Title: 3-CYCLOHEXYL AND CYCLOHEXYL SUBSTITUTED INDOLE AND IND AZOLE COMPOUNDS AS ROR-gammaT INHIBITORS AND USES THEREOF

Abstract: The present invention relates to compounds according to Formula I and pharmaceutically acceptable salts or solvates thereof. Such compounds can be used in the treatment of RORgammaT-mediated diseases or conditions.
Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))
— with sequence listing part of description (Rule 5.2(a))
TITLE OF THE INVENTION
3-CYCLOHEXENYL AND CYCLOHEXYL SUBSTITUTED INDOLE AND INDAZOLE COMPOUNDS AS RORgammaT INHIBITORS AND USES THEREOF

BACKGROUND OF THE INVENTION

Upon activation by antigen-presenting cells naive 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 Thl7 (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 Thl7 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 (green fluorescent protein), revealed a constitutive expression of GFP in approximately 10% of the CD4+ T cells in the small intestinal lamina propria (LP), co-expressing the Thl7 cytokines IL-17/F and IL-22 (Ivanov et al., Cell 126: 1121-1133, 2006). In mice deficient for RORgammaT, the number of Thl7 cells was markedly decreased in the LP; and in vitro stimulation of CD4+ T cells under Thl7 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). The foregoing studies demonstrate 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 Thyl, 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 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; Annunziato 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 126:1 121-33, 2006; Buonocore et al, Nature 464: 1371-1375, 2010).

With RORgammaT being a critical mediator in Th17-cells and 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 that 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, antagonists have been reported such as 7-oxygenated sterols (Wang et al, *J. Biol. Chem.* 285: 5013-5025, 2009) and compounds described in EP2181710 Al.

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 immune 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 that 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

or a pharmaceutically acceptable salt or solvate thereof, wherein:

- $a$ is a bond or no bond;
- $X$ is $\text{CH}_2$, $\text{C(O)}$, $\text{CR}^b$;
- $Y$ is $\text{CH}$, $\text{N}$, $\text{CR}^a$;
- $n = 0$, $1$, $2$, $3$ or $4$;
- $A^4$ is $\text{CR}^4$ or $\text{N}$;
- $A^5$ is $\text{CR}^5$ or $\text{N}$;
- $A^6$ is $\text{CR}^6$ or $\text{N}$;
- $A^7$ is $\text{CR}^7$ or $\text{N}$;
- with the proviso that no more than two of $A^4$-$A^7$ can be $\text{N}$;
- $R^a$ is $(\text{C}_{i_4})$alkyl;
- $R^b$ is $(\text{C}_{i_4})$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 $R^b$;
- $R^2$ is hydroxy carbonyl, hydroxy carbonyl$(\text{Cl}_{i_0})$alkyl, $(\text{Cl}_{i_0})$alkyl sulfoxynaminocarbonyl, or carbamoyl;
R⁴ is hydrogen, halogen, cyano, nitro, hydroxy, (Cᵢ₃)alkylC(0)0-, (Cᵢ₄)alkyl, or (Cᵢ₄)alkoxy, wherein (Cᵢ₄)alkyl and (Cᵢ₄)alkoxy are optionally substituted with one or more halogen; R⁴-R⁷ independently are H, halogen, amino, cyano, hydroxy, (Cᵢ₃)alkoxy, (Cᵢ₄)alkyl, (Cₙ-io)alkyl)aminocarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl or amino(Cᵢ₄)alkyl, wherein (Cᵢ₃)alkoxy, (Cᵢ₄)alkyl, (Cₙ-io)alkyl)aminocarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl and amino(Cᵢ₄)alkyl are optionally substituted with one or more halogen, hydroxyl or (Cᵢ₃)alkoxy; or a group having the formula \( \text{O} \), optionally substituted with one or more of the following: (Cᵢ₅)alkyl, halogen, amino, cyano, hydroxy, (Cᵢ₃)alkoxy, and wherein m is 1, 2, 3, or 4; R⁸ is halogen, cyano, amino, nitro, hydroxy, H₂NC(0)-, (Cᵢ₃)alkoxycarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl, (Cᵢ₄)alkyl, (Cₙ-6)cycloalkyl, (Cₙ-6)cycloalkylaminocarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl or amino(Cᵢ₄)alkoxycarbonyl or (Cᵢ₃)alkoxy, wherein (Cᵢ₃)alkoxycarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl, (Cᵢ₄)alkyl, (Cₙ-6)cycloalkylaminocarbonyl, amino(Cᵢ₄)alkoxycarbonyl or (Cᵢ₃)alkoxy, wherein (Cᵢ₃)alkoxycarbonyl, (di)(Cᵢ₆)alkylaminocarbonyl, (Cᵢ₄)alkyl, (Cₙ-6)cycloalkylaminocarbonyl, amino(Cᵢ₄)alkoxycarbonyl or (Cᵢ₃)alkoxy are optionally substituted with oxo, (Cᵢ₄)alkyl, hydroxy(Cᵢ₃)alkyl, or one, two or three halogens.

In a first embodiment of the compound having Formula I is a compound having Formula IX.

\[
\begin{array}{c}
\text{In a first embodiment of the compound having Formula I is a compound having} \\
\text{Formula IX}
\end{array}
\]

\[
\text{IX}
\]

\[
\begin{array}{c}
\text{IX}
\end{array}
\]
or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is CH₂, C(O), CRᵇ;
Y is CH, N, CRᵃ;
n = 0, 1, 2, 3 or 4;
A⁴ is CR⁴ or N,
A⁵ is CR⁵ or N,
A⁶ is CR⁶ or N,
A⁷ is CR⁷ or N,
with the proviso that no more than two of A⁴-A⁷ can be N;
Rᵃ is (Ci₋₄)alkyl;
Rᵇ is (Ci₋₄)alkyl;
R¹ is

(i) (C₃₋₁₂)carbocyclyl; or
(ii) a 4- to 12-membered heterocyclyl,
both (i) and (ii) optionally substituted with one, two, three, four or five R⁸;
R² is hydroxycarbonyl, hydroxycarbonyl(Ci₋₁₀)alkyl, (Ci₋₁₀)alkylsulfoxaminocarbonyl, or carbamoyl;
R³ is hydrogen, halogen, cyano, nitro, hydroxy, (Ci₋₃)alkylC(0)₀⁻, (Ci₋₄)alkyl, or (Ci₋₄)alkoxy, wherein (Ci₋₄)alkyl and (Ci₋₄)alkoxy are optionally substituted with one or more halogen;
R⁴-R⁷ independently are H, halogen, amino, cyano, hydroxy, (Ci₋₃)alkoxy, (Ci₋₄)alkyl, (Co₋io)alkylaminocarbonyl, (di)(Ci₋₆)alkylaminocarbonyl or amino(Ci₋₄)alkyl, wherein (Ci₋₃)alkoxy, (Ci₋₄)alkyl, (Co₋io)alkylaminocarbonyl, (di)(Ci₋₆)alkylaminocarbonyl and amino(Ci₋₄)alkyl are optionally substituted with one or more halogen, hydroxyl or (Ci₋₃)alkoxy; or a group having the formula

![Chemical Structure](image)

, optionally substituted with one or more of the following: (Ci₋io)alkyl, halogen, amino, cyano, hydroxy, (Ci₋₃)alkoxy, and wherein m is 1, 2, 3, or 4; R⁸ is halogen, cyano, amino, nitro, hydroxy, H₂NC(0)₀⁻, (Ci₋₃)alkoxycarbonyl, (di)(Ci₋₆)alkylaminocarbonyl, (Ci₋₄)alkyl, (C₃₋₂)cycloalkyl, (C₃₋₅)heterocycloalkyl, (Ci₋₃)alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C₁₋₈)cycloalkylaminocarbonyl, amino(Ci₋₄)alkyloxycarbonyl or (Ci₋₃)alkoxy, wherein
(C₃)alkoxycarbonyl, (di)(C₆)alkylaminocarbonyl, (C₄)alkyl, (Cl-3)alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C₃-6)cycloalkylaminocarbonyl, amino(C₄)alkyloxycarbonyland (C₃)alkoxy are optionally substituted with oxo, (C₄)alkyl, hydroxy(C₃)alkyl, or one, two or three halogens.

In a second embodiment of the compound having Formula I is a compound having Formula 1a

![Formula 1a](image)

and a pharmaceutically acceptable salt or solvate thereof.

In a third embodiment of the compound having Formula I is a compound having Formula 1b

![Formula 1b](image)
and a pharmaceutically acceptable salt or solvate thereof.

In a first subset of the third embodiment is a compound wherein \( Y \) is N.

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

\[
\text{Ic}
\]

and a pharmaceutically acceptable salt or solvate thereof.

In a second subset of the first embodiment is a compound having Formula Id

\[
\text{Id}
\]

wherein \( x \) is 1, 2, 3, 4 or 5,

and a pharmaceutically acceptable salt or solvate thereof.
In a subset of the compound having Formula Ie is a compound having Formula If

and a pharmaceutically acceptable salt or solvate thereof.

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

and a pharmaceutically acceptable salt or solvate thereof.
and a pharmaceutically acceptable salt or solvate thereof.

In a third subset of the first embodiment is a compound wherein \( \text{A}^4, \text{A}^5, \text{A}^6, \text{A}^7 \) are selected from the group consisting of:

- (i) \( \text{CR}^4, \text{CR}^5, \text{CR}^6, \text{CR}^7 \);
- (ii) \( \text{N}, \text{CR}^5, \text{CR}^6, \text{CR}^7 \);
- (iii) \( \text{CR}^4, \text{N}, \text{CR}^6, \text{CR}^7 \);
- (iv) \( \text{CR}^4, \text{CR}^5, \text{N}, \text{CR}^7 \);
- (v) \( \text{CR}^4, \text{CR}^5, \text{CR}^6, \text{N} \);
- (vi) \( \text{N}, \text{N}, \text{CR}^6, \text{CR}^7 \);
- (vii) \( \text{CR}^4, \text{CR}^5, \text{N}, \text{N} \);
- (viii) \( \text{CR}^4, \text{CR}^5, \text{N}, \text{CR}^7 \);
- (ix) \( \text{CR}^4, \text{N}, \text{CR}^6, \text{N} \);
- (x) \( \text{CR}^4, \text{N}, \text{CR}^6, \text{N} \);
- and (xi) \( \text{N}, \text{CR}^5, \text{CR}^6, \text{N} \).

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

In a fifth subset of the first embodiment is compound wherein \( \text{R}^1 \) is (i) \( \text{(C}_3\text{)}\text{cycloalkyl} \) or \( \text{(C}_3\text{)}\text{heterocycloalkyl} \), both optionally substituted with one or more \( \text{R}^8 \), wherein \( \text{R}^8 \) is selected from halogen, amino, cyano, nitro, hydroxy, \( \text{H}_2\text{N}_{\text{C}}(\text{0}) \), \( \text{(C}_3\text{)}\text{alkoxycarbonyl} \), (di)(\( \text{C}_3\text{)}\text{alkylaminocarbonyl} \), (\( \text{C}_3\text{)}\text{alkyl} \) or (\( \text{C}_3\text{)}\text{alkoxy} \), wherein (\( \text{C}_3\text{)}\text{alkoxycarbonyl} \), (di)(\( \text{C}_3\text{)}\text{alkylaminocarbonyl} \), (\( \text{C}_3\text{)}\text{alkyl} \) and (\( \text{C}_3\text{)}\text{alkoxy} \) are optionally substituted with one or more halogens; (ii) \( \text{(C}_2\text{)}\text{heteroaryl} \), optionally substituted with one or more \( \text{R}^8 \), wherein \( \text{R}^8 \) is selected from halogen, amino, cyano, nitro, hydroxy, \( \text{H}_2\text{N}_{\text{C}}(\text{0}) \), \( \text{(C}_3\text{)}\text{alkoxycarbonyl} \), (di)(\( \text{C}_3\text{)}\text{alkylaminocarbonyl} \), (\( \text{C}_3\text{)}\text{alkyl} \) or (\( \text{C}_3\text{)}\text{alkoxy} \), wherein (\( \text{C}_3\text{)}\text{alkoxycarbonyl} \),
(di)(Ci_6)alkylaminocarbonyl, (Ci_4)alkyl and (Ci_3)alkoxy are optionally substituted with one or more halogens; or (iii) (Ci_6)aryl, optionally substituted with one or more R^8, wherein R^8 is selected from halogen, amino, cyano, nitro, hydroxy, H_2NC(0)-, (Ci_3)alkoxycarbonyl, (di)(Ci_6)alkylaminocarbonyl, (Ci_4)alkyl or (Ci_3)alkoxy, wherein (Ci_3)alkoxycarbonyl, (di)(Ci_6)alkylaminocarbonyl, (Ci_4)alkyl or (Ci_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, (Ci_3)alkoxycarbonyl, (Ci_4)alkyl, (Ci_3)alkoxy, wherein (Ci_3)alkoxycarbonyl, (Ci_4)alkyl and (Ci_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, (Ci_1-3)-alkoxycarbonyl, (Ci_4)alkyl or (Ci_3)alkoxy, wherein (Ci_3)alkoxycarbonyl, (Ci_4)alkyl and (Ci_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, (Ci_3)alkoxycarbonyl, (Ci_4)alkyl or (Ci_3)alkoxy, wherein (Ci_3)alkoxycarbonyl, (Ci_4)alkyl and (Ci_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, (Ci_3)alkoxycarbonyl, (Ci_4)alkyl or (Ci_3)alkoxy, wherein (Ci_3)alkoxycarbonyl, (Ci_4)alkyl and (Ci_3)alkoxy are optionally substituted with one or more halogens.

In a tenth subset of the first embodiment, R^2 is C(0)OH.
A still further embodiment of the compounds of Formula I, IX, la, lb, Id, If or Ig 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 $A_1$, $A_2$, $A_3$, $A_4$, $R_1$, $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $Y$, $m$, $n$ and $x$ and all substituent groups in the various aspects of the inventions defined hereinabove 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)benzoyl)-6-(dimethylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
- 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
- 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acidfluorobenzoic acid;
- 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-hydroxyethylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
- 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-enecarboxylic acid;
- 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-enecarboxylic acid;
(R or S)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy 5-azetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

(S or R)-4-((2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy 5-azetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

(R or S)-4-((2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy 5-azetidine-1-carbonyl)-1H-indazol-3-yl)-l-methylcyclohex-3-enecarboxylic acid;

(S or R)-4-((2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy 5-azetidine-1-carbonyl)-1H-indazol-3-yl)-l-methylcyclohex-3-enecarboxylic acid;

(R or S)-4-((2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

(S or R)-4-((2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(3,3-difluoro 5-azetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(cyclopropylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(cyclopropyl(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(azetidine-1-carbonyl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(pyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-((S)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-((R)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(3-methoxypyrrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-((S)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-((R)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;

4-((2-(trifluoromethyl)benzoyl)-6-(2-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclohexyl(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(morpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2R,6S)-2,6-dimethylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(4-methyl-3-oxopiperazine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-3-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2R,6S)-2,6-dimethylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethylaminopropyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-3-methoxypyrrolidin-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((R)-3-methoxypyrrolidin-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxycyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6-hydroxycyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxy-6-methylcyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-methylcyclohexanecarboxylic acid;
(trans)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-methylcyclohexanecarboxylic acid;
(cis)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-methylcyclohexanecarboxylic acid;
(trans)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-1-methylcyclohexanecarboxylic acid;
(cis)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-1-methylcyclohexanecarboxylic acid;
(R and S)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylcyclohex-3-enecarboxylic acid;
(R and S)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylic acid;
(trans)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid;
(cis)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid; 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-5-methylycyclohex-3-ene carboxylic acid; and 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-4-fluoro-1H-indazol-3-yl)-4-hydroxy cyclohexanecarboxylic 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 (C1-C6 alkyl) or from 1 to 3 carbon atoms (C1-C3 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, "C1-C6 alkyl" (or "C1-C6 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 alkylene-B" represents, for example, A-CH₂-CH₂-CH₂-B, A-CH₂-CH₂-CH(CH₃)-CH₂-B, A-CH₂-CH(CH₂CH₃)-B, A-CH₂-C(CH₂)(CH₃)-B, and the like. "Alkoxyl" represents a linear or branched alkyl group of indicated number of carbon atoms attached through an oxygen bridge; for example "Ci-Ce alkoxy" includes -OCH₃, -OCH₂CH₃, -OCH(CH₃)₂, -O(CH₂)₃CH₃, 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, Ci-C₂₀ alkyl, CF₃, NH₂, N(Ci-C₆ alkyl)₂, N0₂, oxo, CN, N₃, -OH, -0(Ci-C₆ alkyl), C₃-, C₅- cycloalkyl, (C₁₋₇)cycloalkyl, (C₃₋₅)heterocycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, (Co-C₆ alkyl) S(0)₂₋₄, (C₀₋₆ alkyl)S(O)₂₋₄(C₀₋₆ alkyl), (C₀₋₆ alkyl)C(0)NH-, H₂N-C(NH)ₐ, H₂N-C(0)(NH)-, -0(Ci-C₆ alkyl)CF₃, (C₀₋₆ alkyl)C(O)-, (C₀₋₆ alkyl)OC(O)-, (C₀₋₆ alkyl)O(0)Ci-C₆ alkyl)-, (Co-C₆ alkyl)NH(Ci-C₆ alkyl), NH(Ci-C₆ alkyl)OCi-C₆ alkyl, -NH(Ci-C₆ alkyl)NH(Ci-C₆ alkyl), -(Co-C₆ alkyl)NHSO₂₋₄(Ci-C₆ alkyl), aryl, aralkyl, heterocycle, heterocyclylalkyl, haloaryl, 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-butylnyl, and the like.

