

SOLID AND SALT FORMS OF TCR-NcK MODULATORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 63/614,181, filed on December 22, 2023, the entirety of which is hereby incorporated by reference.

TECHNICAL FIELD OF THE DISCLOSURE

[0002] The present disclosure relates to the solid and salt forms of Compound A, 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2H-chromen-6-yl)oxy)propanoic acid, and to methods of making such solid and salt forms. This disclosure also provides methods of compounds having the ability to inhibit lymphocyte proliferation by blocking the interaction of TCR with Nck. Therefore, such forms and compositions are useful for treating diseases, disorders, or conditions where such interaction triggers a complication such as transplant rejection reactions, immune or autoimmune disease or proliferation.

BACKGROUND OF THE DISCLOSURE

[0003] Autoimmune and inflammatory diseases such as asthma, multiple sclerosis (MS), allergies, rheumatoid arthritis (RA), Crohn's disease, or psoriasis are a diverse group of disease in which the adaptive immune system, particularly via T-lymphocytes, attack of the body's own antigens. It is commonly accepted that T-cells are at the center of all immunological mechanisms. T-cells can recognize both foreign and self-antigens and activate the immune response against them. T-cells recognize antigens via the T-cell antigen receptor (TCR), which is responsible for the transmission of signals to the cytoplasm. Indeed, the fact that the haplotype of the major histocompatibility complex (MHC) is the most important genetic risk factor to the human autoimmune disease places T-cells in the center of all immunopathological events.

[0004] The T-cell recognizes the antigen peptide associated with MHC (pMHC) via the TCR and can translate the small differences in the chemical composition of the pMHC into different quantitative and qualitative results. While a variety of control mechanisms to prevent activation of T-cells bearing TCRs with significant affinity for MHC loaded with self-peptides exists, including suppression of potentially auto-reactive T-cells during maturation in the thymus, these

mechanisms are somewhat insufficient in patients what develop autoimmune diseases and auto-reactive T-cells are activated and expand, overcoming homeostatic controls.

[0005] Upon stimulation, the TCR is activated and undergoes a conformational change that results in the recruitment of different proteins forming the “TCR signalosome” responsible for signal transduction and cell activation. This complex includes the cytosolic protein non-catalytic region of tyrosine kinase protein (Nck) that binds to the proline-rich sequence (PRS) motif present in the CD3 ϵ subunit of the TCR. As a result, the TCR conformational change stabilizes, and the activation signal is efficiently transmitted.

[0006] Current therapies for immune diseases appear as immunosuppressive strategies rather than tolerogenic/immunomodulatory approaches. Azathioprine, methotrexate, mycophenolate, and cladribine are cytostatic. Other therapies force the depletion of T-cells (Alemtuzumab, anti-CD25) or their retention in the lymph nodes (Fingolimod). Alternatively, indirect modulation of the immune system is also being used as a powerful strategy (BG-12). Therefore, despite the central role of TCR signal for activating T-cells in autoimmune diseases, recent efforts to modulate activation of T-cells are focused on modulating co-stimulatory signals, cytokine receptors, etc., with the consequent lack of specificity and many associated side effects.

[0007] To develop a specific immunomodulatory therapy, many efforts have been focused on characterizing the role of Nck in T-cell activation by means of many different research groups. Nck has been attributed an important role in the function of mature T-cells through studies in knock-out mice lacking Nck1 in all tissues and lacking Nck2 conditionally only in T-cells. In these models, the number of peripheral T-cells expressing a TCR with low avidity for self-antigens fell sharply, and a general deterioration in the activation of T-cells by stimulation with weak antigens was observed. Moreover, the importance of Nck was also addressed by generating bone marrow chimeras showing that the PRS motif (Nck binding site in the TCR) is important for the activation of mature T-cells by weak agonists but not strong ones. Similarly, mutation of the PRS motif altered the ability of mice to activate an adaptive immune response in vivo. Furthermore, an inhibitor peptide with high affinity for the SH3.1 domain of Nck alters the assembly of the TCR signalosome, suggesting that the recruitment of Nck is a critical early step in TCR signaling, which represents a target for the modulation of the immune system.

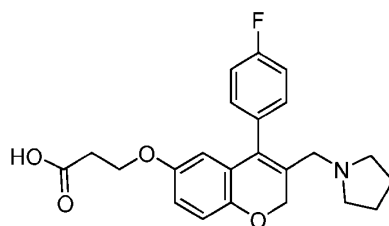
[0008] The document WO 2010/064707 describes a series of compounds derived from 2*H*-chromene for the prevention or treatment of a disease induced by an undesired lymphocyte infiltration mediated by sphingosine-1-phosphate (S1P1).

[0009] The document WO 2012/042078 also describes chrome derivative with inhibitory capacity of the TCR-Nck interaction in T-cells and their use for the treatment of autoimmune diseases, inflammatory diseases, or transplant rejection.

[0010] It would therefore be desirable to provide novel compounds which are capable of inhibiting TCR-Nck interactions in T lymphocytes, and that are good drug candidates. The 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 favourable pharmacokinetic profile. Moreover, the compounds should not be toxic and present minimal side effects.

SUMMARY OF THE DISCLOSURE

[0011] Compounds of the present disclosure, and pharmaceutically acceptable salts and compositions thereof, are effective at modulating the interaction of TCR with Nck and are useful for treating a variety of diseases, disorders, or conditions where such interaction triggers a complication such as transplant rejection reactions, immune or autoimmune disease or proliferation. In general, salt forms or freebase forms, and pharmaceutically acceptable compositions thereof, are useful for treating or lessening the severity of a variety of diseases or disorders as described in detail herein. Such compounds are represented by the chemical structure below, denoted as compound A:



[0012] Compounds of the present 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.

BRIEF DESCRIPTION OF THE FIGURES

[0013] FIG. 1 depicts the XRPD pattern of Compound 1, Form A.

[0014] FIG. 2 depicts the DSC trace of Compound 1, Form A.

[0015] FIG. 3 depicts the XRPD pattern of Compound 1, Form A.

[0016] FIG. 4 depicts the DSC trace of Compound 1, Form A.

[0017] FIG. 5A and FIG. 5B depicts the DSC trace of Compound 2.

[0018] FIG. 6 depicts the DSC trace of Compound 4.

[0019] FIG. 7A and FIG. 7B depicts the DSC trace of Compound 6.

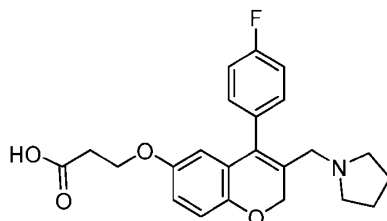
[0020] FIG. 8A and FIG. 8B depicts the DSC trace of Compound 7.

[0021] FIG. 9A and FIG. 9B depicts the DSC trace of Compound 8.

DETAILED DESCRIPTION OF THE DISCLOSURE

General Description of Certain Aspects of the Disclosure

[0022] United States Patent No. 10,696,663 ("the '663 patent," the entireties of which are incorporated herein by reference), describes certain compounds that are effective at modulators of the interaction of TCR with Nck. Such compounds include compound A:



[0023] Compound A, 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2H-chromen-6-yl)oxy)propanoic acid is designated as compound I-33 in the '792 publication.

[0024] It would be desirable to provide a solid form of compound A, or a salt of compound A, that imparts characteristics such as improved aqueous solubility, stability, and ease of formulation. Accordingly, the present disclosure provides solid forms of compound A, salts of compound A, and solid forms of the salts.

Compound A

[0025] It is contemplated that Compound A can exist in a variety of physical forms. For example, Compound A can be in solution, suspension, or in solid form. In certain embodiments, Compound

A is in solid form. When Compound A is in solid form, the Compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0026] In some embodiments, the present disclosure provides a form of Compound A substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include different forms of Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound A. In certain embodiments, at least about 95% by weight of a form of Compound A is present. In still other embodiments of the disclosure, at least about 99% by weight of a form of Compound A is present.

[0027] According to one embodiment, a form of Compound A is present in an amount of at least about 97.0, 97.5, 98.0, 98.5, 99.0, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, a form of Compound A contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, a form of Compound A contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0028] The structure depicted for a form of Compound A is also meant to include all tautomeric forms of Compound A. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure.

[0029] In certain embodiments, Compound A is a crystalline solid. In other embodiments, Compound A is a crystalline solid substantially free of amorphous Compound A. As used herein, the term "substantially free of amorphous Compound A" means that the compound contains no significant amount of amorphous Compound A. In certain embodiments, at least about 95% by weight of crystalline Compound A is present. In still other embodiments of the disclosure, at least about 99% by weight of crystalline Compound A is present.

[0030] In some embodiments, Compound A is amorphous. In some embodiments, Compound A is amorphous, and is substantially free of crystalline Compound A.

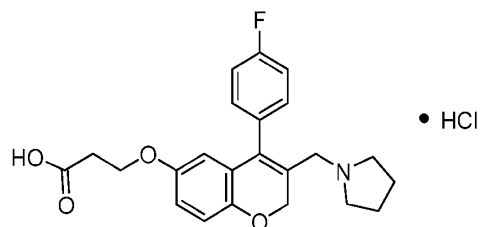
[0031] In some embodiments, the present disclosure provides a composition comprising Compound A and a pharmaceutically acceptable carrier or excipient.

[0032] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound A or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0033] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound A or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 1 (HCl salt of Compound A)

[0034] According to one embodiment, the present invention provides a hydrochloride salt of Compound A, represented by compound 1:



Compound 1

[0035] It will be appreciated by one of ordinary skill in the art that the hydrogen chloride and Compound A are ionically bonded to form Compound 1. It is contemplated that Compound 1 can exist in a variety of physical forms. For example, Compound 1 can be in solution, suspension, or in solid form. In certain embodiments, Compound 1 is in solid form. When Compound 1 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0036] In some embodiments, the present invention provides a method of making a hydrochloride salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the hydrochloride salt of Compound A is Compound 1. In some embodiments, the suitable acid is hydrochloride acid. In some embodiments, the suitable solvent is selected from the group consisting of n-heptane, diisopropyl ether, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, n-butyl acetate, methanol, ethanol, isopropanol, n-propanol, n-butanol, acetic acid, methyl isobutyl ketone, tetrahydrofuran, acetone, methyl ethyl ketone, methyl *tert*-butyl ether, 10% aq. methanol, 10% aq. isopropanol, and water, or a mixture thereof. In certain embodiments, Compound 1 is crystalline. In certain embodiments, Compound 1 is amorphous.

[0037] In some embodiments, the present disclosure provides a form of Compound 1 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include different forms of Compound 1, residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 1. In certain embodiments, at least about 95% by weight of a form of Compound 1 is present. In still other embodiments of the disclosure, at least about 99% by weight of a form of Compound 1 is present. In some embodiments, the residual solvent is selected from the group consisting of n-heptane, diisopropyl ether, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, n-butyl acetate, methanol, ethanol, isopropanol, n-propanol, n-butanol, acetic acid, methyl isobutyl ketone, tetrahydrofuran, acetone, methyl ethyl ketone, methyl *tert*-butyl ether, and water, or a mixture thereof.

[0038] According to one embodiment, a form of Compound 1 is present in an amount of at least about 97.0, 97.5, 98.0, 98.5, 99.0, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, a form of Compound 1 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, a form of Compound 1 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0039] The structure depicted for a form of Compound **1** is also meant to include all tautomeric forms of Compound **1**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this disclosure.

[0040] It has been found that Compound **1** can exist in a variety of solid forms. Exemplary forms include polymorphs such as those described herein.

[0041] In certain embodiments, Compound **1** is a crystalline solid. In other embodiments, Compound **1** is a crystalline solid substantially free of amorphous Compound **1**. As used herein, the term "substantially free of amorphous Compound **1**" means that the compound contains no significant amount of amorphous Compound **1**. In certain embodiments, at least about 95% by weight of crystalline Compound **1** is present. In still other embodiments of the disclosure, at least about 99% by weight of crystalline Compound **1** is present.

[0042] It has been found that Compound **1** can exist in at least one distinct polymorphic form. In certain embodiments, the present disclosure provides a polymorphic form of Compound **1** referred to herein as Form A.

[0043] In some embodiments, Compound **1** is amorphous. In some embodiments, Compound **1** is amorphous, and is substantially free of crystalline Compound **1**.

[0044] Methods for preparing Compound **1** are described *infra*.

[0045] In some embodiments, the present disclosure provides Compound **1**, wherein said compound has a XRPD substantially similar to that depicted in **FIG. 1**. In some embodiments, the present disclosure provides Compound **1**, wherein said compound has a XRPD substantially similar to that depicted in **FIG. 3**.

[0046] In some embodiments, the present disclosure provides Compound **1**, wherein said compound has a DSC substantially similar to that depicted in **FIG. 2**. In some embodiments, the present disclosure provides Compound **1**, wherein said compound has a DSC substantially similar to that depicted in **FIG. 4**.

[0047] In some embodiments, the present disclosure provides a composition comprising Compound **1** and a pharmaceutically acceptable carrier or excipient.

[0048] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **1** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0049] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound **1** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Form A of Compound 1

[0050] In some embodiments, Form A of Compound **1** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 1.1 below. In some embodiments, Form A of Compound **1** has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 1.2 below.

Table 1.1 - XRPD Peak Positions for Form A of Compound 1

Position [$^{\circ}2\theta$] ¹	d (Angstroms)	Intensity [%]
3.9	22.7	1.2
5.9	15.0	2.3
7.8	11.3	1.2
8.9	10.0	5.3
9.7	9.1	39.7
10.5	8.4	9.2
11.6	7.7	12.9
13.3	6.7	7.2
15.1	5.9	5.2
15.5	5.7	5.4
16.1	5.5	7.4
16.4	5.4	21.7
16.9	5.2	37.1
17.6	5.1	16.5

18.1	4.9	19.3
18.4	4.8	4.5
18.9	4.7	9.3
19.4	4.6	49.7
19.5	4.6	64.9
19.7	4.5	27.8
20.1	4.4	6.7
20.5	4.3	11.8
21.0	5.2	8.3
21.5	4.1	16.8
21.8	4.1	20.2
22.4	4.0	29.7
23.0	3.9	56.6
23.2	3.8	37.3
23.9	3.7	14.2
24.7	3.6	100
25.7	3.5	22.5
26.7	3.4	8.1
27.0	3.3	13.7
27.5	3.2	8.2
28.1	3.2	2.1
28.4	3.2	12.1
29.1	3.1	3.3
29.6	3.0	1.6
30.6	2.9	5.1
31.2	2.9	14.1
31.6	2.8	6.5
32.5	2.8	9.8
33.6	2.7	2.6

34.4	2.6	6.2
35.3	2.6	1.1
36.4	2.5	2.8
37.2	2.4	2.4
37.9	2.4	3
40.4	2.2	2.1
41.0	2.2	3.7
41.5	2.2	4.6
44.7	2.0	4.2
45.6	2.0	5.7
48.8	1.9	1.4

¹ In this and all subsequent tables, the position 2θ is within ± 0.2 .

Table 1.2 - XRPD Peak Positions for Form A of Compound 1

Position [2θ] ¹	d (Angstroms)	Intensity [%]
4.0	22.1	1.5
7.7	11.6	1.8
9.6	9.3	47.4
11.5	7.8	10.4
13.1	6.8	7.7
14.8	6.1	2.1
15.4	5.8	7.9
15.9	5.6	5.4
16.3	5.5	62.2
16.8	5.3	57.1
17.4	5.2	6.0
17.9	5.0	18.8
18.8	4.8	12.9
19.2	4.7	30.4
19.4	4.6	45.1

19.6	4.6	100.0
20.1	4.5	4.3
20.4	4.4	10.8
21.4	4.2	10.0
21.7	4.2	24.7
22.3	4.0	20.1
22.9	3.9	46.3
23.1	3.9	50.4
23.8	3.8	14
24.5	3.7	70.0
25.6	3.5	33.9
26.0	3.5	3.5
26.3	3.4	4.1
26.6	3.4	9.3
27.0	3.4	6.6
28.4	3.2	17.8
29.0	3.1	4.8
30.4	3.0	4.8
31.1	2.9	10.5
31.5	2.9	6.4
32.4	2.8	11.6
32.7	2.8	7.6
33.1	2.8	4.9
33.4	2.7	2.1
34.0	2.7	2.7
34.5	2.7	13.3
36.2	2.5	1.4
36.7	2.5	1.7
37.2	2.5	3.1

37.9	2.4	1.4
39.0	2.4	1.8
39.9	2.3	2.5
40.3	2.3	1.8
40.9	2.3	3.3
41.5	2.2	8.2
42.6	2.2	2.3
44.5	22.1	9.2
45.5	11.6	3.2
49.5	9.3	1.6

¹ In this and all subsequent tables, the position 2θ is within ± 0.2 .

[0051] As used herein, the term “about” in the context of peaks at degrees 2θ means that a peak can be the given 2θ value ± 0.2 , or the given 2θ value ± 0.1 , or the given value. For example, a peak of “about 12.0 2θ ” means a peak can be 11.8 2θ , 11.9 2θ , 12.0 2θ , 12.1 2θ , or 12.2 2θ .

[0052] In some embodiments, Form A of Compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 19.5, about 23.0, and about 24.7 degrees 2-theta.

[0053] In some embodiments, Form A of Compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 9.7, about 19.4, about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 9.7, about 19.4, about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has three or more peaks in its X-ray powder diffraction pattern selected from those at about 9.7, about 19.4, about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has four or more peaks in its X-ray powder diffraction pattern selected from

those at about 9.7, about 19.4, about 19.5, about 23.0, and about 24.7 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has all five peaks in its X-ray powder diffraction pattern selected from those at about 9.7, about 19.4, about 19.5, about 23.0, and about 24.7 degrees 2-theta.

[0054] In some embodiments, Form A of Compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 19.6, about 23.1, and about 24.5 degrees 2-theta.

[0055] In some embodiments, Form A of Compound **1** is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 16.3, about 16.8, about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 16.3, about 16.8, about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has three or more peaks in its X-ray powder diffraction pattern selected from those at about 16.3, about 16.8, about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has four or more peaks in its X-ray powder diffraction pattern selected from those at about 16.3, about 16.8, about 19.6, about 23.1, and about 24.5 degrees 2-theta. In some embodiments, Form A of Compound **1** is characterized in that it has all five peaks in its X-ray powder diffraction pattern selected from those at about 16.3, about 16.8, about 19.6, about 23.1, and about 24.5 degrees 2-theta.

[0056] In certain embodiments, the X-ray powder diffraction pattern of Form A of Compound **1** is substantially similar to the XRPD provided in **FIG. 1**. In certain embodiments, the Differential Scanning Calorimetry (DSC) of Form A of Compound **1** is substantially similar to the DSC provided in **FIG. 2**. In certain embodiments, the X-ray powder diffraction pattern of Form A of Compound **1** is substantially similar to the XRPD provided in **FIG. 3**. In certain embodiments, the Differential Scanning Calorimetry (DSC) of Form A of Compound **1** is substantially similar to the DSC provided in **FIG. 4**.

[0057] In some embodiments, Form A of Compound **1** can be characterized by substantial similarity to two or more figures simultaneously (e.g., **FIG. 1** and **FIG. 2**). In some embodiments, Form A of Compound **1** can be characterized by substantial similarity to two or more figures simultaneously (e.g., **FIG. 3** and **FIG. 4**).

[0058] Method for preparing Form A of Compound **1** is described *infra*.

[0059] In some embodiments, the present invention provides Form A of Compound **1**.

[0060] In some embodiments, the present invention provides Compound **1**, wherein said compound is crystalline.

[0061] In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound is substantially free of amorphous Compound **1**.

[0062] In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound is substantially free of impurities.

[0063] In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound has an XRPD substantially similar to that depicted in **FIG. 1**. In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound has an XRPD substantially similar to that depicted in **FIG. 3**.

[0064] In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound has a DSC substantially similar to that depicted in **FIG. 2**. In some embodiments, the present invention provides Form A of Compound **1**, wherein said compound has a DSC substantially similar to that depicted in **FIG. 4**.

[0065] In some embodiments, the present invention provides a composition comprising Form A of Compound **1** and a pharmaceutically acceptable carrier or excipient.

[0066] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Form A of Compound **1** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0067] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Form A of Compound **1** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

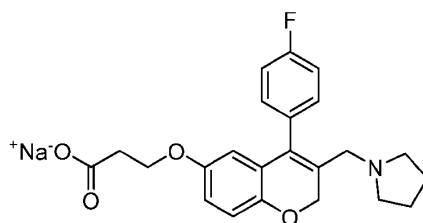
Other Salt Forms of Compound A

[0068] In some embodiments, the present invention provides a salt form of Compound A selected from sodium salt (Compound 2), potassium salt (Compound 3), calcium salt (Compound 4), and magnesium salt (Compound 5), described below. In some embodiments, an acid and Compound A are ionically bonded to form one of compounds 6 through 15, described below. It is contemplated that compounds 2 through 15 can exist in a variety of physical forms. For example, compounds 2 through 15 can be in solution, suspension, or in solid form. In certain embodiments, compounds 2 through 15 are in solid form. When compounds 2 through 15 are in solid form, said compounds may be amorphous, crystalline, or a mixture thereof. Exemplary such solid forms of compounds 2 through 15 are described in more detail below.

