(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 November 2014 (13.11.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/181287 Al

(51) International Patent Classification:

C07D 413/02 (2006.01)	***A61K 31/4192*** (2006.01)
C07D 413/14 (2006.01)	***A61K 31/4196*** (2006.01)
C07D 417/12 (2006.01)	***A61K 31/4164*** (2006.01)
C07D 207/30 (2006.01)	***A61K 31/422*** (2006.01)
C07D 213/02 (2006.01)	***A61K 31/426*** (2006.01)
C07D 231/10 (2006.01)	***A61K 31/44*** (2006.01)
C07D 239/20 (2006.01)	***A61K 31/495*** (2006.01)
C07D 247/02 (2006.01)	***A61K 31/506*** (2006.01)
C07D 249/06 (2006.01)	***A61P 3/08*** (2006.01)
C07D 261/02 (2006.01)	***A61P 9/00*** (2006.01)
C07D 263/02 (2006.01)	***A61P 11/00*** (2006.01)
C07D 275/02 (2006.01)	***A61P 17/00*** (2006.01)
C07D 277/20 (2006.01)	***A61P 31/12*** (2006.01)

(21) International Application Number:
PCT/IB20 14/06 1299

(22) International Filing Date:
8 May 2014 (08.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/821,287 9 May 2013 (09.05.2013) US

(71) Applicant: **PIRAMAL ENTERPRISES LIMITED** [IN/IN]; Piramal Tower, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400013 (IN).

(72) Inventors: **SHARMA, Rajiv;** 1, Nirlon Complex, Off Western Express Highway, Goregaon (East), Mumbai 400063 (IN). **JAIN, Arunkumar;** 1106 Opal Building, Nirmal Lifestyle, L.B.S. Road, Mulund (West), Mumbai 400080 (IN). **SAHU, Bichismita;** 1, Nirlon Complex, Off Western Express Highway, Goregaon (East), Mumbai 400063 (IN). **SINGH, Deepak;** 1, Nirlon Complex, Off Western Express Highway, Goregaon (East), Mumbai 400063 (IN). **MALI, Sunil;** 1, Nirlon Complex, Off Western Express Highway, Goregaon (East), Mumbai 400063 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, FT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2014/181287 A1

(54) **Title:** HETEROCYCLYL COMPOUNDS AND USES THEREOF

(57) **Abstract:** The present invention provides heterocyclyl compounds of formula I, isotopic forms, stereoisomers or tautomers thereof, or pharmaceutically acceptable salts, solvates, N- oxides, S-oxides and polymorphs thereof, and processes for their preparation. The invention further relates to pharmaceutical compositions containing the compounds and their use in the treatment of inflammatory diseases, autoimmune disorders and other related disorders. The heterocyclyl compounds find use as Interleukin 17 (IL-17) inhibitors and Tumor Necrosis Factor alpha (TNF-a) inhibitors.

HETEROCYCLYL COMPOUNDS AND USES THEREOF

FIELD OF THE INVENTION

The present invention relates to heterocyclyl compounds (the compounds of formula I as described herein), processes for their preparation, pharmaceutical compositions containing the said compounds, their use as Interleukin 17 (IL-17) inhibitors or Tumor Necrosis Factor alpha (TNF-a) inhibitors, and methods for using said compounds in the treatment or prevention of diseases or disorders mediated by IL-17 and TNF-a, such as autoimmune or inflammatory diseases or disorders; and metabolic diseases or disorders.

BACKGROUND OF THE INVENTION

Inflammation is part of the non-specific immune response that occurs in reaction to body injury (e.g. trauma, ischemia, and foreign particles) or infection (e.g. bacterial or viral infection). Inflammation is an inherent part of various autoimmune or inflammatory disorders, such as rheumatoid arthritis, atherosclerosis, inflammatory myopathies, septic shock syndrome, ulcerative colitis, inflammatory bowel disease, psoriasis, multiple sclerosis, and others. It has been reported that inflammation is commonly associated with the metabolic diseases and disorders such as insulin resistance and obesity (Brent E. Wisse, Journal of the American Society of Nephrology, 2004, 15, 2792-2800).

Inflammation can be classified as either acute or chronic. Infiltration of innate immune system cells, specifically neutrophils and macrophages, characterizes the acute inflammation, while infiltration of T lymphocytes and plasma cells are features of chronic inflammation.

Recent studies have established that Th_{17} cells are involved in mediating inflammatory diseases and immune defense against extracellular bacteria. Th_{17} cells are a subset of T cells that produce pro-inflammatory cytokines such as the interleukins (IL-6, IL-17A, IL-17F, IL-21, IL-22), and TNF-a (Tumor necrosis factor-alpha). Th_{17} cells can be generated from naive precursors in the presence of TGF-β and IL-6 or IL-21, which can be further augmented by TNF or IL-1β which are the inflammatory cytokines that inhibit

Th1 and Th2 cell differentiation. Developments of Th1 , Th2, and regulatory T cells (T reg cells) are specified by transcription factors such as Tbet, GATA3, and Foxp3, respectively, whereas that of Th-$|_7$ cells appears to depend on the retinoid-related orphan receptor RORgt, RORa, and signal transducer and activator of transcription (J *Exp Med.* 201 1 October 24; 208(1 1): 2321-2333).

The pro-inflammatory cytokine, Interleukin 17 (family) comprises six members namely IL-1 7A, IL-1 7B, IL-1 7C, IL-1 7D, IL-1 7E, and IL-1 7F, out of which IL-1 7A and IL-1 7F are clearly associated with inflammation as these are produced by Th_{17} cells. IL-1 7 deploys neutrophils to the site of inflammation and this ability imparts IL-1 7 with a key role in several types of diseases. IL-1 7 is predominantly produced by activated memory T cells and acts on the cell by binding to a specific cell surface receptor IL-1 7R. Human IL-1 7 is a 20-30 kDa glycoprotein configured with 155 amino acids, comprising a signal peptide at the N-end. The expression of IL-1 7 has been found to be elevated in patients with rheumatoid arthritis, systemic lupus erythematosus (SLE), Behget's disease, inflammatory bowel disease, asthma, multiple sclerosis, and other related diseases or disorders. It has further been reported that IL-1 7 plays a pivotal role in the obesity induced inflammatory conditions (Mario Galgani et al., Journal of Leukocyte Biology, 201 0, 87, 17-1 8).

It is indicated herein above that Th_{17} cells, which stimulate the secretion of a wide range of pro-inflammatory cytokines including IL-1 7A and TNF-α among others, appear to depend on the retinoid-related orphan receptor RORgt. Accordingly, transcription factor 'Retinoid-related orphan receptor gamma t (RORgt)' plays a pivotal role in the production of IL-1 7. RORgt is a member of steroid hormone nuclear receptor superfamily and it is encoded by ROR_c gene. RORgt is exclusively expressed in the T cells of the immune system. It is known that RORgt controls differentiation of pro-inflammatory T helper 17 (Th_{17}) cells. It is reported that RORgt is required for the induction of IL-1 7 transcription and for the manifestation of Th1 7-dependent autoimmune disease. Multiple other transcription factors have also been shown to be important for the development of Th1 7 cells: BATF, STAT3, IRF4, RUNX1 , and IκBζ. Unlike RORgt, these factors are not NHRs (Nuclear hormone receptors) and thus do not contain ligand binding domains, which renders them less attractive targets for drug development.

Tumor Necrosis Factor-alpha (TNF-a) / cachectin is a pleiotrophic cytokine that plays pivotal role in inflammatory disorders and conditions. TNF-a is a soluble homotrimer of 17 kD protein subunits. TNF-a is produced by monocytes, macrophages, and T lymphocytes. It shows self-regulatory, growth stimulating and growth inhibitory properties. Following to infection or injury, TNF-a initiates inflammatory cascade of cytokines, thereby recruiting macrophage and neutrophils to a site of infection. It activates granulocytes, and increases Major Histocompatibility Complex class II (MHC Class II) expression. It also promotes secretion of matrix metalloproteinases (MMPs), leading to cartilage matrix degradation. Because TNF-a initiates an inflammatory cascade, and has been found to be increased in close proximity to inflamed or injured tissue, TNF-a inhibition is an appealing target for the development of new anti-inflammatory drugs.

Although, significant advances have been made in providing treatment options for inflammatory and autoimmune disorders, the treatment options do not provide satisfactory results for all the patients due to, for example, detrimental side effects or efficacy, or inadequacy as to patient compliance. Treatments for autoimmune and inflammatory disorders vary depending on the particular medical disorder, and often involve use of immunosuppressive drugs. In view of this, there is a continuing need to provide newer and effective treatment options to the patients suffering from autoimmune, inflammatory and related disorders.

It is evident from the above discussion that the pro-inflammatory cytokines such as IL-17 and TNF-a constitute attractive targets for new drug developments for inflammatory disorders, autoimmune disorders and other related disorders. The present invention addresses the need of newer and effective treatment options to the patients suffering from autoimmune, inflammatory and related disorders by providing compounds that are IL-17 and/or TNF-a inhibitors.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to a compound of formula I (as described herein), or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, S-oxide or N-oxide thereof.

According to another aspect of the present invention, there are provided processes for the preparation of the compounds of formula I, or pharmaceutically acceptable salts thereof.

According to a further aspect of the present invention, there is provided a pharmaceutical composition comprising one or more of the compounds of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; and at least one pharmaceutically acceptable carrier or excipient.

According to a further aspect of the present invention, there is provided a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as IL-17 inhibitor.

According to another aspect of the present invention, there is provided a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as TNF-a inhibitor.

According to yet another aspect of the present invention, there is provided a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use in the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

According to a further aspect of the present invention, there is provided a method for the treatment of a disease or disorder mediated by IL-17 or TNF-a, comprising administering to a subject in need thereof; a therapeutically effective amount of the compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof.

According to yet another aspect of the present invention, there is provided use of a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for the manufacture of a medicament for the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

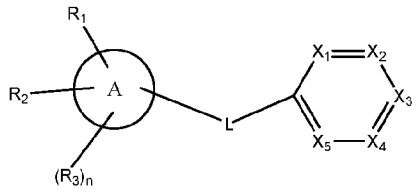
In a further aspect, the present invention relates to use of a compound of formula I or a stereoisomer, a tautomer, or a pharmaceutically acceptable salt or a solvate thereof; in

combination with at least one further therapeutically active agent for the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

One or more further aspects of the present inventions are discussed in detail herein below. These and other objectives and advantages of the present invention will be apparent to those skilled in the art from the following description.

DETAILED DESCRIPTION OF THE INVENTION

According to the first aspect, the present invention relates to a compound of formula I:

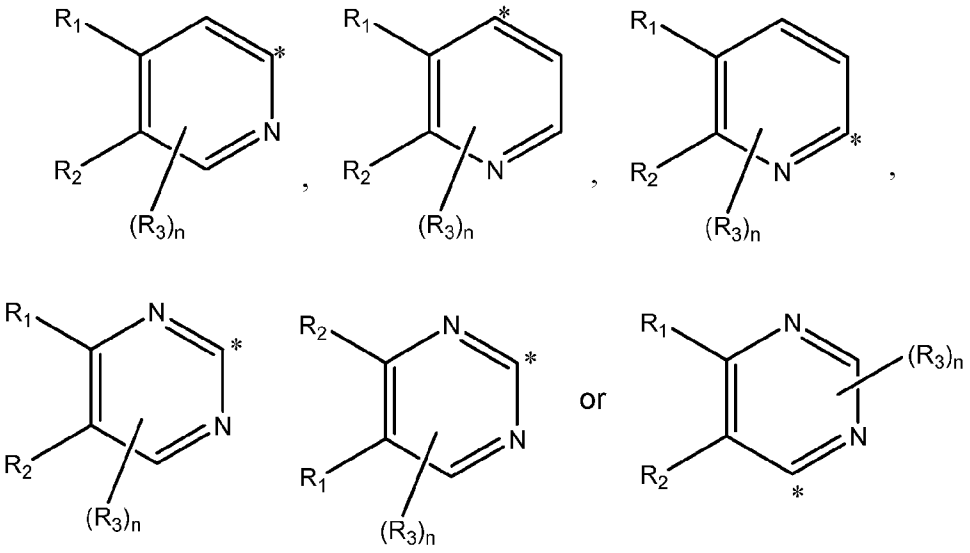


Formula I

or an isotopic form, a stereoisomer or a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof;

wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole, pyrrole, a 5- or 6-membered saturated heterocyclic ring system or a heteroaryl ring system selected from:



wherein * indicates the point of attachment to L;

R_1 and R_3 are independently selected from the group consisting of hydrogen, hydroxy, halogen, cyano, nitro, (CrC $_6$)-alkyl, (CrC $_6$)-alkoxy, (CrC $_6$)-alkoxyalkyl, (CrC $_6$)-alkylamino, (C_3-Ci $_2$)-cycloalkyl, 0-(C_3-Ci $_2$)-cycloalkyl, halo(CrC $_6$)alkyl, halo(d-C_6)alkoxy, (C_6-C_{14})-aryl, heterocyclyl, 0-(C_6-C_{14})aryl, (C_6-C_{14})ar(C_1-C_6)alkyl, (C_6-Ci $_4$)ar(C_1-C_6)alkyloxy, heteroaryl, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$R$_a$, NR$_a$R$_b$ and C(0)NR $_a$R$_b$;

n is an integer from 0 to 2;

R_2 is (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-Ce)-alkoxy(C_1-C_6)-alkyl, (C_3-C_{12})-cycloalkyl, O-(C_3-C_{12})-cycloalkyl, (C_6-C_{14})-aryl, 0-(C_6-C_{14})aryl, (C_6-C_{14})ar(CrC $_6$)alkyl, (C_6-C_{14})ar(C_1-C_6)alkyloxy, heterocyclyl or heteroaryl;

R_2 together with R_1 can form a 5- or 6- membered saturated or unsaturated ring optionally containing 1 to 3 heteroatoms independently selected from the group consisting of O, N and S, which ring is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (d-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkoxyalkyl, (CrC $_6$)-alkylamino, (C_3-C_{12})-cycloalkyl, O-(C_3-C_{12})-cycloalkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl, 0-(C_6-Ci $_4$)aryl, (C_6-Ci $_4$)ar(Ci-C $_6$)alkyl, (C_6-Ci $_4$)ar(Ci-C $_6$)alkyloxy, heterocyclyl, heteroaryl, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$Ra, NR$_a$R$_b$ and C(0)NR $_a$R$_b$;

L is *N(R $_4$)-C(0)-N(R $_5$), *C(0)N(R $_5$), *N(R $_4$)-C(0), *CH(R $_6$)-C(0)-N(R $_5$), *CH(R $_6$)N(R $_5$), *N(R $_4$)-S(0) $_2$ or *NR$_4$; wherein * indicates the point of attachment to A;

