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Title: PYRAZOLE DERIVATIVES AS MODULATORS OF CALCIUM RELEASE-ACTIVATED CALCIUM CHANNEL

Abstract: Disclosed are novel calcium release-activated calcium (CRAC) channel inhibitors, methods for preparing them, pharmaceutical compositions containing them, and methods of treatment using them. The present disclosure also relates to methods for treating non-small cell lung cancer (NSCLC) with CRAC inhibitors, and to methods for identifying therapeutics for treating and diagnosing cancer.
PYRAZOLE DERIVATIVES AS MODULATORS OF CALCIUM RELEASE–ACTIVATED CALCIUM CHANNEL


FIELD OF THE INVENTION

[02] The present invention relates to calcium release-activated calcium (CRAC) channel inhibitors of formula I and pharmaceutically acceptable salts thereof, methods for preparing them, pharmaceutical compositions containing them, and methods of treatment with them.

BACKGROUND OF THE INVENTION

[03] The regulation of intracellular calcium is a key element in the transduction of signals into and within cells. Cellular responses to growth factors, neurotransmitters, hormones and a variety of other signal molecules are initiated through calcium-dependent processes. The importance of calcium ion as a second messenger is emphasised by many different mechanisms which work together to maintain calcium homeostasis. Changes in intracellular free calcium ion concentration represent the most wide-spread and important signalling event for regulating a plethora of cellular responses. A widespread route for calcium ion entry into the cell is through store-operated channels (SOCs), i.e. many cell types employ store-operated calcium ion entry as their principal pathway for calcium ion influx. This mechanism is engaged following calcium ion release from stores, where the depleted stores lead to activation of calcium release-activated calcium (CRAC) channels.

[04] CRAC channels, a subfamily of store-operated channels, are activated by the release of calcium from intracellular stores, particularly from the endoplasmic reticulum (ER). These channels are key factors in the regulation of a wide range of cellular function, including muscle contraction, protein and fluid secretion and control over cell
growth and proliferation and hence play an essential role in various diseases such as immune disorders and allergic responses. Among several biophysically distinct store-operated currents the best characterized and most calcium ion selective one is the CRAC current. Thus, CRAC channels mediate essential functions from secretion to gene expression and cell growth and form a network essential for the activation of immune cells that establish the adaptive immune response. Recently two proteins, stromal interaction molecule (STIM1) and CRAC Modulator 1 (CRACM1 or Orail), have been identified as the essential components that fully reconstitute and amplify CRAC currents in heterologous expression systems with a similar biophysical fingerprint. In mammals, there exist several homologs of these proteins: STIM1 and STIM2 in the endoplasmic reticulum and CRACM1, CRACM2, and CRACM3 in the plasma membrane.

CRAC currents were initially discovered in lymphocytes and mast cells, and at the same time have been characterized in various cell lines such as S2 drosophila, DT40 B cells, hepatocytes, dendritic, megakaryotic, and Madin-Darby canine kidney cells. In lymphocytes and in mast cells, activation through antigen or Fc receptors initiates the release of calcium ion from intracellular stores caused by the second messenger inositol (1,4,5)-triphosphate (Ins(1,4,5)P₃), which in turn leads to calcium ion influx through CRAC channels in the plasma membrane. Store-operated Ca²⁺ currents characterized in smooth muscle, A431 epidermal cells, endothelial cells from various tissues, and prostate cancer cell lines show altered biophysical characteristics suggesting a distinct molecular origin.


It is well established now that intracellular calcium plays an important role in various cellular functions, and that its concentration is regulated by calcium ion influx through calcium channels on the cell membrane. Ca²⁺ ion channels, which are located
in the nervous, endocrine, cardiovascular, and skeletal systems and are modulated by membrane potential, are called voltage-operated Ca\textsuperscript{2+} (VOC) channels. These channels are classified into L, N, P, Q, R, and T subtypes. Excessive Ca\textsuperscript{2+} influx through the VOC channels causes hypertension and brain dysfunction. In contrast, calcium ion channels on inflammatory cells, including lymphocytes, mast cells, and neutrophils, can be activated regardless of their membrane potential. This type of calcium ion channel has been reported to act in the crisis and exacerbation of inflammation and autoimmune diseases. In the T cells, it has been reported that the early stages of activation consist of pre- and post-Ca\textsuperscript{2+} events. The stimulation of T cell receptors induces pre-Ca\textsuperscript{2+} events, including the generation of IP3, followed by the release of Ca\textsuperscript{2+} from the endoplasmic reticulum (ER). In post-Ca\textsuperscript{2+} events, depletion of Ca\textsuperscript{2+} in the ER induces the activation of CRAC channels, and capacitative Ca\textsuperscript{2+} influx through the CRAC channel sustains high intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]\textsubscript{i}). This prolonged high [Ca\textsuperscript{2+}]\textsubscript{i} activates cytosolic signal transduction to produce lipid mediators (e.g., LTD\textsubscript{4}), cytokines [e.g., interleukin-2 (IL-2)], and matrix metalloproteinases, which participate in the pathogenesis of inflammation and autoimmune diseases.

These facts suggest that CRAC channel modulators can be useful for the treatment of diseases caused by the activation of inflammatory cells without side effects observed in steroids. Since VOC channel modulators would cause adverse events in the nervous and cardiovascular systems, it may be necessary for CRAC channel modulators to exhibit sufficient selectivity over VOC channels if they are to be used as anti-inflammatory drugs.

Accordingly, CRAC channel modulators have been said to be useful in treatment, prevention and/or amelioration of diseases or disorders associated with calcium release-activated calcium channel including, but not limited to, inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, type I diabetes, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis and atopic dermatitis.

[10] CRAC channel inhibitors which have been identified include SK&F 96365 (1), Econazole (2) and L-651582 (3).

[11] However, these molecules lack sufficient potency and selectivity over VOC channels and hence are not suitable for therapeutic use.

[12] Recent publications by Taiji et al. (European Journal of Pharmacology, 560, 225-233, 2007) and Yasurio Yonetoky et al. (Bio. & Med. Chem., 16, 9457-9466, 2008) describe a selective CRAC channel inhibitor coded YM-58483 that is capable of inhibiting T cell function and proposed to be of some benefit in the treatment of inflammatory diseases including bronchial asthma.

YM-58483

[13] Yasurio Yonetoky et al. disclose YM-58483 to be selective for CRAC channels over the voltage operated channels (VOC) with a selective index of 31.

[14] Other CRAC channel modulators disclosed include various biaryl and/or heterocyclic carboxanilide compounds including for example PCT or US patent


[17] Cancer is a major public health problem in India, the U.S. and many other parts of the world. Currently, 1 in 4 deaths in India is due to cancer. Lung cancer is the leading cause of cancer deaths worldwide because of its high incidence and mortality, with 5-year survival estimates of 10% for non-small cell lung cancer (NSCLC). It has been reported that further investigations on the mechanisms of tumorigenesis and chemoresistance of lung cancer are needed to improve the survival rate (Jemal A, et al, Cancer Statistics, CA Cancer. J. Clin., 56, 106-130, 2006). There are four major types of NSCLC, namely, adenocarcinoma, squamous cell carcinoma, bronchoalveolar carcinoma, and large cell carcinoma. Adenocarcinoma and squamous cell carcinoma are the most common types of NSCLC based on cellular morphology (Travis et al, Lung Cancer Principles and Practice, Lippincott-Raven, New York, 361-395, 1996). Adenocarcinomas are characterized by a more peripheral location in the lung and often

[18] The majority of NSCLCs are characterized by the presence of the ras mutation thereby rendering the patient relatively insensitive to treatment by known kinase inhibitors. As a result, current treatments of lung cancer are generally limited to cytotoxic drugs, surgery, and radiation therapy. There is a need for treatments which have fewer side effects and more specifically target the cancer cells, are less invasive, and improve the prognosis of patients.

[19] The identification of lung tumor-initiating cells and associated markers may be useful for optimization of therapeutic approaches and for predictive and prognostic information in lung cancer patients. Accordingly, a need remains for new methods of predicting, evaluating and treating patients afflicted with lung cancer.

[20] There still remains an unmet and dire need for small molecule modulators having specificity towards Stiml and/or Orail in order to regulate and/or modulate activity of CRAC channels, particularly for the treatment of diseases and disorders associated with the CRAC.

**SUMMARY OF THE INVENTION**

[21] The present invention relates to compounds of formula (I), methods for their preparation, pharmaceutical compositions containing them, and methods of treatment with them.

[22] In particular, compounds of formula (I) and their pharmaceutically acceptable salts thereof are calcium release-activated calcium channel modulators useful in the treatment, prevention, inhibition and/or amelioration of diseases or disorders associated with calcium release-activated calcium channel.

[23] In one aspect, the present invention relates to a compound of formula (I):

![Chemical Structure](I)
or a tautomer thereof, prodrug thereof, N-oxide thereof, pharmaceutically acceptable ester thereof or pharmaceutically acceptable salt thereof,

wherein

Ring Hy represents

\[ \text{Ring Hy is optionally substituted with } R''''; \]

R\(^1\) and R\(^2\) are the same or different and are independently selected from CH\(_3\), CH\(_2\)F, CHF\(_2\), CF\(_3\), substituted or unsubstituted C\(_x\)\(_y\), cycloalkyl, CH\(_2\)-OR\(^a\), CH\(_2\)-NR\(^a\)R\(^b\), CN and COOH with the proviso that:

a) both R\(^1\) and R\(^2\) at the same time do not represent CF\(_3\),

b) both R\(^1\) and R\(^2\) at the same time do not represent CH\(_3\),

c) when R\(^1\) is CF\(_3\) then R\(^2\) is not CH\(_3\) and

d) when R\(^1\) is CH\(_3\) then R\(^2\) is not CF\(_3\);

Ring Ar represents:

\[ T, U, V \text{ and } W \text{ are the same or different and are independently selected from } CR^8 \text{ and } N; \]

Z\(^1\), Z\(^2\) and Z\(^3\) are the same or different and are independently selected from CR\(^\Lambda\), CR\(^\Lambda\)R\(^B\), O, S and -NR\(^\Lambda\), with the proviso that at least one of Z\(^1\), Z\(^2\) and Z\(^3\) represents O, S or -NR\(^\Lambda\);

L\(_1\) and L\(_2\) together represent -NH -C(=X)-, -NH-S(=0) q, -C(=X)NH- q, -NH-CR'R'''' q or -S(=0) q NH-;

A is absent or selected from -(CR'\(^R\)'\(^-\))-, O, S(=0) q, C(=X) and -NR\(^\Lambda\);

each occurrence of R' and R'' are the same or different and are independently selected from hydrogen, hydroxy, cyano, halogen, -OR\(^\Lambda\), -COOR\(^\Lambda\), -S(=0) q, -R\(^A\) -NR\(^B\), -C(=X)-R\(^\Lambda\), substituted or unsubstituted C\(_{1-6}\) alkyl group, substituted or unsubstituted C\(_{6-9}\) alkenyl, substituted or unsubstituted C\(^\Lambda\)alkynyl, and substituted or unsubstituted C\(_{1,5}\) cycloalkyl, or
R’ and R”, when directly bound to a common atom, may be joined to form a substituted or unsubstituted saturated or unsaturated 3-6 member ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR² and S;

R” is selected from hydrogen, hydroxy, cyano, halogen, -OR², -COOR², -S(=0)² -R³, -NR²R⁴, -C(=X)-R³, substituted or unsubstituted C(i,6) alkyl group, substituted or unsubstituted C(i,6) alkenyl, substituted or unsubstituted C(i,6) alkynyl, and substituted or unsubstituted Cp⁺cycloalkyl;

each occurrence of X is independently selected from O, S and -NR²;

Cy is selected from monocyclic substituted or unsubstituted cycloalkyl group, monocyclic substituted or unsubstituted heterocyclic, monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl;

each occurrence of R³ and R⁴ are the same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, -OR⁵, -S(=0)⁵ -R⁶, -NR⁵R⁷, -C(=Y)-R⁶, -CR⁵R⁷-C(=Y)-R⁶, -CR⁵R⁷-C(=Y)-CR⁶R⁷, -C(=Y)-NR⁵R⁷, -NR⁵R⁷-C(=Y)-NR⁶R⁷, -S(=0)⁵ -NR⁵R⁷, -NR⁵R⁷-S(=0)⁵ -NR⁶R⁷, -NR⁵R⁷-NR⁶R⁷, substituted or unsubstituted alkenyl, substituted or unsubstituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclic, substituted or unsubstituted heterocyclicalkyl, substituted or unsubstituted aroyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl, or when R³ and R⁴ are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR⁵ and S;

each occurrence of R⁵ and R⁶ may be same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclicalkyl, or when two R⁵ and/or R⁶ substituents are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 membered ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NH and S;
each occurrence of \( Y \) is selected from \( O, S \) and \(-NR^a\); and

each occurrence of \( q \) independently represents an integer 0, 1 or 2;

with Proviso (e) that the compound of formula (I) is not:

- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-(difluoromethyl)-5-methyl-1H-pyrazole-3-carboxamide;} \)
- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-4-nitro-1H-pyrazole-5-carboxamide;} \)
- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(1-ethyl-5-methyl-1H-pyrazol-4-yl)-5-isoxazolecarboxamide;} \)
- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4,5-dihydro-3-(2-methoxyphenyl)-5-isoxazolecarboxamide;} \)
- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-[4-(1,1-dimethylethyl)phenyl]-cyclopropanecarboxamide;} \)
- \( \text{N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-pyridine carboxamide;} \)
- \( \text{N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-pyridine carboxamide;} \)
- \( \text{N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-pyridine carboxamide;} \)

N-benzyl-6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridazin-3-amine.

[24] In one preferred embodiment, \( R^1 \) is cyclopropyl.

[25] In one preferred embodiment, \( R^2 \) is \( CF_3 \).

[26] According to one preferred embodiment, \( Hy \) is
[27] Further preferred is a compound of formula (I) wherein Hy is

[28] Further preferred is a compound of formula (I) wherein Hy is

[29] According to one preferred embodiment, Ar is
Further preferred is a compound of formula (I) wherein Ar is

Further preferred is a compound of formula (I) wherein Ar is

According to one preferred embodiment, Li and L₂ together represent -NH-C(=0)-, -NH-S(=0)-, -C(=0)NH- or NH-CH₂-.

According to one preferred embodiment, A is absent or selected from -(CR'R")-, O, S(=0), C(=X) and -NR₃. More preferably, A is -CH₂-, -CHMe- or -(CR'R")-, where R' and R" are joined to form a substituted or unsubstituted saturated or unsaturated 3-6 member ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NR₃ (such as NF₃) and S;

Further preferred is a compound of formula (I) wherein A is

Further preferred is a compound of formula (I) wherein A is

Further preferred is a compound of formula (I) wherein A is absent.

Further preferred is a compound of formula (I) wherein A is -CH₂-.

According to one preferred embodiment, Cy is
Further preferred is a compound of formula (I) wherein Cy is

Further preferred is a compound of formula (I) wherein Cy is

Further preferred is a compound of formula (I) wherein Cy is
Yet another embodiment is a compound having the formula (IA):

or a tautomer thereof, prodrug thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof, wherein the variables (e.g., $R''$, $R^1$, $R^2$, $T$, $U$, $V$, $W$, $Li$, $L_2$, $A$ and $Cy$) are defined as described above in relation to formula (I), with the proviso that the compound of formula (IA) is not any of the compounds in Proviso (a-e) as defined above.

Further preferred is a compound of formula (IA-I)

or a tautomer thereof, prodrug thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof, wherein the variables (e.g., $R''$, $R^1$, $R^2$, $T$, $U$, $V$, $W$, $A$ and $Cy$) are defined as described above in relation to formula (I), with the proviso that the compound of formula (IA) is not any of the compounds in Proviso (a-e) defined above.

Further preferred is a compound of formula (IA-I)
or a tautomer thereof, prodrug thereof, N-oxide thereof, pharmaceutically acceptable ester thereof, or pharmaceutically acceptable salt thereof, wherein

R<sup>1</sup> and R<sup>2</sup> are the same or different and are independently selected from CH<sub>2</sub>F, CHF<sub>2</sub>, CF<sub>3</sub> and cyclopropyl; with the proviso that

a) both R<sup>1</sup> and R<sup>2</sup> at the same time do not represent CF<sub>3</sub>,

; R<sup>***</sup> is hydrogen or halogen;
T, U, V, W are independently CR<sup>8</sup> or N;
R<sup>8</sup> is hydrogen or halogen;
A is absent; and
Cy is selected from monocyclic substituted or unsubstituted aryl or monocyclic substituted or unsubstituted heteroaryl,

with the proviso that the compound of formula (IA) is not any of the compounds in Proviso (e) defined above.

[45] Further preferred is a compound of formula (IA-I) wherein both R<sup>1</sup> and R<sup>2</sup> represent cyclopropyl.
[46] Further preferred is a compound of formula (IA-I) wherein one of R<sup>1</sup> and R<sup>2</sup> is CF<sub>3</sub> and the other is cyclopropyl.
[47] Further preferred is a compound of formula (IA-I) wherein R<sup>1</sup> is cyclopropyl and R<sup>2</sup> is CF<sub>3</sub>.
[48] Further preferred is a compound of formula (IA-I) wherein T, U, V, W are CH, CF or N.
[49] Further preferred is a compound of formula (IA-I) wherein T is CF or N and each of U, V and W is CH.
[50] Further preferred is a compound of formula (IA-I) wherein each of T and V is CF or N and each of U and W is CH.
[51] Further preferred is a compound of formula (IA-I) wherein A is absent
Further preferred is a compound of formula (IA-I) wherein Cy is selected from

Further preferred is a compound of formula (IA-I) wherein Cy is

Yet another embodiment is a compound having the formula (IA-III)

Yet another embodiment is a compound having the formula (IA-III)
or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester, or pharmaceutically acceptable salt thereof,

wherein

R\(^1\) and R\(^2\) are the same or different and are independently selected from CH\(_2\)F, CHF\(_2\), CF\(_3\), Cyclopropyl with the proviso that both R\(^1\) and R\(^2\) at the same time do not represent CF\(_3\);

T and V are the same or different and are independently selected from CF and N;

Each of U and V is CR\(^a\);

L\(_1\) and L\(_2\) together represent -NH-C(=X)-, -NH-S(=0)\(_q\)-, C(=X)NH- or S(=0)\(_q\)NH- or NH-CR'R\(^b\)-;

A is absent or selected from -(CR'R\(^b\))- and -NR\(^b\);

each occurrence of R' and R'' are the same or different and are independently selected from hydrogen or substituted or unsubstituted C\(_{1-6}\) alkyl group or R' and R'' may be joined to form a substituted or unsubstituted saturated or unsaturated 3-6 membered ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR\(^a\) and S;

R'' is selected from the group consisting of hydrogen, or halogen

each occurrence of X is independently selected from O, S and -NR\(^a\);

Cy is selected from monocyclic substituted or unsubstituted heterocyclyl, monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl.

each occurrence of R\(^a\) and R\(^b\) are the same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, -OR\(^c\), -S(=0)\(_q\)-R\(^c\), -NR\(^a\)R\(^d\)-, -C(=Y)-R\(^o\), -CR\(^a\)R\(^d\)-C(=Y)-R\(^e\), -CR\(^a\)R\(^d\)-Y-CR\(^a\)R\(^d\), -C(=Y)-NR\(^a\)R\(^d\), -NRR\(^a\)-C(=Y)-NR\(^a\)R\(^d\), -S(=0)\(_q\)-NR\(^a\)R\(^d\), -NR\(^a\)R\(^d\)-S(=0)\(_q\)-NR\(^a\)R\(^d\), -NR\(^a\)R\(^d\)-NR\(^a\)R\(^d\), substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted aryl.
arylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl, or when R³ and R⁴ substituent are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR³ and S;

each occurrence of R³ and R⁴ may be same or different and are independently selected from the group consisting of hydrogen, nitro, hydroxy, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heterocycloalkenyl, or when two R³ and/or R⁴ substitutents are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NH and S;

each occurrence of Y is selected from O, S and -NR³; and

each occurrence of q independently represents 0, 1 or 2.

[55] Further preferred is a compound of formula (IA-IH) wherein both R¹ and R² represent cyclopropyl.

[56] Further preferred is a compound of formula (IA-III) wherein one of R¹ and R² is CF₃ and the other is cyclopropyl.

[57] Further preferred is a compound of formula (IA-III) wherein one of R¹ and R² is CF₃ and the other is CH₂F, CHF₂.

[58] Further preferred is a compound of formula (IA-III) wherein R¹ is cyclopropyl and R² is CF₃.

[59] Further preferred is a compound of formula (IA-III) wherein T is CF or N.

[60] Further preferred is a compound of formula (IA-III) wherein U, V, W are CH, CF or N.

[61] Further preferred is a compound of formula (IA-III) wherein Li and L₂ together represent -NH-C(=0)-, C(=0)NH- or -NH-CH₂-;

[62] Further preferred is a compound of formula (IA-III) wherein A is absent,-NH- or-CH₂-.

[63] Further preferred is a compound of formula (IA-III) wherein Cy is selected from
Further preferred is a compound of formula (1A-III) wherein Cy is selected from

Representative compounds of the present invention include those specified below and in Table 1 and pharmaceutically acceptable salts thereof. The present invention should not be construed to be limited to them.
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-4-methylthiazole-5-carboxamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2,4-dimethylthiazole-5-carboxamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-5-methylisoxazole-4-carboxamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-3,5-dimethylisoxazole-4-carboxamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]benzamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2-methylbenzamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2,6-difluorobenzamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2,3-difluorobenzamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-3-(methylsulfonyl)benzamide
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-4-(methylsulfonyl)benzamide
2-chloro-N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-5-(methylthio)benzamide
2-chloro-N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-5-(methylsulfonyl)benzamide
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N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]isonicotinamide hydrochloride
N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-3-fluoroisonicotinamide
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N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2-(pyridin-4-yl)acetamide hydrochloride
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N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-2,3-difluorobenzamide
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N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]isonicotinamide hydrochloride
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N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-4-yl)acetamide hydrochloride
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1-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(4-methylthiazol-5-yl)urea
1-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(4-methylpyrimidin-5-yl)urea
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-methylthiazol-5-yl)benzamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,6-difluorophenyl) benzamide
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N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-4-methylthiazole-5-carboxamide
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nicotinamide
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nicotinamide
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methylthiazole-5-carboxamide
N-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-2,6-
difluorobenzamide
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carboxamide
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5-carboxamide
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N-(2-chloro-6-fluorophenyl)-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-
fluorobenzamide
N-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-4-
methylthiazole-5-carboxamide
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methylpyrimidine-5-carboxamide
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phenylcyclobutanecarboxamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-4-
methyloxazole-5-carboxamide
N-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-4-
methylpyrimidine-5-carboxamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluoro-N-(4-methylpyrimidin-5-yl) benzamide or
N-4-[3-cyclopropyl-5-(difluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-2,6-difluorobenzamide and N-4-[5-cyclopropyl-3-(difluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-2,6-difluorobenzamide
or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester, or pharmaceutically acceptable salt thereof.

**Table 1**

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</table>
[66] The compounds of the present invention (e.g., compounds of formulas I, IA, IA-I, and/or IA-III including their pharmaceutically acceptable esters and salts) are useful for the treatment, prevention, inhibition, and/or amelioration of diseases and disorders associated with calcium release-activated calcium (CRAC) channel.

[67] Another embodiment of the present invention is a method for treating a disease or disorder via modulation of CRAC channels by administering to a patient in need of such treatment an effective amount of a compound of the present invention (e.g., a compound of formula I, IA, IA-I, and/or IA-III as defined above).

[68] Yet another embodiment of the present invention is a method for treating a disease or disorder via modulation of CRAC channels by administering to a patient in need of such treatment an effective amount of a compound of the present invention (e.g.,
a compound of formula I, IA, IA-I, and/or IA-III as defined above), in combination (simultaneously or sequentially) with at least one other anti-inflammatory agent.

[69] The compounds of the present invention may inhibit store operated calcium entry, interrupt the assembly of SOCE units, alter the functional interactions of proteins that form store operated calcium channel complexes, and alter the functional interactions of STIM1 with Orail. These compounds are SOC channel pore blockers, and are CRAC channel pore blockers.

[70] The compounds described herein modulate intracellular calcium and are used in the treatment of diseases, disorders or conditions where modulation of intracellular calcium has a beneficial effect. In one embodiment, the compounds described herein inhibit store operated calcium entry. In one embodiment, the compounds of the present invention capable of modulating intracellular calcium levels interrupt the assembly of SOCE units. In another embodiment, the compounds of the present invention capable of modulating intracellular calcium levels alter the functional interactions of proteins that form store operated calcium channel complexes. In one embodiment, the compounds of the present invention capable of modulating intracellular calcium levels alter the functional interactions of STIM1 with Orail. In other embodiments, the compounds of the present invention capable of modulating intracellular calcium levels are SOC channel pore blockers. In other embodiments, the compounds of the present invention capable of modulating intracellular calcium levels are CRAC channel pore blockers.

[71] In one aspect, the compounds of the present invention capable of modulating intracellular calcium levels inhibit the electrophysiological current (Isoc) directly associated with activated SOC channels. In one aspect, compounds capable of modulating intracellular calcium levels inhibit the electrophysiological current (I_{CRA C}) directly associated with activated CRAC channels.

[72] The compounds of the present invention are useful in the treatment of diseases, conditions or disorders that benefit from modulation of intracellular calcium, including, but not limited to, an immune system-related disease (e.g., an autoimmune disease), a disease or disorder involving inflammation (e.g., asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, glomerulonephritis, neuroinflammatory diseases, multiple sclerosis, uveitis and disorders of the immune system), cancer or other proliferative disease, hepatic diseases or disorders, and renal diseases or disorders. In one embodiment, the compounds described
herein are used as immunosuppressants to prevent (or inhibit) transplant graft rejections, allogeneic or xenogeneic transplantation rejection (organ, bone marrow, stem cells, other cells and tissues), and/or graft-versus-host disease. For instance, the compounds of the present invention can be used to prevent (or inhibit) transplant graft rejections result from tissue or organ transplants. The compounds of the present invention can also be used to prevent (or inhibit) graft-versus-host disease resulting from bone marrow or stem cell transplantation.

[73] More particularly, the compounds of formula I, IA, IA-I, and/or IA-III are useful in the treatment of a variety of inflammatory diseases including, but not limited to, inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, type I diabetes, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis and atopic dermatitis, asthma and Sjogren's syndrome.

[74] The compounds described herein modulate an activity of, modulate an interaction of, or bind to, or interact with at least one portion of a protein in the store operated calcium channel complex. In one embodiment, the compounds described herein modulate an activity of, modulate an interaction of, or bind to, or interact with at least one portion of a protein in the calcium release activated calcium channel complex. In one embodiment, the compounds described herein reduce the level of functional store operated calcium channel complexes. In another embodiment, the compounds described herein reduce the level of activated store operated calcium channel complexes. In a further embodiment, the store operated calcium channel complexes are calcium release activated calcium channel complexes.

[75] The compounds of the present invention which are capable of modulating intracellular calcium levels for treatment of a disease or disorder, when administered to a subject having a disease or disorder, effectively reduce, ameliorate or eliminate a symptom or manifestation of the disease, condition or disorder. In other embodiments, the compounds described herein are administered to a subject predisposed to a disease,
condition or disorder that does not yet manifest a symptom of the disease, condition or disorder, and prevents or delays development of the symptoms. In further embodiments, the compound of the present invention has such effects alone or in combination with other agents, or functions to enhance a therapeutic effect of another agent.

[76] Due to the key role of calcium in the regulation of cellular proliferation in general, calcium channel inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostatic hyperplasia, familial adenomatosis polyposis, neurofibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

[77] The compounds of the present invention, as modulators of apoptosis, are useful in the treatment of cancer (including, but not limited to, those types mentioned herein above), viral infections (including, but not limited, to herpevirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including, but not limited, to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including, but not limited to, Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including, but not limited to, osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

[78] The compounds of present invention can modulate the level of cellular RNA and DNA synthesis. These agents are therefore useful in the treatment of viral infections (including, but not limited to, HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).
The compounds of the present invention are useful in the chemoprevention of cancer. Chemoprevention is defined as inhibiting the development of invasive cancer by either blocking the initiating mutagenic event or by blocking the progression of premalignant cells that have already suffered an insult or inhibiting tumor relapse. The compounds are also useful in inhibiting tumor angiogenesis and metastasis.

The compounds of the present invention are also useful in combination (administered together or sequentially) with known anti-cancer treatments such as radiation therapy or with cytostatic or cytotoxic or anticancer agents, such as for example, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents, such as paclitaxel, docetaxel or the epothilones (for example, ixabepilone), either naturally occurring or synthetic; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; and anti-metabolites, such as methotrexate, other tyrosine kinase inhibitors such as Iressa and OSI-774; angiogenesis inhibitors; EGF inhibitors; VEGF inhibitors; CDK inhibitors; SRC inhibitors; c-Kit inhibitors; Herl/2 inhibitors and monoclonal antibodies directed against growth factor receptors such as erbitux (EGF) and herceptin (Her2) and other protein kinase modulators as well.

The invention further provides a pharmaceutical composition comprising one or more compounds of formula I, IA, IA-I, and/or IA-III and a pharmaceutically acceptable carrier.

Yet another embodiment of the invention is a dosage form comprising one or more compounds of the present invention, optionally with a pharmaceutically acceptable carrier. The dosage form can be, for example, a solid oral dosage form such as a tablet or capsule.

**DETAIL DESCRIPTION OF THE INVENTION**

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood in the field to which the claimed subject matter belongs. In the event that there is a plurality of definitions for terms herein, those in this section prevail.

It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any
subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.


[86] Unless specific definitions are provided, the nomenclature employed in connection with, and the laboratory procedures and techniques of, analytical chemistry, and medicinal and pharmaceutical chemistry described herein are those generally used. In some embodiments, standard techniques are used for chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. In other embodiments, standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). In finer embodiments, reactions and purification techniques are performed e.g., using kits of manufacturer's specifications or as described herein. The foregoing techniques and procedures are generally performed by conventional methods and as described in various general and more specific references that are cited and discussed throughout the present specification.

[87] As used herein the following definitions shall apply unless otherwise indicated. Further many of the groups defined herein can be optionally substituted. The listing of substituents in the definition is exemplary and is not to be construed to limit the substituents defined elsewhere in the specification.

[88] The term 'alkyP refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single
bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, and 1,1-dimethylethyl (t-butyl).

[89] The term substituted or unsubstituted (Ci-6) alkyl refers to an alkyl group as defined above having up to 6 carbon atoms.

[90] The term "alkenyl" refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-buteny1, and 2-butenyl.

[91] The term substituted or unsubstituted (Ci,s)alkenyl refers to an alkenyl group as defined above having up to 6 carbon atoms.

[92] The term "alkynyl" refers to a straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, and butynyl.

[93] The term substituted or unsubstituted (Ci-6) alkynyl refers to an alkynyl group as defined above having up to 6 carbon atoms.

[94] The term "alkoxy" denotes an alkyl group as defined above attached via an oxygen linkage to the rest of the molecule. Representative examples of those groups are -OCH3 and -OC2H5.

[95] The term "cycloalkyl" denotes a non-aromatic mono or multicyclic ring system of about 3 to 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. Non-limiting examples of multicyclic cycloalkyl groups include perhydronaphthyl, adamantyl, norbornyl groups (bridged cyclic group), or spirobicyclic groups e.g. spiro (4,4) non-2-yl.

[96] The term "cycloalkylalkyl" refers to a cyclic ring-containing radical containing in the range of about 3 up to 8 carbon atoms directly attached to an alkyl group which is then attached to the main structure at any carbon in the alkyl group that results in the creation of a stable structure such as cyclopropymethyl, cyclobuylethyl, and cyclopentylethyl.

[97] The term "cycloalkenyl" refers to a cyclic ring-containing radical containing in the range of about 3 up to 8 carbon atoms with at least one carbon-carbon double bond such as cyclopropenyl, cyclobutenyl, and cyclopentenyl.
The term "aryl" refers to an aromatic radical having in the range of 6 up to 20 carbon atoms such as phenyl, naphthyl, tetrahydronaphthyl, indanyl, and biphenyl.

The term "arylalkyl" refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g., -CH₂C₆H₅, and -C₂H₅C₆H₅.

The term "heterocyclic ring" refers to a non-aromatic 3 to 15 member ring radical which, consists of carbon atoms and at least one heteroatom selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a mono-, bi-, tri- or tetracyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quatemized. The heterocyclic ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "heteroaryl" refers to an optionally substituted 5-14 member aromatic ring having one or more heteroatoms selected from N, O, and S as ring atoms. The heteroaryl may be a mono-, bi- or tricyclic ring system. Examples of such heteroaryl ring radicals includes but are not limited to oxazolyl, thiazolyl imidazolyl, pyrrolyl, furanyl, pyridinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzoazolyl, benzoazolyl, carbazolyl, quinolyl and isoquinolyl. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

Examples of such "heterocyclic ring" or "heteroaryl" radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofuranyl, carbazolyl, cinnolinyl, dioxolanyl, indoliziny, naphthridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl, pteridinyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisoquinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolonyl, oxasolidinyl, triazolyl, indanyl, isoazolyl, isoxasolidinyl, morpholinyl, thiazoyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindoliny, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl,
benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurfuryl, tetrahydropyranyl, thiophenyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl, oxadiazolyl, chromanyl, isochromanyl and the like.

[103] The term "heteroarylalkyl" refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from the alkyl group that results in the creation of a stable structure.

[104] The term "heterocyclylalkyl" refers to a heterocyclic ring radical as defined above directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

[105] The term "substituted" unless otherwise specified refers to substitution with any one or any combination of the following substituents: hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=0), thio(=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, -COOR, -C(0)R, -C(S)R, -C(O)NR 2R, -C(0)ONR 2R, -NR 2R, -NR 2CONR 2R, -N(R)S0 2R, -N(N-R(R)R), -NR 2C(0)OR, -NR 2R, -NR 2C(0)R, -NR 2C(S)R, -NR 2C(0)NR 2R, -OR 2R, -OR 2C(0)NR 2R, -OR 2C(0)OR 2R, -OC(0)R, -OC(0)NR 2R, -R 2NR 2C(0)R, -R 2OR 2R, -R 2C(0)OR, -R 2C(0)R, -R 2C(0)R, -R 2C(0)OR 2R, -R 2C(0)NR 2R, -R 2C(0)OR, -R 2C(0)R, -R 2C(0)OR, and -ONO 2R, wherein R, R' and R'' in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, or any two
of $R^x$, $R^y$ and $R^z$ may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include heteroatoms which may be same or different and are selected from O, NR$^X$ or S. The substituents in the aforementioned "substituted" groups cannot be further substituted. For example, when the substituent on "substituted alkyl" is "substituted aryl", the substituent on "substituted aryl" cannot be "substituted alkenyl". Substitution or the combination of substituents envisioned by this invention are preferably those resulting in the formation of a stable compound.

[106] The term "halogen" or "halo" refers to radicals of fluorine, chlorine, bromine and iodine.

