaneous lupus erythematosus, atopic dermatitis, mast cell-mediated allergic reactions, autoimmune hepatitis, ~~myanstheniamyasthenia~~ gravis, ankylosing spondylitis, Crohn's disease, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.

37. The use of claim 36, wherein the disease, disorder, or condition is leukemia or lymphoma.

38. The use of claim 37, wherein the leukemia is selected from acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, B-cell prolymphocytic leukemia, Burkitt leukemia, and mast cell leukemia.

39. The use of claim 37, wherein the lymphoma is selected from diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma, and lymphomatoid granulomatosis.

~~24.~~40. The ~~method~~ use according to any one of claims 35-39~~22~~, wherein the compound is to be administered to the patient, and wherein ~~further comprising administering~~ an additional therapeutic agent is to be administered in combination with said compound.