R_4, R_5 and R_6 are independently selected from the group consisting of hydrogen, hydroxy, cyano, (Ci -C6)-alkyl, (Ci -C6)-alkoxy, (Ci-C6)-alkoxyalkyl, (Ci -C6)-alkylamino, (C_3-Ci $_2$)-cycloalkyl, 0-(C_3-Ci $_2$)-cycloalkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, hydroxy(Ci-C $_6$)-alkyl, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$R$_a$, P(0)n(0(Ci-C $_6$)alkyl)$_2$, O-P(O) (0(C_1-C_6)alkyl)$_2$ and C(0)NR $_a$R$_b$;

Xi, X_2, X_4 and X_5 are independently selected from N and C(R_7); wherein R_7 is hydrogen, halogen, hydroxy, nitro, cyano, (CrC $_6$)-alkyl, (CrC $_6$)-alkoxy, (d-C $_6$)-alkoxy(CrC $_6$)-alkyl, (Ci-C $_6$)-alkylamino, (C_3-Ci $_2$)-cycloalkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_6-Ci $_4$)-aryl, 0-(C_6-Ci $_4$)aryl, (C_6-Ci $_4$)ar(C_1-C_6)alkyl, (C_6-Ci $_4$)ar(Ci-C $_6$)alkyloxy, heterocyclyl, O-heterocyclyl, heteroaryl, C(0)R $_a$,

C(0)OR $_a$, S(0) $_n$R$_a$, P(0)n(0(Ci -C$_e$)alkyl)$_2$, 0-P(0)(0(C $_1$-C$_6$)alkyl)$_2$, NR$_a$R$_b$ or C(0)NR $_a$R$_b$;

X$_3$ is N or C(R $_8$), wherein R$_8$ is hydrogen, halogen, hydroxy, cyano, nitro, (CrC $_6$)-alkyl, (Ci -C$_6$)-alkoxy, (C$_1$-C$_6$)-alkoxy(Ci -C$_6$)alkyl, (C$_1$-C$_6$)-alkylamino, (C$_3$-C$_{12}$)-cycloalkyl, O-(C$_3$-Ci $_2$)-cycloalkyl, halo(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-Ci $_4$)-aryl, 0-(C $_6$-Ci $_4$)aryl, (C6-Ci $_4$)ar(CrC6)alkyl, (C6-Ci $_4$)ar(CrC6)alkyloxy, heterocyclyl, O-heterocyclyl, heteroaryl, C(0)R $_a$,C(0)OR $_a$, S(0) $_n$R$_a$, NR$_a$R$_b$ or C(0)NR $_a$R$_b$;
provided that no more than three of the X$_1$ to X$_5$ positions can be simultaneously N;

when two or more of X-i , X$_2$, X$_4$ and X$_5$ represent C(R $_7$) then R$_7$ groups on the two adjacent carbon atoms can form a 3-7 membered unsaturated or saturated fused ring optionally containing 1 to 3 heteroatoms independently selected from the group consisting of O, N and S; wherein the ring can be unsubstituted or substituted with 1-3 groups of R$_c$; or
when any one of X$_2$ and X$_4$ represent C(R $_7$) and X$_3$ represents C(R $_8$) then the R$_7$ group together with the R$_8$ group can form a 3-7 membered fused ring optionally containing 1 to 3 heteroatoms selected from O, N or S; wherein the ring can be unsubstituted or substituted with 1-3 groups of R$_c$;
R$_a$ and R$_b$ are independently selected from the group consisting of hydrogen, (CrC $_6$)-alkyl, (C$_3$-C$_{12}$)-cycloalkyl, halo(C$_1$-C$_6$)alkyl, (C$_6$-C$_{14}$)-aryl, (C$_6$-C$_1$4)ar(CrC6)alkyl, heterocyclyl, heteroaryl, and S(0) $_n$R$_a$; or
R$_a$ and R$_b$, can form a 3-7 membered saturated or unsaturated ring optionally containing one or more heteroatoms selected from N, O or S, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, cyano, nitro, (C$_1$-C$_6$)-alkyl, (CrC $_6$)-alkoxy, (CrC $_6$)-alkylamino, (C$_3$-C$_{12}$)-cycloalkyl, 0-(C $_3$-Ci $_2$)-cycloalkyl, halo(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-Cu)-aryl, 0-(C $_6$-Cu)aryl, (C$_6$-Ci $_4$)ar(Ci -C$_6$)alkyl, heterocyclyl, heteroaryl, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$R$_a$, P(0)n(0(Ci -C$_6$)alkyl)$_2$, 0-P(0)(0(C $_1$-C$_6$)alkyl)$_2$, NR$_a$R$_b$ and C(0)NR $_a$R$_b$;

wherein:
each of the (CrC $_6$)alkyl and (C-| -C$_6$)-alkoxy can be unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (Ci -C$_6$)-alkoxy-(R$_c$)o-3, (C$_3$-Ci $_2$)-cycloalkyl-(R$_c$)o-3, 0-(C $_3$-Ci $_2$)-cycloalkyl-(R$_c$)o-3, halo(CrC $_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-Ci $_4$)-aryl-(R$_c$)$_0$-3, 0-(C $_6$-Ci $_4$)aryl-(R$_c$)o-3,

$(C_6$-$C_{14})$ar(CrC $_6$)alkyl-(R $_c)_{o-3}$, heterocyclyl-(R $_c)_{0-3}$, heteroaryl-(R $_c)_{0-3}$, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$Ra, P(0)n(0(Ci-C $_6$)alkyl) $_2$, 0-P(0)(0(Ci-C $_6$)alkyl) $_2$, N R_aR_b and C(0)NR $_a$ R_b;

heterocyclyl refers to a 3-12 membered saturated or partially unsaturated monocyclic or bicyclic ring system containing one to four identical or different heteroatoms independently selected from the group consisting of N, S and O;

heteroaryl refers to a 5-10 membered aromatic monocyclic or bicyclic ring system containing one to four identical or different heteroatoms independently selected from the group consisting of N, S and O;

each of the $(C_2$-$C_6)$-alkenyl, $(C_2$-$C_6)$-alkynyl, $(C_3$-Ci $_2)$-cycloalkyl, $(C_6$-Ci $_4)$-aryl, $(C_6$-$C_{14})$ar(CrC6)alkyl, heterocyclyl and heteroaryl can be unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (Ci-C $_6$)alkyl-(Rc)o-3, (CrC $_6$)-alkoxy-(R $_c)_{o-3}$, $(C_3$-$C_{12})$-cycloalkyl-(Ftc)o-3, 0-(C $_3$-Ci $_2$)-cycloalkyl-(Rc)o-3, halo$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkoxy, $(C_6$-Cu)-aryl-(Rc)o-3, 0-(C $_6$-Ci $_4$)aryl-(R $_c)_{o-3}$, $(C_6$-Ci4)ar(Ci-C $_6$)alkyl-(R $_c)_{o-3}$, heterocyclyl-(R $_c)_{0-3}$, heteroaryl-(R $_c)_{o-3}$, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$ R_a, P(0) $_n$(0(Ci-C $_6$)alkyl) $_2$, O-P(O) (0(C $_1$-$C_6)$alkyl) $_2$, N R_aR_b and C(0)NR $_a$ R_b; and

R_c is halogen, hydroxy, cyano, nitro, (Ci-C $_6$)-alkyl-(R $_c)_{o-i}$, (Ci-C $_6$)-alkoxy-(R $_c)_{o-i}$, $(C_3$-$C_{12})$-cycloalkyl-(R $_c)_{o-i}$, O-(C $_3$-Ci $_2$)-cycloalkyl-(R $_c)_0$-i, hydroxy(Ci-C $_6$)-alkyl-(R $_c)_{o-i}$, halo(CrC $_6$)alkyl, halo$(C_1$-$C_6)$alkoxy, $(C_6$-$C_{14})$-aryl-(R $_c)_0$-i, O-(C $_6$-Ci $_4$)aryl-(R $_c)_0$-i, $(C_6$-$C_{14})$ar(CrC $_6$)alkyl-(R $_c)_0$-i, heterocyclyl-(R $_c)_0$-i, heteroaryl-(R $_c)_0$-i, C(0)R $_a$, C(0)OR $_a$, S R_a, S(0) $_n$ R_a, P(0) $_n$(0(Ci-C $_6$)alkyl) $_2$, 0-P(0)(0(C $_1$-$C_6)$alkyl) $_2$, N R_aR_b or C(0)NR $_a$ R_b; and

with the provisos that:

(a) when A is pyrazole then L is a group other than *C(0)N(R $_5$) and *N(R $_4$)-C(0); and

(b) when A is pyrazole and L is *N(R $_4$)-C(0)-N(R $_5$), then said L group is not attached to 5-position of pyrazole.

Definitions

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein and

the appended claims. These definitions should not be interpreted in the literal sense as they are not general definitions and are relevant only for this application.

It will be understood that "substitution", "substituted" or "substituted with" means that one or more hydrogens of the specified moiety are replaced with a suitable substituent and includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and results in a stable compound.

The terms "a", "an" and "the" refers to "one or more" when used in the subject specification, including the claims. Thus, for example, reference to "a compound" may include a plurality of such compounds, or reference to "a disease" or "a disorder" includes a plurality of diseases or disorders.

It should also be noted that the term "or" is generally employed in its sense including "and/or" unless the content clearly dictates otherwise.

Also, use of "(s)" as part of a term, includes reference to the term singly or in plurality, e.g. the term compound(s) may indicate a single compound or more compounds.

The term "independently" when used in the context of selection of substituents for a variable, it means that where more than one substituent is selected from a number of possible substituents, those substituents may be the same or different.

As used herein, the term "(C_1-C_6)-alkyr or "alkyl" whether used alone or as part of a substituent group, refers to the radical of saturated aliphatic groups, including straight or branched-chain alkyl groups. An alkyl group can have a straight chain or branched chain containing carbon atoms. A straight-chain or branched chain alkyl has six or fewer carbon atoms in its backbone, for instance, CrC_6 for straight chain and C_3-C_6 for branched chain. Suitable alkyl groups containing from one to six carbon atoms, for example, include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, iso-butyl, sec-butyl, n-pentyl, isopentyl, 2-pentyl, 3-pentyl, neo-pentyl, n-hexyl, isohexyl, 2-hexyl and 3-hexyl.

Furthermore, unless stated otherwise, the alkyl groups may be unsubstituted or substituted with one or more substituents. A substituted alkyl refers to a (CrC_6)-alkyl substituted with one or more groups, preferably 1-3 groups independently selected from

the group consisting of halogen, hydroxy, nitro, cyano, (C-i-C$_6$)-alkoxy-(R$_c$)o-3, (C$_3$-C$_{12}$)-cycloalkyl-(R$_c$)o-3, 0-(C$_3$-Ci$_2$)-cycloalkyl-(R$_c$)o-3, halo(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-**Ci4**)-aryl-(R$_c$)o-3, 0-(C$_6$-Ci$_4$)aryl-(R$_c$)o-3, (C$_6$-Ci$_4$)ar(Ci-C$_6$)alkyl-(R$_c$)o-3, heterocyclyl-(R$_c$)$_0$-3, heteroaryl-(R$_c$)o-3, C(0)R$_a$, C(0)OR$_a$, S(0)$_n$R$_a$, P(0)$_n$(0(Ci-C$_6$)alkyl)$_2$, 0-P(0)(0(C$_1$-C$_6$)alkyl)$_2$, NR$_a$R$_b$ and C(0)NR$_a$R$_b$;

wherein n is 0-2; R$_a$ and R$_b$ are independently selected from the group consisting of hydrogen, (C$_1$-C$_6$)-alkyl, (C$_3$-Ci$_2$)-cycloalkyl, halo(C$_1$-C$_6$)alkyl, (C$_6$-Ci$_4$)-aryl, (C$_6$-C$_{14}$)ar(CrC$_6$)alkyl, heterocyclyl, heteroaryl, and S(0)$_n$R$_a$; or

R$_a$ and R$_b$ can form a 3-7 membered saturated or unsaturated ring optionally containing one or more heteroatoms selected from N, O or S, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, cyano, nitro, (Ci-C6)-alkyl, (Ci-**C6**)-alkoxy, (Ci-**C6**)-alkylamino, (C$_3$-Ci$_2$)-cycloalkyl, 0-(C$_3$-Ci$_2$)-cycloalkyl, halo(C$_1$-C$_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-C$_{14}$)-aryl, O-(C$_6$-C$_{14}$)aryl, (C$_6$-Ci$_4$)ar(C$_1$-C$_6$)alkyl, heterocyclyl, heteroaryl, C(0)R$_a$, C(0)OR$_a$, S(0)$_n$Ra, P(0)n(0(CrC$_6$)alkyl)$_2$, 0-P(0)(0(CrC$_6$)alkyl)$_2$, NR$_a$R$_b$ and C(0)NR$_a$R$_b$; and

R$_c$ is halogen, hydroxy, cyano, nitro, (C$_1$-C$_6$)-alkyl-(R$_c$)$_0$-i, (CrC$_6$)-alkoxy-(R$_c$)o-i, (C$_3$-C$_{12}$)-cycloalkyl-(R$_c$)o-i, O-(C$_3$-C$_{12}$)-cycloalkyl-(R$_c$)$_0$-i, hydroxy(C$_1$-C$_6$)-alkyl-(R$_c$)o-i, halo(CrC$_6$)alkyl, halo(C$_1$-C$_6$)alkoxy, (C$_6$-C$_{14}$)-aryl-(R$_c$)$_0$-1, O-(C$_6$-Ci$_4$)aryl-(R$_c$)$_0$-1, (C$_6$-**Ci4**)ar(Ci-C$_6$)alkyl-(R$_c$)o-i, heterocyclyl-(R$_c$)$_0$-1, heteroaryl-(R$_c$)$_0$-i, C(0)R$_a$, C(0)OR$_a$, SR$_a$, S(0)nR$_a$, P(0)$_n$(0(Ci-C$_6$)alkyl)$_2$, 0-P(0)(0(C$_1$-C$_6$)alkyl)$_2$, NR$_a$R$_b$ or C(0)NR$_a$R$_b$.

Examples of substituted alkyls include, but are not limited to, chloromethyl, hydroxymethyl, hydroxyethyl, aminoethyl and the like.

The term "halogen" refers to a fluorine, chlorine, bromine, or iodine atom.

When the alkyl group is substituted with one or more halogens, it is specifically referred to as "halo(Ci-C$_6$)alkyr or "haloalkyl". A monohalo(Ci-C$_6$)alkyl radical, for example, may have a chlorine, bromine, iodine or fluorine atom. Dihalo and polyhalo **(CrC6)**alkyl radicals may have two or more of the same or different halogen atoms. Examples of halo(CrC$_6$)alkyl include, but are not limited to, chloromethyl, dichloromethyl, trichloromethyl, dichloroethyl, dichloropropyl, fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl or the like groups.

As used herein, the term "halo(d -C6)alkoxy" or "haloalkoxy" refers to radicals wherein one or more of the hydrogen atoms of the alkoxy group are substituted with one or more halogens. Representative examples of "haloalkoxy" or "halo(CrC $_6$)alkoxy" groups include, but not limited to, difluoromethoxy ($OCHF_2$), trifluoromethoxy (OCF_3) or trifluoroethoxy (OCH_2CF_3).