[107] The term "protecting group" or "PG" refers to a substituent that is employed to block or protect a particular functionality. Other functional groups on the compound may remain reactive. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include, but are not limited to, acetyl, trifluoroacetyl, tert-butoxycarbonyl (BOC), benzylxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include, but are not limited to, acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Suitable carboxy-protecting groups include, but are not limited to, -CH$_2$CH$_2$S02Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-diphenyl-1-phosphino)-ethyl and nitroethyl. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

[108] The term "stereoisomer" refers to compounds, which have identical chemical composition, but differ with regard to arrangement of the atoms and the groups in space. These include enantiomers, diastereomers, geometrical isomers, atropisomer or conformational isomers.

[109] All the stereoisomers of compounds described herein are within the scope of this invention. Racemic mixtures are also encompassed within the scope of this invention. Therefore, single stereochemical isomers as well enantiomeric,
diastereoisomeric and geometric (or conformational) mixtures of the present compounds fall within the scope of the invention.

[110] The term "tautomers" refers to compounds, which are characterized by relatively easy interconversion of isomeric forms in equilibrium. These isomers are intended to be covered by this invention.

[III] The term "prodrug" refers to compounds, which are an inactive precursor of a compound, converted into its active form in the body by normal metabolic processes.

[112] The term "ester" refers to compounds, which are formed by reaction between an acid and an alcohol with elimination of water. An ester can be represented by the formula RCOOR', where R is the base compound and R' is the ester moiety (e.g., an ethyl group).

[113] Additionally the instant invention also includes the compounds which differ only in the presence of one or more isotopically enriched atoms for example replacement of hydrogen with deuterium and the like.

[114] Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, and Mn; salts of organic bases such as N,N'-diacetyldihexylenediamine, glucamine, triethylamine, choline, hydroxide, dicyclohexylamine, metformin, benzylamine, trialkylamine, and thiamine; chiral bases such as alkylyphenylamine, glycinol, and phenyl glycinol; salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, ornithine, lysine, arginine, and serine; quaternary ammonium salts of the compounds of invention with alkyl halides or alkyl sulphates such as Mel and (Me)₂S0₄; non-natural amino acids such as D-isomers or substituted amino acids; guanidine or substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium or substituted ammonium salts and aluminum salts. Salts may include acid addition salts where appropriate which are sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, maleates, citrates, fumarates, succinates, palmoates, methanesulphonates, benzoates, salicylates, benzenesulphonates, ascorbates, glycerophosphates, and ketoglutarates.

[115] The term "subject" or "patient" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey
species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; and laboratory animals including rodents, such as rats, mice and guinea pigs. Examples of non-mammals include, but are not limited to, birds, and fish. In one embodiment of the methods and compositions provided herein, the mammal is a human.

116 The terms "treat," "treating" or "treatment," as used herein, include relieving, abating or ameliorating a disease, disorder or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying causes of symptoms, inhibiting the disease, disorder or condition, e.g., arresting the development of the disease, disorder or condition, relieving the disease, disorder or condition, causing regression of the disease, disorder or condition, relieving a condition caused by the disease, disorder or condition, or stopping the symptoms of the disease, disorder or condition either prophylactically and/or therapeutically.

117 As used herein, the term "target protein" refers to a protein or a portion of a protein capable of being bound by, or interacting with a compound described herein, such as a compound capable of modulating a STIM protein and/or an Orai protein. In certain embodiments, a target protein is a STIM protein. In other embodiments, a target protein is an Orai protein, and in yet other embodiments, the compound targets both STIM and Orai proteins.

118 The term "STIM protein" refers to any protein situated in the endoplasmic reticular or plasma membrane which activates an increase in rate of calcium flow into a cell by a CRAC channel. (STIM refers to a stromal interaction molecule.) As used herein, "STIM protein" includes but is not limited to, mammalian STIM-1, such as human and rodent (e.g., mouse) STIM-1, Drosophila melanogaster D-STIM, C. elegans C-STIM, Anopheles gambiae STIM and mammalian STIM-2, such as human and rodent (e.g., mouse) STIM-2. As described herein, such proteins have been identified as being involved in, participating in and/or providing for store-operated calcium entry or modulation thereof, cytoplasmic calcium buffering and/or modulation of calcium levels in or movement of calcium into, within or out of intracellular calcium stores (e.g., endoplasmic reticulum).

119 It will be appreciated by "activate" or "activation" it is meant the capacity of a STIM protein to up-regulate, stimulate, enhance or otherwise facilitate calcium flow into a cell by a CRAC channel. It is envisaged that cross-talk between the STIM protein and
the CRAC channel may occur by either a direct or indirect molecular interaction. Suitably, the STIM protein is a transmembrane protein which is associated with, or in close proximity to, a CRAC channel.

[120] The term "fragment" or "derivative" when referring to a protein (e.g. STIM, Orai) means proteins or polypeptides which retain essentially the same biological function or activity in at least one assay as the native protein(s). For example, the fragment or derivative of the referenced protein preferably maintains at least about 50% of the activity of the native protein, at least 75%, or at least about 95% of the activity of the native protein, as determined, e.g., by a calcium influx assay.

[121] As used herein, "amelioration" refers to an improvement in a disease or condition or at least a partial relief of symptoms associated with a disease or condition. As used herein, amelioration of the symptoms of a particular disease, disorder or condition by administration of a particular compound or pharmaceutical composition refers to any lessening of severity, delay in onset, slowing of progression, or shortening of duration, whether permanent or temporary, lasting or transient that are attributed to or associated with administration of the compound or composition.

[122] The term "modulate," as used herein, means to interact with a target protein either directly or indirectly so as to alter the activity of the target protein, including, by way of example only, to inhibit the activity of the target, or to limit or reduce the activity of the target.

[123] As used herein, the term "modulator" refers to a compound that alters an activity of a target (e.g., a target protein). For example, in some embodiments, a modulator causes an increase or decrease in the magnitude of a certain activity of a target compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a target. In certain embodiments, an inhibitor completely prevents one or more activities of a target.

[124] As used herein, "modulation" with reference to intracellular calcium refers to any alteration or adjustment in intracellular calcium including but not limited to alteration of calcium concentration in the cytoplasm and/or intracellular calcium storage organelles, e.g., endoplasmic reticulum, or alteration of the kinetics of calcium fluxes into, out of and within cells. In aspect, modulation refers to reduction.
The terms "inhibits", "inhibiting", or "inhibitor" of SOC channel activity or CRAC channel activity, as used herein, refer to inhibition of store operated calcium channel activity or calcium release activated calcium channel activity.

The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

The term "pharmaceutically acceptable," molecular entities and compositions that are physiologically tolerable and do not typically produce an allergic or similar untoward reaction, such as gastric upset, and dizziness, when administered to a human. Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

The term "pharmaceutical composition" refers to a mixture of a compound of the present invention with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

The compounds and pharmaceutical compositions of the present invention can be administered by various routes of administration including, but not limited to, intravenous, oral, aerosol, parenteral, ophthalmic, pulmonary and topical administration.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result is reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of a compound of the present invention required to provide a clinically significant decrease in disease symptoms. In some embodiments, an appropriate "effective" amount in any individual case is determined using techniques, such as a dose escalation study.

The terms "enhance" or "enhancing," as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system.
An "enhancing-effective amount," as used herein, refers to an amount adequate to
enhance the effect of another therapeutic agent in a desired system.

[132] The term "carrier," as used herein, refers to relatively nontoxic chemical
compounds or agents that facilitate the incorporation of a compound into cells or tissues.

[133] The term "diluent" refers to chemical compounds that are used to dilute the
compound of interest prior to delivery. In some embodiments, diluents are used to
stabilize compounds because they provide a more stable environment. Salts dissolved in
buffered solutions (which also provide pH control or maintenance) are utilized as
diluents, including, but not limited to a phosphate buffered saline solution.

[134] As used herein, "intracellular calcium" refers to calcium located in a cell
without specification of a particular cellular location. In contrast, "cytosolic" or
"cytoplasmic" with reference to calcium refers to calcium located in the cell cytoplasm.

[135] As used herein, an effect on intracellular calcium is any alteration of any
aspect of intracellular calcium, including but not limited to, an alteration in intracellular
calcium levels and location and movement of calcium into, out of or within a cell or
intracellular calcium store or organelle. For example, in some embodiments, an effect on
intracellular calcium is an alteration of the properties, such as, for example, the kinetics,
sensitivities, rate, amplitude, and electrophysiological characteristics, of calcium flux or
movement that occurs in a cell or portion thereof. In some embodiments, an effect on
intracellular calcium is an alteration in any intracellular calcium-modulating process,
including, store-operated calcium entry, cytosolic calcium buffering, and calcium levels
in or movement of calcium into, out of or within an intracellular calcium store. Any of
these aspects are assessed in a variety of ways including, but not limited to, evaluation of
calcium or other ion (particularly cation) levels, movement of calcium or other ion
(particularly cation), fluctuations in calcium or other ion (particularly cation) levels,
kinetics of calcium or other ion (particularly cation) fluxes and/or transport of calcium or
other ion (particularly cation) through a membrane. An alteration is any such change that
is statistically significant. Thus, for example, in some embodiments, if intracellular
calcium in a test cell and a control cell is said to differ, such differences are a statistically
significant difference.

[136] Modulation of intracellular calcium is any alteration or adjustment in
intracellular calcium including but not limited to alteration of calcium concentration or
level in the cytoplasm and/or intracellular calcium storage organelles, e.g., endoplasmic
reticulum, alteration in the movement of calcium into, out of and within a cell or intracellular calcium store or organelle, alteration in the location of calcium within a cell, and alteration of the kinetics, or other properties, of calcium fluxes into, out of and within cells. In some embodiments, intracellular calcium modulation involves alteration or adjustment, e.g. reduction or inhibition, of store-operated calcium entry, cytosolic calcium buffering, calcium levels in or movement of calcium into, out of or within an intracellular calcium store or organelle, and/or basal or resting cytosolic calcium levels. The modulation of intracellular calcium involves an alteration or adjustment in receptor-mediated ion (e.g., calcium) movement, second messenger-operated ion (e.g., calcium) movement, calcium influx into or efflux out of a cell, and/or ion (e.g., calcium) uptake into or release from intracellular compartments, including, for example, endosomes and lysosomes.

[137] As used herein, "involved in", with respect to the relationship between a protein and an aspect of intracellular calcium or intracellular calcium regulation means that when expression or activity of the protein in a cell is reduced, altered or eliminated, there is a concomitant or associated reduction, alteration or elimination of one or more aspects of intracellular calcium or intracellular calcium regulation. Such an alteration or reduction in expression or activity occurs by virtue of an alteration of expression of a gene encoding the protein or by altering the levels of the protein. A protein involved in an aspect of intracellular calcium, such as, for example, store-operated calcium entry, thus, are one that provides for or participates in an aspect of intracellular calcium or intracellular calcium regulation. For example, a protein that provides for store-operated calcium entry are a STIM protein and/or an Orai protein.

[138] As used herein, a protein that is a component of a calcium channel is a protein that participates in multi-protein complex that forms the channel.

[139] As used herein, "cation entry" or "calcium entry" into a cell refers to entry of cations, such as calcium, into an intracellular location, such as the cytoplasm of a cell or into the lumen of an intracellular organelle or storage site. Thus, in some embodiments, cation entry is, for example, the movement of cations into the cell cytoplasm from the extracellular medium or from an intracellular organelle or storage site, or the movement of cations into an intracellular organelle or storage site from the cytoplasm or extracellular medium. Movement of calcium into the cytoplasm from an intracellular
organelle or storage site is also referred to as "calcium release" from the organelle or storage site.

[140] As used herein, "cell response" refers to any cellular response that results from ion movement into or out of a cell or within a cell. In some embodiments, the cell response is associated with any cellular activity that is dependent, at least in part, on ions such as, for example, calcium. Such activities optionally include, for example, cellular activation, gene expression, endocytosis, exocytosis, cellular trafficking and apoptotic cell death.

[141] As used herein, "immune cells" include cells of the immune system and cells that perform a function or activity in an immune response, such as, but not limited to, T-cells, B-cells, lymphocytes, macrophages, dendritic cells, neutrophils, eosinophils, basophils, mast cells, plasma cells, white blood cells, antigen presenting cells and natural killer cells.

[142] As used herein, "cytokine" or "cytokines" refers to small soluble proteins secreted by cells that in some embodiments, alter the behavior or properties of the secreting cell or another cell. Cytokines bind to cytokine receptors and trigger a behavior or properly within the cell, for example, cell proliferation, death or differentiation. Exemplary cytokines include, but are not limited to, interleukins (e.g., IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-16, IL-17, IL-18, IL-1.alpha., IL-1.beta., and IL-1 RA), granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), oncostatin M, erythropoietin, leukemia inhibitory factor (LIF), interferons, B7.1 (also known as CD80), B7.2 (also known as B70, CD86), TNF family members (TNF-.alpha., TNF-.beta., LT-.beta., CD40 ligand, Fas ligand, CD27 ligand, CD30 ligand, 4-1BBL, Trail), and MIF.

[143] "Store operated calcium entry" or "SOCE" refers to the mechanism by which release of calcium ions from intracellular stores is coordinated with ion influx across the plasma membrane.

[144] Cellular calcium homeostasis is a result of the summation of regulatory systems involved in the control of intracellular calcium levels and movements. Cellular calcium homeostasis is achieved, at least in part, by calcium binding and by movement of calcium into and out of the cell across the plasma membrane and within the cell by movement of calcium across membranes of intracellular organelles including, for
example, the endoplasmic reticulum, sarcoplasmic reticulum, mitochondria and endocytic organelles including endosomes and lysosomes.

[145] Movement of calcium across cellular membranes is carried out by specialized proteins. For example, calcium from the extracellular space enters the cell through various calcium channels and a sodium/calcium exchanger and is actively extruded from the cell by calcium pumps and sodium/calcium exchangers. Calcium is also released from internal stores through inositol trisphosphate or ryanodine receptors and is likely taken up by these organelles by means of calcium pumps.

[146] Calcium enters cells by any of several general classes of channels, including but not limited to, voltage-operated calcium (VOC) channels, store-operated calcium (SOC) channels, and sodium/calcium exchangers operating in reverse mode. VOC channels are activated by membrane depolarization and are found in excitable cells like nerve and muscle and are for the most part not found in nonexcitable cells. Under some conditions, Ca\(^{2+}\) also enters cells via Na\(^+\) - Ca\(^{2+}\) exchangers operating in reverse mode.

[147] Endocytosis provides another process by which cells take up calcium from the extracellular medium through endosomes. In addition, some cells, e.g., exocrine cells, release calcium via exocytosis.

[148] Cytosolic calcium concentration is tightly regulated with resting levels usually estimated at approximately 0.1 \(\mu\text{M}\) in mammalian cells, whereas the extracellular calcium concentration is typically about 2 mM. This tight regulation facilitates transduction of signals into and within cells through transient calcium flux across the plasma membrane and membranes of intracellular organelles. There is a multiplicity of intracellular calcium transport and buffer systems in cells that serve to shape intracellular calcium signals and maintain the low resting cytoplasmic calcium concentration. In cells at rest, the principal components involved in maintaining basal calcium levels are calcium pumps and leaks in the endoplasmic reticulum and plasma membrane. Disturbance of resting cytosolic calcium levels effects transmission of such signals and give rise to defects in a number of cellular processes. For example, cell proliferation involves a prolonged calcium signalling sequence. Other cellular processes include, but are not limited to, secretion, signalling, and fertilization, involve calcium signalling.

[149] Cell-surface receptors that activate phospholipase C(PLC) create cytosolic Ca\(^{2+}\) signals from intra- and extra-cellular sources. An initial transient rise of \([\text{Ca}^{2+}]_i\) (intracellular calcium concentration) results from the release of \(\text{Ca}^{2+}\) from the
endoplasmic reticulum (ER), which is triggered by the PLC product, inositol-1,4,5-trisphosphate (P3), opening IP3 receptors in the ER (Streb et al. Nature, 306, 67-69, 1983). A subsequent phase of sustained Ca\(^{2+}\) entry across the plasma membrane then ensues, through specialized store operated calcium (SOC) channels (in the case of immune cells the SOC channels are calcium release-activated calcium (CRAC) channels) in the plasma membrane. Store-operated Ca\(^{2+}\) entry (SOCE) is the process in which the emptying of Ca\(^{2+}\) stores itself activates Ca\(^{2+}\) channels in the plasma membrane to help refill the stores (Putney, Cell Calcium, 7, 1-12, 1986; Parekh et al, Physiol. Rev. 757-810; 2005). SOCE does more than simply provide Ca\(^{2+}\) for refilling stores, but itself generates sustained Ca\(^{2+}\) signals that control such essential functions as gene expression, cell metabolism and exocytosis (Parekh and Putney, Physiol. Rev. 85, 757-810 (2005).

[150] In lymphocytes and mast cells, activation of antigen or Fc receptors causes the release of Ca\(^{2+}\) from intracellular stores, which in turn leads to Ca\(^{2+}\) influx through CRAC channels in the plasma membrane. The subsequent rise in intracellular Ca\(^{2+}\) activates calcineurin, a phosphatase that regulates the transcription factor NFAT. In resting cells, NFAT is phosphorylated and resides in the cytoplasm, but when dephosphorylated by calcineurin, NFAT translocates to the nucleus and activates different genetic programmes depending on stimulation conditions and cell type. In response to infections and during transplant rejection, NFAT partners with the transcription factor AP-1 (Fos-Jun) in the nucleus of "effector" T cells, thereby transactivating cytokine genes, genes that regulate T cell proliferation and other genes that orchestrate an active immune response (Rao et al., Annu Rev Immunol, 1997; 15:707-47). In contrast, in T cells recognizing self antigens, NFAT is activated in the absence of AP-1, and activates a transcriptional programme otherwise known as "anergy" that suppresses autoimmune responses (Macian et al., Transcriptional mechanisms underlying lymphocyte tolerance. Cell. 2002 Jun. 14; 109(6):719-31). In a subclass of T cells, known as regulatory T cells which suppress autoimmunity mediated by self-reactive effector T cells, NFAT partners with the transcription factor FOXP3 to activate genes responsible for suppressor function (Wu et al., Cell. 2006 Jul. 28; 126(2):375-87; Rudensky A Y, Gavin M, Zheng Y. Cell. 2006 Jul. 28; 126(2):253-256).

[151] The endoplasmic reticulum (ER) carries out a variety processes. The ER has a role as both an agonist-sensitive Ca\(^{2+}\) store and sink, protein folding/processing takes place within its lumen. Here, numerous Ca\(^{2+}\)-dependent chaperone proteins ensure that
newly synthesized proteins are folded correctly and sent off to the appropriate
destination. The ER is also involved in vesicle trafficking, release of stress signals,
regulation of cholesterol metabolism, and apoptosis. Many of these processes require
intraluminal Ca\(^{2+}\), and protein misfolding, ER stress responses, and apoptosis are all
likely induced by depleting the ER of Ca\(^{2+}\) for prolonged periods of time. Because of its
role as a source of Ca\(^{2+}\), it is clear that ER Ca\(^{2+}\) content must fall after stimulation.
However, to preserve the functional integrity of the ER, it is vital that the Ca\(^{2+}\) content
does not fall too low or is maintained at a low level. Replenishment of the ER with Ca\(^{2+}\)
is therefore a central process to all eukaryotic cells. Because a fall in ER Ca\(^{2+}\) content
activates store-operated Ca\(^{2+}\) channels in the plasma membrane, a major function of this
Ca\(^{2+}\) entry pathway is believed to be maintenance of ER Ca\(^{2+}\) levels that are necessary for
proper protein synthesis and folding. However, store-operated Ca\(^{2+}\) channels have other
important roles.

[152] The understanding of store operated calcium entry was provided by
electrophysiological studies which established that the process of emptying the stores
activated a Ca\(^{2+}\) current in mast cells called Ca\(^{2+}\) release-activated Ca\(^{2+}\) current or I\(\text{CRAC}\)-
ICRAC is non-voltage activated, inwardly rectifying, and remarkably selective for Ca\(^{2+}\). It
is found in several cell types mainly of hemopoietic origin. I\(\text{CRAC}\) is not the only store-
operated current, and it is now apparent that store-operated influx encompasses a family
of Ca\(^{2+}\)-permeable channels, with different properties in different cell types. I\(\text{CRAC}\) was
the first store-operated Ca\(^{2+}\) current to be described and remains a popular model for
studying store-operated influx.

[153] Effects of compounds or agents on intracellular calcium can be monitored
using various screening/identification methods which provide for a direct or indirect
evaluation or measurement of cellular (including cytosolic and intracellular organelle or
compartment) calcium and/or movement of ions into, within or out of a cell, organelle,
calcium store or portions thereof (e.g., a membrane). A variety of methods can be used
for evaluating calcium levels and ion movements or flux. The particular method used and
the conditions employed would depend on whether a particular aspect of intracellular
calcium is being monitored or assessed. For example, in some aspects, reagents and
conditions may be used for specifically evaluating store-operated calcium entry, resting
cytosolic calcium levels, calcium buffering and calcium levels and uptake by or release
from intracellular organelles and calcium stores. Alternately, the effect of a compound or
agent on intracellular calcium can be monitored or assessed using, for example, a cell, an
intracellular organelle or calcium storage compartment, a membrane (including, e.g., a
detached membrane patch or a lipid bilayer) or a cell-free assay system (e.g., outside-out
membrane vesicle). Generally, some aspect of intracellular calcium is monitored or
assessed in the presence of test agent and compared to a control, e.g., intracellular
calcium in the absence of test agent.

**Diseases, Disorders or Conditions**

[154] Clinical studies demonstrate that the CRAC channel is absolutely required for
the activation of genes underlying the T cell response to antigen. Sustained calcium entry
is needed for lymphocyte activation and adaptive immune response. Calcium entry into
lymphocytes occurs primarily through the CRAC channels. Increased calcium leads to
NFAT activation and expression of cytokines required for immune response. Inhibiting
the store operated calcium entry is an efficient way to prevent T cell activation.

[155] Inhibition of CRAC channel activity with the compounds that modulate
intracellular calcium levels provide a means for providing immunosuppressive therapy as
demonstrated by the elimination of store-operated calcium entry noted in patients with
severe-combined immunodeficiency (SCID). T cells, fibroblasts, and in some cases B
cells, from patients with T cell immunodeficiency or SCID having a principal defect in T
cell activation show a strong defect in store-operated calcium entry. SCID patients lack
adaptive immune response, but without any impairment or toxicity in major organs. The
SCID patient phenotype indicates that inhibition of CRAC channels is an effective
strategy for immunosuppression.

**Diseases/Disorders Involving Inflammation and Diseases/Disorders Related to the
Immune System**

[156] In some embodiments, diseases, disorders or conditions that are treated or
prevented using compounds disclosed herein that are capable of modulating intracellular
calcium levels, compositions thereof, and methods provided herein to identify
compounds capable of modulating intracellular calcium levels, include diseases,
conditions or disorders involving inflammation and/or that are related to the immune
system. These diseases include, but are not limited to, asthma, chronic obstructive
pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, glomerulonephritis, neuroinflammatory diseases such as multiple sclerosis, and disorders
of the immune system.
The activation of neutrophils (PMN) by inflammatory mediators is partly achieved by increasing cytosolic calcium concentration. Store-operated calcium influx in particular is thought to play an important role in PMN activation. It has been shown that trauma increases PMN store-operated calcium influx and that prolonged elevations of cytosolic calcium concentration due to enhanced store-operated calcium influx likely alters stimulus-response coupling to chemotaxins and contribute to PMN dysfunction after injury. Modulation of PMN cytosolic calcium concentration through store-operated calcium channels might therefore be useful in regulating PMN-mediated inflammation and spare cardiovascular function after injury, shock or sepsis.

Calcium plays a critical role in lymphocyte activation. Activation of lymphocytes, e.g., by antigen stimulation, results in rapid increases in intracellular free calcium concentrations and activation of transcription factors, including nuclear factor of activated T cells (NFAT), NF-κB, JNK1, MEF2 and CREB. NFAT is a key transcriptional regulator of the IL-2 (and other cytokine) genes. A sustained elevation of intracellular calcium level is required to keep NFAT in a transcriptionally active state, and is dependent on store-operated calcium entry. Reduction or blocking of store-operated calcium entry in lymphocytes blocks calcium-dependent lymphocyte activation. Thus, in some embodiments, modulation of a STIM protein and/or an Orai protein, and particularly store-operated calcium entry (e.g., reduction in, elimination of store-operated calcium entry), in lymphocytes is a method for treating immune and immune-related disorders, including, for example, chronic immune diseases/disorders, acute immune diseases/disorders, autoimmune and immunodeficiency diseases/disorders, diseases/disorders involving inflammation, organ transplant graft rejections and graft-versus-host disease and altered (e.g., hyperactive) immune responses. For example, in some embodiments treatment of an autoimmune disease/disorder involves reducing, blocking or eliminating store-operated calcium entry in lymphocytes.

Examples of immune disorders include, for example, psoriasis, rheumatoid arthritis, vasculitis, inflammatory bowel disease, dermatitis, osteoarthritis, asthma, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation (organ, bone marrow, stem cells and other cells and tissues) graft rejection, graft-versus-host disease, lupus erythematosus, inflammatory disease, type I diabetes, pulmonary fibrosis, dermatomyositis, Sjogren’s syndrome, thyroiditis (e.g., Hashimoto’s and autoimmune
thyroiditis), myasthenia gravis, autoimmune hemolytic anemia, multiple sclerosis, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis and atopic dermatitis.

[160] In other embodiments, compounds disclosed herein that are capable of modulating intracellular calcium levels, compositions thereof, and methods provided herein to identify compounds capable of modulating intracellular calcium levels, are used in connection with treatment of malignancies, including, but not limited to, malignancies of lymphoreticular origin, bladder cancer, breast cancer, colon cancer, endometrial cancer, head and neck cancer, lung cancer, melanoma, ovarian cancer, prostate cancer and rectal cancer. Store-operated calcium entry is thought to play an important role in cell proliferation in cancer cells.

[161] Inhibition of SOCE is sufficient to prevent tumor cell proliferation. The pyrazole derivative BTP-2, a direct $I_{\text{CRAC}}$ blocker inhibits SOCE and proliferation in Jurkat cells and in colon cancer cells. Moreover, sustained SOCE requires mitochondrial Ca$^{2+}$ uptake and that prevention of mitochondrial Ca$^{2+}$ uptake leads to SOCE inhibition. Stimulation of Jurkat cells induces sustained SOCE and activation of the Ca$^{2+}$-dependent phosphatase calcineurin that dephosphorylates NFAT, promoting expression of interleukin-2 and proliferation. In other embodiments, compounds capable of modulating intracellular calcium levels inhibit SOCE and are used in the treatment of cancer or other proliferative diseases or conditions.

[162] In some embodiments, diseases, disorders or conditions that are treated or prevented using compounds disclosed herein that are capable of modulating intracellular calcium levels, compositions thereof, and methods provided herein to identify compounds capable of modulating intracellular calcium levels, include, for example, hepatic or liver diseases and disorders. These diseases, conditions or disorders include but are not limited to liver injury, for example, due to transplantation, hepatitis and cirrhosis.

[163] Store-operated calcium entry has been implicated in chronic liver disease as well as transplantation injury after cold preservation-warm deoxygenation.

[164] In some embodiments, diseases, conditions or disorders that are treated or prevented using the compounds disclosed herein that are capable of modulating intracellular calcium levels, compositions thereof, and methods provided herein to identify compounds capable of modulating intracellular calcium levels, include kidney or
renal diseases and disorders. Mesangial cell hyperplasia is often a key feature of such diseases and disorders. In other embodiments, such diseases and disorders are caused by immunological or other mechanisms of injury, including IgAN, membranoproliferative glomerulonephritis or lupus nephritis. Imbalances in the control of mesangial cell replication also appear to play a key role in the pathogenesis of progressive renal failure. The turnover of mesangial cells in normal adult kidney is very low with a renewal rate of less than 1%. A prominent feature of glomerular/kidney diseases is mesangial hyperplasia due to elevated proliferation rate or reduced cell loss of mesangial cells. When mesangial cell proliferation is induced without cell loss, for example due to mitogenic stimulation, mesangioproliferative glomerulonephritis does result. Data have indicated that regulators of mesangial cell growth, particularly growth factors, are thought to act by regulating store-operated calcium channels. In yet other embodiments, modulators of store-operated calcium influx aids in the treatment of glomerular diseases by inhibiting mesangial cell proliferation.

[165] In one aspect, compounds described herein modulate intracellular calcium, such as but not limited to, modulation (e.g. reduction or inhibition) of SOC channel activity, such as inhibition of CRAC channel activity (e.g. inhibition of \( I_{\text{CRAC}} \), inhibition of SOCE), in an immune system cell (e.g., a lymphocyte, white blood cell, T cell, B cell), a fibroblast (or a cell derived from a fibroblast), or an epidermal, dermal or skin cell (e.g., a keratinocyte). In some embodiments, the step of modulating one or more proteins involved in modulating intracellular calcium (e.g. a STIM protein and/or Orai protein) involves, for example, reducing the level, expression of, an activity of, function of and/or molecular interactions of a protein. For instance, if a cell exhibits an increase in calcium levels or lack of regulation of an aspect of intracellular calcium modulation, e.g., store-operated calcium entry, then in other embodiments, modulating involves reducing the level of, expression of, an activity or function of, or a molecular interaction of a protein, e.g. a STIM protein and/or Orai protein.

[166] The following general methodology described herein provides the manner and process of making and using the compound of the present invention and are illustrative rather than limiting. Further modification of provided methodology and additionally new methods may also be devised in order to achieve and serve the purpose of the invention. Accordingly, it should be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the specification hereto.
General Method of Preparation of Compound of Formula (I)

The compounds of the present invention may be prepared by the following processes. Unless otherwise indicated, all the variables when used in the below formulae are to be understood to present those groups described above in relation to formula (IA). These methods can similarly be applied to other compounds of formula (I) (e.g., I, IA, IA-I, and/or IA-III).

Scheme 1 provides a general process for synthesis of a compound of formula (IA) wherein L₁ & L₂ together are -NH-CO-, R'' is hydrogen or halogen, and all other variables R, R¹, R², T, U, V, W, A and Cy are as described above in relation to formula (IA).

A compound of formula 1 can be reacted with a compound of formula 2 (e.g., phenyl hydrazine) to form a compound of formula 3. The compound of formula 3 can then be nitrated, e.g., using a mixture of concentrated H₂SO₄ and concentrated HNO₃ to form a compound of formula 4. Reduction of the compound of formula 4, such as with FeCl₃ and hydrazine in the presence of activated charcoal, yields the corresponding amine compound of formula 5a wherein R'' is Hydrogen. Alternately halogenation followed by reduction of the compound of formula 4, yields the corresponding amine compound of formula 5b wherein R'' is Halogen. The compound of formula 5a or 5b can be coupled with various other intermediates in the presence of a suitable coupling reagent to provide a compound of formula (IA). The compound of formula 5a or 5b can be coupled with i. Cy-A-COOH using one or more amide coupling reagents such as (benzotriazol-1-yloxy)tris(dimethylamino) phosphoniumhexafluoro phosphate (BOP...
reagent) or N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC); ii. with acid chlorides of formula Cy-A-COCl; or iii. isocyanates of formula Cy-NCO where A is NH.

Scheme 2 provides a general process for synthesis of a compound of formula (IA) wherein Li & L₂ together i -NH-CO- , R" is hydrogen or halogen and all other variables R, R¹, R², T, U, V, W, A and Cy are those described above in relation to formula (IA).

Step-1

[170] Step-1: A ketone of formula a can be condensed with an ester of formula b in the presence of a base such as a metal alkoxide, e.g., sodium ethoxide, to give a diketone of formula 1.

[171] Step-2: The compound of formula 1 can be converted to a pyrazole compound of formula 2a by reacting it with hydrazine. The compound of formula 2a can be reacted, with a compound of formula 2b wherein L₉ is a leaving group (such as a halogen) in the presence of a suitable base such as an alkali metal carbonate, e.g., Cs₂CO₃, to give a compound of formula 4, which can be subjected to a similar sequence of transformations as described above in scheme 1 to afford a compound of formula IA.

56
Scheme 2 provides a general process for synthesis of a compound of formula (IA) wherein $L_1$ & $L_2$ together is $-\text{CO-NH}$-, $R''$ is hydrogen or Halogen and all other variables $R$, $R^1$, $R^2$, $T$, $U$, $V$, $W$, $A$ and $\text{Cy}$ are those described above in relation to formula (IA).

The compound of formula 2a can be reacted with a compound of formula 2c wherein $L_g$ is a leaving group (such as a halogen) in the presence of a suitable base such as an alkali metal carbonate, e.g., $\text{Cs}_2\text{C}O_3$, to give a compound of formula 4a, which can then be hydrolysed to give a compound of formula 5c. The compound of formula 5c can be coupled with $\text{Cy}-\text{A-NH}_2$ using one or more amide coupling reagents such as (benzotriazol-1-yloxy)tris(dimethylamino) phosphoniumhexafluoro phosphate (BOP reagent) or $N$-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide hydrochloride (EDC).

Similar methodologies with certain modifications as known to those skilled in the art can be used to synthesize compounds of formula I, IA, IA-I, and/or IA-III wherein the variables are to be understood to present those groups described above in relation to formula I, IA, IA-I, and/or IA-III using suitable intermediates and reagents.

Experimental

The following abbreviations are used throughout this disclosure: EDC.HCl [N-(3-dimethylaminopropyl)-$N'$-ethylcarbodiimide hydrochloride], HOBt [Hydroxybenzotriazole], TEA (triethylamine), DMF (dimethyl formamide), AcOEt (ethyl acetate), DCM (dichloromethane), DMSO (dimethyl sulfoxide), THF (tetrahydrofuran). Unless otherwise mentioned, work-up implies distribution of reaction mixture between the aqueous and organic phases indicated within parentheses, separation and drying over $\text{Na}_2\text{SO}_4$ of the organic layer and evaporating the solvent to afford a residue. Unless otherwise stated, purification implies column chromatography using
silica gel as the stationary phase and a mixture of petroleum ether (boiling at 60-80 °C) and ethyl acetate or dichloromethane and methanol of suitable polarity as the mobile phases. RT (or rt, implies ambient temperature (-25-28 °C).

[177] **Intermediate 1: 1,3-dicyclopopylpropane-1,3-dione:** Sodium ethoxide (8g, 117.64 mmol) was added to a solution of cyclopropyl methyl ketone (5g, 59.4 mmol) and methyl cyclopropane carboxylate (12 ml, 118.9 mmol) in DMSO (30 mL). The resulting mixture was heated at 60 °C overnight and then cooled to 0 °C. After quenching the reaction with 6N HCl, work-up (H2O/AcOEt) gave the title compound as a brown liquid which was used without any purification. 1H-NMR (δ ppm, CDC13, 400 MHz): 16.05 (bs, 0.6H), 5.72 (s, 0.6H) 3.78 (s, 0.8H), 2.08-2.0 (m, 0.8H), 1.62-1.53 (m, 1.2H), 1.12-1.05 (m, 4H), 0.97-0.83 (m, 4H). MS (m/z): 153.2 [M+H]+.

[178] **Intermediate 2: l-cyclopropyl-1,4,4-trifluorobutane-1,3-dione:** A procedure similar to that described for intermediate 1 was followed. From cyclopropyl methyl ketone (10 g, 119 mmol), ethyl 2,2,2-trifluoroacetate (29 ml, 237 mmol), DMSO (60 mL) and sodium ethoxide (16.1 g, 237 mmol), the title compound (15 g) was obtained as a brown liquid and was used in the next step without purification. 1H-NMR (δ ppm, CDC13, 400 MHz): 5.65 (s, 2H), 2.16-2.04 (m, 1H), 1.18-1.12 (m, 2H), 0.98-0.94 (m, 2H).