The term "carbocycle" (and variations thereof such as "carbocycllic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to (i) a C₃ to C₅ monocyclic, saturated or unsaturated ring or (ii) a C₇ to C₁₂ 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 that results in a stable compound.

Saturated carbocycles 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 Cl-6 alkyl, Cl-6 alkenyl, Cl-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 "heterocycl") 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 that 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, iso-thiazolidinyl, 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 to a 5- or 6-membered monocyclic aromatic ring or a 7- to 12-membered bicyclic aromatic ring, and that 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, thiényl (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, naphthrydinyll, pyrazolo[3,4-b]pyridine, imidazo[2,1-b](1,3)thiazole, (i.e., \( \text{S-N} = \text{S} \)), 6-(1-pyrrolyl)-3-pyridyl, 4-(1-pyrrolyl)phenyl, 4-(pyrid-3-yl)phenyl, 4-(pyrid-4-yl)phenyl, and benzothiophenyl (i.e., \( \text{S} \)).

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., \( \text{O} \cdot \text{O} \)), and benzo-
1,3-dioxolyl (i.e., \( \text{O} \cdot \text{O} \)). In certain contexts herein, \( \text{O} \cdot \text{O} \) 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, 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), Ci-C_{6} alkyl optionally substituted with one to
two fluorine, NH_{2}, N(Ci-C_{6} alkyl)_{2}, N0_{2}, oxo, CN, N_{3}, -OH, -0(Ci-C_{6} alkyl) optionally
substituted with one to five fluorine, C^{3}_{3}Cio cycloalkyl, (C^{3}_{3}2)cycloalkyl, (C^{3}_{3}3)heterocycloalkyl, C_{2}-C_{6} alkenyl, C_{2}-C_{6} alknyl, (Co-C_{6} alkyl)S(0)O-2, aryl-S(O)_{0}, (Co-C_{6}
alkyl)S(0)O-2(Co-C_{6} alkylene), (Co-C_{6} alkyl)C(0)NH-, H_{2}N-C(NH)_{2}, C_{0}O-6 alkyl)C(O)-,
(Not-C_{6} alkyl)OC(O)-, (C_{0}-C_{6} alkyl)OC(O-C_{6} alkylene), (Co-C_{6} alkyl)C(O)O-2(C_{0}-C_{6} alkylene),
(Co-C_{6} alkyl)O{\text{NC}_{0}}-2, (Co-C_{6} alkyl)OC(0)NH-, aryl, aralkyl, heteroaryl, heteroaralkyl, haloo-
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 C1 to C_{4} alkylene.

The term "C_{0}" as employed in expressions such as "C_{0}-alkylene" means a direct
covalent bond; or when employed in expressions such as "C_{0}-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 \( \text{Q} \), wherein \( s \) is an integer equal to zero, 1 or 2, the structure is \( \text{T} \) when \( s \) is zero; or it means that the indicated atom is absent; for example -\( S(0)\) 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

\[
\begin{align*}
\text{H3CH2C} & \text{--C--CH3} \\
\text{H2CH2CH2CH2C} & \text{--C--CH2CH2CH2} \\
\end{align*}
\]

The term (Ci,\(_\circ\))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 (Ci,\(_4\))alkyl.

The term (Ci,\(_5\))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 \((\text{Ci}_4)\)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 \((\text{Ci}_3)\)alkoxy means an alkoxy group having 1-3 carbon atoms, the alkoxy moiety being branched or unbranched.

The term \((\text{Ci}_3)\)alkoxycarbonyl means an alkoxy group having 1-3 carbon atoms in the alkoxy moiety, the alkoxy moiety having the same meaning as previously defined.

The term \((\text{di})(\text{Ci}_6)\)alkaminocarbonyl means an alkaminocarbonyl 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 \((\text{Ci}_4)\)alkyl.

The term \((\text{Ci}_3)\)alkoxyaminocarbonyl means an alkoxyaminocarbonyl group, the amino group of which is substituted with an alkoxy group which contains 1-3 carbon atoms and which has the same meaning as previously defined.

The term amino\((\text{Ci}_4)\)alkyloxyxycarbonyl means an aminoalkyloxycarbonyl group in which the alkyl group contains 1-4 carbon atoms.

The term \((\text{C}_3\text{C}_7)\)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 \((\text{C}_3\text{C}_5)\)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 \[\begin{array}{c}
\text{N} \\
\text{O}
\end{array}\] \(m\), means a heterocyclocarbonyl group such as \[\begin{array}{c}
\text{N} \\
\text{O}
\end{array}\] and \[\begin{array}{c}
\text{N} \\
\text{O}
\end{array}\], each optionally substituted with one or more \((\text{Ci}_1)\)alkyl, halogen, amino, cyano, hydroxy, and \((\text{Ci}_3)\)alkoxy.

The term \((\text{C}_2\text{C}_9)\)heteroaryl means an aromatic group having 2-9 carbon atoms and 1-3 heteroatoms selected from N, O and S, like imidazolyl, thiazolyl, 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 (C2-5)heteroaryl group may be attached via a carbon atom or a nitrogen, if feasible.

The term (C6-i4)aryl means an aromatic hydrocarbon group having 6-14 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl, indenyl, anthracyl. More preferred are (C6-i0)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, "C1-C4" shall have the same meaning as "C_{1,4}". Additionally, when referring to a functional group generically, "Ax" 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^{1n}" shall have the same meaning, and be interchangeable with, "R_1".

In the above definitions with multifunctional groups, the attachment point is at the last group. For example, the term (Cl_3)alkoxycarbonyl refers to, e.g., \(H_3C-O-C(\text{Cl}_4)\), and the term (Cl-4)alkylcarbonyloxy refers to, e.g., \(H_3C-CO(\text{Cl}_4)\).

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, it 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. Such compounds are referred to as tautomers. For example, compounds including carbonyl \(-\text{CH}_2\text{C}(0)\)- groups (keto forms) may undergo tautomerism to form hydroxyl \(-\text{CH}=\text{C(OH)}\)- 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 that 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'-dibenzylethlenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydabamine, isopropylamine, dicyclohexylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polamine 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 that are, within the scope of medical judgment, 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 that may not be a compound of formula I, but that 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.

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 prodrugs and the use of prodrugs is provided by T. Higuchi and W. Stella, "Prodrugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, 1987; 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. In light of the present disclosure, 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 activity, 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, la, lb, lc, ld, le, lf or lg 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 Thl7 cells and non-Thl7 cells, which express Thl7 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, ankylosing spondylitis 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 Thl7 cells and/or non-Thl7 cells, which express Thl7 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 Thl7 cells and/or non-Thl7 cells, which express Thl7 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 Thl7 cells and/or non-Thl7 cells, which express Thl7 hallmark cytokines, play a prominent role, such as but not limited to Kawasaki disease and Hashimoto’s thyroiditis.

In one aspect 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, la, lb, Ic, Id, Ie, If or Ig, 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 that 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 that 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 that 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, dragees, 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 glycols 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 nebulizers. 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 H1 receptor antagonists; (9) al- and a2-adrenoceptor agonist; (10) anticholinergic agents; (11) 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 optimize 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, la, lb, Ic, Id, Ie, If or Ig.

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 in light of the present disclosure. 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 and/or 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; Dppf: 1,1’-Bis(diphenylphosphino) ferrocene; AcOH: Acetic acid; DMAC: N,N-Dimethylacetamide; Pd(PPh₃)₄: Tetrakis(Triphenylphosphine)Palladium(0); Pd(dppf)Cl₂: [1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium (II); Ac₂O: Acetic anhydride; LiHMDS: Lithium bis(trimethylsilyl)amide; PhNTf₂: N-Phenyl-bis(trifluoromethanesulfonimide); S-Phos: 2-Dicyclohexylphosphino-2’,6’-dimethoxybiphenyl; X-Phos: 2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl; CPME: Cyclopentyl methyl ether; DMAP: 4-Dimethylaminopyridine; TEA: Triethylamine; THF: Tetrahydrofuran; PYAOP: (7-Azabenzotriazol-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate.

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

Scheme 2 illustrates a general method for the preparation of compounds of formula I that contain an amide moiety at A<sup>6</sup> position. Starting from halide A, acylation followed by ester hydrolysis gave intermediate B. Standard amide coupling furnished intermediate C. Subsequent Suzuki coupling followed by ester hydrolysis led to the formation of the final product I.

Scheme 3 illustrates an alternative method for the preparation of compounds of formula I that contain an amide moiety at A<sup>6</sup> position. Starting from halide A, N-acylation followed by Suzuki coupling gave intermediate C. Selective ester hydrolysis and subsequent amide coupling led to the formation of compound D. Final t-Bu removal under acidic conditions gave the desired product I.
Scheme 4 illustrates a general method toward the preparation of compounds of formula I that contain a cyclohexyl instead of cyclohexenyl motif. Starting from halide A, which can be obtained following those methods described previously, hydrogenation led to the formation of saturated cyclohexyl intermediate B. Ester hydrolysis gave the desired product I.

Scheme 5 illustrates a general method for the preparation of compounds of formula I that often are more difficult to access in comparison to those from general methods described previously. N-acylation followed by carbonylation gave intermediate C. Ester hydrolysis, Weinreb formation, and vinyl Grignard addition led to the formation of key intermediate E. Condensation with β-ketone ester afforded two region-isomers F and G. Final ester hydrolysis gave the final product I. Corresponding saturated cyclohexyl analogs could also be obtained from either intermediate F or G via hydrogenation and ester hydrolysis.
The following table lists commercial sources, and previously disclosed synthetic routes for chemical materials employed in the synthesis of intermediates and that can be used in the synthesis of examples of the instant invention. The list is not intended to be exhaustive, exclusive, or limiting in any way.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>LabPartner</td>
</tr>
</tbody>
</table>
Intermediates

Example i-1: Preparation of ethyl l-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (i-l).

Scheme i-1
Step 1. Preparation of 1,4-dioxa-spiro[4.5]decane-8-carboxylic acid ethyl ester (i-lb).

A mixture of ethyl 4-oxocyclohexanecarboxylate (i-la) (5.0 g, 29.41 mmol), ethane-1,2-diol (7.30 g, 117.65 mmol) and 4-methylbenzenesulfonic acid (0.51 g, 2.94 mmol) in toluene (50 mL) was stirred at 100°C overnight. The solvent was removed under reduced pressure and the residue was diluted with H₂O (50 mL). The aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with saturated NaHCO₃ solution (50 mL) then brine (50 mL), dried over anhydrous Na₂S₀₄ and concentrated to obtain the desired product as a pale yellow oil. LCMS (ESI) calc'd for C₉H₁₈O₂ [M+H]⁺: 215, found: 215.

Step 2. Preparation of ethyl 8-methyl-1,4-dioxa-spiro[4.5]decane-8-carboxylate (i-lc).

A mixture of 1,4-dioxa-spiro[4.5]decane-8-carboxylic acid ethyl ester (i-lb) (4.0 g, 18.69 mmol) in anhydrous THF (40 mL) was cooled to -78°C in a dry ice-acetone bath and LiHMDS (28 mL, 28.0 mmol) was added dropwise. The mixture was stirred at -78°C for 1 h. Then CH₃I (5.3 g, 37.38 mmol) was added dropwise. The resulting solution was warmed to room temperature and stirring continued overnight. Saturated NH₄Cl solution (50 mL) was added to quench the reaction and the aqueous layer was extracted with EA (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂S₀₄ and concentrated to obtain the desired product as a pale yellow oil. LCMS (ESI) calc'd for C₁₀H₂₀O₄ [M+H]⁺: 229, found: 229.

Step 3. Preparation of ethyl 1-methyl-4-oxocyclohexanecarboxylate (i-ld).

A mixture of ethyl 8-methyl-1,4-dioxa-spiro[4.5]decane-8-carboxylate (i-lc) (2.0 g, 8.77 mmol) in acetone (20 mL) and IN H₂S₀₄ (20 mL) was stirred at room temperature overnight. The mixture was diluted with H₂O (50 mL). The aqueous layer was extracted with DCM (3x30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na₂S₀₄ and concentrated to obtain the desired product as a pale yellow oil. LCMS (ESI) calc'd for C₁₀H₁₈O₃ [M+H]⁺: 185, found: 185.

Step 4. Preparation of ethyl 1-methyl-4-(trifluoromethylsulfonyloxy)cyclohex-3-ene carboxylate (i-le).

A mixture of ethyl 1-methyl-4-oxocyclohexanecarboxylate (i-ld) (3.0 g, 16.3 mmol) in anhydrous THF (20 mL) was cooled to -78°C in a dry ice-acetone bath and LiHMDS (18 mL, 17.9 mmol) was added dropwise. The mixture was stirred at -78°C for 30 min. Then a solution
of trifluoro-N-phenyl-N-(trifluoromethylsulfonyl) methanesulfonamide 5 (5.37 g, 14.7 mmol) in anhydrous THF (20 mL) was added dropwise. The resulting solution was warmed to room temperature and continued to stir for 3 h. Saturated NH₄Cl solution (50 mL) was added to quench the reaction and the aqueous layer was extracted with EA (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was chromatographed on silica gel (PE:EA 100:1) to obtain the desired product as a colorless oil. LCMS (ESI) calc’d for C₅F₃O₅S [M+H]+: 317, found: 317;

Step 5. Preparation of ethyl 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (i-1).

A mixture of ethyl 1-methyl-4-(trifluoromethylsulfonyloxy)cyclohex-3-enecarboxylate (i-le) (2.7 g, 8.54 mmol), 4,4,4′,5,5,5′-octamethyl-2,2’-bi(1,3,2-dioxaborolane) (2.39 g, 9.40 mmol), KOAc (2.51 g, 25.62 mmol), dppf (0.31 g, 0.56 mmol) and Pd(dppf)Cl₂ (0.3 g, 0.43 mmol) in 1,4-dioxane (50 mL) was heated to 80°C and stirred at this temperature for 3 h. The solvent was removed under reduced pressure and the residue was diluted with 100 mL of water. The aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by silica gel chromatograph (PE:EA 100:1) to provide the desired product as a colorless oil. LCMS (ESI) calc’d for C₁₆H₂₇B₀₄ [M+H]+: 295, found: 295;

Example i-2: Preparation of 3-bromo-lH-pyrazolo[4,3-b]pyridine

Scheme i-2

Step 1. Preparation of (3-bromo-lH-pyrazolo[4,3-b]pyridin-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (i-2).

To a flask was added 3-bromo-lH-pyrazolo[4,3-b]pyridine (i-2a) (3.2 g, 16.2 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (3.9 g, 16.2 mmol), DMAP (1.97 g, 16.2 mmol)
and DCM (60 mL), followed by the addition of TEA (3.26 g, 32.4 mmol) slowly. The reaction mixture was stirred at 40°C for 3 h. The mixture was diluted with H₂O, and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with H₂O, brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (Petroleum/EtOAc, 5/1) to afford 3.0 g (46%) of the title compound. LCMS (ESI) calc'd for C₁₅H₇BrClF₄N₂O [M+H]^+: 421, found: 421.