As used herein, the term "(C_2-C_6)-alkenyr or "alkenyl", as used herein; alone or as part of a substituent group, refers to a straight or branched chain hydrocarbon radical containing the indicated number of carbon atoms and at least one carbon-carbon double bond (two adjacent sp^2 carbon atoms). For example, (C_2-C_6)-alkenyl refers to an alkenyl group having 2 to 6 (both inclusive) carbon atoms. Depending on the placement of double bond and substituents if any, the geometry of the double bond may be entgegen (E), or zusammen (Z), cis or trans. Examples of alkenyl include, but are not limited to, vinyl, allyl and 2-propenyl.

Unless stated otherwise, the alkenyl groups can be unsubstituted or substituted with one or more groups, preferably 1-3 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, **(CrC6**)alkyl-(R_c)o-3, (Ci-**C6**)-alkoxy-(R_c)o-3, (C_3-C_{12})-cycloalkyl-(R_c)o-3, 0-(C_3-C_{12})-cycloalkyl-(R_c)o-3, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl-(R_c)0-3, O-(C_6-C_{14})aryl-(R_c)0-3, (C_6-C_{14})ar(C_1-C_6)alkyl-(R_c)o-3, heterocyclyl-(R_c)o-3, heteroaryl-(R_c)0-3, C(0)R_a, C(0)OR_a, S(0)$_n$$R_a$, P(0)$_n$(0($C_1$-$C_6$)alkyl)$_2$, O-P(O) (0($C_1$-$C_6$)alkyl)$_2$, N$R_a$$R_b$ and C(0)N$R_a$$R_b$; wherein R_a, R_b, R_c and n are as defined herein above.

As used herein, the term "alkynyl" or "(C_2-C6)alkynyl" whether used alone or as part of a substituent group, refers to a straight or branched chain hydrocarbon radical containing the indicated number of carbon atoms and at least one carbon-carbon triple bond (two adjacent sp carbon atoms). For example, (C_2-C_6)alkynyl refers to an alkynyl group having 2 to 6 (both inclusive) carbon atoms. Examples of (C_2-Ce)alkynyl include, but are not limited to, ethynyl, 1-propynyl, 3-propynyl and 3-butynyl. Unless stated otherwise, the "alkynyl" can be unsubstituted or substituted with one or more groups, preferably 1-3 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (Ci-C_6)alkyl-(R_c)0-3, (Ci-C_6)-alkoxy-(R_c)o-3, (C_3-Ci$_2$)-cycloalkyl-(R_c)0-3, 0-(C_3-Ci$_2$)-cycloalkyl-(R_c)o-3, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-Ci$_4$)-aryl-(R_c)o-3, 0-(C_6-

C_{14})aryl-(R_c)o-3, (C_6-C_{14})ar(C_1-C_6)alkyl-(R_c)o-3, heterocyclyl-(R_c)o-3, heteroaryl-(R_c)0-3, C(0)R_a, C(0)OR_a, S(0)$_n$Ra, P(0)n(0(Ci-C$_6$)alkyl)$_2$, O-P(O) (0(Ci-C$_6$)alkyl)$_2$, N$R_a$$R_b$ and C(0)NR_aRb; wherein R_a, Rb, R_c and n are as defined herein above.

As used herein, the term "(C_3-C-|$_2$)-cycloalkyr or "cycloalkyl" whether used alone or as part of a substituent group, refers to a saturated or partially unsaturated cyclic hydrocarbon radical including 1, 2 or 3 rings and including a total of 3 to 12 carbon atoms forming the rings. The term cycloalkyl includes bridged, fused and spiro ring systems. For example, (C_3-C_{12})-cycloalkyl refers to a cycloalkyl group having 3 to 8 (both inclusive) carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, norbornyl, bicyclo[2.1 .0]pentane, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]hept-2-ene, spiro[3.3]heptane, 1,2,3,3a-tetrahydropentalene and the like.

Unless stated otherwise, the "cycloalkyl" group can be unsubstituted or substituted with one or more groups, preferably 1-3 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (Ci-C$_6$)alkyl-(Rc)o-3, (Ci-C$_6$)-alkoxy-(R_c)o-3, (C_3-C_{12})-cycloalkyl-(R_c)o-3, 0-(C_3-C_{12})-cycloalkyl-(R_c)o-3, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-Ci$_4$)-aryl-(R_c)o-3, 0-(C_6-Ci$_4$)aryl-(R_c)o-3, (C_6-Ci$_4$)ar(Ci-C$_6$)alkyl-(R_c)o-3, heterocyclyl-(R_c)o-3, heteroaryl-(R_c)0-3, C(0)R_a, C(0)OR_a, S(0)$_n$$R_a$, P(0)$_n$(0($C_1$-$C_6$)alkyl)$_2$, O-P(O) (0(CrC$_6$)alkyl)$_2$, N$R_a$$R_b$ and C(0)N$R_a$$R_b$; wherein R_a, R_b, R_c and n are as defined herein above.

As used herein, the term "(CrC$_6$)alkoxy" or "alkoxy" refers to a (C_1-C_6)-alkyl having an oxygen radical attached thereto. Representative alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy and the like.

The term, (C_3-Ci$_2$)-cycloalkyloxy or cycloalkyloxy or 0-(C_3-Ci$_2$)-cycloalkyl refers to a (C3 -Ci$_2$)-cycloalkyl having an oxygen radical attached thereto. Representative cycloalkyloxy groups include, but are not limited to, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.

Unless stated otherwise, the alkoxy and cycloalkyloxy can be unsubstituted or substituted with one or more groups selected from the group consisting of halogen,

hydroxy, nitro, cyano, $(C_1\text{-}C_6)$alkyl-$(R_c)_{0\text{-}3}$, $(Ci\text{-}C_6)$-alkoxy-$(R_c)_{0\text{-}3}$, $(C_3\text{-}C_{12})$-cycloalkyl-$(R_c)_{0\text{-}3}$, 0-$(C_3\text{-}C_{12})$-cycloalkyl-$(R_c)_{0\text{-}3}$, halo$(C_1\text{-}C_6)$alkyl, halo(CrC_6)alkoxy, $(C_6\text{-}Ci_4)$-aryl-$(R_c)_{0\text{-}3}$, 0-$(C_6\text{-}Ci4)$aryl-$(R_c)_{0\text{-}3}$, $(C_6\text{-}Ci4)$ar$(Ci\text{-}C_6)$alkyl-$(R_c)_{0\text{-}3}$, heterocyclyl-$(R_c)_{0\text{-}3}$, heteroaryl-$(R_c)_{0\text{-}3}$, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, $P(0)_n(0(Ci\text{-}C_6)alkyl)_2$, O-P(O) $(0(C_1\text{-}C_6)alkyl)_2$, NR_aRb and $C(0)NR_aRb$; wherein R_a, R_b, R_c and n are as defined herein above.

Examples of substituted (CrC_6)-alkoxy include, but are not limited to, chloromethoxy, 2-cyanoethoxy, trifluoromethoxy and benzyloxy group. A benzyloxy group refers to a benzyl having an oxygen radical attached thereto.

The term "$(Ci\text{-}C_6)$-alkoxyalkyl" or "alkoxyalkyl" as used herein refers to a $(C\text{-}|\text{-}C_6)$-alkyl group, which is substituted by a (CrC_6)-alkoxy group.

The term "$(C_6\text{-}C_{14})$-aryr or "aryl" as used herein refers to monocyclic or bicyclic hydrocarbon groups having 6 to 14 ring carbon atoms, preferably 6 to 10 carbon atoms in which the carbocyclic ring(s) present have a conjugated pi electron system. Examples of $(C_6\text{-}Ci_4)$-aryl residues are phenyl, naphthyl, fluorenyl or anthracenyl. Preferred examples of $(C6\text{-}Cu)$-aryl residues are phenyl or naphthyl. Aryl groups can be unsubstituted or substituted by one or more groups, for example 1, 2, 3, 4 or 5 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, $(C_1\text{-}C_6)$alkyl-$(R_c)_{0\text{-}3}$, $(Ci\text{-}C_6)$-alkoxy-$(R_c)_{0\text{-}3}$, $(C_3\text{-}Ci_2)$-cycloalkyl-$(R_c)_{0\text{-}3}$, 0-$(C_3\text{-}Ci_2)$-cycloalkyl-$(R_c)_{0\text{-}3}$, halo(CrC_6)alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}Ci_4)$-aryl-$(R_c)_{0\text{-}3}$, 0-$(C_6\text{-}Ci_4)$aryl-$(R_c)_{0\text{-}3}$, $(C_6\text{-}C_{14})$ar$(Ci\text{-}C_6)$alkyl-$(R_c)_{0\text{-}3}$, heterocyclyl-$(R_c)_{0\text{-}3}$, heteroaryl-$(R_c)_{0\text{-}3}$, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, P(0)n(0(CrC$_6$)alkyl)$_2$, O-P(O) $(0(CrC_6)alkyl)_2$, NR_aR_b and $C(0)NR_aR_b$; wherein R_a, R_b, R_c and n are as defined herein above. In monosubstituted phenyl, the substituent can be located in the 2-position, the 3-position or the 4-position. If the phenyl carries two substituents, they can be located in 2, 3-position, 2, 4-position, 2, 5-position, 2, 6-position, 3, 4-position or 3, 5-position. Examples of monosubstituted phenyl groups include, but are not limited to, 3-trifluoromethylphenyl, 4-chlorophenyl and 4-cyanophenyl. Examples of disubstituted phenyl groups include, but are not limited to, 3, 5-difluorophenyl, and 3, 4-dimethoxyphenyl.

As used herein, the term "$(C_6\text{-}Ci_4)$-aryloxy" or "aryloxy" or "0-$(C_6\text{-}Ci_4)$aryl" refers to an "$(C_6\text{-}Ci_4)$-aryr group having an oxygen radical attached thereto. The aryl of aryloxy

group can be unsubstituted or substituted as explained in the definition of substituted (C_6-Ci_4)-aryl herein above. Examples of aryloxy groups include, but not limited to, phenoxy, 4-chlorophenoxy, and 3, 4-dimethoxyphenoxy.

As used herein, the term "aralkyl" or "(C_6-C_{14})ar(C-|-C_6)alkyr refers to (CrC_6)alkyl group substituted with an (C_6-Ci_4)-aryl group, wherein the terms alkyl and aryl are as defined above. Exemplary aralkyl groups include (CH_2)p-phenyl, wherein p is an integer from 1 to 6, such as benzyl wherein p is 1. The aryl of the (C_6-Ci_4)-aralkyl group can be unsubstituted or substituted as explained in the definition of substituted aryl herein above.

As used herein, the term "aralkyloxy" or "(C_6-C_{14})ar(C-|-C_6)alkyloxy" refers to an aralkyl group having an oxygen radical attached thereto. The aryl of aralkyloxy group may be unsubstituted or substituted as explained in the definition of substituted aryl herein above.

The term "heteroatom" as used herein, includes nitrogen (N), oxygen (O) and sulfur (S). Any heteroatom with unsatisfied valency is assumed to have a hydrogen atom to satisfy the valency.

As used herein, the terms "heterocyclyl" or "heterocyclic" whether used alone or as part of a substituent group, unless indicated otherwise, refers to a saturated, partially unsaturated, monocyclic or polycyclic ring system containing 1 to 10 carbon atoms and 1 to 4 identical or different heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. Unless indicated otherwise, the term "heterocyclyl" primarily refers to a 3- to 12- membered ring system, preferably, 3- to 10- membered ring system which can be a monocyclic or a bicyclic ring. Representative examples of heterocyclyls include, but are not limited to, pyrrolyl, pyrrolidinyl, pyrazolyl, imidazolyl, pyrazinyl, piperazinyl, oxazolyl, oxadiazolyl, isoxazolyl, triaziolyl, thiazolyl, tetrazolyl, furyl, thienyl, purinyl, pyridinyl, pyridazinyl, pyrimidinyl, piperidyl, benzoxazolyl, benzothiazolyl, benzofuranyl, purinyl, benzirmidazolyl, benzoxazolyl, indolyl, indazolyl, isoindolyl, isothiazolyl, isoquinolyl, isoquinolyl, morpholinyl, thiomorpholinyl, thiomorpholinyl-1 , 1-dioxide, quinoxalinyl, quinolinyl and thiophenyl. The oxidized form of the ring nitrogen and sulfur atom of the heterocyclyl to provide N-oxide, S-oxide or S, S-dioxide is also encompassed.

Heterocyclyl having an aromatic ring containing heteroatom/s are herein referred to by the customary term "heteroaryl". Unless indicated otherwise, within the context of the present invention and as used herein, the term "heteroaryl" refers to a 5- to 10-membered aromatic monocyclic or bicyclic ring system containing 1 to 4 identical or different hetero atoms selected from the group consisting of nitrogen, sulphur and oxygen. Examples of heteroaryls include, but are not limited to, pyrrole, pyrazole, imidazole, pyrazine, furan, thiophene, oxazole, thiazole, benzimidazole, benzoxazole, benzothiazole, benzofuran, indole, indazole, isoindole, isoquinoline, isooxazole, triazine, purine, pyridine, quinoline, oxadiazole, thiene, pyridazine, pyrimidine, isothiazole, quinoxaline (benzopyrine) and tetrazole. The oxidized form of the ring nitrogen and sulfur atom of the heteroaryl to provide N-oxide, S-oxide or S,S-dioxide is also encompassed.

Unless stated otherwise, heterocyclyl or heteroaryl group can be unsubstituted or substituted. A substituted heterocyclyl or heteroaryl refers to a heterocyclyl or heteroaryl substituted with 1-5 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (Ci-C_6)alkyl-(R_c)$_{0-3}$, (CrC_6)-alkoxy-(R_c)$_{0-3}$, (C_3-Ci_2)-cycloalkyl-(R_c)$_{0-3}$, O-(C_3-Ci_2)-cycloalkyl-(R_c)$_{0-3}$, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl-(R_c)$_{0-3}$, O-(C_6-C_{14})aryl-(R_c)$_{0-3}$, (C_6-Ci4)ar(Ci-C_6)alkyl-(R_c)$_{0-3}$, heterocyclyl-(R_c)$_{0-3}$, heteroaryl-(R_c)$_{0-3}$, C(0)R_a, C(0)OR_a, S(0)$_n$$R_a$, P(0)$_n$(0($C_1$-$C_6$)alkyl)$_2$, O-P(O) (0(Cr$C_6$)alkyl)2, N$R_a$$R_b$ and C(0)N$R_a$$R_b$; wherein R_a, R_b, R_c and n are as defined herein above. The substituents can be present on either the ring carbon or the ring nitrogen atom(s). The substituents can be present at one or more positions provided that a stable molecule results.

Within the context of this present application and as used herein the term "isotopic forms" or "isotopically labeled forms" is a general term used for isotopic forms of compounds of formula I, wherein one or more atoms of compounds of formula I are replaced by their respective isotopes. All isotopes of any particular atom or element as specified are contemplated within the scope of the compounds of the invention. Examples of isotopes that can be incorporated into the compounds disclosed herein include, but are not limited to, isotopes of hydrogen such as ^{2}H (deuterium or D) and ^{3}H, carbon such as ^{11}C, ^{13}C and ^{14}C, nitrogen such as ^{13}N and ^{15}N, oxygen such as ^{15}0 , ^{17}0 and ^{18}0 , chlorine such as ^{36}Cl, fluorine such as ^{18}F and sulphur such as ^{35}S.