Cationic Salts of Compound A

Compound 2 (Sodium Salt of Compound A)

[0069] According to one embodiment, the present invention provides a sodium salt of Compound A, represented by Compound 2:



Compound 2

[0070] It is contemplated that Compound 2 can exist in a variety of physical forms. For example, Compound 2 can be in solution, suspension, or in solid form. In certain embodiments, Compound 2 is in solid form. When Compound 2 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. Exemplary solid forms are described in more detail below.

[0071] In some embodiments, the present invention provides a method of making Compound 2 by mixing a sodium containing reagent and Compound A. In some embodiments, a sodium containing reagent is sodium carbonate. In some embodiments, a sodium containing reagent is sodium-

methoxide. In certain embodiments, Compound **2** is crystalline. In certain embodiments, Compound **2** is amorphous.

[0072] In some embodiments, the present invention provides Compound **2** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess sodium containing reagent, excess Compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound **2**. In certain embodiments, at least about 95% by weight of Compound **2** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **2** is present. In some embodiments, a sodium containing reagent is sodium carbonate or sodium methoxide.

[0073] According to one embodiment, Compound **2** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **2** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 2.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **2** contains no more than about 2.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0074] The structure depicted for Compound **2** is also meant to include all tautomeric forms of Compound **2**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0075] Methods for preparing Compound **2** are described *infra*.

[0076] In some embodiments, the present disclosure provides Compound **2**, wherein said compound has a DSC substantially similar to that depicted in **FIGs. 5A** and **5B**.

[0077] In some embodiments, the present disclosure provides a composition comprising Compound **2** and a pharmaceutically acceptable carrier or excipient.

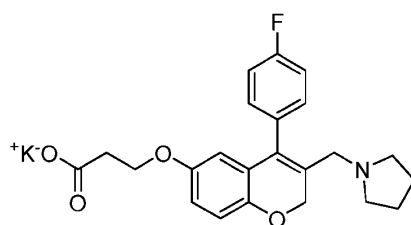
[0078] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said

patient Compound **2** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0079] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound **2** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 3 (Potassium Salt of Compound A)

[0080] According to one embodiment, the present invention provides a potassium salt of Compound **A**, represented by Compound **3**:



Compound 3

[0081] It is contemplated that Compound **3** can exist in a variety of physical forms. For example, Compound **3** can be in solution, suspension, or in solid form. In certain embodiments, Compound **3** is in solid form. When Compound **3** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0082] In some embodiments, the present invention provides a method of making Compound **3** by mixing a potassium containing reagent and Compound **A**. In certain embodiments, the potassium salt of Compound **A** is Compound **3**. In some embodiments, a potassium containing reagent is potassium carbonate. In some embodiments, a potassium containing reagent is potassium *tert*-butoxide. In certain embodiments, Compound **3** is crystalline or amorphous.

[0083] In some embodiments, the present invention provides Compound **3** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess potassium containing reagent, excess Compound **A**, residual solvents, or any other impurities that

may result from the preparation of, and/or isolation of, Compound **3**. In certain embodiments, at least about 95% by weight of Compound **3** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **3** is present. In some embodiments, a potassium containing reagent is potassium carbonate. In some embodiments, a potassium containing reagent is potassium *tert*-butoxide.

[0084] According to one embodiment, Compound **3** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **3** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **3** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0085] The structure depicted for Compound **3** is also meant to include all tautomeric forms of Compound **3**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0086] Methods for preparing Compound **3** are described *infra*.

[0087] In some embodiments, the present disclosure provides a composition comprising Compound **3** and a pharmaceutically acceptable carrier or excipient.

[0088] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **3** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0089] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **3** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 4 (Calcium Salt of Compound A)

[0094] According to one embodiment, Compound **4** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **4** contains no more than about 4.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **4** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0095] The structure depicted for Compound **4** is also meant to include all tautomeric forms of Compound **4**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0096] Methods for preparing Compound **4** are described infra.

[0097] In some embodiments, the present disclosure provides Compound **4**, wherein said compound has a DSC substantially similar to that depicted in **FIG. 6**.

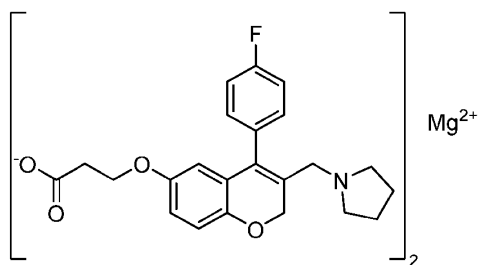
[0098] In some embodiments, the present disclosure provides a composition comprising Compound **4** and a pharmaceutically acceptable carrier or excipient.

[0099] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **4** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0100] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound **4** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 5 (Magnesium Salt of Compound A)

[0101] According to one embodiment, the present invention provides a magnesium salt of Compound A, represented by Compound 5:



Compound 5

[0102] It is contemplated that Compound 5 can exist in a variety of physical forms. For example, Compound 5 can be in solution, suspension, or in solid form. In certain embodiments, Compound 5 is in solid form. When Compound 5 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0103] In some embodiments, the present invention provides a method of making Compound 5 by mixing a magnesium containing reagent and Compound A. In some embodiments, a magnesium containing reagent is magnesium chloride. In certain embodiments, the magnesium salt of Compound A is Compound 5. In certain embodiments, Compound 5 is crystalline or amorphous.

[0104] In some embodiments, the present invention provides Compound 5 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess magnesium containing reagent, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 5. In certain embodiments, at least about 95% by weight of Compound 5 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 5 is present. In some embodiments, a magnesium containing reagent is magnesium chloride.

[0105] According to one embodiment, Compound 5 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 5 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC

chromatogram. In other embodiments, Compound **5** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0106] The structure depicted for Compound **5** is also meant to include all tautomeric forms of Compound **5**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0107] Methods for preparing Compound **5** are described *infra*.

[0108] In some embodiments, the present disclosure provides a composition comprising Compound **5** and a pharmaceutically acceptable carrier or excipient.

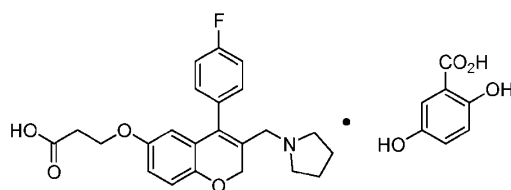
[0109] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **5** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0110] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **5** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Anionic salts of Compound A

Compound 6 (Gentisate Salt of Compound A)

[0111] According to one embodiment, the present invention provides a gentisate salt of Compound **A**, represented by Compound **6**:

**Compound 6**

[0112] It is contemplated that Compound 6 can exist in a variety of physical forms. For example, Compound 6 can be in solution, suspension, or in solid form. In certain embodiments, Compound 6 is in solid form. When Compound 6 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0113] In some embodiments, the present invention provides a method of making a gentisate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the gentisate salt of Compound A is Compound 6. In some embodiments, a suitable acid is gentisic acid. In some embodiments, a suitable solvent is tetrahydrofuran or acetone. In certain embodiments, Compound 6 is crystalline or amorphous.

[0114] In some embodiments, the present invention provides Compound 6 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 6. In certain embodiments, at least about 95% by weight of Compound 6 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 6 is present. In some embodiments, the residual acid is gentisic acid. In some embodiments, the residual solvent is tetrahydrofuran or acetone.

[0115] According to one embodiment, Compound 6 is present in an amount of at least about 97, 97.5, 98.0, 98.6, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 6 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound 6 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single

impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0116] The structure depicted for Compound **6** is also meant to include all tautomeric forms of Compound **6**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0117] Methods for preparing Form A of Compound **6** are described *infra*.

[0118] In some embodiments, the present disclosure provides Compound **6**, wherein said compound has a DSC substantially similar to that depicted in **FIGs. 7A** and **7B**.

[0119] In some embodiments, the present disclosure provides a composition comprising Compound **6** and a pharmaceutically acceptable carrier or excipient.

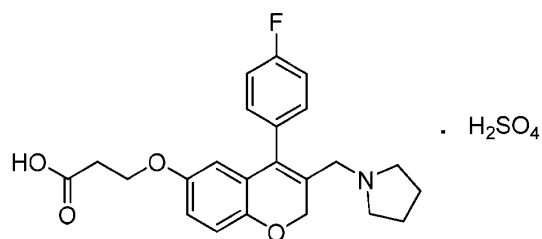
[0120] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **6** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0121] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **6** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

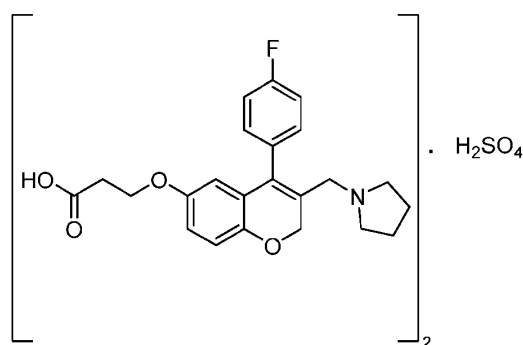
Compound 7 (Sulfate Salt of Compound A)

[0122] According to one embodiment, the present invention provides a sulfate salt of Compound **A**.

[0123] In some embodiments, the sulfate salt of Compound **A** comprises Compound **A** and sulfuric acid at a molar ratio of 1:1 and has the following formula:



[0124] In some embodiments, the sulfate salt of Compound A comprises Compound A and sulfuric acid at a molar ratio of 2:1 and is represented by Compound 7 having the following formula:



Compound 7

[0125] It is contemplated that Compound 7 can exist in a variety of physical forms. For example, Compound 7 can be in solution, suspension, or in solid form. In certain embodiments, Compound 7 is in solid form. When Compound 7 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0126] In some embodiments, the present invention provides a method of making a sulfate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the sulfate salt of Compound A is Compound 7. In some embodiments, the suitable acid is sulfuric acid. In some embodiments, the suitable solvent is methyl iso-butyl ketone. In certain embodiments, Compound 7 is crystalline or amorphous.

[0127] In some embodiments, the present invention provides Compound 7 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 7. In certain embodiments, at least about 95% by

weight of Compound 7 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 7 is present. In some embodiments, the residual acid is sulfuric acid. In some embodiments, the residual solvent is methyl iso-butyl ketone.

[0128] According to one embodiment, Compound 7 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 7 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound 7 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.7 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0129] The structure depicted for Compound 7 is also meant to include all tautomeric forms of Compound 7. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0130] Methods for preparing Form A of Compound 7 are described *infra*.

[0131] In some embodiments, the present disclosure provides Compound 7, wherein said compound has a DSC substantially similar to that depicted in **FIGs. 8A** and **8B**.

[0132] In some embodiments, the present disclosure provides a composition comprising Compound 7 and a pharmaceutically acceptable carrier or excipient.

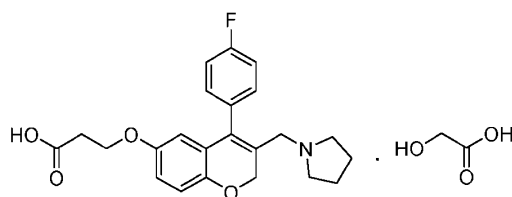
[0133] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound 7 or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0134] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound 7 or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

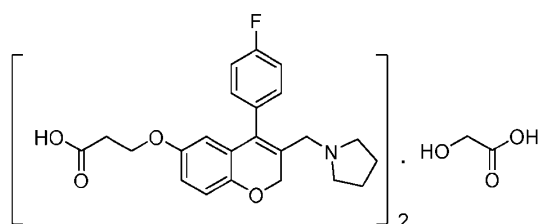
Compound 8 (Glycolate Salt of Compound A)

[0135] According to one embodiment, the present invention provides a glycolate salt of Compound A.

[0136] In some embodiments, the glycolate salt of Compound A comprises Compound A and glycolic acid at a molar ratio of 1:1 and has the following formula:



[0137] In some embodiments, the glycolate salt of Compound A comprises Compound A and glycolic acid at a molar ratio of 2:1 and is represented by Compound 8 having the following formula:



Compound 8

[0138] It is contemplated that Compound 8 can exist in a variety of physical forms. For example, Compound 8 can be in solution, suspension, or in solid form. In certain embodiments, Compound 8 is in solid form. When Compound 8 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0139] In some embodiments, the present invention provides a method of making a glycolate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the glycolate salt of Compound A is Compound 8. In some embodiments, the suitable acid is glycolic acid. In some embodiments, the suitable solvent is acetone. In certain embodiments, Compound 8 is crystalline or amorphous.

[0140] In some embodiments, the present invention provides Compound 8 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound

contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 8. In certain embodiments, at least about 95% by weight of Compound 8 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 8 is present. In some embodiments, the residual acid is glycolic acid. In some embodiments, the residual solvent is acetone.

[0141] According to one embodiment, Compound 8 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 8 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound 8 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0142] The structure depicted for Compound 8 is also meant to include all tautomeric forms of Compound 8. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0143] Methods for preparing Compound 8 are described *infra*.

[0144] In some embodiments, the present disclosure provides Compound 8, wherein said compound has a DSC substantially similar to that depicted in **FIGs. 9A** and **9B**.

[0145] In some embodiments, the present disclosure provides a composition comprising Compound 8 and a pharmaceutically acceptable carrier or excipient.

[0146] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound 8 or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

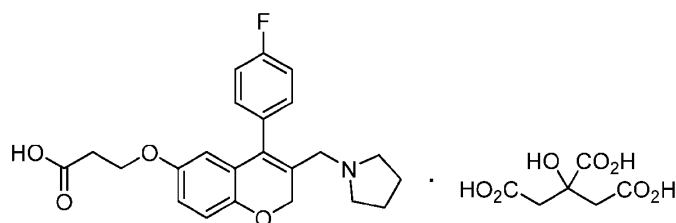
[0147] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound 8 or a composition

thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 9 (Citrate Salt of Compound A)

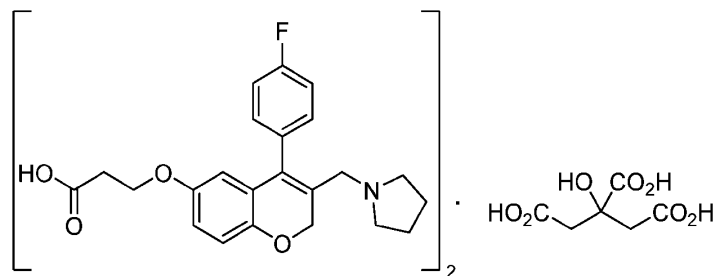
[0148] According to one embodiment, the present invention provides a citrate salt of Compound A.

[0149] In some embodiments, the citrate salt of Compound A comprises Compound A and citric acid at a molar ratio of 1:1 and is represented by Compound 9 having the following formula:

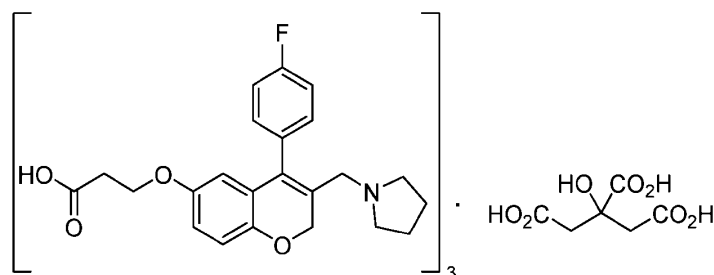


Compound 9

[0150] In some embodiments, the citrate salt of Compound A comprises Compound A and citric acid at a molar ratio of 2:1 and is represented by the following formula:



[0151] In some embodiments, the citrate salt of Compound A comprises Compound A and citric acid at a molar ratio of 3:1 and is represented by the following formula:



[0152] It is contemplated that Compound 9 can exist in a variety of physical forms. For example, Compound 9 can be in solution, suspension, or in solid form. In certain embodiments, Compound 9 is in solid form. When Compound 9 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0153] In some embodiments, the present invention provides a method of making a citrate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the citrate salt of Compound A is Compound 9. In some embodiments, the suitable acid is citric acid. In some embodiments, the suitable solvent is acetone. In certain embodiments, Compound 9 is crystalline or amorphous.

[0154] In some embodiments, the present invention provides Compound 9 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 9. In certain embodiments, at least about 95% by weight of Compound 9 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 9 is present. In some embodiments, the residual acid is citric acid. In some embodiments, the residual solvent is acetone.

[0155] According to one embodiment, Compound 9 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 9 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound 9 contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single

impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0156] The structure depicted for Compound **9** is also meant to include all tautomeric forms of Compound **9**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0157] Methods for preparing Compound **9** are described *infra*.

[0158] In some embodiments, the present disclosure provides a composition comprising Compound **9** and a pharmaceutically acceptable carrier or excipient.

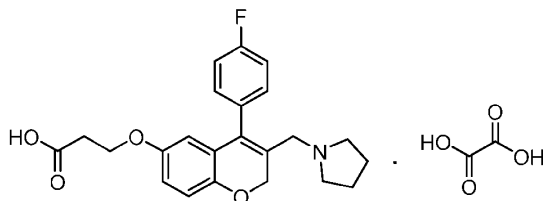
[0159] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **9** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0160] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **9** or a composition thereof. In some embodiments the method of modulating TCR-Nck is used to treat autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

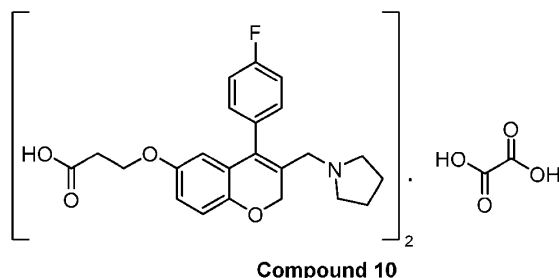
Compound 10 (Oxalate Salt of Compound A)

[0161] According to one embodiment, the present invention provides an oxalate salt of Compound **A**.

[0162] In some embodiments, the oxalate salt of Compound **A** comprises Compound **A** and oxalic acid at a molar ratio of 1:1 and is represented by the following formula:



[0163] In some embodiments, the oxalate salt of Compound A comprises Compound A and oxalic acid at a molar ratio of 2:1 and is represented as Compound 10 having the following formula:



[0164] It is contemplated that Compound 10 can exist in a variety of physical forms. For example, Compound 10 can be in solution, suspension, or in solid form. In certain embodiments, Compound 10 is in solid form. When Compound 10 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0165] In some embodiments, the present invention provides a method of making an oxalate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the oxalate salt of Compound A is Compound 10. In some embodiments, the suitable reagent is oxalic acid. In some embodiments, the suitable solvent is tetrahydrofuran. In certain embodiments, Compound 10 is crystalline or amorphous.

[0166] In some embodiments, the present invention provides Compound 10 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 10. In certain embodiments, at least about 95% by weight of Compound 10 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 10 is present. In some embodiments, the residual acid is oxalic acid. In some embodiments, the residual solvent is tetrahydrofuran.

[0167] According to one embodiment, Compound 10 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 10 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC

chromatogram. In other embodiments, Compound **10** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0168] The structure depicted for Compound **10** is also meant to include all tautomeric forms of Compound **10**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0169] Methods for preparing Compound **10** are described *infra*.

[0170] In some embodiments, the present disclosure provides a composition comprising Compound **10** and a pharmaceutically acceptable carrier or excipient.

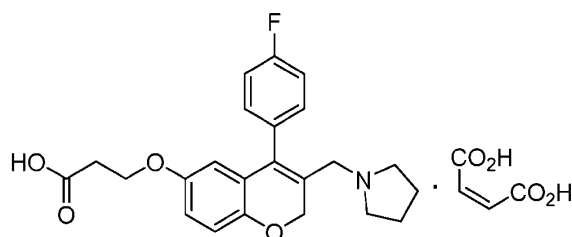
[0171] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **10** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0172] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **10** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

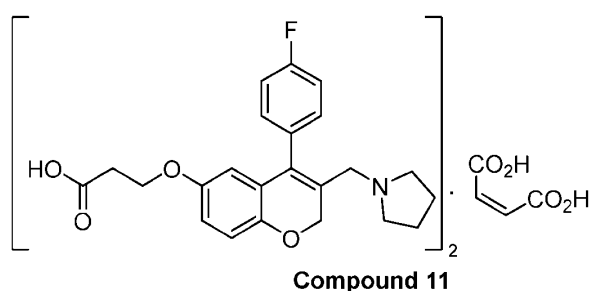
Compound 11 (Maleate Salt of Compound A)

[0173] According to one embodiment, the present invention provides a maleate salt of Compound **A**.