Example i-3: Preparation of (3-bromo-4-fluoro-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone

Scheme i-3

Step 1. Preparation of 3-bromo-4-fluoro-1H-indazole (i-3b). To a suspension of 4-fluoro-1H-indazole (i-3a) (5 g, 36.8 mmol) in 2M sodium hydroxide solution (100 ml) at room temperature was added a solution of bromine (5.8 g, 36.8 mmol) in 2M sodium hydroxide solution (60 ml). The reaction mixture was stirred at room temperature for 3 h. To the reaction mixture was added sodium bisulfite aqueous solution (10%, 100 mL). The solution was extracted with ethyl acetate (2 x 150 mL). The combined organic layer was washed with H₂O (3 x 100 mL) and brine (2 x 150 mL). The solution was dried over anhydrous Na₂SO₄ and evaporated. 5.47 g product was obtained. Yield 69%. LCMS (ESI) calc'd for C₇H₄BrFN₂ [M+H]^+: 215, found: 215.

Step 2 Preparation of (3-bromo-4-fluoro-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (i-3). To a flask was added 3-bromo-4-fluoro-1H-indazole (i-3b) (3.2 g, 14.9 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (5.43 g, 22.35 mmol), DMAP (1.82 g, 14.9 mmol), and TEA (3.02 g, 29.8 mmol). The mixture was stirred at 40°C for 3 h. The mixture was diluted with H₂O, and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂. The combined organics were washed with H₂O, brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography (Petroleum/EtOAc, 5/1) to afford 2.8 g (45%) of the title compound. LCMS (ESI) calc'd for C₁₅H₆BrClF₄N₂O [M+H]^+: 421, found: 421.
Example i-4: (4-chloro-3-iodo-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl) methanone

To a flask was added 4-chloro-3-iodo-1H-indazole (i-4a) (1 g, 3.59 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (1.05 g, 4.31 mmol), DMAP (0.44 g, 3.6 mmol), DCM (7.2 ml) and Et₃N (0.75 ml, 5.4 mmol) slowly. The reaction was allowed to stir at room temperature overnight. The mixture was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. Aqueous layers were back extracted once with ethyl acetate, and combined organic layers were dried over Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 0-50%) to give the desired product as a colorless solid (1.5 g, 86%). LCMS (ESI) calc’d for C₁₅H₆Cl₂F₃I₂O [M+H]+: 484.8, found: 484.8.

Example i-5: Preparation of 2-chloro-6-cyclopropylbenzoic acid

Step 1. Preparation of methyl 2-chloro-6-cyclopropylbenzoate (i-5b).
Methyl 2-bromo-6-chlorobenzoate (i-5a) (1.0 g, 4.0 mmol), cyclopropylboronic acid (516 mg, 6.0 mmol), Pd(OAc)₂ (90 mg, 0.4 mmol), Cy₃P (224 mg, 0.8 mmol) and K₃PO₄ (2.5 g, 12.0 mmol) were mixed in toluene (20 ml) and H₂O (2.5 ml). The mixture was stirred at 100°C overnight under N₂ atmosphere. The mixture was cooled down and poured into water (50 ml). The mixture was extracted with EA (50 ml). The organic layer was dried over Na₂SO₄.
filtered, and concentrated. The residue was purified by flash chromatography (Petroleum/EtOAc 15/1) to give 0.6 g (71%) of the title compound. LCMS (ESI) calc'd for C_{11}H_{11}ClO_2 [M+H]^+: 211, found: 211.

5 Step 2. Preparation of 2-chloro-6-cyclopropylbenzoic acid (i-5c).
NaOH (380 mg, 9.5 mmol) was added to a solution of methyl 2-chloro-6-cyclopropylbenzoate (i-5b) (200 mg, 0.95 mmol) in EtOH (15 ml) and H_2O (6 ml). The resulting solution was stirred at 80°C overnight. The mixture was cooled down and acidified with diluted HCl to pH=2-3. The mixture was extracted with EA (50 ml). The organic layer was dried over Na_2SO_4 and concentrated to afford 160 mg (86%) of the title compound. LCMS (ESI) calc'd for C_{10}H_{10}ClO_2 [M+H]^+: 197, found: 197.

Step 3. Preparation of 2-chloro-6-cyclopropylbenzoyl chloride (i-5).
To a solution of 2-chloro-6-cyclopropylbenzoic acid (i-5c) (1 g, 7.19 mmol) in 50 mL of DCM was added oxalyl dichloride (13 mL) at 0 °C dropwise, and the mixture was stirred at 25 °C for 12h. The mixture was evaporated to dryness. The residue was distilled under reduced pressure to afford 12 g (86%) of the title compound as a yellow oil. LCMS (ESI) calc'd for C_{10}H_{8}ClO_2 [M+H]^+: 215, found: 215.

Example i-6: Preparation of (2-chloro-6-cycloproplyphenyl)(4-fluoro-3-iodo-1H-indazol-1-yl)methanone

Scheme i-6

To a suspension of 4-fluoro-3-iodo-1H-indazole (1.14 g, 4.65 mmol) in 20 mL of THF was added NaH (279 mg, 6.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 minutes. A solution of 2-chloro-6-cyclopropylbenzoyl chloride (i-6a) (1 g, 4.65 mmol) in anhydrous THF (20 mL) was added dropwise to the mixture. The mixture was stirred at 25 °C for an additional 30 minutes. The reaction mixture was quenched with a sat. NH_4Cl solution, and was diluted with water (100 mL) and extracted with EtOAc (150 mLx3). The combined organic layers were washed with brine (50 mLx2), dried over Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography on silica gel (PE: EtOAc =
5:1) to give 1.7 g (86.3%) of the title compound as a yellow solid. LCMS (ESI) calc'd for C_{17}H_{11}ClN_2O [M+H]^+: 441, found: 441.

Example i-7: Preparation of l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazole-6-carboxylic acid

Scheme i-7

Step 1: Preparation of l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazole-6-carboxylate (i-7b).

To a flask was added methyl 3-iodo-lH-indazole-6-carboxylate (i-7a) (1.5 g, 4.97 mmol), TEA (1.730 ml, 12.41 mmol), DMAP (0.061 g, 0.497 mmol), and DCM (9.93 ml). To the solution was added a solution of 2-chloro-6-cyclopropylbenzoyl chloride (1.282 g, 5.96 mmol) in DCM (9.93 ml). The resulting solution was allowed to stir at room temperature for 3 hours. The mixture was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. Aqueous layers were back extracted once with ethyl acetate. Combined organic layers were dried with Na2SO4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 10-75%) to give the title product as a colorless solid. (2.06 g, 87%) LCMS (ESI) calc'd for C_{19}H_{14}ClIN_2O_3 [M+H]^+: 480.9, found: 480.9.

Step 2: Preparation of l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazole-6-carboxylic acid (i-7).

To a vial was added methyl l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazole-6-carboxylate (i-7b) (1.1 g, 2.288 mmol), lithium hydroxide (1.096 g, 45.8 mmol), THF (3.81 ml), and water (3.81 ml). The reaction was allowed to stir at room temperature overnight.
The reaction was concentrated and the residue was purified by flash chromatography (EtOAc/Hexane 0-100%) to give desired product as a colorless solid. (889 mg, 83%) LCMS (ESI) calc'd for C_{18}H_{12}CIIN_{2}O_{3} [M+H]^+: 466.9, found: 466.9.

Example i-8: Preparation of 3-(4-(tert-butoxycarbonyl)cyclohex-1-en-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazole-6-carboxylic acid

Scheme i-8

Step 1: methyl 3-(4-(tert-butoxycarbonyl)cyclohex-1-en-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazole-6-carboxylate (i-8b).

To a microwave reaction vial was added methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylate (lg, 1.97 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolo lan-2-yl)cyclohex-3-enecarboxylate (0.91 g, 2.95 mmol), THF (9.8 ml), and 2M Na_{2}C0_{3} (2.95 ml, 5.90 mmol). The mixture was degassed by bubbling N_{2} for 5min. 1,1-Bis(diphenylphosphino)ferrocene-palladium(ii)dichloride dichloro methane complex (0.16 g, 0.20 mmol) was added, and the mixture was heated at 50 °C for 2h. The mixture was cooled down, diluted with H_{2}O, and extracted with EtOAc. The organic layer was washed with brine, dried over MgSC\^\_2, and concentrated. The residue was purified by flash chromatography (0-50% EtOAc/hexanes) to give the title compound (0.8g, 72%). LCMS (ESI) calc'd for: C_{28}H_{27}C1F_{3}N_{2}O_{5} [M+H]^+: 563, found: 563.
Step 2: Preparation of 3-(4-(tert-butoxycarbonyl)cyclohex-1-en-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazole-6-carboxylic acid (i-8).

To a solution of methyl 3-(4-(tert-butoxycarbonyl)cyclohex-1-en-1-yl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazole-6-carboxylate (i-8b) (0.8g, 1.421 mmol) in THF (10.66 ml)/MeOH (3.55 ml) was added a solution of LiOH (1M, 2.8 ml). The mixture was stirred at room temperature for 14h. The mixture was acidified with 2N HCl to pH 3-4, and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and concentrated. The residue was used without purification. LCMS (ESI) calc’d for: C₂₇H₂₅C₁F₃₂O₅ [M+H]+: 549, found: 549.

Example i-9: l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-N-methoxy-N-methyl-1H-indazole-3-carboxamide.

Scheme i-9

Step 1. Preparation of ethyl l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazole-3-carboxylate (i-9b).

A mixture of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-iodo-1H-indazol-1-yl)methanone (i-9a) (2.2 g, 4.72 mmol), Et₃N (1.43 g, 14.2 mmol) and Pd(dppf)Cl₂ (200 mg) in EtOH (80 mL) was degassed with CO at 50 Psi and stirred at 80 °C for 20 hours. The mixture was then filtrated and concentrated. The residue was extracted with EA and dried over Na₂SO₄. The crude product was purified by column chromatography (PE : EA = 10 : 1) to give the title compound as a white solid (1.3 g, yield: 66%). LCMS (ESI) calc’d for C₁₈H₁₁C₁F₄N₂O₃ [M+H]+: 415, found: 415.
**Step 2. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazole-3-carboxylic acid (i-9c).**

A solution of ethyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazole-3-carboxylate (i-9b) (500 mg, 1.21 mmol) and LiOH H₂O (152 mg, 3.62 mmol) in THF / H₂O (5 mL / 1 mL) was stirred at 25 °C for 10 hours. The mixture was acidified with HCl (aq.) to pH = 1 and was then extracted with EtOAc (100 mLx5). The combined organics were washed with brine and dried over Na₂SO₄. The title compound (420 mg, yield: 90%) was used in the next step without further purification. LCMS (ESI) calc'd for C₁₆H₁₇ClF₄N₂O₃ [M+H]⁺: 387, found: 387.

**Step 3. Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-N-methoxy-N-methyl-1H-indazole-3-carboxamide (i-9).**

To a solution of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazole-3-carboxylic acid (i-9c) (5 g, 12.95 mmol), HATU (7.38 g, 19.43 mmol) and N, O-dimethylhydroxylamine hydrochloride (1.89 g, 19.43 mmol) in THF (90 mL) was added Et₃N (2.62 g, 25.9 mmol) under N₂. The mixture was stirred at 25°C for 10 hours. The mixture was quenched with H₂O and extracted with EtOAc (500 mLx5). The combined organic phase was washed with brine and dried over Na₂SO₄. The product was purified by column chromatography (PE : EA = 10 : 1) to afford the title compound as a white solid (5 g, yield: 95%). LCMS (ESI) calc'd for C₁₈H₁₂ClF₄N₃O₃ [M+H]⁺: 430, found: 430.

**Example i-10: (2-chloro-6-(trifluoromethyl)phenyl)(3-iodo-1H-pyrazolo[4,3-b]pyridin-1-yl)methanone**

**Scheme i-10**

To a suspension of NaH (16 mg, 3.8 mmol, 60% in mineral oil) in 10 mL of dry THF was added 3-iodo-1H-pyrazolo[4,3-b]pyridine (i-10a) (400 mg, 1.6 mmol) portionwise at 0°C. After stirring for 30 min, 2-chloro-6-(trifluoromethyl)benzoyl chloride (480 mg, 1.9 mmol) was added dropwise and the mixture was stirred at 15 °C for 1 h. The resulting mixture was
quenched with water (10 mL) and the aqueous layer was extracted with DCM (20 mLx3). The combined organic layer was washed with brine (25 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to afford the title compound (600 mg, 85%). LCMS (ESI) calc'd for C_{44}H_{66}ClF_{3}I_{3}N_{3}O [M+H]^+: 452, found: 452.

Example i-11: Preparation of ethyl 4-((1)-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylate

Step 1. ethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (i-llb).
To a solution of pyridine (5.2 mL, 6.5 mmol)/toluene (150 mL) was added trifluoromethanesulfonic anhydride (11 mL, 6.5 mmol), over 30 minutes at 15 °C, while under nitrogen. A solution of ethyl 4-oxocyclohexanecarboxylate (i-lla) (10 g, 5.88 mmol) in toluene (5 mL) was added, and the mixture was heated to 40 °C. An additional batch of trifluoromethanesulfonic anhydride (0.05 mmol) was added after 10 h and 12 h respectively, to push the reaction to completion. The resulting mixture was poured into ice water (200 mL) and extracted with ethyl acetate (200 mLx3). The combined organic layer was washed with brine (200 mL), dried over anhydrous Na_{2}SO_{4} and concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE: EtOAc = 30:1) to give the title compound (8 g, 47%) as a yellow oil. LCMS (ESI) calc'd for C_{40}H_{34}F_{3}O_{5}S [M+H]^+: 303, found: 303.

Step 2 Preparation of ethyl 4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (i-llc).
To a solution of ethyl 4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (i-llb) (20 g, 66.2 mmol) in 1,4-dioxane (500 mL) was added bis(pinacolato)diboron (34 g, 132.4 mmol) and potassium acetate (19 g, 198 mmol). The mixture was purged with nitrogen for 20 minutes, Pd(dppf)Cl_{2} (4.9 g, 6.6 mmol) was added and the reaction was stirred at 100 °C for 2 h. The resulting mixture was filtered over Celite and the filtrate was diluted with water (500
mL) and extracted with ethyl acetate (500 mL x 3). The combined organic layer was washed with brine (500 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (PE: EtOAc = 20:1) to give the title compound (12 g, 67%) as a yellow oil. LCMS (ESI) calc’d for C$_{13}$H$_{25}$B$_2$O$_4$ [M+H]$^+$: 281, found: 281.

**Step 3 Preparation of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylate (i-11).**

To a mixture of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-iodo-1H-indazol-1-yl)methanone (i-9a) (1 g, 2.1 mol) in THF/H$_2$O (40 mL/10mL) was added ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (i-11c) (897 mg, 3.2 mmol) and Na$_2$C$_6$O$_3$ (667 mg, 6.3 mmol). The mixture was purged with nitrogen for 20 minutes, and then Pd(dppf)Cl$_2$ (726 mg, 0.63 mmol) was added. The reaction was stirred at 80 °C for 10 h. The resulting mixture was filtered over Celite and the filtrate was diluted with water (50 mL) and extracted with ethyl acetate (50 mLx3). The combined organic layer was washed with brine (50 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The product was purified by column chromatography on silica gel (PE: EtOAc = 10:1) to give the title compound (300 mg, 29%) as a brown oil. LCMS (ESI) calc’d for C$_{24}$H$_{19}$ClF$_4$N$_2$0$_3$ [M+H]$^+$: 495, found: 495.