Substitution with heavier isotopes, for example, replacing one or more key carbon-hydrogen bonds with carbon-deuterium bond may show certain therapeutic advantages, resulting from longer metabolism cycles, (e.g., increased in vivo half life or reduced dosage requirements), improved safety or greater effectiveness and hence may be preferred in certain circumstances.

Representative examples of isotopic forms of the compounds of formula I can include, without limitation, deuterated compounds of formula I. The term "deuterated" as used herein, by itself or used to modify a compound or group, refers to replacement of one or more hydrogen atom(s), which is attached to carbon(s), with a deuterium atom. For example, the compounds of formula I can include in the definitions of one or more of its various variables, wherever applicable, deuterium, deuterated-alkyl, deuterated-alkoxy, deuterated-cycloalkyl, deuterated-heterocyclyl, deuterated-aryl, deuterated-heteroaryl and the like. The term "deuterated-alkyl" refers to an (d-C6)-alkyl group as defined herein, wherein at least one hydrogen atom bound to carbon is replaced by a deuterium. That is, in a deuterated alkyl group, at least one carbon atom is bound to a deuterium. In a deuterated alkyl group, it is possible for a carbon atom to be bound to more than one deuterium; it is also possible that more than one carbon atom in the alkyl group is bound to a deuterium. Analogously, the term "deuterated" and the terms deuterated-heterocyclyl, deuterated-heteroaryl, deuterated-cycloalkyl, deuterated-aryl, deuterated-alkoxy each refer to the corresponding chemical moiety wherein at least one carbon is bound to a deuterium.

The term "pharmaceutically acceptable solvate(s)" or "solvate(s)" as used herein refers to a compound formed by the interaction of a solute (in the present invention, a compound of formula I or a pharmaceutically acceptable salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Preferably, the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably, the solvent used is water and the solvates obtained are referred to as hydrates. Examples for suitable solvates are the mono- or di-hydrates or alcoholates of the compounds according to the invention.
Within the context of the present invention and as used herein, the term "stereoisomer" or "stereoisomeric form" is a general term used for all isomers of individual compounds

(in the present invention, a compound of formula I) that differ only in the orientation of their atoms in space. The term stereoisomer includes mirror image isomers (enantiomers), mixtures of mirror image isomers (racemates, racemic mixtures), geometric (cis/trans or E/Z) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

The term "tautomer" or "tautomeric form" refers to the coexistence of two (or more) compounds that differ from each other only in the position of one (or more) mobile atoms and in electron distribution, for example, keto-enol tautomers.

As used herein, the term "pharmaceutically acceptable" means that the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

The term "pharmaceutically acceptable salt(s)" as used herein includes salts of the active compound i.e. the compound of formula I, which retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects; and are prepared with suitable acids or bases, depending on the particular substituents found on the compounds described herein.

Within the context of the present invention and as used herein the term "polymorph(s)" or "polymorphic form" refers to crystals of the same compound that differs only in the arrangement and/or conformation of the molecule in the crystal lattice.

Within the context of the present invention and as used herein, "N-oxide" refers to the oxide of the nitrogen atom of a nitrogen-containing heteroaryl or heterocycle. N-oxide can be formed in the presence of an oxidizing agent such as m-chloro-perbenzoic acid or hydrogen peroxide. N-oxide refers to an amine oxide, also known as amine-N-oxide, and is a chemical compound that contains N→0 bond.

Within the context of the present invention and as used herein, "a prodrug" or "prodrugs" refers to any compound, which are derivatives of parent compound (in the context of the present invention, a compound of formula I), which following administration, release(s) the parent compound *in vivo* via a chemical or physiological process, e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the parent compound.

In the context of the present invention, the term "compound(s) of formula I" or "compounds of the present invention" are used interchangeably and includes all the stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and pharmaceutically acceptable salts, pharmaceutically acceptable solvates, pharmaceutically acceptable prodrugs, N-oxides and pharmaceutically acceptable polymorphs thereof. The compound(s) of formula I can also be referred to herein as "the active compound" or "the active ingredient".

The term, "therapeutically effective amount" as used herein means an amount of a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; or a composition comprising the compound of formula I or a pharmaceutically acceptable salt thereof, effective in producing the desired therapeutic response in a particular patient suffering from a disease or disorder mediated by IL17 or TNF-a. Particularly, the term "therapeutically effective amount" includes the amount of the compound, when administered, that induces a positive modification in the disease or disorder to be treated or is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disease or disorder being treated in a subject. In respect of the therapeutic amount of the compound, consideration is also given that the amount of the compound used for the treatment of a subject is low enough to avoid undue or severe side effects, within the scope of sound medical judgment. The therapeutically effective amount of the compound or composition will vary with the particular condition being treated, the age and physical condition of the end user, the severity of the condition being treated or prevented, the duration of the treatment, the nature of concurrent therapy, the specific compound or composition employed the particular pharmaceutically acceptable carrier utilized.

As used herein, the term "pharmaceutically acceptable carrier" refers to a material that is non-toxic, inert, solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type which is suitable for a subject, preferably a mammal, more preferably a human, and is suitable for delivering an active agent to the target site without terminating the activity of the agent.

The term "disease(s) or disorder(s) mediated by IL-17 or TNF-a" encompasses all diseases, disorders and medical conditions in which pro-inflammatory cytokines IL-17

or TNF-α plays a role, whether directly or indirectly, including the causation, development, progression, persistence or pathology of the disease or disorder.

The term "disease(s) or disorder(s) mediated by IL-17" encompasses all diseases, disorders and medical conditions in which pro-inflammatory cytokine IL-17 plays a role, whether directly or indirectly, including the causation, development, progression, persistence or pathology of the disease or disorder.

The term "disease(s) or disorder(s) mediated by TNF-a" encompasses all diseases, disorders and medical conditions in which pro-inflammatory cytokine TNF-a plays a role, whether directly or indirectly, including the causation, development, progression, persistence or pathology of the disease or disorder.

The diseases or disorders mediated by IL-17 or TNF-a can be selected from the group consisting of an autoimmune or inflammatory disease or disorder; and a metabolic disease or disorder.

The term "subject" as used herein refers to an animal, preferably a mammal, and most preferably a human. The term "mammal" used herein refers to warm-blooded vertebrate animals of the class 'mammalia', including humans, characterized by a covering of hair on the skin and, in the female, milk-producing mammary glands for nourishing the young. The term mammal includes animals such as cat, dog, rabbit, bear, fox, wolf, monkey, deer, mouse, pig and human. The term "subject" may be used interchangeably with the term patient. In the context of the present invention the phrase "a subject in need thereof" means a subject in need of the treatment for the disease or disorder that is mediated by IL17 or TNF-a. Alternatively, the phrase "a subject in need thereof means a subject (patient) diagnosed having a disease or disorder that is mediated by IL17 or TNF-a.

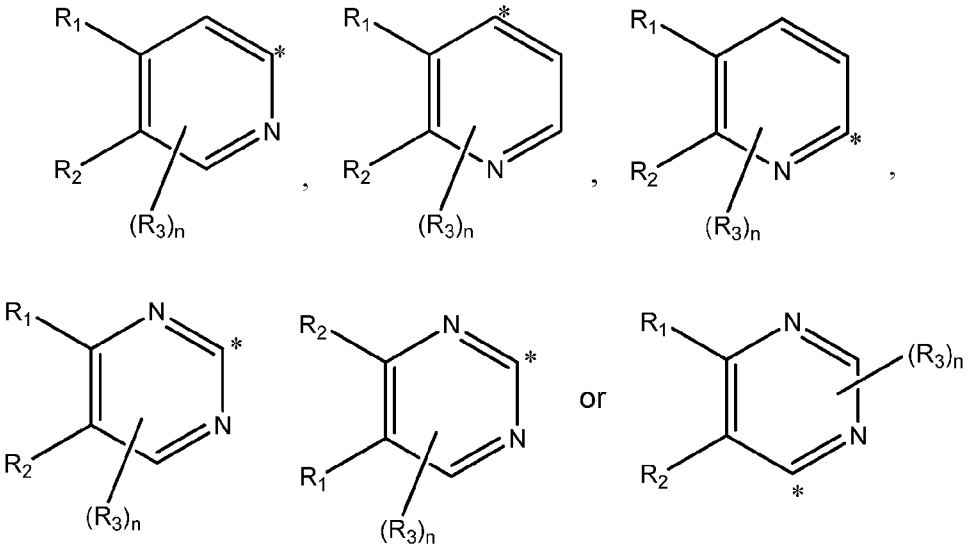
As used herein, the terms "treatment" "treat" and "therapy" and the like refer to alleviate, slow the progression, attenuation or cure of existing diseases or condition (e.g. rheumatoid arthritis). Treatment also includes treating, preventing development of, or alleviating to some extent, one or more of the symptoms of the diseases or condition.

Embodiments

The invention encompasses all the compounds described by the formula I without limitation, however, for the purpose of further illustrations, preferred aspects and elements of the invention are discussed herein in the form of the following embodiments.

In an embodiment, the present invention relates to a compound of formula I, wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole, pyrrole or a heteroaryl ring system selected from:



wherein * indicates the point of attachment to L; and

L, R_1, R_2, R3 and n are as defined in the first aspect with the provisos that:

(a) when A is pyrazole then L is a group other than *C(0)N(R_5) and *N(R_4)-C(0); and

(b) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I, wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole or pyrrole;

with the provisos that:

(a) when A is pyrazole then L is a group other than $^*C(0)N(R_5)$ and $^*N(R_4)$-C(0); and

(b) when A is pyrazole and L is $^*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein,

A is triazole, pyrazole, isoxazole or thiazole;

L is $^*N(R_4)$-C(0)-N(R_5), $^*C(0)N(R_5)$, $^*N(R_4)$-C(0), $^*CH(R_6)$-C(0)-N(R_5), $^*CH(R_6)N(R_5)$, $^*N(R_4)$-$S(0)_2$ or $^*NR_4$; wherein * indicates the point of attachment to A;

R_4, R_5 and R_6, are as defined in the first aspect with the provisos that:

(c) when A is pyrazole then L is a group other than $^*C(0)N(R_5)$ and $^*N(R_4)$-C(0); and

(d) when A is pyrazole and L is $^*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein,

A is triazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein:

A is pyrazole;

L is $^*N(R_4)$-C(0)-N(R_5); $^*CH(R_6)$-C(0)-N(R_5); $^*CH(R_6)N(R_5)$; $^*N(R_4)$-$S(0)_2$ or $^*NR_4$; wherein * indicates the point of attachment to A;

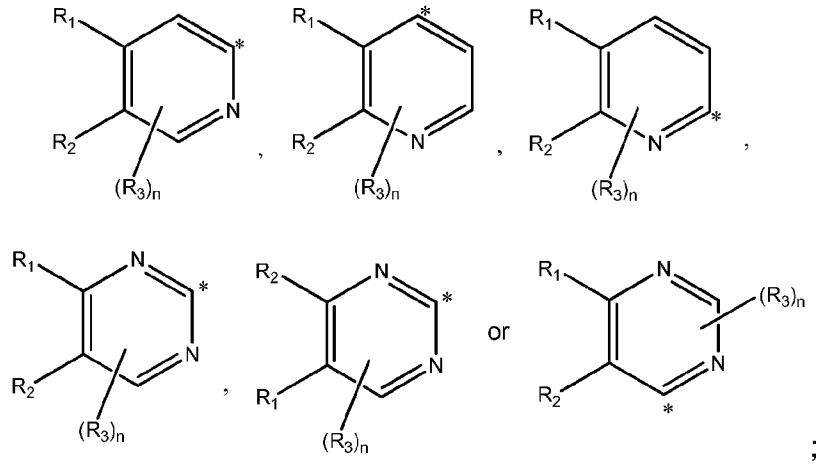
R_4, R_5 and R_6, are as defined in the first aspect with the proviso that when L is $^*N(R_4)$-C(0)-N(R_5), then the said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is isoxazole; or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

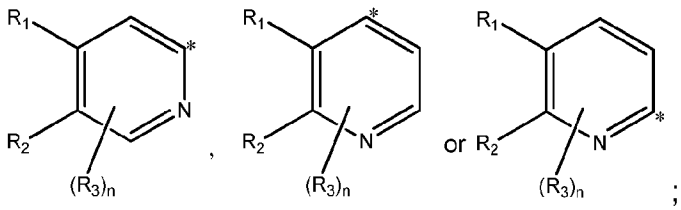
In another embodiment, the present invention relates to a compound of formula I; wherein A is thiazole; or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention provides a compound of formula I; wherein A is



wherein * indicates the point of attachment to L; and L, R_1, R_2, R3 and n are as defined in the first aspect; or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

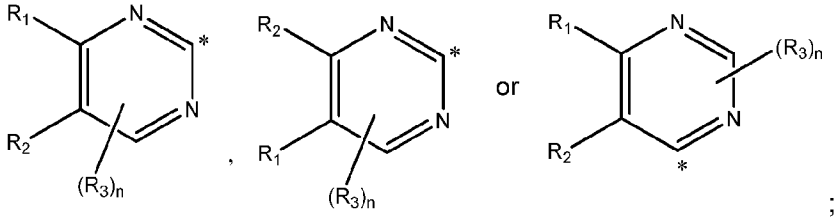
In another embodiment, the present invention provides a compound of formula I; wherein A is



wherein * indicates the point of attachment to L;

and L, R_1, R_2, R_3 and n are as defined in the first aspect;
or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is



wherein * indicates the point of attachment to L;
and L, R_1, R_2, R_3 and n are as defined in the first aspect;
or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein each of **Xi, X_2, X_4** and **X_5** is $C(R_7)$; and **X_3** is $C(R_8)$; and
R_7 and R_8 are as defined in the first aspect; with the provisos that:

(a) when A is pyrazole then L is a group other than $^*C(0)N(R_5)$ or $^*N(R_4)$-C(0); and
(b) when A is pyrazole and L is $^*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is selected from a triazole, pyrazole, isoxazole or thiazole;
each of **Xi, X_2, X_4** and **X_5** is $C(R_7)$; and **X_3** is $C(R_8)$; and
R_7 and R_8 are as defined in the first aspect; with the provisos that:

(a) when A is pyrazole then L is a group other than $^*C(0)N(R_5)$ or $^*N(R_4)$-C(0); and
(b) when A is pyrazole and L is $^*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is triazole or pyrazole;

L is *N(R_4)-C(0)-N(R_5); wherein * indicates the point of attachment to A;

each of **Xi, X_2, X_4** and X_5 is C(R_7); and X_3 is C(R_8); and

R_4, R_5, R_7 and R_8 are as defined in the first aspect; with the proviso that when A is pyrazole the said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is triazole;