[0174] In some embodiments, the maleate salt of Compound **A** comprises Compound **A** and maleic acid at a molar ratio of 1:1 and represented by the following formula:



[0175] In some embodiments, the maleate salt of Compound A comprises Compound A and maleic acid at a molar ratio of 2:1 and is represented as Compound 11 having the following formula:



[0176] It is contemplated that Compound 11 can exist in a variety of physical forms. For example, Compound 11 can be in solution, suspension, or in solid form. In certain embodiments, Compound 11 is in solid form. When Compound 11 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0177] In some embodiments, the present invention provides a method of making maleate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the maleate salt of Compound A is Compound 11. In some embodiments, the suitable acid is maleic acid. In some embodiments, the suitable solvent is acetone, tetrahydrofuran, or methyl iso-butyl ketone. In some embodiments, the suitable solvent is acetone. In some embodiments, the suitable solvent is tetrahydrofuran. In some embodiments, the suitable solvent is methyl iso-butyl ketone. In certain embodiments, Compound 11 is crystalline or amorphous.

[0178] In some embodiments, the present invention provides Compound 11 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 11. In certain embodiments, at least about 95% by

weight of Compound **11** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **11** is present. In some embodiments, the residual acid is maleic acid. In some embodiments, the residual solvent is acetone, tetrahydrofuran, or methyl iso-butyl ketone. In some embodiments, the residual solvent is acetone. In some embodiments, the residual solvent is tetrahydrofuran. In some embodiments, the residual solvent is methyl iso-butyl ketone.

[0179] According to one embodiment, Compound **11** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **11** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **11** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0180] The structure depicted for Compound **11** is also meant to include all tautomeric forms of Compound **11**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0181] Methods for preparing Compound **11** are described *infra*.

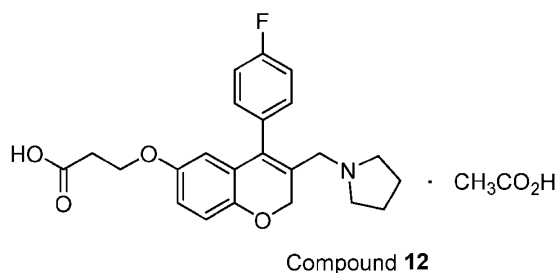
[0182] In some embodiments, the present disclosure provides a composition comprising Compound **11** and a pharmaceutically acceptable carrier or excipient.

[0183] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **11** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0184] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **11** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 12 (Acetate Salt of Compound A)

[0185] According to one embodiment, the present invention provides an acetate salt of Compound A, represented by Compound 12:



[0186] It is contemplated that Compound 12 can exist in a variety of physical forms. For example, Compound 12 can be in solution, suspension, or in solid form. In certain embodiments, Compound 12 is in solid form. When Compound 12 is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0187] In some embodiments, the present invention provides a method of making an acetate salt of Compound A by mixing a suitable acid and Compound A in a suitable solvent. In certain embodiments, the acetate salt of Compound A is Compound 12. In some embodiments, the suitable acid is acetic acid. In some embodiments, the suitable solvent is tetrahydrofuran. In certain embodiments, Compound 12 is crystalline or amorphous.

[0188] In some embodiments, the present invention provides Compound 12 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound A, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound 12. In certain embodiments, at least about 95% by weight of Compound 12 is present. In still other embodiments of the invention, at least about 99% by weight of Compound 12 is present. In some embodiments, the residual acid is acetic acid. In some embodiments, the residual solvent is tetrahydrofuran.

[0189] According to one embodiment, Compound 12 is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound 12 contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about

1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **12** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0190] The structure depicted for Compound **12** is also meant to include all tautomeric forms of Compound **12**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0191] Methods for preparing Compound **12** are described *infra*.

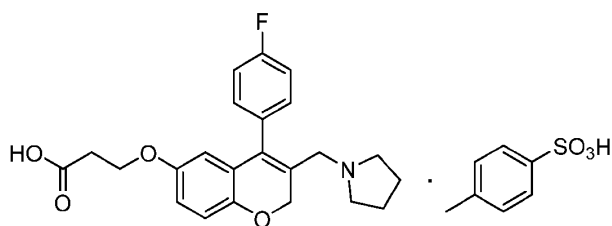
[0192] In some embodiments, the present disclosure provides a composition comprising Compound **12** and a pharmaceutically acceptable carrier or excipient.

[0193] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **12** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0194] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **12** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 13 (Tosylate Salt of Compound A)

[0195] According to one embodiment, the present invention provides a tosylate salt of Compound **A**, represented by Compound **13**:

**Compound 13**

[0196] It is contemplated that Compound **13** can exist in a variety of physical forms. For example, Compound **13** can be in solution, suspension, or in solid form. In certain embodiments, Compound **13** is in solid form. When Compound **13** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0197] In some embodiments, the present invention provides a method of making a tosylate salt of Compound **A** by mixing a suitable acid and Compound **A** in a suitable solvent. In certain embodiments, the tosylate salt of Compound **A** is Compound **13**. In some embodiments, the suitable acid is *p*-toluene sulfonic acid. In some embodiments, the suitable solvent is tetrahydrofuran. In certain embodiments, Compound **13** is crystalline or amorphous.

[0198] In some embodiments, the present invention provides Compound **13** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound **13**. In certain embodiments, at least about 95% by weight of Compound **13** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **13** is present. In some embodiments, the residual acid is *p*-toluene sulfonic acid. In some embodiments, the residual solvent is tetrahydrofuran.

[0199] According to one embodiment, Compound **13** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **13** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **13** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single

impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0200] The structure depicted for Compound **13** is also meant to include all tautomeric forms of Compound **13**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0201] Methods for preparing Compound **13** are described *infra*.

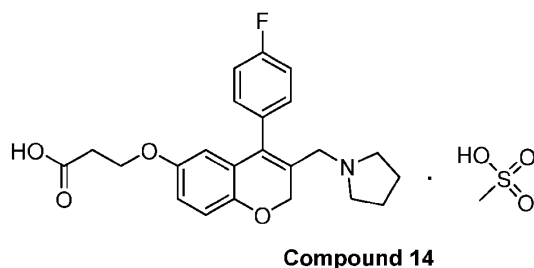
[0202] In some embodiments, the present disclosure provides a composition comprising Compound **13** and a pharmaceutically acceptable carrier or excipient.

[0203] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **13** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0204] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound **13** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

Compound 14 (Mesylate Salt of Compound A)

[0205] According to one embodiment, the present invention provides a mesylate salt of Compound **A**, represented by Compound **14**:



[0206] It is contemplated that Compound **14** can exist in a variety of physical forms. For example, Compound **14** can be in solution, suspension, or in solid form. In certain embodiments, Compound **14** is in solid form. When Compound **14** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0207] In some embodiments, the present invention provides a method of making a mesylate salt of Compound **A** by mixing a suitable acid and Compound **A** in a suitable solvent. In certain embodiments, the mesylate salt of Compound **A** is Compound **14**. In some embodiments, the suitable acid is methane sulfonic acid. In some embodiments, the suitable solvent is tetrahydrofuran. In certain embodiments, Compound **14** is crystalline or amorphous.

[0208] In some embodiments, the present invention provides Compound **14** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound **14**. In certain embodiments, at least about 95% by weight of Compound **14** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **14** is present. In some embodiments, the residual acid is methane sulfonic acid. In some embodiments, the residual solvent is tetrahydrofuran.

[0209] According to one embodiment, Compound **14** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **14** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **14** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0210] The structure depicted for Compound **14** is also meant to include all tautomeric forms of Compound **14**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0211] Methods for preparing Compound **14** are described *infra*.

[0212] In some embodiments, the present disclosure provides a composition comprising Compound **14** and a pharmaceutically acceptable carrier or excipient.

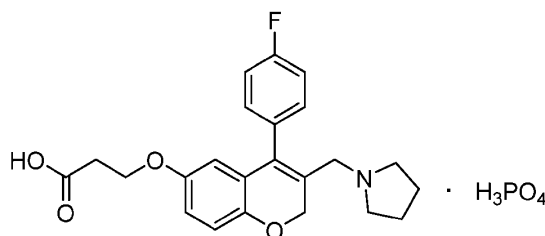
[0213] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **14** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0214] In some embodiments, the present invention provides a method of modulating TCR-NcK interaction in a patient, comprising administering to said patient Compound **14** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

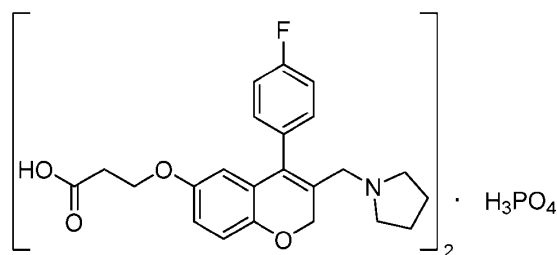
Compound 15 (Phosphate Salt of Compound A)

[0215] According to one embodiment, the present invention provides a phosphate salt of Compound **A**.

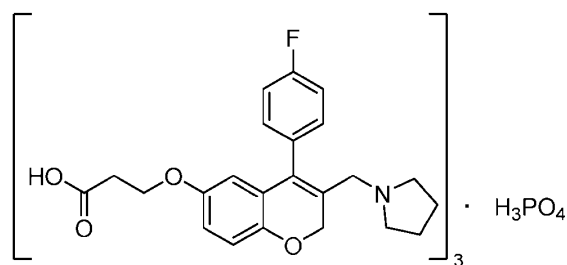
[0216] In some embodiments, the phosphate salt of Compound **A** comprises Compound **A** and *o*-phosphoric acid at a molar ratio of 1:1 and is represented by the following formula:



[0217] In some embodiments, the phosphate salt of Compound **A** comprises Compound **A** and *o*-phosphoric acid at a molar ratio of 2:1 and is represented by the following formula:



[0218] In some embodiments, the phosphate salt of Compound **A** comprises Compound **A** and *o*-phosphoric acid at a molar ratio of 3:1 and is represented as Compound **15** having the following formula:



Compound 15

[0219] It is contemplated that Compound **15** can exist in a variety of physical forms. For example, Compound **15** can be in solution, suspension, or in solid form. In certain embodiments, Compound **15** is in solid form. When Compound **15** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof.

[0220] In some embodiments, the present invention provides a method of making Compound **15** by mixing a suitable acid and Compound **A**. In certain embodiments, the phosphate salt of Compound **A** is Compound **15**. In some embodiments, a suitable acid is *o*-phosphoric acid. In some embodiments, the suitable solvent is ethanol or tetrahydrofuran. In some embodiments, the suitable solvent is ethanol. In some embodiments, the suitable solvent is tetrahydrofuran. In certain embodiments, Compound **15** is crystalline or amorphous.

[0221] In some embodiments, the present invention provides Compound **15** substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include residual acid, excess Compound **A**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, Compound **15**. In certain embodiments, at least about 95% by

weight of Compound **15** is present. In still other embodiments of the invention, at least about 99% by weight of Compound **15** is present. In some embodiments, the residual acid is *o*-phosphoric acid. In some embodiments, the residual solvent is ethanol or tetrahydrofuran. In some embodiments, the residual solvent is ethanol. In some embodiments the residual solvent is tetrahydrofuran.

[0222] According to one embodiment, Compound **15** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, Compound **15** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, Compound **15** contains no more than about 1.0% area percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[0223] The structure depicted for Compound **15** is also meant to include all tautomeric forms of Compound **15**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0224] Methods for preparing Compound **15** are described *infra*.

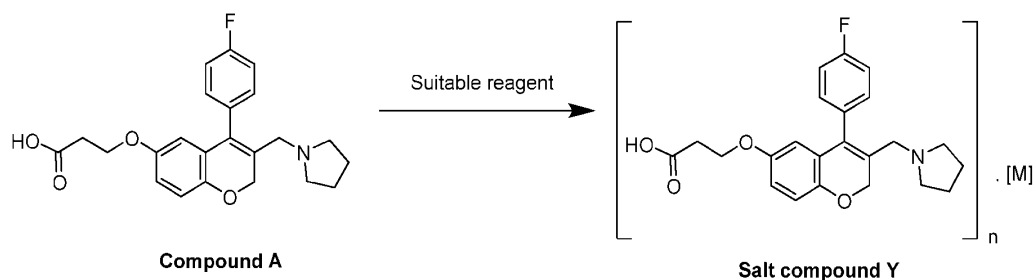
[0225] In some embodiments, the present disclosure provides a composition comprising Compound **15** and a pharmaceutically acceptable carrier or excipient.

[0226] In some embodiments, the present invention provides a method of treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising administering to said patient Compound **15** or a composition thereof. In some embodiments, a disorder mediated by TCR-Nck interaction is selected from those as described herein.

[0227] In some embodiments, the present invention provides a method of modulating TCR-Nck interaction in a patient, comprising administering to said patient Compound **15** or a composition thereof. In some embodiments, a patient has a disorder selected from autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

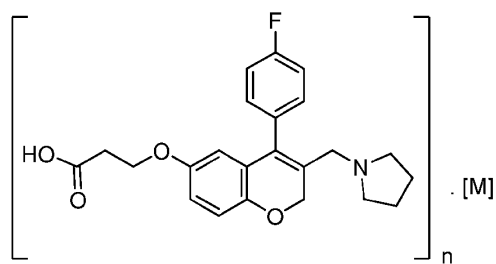
General Methods of Providing a Salt Compound

[0228] Compound **A** is prepared according to the methods described in detail in United States Patent No. 10,696,663 (the '663 patent), the entirety of which is hereby incorporated herein by reference. Salt compounds of general formula **Y**, which formula encompasses, *inter alia*, salt compounds **2** through **5**, and/or particular forms thereof, are prepared from Compound **A**, according to the general Scheme below.



[0229] For instance, each of compounds **2** through **5**, and forms thereof, are prepared from Compound **A** by combining Compound **A** with an appropriate or suitable reagent to form a salt Compound **Y**. Thus, another aspect of the present invention provides a method for preparing compounds **2** through **5**, and solid forms thereof.

[0230] As described generally above, in some embodiments, the present invention provides a method for preparing a salt Compound of the general formula **Y**:

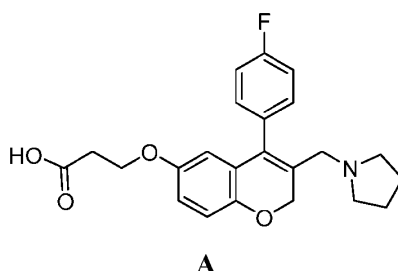


salt Compound **Y**

wherein $n = 1$ or 2 ;

comprising steps of:

combining Compound **A**:



with a suitable reagent and optionally a solvent under conditions for forming a salt compound of formula **Y**.

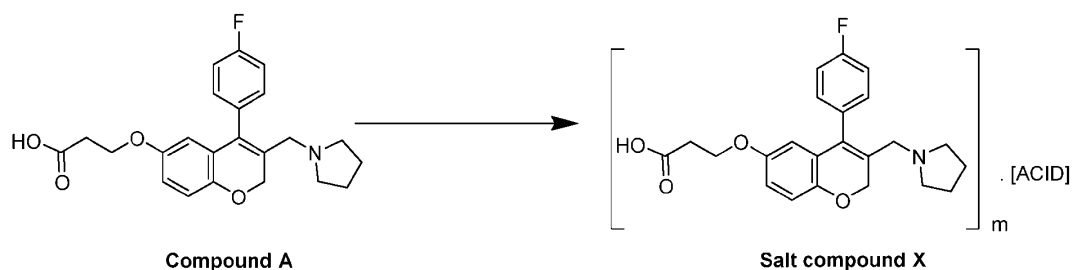
[0231] In some embodiments, the suitable reagent is sodium carbonate or sodium methoxide. In some embodiments, the suitable reagent is sodium carbonate. In some embodiments, the suitable reagent is sodium methoxide. In some embodiments, the present invention provides a method of making a sodium salt of Compound **A**. In certain embodiments, the sodium salt of Compound **A** is Compound **2**.

[0232] In some embodiments, the suitable reagent is potassium carbonate or potassium *tert*-butoxide. In some embodiments, the suitable reagent is potassium carbonate. In some embodiments, the suitable reagent is potassium *tert*-butoxide. In some embodiments, the present invention provides a method of making a potassium salt of Compound **A**. In certain embodiments, the potassium salt of Compound **A** is Compound **3**.

[0233] In some embodiments, the suitable reagent is calcium carbonate or calcium hydroxide. In some embodiments, the suitable reagent is calcium carbonate. In some embodiments, the suitable reagent is calcium hydroxide. In some embodiments, the present invention provides a method of making a calcium salt of Compound **A**. In certain embodiments, the calcium salt of Compound **A** is Compound **4**.

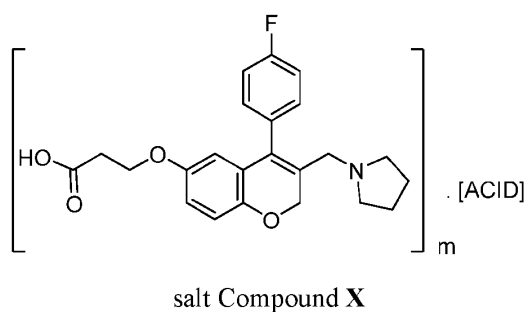
[0234] In some embodiments, the suitable reagent is magnesium chloride. In some embodiments, the present invention provides a method of making a magnesium salt of Compound **A**. In certain embodiments, the magnesium salt of Compound **A** is Compound **5**.

[0235] Salt compounds of general formula **X**, which formula encompasses, *inter alia*, salt compounds **1** and **6** through **15**, and/or particular forms thereof, are prepared from Compound **A**, according to the general Scheme below.



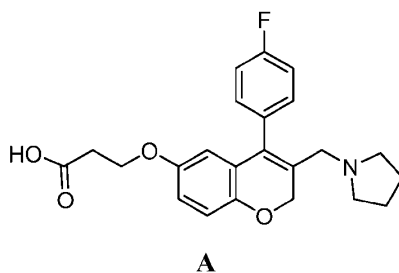
[0236] For instance, each of compounds **1** and **6** through **15**, and forms thereof, are prepared from Compound **A** by combining Compound **A** with an appropriate acid to form a salt of that acid. Thus, another aspect of the present invention provides a method for preparing compounds **1** and **6** through **15**, and solid forms thereof.

[0237] As described generally above, in some embodiments, the present invention provides a method for preparing a salt Compound of the general formula **X**:



wherein $m = 1, 2, 3$ or 4 comprising steps of:

combining Compound **A**:



with a suitable acid and optionally a solvent under conditions for forming a salt compound of formula **X**.

[0238] In some embodiments, the suitable acid is hydrochloric acid. In some embodiments, the present invention provides a method of making a hydrochloride salt of Compound **A**. In certain

embodiments, the hydrochloride salt of Compound **A** is Compound **1**. In certain embodiments, the hydrochloride salt of Compound **A** is Form A of Compound **1**.

[0239] In some embodiments, the suitable acid is gentisic acid. In some embodiments, the present invention provides a method of making a gentisate salt of Compound **A**. In certain embodiments, the gentisate salt of Compound **A** is Compound **6**.

[0240] In some embodiments, the suitable acid is sulfuric acid. In some embodiments, the present invention provides a method of making a sulfate salt of Compound **A**. In certain embodiments, the sulfate salt of Compound **A** is Compound **7**.

[0241] In some embodiments, the suitable acid is glycolic acid. In some embodiments, the present invention provides a method of making a glycolate salt of Compound **A**. In certain embodiments, the glycolate salt of Compound **A** is Compound **8**.

[0242] In some embodiments, the suitable acid is citric acid. In some embodiments, the present invention provides a method of making a citrate salt of Compound **A**. In certain embodiments, the citrate salt of Compound **A** is Compound **9**.

[0243] In some embodiments, the suitable acid is oxalic acid. In some embodiments, the present invention provides a method of making an oxalate salt of Compound **A**. In certain embodiments, the oxalate salt of Compound **A** is Compound **10**.

[0244] In some embodiments, the suitable acid is maleic acid. In some embodiments, the present invention provides a method of making a maleate salt of Compound **A**. In certain embodiments, the maleate salt of Compound **A** is Compound **11**.

[0245] In some embodiments, the suitable acid is acetic acid. In some embodiments, the present invention provides a method of making an acetate salt of Compound **A**. In certain embodiments, the acetate salt of Compound **A** is Compound **12**.

[0246] In some embodiments, the suitable acid is *p*-toluene sulfonic acid. In some embodiments, the present invention provides a method of making a tosylate salt of Compound **A**. In certain embodiments, the tosylate salt of Compound **A** is Compound **13**.