**Example i-12: Preparation of 3-((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-4-fluoro-1H-indazole**

Scheme i-12
Step 1. Preparation of 4-(methoxycarbonyl)cyclohexanecarboxylic acid (i-12b).
A mixture of dimethyl cyclohexane-1,4-dicarboxylate (i-12a) (8 g, 40 mmol) and barium hydroxide (6.3 g, 20 mmol) in 80% aqueous methanol (150 mL) was stirred at 25 °C for 12 h. The mixture was diluted with water (200 mL) and washed with hexane (100 mLx2) to remove remaining starting material. The aqueous layer was then acidified with 2 M HCl to pH = 3 and extracted with EtOAc (100 mL x 3). The organic layer was washed with water (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The mixture was purified by column chromatography on silica gel (PE: EtOAc = 50:1 to 3:1) to afford the title compound (3.2 g, 43%) as a white solid. LCMS (ESI): calc'd for C₁₅H₂₁O₃S: [M+H]⁺: 287, found: 287;

Step 2. Preparation of methyl 4-(hydroxymethyl)cyclohexanecarboxylate (i-12c).
To a solution of 4-(methoxycarbonyl)cyclohexanecarboxylic acid (i-12b) (1.5 g, 8.1 mmol) in 15 mL of THF was added dropwise, borane in dimethylsulfane (10 M, 1.6 mL, 16.0 mmol), while cooling to 15 °C in an ice bath. The reaction was stirred at 15 °C for 3 h. The reaction mixture was slowly poured into methanol (500 mL) (cooled in an ice bath), stirred at 15 °C for 30 min and concentrated in vacuo. The residue was partitioned with water (300 mL) and EtOAc (300 mL). The aqueous layer was extracted with EtOAc (300 mL x 2) and the combined organic layer was washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (1.3 g, 90%) as a yellow oil. LCMS (ESI): calc'd for C₉H₁₆O₃ [M+H]⁺: 173, found: 173;

Step 3. Preparation of methyl 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexane carboxylate (i-12d).
To a solution of methyl 4-(hydroxymethyl)cyclohexanecarboxylate (i-12c) (1.3 g, 7.5 mmol) in 30 mL of DCM, was added triethylamine (2.3 g, 22.6 mmol) and DMAP (46 mg, 0.37 mmol). The reaction was stirred at 15 °C for 30 min. Tert-butylchlorodimethylsilane (1.4 g, 9.1 mmol) was added dropwise, while cooling in an ice bath. The mixture was stirred at 15 °C for 12 h, and was then diluted with DCM (100 mL), and washed with water (100 mLx2). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The mixture was purified by column chromatography on silica gel (PE: EtOAc = 50:1) to afford the title compound (2 g, 92%) as a yellow oil. LCMS (ESI): calc'd for C₁₅H₃₀O₃Si [M+H]⁺: 287, found: 287;
Step 4. Preparation of methyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-l-methylcyclohexanecarboxylate (i-12e).

To a solution of 1,2-diisopropylhydrazine (14.1 g, 140 mmol) in 200 mL of anhydrous THF at 0 °C, was added dropwise n-BuLi (47.5 mL, 118 mmol). The mixture was stirred at 0 °C for 20 min. A solution of methyl 4-(((tert-butyldimethylsilyl)oxy)methyl)cyclohexanecarboxylate (i-12d) (20 g, 70 mmol) in 100 mL of THF was added dropwise. The mixture was then stirred at 0 °C for 1 h. It was then cooled to -78 °C, and iodomethane (19.8 g, 140 mmol) was added dropwise. After the addition was complete, the mixture was stirred at -78 °C for an additional 1 h and then stirred at 15 °C for 12 h. The resulting mixture was poured into saturated aq. NH₄Cl (200 mL) solution, and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (20 g, 95%) as a yellow oil. LCMS (ESI): calc'd for C₂₁H₃₃F₂O₂Si [M+H]⁺: 301; found: 301;

Step 5. Preparation of (4-(((tert-butyldimethylsilyl)oxy)methyl)-l-methylcyclohexyl)-(2,6-difluorophenyl)methanone (i-12f).

To a solution of 1,3-difluorobenzene (4.6 g, 40 mmol) and TMEDA (3.8 g, 33.3 mmol) in 50 mL of THF was added s-BuLi (28.1 mL, 36.6 mmol) at -78 °C. The mixture was stirred at -78 °C for 2 h. A solution of methyl 4-(((tert-butyldimethylsilyl)oxy)methyl)-l-methylcyclohexanecarboxylate (i-12e) (10 g, 33.3 mmol) in 50 mL of THF was added. The mixture was stirred at -78 °C for 1 h, and then warmed to 15 °C while stirring for 12 h. The resulting mixture was quenched with saturated aq. NH₄Cl (200 mL), and extracted with EtOAc (300 mL x 3). The combined organic layer was washed with brine (100 mL x 2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (11 g, 86%) as yellow oil. LCMS (ESI): calc'd for C₂₁H₂₁F₂O₂Si [M+H]⁺: 383; found: 383;

Step 6. Preparation of 3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-l-methylcyclohexyl)-4-fluoroIH-indazole (i-12).

A mixture of (4-(((tert-butyldimethylsilyl)oxy)methyl)-l-methylcyclohexyl)(2,6-difluorophenyl)methanone (i-12f) (1 g, 2.6 mmol) in 15 mL of H₂N-NH₂·H₂O (85%) was stirred at 110 °C for 30 h. The resulting mixture was poured into 100 mL of water and extracted with EtOAc (300 mLx3). The organic layer was washed with brine (100 mLx2), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The mixture was purified by column chromatography on silica gel (PE to PE: EtOAc = 20:1) to afford the title compound (300 mg, 31%) as a yellow oil. LCMS (ESI): calc'd for C₂₁H₂₃FN₂OSi [M+H]⁺: 377; found: 377.
Method for preparation of the compound

Example 1 A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethyl carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (1A)

Step 1: Preparation of methyl 1H-indazole-6-carboxylate (A-2).

Methyl 3-amino-4-methylbenzoate (A-1) (5.0 g, 30.2 mmol) was dissolved in AcOH (140 mL). Sodium nitrite (2.1 g, 30.2 mmol) in water (3.5 mL) was added drop-wise to the solution while stirring at 0 °C. The ice bath was removed and the mixture was stirred overnight. Solvents were evaporated, and the mixture was diluted with water (80 mL) and extracted with EtOAc(3x30 mL). The combined organics were washed with water and brine (2x200 mL), dried and evaporated to afford 2 (4.4 g), yield 83%. LCMS (ESI): calc'd for C_{19}H_{18}N_{2}O_{2}, [M+H]^+: 177, found: 177.
Step 2: Preparation of Methyl 3-iodo-1H-indazole-6-carboxylate (A-3).

Methyl 1H-indazole-6-carboxylate (A-2) (5.0 g, 28.3 mmol) was dissolved in anhydrous DMAC (50 mL). Iodine (14.4 g, 56.7 mmol) and potassium hydroxide (6.3 g, 113.5 mmol) were added in portions while stirring at 0 °C. The ice bath was removed and the mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC (25% MeOH in chloroform) then it was slowly quenched with Na₂S₂O₃ (sat. sol. in water, 100 mL), diluted with water (50 mL) and extracted with EtOAc (3x100 mL). The organic phase was evaporated and triturated with n-hexane. The precipitated material was filtered and dried to afford a brown solid (5.3 g), yield 62%. LCMS(ESI): calc'd for C₁₇H₉ClF₃IN₂O₃, [M+H]+: 495, found: 495.

Step 3: Preparation of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylate (A-4).

To a 250 mL round-bottomed flask, was added Methyl 3-iodo-1H-indazole-6-carboxylate (11.7 g, 38.7 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (A-3) (9.1 g, 38.7 mmol), DMAP (4.72 g, 38.7 mmol) and CH₂Cl₂ (30 mL). After stirring at room temperature for 3 minutes, TEA (11.2 mL, 77 mmol) was added slowly. The reaction mixture was stirred at room temperature overnight. LCMS indicated that the starting material had been consumed. The mixture was poured into 30 mL of water. The aqueous layer was extracted twice with 20 mL of CH₂Cl₂. The combined organic layer was washed with 20 mLx2 water followed by 10 mL of brine. The resulting organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The residue was purified by column chromatography on 60 g of silica gel eluting with Petroleum ether/EtOAc from 50/1 to 10/1, to give a fawn solid (16.5 g), yield 84%. LCMS (ESI): calc'd for C₁₇H₉ClF₃IN₂O₃, [M+H]+: 509, found: 509.

Step 4: Preparation of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylic acid (A-5).

A mixture of methyl 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-1H-indazole-6-carboxylate (A-4) (16.5g, 32.48 mmol) and LiOH (3.40g, 162.40 mmol) in 10 ml THF/50 ml H₂O was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in water. HC1 (5%> sol in water) was added to achieve pH=4-5. The precipitated solid was filtered, washed with water and n-hexane, and dried to afford an off-white solid (16.0g), yield 83%. LCMS(ESI): calc'd for C₁₀H₇ClF₃IN₂O₃, [M+H]+: 495, found: 495.
Step 5: Preparation of l-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-N,N-dimethyl-lH-indazole-6-carboxamide (A-6).

1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-lH-indazole-6-carboxylic acid (A-5) (178 mg, 0.36mmol) was dissolved in CH₂Cl₂ (15 mL). Dimethylamine (19 mg, 0.42mmol) and PYAOP (374 mg, 0.72mmol) were added and the mixture was stirred at room temperature for 2 minutes. TEA (0.16mL, 1.08mmol) was added and the mixture was stirred at room temperature for 2h. The reaction mixture was diluted with EtOAc (20 ml), washed with brine (2x20 ml), dried over anhydrous Na₂SO₄, and concentrated to obtain a white solid 7 (191 mg), yield 97%. LCMS (ESI): calc'd for C₁₅H₁₂ClF₃IN₃O₂, [M+H]⁺: 522, found: 522.

Step 6: Preparation of methyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl))-6-(dimethylcarbamoyl)-lH-indazol-3-yl)cyclohex-3-enecarboxylate (A-7).

A mixture of 1-(2-chloro-6-(trifluoromethyl)benzoyl)-3-iodo-N,N-dimethyl-lH-indazole-6-carboxamide (A-6) (318 mg, 0.61 mmol), 4-(methoxycarbonyl)cyclohex-1-enylboronic acid (169 mg, 0.92 mmol), Pd(dppf)Cl₂ (50 mg, 0.061 mmol) and KOAc (181 mg, 1.83mmol) in 10 ml Dioxane/2 ml H₂O was heated to 95°C for 2h under microwave irradiation. The crude was diluted with EtOAc (50 ml), washed with brine (2x50 ml), dried over anhydrous Na₂SO₄, and concentrated. The mixture was purified by silica gel column (Petroleum ether/EtOAc =20/1) to afford a white solid 8, 192 mg (59%). LCMS (ESI): calc'd for C₂₆H₂₃ClF₃N₃O₄, [M+H]⁺: 534, found: 534.

Step 7: Preparation of 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl))-6-(dimethyl carbamoyl)-lH-indazol-3-yl)cyclohex-3-enecarboxylic acid (1A).

A mixture of methyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl))-6-(dimethylcarbamoyl)-lH-indazol-3-yl)cyclohex-3-enecarboxylate (A-7) (37 mg, 0.07 mmol) and LiOH H₂O (16mg, 0.37mmmol) in 10 ml THF/10 ml H₂O was stirred at room temperature for 2 hours. The solvent was evaporated and the residue was dissolved in water. HCl (5% sol in water) was added until pH =4-5 was acheived. The precipitated solid was filtered, washed with water (10 mL), n-hexane (10 mL), and dried to afford an off-white solid 1A. LCMS (ESI): calc'd for C₂₆H₂₃ClF₃N₃O₄, [M+H]⁺: 520, found: 520; ¹HNMR (400MHz, MEOD) δ 8.60 (1H, s), 8.19-8.21 (1H, d, J = 8.4Hz), 7.83-7.87 (2H, m), 7.73-7.77 (1H, m), 7.57-7.59 (1H, m), 6.85 (1H, s), 3.21 (3H, s), 3.09 (3H, s), 2.48-2.67 (4H, m), 2.35-2.38 (1H, m), 2.09-2.12 (1H, m), 1.77-1.80 (1H, m).
Example IB: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (IB)

Step 1: Preparation of 4-fluoro-3-iodo-1H-indazole (B-2). To a solution of 4-fluoroindazole (B-1) (5.00 g, 36.73 mmol) in DMF (80 mL), was added I$_2$ (18.64 g, 73.46 mmol) and KOH (7.73 g, 137.7 mmol) at room temperature while stirring. After 2 hours, TLC indicated that the reaction was complete. The reaction mixture was poured into aq. NaHSC$_3$ (10%, 200 mL) and extracted with EA (3x200 mL). The combined organic layer was washed with H$_2$O (100 mL) and brine (2x200 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The crude (solid) was washed with PE to give a yellow solid B-2 (8.33 g), yield 86.5%. Physical characterization data for B-2 was as follows: LCMS(ESI): calc. C$_7$H$_4$FIN$_2$, 261.9; obs. M+H=262.9

Step 2: Preparation of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-iodo-1H-indazol-1-yl)methanone (B-3). To a 250 mL round-bottomed flask was added compound B-2 (5.24 g, 20 mmol), 2-chloro-6-(trifluoromethyl)benzoyl chloride (4.86 g, 20 mmol), DMAP (2.44 g, 20 mmol) and DCM (30mL). The reaction was stirred at room temperature for 3 minutes. TEA (5.8 mL, 40 mmol) was then added slowly. The reaction mixture was stirred at room temperature overnight. LCMS indicated little starting material remaining. The mixture was poured into water (30mL). The aqueous phase was extracted twice with DCM (20 mL). The
combined organic phase was washed with water (2x20mL), followed by brine (10mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow solid. The residue was purified by column chromatography on 30 g of silica gel eluting with PE/EA from 50/1 to 10/1, to give a fawn solid B-3 (7.8 g), yield 83%. LCMS(ESI): calc'd for C_{19}H_{16}ClF_{4}N_{2}O, [M+H]+: 469, Found:469.

**Step 3: Preparation of methyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylate (B-4).** A mixture of B-3 (300 mg, 0.64 mmol), 4-(ethoxycarbonyl)-4-methylcyclohex-1-enylboronic acid (203 mg, 0.96 mmol), Pd(dppf)Cl\(_2\) (52.2 mg, 0.064 mmol) and KOAc (190 mg, 1.92mmol) in Dioxane (10 ml)/H\(_2\)O (2ml) was heated to 90°C for 2h under microwave irradiation. The mixture was diluted with CH\(_2\)Cl\(_2\) (50 ml), washed with brine (2x50 ml), dried over anhydrous Na\(_2\)SO\(_4\), and concentrated. The mixture was purified by silica gel column (PE/EA=20/1) to afford 172 mg of a yellow solid B-4. LCMS(ESI): calc'd for C_{25}H_{21}ClF_{4}N_{2}O, [M+H]+: 509, Found: 509.

**Step 4: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (B-5).** A mixture of B-4 (182 mg, 0.36 mmol) and LiOH (350 mg, 1.44 mmol) in 5 ml THF/5 ml H\(_2\)O was stirred at room temperature for one week. HCl (2mol/L) was added slowly to maintain the PH<7. The mixture was concentrated under reduced pressure, and filtered to afford a white solid. The white solid was washed with H\(_2\)O and dried to yield 100 mg of white solid IB. LCMS(ESI): calc'd for C_{23}H_{17}ClF_{4}N_{2}O_{3}, [M+H]+:481, Found, 481. \(^1\)HNMR (400MHz, MeOD) \(\delta\) 8.39(1H, d, J=8.0 Hz), 7.86-7.83(2H, m), 7.77-7.70(2H, m), 7.27-7.22(2H, m), 6.66(1H, s), 2.84-2.78(2H, m), 2.39-2.38(2H, m), 2.20-2.14(1H, m), 2.07-1.95(1H, m), 1.71-1.64(1H, m), 1.27(3H, d, J=0.8 Hz)

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

**Table 1**

![Chemical Structure Diagram]
<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>A ring</th>
<th>P</th>
<th>Q</th>
<th>LCMS [M+H]$^+$ Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>1C 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>467</td>
</tr>
<tr>
<td>1D 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-hydroxyethylcarbamoil)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>536</td>
</tr>
<tr>
<td>1E 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>450</td>
</tr>
<tr>
<td>1F 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-1-methylcyclohex-3-enecarboxylic acid</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>464</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Molecular Formula</td>
<td>Molecular Weight</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>IG</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-methylcyclohex-3-ene-2-carboxylic acid</td>
<td>464</td>
<td></td>
</tr>
<tr>
<td>IH</td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-2-methylcyclohex-3-ene-2-carboxylic acid</td>
<td>449</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td>4-(4-chloro-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-1-methylcyclohex-3-ene-2-carboxylic acid</td>
<td>497</td>
<td></td>
</tr>
<tr>
<td>IJ</td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
<td>4-(1-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)-1-methylcyclohex-3-ene-2-carboxylic acid</td>
<td>453</td>
<td></td>
</tr>
<tr>
<td>IK</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td>4-(1-(2-chloro-6-methylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-ene-2-carboxylic acid</td>
<td>413</td>
<td></td>
</tr>
<tr>
<td>IL</td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
<td>4-(1-(2-chloro-6-methylbenzoyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)cyclohex-3-ene-2-carboxylic acid</td>
<td>396</td>
<td></td>
</tr>
</tbody>
</table>
Example 2A and 2B: Preparation of (R or S)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy azetidine-l-carbonyl)-lH-indazol-3-yl)cyclohex-3-enecarboxylic acid (2A) and (S or R)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy azetidine-l-carbonyl)-lH-indazol-3-yl)cyclohex-3-enecarboxylic acid (2B).