L is *N(R_4)-C(0)-N(R_5); *C(0)N(R_5), *CH(R_6)-C(0)-N(R_5); *CH(R_6)N(R_5) or *N(R_4)-S(0)$_2$;wherein * indicates the point of attachment to A;

each of **Xi, X_2, X_4** and X_5 is C(R_7); and X_3 is C(R_8); and

R_4, R_5, R_6, R_7 and R_8 are as defined in the first aspect;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A pyrazole;

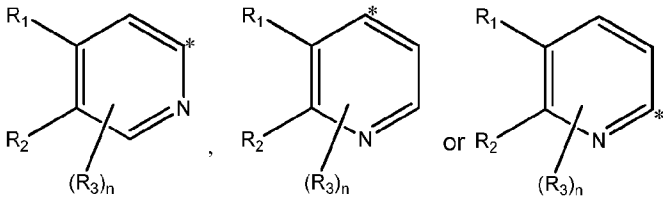
L is *N(R_4)-C(0)-N(R_5); N(R_4)-S(0)$_2$ or *CH(R_6)N(R_5); wherein * indicates the point of attachment to A;

each of **Xi, X_2, X_4** and X_5 is C(R_7); and X_3 is C(R_8); and

R_4, R5, R_7 and R_8 are as defined in the first aspect; with the proviso that when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then the said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is



wherein * indicates the point of attachment to L;

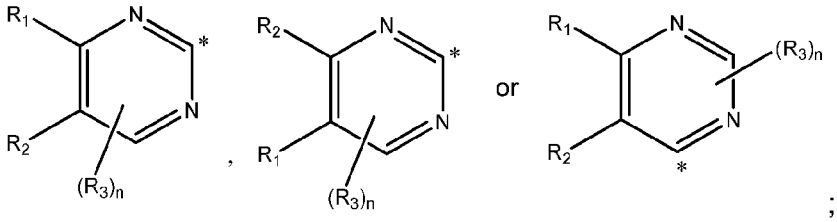
L is *N(R_4)-C(0)-N (R_5); *C(0)N (R_5); *N(R_4)-S(0)$_2$ or *NR_4; wherein * indicates the point of attachment to A;

each of X_1, X_2, X_4 and X_5 is C(R_7); and X_3 is C(R_8); and

Ri, R2, R3, R4, R5, R7, R8 and n are as defined in the first aspect;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein A is



wherein * indicates the point of attachment to L;

L is *N(R_4)-C(0)-N(R_5); *C(0) N(R_5); N(R_4)-S(0)$_2$ or *NR_4; wherein * indicates the point of attachment to A;

each of X_1, X_2, X_4 and X_5 is C(R_7); and X_3 is C(R_8); and

Ri, R2, R3, R4, R5, R7, R8 and n are as defined in the first aspect;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

In another embodiment, the present invention relates to a compound of formula I; wherein one of X_1, X_2, X_4 or X_5 is N, while the remaining are C(R_7); X3 is N or C(Rs); or any two of X_1, X_2, X_4 or X_5 are N, while the remaining are C(R_7); X3 is N or C(Rs); and R_7 and R_8 are as defined in the first aspect; with the provisos that:

(a) when A is pyrazole then L is a group other than *C(0) N(R_5) or *N(R_4)-C(0); and

(b) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, stereoisomer or a tautomer or a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

Representative compounds of formula I encompassed in accordance with the present invention include:

1-(5-Methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)-3-(2-(trifluoromethyl)-1 H-benzo[d]imidazol-6-yl)urea;

1-(4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1 -yl)-3-cyanophenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(3-Cyano-4-(4-(2-hydroxyethyl)piperidin-1 -yl)phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(5-Methyl-1 -phenyl-1 H-pyrazol-4-yl)-3-(naphthalen-1 -yl)urea;

1-(1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1-yl) phenyl) urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(3-Cyano-4-(piperazin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(5-Chloro-6-morpholinopyridin-3-yl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(3-Cyano-4-(4-(4-fluoro-3-(trifluoromethyl) benzoyl) piperazin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-1 -methyl-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholinopiperidin -1-yl)phenyl)urea;

1-(4-([1 ,4'-Bipiperidin]-1 '-yl)-3-cyanophenyl)-3-(1 -(4-chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

2-(1 -(4-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-2-cyanophenyl) piperidin-4-yl)ethyl diethyl phosphate;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(2-methoxyethyl) piperidin-1 -yl)phenyl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(4-(4-morpholinopiperidin-1 -yl)-2-(trifluoromethyl)phenyl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(1 -(4-morpholinophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(4-(1 ,1 ,1 ,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-3-(1 -(4-isopropylphenyl) -1H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-5-methyl-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1 -yl)phenyl)urea;

3-(3-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-N-(4-hydroxy-3-methoxy benzyl)benzamide;

4-(1 -(2-Cyano-4-(3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido) phenyl)piperidin-4-yl)butanoic acid;

1-(3-Cyano-4-(4-(pyrimidin-2-yl)piperazin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl) phenyl)-1H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(piperazin-1 -yl)phenyl) urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-(4-morpholinopiperidin-1 -yl) pyridin-2-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(4-cyano-5-(4-morpholinopiperidin -1-yl)pyridin-2-yl)urea;

1-(6-(4-Morpholinopiperidin-1 -yl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(5-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)pyridin-2-yl)piperidine-4-carboxylic acid;

1-(6-(4-(Pyrimidin-2-yl)piperazin-1 -yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(5-Chloro-6-(4-morpholinopiperidin-1 -yl)pyridin-3-yl)-3-(1 -(4-chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-methyl-6-(4-morpriolino piperidin-1-yl)pyridin-3-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1 -yl)pyridin-3-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-cyano-6-(4-(pyrimidin-2-yl)piperazin-1 -yl)pyridin-3-yl)urea;

1-(6-(4-Cyano-4-phenylpiperidin-1 -yl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl) phenyl)-1 H-1,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(piperidin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)-3-(1 -(4-(trifluoro methyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(cyclopropylmethyl) piperazin-1 -yl)phenyl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-methoxypiperidin-1 -yl)phenyl)urea;

1-(3-Cyano-4-(4-(3-hydroxyphenyl)piperazin-1 -yl)phenyl)-3-(1 -(p-tolyl)-l H-1 ,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(1 -(3-(trifluoromethyl) phenyl)-1 H-1,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-hydroxypiperidin-1 -yl)phenyl)-1 ,3-dimethylurea;

1-(4-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-2-cyanophenyl)-4-(2-hydroxypropan-2-yl)piperidin-1 -ium methanesulfonate;

1-(3-Cyano-4-(piperazin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea hydrochloride;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)urea;

1-(4-(Tert-butyl) phenyl)-N-(3-cyano-4-(4-(2-hydroxyethyl) piperidin-1 -yl) phenyl)-1 H-1 , 2, 3-triazole-4-carboxamide;

1-(4-(Tert-butyl) phenyl)-N-(3-cyano-4-(4-hydroxypiperidin-1 -yl) phenyl)-1 H-1 , 2, 3-triazole-4-carboxamide;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide hydrochloride;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-(pyrimidin-2-yl)piperazin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

N-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-5-pentyl-1 -(3-(trifluoromethyl) phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

N-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(4-fluorophenyl)-4-rnethylisoxazole-5-carboxamide;

3-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)isoxazole-5-carboxamide;

N-(1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-cyano-4-(4-morpholino piperidin-1 -yl)benzenesulfonamide;

N-(4-(3-Methoxyphenyl)pyrimidin-2-yl)-5^henylthiazol-2-arnine;

5-Phenyl-N-(4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)thiazol-2-arnine;

N-(4-(2-Methoxyphenyl)pyrimidin-2-yl)-5-phenylthiazol-2-arnine;

5-((6-Fluorobenzo[d]thiazol-2-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;

5-((4-(3, 5-Dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;

5-((4-(3, 5-Dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-(hydroxymethyl) piperidin-1 -yl) benzonitrile;

4-(2-Methoxyphenyl)-N-(4-(4-(pyrimidin-2-yl)piperazin-1 -yl)-3-(trifluoromethyl) phenyl) pyrimidin-2-amine;

1,1,1,3,3,3-Hexafluoro-2-(4-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino)phenyl) propan-2-ol;

2-(4-Hydroxypiperidin-1 -yl)-5-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino) benzonitrile;

5-((4-Morpholinopyrimidin-2-yl)amino)-2-(4-(pyridin-2-yl)piperazin-1 -yl)benzonitrile

2-morpholino-5-((4-morpholinopyrimidin-2-yl)amino)benzonitrile;

5-((4-((2-Morpholinoethyl)amino)pyrimidin-2-yl)amino)-2-(4-morpholino piperidin-1 -yl)benzonitrile;

5-((2-Chloro-6-methoxyquinolin-4-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;

2-(4-Morpholinopiperidin-1 -yl)-5-(quinolin-2-ylamino) benzonitrile;

5-((Cyano(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(2-hydroxypropan-2-yl)piperidin-1 -yl)benzonitrile;

5-((Cyano(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1 -yl)benzonitrile;

2-Chloro-5-(((1 -(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino) benzonitrile;

5-(((1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino)-2-(4-morpholino piperidin-1 -yl)benzonitrile;

Diethyl (((4-chloro-3-cyanophenyl)amino)(1 -(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)phosphonate;

N-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxy-2-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide; or

N-(3-Cyano-4-(4-methoxypiperidin-1 -yl)phenyl)-2-hydroxy-2-(1 -(3 (trifluoromethyl) phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide; or
a stereoisomer, a tautomer or a pharmaceutically acceptable salt thereof.

The compounds of the present invention include all isotopic forms, stereoisomeric and tautomeric forms and mixtures thereof in all ratios and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, prodrugs, N-oxides, S-oxides and polymorphs.

According to another aspect of the present invention, there are provided processes for the preparation of the compounds of formula I.

Thus, the compound of formula I can be prepared by various methods including using methods well known to the person skilled in the art. Examples of processes for the preparation of the compounds of formula I are described below and illustrated in the following scheme, but are not limited thereto. It will be appreciated by the person skilled in the art that within certain of the processes described herein, the order of the synthetic steps employed can be varied and will depend *inter alia* on factors such as the nature of functional groups present in a particular substrate and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent such as bases, solvents, coupling agents to be used in the reaction steps.

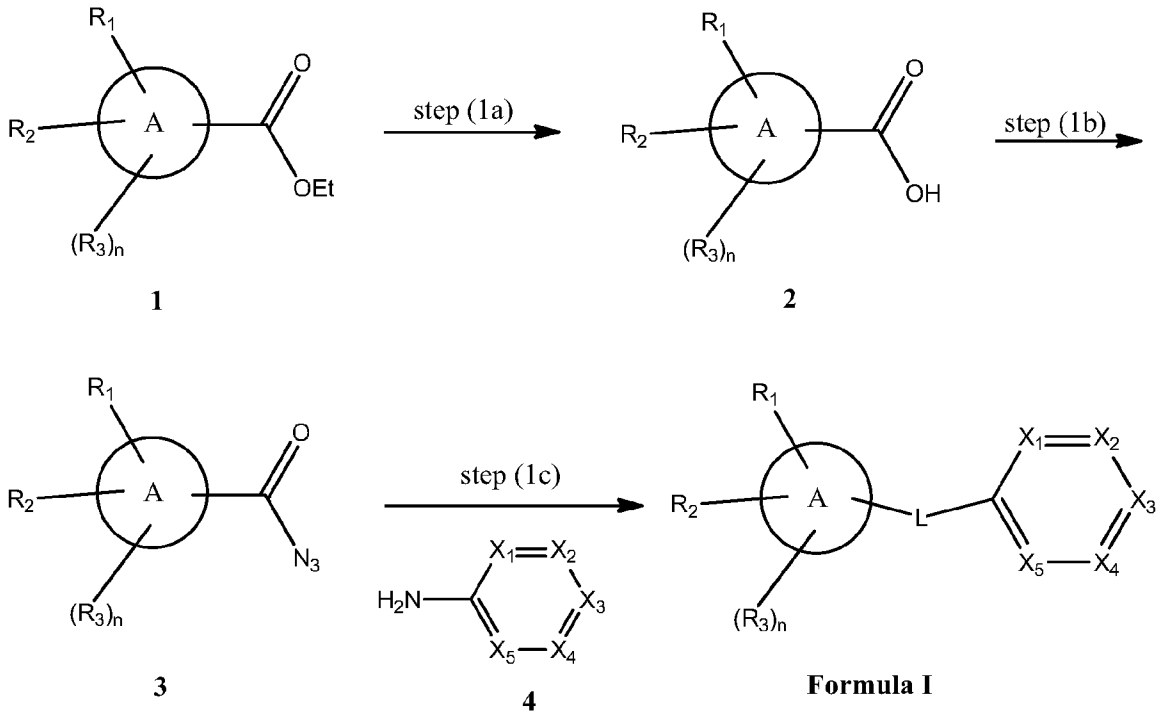
The reagents, reactants and intermediates used in the following process are either commercially available or can be prepared according to standard procedures known in the art, for instance those reported in the literature references. In the following schemes and the description of the processes for the synthesis of the compounds of formula I, the starting compounds and the intermediates used for the synthesis of compounds of the present invention, are designated as intermediates 1-13 respectively, for ease of reference. Throughout the process description, the corresponding substituent groups in the various formulae representing starting compounds and intermediates have the same meanings as that for the compound(s) of formula I as indicated in one or more embodiments described above, unless stated otherwise.

The processes for the preparation of the compounds of formula I of the present invention are depicted in schemes 1 to 7 presented below. For ease of reference, the

reaction steps shown in schemes 1 to 7, are referred to by using general symbols namely (1a), (1b) and (1c) in the scheme 1; (2a) in the scheme 2, and the like.

Scheme 1 depicts a process for the preparation of the compounds of formula I, wherein A, R-i, R_2, F?3, X-i, X2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is $^*N(R_4)$-C(0)-N(R_5); wherein * indicates the point of attachment to A; and R_4 and R5 are hydrogen.

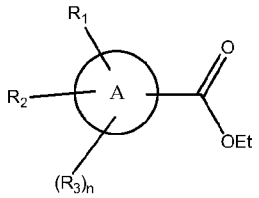
Scheme 1



1 2 3 4 Formula I

Step (1a)

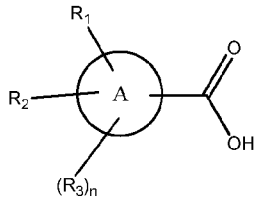
A compound 1 of the following formula;



1

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect;

is hydrolysed by reacting it with NaOH in a solvent such as a mixture of tetrahydrofuran (THF) and water at a temperature ranging from 70 °C to 90 °C to obtain a compound 2 of the following formula;



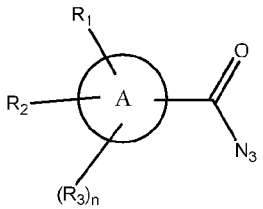
2

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect.