[0247] In some embodiments, the suitable acid is methanesulfonic acid. In some embodiments, the present invention provides a method of making a mesylate salt of Compound **A**. In certain embodiments, the mesylate salt of Compound **A** is Compound **14**.

[0248] In some embodiments, the suitable acid is *o*-phosphoric acid. In some embodiments, the present invention provides a method of making a phosphate salt of Compound A. In certain embodiments, the phosphate salt of Compound A is Compound 15.

[0249] In certain embodiment, Compound A and the suitable acid is present in a molar ratio of 1:1. In certain embodiment, Compound A and the suitable acid is present in a molar ratio of 2:1. In certain embodiment, Compound A and the suitable acid is present in a molar ratio of 3:1. As described generally above, the molar ratio of Compound A and the suitable acid in a salt Compound of formula X can be readily determined by a person skilled in the art.

[0250] A suitable solvent may be any solvent system (e.g., one solvent or a mixture of solvents) in which Compound A and/or an acid are soluble or are at least partially soluble.

[0251] Examples of suitable solvents useful in the present invention include, but are not limited to protic solvents, aprotic solvents, polar aprotic solvent, or mixtures thereof. In certain embodiments, suitable solvents include an ether, an ester, an alcohol, a ketone, or a mixture thereof. In some embodiments, the solvent is one or more organic alcohols. In some embodiments, the solvent is chlorinated. In some embodiments, the solvent is an aromatic solvent.

[0252] In certain embodiments, a suitable solvent is methanol, ethanol, isopropanol, or acetone wherein said solvent is anhydrous or in combination with water or heptane. In some embodiments, suitable solvents include tetrahydrofuran, dimethylformamide, dimethylsulfoxide, glyme, diglyme, methyl t-butyl ether, t-butanol, n-butanol, and acetonitrile. In some embodiments, a suitable solvent is ethanol. In some embodiments, a suitable solvent is anhydrous ethanol. In some embodiments, the suitable solvent is MTBE.

[0253] In some embodiments, a suitable solvent is ethyl acetate. In some embodiments, a suitable solvent is a mixture of methanol and methylene chloride. In some embodiments, a suitable solvent is a mixture of acetonitrile and water. In certain embodiments, a suitable solvent is methyl acetate, isopropyl acetate, acetone, or tetrahydrofuran. In certain embodiments, a suitable solvent is diethylether. In certain embodiments, a suitable solvent is water. In certain embodiments, a suitable solvent is methyl ethyl ketone. In certain embodiments, a suitable solvent is methyl iso-butyl ketone. In certain embodiments, a suitable solvent is toluene.

[0254] In some embodiments, the present invention provides a method for preparing a salt compound of the general formula X or Y, comprising one or more steps of removing a solvent and adding a solvent. In some embodiments, an added solvent is the same as the solvent removed. In

some embodiments, an added solvent is different from the solvent removed. Means of solvent removal are known in the synthetic and chemical arts and include, but are not limited to, any of those described herein and in the Exemplification. In some embodiments, a solvent is selected from the group consisting of n-heptane, diisopropyl ether, 2-methyltetrahydrofuran, ethyl acetate, isopropyl acetate, n-butyl acetate, methanol, ethanol, isopropanol, n-propanol, n-butanol, acetic acid, methyl isobutyl ketone, tetrahydrofuran, acetone, methyl ethyl ketone, methyl *tert*-butyl ether, 10% aq. methanol, 10% aq. isopropanol, and water, or a mixture thereof.

[0255] In some embodiments, a method for preparing a salt compound of the general formula **X** or **Y** comprises one or more steps of heating or cooling a preparation.

[0256] In some embodiments, a method for preparing a salt compound of the general formula **X** or **Y** comprises one or more steps of agitating or stirring a preparation.

[0257] In some embodiments, a method for preparing a salt compound of the general formula **X** or **Y** comprises a step of heating.

[0258] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises a step of adding a suitable acid to a solution or slurry of Compound **A**.

[0259] In some embodiments, a method for preparing a salt compound of the general formula **Y** comprises a step of adding a suitable reagent to a solution or slurry of Compound **A**.

[0260] In some embodiments, a method for preparing a salt compound of the general formula **X** or **Y** comprises a step of adding the suitable reagent to a heated solution or slurry of Compound **A**.

[0261] In some embodiments, a method for preparing a salt compound of the general formula **X** comprises a step of stirring or agitating the heated mixture containing Compound **A** and the suitable acid for a brief period before cooling and stirring the mixture at ambient temperature.

[0262] In some embodiments, a method for preparing a salt compound of the general formula **Y** comprises a step of adding the suitable reagent to a solution or slurry of Compound **A** at 0-5°C.

[0263] In some embodiment, a method for preparing a salt compound of the general formula **Y** comprises a step of adding the suitable reagent to a solution or slurry of Compound **A** at ambient temperature.

[0264] In some embodiments, a method for preparing a salt compound of the general formula **Y** comprises a step of adding a combination of suitable reagents to a solution or slurry of Compound **A** at ambient temperature.

[0265] In certain embodiments, a salt compound of formula **X** or **Y** precipitates from the mixture. In another embodiment, a salt compound of formula **X** or **Y** crystallizes from the mixture. In other embodiments, a salt compound of formula **X** or **Y** crystallizes from solution following seeding of the solution (i.e., adding crystals of a salt compound of formula **X** or **Y** to the solution).

[0266] A salt compound of formula **X** or **Y** can precipitate out of the reaction mixture or be generated by removal of part or all of the solvent through methods such as evaporation, distillation, filtration (ex. nanofiltration, ultrafiltration), reverse osmosis, absorption and reaction, by adding an anti-solvent such as heptane, by cooling or by different combinations of these methods.

[0267] As described generally above, a salt compound of formula **X** or **Y** is optionally isolated. It will be appreciated that a salt compound of formula **X** or **Y** may be isolated by any suitable physical means known to one of ordinary skill in the art. In certain embodiments, precipitated solid salt compound of formula **X** or **Y** is separated from the supernatant by filtration. In other embodiments, precipitated solid salt compound of formula **X** or **Y** is separated from the supernatant by decanting the supernatant.

[0268] In certain embodiments, a salt compound of formula **X** or **Y** is separated from the supernatant by filtration.

[0269] In certain embodiments, an isolated salt compound of formula **X** or **Y** is dried in air. In other embodiments, isolated salt compound of formula **X** or **Y** is dried under reduced pressure, optionally at elevated temperature.

[0270] In certain embodiments, Compound **1** is suspended in suitable solvent to form a suspension or a solution. In certain embodiments, the suspension is heated for a brief period before stirring it at ambient temperature to obtain Form A of Compound **1**. In certain embodiments, the suspension is heated for a brief period to form a solution before stirring it at ambient temperature to obtain Form A of Compound **1**. In certain embodiment, the Form A of Compound **1** is obtained by cooling a heated solution of Compound **1** in a suitable solvent. In certain embodiment, the Form A of Compound **1** is obtained by cooling a heated suspension of Compound **1** in a suitable solvent.

[0271] In certain embodiments Form A of Compound **1** can precipitate out of the reaction mixture or be generated by removal of part or all of the solvent through methods such as evaporation, distillation, filtration (ex. nanofiltration, ultrafiltration), reverse osmosis, absorption and reaction, by adding an anti-solvent such as heptane, by cooling or by different combinations of these methods.

[0272] In certain embodiments, precipitated solid Form A of Compound 1 is separated from the supernatant by filtration. In other embodiments, Form A of Compound 1 is separated from the supernatant by decanting the supernatant. In certain embodiments, Form A of Compound 1 is separated from the supernatant by filtration.

[0273] In certain embodiments, Form A of Compound 1 is dried in air. In other embodiments, Form A of Compound 1 is dried under reduced pressure, optionally at elevated temperature.

[0274] In certain embodiments, Compound 1 is suspended in n-heptane and the suspension is heated for a brief period (*e.g.*, reflux at 95-100°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0275] In certain embodiments, Compound 1 is suspended in diisopropyl ether and the suspension is heated for a brief period (*e.g.*, reflux at 65-70°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0276] In certain embodiments, Compound 1 is suspended in 2-methyltetrahydrofuran and the suspension is heated for a brief period (*e.g.*, reflux at 80-85°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0277] In certain embodiments, Compound 1 is suspended in ethyl acetate and the suspension is heated for a brief period (*e.g.*, reflux at 75-80°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0278] In certain embodiments, Compound 1 is suspended in isopropyl acetate and the suspension is heated for a brief period (*e.g.*, reflux at 85-90°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0279] In certain embodiments, Compound 1 is suspended in *n*-butyl acetate and the suspension is heated for a brief period (*e.g.*, reflux at 125-130°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0280] In certain embodiments, Compound 1 is suspended in methanol and the solution is heated for a brief period (*e.g.*, reflux at 60-65°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0281] In certain embodiments, Compound 1 is suspended in ethanol and the solution is heated for a brief period (*e.g.*, reflux at 75-80°C), before stirring it at ambient temperature to obtain Form A of Compound 1.

[0282] In certain embodiments, Compound 1 is suspended in isopropanol and the suspension is heated for a brief period (*e.g.*, reflux at 80-85°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0283] In certain embodiments, Compound 1 is suspended in *n*-propanol and the solution is heated for a brief period (*e.g.*, reflux at 95-100°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0284] In certain embodiments, Compound 1 is suspended in *n*-butanol and the suspension is heated for a brief period (*e.g.*, reflux at 115-120°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0285] In certain embodiments, Compound 1 is suspended in acetic acid and the solution is heated for a brief period (*e.g.*, reflux at 110-120°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0286] In certain embodiments, Compound 1 is suspended in methyl isobutyl ketone and the suspension is heated for a brief period (*e.g.*, reflux at 115-120°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0287] In certain embodiments, Compound 1 is suspended in tetrahydrofuran and the suspension is heated for a brief period (*e.g.*, reflux at 65-70°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0288] In certain embodiments, Compound 1 is suspended in acetone and the suspension is heated for a brief period (*e.g.*, reflux at 55-60°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0289] In certain embodiments, Compound 1 is suspended in methyl ethyl ketone and the suspension is heated for a brief period (*e.g.*, reflux at 80-85°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0290] In certain embodiments, Compound 1 is suspended in methyl *tert*-butyl ether and the suspension is heated for a brief period (*e.g.*, reflux at 55-60°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0291] In certain embodiments, Compound 1 is suspended in 10% aqueous methanol and the solution is heated for a brief period (*e.g.*, reflux at 100-110°C), before stirring it at ambient temperature to obtain Form A of Compound 1 as a white crystalline solid.

[0292] In certain embodiments, Compound **1** is suspended in 10% aqueous isopropanol and the solution is heated for a brief period (e.g., reflux at 100-110°C), before stirring it at ambient temperature to obtain Form A of Compound **1** as a white crystalline solid.

[0293] In certain embodiments, Compound **1** is suspended in water and the solution is heated for a brief period (e.g., reflux at 100-110°C), before stirring it at ambient temperature to obtain Form A of Compound **1** as a white crystalline solid.

Uses, From Formulation and Administration

Pharmaceutically acceptable compositions

[0294] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably modulate the interaction between TCR and Nck, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably modulate the interaction between TCR and Nck in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[0295] The term “patient,” as used herein, means an animal, preferably a mammal, and most preferably a human.

[0296] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants, or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts, or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol,

sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0297] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0298] For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0299] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions, or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with

emulsifying and suspending agents. If desired, certain sweetening, flavoring, or coloring agents may also be added.

[0300] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0301] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0302] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (*see supra*) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[0303] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax, and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0304] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[0305] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known

in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0306] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[0307] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[0308] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[0309] Compounds and compositions described herein are generally useful for the modulation of TCR signaling and T-cell activation via modulation of the interaction between TCR and Nck.

[0310] The activity of a compound utilized in this invention as a modulator of the TCR-Nck interaction, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include, for example, assays that measure the proliferation of T-lymphocytes (*e.g.*, Tse, W.T. *et al.*, Transplantation, 2003, 75(3): 389-97, whose contents is incorporated here by reference); measure the polymerization of the actin cytoskeleton induced in T-cells after TCR stimulation (*e.g.*, Fuller, C.L. *et al.*, Immunol. Rev. 2003, 292: 220-36, whose contents is incorporated here by reference); and measure the secretion of cytokines by T-cells caused by stimulation of the TCR (*e.g.*, Finco, D. *et al.*, Cytokine, 2014, 66(2): 143-55, whose contents is incorporated here by reference). *In*

vivo assays include standard animal models for immune and autoimmune disease, which are well-known and are part of the state of the art such as, for example, delayed hypersensitivity (*e.g.*, Kudlacz, E. *et al.*, Am. J. Transplant., 2004, 4(1): 51-7, whose contents is incorporated here by reference); models for rheumatoid arthritis (*e.g.*, Holmdahl, R. *et al.*, APMIS, 1989, 97(7): 575-84, whose contents is incorporated here by reference); models of multiple sclerosis (experimental autoimmune encephalomyelitis) (*e.g.*, Gonzalez-Rey, E. *et al.*, Am. J. Pathol. 2006, 168(4): 1279-88, whose contents is incorporated here by reference); and models of transplant rejection (*see, e.g.*, various animal models described in the references above in relation to the treatment of transplant rejection, incorporated here by reference).

[0311] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0312] Provided compounds are modulators of the TCR-Nck interaction and are therefore useful for treating one or more disorders associated with activity of TCR. Thus, in certain embodiments, the present invention provides a method for treating a TCR-Nck mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[0313] As used herein, the terms “TCR-Nck mediated” disorders, diseases, and/or conditions means any disease, or other deleterious condition, in which the TCR is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which TCR is known to play a role. Such TCR-Nck mediated disorders include, without limitation, autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders. (*See, e.g.*, O’Sea, J. *et al.*, Nat. Rev. Drug Discov. 2004, 3(7): 555-64; Cetkovic-Cvrlje, M. *et al.*, Curr. Pharm. Des. 2004, 10(15): 1767-84; Cetkovic-Cvrlje, M. *et al.*, Arch. Immunol. Ther. Exp. 2004, 52(2): 69-82).

Autoimmune and Inflammatory Disorders

[0314] As used herein, “autoimmune and inflammatory disorder” refers to those diseases, illnesses, or conditions engendered when the host's systems are attacked by the host's own immune system. The targets of autoimmune interaction can range anywhere from the cellular level (e.g., myelin basic protein in multiple sclerosis, or the thyrotropin receptor in Graves' disease) to organ specific effects in rheumatoid arthritis or Crohn's disease to system wide effects as seen in systemic lupus erythematosus. Some of the events that have been postulated in the causation of autoimmune diseases have included cytokine over expression, for example TNF- α , IL-2, or IL-2 receptor in inflammatory bowel disease, or under expression (IL-10 under expression in Type 1 diabetes), to defects in allele expression (HLA Class I B27 in ankylosing spondylitis), to altered expression of apoptosis proteins (under expression of Fas in autoimmune lymphoproliferative syndrome type I (ALPS 1). See “Harrison's Principles of Internal Medicine”, 16th ed., McGraw-Hill, N.Y., 2005; Chapter 295 for additional information on autoimmune diseases.

[0315] In certain embodiments, the autoimmune or inflammatory disorder is Addison's disease, agammaglobulinemia, alopecia areata, alopecia universalis, amyloidosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (Meniere's disease), autoimmune myocarditis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticarial, axon and neuronal neuropathy, Baló disease, Behçet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease, Celiac disease, Chagas disease, chronic inflammatory demyelination polyneuropathy, chronic recurrent multifocal osteomyelitis, Churg-Strauss, cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis, eosinophilic fasciitis, erythema nodosum, essential mixed cryoglobulinemia, Evan's syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis, giant cell myocarditis, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangitis, Grave's disease, Guillain-Barre Syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schönlein purpura, herpes gestationis or pemphigoid

gestationis, hypogammaglobulinemia, IgA nephropathy, IgG4-related sclerosing disease, immune thrombocytopenic purpura, inclusion body myositis, inflammatory bowel disease, interstitial cystitis, juvenile arthritis, juvenile diabetes, juvenile myositis, Kawasaki disease, Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosis, ligneous conjunctivitis, linear IgA disease, lupus erythematosus, Lyme disease chronic, Lyme neuroborreliosis, microscopic polyangiitis, mixed connective tissue disease, Mooren's ulcer, Mucha-Habermann disease, multiple sclerosis, myasthenia gravis, myositis, neuromyelitis optica, neutropenia, ocular cicatricial pemphigoid, optic neuritis, palindromic rheumatism, PANDAS, paraneoplastic cerebellar degeneration, paroxysmal nocturnal hemoglobinuria, Parry-Romberg syndrome, Pars planitis, Parsonage-Turner syndrome, pemphigus, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia, POEMS syndrome, polyarteritis nodosa, polyglandular syndromes types I, II, and III, polymyalgia rheumatica, polymyositis, postmyocardial infarction syndrome, postpericardiotomy syndrome, primary biliary cirrhosis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia, pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjogren's syndrome, sperm & testicular autoimmunity, stiff person syndrome, subacute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia, Takayasu's arteritis, temporal arteritis, thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, transverse myelitis, type 1 diabetes, ulcerative colitis, undifferentiated connective tissue disease, uveitis, vasculitis, vitiligo and Wegener's granulomatosis (or granulomatosis with polyangiitis).

Disorders Associated with Transplantation

[0316] In some embodiments, the disorder is associated with transplantation. In some embodiments the disorder associated with transplantation is transplant rejection. In some embodiments the disorder associated with transplantation is graft-versus-host disease.

Proliferative Disorders

[0317] In some embodiments, the disorder is a proliferative disorder. In some embodiments, the proliferative disorder is a cancer.

[0318] As used herein, the term “cancer” refers to cells having the capacity for autonomous growth, *i.e.*, an abnormal state or condition characterized by rapidly proliferating cell growth. The term is meant to include all types of cancerous growths or oncogenic processes, metastatic tissues or malignantly transformed cells, tissues, or organs, irrespective of histopathologic type or stage of invasiveness. The term “tumor” as used herein refers to cancerous cells, *e.g.*, a mass of cancer cells. The term “carcinoma” is art recognized and refers to malignancies of epithelial or endocrine tissues including respiratory system carcinomas, gastrointestinal system carcinomas, genitourinary system carcinomas, testicular carcinomas, breast carcinomas, prostatic carcinomas, endocrine system carcinomas, and melanomas. An “adenocarcinoma” refers to a carcinoma derived from glandular tissue or in which the tumor cells form recognizable glandular structures. The term “sarcoma” is art recognized and refers to malignant tumors of mesenchymal derivation.

[0319] Cancers include, without limitation, leukemias (*e.g.*, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (*e.g.*, Hodgkin's disease or non-Hodgkin's disease), Waldenstrom's macroglobulinemia, multiple myeloma, heavy chain disease, and solid tumors such as sarcomas and carcinomas (*e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

[0320] In some embodiments the proliferative disorder is a hematological cancers. In some embodiments the proliferative disorder is a leukemia. In some embodiments, the leukemia is a T-cell leukemia.

Neurological Disorders

[0321] In some embodiments, the disorder is a neurological disorder. In some embodiments, the neurological disorder is Balo's disease, chronic inflammatory demyelinating polyneuropathy, Devic's neuromyelitis optica, Marburg acute multiple sclerosis, multiple sclerosis, Schilder's disease, or perivenous encephalomyelitis.

Acceptable Compositions

[0322] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0323] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0324] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution,

suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[0325] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[0326] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[0327] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[0328] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin,

polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[0329] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well-known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[0330] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well-known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[0331] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[0332] The term “biological sample”, as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Methods of Treatment

[0333] In other embodiments, the present invention provides a method for treating a disorder mediated by TCR-Nck interaction in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. In some embodiments the method of modulating TCR-Nck is used to treat autoimmune and inflammatory disorders; disorders associated with transplantation; proliferative disorders; and neurological disorders.