[179] **Intermediate 3: 4,4,4-trifluoro-l-(furan-2-yl)butane-1,3-dione:** A procedure similar to that described for intermediate 1 was followed. From 1-(furan-2-yl)ethanone (5 g, 45.4 mmol), ethyl 2,2,2-trifluoroacetate (12.9 g, 90.8 mmol), DMSO (30 mL) and sodium ethoxide (6.2 g, 90.8 mmol), the title compound was obtained as a brown liquid quantitatively and was used without purification. 1H-NMR (δ ppm, DMSO-d6, 400 M Hz): 9.10 (bs, 1H), 8.15 (s, 1H), 7.96 (d, J 1, 1H), 6.85-6.81 (m, 1H), 6.70 (s, 1H).

[180] **Intermediate 4: 3,5-dicyclopopyl-1H-pyrazole:** Intermediate 1 (5.3 g, 35 mmol) and hydrazine hydrate (1.8 mL, 38.3 mmol) in ethanol (20 mL) were refluxed overnight. Work-up (H2O/AcOEt) after cooling the mixture to ambient temperature gave the title compound as a brown solid. M. P.: 161-164 °C. 1H-NMR (δ ppm, CDC13, 400 MHz): 15.2 (bs, 1H), 5.65 (s, 1H), 2.16-2.09 (m, 2H), 1.18-1.14 (m, 4H), 0.98-0.94 (m, 4H). MS (m/z): 149.04 [M+H]+.

[181] **Intermediate 5: 5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazole:** Intermediate 2 (0.120 g, 0.66 mmol) and hydrazine hydrate (0.04 mL, 0.72 mmol) were
dissolved in ethanol (6 mL) and refluxed overnight. Work-up (H₂O/AcOEt) after cooling the mixture to RT gave the title compound as a brown solid (0.114 g).

[182] **Intermediate 6: 5-(furan-2-yl)-1-phenyl-3-(trifluoromethyl)-1 H-pyrazole:**
A procedure similar to that described for intermediate 4 was followed. From intermediate 3 (4 g, 19.4 mmol) and phenyl hydrazine (2.31 g, 21.3 mmol), title compound obtained as a white solid. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.52-7.48 (m, 3H), 7.46-7.40 (m, 3H), 6.91 (s, 1H), 6.36-6.33 (m, 1H), 5.96 (d, J 7.4, 1H).

[183] **Intermediate 7: 1-phenyl-3-(trifluoromethyl)-1 H-pyrazole-5-carboxylic acid:** Intermediate 6 (2.84 g, 10.2 mmol) was dissolved in acetone (120 ml) and KMnO₄ (11.2 gms, 71.45 mmol in 135 ml water) solution was added to it. This mixture was heated at 60 °C for 3h and then cooled to rt. Then isopropyl alcohol was added to the reaction mixture and stirred at rt overnight. The reaction mixture filtered through celite and filtrate was evaporated on high vacuum. The residue was dissolved in IN NaOH and washed with petether. Aqueous layer was acidified with 2N HCl solution to obtain the solid. Solid was filtered and dried on high vacuum to obtain the title compound (2.3 g) as a white solid. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.57-7.42 (m, 5H), 7.30 (s, 1H).

[184] **Intermediate 8: methyl 1-phenyl-3-(trifluoromethyl)-1 H-pyrazole-5-carboxylate:** Intermediate 7 (1.55 g, 6.0 mmol) was dissolved in MeOH (15 ml), cooled to 0 °C and thionyl chloride (1.3 ml, 18.2 mmol) was added. Reaction mixture was heated to 60 °C for overnight. Work up (AcOEt : H₂O ) followed by evaporation on high vacuum obtained the title compound as an yellow solid. ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 7.51-7.47 (m, 3H), 7.46-7.41 (m, 2H), 7.50 (s, 1H), 3.82 (s, 3H).

[185] **Intermediate 9: 3,5-dicyclopropyl-1-(4-nitrophenyl)-1 H-pyrazole:**
A solution of intermediate 4 (2.0 g, 13.5 mmol) and Cs₂CO₃ (5.51 g, 40.5 mmol) in DMSO (15 mL) was heated at 160 °C under nitrogen for 0.5 h. To the mixture, 4-chloro-l-nitrobenzene (6.38 g, 40.5 mmol) was added and stirred at the same temperature for 4 h. Work-up (H₂O/AcOEt) and purification afforded the title compound (0.8 g). ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 8.32 (d, J 9.0, 2H), 7.92 (d, J 9.0, 2H), 5.76 (s, 1H), 1.97-1.91 (m, 1H), 1.86-1.80 (m, 1H), 1.09-1.04 (m, 2H), 0.98-0.94 (m, 2H), 0.83-0.75 (m, 4H).

[186] **Intermediate 10: 3,5-dicyclopropyl-1-(2-fluoro-4-nitrophenyl)-1 H-pyrazole:**
A solution of intermediate 4 (2.0 g, 13.5 mmol) and K₂CO₃ (5.5 g, 40.6 mmol) in DMSO (20 mL) were heated at 120 °C under nitrogen for 0.5 h. To this mixture, 3,4-difluoro-l-nitrobenzene (2.15 g, 13.5 mmol) was added and stirred at the same
temperature for 2 h. Work-up (H₂O/AcOEt) and purification afforded the title compound as a yellow solid (3.16 g). ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 8.19-8.12 (m, 2H), 7.78 (t, J 7.9, IH), 5.70 (s, IH), 2.10-2.00 (m, IH), 1.68-1.58 (m, IH), 1.08-0.92 (m, 4H), 0.82-0.74 (m, 2H), 0.72-0.65 (m, 2H).

Intermediate 11: 2-(3,5-dicyclopentyl-H-pyrazol-1-yl)-5-nitropyridine: A solution of intermediate 4 (8.0 g, 54.05 mmol) and K₂C₅O₃ (27.96 g, 202.6 mmol) in DMSO (60 mL) was heated at 110 °C under nitrogen for 0.5 h. To the mixture, 2-chloro-5-nitropyridine (12.8 g, 80.75 mmol) was added and stirred at the same temperature for 2 h. Work-up (H₂O/AcOEt) and purification afforded the title compound (3.03 g). ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 9.24 (d, J 2.6, IH), 8.51 (dd, J 2.6, 9.9, IH), 8.10 (d, J 9.2, IH), 5.72 (s, IH), 2.90-2.75 (m, IH), 1.99-1.90 (m, IH), 1.06-0.93 (m, 4H), 0.82-0.64 (m, 4H).

Intermediate 12: ethyl 6-(3,5-dicyclopentyl-H-pyrazol-1-yl)nicotinate: A solution of intermediate 4 (2.0 g, 13.5 mmol) and K₂C₅O₃ (5.6 g, 40.5 mmol) in DMSO (15 mL) was heated at 120 °C under nitrogen for 0.5 h. To the mixture, ethyl-6-chloronicotinate (3.8 g, 20.3 mmol) was added and stirred at 160 °C for 4 h. Work-up (H₂O/AcOEt) and purification afforded the title compound (0.26 g). ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 8.95-8.90 (m, IH), 8.38 (dd, J 2.2, 8.7, IH), 7.91 (d, J 8.7, IH), 5.93 (s, IH), 4.35 (q, J 4.12, 2H), 2.88-2.78 (m, IH), 1.91-1.83 (m, IH), 1.33 (t, J 7.1, 3H), 0.99-0.85 (m, 4H), 0.62-0.55 (m, 4H). MS (m/z): 298.3 ([M+H]+).

Intermediate 13: 5-cyclopropyl-l-(4-nitrophenyl)-3-(trifluoromethyl)-lH-pyrazole: A procedure similar to that followed for intermediate 9 was employed. From intermediate 5 (1.0 g, 5.67 mmol), Cs₂C₅O₃ (5.5 g, 16.9 mmol), DMSO (4 mL) and 4-chloro-l-nitrobenzene (1.93 g, 14.1 mmol) was obtained the title compound (0.7 g). ¹H-NMR (δ ppm, CDCl₃, 400 MHz): 8.38 (d, J 7.08, 2H), 7.92 (d, J 7.08, 2H), 6.32 (s, IH), 1.89-1.82 (m, IH), 1.19-1.11 (m, 2H), 0.89-0.85 (m, 2H). MS (m/z): 298.15 [M+H]+.

Intermediate 14: 5-cyclopropyl-l-(2-fluoro-4-nitrophenyl)-3-(trifluoromethyl)-IH-pyrazole: A solution of intermediate 5 (6.3 g, 35 mmol) and K₂C₅O₃ (14.6 g, 105 mmol) in DMSO (20 mL) was heated at 120 °C under nitrogen for 30 mins. To this mixture, 1,2-difluoro nitrobenzene (5.68 g, 35 mmol) was added and stirred at the same temperature for 2 h. Work-up (H₂O/AcOEt) and purification afforded the title compound (7.52 g). ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 8.49 (dd, J 2.4, 9.9,
1H), 8.47-8.27 (m, 1H), 8.04-8.02 (m, 1H), 6.73 (s, 1H), 1.76-1.68 (m, 1H), 0.99-0.90 (m, 2H), 0.84-0.74 (m, 2H).

[191] Intermediate 15: 5-cyclopropyl-1-(2,6-difluoro-4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole: Intermediate 5 (1g, 5.7 mmol) and 3,4,5-trifluoronitrobenzene (lg 5.7 mmol) were dissolved in THF and added sodium hydride (274 mg, 11.3 mmol). Mixture was refluxed for 2h and reaction mixture cooled to rt and quenched with water. Work-up (H2O/acetone) gave the desired product as a yellow gummy liquid. 1H-NMR (δ ppm, CDC13, 400 MHz): 8.37 (d, J 9, 2H), 7.68 (d, J 9, 2H), 7.31 (s, 1H), 3.87 (s, 3H).

[192] Intermediate 16: 2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-nitropyridine: A solution of intermediate 5 (1.0 g, 5.67 mmol) and K2CO3 (2.35 g, 17.03 mmol) in DMSO (10 mL) was heated at 90 °C under nitrogen for 30 mins. To the mixture, 2-chloro-5-nitropyridine (1.35 g, 8.5 mmol) was added and stirred at the same temperature for 2 h. Work-up (H2O/acetone) and purification afforded the title compound (0.30 g). 1H-NMR (δ ppm, CDC13, 400 MHz): 9.33 (d, J 2.5, 1H), 8.62 (dd, J 2.8, 9.0, 1H), 8.19 (d, J 9.0, 1H), 6.29 (s, 1H), 2.92-2.83 (m, 1H), 1.60-1.50 (m, 2H), 0.79-0.70 (m, 2H).

[193] Intermediate 17: 2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-nitropyrimidine: Intermediate 5 (500 mg, 2.84 mmol) and 2-chloro-4-nitropyrimidine (452 mg, 2.84 mmol) were dissolved in THF and cooled to 0 °C. To this mixture sodium hydride (136 mg, 5.7 mmol) was added slowly and reaction mixture was heated to reflux. After one hour reaction mixture cooled to rt and quenched with water. Work up (H2O/acetone) and purification gave the desired product (455 mg) as a white solid. 1H-NMR (δ ppm, CDC13, 400 MHz): 9.58 (s, 2H), 6.37 (s, 1H), 2.82-2.74 (m, 1H), 1.18-1.10 (m, 2H), 0.82-0.75 (m, 2H).

[194] Intermediate 18: methyl 1-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate: Intermediate 8 (2 g, 7.4 mmol) was dissolved in acetic acid (15 ml), cooled to 0 °C and added nitration mixture (6 ml HNO3 and 6 ml H2SO4) drop-wise. Reaction mixture was heated to 60 °C for overnight. Work up (AcOEt : H2O) and purification on silicagel (60-120 mesh silicagel) using EA and pet ether (3: 97) as eluent afforded the title compound (850 mg) as a white solid. 1H-NMR (δ ppm, CDC13, 400 MHz): 8.37 (d, J 9, 2H), 7.68 (d, J 9, 2H), 7.31 (s, 1H), 3.87 (s, 3H).
Intermediate 19: [l-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl]methanol: Intermediate 18 (0.662 g, 2.1 mmol) dissolved in a mixture of THF (5 ml) and MeOH (5 ml) and added sodium borohydride (79 mg, 2.1 mmol). Colour of the reaction mixture changed to pink and then two drops of water added to it. Reaction mixture allowed to stir at rt for 1 h and at this stage colour changed to pink to pale yellow. Reaction mixture was allowed to stir further overnight. Work up (AcOEt/H2O) and evaporation of organic layer on vacuum afforded the title compound (558 mg) as a white solid. 1H-NMR (δ ppm, DMSO-4, 400 MHz): 8.42 (d, J 8.9, 2H), 8.01 (d, J 8.9, 2H), 7.01 (s, 1H), 5.77 (t, J 5.4, 1H), 4.63 (d, J 5.4, 2H).

Intermediate 20: 1-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carbaldehyde: Oxalyl chloride (0.32 ml, 3.8 mmol) was dissolved in DCM, cooled to -78 °C and added DMSO (0.5 ml 7.6 mmol) and stirred for 30 mins. To this intermediate 19 (550 mg, 1.9 mmol) was added, stirred at -78 °C for 20 mins and added triethyl amine (1.06 ml, 7.6 mmol). Reaction mixture warmed to 0 °C and then slowly heated to rt. Work up (H2O/AcOEt) afforded the title compound (375 mg). 9.85 (s, 1H), 8.41 (d, J 8.6, 2H), 7.99 (d, J 8.5, 2H), 7.84 (s, 1H).

Intermediate 21: 5-(fluoromethyl)-l-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole: Intermediate 19 (0.5 g, 1.75 mmol) was dissolved in DCM (10 ml) and reaction mixture cooled to 0 °C. To this (Diethylamino)sulphur trifluoride (0.46 ml, 3.5 mmol) was added drop-wise and allowed the reaction mixture to stir at rt for 30 mins. After completion of the reaction, reaction mixture diluted with DCM and washed with water. DCM removed on rotavapour to obtain the crude. Crude was purified by column chromatography using EA and petether (7: 97) as eluent to afford the title compound (0.41 g) as an yellow solid. 1H-NMR (δ ppm, CDC13, 400 MHz): 8.42 (d, J 9, 2H), 7.86 (d, J 9, 2H), 6.94 (d, J 3.4, 1H), 5.42 (d, J 48.4, 2H).

Intermediate 22: 5-(difluoromethyl)-l-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole: Intermediate 20 (500 mg, 1.75 mmol) was dissolved in DCM, cooled to 0 °C and added (Diethylamino) sulphur trifluoride (0.46 ml, 3.5 mmol). This mixture was stirred at ambient temperature for 30 mins. Water added to reaction mixture and DCM layer separated was dried on anhydrous Na2SO4 and DCM was removed on rotavapour to obtain the crude. Purification (60-120 mesh silica gel) [EA:Petether (60:40)] afforded the title compound as an yellow solid. 1H-NMR (δ ppm,
CDCl₃, 400 MHz): 8.42 (d, J 9.1, 2H), 7.79 (d, J 9.1, 2H), 7.06 (s, 1H), 6.73 (t, J 53, 1H).

[199] Intermediate 23: 4-chloro-3,5-dicyclopropyl-l-(2-fluoro-4-nitrophenyl)-1H-pyrazole: Intermediate 10 (1.15 g, 3.40 mmol) was dissolved in DMF and to this N-Chlorosuccinimide (0.64 g, 4.8 mmol) was added at 0 °C. Then reaction was allowed to stir at rt for 2h. After completion of the reaction, work up (EtOAc) and purification afforded the title compound (0.575 g). ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 8.18-8.09 (m, 2H), 7.64 (t, δ 8.3, 1H), 1.98-1.90 (m, 1H), 1.82-1.72 (m, 1H), 0.90-0.80 (m, 4H), 0.68-0.60 (m, 4H).

[200] Intermediate 24: 4-chloro-5-cyclopropyl-l-(4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole: Intermediate 13 (0.8 g, 3.36 mmol) was dissolved in DMF and to this N-Chlorosuccinimide (0.54 g, 4.0 mmol) was added at 0 °C. Then reaction was allowed to stir at rt for 2h. After completion of the reaction, work up (EtOAc) afforded the title compound (0.802 g). ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 8.39 (d, J 9, 2H), 7.82 (d, J 9, 2H), 1.91-1.80 (m, 1H), 1.10-1.00 (m, 2H), 0.80-0.72 (m, 2H).

[201] Intermediate 25: 5-cyclopropyl-l-(2-fluoro-4-nitrophenyl)-3-(trifluoromethyl)-1H-pyrazole: Intermediate 14 (1.05 g, 3.40 mmol) was dissolved in DMF and to this N-Chlorosuccinimide (0.545 g, 4.08 mmol) was added at 0 °C. Then reaction was allowed to stir at rt for 2h. After completion of the reaction, work up (EtOAc) and purification afforded the title compound (1 g). ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 8.23-8.16 (m, 2H), 7.72 (t, J 7.5, 1H), 1.82-1.70 (m, 1H), 0.99-0.82 (m, 2H), 0.74-0.65 (m, 2H).

[202] Intermediate 26: 2-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-nitropyridine: Intermediate 16 (1.5 g, 5.0 mmol) was dissolved in DMF and to this N-Chlorosuccinimide (0.8 g, 6 mmol) was added at 0 °C. Then reaction was allowed to stir at rt for 2h. After completion of the reaction, work up (EtOAc) and purification afforded the title compound (0.802 g). ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 9.34 (d, J 2.5, 1H), 8.65 (dd, J 2.5, 9, 1H), 8.09 (d, J 9, 1H), 2.48-2.38 (m, 1H), 1.13-1.03 (m, 2H), 0.90-0.82 (m, 2H).

[203] Intermediate 27: 4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)aniline: Iron powder (0.88 g, 15.8 mmol) and ammonium chloride (17 mg, 0.3 mmol) were added to a solution of intermediate 9 (0.85 g, 3.15 mmol) in EtOH/H₂O (2:1, 15 mL) and the mixture
refluxed for half an hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H₂O/AcOEt) after concentration of the combined layers afforded title compound as a yellow solid (0.68 g). 'H-NMR (δ ppm, DMSO-d₆, 400 MHz): 7.11 (d, J 8.6, 2H), 6.61 (d, J 8.6, 2H), 5.65 (s, 1H), 5.24 (s, 2H), 1.81-1.74 (m, 1H), 1.67-1.60 (m, 1H), 0.86-0.77 (m, 4H), 0.61-0.56 (m, 4H). MS (m/z): 240.3 [M+H]+.

[204] Intermediate 28: 4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluoroaniline: Iron powder (1.86 g, 34.8 mmol) and ammonium chloride (30 mg, 0.7 mmol) were added to a solution of intermediate 10 (2 g, 7.0 mmol) in EtOH/H₂O (2:1, 30 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H₂O/AcOEt) and concentration of the combined layers afforded title compound as a yellow solid (1.34 g).

[205] Intermediate 29: 4-(4-chloro-3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluoroaniline: Iron powder (0.48 g, 8.9 mmol) and ammonium chloride (9 mg, 0.17 mmol) were added to a solution of intermediate 23 (0.57 g, 1.8 mmol) in EtOH/H₂O (2:1, 7.5 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H₂O/AcOEt) after concentration of the combined layers afforded intermediate 29 as a yellow solid (0.46 g). 'H-NMR (δ ppm, DMSO-d₆, 400 MHz): 7.02 (t, J 8.6, 1H), 6.45-6.38 (m, 2H), 5.74 (s, 2H), 1.85-1.76 (m 1H), 1.61-1.52 (m, 1H), 0.90-0.82 (m, 2H), 0.78-0.70 (m, 4H), 0.69-0.60 (m, 2H). MS (m/z): 291.98 [M+H]+.

[206] Intermediate 30: 6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-amine: Iron powder (0.79g, 14.17 mmol) and ammonium chloride (15 mg, 0.28 mmol) were added to a solution of intermediate 11 (0.77g, 2.86 mmol) in EtOH/H₂O (2:1, 15 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H₂O/AcOEt) after concentration of the combined layers afforded intermediate 30 as a yellow solid (0.570 g). 'H-NMR (δ ppm, DMSO-d₆, 400 MHz): 7.75 (d, J 2.5, 1H), 7.27 (d, J 8.6, 1H), 7.06 (dd, J 2.7, 8.6, 1H), 5.67 (s, 1H), 5.43 (s, 2H), 2.39-2.27 (m, 1H), 1.88-1.74 (m, 1H), 0.90-0.72 (m, 4H), 0.69-0.50 (m, 4H).

[207] Intermediate 31: 4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]aniline: A procedure similar to that employed for intermediate 27 was followed. From intermediate 13 (0.69g, 2.32 mmol), EtOH-H₂O (2:1, 12 mL), Fe (0.64 g, 15.8 mmol) and NH₄Cl (0.012 mg, 0.22 mmol), the title compound was obtained as yellow solid (0.49 g). 'H-NMR (δ ppm, DMSO-d₆, 400 MHz): 7.19 (d, J 8.64, 2H), 6.65 (d, J 8.64,
2H), 6.47 (s, 1H), 5.46 (s, 2H), 1.75-1.69 (m, 1H), 0.94-0.89 (m, 2H), 0.77-0.73 (m, 2H).

MS (m/z): 268.1 [M+H]^+.

[208] **Intermediate 32**: 4-(4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)aniline: Iron powder (0.67 g, 12.05 mmol) and ammonium chloride (25 mg, 4.8 mmol) were added to a solution of intermediate 24 (0.800 g, 2.41 mmol) in EtOH/H_2O (2:1, 15 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H_2O/AcOEt) and concentration of the combined layers afforded title compound (680 mg) as a yellow solid.

1H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 7.19 (d, J 8.6, 2H), 6.63 (d, J 8.6, 2H), 5.51 (s, 2H), 1.89-1.80 (m, 1H), 0.88-0.80 (m, 2H), 0.65-0.61 (m, 2H).

[209] **Intermediate 33**: 4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluoroaniline: Iron powder (4.75 g, 85.1 mmol) and ammonium chloride (90 mg, 1.7 mmol) were added to a solution of intermediate 14 (5 g, 17.00 mmol) in EtOH/H_2O (2:1, 45 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H_2O/AcOEt) after concentration of the combined layers afforded title compound as a yellow solid (4.3 g). 1H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 7.16 (t, J 8.5, 1H), 6.50-6.45 (m, 3H), 5.86 (s, 2H), 1.60-1.51 (m, 1H), 0.91-0.82 (m, 2H), 0.76-0.69 (m, 2H).

[210] **Intermediate 34**: 4-(4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-3-fluoroaniline: Iron powder (0.8 g, 56 mmol) and ammonium chloride (300 mg, 5.8 mmol) were added to a solution of intermediate 26 (1.0 g, 2.88 mmol) in EtOH/H_2O (2:1, 15 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H_2O/AcOEt) and concentration of the combined layers afforded intermediate 34 as a pale-yellow solid (0.87 g). 1H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 7.19 (t, J 8.6, 1H), 6.50-6.45 (m, 2H), 5.91 (s, 2H), 1.72-1.62 (m, 1H), 0.87-0.79 (m, 2H), 0.76-0.67 (m, 2H).

[211] **Intermediate 35**: 4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)-3,5-difluoroaniline: Iron powder (1.14 g, 20.5 mmol) and ammonium chloride (21 mg 0.41 mmol) were added to a solution of intermediate 15 (1.36 g, 4.1 mmol) in EtOH/H_2O (2:1, 30 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H_2O/AcOEt) and concentration of the combined layers afforded title compound (680 mg) as a yellow solid. 1H-NMR (δ ppm,
DMSO-d$_6$, 400 MHz): 6.54 (s, 1H), 6.37 (d, J 10.6, 2H), 6.24 (s, 2H), 1.59-1.49 (m, 1H),
0.92-0.84 (m, 2H), 0.74-0.66 (m, 2H). MS (m/z): 304.06 ([M+H]$^+$).

[212] Intermediate 36: 6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] pyridin-3-amine: Iron powder (0.279g, 5.00 mmol) and ammonium chloride (5 mg, 0.09 mmol) were added to a solution of intermediate 16 (0.77g, 2.86 mmol) in EtOH/H$_2$O (2:1, 9 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H$_2$O/AcOEt) after concentration of the combined layers afforded intermediate 36 as a yellow solid (0.239 g). $^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 7.84 (d, J 2.6, 1H), 7.33 (d, J 8.6, 1H), 7.12 (dd, J 2.6, 8.6, 1H), 6.49 (s, 1H), 5.69 (s, 2H), 2.45-2.36 (m, 1H), 0.90-0.81 (m, 2H), 0.74-0.65 (m, 2H). MS (m/z): 269.2 [M+H]$^+$.

[213] Intermediate 37: 6-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] pyridin-3-amine: Iron powder (1.56 g, 28.0 mmol) and ammonium chloride (600 mg, 11.2 mmol) were added to a solution of intermediate 26 (1.7 g, 5.60 mmol) in EtOH/H$_2$O (2:1, 15 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H$_2$O/AcOEt) and concentration of the combined layers afforded intermediate 37 as a yellow solid (1.1 g). $^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 8.04 (s, 1H), 7.39 (d, J 8.2, 1H), 7.20 (d, J 8, 1H), 4.26 (s, 2H), 2.10-1.99 (m, 1H), 1.96-1.85 (m, 2H), 1.84-1.70 (m, 2H).

[214] Intermediate 38: 2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] pyrimidin-5-amine: Iron powder (466 mg, 1.67 mmol) and ammonium chloride (8 mg, 0.17 mmol) were added to a solution of intermediate 17 (0.41 g, 1.41 mmol) in EtOH/H$_2$O (2:1, 7.5 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H$_2$O/AcOEt) and concentration of the combined layers afforded intermediate 38 (0.35 g) as a yellow solid. $^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 8.20 (s, 2H), 6.52 (s, 1H), 5.99 (s, 2H), 2.22-2.12 (m, 1H), 1.00-0.85 (m, 2H), 0.80-0.68 (m, 2H). MS (m/z): 267.73 ([M-H]$^-$).

[215] Intermediate 39: 4-[5-(fluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] aniline: Iron powder (434 mg, 7.78 mmol) and ammonium chloride (8 mg, 0.15 mmol) were added to a solution of intermediate 21 (450 mg, 1.56 mmol) in EtOH/H$_2$O (2:1, 15 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H$_2$O/AcOEt) and concentration of the combined layers afforded title compound (335 mg) as a yellow solid (460 mg). $^1$H-NMR (δ ppm,
DMSO-d/e, 400 MHz): 7.16 (d, J 8.6, 2H), 7.12 (d, J 2.8, 1H), 6.65 (d, J 8.6, 2H), 5.5 (s, 2H), 5.4 (d, J 48.3, 2H).

[216] Intermediate 40: 4-(5-(difluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenylacetamide: Iron powder (0.39 g, 7.78 mmol) and ammonium chloride (90 mg, 1.7 mmol) were added to a solution of intermediate 22 (0.41 g, 1.41 mmol) in EtOH/H2O (2:1, 7.5 mL) and the mixture refluxed for one hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H2O/ACOEt) and concentration of the combined layers afforded intermediate 40 (0.35 g) as a yellow solid. 1H-NMR (δ ppm, DMSO-d/e, 400 MHz): 7.92 (d, J 8.6, 2H), 7.47 (d, J 8.6, 2H), 6.65 (s, 1H), 1.90-1.80 (m, 1H), 1.00-0.90 (m, 2H), 0.85-0.77 (m, 2H).

[217] Intermediate 41: 2-chloro-iV-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]acetamide: Chloroacetyl chloride (0.2 mL, 2.39 mmol) was added to a solution of intermediate 27 (600 mg, 2.24 mmol) in dichloromethane (DCM) at 0 °C. The mixture was stirred for 15 mins. Work-up (H2O/DCM) gave the intermediate 41 which was used in the next step without further purification.

[218] Intermediate 42: 2-chloro-N-[4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl] acetamide: Chloroacetyl chloride (0.05 mL, 0.62 mmol) was added to a solution of intermediate 31 (150 mg, 0.561 mmol) in dichloromethane (DCM) at 0 °C. The mixture was stirred for 15 mins. Work-up (H2O/DCM) gave the titled compound, which was used in the next step without further purification.

[219] Intermediate 43: 2-chloro-N-[6-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)pyridin-3-yl]acetamide: Chloroacetyl chloride (0.16 mL, 2.00 mmol) was added to a solution of intermediate 36 (500 mg, 1.86 mmol) in dichloromethane (DCM) at 0 °C. The mixture was stirred for 15 mins. Work-up (H2O/DCM) gave the intermediate 43 which was used in the next step without further purification.

[220] Intermediate 44: 5-cyclopropyl-1-(4-iodophenyl)-3-(trifluoromethyl)-1H-pyrazole: To the intermediate 31 (2g, 7.49 mmol) in 5ml water was added Cone. HCl (5 ml) and cooled to 0 °C. To this sodium nitrite solution (lg, 15 mmol) was added slowly and stirred for 15 mins at 0 °C. To this mixture potassium iodide solution (2.5 g, 15 mmol), was added at same temperature and stirred the reaction mixture at rt. Work-up (H2O/ACOEt) and purification gave the desired product as a yellow liquid. 1H-NMR (δ ppm, CDCl3, 400 MHz): 7.92 (d, J 8.6, 2H), 7.47 (d, J 8.6, 2H), 6.65 (s, 1H), 1.90-1.80 (m, 1H), 1.00-0.90 (m, 2H), 0.85-0.77 (m, 2H).
Intermediate 45: 5-cyclopropyl-1-(2-fluoro-4-iodophenyl)-3-(trifluoromethyl)-1H-pyrazole: To the intermediate 33 (1.9g, 7.20 mmol) in 5ml water was added Cone. HCl (5 ml) and cooled to 0 °C. To this sodium nitrite solution (1g, 15 mmol) was added slowly and stirred for 15 mins at 0 °C. To this mixture potassium iodide solution (2.5 g, 15 mmol) was added at same temperature and stirred the reaction mixture at rt. Work-up (H$_2$O/AcOEt) and purification gave the desired product as a yellow colour liquid. $^1$H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 8.01 (dd, $J$ 1.7, 9.5, 1H), 7.79 (dd, $J$ 1.7, 8.4, 1H), 7.45 (t, $J$ 8.1, 1H), 6.63 (s, 1H), 1.64-1.56 (m, 1H), 0.92 -0.84 (m, 2H), 0.79-0.71 (m, 2H).

Intermediate 46: 6-(3,5-dicyclopentyl-1H-pyrazol-1-yl)nicotinic acid: To a solution of intermediate 12 (300 mg, 1 mmol) in THF:H$_2$O (1:1) added Potassium hydroxide (83 mg, 1.5 mmol) and refluxed for 5 h. After completion of the reaction, reaction mixture was acidified with 2N HCl and worked up (H$_2$O/AcOEt) to afford the title compound (240 mg). 1H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 13.3 (bs, 1H), 8.90 (d, $J$ 2.0, 1H), 8.35 (dd, $J$ 2.2, 8.6, 1H), 7.89 (d, $J$ 8.6, 1H), 5.93 (s, 1H), 2.90-2.80 (m, 1H), 1.90-1.80 (m, 1H), 1.00-0.82 (m, 4H), 0.75-0.62 (m, 4H).

Intermediate 47: 4-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzoic acid: Magnesium (32 mg, 1.32 mmol) and a pinch of iodine suspended in ether under inert atmosphere. To this small amount of methyl iodide was added and refluxed the reaction mixture to start Grignard formation. At this stage intermediate 44 (500 mg, 1.32 mmol) was added and continued the reaction under reflux condition. After complete consumption of the starting material, reaction mixture cooled to rt and added dry ice pieces into it followed by con. HCl. Solid that formed was filtered and dried on high vacuum to obtain the title compound (100 mg) as a yellow solid. $^1$H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 13.2 (bs, 1H), 8.11 (d, $J$ 8.6, 2H), 7.82 (d, $J$ 8.6, 2H), 6.7 (s, 1H), 1.99-1.90 (m, 1H), 1.04-0.94 (m, 2H), 0.88-0.80 (m, 2H).

Intermediate 48: 4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorobenzoic acid: Magnesium (143 mg, 6 mmol) and a pinch of iodine suspended in ether under inert atmosphere. To this small amount of methyl iodide was added and refluxed the reaction mixture to start Grignard formation. At this stage intermediate 45 (790 mg, 2 mmol) was added and continued the reaction under reflux condition. After complete consumption of the starting material, reaction mixture cooled to rt and added dry ice pieces into it followed by 2N HCl. Solid that formed was filtered and dried on
high vacuum to obtain the title compound (160 mg) as an off-white solid. 1H-NMR (δ ppm, DMSO-d4, 400 MHz): 13.6 (bs, 1H), 7.97-7.92 (m, 2H), 7.84-7.78 (m, 1H), 6.68 (s, 1H), 1.69-1.61 (m, 1H), 0.94-0.87 (m, 2H), 0.80-0.74 (m, 2H).

Intermediate 49: Ethyl 6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl] nicotinate:

A solution of intermediate 5 (0.84 g, 4.7 mmol) and K2CO3 (1.9 g, 14.1 mmol) in DMSO (10 mL) was heated at 80 °C under nitrogen for 0.5 h. To the mixture, ethyl-6-chloronicotinate (3.8 g, 20.3 mmol) was added and stirred at 80 °C for 4 h. Work-up (H2O/AcOEt) and purification afforded the title compound (0.26 g). 1H-NMR (δ ppm, CDC13, 400 MHz): 9.11 (d, J 1.1 H), 8.44 (d, J 2.2, 8.6, 1H), 8.00 (d, J 8.6, 1H), 6.25 (s, 1H), 4.45 (q, J 7.1, 2H), 2.91-2.80 (m, 1H), 1.43 (t, J 7.1, 3H), 1.11-1.01 (m, 2H), 0.79-0.70 (m, 2H).

Intermediate 50: 6-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl) nicotinic acid: To a solution of intermediate 49 (600 mg, 1.8 mmol) in MeOH:H2O (2:1) added sodium hydroxide (221 mg, 5.4 mmol) and refluxed for 2 h. After completion of the reaction, reaction mixture was acidified with 2N HCl and worked up (H2O/AcOEt) to afford the pure compound (452 mg). 1H-NMR (δ ppm, DMSO-J6, 400 MHz): 9.18 (d, J 2.0, 1H), 8.50 (dd, J 2.2, 8.6, 1H), 8.07 (d, J 8.6, 1H), 6.27 (s, 1H), 2.92-2.82 (m, 1H), 1.14-1.04 (m, 2H), 0.78-0.71 (m, 2H).

Intermediate 51: ethyl 2-[(dimethylamino)methylene]-3-oxobutanoate: Ethyl acetoacetate (15 g, 115 mmol) and N,N-Dimethylformamide dimethyl Acetal (13.7 g, 115 mmol) stirred at rt for overnight. After completion of the reaction, reaction mixture distilled on rotavapour to obtain the crude. Crude was purified by column chromatography over 60-120 mesh silica gel using EtOAc and petether (10:90) as eluent to obtain the title compound (20 g).