Step (1b)

Method A:

The compound of formula 2 as obtained in step (1a) is reacted with reagents namely trichloroacetonitrile, triphenyl phosphine and sodium azide in a solvent such as acetone at a temperature ranging from 20 °C to 35 °C to obtain a compound 3 of the following formula;



3

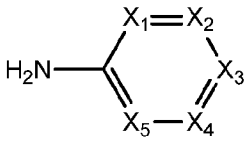
wherein, A, R_1, R_2, R3 and n are as defined in the first aspect.

Method B:

The compound of formula 2 as obtained in step (1a) is reacted with reagents namely sodium azide and triphosgene in the presence of a base such as triethylamine (TEA) in a solvent such as acetone or THF at a temperature ranging from 20 °C to 35 °C to obtain a compound 3 of the above formula.

Step (1c)

The compound of formula 3 as obtained in step (1b) is reacted with a compound 4 of the following formula;



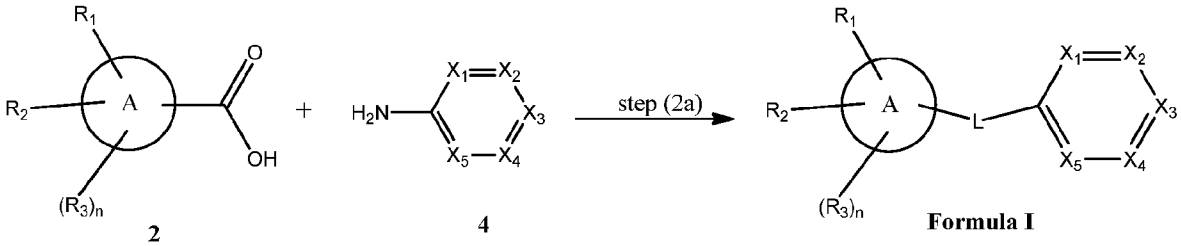
4

wherein, X_1, X_2, X_3, X_4 and X_5 are as defined in the first aspect;

in a solvent such as DMF (N, N-Dimethylformamide) or toluene at a temperature ranging from 100 °C to 120 °C to obtain a compound of formula I; wherein R-i, R_2, R3, X_1, X_2, X_3, X_4, X5 and n are as defined in the first aspect, L is $^*N(R_4)$-C(0)-$N(R_5)$; wherein * indicates the point of attachment to A; and R_4 and R_5 are hydrogen.

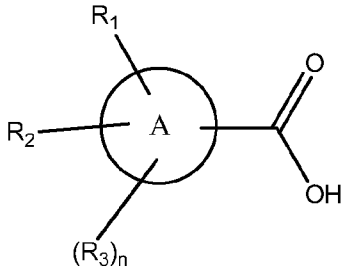
Scheme 2 depicts a process for the preparation of the compounds of formula I, wherein A, R-i, R_2, R3, X-i, X_2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is $^*C(0)N(R_5)$; wherein * indicates the point of attachment to A; and R_5 is hydrogen.

Scheme 2



Step 2(a)

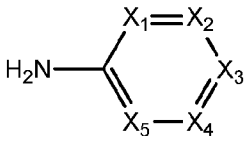
The compound 2 of the following formula;



2

wherein, A, R-i, R_2, R_3 and n are as defined in the first aspect;

is reacted with the compound 4 of the following formula;



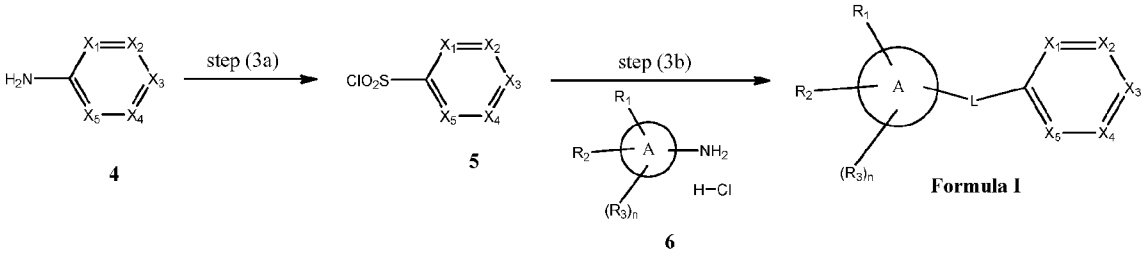
4

wherein, X_1, X_2, X3, X_4 and X_5 are as defined in the first aspect;

in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) as a catalysts, in the presence of a base such as tnethylamine, in a solvent such as DMF (N, N-Dimethylformamide) at a temperature ranging from 20 °C to 35 °C to obtain a compound of formula I, wherein A, R_1, R_2, R3, Xi, X2, X3, X4, X5 and n are as defined in the first aspect of the present invention, and L is *C(0)N (R_5); wherein * indicates the point of attachment to A; and R_5 is hydrogen.

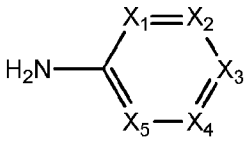
Scheme 3 depicts a process for the preparation of the compounds of formula I, wherein A, R-i, R_2, R3, X-i, X_2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *N(R_4)-S(0)$_2$; wherein * indicates the point of attachment to A; and R_4 is hydrogen.

Scheme 3



Step (3a)

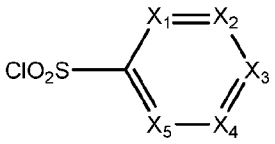
Compound 4 of the following formula;



4

wherein, X_1, X_2, X_3, X_4 and X_5 are as defined in the first aspect;

is reacted with cuprous chloride and sulphur dioxide in the presence of a base such as sodium nitrite in a solvent such as mixture of concentrated HCl and glacial acetic acid or acetic acid at a temperature ranging from -5 °C to 5 °C to obtain a compound 5 of the following formula;

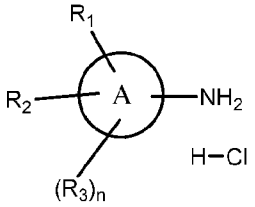


5

wherein, X_1, X_2, X3, X_4 and X_5 are as defined in the first aspect;

Step 3(b)

The compound of formula 5 as obtained in step 3(a) is reacted with a compound 6 of the following formula;



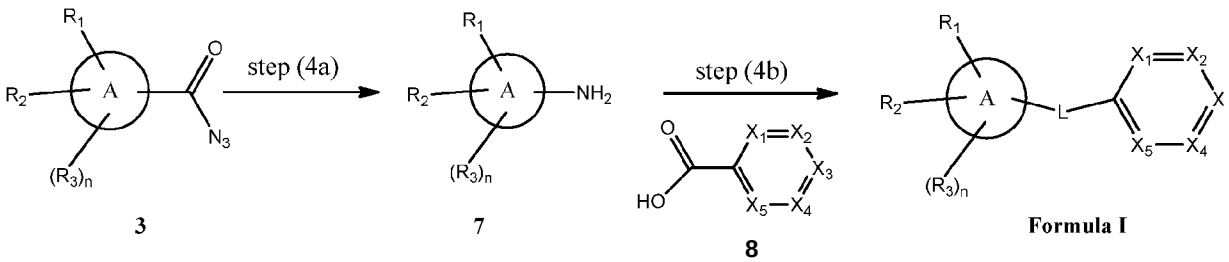
6

wherein, A, R_1, R_2, R3 and n are as defined in the first aspect;

in the presence of a base such as triethylamine (TEA) in a solvent such dichloromethane (MDC) at a temperature ranging from 20 °C to 35 °C to obtain a compound of formula I, wherein A, R_1, R_2, R3, Xi, X2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *N(R_4)-S(0) $_2$; wherein * indicates the point of attachment to A; and R_4 is hydrogen.

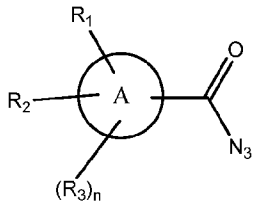
Scheme **4** depicts a process for the preparation of the compounds of formula I, wherein A, R-i, R_2, R3, Xi, X_2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *N(R_4)-C(0); wherein * indicates the point of attachment to A; and R_4 is hydrogen.

Scheme 4



Step 4(a)

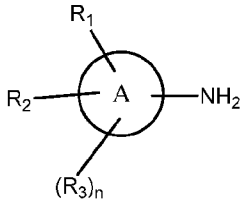
Compound 3 of following formula;



3

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect;

is refluxed in a solvent such as terf-butanol and reacted with saturated HCI in ethyl acetate at a temperature ranging from 20 °C to 35 °C to obtain a compound 7 of the following formula;

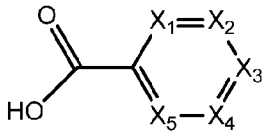


7

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect.

Step 4(b)

The compound of formula 7 as obtained in step 4(a) is reacted with compound 8 of the following formula;



8

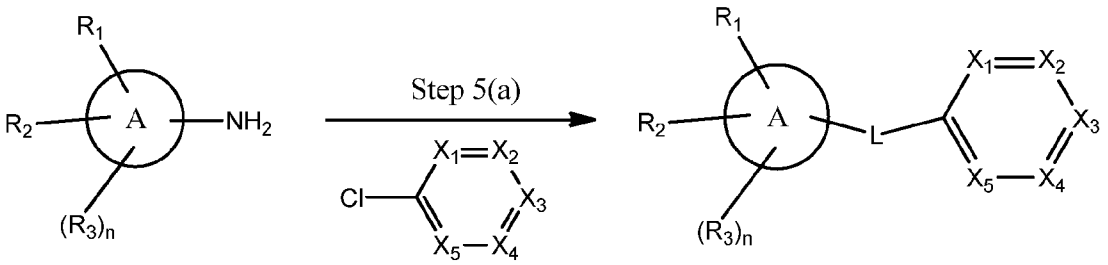
wherein, X_1, X_2, X_3, X_4 and X_5 are as defined in the first aspect;

in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) as a catalysts in a solvent such as dichloromethane at a temperature ranging from 20 °C to 35 °C to obtain a compound of formula I, wherein A, R_1, R_2, R3, X-i, X_2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *N(R_4)-C(O); wherein * indicates the point of attachment to A; and R_4 is hydrogen.

Scheme 5 depicts a process for the preparation of the compounds of formula I wherein, A, R_1, R_2, R3, X-i, X2, X3, X4, X5 and n are as defined in the first aspect of the present

invention, and L is $^*NR_4$; wherein * indicates the point of attachment to A; and R_4 is hydrogen.

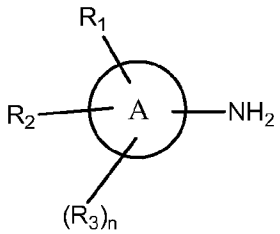
Scheme 5



7 **9** **Formula I**

Step 5(a)

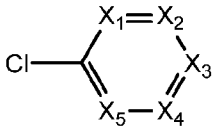
Compound 7 of the following formula;



7

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect;

is reacted with a compound 9 of the following formula;



9

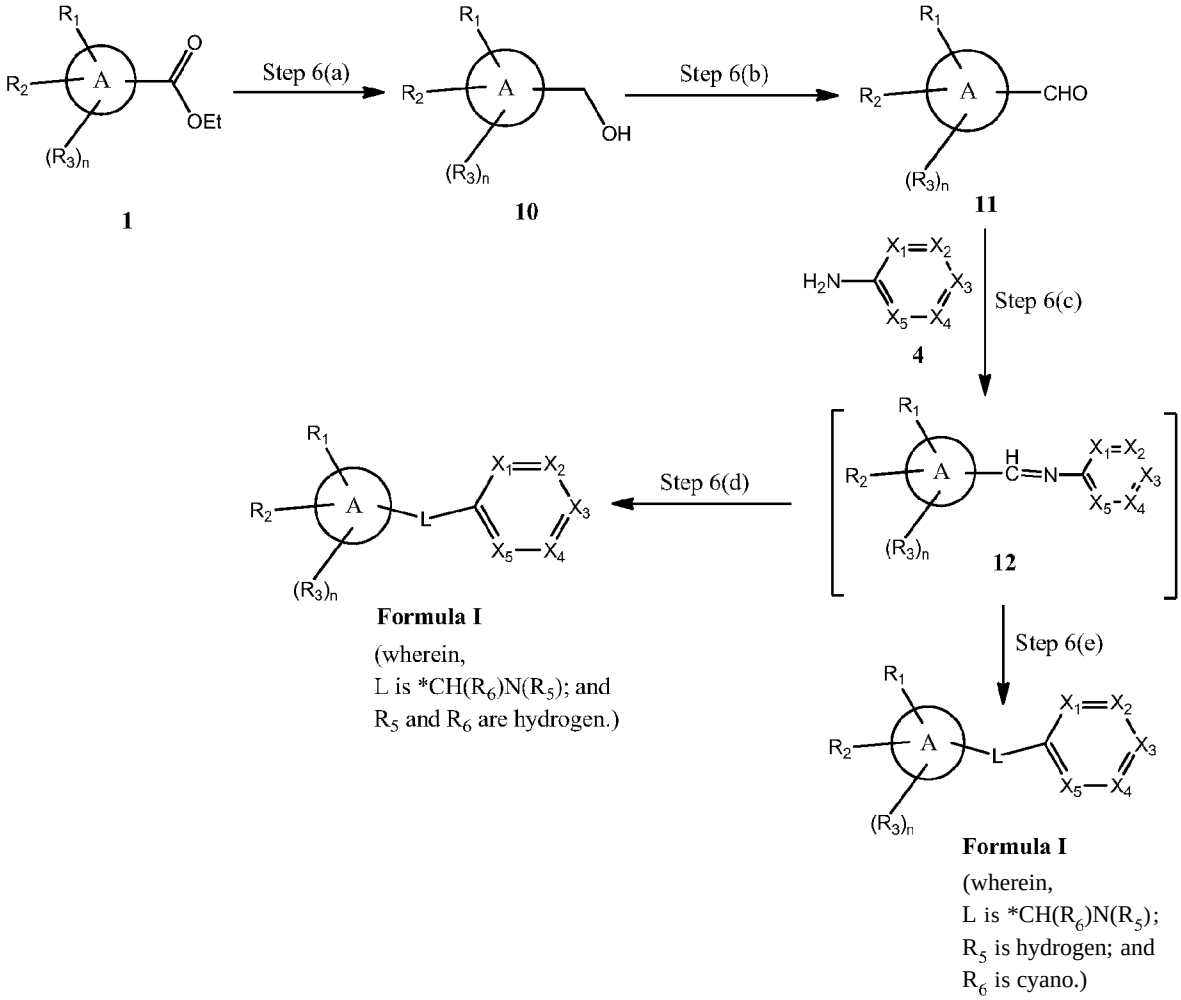
wherein, X_1, X_2, X3, X_4 and X5 are as defined in the first aspect;

in presence of a base such as xantphos and cesium carbonate and a catalyst namely tris(dibenzylidineacetone)dipd(0) in a solvent such as dioxane at a temperature ranging from 80 °C to 120 °C to obtain a compound of formula I, wherein A, R_1, R_2, R3, X-i, X_2, X_3, X_4, X_5 and n are as defined in the first aspect of the present invention, and L is $^*NR_4$; wherein * indicates the point of attachment to A; and R_4 is hydrogen.