[0334] In some embodiments, the method of modulating TCR-Nck is used to treat alopecia areata. (See, e.g., Petukhova, L. *et al.*, Nature, 2010, 466(7302): 123-17). Accordingly, in some embodiments, the present invention provides a method of treating alopecia areata, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0335] In some embodiments, the method of modulating TCR-Nck is used to treat ankylosing spondylitis. (See, e.g., Smith, J.A., Curr Allergy Asthma Rep. 2015, 15(1): 489). Accordingly, in some embodiments, the present invention provides a method of treating ankylosing spondylitis, in

a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0336] In some embodiments, the method of modulating TCR-Nck is used to treat asthma. (*See, e.g., Robinson, D.S., J. Allergy Clin. Immunol.*, 2010, 126(6): 1081-91). Accordingly, in some embodiments, the present invention provides a method of treating asthma, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0337] In some embodiments, the method of modulating TCR-Nck is used to treat autoimmune hepatitis. (*See, e.g., Manns, M.P. et al., Hepatology*, 2010, 51(6), 2193-213. Accordingly, in some embodiments, the present invention provides a method of treating autoimmune hepatitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0338] In some embodiments, the method of modulating TCR-Nck is used to treat autoimmune lymphoproliferative syndrome (ALPS). (*See, e.g., Sneller, M.C. et al., Curr. Opin. Rheumatology*, 2003, 15(4) 417-21). Accordingly, in some embodiments, the present invention provides a method of treating ALPS, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0339] In some embodiments, the method of modulating TCR-Nck is used to autoimmune myocarditis. (*See, e.g., Caforio, A.L. and Iliceto, S., Curr. Opin. Cardiol.*, 2008, 23(3): 219-26). Accordingly, in some embodiments, the present invention provides a method of treating autoimmune myocarditis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0340] In some embodiments, the method of modulating TCR-Nck is used to autoimmune orchitis. (*See, e.g., Silva, C.A. et al., Autoimmun Rev.*, 2014, 13(4-5): 431-34). Accordingly, in some embodiments, the present invention provides a method of treating autoimmune orchitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0341] In some embodiments, the method of modulating TCR-Nck is used to autoimmune pancreatitis. (*See, e.g., Fan, B.G. and Andren-Sandberg, A., N. Am. J. Med. Sci.* 2009, 1(2): 148-51). Accordingly, in some embodiments, the present invention provides a method of treating

autoimmune pancreatitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0342] In some embodiments, the method of modulating TCR-Nck is used to treat atopic dermatitis. (*See, e.g.*, Nograles, K.E. *et al.*, J. Allergy Clin. Immunol., 2009, 123(6): 1244-52). Accordingly, in some embodiments, the present invention provides a method of treating systemic atopic dermatitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0343] In some embodiments, the method of modulating TCR-Nck is used to treat Behçet's disease. (*See, e.g.*, Direskeneli, H., Genetics Research International, 2013, Article ID 249157 doi:10.1255/2013/249157). Accordingly, in some embodiments, the present invention provides a method of treating Behçet's disease, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0344] In some embodiments, the method of modulating TCR-Nck is used to treat Castleman disease. (*See, e.g.*, Al-Maghrabi, J. *et al.*, Histopathology, 2005, 48(3): 233-38). Accordingly, in some embodiments, the present invention provides a method of treating Castleman disease, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0345] In some embodiments, the method of modulating TCR-Nck is used to treat Celiac disease. (*See, e.g.*, Mazzarella, G., World J. Gastroenterol., 2015, 21(24): 7349-56). Accordingly, in some embodiments, the present invention provides a method of treating Celiac disease, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0346] In some embodiments, the method of modulating TCR-Nck is used to treat chronic inflammatory demyelinating polyneuropathy. (*See, e.g.*, Notturmo, F. *et al.*, J. Neuroimmunol. 2008, 197(2): 124-7). Accordingly, in some embodiments, the present invention provides a method of treating chronic inflammatory demyelinating polyneuropathy, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0347] In some embodiments, the method of modulating TCR-Nck is used to treat Cogan's syndrome. (*See, e.g.*, Greco, A. *et al.*, Autoimmunity Rev. 2013, 12(3): 396-400). Accordingly, in some embodiments, the present invention provides a method of treating Cogan's syndrome, in

a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0348] In some embodiments, the method of modulating TCR-Nck is used to treat Churg-Strauss syndrome. (*See, e.g., Guida, G. et al., Clin. Immunol., 2008 128(1): 94-102*). Accordingly, in some embodiments, the present invention provides a method of treating Churg-Strauss syndrome, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0349] In some embodiments, the method of modulating TCR-Nck is used to treat Crohn's disease. (*See, e.g., Roche, J.K. et al., J. Clin. Invest. 1985, 75(2):522-530; Marks, D.J. and Segal, A.W. J. Pathol. 2008, 214(2): 260-66; Cobrin, G.M. and Abreu, M.T. Immunol. Rev. 2005, 206(1): 277-95*). Accordingly, in some embodiments, the present invention provides a method of treating Crohn's disease, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0350] In some embodiments, the method of modulating TCR-Nck is used to treat Evans syndrome. (*See, e.g., Teachery, D.T. et al., Blood, 2004, 105(6):2443-48*). Accordingly, in some embodiments, the present invention provides a method of treating Evans syndrome, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0351] In some embodiments, the method of modulating TCR-Nck is used to treat inclusion body myositis. (*See, e.g., Kitazawa, M. et al., J. Neuroscience, 2009, 29(19): 6132-41*). Accordingly, in some embodiments, the present invention provides a method of treating inclusion body myositis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0352] In some embodiments, the method of modulating TCR-Nck is used to treat inflammatory bowel disease. (*See, e.g., Zenewicz, L.A. et al., Trends Mol. Med., 2009, 15(5): 199-207*). Accordingly, in some embodiments, the present invention provides a method of treating inflammatory bowel disease, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0353] In some embodiments, the method of modulating TCR-Nck is used to treat Kawasaki disease. (*See, e.g., Onouchi, Y. et al., Nature Genetics, 2008, 40: 35-42*). Accordingly, in some embodiments, the present invention provides a method of treating Kawasaki disease, in a patient

in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0354] In some embodiments, the method of modulating TCR-Nck is used to treat Lyme disease (chronic). (*See, e.g.*, Singh, S.K. and Girschick, H.J. *Paediatric Rheumatology*, 2004, 10(7): 598-614; Raveche, E.S. *et al.*, *J. Clin. Microbiol.* 2005, 43(2): 850-56). Accordingly, in some embodiments, the present invention provides a method of treating Lyme disease (chronic), in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0355] In some embodiments, the method of modulating TCR-Nck is used to treat multiple sclerosis. (*See, e.g.*, Babbe, H. *et al.*, *J. Exp. Med.*, 2000, 192(3): 393-404; Dai, K.Z. *et al.*, *Genes Immun.* 2001, 2(5): 263-8). Accordingly, in some embodiments, the present invention provides a method of treating multiple sclerosis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0356] In some embodiments, the method of modulating TCR-Nck is used to treat myasthenia gravis. (*See, e.g.*, Meriggioli, M.N. and Sanders, D.B.S., *Lancet Neurology*, 2009, 8(5): 475-90). Accordingly, in some embodiments, the present invention provides a method of treating myasthenia gravis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0357] In some embodiments, the method of modulating TCR-Nck is used to treat psoriasis. (*See, e.g.*, Cai, Y. *et al.*, *Cell Mol. Immunol.*, 2012, 9(4): 302-09). Accordingly, in some embodiments, the present invention provides a method of treating psoriasis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0358] In some embodiments, the method of modulating TCR-Nck is used to treat psoriatic arthritis. (*See, e.g.*, Choy, E., *Curr. Rheumatol. Rep. Exp.*, 2007, 9(6): 437-41). Accordingly, in some embodiments, the present invention provides a method of treating psoriatic arthritis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0359] In some embodiments, the method of modulating TCR-Nck is used to treat rheumatoid arthritis. (*See, e.g.*, Cope, A.P. *et al.*, *Clin. Exp. Rheumatol.*, 2007, 25(5): S4-12). Accordingly, in some embodiments, the present invention provides a method of treating rheumatoid arthritis, in a

patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0360] In some embodiments, the method of modulating TCR-Nck is used to treat systemic lupus erythematosus. (*See, e.g.,* Crispin, J.C. *et al.*, J. Immunol., 2008, 181(12): 8761-66; Linterman, M.A. *et al.*, J. Exp. Med. 2009, 206(3): 561-76). Accordingly, in some embodiments, the present invention provides a method of treating systemic lupus erythematosus, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0361] In some embodiments, the method of modulating TCR-Nck is used to treat type I diabetes. (*See, e.g.,* Roep, B.O., Diabetologia, 46(3): 305-21). Accordingly, in some embodiments, the present invention provides a method of treating type I diabetes, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0362] In some embodiments, the method of modulating TCR-Nck is used to treat ulcerative colitis. (*See, e.g.,* Kappeler, A. and Mueller, C., Histol Histopathol., 2000, 15(1): 167-72). Accordingly, in some embodiments, the present invention provides a method of treating ulcerative colitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0363] In some embodiments, the method of modulating TCR-Nck is used to treat uveitis. (*See, e.g.,* Horai, R. *et al.*, Immunity, 2015, 43(2): 343-53). Accordingly, in some embodiments, the present invention provides a method of treating uveitis, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0364] In some embodiments, the method of modulating TCR-Nck is used to treat vitiligo. (*See, e.g.,* Van den Wijngaard, R. *et al.*, Lab Invest. 2000, 80(8): 1299-309). Accordingly, in some embodiments, the present invention provides a method of treating vitiligo, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0365] In some embodiments, the method of modulating TCR-Nck is used to treat rejection of transplants. (*See, e.g.,* Issa, F. *et al.*, Expert Rev. Clin. Immunol. 2010, 6(1): 155-69). Accordingly, in some embodiments, the present invention provides a method of treating rejection of transplants,

in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0366] In some embodiments, the method of modulating TCR-Nck is used to treat granulomatosis with polyangiitis (Wegener's granulomatosis). (*See, e.g., Morgan, M.D. et al., Arthritis & Rheumatism, 2012, 63(7): 2127–37.*) Accordingly, in some embodiments, the present invention provides a method of treating granulomatosis with polyangiitis (Wegener's granulomatosis), in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0367] In some embodiments, the method of modulating TCR-Nck is used to treat hematological cancer. Accordingly, in some embodiments, the present invention provides a method of treating hematological cancer, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

[0368] In some embodiments, the method of modulating TCR-Nck is used to treat transplant rejection. (*See, e.g., Issa, F. et al., Expert Rev. Clin. Immunol. 2010, 6(1): 155-69.*) In some embodiments, the method of modulating TCR-Nck is used to treat graft-versus-host disease. (*See, e.g., W.D., Nature Rev. Immunology, 2007, 7: 340-52.*) Accordingly, in some embodiments, the present invention provides a method of treating a disorder associated with transplantation, in a patient in need thereof, comprising the step of administering to said patient a provided compound or a pharmaceutically acceptable salt thereof.

Combinations

[0369] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as “appropriate for the disease, or condition, being treated.”

[0370] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be

part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[0371] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0372] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[0373] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 µg/kg body weight/day of the additional therapeutic agent can be administered.

[0374] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[0375] In one embodiment, the present invention provides a composition comprising a compound of formula I and one or more additional therapeutic agents. The therapeutic agent may be administered together with a compound of formula I, or may be administered prior to or following administration of a compound of formula I. Suitable therapeutic agents are described

in further detail below. In certain embodiments, a compound of formula I may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours before the therapeutic agent. In other embodiments, a compound of formula I may be administered up to 5 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5, hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 12 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, or 18 hours following the therapeutic agent.

[0376] In another embodiment, the present invention provides a method of treating a TCR-Nck mediated disease, disorder or condition by administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents. Such additional therapeutic agents may be small molecules or recombinant biologic agents and include, for example, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, colchicine (Colcrys®), corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, probenecid, allopurinol, febuxostat (Uloric®), sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytosan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol (Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), canakinumab (Ilaris®), anti-Jak inhibitors such as tofacitinib, antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®), “anti-IL-6” agents such as tocilizumab (Actemra®), diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®), monoclonal antibodies such as tanezumab, anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot®, anticholinergics or antispasmodics such as dicyclomine (Bentyl®), Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®),

pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®) and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as beclomethasone dipropionate (Beclivent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmicort®), and flunisolide (Aerobid®), Afviar®, Symbicort®, Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, IgE antibodies such as omalizumab (Xolair®), nucleoside reverse transcriptase inhibitors such as zidovudine (Retrovir®), abacavir (Ziagen®), abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®), didanosine (Videx®), emtricitabine (Emtriva®), lamivudine (Epivir®), lamivudine/zidovudine (Combivir®), stavudine (Zerit®), and zalcitabine (Hivid®), non-nucleoside reverse transcriptase inhibitors such as delavirdine (Rescriptor®), efavirenz (Sustiva®), nevirapine (Viramune®) and etravirine (Intelence®), nucleotide reverse transcriptase inhibitors such as tenofovir (Viread®), protease inhibitors such as amprenavir (Agenerase®), atazanavir (Reyataz®), darunavir (Prezista®), fosamprenavir (Lexiva®), indinavir (Crixivan®), lopinavir and ritonavir (Kaletra®), nelfinavir (Viracept®), ritonavir (Norvir®), saquinavir (Fortovase® or Invirase®), and tipranavir (Aptivus®), entry inhibitors such as enfuvirtide (Fuzeon®) and maraviroc (Selzentry®), integrase inhibitors such as raltegravir (Isentress®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), bortezomib (Velcade®), and dexamethasone (Decadron®) in combination with lenalidomide (Revlimid®), or any combination(s) thereof.

[0377] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, sulfasalazine (Azulfidine®), antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), methotrexate (Rheumatrex®), gold salts such as gold thioglucose (Solganal®), gold thiomalate (Myochrysine®) and auranofin (Ridaura®), D-penicillamine (Depen® or Cuprimine®), azathioprine (Imuran®), cyclophosphamide (Cytosan®), chlorambucil (Leukeran®), cyclosporine (Sandimmune®), leflunomide (Arava®) and “anti-TNF” agents such as etanercept (Enbrel®), infliximab (Remicade®), golimumab (Simponi®), certolizumab pegol

(Cimzia®) and adalimumab (Humira®), “anti-IL-1” agents such as anakinra (Kineret®) and rilonacept (Arcalyst®), antibodies such as rituximab (Rituxan®), “anti-T-cell” agents such as abatacept (Orencia®) and “anti-IL-6” agents such as tocilizumab (Actemra®).

[0378] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, diclofenac, cortisone, hyaluronic acid (Synvisc® or Hyalgan®) and monoclonal antibodies such as tanezumab.

[0379] In some embodiments, the present invention provides a method of treating systemic lupus erythematosus comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, naproxen, etodolac (Lodine®) and celecoxib, corticosteroids such as prednisone, prednisolone, methylprednisolone, hydrocortisone, and the like, antimalarials such as hydroxychloroquine (Plaquenil®) and chloroquine (Aralen®), cyclophosphamide (Cytoxan®), methotrexate (Rheumatrex®), azathioprine (Imuran®) and anticoagulants such as heparin (Calcinparine® or Liquaemin®) and warfarin (Coumadin®).

[0380] In some embodiments, the present invention provides a method of treating Crohn’s disease, ulcerative colitis, or inflammatory bowel disease comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from mesalamine (Asacol®) sulfasalazine (Azulfidine®), antidiarrheals such as diphenoxylate (Lomotil®) and loperamide (Imodium®), bile acid binding agents such as cholestyramine, alosetron (Lotronex®), lubiprostone (Amitiza®), laxatives such as Milk of Magnesia, polyethylene glycol (MiraLax®), Dulcolax®, Correctol® and Senokot® and anticholinergics or antispasmodics such as dicyclomine (Bentyl®), anti-TNF therapies, steroids, and antibiotics such as Flagyl or ciprofloxacin.

[0381] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from Singulair®, beta-2 agonists such as albuterol (Ventolin® HFA, Proventil® HFA), levalbuterol (Xopenex®), metaproterenol (Alupent®), pirbuterol acetate (Maxair®), terbutaline sulfate (Brethaire®), salmeterol xinafoate (Serevent®)

and formoterol (Foradil®), anticholinergic agents such as ipratropium bromide (Atrovent®) and tiotropium (Spiriva®), inhaled corticosteroids such as prednisone, prednisolone, beclomethasone dipropionate (Beclivent®, Qvar®, and Vanceril®), triamcinolone acetonide (Azmacort®), mometasone (Asthmanex®), budesonide (Pulmicort®), flunisolide (Aerobid®), Afvair®, Symbicort®, and Dulera®, cromolyn sodium (Intal®), methylxanthines such as theophylline (Theo-Dur®, Theolair®, Slo-bid®, Uniphyll®, Theo-24®) and aminophylline, and IgE antibodies such as omalizumab (Xolair®).

[0382] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (Hydrodaunorubicin®), vincristine (Oncovin®), prednisone, a hedgehog signaling inhibitor, a BTK inhibitor, a JAK/pan-JAK inhibitor, a PI3K inhibitor, a SYK inhibitor, and combinations thereof.

[0383] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula I and a BTK inhibitor, wherein the disease is selected from inflammatory bowel disease, arthritis, systemic lupus erythematosus (SLE), vasculitis, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune thyroiditis, Sjogren's syndrome, multiple sclerosis, systemic sclerosis, Lyme neuroborreliosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, autoimmune gastritis, pernicious anemia, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behçet's disease, chronic fatigue, dysautonomia, membranous glomerulonephropathy, endometriosis, interstitial cystitis, pemphigus vulgaris, bullous pemphigoid, neuromyotonia, scleroderma, vulvodynia, a hyperproliferative disease, rejection of transplanted organs or tissues, Acquired Immunodeficiency Syndrome (AIDS, also known as HIV), type 1 diabetes, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (*e.g.*, allergies to plant pollens,

latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis, asthma, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis, B-cell proliferative disorder, *e.g.*, diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, 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/leukemia, or lymphomatoid granulomatosis, breast cancer, prostate cancer, or cancer of the mast cells (*e.g.*, mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis), bone cancer, colorectal cancer, pancreatic cancer, diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behçet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, bone metastasis, a thromboembolic disorder, (*e.g.*, myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, deep venous thrombosis), inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholecystitis, agammaglobulinemia, psoriasis, allergy,

Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behçet's disease, scleroderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[0384] In another embodiment, the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula I and a PI3K inhibitor, wherein the disease is selected from a cancer, a neurodegenerative disorder, an angiogenic disorder, a viral disease, an autoimmune disease, an inflammatory disorder, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), liver disease, pathologic immune conditions involving T-cell activation, a cardiovascular disorder, and a CNS disorder.

[0385] In some embodiments the present invention provides a method of treating or lessening the severity of a disease comprising administering to a patient in need thereof a compound of formula I and a Bcl-2 inhibitor, wherein the disease is an inflammatory disorder, an autoimmune disorder, a proliferative disorder, an endocrine disorder, a neurological disorder, or a disorder associated with transplantation.

[0386] A compound of the current invention may also be used to advantage in combination with antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds

which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin. The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin™. Formestane is marketed under the trade name Lentaron™. Fadrozole is marketed under the trade name Afema™. Anastrozole is marketed under the trade name Arimidex™. Letrozole is marketed under the trade names Femara™ or Femar™. Aminoglutethimide is marketed under the trade name Orimeten™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[0387] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name Nolvadex™. Raloxifene hydrochloride is marketed under the trade name Evista™. Fulvestrant can be administered under the trade name Faslodex™.

[0388] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (Casodex™). The term "gonadorelin agonist" as used herein includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin can be administered under the trade name Zoladex™.

[0389] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to, topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, *e.g.*, in the form as it is marketed, *e.g.*, under the trademark Camptosar™. Topotecan is marketed under the trade name Hycamptin™.

[0390] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as Caelyx™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophyllotoxines etoposide and teniposide. Etoposide is marketed under the trade name Etopophos™. Teniposide is marketed under the trade name VM 26-Bristol. Doxorubicin is marketed under the trade name Acriblastin™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron.

[0391] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is marketed under the trade name Farmistin™.

[0392] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[0393] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[0394] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[0395] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.*, under the trademark Carboplat™. Oxaliplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.*, under the trademark Eloxatin™.

[0396] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-121; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the AxI receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine

kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (*e.g.*, BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safinol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofofosine; RO 318220 and RO 320432; GO 6976; Ixis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a PI3K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (Gleevec™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-[(2,5- dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR₁ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (Herceptin™), cetuximab (Erbix™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.12, E6.3 or E7.6.3, and 7*H*-pyrrolo-[2,3-*d*]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase

activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1226, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[0397] The term “PI3K inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3K α , PI3K γ , PI3K δ , PI3K β , PI3K-C2 α , PI3K-C2 β , PI3K-C2 γ , Vps34, p120- α , p120- β , p120- γ , p120- δ , p85- α , p85- β , p55- γ , p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1226, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[0398] The term “Bcl-2 inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta’s pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; *see* WO 2008/128802), navitoclax (and analogs thereof, *see* US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, *see* WO 2004/106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[0399] The term “BTK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against Bruton’s Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[0400] The term “SYK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib

[0401] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2008/039218 and WO 2012/090760, the entirety of which are incorporated herein by reference.

[0402] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2003/063794, WO 2005/007623, and WO 2006/078846, the entirety of which are incorporated herein by reference.

[0403] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2004/019973, WO 2004/089925, WO 2007/016176, US8138347, WO 2002/088122, WO 2007/084786, WO 2007/129161, WO 2006/122806, WO 2005/123554, and WO 2007/044729 the entirety of which are incorporated herein by reference.

