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(71) Applicant *(for all designated States except US)*: **MERCK SHARP & DOHME CORP.** [US/US]; 126 E. Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARR, Kenneth Jay** [US/US]; 261 Commonwealth Avenue, No. 7 Boston, MA 02116 (US). **BEINSTOCK, Corey** [US/US]; 26 Homeward Lane, Natick, MA 01760 (US). **MACLEAN, John** [GB/US]; 431 Washington Street, Unit 4 Brookline, MA 02446 (US). **ZHANG, Hongjun** [CN/US]; 8 Town House Drive, Newton, MA 02460 (US). **BERESIS, Richard Thomas** [US/CN]; Apartment 2504, Building 1, 2504 Shimen #2 Road, Shanghai 200040 (CN).

(74) Agent: **LIU, SHEN & ASSOCIATES**; A0601, Huibin Building, No.8 Beichen Dong Street, Chaoyang District, Beijing 100101 (CN).

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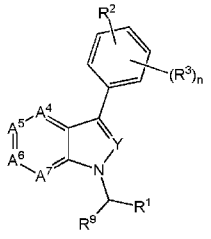

(I)

(57) Abstract: Disclosed are compounds of Formula I or a pharmaceutically acceptable salt or solvate thereof. Such compounds can be used in the treatment of RORgammaT-mediated diseases or conditions.

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N-ALKYLATED INDOLE AND INDAZOLE COMPOUNDS AS RORGAMMAT INHIBITORS AND USES THEREOF

BACKGROUND OF THE INVENTION

Upon activation by antigen-presenting cells naïve T helper cells undergo clonal expansion and will ultimately differentiate in cytokine secreting effector T cells, such as Th1 and Th2 subtypes. A third and distinct effector subset has been identified, which plays a key role in providing immunity to bacteria and fungi at mucosal surfaces (Kastelein et al., *Annu. Rev. Immunol.* 25: 221-242, 2007). This effector T helper cell subset can be distinguished based on its ability to produce large quantities of IL-17/F, IL-21 and IL-22, and is named Th17 (Miossec et al., *New Eng. J. Med.* 2361: 888-898, 2009).

Different T helper subsets are characterized by the expression of lineage specific master transcription factors. Th1 and Th2 effector cells express Tbet and GATA3, respectively. A Thymocyte/T cell specific variant of Retinoic Acid Receptor-related Orphan Receptor (ROR), RORgammaT, is highly expressed in Th17 cells (He et al., *Immunity* 9: 797-806, 1998). RORgammaT belongs to the nuclear hormone receptor superfamily (Hirose et al., *Biochem. Biophys. Res. Comm.* 205: 1976-1983, 1994). RORgammaT is a truncated form of RORgamma, lacking the first N-terminal 21 amino acids and is, in contrast to RORgamma which is expressed in multiple tissues (heart, brain, kidney, lung, liver and muscle), exclusively expressed in cells of the lymphoid lineage and embryonic lymphoid tissue inducers (Sun et al., *Science* 288: 2369-2372, 2000; Eberl et al., *Nat Immunol.* 5: 64-73, 2004).

Studies using heterozygous knock-in mice replacing the RORgammaT open reading frame with GFP, revealed a constitutive expression of GFP in approximately 10% of the CD4+ T cells in the small intestinal lamina propria (LP), co-expressing the Th17 cytokines IL-17/F and IL-22 (Ivanov et al., *Cell* 126: 1121-1133, 2006). In mice deficient for RORgammaT, the number of Th17 cells was markedly decreased in the LP and in vitro stimulation of CD4+ T cells, under Th17 polarizing conditions resulted in a drastic decrease of IL-17 expression. These results were further substantiated via forced expression of RORgammaT in naïve CD4+ T cells, which resulted in an induction of IL-17/F and IL-22

(Ivanov et al., *Cell* 126: 1121-1133, 2006). Taken together demonstrating the importance of RORgammaT in differentiation and stabilization of the Th17 lineage. In addition, a ROR family member, RORalpha has been demonstrated to be involved in Th17 differentiation and stabilization (Yang et al., *Immunity* 28: 29-39, 2008).

Recently, RORgammaT was shown to play a crucial role in non-Th17 lymphoid cells. In these studies, RORgammaT was critically important in innate lymphoid cells expressing Thy1, SCA-1 and IL-23R proteins. Genetic disruption of RORgamma in a mouse colitis model dependent on these innate lymphoid cells, prevented colitis development (Buonocore et al., *Nature* 464: 1371-1375, 2010). In addition, RORgammaT was shown to play a crucial role in other non-Th17 cells, such as mast cells (Hueber et al., *J. Immunol.* 184: 3336-3340, 2010). Finally, RORgammaT expression and secretion of Th17-type of cytokines was reported for Lymphoid Tissue Inducer cells, NK T-cells, NK cells (Eberl et al., *Nat. Immunol.* 5: 64-73, 2004) and gamma-delta T-cells (Sutton et al., *Nat. Immunol.* 31: 331-341, 2009; Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009), suggesting an important function for RORgammaT in these subtypes of cells.

Based on the role of IL-17 producing cells (either Th17 or non-Th17 cells) RORgammaT has been identified as a key mediator in the pathogenesis of several diseases (Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009; Annuziato et al., *Nat. Rev. Rheumatol.* 5: 325-331, 2009). This was confirmed using several disease models representative of autoimmune diseases. Genetic ablation of the RORgamma gene in mice prevented the development of experimental autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE) and colitis (Ivanov et al., *Cell* 126:1121-33, 2006; Buonocore et al., *Nature* 464: 1371-1375, 2010).

Being a critical mediator in Th17-cells and other non-Th17 cells, antagonism of the transcriptional activity of RORgammaT is expected to have a beneficial effect on autoimmune diseases, such as, but not limited to rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, Crohn's disease, and asthma (Annunziato et al., *Nat. Rev. Immunol.* 5: 325-331, 2009; Louten et al., *J. Allergy Clin. Immunol.* 123: 1004-1011, 2009). Antagonism of RORgammaT may also be beneficial in other diseases, which are characterized by increased levels of Th17 cells and/or elevated levels of Th17 hallmark cytokines such as IL-17, IL-22 and IL-23. Examples of such diseases are Kawasaki Disease (Jia et al., *Clin. Exp. Immunol.* 162: 131-137, 2010) and Hashimoto's thyroiditis (Figueroa-

Vega et al., *J. Clin. Endocrinol. Metab.* 95: 953-62, 2010). Another example includes infectious diseases, such as, but not limited to, mucosal leishmaniasis (Boaventura et al., *Eur. J. Immunol.* 40: 2830-2836, 2010). In each of the above examples the inhibition may be enhanced by simultaneous inhibition of RORalpha.

Compounds modulating RORgammaT have been reported. Examples of agonists include T0901317 and SR1078 (Wang et al., *ACS Chem. Biol.* 5:1029-1034, 2010). In addition, antagonist have been reported such as 7-oxygenated sterols (Wang et al., *J. Biol. Chem.* 285: 5013-5025, 2009) and compounds described in EP2181710 A1.

Numerous immune and inflammatory disorders continue to afflict millions of patients worldwide. Although significant advances have been made in treating these disorders, current therapies do not provide satisfactory results for all patients due to, for example, detrimental side effects or insufficient efficacy. One exemplary immue disorder in need of better therapy is psoriasis. Various therapeutics have been developed in an attempt to treat psoriasis. However, the traditional therapies for psoriasis often have toxic adverse effects. An exemplary inflammatory disorder in need of better treatment is rheumatoid arthritis. Numerous therapeutics have been developed in an attempt to treat this disorder. However, some patients develop resistance to current therapies.

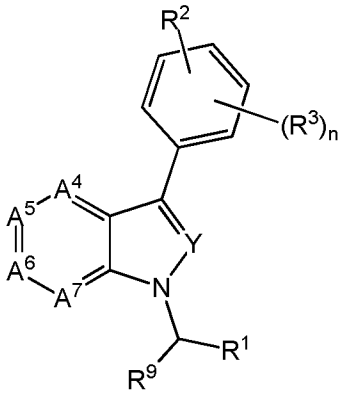
Accordingly, a need exists for improved treatments for immune disorders and inflammatory disorders. The present invention addresses this need and provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds which alter the interaction of coregulator proteins with RORgammaT and thereby antagonize RORgammaT-mediated transcriptional activity, their use for the treatment of RORgammaT-mediated diseases or conditions, in particular autoimmune diseases and inflammatory diseases, as well as pharmaceutical compositions comprising such compounds and pharmaceutical carriers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound according to Formula I



I

or a pharmaceutically acceptable salt or solvate thereof wherein,

Y is CH, N or CR^a;

n = 0, 1, 2, 3 or 4;

A^4 is CR^4 or N,

A^5 is CR^5 or N,

A^6 is CR^6 or N,

A^7 is CR^7 or N,

with the proviso that no more than one or two of A^4-A^7 can be N;

R^a is (C_{1-4})alkyl;

R^1 is

(i) (C_{3-12})carbocyclyl; or

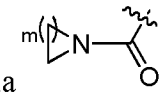
(ii) a 4- to 12-membered heterocyclyl,

both (i) and (ii) optionally substituted with one, two, three, four or five R^8;

R^2 is hydroxycarbonyl, hydroxycarbonyl(C_{1-10})alkyl, (C_{1-10})alkylsulfoxyaminocarbonyl, or carbamoyl;

R^3 is hydrogen, halogen, cyano, nitro, hydroxy, (C1-3)alkylC(O)O-, (C_{1-4})alkyl, or $(C_{1-}$

$_4$)alkoxy, wherein (C_{1-4})alkyl and (C_{1-4})alkoxy are optionally substituted with one or more halogen;

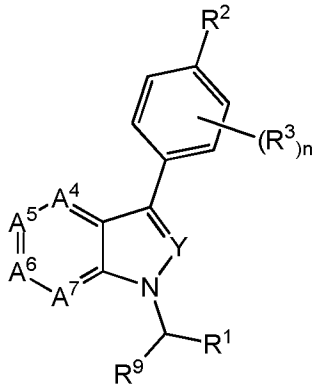
R^4-R^7 independently are H, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl or amino(C_{1-4})alkyl, wherein (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl and amino(C_{1-4})alkyl are optionally substituted with one or more halogen, hydroxyl or (C_{1-3})alkoxy; or a group having the formula  , optionally substituted with one or more of the following: (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, and wherein m is 1, 2, 3, or 4;

R^8 is halogen, cyano, amino, nitro, hydroxy, $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one, two or three halogens;

x is 0, 1, 2, 3, 4 or 5;

R^9 is hydrogen or (C_{1-4})alkyl.

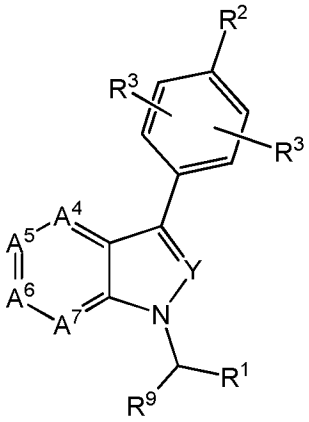
In a first embodiment of the compound having Formula I is a compound having Formula Ia



Ia

and a pharmaceutically acceptable salt or solvate thereof.

In a second embodiment of the compound having Formula I is a compound having Formula Ib

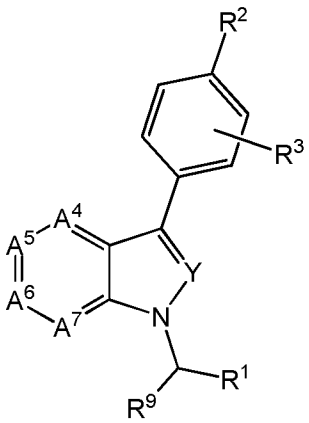


Ib

and a pharmaceutically acceptable salt or solvate thereof.

In a first subset of the second embodiment is a compound wherein Y is N.