Scheme 6 depicts a process for the preparation of the compounds of formula I wherein, A, R-i, R_2, R3, X-i, X_2, X3, X4, X5 and n are as defined in the first aspect of the present

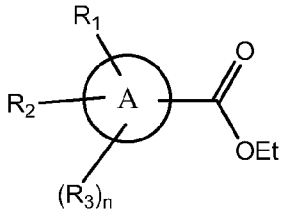
invention, and L is *CH(R_6)N(R_5); wherein * indicates the point of attachment to A; R_5 is hydrogen and R_6 is hydrogen or cyano.

Scheme 6



Step 6(a)

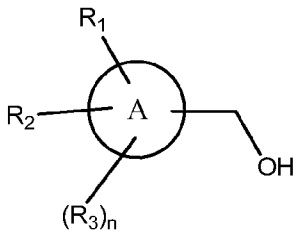
Compound 1 of the following formula;



1

wherein, A, **Ri, R_2,** R3 and n are as defined in the first aspect;

is reacted with lithium aluminium hydride (LAH) in a solvent such as tetrahydrofuran at a temperature ranging from -5 °C to 5 °C to obtain a compound 10 of the following formula;

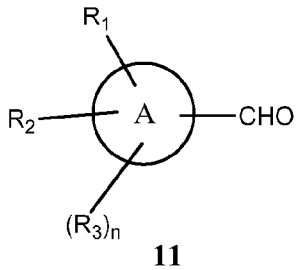


10

wherein, A, R_1, R_2, R3 and n are as defined in the first aspect.

Step 6(b)

The compound of formula 10 as obtained in step 6(a) is reacted with manganese dioxide in a solvent such as chloroform at a temperature ranging from 65 °C to 75 °C to obtain a compound 11 of the following formula;

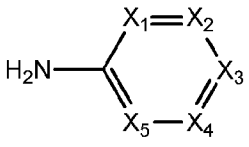


11

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect.

Step 6(c)

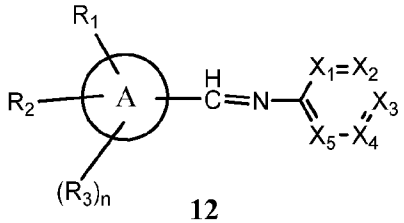
The compound of formula 11 as obtained in step 6(b) is reacted with compound 4 of the following formula;



4

wherein, $\mathbf{X_1}$, $\mathbf{X_2}$, X3, $\mathbf{X_4}$ and X5 are as defined in the first aspect;

and trifluoroacetic acid in a solvent such as tetrahydrofuran at a temperature ranging from 25 °C to 30 °C to obtain a compound 12 of the following formula;



12

wherein, A, R-i, R_2, R3,n, X-i, X_2, X3, X_4 and X_5 are as defined in the first aspect; which is telescoped to next step without isolation.

Step 6(d)

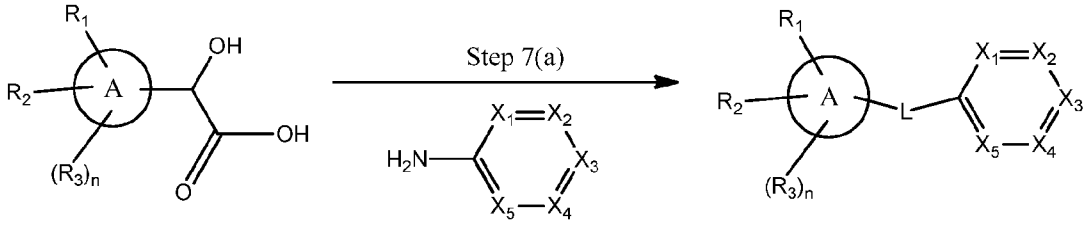
The compound of formula 12 as obtained in step 6(c) is reduced by using a reducing agent such as sodium borohydride or sodium cyanoborohydride in a solvent such as tetrahydrofuran at a temperature ranging from 0 °C to 25 °C to obtain a compound of formula I wherein, A, R-i, R_2, R3, X-i, X2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *CH(R_6)N(R_5); wherein * indicates the point of attachment to A; and R_5 and R_6 are hydrogen.

Step 6(e)

The compound of formula 12 as obtained in step 6(c) is reacted with trimethylsilanecarbonitrile and tetrabutylammonium difluorotriphenylsilicate in a solvent such as tetrahydrofuran at a temperature ranging from 0 °C to 25 °C to obtain a compound of formula I; wherein, A, R_1, R_2, R3, Xi, X2, X3, X4, X5 and n are as defined in the first aspect of the present invention, and L is *CH(R_6)N(R_5); wherein * indicates the point of attachment to A; R_5 is hydrogen and R_6 is cyano.

Scheme 7 depicts a process for the preparation of the compounds of formula I wherein, A, R-i, R_2, R_3, X-i, X_2, X3, X_4, X5 and n are as defined in the first aspect of the present invention, and L is *CH(R_6)-C(0)-N(R_5); wherein * indicates the point of attachment to A; R_5 is hydrogen and R_6 is hydroxy.

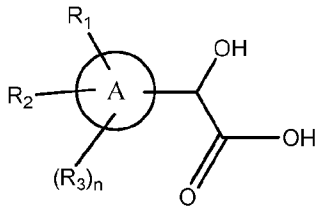
Scheme 7



13 4 Formula I

Step 7(a)

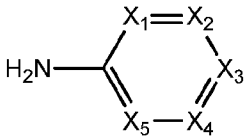
Compound 13 of the following formula;



13

wherein, A, R-i, R_2, R3 and n are as defined in the first aspect;

is reacted with the compound 4 of the following formula;



4

wherein, **X i, X_2,** X3, X_4 and X_5 are as defined in the first aspect;

in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) as a catalysts, in presence of a base such as triethylamine, in a solvent such as DMF (N, N-Dimethylformamide) at a temperature ranging from 20 °C to 35 °C to obtain a compound of formula I, wherein A, **R-i,** R_2, R3, **X i, X2,** X3, X4, X5 and n are as defined in the first aspect of the present invention, and L is *CH(R_6)-C(0)-N(R_5); wherein * indicates the point of attachment to A; R_5 is hydrogen and R_6 is hydroxy.

The compound of formula I, as obtained in Schemes 1, 2, 3, 4, 5, 6 and 7 can be optionally converted into its corresponding pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salts" as used herein refers to organic and inorganic salts of a compound of the invention, depending on the particular group (acidic or basic group) present in the compounds of formula I described herein. When compounds of the present invention contain relatively acidic groups, base addition salts can be obtained by contacting the compounds of formula I with a sufficient amount of an appropriate base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, magnesium, calcium, ammonium, zinc or organic base salt. Examples of pharmaceutically acceptable organic base addition salts include those derived from

organic bases such as lysine, arginine, choline, guanidine, diethanolamine, tromethamine, metformin and the like.

When compounds of the present invention contain relatively basic groups, acid addition salts can be obtained by contacting the compounds of formula I with a sufficient amount of an appropriate acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric or hydriodic acids and the like, as well as the salts derived from organic acids such as acetic, ascorbic, isobutyric, benzoic, citric, oxalic, succinic, suberic, fumaric, propionic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, lactic, maleic, malonic, mandelic, tartaric, methanesulfonic, ethanesulfonic, glucuronic or galacturonic acids and the like.

The pharmaceutically acceptable salts of the compounds of formula I can be synthesized from the compound of formula I, which contains a basic or an acidic group, by using conventional chemical methods. Generally, the salts are prepared by treating the compound of formula I which may be a free base or an acid with a suitable salt-forming inorganic or an organic acid or a base in a suitable solvent or dispersant or from another salt by cation or anion exchange. Suitable solvents that can be used for the preparation of pharmaceutically acceptable salts include, but are not limited to, ethyl acetate, diethyl ether, methanol, ethanol, acetone, tetrahydrofuran, dioxane or mixtures of these solvents.

The compounds of formula I can be regenerated from their corresponding salts by contacting the salt with an appropriate base or acid depending on the type of salt and isolating the parent compound in the conventional manner. The compound differs from the various salt forms in certain physical properties. An example of physical properties that may differ is solubility in polar solvents.

The present invention also encompasses within its scope the solvates of the compounds of formula I.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are suitable for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Various polymorphs of compounds of formula I can be prepared by crystallization of the compounds under different conditions. The different conditions are, for example, using different solvents or their mixtures for crystallization; crystallization at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs can also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs can be determined by IR (infra-red) spectroscopy, solid probe NMR (nuclear magnetic resonance) spectroscopy, differential scanning calorimetry, powder x-ray diffraction or such other techniques.

Those skilled in the art will recognize that stereocentres exist in compounds of formula I. Accordingly, the present invention includes all possible stereoisomers and geometric isomers of formula I and includes not only racemic compounds but also the optically active isomers as well. When a compound of formula I is desired as a single enantiomer, it can be obtained either by resolution of the final product or by stereospecific synthesis from either isomerically pure starting material or an appropriate intermediate. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art, for example, *Chiral reagents for asymmetric synthesis* by Leo A. Paquette; John Wiley & Sons Ltd (2003).

Additionally, in situations wherein tautomers of the compounds of formula I are possible, the present invention is intended to include all tautomeric forms of the compounds.

The present invention also encompasses within its scope prodrugs of the compound of formula I. Preferably, prodrugs are those compounds that are converted to their parent compound intracellular^, where the cellular converting location is the site of therapeutic action. The prodrugs of the compounds of the present invention are derivatives, particularly simple derivatives of the said compounds which upon administration to a

subject in need thereof undergoes conversion by metabolic or chemical processes to release the parent drug (e.g. the compound of formula I) *in vivo* from which the prodrug is derived. For instance, preferred produgs are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, e.g., alkyl esters, cycloalkyl esters, alkenyl esters, benzyl esters, mono- or di-substituted alkyl esters such as the pivaloyloxymethyl ester and the like conventionally used in the art (An introduction to Medicinal Chemistry, Graham. L. Patrick, Second Edition, Oxford University Press, pg 239-248; Prodrugs: Challenges and Rewards, Part 1 and Part 2, AAPS Press, Edited by Valentino J. Stella, Renald T. Borchardt, Michael J. Hagemon, Reza Oliyai, Hans Maag, Jefferson W. Tilley).

In one aspect, the present invention relates to a method for the treatment of a disease or disorder mediated by IL-17 or TNF-α, comprising administering to a subject in need thereof; a therapeutically effective amount of the compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof.

In another aspect, the present invention provides a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as IL-17 inhibitor.

In another aspect, the present invention provides a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as TNF-a inhibitor.

In yet another aspect of the present invention, there is provided a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or solvate thereof; for use in the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

In yet another aspect, the present invention provides use of a compound of formula I or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for the manufacture of a medicament for the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

In an embodiment of the present invention, the present invention encompasses within its scope all the diseases or disorders wherein IL-17 is implicated.

In another embodiment of the present invention, the present invention encompasses within its scope all the diseases or disorders wherein TNF-a is implicated.

In an embodiment of the present invention, the disease or disorder mediated by the pro-inflammatory cytokines IL-17 or TNF-a is selected from the group consisting of an autoimmune or inflammatory disease or disorder; and a metabolic disease or disorder.

In an embodiment of the present invention, the autoimmune disorder, inflammatory disorder or metabolic disorder can be selected from the group consisting of: inflammatory bowel disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, refractory rheumatoid arthritis, chronic non-rheumatoid arthritis, ankylosing spondylitis, osteoporosis/bone resorption, chronic graft-versus-host disease, acute graft-versus-host disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, asthma, bronchitis, epidermal hyperplasia, Crohn's disease, atherosclerosis, septic shock syndrome, coronary heart disease, vasculitis, ulcerative colitis, psoriasis, adult respiratory distress syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Type I diabetes, Graves' disease, Addison's disease, Raynaud's phenomenon, autoimmune hepatitis, psoriatic epidermal hyperplasia and delayed type hypersensitivity in skin disorders.

In an embodiment of the present invention, the metabolic disease or disorder is selected from the group consisting of obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, low adiponectin level, dyslipoproteinemia, impaired glucose tolerance, insulin resistance, increase in HbA1c (glycosylated haemoglobin) level, reduced metabolic activity and Type II diabetes.

The present invention also encompasses within its scope the use of a compound of formula I or its pharmaceutically acceptable salt or a solvate in combination with other therapeutically active agents; wherein the compound of formula I and the further therapeutic agent are administered either simultaneously or sequentially.

In another further aspect, the present invention relates to pharmaceutical composition(s) containing a therapeutically effective amount of at least one compound of formula I or its pharmaceutically acceptable salt or solvate thereof and a conventional pharmaceutically acceptable carrier. The present invention also relates to a process for the production of a pharmaceutical composition, which includes bringing at least one compound of formula I, into a suitable administration form using a pharmaceutically acceptable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries can be added.

The pharmaceutical composition(s) of the present invention can be administered orally, for example in the form of pills, tablets, coated tablets, capsules, granules or elixirs. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injectable sterile solutions or suspensions, or topically, for example in the form of ointments or creams or transdermal^, in the form of patches, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical composition(s) according to the invention is/are prepared in a manner known and familiar to one skilled in the art. Pharmaceutically acceptable inert inorganic and/or organic carriers and/or additives can be used in addition to the compound(s) of formula I, and/or its (their) physiologically tolerable salt(s). For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, gum arabica, magnesia or glucose, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological sodium chloride solution or alcohols, for example, ethanol, propanol or glycerol, sugar solutions, such as glucose solutions or mannitol solutions, or a mixture of the various solvents which have been mentioned.

The pharmaceutical composition(s) normally contain about 1 % to 99 %, for example, about 5 % to 70 %, or from about 10 % to about 30 % by weight of the compound of formula I or its pharmaceutically acceptable salt. The amount of the compound of formula I or its pharmaceutically acceptable salt in the pharmaceutical composition(s) can range from about 1 mg to about 1000 mg or from about 2.5 mg to about 500 mg or

from about 5 mg to about 250 mg or in any range falling within the broader range of 1 mg to 1000 mg or higher or lower that the specified range.

As is customary, the dosage range which are suitable in a specific case depend on the type of inflammatory disorder or autoimmune disorder to be treated and on the state of the respective condition or disorder. The selected dosage level can be readily determined by a skilled medical practitioner in the light of the relevant circumstances, including the condition (inflammatory disorder or autoimmune disorder) to be treated, the chosen route of administration including other factors such as age, weight and physical health and response of the individual patient, pharmacokinetics, severity of the disease and the like, factors known in the medical art. Actual dosage levels of the active ingredients i.e. the compounds of formula I in the pharmaceutical composition of this present invention can be varied so as to obtain an amount of the active ingredient, which is effective to achieve the desired therapeutic response for a particular patient (subject in need of the treatment), composition, and mode of administration without being toxic to the patient. Typically, the dose of the compounds of formula I or pharmaceutically acceptable salts thereof, which is to be administered, can cover a wide range. The dose to be administered daily is to be selected to suit the desired effect. A suitable dosage is about 0.01 mg/kg/day to about 200 mg/kg/day of the compound of formula I or its pharmaceutically acceptable salt, for example, about 0.1 mg/kg/day to 100 mg/kg/day of a compound of formula I or its pharmaceutically acceptable salt. If required, higher or lower daily doses can also be administered.