[0404] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO 2009/124512, WO 2008/109943, WO 2007/053452, WO 2000/142246, and WO 2007/070514, the entirety of which are incorporated herein by reference.

[0405] Further anti-angiogenic compounds include compounds having another mechanism for their activity, *e.g.*, unrelated to protein or lipid kinase inhibition *e.g.*, thalidomide (Thalomid™) and TNP-470.

[0406] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[0407] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are *e.g.*, inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[0408] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α - γ - or δ - tocopherol or α - γ - or δ -tocotrienol.

[0409] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (Celebrex™), rofecoxib (Vioxx™), etoricoxib, valdecoxib or a 5-alkyl-2- arylaminophenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[0410] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid is marketed under the trade name Didronel™. Clodronic acid is marketed under the trade name Bonefos™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name Aredia™. Alendronic acid is marketed under the trade name Fosamax™. Ibandronic acid is marketed under the trade name Bondranat™. Risedronic acid is marketed under the trade name Actonel™. Zoledronic acid is marketed under the trade name Zometa™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[0411] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[0412] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R125777 (Zarnestra™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[0413] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[0414] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™) and MLN 341.

[0415] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, *e.g.*, hydroxamate peptidomimetic inhibitor batimastat and its orally

bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA212, MMI270B or AAJ996.

[0416] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1- β -D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[0417] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU12248 and MLN518.

[0418] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[0419] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[0420] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[0421] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the

purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. *See* Hellman, "Principles of Radiation Therapy", Cancer, in Principles and Practice of Oncology", Devita *et al.*, Eds., 4th Edition, Vol. 1, pp. 248-275 (1993). [0422] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1*H*-isoindole-1,3-dione derivatives.

[0423] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; AngiostatinTM; EndostatinTM; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (AvastinTM).

[0424] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as Visudyne™ and porfimer sodium.

[0425] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, *e.g.*, anecortave, triamcinolone, hydrocortisone, 12- α -epihydrocortisol, corticosterone, 17 α -hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[0426] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[0427] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[0428] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, *e.g.*, Patents International (*e.g.*, IMS World Publications).

[0429] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[0430] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

EXEMPLIFICATION

[0431] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

General Procedures

[0432] X-ray powder diffraction (XRPD) analysis was carried out in reflection-transmission mode on a Panalytical X'Pert 3 Powder with X'Celerator detector using a standard Aptuit method. The data were evaluated using the HighScore Plus software. The instrumental parameters used are listed below in Table 2.

Table 2: Parameters used for X-ray powder diffraction (XRPD) analysis.

Instrumental Parameter	Value
Scan Axis	Gonio
Start position [$^{\circ}2\theta$]	2.5066
End position [$^{\circ}2\theta$]	49.9956
Step Size [$^{\circ}2\theta$]	0.0130
Scan Step Time [s]	18.8700
Scan type	Continuous
PSD Mode	Scanning
PSD Length [$^{\circ}2\theta$]	3.35
Offset [$^{\circ}2\theta$]	0.0000
Divergence slit type	Fixed
Divergence slit size [$^{\circ}$]	0.4354
Specimen length [mm]	10.00
Measurement temperature [$^{\circ}\text{C}$]	25.00
Anode material	Cu
K-Alpha1 [$\text{\AA}$]	1.54060
K-Alpha2 [$\text{\AA}$]	1.54443
K-beta [$\text{\AA}$]	1.39225
K-A2/K-A1 Ratio	0.50000
Generator settings	40 mA, 45kV
Diffractometer type	0000000011181744
Diffractometer number	0

Goniometer radius [mm]	240.00
Distant focus divergent slit [mm]	100.00
Incident beam monochromator	No
spinning	Yes
PHD lower level	4.02 (keV)
PHD upper level	11.27 (keV)

[0433] Differential Scanning Calorimetry (DSC) analyses were carried out using a TA Q2000 MDSC instrument.

Primary Salt Screening

[0434] Salt screening experiments were conducted using twelve (14) acid salt formers and seven base salt formers being employed. The experimental details for each salt forming attempt are described in Table 3.

Table 3: Salt screening results of compound A

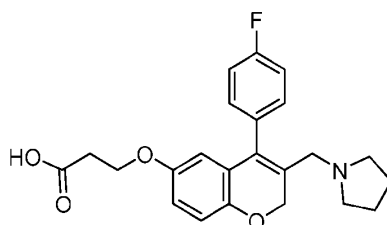
Exp. ID	Salts	Acid/base	Solvent	Conditions	Results
1	Hydrogen chloride salt of Compound A	HCl			Compound 1 Slightly hygroscopic
2	Sodium salt of Compound A	Sodium carbonate	Methanol	Ambient temperature	Compound 2 Deliquescent
3		Sodium methoxide	Methanol	Ambient temperature	Compound 2 Deliquescent
4	Potassium salt of Compound A	Potassium carbonate	Methanol	Ambient temperature	Compound 3 Highly hygroscopic solid and becomes viscous after filtration
5		Potassium <i>tert</i> -butoxide	Methanol	Ambient temperature	Compound 3 Highly hygroscopic solid and becomes viscous after filtration

6	Calcium salt of Compound A	Sodium hydroxide/Calcium chloride	Water	Ambient temperature	Compound 4 Poor aqueous solubility
7		Calcium hydroxide	Methanol	Ambient temperature	Compound 4 Poor aqueous solubility
8	Magnesium salt of Compound A	Magnesium Chloride	Water	Ambient temperature	Compound 5 Poor aqueous solubility
9	L-lysine salt of compound A	L-lysine	Methanol	55-60 °C followed by ambient temperature	Viscous or syrupy salt
10			THF	55-60 °C followed by ambient temperature	Viscous or syrupy salt
12	L-arginine salt of Compound A	L-arginine	Methanol	55-60 °C followed by ambient temperature	Viscous or syrupy salt
12			THF	55-60 °C followed by ambient temperature	Viscous or syrupy salt
13	L-histidine salt of Compound A	L-histidine	Methanol	55-60 °C followed by ambient temperature	No salt formation
14			THF	55-60 °C followed by ambient temperature	No salt formation
15	Gentisate salt of Compound A	Gentisic acid	THF	55-60 °C followed by ambient temperature	Syrupy liquid of compound 6
16			Acetone	55-60 °C followed by ambient temperature	Compound 6
17	Sulphate salt of Compound A	Sulphuric acid	Methyl iso-butyl ketone	Ambient temperature	Compound 7
18	Glycolate salt of	Glycolic acid	Acetone	55-60 °C followed by	Compound 8

	Compound A			ambient temperature	
19	Citrate salt of Compound A	Citric acid	Acetone	55-60 °C followed by ambient temperature	Compound 9
20	Oxalate salt of Compound A	Oxalic acid	Tetrahydrofuran	55-60 °C followed by ambient temperature	Compound 10
21	Malcate salt of Compound A	Maleic acid	Tetrahydrofuran	55-60 °C followed by ambient temperature	Compound 11
22			Methyl iso-butyl ketone	70-75 °C followed by ambient temperature	Compound 11
23			Acetone	50-55 °C followed by ambient temperature	Compound 11
24	Fumarate salt of Compound A	Fumaric acid	acetone	50-55 °C followed by ambient temperature	No salt formation; obtained the free base
25	Mandelate salt of Compound A	Mandelic acid	Tetrahydrofuran	50-55 °C followed by ambient temperature	No salt formation; obtained the free base
			Acetone	50-55 °C followed by ambient temperature	No salt formation; obtained the free base
26	Tartrate salt of Compound A	Tartaric acid	Acetone	50-55 °C followed by ambient temperature	No salt formation; obtained the free base
27	Succinate salt of Compound A	Succinic acid	Acetone	50-55 °C followed by ambient temperature	No salt formation; obtained the free base
28	Acetate salt of compound A	Acetic acid	tetrahydrofuran	50-55 °C followed by ambient temperature	Compound 12 Highly hygroscopic in nature
29	Tosylate salt of	p-toluene sulfonic acid	Tetrahydrofuran	50-55 °C followed by	Compound 13

	Compound A			ambient temperature	Highly hygroscopic in nature
30	Mesylate salt of compound A	Methane sulfonic acid	Tetrahydrofuran	Ambient temperature	Compound 14 Highly hygroscopic in nature
31	Phosphate salt of Compound A	o-phosphoric acid	Ethanol	Ambient temperature	Compound 15

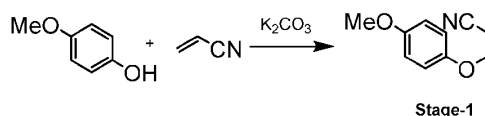
Example 1 - General Preparation of Compound 1



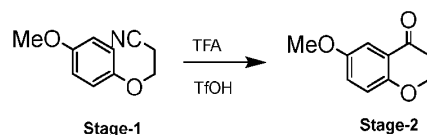
Compound A

[0435] The title compound was prepared according to the steps and intermediates (e.g., Scheme 1) described below and in the '792 publication, the entirety of which is incorporated herein by reference.

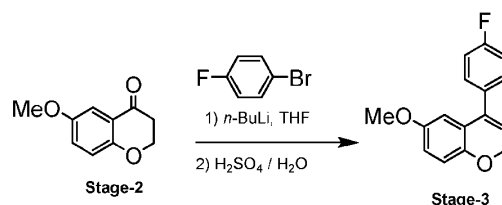
Step 1: Synthesis of 3-(4-methoxyphenoxy)propanenitrile:



[0436] 4-Methoxyphenol (125 g, 1.0 mol) and acrylonitrile (198 mL, 3.0 mol) were taken in a reactor and K_2CO_3 (417 g, 3.0 mol) was added followed by t-butanol (90 mL) at 25 °C. the mass was heated to 80-85 °C for 24 h. The reaction mixture was then cooled to RT and filtered to remove the inorganics. The clear filtrate was quenched with ice water (300 mL) and the aqueous layer was extracted with DCM (300 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 3-(4-methoxyphenoxy)propanenitrile (160 g, 90%).

Step 2: Synthesis of 6-methoxychroman-4-one:

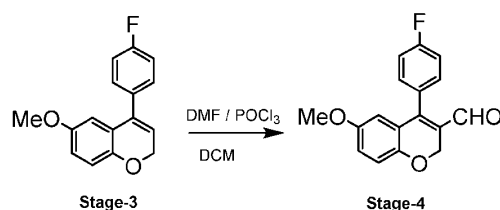
[0437] 3-(4-Methoxyphenoxy)propanenitrile (160 g, 0.90 mol) and TFA (277 mL, 3.6 mol) were added to a reaction vessel and cooled to 0 °C. Trifluoromethanesulfonic acid (120 ml, 1.35 mol) was slowly added through an addition funnel over a period of 20-30 min. After completion of addition, the reaction was stirred at 25-30 °C for 22-24 h. The reaction was then quenched with water (480 ml). The resulting mixture was extracted with EtOAc (500 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain brown colored gummy mass of 6-methoxy-4-chromanone. Diisopropylether (800 mL) was added to the gummy mass of 6-methoxy-4-chromanone and stirred for 5-10 min. The mixture was cooled to 0 °C and stirred for 30 min. The reaction mixture was then filtered with a buchner funnel to separate the pale yellow solid. The compound was dried under vacuum at 25-30 °C to generate 6-methoxychroman-4-one (120 g, 75%).

Step 3: Synthesis of 4-(4-fluorophenyl)-6-methoxy-2H-chromene:

[0438] A reaction vessel was charged with 1-Bromo-4-fluorobenzene (153 mL) and THF (1.125 L) and cooled to -78°C to -70°C. Bu-Li in hexane (1.6M; 1.0 L) was added drop-wise to the reaction at -78°C to -70°C through an addition funnel over a period of 15-20 min. 6-methoxychroman-4-one (225 g, 1.26 mol) dissolved in THF (1.125 L) was added drop-wise to the reaction at -78°C to -70°C through an addition funnel over a period of 15-20 min and the reaction was stirred for 2 h at the same temperature. After completion of the reaction, 10% NH₄Cl solution was added to the reaction at -78°C to -70°C and the reaction mixture was gradually warmed to RT. The reaction mixture was extracted with ethyl acetate (1.125 L) and the combined organics were

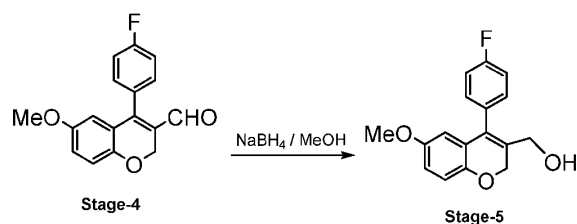
dried over anhydrous Na₂SO₄. The solvent was distilled off to yield a gummy mass of 4-(4-fluoro phenyl)-6-methoxy chroman-4-ol. The crude alcohol was dissolved in 1,4-dioxane and 20% H₂SO₄ solution (1.125 L) was added. The mixture was heated to reflux and maintained for 1 h. After completion of the reaction, the reaction was cooled to RT and extracted with ethyl acetate (1.125 L). The organic phase was dried over anhydrous Na₂SO₄ and the solvent distilled off completely to yield brown colored gummy mass of crude 4-(4-fluorophenyl)-6-methoxy-2*H*-chromene. Methanol (500 mL) was added to the crude mass of 4-(4-fluorophenyl)-6-methoxy-2*H*-chromene and cooled to 0 °C. The precipitated solids were filtered to get pure 4-(4-fluorophenyl)-6-methoxy-2*H*-chromene (160 g, 49%).

Step 4: Synthesis of 4-(4-fluorophenyl)-6-methoxy-2H-chromene-3-carbaldehyde:



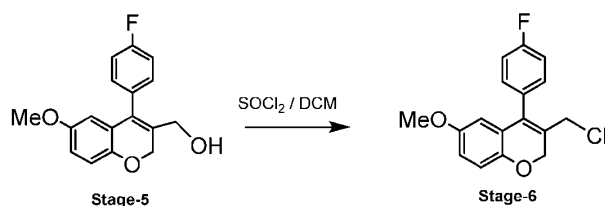
[0439] DMF (75 mL) was added to a reactor and cooled to 0 °C. POCl₃ (73 mL) was added slowly while maintaining the temperature between 0-5°C and stirred for 30 min. 4-(4-Fluorophenyl)-6-methoxy-2H-chromene (100 g, 0.39 mol) in DCM (250 mL) was added dropwise at 0-10°C. The reaction was allowed to warm to RT and then heated to 45°C for 7h. On completion, reaction was cooled to 20-25°C and then poured it into ice cold water, extracted with ethyl acetate (400 mL x 2), then the organics were dried over anhydrous Na₂SO₄. The solvent was distilled off completely to obtain a yellow colored solid as crude product. The product was recrystallized in diisopropylether to obtain pure 4-(4-fluorophenyl)-6-methoxy-2H-chromene-3-carbaldehyde (77 g, 69%).

Step 5: Synthesis of (4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methanol:



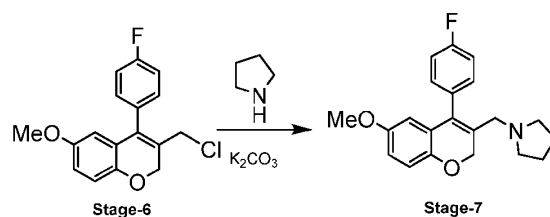
[0440] Methanol (50 mL) was added to a solution of 4-(4-fluorophenyl)-6-methoxy-2H-chromene-3-carbaldehyde (100 g, 0.35 mol) in toluene (400 mL) at 25-30 °C. The reaction was cooled to 5-10 °C and sodium borohydride was added into the reaction mass at 5-10 °C in small portions over a period of 10 min. After completion of the addition, the reaction was allowed to warm to RT and stirred over a period of 1 h. After this time, 200 mL of water was added to the mixture and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to give the title compound (4-(4-fluorophenyl)-6-methoxy-2H-chromen-3-yl)methanol (90 g, 90%).

Step 6: Synthesis of 3-(chloromethyl)-4-(4-fluorophenyl)-6-methoxy-2H-chromene:



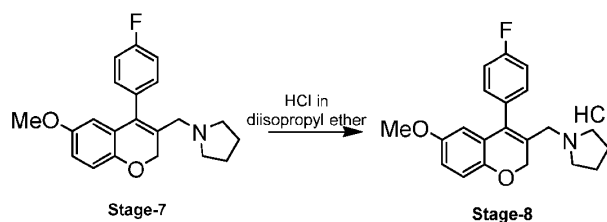
[0441] Thionyl chloride (33 mL) was added to a mixture of (4-(4-fluorophenyl)-6-methoxy-2H-chromen-3-yl)methanol (90 g, 0.31 mmol) in toluene (200 mL) at 5-10°C and then stirred at 5-10 °C for 1h. The reaction was quenched with water (2500 mL) and stirred for 15 min and organic layer dried over anhydrous Na₂SO₄ and concentrated *in vacuo* to obtain 3-(chloromethyl)-4-(4-fluorophenyl)-6-methoxy-2H-chromene as a light brown colored gummy mass (83 g, 88%).

Step 7: Synthesis of 1-((4-(4-fluorophenyl)-6-methoxy-2H-chromen-3-yl)methyl)pyrrolidine:



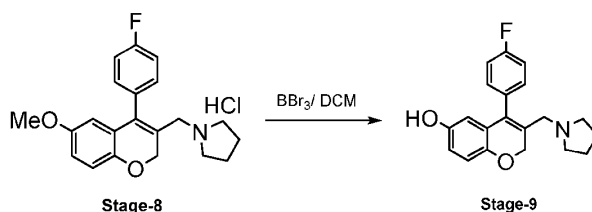
[0442] Pyrrolidine (33 mL) was added to a solution of 3-(chloromethyl)-4-(4-fluorophenyl)-6-methoxy-2*H*-chromene (100 g, 0.33 mmol) in diisopropylether (400 mL) and the mixture was cooled to 5-10 °C. Anhydrous potassium carbonate (138 g, 1.0 mol) was added at 5-10°C and the reaction was then heated to 55-60°C for 1 h. After this time, reaction mass was cooled to 25-30°C and filtered. The clear filtrate was washed with water (250 mL) and the organic layer was dried over anhydrous sodium sulfate and concentrated to obtain a light brown colored gummy mass of 1-((4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methyl)pyrrolidine (100 g, 89%).

Step 8: Synthesis of 1-((4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methyl)pyrrolidine hydrochloride:



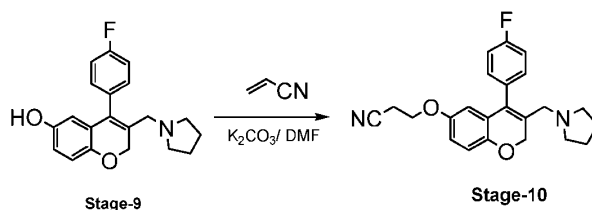
[0443] HCl in diisopropylether (250 mL) was added to a solution of 1-((4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methyl)pyrrolidine (100 g, 0.29 mol) in diisopropylether (400 mL) between 5-10°C in a drop wise manner over a period of 1h, followed by stirring for 30 min at 5-10°C. The precipitated solid was filtered and dried under vacuum at 40-45°C to yield 1-((4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methyl)pyrrolidine hydrochloride (100 g, 91%).

Step 9: Synthesis of 4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-ol:



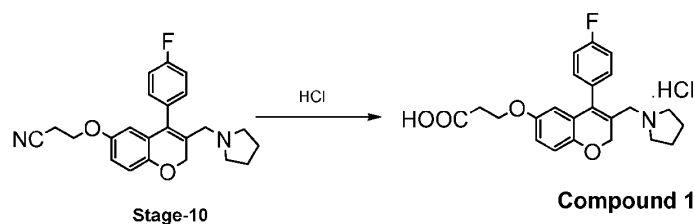
[0444] Neat BBr_3 (100 g, 38 mL, 0.4 mol) was added to a solution of 1-((4-(4-fluorophenyl)-6-methoxy-2*H*-chromen-3-yl)methyl)pyrrolidine hydrochloride (100 g, 0.27 mol) in dry DCM (1500 mL) at 0-10°C and after completion of the addition the mixture was stirred at RT for 16 h. The DCM layer was decanted to separate the gummy product mass. The product was quenched with methanol and diluted with water to precipitate out the product. The precipitated solid was filtered and suck dried to yield 4-(4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-ol (75 g, 86%).