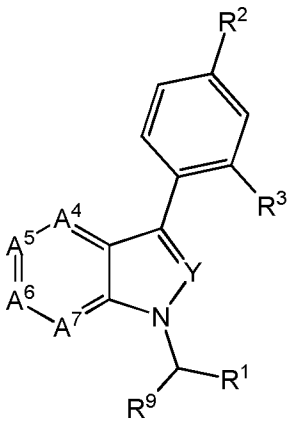
In a second subset of the second embodiment is a compound having Formula Ic



Ic

and a pharmaceutically acceptable salt or solvate thereof.

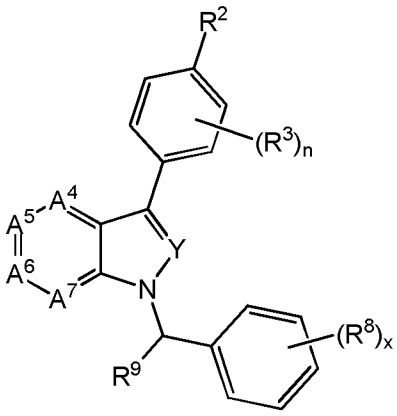
In a subset of the compound having Formula Ic, is a compound having Formula Id



Id

and a pharmaceutically acceptable salt or solvate thereof. In a further subset, Y is N.

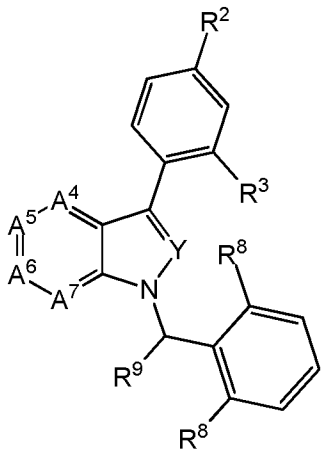
In a first subset of the first embodiment is a compound having Formula Ie



Ie

and a pharmaceutically acceptable salt or solvate thereof.

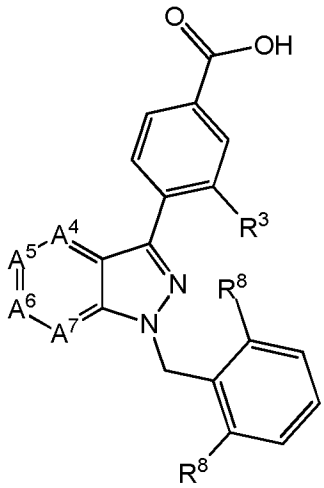
In a subset of the compound having Formula Ie is a compound having Formula If



If

and a pharmaceutically acceptable salt or solvate thereof.

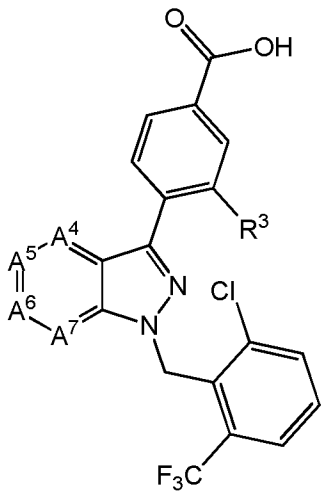
In a subset of the compound having Formula If is a compound having Formula Ig



Ig

and a pharmaceutically acceptable salt or solvate thereof.

In a subset of the compound having Formula Ig is a compound having Formula Ih



Ih

and a pharmaceutically acceptable salt or solvate thereof.

In a second subset of the first embodiment is a compound wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; (iii) CR^4, N, CR^6, CR^7; (iv) CR^4, CR^5, N, CR^7; (v) CR^4, CR^5, CR^6, N; (vi) N, N, CR^6,CR^7; (vii) CR^4, N, N, CR^7; (viii) CR^4, CR^5, N, N; (ix) N, CR^5, N, CR^7; (x) CR^4, N, CR^6, N; and (xi) N, CR^5, CR^6, N.

In a third subset of the first embodiment is a compound wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; and (iii) CR^4, CR^5, N, CR^7.

In a fourth subset of the first embodiment is a compound wherein A^4, A^5, A^6, A^7 is (i) CR^4, CR^5, CR^6, CR^7, or (ii) N, CR^5, CR^6, CR^7; and Y is N.

In a fifth subset of the first embodiment is compound wherein R^1 is (i) (C_{3-7})cycloalkyl or (C_{3-5})heterocycloalkyl, both optionally substituted with one or more R^8, wherein R^8 is selected from halogen, amino, cyano, nitro, hydroxy, $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogens; (ii) (C_{2-9})heteroaryl, optionally substituted with one or more R^8, wherein R^8

is selected from halogen, amino, cyano, nitro, hydroxy, $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogens; or (iii) (C_{6-14})aryl, optionally substituted with one or more R^8, wherein R^8 is selected from halogen, amino, cyano, nitro, hydroxy, $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy are optionally substituted with one or more halogens.

In a sixth subset of the first embodiment is compound wherein R^1 is (C_{2-9})heteroaryl, or (ii) (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8. In a further subset R^8 is selected from halogen, amino, cyano, nitro, hydroxy, (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl, (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogens.

In a seventh subset of the first embodiment, R^1 is (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8. In a further subset R^8 is selected from halogen, cyano, (C_{1-3})-alkoxycarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one, two or three halogens.

In an eighth subset of the first embodiment, R^1 is phenyl, naphthyl, pyridinyl, quinolinyl, benzooxadiazolyl, thiophenyl, isoxazolyl, or benzothiophenyl, each optionally substituted with one or more R^8. In a further subset R^8 is selected from halogen, amino, cyano, nitro, hydroxy, (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogens.

In a ninth subset of the first embodiment, R^1 is phenyl, optionally substituted with one, two or three R^8. In a further subset R^8 is selected from halogen, amino, cyano, nitro, hydroxy, (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one or more halogens.

In a tenth subset of the first embodiment, R^2 is C(O)OH.

A still further embodiment of the compounds of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig, and Ih are compounds wherein one of R^4, R^5, R^6, and R^7 is other than hydrogen.

The invention also relates to those compounds wherein all specific definitions for A^1 through A^4, R^1 through R^9, R^a, Y, m, n and x and all substituent groups in the various aspects of the inventions defined here above occur in any combination within the definition of the compound of Formula I.

Non-limiting examples of the compound of the present invention include:

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[3,4-c]pyridin-3-yl}-3-fluorobenzoic acid;

4-[1-(2-bromo-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}-3-fluorobenzoic acid;

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}benzoic acid;

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}-2,5-difluorobenzoic acid;

4-(1-{1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-{(1R or 1S)-1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-(1-{(1S or 1R)-1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;

4-[1-(2-bromo-3-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(5-chloro-2-cyanobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

3-fluoro-4-(1-{1-[2-(trifluoromethyl)phenyl]ethyl}-1H-pyrazolo[4,3-b]pyridin-3-yl)benzoic acid;

4-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(2-chloro-3,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

3-fluoro-4-[1-(2,3,6-trifluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]benzoic acid;

3-fluoro-4-{1-[2-fluoro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}benzoic acid;

4-[1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(2-chloro-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(2-chloro-6-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(2,3-dichloro-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(1-benzothiophen-7-ylmethyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;

4-[1-(3,6-dichloro-2-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-{1-[2-chloro-6-(methoxycarbonyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;

4-[1-(2-bromo-6-chlorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrrolo[3,2-b]pyridin-3-yl}-3-fluorobenzoic acid; and

4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrrolo[2,3-c]pyridin-3-yl}-3-fluorobenzoic acid.

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding, and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name, and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl"

applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "fluoroalkyl," "alkoxy", etc.

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term "alkyl," as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond having the specified number of carbon atoms. In different embodiments, an alkyl group contains, for example, from 1 to 6 carbon atoms (C_1-C_6 alkyl) or from 1 to 3 carbon atoms (C_1-C_3 alkyl). Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched.

Unless specified otherwise, "alkyl" includes both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbon atoms; for example, "$C_{1\text{-}6}$ alkyl" (or "C_1-C_6 alkyl") includes all of the hexyl alkyl and pentyl alkyl isomers as well as n-, iso-, sec- and t-butyl, n- and isopropyl, ethyl and methyl. "Alkylene" refers to both branched- and straight-chain saturated aliphatic hydrocarbon groups, including all isomers, having the specified number of carbons, and having two terminal end chain attachments; for example, the term "A-C_4alkylene-B" represents, for example, A-CH_2-CH_2-CH_2-CH_2-B, A-CH_2-CH_2-$CH(CH_3)$-CH_2-B, A-CH_2-$CH(CH_2CH_3)$-B, A-CH_2-$C(CH_3)(CH_3)$-B, and the like. "Alkoxy" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge; for example "C_1-C_6 alkoxy" includes -OCH_3, -OCH_2CH_3, -$OCH(CH_3)_2$, -$O(CH_2)_5CH_3$, and the like.

Unless otherwise specifically noted as only "unsubstituted" or only "substituted", alkyl groups are unsubstituted or substituted with 1 to 3 substituents on each carbon atom, with halo, C_1-C_{20} alkyl, CF_3, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -$O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, $(C_{3\text{-}7})$cycloalkyl, $(C_{3\text{-}5})$heterocycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl) $S(O)_{0\text{-}2}$-, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, H_2N-C(O)(NH)-, -$O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6 alkyl)$O(C_1$-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)OC(O)NH-, -$NH(C_1$-C_6 alkyl)NHC(O)NH(C_1-C_6 alkyl), NHC(O)OC_1-C_6 alkyl, -$NH(C_1$-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), -(C_0-C_6 alkyl)$NHSO_2(C_1$-C_6 alkyl), aryl, aralkyl, heterocycle, heterocyclylalkyl, halo-

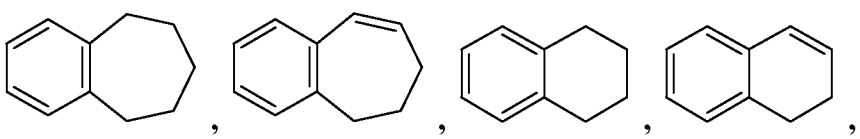
aryl, halo-aralkyl, halo-heterocycle, halo-heterocyclylalkyl, cyano-aryl, cyano-aralkyl, cyano-heterocycle and cyano-heterocyclylalkyl.

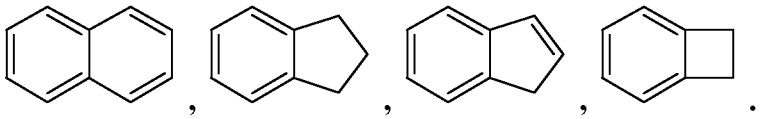
The term "alkenyl" means a straight or branched carbon chain having the specified number of carbon atoms with at least one carbon-carbon double bond. Examples of alkenyl include, but are not limited to, vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, 2,4-hexadienyl, and the like.

The term "alkynyl" means a straight or branched carbon chain having the specified number of carbon atoms with at least one carbon-carbon triple bond. Examples of alkynyl include, but are not limited to ethynyl, propargyl, 1-propynyl, 2-butynyl, and the like.

The term “carbocycle” (and variations thereof such as “carbocyclic” or “carbocyclyl”) as used herein, unless otherwise indicated, refers to (i) a C_3 to C_8 monocyclic, saturated or unsaturated ring or (ii) a C_7 to C_{12} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either attached via a bond to, or fused (including spirofused) to, the other ring, and each ring is saturated or unsaturated. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound.

Saturated carbocyclics form a subset of carbocycles in which the entire ring system (mono- or polycyclic) is saturated. Saturated monocyclic carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc. The fused bicyclic carbocycles are a further subset of the carbocycles in which a C_7 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms (or in the case of spirofused, one carbon atom) are shared by each of the rings in the ring system. A saturated bicyclic carbocycle is one in which both rings are saturated. An unsaturated bicyclic carbocycle is one in which one ring is unsaturated and the other is unsaturated or saturated. Unless otherwise noted, carbocycle is unsubstituted or substituted with C_{1-6} alkyl, C_{1-6} alkenyl, C_{1-6} alkynyl, aryl, halogen, NH_2 or OH. A subset of the fused bicyclic unsaturated carbocycles are those bicyclic carbocycles in which one ring is a benzene ring and the other ring is saturated or unsaturated, with attachment via any carbon atom that results in a stable compound. Representative examples of this subset include the following:





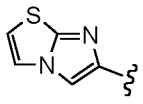
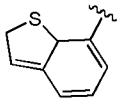
Aromatic carbocycles form another subset of the carbocycles. The term "aryl" refers to aromatic mono- and poly-carbocyclic ring systems in which the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. Suitable aryl groups include phenyl, naphthyl, and biphenyl.