Intermediate 52: ethyl 4-methylpyrimidine-5-carboxylate: Intermediate 51 (9.7 g, 52.4 mmol) and Formamidine acetate (5.4 g, 52.4 mmol), were dissolved in EtOH and added NaOEt (3.6 g, 52.4 mmol). This mixture was refluxed for 6h. After that, ethanol removed on rotavapour followed by work-up (AcOEt/H2O) to obtain the crude. Crude was purified by column chromatography using 60-120 mesh silicagel and AcOEt and Petether (25:75) as eluent to obtain the title compound (2.7 g).

Intermediate: 53: 4-methylpyrimidine-5-carboxylic acid: Intermediate 52 (2.6 g, 15.64 mmol) dissolved in sodium hydroxide solution (1.88 g, 47 mmol in 4 ml
water) and refluxed. The reaction mixture was cooled to rt and acidified with con HCl to obtain the solid. Solid that obtained was filtered and dried to obtain the title compound (1.5 g) as an yellow solid. $^1$H-NMR (δ ppm, DMSO-d$_4$, 400 MHz): 13.5 (bs, 1H), 9.14 (s, 1H), 9.05 (s, 1H), 2.71 (s, 3H).

[230] Intermediate 54: ethyl 2,4-dimethylpyrimidine-5-carboxylate: Intermediate 51 (17.6 g, 95 mmol) and acetamide hydrochloride (17.6 g, 95 mmol), were dissolved in EtOH and added NaOEt (6.5 g, 95 mmol). This mixture was refluxed for 4h. After that, ethanol removed on rotavapour followed by work-up (AcOEt/H$_2$O) to obtain the crude. Crude was purified by column chromatography using 60-120 mesh silicagel and AcOEt and Petether (25:75) as eluent to obtain the title compound (7.3 g).

[231] Intermediate 55: 2,4-dimethylpyrimidine-5-carboxylic acid: Intermediate 54 (7.3 g, 40.5 mmol) dissolved in sodium hydroxide solution (4.86 g, 121.6 mmol in 10 ml water) and refluxed. The reaction mixture was cooled to rt and acidified with con HCl to obtain the solid. Solid that obtained was filtered and dried to obtain the title compound quantitatively as an yellow solid. $^1$H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 13.5 (bs, 1H), 8.93 (s, 1H), 2.66 (s, 3H), 2.60 (s, 3H).

[232] Intermediate 56: ethyl 4-methylthiazole-5-carboxylate: 4-methylthiazole-5-carboxylic acid was dissolved in DCM, cooled to 0 °C, added oxalyl chloride (7.6 ml, 88 mmol) and DMF (2 drops). Reaction mixture was stirred for 30 mins and DCM was removed on rotavapour. Residue was dissolved in MeOH at 0 °C and stirred for 30 mins at rt. MeOH was removed on rotavapour and crude was worked up (AcOEt/H$_2$O) to obtain the title compound (4.1 g) as a white solid. $^1$H-NMR (δ ppm, CDC$_1$3, 400 MHz): 8.83 (s, 1H), 4.35 (q, J 7.2, 2H), 2.78 (s, 3H), 1.37 (t, J 7.2, 3H).

[233] Intermediate 57: (4-methylthiazol-5-yl) methanol: Intermediate 56 (262 mg, 1.6 mmol) was dissolved in MeOH and added sodium borohydride (126 mg, 3.2 mmol) and stirred the reaction mixture at rt for overnight. MeOH was removed on rotavapour and residue was worked up (AcOEt/H$_2$O) to obtain the title compound (183 mg) as a white solid. $^1$H-NMR (δ ppm, CDC$_1$3, 400 MHz): 8.67 (s, 1H), 4.82 (s, 2H), 2.44 (s, 3H).

[234] Intermediate 58: 4-methylthiazole-5-carbaldehyde: Oxalyl chloride (0.8 ml, 9.8 mmol) was dissolved in DCM, cooled to -78 °C and added DMSO (1.39 ml 19.6 mmol) and stirred for 30 mins. To this intermediate 57 (630 mg, 4.9 mmol) was added, stirred at -78 °C for 20 mins and added triethyl amine (2.7 ml, 7.6 mmol). Reaction
mixture warmed to 0 °C and then slowly heated to rt. Work up (H₂O/AcOEt) afforded the title compound (408 mg) as a yellow solid. 10.13 (s, 1H), 9.37 (s, 1H), 2.71 (s, 3H).

[235] **Intermediate 59: 4-methylthiazol-5-amine:** 4-Methylthiazole-5-carboxylic acid (lg, 7 mmol) was dissolved in acetone (50 mL) and cooled to 0 °C. To this mixture triethyl amine (0.84 g, 8.3 mmol) was added and after 5 mins ethylchloroformate (0.9 g, 8.3 mmol) was added slowly. This mixture stirred at rt for 1 h and then Sodium azide solution (0.9 g, 13.8 mmol in 5 ml H₂O) was added to it at 0 °C. The reaction mixture was stirred for half an hour at rt, acetone was removed and residue was extracted with ether. Ether removed on rotavapour to obtain the crude. Crude was dissolved in 1,4-dioxane, added Cone. H₂SO₄ and refluxed for lh. The reaction mixture cooled to rt, pH adjusted to 9 with aq NaOH and extracted with EtOAc to obtain the title compound (0.24 g) as a brown solid. 'H-NMR (δ ppm, OMSO-d₆, 400 MHz): 7.98 (s, 1H), 5.13 (s, 2H), 2.11 (s, 3H).

[236] **Intermediate 60: 1-phenylcyclobutanecarbonitrile:** Sodium hydride (1.54 g, 64.1 mmol) dissolved in DMF (15 ml) and cooled to 0 °C. Phenyl acetonitrile (3 g, 25.6 mmol) and 1,3-dibromopropane (5.2 g, 25.6 mmol) were dissolved in DMF (15 ml) and added to above mixture drop-wise at 0 °C. This mixture was heated to rt and continued stirring for 2h. Work up (H₂O/Toluene) afforded the title compound (2.61 g) as crude, which was used in the next without further purification.

[237] **Intermediate 61: 1-phenylcyclobutanecarboxylic acid:** Intermediate 60 (2.6 g, 16.54 mmol) was dissolved in ethylene glycol and added potassium hydroxide (5.6 g, 99.2 mmol). This mixture was heated to 160 °C for 2h. After two hours reaction mixture was cooled to rt and toluene and water were added. Aqueous layer separated and acidified with HCl and pH adjusted to 4. Aqueous layer extracted with ethyl acetate and ethyl acetate layer was dried on anhydrous sodium sulphate. Ethyl acetate removed on rotavapour to obtain the title compound (930 mg) as a white solid.

[238] **Intermediate 62: (Z)-1-cyclopropyl-4,4-difluoro-3-hydroxybut-2-en-1-one:** Hexamethyl disilazane (1 g, 6.2 mmol) and diethylether were taken in RBF and cooled to -78 °C under nitrogen atmosphere. n-BuLi (7.7 ml) was added and stirred for 15 mins. Cyclopropyl methyl ketone (0.66 ml, 6.8 mmol) was added and stirred at -78 °C for 45 mins. At this stage methyl 2,2-difluoroacetate (1.62 ml, 18.58 mmol) was added and brought the reaction mixture to rt and allowed to stir for overnight. Reaction mixture quenched with water, ether layer separated and aqueous layer was acidified with IN HCl.
Aqueous layer extracted with diethyl ether and ether was dried over anhydrous Na₂SO₄. Diethyl ether was removed on rotavapour to obtain the title compound (390 mg) which was used in the next step without further purification. 1H-NMR (δ ppm, CDCl₃, 400 MHz): 6.08 (s, 1H), 5.95 (t, J 54.2, 1H), 1.84-1.76 (m, 1H), 1.34-1.29 (m, 2H), 1.10-1.03 (m, 2H).

[239] **Intermediate 63:** 5-cyclopropyl-3-(difluoromethyl)-1H-pyrazole:
Intermediate 62 (390 mg, 2.4 mmol) dissolved in ethanol (2 ml), added hydrazine hydrate (0.13 ml, 2.65 mmol) and HCl (0.18 ml). This mixture was refluxed for 3 h. After 3 h, ethanol was removed on rotavapour and work up (H₂O/ AcOEt) afforded the title compound (290 mg) which was used in the next step without further purification. 1H-NMR (δ ppm, CDCl₃, 400 MHz): 12.96 (s, 1H), 6.84 (t, J 54.8, 1H), 6.15 (s, 1H), 1.95-1.87 (m, 1H), 0.99-0.91 (m, 2H), 0.74-0.66 (m, 2H).

[240] **Intermediate 64:** Mixture of 3-cyclopropyl-5-(difluoromethyl)-1-(2-fluoro-4-nitrophenyl)-1H-pyrazole and 5-cyclopropyl-3-(difluoromethyl)-1-(2-fluoro-4-nitrophenyl)-1H-pyrazole: Intermediate 63 (100 mg, 0.63 mmol), CS₂CO₃ (622 mg, 1.9 mmol), acetone (5 mL) were mixed and heated to reflux. After 30 mins, 1,2-difluoro-4-benzene (253 mg, 1.59 mmol) was added and continued the reaction for 1 h. Work up (H₂O/ AcOEt) followed by purification using 60-120 mesh silica gel and EtOAc and Petether (3:97) as eluent afforded the title compound (65 mg). 1H-NMR (δ ppm, CDCl₃, 400 MHz): 8.23-8.10 (m, 2H), 7.78-7.72 (m, 1H), 6.71 (t, J 54.8, 0.37H), 6.66 (t, J 54.8, 0.63H), 6.43 (s, 0.37 H), 6.25 (s, 0.63H), 2.05-1.95 (m, 0.37H), 1.70-1.61 (m, 0.63H), 1.04-0.94 (m, 2H), 0.86-0.80(m, 0.74H), 0.77-0.71 (m, 1.26H).

[241] **Intermediate 65:** Mixture of 4-(3-cyclopropyl-5-(difluoromethyl)-1H-pyrazolyl)-3-fluoroaniline and 4-(5-cyclopropyl-3-(difluoromethyl)-1H-pyrazolyl)-3-fluoroaniline: Iron powder (120 mg, 2.31 mmol) and ammonium chloride (2 mg, 0.046 mmol) were added to a solution of intermediate 64 (130 mg, 0.46 mmol) in EtOH/H₂O (2:1, 1.65 mL) and the mixture refluxed for half an hour. The mixture was filtered through celite and celite washed with ethanol. Work-up (H₂O/ AcOEt) and concentration of the combined layers afforded title compound as a yellow solid (90 mg). 1H-NMR (δ ppm, DMSO-d₆, 400 MHz): 7.12 (t, J 8.5, 0.63 H), 7.08-7.03 (m, 0.37H), 6.90 (t, J 54.8, 0.63H), 6.84 (t, J 54.8, 0.37H), 6.50-6.38 (m, 2.37H), 6.25 (s, 0.63H), 5.81 (s, 2H), 1.95-1.86 (m, 0.37H), 1.57-1.48 (m, 0.63H), 0.90-0.82 (m, 2H), 0.71-0.64 (m, 2H).
General Procedure for Amide Formation:

[242] Procedure-1: A solution of an appropriate aniline (leq.), the requisite acid (1.1 eq.), EDC.HCl (1.2 eq.), HOBt (0.5 eq.) and TEA (3 eq.) in DMF was stirred at RT overnight. Work-up (H₂O/AcOEt) and purification gave the desired product.

[243] Procedure-2: Acid (1 eq.) was dissolved in DCM, cooled to 0 °C, added oxalyl chloride (3 eq.) and three drops of DMF. The reaction mixture was stirred at room temperature for 30 mins and DCM was removed on rotavapour to obtain the acid chloride. Amine was dissolved in DCM under N₂ atmosphere and added Pyridine (1.3 eq.). To this mixture acid chloride in DCM was added and allowed to stir at room temperature until amine was totally consumed. Work-up (H₂O/AcOEt) and purification gave the desired product.

[244] The following compounds were prepared using these procedures:

Example 1

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide:

[245] Following the general procedure-1, the title compound (60 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (86 mg, 0.60 mmol) and intermediate 27 (120 mg, 0.50 mmol) as a white solid. M. P.: 117-120 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.86 (s, 1H), 7.79 (d, J 8.8, 2H), 7.59 (d, J 8.8, 2H), 5.81 (s, 1H), 2.81 (s, 3H), 1.84-1.77 (m, 2H), 0.92-0.90 (m, 2H), 0.89-0.81 (m, 2H), 0.68-0.61 (m, 4H). MS (m/z): 363.96 [M-H]⁻.

Example 2

A'-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-4-methylthiazole-5-carboxamide

[246] Following the general procedure-1, the title compound (102 mg) was prepared from 4-methylthiazole-5-carboxylic acid (78 mg, 0.54 mmol) and intermediate 27 (120 mg, 0.50 mmol) as an off-white solid. M. P. 110-114 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.37 (s, 1H), 9.13 (s, 1H), 7.78 (d, J 8.7, 2H), 7.55 (d, J 8.7, 2H), 5.79 (s, 1H), 2.61 (s, 3H), 1.89-1.71 (m, 2H), 0.94-0.80 (m, 2H), 0.69-0.60 (m, 4H). MS (m/z): 363.11 [M-H]⁺.
Example 3

\[N-\{4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl\} \cdot 2,4\text{-dimethylthiazole-5-carboxamide:}\]

[247] Following the general procedure-1, the title compound (87 mg) was prepared from 2,4-dimethylthiazole-5-carboxylic acid (94 mg, 0.59 mmol) and intermediate 27 (120 mg, 0.50 mmol) as an off-white solid. M. P. 98-114 °C. \(^1\text{H}\)-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 10.22 (s, 1H), 7.76 (d, \(J\ 8.4\), 2H), 7.52 (d, \(J\ 8.4\), 2H), 5.79 (s, 1H), 2.66 (s, 3H), 2.54 (s, 3H), 1.88-1.73 (m, 2H), 0.95-0.82 (m, 4H), 0.69-0.61 (m, 4H). MS (m/z): 379.20 [M+H]+.

Example 4

\[N-\{4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl\}-5-methylisoxazole-4-carboxamide\]

[248] Following the general procedure-2, the title compound (55 mg) was prepared from 5-methylisoxazole-4-carbonyl chloride (79 mg) and intermediate 27 as a white solid. M. P. 153-158 °C. \(^1\text{H}\)-NMR (δ ppm, DMSO-d/6, 400 MHz): 10.17 (s, 1H), 9.06 (s, 1H), 7.79 (d, \(J\ 7.6\), 2H), 7.56 (d, \(J\ 7.6\), 2H), 5.80 (s, 1H), 2.68 (s, 3H), 1.84-1.78 (m, 2H), 0.91-0.70 (m, 4H), 0.69-0.55 (m, 4H). MS (m/z): 347.08 [M-H]-.

Example 5

\[N-\{4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl\}-3,5-dimethylisoxazole-4-carboxamide\]

[249] Following the general procedure-1, the title compound (147 mg) was prepared from 3,5-dimethylisoxazole-4-carboxylic acid (155 mg, 1 mmol) and intermediate 27 (150 mg, 0.62 mmol) as a yellow solid. M. P.: 115-119 °C. \(^1\text{H}\)-NMR (δ ppm, DMSO-d/4, 400 MHz): 10.18 (s, 1H), 7.76 (d, \(J\ 8.7\), 2H), 7.55 (d, \(J\ 8.7\), 2H), 5.79 (s, 1H), 2.55 (s, 3H), 2.33 (s, 3H), 1.88-1.73 (m, 2H), 0.94-0.80 (m, 4H), 0.70-0.61 (m, 4H). MS (m/z): 363.27 [M+H]+.

Example 6

\[N-\{4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl\}benzamide\]

[250] Following the general procedure-2, title compound (90 mg) was prepared from benzoyl chloride (64 mg, 0.45 mmols) and intermediate 27 (100 mg, 0.41 mmols) as a pale yellow solid. M. P. 133-138.5 °C. \(^1\text{H}\)-NMR (δ ppm, DMSO-d/6, 400 MHz): 10.39 (s, 1H), 7.96 (d, \(J\ 7.1\), 2H), 7.91 (d, \(J\ 9.0\), 2H), 7.61-7.51 (m, 5H), 5.79 (s, 1H), 1.85-1.76 (m, 2H), 0.93-0.81 (m, 4H), 0.68-0.61 (m, 4H). MS (m/z): 341.9 [M-H]+.
Example 7

\[ \text{N-[4-(3,5-dicyclopropyl-\textit{H}-pyrazol-1-yl)phenyl]-2-niethylbenzainide:} \]

[251] Following the general procedure-1, the title compound (130 mg) was prepared from intermediate 27 (200 mg, 0.84 mmol) and p-toluic acid (182 mg, 1.34 mmol) as an yellow solid. M. P.: 127.5-129.8 °C. \(^1\text{H}\)-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.44 (s, 1H), 7.85 (d, \(J\) 8.8, 2H), 7.57 (d, \(J\) 8.7, 1H), 7.53 (d, \(J\) 8.8, 2H), 7.47 (d, \(J\) 7.5, 1H), 7.42-7.37 (m, 1H), 7.33-7.27 (m, 2H), 2.38 (s, 3H), 1.90-1.73 (m, 2H), 0.93-0.80 (m, 4H), 0.69-0.61 (m, 4H). MS (m/z): 358.03 [\(\text{M+H}\)]\(^+\).

Example 8

\[ \text{N-[4-(3,5-dicyclopropyl-\textit{H}-pyrazol-1-yl)phenyl]-2,6-difluorobenzamide:} \]

[252] The title compound (77 mg) was prepared from 2,6-difluorobenzoic acid and intermediate 27 (120 mg, 0.50 mmol) as a white solid. M. P. 158-163 °C. \(^1\text{H}\)-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.93 (s, 1H), 7.79 (d, \(J\) 8.8, 2H), 7.63-7.56 (m, 3H), 7.25 (t, \(J\) 8.0, 2H), 1.85-1.80 (m, 2H), 0.89-0.85 (m, 2H), 0.84-0.81 (m, 2H), 0.68-0.61 (m, 4H). MS (m/z): 378.4 [\(\text{M-H}\)]\(^-\).

Example 9

\[ \text{N-[4-(S^-dicyclopropyl-\textit{H}-pyrazol-1-yl)phenyl]-2,3-difluorobenzamide:} \]

[253] Following the general procedure-1, the title compound (120 mg) was prepared from 2,3-difluorobenzoic acid and intermediate 27 (95 mg, 0.60 mmol) as a white solid. M. P. 135-142 °C. \(^1\text{H}\)-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.69 (s, 1H), 7.81 (d, \(J\) 8.8, 2H), 7.65-7.61 (m, 1H), 7.57 (d, \(J\) 8.8, 2H), 7.51-7.48 (m, 1H), 7.37-7.32 (m, 1H), 1.87-1.75 (m, 2H), 0.93-0.85 (m, 2H), 0.84-0.81 (m, 2H), 0.68-0.61 (m, 4H). MS (m/z): 380.26 [\(\text{M+H}\)]\(^+\).

Example 10

\[ \text{N-[4-(3,5-dicyclopropyl-\textit{H}-pyrazol-1-yl)phenyl]-3-(methylsulfonyl)benzamide} \]

[254] Following the general procedure-2, the title compound (63 mg) was prepared from 3-(methylsulfonyl)benzoyl chloride (100 mg, 0.45 mmol) and intermediate 27 (120 mg, 0.50 mmol) as a pale yellow solid. M. P. 203-208 °C. \(^1\text{H}\)-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.66 (s, 1H), 8.48 (s, 1H), 8.30 (d, \(J\) 7.5, 1H), 8.14 (d, \(J\) 7.5, 1H), 7.89 (d, \(J\)
N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-4-(methylsulfonyl)benzamide

[255] Following the general procedure-2, the title compound (97 mg) was prepared from 4-(methylsulfonyl)benzoyl chloride (100 mg, 0.46 mmol) and intermediate 27 (110 mg, 0.45 mmol) as an yellow solid. M. P. 171-176 °C. \(^1\)H-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 10.64 (s, 1H), 8.18 (d, J 8.3, 2H), 8.09 (d, J 8.3, 2H), 7.89 (d, J 8.8, 2H), 7.58 (d, J 8.8, 2H), 5.80 (s, IH), 3.29 (s, 3H), 1.92-1.85 (m, 2H), 0.90-0.81 (m, 4H), 0.68-0.61 (m, 4H). MS (m/z): 422.29 [M+H]^+.

Example 12

2-chloro-/V-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-5-(methylthio)benzamide:

[256] Following the general procedure-1, the title compound (24 mg) was prepared from 2-chloro-5-(methylthio)benzoic acid (109 mg, 0.54 mmol) and intermediate 27 (120 mg, 0.45 mmol) as a pale yellow solid. M. P. 168-173 °C. \(^1\)H-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 10.66 (s, IH), 7.82 (d, J 8.8, 2H), 7.55 (d, J 8.8, 2H), 7.49-7.45 (m, 2H), 7.39-7.36 (m, IH), 5.79 (s, IH), 2.52 (s, 3H), 1.87-1.74 (m, 2H), 0.93-0.88 (m, 2H), 0.67-0.61 (m, 4H). MS (m/z): 420.23 [M-H].

Example 13

2-chloro-7V-[\(^1\)-3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-5-(methylsulfonyl)benzamide

[257] Following the general procedure-2, the title compound (58 mg) was prepared from 2-chloro-5-(methylsulfonyl)benzoyl chloride (120 mg, 0.47 mmol) and intermediate 27 (120 mg, 0.45 mmol) as a pale yellow solid. M. P. 60-65 °C. \(^1\)H-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 10.85 (s, IH), 8.16 (d, J 2.1, IH), 8.03 ((dd, J 2.0, 8.4, IH), 7.88 (d, J 8.4, 1H) 7.81 (d, J 8.8, 2H), 7.58 (d, J 8.8, 2H), 5.80 (s, IH), 3.31 (s, 3H), 1.86-1.74 (m, 2H), 0.95-0.82 (m, 4H), 0.70-0.59 (m, 4H). MS (m/z): 454.07 [M-H]^+.
Example 14

*N-[4-(3,5-dicyclop-ropyl-lH-pyrazol-l-yl)phenyl]nicotinamide hydrochloride:

[258] Following the general procedure-1, *N-[4-(3,5-dicyclop-ropyl-l H-pyrazol-l-yl)phenyl] nicotinamide (220 mg) was prepared from intermediate 27 (200 mg, 0.84 mmol) and isonicotinic acid (164 mg, 1.34 mmol) as an off-white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (190 mg) as an off-white solid. M. P.: 230.2-232.9 °C. 1H-NMR (δ ppm, DMSO-**d**6, 400 MHz): 10.97 (s, 1H), 9.34 (s, 1H), 8.94 (d, J 3.6, 1H), 8.74 (bs, 1H), 7.93 (d, J 8.8, 3H), 7.60 (d, J 8.8, 2H), 5.82 (s, 1H), 1.90-1.74 (m, 2H), 0.95-0.80 (m, 4H), 0.70-0.60 (m, 4H). MS (m/z): 345.15 [M+H-HCl]**+. 

Example 15

*N-[4-(3,5-dicyclop-ropyl-lH-pyrazol-l-yl)phenyl]isonicotinamide hydrochloride

[259] Following the general procedure-1 *N-[4-(3,5-dicyclop-ropyl-l H-pyrazol-l-yl)phenyl] isonicotinamide (40 mg) was prepared from isonicotinic acid (74 mg, 0.60 mmol) and intermediate 27 (120 mg, 0.50 mmol) as a pale yellow solid and dissolved in TFIF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (47 mg) as an yellow solid. M. P. 232-238 °C. 1H-NMR (δ ppm, DMSO-**d**6, 400 MHz): 11.08 (s, 1H), 9.01 (d, J 6.0, 2H), 8.30 (d, J 6.0, 2H), 7.94 (d, J 8.8, 2H), 7.61 (d, J 8.8, 2H), 5.83 (s, 1H), 1.90-1.74 (m, 2H), 0.95-0.80 (m, 4H), 0.70-0.60 (m, 4H).MS (m/z): 345.22 [M-H-HCl]**+. 

Example 16

*iV-[4-(3,5-dicyclop-ropyl-lH-pyrazol-l-yl)phenyl]-3-fluoroisonicotinamide:

[260] Following the general procedure-1, the title compound (60 mg) was prepared from intermediate 27 (200 mg, 0.84 mmol) and 3-fluoroisonicotinic acid (188 mg, 1.3 mmol) as an off-white solid. M. P.: 135.2-139.3 °C. 1H-NMR (δ ppm, DMSO-**d**6, 400 MHz): 10.84 (s, 1H), 8.77 (s, 1H), 8.60 (d, J 4.7, 1H), 7.81 (d, J 8.9, 2H), 7.71 (t, J 5.4, 1H), 7.59 (d, J 8.9, 2H), 5.80 (s, 1H), 1.90-1.73 (m, 2H), 0.95-0.79 (m, 4H), 0.69-0.60 (m, 4H). MS (m/z): 363.14 [M+H]**+. 

77
Example 17

3,5-dichloro-N-(4-(3,5-dicyclopentyl-1H-pyrazol-1-yl)phenyl)isonicotinamide:

[261] Following the general procedure-2, the title compound (168 mg) was prepared from intermediate 27 (200 mg, 0.84 mmol) and 3,6-dichloropyridine-4-carboxylic acid (211 mg, 1 mmol) as a white solid. M. P.: 159-164 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.09 (s, 1H), 8.81 (s, 2H), 7.76 (d, J 8.9, 2H) 7.60 (d, J 8.9, 2H), 5.80 (s, 1H), 1.88-1.75 (m, 2H), 0.95-0.89 (m, 2H), 0.87-0.81 (m, 2H), 0.71-0.60 (m, 4H). MS (m/z): 413.30 [M+H]+.

Example 18

A’-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-4-methylpyrimidine-5-carboxamide:

[262] Following the general procedure-1, the title compound (129 mg) was prepared from intermediate 27 (200 mg, 0.87 mmol) and 4-methylpyrimidine-5-carboxylic acid (360 mg, 2.63 mmol) as a yellow solid. M. P.: 89-95 ºC. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.75 (s, 1H), 9.15 (s, 1H), 8.90 (s, 1H), 7.83 (d, J 8.8, 2H), 7.58 (d, J 8.8, 2H), 5.80 (s, 1H), 2.59 (s, 3H), 1.90-1.78 (m, 2H), 0.99-0.82 (m, 4H), 0.70-0.58 (m, 4H). MS (m/z): 359.99 [M+H]+.

Example 19

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-2-phenylacetamide:

[263] Following the general procedure-1, title compound (100 mg) was prepared from 2-phenylacetic acid (68 mg, 0.501 mmol) and intermediate 27 (100 mg, 0.41 mmol) as a pale yellow solid. M. P. 133-138.5 ºC. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.30 (s, 1H), 7.69 (d, J 8.8, 2H), 7.48 (d, J 8.8, 2H), 7.35-7.30 (m, 4H), 7.26-7.22 (m, 1H), 5.77 (s, 1H), 3.65 (s, 2H), 1.84-1.70 (m, 2H), 0.90-0.80 (m, 4H), 0.65-0.59 (m, 4H). MS (m/z): 358.29 [M+H]+.

Example 20

/N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)phenyl]-2-(4-fluorophenyl)acetamide:

[264] Following the general procedure-1, the title compound (120 mg) was prepared from 2-(4-fluorophenyl)acetic acid (92 mg, 0.60 mmol) and intermediate 27 (120 mg, 0.60 mmol) as an off-white solid. M. P. 141-148 ºC. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.30 (s, 1H), 7.68 (d, J 8.8, 2H), 7.48 (d, J 8.8, 2H), 7.38-7.34 (m, 2H), 7.14 (t, J
8.9, 2H), 5.77 (s, 2H), 1.84-1.70 (m, 2H), 0.89-0.80 (m, 4H), 0.65-0.59 (m, 4H). MS (m/z): 374.1 [M-H]⁻.

Example 21

N-[4-(3,5-dicyclopropyl-1H-pyrazol-l-yl)phenyl]-1-phenylcyclopropanecarboxainide:

[265] Following the general procedure-2, the title compound (40 mg) was prepared from 1-phenylcyclopropanecarbonyl chloride (82 mg, 0.45 mmol) and intermediate 27 (100 mg, 0.42 mmol) as a brown viscous liquid. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 9.24 (s, 1H), 7.65 (d, J 8.9, 2H), 7.45 (d, J 8.9, 2H), 7.42-7.33 (m, 4H), 7.28 (d, J 7.0, 1H), 5.76 (s, 1H), 1.83-1.79 (m, 1H), 1.75-1.70 (m, 1H), 1.46-1.41 (m, 2H), 1.31-1.10 (m, 2H), 0.89-0.79 (m, 4H), 0.65-0.59 (m, 4H). MS (m/z): 384.27 [M+H]⁺.

Example 22

iV-[4-(3,5-dicyclopropyl-1H-pyrazol-l-yl)phenyl]-2-(pyridin-2-yl)acetamide hydrochloride

[266] Following the general procedure-1, N-[4-(3,5-dicyclopropyl-1H-pyrazol-l-yl)phenyl]-2-(pyridin-2-yl)acetamide (85 mg) was prepared from 2-pyridylacetic acid (139 mg, 0.8 mmol) and intermediate 27 (120 mg, 0.5 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (75 mg) as a pale yellow solid. M. P. 157-162 °C. 1H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.90 (s, 1H), 8.89 (d, J 5.1, 1H), 8.53 (t, J 8.0, 1H), 8.05 (d, J 8.0, 1H), 7.95 (t, J 6.5, 1H), 7.72 (d, J 8.8, 2H), 7.52 (d, J 8.8, 2H), 5.79 (s, 1H), 4.34 (s, 2H), 1.87-1.70 (m, 2H), 0.95-0.81 (m, 4H), 0.67-0.59 (m, 4H). MS (m/z): 359.29 [M+H-HCl]⁺.

Example 23

A^-[4-(3,5-dicyclopropyl-lH-pyrazol-l-yl)phenyl]-2-(pyridin-3-yl)acetamide hydrochloride

[267] Following the general procedure-1, N-[4-(3,5-dicyclopropyl-1H-pyrazol-l-yl)phenyl]-2-(pyridin-3-yl)acetamide (86 mg) was prepared from 3-pyridylacetic acid (139 mg, 0.8 mmol) and intermediate 27 (120 mg, 0.5 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title
compound (75 mg) as a pale yellow solid. M. P. 103-108 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.71 (s, 1H), 8.92 (s, 1H), 8.84 (d, J 5.1, 1H), 8.55 (d, J 7.8, 1H), 8.06-8.01 (m, 1H), 7.72 (d, J 8.8, 2H), 7.51 (d, J 8.8, 2H), 5.78 (s, 1H), 4.05 (s, 2H), 1.85-1.69 (m, 2H), 0.91-0.79 (m, 4H), 0.68-0.58 (m, 4H). MS (m/z): 393.05 [MH⁺].

Example 24

A'-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2-(pyridin-4-yl)acetamide hydrochloride:

Following the general procedure-1, N-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2-(pyridin-4-yl)acetamide (89 mg) was prepared from 2-(pyridin-4-yl)acetic acid (104 mg, 0.60 mmol) and intermediate 27 (120 mg, 0.50 mmol) as an off-white solid. This amide was dissolved in saturated HCl in diethyl ether at 0 °C and stirred for 15min. Solid that separated out was filtered and dried to give the title compound (12 mg). M. P. 175-181 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.75 (s, 1H), 8.86 (d, J 6.2, 2H), 8.04 (d, J 5.8, 2H), 7.71 (d, J 8.8, 2H), 7.51 (d, J 8.8, 2H), 5.78 (s, 1H), 4.12 (s, 2H), 1.84-1.72 (m, 2H), 0.91-0.80 (m, 4H), 0.66-0.60 (m, 4H). MS (m/z): 393.09 [MH⁺].

Example 25

IV-[4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenyl]-2-(piperazin-1-yl)acetamide hydrochloride:

Intermediate 41 (150 mg, 0.475 mmol) and piperazine (40 mg, 0.464 mmol) were dissolved in DMF (3 mL) at 0 °C and Sodium Hydroxide (30 mg, 1.25 mmol) was added to the reaction mixture. Then reaction was allowed to stir at ambient temperature overnight. Work-up (H₂O:AcOEt) followed by purification on column afforded both mono and di substituted piperazines. They were separated by column chromatography. Mono substituted piperazine was protected with di-tert-butyl dicarbonate (100 mg, 0.46 mmol) in presence of tri ethyl amine (0.11 ml, 0.82 mmol) in DCM. Work up followed by purification afforded the tert-butyl 4-(2-(4-(3,5-dicyclopropyl-lH-pyrazol-1-yl)phenylamino)-2-oxoethyl)piperazin-1-ylcarboxylate (98 mg). Saturated HCl in diethyl ether was added at 0 °C to it and stirred for 15min. Solid that separated out was filtered and dried to give the title compound (40 mg) as an off-white solid. M. P. 218-226 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.99 (bs, 1H), 9.69 (bs, 2H), 7.74 (d, J 8.7, 2H),
Example 26

7\textsubscript{V}·-[4-(3,5-dicyclopropyl-1\textsubscript{H}-pyrazol-1-yl)phenyl]-2-morpholinoacetamide

[270] Intermediate 41 (150 mg, 0.475 mmol) and morpholine (40 mg, 0.475 mmol) were dissolved in DMF (3 mL) at 0 °C and Sodium Hydride (30 mg, 1.25 mmol) was added to the reaction mixture. Reaction was allowed to stir at ambient temperature overnight. Work-up (H\textsubscript{2}O:AcOEt) followed by purification on column afforded the title compound as a white solid. M. P. 178-184 °C. \textsuperscript{1}H-NMR (\(\delta\) ppm, DMSO-\textsubscript{d6}, 400 MHz): 9.87 (s, 1H), 7.74 (d, \(J = 8.7\), 2H), 7.49 (d, \(J = 8.7\), 2H), 5.77 (s, 1H), 3.63 (t, \(J = 4.2\), 4H), 3.13 (s, 2H), 2.48-2.45 (m, 4H), 1.89-1.69 (m, 2H), 0.92-0.81 (m, 4H), 0.69-0.60 (m, 4H). MS (m/z): 393.05 [M+H\textsubscript{-HCl}]\textsuperscript{+}.

Example 27

\textsuperscript{1}V·-[4-(3,5-dicyclopropyl-1\textsubscript{H}-pyrazol-1-yl)phenyl]benzenesulfonamide:

[271] Following the general procedure-2, title compound (90 mg) was prepared from benzene sulphonyl chloride (81 mg, 0.458 mmol) and intermediate 27 (100 mg, 0.42 mmol) as a yellow solid. M. P 180-184.5 °C. \textsuperscript{1}H-NMR (\(\delta\) ppm, DMSO-\textsubscript{d6}, 400 MHz): 10.43 (s, 1H), 7.77 (d, \(J = 7.2\), 2H), 7.64-7.59 (m, 1H), 7.58-7.52 (m, 2H), 7.43 (d, \(J = 8.7\), 2H), 7.17 (d, \(J = 8.7\), 2H), 5.75 (s, 1H), 1.81-1.75 (m, 1H), 1.69-1.64 (m, 1H), 1.16-0.78 (m, 4H), 0.62-0.57 (m, 4H). MS (m/z): 378.05 [M-H]\textsuperscript{-}.