Step 10: Synthesis of 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-yl)oxy)propanenitrile:



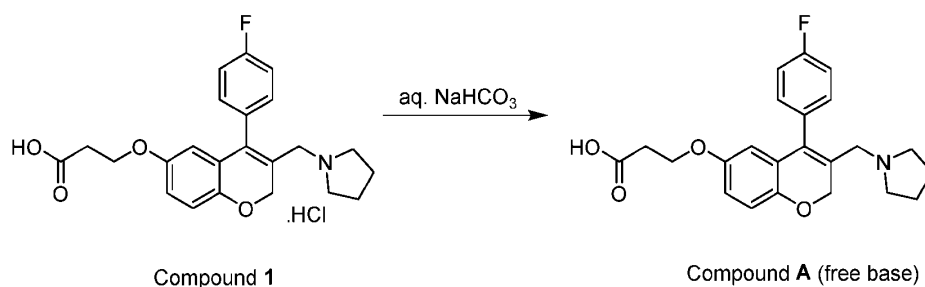
[0445] DMF (125 mL) and potassium carbonate (25.5 g, 185.0 mmol) were added to a solution of 4-(4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-ol (25 g, 61.7 mmol) in acrylonitrile (250 mL). The mixture was heated to 80 -85°C for 24 h. After this time, the reaction mixture was concentrated *in vacuo*. The resulting residue was quenched with water and extracted with ethyl acetate (300 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated to obtain a light brown colored gummy mass which was further purified by column chromatography to yield 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-yl)oxy)propanenitrile as a light brown solid (12 g, 47%).

Step 11: Synthesis of 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2*H*-chromen-6-yl)oxy)propanoic acid hydrochloride:



[0446] Concentrated HCl (1.0 L) was added to 3-((4-(4-fluorophenyl)-3-(pyrrolidin-1-ylmethyl)-2H-chromen-6-yl)oxy)propanenitrile (100 g, 26 mol) and the reaction was heated to 95-100 °C for 4 h. The reaction was then cooled to RT and stirred for 3 h. The Precipitated solids were filtered and suck dried to obtain crude Compound 1 (60 g) with HPLC purity 92-95 % a/a.

Example 1.1 - Preparation of Compound A

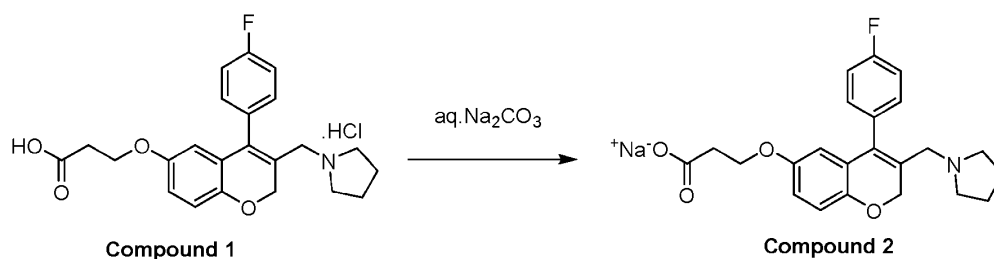


[0447] To a mixture of Compound 1 (5.0 g) and water (100 ml), was added sodium bicarbonate (1.0 eq.) at ambient temperature and adjusted pH of the aqueous suspension to 5.5-6.0. The suspension becomes clear and reprecipitated. Then the slurry was stirred for 1 h at ambient temperature. The solid was isolated by filtration and washed with water (2 volumes). The wet solid was then dried at 55-60 °C in hot air oven for 5-6 h to obtain 4.5 g of Compound A (free base).

Preparation of salts of Compound A using basic counter ions

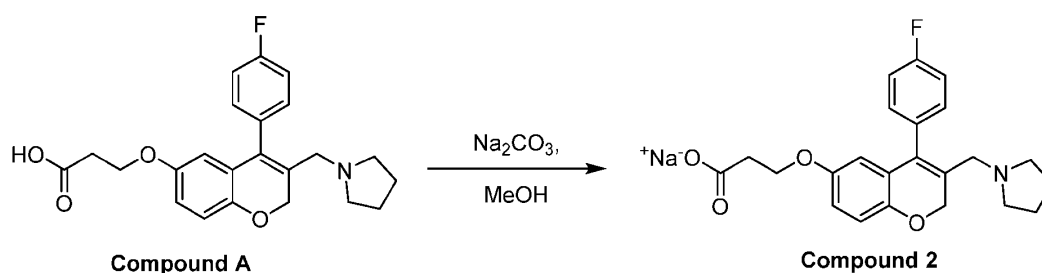
Example 2 - Preparation of Compound 2

(a) Preparation of Compound 2 using sodium carbonate



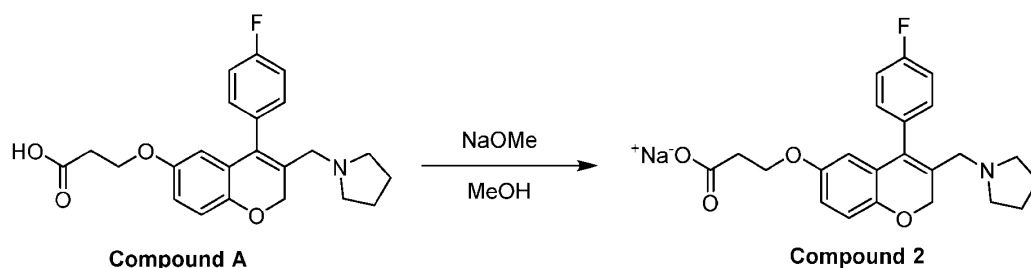
[0448] Compound **1** (0.5 g) was dissolved in methanol (15 ml). To this solution, was added sodium carbonate (1.05 eq.) at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. Then methanol was removed under reduced pressure at 40-45°C. Diethyl ether (15 ml) was added to the obtained residue and the resulting slurry was stirred for 1 h at ambient temperature. The solid obtained was filtered and washed with diethyl ether (~4 vol.). The wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.46 g of Compound **2**.

(b) Preparation of Compound 2 using sodium carbonate



[0449] To a suspension of Compound **A** free base (0.5 g) in methanol (15 ml), was added sodium carbonate (1.0 eq.) at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. The reaction mass was filtered to remove undissolved solid, and filtrate was concentrated under reduced pressure at 40-45°C. Diethyl ether (15 ml) was added to the residue after distillation and the resulting slurry was stirred for 1 h at ambient temperature. The solid obtained was isolated by filtration and washed with diethyl ether (4 volumes). The obtained solid was unloaded and dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.23 g of Compound **2**.

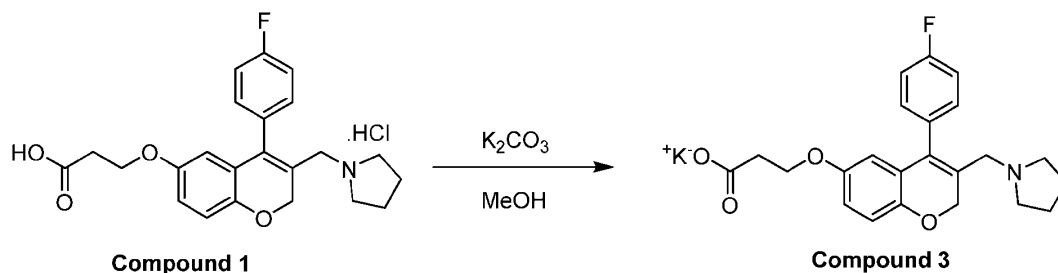
(c) Preparation of Compound 2 using sodium methoxide



[0450] To a suspension of Compound A free base (0.5 g) in methanol (15 ml) was added sodium methoxide (1.0 eq.) at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. Methanol was removed under reduced pressure at 40-45°C, diethyl ether (15 ml) was added to the obtained residue and the resulting slurry was stirred for 1 h at ambient temperature. The solid obtained was isolated by filtration and washed with diethyl ether (4 volumes). Wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.41 g of Compound 2.

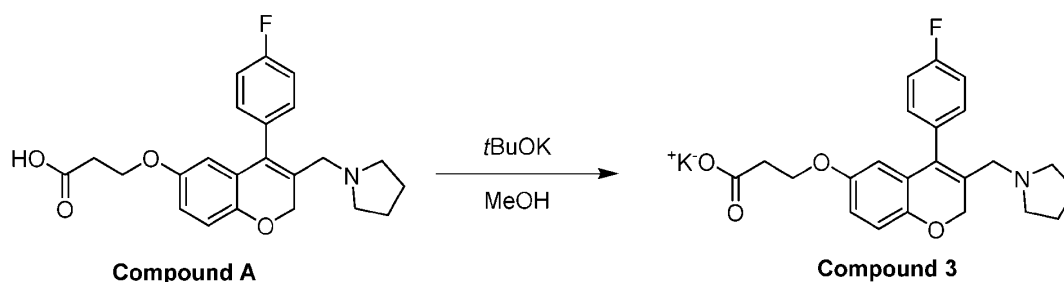
Example 3 - Preparation of Compound 3

(a) Preparation of Compound 3 from Compound 1 using potassium carbonate



[0451] Compound 1 (0.5 g) was dissolved in methanol (15 ml). To this solution, was added potassium carbonate (1.05 eq.) at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. Then methanol was removed under reduced pressure at 40-45°C. Diethyl ether (15 ml) was added to the obtained residue and the resulting slurry was stirred for 1 h at ambient temperature. The solid was found highly hygroscopic in nature and difficult to isolate by filtration as it became viscous immediately after filtration. This viscous solid was collected and analysed by ¹H-NMR.

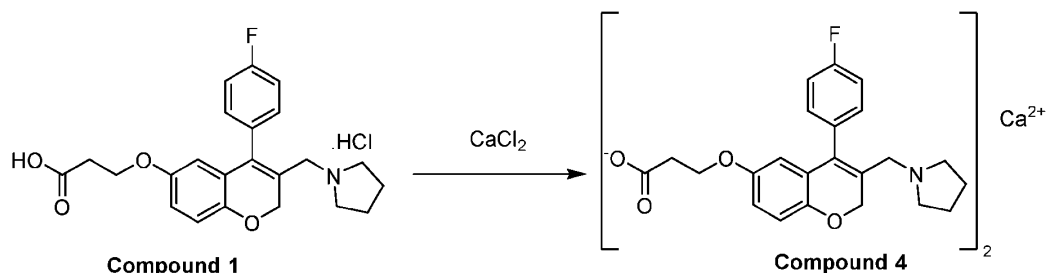
(b) Preparation of Compound 3 using potassium tert-butoxide



[0452] To a suspension of Compound **A** free base (0.5 g) in methanol (15 ml) was added potassium *tert*-butoxide (1.0 eq.) at 0-5 °C. The reaction mixture was stirred for 16 h at ambient temperature. Reaction mixture was filtered to remove undissolved particles and the filtrate was concentrated under reduced pressure at 40-45°C. Diethyl ether (15 ml) was added to the residue and the resulting slurry was stirred for 1 h at ambient temperature. The solid was found highly hygroscopic in nature and difficult to isolate by filtration as it became viscous immediately after filtration..

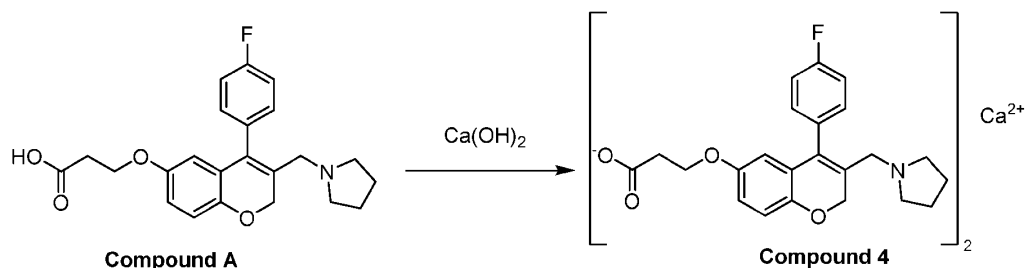
Example 4 - Preparation of Compound 4

(a) *Preparation of Compound 4 using calcium chloride (via in situ preparation of sodium salt)*



[0453] To a mixture of compound **1** (1.0 g) and water (30 ml), was added sodium hydroxide (2.0 eq.) at ambient temperature. The reaction mixture was stirred for 1 h at ambient temperature and then added calcium chloride (0.5 eq.) into the reaction mixture and the reaction mixture was stirred for 1 h at ambient temperature. The solid was isolated by filtration and washed with water (4 volumes). Then the wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.74 g of compound **4**.

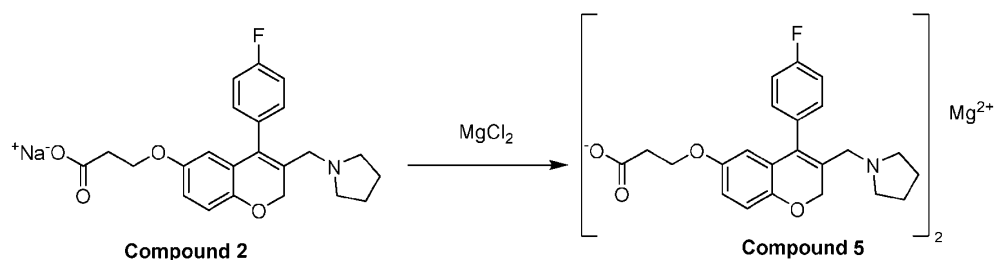
(b) Preparation of Compound 4 using calcium hydroxide (via in situ preparation of sodium salt)



[0454] To a mixture of compound **A** free base (0.5 g) and methanol (15 ml), was added calcium hydroxide (0.5 eq.) at ambient temperature. The reaction mixture was stirred for 16 h at ambient temperature. The solid was isolated by filtration and it was washed with methanol (4 volumes). The wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.4 g of compound **4**.

Example 5 - Preparation of Compound 5

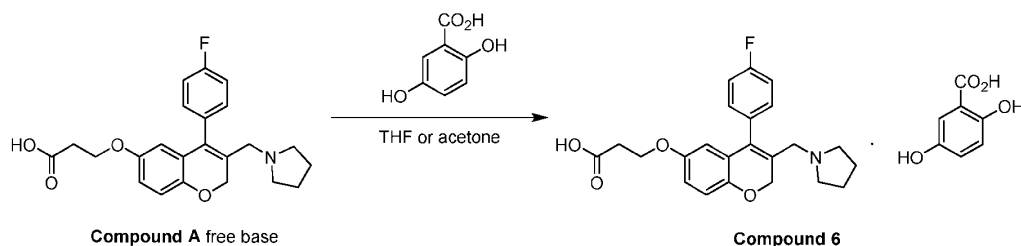
(b) *Preparation of Compound 5 using Magnesium chloride*



[0455] Compound **2** (0.4 g) was dissolved in water (40 ml). To this solution, was added magnesium chloride (0.5 eq) at 40-45 °C. Then heating was stopped, and the reaction mixture was stirred for 16 h at ambient temperature. The precipitated solid was isolated by filtration and washed by water (10 volumes). The wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.3 g of Compound **5**.

Preparation of salts of Compound A using acidic counter ions

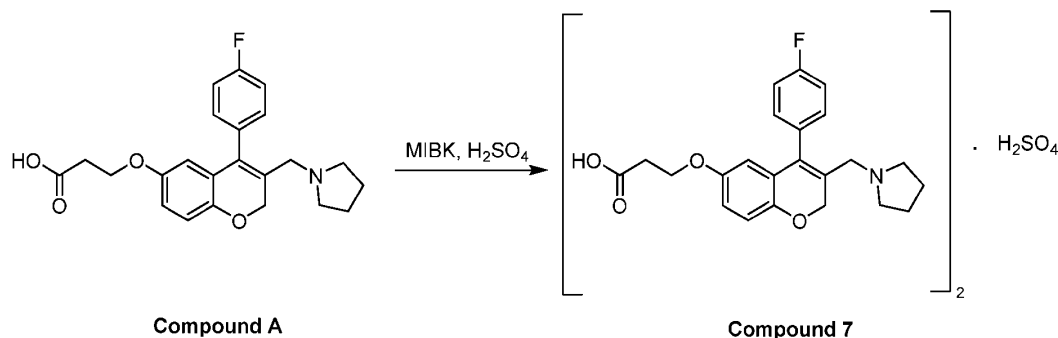
Example 6: Preparation of Compound 6



[0456] Compound **A** free base (0.5 g) was dissolved in tetrahydrofuran (15 ml) at 55-60 °C. To this solution was added gentisic acid (1.0 eq.) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60 °C. Then Reaction mixture was cooled to ambient temperature and stirred for 3 h. Tetrahydrofuran was removed under vacuum at 40-45°C to obtain syrupy liquid of compound **6**

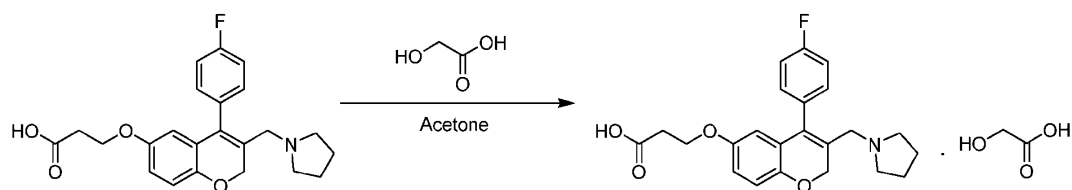
[0457] Compound **A** free base 0.3 g was dissolved in acetone (12 ml) at 50-55 °C. To this solution, was added gentisic acid (1.0 eq.) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60°C. Reaction mixture was cooled to ambient temperature and stirred for 3 h. The solvent was removed under reduced pressure at 40-45°C to obtain compound **6**.

Example 7: Preparation of Compound 7



[0458] To a mixture of compound **A** free base (0.5 g) and methyl iso-butyl ketone (15 ml), was added sulphuric acid solution (0.5 eq. of sulphuric acid in 5 ml of methyl iso-butyl ketone) at -5-0 °C. The reaction mixture was stirred for 16 h at ambient temperature. The obtained solid was filtered and washed with methyl iso-butyl ketone (10 vol.) and dried at 55-60 °C in hot air oven for 5-6 h to obtain compound **7**.

Example 8: Preparation of Compound 8

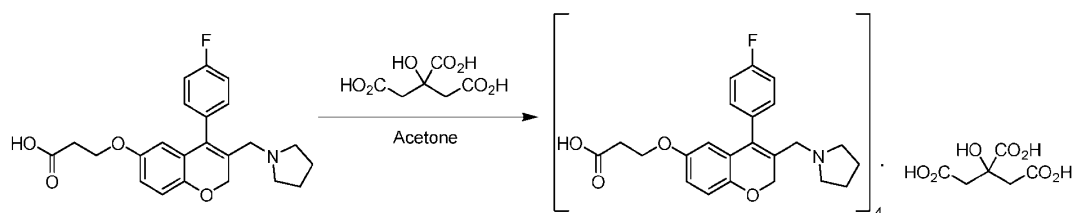


Compound A

Compound 8

[0459] Compound A free base (0.5 g) was dissolved in acetone (20 ml) at 55-60 °C. To this solution, was added glycolic acid (0.5 eq) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60 °C. Then reaction mixture was cooled to ambient temperature and stirred for 3 h. The solid precipitated was filtered and washed with acetone (4 volumes). The wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.46 g of Compound 8.

Example 9: Preparation of Compound 9

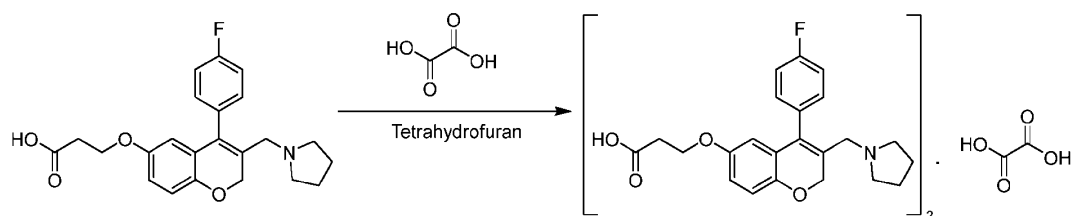


Compound A

Compound 9

[0460] Compound A free base (0.5 g) was dissolved in acetone (20 ml) at 50-55 °C. To this solution was added citric acid (1.0 eq) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60 °C. Reaction mixture was cooled to ambient temperature and stirred for 3 h. The solvent was removed under reduced pressure at 40-45°C to obtain Compound 9.

Example 10: Preparation of Compound 10

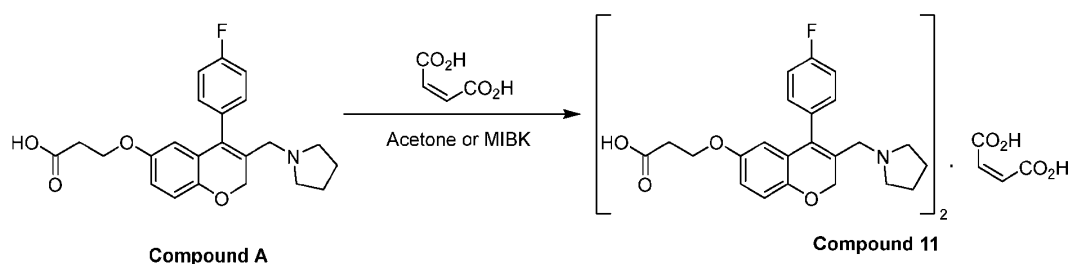


Compound A

Compound 10

[0461] Compound **A** free base (0.5 g) was dissolved in tetrahydrofuran (15 ml) at 55-60 °C. To this solution was added oxalic acid (0.5 eq.) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60 °C and cooled to ambient temperature and stirred for 4 h. The solid obtained was filtered and washed with tetrahydrofuran (4 volumes). The wet solid was dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.35 g of solid Compound **10**.