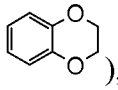
The term “cycloalkyl” means a cyclic ring of an alkane having the specified total ring carbon atoms; for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term “heterocycle” (and variations thereof such as “heterocyclic” or “heterocyclyl”) broadly refers to (i) a stable 4- to 8-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 7- to 12-membered bicyclic ring system, wherein each ring in (ii) is either attached via a bond to, or fused (including spirofused) to, the other ring, and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

Saturated heterocyclics form a subset of the heterocycles; i.e., the term "saturated heterocyclic" generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is saturated. The term "saturated heterocyclic ring" refers to a 4- to 8-membered saturated monocyclic ring or a stable 7- to 12-membered bicyclic ring system which consists of carbon atoms and one or more heteroatoms selected from N, O and S. Representative examples include piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, 1,4-dioxanyl, 1,4-thioxanyl,

tetrahydropyranyl, tetrahydrofuryl (or tetrahydrofuranyl), tetrahydrothienyl, and tetrahydrothiopyranyl.

Heteroaromatics form another subset of the heterocycles; i.e., the term "heteroaromatic" (alternatively “heteroaryl”) generally refers to a heterocycle as defined above in which the entire ring system (whether mono- or poly-cyclic) is an aromatic ring system. The term "heteroaromatic ring" refers a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic aromatic ring, and which consists of carbon atoms and one or more heteroatoms selected from N, O and S. In the case of substituted heteroaryl rings containing at least one nitrogen atom (e.g., pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of monocyclic heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Examples of bicyclic heteroaromatic rings include benzotriazolyl, indolyl, benzoxazolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, isoindolyl, indazolyl, quinoxalinyl, quinazolinyl, cinnolinyl, quinolinyl, isoquinolinyl, naphthyridinyl, pyrazolo[3,4-b]pyridine, imidazo[2,1-b](1,3)thiazole, (i.e., ), 6-(1-pyrrolyl)-3-pyridyl, 4-(1-pyrrolyl)phenyl, 4-(pyrid-3-yl)phenyl, 4-(pyrid-4-yl)phenyl, and benzothiophenyl (i.e. ).

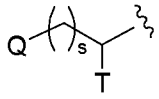
Another subset of heterocycles is unsaturated heterocycles in which one or both rings are unsaturated (provided the entire ring system is not aromatic). Representative examples of unsaturated heterocycles include dihydrofuranyl, dihydrothienyl, dihydropyranyl, dihydroimidazolyl, indolinyl, isoindolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, tetrahydronaphthyridinyl, 2,3-dihydrobenzofuranyl, 1,4-benzoxazinyl, 1,3-benzoxazolinyl, 2,3-dihydrobenzo-1,4-dioxinyl (i.e., ), and benzo-1,3-dioxolyl (i.e., ). In certain contexts herein,  is alternatively referred to as phenyl having as a substituent methylenedioxy attached to two adjacent carbon atoms. Also included are groups such as chromone and coumarin.

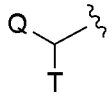
Unless otherwise specifically noted as only unsubstituted or only substituted, cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl (including phenyl) and heteroaryl groups are unsubstituted or substituted (also referred to as "optionally substituted"). Unless the substituents are specifically provided, substituents for substituted or optionally substituted cycloalkyl, heterocycloalkyl, cycloalkenyl, aryl (including phenyl, and as an isolated substituent or as part of a substituent such as in aryloxy and aralkyl), heteroaryl (as an isolated substituent or as part of a substituent such as in heteroaryloxy and heteroaralkyl) are one to three groups independently selected from halogen (or halo), C_1-C_6 alkyl optionally substituted with one to five fluorine, NH_2, $N(C_1$-C_6 alkyl$)_2$, NO_2, oxo, CN, N_3, -OH, -O(C_1-C_6 alkyl) optionally substituted with one to five fluorine, C_3-C_{10} cycloalkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)S(O)$_{0-2}$-, aryl-S(O)$_{0-2}$-, (C_0-C_6 alkyl)S(O)$_{0-2}$(C_0-C_6 alkylene)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkylene)-, (C_0-C_6 alkyl)C(O)$_{1-2}$(C_0-C_6 alkylene)-, (C_0-C_6 alkyl)$_2$NC(O)-, (C_0-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heteroaralkyl, halo-aryl, halo-aralkyl, halo-heteroaryl, halo-heteroaralkyl, cyano-aryl, cyano-aralkyl, cyano-heteroaryl and cyano-heteroaralkyl.

The term "halogen" (or “halo”) refers to fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro (F), chloro (Cl), bromo (Br), and iodo (I)).

The term "haloalkyl" means alkyl having the specified number of carbon atoms in which from one to all of the hydrogen atoms have been replaced by a halogen atom.

The terms "aralkyl" and "heteroaralkyl" refer to an aryl/heteroaryl linked to the rest of the molecule via a C_1 to C_4 alkylene.

The term “C_0” as employed in expressions such as “C_{0-6} alkylene” means a direct covalent bond; or when employed in experessions such as "C_{0-6} alkyl" means hydrogen. Similarly, when an integer defining the presence of a certain number of atoms in a group is equal to zero, it means that the atoms adjacent thereto are connected directly by a bond; for example, in the structure 

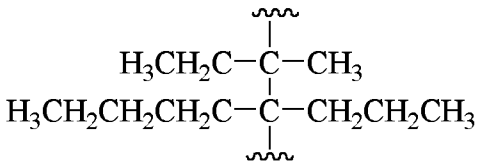
, wherein s is an integer equal to zero, 1 or 2, the structure is 

when s is zero; or it means that the indicated atom is absent; for example -S(O)$_0$- means -S-.

Unless expressly stated to the contrary, an "unsaturated" ring is a partially or fully unsaturated ring. For example, an "unsaturated monocyclic C_6 carbocycle" refers to cyclohexene, cyclohexadiene, and benzene.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heterocycle described as containing from "1 to 4 heteroatoms" means the heterocycle can contain 1, 2, 3 or 4 heteroatoms.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. For variable definitions containing terms having repeated terms, e.g., $(CRiRj)_r$, where r is the integer 2, Ri is a defined variable, and Rj is a defined variable, the value of Ri may differ in each instance in which it occurs, and the value of Rj may differ in each instance in which it occurs. For example, if Ri and Rj are independently selected from the group consisting of methyl, ethyl, propyl and butyl, then $(CRiRj)_2$ can be



The term (C_{1-6})alkyl as used hereinabove means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, n-pentyl and n-hexyl. Preferred is (C_{1-4})alkyl.

The term (C_{1-5})alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, tert-butyl and n-pentyl.

The term (C_{1-4})alkyl as used herein means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

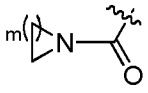
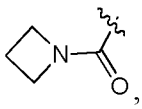
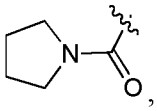
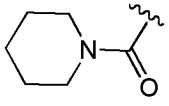
The term (C_{1-3})alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety being branched or unbranched.

The term (C_{1-3})alkoxycarbonyl means an alkoxycarbonyl group having 1-3 carbon atoms in the alkoxy moiety, the alkoxy moiety having the same meaning as previously defined.

The term (di)(C_{1-6})alkylaminocarbonyl means an alkylaminocarbonyl group, the amino group of which is monosubstituted or disubstituted independently with an alkyl group which contains 1-6 carbon atoms and which has the same meaning as previously defined. Preferred alkyl group is (C_{1-4})alkyl.

The term (C_{3-7})cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. 5-6 Carbon atoms are preferred.

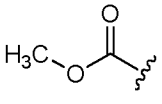
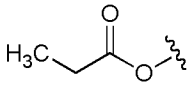
The term (C_{3-5})heterocycloalkyl means a heterocycloalkyl group having 3-5 carbon atoms, including 1-3 heteroatoms selected from N, O and/or S, which may be attached via a nitrogen if feasible, or a carbon atom. Preferred number of heteroatoms is one or two. Most preferred number is one. Preferred heteroatoms are N or O. Most preferred are piperazinyl, tetrahydropyranyl, morpholinyl and pyrrolidinyl.

A group having the formula  , means a heterocyclocarbonyl group such as  ,  , and  , each optionally substituted with one or more (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, and (C_{1-3})alkoxy.

The term (C_{2-9})heteroaryl means an aromatic group having 2-9 carbon atoms and 1-3 heteroatoms selected from N, O and S, like imidazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, thiophenyl or furyl, pyrazolyl, isoxazolyl or quinolyl. Preferred number of heteroatoms is one or two. Preferred heteroaryl groups are pyrazolyl, thiophenyl, isoxazolyl, pyridyl and quinolyl. The (C_{2-5})heteroaryl group may be attached via a carbon atom or a nitrogen, if feasible.

The term (C_{6-14})aryl means an aromatic hydrocarbon group having 6-14 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl, indenyl, anthracyl, More preferred are (C_{6-10})aryl groups. The most preferred aromatic hydrocarbon group is phenyl.

As used herein, the term "X_a-X_b", shall have the same meaning as the term "X_{a-b}", wherein X is any atom and a and b are any integers. For example, "C_1-C_4" shall have the same meaning as "C_{1-4}". Additionally, when referring to a functional group generically, "A^x" shall have the same meaning, and be interchangeable with, "AX", wherein "A" is any atom and "x" or "X" are any integer. For example, "R^1" shall have the same meaning, and be interchangeable with, "R1".

In the above definitions with multifunctional groups, the attachment point is at the last group. For example, the term (C_{1-3})alkoxycarbonyl refers to, e.g.  , and the term (C1-4)alkylcarbonyloxy refers to, e.g.  .

The term “substituted” means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. “Stable compound” or “stable structure” is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. Accordingly, the term "one or more" when referring to a substituent and/or variable means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom’s normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound.

The term “optionally substituted” means that a substitution with the specified groups, radicals or moieties, may or may not be made on the specified group.

When, in the definition of a substituent, is indicated that “all of the alkyl groups” of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

The term "effective amount" as used herein, refers to an amount of the compound of Formula (I) and/or an additional therapeutic agent, or a composition thereof, that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from an RORgammaT-mediated disease or disorder. In the combination therapies of the present invention, as effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

A “subject” is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, a subject is a chimpanzee.

It should be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

The compounds of this invention include the prodrugs, hydrates or solvates of the compounds.

Optical Isomers - Diastereomers - Geometric Isomers – Tautomers

The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

Compounds described herein may contain an asymmetric center and may thus exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centers, they may additionally exist as diastereomers. The present invention includes all such possible stereoisomers as substantially pure resolved enantiomers, racemic mixtures thereof, as well as mixtures of diastereomers. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Diastereoisomeric pairs of enantiomers may be separated by, for example, fractional crystallization from a

suitable solvent, and the pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid or base as a resolving agent or on a chiral HPLC column. Further, any enantiomer or diastereomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

When compounds described herein contain olefinic double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl $-CH_2C(O)-$ groups (keto forms) may undergo tautomerism to form hydroxyl –CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are included within the scope of the present invention.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds of Formula (I) may be atropisomers (e.g. substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula I may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may, for example, be

substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts prepared from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines derived from both naturally occurring and synthetic sources. Pharmaceutically acceptable organic non-toxic bases from which salts can be formed include, for example, arginine, betaine, caffeine, choline, N,N'-dibenzyl-ethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated.