**Scheme C**

Step 1: Preparation of (l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazol-6-yl)(3-methoxyazetidin-l-yl)methanone (C-1).

To a vial was added l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-lH-indazole-6-carboxylic acid (889 mg, 1.905 mmol), 3-methoxy azetidine hydrochloride (330 mg, 2.67 mmol), HATU (1449 mg, 3.81 mmol), DIPEA (1331 µl, 7.62 mmol), and DMF (3810 µl). The solution was stirred at room temperature overnight. The mixture was diluted with ethyl acetate, washed 2x
with aqueous sodium hydrogen carbonate and 1x with brine. The aqueous layer was back extracted once with ethyl acetate, combined organic layers were dried with Na2SO4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 10-95%) to give desired product as a yellow solid. (1.02 g, 100%) LCMS (ESI) calc'd for C_{22}H_{19}ClIN_{3}O_{3} [M+H]^+: 536, found: 536.

**Step 2: Preparation of tert-butyl 4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-IH-indazol-3-yl)cyclohex-3-enecarboxylate (C-2).**

To a vial was added (l-(2-chloro-6-cyclopropylbenzoyl)-3-iodo-IH-indazol-6-yl)(3-methoxyazetidin-1-yl)methanone (C-I) (300 mg, 0.560 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (259 mg, 0.840 mmol), (2-dicyclohexylphosphino-2′,4′,6′-trisopropyl-1,1′-biphenyl)[(2-(2-aminoethyl)phenyl)palladium(ii) chloride (83 mg, 0.12 mmol), and THF (2800 µl). The reaction was degassed with argon for 5 minutes. To the solution was added potassium phosphate tribasic (700 µl, 1.400 mmol) and the resulting solution was heated to 80°C overnight. The mixture was cooled, diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. Aqueous layers were back extracted once with ethyl acetate, combined organic layers were dried over Na2SO4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by Prep-HPLC (Acetonitrile/Water + 0.10% TFA 50-100%) to give the desired product as a colorless solid.

Chiral separation afforded two separate enantiomers: (Peak 1 - C-2a, 126.9 mg, 38%) (Peak 2 - C-2b, 136 mg, 41%) LCMS (ESI) calc'd for C_{33}H_{36}C_{1}N_{3}O_{5} [M+H]^+: 590, found: 590.

**Step 3: Preparation of (R or S)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-IH-indazol-3-yl)cyclohex-3-enecarboxylic acid (2A).**

To a vial was added tert-buty1 4-(l-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-IH-indazol-6-yl)cyclohex-3-enecarboxylate (peakl, C-2a, 126 mg, 0.214 mmol), DCM (1601 µl), TFA (534 µl) and the solution was allowed to stir for 2 hours. The reaction was concentrated and the residue was purified by Prep-HPLC (Acetonitrile/Water + 0.10% TFA 35-100%) to give the title compound as a colorless solid. (48 mg, 42%) LCMS (ESI) calc'd for C_{29}H_{28}C_{1}N_{3}O_{5} [M+H]^+: 534, found: 534. ^1H NMR (600 MHz, DMSO) δ 8.71 (s, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.05 (d, J = 7.7 Hz, 1H), 6.78 (s, 1H), 4.46 (s, 1H), 4.32-4.20 (m, 2H), 4.13 (d, J = 7.9 Hz, 1H), 3.88 (d, J = 8.4 Hz, 1H), 3.2 (s, 3H), 2.59-2.48 (m, 2H), 2.41-2.18 (m, 3H), 1.96 (d, J = 12.1 Hz, 1H), 1.72-1.51 (m, 2H), 0.86-0.48 (m, 4H).
Step 4: Preparation of \((S \text{ or } R)-4-(1-(2\text{-chloro-6-cyclopropylbenzoyl})-6-(3\text{-methoxyazetidine-1-carbonyl})-1H\text{-indazol-3-yl})\text{cyclohex-3-ene}c\text{arboxylic acid (2B)}\). Preparation was similar to that for the other enantiomeric ester (peak2, C-2b), and can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.

The following examples shown in Table 2 were made using the same procedures described for Example 2A and 2B, which can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.

Table 2

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Structure</th>
<th>LCMS [M+H]$^+$ Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>2C</td>
<td><img src="image" alt="Structure" /></td>
<td>548</td>
</tr>
<tr>
<td>(R or S)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-indazol-3-yl)-1-methylcyclohex-3-enecarboxylic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D</td>
<td><img src="image" alt="Structure" /></td>
<td>548</td>
</tr>
<tr>
<td>(S or R)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-indazol-3-yl)-1-methylcyclohex-3-enecarboxylic acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Example 3A and 3B: Preparation (R or S)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-lH-indazol-3-yl)cyclohex-3-enecarboxylic acid (3A) and (S or R)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-lH-indazol-3-yl)cyclohex-3-enecarboxylic acid (3B)

Scheme D

Step 1: Preparation of tert-butyl 4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-lH-indazol-3-yl)cyclohex-3-enecarboxylate (D-1).

To a vial was added (2-chloro-6-cyclopropyl phenyl)(4-fluoro-3-iodo-lH-indazol-l-yl)methanone (220 mg, 0.499 mmol), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (231 mg, 0.749 mmol), PdCl$_2$(dpff)-CH$_2$Cl$_2$ adduct (82 mg, 0.100 mmol), sodium carbonate (159 mg, 1.498 mmol), and THF (2496 µL). The reaction
was degassed with argon for 5 minutes. The reaction was then heated to 80°C overnight. The next morning the mixture was cooled, diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The aqueous layer was back extracted once with ethyl acetate, combined organics were dried with Na2SO4, filtered and the solvent was evaporated under reduced pressure. The residue was purified by Prep-HPLC (Acetonitrile/Water + 0.10% TFA 65-100%) to give the desired product as a brown solid. Chiral purification afforded two separate enantiomers. (Peak 1 - D-la, 26 mg, 10%) (Peak 2 - D-lb, 25 mg, 10%) LCMS (ESI) calc’d for C28H28ClFN2O3 [M+H]+: 495, found: 495.

Step 2: Preparation (R or S)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (3A) To a vial was added tert-butyl 4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylate (peak1, D-la, 26 mg, 0.053 mmol), DCM (2 mL), and TFA (0.202 mL, 2.63 mmol). The solution was stirred for two days. The reaction was concentrated and the residue was brought up in methanol, and submitted for Prep-HPLC purification (Acetonitrile/Water + 0.10% TFA) to give the product as a colorless solid. (7.6 mg, 33%) LCMS (ESI) calc’d for C24H20ClFN2O3 [M+H]+: 439, found: 439. 1H NMR (600 MHz, DMSO) δ 12.21 (s, 1H), 8.35 (s, 1H), 7.73 (s, 1H), 7.47 - 7.25 (m, 3H), 7.04 (s, 1H), 6.51 (s, 1H), 2.42 - 2.19 (m, 5H), 1.94 (s, 1H), 1.62 (s, 2H), 0.83 - 0.48 (m, 4H).

Step 4: Preparation (S or R)-4-(l-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (3B). Preparation was similar to that for the other enantiomeric ester (peak2, D-lb), and can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.

Example 4A: Preparation of 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3,3-difluoroazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid
**Scheme E**

**Step 1: Preparation of tert-Butyl 4-[(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3,3-difluoroazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylate (E-1).**

To a vial containing 3,3-difluoroazetidine hydrogen chloride salt (11.5mg, 0.089 mmol) dissolved in DMA (1.0mL) was added 3-(4-(tert-butoxycarbonyl)cyclohex-1-en-1-yl)-1-(2-chloro-6-(trifluoromethyl) benzoyl)-1H-indazole-6-carboxylic acid (30 mg, 0.055 mmol), N-ethyl-N-isopropylpropan-2-amine (0.050 ml, 0.055 mmol) and HATU (25mg, 0.066 mmol). The reaction mixture was stirred at room temperature overnight. The following morning the solvent was evaporated under reduced pressure and the material was carried into step 2 without purification. LCMS (ESI) calc’d for C$_{30}$H$_{28}$ClF$_5$N$_4$O$_4$ [M+H$^+$]: 624, found: 624.

**Step 2: Preparation of 4-[(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3,3-difluoroazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid (4A).**

Tert-Butyl 4-[(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3,3-difluoroazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylate (E-1) was dissolved in a 1:1 solution of DCM:TFA (0.5mL) and stirred at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure. DMSO (1.2mL) was added to dissolve the crude sample and the material was purified by mass triggered prep-HPLC (CH$_3$CN/H$_2$O) to obtain 17.9 mg
of the title compound. LCMS (ESI) calc’d for C_{26}H_{20}ClF_{5}N_{3}O_{4} [M+H]^+: 568, found: 568.

The following examples shown in **TABLE 3** were prepared following similar procedures described for **Examples 4A** in **Scheme E**, which can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.

**Table 3**

<table>
<thead>
<tr>
<th>IUPAC Name</th>
<th>Structure</th>
<th>LCMS [M+H]^+ Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>4B 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image" alt="Structure 4B" /></td>
<td>532</td>
</tr>
<tr>
<td>4C 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclopropyl(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image" alt="Structure 4C" /></td>
<td>546</td>
</tr>
<tr>
<td>4D 4-(6-(azetidine-1-carbonyl)-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td><img src="image" alt="Structure 4D" /></td>
<td>532</td>
</tr>
<tr>
<td>4E</td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>---------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image1" alt="Chemical Structure 4E" /></td>
<td>562</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4F</th>
<th>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(pyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image2" alt="Chemical Structure 4F" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4G</th>
<th>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image3" alt="Chemical Structure 4G" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4H</th>
<th>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((R)-2-methylpyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image4" alt="Chemical Structure 4H" /></td>
</tr>
<tr>
<td></td>
<td>Molecule Structure</td>
</tr>
<tr>
<td>---</td>
<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>4I</td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-methoxypyrrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid</td>
</tr>
<tr>
<td>4J</td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid</td>
</tr>
<tr>
<td>4K</td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(cyclohexyl(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid</td>
</tr>
<tr>
<td>4L</td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(morpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>4M</strong></td>
<td><img src="image" alt="Molecule Image" /></td>
</tr>
<tr>
<td><strong>4N</strong></td>
<td><img src="image" alt="Molecule Image" /></td>
</tr>
<tr>
<td><strong>4O</strong></td>
<td><img src="image" alt="Molecule Image" /></td>
</tr>
<tr>
<td><strong>4P</strong></td>
<td><img src="image" alt="Molecule Image" /></td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>4Q</strong></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((R)-3-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
</tr>
<tr>
<td><strong>4R</strong></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-2-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
</tr>
<tr>
<td><strong>4S</strong></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2-hydroxyethyl)(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
</tr>
<tr>
<td><strong>4T</strong></td>
<td>4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(isopropylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>4U</strong></td>
<td><img src="4U_image" alt="" /></td>
</tr>
<tr>
<td><strong>4V</strong></td>
<td><img src="4V_image" alt="" /></td>
</tr>
<tr>
<td><strong>4W</strong></td>
<td><img src="4W_image" alt="" /></td>
</tr>
<tr>
<td><strong>4X</strong></td>
<td><img src="4X_image" alt="" /></td>
</tr>
</tbody>
</table>
4Y
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(piperidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid

4Z
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(((1-hydroxy-3-(methylamino)propan-2-yl)oxy)carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid

4AA
Enantiomer 1: 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-3-methoxypyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid

4AB
Enantiomer 2: 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((R)-3-methoxypyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-ene carboxylic acid
Example 5A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indol-3-yl)cyclohex-3-enecarboxylic acid

**Step 1: Preparation of 4-fluoro-l-tosyl-lH-indole** (F-1).
To a flask was added 4-fluoro-lH-indole (1000 mg, 7.40 mmol), sodium hydride (326 mg, 8.14 mmol), and DMF (14.8 mL). The solution was allowed to stir at room temperature for 30 min. 4-methylbenzene-1-sulfonyl chloride (2116 mg, 11.10 mmol) was then added to the flask and the resulting solution was allowed to stir for 3 hours. The mixture was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The combined aqueous layer was back extracted once with ethyl acetate, combined organic layers were dried with Na₂SO₄, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 0-75%) to give the desired product as a colorless solid. (1.76 g, 82%) LCMS (ESI) calc'd for C₁₅H₁₂FN₂O₂S [M+H]⁺: 290, found: 290.
Step 2: Preparation of 3-bromo-4-fluoro-l-tosyl-lH-indole (F-2).
To a flask was added 4-fluoro-l-tosyl-lH-indole (F-1) (784 mg, 2.71 mmol) and DCM (8 mL) and the reaction was cooled to 0°C. A solution of bromine (0.154 mL, 2.98 mmol) in DCM (8 mL) was added dropwise and the resulting solution was allowed to stir for 1 hour. The mixture was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The combined aqueous layer was back extracted once with ethyl acetate, and the combined organics were dried over Na2S04, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 0-75%) to give the desired product as a colorless solid. (217 mg, 53%) LCMS (ESI) calc’d for C19H22FNO2 [M-tBu]+: 260, found: 260.

Step 3: Preparation of tert-butyl 4-(4-fluoro-l-tosyl-lH-indol-3-yl)cyclohex-3-ene carboxylate (F-3).
To a flask was added 3-bromo-4-fluoro-l-tosyl-lH-indole (F-2) (471 mg, 1.279 mmol), (2-dicyclohexylphosphino-2’,4’,6’-trisopropyl-lr-biphenyl)[2-(2-aminoethyl)phenyl]palladium (II) chloride (94 mg, 0.128 mmol), THF (639 ε) and the vial was thoroughly degassed with argon. Potassium phosphate tribasic (2558 μ, 2.56 mmol) was added and the reaction was heated to 80°C and allowed to stir overnight. The mixture was cooled, diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The combined aqueous layer was back extracted once with ethyl acetate, and the combined organics were dried over Na2S04, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 10-75%) to give the desired product as a colorless solid. LCMS (ESI) calc’d for C26H28FNG4S [M-tBu]+: 414, found: 414.

Step 4: Preparation of tert-butyl 4-(4-fluoro-lH-indol-3-yl)cyclohex-3-ene carboxylate (F-4).
To a flask was added tert-butyl 4-(4-fluoro-l-tosyl-lH-indol-3-yl)cyclohex-3-ene carboxylate (F-3) (550 mg, 1.171 mmol), THF (3904 μ), ethanol (7809 μ) and KOH (657 mg, 11.71 mmol) and the reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was diluted with methanol and filtered. The resulting solution was concentrated and the residue was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The combined aqueous layer was back extracted once with ethyl acetate, and the combined organics were dried with Na2S04, filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 10-75%) to give the desired product as a colorless solid. (217 mg, 53% over two steps) LCMS (ESI) calc’d for C19H22FNO2 [M-tBu]+: 260, found: 260.
Step 5: Preparation of tert-butyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indol-3-yl)cyclohex-3-enecarboxylate (F-5).

To a vial was added tert-butyl 4-(4-fluoro-lH-indol-3-yl)cyclohex-3-enecarboxylate (F-4) (58 mg, 0.184 mmol), and DMF (1839 µl), followed by sodium hydride (8.83 mg, 0.221 mmol) portionwise. The reaction was stirred for 30 min at room temperature. 2-chloro-6-(trifluoromethyl)benzoyl chloride (53.6 mg, 0.221 mmol) was added dropwise to the solution and the resulting mixture was stirred for an additional hour. The mixture was diluted with ethyl acetate, washed 2x with aqueous sodium hydrogen carbonate and 1x with brine. The combined aqueous layer was back extracted once with ethyl acetate, and the combined organics were dried with Na2SO4, filtered, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/Hexane 10-75%) to give the desired product. (93 mg, 98%) LCMS (ESI) calc'd for C27H24ClF4N3O3 [M-tBu]+: 466, found: 466.