Example 28

\textsuperscript{2}V·-[4-(3,5-dicyclopropyl-1\textsubscript{H}-pyrazol-1-yl)-3-fluorophenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide:

[272] Following the general procedure-2, the title compound (34 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (90 mg, 0.56 mmol) and intermediate 28 (120 mg, 0.47 mmol) as a white solid. M. P.: 148-152 °C. \textsuperscript{1}H-NMR (\(\delta\) ppm, DMSO-\textsubscript{d6}, 400 MHz): 11.07 (s, 1H), 7.83 (d, \(J = 10.8\), 1H), 7.57-7.50 (m, 2H), 5.76 (s, 1H), 2.82 (s, 3H), 1.87-1.79 (m, 1H), 1.56-1.48 (m, 1H), 0.89-0.77 (m, 4H), 0.66-0.54 (m, 4H). MS (m/z): 384.28 [M+H]\textsuperscript{+}.
Example 29

A’-[4-(3,5-dicyclopentyH-pyrazol-1-yH)-3-fluorophenyl]-4-methylthiazole-5-carboxamide:

[273] Following the general procedure-1, the title compound (48 mg) was prepared from 4-methylthiazole-5-carboxylic acid (106 mg, 0.75 mmol) and intermediate 28 (120 mg, 0.47 mmol) as a pale-yellow solid. M. P.: 102-106 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.58 (s, 1H), 9.16 (s, 1H), 7.83 (dd, J 2.2, 12.6, 1H), 7.57 (dd, J 1.9, 8.8, 1H), 7.48 (t, J 8.6, 1H), 5.75 (s, 1H), 2.62 (s, 3H), 1.85-1.79 (m, 1H), 1.55-1.45 (m, 1H), 0.90-0.77 (m, 4H), 0.68-0.55 (m, 4H). MS (m/z): 383.05 [M+H]+.

Example 30

N-[4-(3,5-dicyclopentyH-pyrazol-1-yH)-3-fluorophenyl]-3,5-dimethylisoxazole-4-carboxamide:

[274] Following the general procedure-2, the title compound (70 mg) was prepared from intermediate 28 (200 mg, 0.78 mmol) and 3,5-dimethylisoxazole-4-carboxylic acid (150 mg, 0.95 mmol) as a pale-yellow solid. M. P.: 166-168 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.40 (s, 1H), 7.84-7.81 (m, 1H), 7.52-7.46 (m, 2H), 5.74 (s, 1H), 2.58 (s, 3H), 2.31 (s, 3H), 1.88-1.79 (m, 1H), 1.54-1.46 (m, 1H), 0.90-0.78 (m, 4H), 0.64-0.55 (m, 4H). MS (m/z): 381.32 [M+H]+.

Example 31

iV-[4-(3,5-dicyclopentyH-pyrazol-1-yH)-3-fluorophenyl]-2-methyl benzamide:

[275] Following the general procedure-2, the title compound (25 mg) was prepared from intermediate 28 (200 mg, 0.78 mmol) and o-toluic acid (143 mg, 0.93 mmol) as a yellow solid. M. P.: 105-107 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.67 (s, 1H), 7.92 (d, J 11.4, 1H), 7.59 (d, J 8, 1H), 7.52-7.47 (m, 2H), 7.46-7.38 (m, 2H), 7.32 (d, J 7.4, 2H), 5.74 (s, 1H), 2.39 (s, 3H), 1.90-1.80 (m, 1H), 1.59-1.50 (m, 1H), 0.90-0.78 (m, 4H), 0.68-0.54 (m, 4H). MS (m/z): 375.86 [M+H]+.

Example 32

N-[4-(3,5-dicyclopentyH-pyrazol-1-yH)-3-fluorophenyl]-2,3-difluorobenzamide:

[276] Following the general procedure-1, the title compound (50 mg) was prepared from intermediate 28 (200 mg, 0.77 mmol) and 2,3-difluorobenzoic acid (196 mg, 1.24
mmol) as a pale-yellow solid. M. P.: 132-135 °C. \(^1\)H-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 10.93 (s, IH), 7.87 (d, J 10.8, IH), 7.65 (q, J 8.3, IH), 7.59-7.48 (m, 3H), 7.41-7.34 (m, IH), 5.75 (s, IH), 1.88-1.79 (m, IH), 1.56-1.48 (m, IH), 0.90-0.78 (m, 4H), 0.65-0.55 (m, 4H). MS (m/z): 396.16 [M-H]^+.

Example 33

N-[4-(3,5-dicyclopropyl-l H-pyrazol-l-yl)-3-fluorophenyl]-2,6-difluorobenzamide:

[277] Following the general procedure-1, the title compound (50 mg) was prepared from intermediate 28 (200 mg, 0.78 mmol) and 2,6-difluorobenzoic acid (196 mg, 1.2 mmol) as a yellow solid. M. P.: 182.2-185.7 °C. \(^1\)H-NMR (δ ppm, DMSO-\(d_6\), 400 MHz): 11.20 (s, IH), 7.84 (d, J 11.4, IH), 7.68-7.59 (m, IH), 7.59-7.50 (m, 2H), 7.28 (t, J 8, 2H), 5.75 (s, IH), 1.89-1.79 (m, IH), 1.60-1.50 (m, IH), 0.90-0.78 (m, 4H), 0.66-0.58 (m, 4H). MS (m/z): 398.07 [M+H]^+.

Example 34

iV-[4-(3,5-dicyclopropyl-lH-pyrazol-l-yl)-3-fluorophenyl]nicotinamide hydrochloride:

[278] Following the general procedure-1, N-[4-(3,5-dicyclopropyl-l H-pyrazol-l-yl)-3-fluorophenyl]nicotinamide (130 mg) was prepared from intermediate 28 (200 mg, 0.78 mmol) and nicotinic acid (153 mg, 1.2 mmol) as an off-white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (70 mg) as a white solid. M. P.: 201.2-203.4 °C. \(^1\)H-NMR (δ ppm, DMSO-de, 400 MHz): 11.04 (s, IH), 9.26 (s, IH), 8.87 (d, J 4.8, IH), 8.58 (d, J 4.8, IH), 7.97 (d, J 12.8, IH), 7.81 (d, J 5, IH), 7.71 (d, J 8.6, IH), 7.52 (t, J 8.7, IH), 5.76 (s, IH), 1.90-1.80 (m, IH), 1.58-1.48 (m, IH), 0.90-0.78 (m, 4H), 0.65-0.55 (m, 4H). MS (m/z): 363.14 [M+H-HCl]^+.

Example 35

iV-[4-(3,5-dicyclopropyl-lH-pyrazol-l-yl)-3-fluorophenyl]isonicotinamide hydrochloride:

[279] Following the general procedure-1, N-[4-(3,5-dicyclopropyl-l H-pyrazol-l-yl)-3-fluorophenyl]isonicotinamide (107 mg) was prepared from intermediate 28 (200 mg, 0.78 mmol) and nicotinic acid (153 mg, 1.2 mmol) as a yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15
Solid that separated out was filtered and dried to give the title compound (70 mg) as a pale-yellow solid. M. P.: 201.2-203.4 °C. $^1$H-NMR ($\delta$ ppm, DMSO-$d_6$, 400 MHz): 10.83 (s, 1H), 8.81 (d, $J$ 5.9, 2H), 7.94 (dd, $J$ 1.9, 12.6, IH), 7.87 (d, $J$ 5.9, 2H), 7.67 (dd, $J$ 1.4, 8.6, IH), 7.51 (t, $J$ 8.7, IH), 5.76 (s, IH), 1.88-1.78 (m, 1H), 1.58-1.48 (m, 1H), 0.88-0.78 (m, 4H), 0.62-0.50 (m, 4H). MS (m/z): 363.14 [M+H-HCl]+.

Example 36

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-4-methylpyrimidine-5-carboxamide:

[280] Following the general procedure-1, the title compound (44 mg) was prepared from 4-methylpyrimidine-5-carboxylic acid (144 mg, 0.75 mmol) and intermediate 28 (120 mg, 0.47 mmol) as a pale-brown solid. M. P.: 123-125 °C. $^1$H-NMR ($\delta$ ppm, DMSO-$d_6$, 400 MHz): 11.00 (s, 1H), 9.16 (s, 1H), 8.93 (s, 1H), 7.91-7.87 (m, 1H), 7.60-7.47 (m, 2H), 5.75 (s, 1H), 2.6 (s, 3H), 1.90-1.78 (m, 1H), 1.66-1.56 (m, 1H), 0.90-0.78 (m, 4H), 0.67-0.59 (m, 4H). MS (m/z): 377.86 [M+H]+.

Example 37

N-[4-(4-chloro-3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-4-methyl-1,3-thiadiazole-5-carboxamide:

[281] Following the general procedure-2, the title compound (43 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (80 mg, 0.49 mmol) and intermediate 29 (120 mg, 0.41 mmol) as a white solid. M. P.: 153-156 °C. $^1$H-NMR ($\delta$ ppm, DMSO-$d_6$, 400 MHz): 11.09 (s, 1H), 7.84 (d, $J$ 12, IH), 7.58-7.49 (m, 2H), 2.82 (s, 3H), 1.89-1.81 (m, 1H), 1.69-1.61 (m, 1H), 0.92-0.85 (m, 2H), 0.82-0.72 (m, 4H), 0.64-0.55 (m, 2H). MS (m/z): 415.57 [M-H]-.

Example 38

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-methyl-1,2,3-thiadiazole-5-carboxamide hydrochloride:

[282] Following the general procedure-1, the title compound (32 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (80 mg, 0.47 mmol) and intermediate 30 (120 mg, 0.40 mmol) as a white solid. M. P.: 215-219 °C. $^1$H-NMR ($\delta$ ppm, DMSO-$d_6$, 400 MHz): 11.09 (s, 1H), 8.74 (d, $J$ 2.2, IH), 8.24 (dd, $J$ 2.4, 8.8, IH), 7.77 (d, $J$ 8.8,
IH), 5.83 (s, IH), 3.87 (s, 3H), 2.70-2.61 (m, IH), 1.90-1.81 (m, IH), 0.95-0.82 (m, 4H), 0.70-0.58 (m, 4H). MS (m/z): 365.03 [M-HCl]⁺.

Example 39

iV-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-methylthiazole-5-carboxamide hydrochloride

[283] Following the general procedure-1, N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-methylthiazole-5-carboxamide (55 mg) was prepared from 4-methylthiazole-5-carboxylic acid (130 mg, 0.83 mmol) and intermediate 30 (200 mg, 0.83 mmol) as a brown solid and dissolved in THF. Saturated HC1 in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (50 mg) as an off-white solid. M. P. 93-98 °C. 1H-NMR (δ ppm, DMSO-400 MHz): 10.57 (s, IH), 9.16 (s, IH), 8.74 (s, IH), 8.23 (dd, J 2.4, 8.9, IH), 7.73 (d, J 8.9, IH), 5.82 (s, IH), 2.70-2.60 (m, 4H), 1.88-1.80 (m, IH), 0.93-0.81 (m, 4H), 0.69-0.58 (m, 4H). MS (m/z): 366.36 [M+H-HC1]⁺.

Example 40

^e-iS^-dicyclopropyl-lH-pyrazol-1-y^pyridin-S-ylj-l^-dimethylthiazole-S-carboxamide:

[284] Following the general procedure-1, title compound (48 mg) was prepared from 2,4-dimethylthiazole-5-carboxylic acid (94 mg, 0.59 mmol) and intermediate 30 (120 mg, 0.49 mmol) as a pale yellow solid. M. P. 108-113 °C. 1H-NMR (δ ppm, DMSO-400 MHz): 10.38 (s, IH), 8.71 (d, J 2.0, IH), 8.20 (dd, J 2.0, 8.8, IH), 7.71 (d, J 8.8, IH), 5.81 (s, IH), 2.66 (s, 3H), 2.64-2.58 (m, IH), 2.56 (s, 3H), 1.89-1.81 (m, IH), 0.92-0.84 (m, 4H), 0.67-0.59 (m, 4H). MS (m/z): 380.23 [M+H-HCl]⁺.

Example 41

iV-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-3,5-dimethylisoxazole-4-carboxamide:

[285] Following the general procedure-1, the title compound (68 mg) was prepared from 3,5-dimethylisoxazole-4-carboxylic acid (112 mg, 0.8 mmol) and intermediate 30 (120 mg, 0.5 mmol) as a pale-yellow solid. M. P.: 208-210 °C. 1H-NMR (δ ppm, DMSO-d6 400 MHz): 10.32 (s, IH), 8.70 (d, J 2.5, 8.8, IH), 8.20 (dd, J 2.5, 8.8, IH), 7.73 (d, J
Example 42

6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-A'-o-tolynicotinamide:

[286] Following the general procedure-2, the title compound (10 mg) was prepared from o-toluidine (60 mg, 0.56 mmol) and intermediate 30 (177 mg, 0.62 mmol) as a white solid. M. P.: 123-126 °C. 1H-NMR (δ ppm, DMSO-\textsubscript{d}\textsubscript{6}, 400 MHz): 10.05 (s, 1H), 9.00 (s, 1H), 8.44 (d, J 8.2, 1H), 7.92 (d, J 8.6, 1H), 7.36 (d, J 7.6, 2H), 7.28 (d, J 7.5, 1H), 7.26-7.19 (m, 1H), 5.92 (s, 1H), 2.89-2.81 (m, 1H), 2.25 (s, 3H), 1.94-1.84 (m, 1H), 1.00-0.87 (m, 4H), 0.74-0.62 (m, 4H). MS (m/z): 357.02 [M-H]^-.

Example 43

/V-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-2-fluorobenzaniide:

[287] Following the general procedure-1, the title compound (121 mg) was prepared from 2-fluorobenzoic acid (111 mg, 0.8 mmol) and intermediate 30 (120 mg, 0.5 mmol) as a pale-yellow solid M. P.: 121-126 °C. 1H-NMR (δ ppm, DMSO-\textsubscript{d}\textsubscript{6}, 400 MHz): 10.75 (s, 1H), 8.76 (d, J 2.4, 1H), 8.28 (dd, J 2.6, 8.9, 1H), 7.79 -7.70 (m, 2H), 7.65-7.54 (m, 1H), 7.52-7.30 (m, 2H), 5.82 (s, 1H), 2.71-2.60 (m, 1H), 1.94-1.80 (m, 1H), 0.94-0.80 (m, 4H), 0.72-0.59 (m, 4H). MS (m/z): 362.95 [M+H]^+.

Example 44

7V-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-2,3-difluorobenzamide hydrochloride:

[288] Following the general procedure-1, title compound (68 mg) was prepared from 2,3-difluorobenzoic acid (126 mg, 0.5 mmol) and intermediate 30 (120 mg, 0.5 mmol) as a pale yellow solid M. P. 172-177 °C. 1H-NMR (δ ppm, DMSO-\textsubscript{d}\textsubscript{6}, 400 MHz): 10.84 (s, 1H), 8.75 (d, J 1, 1H), 8.26 (dd, J 1, 8.8, 1H), 7.75 (d, J 8.8, 1H), 7.64 (q, J 8.3, 1H), 7.53 (t, J 6.6, 1H), 7.35 (q, J 7.5, 1H), 5.82 (s, 1H), 2.70-2.61 (m, 1H), 1.91-1.80 (m, 1H), 0.99-0.81 (m, 4H), 0.69-0.52 (m, 4H). MS (m/z): 378.88 [M-H-HCl]^-. 
Example 45

\[
N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]-2,6-difluorobenzamide hydrochloride:
\]

[289] Following the general procedure-1, \(N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]-2,6-difluorobenzamide\) (71 mg) was prepared from 2,6-difluorobenzoic acid (126 mg, 0.799 mmol) and intermediate 30 (120 mg, 0.5 mmol) as a brown solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0°C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (69 mg) as a brown solid. M. P. 196-201 °C. \(^1\)H-NMR (δ ppm, DMSO-\(_d_6\), 400 MHz): 11.16 (s, 1H), 8.72 (d, J 2.3, 1H), 8.26 (dd, J 2.5, 8.9, 1H), 7.75 (d, J 8.8, 1H), 7.65-7.60 (m, 1H), 7.27 (t, J 8.0, 2H), 5.82 (s, 1H), 2.69-2.60 (m, 1H), 1.90-1.82 (m, 1H), 0.94-0.82 (m, 4H), 0.70-0.59 (m, 4H). MS (m/z): [M+H-HCl]+.

Example 46

\[
N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]nicotinamide dihydrochloride:
\]

[290] Following the general procedure-1, \(N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]nicotinamide\) (82 mg) was prepared from intermediate 30 (120 mg, 0.5 mmol) and nicotinic acid (98 mg, 0.65 mmol) as a yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0°C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (80 mg) as an yellow solid. M. P.: 164.6-169.5 °C. \(^1\)H-NMR (δ ppm, DMSO-\(_d_6\), 400 MHz): 11.19 (s, 1H), 9.36 (s, 1H), 8.95 (d, J 5.2, 1H), 8.88 (d, J 2.5, 1H), 8.75 (d, J 8.9, 1H), 8.36 (dd, J 2.5, 8.9, 1H), 7.92 (dd, J 5.3, 8, 1H), 7.77 (d, J 8.9, 1H), 5.83 (s, 1H), 2.71-2.61 (m, 1H), 1.91-1.81 (m, 1H), 0.95-0.82 (m, 4H), 0.70-0.55 (m, 4H). MS (m/z): 346.27 [M+2HCl]+.

Example 47

\[
N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]isonicotinamide dihydrochloride:
\]

[291] Following the general procedure-1, \(N-[6-(3,5-dicyclop propel-1H-pyrazol-1-yl)pyridin-3-yl]isonicotinamide\) (220 mg) from intermediate 30 (200 mg, 0.83 mmol) and isonicotinic acid (163 mg, 1.3 mmol) as a pale-yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0°C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (190 mg) as a pale-yellow solid. M. P.: 200.3-202.4 °C. \(^1\)H-NMR (δ ppm, DMSO-\(_d_6\), 400 MHz): 11.26
(s, IH), 8.99 (t, J 5.4, 2H), 8.88 (s, IH), 8.35 (dd, J 2.6, 6.3, IH), 8.30-8.25 (m, 2H), 7.78 (d, J 8.9, IH), 5.83 (s, IH), 2.72-2.62 (m, IH), 1.90-1.81 (m, IH), 0.94-0.82 (m, 4H), 0.70-0.59 (m, 4H). MS (m/z): 346.13 [M+H-2HCl]+.

Example 48

N-{6-(3,5-dicyclopentyl) H-pyrazol-1-yl}pyridin-3-yl]-3-fluoroisonicotinamide:

[292] Following the general procedure-1, the title compound (97 mg) was prepared from intermediate 30 (120 mg, 0.5 mmol) and 3-fluoroisonicotinic acid (112 mg, 0.8 mmol) as a brown solid. M. P.: 192.3-195.4 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.00 (s, IH), 8.79 (s, IH), 8.74 (d, J 2.5, IH), 8.61 (d, J 4.8, IH), 8.26 (dd, J 2.8, 8.9, IH), 7.78-7.72 (m, 2H), 5.83 (s, IH), 2.61-2.51 (m, IH), 1.90-1.80 (m, IH), 0.94-0.82 (m, 4H), 0.70-0.58 (m, 4H). MS (m/z): 364.19 [M+H]+.

Example 49

3,5-dichloro-N-{4-[5-cyclopentyl-3-(trifluoromethyl)] H-pyrazol-1-yl}phenyl]isonicotinamide:

[293] Following the general procedure-2, the title compound (60 mg) was prepared from 3,5-dichloroisonicotinoyl chloride (313 mg, 1.5 mmol) and intermediate 31 (200 mg, 0.75 mmol) as a white solid. M. P.: 182-184 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.21 (s, IH), 8.82 (s, 2H), 7.85 (d, J 8.8, 2H), 7.65 (d, J 8.8, 2H), 6.62 (s, IH), 1.90-1.80 (m, IH), 1.00-0.91 (m, 2H), 0.78-0.85 (m, 2H). MS (m/z): 371.76 [M-H-2Cl]−.

Example 50

3,5-dichloro/N-[6-(3,5-dicyclopentyl) H-pyrazol-1-yl]pyridin-3-yl]isonicotinamide hydrochloride:

[294] Following the general procedure-2, 3,5-dichloro-N-[6-(3,5-dicyclopentyl) H-pyrazol-1-yl]pyridin-3-yl]isonicotinamide (24 mg) was prepared from 3,5-dichloroisonicotinoyl chloride (313 mg, 1.5 mmol) and intermediate 30 (200 mg, 0.75 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (7 mg) as a pale-yellow solid. M. P.: 193-195 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.34 (s, IH), 8.82 (s, 2H), 8.69 (d, J 2.4, IH), 8.24 (dd, J 2.6, 8.9, IH), 7.78 (d, J 8.9, IH), 5.83 (s, IH), 2.72-2.64 (m, IH), 1.80-1.70 (m, IH), 0.92-0.82 (m, 4H), 0.70-0.58 (m, 4H). MS (m/z): 413.40 [M-H-HCl]+.
Example 51

N-[6-(3,5-dicyclop rypyl-lH-pyrazol-l-yl)pyridin-3-yl]-4-methylpyrimidine-5-carboxamide hydrochloride:

[295] Following the general procedure-1, N-[6-(3,5-dicyclop ry opl-lH-pyrazol-l-yl)pyridin-3-yl]-4-methylpyrimidine-5-carboxamide (230 mg) from intermediate 30 (200 mg, 0.83 mmol) and intermediate 53 (350 mg, 2.49 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (120 mg) as a yellow solid. M. P.: 192-197 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.92 (s, 1H), 9.16 (s, 1H), 8.94 (s, 1H), 8.75 (d, J 2.5, 1H), 8.27 (dd, J 2.6, 8.8, 1H), 7.76 (d, J 8.8, 1H), 5.82 (s, 1H), 2.70-2.62 (m, 1H), 2.61 (s, 3H), 1.92-1.84 (m, 1H), 0.95-0.85 (m, 4H), 0.70-0.58 (m, 4H). MS (m/z): 360.97 [M+H-HCl]+.

Example 52

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-l-yl]phenyl}-4-methyl-l'^,3-thiadiazole-5-carboxamide:

[296] Following the general procedure-2, the title compound (15 mg) was prepared from 4-methyl-l,2,3-thiadiazole-5-carbonyl chloride (80 mg, 0.49 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a white solid. M. P. 84-89 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.95 (s, 1H), 7.87 (d, J 8.8, 2H), 7.66 (d, J 8.8, 2H), 6.62 (s, 1H), 2.82 (s, 3H), 1.85-1.81 (m, 1H), 0.99-0.94 (m, 2H), 0.86-0.79 (m, 2H). MS (m/z): 392.08 [M-H]-.

Example 53

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-l-yl]phenyl}-4-methylthiazole-5-carboxamide:

[297] Following the general procedure-2, the title compound (20 mg) was prepared from 4-methylthiazole-5-carbonyl chloride (78 mg) and intermediate 31 (120 mg, 0.45 mmol) as brown solid. M. P. 137-141 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.47 (s, 1H), 9.14 (s, 1H), 7.87 (d, J 8.8, 2H), 7.62 (d, J 8.8, 2H), 6.61 (s, 1H), 2.62 (s, 3H), 1.85-1.81 (m, 1H), 0.99-0.94 (m, 2H), 0.88-0.83 (m, 2H). MS (m/z): 391.15 [M-H]-.
Example 54

\[ \text{N-}[4-\{5\text{-cyclopropyl}-3\text{-}(\text{trifluoromethyl})-1\text{H}\text{-pyrazol-1-yl}\}\text{phenyl}]\text{-N,4-dimethylthiazole-5-carboxamide:} \]

[298] \text{N-}[4-\{3\text{-cyclopropyl}-5\text{-}(\text{trifluoromethyl})-1\text{H}\text{-pyrazol-1-yl}\}\text{phenyl}]\text{-4-methylthiazole-5-carboxamide (500 mg, 1.27 mmol) was dissolved in THF, cooled to 0 °C and added sodium hydride (61 mg, 2.54 mmol) and stirred the mixture for 30 mins at the same temperature. Methyl Iodide (210 mg, 1.52 mmol) was added and heated the reaction mixture to rt. After 3h, reaction mixture quenched with water. Work up (H\textsubscript{2}O/AcOEt) and purification afforded the title compound (150 mg) as a gummy liquid.} \]

\[ \text{\^{1}H-NMR (δ ppm, CDCl}_3\text{, 400 MHz): 8.59 (s, 1H), 7.63 (d, J 8.6, 2H), 7.27 (d, J 8.6, 2H), 6.26 (s, 1H), 3.53 (s, 3H), 2.56 (s, 3H), 1.82-1.72 (m, 1H), 1.10-1.00 (m, 2H), 0.81-0.75 (m, 2H). MS (m/z): 406.96 [M+H].} \]

Example 55

\[ \text{A'-[4-\{5\text{-cyclopropyl}-3\text{-}(\text{trifluoromethyl})-1\text{H}\text{-pyrazol-1-yl}\}\text{phenyl}]\text{-2,4-dimethylthiazole-5-carboxamide:} \]

[299] \text{Following the general procedure-1, the title compound (58 mg) was prepared from 2,4-dimethylthiazole-5-carboxylic acid (77 mg, 0.49 mmol) and intermediate 31 (120 mg, 0.45 mmol) as an off-white solid. M. P. 117-122 °C. ^{1}H-NMR (δ ppm, DMSO-\textsubscript{d\textsubscript{6}}, 400 MHz): 10.32 (s, 1H), 7.85 (d, J 8.8, 2H), 7.61 (d, J 8.8, 2H), 6.61 (s, 1H), 2.66 (s, 3H), 2.55 (s, 3H), 1.84-1.79 (m, 1H), 0.97-0.94 (m, 2H), 0.83-0.79 (m, 2H). MS (m/z): 405.17 [M-H].} \]

Example 56

\[ \text{A'-[4-\{5\text{-cyclopropyl}-3\text{-}(\text{trifluoromethyl})-1\text{H}\text{-pyrazol-1-yl}\}\text{phenyl}]\text{-5-methylisoxazole-4-carboxamide:} \]

[300] \text{Following the general procedure-2, title compound (50 mg) was prepared from 5-methylisoxazole-4-carbonyl chloride (71 mg, 0.489 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a brown solid. M. P. 90-95 °C. \textsuperscript{1}H-NMR (δ ppm, DMSO-\textsubscript{d\textsubscript{6}}, 400 MHz): 10.44 (s, 1H), 8.76 (s, 1H), 7.88 (d, J 8.8, 2H), 7.63 (d, J 9.5, 2H), 6.61 (s, 1H), 2.63 (s, 3H), 1.85-1.80 (m, 1H), 0.99-0.93 (m, 2H), 0.84-0.79 (m, 2H). MS (m/z): 375.10 [M-H].}
Example 57

A'-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3,5-dimethylisoxazole-4-carboxamide:

Following the general procedure-2, the title compound (130 mg) was prepared from 3,5-dimethylisoxazole-4-carbonyl chloride (85 mg, 0.54 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a pale-yellow solid. M. P.: 170-172 °C. 1H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 10.29 (s, 1H), 7.85 (d, J 8.9, 2H), 7.62 (d, J 8.9, 2H), 6.61 (s, 1H), 2.56 (s, 3H), 2.34 (s, 3H), 1.90-1.80 (m, 1H), 1.01-0.94 (m, 2H), 0.86-0.78 (m, 2H). MS (m/z): 388.61 [M-H].

Example 58

iV-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-1-methyl-1H-imidazole-2-carboxamide:

Following the general procedure-1, the title compound (25 mg) was prepared from intermediate 31 (220 mg, 0.79 mmol) and 1-methyl-1H-imidazole-2-carboxylic acid (100 mg, 0.79 mmol) as a white solid. M. P.: 132.1-134.5 °C. 1H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 10.63 (s, 1H), 8.03 (d, J 8.9, 2H), 7.59 (d, J 8.9, 2H), 7.46 (s, 1H), 7.10 (s, 1H), 6.60 (s, 1H), 4.00 (s, 3H), 1.86-1.80 (m, 1H), 0.99-0.92 (m, 2H), 0.85-0.78 (m, 2H). MS (m/z): 376.09 [M+H].

Example 59

N-{4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methyl-1H-imidazole-5-carboxamide:

Following the general procedure-1, the title compound (150 mg) was prepared from intermediate 31 (150 mg, 0.56 mmol) and 4-methyl-1H-imidazole-5-carboxylic acid (85 mg, 0.67 mmol) as an off-white solid. M. P.: 245-250 °C. 1H-NMR (δ ppm, DMSO-d$_6$, 400 MHz): 12.46 (bs, 1H), 9.99 (s, 1H), 8.02 (d, J 8.9, 2H), 7.67 (s, 1H), 7.54 (d, J 8.9, 2H), 6.59 (s, 1H), 2.48 (s, 3H), 1.86-1.76 (m, 1H), 1.00-0.92 (m, 2H), 0.82-0.74(m, 2H). MS (m/z): 374.04 [M+H].

Example 60

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-methylbenzamide:

Following the general procedure-1, the title compound (80 mg) was prepared from intermediate 31 (200 mg, 0.75 mmol) and o-toluic acid (163 mg, 1.2 mmol) as an
off-white solid. M. P.: 143.2-145.8 °C. $^1$H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 10.56 (s, IH), 7.93 (d, J 8.8, 2H), 7.60 (d, J 8.8, 2H), 7.48 (d, J 7.6, IH), 7.42-7.38 (m, 1H), 7.32-7.29 (m, 2H), 6.61 (s, IH), 2.39 (s, 3H), 1.88-1.78 (m, IH), 1.00-0.92 (m, 2H), 0.84-0.76 (m, 2H). MS (m/z): 383.62 [M-H]$^+$.

Example 61

iV-\{4-\{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl\}phenyl\}-2,3-
difluorobenzamide:

[305] The title compound (28 mg) was prepared from 2,3-difluorobenzoic acid (71 mg, 0.45 mmol) and intermediate 31 (100 mg, 0.374 mmol) as a white solid. M. P. 147-152 °C. $^1$H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 10.80 (s, IH), 7.90 (d, J 8.7, 2H), 7.64 (d, J 8.7, 2H), 7.53-7.50 (m, 1H), 7.37-7.34 (m, 2H), 6.62 (s, IH), 1.83-1.82 (m, IH), 0.83-0.79 (m, 2H'), 0.99-0.94 (m, 2H). MS (m/z): 406.05 [M-H]$^+$.

Example 62

N-\{4-\{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl\}phenyl\}-2,6-
difluorobenzamide:

[306] Following the general procedure-1, the title compound (20 mg) was prepared from 2,6-difluorobenzoic acid (142 mg, 0.89 mmol) and intermediate 31 (100 mg, 0.374 mmol) as a pale yellow solid. M. P. 188-191 °C. 1H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 11.06 (s, IH), 7.87 (d, J 8.8, 2H), 7.64 (d, J 8.8, 2H), 7.63-7.59 (m, IH), 7.29-7.25 (m, 2H), 6.62 (s, IH), 1.85-1.82 (m, IH), 0.99-0.94 (m, 2H), 0.83-0.79 (m, 2H). MS (m/z): 406.05 [M-H]$^+$.

Example 63

iV-\{4-\{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl\}phenyl\}-3-
(methylsulfonyl)benzamide

[307] Following the general procedure-2, the title compound (43 mg) was prepared from 3-(methylsulfonyl)benzoyl chloride (108 mg, 0.49 mmol) and intermediate 31 (100 mg, 0.45 mmol) as a white solid. M. P. 178-184 °C. $^1$H-NMR (δ ppm, DMSO-$d_6$, 400 MHz): 10.76 (s, IH), 8.49 (s, IH), 8.31 (d, J 7.5, IH), 8.15 (d, J 7.5, IH), 7.98 (d, J 8.6, 2H), 7.84 (t, J 7.8, IH), 7.66 (d, J 8.6, 2H), 6.62 (s, IH), 3.21 (s, 3H), 1.98-1.82 (m, IH), 1.07-0.94 (m, 2H), 0.90-0.75 (m, 2H). MS (m/z): 448.22 [M-H]$^+$.
Example 64

2-chloro-N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-5-(methylthio)benzamide:

[308]  Following the general procedure-1, the title compound (63 mg) was prepared from 2-chloro-5-(methylthio)benzoic acid (100 mg, 0.49 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a white solid. M. P.: 172-177 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.90 (s, 1H), 8.90 (d, J 5.40, 2H), 8.07 (d, J 5.40, 2H), 7.99 (d, J 8.8, 2H), 7.39 (dd, J 2.4, 8.4, 1H), 6.61 (s, 1H), 2.52 (s, 3H), 1.86-1.79 (m, 1H), 0.99-0.94 (m, 2H), 0.84-0.79 (m, 2H). MS (m/z): 449.96 [M-H]⁻.

Example 65

2-chloro-N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-5-(methylsulfonyl)benzamide:

[309]  2-chloro-N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-5-(methylthio)benzamide (40 mg, 0.08 mmols) was dissolved in a 5 mL mixture of H₂O and acetone (1:1) at 0 °C and added Oxone (108 mg, 0.16 mmols). The mixture was stirred at ambient temperature for one hour. The reaction mixture was filtered to remove oxone and filtrate was worked up (AcOEt: H₂O). Title compound (38 mg) was obtained as a white solid. M. P. 132-135 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.97 (s, 1H), 8.19 (d, J 2.2, 1H), 8.04 (dd, J 8.4, 2.2, 1H), 7.89 (d, J 8.6, 3H), 7.65 (d, J 8.8, 2H), 6.62 (s, 1H), 3.30 (s, 3H), 1.97-1.81 (m, 1H), 0.99-0.94 (m, 2H), 0.86-0.79 (m, 2H). MS (m/z): 481.85 [M-H]⁻.

Example 66

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}pyridine-4-carboxamide hydrochloride:

[310]  Following general procedure-1, N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}pyridine-4-carboxamide (120 mg) was prepared from pyridine-4-carboxylic acid (66 mg, 0.54 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added at 0 °C to it and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (70 mg) as a yellow solid. M. P. 210-215 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.90 (s, 1H), 8.90 (d, J 5.40, 2H), 8.07 (d, J 5.40, 2H), 7.99 (d, J 8.8, 2H).
7.66 (d, J 8.8, 2H), 6.62 (s, 1H), 1.86-1.82 (m, 1H), 0.99-0.95 (m, 2H), 0.83-0.79 (m, 2H). MS (m/z): 406.89 [M-H]−.

Example 67

A′-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3-fluoroisonicotinamide:

Following the general procedure-1, the title compound (160 mg) was prepared from intermediate 31 (200 mg, 0.75 mmol) and 3-fluoroisonicotinic acid (168 mg, 1.2 mmol) as a brown solid. M. P.: 143.2-145.9 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.95 (s, 1H), 8.78 (d, J 1, 1H), 8.60 (dd, J 1, 4.8, 1H), 7.89 (d, J 8.9, 2H), 7.73 (d, J 5.3, 1H), 7.66 (d, J 8.9, 2H), 6.62 (s, 1H), 1.88-1.79 (m, 1H), 1.00-0.93 (m, 2H), 0.85-0.78 (m, 2H). MS (m/z): 391.14 [M+H]+.

Example 68

A′-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylpyrimidine-5-carboxamide:

Following the general procedure-1, the title compound (17 mg) was prepared from intermediate 31 (200 mg, 0.75 mmol) and intermediate 53 (123 mg, 0.89 mmol) as an off-white solid. M.P.: 163.4-165.5 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.87 (s, 1H), 9.16 (s, 1H), 8.92 (s, 1H), 7.91 (d, J 8.8, 2H), 7.65 (d, J 8.8, 2H), 6.62 (s, 1H), 2.60 (s, 3H), 1.90-1.78 (m, 1H), 1.00-0.92 (m, 2H), 0.85-0.76 (m, 2H). MS (m/z): 387.36 [M+H]+.