The term pharmaceutically acceptable salt represents those salts which are, within the scope of medical judgement, suitable for use in contact for the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. They may be obtained during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable mineral acid such as hydrochloric acid, phosphoric acid, or sulfuric acid, or with an organic acid such as for example ascorbic acid, citric acid, tartaric acid, lactic acid, maleic acid, malonic acid, fumaric acid, glycolic acid, succinic acid, propionic acid, acetic acid, methanesulfonic acid, and the like. The acid function can be reacted with an organic or a mineral base, like sodium hydroxide, potassium hydroxide, calcium hydroxide, calcium carbonate, ammonium (e.g. diethylamine) or lithium hydroxide.

Solvates

The present invention includes within its scope solvates of compounds of Formula I.As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (i.e., a compound of Formula I) or a pharmaceutically acceptable salt thereof and a solvent that does not interfere with the biological activity of the solute. Examples of solvents include, but are not limited to water, ethanol, and acetic acid. When the solvent is water, the solvate is known as hydrate; hydrate includes, but is not limited to, hemi-, mono, sesqui-, di- and trihydrates.

The compounds of the invention may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" may also mean a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-

limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

Prodrugs

The present invention includes within its scope the use prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with a compound of formula I or with a compound which may not be a compound of formula I, but which converts to a compound of formula I in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs," ed. H. Bundgaard, Elsevier, 1985.

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (e.g, a drug precursor) that is transformed in vivo to yield a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, “Pro-drugs as Novel Delivery Systems,” Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Isotopes

In the compounds of generic Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^1H) and deuterium (^2H).

Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Utilities

Compounds of the present invention alter the interaction of coregulator proteins with Retinoic Acid Receptor-related Orphan Receptor gamma t (RORgammaT) and thereby antagonize RORgammaT-mediated transcriptional actvity, and as such are useful in the treatment of diseases and conditions in which inhibition of RORgammaT is desirable, such as autoimmune and inflammatory diseases and disorders.

Accordingly, another embodiment of the present invention provides a method for treating a disease or condition mediated by RORgammaT in a subject comprising administering to the subject an amount of a compound having Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih, or a pharmaceutically acceptable salt or solvate thereof, that is effective for treating the disease or condition mediated by RORgammaT in the subject.

The compounds according to the invention can be used in therapy.

A further aspect of the invention resides in the use of compounds according to the invention or a pharmaceutically acceptable salt thereof for the treatment of RORgammaT-mediated diseases or RORgammaT mediated conditions.

Another aspect of the invention resides in the use of compounds or a pharmaceutically acceptable salt thereof having the general formula I for the treatment of autoimmune diseases, in particular those diseases in which Th17 cells and non-Th17 cells, which express Th17 hallmark cytokines play a prominent role. These include, but are not limited to, the treatment of rheumatoid arthritis, psoriasis, inflammatory bowel disease, Crohn's disease and multiple sclerosis.

In another aspect, compounds or a pharmaceutically acceptable salt thereof having the general formula I can be used for treatment of inflammatory diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as,

but not limited to respiratory diseases, osteoarthritis and asthma. Also, compounds or a pharmaceutically acceptable salt thereof having the general formula I can be used for treatment of infectious diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to mucosal leishmaniasis.

Compounds or a pharmaceutically acceptable salt thereof having the general formula I can also be used for treatment of other diseases in which Th17 cells and/or non-Th17 cells, which express Th17 hallmark cytokines play a prominent role such as, but not limited to Kawasaki disease and Hashimoto's thyroiditis.

In one aspect is the disease or condition is an autoimmune disease or inflammatory disease. The disease or condition includes, but is not limited to, multiple sclerosis, inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis or mucosal leishmaniasis.

In another aspect, the compounds according to the invention can be used in therapies to treat or prevent multiple sclerosis, inflammatory bowel disease, Crohn's disease, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis and mucosal leishmaniasis.

In another aspect the compounds according to the invention can be used to treat or prevent psoriasis.

In yet another aspect the compounds according to the invention can be used to treat inflammatory bowel disease.

This aspect of the present invention further includes the use of a compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a disease or condition mediated by RORgammaT.

Route of Administration/Dosage

The compounds of this invention can be administered for the treatment or prevention of afflictions, diseases and illnesses according to the invention by any means that effects contact of the active ingredient compound with the site of action in the body of a warm-blooded animal. For example, administration can be oral, topical, including transdermal, ocular,

buccal, intranasal, inhalation, intravaginal, rectal, intracisternal and parenteral. The term "parenteral" as used herein refers to modes of administration which include subcutaneous, intravenous, intramuscular, intraarticular injection or infusion, intrasternal and intraperitoneal. For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

The compounds can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage administered will be dependent on the age, health and weight of the recipient, the extent of disease, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. Usually, a daily dosage of active ingredient compound will be from about 1.0-2000 milligrams per day. Ordinarily, from 10 to 500 milligrams per day in one or more applications is effective to obtain desired results. These dosages are the effective amounts for the treatment and prevention of afflictions, diseases and illnesses described above, e.g., autoimmune and inflammatory diseases and disorders.

Compositions include e.g. those suitable for oral, sublingual, subcutaneous, intravenous, intramuscular, nasal, local, or rectal administration, and the like, all in unit dosage forms for administration.

For oral administration, the active ingredient may be presented as discrete units, such as tablets, capsules, powders, granulates, solutions, suspensions, and the like.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically

acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

Pharmaceutical Compositions

Another aspect of the present invention provides pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable excipients. The term "excipient" and "carrier" may be used interchangeably. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The

pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, troches, dragées, granules and powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, dispersions, and suspensions. The active ingredient can also be administered parenterally, in sterile liquid dosage forms, such as dispersions, suspensions or solutions. Other dosages forms that can also be used to administer the active ingredient as an ointment, cream, drops, transdermal patch or powder for topical administration, as an ophthalmic solution or suspension formation, i.e., eye drops, for ocular administration, as an aerosol spray or powder composition for inhalation or intranasal administration, or as a cream, ointment, spray or suppository for rectal or vaginal administration.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene gycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field.

For administration by inhalation, the compounds of the present invention may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or

nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons.

For ocular administration, an ophthalmic preparation may be formulated with an appropriate weight percent solution or suspension of the compounds of Formula I in an appropriate ophthalmic vehicle, such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention include, but are not limited to, hard and soft gelatin capsules, tablets, parenteral injectables, and oral suspensions.

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

A large number of tablets are prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol. The solution is made to volume with water for injection and sterilized.

An aqueous suspension is prepared for oral administration so that each 5 milliliters contain 100 milligrams of finely divided active ingredient, 100 milligrams of sodium carboxymethyl cellulose, 5 milligrams of sodium benzoate, 1.0 grams of sorbitol solution, U.S.P., and 0.025 milliliters of vanillin.

The same dosage forms can generally be used when the compounds of this invention are administered stepwise or in conjunction with another therapeutic agent. When drugs are administered in physical combination, the dosage form and administration route should be selected depending on the compatibility of the combined drugs. Thus the term coadministration is understood to include the administration of the two agents concomitantly or sequentially, or alternatively as a fixed dose combination of the two active components.

The present invention also relates to a pharmaceutical composition comprising compounds or pharmaceutically acceptable salts thereof having the general formula I in admixture with pharmaceutically acceptable auxiliaries and optionally other therapeutic agents. The auxiliaries must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The exact dose and regimen of administration of the active ingredient, or a pharmaceutical composition thereof, may vary with the particular compound, the route of administration, and the age and condition of the individual subject to whom the medicament is to be administered.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-100 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day. The dosage as well as the regimen of administration may differ between a female and a male recipient.

Combination Therapy

Compounds of the present invention, and their salts and solvates, and physiologically functional derivatives thereof, may be employed alone or in combination with other therapeutic agents for the treatment of diseases and conditions associated with inappropriate IL-17 pathway activity. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) or a pharmaceutically

acceptable salt or solvate thereof, or a physiologically functional derivative thereof, and the use of at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. For the treatment of the inflammatory and autoimmune diseases, rheumatoid arthritis, psoriasis, inflammatory bowel disease, ankylosing spondylitis, SLE, uveitis, atopic dermatitis, COPD, asthma and allergic rhinitis a compound of formula (I) may be combined with one or more other active agents such as: (1) TNF-a inhibitors; (2) non-selective COX-I/COX-2 inhibitors; (3) COX-2 inhibitors; (4) other agents for treatment of inflammatory and autoimmune diseases including glucocorticoids, methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporin, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, Lymphostat-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetics thereof; (5) leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist; (6) LTD4 receptor antagonist; (7) PDE4 inhibitor; (8) antihistamine HI receptor antagonists; (9) al- and a2-adrenoceptor agonist; (10) anticholinergic agents; (1 1) β-adrenoceptor agonists; (12) insulin-like growth factor type I (IGF-1) mimetic; (13) glucocorticosteroids; (14) kinase inhibitors such as inhibitors of the Janus Kinases (JAK 1 and/or JAK2 and/or JAK 3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologies such as rituximab; (16) selective costimulation modulators such as abatacept; (17) interleukin inhibitors, such as IL-1 inhibitor anakinra, IL-6 inhibitor tocilizumab, and IL12/IL-23 inhibitor ustekinumab. It could also be combined with anti-IL17 antibodies to obtain additive/synergistic responses for the treatment of inflammatory and autoimmune diseases.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent or carrier represent a further aspect of the invention. These combinations are of particular interest in respiratory diseases and are conveniently adapted for inhaled or intranasal delivery.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions. Preferably, the individual compounds will be administered simultaneously in a combined pharmaceutical composition. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Accordingly, the pharmaceutical compositions of the present invention include those that also comprise at least one additional therapeutically active agent, in addition to the compound of Formula I, Ia, Ib, Ic, Id, Ie, If, Ig or Ih.

The invention further includes a compound of Formula I in combination with one or more other drug(s).

METHODS OF SYNTHESIS

Methods for preparing the compounds of this invention are illustrated in the following schemes and examples. Other synthetic protocols will be readily apparent to those skilled in the art. The examples illustrate the preparation of the compounds of Formula I and as such are not to be considered as limiting the invention set forth in the claims appended hereto. Unless otherwise indicated, all variables are as previously defined.

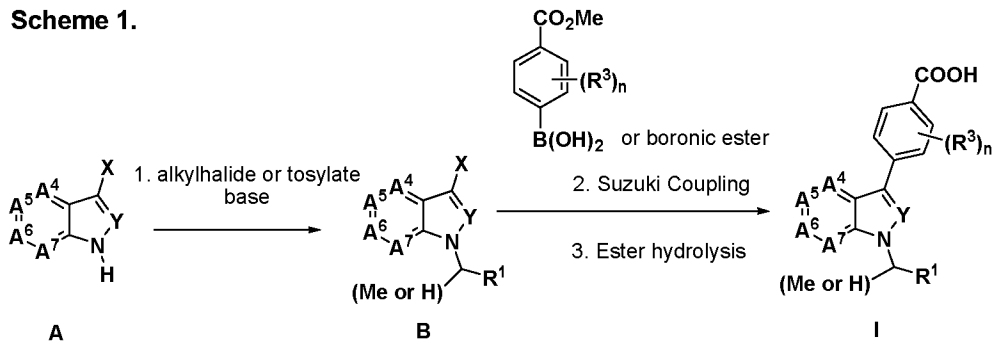
All the end products of the formula I were analyzed by NMR, LCMS. Intermediates were analyzed by NMR and/or TLC and/or LCMS. Most compounds were purified by reverse phase HPLC, MPLC on silica gel, recrystallization and/or swish (suspension in a solvent followed by filtration of the solid). The course of the reactions was followed by thin layer chromatography (TLC) and/or LCMS and/or NMR and reaction times are given for illustration only.

Abbreviations used herein are as follows: EtOAc: Ethyl acetate; PE: Petroleum ether; EA: Ethyl acetate; DCM: Dichloro methane; DMF: N,N-dimethylformamide; THF: tetrahydrofuran; DMSO: Dimethyl sulfoxide; TBAI: Tetrabutylammonium iodide;

TsCl: 4-toluene sulfonyl chloride; DMAP: N,N-dimethylpyridin-4-amine; Et3N: triethylamine; ACN: acetonitrile; MsCl: methanesulfonyl chloride; $(COCl)_2$: oxalyl dichloride; $LiBH_4$: lithium tetrahydroborate; t-BuOK: Potassium tert-butoxide.