Step 6: Preparation of 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indol-3-yl)cyclohex-3-enecarboxylic acid (5A).

To a vial was added tert-butyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indol-3-yl)cyclohex-3-enecarboxylate (F-5) (90 mg, 0.172 mmol), DCM (1724 µl), and TFA (332 µl, 4.31 mmol); the solution was stirred at room temperature for 2 hours. The reaction was concentrated and the residue was purified by Prep-HPLC (Acetonitrile/Water + 0.10% TFA 60-95%) to obtain the desired product as a colorless solid. (41 mg, 51%) LCMS (ESI) calc'd for C23H16ClF4NO3 [M+H]+: 466, found: 466. H NMR (600 MHz, DMSO) δ 8.31 (d, J = 8.2, 1H), 8.00 (d, J = 8.2, 1H), 7.96 (d, J = 8.1, 1H), 7.84 (t, J = 8.1, 1H), 7.49 - 7.41 (m, 1H), 7.23 - 7.16 (m, 1H), 7.04 (d, J = 3.6, 1H), 5.90 (s, 1H), 2.36 - 2.13 (m, 5H), 2.00 - 1.91 (m, 1H), 1.65 - 1.52 (m, 1H).

Example 6A and 6B: Preparation of 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-2-hydroxycyclohex-3-enecarboxylic acid (6A) and 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-6-hydroxycyclohex-3-enecarboxylic acid (6B)
Step 1. Preparation of \(1-\{(1-2\text{-chloro}-6\text{-}(\text{trifluoromethyl})\text{benzoyl})-4\text{-fluoro-}1H\text{-indazol-3-yl}\}\)prop-2-en-l-one (G-1).

To a solution of \(1-(2\text{-chloro}-6\text{-}(\text{trifluoromethyl})\text{benzoyl})-4\text{-fluoro-N-methoxy-N-methyl-}1H\text{-indazole-3-carboxamide}\) (3.2 g, 7.44 mmol) in THF (32 mL) was added vinylmagnesium bromide (26 mL, 26 mmol) under \(N_2\) at 10-20°C. After 15-20 mins, the mixture was poured into a mixture of ice and aqueous HC1. Extracted with DCM (500 mLx5) and the combined organic phase was washed with brine and dried over \(\text{Na}_2\text{SO}_4\). The crude product was purified with column chromatography \((\text{PE : DCM} = 3 : 1)\) to give the title compound \((2.5 \text{ g}, \text{yield: 74}\%)\) as a white solid. LCMS (ESI): calc'd for \(\text{C}_{18}\text{H}_{12}\text{ClF}_4\text{N}_2\text{O}_2 \{\text{M+H}\}^+\): 397, found: 397;

Step 2. Preparation of ethyl \(4-\{(1-2\text{-chloro}-6\text{-}(\text{trifluoromethyl})\text{benzoyl})-4\text{-fluoro-}1H\text{-indazol-3-yl}\}\)-2-oxocyclohex-3-enecarboxylate (G-2a) and ethyl \(4-\{(1-2\text{-chloro}-6\text{-}(\text{trifluoromethyl})\text{benzoyl})-4\text{-fluoro-}1H\text{-indazol-3-yl}\}\)-6-oxocyclohex-3-enecarboxylate (G-2b).

To a solution of \(1-(1-2\text{-chloro}-6\text{-}(\text{trifluoromethyl})\text{benzoyl})-4\text{-fluoro-}1H\text{-indazol-3-yl\})\)prop-2-en-l-one (G-1) (2.35 g, 6.43 mmol) in EtOH (306 mL) was added ethyl 3-oxobutanoate (837 mg, 6.43 mmol) and EtONa (437 mg, 6.43 mmol) while stirring under \(N_2\). The reaction was heated to 80°C for 10 hours, and then concentrated to remove EtOH. The residue was diluted with \(H_2O\) and extracted with EtOAc (500 mLx5). The combined organic phase was washed
with brine and dried over Na₂SO₄. The crude product was purified by column chromatography (PE : EA = 50 : 1, 30 : 1 to 10 : 1) to give the title compound (G-2a) (600 mg, yield: 18%) as colorless oil and (G-2b) (300 mg, yield: 9%) as a white solid. LCMS (ESI): calc'd for C₂₄H₁₇ClF₄N₂O₄ [M+H]⁺: 509, found: 509;

Step 3. Preparation of ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxycyclohex-3-enecarboxylate (G-3).
To a solution of ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-oxocyclohex-3-enecarboxylate (G-2) (285 mg, 0.56 mmol) in MeOH (5 mL) was added CeCl₃·7H₂O (1.0 g, 2.80 mmol) and NaBH₄ (66 mg, 1.75 mmol) at 0 °C under N₂. The mixture was stirred for 0.5 h and then quenched with H₂O, and extracted with EtOAc (50 mLx5). The combined organics were washed with brine and dried over Na₂SO₄. The crude product was purified by prep-TLC (PE : EA = 3 : 1) to give the title compound (260 mg, yield: 90%) as a colorless oil. LCMS (ESI): calc'd for C₂₄H₁₇ClF₄N₂O₄ [M+H]⁺: 511, found: 493;

Step 4. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxycyclohex-3-enecarboxylic acid (6A).
To a solution of ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxycyclohex-3-enecarboxylate (G-3) (60 mg, 0.12 mmol) in THF/H₂O (3 mL/1 mL) was added LiOH·H₂O (25 mg, 0.59 mmol) under N₂. The reaction was stirred at 20 °C for 10 hours and was then quenched with H₂O and extracted with EtOAc (50 mLx3). The combined organics were washed with brine and dried over Na₂SO₄. The product was purified to give the title compound as a white solid (40 mg, yield: 71%) with prep-TLC (PE : EA = 1 : 1).
LCMS (ESI): calc'd for C₂₂H₁₅ClF₄N₂O₄ [M+H]⁺: 483, found: 465; 1H-NMR (400 MHz, Methanol-δ) δ 8.38 (1H, d, J = 8.0 Hz), 7.72-7.85 (4H, m), 7.23-7.28 (1H, m), 6.70 (0.6H, s), 6.60 (0.4H, s), 4.59-4.62 (1H, m), 1.81-2.66 (5H, m).

Step 5. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6-hydroxycyclohex-3-enecarboxylic acid (6B). Preparation from the other regioisomer G-2b was similar to the preparation of 6A, and can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.

The following example shown in TABLE 4 was prepared following similar procedures described for Example 6A and 6B in Scheme G, which can be achieved by those of ordinary skill in the art of organic synthesis in light of the present disclosure.
### Table 4

<table>
<thead>
<tr>
<th>Chemical Name</th>
<th>Structure</th>
<th>LCMS [M+H]^+ Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>6C</td>
<td>![Structure Image]</td>
<td>479</td>
</tr>
</tbody>
</table>

Example 7A, 7B and 7C: Preparation of 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2-hydroxy-6-methylcyclohex-3-enecarboxylic acid (7A)

Scheme H

![Scheme Image]
Step 1. Preparation of (3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-4-fluoro-1H-indazol-1-yl)-(2-chloro-6-(trifluoromethyl)phenyl)methanone (H-1).

To a solution of compound 3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-4-fluoro-1H-indazole (300 mg, 0.8 mmol) in 10 mL of THF, was added NaH (39 mg, 1.0 mmol, 60% in mineral oil) at 0 °C. The mixture was stirred at 15 °C for 30 min. 2-chloro-6-(trifluoromethyl)benzoyl chloride (212 mg, 0.9 mmol) in 5 mL of THF was added dropwise at 0 °C. The mixture was stirred at 15 °C for 2h, poured into water (150 mL) and extracted with EtOAc (100 mLx3). The combined organic layer was washed with brine (100 mLx2), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (PE: EtOAc = 100:1 to PE: EtOAc = 20:1) to afford the title compound (400 mg, 86.4%) as a yellow solid. LCMS (ESI): calc'd for C29H35ClF4N2O2Si [M+H]+: 583, found: 583.

Step 2. Preparation of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-(4-(hydroxyl methyl)-1-methylcyclohexyl)-1H-indazol-1-yl)methanone (H-2).

To a solution of compound 3-(4-(((tert-butyldimethylsilyl)oxy)methyl)-1-methylcyclohexyl)-4-fluoro-1H-indazol-1-yl)(2-chloro-6-(trifluoromethyl)phenyl)methanone (H-I) (360 mg, 0.6mmol) in 10 mL of THF was added TBAF (323 mg, 1.2 mmol) dropwise, while cooling the reaction to 0 °C. The mixture was stirred at 15 °C for 24 h. The resulting mixture was poured into 100 mL of water and extracted with EtOAc (200 mL x 3). The combined organics were washed with brine (100 mL x 2), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (PE: EtOAc = 100:1 to PE: EtOAc = 1:1) to afford the title compound (250 mg, 86 %) as a yellow oil. LCMS (ESI): calc'd for C23H23ClF4N2O2 [M+H]+: 469, found: 469;

Step 3. Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-methylcyclohexanecarboxylic acid (7A).

To a solution of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-(4-(hydroxymethyl)-1-methylcyclohexyl)-1H-indazol-1-yl)methanone (H-2) (100 mg, 0.2 mmol) in acetone (10 mL) was added dropwise 0.2 mL of Jones reagent, while cooling to 0 °C. The mixture was stirred at 15 °C for 20 min. The resulting mixture was quenched with 10 mL of propan-2-ol, diluted with 100 mL of water and extracted with EtOAc (100 mLx3). The organic layer was washed with brine (100 mLx2), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (PE: EtOAc = 100:1 to PE: EtOAc = 5:1) to afford the title compound (76 mg, 75 %) as a white solid. LCMS (ESI): calc'd for C23H19ClF4N2O3 [M+H]+: 483, found: 483; H NMR (400 MHz, CDCl3) δ 1.27-1.47
Further separation by SFC afforded two isomers:

(\textit{trans})-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-methyl
cyclohexanecarboxylic acid (7B) and (\textit{cis})-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-
fluoro-1H-indazol-3-yl)-4-methylcyclohexanecarboxylic acid (7C)

Example 8A and 8B: Preparation of (\textit{trans})-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-
4-fluoro-1H-indazol-3-yl)cyclohexanecarboxylic acid (8A) and (\textit{cis})-4-(1-(2-chloro-6-
(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohexanecarboxylic acid (8B).

\textbf{Scheme 1}

\textbf{Step 1. Preparation of (Racemic) ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-
fluoro-1H-indazol-3-yl)cyclohexanecarboxylate} (1-1).

To a solution of (Racemic) ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-
indazol-3-yl)cyclohex-3-enecarboxylate (100 mg, 0.2 mmol) in ethyl acetate (20 mL) was added 10\% Pd/C (20 mg) while stirring under nitrogen. The suspension was degassed and
purged with \(\frac{3}{4}\) several times, and then stirred under \(\frac{3}{4}\) (balloon) at 40 °C for 4 h. The
resulting mixture was filtered over Celite, rinsing with ethyl acetate (50 mL). The combined
organic layers were concentrated \textit{in vacuo} to dryness to give the crude product, which was
further purified by column chromatography on silica gel (PE: EtOAc = 10:1) to afford the
title compound (60 mg, 60\%) as a colorless oil. LCMS (ESI) calc’d for C_{24}H_{21}ClF_{4}N_{2}O_{3}
Step 2. Preparation of (trans)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)cyclohexanecarboxylic acid (8A) and (cis)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)cyclohexanecarboxylic acid (8B).

To a mixture of (Racemic) ethyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)cyclohexanecarboxylate (1-1) (150 mg, 0.30 mmol) in EtOH (5 mL) was added LiOH (22 mg, 0.91 mmol). The reaction was stirred at 20 °C for 4 h. The resulting mixture was concentrated in vacuo and water (15 mL) was added. The aqueous solution was washed with ethyl acetate (15 mL), and acidified with 2 M HCl to pH = 2. The precipitate was collected by filtration to give the crude product (70 mg, cis: trans = 3:1) as a white solid, which was separated by prep-HPLC (acetonitrile + 0.75% trifluoroacetic acid in water) to afford two isomers:

(i trans)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)cyclohexanecarboxylic acid (8A) (2 mg). LCMS (ESI) calc'd for C_{22}H_{17}ClF_{4}N_{2}O_{3} [M+H]^{+}: 469, found: 469. H NMR (400MHz, CDCl_{3}) δ 8.35 (1H, d, J = 8.53 Hz), 7.67-7.70 (2H, m), 7.55-7.60 (2H, m), 7.06-7.1 (1H, m), 3.04-3.09 (1H, m), 2.35-2.40 (1H, t, J = 11.2 Hz), 2.10 (4H, br s.), 1.51-1.64 (4H, m).

(cis)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)cyclohexanecarboxylic acid (8B) (6 mg). LCMS (ESI) calc'd for C_{22}H_{17}ClF_{4}N_{2}O_{3} [M+H]^{+}: 469, found: 469. H NMR (400MHz, CDCl_{3}) δ 8.35 (1H, d, J = 8.28 Hz), 7.37 -7.74 (4H, m), 6.92 - 7.13 (1H, m), 3.37 (1H, br s.), 2.52 (1H, br s.), 1.76-2.00 (6H, m), 1.66 (2H, d, J = 4.52 Hz).

Example 9A and 9B: Preparation of (trans)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-l-methylcyclohexanecarboxylic acid (9A) and (cis)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-l-methylcyclohexanecarboxylic acid (9B)
Step 1: Preparation of ethyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylate (J-l).

To a cis/trans mixture of ethyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohex-3-enecarboxylic acid (300 mg, 0.606 mmol) in EtOAc (30 mL) was added Pd/C (6.5 mg, 0.061 mmol) while stirring under nitrogen. The suspension was degassed in vacuo and purged with H₂ several times, and then stirred under H₂ (balloon) at 40°C for 4 h. The resulting mixture was filtered over a Celite pad, rinsing with ethyl acetate (50 mL). The combined filtrates were concentrated in vacuo to dryness. The crude product was purified by column chromatography on silica gel (ethyl acetate/ petroleum ether = 1/10) to afford the title compound (150 mg, yield: 47.3%) as a colorless oil. LCMS (ESI) calc'd for C₂₅H₂₃ClF₄N₂O₃ [M+H]^+: 511, found: 511.

Step 2: Preparation of (trans)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylic acid (9A) and (cis)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylic acid (9B).

To a mixture of ethyl 4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylate (J-l) (100 mg, 0.196 mmol) in EtOH (10 mL) was added NaOH (24 mg, 0.59 mmol) and the reaction was stirred at 40°C for 12 h. The resulting mixture was concentrated in vacuo, diluted with water (10 mL), and washed with ethyl acetate (10 mL×2). The aqueous layer was acidified with 2 M HCl to pH = 2. The precipitate was collected by filtration and purified by preparative HPLC (acetonitrile + 0.75% trifluoroacetic acid in water) to give two separate isomers:

(trans)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylic acid (9A): 5 mg, LCMS (ESI) calc'd for C₂₅H₁₉ClF₄N₂O₃ [M+H]^+: 483, found: 483; ¹H NMR (400 MHz, CDC₁₃) δ 8.35 (1H, d, J=8.03 Hz), 7.69 (2H, m), 7.53-7.63 (2H, m), 6.91-7.16 (1H, m), 3.21 (1H, br.s.), 1.72-1.96 (6H, m), 1.61 (2H, br.s.), 1.18 (3H, s).

(cis)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-l-methylocyclohexanecarboxylic acid (9B): 6 mg, LCMS (ESI) calc'd for C₂₅H₁₉ClF₄N₂O₃ [M+H]^+: 483, found: 483; ¹H NMR(400 MHz, CDC₁₃) δ 8.35 (1H, d, J=8.53 Hz), 7.60-7.69 (2H, m), 7.47 - 7.60 (2H, m), 6.95-7.10 (1H, m), 3.50 (1H, s), 2.82-3.15 (1H, m), 2.28 (2H, J=13.05 Hz, d), 1.92 (2H, d, J=12.55 Hz), 1.67 (1H, t, J=10.29 Hz), 1.28-1.38 (2H, m), 1.27 (3H, s).

Example 10A and 10B: Preparation of (R and S)-4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylocyclohex-3-ene carboxylic acid...
(10A) and (R and S) 4-[(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylic acid (10B).