Example 69

iV-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2,4-dimethylpyrimidine-5-carboxamide:

Following the general procedure-1, the title compound (150 mg) was prepared from intermediate 31 (150 mg, 0.56 mmol) and intermediate 55 (170 mg, 1.12 mmol) as a pale-yellow solid. M. P.: 144.8-146.8 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.78 (s, 1H), 8.80 (s, 1H), 7.90 (d, J 8, 2H), 7.64 (d, J 8, 2H), 6.63 (s, 1H), 2.63 (s, 3H), 2.55 (s, 3H), 1.90-1.78 (m, 1H), 1.01-0.90 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 402.06 [M+H]+.
Example 70

*N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(4-fluorophenyl)acetamide:

[314] The title compound (14 mg) was prepared from 2-(4-fluorophenyl)acetic acid (83 mg, 0.54 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a pale yellow colour solid. M. P. 135-140 °C. \[^1\text{H}-\text{NMR}\] (δ ppm, DMSO-\[^{d_6}\], 400 MHz): 10.42 (s, 1H), 7.77 (d, J 8.8, 2H), 7.50 (d, J 8.8, 2H), 7.38-7.35 (m, 2H), 7.12 (t, J 8.8, 2H), 6.81 (s, 1H), 3.70 (s, 2H), 3.61-1.73 (m, 1H), 0.96-0.91 (m, 2H), 0.86-0.77 (m, 2H). MS (m/z): 402.01 [M+H]^+

Example 71

*N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-2-yl)acetamide hydrochloride

[315] Following the general procedure-1, *N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-2-yl)acetamide* (107 mg) was prepared from 2-pyridylacetic acid (124 mg, 0.71 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (90 mg) as a pale yellow solid. M. P. 210-215 °C. \[^1\text{H}-\text{NMR}\] (δ ppm, DMSO-\[^{d_6}\], 400 MHz): 10.80 (s, 1H), 8.79 (d, J 4.8, 1H), 8.31 (t, J 7.2, 1H), 7.86 (d, J 7.4, 1H), 7.84-7.79 (m, 4H), 7.59 (d, J 8.8, 2H), 6.60 (s, 1H), 4.20 (s, 2H), 1.85-1.75 (m, 1H), 0.99-0.90 (m, 2H), 0.82-0.75 (m, 2H). MS (m/z): 420.89 [M+H]^+

Example 72

*N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-3-yl)acetamide hydrochloride

[316] Following the general procedure-1, *N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-3-yl)acetamide* (140 mg) was prepared from 3-pyridylacetic acid (124 mg, 0.714 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (101 mg) as a pale yellow solid. M. P. 196-201 °C. \[^1\text{H}-\text{NMR}\] (δ ppm, DMSO-\[^{d_6}\], 400 MHz): 10.81 (s, 1H), 8.89 (s, 1H), 8.81 (d, J 5.4, 1H), 8.48 (d, J
7.4, 1H) 8.00-7.97 (m, 1H), 7.80 (d, J 8.7, 2H), 7.58 (d, J 8.7, 2H), 6.59 (s, 1H), 4.04 (s, 2H), 1.84-1.75 (m, 1H), 0.97-0.91 (m, 2H), 0.80-0.75 (m, 2H). MS (m/z): 423.2 [M+H]^+

Example 73

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]phenyl}-2-(pyridin-4-yl)acetamide hydrochloride:

[317] Following the general procedure-1, N-{4-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]phenyl}-2-(pyridin-4-yl)acetamide (38 mg) was prepared from 2-(pyridin-4-yl)acetic acid (94 mg, 0.54 mmol) and intermediate 31 (120 mg, 0.45 mmol) as a pale-yellow solid and dissolved in THF. Saturated HC1 in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (30 mg) as a brown solid. M. P. 135-139 ºC. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.93 (s, 1H), 8.85 (d, J 5.8, 2H), 8.01 (d, J 5.8, 2H), 7.81 (d, J 8.6, 2H), 7.58 (d, J 8.6, 2H), 6.59 (s, 1H), 4.13 (s, 2H), 1.83-1.74 (m, 1H), 0.99-0.91 (m, 2H), 0.83-0.76 (m, 2H). MS (m/z): 387.27 [M+H-HC1]^+.  

Example 74

4-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]-A'-(4-methylthiazol-5-yl)methyl]aniline:

[318] Intermediate 31 (600 mg, 2.24 mmol) was dissolved in THF, added intermediate 58 (338 mg, 2.7 mmol), sodium triacetoxy borohydride (710 mg, 3.4 mmol) and AcOH (0.12 ml, 2.24 mmol). The mixture was stirred at rt for 48 hrs. After completion of the reaction, THF was removed on rotavapour to obtain the residue. Work up (AcOEt/H2O) and purification on silicagel (60-120 mesh) using EA and Petether (25:75) afforded the title compound (31 mg) as a white solid. M. P.: 59.2-61.2 ºC. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 8.84 (s, 1H), 7.28 (d, J 8.8, 2H), 6.71 (d, J 8.8, 2H), 6.66 (t, J 5.7, IH), 6.49 (s, IH), 4.45 (d, J 5.7, 2H), 2.49 (s, 3H), 1.79-1.69 (m, IH), 0.98-0.90 (m, 2H), 0.80-0.74 (m, 2H). MS (m/z): 376.98 [M-H]^−.
Example 75

1-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}phenyl]-3-(4-methyl-1,2,3-thiadiazol-5-yl)urea:

[319] 4-methylthiadiazole-5-carboxylic acid (300 mg, 1.92 mmol) was dissolved in acetone, water mixture (15 ml and 1.5 ml) and cooled to -5 °C. Ethyl chloroformate (0.32 ml, 2.3 mmol) was added slowly to this mixture and stirred at same temperature for 30 mins. At this stage sodium azide (250 mg, 3.84 mmol) was added and stirred for 30 mins at the same temperature. Water was added to the reaction mixture and extracted with Et₂O and ether was removed to obtain the crude. Crude was dissolved in dioxane, intermediate 31 (90 mg, 0.33mmol) was added and refluxed for 30 mins. Work up (AcOEt:H₂O) followed by purification on 60-120 mesh silica gel using EA and Petether (45:50) as eluent afforded the title compound (150 mg) as a white solid. M. P.: 124-128 °C. 1H-NMR (δ ppm, DMSO-₆, 400 MHz): 10.27 (s, 1H), 9.45 (s, 1H), 7.68 (d, J 8.9, 2H), 7.60 (d, J 8.9, 2H), 6.61 (s, 1H), 2.60 (s, 3H), 1.88-1.78 (m, 1H), 1.00-0.92 (m, 2H), 0.84-0.76 (m, 2H). MS (m/z): 394. \[M-H]^+\]. MS (m/z): 407.01 \[M-H]^+\).

Example 76

1-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}phenyl]-3-(4-methylthiazol-5-yl)urea:

[320] 4-methylthiazole-5-carboxylic acid (lg, 6.99 mmol) was dissolved in acetone, water mixture (50 ml and 5 ml) and cooled to -5 °C. Ethyl chloroformate was added slowly to this mixture and stirred at same temperature for 30 mins. At this stage sodium azide (0.9 g, 13.8 mmol) was added and stirred for 30 mins at the same temperature. Water was added to the reaction mixture and extracted with Et₂O and ether was removed to obtain the crude. Crude was dissolved in dioxane, intermediate 31 was added and refluxed for 30 mins. Work up (AcOEt:H₂O) followed by purification on 60-120 mesh silica gel using EA and Petether (45:50) as eluent afforded the title compound (2.1 g) as a pale yellow solid. M. P.: 124-126 °C. ¹H-NMR (δ ppm, DMSO-₆, 400 MHz): 9.17 (s, 1H), 9.15 (s, 1H), 8.50 (s, 1H), 7.64 (d, J 8.9, 2H), 7.55 (d, J 8.9, 2H), 6.59 (s, 1H), 2.32 (s, 3H), 1.84-1.74 (m, 1H), 1.02-0.92 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 405.49 \[M-H]^+\).
Example 77

1-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(4-methylpyrimidin-5-yl)urea:

[321] 4-methylpyrimidine-5-carbonyl azide (450 mg, 2.43 mmol) and intermediate 31 (649 mg, 2.43 mmol) were dissolved in dioxane and refluxed for 30 mins. Work up (AcOEt:H2O) followed by purification on 60-120 mesh silica gel using EA and Petether (10:90) as eluent afforded the title compound (200 mg) as a pale yellow solid. M. P.: 190-192 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 9.23 (s, 1H), 8.78 (s, 1H), 8.69 (s, 1H), 7.86 (s, 1H), 7.50 (dd, J 2, 6.9, 4H), 6.10 (s, 1H), 2.44 (s, 3H), 1.74-1.66 (m, 1H), 0.97-0.91 (m, 2H), 0.75-0.65 (m, 2H). MS (m/z): 401.27 [M-H]+.

Example 78

4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-A'-(4-methylthiazol-5-yl)benzamide:

[322] Following the general procedure-1, the title compound (40 mg) was prepared from intermediate 47 (98 mg, 0.86 mmol) and intermediate 59 (170 mg, 0.57 mmol) as an off-white solid. M. P.: 125-128 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.83 (s, 1H), 8.70 (s, 1H), 8.15 (d, J 8.4, 2H), 7.86 (d, J 8.4, 2H), 6.72 (s, 1H), 2.42 (s, 3H), 1.99-1.88 (m, 1H), 1.05-0.97 (m, 2H), 0.89-0.79 (m, 2H). MS (m/z): 392.84 [M+H]+.

Example 79

4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-A'-(2,6-difluorophenyl)benzamide:

[323] Following the general procedure-2, the title compound (8 mg) was prepared from intermediate 47 (150 mg, 0.53 mmol) and 2,6-difluoroaniline (194 mg, 0.63 mmol) as a white solid. M. P.: 145.2-147.3 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.33 (s, 1H), 8.18 (d, J 8.6, 2H), 7.86 (d, J 8.6, 2H), 7.44-7.40 (m, 1H), 7.23 (t, J 8.1, 2H), 6.72 (s, 1H), 2.00-1.90 (m, 1H), 1.03-0.97 (m, 2H), 0.90-0.80 (m, 2H). MS (m/z): 405.70 [M-H]+.
Example 80

\[N-\{4-[4\text{-chloor-5-cyclop'ropyl-3-(trifluoromethyl)-1\text{H}-pyrazol-l-yl}\}phenyl\}-4-methylthiazole-5-carboxamide:\]

Following the general procedure-2, the title compound (71 mg) was prepared from 4-methylthiazole-5-carbonyl chloride (70 mg, 0.44 mmol) and intermediate 32 (120 mg, 0.4 mmol) as a white solid. M. P.: 161-164 °C. \( ^1\text{H-NMR} (\delta \text{ ppm, DMSO-d}_6, 400 \text{ MHz})\): 10.47 (s, 1H), 9.14 (s, 1H), 7.86 (d, \( J = 8.7 \), 2H), 7.63 (d, \( J = 8.7 \), 2H), 3.29 (s, 3H), 2.01-1.94 (m, 1H), 0.90-0.86 (m, 2H), 0.65-0.61 (m, 2H). MS (m/z): 425.08 [\text{M-H}]^-. 

Example 81

\[N-\{4-[4\text{-chloor-5-cyclop'ropyl-3-(trifluoromethyl)-1\text{H}-pyrazol-l-yl}\}-2-(pyridin-2-yl)acetamide hydrochloride\]

Following the general procedure-1, the title compound (32 mg) was prepared from 2-(pyridin-2-yl)acetic acid (80 mg, 0.47 mmol) and intermediate 32 (120 mg, 0.40 mmol) as a white solid. M. P.: 215-219 °C. \( ^1\text{H-NMR} (\delta \text{ ppm, DMSO-d}_6, 400 \text{ MHz})\): 10.82 (s, 1H), 8.78 (d, \( J = 5 \), 2H), 8.31 (t, \( J = 7 \), 1H), 7.86 (d, \( J = 7.8 \), 1H), 7.81 -7.73 (m, 3H), 7.59 (d, \( J = 8.7 \), 1H), 4.20 (s, 2H), 2.00-1.91 (m, 1H), 0.90-0.81 (m, 2H), 0.63-0.54 (m, 2H). MS (m/z): 421.23 [\text{M+H-HCl}]^+. 

Example 82

\[N-\{5\text{-cyclop'ropyl-3-(trifluoromethyl)-1\text{H}-pyrazoH-y]l\}-3\text{-fluorophenyl}\}-4\text{-methyl-1,2,3-thiadiazole-5-carboxamide}\]

Following the general procedure-2, the title compound (33 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (147 mg, 0.76 mmol) and intermediate 33 (200 mg, 0.76 mmol) as a white solid. M. P.: 105-112 °C. 1H-NMR (\( \delta \text{ ppm, DMSO-d}_6, 400 \text{ MHz})\): 1.17 (s, 1H), 7.93 (d, \( J = 12.2 \), \( IH \)), 7.72-7.60 (m, 2H), 6.6 (s, \( IH \)), 3.31 (s, 3H), 1.66-1.58 (m, 1H), 0.94-0.84 (m, 2H), 0.8-0.72 (m, 2H). MS (m/z): 410.09 [\text{M-H}]^-. 

Example 83

\[V-\{5\text{-cyclop'ropyl-3-(trifluoromethyl)-1\text{H}-pyrazol-l-yl\}-3\text{-fluorophenyl}\}-4-methylthiazole-5-carboxamide\]

Following the general procedure-2, the title compound (37 mg) was prepared from 4-methylthiazole-5-carbonyl chloride (60 mg, 0.37 mmol) and intermediate 33 (100
mg, 0.37 mmol) as a white solid. M. P.: 95-97.6 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.66 (s, IH), 9.17 (s, IH), 7.92 (d, J 12.5, IH), 7.64 (d, J 2.4, 2H), 6.61 (s, IH), 2.63 (s, 3H), 1.70-1.56 (m, IH), 1.00-0.89 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 408.98 \([M-H]^-\).

**Example 84**

\(-\{4-\left[5\text{-cyclopropyl-3-(trifluoromethyl)}-\text{H} \right] \text{pyrazol-1-y1}\}-3\text{-fluorophenyl}\}-5\text{-methylisoxazole-4-carboxamide:}

[328] Following the general procedure-2, the title compound (37 mg) was prepared from 5-methylisoxazole-4-carbonyl chloride (73 mg, 0.50 mmol) and intermediate 33 (120 mg, 0.42 mmol) as a white solid. M. P.: 125-128 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.47 (s, IH), 9.08 (s, IH), 7.95 (dd, J 2, 12.9, IH), 7.68-7.60 (m, 2H), 6.62 (s, IH), 2.69 (s, 3H), 1.67-1.58 (m, IH), 0.95-0.85 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 392.61 \([\text{M}+\text{H}]^+\).

**Example 85**

\(-\{4-\left[5\text{-cyclopropyl-3-(trifluoromethyl)}-\text{H} \right] \text{pyrazol-1-y1}\}-3\text{-fluorophenyl}\}-3,5\text{-dimethylisoxazole-4-carboxamide:}

[329] Following the general procedure-2, the title compound (54 mg) was prepared from intermediate 33 (200 mg, 0.70 mmol) and 3, 5-dimethylisoxazole-4-carboxylic acid (120 mg, 0.85 mmol) as a white solid. M. P.: 163-165 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.50 (s, IH), 7.91 (dd, J 2, 12.6, IH), 7.65 (t, J 8.6, IH), 7.57 (dd, J 2, 8.8, IH), 6.61 (s, IH), 2.56 (s, 3H), 2.34 (s, 3H), 1.94-1.87 (m, IH), 0.94-0.86 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 409.04 \([\text{M}+\text{H}]^+\).

**Example 86**

\(-\{4-\left[5\text{-cyclopropyl-3-(trifluoromethyl)}-\text{H} \right] \text{pyrazol-1-y1}\}-3\text{-fluorophenyl}\}-2\text{-methylbenzamide:}

[330] Following the general procedure-1, the title compound (24 mg) was prepared from intermediate 33 (200 mg, 0.7 mmol) and o-toluic acid (153 mg, 1.1 mmol) as a pale-yellow solid. M. P.: 141.6-143.7 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.78 (s, IH), 8.01-7.98 (m, IH), 7.69-7.60 (m, 2H), 7.50 (d, J 7.6, IH), 7.44-7.40 (m, IH), 7.33 (d, J 7.5, 2H), 6.61 (s, IH), 2.39 (s, 3H), 1.69-1.60 (m, IH), 0.94-0.88 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 401.54 \([\text{M}+\text{H}]^+\).
Example 87

**N-(4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]-3-fluorophenyl)-2,3-difluorobenzamide:**

[331] Following the general procedure-2, the title compound (156 mg) was prepared from intermediate 33 (200 mg, 0.70 mmol) and 2,3-difluorobenzoic acid (150 mg, 0.95 mmol) as a white solid. M. P.: 132-135 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.03 (s, 1H), 7.96 (dd, J 1.9, 12.7, 1H), 7.71-7.61 (m, 3H), 7.56-7.51 (m, 1H), 7.42-7.34 (m, 1H), 6.62 (s, 1H), 1.67-1.58 (m, 1H), 0.94-0.86 (m, 2H), 0.79-0.72 (m, 2H). MS (m/z): 424.02 [M-H]+.

Example 88

**7V-4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]-3-fluorophenyl)-2,6-difluorobenzamide:**

[332] Following the general procedure-1, the title compound (195 mg) was prepared from intermediate 33 (200 mg, 0.75 mmol) and 2,6-difluorobenzoic acid (189 mg, 1.2 mmol) as a white solid. M. P.: 193.1-196.4 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.30 (s, 1H), 7.92 (dd, J 2, 12.3, 1H), 7.69-7.58 (m, 3H), 7.29 (t, J 8.1, 2H), 6.62 (s, 1H), 1.70-1.60 (m, 1H), 0.95-0.88 (m, 2H), 0.80-0.74 (m, 2H). MS (m/z): 423.51 [M-H]+.

Example 89

**N-(4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]nicotinamide hydrochloride:**

[333] Following the general procedure-1, N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]nicotinamide (30 mg) from intermediate 33 (200 mg, 0.7 mmol) and nicotinic acid (138 mg, 1.12 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (68 mg) as an Off-white solid M. P.: 170-172 °C. 1H-NMR (δ ppm, OMSO-d6, 400 MHz): 10.98 (s, 1H), 9.18 (d, J 1.4, 1H), 8.84 (d, J 3.7, 1H), 8.42 (d, J 8, 1H), 8.04 (dd, J 2.1, 12.6, 1H), 7.77-7.74 (m, 1H), 7.70-7.65 (m, 2H), 6.62 (s, 1H), 1.69-1.59 (m, 1H), 0.96-0.88 (m, 2H), 0.76-0.70 (m, 2H). MS (m/z): 390.93 [M-H-HCl]+.
Example 90

A^4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]isonicotinamide hydrochloride:

[334] Following the general procedure-1, N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]isonicotinamide (60 mg) prepared from intermediate 33 (200 mg, 0.7 mmol) and isonicotinic acid (138 mg, 1.12 mmol) as a pale yellow solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (53 mg) as a pale-yellow solid. M. P.: 148-153 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.12 (s, IH), 8.90 (d, J 1.9, 2H), 8.07-8.03 (m, 3H), 7.77 (dd, J 1.9, 8.8, IH), 7.68 (t, J 8.6, IH), 6.63 (s, IH), 1.78-1.68 (m, IH), 0.95-0.85 (m, 2H), 0.80-0.73 (m, 2H). MS (m/z): 390.93 [M-H-HCl].

Example 91

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-3-fluoroisonicotinamide:

[335] Following the general procedure-1, the title compound (25 mg) was prepared from intermediate 33 (200 mg, 0.7 mmol) and 3-fluoronicotinic acid (158 mg, 1.1 mmol) as a black solid. M. P.: 161-165 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.17 (s, IH), 8.80 (s, 2H), 8.61 (d, J 4.8, IH), 7.94 (d, J 11.8, IH), 7.75 (t, J 5.2, IH), 7.68 (t, J 8.2, IH), 7.62 (d, J 9.1, IH), 6.62 (s, IH), 1.70-1.58 (m, IH), 0.96-0.88 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 408.32 [M+H].

Example 92

3,5-dichloro-A^4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]isonicotinamide:

[336] Following the general procedure-2, the title compound (86 mg) was prepared from intermediate 33 (150 mg, 0.55 mmol) and 3,5-dichloroisonicotinoyl chloride (132 mg, 0.63 mmol) as a white solid. M. P.: 218-223 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.48 (s, IH), 8.84 (s, 2H), 7.89 (dd, J 2.2, 12.04, IH), 7.70 (t, J 8.6, IH), 7.56 (dd, J 1.6, 8.6, IH), 6.63 (s, IH), 1.70-1.60 (m, IH), 0.96-0.88 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 458.33 [M-H].
Example 93

\( N\{4-[5\text{-cyclopropyl}-3-(\text{trifluoromethyl})-1H-pyrazol-1-yl]-3\text{-fluorophenyl}\}-4\text{-methylpyrimidine-5-carboxamide}: \)

[337] Following the general procedure-1, the title compound (150 mg) was prepared from intermediate 53 (130 mg, 0.67 mmol) and intermediate 33 (150 mg, 0.57 mmol) as a pale-yellow solid. M. P.: 101-103 °C. 1H-NMR (\( \delta \) ppm, DMSO-\( d_6 \), 400 MHz): 11.08 (s, 1H), 9.17 (s, 1H), 8.94 (s, 1H), 7.97 (d, \( J \) 12.2, 1H), 7.70-7.61 (m, 2H), 6.62 (s, 1H), 1.70-1.57 (m, 1H), 0.98-0.90 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 403.71 \([M-H]^+\).

Example 94

\( N\{4-[5\text{-cyclopropyl}-3-(\text{trifluoromethyl})-1H-pyrazol-1-yl]-3\text{-fluorophenyl}\}-4\text{-methylpyrimidine-5-carboxamide}: \)

[338] Following the general procedure-2, the title compound (150 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carbonyl chloride (150 mg, 0.94 mmol) and intermediate 34 (150 g, 0.47 mmol) as a white solid. M. P.: 143-147 °C. 1H-NMR (\( \delta \) ppm, CDC\textsubscript{3}, 400 MHz): 1.18 (s, 1H), 7.93 (dd, \( J \) 1.8, 12.5, 1H), 7.62 (d, \( J \) 9, 1H), 7.08-7.01 (m, 2H), 6.21 (s, 1H), 3.53 (s, 3H), 2.58 (s, 3H), 1.60-1.51 (m, 1H), 0.98-0.88 (m, 2H), 0.70-0.60 (m, 2H). MS (m/z): 418.35 \([M-H]^+\).
Example 96

iV-{4-[4-chloro-5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-2-\((\text{pyridin-2-yl})\)acetamide hydrochloride:

[340] Following the general procedure-1, \(N\)-{4-[4-chloro-5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-2-(pyridin-2-yl)acetamide (150 mg) was prepared from 2-(pyridin-2-yl)acetic acid (97 mg, 0.56 mmol) and intermediate 34 (150 mg, 0.47 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (25 mg) as a white solid. M. P.: 169-171 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 11.03 (s, 1H), 8.75 (d, J 3.9, 1H), 8.29-8.20 (m, 1H), 8.17 (d, J 12.6, 1H), 7.79 (d, J 7.4, 1H), 7.73-7.69 (m, 1H), 7.67 (t, J 8.7, 1H), 7.51 (d, J 8.6, 1H), 4.17 (s, 2H), 1.80-1.70 (m, 1H), 0.90-0.80 (m, 2H), 0.72-0.60 (m, 2H). MS (m/z): 439.15 [M+H-HCl]+.

Example 97

l-{4-[5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-3-(4-methylpyrimidin-5-yl)urea:

[341] 4-methylpyrimidine-5-carboxylic acid (500 mg, 3.62 mmol) was dissolved in acetone, water mixture (20 ml and 2 ml) and cooled to -5 °C. Ethyl chloroformate (0.47 ml, 4.34 mmol) was added slowly to this mixture and stirred at same temperature for 30 mins. At this stage sodium azide (470 mg, 7.24 mmol) was added and stirred for 30 mins at the same temperature. Water was added to the reaction mixture and extracted with \(\text{Et}_2\)\(\text{O}\) and ether was removed to obtain the crude. Crude was dissolved in dioxane, intermediate 33 (764 mg, 2.68 mmol) was added and refluxed for 30 mins. Work up (AcOEt:H\(_2\)O) followed by purification on 60-120 mesh silica gel using EA and Petroleum (10:90) as eluent afforded the title compound (403 mg) as a pale yellow solid. M. P.: 197.8-202.4°C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 9.63 (s, 1H), 9.04 (s, 1H), 8.75 (s, 1H), 8.49 (s, 1H), 7.76 (dd, J 2.2, 12.8, 1H), 7.56 (t, J 8.7, 1H), 7.00 (dd, J 1.8, 8.7, 1H), 6.60 (s, 1H), 2.48 (s, 3H), 1.64-1.57 (m, 1H), 0.94-0.86 (m, 2H), 0.78-0.72 (m, 2H). MS (m/z): 419.26 [M-H]-.
Example 98

A’-[4-[5]-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-2,6-dichlorobenzamide:

Following the general procedure-2, the title compound (15 mg) was prepared from intermediate 48 (220 mg, 0.74 mmol) and 2,6-dichloroaniline (100 mg, 0.62 mmol) as a white solid. M. P.: 175-180 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.63 (s, 1H), 8.11-8.02 (m, 2H), 7.91 (t, J 7.8, 1H), 7.62 (d, J 8.2, 2H), 7.41 (t, J 8, 1H), 6.70 (s, 1H), 1.73-1.64 (m, 1H), 0.97-0.90 (m, 2H), 0.84-0.77 (m, 2H). MS (m/z): 455.94 [M-H]⁺.

Example 99

4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)-3-fluorobenzamide:

Following the general procedure-2, the title compound (100 mg) was prepared from intermediate 48 (220 mg, 0.67 mmol) and 2,3-difluoroaniline (216 mg, 0.65 mmol) as a white solid. M. P.: 175-180 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.6 (s, 1H), 8.09 (d, J 9.3, 1H), 8.01 (d, J 8.5, 1H), 7.88 (t, J 7.8, 1H), 7.49-7.41 (m, 1H), 7.39-7.31 (m, 1H), 7.29-7.22 (m, 1H), 6.70 (s, 1H), 1.71-1.62 (m, 1H), 0.99-0.91 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 424.23 [M-H]⁺.

Example 100

4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-A’-(2,6-difluorophenyl)-3-fluorobenzamide:

Following the general procedure-2, the title compound (15 mg) was prepared from intermediate 48 (150 mg, 0.55 mmol) and 2,6-difluoroaniline (69 mg, 0.54 mmol) as a white solid. M. P.: 168.2-170.2 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.46 (s, 1H), 8.09 (d, J 8, 1H), 8.03 (d, J 8.3, 1H), 7.89 (t, J 7.9, 1H), 7.50-7.40 (m, 1H), 7.24 (t, J 8.2, 2H), 6.70 (s, 1H), 1.75-1.65 (m, 1H), 0.98-0.90 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 425.79 [M+H]⁺.

Example 101

N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4-methyl-1,2,3-thiadiazole-5-carboxamide:

Following the general procedure-1, title compound (18 mg) was prepared from 4-methyl-1,2,3-thiadiazole-5-carboxylic acid (102 mg, 0.71 mmol) and intermediate 36.
(120 mg, 0.45 mmol) as a pale yellow solid. M. P. 170-172 °C. ¹H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.15 (s, IH), 8.86 (d, J 2.2, IH), 8.36 (dd, J 2.4, 8.8, IH), 7.85 (d, J 8.8, IH), 6.66 (s, IH), 2.85 (s, 3H), 2.60-2.50 (m, IH), 1.08-0.98 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 392.79 [M-H-HC1]⁺.

Example 102

N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4-methylthiazole-5-carboxamide hydrochloride:

[346] Following the general procedure-2, N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4-methylthiazole-5-carboxamide (45 mg) was prepared from 4-methylthiazole-5-carbonyl chloride (132 mg, 0.82 mmol) and intermediate 36 (200 mg, 0.75 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0°C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (69 mg) as a pale yellow solid. M. P.: 180-183 °C. ¹H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.68 (s, IH), 9.18 (s, IH), 8.85 (d, J 2.4, IH), 8.35 (dd, J 2.5, 8.8, IH), 7.79 (d, J 8.8, IH), 6.64 (s, IH), 2.64 (s, 3H), 2.51-2.40 (m, IH), 1.10-0.95 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 394.23 [M+H]⁺.

Example 103

N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-3,5-dimethylisoxazole-4-carboxamide:

[347] Following the general procedure-1, the title compound (34 mg) was prepared from 3,5-dimethylisoxazole-4-carboxylic acid (101 mg, 0.71 mmol) and intermediate 36 (120 mg, 0.45 mmol) as a white solid. M. P.: 139-142 °C. ¹H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.47 (s, IH), 8.82 (d, J 2.5, IH), 8.33 (dd, J 2.5, 8.8, IH), 7.80 (d, J 8.8, IH), 6.64 (s, IH), 2.58 (s, 3H), 2.57-2.50 (m, IH), 2.49 (s, 3H), 1.00-0.92 (m, 2H), 0.80-0.74 (m, 2H). MS (m/z): 389.67 [M-H]⁻.

Example 104

N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2-methylbenzamide:

[348] Following the general procedure-1, the title compound (19 mg) was prepared from o-toluic acid (58 mg, 0.43 mmol) and intermediate 36 (80 mg, 0.26 mmol) as a white solid. M. P.: 134-138 °C. ¹H-NMR (δ ppm, DMSO-d6, 400 MHz): 10.76 (s, IH),
8.88 (d, J 2.4, IH), 8.43 (dd, J 2.4, 8.9, IH), 7.79 (d, J 8.8, 1H), 7.53 (d, J 7.3, IH), 7.44-
7.40 (m, IH), 7.34-7.31 (m, 2H), 6.63 (s, IH), 2.41 (s, 3H), 2.55-2.45 (m, 1H), 1.01-0.92
(m, 2H), 0.81-0.72 (m, 2H). MS (m/z): 384.63 [M-H]⁺.

**Example 105**

2-chloro-N-[(6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-
yl)benzamide hydrochloride

[349] Following the general procedure-2, 2-chloro-N-[(6-[5-cyclopropyl-3-
(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl)benzamide (65 mg) was prepared from
2-chlorobenzoic acid (107 mg, 0.61 mmol) and intermediate 36 (150 mg, 0.56 mmol)
and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C
and stirred for 15 min. Solid that separated out was filtered and dried to give the title
compound (52 mg) as a pale-yellow solid. M. P. 145-148 °C. ¹H-NMR (δ ppm, DMSO-
₆): 10.99 (s, IH), 8.86 (s, IH), 8.39 (d, J 8.7, IH), 7.82 (d, J 8.7, IH), 7.65 (q, J 8.6, IH),
7.66 (d, J 7, IH), 7.60 (d, J 7.8, IH), 7.54 (t, J 7.3, IH), 7.48 (t, J 7.3, IH), 6.64 (s, IH),
2.60-2.48 (m, IH), 1.04-0.92 (m, 2H), 0.82-0.70 (m, 2H). MS (m/z): 405.13 [M-H-HC1]⁺.

**Example 106**

N-(6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl)-2-
fluorobenzamide:

[350] Following the general procedure-1, the title compound (110 mg) was prepared
from 2-fluorobenzoic acid (112 mg, 0.80 mmol) and intermediate 36 (150 mg, 0.50
mmol) as a white solid M. P.: 102-106 °C. ¹H-NMR (δ ppm, DMSO-₆): 10.89 (s, IH), 8.87 (d, J 2.4, IH), 8.40 (dd, J 2.5, 8.8, IH), 7.81 (d, J 8.8, IH), 7.73 (dt, J
1.6, 7.5, IH), 7.67-7.59 (m, IH), 7.44-7.34 (m, 2H), 6.64 (s, IH), 2.58-2.50 (m, IH),
1.02-0.94 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 389.09 [M-H]⁺.

**Example 107**

N-{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2,3-
difluorobenzamide:

[351] Following the general procedure- 1, the title compound (22 mg) was prepared
from 2,3-difluorobenzoic acid (113 mg, 0.70 mmol) and intermediate 36 (120 mg, 0.45
mmol) as a white solid. M. P.: 151-156 °C. ¹H-NMR (δ ppm, OMSO-₆: 400 MHz):
10.99 (s, IH), 8.86 (s, IH), 8.39 (d, J 8.7, IH), 7.82 (d, J 8.7, IH), 7.65 (q, J 8.6, IH),
7.55 (t, J 6.4, IH), 7.42-7.34 (m, IH), 6.63 (s, IH), 2.51-2.40 (m, IH), 1.02-0.94 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 406.94 [M-H]+.

Example 108

iV-{6-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]pyridin-3-yl}-2,6-difluorobenzamide:

[352] Following the general procedure-1, the title compound was prepared from 2,6-difluorobenzoic acid (113 mg, 0.70 mmol) and intermediate 36 (120 mg, 0.45 mmol) as a pale yellow solid. M. P.: 157-162 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 1.30 (s, IH), 8.83 (s, IH), 8.39 (d, J 8.8, IH), 7.83 (d, J 8.8, IH), 7.65-7.60 (m, IH), 7.29 (t, J 8, 2H), 6.64 (s, IH), 2.58-2.48 (m, IH), 1.00-0.94 (m, 2H), 0.81-0.75 (m, 2H). MS (m/z): 406.87 [M-H]+.

Example 109

A’-{6-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]pyridin-3-yl}picolinamide:

[353] Following the general procedure-1, the title compound (200 mg) was prepared from picolinic acid (146 mg, 1.2 mmol) and intermediate 36 (200 mg, 0.75 mmol) as a white solid. M. P.: 159-162 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.19 (s, IH), 9.09 (d, J 2.4, IH), 8.78 (d, J 4, IH), 8.62 (dd, J 2.6, 8.8, IH), 8.19 (d, J 7.8, IH), 8.10 (td, J 1.7, 7.7, IH), 7.80 (d, J 8.8, IH), 7.73-7.70 (m, IH), 6.63 (s, IH), 2.66-2.58 (m, IH), 1.06-0.98 (m, 2H), 0.84-0.76 (m, 2H). MS (m/z): 372.09 [M-H]+.