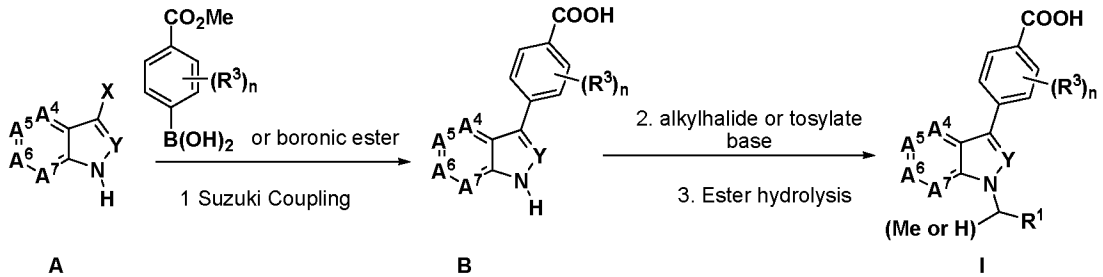
Scheme **1** illustrates a genera method toward the preparation of compounds of formula **I**. Starting from halide **A**, N-acylation with either carboxylic acids or corresponding acid chloride in the presence of base led to the formation of compound **B**. Subsequent Suzuki coupling with pinacol boronic ester or acid followd by ester hydrolysis afforded the final compound. In certain cases, ester hydrosis occurred under the suzuki coupling condition and led to the formation of final product.

Scheme 1.



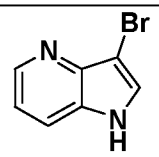
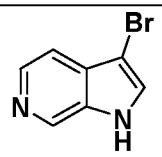
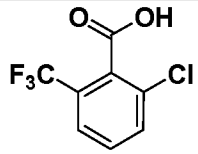
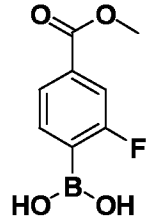
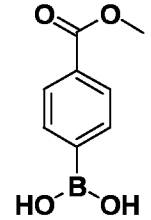
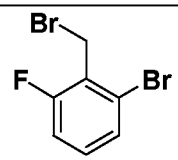
Alternatively the final compound I could also be prepared by switching the order of reaction sequence between N-alkylation and Suzuki coupling (see Scheme 2). Suzuki coupling first by reacting halide A with pinacol boronic ester or acid gave intermediate B. Subsequent N-alkylation followed by hydrolysis furnished final product.

Scheme 2.



COMMERCIALLY AVAILABLE / PREVIOUSLY DESCRIBED MATERIALS

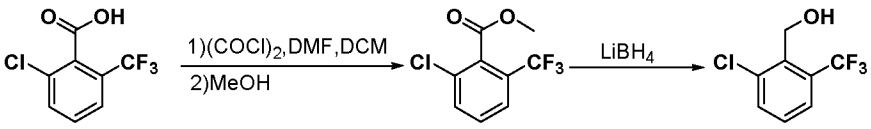
The following table lists commercial sources, and previously disclosed synthetic routes for chemical materials employed in the synthesis of intermediates, and examples of the instant invention. The list is not intended to be exhaustive, exclusive, or limiting in any way.

Structure	Source
	FRONTIERSCI
	Bellen
	Alfa
	Alfa
	APOLLO
	ACROS
	ACC

INTERMEDIATES

Example i-1: Preparation of (2-chloro-6-(trifluoromethyl)phenyl)methanol (i-1)

Scheme i-1



i-1a i-1b i-1

i). Preparation of methyl 2-chloro-6-(trifluoromethyl)benzoate (i-1b).

The mixture of 2-chloro-6-(trifluoromethyl)benzoic acid (**i-1a)** (1.5 g, 6.70 mol) and $(COCl)_2$ (1.1 ml, 13.4 mol) in DCM (20 ml) and DMF (5drops) was stirred at room temperature for 2h.Then MeOH (0.41 ml, 13.4 mol) was added dropwise and the reaction mixture was stirred at room temperature for another 30min.The result solution was diluted with H_2O (50 ml) and the aqueous layer was extracted with DCM(50ml×2). The combined organic layers were washed with brine (50 ml ×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **i-1b** as a pale yellow oil. LCMS (ESI) calc'd for $C_9H_6ClF_3O_2$ $[M+H]^+$: 239, found: 239.

ii) Preparation of (2-chloro-6-(trifluoromethyl)phenyl)methanol (i-1).

The mixture of methyl 2-chloro-6-(trifluoromethyl)benzoate **(i-1b)** (1.0 g, 4.20 mol) and $LiBH_4$ (0.18 g, 8.40 mol) in THF (10 ml) was stirred at room temperature for overnight. 2 M HCl solutions (10 ml) were added to quench the reaction and the aqueous layer was extracted with EtOAc (20 ml ×3). The combined organic layers were washed with brine (20 ml×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **i-1** as a pale yellow oil. LCMS (ESI) calc'd for $C_8H_6ClF_3O$ $[M+H]^+$: 211, found: 211.

Example i-2: Preparation of 1-(2-chloro-6-(trifluoromethyl)phenyl)ethanol (i-2)

Scheme i-2

i-1 i-2b i-2

i) Preparation of 2-chloro-6-(trifluoromethyl)benzaldehyde (i-2b).

The mixture of (2-chloro-6-(trifluoromethyl)phenyl)methanol (**i-1)** (0.7 g, 3.33 mol) and Dess-Martin periodinane (2.8g, 6.66 mol) in DCM (15 ml) was stirred at room temperature for overnight. The result solution was diluted with H_2O (30mL) and the aqueous layer was extracted with DCM (30 ml×3). The combined organic layers were washed with brine (30 ml×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (PE/EA=10:1) to get the desired product **i-2b** as a pale yellow solid. LCMS (ESI) calc'd for $C_8H_4ClF_3O$ $[M+H]^+$: 209, found: 209.

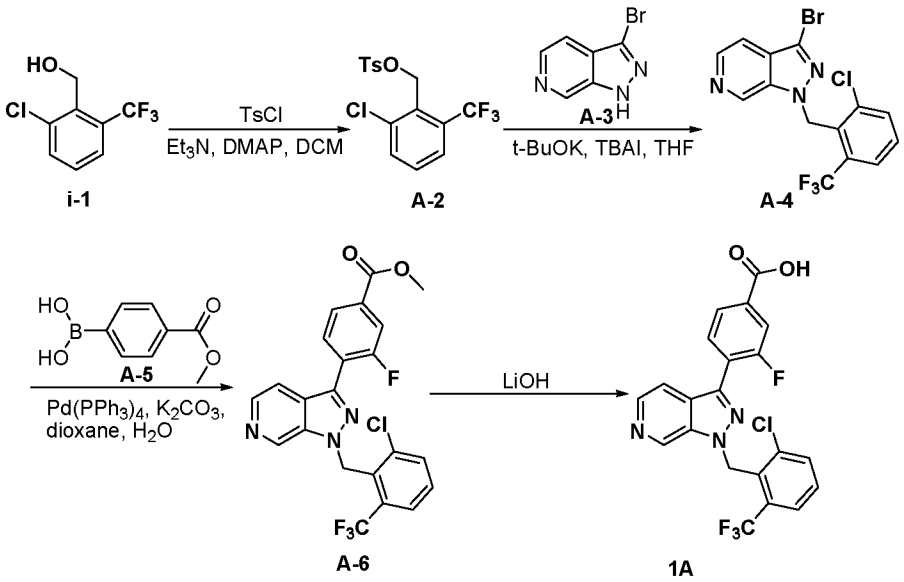
ii) Preparation of 1-(2-chloro-6-(trifluoromethyl)phenyl)ethanol (i-2).

The mixture of 2-chloro-6-(trifluoromethyl)benzaldehyde (**i-2b)** (0.25 g, 1.20 mol) in anhydrous THF (10 ml) was cooled to 0°C in an ice-water bath and CH_3MgBr (3.0M solution in ether, 2.0 ml, 6.0 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2h. Saturated NH_4Cl solution (20 ml) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (20 ml×3). The combined organic layers were washed with brine (20 ml×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **i-2** as a pale yellow oil. LCMS (ESI): calc'd for $C_9H_8ClF_3O$ $[M+H]^+$: 225, found: 225.

EXAMPLES

Example 1A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo[3,4-c]pyridin-3-yl)-3-fluorobenzoic acid (1A).

Scheme A



i) Preparation of 2-chloro-6-(trifluoromethyl)benzyl 4-methylbenzenesulfonate (A-2).

The mixture of (2-chloro-6-(trifluoromethyl)phenyl)methanol **(i-1)** (0.35 g, 1.67 mol), TsCl (0.64 g, 3.34 mol), DMAP (0.20 g, 1.67 mol) and Et_3N (0.48 ml, 3.34 mol) in DCM (10 ml) was stirred at 25 °C for 23h. The result solution was diluted with H_2O (30 ml) and the aqueous layer was extracted with DCM (20 ml ×3). The combined organic layers were washed with 1M HCl solution (10 ml×2), then brine (20 ml ×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **A-2** as a yellow oil. LCMS (ESI) calc'd for $C_{15}H_{12}ClF_3O_3S$ $[M+NH_4]^+$: 382, found: 382.

ii) Preparation of 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo [4,3-b]pyridine (A-4).

The mixture of 2-chloro-6-(trifluoromethyl)benzyl 4-methylbenzenesulfonate **(A-2)** (0.19 g, 0.51 mol), 3-bromo-1H-pyrazolo[3,4-c]pyridine **(A-3)** (0.1 g, 0.51 mol), t-BuOK (0.11 g, 1.02 mol) and TBAI (75 mg, 0.20 mol) in THF (5 ml) was heated to 60 °C and stirred at this temperature for overnight. Saturated NH_4Cl solution (20 ml) was added to quench the reaction and the aqueous layer was extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with brine (20 ml ×1), dried over anhydrous Na_2SO_4 and concentrated to get the desired product **A-4** as a brown oil. LCMS (ESI) calc'd for $C_{14}H_8BrClF_3N_3$ $[M+H]^+$: 390, found: 390.

iii) Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo [4,3-b]pyridin-3-yl)-3-fluorobenzoate (A-6).

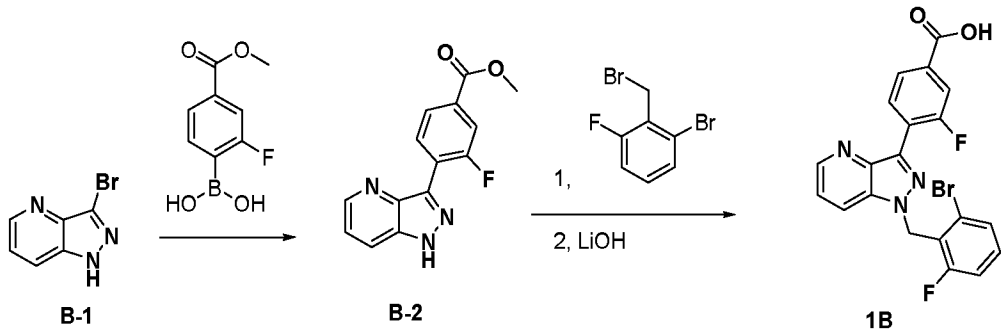
A mixture of 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo[4,3-b]pyri dine **(A-4)** (120 mg, 0.31 mol), 4-(methoxycarbonyl)phenylboronic acid **(A-5)** (73 mg, 0.37 mol), $Pd(PPh_3)_4$ (36 mg, 0.031 mol) and K_2CO_3 (128 mg, 0.93 mol) were suspended in 1,4-dioxane (5 ml) and H_2O (1 ml). The reaction mixture was heated at 110°C in a microwave reactor for 2h. The result mixture was diluted with H_2O (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with brine (30 ml ×1), dried over anhydrous Na_2SO_4 and concentrated to get the crude product **A-6** as a brown oil. LCMS (ESI) calc'd for $C_{22}H_{14}ClF_4N_3O_2$ $[M+H]^+$: 464, found: 464.

iv) Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo[3,4-c]p yridin-3-yl)-3-fluorobenzoic acid (1A).