Example 11: Preparation of Compound 11

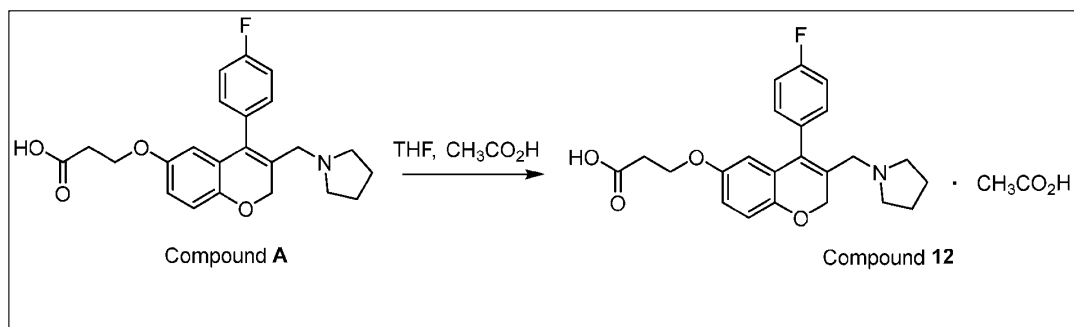


[0462] Compound **A** free base (0.5 g) was dissolved in tetrahydrofuran (15 ml) at 55-60 °C. To this solution was added maleic acid (0.5 eq.) at 55-60 °C. The reaction mixture was stirred for 1 h at 55-60 °C. Reaction mixture was cooled to ambient temperature and stirred for 16 h. Tetrahydrofuran was removed under vacuum at 40-45 °C to obtain syrupy liquid (0.8 g).

[0463] Compound **A** free base (0.5 g) was dissolved in methyl iso-butyl ketone (20 ml) at 70-75 °C. To this solution was added maleic acid (0.5 eq.) at 70-75 °C. The reaction mixture was stirred for 1 h at 70-75 °C. Reaction mixture was cooled to ambient temperature and stirred for 16 h. Methyl iso-butyl ketone was removed under vacuum at 40-45 °C to obtain solid compound **11**.

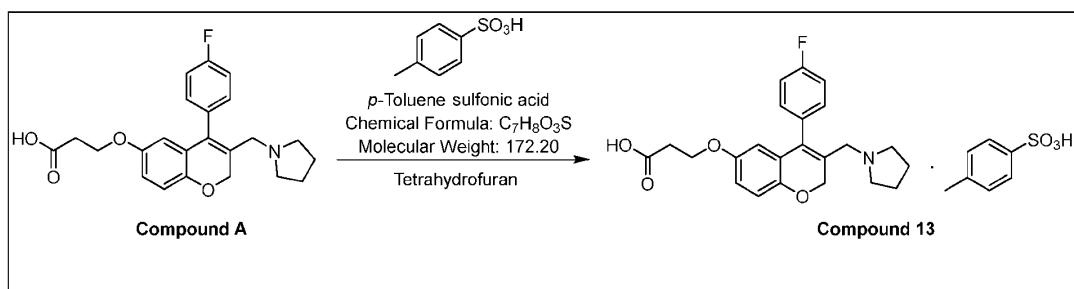
[0464] Compound **A** free base (0.5 g) was dissolved in acetone (20 ml) at 50-55 °C. To this solution was added maleic acid (0.5 eq) at 50-55 °C. The reaction mixture is stirred for 1 h at 50-55 °C. Reaction mixture was cooled to ambient temperature and stirred for 16 h. Acetone was removed under vacuum at 40-45 °C to obtain solid Compound **11**.

Example 12: Preparation of Compound 12



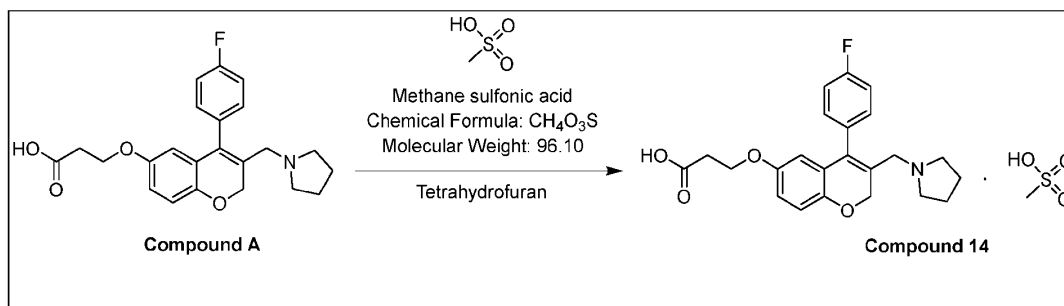
[0465] Compound A free base (0.5 g) was dissolved in tetrahydrofuran (20 ml) at 50-55 °C. To this solution, was added acetic acid (1.0 eq.) at 50-55 °C. The reaction mixture was stirred for 1 h at 50-55 °C. Reaction mixture was cooled to ambient temperature and stirred for 16 h. Tetrahydrofuran was removed under vacuum at 40-45°C to obtain Compound 12 as a solid.

Example 13: Preparation of Compound 13



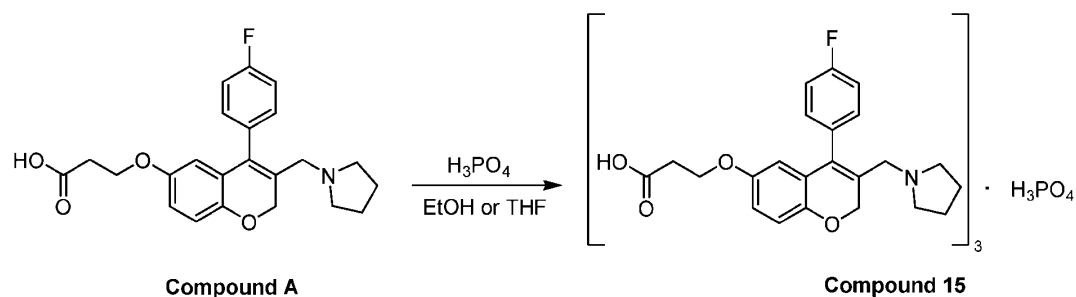
[0466] Compound A free base (0.5 g) was dissolved in tetrahydrofuran (20 ml) at 50-55 °C. To this solution, was added *p*-toluene sulfonic acid (1.0 eq.) at 50-55 °C. The reaction mixture was stirred for 1 h at 50-55 °C. Reaction mixture was cooled to ambient temperature and stirred for 16 h. Tetrahydrofuran was removed under vacuum at 40-45°C to obtain Compound 13 as a solid.

Example 14: Preparation of Compound 14



[0467] To a mixture of compound **A** free base (0.5 g) and tetrahydrofuran (20 ml) was added methane sulfonic acid (1.0 eq.) at -5-0 °C. The reaction mixture was stirred for 16 h at ambient temperature. The solid precipitated was filtered, washed with tetrahydrofuran (10 volumes) and dried in hot air oven at 55-60 °C for 5-6 h to obtain 0.3 g of Compound **14** mesylate salt.

Example 15: Preparation of Compound 15



[0468] To a mixture of compound **A** free base (0.5 g) and ethanol (15 ml), was added *o*-phosphoric acid solution (0.35 eq of *o*-phosphoric in 5 ml of ethanol) at -5-0 °C. The reaction mixture was stirred for 16 h at ambient temperature. The solid precipitated was filtered, washed with ethanol (10 volumes) and dried at 55-60 °C in hot air oven for 5-6 h to obtain 0.46 g of solid Compound **15**.

[0469] To a mixture of compound **A** free base (0.5) g and tetrahydrofuran (15 ml) was added *o*-phosphoric acid solution (0.35 eq of *o*-phosphoric in 5 ml of tetrahydrofuran) at -5-0 °C. The reaction mixture was stirred for 16 h at 20-30 °C. The solid obtained was filtered and washed tetrahydrofuran (10 vol.). Dried at 55-60 °C in hot air oven for 4-6 h to obtain 0.40 g of solid Compound **15**.

Example 16: Polymorph Screening to identify the stable polymorph

[0470] The results of the polymorph screening to identify the suitable and stable polymorph of Compound **1** are summarized in Table 4.

[0471] Compound **1**, which was isolated as hydrochloride salt, was selected as a suitable candidate to perform the polymorphism study as it was found to be superior in terms of solubility and hygroscopicity and further confirmed after performing salt screening study on compound A using different acid and base counterions.

[0472] Form A of Compound **1** was subject to slurry analysis performed at reflux conditions. As the results summarized in Table 4, Form A was obtained in all the experiments, indicating Form A of Compound **1** is thermodynamically stable that is supported by repeated recrystallizations.

Table 4: Stable Form Screen Slurries of Compound 1

Solvent	Conditions	Type of experiment	Observations	XRPD Result
n-heptane	Reflux, 95-100°C	Suspension or slurry	White crystalline solid	Form A
Diisopropyl ether	Reflux, 65-70°C	Suspension or slurry	White crystalline solid	Form A
2-Methyltetrahydrofuran	Reflux, 80-85°C	Suspension or slurry	White crystalline solid	Form A
Ethyl acetate	Reflux, 75-80°C	Suspension or slurry	White crystalline solid	Form A
Isopropyl acetate	Reflux 85-90°C	Suspension or slurry	White crystalline solid	Form A

n-butyl acetate	Reflux 125-130°C	slurry	White crystalline solid	Form A
Methanol	Reflux 60-65°C	Recrystallization	White crystalline solid	Form A
Ethanol	Reflux 75-80°C	Recrystallization	White crystalline solid	Form A
Isopropanol	Reflux 80-85°C	Slurry or suspension	White crystalline solid	Form A
n-propanol	Reflux 95-100°C	Recrystallization	White crystalline solid	Form A
n-butanol	Reflux 115-120°C	Suspension or slurry	White crystalline solid	Form A
Acetic acid	Reflux 110-120°C	Recrystallization	White crystalline solid	Form A
Methyl isobutyl ketone	Reflux 115-120°C	Suspension or slurry	White crystalline solid	Form A
Tetrahydrofuran	Reflux 65-70°C	Suspension or slurry	White crystalline solid	Form A
Acetone	Reflux 55-60°C	Suspension or slurry	White crystalline solid	Form A

Methyl ethyl ketone	Reflux 80-85°C	Suspension or slurry	White crystalline solid	Form A
Methyl <i>tert</i> -butyl ether	Reflux 55-60°C	Suspension or slurry	White crystalline solid	Form A
10% aq. methanol	Reflux 100-110°C	Recrystallization	White crystalline solid	Form A
10% aq. Isopropanol	Reflux 100-110°C	Recrystallization	White crystalline solid	Form A
Water	Reflux 100-110°C	Recrystallization	White crystalline solid	Form A

Example 17 - Preparation of Form A of Compound 1

[0473] Form A of Compound 1 was prepared as described above.

[0474] Table 1.1 and 1.2, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of compound 1.

Table 1.1 - XRPD Peak Positions for Form A of Compound 1

Position [°2 θ] ¹	d (Angstroms)	Intensity [%]
3.9	22.7	1.2
5.9	15.0	2.3
7.8	11.3	1.2
8.9	10.0	5.3
9.7	9.1	39.7
10.5	8.4	9.2
11.6	7.7	12.9
13.3	6.7	7.2

15.1	5.9	5.2
15.5	5.7	5.4
16.1	5.5	7.4
16.4	5.4	21.7
16.9	5.2	37.1
17.6	5.1	16.5
18.1	4.9	19.3
18.4	4.8	4.5
18.9	4.7	9.3
19.4	4.6	49.7
19.5	4.6	64.9
19.7	4.5	27.8
20.1	4.4	6.7
20.5	4.3	11.8
21.0	5.2	8.3
21.5	4.1	16.8
21.8	4.1	20.2
22.4	4.0	29.7
23.0	3.9	56.6
23.2	3.8	37.3
23.9	3.7	14.2
24.7	3.6	100
25.7	3.5	22.5
26.7	3.4	8.1
27.0	3.3	13.7
27.5	3.2	8.2
28.1	3.2	2.1
28.4	3.2	12.1
29.1	3.1	3.3

29.6	3.0	1.6
30.6	2.9	5.1
31.2	2.9	14.1
31.6	2.8	6.5
32.5	2.8	9.8
33.6	2.7	2.6
34.4	2.6	6.2
35.3	2.6	1.1
36.4	2.5	2.8
37.2	2.4	2.4
37.9	2.4	3
40.4	2.2	2.1
41.0	2.2	3.7
41.5	2.2	4.6
44.7	2.0	4.2
45.6	2.0	5.7
48.8	1.9	1.4

¹ In this and all subsequent tables, the position 2 θ is within ± 0.2 .

Table 1.2 - XRPD Peak Positions for Form A of Compound 1

Position [$^{\circ}2\theta$] ¹	d (Angstroms)	Intensity [%]
4.0	22.1	1.5
7.7	11.6	1.8
9.6	9.3	47.4
11.5	7.8	10.4
13.1	6.8	7.7
14.8	6.1	2.1
15.4	5.8	7.9
15.9	5.6	5.4
16.3	5.5	62.2

16.8	5.3	57.1
17.4	5.2	6.0
17.9	5.0	18.8
18.8	4.8	12.9
19.2	4.7	30.4
19.4	4.6	45.1
19.6	4.6	100.0
20.1	4.5	4.3
20.4	4.4	10.8
21.4	4.2	10.0
21.7	4.2	24.7
22.3	4.0	20.1
22.9	3.9	46.3
23.1	3.9	50.4
23.8	3.8	14
24.5	3.7	70.0
25.6	3.5	33.9
26.0	3.5	3.5
26.3	3.4	4.1
26.6	3.4	9.3
27.0	3.4	6.6
28.4	3.2	17.8
29.0	3.1	4.8
30.4	3.0	4.8
31.1	2.9	10.5
31.5	2.9	6.4
32.4	2.8	11.6
32.7	2.8	7.6
33.1	2.8	4.9

33.4	2.7	2.1
34.0	2.7	2.7
34.5	2.7	13.3
36.2	2.5	1.4
36.7	2.5	1.7
37.2	2.5	3.1
37.9	2.4	1.4
39.0	2.4	1.8
39.9	2.3	2.5
40.3	2.3	1.8
40.9	2.3	3.3
41.5	2.2	8.2
42.6	2.2	2.3
44.5	22.1	9.2
45.5	11.6	3.2
49.5	9.3	1.6

¹ In this and all subsequent tables, the position 2θ is within ± 0.2 .

[0475] FIGs. 1 and 3 depict the XRPD diffractograms of Form A of compound 1.

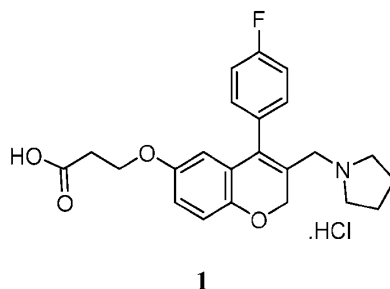
[0476] FIGs. 2 and 4 depict the DSC thermograms of Form A of compound 1.

[0477] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

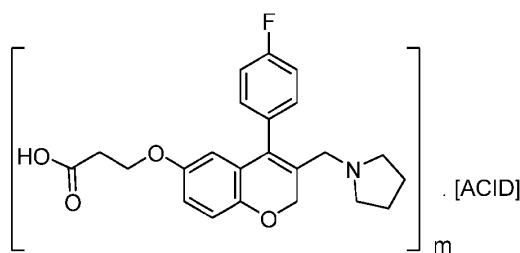
1. A crystalline form of Compound **1**:



wherein said form is of Form A.

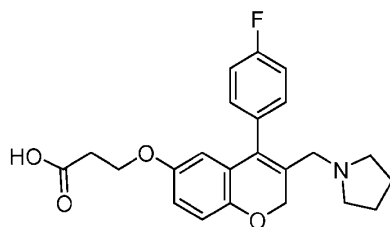
2. The compound according to claim 1, wherein said compound is substantially free of amorphous compound **1**.
3. The compound according to claim 1 or 2, having one or more peaks in its XRPD selected from those at about 19.5, about 23.0 and about 24.7 degrees 2-theta.
4. The compound according to claim 1 or 2, having one or more peaks in its XRPD selected from those at about 19.6, about 23.1 and about 24.5 degrees 2-theta.
5. The compound according to any one of claims 1-4, having an XRPD substantially similar to that depicted in **FIG. 1** or **FIG. 3**.
6. A pharmaceutically acceptable composition comprising the compound according to any one of claims 1-5 and a pharmaceutically acceptable carrier, excipient, or vehicle.
7. A method of modulating the protein-protein interaction between TCR-Nck in a patient comprising administering to the patient the compound according to any one of claims 1 through 5, or a pharmaceutically acceptable composition thereof.

8. A method of treating a TCR-Nck mediated disease, disorder, or condition in a patient in need thereof, comprising administering to the patient the compound according to any one of claims 1 through 5, or a pharmaceutically acceptable composition thereof.
9. A method of treating a disease, disorder, or condition in a patient in need thereof, comprising administering to the patient the compound according to any one of claims 1 through 5, 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, myasthenia gravis, ankylosing spondylitis, Crohn's disease, leukemias, lymphomas, and thromboembolic and allergic complications associated with leukemias and lymphomas.
10. The method according to claim 9, wherein the compound or composition thereof is administered orally.
11. The method according to claim 9 or 10, wherein the compound or composition thereof is administered in a range of 0.01 - 100 mg/kg body weight of the patient.
12. The method according to any one of claims 9-11, further comprising administering to the patient an additional therapeutic agent.
13. A method for preparing a salt compound of formula **X**:



wherein m is 1, 2, 3, or 4, comprising steps of:

combining **A**:



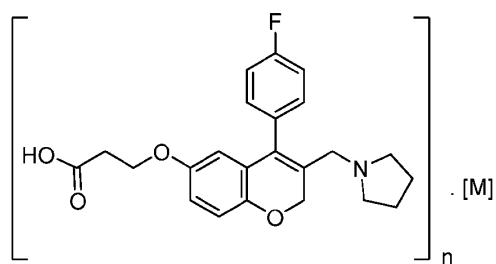
A

with a suitable acid and optionally a solvent under conditions for forming a salt compound of formula **X**.

14. The method of claim 13, wherein:

- (a) the suitable acid is hydrochloride acid thereby forming a hydrochloride salt of compound **A**;
 - (b) the suitable acid is gentisic acid thereby forming a gentisate salt of compound **A**;
 - (c) the suitable acid is sulfuric acid thereby forming a sulfate salt of compound **A**;
 - (d) the suitable acid is glycolic acid thereby forming a glycolate salt of compound **A**;
 - (e) the suitable acid is citric acid thereby forming a citrate salt of compound **A**;
 - (f) the suitable acid is oxalic acid thereby forming an oxalate salt of compound **A**;
 - (g) the suitable acid is maleic acid thereby forming a maleate salt of compound **A**;
 - (h) the suitable acid is acetic acid thereby forming an acetate salt of compound **A**;
 - (i) the suitable acid is *p*-toluene sulfonic acid thereby forming a tosylate salt of compound **A**;
 - (j) the suitable acid is methyl sulfonic acid thereby forming a mesylate salt of compound **A**;
- or
- (k) the suitable acid is *o*-phosphoric acid thereby forming a phosphate salt of compound **A**.

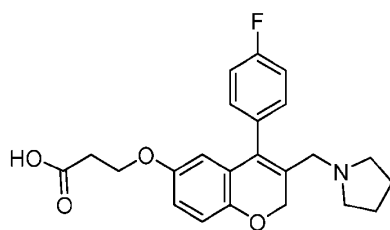
15. A method for preparing a salt compound of formula **Y**:

**Y**

wherein $n = 1$ or 2

comprising steps of:

combining **A**:

**A**

with a suitable reagent and optionally a solvent under conditions for forming a salt compound of formula **Y**.

16. The method of claim 15, wherein:

- (a) the suitable reagent is sodium carbonate or sodium methoxide thereby forming a sodium salt of compound **A**;
- (b) the suitable reagent is potassium carbonate or potassium tert-butoxide thereby forming a potassium salt of compound **A**;
- (c) the suitable reagent is calcium carbonate or calcium hydroxide thereby forming a calcium salt of compound **A**; or
- (d) the suitable reagent is magnesium chloride thereby forming a magnesium salt of compound **A**.