Example 110

iV-{6-[5-cyclopropyl-3-(trifluoromethyl)-lH-pyrazol-1-yl]pyridin-3-yl}-3-methylpicolinamide:

[354] Following the general procedure-1, the title compound (140 mg) was prepared from 3-methylpicolinic acid (163 mg, 1.2 mmol) and intermediate 36 (200 mg, 0.75 mmol) as an off-white solid. M. P.: 197-199 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.05 (s, IH), 9.00 (d, J 2.5, IH), 8.58-8.53 (m, 2H), 7.84 (d, J 7.8, IH), 7.79 (d, J 8.8, IH), 7.57-7.54 (m, IH), 6.63 (s, IH), 2.60 (s, 3H), 2.55-2.45 (m, IH), 1.04-0.94 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 385.53 [M-H]+.
Example 111

\[\text{N-}[6-[5\text{-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]}\text{nicotinamide hydrochloride:}\]

[355] Following the general procedure-1, \(\text{N-}[6-[5\text{-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]}\text{nicotinamide (200 mg) was prepared from nicotinic acid (132 mg, 1.2 mmol) and intermediate 36 (290 mg, 0.67 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (192 mg) as a white solid M. P.: 211-213 °C. }^{1}H\text{-NMR (δ ppm, DMSO-}d_{6}, 400 MHz): 11.11 \text{ (s, IH), 9.27 (d, J 2, IH), 8.98 (d, J 2, IH), 8.89-8.86 (m, IH), 8.59-8.51 (m, IH), 8.48-8.46 (m, IH), 7.83 (d, J 8.8, IH), 7.79-7.73 (m, IH), 6.65 (s, IH), 2.58-2.50 (m, IH), 1.04-0.94 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 371.90 [M-H]^+].

Example 112

\^[6-IS-cyclopropyl-S-itrifluoromethyO-1H-pyrazol-1-yl]pyridin-S-yli\text{l-1-methyl nicotinamide hydrochloride:}\]

[356] Following the general procedure-1, \(\text{N-}[6-[5\text{-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]}\text{-2-methylnicotinamide (35 mg) was prepared from 2-methylnicotinic acid (110 mg, 0.80 mmol) and intermediate 36 (150 mg, 0.5 mmol) as a white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (20 mg) as a white solid. M. P.: 241-245 °C. }^{1}H\text{-NMR (δ ppm, DMSO-}d_{6}, 400 MHz): 11.15 \text{ (s, IH), 8.89 (d, J 2.5, IH), 8.74 (d, J 4.1 IH), 8.42 (dd, J 2.6, 8.8, IH), 8.32 (d, J 7.7, IH), 7.83 (d, J 8.8, IH), 7.72-7.64 (m, IH), 6.65 (s, IH), 2.70 (s, 3H), 2.58-2.50 (m, IH), 1.00-0.95 (m, 2H), 0.81-0.76 (m, 2H). MS (m/z): 385.64 [M-H-HCl]^+].

Example 113

\^[A'-ie-fS-cyclopropyl-S-itrifluoromethy^-1H-pyrazol-1-yl]pyridin-S-ylisonicotinamide hydrochloride:}\]

[357] Following the general procedure-1, \(\text{N-}[6-[5\text{-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]}\text{isonicotinamide (160 mg) was prepared from isonicotinic acid (132 mg, 1.2 mmol) and intermediate 36 (290 mg, 0.67 mmol) as an off-white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (192 mg) as a white solid. M. P.: 241-245 °C. }^{1}H\text{-NMR (δ ppm, DMSO-}d_{6}, 400 MHz): 11.15 \text{ (s, IH), 8.89 (d, J 2.5, IH), 8.74 (d, J 4.1 IH), 8.42 (dd, J 2.6, 8.8, IH), 8.32 (d, J 7.7, IH), 7.83 (d, J 8.8, IH), 7.72-7.64 (m, IH), 6.65 (s, IH), 2.70 (s, 3H), 2.58-2.50 (m, IH), 1.00-0.95 (m, 2H), 0.81-0.76 (m, 2H). MS (m/z): 385.64 [M-H-HCl]^+.}
and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (137 mg) as an yellow solid. M. P.: 186-188 °C. \textsuperscript{1}H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 11.23 (s, 1H), 8.99 (d, J 2.5, 1H), 8.94 (d, J 6.2, 2H), 8.47 (dd, J 2.5, 8.8, 1H), 8.14 (d, J 6.2, 2H), 7.86 (d, J 8.8, 1H), 6.65 (s, 1H), 2.60-2.52 (m, 2H), 1.04-0.94 (m, 2H), 0.80-0.73 (m, 2H). MS (m/z): 371.65 [M-H].

Example 114

\textit{iV-\{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-yl]pyridin-3-yl\}-3-fluoroisonicotinamide:}

Following the general procedure-1, the title compound (90 mg) was prepared from 3-fluoroisonicotinic acid (113 mg, 0.80 mmol) and intermediate 36 (150 mg, 0.5 mmol) as a brown solid. M. P.: 162-164 °C. \textsuperscript{1}H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 11.16 (s, 1H), 8.87 (d, J 2.5, 1H), 8.80 (d, J 2.5, 1H), 8.64-8.62 (m, 1H), 8.37 (dd, J 2.1, 8.8, 1H), 7.87 (d, J 8.8, 1H), 7.77 (t, J 5.4, 1H), 6.65 (s, 1H), 2.592.52 (m, 1H), 1.05-0.97 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 389.60 [M-H].

Example 115

\textit{3,5-dichloro-N-\{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-yl]pyridin-3-y]isonicotinamide:}

Following the general procedure-2, the title compound (45 mg) was prepared from intermediate 36 (200 mg, 0.75 mmol) and 3,5-dichloroisonicotinic acid (390 mg, 1.56 mmol) as a pale-yellow solid. M. P.: 223-225 °C. \textsuperscript{1}H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 11.49 (s, 1H), 8.84 (s, 2H), 8.80 (d, J 2.6, 1H), 8.37 (dd, J 2.6, 8.8, 1H), 7.86 (d, J 8.8, 1H), 6.65 (s, 1H), 2.60-2.52 (m, 1H), 1.02-0.94 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 441.94 [M-H].

Example 116

\textit{\textsuperscript{3}-\{ e-IS-cyclopropyl-S-trifluoromethyl\}-1H-pyrazol-yl]pyridin-3-yl\}-4-methylpyrimidine-5-carboxamide:}

Following the general procedure-1, the title compound (17 mg) was prepared from intermediate 36 (200 mg, 0.75 mmol) and intermediate 53 (123 mg, 0.89 mmol) as an off-white solid. M. P.: 159.2-160.3 °C. \textsuperscript{1}H-NMR (δ ppm, DMSO-\textit{d}_6, 400 MHz): 11.08 (s, 1H), 9.17 (s, 1H), 8.96 (s, 1H), 8.86 (s, 1H), 8.45-8.38 (m, 1H), 7.83 (d, J 6.9, 1H),
6.65 (s, 1H), 2.61 (s, 3H), 2.50-2.40 (m, 1H), 1.02-0.90 (m, 2H), 0.86-0.70 (m, 2H). MS (m/z): 386.77 [M-H]+.

Example 117

A’-{[6-[5-cyclopropyl-3-(trifluoromethyl)]-H-pyrazol-1-yl]pyridin-3-yl}-2-(pyridin-2-yl)acetamide hydrochloride:

[361] Following the general procedure-1, N-{[5-cyclopropyl-3-(trifluoromethyl)]-1H-pyrazol-1-yl]pyridin-3-yl}2-(pyridin-2-yl)acetamide (200 mg) was prepared from 2-(pyridin-2-yl)acetic acid (207 mg, 1.2 mmol) and intermediate 36 (200 mg, 0.75 mmol) as an off-white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (210 mg) as an Off-white solid M. P.: 179-181 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.38 (s, 1H), 8.90 (dd, J 0.8, 5.7, 1H), 8.82 (d, J 2.5, 1H), 8.54 (t, J 6.7, 1H) 8.30 (dd, J 2.6, 8.8, 1H), 8.06 (d, J 8, 1H), 7.96 (t, J 6.7, 1H), 7.77 (d, J 8.8, 1H), 6.63 (s, 1H), 4.41 (s, 2H), 2.50-2.41 (m, 1H), 1.00-0.91 (m, 2H), 0.79-0.72 (m, 2H). MS (m/z): 385.60 [M-H-HCl].

Example 118

7V-{[6-[5-cyclopropyl-3-(trifluoromethyl)]-H-pyrazol-1-yl]pyridin-3-yl}-2-(pyridin-4-yl)acetamide hydrochloride:

[362] Following the general procedure-1, N-{[5-cyclopropyl-3-(trifluoromethyl)]-1H-pyrazol-1-yl]pyridin-3-yl}-2-(pyridin-4-yl)acetamide (280 mg) was prepared from 4-(pyridin-4-yl)acetic acid (310 mg, 1.78 mmol) and intermediate 36 (300 mg, 1.12 mmol) as an off-white solid and dissolved in THF. Saturated HCl in diethyl ether was added to this solution at 0 °C and stirred for 15 min. Solid that separated out was filtered and dried to give the title compound (68 mg) as an Off-white solid M. P.: 185.2-188 °C. 1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.26 (s, 1H), 8.87 (d, J 6.6, 2H), 8.81 (d, J 2.5, 1H), 8.30 (dd, J 2.6, 8.8, 1H), 8.06 (d, J 6.6, 2H), 7.76 (d, J 8.8, 1H), 6.62 (s, 1H), 4.19 (s, 2H), 2.52-2.42 (s, 1H), 1.00-0.91 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 385.53 [M-H-HCl].

Example 119

N-{[4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)]-1H-pyrazol-1-yl]-3-fluorophenyl]-4-methylpyrimidine-S-carboxamide:
[363] **Step-1:** Intermediate 34 (1.83 g, 5.72 mmol) and t-Butylacetoacetate (1.9 ml, 11.4 mmol) were dissolved in xylene (5 ml) and heated to 145 °C for 90 mins. Reaction mixture was cooled to rt to obtain a solid. Solid that formed was filtered, washed with petether and dried to obtain \( N\{-4\{4\text{-chloro-5-cyclopropyl-3\{trifluoromethyl\}\}1\text{H-pyrazol-1-yl\}phenyl\}\}3\text{-oxobutanamide} (1.6 g).

[364] **Step-2:** \( N\{-4\{4\text{-chloro-5-cyclopropyl-3\{trifluoromethyl\}\}1\text{H-pyrazol-1-yl\}phenyl\}\}3\text{-oxobutanamide} (1.6 g, 3.98 mmol) and N,N-Dimethylformamide dimethylacetal (2.6 g, 21.9 mmol) were mixed and stirred at rt for overnight. Workup (AcOEt:H\(_2\)O) followed by purification on 60-120 mesh silica gel using EA and petether (1:1) as eluent afforded \( N\{-4\{4\text{-chloro-5-cyclopropyl-3\{trifluoromethyl\}\}1\text{H-pyrazol-1-yl\}phenyl\}\}2\{\{\text{dimethylamino}\}\text{methylene}\}3\text{-oxobutanamide} (1.3 g).

[365] **Step-3:** \( N\{-4\{4\text{-chloro-5-cyclopropyl-3\{trifluoromethyl\}\}1\text{H-pyrazol-1-yl\}phenyl\}\}2\{\{\text{dimethylamino}\}\text{methylene}\}3\text{-oxobutanamide} (1.3 g, 2.8 mmol) and formamidine acetate (354 mg, 3.4 mmol) were dissolved in ethanol and added NaOEt (202 mg, 3.4 mmol). The above mixture was refluxed for 3 h. Ethanol was removed on rotavapour and worked up (H\(_2\)O/ AcOEt) to obtain the crude. Crude was purified by column on 60-120 mesh silica gel using AcOEt and Petether (35:65) as eluent to obtain the title compound (150 mg) as a pale-yellow solid. M. P.: 183-185 °C. 1H-NMR (\(\delta\) ppm, OMSO-de, 400 MHz): 11.11 (s, 1H), 9.17 (s, 1H), 8.95 (s, 1H), 7.99 (dd, \(J\) 1.8, 12.4, 1H), 7.71 (t, \(J\) 8.7, 1H), 7.62 (d, \(J\) 8.7, 1H), 2.60 (s, 3H), 1.81-1.72 (m, 1H), 0.89-0.81 (m, 2H), 0.74-0.67 (m, 2H). MS (m/z): 405.89 [M+H-C\(_1\)]\(^{+}\).

### Example 120

\(1\{-6\{3\text{-cyclopropyl-5\{trifluoromethyl\}\}1\text{H-pyrazol-1-yl\}pyridin-3-yl\}\}-3\{4\text{-methylthiazol-5-yl\}urea}\):

[366] 4-methylthiazole-5-carboxylic acid (300 mg, 2.09 mmol) was dissolved in acetone, water mixture (15 ml and 1.5 ml) and cooled to -5 °C. Ethyl chloroformate (270 mg, 2.5 mmol) was added slowly to this mixture and stirred at same temperature for 30 mins. At this stage sodium azide (270 mg, 4.2 mmol) was added and stirred for 30 mins at the same temperature. Water was added to the reaction mixture and extracted with Et\(_2\)O and ether was removed to obtain the crude. Crude was dissolved in dioxane, intermediate 36 (240 mg, 0.89 mmol) was added and refluxed for 30 mins. Work up (AcOEt:H\(_2\)O) followed by purification on 60-120 mesh silica gel using EA and petether
(45:50) as eluent afforded the title compound (200 mg) as a pale yellow solid. M. P.: 244-247°C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 9.49 (s, 1H), 9.45 (s, 1H), 8.60-8.53 (m, 2H), 8.20 (m, 1H), 7.70 (m, 1H), 6.60 (s, 1H), 2.30 (s, 3H), 1.06-0.96 (m, 2H), 0.82-0.72 (m, 2H). MS (m/z): 409.06 \([M+H]^+\).

Example 121

6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)nicotinamide:

Following the general procedure-2, the title compound (100 mg) was prepared from intermediate 50 (220 mg, 0.74 mmol) and 2,3-difluoroaniline (100 mg, 0.77 mmol) as a white solid. M. P.: 155-160 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.66 (s, 1H), 9.10 (d, \(J\) 2.2, 1H), 8.60 (dd, \(J\) 2.3, 8.6, 1H), 8.00 (d, \(J\) 8.6, 1H), 7.47-7.44 (m, 1H), 7.35-7.30 (m, 1H), 7.29-7.23 (m, 1H), 6.74 (s, 1H), 2.90-2.72 (m, 1H), 1.10-1.00 (m, 2H), 0.90-0.81 (m, 2H). MS (m/z): 407.22\([M-H]\).

Example 122

6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-7V-(2,6-difluorophenyl)nicotinamide:

Following the general procedure-2, the title compound (36 mg) was prepared from intermediate 50 (150 mg, 0.46 mmol) and 2,6-difluoroaniline (61 mg, 0.46 mmol) as a white solid. M. P.: 192-194 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.52 (s, 1H), 9.11 (d, \(J\) 2.1, 1H), 8.58 (dd, \(J\) 2.1, 8.6, 1H), 8.02 (d, \(J\) 8.4, 1H), 7.50-7.40 (m, 1H), 7.24 (t, \(J\) 8.12, 2H), 6.75 (s, 1H), 2.80-2.70 (m, 1H), 1.09-1.00 (m, 2H), 0.88-0.80 (m, 2H).

Example 123

N-[6-[4-chloro-5-cyclopropyl-3-trifluoromethyl-1H-pyrazol-1-yl]pyridin-3-yl]-4-methylthiazole-5-carboxamide:

Following the general procedure-2, the title compound (21 mg) was prepared from 4-methylthiazole-5-carbonyl chloride (52 mg, 0.36 mmol) and intermediate 37 (100 mg, 0.36 mmol) as a white solid. M. P.: 144-149 °C. \(^1\)H-NMR (\(\delta\) ppm, DMSO-\(d_6\), 400 MHz): 10.68 (s, 1H), 9.17 (s, 1H), 8.87 (s, 1H), 8.37 (d, \(J\) 7.32, 1H), 7.77 (d, \(J\) 8.2, 1H), 2.65 (s, 3H), 2.21-2.08 (m, 1H), 1.93-1.84 (m, 2H), 1.71-1.60 (m, 2H). MS (m/z): 425.95\([M-H]\).
Example 124

N-(2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl)-2,6-difluorobenzamide:

[370] Following the general procedure-2, the title compound (31 mg) was prepared from intermediate 38 (150 mg, 0.55 mmol) and 2,6-difluoroaniline (98 mg, 0.46 mmol) as a white solid. M. P.: 279.7-281.2 °C. 1H-NMR (δ ppm, DMSO-d_6, 400 MHz): 11.54 (s, 1H), 9.24 (s, 2H), 7.71-7.62 (m, 1H), 7.31 (t, J 8.1, 2H), 6.67 (s, 1H), 2.60-2.50 (m, 1H), 1.02-0.94 (m, 2H), 0.82-0.74 (m, 2H). MS (m/z): 409.90 [M+H]^+.

Example 125

A'-{4-[5-(fluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylthiazole-5-carboxamide:

[371] Following the general procedure-1, the title compound (110 mg) was prepared from 4-methylthiazole-5-carboxylic acid (165 mg, 1.15 mmol) and intermediate 39 (150 mg, 0.58 mmol) as an off-white solid. M. P.: 123.9-125.3 °C. 1H-NMR (δ ppm, DMSO-d_6, 400 MHz): 10.51 (s, 1H), 9.15 (s, 1H), 7.88 (d, J 8.9, 2H), 7.57 (d, J 8.9, 2H), 7.23 (d, J 2.6, IH), 5.53 (d, J 48.04, 2H), 2.62 (s, 3H). MS (m/z): 382.86 [M-H]^-.

Example 126

A'-{4-[5-(difluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylthiazole-5-carboxamide:

[372] Following the general procedure-1, the title compound (70 mg) was prepared from 4-methylthiazole-5-carboxylic acid (132 mg, 0.9 mmol) and intermediate 40 (150 mg, 0.58 mmol) as a white solid. M. P.: 124-126 °C. 1H-NMR (δ ppm, DMSO-d_6, 400 MHz): 10.53 (s, IH), 9.15 (s, IH), 7.88 (d, J 8.8, 2H), 7.59 (d, J 8.8, 2H), 7.42 (s, IH), 7.26 (t, J 52.9, IH), 2.62 (s, 3H). MS (m/z): 400.58 [M-H]^-.

Example 127

3,5-dichloro-/V-/4-(3,5-dicyclopentyl-1H-pyrazol-1-yl)-3-fluorophenyl]isonicotinamide:

[373] Following the general procedure-2, the title compound (21 mg) was prepared from intermediate 28 (500 mg, 1.94 mmol) and 2,6-dichloroisonicotinic acid (380 mg, 1.97 mmol) as a yellow solid. M. P.: 279.7-281.2 °C. 1H-NMR (δ ppm, DMSO-d_6, 400 MHz): 11.37 (s, IH), 8.83 (s, 2H), 7.81 (dd, J 2, 12.1, IH), 7.58-7.48 (m, 2H), 5.76 (s,
Example 128

\[ N-(2\text{-chloro}-6\text{-fluorophenyl})-4-[5\text{-cyclopentyl}-3-(trifluoromethyl)-1\text{H}-pyrazol-1\text{-yl}]-3\text{-fluorobenzamide} \]

Following the general procedure-2, the title compound (21 mg) was prepared from intermediate 48 (500 mg, 1.94 mmol) and 2-Chloro-6-fluoroaniline (380 mg, 1.97 mmol) as a white solid. M. P.: 148-152 °C. 1H-NMR (δ ppm, \(\text{OMSO-d}_6\), 400 MHz): 10.51 (s, 1H), 8.09 (d, \(J = 10.7\) Hz, 1H), 8.04 (d, \(J = 8.1\) Hz, 1H), 7.90 (t, \(J = 7.8\) Hz, 1H), 7.50-7.35 (m, 3H), 6.70 (s, 1H), 1.73-1.65 (m, 1H), 0.97-0.90 (m, 2H), 0.80-0.73 (m, 2H). MS (m/z): 442.08 [\(M+H\)]

Example 129

\( \text{A}^2\text{-[5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-4\text{-methylthiazole-5-carboxamide} \)

Following the general procedure-2, the title compound (86 mg) was prepared from intermediate 38 (100 mg, 0.37 mmol) and 4-methylthiazole-5-carbonyl chloride (72 mg, 0.45 mmol) as a white solid. M. P.: 148-152 °C. 1H-NMR (δ ppm, \(\text{DMSO-d}_6\), 400 MHz): 10.81 (s, 1H), 9.23 (s, 2H), 9.20 (s, 1H), 6.67 (s, 1H), 2.66 (s, 3H), 2.55-2.46 (m, 1H), 1.06-0.97 (m, 2H), 0.81-0.74 (m, 2H). MS (m/z): 395.04 [\(M+H\)]

Example 130

\( \text{A}^\text{-[4-[5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]3,5-difluorophenyl]-4-methylpyrimidine-5-carboxamide} \)

Step-1: Intermediate 35 (lg, 3.3 mmol) and \(t\)-Butylacetoacetate (782 mg, 4.94 mmol) were dissolved in xylene (3 ml) and heated to 145 °C for 90 mins. Reaction mixture was cooled to rt to obtain a solid. Solid that formed was filtered, washed with petether and dried to obtain \(N\text{-[4-[5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3,5-difluorophenyl]3-oxobutanamide} \) (1.0 g).

Step-2: \(N\text{-[4-[5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3,5-difluorophenyl]3-oxobutanamide} \) (lg, 2.6 mmol) and N,N-Dimethylformamide dimethylacetal (1.7 g, 14.2 mmol) were mixed and stirred at rt for overnight. Workup
(AcOEt/H\textsubscript{2}O) followed by purification on 60-120 mesh silicagel using AcOEt and Petether (1:1) as eluent afforded \textit{N}-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}\textsubscript{-}3,5-difluorophenyl]-2-[(dimethylamino)methylene]-3-oxobutanamide (0.7 g).

[378] **Step-3:** \textit{N}-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}\textsubscript{-}3,5-difluorophenyl]-2-[(dimethylamino)methylene]-3-oxobutanamide (700 mg, 1.6 mmol) and formamidine acetate (282 mg, 2.7 mmol) were dissolved in ethanol and added NaOEt (120 mg, 3.4 mmol). The above mixture was refluxed for 3 hr. Ethanol was removed on rotavapour and worked up (½0/\textsubscript{AcOEt}) to obtain the crude. Crude was purified by column on 60-120 mesh silica gel using AcOEt and Petether (35:65) as eluent to obtain the title compound (34 mg) as a pale-yellow solid. M. P.: 147-150° C. \textit{\textsuperscript{1}H-NMR} (δ ppm, DMSO-\textsubscript{d}6, 400 MHz): 11.25 (s, 1H), 9.18 (s, 1H), 8.96 (s, 1H), 7.73 (d, \textit{J} 9.9, 2H), 6.69 (s, 1H), 2.61 (s, 3H), 1.65-1.56 (m, 1H), 0.95-0.86 (m, 2H), 0.80-0.72 (m, 2H). MS (m/z): 424.09 [\textit{M+H}]\textsuperscript{+}.

**Example 131**

\textit{N}-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}\textsubscript{-}3-fluorophenyl}-1-phenylcyclobutanecarboxamide:

[379] Following the general procedure-2, the title compound (26 mg) was prepared from intermediate 33 (100 mg, 0.37 mmol) and intermediate 61 (72 mg, 0.45 mmol) as a white solid. M. P.: 72-76° C. \textit{\textsuperscript{1}H-NMR} (δ ppm, DMSO-\textsubscript{d}6, 400 MHz): 9.85 (s, 1H), 7.89 (d, \textit{J} 11.4, 1H), 7.62-7.51 (m, 2H), 7.49-7.43 (m, 2H), 7.36 (t, \textit{J} 7.8, 2H), 7.28-7.22 (m, 1H), 6.58 (s, 1H), 2.91-2.80 (m, 2H), 1.90-1.78 (m, 2H), 1.60-1.50 (m, 1H), 0.90-0.80 (m, 2H), 0.79-0.68 (m, 2H). 444.18 [\textit{M+H}]\textsuperscript{+}

**Example 132**

\textit{7V-[4-{5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl}\textsubscript{-}3-fluorophenyl]-4-methylloxazole-5-carboxamide}:

[380] Following the general procedure-2, the title compound (26 mg) was prepared from intermediate 33 (100 mg, 0.37 mmol) and 4-Methylloxazole-5-carboxylic acid (70 mg, 0.55 mmol) as a white solid. M. P.: 148-150° C. \textit{\textsuperscript{1}H-NMR} (δ ppm, DMSO-\textsubscript{d}6, 400 MHz): 10.74 (s, 1H), 8.59 (s, 1H), 8.0 (d, \textit{J} 12.6, 1H), 7.77 (d, \textit{J} 8.4, 1H), 7.63 (t, \textit{J} 8.8, 1H), 6.61 (s, 1H), 2.44 (s, 3H), 2.66-2.58 (m, 1H), 0.94-0.84 (m, 2H), 0.80-0.71 (m, 2H). MS (m/z): 395.04 [\textit{M+H}]\textsuperscript{+}.
Example 133

A'-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-4-methylpyrimidine-5-carboxamide:

Step-1: Intermediate 38 (1.1 g, 4.08 mmol) and i-Burylacetoacetate (1.29 g, 8.17 mmol) were dissolved in xylene (2.9 ml) and heated to 145 °C for 90 mins. Reaction mixture was cooled to rt to obtain a solid. Solid that formed was filtered, washed with petether and dried to obtain N-[2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl]-3-oxobutanamide (445 mg).

Step-2: N-[2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl]-3-oxobutanamide (445 mg, 1.3 mmol) and N,N-Dimethylformamide dimethylacetal (859 mg, 7.2 mmol) were mixed and stirred at rt for overnight. Workup (AcOEt/H₂O) followed by purification on 60-120 mesh silica gel using AcOEt and Petether (1:1) as eluent afforded N-[2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl]-2-[(dimethylamino)methylene]-3-oxobutanamide (0.3 g).

Step-3: N-[2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl]-2-[(dimethylamino)methylene]-3-oxobutanamide (0.3 g, 0.78 mmol) and formamidine acetate (98 mg, 0.94 mmol) were dissolved in ethanol and added NaOEt (60 mg, 0.94 mmol). The above mixture was refluxed for 3 h. Ethanol was removed on rotavapour and worked up (H₂O/ AcOEt) to obtain the crude. Crude was purified by column on 60-120 mesh silica gel using AcOEt and Petether (1:1) as eluent to obtain the title compound (12 mg) as a brown solid. M. P.: 201-203 °C. ¹H-NMR (δ ppm, DMSO-d₆, 400 MHz): 11.29 (s, 1H), 9.26 (s, 2H), 9.19 (s, 1H), 8.99 (s, 1H), 6.68 (s, 1H), 2.64 (s, 3H), 2.55-2.49 (m, 1H), 1.02-0.94 (m, 2H), 0.83-0.75 (m, 2H). MS (m/z): 389.93 [M+H]⁺.

Example 134

4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluoro-N-(4-methylpyrimidin-5-yl)benzamide:

Following the general procedure-2, the title compound (17 mg) was prepared from intermediate 48 (120 mg, 0.41 mmol) and 4-methylpyrimidin-5-amine (50 mg, 0.46 mmol) as a white solid. M. P.: 150-152 °C. 1H-NMR (δ ppm, DMSO-d₆, 400 MHz): 10.52 (s, 1H), 8.94 (s, 1H), 8.76 (s, 1H), 8.11 (dd, J 1.6, 10.7, 1H), 8.04 (d, J 8.1, 1H),
7.91 (t, J 7.7, 1H), 6.70 (s, 1H), 2.48 (s, 3H), 1.70-1.62 (m, 1H), 0.95-0.88 (m, 2H), 0.83-0.77 (m, 2H). MS (m/z): 406.03 [M+H]+.

Example 135

A'-(4-[3-cyclopropyl-5-(difluoromethyl)-1H-pyrazol-l-yl]-3-fluorophenyl)-2,6-difluorobenzamide and A'-[4-5-cyclopropyl-3-(difluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl]-2,6-difluorobenzamide:

[386] Following the general procedure-2, the title compound (60 mg) was prepared from intermediate 65 (90 mg, 0.36 mmol) and 2,6-difluorobenzoic acid (120 mg, 0.76 mmol) as a white solid. M. P.: 168-171 °C. ^1H-NMR (δ ppm, DMSO-d6, 400 MHz): 11.28 (s, 0.64H), 11.26 (s, 0.36H), 7.92 (d, J 12.4, 0.64H), 7.85 (d, J 12.4, 0.36H), 7.66-7.53 (m, 3H), 7.29 (t, J 8.2, 1.28H), 7.19 (t, J 8.2, 0.72H), 7.00 (t, J 53.3, 0.36H), 6.97 (t, J 53.3, 0.64H), 6.57 (s, 0.36H), 6.38 (s, 0.64H), 2.0-1.94 (m, 0.36H), 1.64-1.56 (m, 0.64H), 0.96-0.86 (m, 2H), 0.75-0.69 (m, 2H). MS (m/z): 408.20 [M+H]+.

BIOLOGICAL ASSAYS

[387] The properties of the compounds of this invention may be confirmed by a number of biological/pharmacological assays. The biological/ pharmacological assay which can be been carried out with the compounds according to the invention and/or their pharmaceutically acceptable salts is exemplified below. Similarly the compounds of the present invention may also be tested using other assays, such as cytokine (IL-2, IL-4, IL-5, IL-10, IL-12, TNF alpha, interferon gamma etc.) estimation in Jurkat as well as human PBMCs The compounds of the invention may also be tested in various aminal models to establish the various theparuetic potential of of the compounds of this invention.

1. IN-VITRO CRAC CHANNEL INHIBITION ASSAYS

1A. IN-VITRO CRAC CHANNEL INHIBITION ASSAY IN Jurkat CELLS

[388] Inhibition of CRAC channels was determined following thapsigargin (Sigma, Cat # T9033) induced endoplasmic calcium release in Jurkat cells, (see Yasurio Yonetoky et.al Bio. & Med Chem. 14 (2006) 4750-4760). Cells were centrifuged and re-suspended in equal volumes of Ca²⁺ and Mg²⁺ free Hanks buffer and Fluo-8 NW dye (ABD Bioquest, Inc., Sunnyvale, CA) loading solution at 2 x 10⁵ cells/100 µl/well in 96-well black plate. Plate is incubated at 37°C,5% CO₂ for 30 min followed by further 15
min incubation at room temperature. Test compounds (DMSO stocks diluted in Ca\textsuperscript{2+} and Mg\textsuperscript{2+} free Hanks buffer) at desired concentrations were added to the wells and incubated for 15 min. Thapsigargin (1 µM final concentration) was added to the wells and incubated for 15 min to inhibit the Sarco-endoplasmic reticulum Ca\textsuperscript{2+} ATPase pump thereby depleting endoplasmic calcium and raising cytosolic calcium concentrations. Store-operated calcium entry was initiated by adding extracellular Ca\textsuperscript{2+} to a final concentration of 1.8 mM. Fluorescence was monitored over 5 min on a plate reader (BMG Labtech., Germany) with excitation at 485 nm and an emission wavelength at 520 nm. Data were analyzed using GraphPad Prism. IC50 for each compound was determined based on the percent inhibition of thapsigargin-induced calcium influx into cells. The results are as provided in Table 1A.

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<th>IC50 (nM)</th>
<th>Compound</th>
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**IB. IN-VITRO CRAC CHANNEL INHIBITION ASSAY IN NCI-H460 CANCER CELL LINE**

Inhibition of CRAC channels was determined following thapsigargin (Sigma, Cat # T9033) induced endoplasmic calcium release in NCI-H460 cells (National Centre For Cell Science (NCCS), Pune).

Cells (30,000 per well) were plated overnight in complete RPMI medium. Medium was substituted with Ca\(^{2+}\) and Mg\(^{2+}\) free Hanks buffer and Fluo-8 NW dye (ABD Bioquest, Inc., Sunnyvale, CA) loading solution in 96-well black plate. Plate was incubated at 37°C/5% CO\(_2\) for 30 min followed by further 15 min incubation at room temperature. Test compounds (DMSO stocks diluted in Ca\(^{2+}\) and Mg\(^{2+}\) free Hanks buffer) at desired concentrations were added to the wells and incubated for 15 min. Thapsigargin (1 μM final concentration) was added to the wells and incubated for 15 min to inhibit the Sarco-endoplasmic reticulum Ca\(^{2+}\) ATPase pump thereby depleting endoplasmic calcium and raising cytosolic calcium concentrations. Store-operated calcium entry was initiated by adding extracellular Ca\(^{2+}\) to a final concentration of 2.5 mM. Fluorescence was
monitored over 30 min on a plate reader (BMG Labtech., Germany) with excitation at 485 nm and an emission wavelength at 520 nm. Data were analyzed using GraphPad Prism. IC50 for each compound was determined based on the percent inhibition of Thapsigargin-induced calcium influx into cells. The results are as provided in Table 2.

1C. IN-VITRO CELL PROLIFERATION ASSAY IN NCI-H460 CANCER CELL LINE (Anticancer Activity)

Growth inhibition assays were carried out using 10% FBS supplemented media. Cells were seeded at a concentration of 5000 cells/well in a 96-well plate. Test compound at a concentration range from 0.01 to 10000 nM were added after 24 h. Growth was assessed using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) dye reduction test at 0 h (prior to the addition of the test compound) and 48 h after the addition of test compound. Absorbance was read on a Fluostar Optima (BMG Labtech, Germany) at a wavelength of 450 nm. Data were analysed using GraphPad Prism. IC-50 for each compound was determined based on the % inhibition due to the test compound compared to the control. The results are as provided in Table 2.