The mixture of 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo[4,3-b]pyridine -3-yl)-3-fluorobenzoate **(A-6)** (100 mg, 0.22 mol) and LiOH (28 mg, 0.66 mol) in THF (4 ml) and H_2O (2 ml) was stirred at room temperature for overnight. The reaction mixture was diluted with H_2O (30 ml). 2M HCl solution was added to adjust the pH=3 and the aqueous layer was extracted with ethyl acetate (20 ml ×3). The combined organic layers were washed with brine (20 ml ×1), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified with Prep-HPLC (ACN/H_2O) to get the desired product **1A** as a white solid.. LCMS (ESI) calc'd for $C_{21}H_{12}ClF_4N_3O_2$ $[M+H]^+$: 450, found: 450; ^{1}HNMR (400 MHz, MeOD) δ 8.63 (1H, d, J=4.4Hz), 8.20 (1H, d, J=8.8Hz), 8.05-8.09 (1H, m), 7.94 (1H, d, J=7.6Hz), 7.79-7.87 (3H, m), 7.62-7.66 (1H, m), 7.52-7.55 (1H, m),5.97 (2H, s).

Example 1B: Preparation of 4-(1-(2-bromo-6-fluorobenzyl)-1H-pyrazolo[4,3-b] pyridin-3-yl)-3-fluorobenzoic acid (1B)

Scheme B



i) Preparation of methyl 3-fluoro-4-(1H-pyrazolo[4,3-b]pyridin-3-yl)benzoate (B-2)

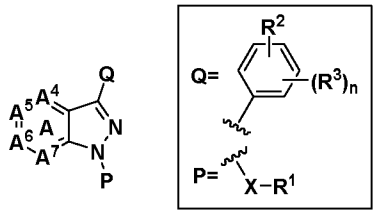
A mixture of 3-bromo-1H-pyrazolo[4,3-b]pyridine (**B-1)** (196.9mg, 1 mol),4-(methoxycarbonyl)phenylboronic acid (198 mg, 1mol), $Pd(PPh_3)_4$ (115mg, 0.1 mol) and K_2CO_3 (420 mg, 3mol) were suspended in 1,4-dioxane (5 ml) and H_2O (1 ml). The reation mixture was heated at 110°C in a microwave reactor for 2h. The result mixture was diluted with H_2O (30 ml) and the aqueous layer was extracted with ethyl acetate (30 ml ×2). The combined organic layers were washed with brine (30 ml ×1), dried over anhydrous Na_2SO_4 and concentrated to get the crude product **B-2** as a brown oil. LCMS (ESI) calc'd for $C_{14}H_{10}FN_3O_2$ $[M+H]^+$: 272.08, found: 272.

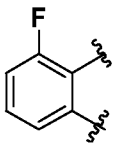
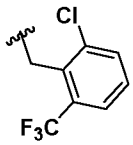
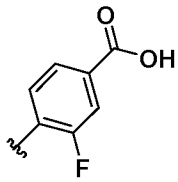
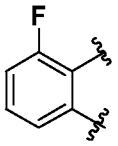
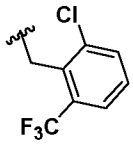
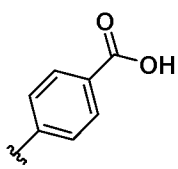
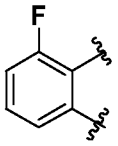
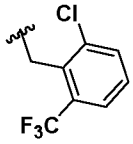
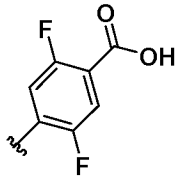
ii) Preparation of 4-(1-(2-bromo-6-fluorobenzyl)-1H-pyrazolo[4,3-b] pyridin-3 -yl)-3-fluorobenzoic acid (1B)

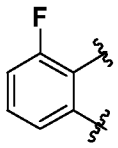
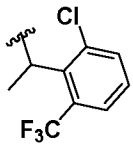
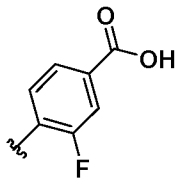
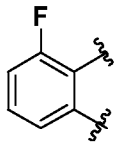
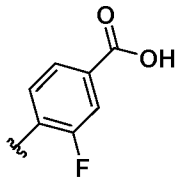
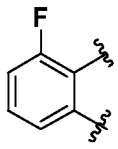
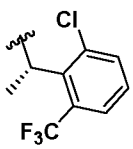
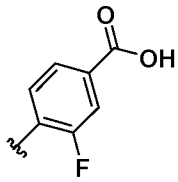
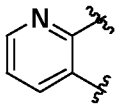
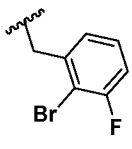
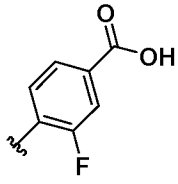
To a 1 dram vial was added methyl 3-fluoro-4-(1H-pyrazolo[4,3-b]pyridin-3-yl)benz oate **(B-2)** (30mg, 0.11mmol), 1-bromo-2-(bromomethyl)-3-fluorobenzene (29.4mg, 0.111mmol), cesium carbonate(72 mg,0.22 mmol), and DMF(1ml), The reaction mixtures were stirred at RT overnight. The mixtures were then evaporated under reduced pressure. THF (0.5ml), Methanol (0.25ml), and LiOH (1M, 0.332mmol) were then added and the reaction mixtures were stirred overnight at room temperature. The mixtures were then evaporated under reduced pressure. The reactions were then diluted with 2.0 ml DMSO, filtered, and purified by purified with Prep-HPLC (ACN/H_2O) to afford desired products. LCMS (ESI) calc'd for $C_{21}H_{12}ClF_4N_3O_2$ $[M+H]^+$: 444, found: 444.

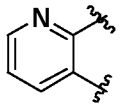
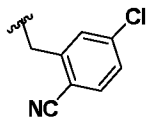
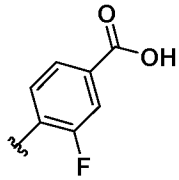
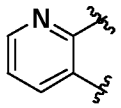
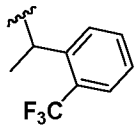
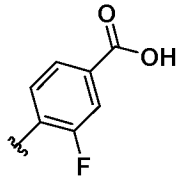
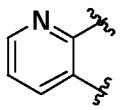
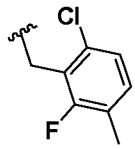
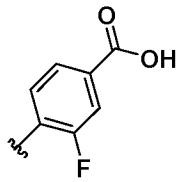
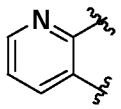
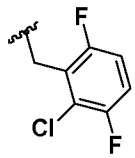
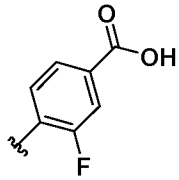
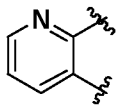
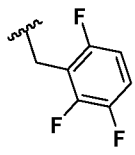
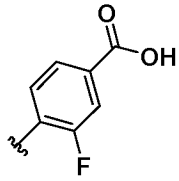
The following examples shown in **TABLE 1** were prepared following similar procedures described for **Examples #1A, 1B** in **Schemes A, B.** which can be achieved by those of ordinary skill in the art of organic synthesis.

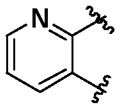
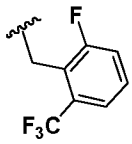
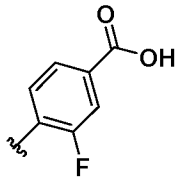
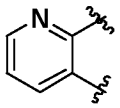
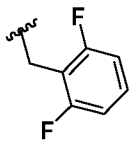
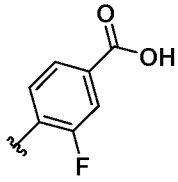
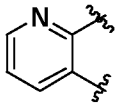
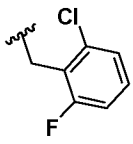
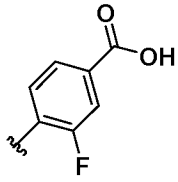
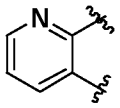
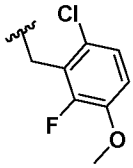
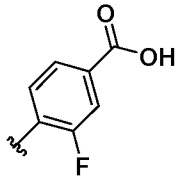
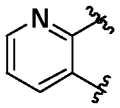
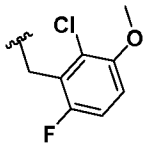
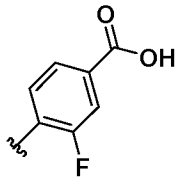
TABLE 1

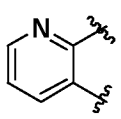
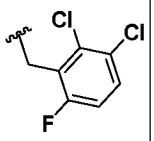
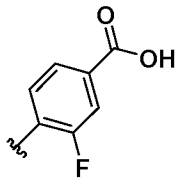
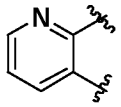
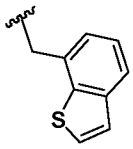
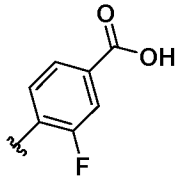
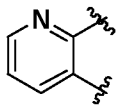
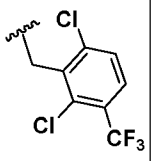
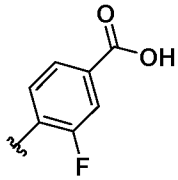
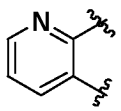
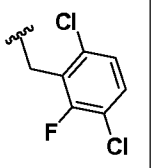
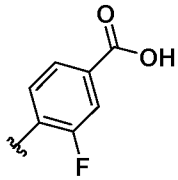
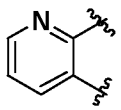
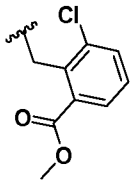
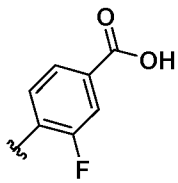


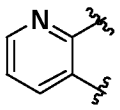
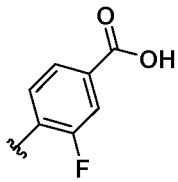
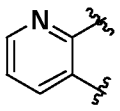
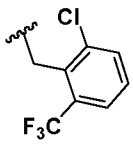
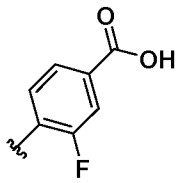
	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
1C	4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid				467
1D	4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-4-fluoro-1H-indazol-3-yl)benzoic acid				449
1E	4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-4-fluoro-1H-indazol-3-yl)-2,5-difluorobenzoic acid				485

1F	4-(1-(1-(2-chloro-6-(trifluoromethyl)phenyl)ethyl)-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid				481
1G	4-(1-((R or S)-1-(2-chloro-6-(trifluoromethyl)phenyl)ethyl)-4-fluoro-1H-indazol-3-yl)-2,5-difluorobenzoic acid				481
1H	4-(1-((S or R)-1-(2-chloro-6-(trifluoromethyl)phenyl)ethyl)-4-fluoro-1H-indazol-3-yl)-2,5-difluorobenzoic acid				481
1I	4-[1-(2-bromo-3-fluorobenzyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				444

1J	4-[1-(5-chloro-2-cyanobenzyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				407
1K	3-fluoro-4-(1-{1-[2-(trifluoromethyl)phenyl]ethyl}-1Hpyrazolo[4,3-b]pyridin-3-yl)benzoic acid				430
1L	4-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				414
1M	4-[1-(2-chloro-3,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				418
1N	3-fluoro-4-[1-(2,3,6-trifluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]benzoic acid				402

1O	3-fluoro-4-{1-[2-fluoro-6-(trifluoromethyl)benzyl]-1Hpyrazolo[4,3-b]pyridin-3-yl}benzoic acid				434
1P	4-[1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				384
1Q	4-[1-(2-chloro-6-fluorobenzyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				400
1R	4-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				430
1S	4-[1-(2-chloro-6-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				430