**Scheme K**

**Step 1: Preparation of mixture of methyl 2,2-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate and methyl 6,6-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (K-1).**

To a solution of methyl 2,2-dimethyl-4-oxocyclohexanecarboxylate (1.5 g, 8.14 mmol) in THF (15 mL), was added dropwise LDA (10 mL, 10 mmol) at -78 °C for 15 min. Tf$_2$NPh (3.78 g, 10.6 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h and stirred at 20 oC for additional 10 h. The resulting mixture was quenched with 30 mL of saturated aqueous NH$_4$Cl and extracted with ethyl acetate (15 mLx2). The combined organic fractions were washed with brine (saturated, 10mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/20) to give the title compounds (ratio = 1:6, 1 g, yield: 34.9%) as yellow oils.

**Step 2: Preparation of mixture of methyl 2,2-dimethyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate and methyl 6,6-dimethyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (K-2).**

To a mixture of methyl 2,2-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate and methyl 6,6-dimethyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-
enececarboxylate (K-1, ratio = 1:6, 900 mg, 2.85 mmol) in 1,4-dioxane (50 mL) was added Bis(pinacolato)diboron (723 mg, 2.85 mmol) and potassium acetate (838 mg, 8.54 mmol). The mixture was purged with nitrogen for 20 minutes, and PdCl$_2$(dppf)-CH$_2$Cl$_2$ (697 mg, 0.854 mmol) and dppf (4732 mg, 8.54 mmol) were added. The mixture was stirred at 100 °C for 2 h. The resulting mixture was filtered over a Celite pad and the filtrate was diluted with water (50 mL) and extracted with ethyl acetate (50 mLx3). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/20) to give the title compound (ratio = 1:6, 400 mg, yield: 43%) as a yellow oil. LCMS (ESI) calc'd for C$_{19}$H$_{27}$B$_{2}$O$_{4}$ [M+H]$^+$. 295, found: 295.

**Step 3: Preparation of mixture of methyl 4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylcyclohex-3-enecarboxylate and methyl 4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylate (K-3).**

To a solution of (2-chloro-6-( trifluoromethyl)phenyl)(4-fluoro-3-iodo-1H-indazol-1-yl)methanone (510 mg, 1.088 mmol) in THF/H$_2$O (40 mL/10mL) was added a mixture of methyl 2,2-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate and methyl 6,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (K-2, ratio = 1:6, 400 mg, 1.36 mmol) and Na$_2$CO$_3$ (432 mg, 4.08 mmol). The mixture was purged with nitrogen for 20 minutes, Pd(dppf)Cl$_2$ (298 mg, 0.408 mmol) was added and the mixture was stirred at 80 °C for 10 h. The resulting mixture was filtered over a Celite pad, and the filtrate was diluted with water (40 mL) and extracted with ethyl acetate (60 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10) to give the title compound (ratio: 1:6, 191 mg, yield: 26.4 %) as a yellow oil. LCMS (ESI) calc'd for C$_{25}$H$_{35}$ClF$_4$N$_2$O$_3$ [M+H]$^+$: 509, found: 509.

**Step 4: Preparation of (R and S)-4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylcyclohex-3-enecarboxylic acid (10A) and (R and S)-4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylic acid (10B).**

A mixture of methyl 4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylcyclohex-3-enecarboxylate, methyl 4-(l-(2-chloro-6-( trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylate (K-3, ratio = 1:6, 200 mg, 0.39 mmol), NaOH (47.2 mg, 1.18 mmol) and methanol (10 mL) was stirred at 40 °C for 10
The resulting mixture was concentrated *in vacuo*, diluted with water (10 mL) and washed with ethyl acetate (10 mLx2). The aqueous layer was acidified with 2 M HCl to pH = 2. The precipitate was collected by filtration and dried *in vacuo*. The desired product was purified by prep-HPLC (acetonitrile + 0.75% trifluoroacetic acid in water) to give two separate isomers:

(R and S)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-dimethylcyclohex-3-enecarboxylic acid (10A): 5 mg. LCMS (ESI) calc’d for C_{24}H_{19}ClF_{4}N_{2}O_{3} [M+H]^+: 495, found: 495; H NMR (400 MHz, CDC1₃) δ 8.43 (1H, d, J = 8.53 Hz), 7.65-7.75 (2H, m), 7.51-7.64 (2H, m), 7.11 (1H, dd, J = 11.04, 8.03 Hz), 6.57 (1H, br.s.), 2.48-2.55 (2H, m), 2.23 (2H, d, J = 8.03 Hz), 1.08 (3H, s), 2.18 (1H, s), 1.02 (3H, d, J = 3.01 Hz).

(R and S)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-dimethylcyclohex-3-enecarboxylic acid (10B): 20 mg, LCMS (ESI) calc’d for C_{24}H_{19}ClF_{4}N_{2}O_{3} [M+H]^+: 495, found: 495; H NMR (400 MHz, CDC1₃) δ 8.43 (1H, d, J = 8.53 Hz), 7.65-7.74 (2H, m), 7.52-7.63 (2H, m), 7.11 (1H, dd, J = 10.54, 8.03 Hz), 6.37 (1H, br.s.), 2.44-2.60 (2H, m), 2.14-2.28 (3H, m), 1.08 (3H, s), 1.02 (3H, d, J = 3.01 Hz).

Example 11A and 11B: Preparation of (trans)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid (11A) and (cis)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid (11B).
Step 1: Preparation of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-enecarboxylate (L-1).
To a mixture of (2-chloro-6-(trifluoromethyl)phenyl)(3-iodo-IH-pyrazolo[4,3-b]pyridin-1-yl)methanone (1 g, 2.2 mmol) and ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (0.8 g, 2.8 mmol) in 40 mL of toluene/EtOH (1:1), was added 1.6 mL of a saturated Na₂CO₃ solution and Pd(dppf)Cl₂·CH₂Cl₂ (182 mg, 0.22 mmol) while stirring under N₂. The reaction mixture was heated to 120 °C for 6 h. Upon completion, the mixture was filtered and the organic layer was concentrated *in vacuo*. The product was purified by silica gel chromatography, eluting with PE:EA=100:1 to PE:EA=10:1 to afford the title compound (500 mg, 47%) as a yellow solid. LCMS (ESI) calc'd for C₂₃H₁₆ClF₃N₃O₃ [M+H]⁺: 478, found: 478.

Step 2: Preparation of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylate (L-2).
To a solution of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-enecarboxylate (L-1) (500 mg, 1.05 mmol) in EtOAc (30 mL), was added Pd/C (50 mg). The resulting reaction mixture was stirred under H₂ (1 atm) for 24 h at 40 °C. The reaction mixture was filtered, and the filtrate was evaporated to give the title compound (500 mg, yield: 99%) as a yellow oil. LCMS (ESI) calc'd for C₂₃H₂₀iClF₃N₃O₃ [M+H]⁺: 480, found: 480.

Step 3: Preparation of (trans)-4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid (11A) and (cis)-4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylic acid (11B).
To a solution of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-IH-pyrazolo[4,3-b]pyridin-3-yl)cyclohexanecarboxylate (L-2) (500 mg, 1.04 mmol) in 10 mL of THF/H₂O (4:1) was added lithium hydroxide monohydrate (175 mg, 4.16 mmol). The reaction mixture was stirred for 24 h at 30 °C. Upon completion, the reaction was diluted with 10 mL of water and extracted with PE (200 mL x 2). The aqueous layer was acidified with 2 M HCl to pH = 3, then extracted with EtOAc (300 mL x 3). The combined organics were washed with brine (200 mL x 2), dried over Na₂SO₄ and concentrated to afford product (300 mg, 64%>) as a yellow solid, which was further separated by SFC to afford two separate isomers (Column: Chiralcel OJ-H 250x4.6mm I.D., 5um ; Mobile phase: ethanol (0.05% DEA) in C0₂ from 5% to 40%) to give two isomers, LCMS (ESI) calc'd for C₂₁H₁₅ClF₃N₃O₃ [M+H]⁺: 452, found: 452:
(irans)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexane carboxylic acid (11A): 1H NMR (400 MHz CDCl₃) δ 8.91 (1H, J = 8.54 Hz, d), 8.83 (1H, d, J = 4.02 Hz), 7.62-7.72 (3H, m), 7.48-7.59 (1H, m), 3.51 (1H, br. s.), 2.55 (1H, br. s.), 1.86-2.01 (6H, m), 1.66-1.76 (2H, m).

cis)-4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohexane carboxylic acid (11B): 1H NMR (400 MHz CDCl₃) δ 8.75-8.83 (2H, m), 7.67-7.72 (2H, m), 7.60 (1H, d, J = 8.04 Hz), 7.54 (1H, dd, J = 8.54, 4.52 Hz), 3.13-3.23 (1H, m), 2.38-2.49 (1H, m), 2.10-2.19 (4H, m), 1.59-1.74 (4H, m).

Example 12A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-5-methylcyclohex-3-enecarboxylic acid

Scheme M

Step 1: Preparation of ethyl 3-methyl-4-oxocyclohexanecarboxylate (M-1).
To a solution of ethyl 4-oxocyclohexanecarboxylate (10 g, 58 mmol) in THF (100 mL) was added LiHMDS (65 mL, 65 mmol) portionwise, while stirring at -78 °C under N₂. After stirring for 1 h, iodomethane (8.34 g, 58 mmol) was added dropwise. The mixture was stirred at ambient temperature for 2 h. The mixture was diluted with water (150 mL) and extracted with EtOAc (100 mL x 3). The combined organics were washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by silica gel chromatography, eluting with PE:EA = 30:1 to afford the title compound (4 g, yield: 37%). LCMS (ESI) calc'd for C₁₀H₁₀O₃ [M+H]+: 185, found: 185.
Step 2: Preparation of ethyl 5-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (M-2).

To a solution of ethyl 3-methyl-4-oxocyclohexanecarboxylate (M-1) (5 g, 27 mmol) in THF (60 mL) was added LDA (13.5 mL, 2.5M in THF, 27 mmol) portionwise while stirring at 0 °C under N₂. After stirring for 1 h, PhNTf₂ (9.64 g, 27 mmol) was added dropwise. The mixture was stirred at ambient temperature for 12 h. The mixture was quenched with water (150 mL) and extracted with EtOAc (50 mL x 3). The combined organic layer was washed with brine, dried over Na₂SO₄ and evaporated. The residue was purified by silica gel chromatography, eluting with PE:EA = 100:1 to afford the title compound (5 g, yield: 63%).


Step 3: Preparation of ethyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (M-3).

To a mixture of ethyl 5-methyl-4-(((trifluoromethyl)sulfonyl)oxy)cyclohex-3-enecarboxylate (M-2) (3.0 g, 9.5 mmol), (Bpin)₂ (2.65 g, 10.4 mmol), KOAc (2.8 g, 28.5 mmol), and Dioxane (50 mL) was added Pd(dppf)Cl₂CH₂Cl₂ (700 mg) while purging with nitrogen. The mixture was heated at 100 °C for 3 h. The solution was cooled and filtered over Celite. The solution was evaporated and purified by column chromatography on silica gel (PE:EA = 200:1) to give the title compound (1 g, yield: 36%). LCMS (ESI) calc’d for C₁₀H₂₇B₄O₄ [M+H]⁺: 295, found: 295.

Step 4: Preparation of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-5-methylcyclohex-3-enecarboxylate (M-4).

A solution of (2-chloro-6-(trifluoromethyl)phenyl)(4-fluoro-3-iido-lH-indazol-1-yl)methanone (2.2 g, 4.6 mmol), ethyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-enecarboxylate (M-3) (1.5 g, 5.1 mmol), Pd(dppf)Cl₂CH₂Cl₂ (340 mg) and Cs₂CO₃ (4.5 g, 13.8 mmol) in THF (30 mL) under N₂ was stirred at 100 °C for 4 h. After 4 hours, the reaction was filtered, and the filtrate was concentrated and purified by column chromatography (PE:EA = 50:1) to give the title compound (1.4 g, yield: 61%). LCMS (ESI) calc’d for C₂₅H₂₁ClF₄N₂0₃ [M+H]⁺: 509, found: 509.

Step 5: Preparation of 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-5-methylcyclohex-3-enecarboxylic acid (12A).

A solution of ethyl 4-((1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-lH-indazol-3-yl)-5-methylcyclohex-3-enecarboxylate (M-4) (100 mg, 0.2 mmol) and LiOH.H₂O (34 mg, 0.8 mmol) in THF/H₂O (3/1 mL) was stirred at room temperature overnight. The next morning the reaction was concentrated, and the residue was diluted with 15 mL of water and acidified
with 1 M HCl to pH = 3-4; was then extracted with EA. The combined organics were washed with brine (200 mL x 2), dried over Na₂SO₄ and concentrated. The residue was purified by prep-TLC to give the title compound as a racemate (50 mg, yield: 52%). LCMS (ESI) calc'd for C₂₃H₁₂ClF₄N₂O₃ [M+H]⁺: 481, found: 481; 1H-NMR (400 MHz, CDCl₃) δ 8.39-8.43 (1H, m), 7.56-7.68 (4H, m), 7.06-7.11 (1H, m), 6.21-6.51 (1H, m), 2.17-2.95 (5H, m), 1.38-1.58 (1H, m), 0.84-0.97 (3H, m).

Example 13A: Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-hydroxycyclohexanecarboxylic acid.

**Scheme N**

![Scheme N](image)

**Step 1:** Preparation of (trans or cis) ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-hydroxycyclohexanecarboxylate (N-la) and (cis or trans)-ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-hydroxycyclohexanecarboxylate (N-lb). To a solution of ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl) cyclohex-3-ene carboxylate (500 mg, 1 mmol) in THF (10 mL) was added BH₃·Me₂S (228 mg, 3 mmol). The reaction mixture was stirred at room temperature overnight. Then aq. NaOH (1 mL, 3M) solution and H₂O₂ (0.5 mL, 30%) was added. The reaction mixture was stirred at room temperature for 3 h. The mixture was extracted with EtOAc. The organic layer was washed with H₂O, brine, dried over Na₂SO₄ and concentrated. The crude product was purified by prep-HPLC (acetonitrile + 0.75% trifluoroacetic acid in water) to give the title compounds (Peak 1 - N-la, 70 mg, 27%) (Peak 2 - N-lb, 70 mg, 27%). LCMS (ESI) calc'd for C₂₄H₂₂ClF₄N₂O₄ [M+H]⁺: 513, found: 513.

**Step 2:** Preparation of 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-hydroxycyclohexanecarboxylic acid (13A). A solution of (cis or trans)-ethyl 4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-hydroxycyclohexanecarboxylate (Peak 2 - N-lb, 70 mg, 0.2 mmol) and LiOH·FLₐ (35 mg, 0.83 mmol) in THF/H₂O (3/1...
mL) was stirred at room temperature overnight. The mixture was concentrated, and the residue was diluted in 5 mL of water and acidified with 1 M HCl to pH = 3-4 and then extracted with EA. The combined organics were washed with brine (200 mL<sup> &gt; 2</sup>), dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by prep-TLC to give the title compound (10 mg, yield: 15 %). LCMS (ESI): calc'd for C<sub>2</sub>H<sub>7</sub>CIF<sub>4</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 485, found: 485; 1H-NMR (400 MHz CDCl<sub>3</sub>) δ 8.42 (1H, d, J = 8.4 Hz), 7.55-7.67 (4H, m), 7.11-7.16 (1H, m), 2.50-2.54 (1H, m), 2.33-2.38 (2H, m), 1.89-1.92 (2H, m), 1.68-1.76 (4H, m).

### 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<sub>2</sub>. This peptide mimics the recruitment of co-activators to RORgammaT through its interaction with the LXXLL (SEQ ID NO:1) (e.g., 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 RORgamma-Ligand Binding Domain TR-FRET Assay was run according to the following protocol.