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<th>NCI-H460 Cell line assay</th>
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2. In Vitro Inhibition of Cytokine Release in Jurkat Cells, Human Whole Blood and Peripheral Blood Mononuclear Cells (PBMC).
Inhibition of cytokine IL-2, IL-4, IL-5 and TNFα was determined as described below.

a. Inhibition of IL-2 in Jurkat cells: Cells were incubated with desired concentrations of the inhibitor for 15 min. Cytokine release was induced by the addition of Concanavalin A (25 µg/ml) + Phorbol Myristate Acetate (50 ng/ml) for IL-2 & TNFα or with Phytohemagglutinin (5 µg/ml) for IL-4 & IL-5 and incubated at 37°C in an atmosphere containing 95% CO₂. Supernatant was collected after 20 h (IL-2 & TNFα) or 48 h (IL-4 & IL-5) for estimation of cytokines by ELISA. Data were analysed using GraphPad Prism. IC₅₀ values for each compound were determined based on the percent inhibition due to the test compound compared to the control.

b. Inhibition of cytokine release in Human Whole Blood (HWB): Freshly collected HVB was diluted with RPMI medium (1:4.5) and added to a 96-well plate. Wells were incubated with desired concentrations of the inhibitor for 15 min. Cytokine release was induced by the addition of Concanavalin A (25 µg/ml) + Phorbol Myristate Acetate (50 ng/ml) for IL-2 & TNFα or with Phytohemagglutinin (5 µg/ml) for IL-4 & IL-5 and incubated at 37°C in an atmosphere containing 95% CO₂. Supernatant was collected after 20 h (IL-2 & TNFα) or 48 h (IL-4 & IL-5) for estimation of cytokines by ELISA. Data were analysed using GraphPad Prism. IC₅₀ values for each compound were determined based on the percent inhibition due to the test compound compared to the control.

c. Inhibition of cytokine release in PBMC: PBMC from freshly collected HVB were isolated by density gradient using Histopaque and seeded in a 96-well plate. Cells were incubated with desired concentrations of the inhibitor for 15 min. Cytokine release was induced by the addition of Concanavalin A (25 µg/ml) + Phorbol Myristate Acetate (50 ng/ml) for IL-2 & TNFα or with Phytohemagglutinin (5 µg/ml) for IL-4 & IL-5 and incubated at 37°C in an atmosphere containing 95% CO₂. Supernatant was collected after 20 h (IL-2 & TNFα) or 48 h (IL-4 & IL-5) for estimation of cytokines by ELISA. Data were analysed using GraphPad Prism. IC₅₀ values for each compound were determined based on the percent inhibition due to the test compound compared to the control. The results are as provided in Table 3.
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<td>Example 93</td>
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<td>65.10</td>
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<td>172.9</td>
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<td>Example 108</td>
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<td>38.41</td>
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<td>Example 111</td>
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<td>-</td>
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<td>Example 143</td>
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<td>Example 144</td>
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<td>243.4</td>
<td>338.4</td>
<td>-</td>
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<td>Example 156</td>
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[389] Example 1: Evaluation of usefulness of CRAC channel modulators in various Anti-inflammatory and Autoimmune disorders using In-vivo animal Models

i. Concanavalin (Con) A induced Hepatitis in Female Balb/C mice: Con A is often used to prepare experimental animals with high levels of cytotoxic T-lymphocytes, because these cells are involved in the development of viral infections in humans. In this model, animals were administered test compounds orally 1 hour prior to intravenous administration of Con A. Blood samples were collected after 24 hours for determination of Serum glutamic oxaloacetic transaminase (SGOT) and Serum glutamic pyruvic transaminase (SGPT) in serum.
Results indicated >85% reduction in serum SGOT & SGPT upon administration of the test compound (example 69) at 10 mg/kg b.w.t.

ii. TNCB induced contact hypersensitivity in female Balb/c mice: Contact hypersensitivity is a simple in vivo assay of cell-mediated immune function. In this procedure, exposure of epidermal cells to exogenous haptens results in a delayed type hypersensitive reaction that can be measured and quantified. Briefly, 7% TNCB solution was applied to the abdominal region of 8 week old Balb/c mice. Ear thickness was measured 7 days after TNCB sensitization. Compounds were administered orally followed by an application of 1% TNCB to inside and outside of ear pinnae. Ear thickness was measured 24 h after TNCB challenge. Data demonstrated >70% reduction in ear inflammation upon administration of the test compound (example 69) at 10 mg/kg b.w.t.

iii. Foot paw Delayed Type Hypersensitivity in male Balb/c mice: DTH swelling responses can be used to follow the activity of immunosuppressive molecules and/or suppressor T cells in vivo. Intradermal antigen (methylated BSA) injections were given to mice (at base of tail) on day 0 and day 7. Compounds were administered once daily from day 0 to day10. Methylated BSA was injected into the right hind footpad of animals on day10. Weight difference induced by antigen was determined by weighing the right and left hind paws 24 h after injection of methylated BSA (day 11). Daily treatment of test compound (example 69) at 10 mg/kg resulted in >40% reduction in antigen-induced paw inflammation in mice.

iv. OVA-Induced Asthma in Guinea Pigs: Pulmonary eosinophilia and airway remodelling in conjunction with altered neural control of airway tone and airway epithelial desquamation contributes to Airway Hyper-responsiveness (AHR) in asthma. For determination of eosinophil reduction, animals were sensitized with OVA on d0, d7, and d14 followed by another round (0.1% w/v) through inhalation on d19 & d20. Compounds were administered orally 1h before OVA challenge (0.3%). BAL fluid was collected on d22 for differential count and cytokine estimation. For determination of change in respiratory parameters, animals were subjected to whole body plethysmography immediately after ova challenge. Results indicated >70% reduction in blood eosinophils along with a concurrent
improvement in respiration upon administration of the test compound (Example 69) at 10 mg/kg b.wt dose.

v. Collagen-induced arthritis in male DBA/1 Ola HSD mice: Collagen induced arthritis in rodent models have been widely used to illustrate and understand the development of the disease besides serving as a surrogate for validation of therapeutic targets for human rheumatoid arthritis. Mice were anesthetized with Isoflurane and given 150µl of Bovine Type II collagen in Freund's complete adjuvant injections (day 0 and day 21). Treatment was initiated on study day 0 and continued once daily, every day (po, qd). Starting on day 18, clinical scores were given daily for each of the paws (right front, left front, right rear, left rear) and continued till the day of sacrifice (day 34). Daily administration of the test compound (Example 69) at 10 mg/kg b.wt alleviated arthritic symptoms, disease progression, and incidence by 30% compared to the control animals.

[390] Other in-vivo models wherein the effect of CRAC channel modulators in various Anti-inflammatory and Autoimmune disorders can be tested include Chronic

Experimental Autoimmune Encephalomyelitis in C57/B16J mice: Experimental Autoimmune Encephalomyelitis (EAE) is an inflammatory disease of the central nervous system and widely used as an animal model of Multiple Sclerosis. Animals are administered pertussis toxin intravenously and myelin oligodendrocyte glycoprotein (MOG) subcutaneously on day 0. Treatment is initiated at day 0 and continued till sacrifice. Development of EAE is observed between day 9 to day 42. At the end of the treatment period, animals are sacrificed for histopathological analysis as well as cytokine estimation in plasma.

[391] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as described in the specification and the claims.

[392] All publications and patent and/or patent applications cited in this application are herein incorporated by reference to the same extent as if each individual publication
or patent application was specifically and individually indicated to be incorporated herein by reference.
We Claim:

1. A compound of formula

![Chemical Structure](image)

or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester or pharmaceutically acceptable salt thereof, wherein

Ring Hy represents

![Chemical Structures](image)

optionally substituted with R'"; 

R¹ and R² are the same or different and are independently selected from CH₃, CH₂F, CHF₂, CF₃, substituted or unsubstituted C₃₋₅cycloalkyl, CH₂-OR, CH₂-NR'R'', CN and COOH with the proviso that:

a) both R¹ and R² at the same time do not represent CF₃;  
b) both R¹ and R² at the same time do not represent CH₃;  
c) when R¹ is CF₃ then R² is not CH₃ and  
d) when R¹ is CH₃ then R² is not CF₃;  

Ring Ar represents:

![Chemical Structures](image)

T, U, V and W are the same or different and are independently selected from CR³ and N;  

Z¹, Z² and Z³ are the same or different and are independently selected from CR³, CR³R⁵, O, S and -NR³, with the proviso that at least one of Z¹, Z² and Z³ represents O, S or -NR³. 

128
Li and L₂ together represent -NH-C(=X)-, -NH-S(=0)₂, -C(=X)NH-, or -S(=0)₂NH- or -NH-CR'R"-;
A is absent or selected from -(CR'R")-, O, S(=0)₂, C(=X) and -NR₄⁺;
R' and R" are the same or different and are independently selected from hydrogen, hydroxy, cyano, halogen, -OR₄, -COOR₄, -S(=0)₂R₄, -NR₄R₂b, -C(=X)-R₄a, substituted or unsubstituted C(1-6) alkyl group, substituted or unsubstituted C(1-6) alkenyl, substituted or unsubstituted C(1-6)alkynyl, and substituted or unsubstituted C(3,5) cycloalkyl, or R' and R" may be joined to form a substituted or unsubstituted saturated or unsaturated 3-6 member ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR₄ and S;
R" is selected from hydrogen, hydroxy, cyano, halogen, -OR₄, -COOR₄, -S(=0)₂R₄, -NR₄R₂b, -C(=X)-R₄a, substituted or unsubstituted C(1-6) alkyl group, substituted or unsubstituted C(1-6) alkenyl, substituted or unsubstituted C(1-6) alkynyl, and substituted or unsubstituted Cp^cycloalkyl.
each occurrence of X is independently selected from O, S and -NR₄⁺;
Cy is selected from monocyclic substituted or unsubstituted cycloalkyl group, monocyclic substituted or unsubstituted heterocyclyl, monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl.
each occurrence of R₄ and R₂b are the same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, -OR₄c, -S(=0)₂R₄c, -NR₄R₂d, -C(=Y)-R₄c, -CR₄d-C(=Y)-R₄c, -CR₄d-Y-CR₄d₂-C(=Y)-NR₄R₄d, -NRR₄d-C(=Y)-NR₄R₂d, -S(=0)₂R₄c-
NR₄R₂d, -NR₄R₂d-S(=0)₂NR₄R₂d, -NR₄R₂d-NR₄R₂d, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl, or when R₄ and R₂b are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which may be the same or different and are selected from O, NR₄ and S;
each occurrence of R₄c and R₄d may be same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, substituted or unsubstituted alkyl, substituted
or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or when two \( R^c \) and/or \( R^d \) substituents are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NH and S;

each occurrence of \( Y \) is selected from O, S and \(-NR^a\); and

each occurrence of \( q \) independently represents 0, 1 or 2;

with the proviso that the compound of formula (I) does not include

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-(difluoromethyl)-5-methyl-1H-Pyrazole-3-carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-4-nitro-1H-Pyrazole-5-carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(1-ethyl-5-methyl-1H-pyrazol-4-yl)-5-Isoxazolecarboxamide; N-[4-[5-cyclopropyl-3-trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4,5-dihydro-3-(2-methoxyphenyl)-5-Isoxazole carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-[4-(1,1-dimethylethyl)phenyl]-Cyclopropanecarboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-Pyridinecarboxamide; N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-Pyridine carboxamide; or N-benzyl-6-(3,5-dicyclopentyl-1H-pyrazol-1-yl)pyridazin-3-amine

2. A compound of claim 1, wherein \( H_y \) is selected from

\[
\begin{align*}
\text{N} & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{CHF}_2 & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{CHF}_2 & \text{N} \quad \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{CHF}_2 & \text{N} \quad \text{N} \\
\text{R}^2 & \text{N} \quad \text{N} \\
\text{CHF}_2 & \text{N} \quad \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{N} \quad \text{N} \\
\text{R}^1 & \text{N} \quad \text{N} \\
\text{R}^1 & \text{N} \quad \text{N} \\
\text{R}^1 & \text{N} \quad \text{N} \\
\text{R}^3 & \text{N} \quad \text{N} \\
\text{R}^3 & \text{N} \quad \text{N} \\
\end{align*}
\]

130
3. A compound of claim 2, wherein \( H_y \) is:

4. A compound of claim 3, wherein \( H_y \) is:

5. A compound of claim 1, wherein \( A_r \) is selected from:

6. A compound of claim 6, wherein \( A_r \) is selected from:

7. A compound of claim 1, wherein \( L_1 \) and \( L_2 \) together represent \(-NH-C(=0)-\), \(-NH-S(=0)\_q\), \(-C(=0)NH\_) or \(-NH-CH\_2\).
8. A compound of claim 7, wherein \( L_1 \) and \( L_2 \) together represent \(-NH-C(=0)-\), \(-C(=0)NH-\) or \( S(=0)_2NH-\) -NH-CH\(_2\)-.

9. A compound of claim 1, wherein \( A \) is absent or is selected from \(-(CR'R^\prime)\)- or \(-NR^3\).

10. A compound of claim 9, wherein \( A \) is \(-CH_2\)- or \(-CHMe-\), \{-CR'R^\prime\}-, where \( R^\prime \) and \( R^\prime\prime \) are joined to form a substituted or unsubstituted saturated or unsaturated 3-6 membered ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NR\(^3\) and S.

11. A compound of claim 9 or 10, wherein \( A \) is

\[ \text{-NH-}, \text{-CH}_2, \text{-CHMe-}, \begin{array}{c} \triangle \end{array} \text{or} \begin{array}{c} \square \end{array}, \text{or} \]

12. A compound of claim 1, wherein \( C_y \) is

![Chemical structures](attachment:chemical_structures.png)

13. A compound of claim 12, wherein \( C_y \) is selected from
A compound of claim 12 or 13, wherein Cy is selected from

14. A compound of formula (IA) or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester, or pharmaceutically acceptable salt thereof, wherein

\[ \text{R}^1 \text{ and } \text{R}^2 \text{ are the same or different and are independently selected from } \text{CH}_3, \text{CH}_2\text{F}, \text{CHF}_2, \text{CF}_3, \text{ substituted or unsubstituted } C_{(3,5)} \text{ cycloalkyl, CH}_2\text{OR}^a, \text{CH}_2\text{NR}^a\text{R}^b, \text{CN and COOH with the proviso that;}
\]

a) both \( \text{R}^1 \text{ and } \text{R}^2 \) at the same time do not represent \( \text{CF}_3 \)
b) both \( \text{R}^1 \text{ and } \text{R}^2 \) at the same time do not represent \( \text{CH}_3 \),
c) when \( \text{R}^1 \) is \( \text{CF}_3 \) then \( \text{R}^2 \) is not \( \text{CH}_3 \) and
d) when \( \text{R}^1 \) is \( \text{CH}_3 \) then \( \text{R}^2 \) is not \( \text{CF}_3 \);
T, U, V and W are the same or different and are independently selected from CR<sup>a</sup> and N;

Li and L<sub>2</sub> together represent -NH-C(=X)-, -NH-S(=0)-, -C(=X)NH-, or -S(=0)-NH- or NH-CR<sup>”</sup>R<sup>”</sup>-

A is absent or selected from -(CR<sup=”</sup>R<sup>”</sup>)-, O, S(=0)-, C(=X) and -NR<sup>a</sup>

each occurrence of R<sup>’</sup> and R<sup>”</sup> are the same or different and are independently selected from hydrogen, hydroxy, cyano, halogen, -OR<sup>a</sup>-, COOR<sup>a</sup>-S(=0)-, NR<sup>a</sup>-R<sup>b</sup>, -C(=X)-R<sup>a</sup>, substituted or unsubstituted C<sub>(3-6)</sub> alkyl group, substituted or unsubstituted C<sub>(i-6)</sub> alkenyl, substituted or unsubstituted C<sub>(i-6)</sub> alkynyl, and substituted or unsubstituted C<sub>(i-6)</sub> cycloalkyl, or R<sup>’</sup> and R<sup>”</sup> may be joined to form a substituted or unsubstituted saturated or unsaturated 3-6 membered ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR<sup>a</sup> and S;

R<sup>”’</sup> is selected from hydrogen, hydroxy, cyano, halogen, -OR<sup>a</sup>-, COOR<sup>a</sup>-S(=0)-, NR<sup>a</sup>-R<sup>b</sup>, -C(=X)-R<sup>a</sup>, substituted or unsubstituted C<sub>(3-6)</sub> alkyl group, substituted or unsubstituted C<sub>(i-6)</sub> alkenyl, substituted or unsubstituted C<sub>(i-6)</sub> alkynyl, and substituted or unsubstituted C<sub>(3-5)</sub>cycloalkyl;

each occurrence of X is independently selected from O, S and -NR<sup>a</sup>;

Cy is selected from monocyclic substituted or unsubstituted cycloalkyl group, monocyclic substituted or unsubstituted heterocyclyl, monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl;

each occurrence of R<sup>a</sup> and R<sup>b</sup> are the same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, -OR<sup>a</sup>-S(=0)-, NR<sup>a</sup>-R<sup>d</sup>, -C(=Y)-R<sup>a</sup>, -CR<sup>d</sup>R<sup>d</sup>-C(=Y)-R<sup>c</sup>, -CR<sup>d</sup>R<sup>d</sup>-Y-CR<sup>d</sup>R<sup>d</sup>-C(=Y)-NR<sup>a</sup>R<sup>d</sup>-NRR<sup>d</sup>-C(=Y)-NR<sup>a</sup>R<sup>d</sup>-S(=0)-, -NR<sup>a</sup>R<sup>d</sup>-NR<sup>a</sup>R<sup>d</sup>-C(=Y)-NR<sup>a</sup>R<sup>d</sup>-S(=0)-, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, and substituted or unsubstituted heteroarylalkyl, or when R<sup>a</sup> and R<sup>b</sup> substituent are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NR<sup>a</sup> and S;
each occurrence of $R^e$ and $R^d$ may be same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, or when two $R^e$ and/or $R^d$ substituents are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NH and S;

- each occurrence of $Y$ is selected from O, S and -NR<sup>b</sup>; and
- each occurrence of $q$ independently represents 0, 1 or 2;”

with the proviso that the compound of formula (I) does not include

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-(difluoromethyl)-5-methyl-IH-Pyrazole-3-carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-1-methyl-4-nitro-IH-Pyrazole-5-carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-3-(1-ethyl-5-methyl-IH-pyrazol-4-yl)-5-Isoxazolecarboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-4,5-dihydro-3-(2-methoxyphenyl)-5-Isoxazole carboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-2-[4-(1,1-dimethylethyl)phenyl]-Cyclopropanecarboxamide; N-[4-[5-cyclopropyl-3-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-3-Pyridinecarboxamide; N-[4-[3-cyclopropyl-5-(trifluoromethyl)-IH-pyrazol-1-yl]phenyl]-3-Pyridine carboxamide; or N-benzyl-6-(3,5-dicyclopropyl-IH-pyrazol-1-yl)pyridazin-3-amine.

16. A compound of claim 15, wherein

L<sub>i</sub> and L<sub>2</sub> together represent -NH-C(O)-; and

Cy is selected from monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl.

17. A compound of any of claims 15-16, wherein both $R^1$ and $R^2$ represent cyclopropyl.

18. A compound of any of claims 15-16, wherein one of $R^1$ and $R^2$ is CF<sub>3</sub> and the other is independently cyclopropyl, CH<sub>2</sub>F or CHF<sub>2</sub>.

19. A compound of any of claims 15-16, wherein T, U, V, and W are independently CH, CF or N.
20. A compound of claim 19, wherein T is CF or N and each of U, V and W is CH.
21. A compound of claim 19, wherein each of T and V is independently CF or N and each of U and W is CH.
22. A compound of claim 15, wherein Li and L2 together represent -NH-C(=0)-, -NH-S(=0)q-, -C(=0)NH- or -NH-CH2-;
23. A compound of any of claims 15-16, wherein A is absent, -NH-, or -CH2-.
24. A compound of claim 23, wherein A is -CH2-.
25 A compound of claim 15, wherein Cy is selected from

26 A compound of claim 15 or 16, wherein Cy is selected from
27. A compound of formula

![Chemical Structure Image]

or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester, or pharmaceutically acceptable salt thereof, wherein

- $R^1$ and $R^2$ are the same or different and are independently selected from $\text{CH}_2\text{F}$, $\text{CHF}_2$, $\text{CF}_3$, cyclopropyl with the proviso that both $R^1$ and $R^2$ at the same time do not represent $\text{CF}_3$;
- $T$ and $V$ are the same or different and are independently selected from $\text{CF}$ and $\text{N}$;
- each of $U$ and $V$ is $\text{CR}_n$;
- $L_1$ and $L_2$ together represent $-\text{NH-C(}=\text{X})-\text{, } -\text{NH-}$-$\text{S(}=\text{0})\text{, } -\text{C(}=\text{X})\text{-NH-}$, or $-\text{S(}=\text{0})\text{NH-}$ or $-\text{NH-CR'}\text{R''}$;
- $A$ is absent or selected from $-(\text{CR'}\text{R'')-}$ and $-\text{NR}^a$;
- each occurrence of $R'$ and $R''$ are the same or different and are independently selected from hydrogen or substituted or unsubstituted $c_{(1,5)}\text{alkyl group or } R' \text{ and } R'' \text{ may be joined to form a substituted or unsubstituted saturated or unsaturated 3-6 membered ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, } \text{NR}^a \text{ and S}$;
- $R''$ is selected from hydrogen or halogen;
each occurrence of X is independently selected from O, S and -NR²;

Cy is selected from monocyclic substituted or unsubstituted heterocyclyl, monocyclic substituted or unsubstituted aryl, and monocyclic substituted or unsubstituted heteroaryl.

each occurrence of R⁷ and R⁸ are the same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, -OR, -S(=0)qR, -NR²R, -CR²R³,C(=Y)-R⁵, -CR²R³-Y-CR³R⁴, -C(=Y)-NR³R⁴, -NRR²C(=Y)-NR³R⁴, -S(=0)qNR³R⁴, -NR³R⁴-S(=0)qNR³R⁴, -NR³R⁴-NR³R⁴, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, and substituted or unsubstituted heteroarylalkyl, or when R⁷ and R⁸ substituent are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which may be same or different and are selected from O, NRC² and S;

each occurrence of R⁶ and R⁷ may be same or different and are independently selected from hydrogen, nitro, hydroxy, cyano, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclyl, or when two R⁶ and/or R⁷ substituents are directly bound to the same atom, they may be joined to form a substituted or unsubstituted saturated or unsaturated 3-10 member ring, which may optionally include one or more heteroatoms which are the same or different and are selected from O, NH and S;

each occurrence of Y is selected from O, S and -NR²; and

each occurrence of q independently represents 0, 1 or 2.

28. A compound of claim 27, wherein one of R¹ and R² is CF₃ and the other is cyclopropyl.

29. A compound of claim 27, wherein one of R¹ and R² is CF₃ and the other is CH₂F, CHF₂.

30 A compound of claim 27, wherein both R¹ and R² represent cyclopropyl.

31. A compound of any of claims 27-30, wherein T is CF or N.
32. A compound of any of claims 27-31, wherein U, V, W are CH, CF or N.
33. A compound of any of claims 27-32, wherein Li and L₂ together represent -NH-C(=0)-, C(=0)NH- or -NH-CH₂-.
34. A compound of any of claims 27-33, wherein A is absent, -NH-, or -CH₂-.
35. A compound of claim 34, wherein A is absent.
36. A compound of claim 34, wherein A is -CH₂-.
37. A compound of claim 34, wherein A is -NH-.
38. A compound of any of claims 27-37, wherein Cy is selected from
39. A compound of claim 38, wherein Cy is
40. A compound selected from:

\[
\begin{align*}
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}4\text{-methyl-1,2,3-thiadiazole-}5\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}4\text{-methylthiazole-}5\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}2,4\text{-dimethylthiazole-}5\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}5\text{-methylisoxazole-}4\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}3,5\text{-dimethylisoxazole-}4\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}benzamide \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}2\text{-methylbenzamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}2,6\text{-difluorobenzamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}2,3\text{-difluorobenzamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}3\text{-}\text{(methylsulfonyl)benzamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}4\text{-}\text{(methylsulfonyl)benzamide} \\
2\text{-chloro-}N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}5\text{-}\text{(methylthio)benzamide} \\
2\text{-chloro-}N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}5\text{-}\text{(methylsulfonyl)benzamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl}\}nicotinamide \text{ hydrochloride} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}isonicotinamide \text{ hydrochloride} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}3\text{-fluoroisonicotinamide} \\
3,5\text{-dichloro-}N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}isonicotinamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}4\text{-methylpyrimidine-}5\text{-carboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-phenylacetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-}(4\text{-fluorophenyl)acetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}1\text{-phenylcyclopropanecarboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}1\text{-phenylcyclopropanecarboxamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-}(pyridin-2-yl)acetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-}(pyridin-3-yl)acetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-}(pyridin-4-yl)acetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-}(piperazin-1-yl)acetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}2\text{-morpholinoacetamide} \\
N\{4-(3,5\text{-dicyclopropyl-}1\text{H-pyrazol-}1\text{-yl)phenyl\}benzenesulfonamide}
\end{align*}
\]
N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-4-methylthiazole-5-carboxamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-3,5-dimethylisoxazole-4-carboxamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-2methyl benzamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-2,3-difluorobenzamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-2,6-difluorobenzamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]nicotinamide

N-[4-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-3-fluorophenyl]-4-methylpyrimidine-5-carboxamide

N-[6-(3,5-dicyclopropyl-1H-pyridin-3-yl)-4-methyl-1,2,3-thiadiazole-5-carboxamide

N-[6-(3,5-dicyclopropyl-1H-pyridin-3-yl)-4-methylthiazole-5-carboxamide

N-[6-(3,5-dicyclopropyl-1H-pyridin-3-yl)-2,4-dimethylthiazole-5-carboxamide

N-[6-(3,5-dicyclopropyl-1H-pyridin-3-yl)-3,5-dimethylisoxazole-4-carboxamide

6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)-N-o-tolynicotinamide

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-2-fluorobenzamide

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-2,3-difluorobenzamide

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-2,6-difluorobenzamide

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]nicotinamide dihydrochloride

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]isonicotinamide

N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]fluoroisonicotinamide

3,5-dichloro-N-[4-[5-cyclopropyl-1,3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl] isonicotinamide

3,5-dichloro-N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]isonicotinamide
N-[6-(3,5-dicyclopropyl-1H-pyrazol-1-yl)pyridin-3-yl]-4-methylpyrimidine-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1,2,3-thiadiazole-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylthiazole-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-N,N,N,N-dimethylthiazole-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,4-dimethylthiazole-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-methylisoxazole-4-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3,5-dimethylisoxazole-4-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-1-methyl-1H-imidazole-2-carboxamide

N-[4-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methyl-1H-imidazole-5-carboxamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2-methylbenzamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,3-difluorobenzamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-2,6-difluorobenzamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-3-(methylsulfonyl)benzamide

2-chloro-N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-(methylthio) benzamide

2-chloro-N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-5-(methylsulfonyl)benzamide

N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]pyridine-4-carboxamide hydrochloride
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3-fluorisonicotinamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylpyrimidine-5-carboxamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2,4-dimethylpyrimidine-5-carboxamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(4-fluorophenyl)acetamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-2-yl)acetamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-3-yl)acetamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]methyl]aniline
1-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3-(4-methyl-1,2,3-thiadiazol-5-yl)urea
1-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3-(4-methylthiazol-5-yl)urea
1-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-3-(4-methylpyrimidin-5-yl)urea
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(4-methylthiazol-5-yl)benzamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,6-difluorophenyl)benzamide
N-{4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylthiazole-5-carboxamide
N-{4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-2-(pyridin-2-yl)acetamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-4-methyl-1,2,3-thiadiazole-5-carboxamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-4-methylthiazole-5-carboxamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-5-methylisoxazole-4-carboxamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-3,5-dimethylisoxazole-4-carboxamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-2-methylbenzamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-2,3-difluorobenzamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl nicotinamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl isonicotinamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl 3,5-dichloroisonicotinamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-4-methylpyrimidine-5-carboxamide
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-N,4-dimethylpyrimidine-5-carboxamide
N-4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-4-methyl-1,2,3-thiadiazole-5-carboxamide
N-4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-2-(pyridin-2-yl)acetamide
N-4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-3-(4-methylpyrimidin-5-yl)urea
N-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl-2,6-dichlorobenzamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)-3-fluorobenzamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,6-difluorophenyl)-3-fluorobenzamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4-methyl-1,2,3-thiadiazole-5-carboxamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-4-methylthiazole-5-carboxamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-3,5-dimethylisoxazole-4-carboxamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2-methylbenzamide
2-chloro-N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]benzamidine
N-(6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl)-2-fluorobenzamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2,3-difluorobenzamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2,6-difluorobenzamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]picolinamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-3-methylpicolinamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]nicotinamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]-2-methylnicotinamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]isonicotinamide
N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]fluoroisonicotinamide
3,5-dichloro-N-[6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl]isonicotinamide
N-{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-4-methylpyrimidine-5-carboxamide
N-{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-2-(pyridin-2-yl)acetamide
N-{6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-2-(pyridin-4-yl)acetamide
N-{4-[4-chloro-5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-4-methylpyrimidine-5-carboxamide
1-{6-[3-cyclopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl]pyridin-3-yl}-3-(4-methylthiazol-5-yl)urea
6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,3-difluorophenyl)nicotinamide
6-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-(2,6-difluorophenyl)nicotinamide
N-{6-[4-[5-(fluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]-4-methylthiazole-5-carboxamide
N-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-2,6-difluorobenzamide
N-{4-[5-(fluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylthiazole-5-carboxamide
N-{4-[5-(difluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl}-4-methylthiazole-5-carboxamide
3,5-dichloro-N-[4-(3,5-dicyclopopyl-1H-pyrazol-1-yl)-3-fluorophenyl]isonicotinamide
N-(2-chloro-6-fluorophenyl)-4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorobenzamide
N-{2-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]pyrimidin-5-yl}-4-methylthiazole-5-carboxamide
N-[4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3,5-difluorophenyl]-4-methylpyrimidine-5-carboxamide
{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-1-phenylcyclobutanecarboxamide
N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-4-methyloxazole-5-carboxamide

N-{4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-4-methylpyrimidine-5-carboxamide
4-[5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]-3-fluoro-N-(4-methylpyrimidin-5-yl) benzamide and
N-{4-[3-cyclopropyl-5-(difluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-2,6-difluorobenzamide and N-{4-[5-cyclopropyl-3-(difluoromethyl)-1H-pyrazol-1-yl]-3-fluorophenyl}-2,6-difluorobenzamide

or a tautomer, prodrug, N-oxide, pharmaceutically acceptable ester, or pharmaceutically acceptable salt thereof.

41. A method of modulating store-operated calcium (SOC) channel activity comprising contacting the SOC channel complex, or portion thereof, with a compound of any one of claims 1-40

42. A method of modulating calcium release activated calcium channel (CRAC) activity in a mammal comprising administering to the mammal a compound of any of claims 1-40, wherein the compound of any one of claims 1-40 modulates CRAC activity in the mammal.

43. A method of inhibiting store-operated calcium entry (SOCE) activation of nuclear factor of activated T cells (NFAT) in a mammal comprising administering to the mammal a compound of any one of claims 1-40, wherein the compound of any one of claims 1-40 inhibits SOCE activation of NFAT in the mammal.

44. A method of decreasing cytokine release by inhibiting the SOCE activation of NFAT in a mammal comprising administering to the mammal a compound of any one of claims 1-40, wherein the compound of any one of claims 1-40 decreases cytokine release in the mammal.

45. Use of a compound in any one of claims 1-40 in the manufacture of a medicament for the treatment of a disease, disorder, or condition that would benefit from modulation of calcium release-activated calcium (CRAC) channel.

46. A method of inhibiting immune cell activation comprising administering to an immune cell a compound of any of claims 1-40.
47. A method of inhibiting T-cell and/or B-cell proliferation in response to an antigen, comprising administering to a T-cell and/or B-cell a compound of any one of claims 1-55.

48. A method of inhibiting cytokine production in a cell, comprising administering to the cell a compound of any one of claims 1-40.

49. The method of claim 48, wherein the cytokine is selected from IL-2, IL-4, IL-5, IL-13, GM-CSF, IFN-γ, TNFα, and combinations thereof.

50. A method of modulating an ion channel in a cell, wherein the ion channel is involved in immune cell activation, comprising administering to the cell a compound of any one of claims 1-40.

51. The method of claim 50, wherein the ion channel is a Ca\(^{2+}\)-release-activated Ca\(^{2+}\) channel (CRAC).

52. A pharmaceutical composition, comprising a compound of any one of claims 1-40 and a pharmaceutically acceptable carrier.

53. The pharmaceutical composition of claim 67, further comprising one or more additional therapeutic agents selected from anti-inflammatory agent, immunosuppressive agents, steroids, non-steroidal anti-inflammatory agents, antihistamines, analgesics, and suitable mixtures thereof.

54. A method of treating cancer comprising the step of administering to a subject in need thereof an effective amount of a compound of any one of claims 1-40.

55. A method of reducing an inflammation in a subject in need thereof comprising the step of administering to a subject in need thereof an effective amount of a compound of any one of claims 1-40.

56. A method of treating an autoimmune disorder comprising the step of administering to a subject in need thereof an effective amount of a compound of any one of claims 1-40.

57. The method of claim 56, wherein the autoimmune disorder is chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, allergic rhinitis, asthma, multiple sclerosis, psoriasis, Crohn's disease, colitis, ulcerative colitis, arthritis, bone diseases associated with increased bone resorption, or chronic obstructive airway disease.

58. The method of claim 56, wherein the autoimmune disorder is rheumatoid arthritis.
59. The method of claim 56, wherein the autoimmune disorder is multiple sclerosis.

60. The method of claim 56, wherein the autoimmune disorder is asthma.

61. A method for the treatment of calcium release-activated calcium (CRAC) channel associated diseases or disorders, comprising the step of administering to a subject in need thereof an effective amount of compound of any one of claims 1-40.

62. A method of claim 61, further comprising the step of administering simultaneously or sequentially to a subject in need thereof at least one other anti-inflammatory agent, immunosuppressive agent, steroid, non-steroidal anti-inflammatory agent, antihistamine, analgesic, or a mixture thereof.

63. A method of claim 61, wherein the calcium release-activated calcium (CRAC) channel associated disease, disorder or condition is an immune system-related disease, a disease or disorder involving inflammation, a hepatic disease or disorder, or a renal disease or disorder.

64. A method of claim 61, wherein the CRAC channel associated disease, disorder or condition is selected from:

- inflammation, glomerulonephritis, uveitis, hepatic diseases or disorders, renal diseases or disorders, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, vasculitis, dermatitis, osteoarthritis, inflammatory muscle disease, allergic rhinitis, vaginitis, interstitial cystitis, scleroderma, osteoporosis, eczema, allogeneic or xenogeneic transplantation, graft rejection, graft-versus-host disease, lupus erythematosus, pulmonary fibrosis, dermatomyositis, thyroiditis, myasthenia gravis, autoimmune hemolytic anemia, cystic fibrosis, chronic relapsing hepatitis, primary biliary cirrhosis, allergic conjunctivitis, hepatitis, atopic dermatitis, asthma, Sjogren's syndrome, organ transplant rejection, multiple sclerosis, Guillain-Barre, autoimmune uveitis, autoimmune hemolytic anemia, pernicious anemia, autoimmune thrombocytopenia, temporal arteritis, anti-phospholipid syndrome, vasculitides such as Wegener's granulomatosis, Behcet's disease, psoriasis, dermatitis herpetiformis, pemphigus vulgaris, vitiligo, Crohn's disease, colitis, ulcerative colitis, primary biliary cirrhosis, autoimmune hepatitis, Type 1 or immune-mediated diabetes mellitus, Grave's disease. Hashimoto's thyroiditis, autoimmune oophoritis and orchitis, autoimmune disorder of the adrenal gland, systemic lupus erythematosus, polymyositis, dermatomyositis, ankylosing spondylitis, transplant rejection, skin graft rejection, arthritis, bone diseases associated with increased bone resorption, ileitis, Barrett's
syndrome, adult respiratory distress syndrome, chronic obstructive airway disease; corneal dystrophy, trachoma, onchocerciasis, sympathetic ophthalmitis, endophthalmitis; gingivitis, periodontitis; tuberculosis; leprosy; uremic complications, nephrosis; scleroderma; psoriasis, chronic demyelinating diseases of the nervous system, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis; viral or autoimmune encephalitis; autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematoses; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma, and cancer.

65. A method for suppressing the immune system of a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-40.

66. A method for treating or preventing an allergic disorder in a subject in need thereof, comprising administering to the subject an effective amount of a compound of any one of claims 1-40.

67. The method of claim 66, wherein the disorder is allergic rhinitis, sinusitis, rhinosinusitis, chronic otitis media, recurrent otitis media, drug reactions, insect sting reactions, latex reactions, conjunctivitis, urticaria, anaphylaxis reactions, anaphylactoid reactions, atopic dermatitis, asthma, or food allergies.
**INTERNATIONAL SEARCH REPORT**

**International application No**

PCT/IB2010/002535

A. **CLASSIFICATION OF SUBJECT MATTER**

INV. C07D231/12 C07D401/04 C07D401/12 C07D401/14 C07D403/04

C07D403/12 C07D403/14 C07D413/12 C07D417/12

C07D417/14 A61P35/00 A61K31/415 A61K31/4155

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

B. **FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic database consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>

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

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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**Date of the actual completion of the international search**

20 January 2011

**Date of mailing of the international search report**

28/01/2011

**Name and mailing address of the ISA**

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Fax: (+31-70) 340-3016

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Fanni, Stefano

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