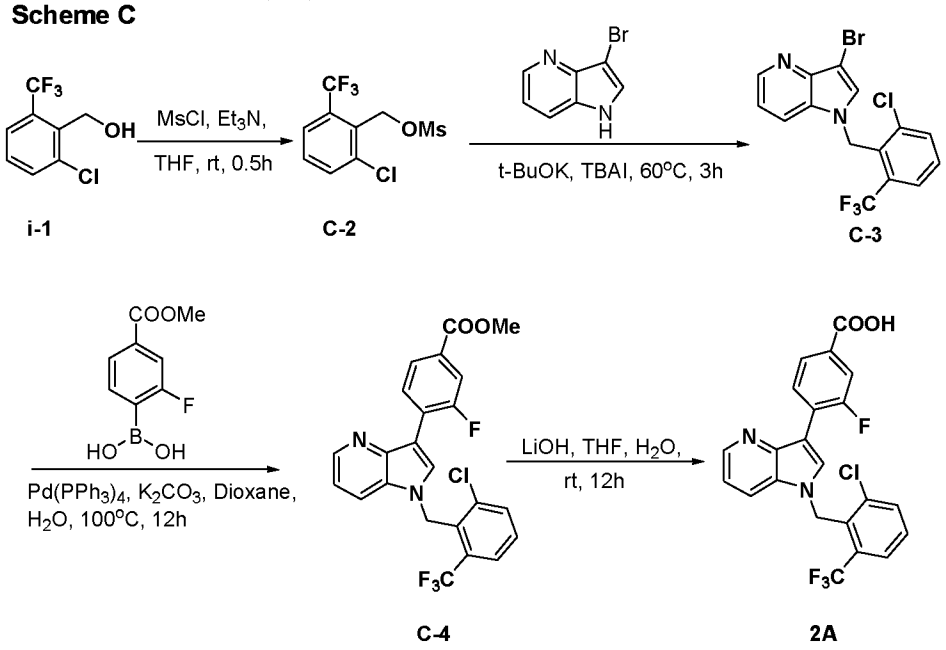
1T	4-[1-(2,3-dichloro-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				434
1U	4-[1-(1-benzothiophen-7-ylmethyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				440
1V	4-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1Hpyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid				484
1W	4-[1-(3,6-dichloro-2-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				434
1X	4-{1-[2-chloro-6-(methoxycarbonyl)benzyl]-1Hpyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid				440

1Y	4-[1-(2-bromo-6-chlorobenzyl)-1Hpyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid				460
1Z	4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-3-fluorobenzoic acid				450

Example 2A

Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[3,2-b]pyridin-3-yl)-3-fluorobenzoic acid (2A).

Scheme C



i) Preparation of 2-chloro-6-(trifluoromethyl)benzyl methanesulfonate (C-2)

To the solution of (2-chloro-6-(trifluoromethyl)phenyl)methanol **(i-1)** (210 mg, 1 mmol) and Et_3N (3 ml) dissolved in anhydrous THF (10 ml) was added MsCl (228 mg,2.0 mmol) drop wise. The mixture solution was protected by N_2 and stirred at r.t for 0.5 h. Then the solution was filtered and concentrated to afford 267 mg product **C-2** (yield: 93%). LCMS (ESI) calc'd [M+H] +: 288.67, found: 288.9.

ii) Preparation of 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[3 ,2-b]pyridine (C-3)

The mixture of 2-chloro-6-(trifluoromethyl)benzyl methanesulfonate **(C-2)** (288 mg, 1mmol), 3-bromo-1H-pyrrolo[3,2-b]pyridine (196 mg, 1.0 mmol), tBuOK (336 mg, 3.0 mmol), TBAI (106 mg, 0.4 mmol), THF(15 ml) and was protected by N_2 and stirred at 60 °C for 3 h. Then the solution was filtered and concentrated to be purified by chromatography column (EA/PE=1:4) to afford 289 mg product **C-3** (yield: 74.5%). LCMS (ESI) calc'd $[M+H]^+$: 389.60, found: 389.8.

iii). Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo [3,2-b]pyridin-3-yl)-3-fluorobenzoate (C-4).

The mixture of 3-bromo-1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[3,2-b]py ridine **(C-3)** (216 mg, 1mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (298 mg, 1.5 mmol), $Pd(PPh_3)_4$ (5 mg), K_2CO_3(414 mg, 3.0 mmol), Dioxane(15 ml) and H_2O(5 ml) was protected by N_2 and stirred at 100°C for 16 h. Then the solution was filtered and concentrated to be purified by chromatography column (EA/PE=1:4) to afford 364 mg product **C-4** (yield: 78.8%). LCMS (ESI) calc'd $[M+H]^+$: 462.86, found: 463.0.

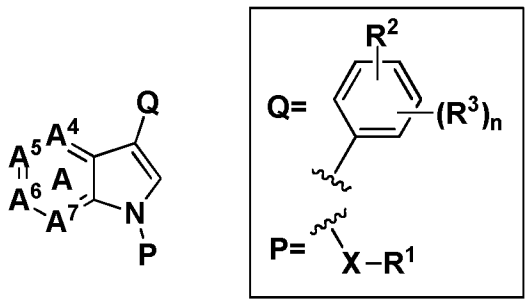
iv). Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[3,2-b]py ridin-3-yl)-3-fluorobenzoic acid (2A)

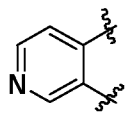
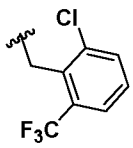
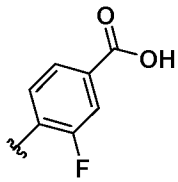
To the solution of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[3,2-b] pyridin-3-yl)-3-fluorobenzoate **(C-4)** (100 mg, 0.21 mmol) in THF (20 ml) and H_2O (5 ml) was added LiOH (48 mg,3.0 mmol). The mixture solution was stirred at r.t for 16 h. Added water (30 ml),acidified by HCl (2M), extracted with EA(20 ml×3), combined the organic layer, dried and concentrated to be purified by pre-HPLC (ACN/H_2O) to afford 79.4 mg

product **2A** (yield: 82.3 %).^{1}HNMR (400 MHz, $CDCl_3$) δ: 8.61(1H,d), 8.52(1H,d), 8.32(1H,t), 7.91(3H,t), 7.82(1H,2), 7.70(2H,m), 7.53(1H,m),5.81(2H,s).

The following examples shown in **TABLE 2** were prepared following similar procedures described for **Example #2A** in **Scheme C.** which can be achieved by those of ordinary skill in the art of organic synthesis.

TABLE 2



	Chemical Name	A ring	P	Q	LCMS $[M+H]^+$ Found
2B	4-(1-(2-chloro-6-(trifluoromethyl)benzyl)-1H-pyrrolo[2,3-c]pyridin-3-yl)-3-fluorobenzoic acid				449

Biological Assays

The compounds of the invention inhibit RORgammaT activity. Activation of RORgammaT activity can be measured using e.g. biochemical TR-FRET assay. In such an assay, interaction of cofactor-derived peptides with human RORgammaT-Ligand Binding Domain (LBD) can be measured. The TR-FRET technique is a sensitive biochemical proximity assay that will give information concerning the interaction of a ligand with the LBD, in the presence of cofactor derived peptides (Zhou et al., Methods 25:54-61, 2001).

To identify novel antagonists of RORgammaT, an assay was developed which employs the interaction of RORgammaT with its co-activator peptide SRC1_2. This peptide mimics the recruitment of co-activators to RORgammaT through its interaction with the LXXLL (eg NR box) motifs (Xie et al., J. Immunol. 175: 3800-09, 2005; Kurebayashi et al., Biochem. Biophys. Res. Commun. 315: 919-27, 2004; Jin et al., Mol. Endocrinology 24:923-29, 2010). The RORγ-Ligand Binding Domain TR-FRET Assay was run according to the following protocol.

HIS-tagged RORγ-LBD protein was expressed in SF9 cells using a baculovirus expression system. The RORγ-LBD protein was purified by glutathione sepharose chromatography. Separately, SF9 cells not expressing any recombinant protein were lysed and the lysate was added to the purified RORγ-LBD at 0.25 µl lysate (from 10,000 SF9 cells)/nM purified protein. The mixture was then diluted in assay buffer (50 mM Tris pH 7.0, 50 mM KCl, 1 mM EDTA, 0.1 mM DTT) to obtain RORγ-LBD final concentration of 3 nM in 384-well assay plate.

Compounds to be tested were injected to the assay plate using Acoustic Droplet Ejection technology by Echo 550 liquid handler (Labcyte, CA).

A stock of biotinylated-LXXLL peptide from coactivator SRC1 (Biotin-CPSSHSSLTERHKILHRLLQEGSPS) was prepared in assay buffer and added to each well (100 nM final concentration). A solution of Europium tagged anti-HIS antibody (1.25 nM final concentration) and APC conjugated streptavidin (8 nM final concentration) were also added to each well.

The final assay mixture was incubated for overnight at 4°C, and the fluorescence signal was measured on an Envision plate reader: (Excitation filter = 340 nm; APC emission = 665 nm; Europium emission = 615 nm; dichroic mirror = D400/D630; delay time = 100 µs, integration time = 200 µs).IC50 values for test compounds were calculated from the quotient of the fluorescence signal at 665 nm divided by the fluorescence signal at 615 nm.

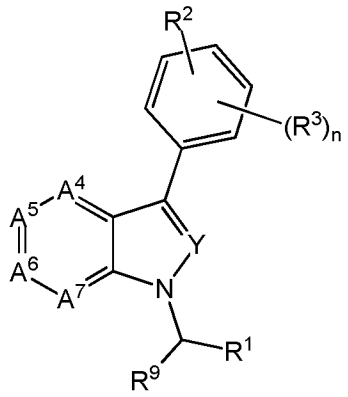
Biological Data

The following table tabulates the biological data disclosed for the instant invention.

Examples	Fret IC_{50} (nM)
1A	142
1B	2293
1C	39
1D	65
1E	219
1F	1553
1G	725
1H	358
1I	8228
1J	>10000
1K	>10000
1L	2122
1M	3102
1N	>10000
1O	1188
1P	>10000
1Q	3792
1R	4306
1S	3708
1T	1916
1U	9120
1V	2170
1W	4199
1X	3264
1Y	599
1Z	380
2A	283
2B	33

CLAIMS

1. A compound according to Formula I



I

or a pharmaceutically acceptable salt or solvate thereof wherein,

Y is CH, N or CR^a;

n = 0, 1, 2, 3 or 4;

A^4 is CR^4 or N,

A^5 is CR^5 or N,

A^6 is CR^6 or N,

A^7 is CR^7 or N,

with the proviso that no more than one or two of A^4-A^7 can be N;

R^a is (C_{1-4})alkyl;

R^1 is

(i) (C_{3-12})carbocyclyl; or

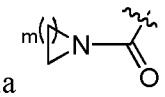
(ii) a 4- to 12-membered heterocyclyl,

both (i) and (ii) optionally substituted with one, two, three, four or five R^8;

R^2 is hydroxycarbonyl, hydroxycarbonyl(C_{1-10})alkyl, (C_{1-10})alkylsulfoxyaminocarbonyl, or carbamoyl;

R^3 is hydrogen, halogen, cyano, nitro, hydroxy, (C1-3)alkylC(O)O-, (C_{1-4})alkyl, or (C_{1-4})alkoxy, wherein (C_{1-4})alkyl and (C_{1-4})alkoxy are optionally substituted with one or

more halogen;

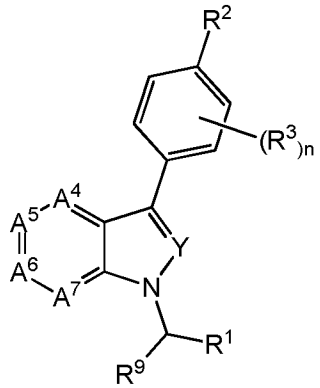
R^4-R^7 independently are H, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl or amino(C_{1-4})alkyl, wherein (C_{1-3})alkoxy, (C_{1-4})alkyl, (C_{0-10})alkyl)aminocarbonyl, (di)(C_{1-6})alkylaminocarbonyl and amino(C_{1-4})alkyl are optionally substituted with one or more halogen, hydroxyl or (C_{1-3})alkoxy; or a group having the formula  , optionally substituted with one or more of the following: (C_{1-10})alkyl, halogen, amino, cyano, hydroxy, (C_{1-3})alkoxy, and wherein m is 1, 2, 3, or 4;

R^8 is halogen, cyano, amino, nitro, hydroxy, $H_2NC(O)$-, (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{3-5})heterocycloalkyl, or (C_{1-3})alkoxy, wherein (C_{1-3})alkoxycarbonyl, (di)(C_{1-6})alkylaminocarbonyl, (C_{1-4})alkyl and (C_{1-3})alkoxy are optionally substituted with one, two or three halogens;

x is 0, 1, 2, 3, 4 or 5;

R^9 is hydrogen or (C_{1-4})alkyl.