**HIS-tagged RORgamma-LBD protein** was expressed in SF9 cells using a baculovirus expression system. The RORgamma-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 purifed RORgamma-LBD at 0.25 µg 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 KC1, 1 mM EDTA, 0.1 mM DTT) to obtain RORgamma-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) (SEQ ID NO:2) 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 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.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Fret IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>18</td>
</tr>
<tr>
<td>1B</td>
<td>21</td>
</tr>
<tr>
<td>1C</td>
<td>13</td>
</tr>
<tr>
<td>1D</td>
<td>774</td>
</tr>
<tr>
<td>1E</td>
<td>76</td>
</tr>
<tr>
<td>1F</td>
<td>170</td>
</tr>
<tr>
<td>1G</td>
<td>182</td>
</tr>
<tr>
<td>1H</td>
<td>20</td>
</tr>
<tr>
<td>1I</td>
<td>14</td>
</tr>
<tr>
<td>1J</td>
<td>7</td>
</tr>
<tr>
<td>1K</td>
<td>31</td>
</tr>
<tr>
<td>1L</td>
<td>123</td>
</tr>
<tr>
<td>2A</td>
<td>2</td>
</tr>
<tr>
<td>2B</td>
<td>2</td>
</tr>
<tr>
<td>2C</td>
<td>4</td>
</tr>
<tr>
<td>2D</td>
<td>5</td>
</tr>
<tr>
<td>3A</td>
<td>6</td>
</tr>
<tr>
<td>3B</td>
<td>5</td>
</tr>
<tr>
<td>4A</td>
<td>5</td>
</tr>
<tr>
<td>4B</td>
<td>143</td>
</tr>
<tr>
<td>4C</td>
<td>9</td>
</tr>
<tr>
<td>4D</td>
<td>177</td>
</tr>
<tr>
<td>4E</td>
<td>2</td>
</tr>
<tr>
<td>4F</td>
<td>30</td>
</tr>
<tr>
<td>4G</td>
<td>6</td>
</tr>
<tr>
<td>----</td>
<td>---</td>
</tr>
<tr>
<td>4H</td>
<td>115</td>
</tr>
<tr>
<td>4I</td>
<td>3</td>
</tr>
<tr>
<td>4J</td>
<td>24</td>
</tr>
<tr>
<td>4K</td>
<td>94</td>
</tr>
<tr>
<td>4L</td>
<td>36</td>
</tr>
<tr>
<td>4M</td>
<td>21</td>
</tr>
<tr>
<td>4N</td>
<td>3</td>
</tr>
<tr>
<td>4O</td>
<td>308</td>
</tr>
<tr>
<td>4P</td>
<td>41</td>
</tr>
<tr>
<td>4Q</td>
<td>380</td>
</tr>
<tr>
<td>4R</td>
<td>21</td>
</tr>
<tr>
<td>4S</td>
<td>40</td>
</tr>
<tr>
<td>4T</td>
<td>1116</td>
</tr>
<tr>
<td>4U</td>
<td>164</td>
</tr>
<tr>
<td>4V</td>
<td>31</td>
</tr>
<tr>
<td>4W</td>
<td>3</td>
</tr>
<tr>
<td>4X</td>
<td>3</td>
</tr>
<tr>
<td>4Y</td>
<td>159</td>
</tr>
<tr>
<td>4Z</td>
<td>258</td>
</tr>
<tr>
<td>4AA</td>
<td>7</td>
</tr>
<tr>
<td>4AB</td>
<td>8</td>
</tr>
<tr>
<td>5A</td>
<td>4</td>
</tr>
<tr>
<td>6A</td>
<td>2</td>
</tr>
<tr>
<td>6B</td>
<td>15</td>
</tr>
<tr>
<td>6C</td>
<td>5</td>
</tr>
<tr>
<td>7A</td>
<td>1879</td>
</tr>
<tr>
<td>7B</td>
<td>663</td>
</tr>
<tr>
<td>7C</td>
<td>872</td>
</tr>
<tr>
<td>8A</td>
<td>16</td>
</tr>
<tr>
<td>8B</td>
<td>505</td>
</tr>
<tr>
<td>9A</td>
<td>50</td>
</tr>
<tr>
<td>9B</td>
<td>5022</td>
</tr>
<tr>
<td>10A</td>
<td>343</td>
</tr>
<tr>
<td>10B</td>
<td>96</td>
</tr>
<tr>
<td>11A</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>11B</td>
<td>10000</td>
</tr>
<tr>
<td>12A</td>
<td>54</td>
</tr>
<tr>
<td>13A</td>
<td>2474</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound according to Formula I

\[ \text{I} \]

or a pharmaceutically acceptable salt or solvate thereof, wherein:

- \( a \) is a bond or no bond;
- \( X \) is \( \text{CH}_2, \text{C(O)}, \text{CR}^b \);
- \( Y \) is \( \text{CH}, \text{N}, \text{CR}^a \);
- \( n = 0, 1, 2, 3 \) or 4;
- \( A^4 \) is \( \text{CR}^4 \) or N,
- \( A^5 \) is \( \text{CR}^5 \) or N,
- \( A^6 \) is \( \text{CR}^6 \) or N,
- \( A^7 \) is \( \text{CR}^7 \) or N,

with the proviso that no more than two of \( A^4-A^7 \) can be N;

- \( R^a \) is \( (\text{Ci}_{-4}) \text{alkyl} \);
- \( R^b \) is \( (\text{Ci}_{-4}) \text{alkyl} \);
- \( R^1 \) is
  - (i) \( (\text{C}_3-\text{i,2}) \text{carbocyclyl} \); 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(\( \text{Ci}_{-\text{i,0}} \)alkyl), or carbamoyl;
- \( R^3 \) is hydrogen, halogen, cyano, nitro, hydroxy, \( (\text{Ci}_{-3}) \text{alkylC(0)O-}, \) \( (\text{Ci}_{-4}) \text{alkyl}, \) or \( (\text{C}_1-\text{i,2}) \text{carbocyclyl} \).
alkoxy, wherein (Ci-4)alkyl and (Ci-4)alkoxy are optionally substituted with one or more halogen;
R^4-R^7 independently are H, halogen, amino, cyano, hydroxy, (Ci-3)alkoxy, (Ci-4)alkyl, (Co-io)alkylaminocarbonyl, (di)(Ci-6)alkylaminocarbonyl or amino(Ci-4)alkyl, wherein (Ci-3)alkoxy, (Ci-4)alkyl, (C0-io)alkylaminocarbonyl, (di)(Ci-6)alkylaminocarbonyl and amino(Ci-4)alkyl are optionally substituted with one or more halogen, hydroxyl or (Ci-
alfinyl); or a group having the formula \( \text{O}^{-} \), optionally substituted with one or more of the following: (Ci-i0)alkyl, halogen, amino, cyano, hydroxy, (Ci-3)alkoxy, and wherein m is 1, 2, 3, or 4;

R^8 is halogen, cyano, amino, nitro, hydroxy, H\textsubscript{2}NC(0)-, (Ci-3)alkoxycarbonyl, (di)(Ci_6)alkylaminocarbonyl, (Ci-4)alkyl, (C1-7)cycloalkyl, (C1-5)heterocycloalkyl, (Cl-3)alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C3-6)cycloalkylaminocarbonyl, amino(Cl-4)alkyloxycarbonyl or (Ci-3)alkoxy, wherein (Ci-3)alkoxycarbonyl, (di)(Ci-6)alkylaminocarbonyl, (Ci-4)alkyl, (Ci-3)alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C3-6)cycloalkylaminocarbonyl, amino(Ci-4)alkyloxycarbonyland (Ci-3)alkoxy are optionally substituted with oxo, (Ci-4)alkyl, hydroxy(Ci-3)alkyl, or one, two or three halogens.

2. The compound of claim 1 having Formula Ix

\[ \text{Ix} \]
or a pharmaceutically acceptable salt or solvate thereof wherein,

X is \( \text{CH}_2, \text{C(O)}, \text{CR}^b \);

Y is \( \text{CH}, \text{N}, \text{CR}^a \);

\( n = 0, 1, 2, 3 \) or 4;

\( A^4 \) is \( \text{CR}^4 \) or \( \text{N} \);

\( A^5 \) is \( \text{CR}^5 \) or \( \text{N} \);

\( A^6 \) is \( \text{CR}^6 \) or \( \text{N} \);

\( A^7 \) is \( \text{CR}^7 \) or \( \text{N} \);

with the proviso that no more than two of \( A^4 \to A^7 \) can be \( \text{N} \);

\( R^a \) is \( (\text{Ci}_{-4}) \text{alkyl} \);

\( R^b \) is \( (\text{Ci}_{-4}) \text{alkyl} \);

\( R^1 \) is

(i) \( (\text{C}_3 \to \text{C}_2) \text{carbocyclyl} \); 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(\( \text{Ci}_{io} \)alkyl), or carbamoyl;

\( R^3 \) is hydrogen, halogen, cyano, nitro, hydroxy, \( (\text{Ci}_3) \text{alkylC}(0)0- \), \( (\text{Ci}_{-4}) \text{alkyl} \), or \( (\text{Ci}_{-4}) \text{alkoxy} \), wherein \( (\text{Ci}_{-4}) \text{alkyl} \) and \( (\text{Ci}_{-4}) \text{alkoxy} \) are optionally substituted with one or more halogen;

\( R^4 \to R^7 \) independently are \( \text{H}, \text{halogen}, \text{amino}, \text{cyano}, \text{hydroxy}, (\text{Ci}_3) \text{alkoxy}, (\text{Ci}_{-4}) \text{alkyl}, (\text{Ci}_{-4}) \text{alkylaminocarbonyl}, (\text{di})(\text{Ci}_6) \text{alkylaminocarbonyl or amino(\text{Ci}_{-4}) \text{alkyl}}, \) where in \( (\text{Ci}_3) \text{alkoxy}, (\text{Ci}_{-4}) \text{alkyl}, (\text{Ci}_{-4}) \text{alkylaminocarbonyl}, (\text{di})(\text{Ci}_6) \text{alkylaminocarbonyl and amino(\text{Ci}_{-4}) \text{alkyl} are optionally substituted with one or more halogen, hydroxyl or (\text{Ci}_3) \text{alkoxy}; or a group having the formula

\[
\begin{align*}
\text{O} & \quad \text{ optionally substituted with one or more of the following: (Ci}_{i,0}) \text{alkyl, halogen, amino, cyano, hydroxy, (Ci}_{-3}) \text{alkoxy}, and wherein m is 1, 2, 3, or 4;}
\end{align*}
\]

\( R^8 \) is halogen, cyano, amino, nitro, hydroxy, \( H_2 \text{NC}(0)- \), \( (\text{Ci}_3) \text{alkoxycarbonyl, (di)(Ci}_6) \text{alkylaminocarbonyl, (Ci}_{-4}) \text{alkyl, (C}_3\text{-cycloalkyl, (C}_3\text{-heterocycloalkyl, (Ci}_3\text{-alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C}_3\text{-cycloalkylaminocarbonyl, amino(Ci}_{-4}) \text{alkyloxycarbonyl or (Ci}_3\text{alkoxy, wherein (Ci}_
3) alkoxycarbonyl, (di)(Cl₆)alkylaminocarbonyl, (Cl₄)alkyl, (Cl₃)alkoxyaminocarbonyl, 4- to 8-membered heterocyclylcarbonyl, (C₃-₆)cycloalkylaminocarbonyl, amino(Cl₄)alkyloxycarbonyland (Cjalkoxy are optionally substituted with oxo, (Cl₄)alkyl, hydroxy(Cl₃)alkyl, or one, two or three halogens.

3. The compound of claim 1 having Formula 1a

![Formula 1a](image)

or a pharmaceutically acceptable salt or solvate thereof.

4. The compound of claim 1 having Formula 1b

![Formula 1b](image)
or a pharmaceutically acceptable salt or solvate thereof.

5. The compound of claim 4, wherein $Y$ is N.

6. The compound of claim 4 having Formula Ic

or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of claim 3 having Formula Id

wherein $x$ is 1, 2, 3, 4 or 5,

or a pharmaceutically acceptable salt or solvate thereof.
8. The compound of claim 7 having Formula Ie

\[ \text{Ie} \]

or a pharmaceutically acceptable salt or solvate thereof.

9. The compound of claim 8 having Formula If

\[ \text{If} \]

or a pharmaceutically acceptable salt or solvate thereof.

10. The compound of claim 9 having Formula Ig
or a pharmaceutically acceptable salt or solvate thereof.

11. The compound of claim 1, 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.

12. The compound of claim 11, wherein $R^1$ is $(C_{6,14})$aryl, optionally substituted with one, two, three, four or five $R^8$.

13. The compound of claim 12, wherein $R^1$ is phenyl, optionally substituted with one, two or three $R^8$.

14. The compound of claim 13, wherein $R^2$ is C(0)OH.

15. A compound according to claim 1 selected from:

4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(dimethylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(l-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-
enecarboxylic acid;  
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(2-hydroxyethylcarbamoyl)-
1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)cyclohex-3-
enecarboxylic acid;  
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-1-
methylcyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-yl)-2-
methylcyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;  
4-(4-chloro-1-(2-chloro-6-(trifluoromethyl)benzoyl)-1H-indazol-3-yl)-1-
methylcyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)-1-
methylcyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-methylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;  
4-(1-(2-chloro-6-methylbenzoyl)-1H-pyrazolo[4,3-b]pyridine-3-yl)cyclohex-3-
enecarboxylic acid;  
(R or S)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy azetidine-1-carbonyl)-1H-
indazol-3-yl)cyclohex-3-enecarboxylic acid;  
(S or R)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxy azetidine-1-carbonyl)-1H-
indazol-3-yl)cyclohex-3-enecarboxylic acid;  
(R or S)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-
indazol-3-yl)-1-methylcyclohex-3-enecarboxylic acid;  
(S or R)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-6-(3-methoxyazetidine-1-carbonyl)-1H-
indazol-3-yl)-1-methylcyclohex-3-enecarboxylic acid;  
(R or S)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-
enecarboxylic acid;  
(S or R)-4-(1-(2-chloro-6-cyclopropylbenzoyl)-4-fluoro-1H-indazol-3-yl)cyclohex-3-
enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(3,3-difluoroazetidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-6-((cyclopropyl)carbamoyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((cyclopropyl(methyl)carbamoyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-6-(azetidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(3-methoxyazetidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-(trifluoromethyl)benzoyl))-6-(pyrrolidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((S)-2-methylpyrrolidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((R)-2-methylpyrrolidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(3-methoxypyrrolidine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(2-methylmorpholine-4-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(cyclohexyl(methyl)carbamoyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(morpholine-4-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((2R,6S)-2,6-dimethylmorpholine-4-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-(4-methyl-3-oxopiperazine-1-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((S)-3-methylmorpholine-4-carbonyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-((1-(2-chloro-6-((trifluoromethyl)benzoyl))-6-((methyl(tetrahydro-2H-pyran-4-yl)carbamoyl))-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((R)-3-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-2-methylmorpholine-4-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2-hydroxyethyl)(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(isopropylcarbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(isopropyl(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2-methoxyethyl)(methyl)carbamoyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-hydroxyazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-(3-fluoroazetidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((2-hydroxy-3-(methylamino)propan-2-yl)oxy)carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-6-((S)-3-methoxypyrrolidine-1-carbonyl)-1H-indazol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-(trifluoromethyl)benzoyl)-4-fluoro-1H-indol-3-yl)cyclohex-3-enecarboxylic acid;
4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-
methylcyclohexanecarboxylic acid; (trans)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-
methylcyclohexanecarboxylic acid; (cis)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-
methylcyclohexanecarboxylic acid; (trans)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohexanecarboxylic acid; (cis)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)cyclohexanecarboxylic acid; (trans)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-1-
methylcyclohexanecarboxylic acid; (cis)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-1-
methylcyclohexanecarboxylic acid; (R and S)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-2,2-
dimethylcyclohex-3-enecarboxylic acid; (R and S) 4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-6,6-
dimethylcyclohex-3-enecarboxylic acid; (trans)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-
b]pyridin-3-
yl)cyclohexanecarboxylic acid; (cis)-4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-1H-pyrazolo[4,3-b]pyridin-3-
yl)cyclohexanecarboxylic acid; 4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-5-
methylcyclohex-3-enecarboxylic acid; and 4-(1-(2-chloro-6-((trifluoromethyl)benzoyl)-4-fluoro-1H-indazol-3-yl)-4-
hydroxycyclohexanecarboxylic acid.

16. A pharmaceutical composition comprising a compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof, and one or more pharmaceutically acceptable excipients.
17. The pharmaceutical composition of claim 16, further comprising at least one additional therapeutically active agent.

18. 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).

19. 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.

20. The method of claim 19, wherein the disease or condition is an autoimmune disease or inflammatory disease.

21. The method of claim 20, 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.