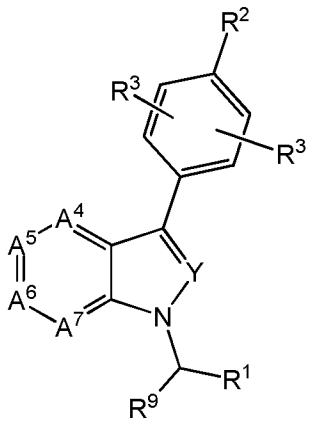
2. The compound of claim 1 having Formula Ia



Ia

and a pharmaceutically acceptable salt or solvate thereof.

3. The compound of claim 1 having Formula Ib

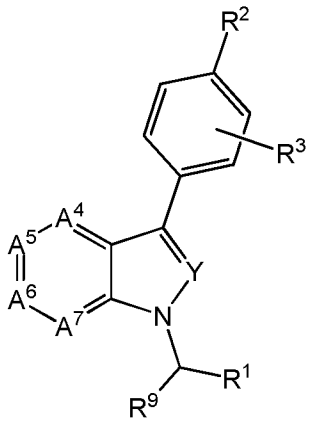


Ib

and a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 3, wherein Y is N.

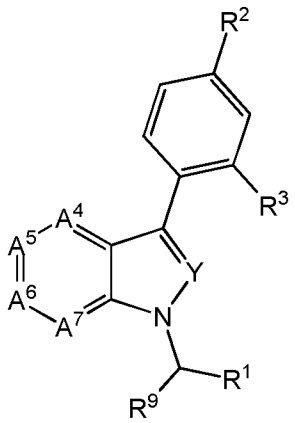
5. The compound of claim 3 having Formula Ic



Ic

and a pharmaceutically acceptable salt or solvate thereof.

6. The compound of claim 5 having Formula Id

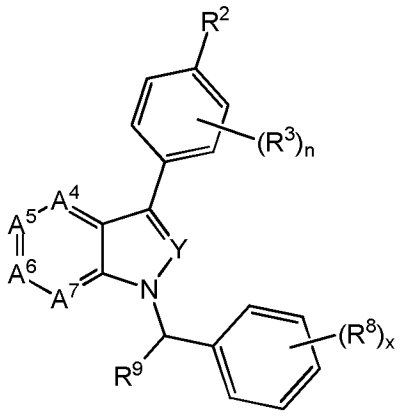


Id

and a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 6, wherein Y is N.

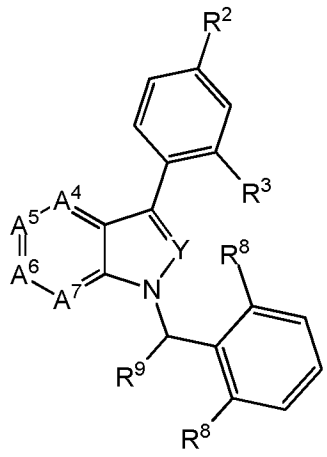
8. The compound of claim 2 having Formula Ie



Ie

and a pharmaceutically acceptable salt or solvate thereof.

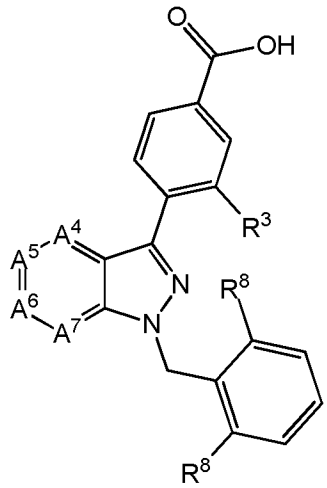
9. The compound of claim 8 having Formula If



If

and a pharmaceutically acceptable salt or solvate thereof.

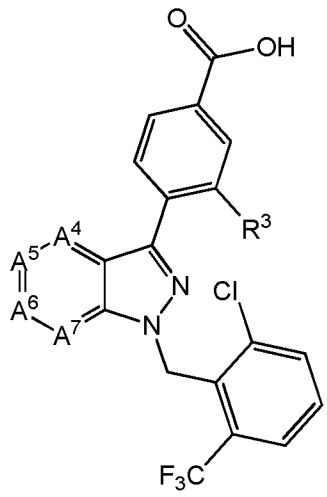
10. The compound of claim 9 having Formula Ig



Ig

and a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 10 having Formula Ih



Ih

and a pharmaceutically acceptable salt or solvate thereof.

12. The compound of claim 1, wherein A^4, A^5, A^6, A^7 are selected from the group consisting of: (i) CR^4, CR^5, CR^6, CR^7; (ii) N, CR^5, CR^6, CR^7; and (iii) CR^4, CR^5, N, CR^7.

13. The compound of claim 12, wherein A^4, A^5, A^6, A^7 is (i) CR^4, CR^5, CR^6, CR^7, or (ii) N, CR^5, CR^6, CR^7; and Y is N.

14. The compound of claim 12, wherein R^1 is (C_{2-9})heteroaryl, or (ii) (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8.

15. The compound of claim 14, wherein R^1 is (C_{6-14})aryl, optionally substituted with one, two, three, four or five R^8.

16. The compound of claim 14, wherein R^1 is phenyl, naphthyl, pyridinyl, quinolinyl, benzooxadiazolyl, thiophenyl, isoxazolyl, or benzothiophenyl, each optionally substituted with one or more R^8.

17. The compound of claim 16, wherein R^1 is phenyl, optionally substituted with one, two or three R^8.

18. The compound of claim 17, wherein R^2 is C(O)OH.

19. A compound according to claim 1 selected from:
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[3,4-c]pyridin-3-yl}-3-fluorobenzoic acid;
4-[1-(2-bromo-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}-3-fluorobenzoic acid;
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}benzoic acid;
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-4-fluoro-1H-indazol-3-yl}-2,5-difluorobenzoic acid;
4-(1-{1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;
4-(1-{(1R or 1S)-1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;
4-(1-{(1S or 1R)-1-[2-chloro-6-(trifluoromethyl)phenyl]ethyl}-4-fluoro-1H-indazol-3-yl)-3-fluorobenzoic acid;
4-[1-(2-bromo-3-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(5-chloro-2-cyanobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
3-fluoro-4-(1-{1-[2-(trifluoromethyl)phenyl]ethyl}-1H-pyrazolo[4,3-b]pyridin-3-yl)benzoic acid;
4-[1-(6-chloro-2-fluoro-3-methylbenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(2-chloro-3,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
3-fluoro-4-[1-(2,3,6-trifluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]benzoic acid;
3-fluoro-4-{1-[2-fluoro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}benzoic acid;
4-[1-(2,6-difluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;

4-[1-(2-chloro-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(6-chloro-2-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(2-chloro-6-fluoro-3-methoxybenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(2,3-dichloro-6-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-[1-(1-benzothiophen-7-ylmethyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-{1-[2,6-dichloro-3-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;
4-[1-(3,6-dichloro-2-fluorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-{1-[2-chloro-6-(methoxycarbonyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;
4-[1-(2-bromo-6-chlorobenzyl)-1H-pyrazolo[4,3-b]pyridin-3-yl]-3-fluorobenzoic acid;
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrazolo[4,3-b]pyridin-3-yl}-3-fluorobenzoic acid;
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrrolo[3,2-b]pyridin-3-yl}-3-fluorobenzoic acid; and
4-{1-[2-chloro-6-(trifluoromethyl)benzyl]-1H-pyrrolo[2,3-c]pyridin-3-yl}-3-fluorobenzoic acid.

20. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof and one or more pharmaceutically acceptable excipients.

21. The pharmaceutical composition of claim 20, which further comprises at least one additional therapeutically active agent.

22. Use of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a disease or condition mediated by Retinoic acid receptor-related Orphan Receptor gamma t (RORgammaT).

23. A method for treating a disease or condition mediated by RORgammaT in a subject comprising administering to the subject an amount of a compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, that is effective for treating the disease or condition mediated by RORgammaT in the subject.

24. The method of claim 23, wherein the disease or condition is an autoimmune disease or inflammatory disease.

25. The method of claim 24, wherein the disease or condition is multiple sclerosis, inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, psoriasis, rheumatoid arthritis, asthma, osteoarthritis, Kawasaki disease, Hashimoto's thyroiditis or mucosal leishmaniasis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080134

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: C07D231/-; C07D471/-; C07D403/-; A61K31/-; A61P43/-; A61P37/-; A61P29/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPI; EPODOC; CNPAT; CNKI; CA ON CD; CAPLUS; REGISTRY(structure search): ROR; retinoic; orphan; *indazol; *immun*; inflammatory; *indol*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US5958683A(NOVARTIS AG), 28 September 1999 (28.09.1999), claims 1-23	1-25
A	WO2011055270A1(WYETH LLC ET AL), 12 May 2011(12.05.2011) , the whole document	1-25
A	CN101087784A(WYETH LLC), 12 December 2007(12.12.2007), the whole document	1-25
A	US7427600B2(SHIRE LLC ET AL), 23 September 2008 (23.09.2008), the whole document	1-25
A	EP0429257A(GLAXO GROUP LTD), 29 May 1991(29.05.1991), the whole document	1-25
A	JP46040946B(SUMITOMO CHEM CO LTD), 03 December 1971 (03.12.1971), the whole document	1-25

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 May 2013 (08.05.2013)	**23 May 2013 (23.05.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HE, Xiaoping Telephone No. (86-10)62084365

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080134

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VOLKER FISCHER ET AL, THE 3-HYDROXY-3-METHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR FLUVASTATIN: EFFECT ON HUMAN CYTOCHROME P-450 AND IMPLICATIONS FOR METABOLIC DRUG INTERACTIONS, drug metabolism and disposition , 1998, vol. 27, no.3, pp. 410-416, Fig. 2	1-25
A	ARMELLE MELET ET AL, ANALYSIS OF HUMAN CYTOCHROME P450 2C8 SUBSTRATE SPECIFICITY USING A SUBSTRATE PHARMACOPHORE AND SITE-DIRECTED MUTANTS, Biochemistry, 2004, vol. 43, pp. 15379-15392, Fig. 1 Fluvastatin	1-25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080134

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23-25
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 23-25 relate to methods for treatment by therapy/diagnostic method of the human or animal body, which belongs to Rule 39.1(iv) of no international searching authority. Nevertheless, a search has been executed for the claims. The search has been carried out for the claims based on the alleged effect i.e. the uses of the compounds for the manufacture of medicaments.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/080134

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO2011055270A1	12.05.2011	US2011105509A1	05.05.2011
		TW201127823A	16.08.2011
US7427600B2	23.09.2008	US2007232529A1	04.10.2007
CN101087784A	12.12.2007	WO2006034419A2	30.03.2006
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		KR20070089908A	04.09.2007
		JP2008513512A	01.05.2008
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US5958683A	28.09.1999	WO9527202A1	12.10.1995
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/080134

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US5958683A	28.09.1999	AU9244798A	04.02.1999
		MX9603966A1	01.12.1997
		US6218359B1	17.04.2001
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		EP0429257A3	29.01.1992
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/080134

CLASSIFICATION OF SUBJECT MATTER

C07D231/56 (2006.01) i

C07D403/10 (2006.01) i

C07D403/12 (2006.01) i

C07D471/04 (2006.01) i

A61K 31/416 (2006.01) i

A61K 31/41 (2006.01) i

A61K 31/422 (2006.01) i

A61K 31/437 (2006.01) i

A61P 37/00 (2006.01) i

A61P 29/00 (2006.01) i