In addition to the compound of the formula I or its pharmaceutically acceptable salt and carrier substances, the pharmaceutical compositions can contain additives such as, for example, fillers, antioxidants, dispersants, emulsifiers, defoamers, flavors, preservatives, solubilizers or colorants. Pharmaceutical compositions can also contain two or more compounds of formula I or their physiologically tolerable salts. Furthermore, in addition to at least one compound of formula I or its physiologically tolerable salt, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

The present invention also encompasses within its scope use of a compound of formula I or its pharmaceutically acceptable salt or a solvate in combination with other therapeutically active agents. The compound of formula I or its pharmaceutically

acceptable salt, can be administered either simultaneously or sequentially in combination with the further therapeutically active agents. For instance, a pharmaceutical composition including a compound of formula I or a pharmaceutically acceptable salt can be administered to a mammal, in particular a human, with any other pharmaceutically active compounds, in mixtures with one another or in the form of pharmaceutical compositions.

The therapeutically active agents that can be used in combination with one or more compounds of formula I or its pharmaceutically acceptable salt can be selected from: monoclonal antibodies, non-steroidal anti-inflammatory drugs (NSAIDs) such as COX inhibitors or PDE4 inhibitors. Examples of monoclonal antibodies include, but not limited to, rituximab, etanercept, infliximab, adalimumab, natalizumab and vedolizumab. Examples of NSAIDs include, but not limited to, diclofenac, indomethacin, sulindac, mefenamic acid, piroxicam, ibuprofen, naproxen, ketoprofen, phenylbutazone, aspirin, diflunisal, nimesulide, celecoxib, valdecoxib, etorcoxib and meloxicam. Examples of PDE4 inhibitors include, but not limited to, rolipram, ibudilast, luteolin and roflumilast.
It is understood that modifications that do not substantially affect the activity of the various aspects of this invention are included. Accordingly, the following examples are intended to illustrate but not to limit the present invention.

Abbreviations, which may be used in the description of the schemes and in the examples that follow, include:

CH_3CN	:	Acetonitrile
DCM	:	Dichloromethane
DMF	:	N, N-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
EDC	:	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
FBS	:	Fetal bovine serum
g / gm	:	Gram
h	:	Hour(s)
^3H	:	Tritium
H_2O	:	Water
HCl	:	Hydrochloric acid
HOBt	:	Hydroxybenzotriazole

hPBMC	:	Human peripheral blood mononuclear cells
IL-17	:	Interleukin-17
LAH	:	Lithium aluminium hydride
MEM EBS	:	Minimum essential medium with Earle's balance salt solution
mmol	:	Millimolar
mL	:	Millilitre
NaOH	:	Sodium hydroxide
Na_2SO_4	:	Sodium sulphate
$NaHCO_3$	:	Sodium bicarbonate
PBS	:	Phosphate buffered saline
PMA	:	Phorpbol myristate acetate
PTSA	:	p-Toluenesulfonic acid
RT	:	Room temperature (25-30 °C)
REG3A	:	Regenerating islet-derived protein 3-alpha
RPMI	:	Roswell Park Memorial Institute Medium
THF	:	Tetrahydrofuran
TEA	:	Triethylamine
Th17	:	T-helper cell - 17
TNF-α	:	Tumor necrosis factor - alpha
t-BuOH	:	tert-Butyl alcohol
Vol	:	Volume
Xantphos	:	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Examples

Example 1:

1-(5-Methyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)-3-(2-(trifluoromethyl)-1H-benzo[d]imidazol-6-yl)urea

Step 1) 1-(4-(trifluoromethyl)phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid (intermediate 1)

To the stirred solution of ethyl 1-(4-(trifluoromethyl)phenyl)-5-methyl-1H-pyrazole-4-carboxylate (12.75 mmol) in THF: H_2O (1:1 vol, 20 mL) was added NaOH (25.50 mmol) and the resulting mixture was heated to reflux for 4 h. The reaction mixture was cooled

to a room temperature and THF was removed. The aqueous layer was separated, washed with ethyl acetate and acidified with dilute HCl to afford the title compound.

Step 2): Azido(1-(4-(trifluoromethyl)phenyl)-5-methyl-1H-pyrazol-4-yl) methanone (intermediate 2)

Method A:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (3.90 mmol) in acetone (10 mL) in an ice bath, was added trichloroacetonitrile (7.81 mmol), triphenyl phosphine (7.81 mmol) and sodium azide (4.68 mmol). The reaction mixture was stirred for 2 h at room temperature. On completion of reaction, the reaction was quenched with water (10 mL). The reaction mixture was extracted with ethyl acetate (25 mL). The organic layer was separated, washed with brine (10 mL), dried with Na_2SO_4, concentrated and purified using column chromatography (silica gel, ethyl acetate and petroleum ether gradient) to afford the title compound.

Method B:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (2.23 mmol) in dry acetone (5 mL) was added sodium azide (4.47 mmol), triethylamine (4.47 mmol) at 0 ^{0}C. Triphosgene (1.11 mmol) dissolved in dry acetone (5 mL) was added to the resulting reaction mixture drop wise over a period of 15 minutes. The resulting reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the white precipitate was filtered out, and washed with acetone. The resulting organic layer was evaporated to afford a crude product, which was further purified using column chromatography (silica gel, ethyl acetate and petroleum ether gradient) to afford the title compound.

Step 3): 1-(5-Methyl-1-(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)-3-(2-(trifluoro methyl)-1H-benzo[d]imidazol-6-yl)urea (final compound)

The compound obtained in step 2 [intermediate 2] (0.339 mmol) and 2-(trifluoromethyl)-3H-benzo[d]imidazol-5-amine (0.339 mmol) in toluene (3 mL) was refluxed for 5 h. The reaction mixture was allowed to cool to the room temperature. The precipitated compound was filtered, washed with petroleum ether and cold dichloromethane, and dried to afford the title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.35 (s, 3H), 7.21 (br s, 1H), 7.62 (m, 1H), 7.79 (d, J= 8.1 Hz, 2H), 7.89 (s, 3H), 8.05 (d, J= 11.7 Hz, 2H), 8.86 (s, 1H), 13.68 (br s, 1H); MS: m/z 469.0 $(M+H)^+$.

Example 2:

1-(4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl)-3-cyanophenyl)-3-(5-methyl-1-(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea

The compound of example 2 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazole-4-carbonyl azide with 5-amino-2-(4-(4-chlorophenyl)-4-hydroxypiperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.68-1 .72 (m, 2H), 1.98-2.00 (m, 2H), 2.29 (s, 3H), 3.22-3.40 (m, 2H), 3.89-3.93 (m, 2H), 7.36 (d, J= 7.2 Hz, 2H), 7.50 (d, J= 8.1 Hz, 2H), 7.79-7.91 (m, 5H), 8.20(s, 1H), 8.27 (s, 1H), 8.44 (s, 1H), 8.74 (s, 1H); MS: m/z 595.8 $(M+H)^+$.

Example 3:

1-(3-Cyano-4-(4-(2-hydroxyethyl)piperidin-1-yl)phenyl)-3-(5-methyl-1-(4-(trifluoro methyl)phenyl)-1H-pyrazol-4-yl)urea

The compound of example 3 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazole-4-carbonyl azide with 5-amino-2-(4-(2-hydroxyethyl)piperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.29-1 .32 (m, 2H), 1.41 - 1 .43 (m, 2H), 1.75-1 .79 (m, 2H), 2.32 (s, 3H), 2.68 (t, J= 11.1 Hz, 2H), 3.46-3.48 (m, 3H), 4.38 (t, J= 4.8 Hz, 1H), 7.1 3 (d, J= 8.7 Hz, 1H), 7.54-7.57 (m, 1H), 7.78-7.90 (m, 6H), 8.14 (s, 1H), 8.74 (s, 1H); MS: m/z 5 13.1 (M+H).

Example 4:

1-(5-Methyl-1 -phenyl-1 H-pyrazol-4-yl)-3-(naphthalen-1 -yl)urea

The compound of example 4 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1 -phenyl-1 H-pyrazole-4-carbonyl azide with naphthalen-1 -amine in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 2.32 (s, 3H), 7.42-7.63 (m, 10H), 7.85 (s, 1H), 7.93 (d, J= 7.8 Hz, 1H), 8.04 (d, J= 7.5 Hz, 1H), 8.1 3 (d, J= 7.8 Hz, 1H), 8.40 (s, 1H), 8.78 (s, 1H); MS: m/z 343.0 (M+H).

Example 5:

1-(1-(4-chlorophenyl)-5-methyl-1H-pyrazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1-yl) phenyl) urea

The compound of example 5 was prepared analogous to the procedure described in example 1 by reaction of 1-(4-chlorophenyl)-5-methyl-1 H-pyrazole-4-carbonyl azide with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.54-1 .58 (m, 2H), 1.88-1 .92 (m, 2H), 2.08 (br s, 1H), 2.20-2.30 (m, 6H), 2.73 (t, J= 11.0 Hz, 2H), 3.39-3.42 (m, 4H), 3.58 (br s, 4H), 7.1 2 (d, J= 8.7 Hz, 1H), 7.58 (br s, 4H), 7.78 (br s, 1H), 7.84 (br s, 1H), 8.1 0 (br s, 1H), 8.74 (s, 1H) ; MS: m/z 520.3 $(M)^+$.

Example 6:

1-(3-cyano-4-(4-morpholinopiperidin-1-yl) phenyl)-3-(5-methyl-1-(4-(trifluoro methyl) phenyl)-1 H-pyrazol-4-yl) urea

The compound of example 6 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazole-4-carbonyl azide with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.51 - 1 .62 (m, 2H), 1.88-1 .92 (m, 2H), 2.25-2.28 (m, 3H), 2.33 (s, 3H), 2.73 (t, 2H, *J* = 11.4 Hz), 3.33-3.42 (m, 4H), 3.58 (br s, 4H), 7.1 3 (d, 1H, *J* = 9.0 Hz), 7.57 (d, 1H, *J* = 7.5 Hz), 7.79-7.91 (m, 6H), 8.1 5 (s, 1H), 8.76 (s, 1H); MS: m/z 554.2 $(M+H)^+$.

Example 7:

1-(3-cyano-4-(piperazin-1-yl) phenyl)-3-(5-methyl-1-(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea

The compound of example 7 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazole-4-carbonyl azide with 5-amino-2-(piperazin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.35 (s, 3H), 2.49 (br s, 4H), 3.84 (br s, 4H), 7.22 (d, 1H, *J* = 8.7 Hz), 7.61 (d, 1H, *J* = 8.7 Hz), 7.80 (d, 2H, *J* = 8.1 Hz), 7.89 (d, 4H, *J* = 8.1 Hz), 8.63 (s, 1H), 9.08 (s, 1H), 9.48 (s, 1H); MS: m/z 470.1 $(M+H)^+$.

Example 8:

1-(5-chloro-6-morpholinopyridin-3-yl)-3-(5-methyl-1-(4-(trifluoromethyl) phenyl)-1H-pyrazol-4-yl) urea

The compound of example 8 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-carbonyl azide with 5-chloro-6-morpholinopyridin-3-amine in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 2.33 (s, 3H), 3.14 (br s, 4H), 3.73 (br s, 4H), 7.80 (d, 2H, *J* = 8.4 Hz), 7.85 (br s, 1H), 7.89 (d, 2H, *J* = 8.1 Hz), 8.11 (s, 1H), 8.25 (br s, 2H), 8.83 (s, 1H); MS: m/z 481.2 $(M+H)^+$.

Example 9:

1-(3-cyano-4-(4-(4-fluoro-3-(trifluoromethyl) benzoyl) piperazin-1-yl) phenyl)-3-(5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazol-4-yl)urea

The compound of example 9 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-carbonyl azide with 5-amino-2-(4-(4-fluoro-3-(trifluoromethyl)benzoyl)piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.29 (s, 3H), 3.07 (br s, 4H), 3.60 (br s, 4H), 7.16 (d, 1H, *J* = 9.0 Hz), 7.60-7.65 (m, 2H), 7.78-7.88 (m, 8H), 8.20 (s, 1H), 8.84 (s, 1H); MS: m/z 659.8 $(M)^+$.

Example 10:

1-(3-Cyano-4-(4-morpholinopiperidin-1-yl) phenyl)-1-methyl-3-(5-methyl-1-(4-(trifluoromethyl) phenyl)-1H-pyrazol-4-yl) urea

The compound of example 10 was prepared analogous to the procedure described in example 1 by reaction of 5-methyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-4-carbonyl azide with 5-(methylamino)-2-(4-morpholinopiperidin-1-yl)benzonitrile in step 3.

Example 11:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)urea

Step 1): 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carboxylic acid (intermediate 1)

To the stirred solution of ethyl 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carboxylate (12.75 mmol) in THF: H_20 (1:1 vol, 20 mL) was added NaOH (25.50 mmol) and the resulting mixture was heated to reflux for 4 h. The reaction mixture was cooled to a room temperature and THF was removed. The aqueous layer was separated, washed with ethyl acetate and acidified with dilute HCl to afford the title compound.

Step 2): 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide (intermediate 2)

Method A:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (3.90 mmol) in acetone (10 mL) in an ice bath, was added trichloroacetonitrile (7.81 mmol), triphenyl phosphine (7.81 mmol) and sodium azide (4.68 mmol). The reaction mixture was stirred for 2 h at room temperature. On completion of reaction, the reaction was quenched with water (10 mL). The reaction mixture was extracted with ethyl acetate (25 mL). The organic layer was separated, washed with brine (10 mL), dried with Na_2SO_4, concentrated and purified using column chromatography (silica gel, ethyl acetate and petroleum ether gradient) to afford the title compound.

Method B:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (2.23 mmol) in dry acetone (5 mL) was added sodium azide (4.47 mmol), triethylamine (4.47 mmol) at 0 ^{0}C. Triphosgene (1.11 mmol) dissolved in dry acetone (5 mL) was added to the resulting reaction mixture drop wise over a period of 15 minutes. The resulting reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the white precipitate was filtered out, and washed with acetone. The resulting organic layer was evaporated to afford a crude product, which was further purified using column chromatography (silica gel, ethyl acetate petroleum and ether gradient) to afford the title compound.

Step 3): 1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin -1-yl)phenyl)urea (final compound)

The compound obtained in step 2 [intermediate 2] (0.339 mmol) and 2-(trifluoromethyl)-3H-benzo[d]imidazol-5-amine (0.339 mmol) in toluene (3 mL) was refluxed for 5 h. The reaction mixture was allowed to cool to the room temperature. The precipitated compound was filtered, washed with petroleum ether and cold dichloromethane, and dried to afford the title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.64(**m**, 2H) 2.00 (m, 2H), 2.79-2.72(m, 2H), 3.43-3.33 (m, 2H), 3.64 (s, 4H), 7.17 (d, J= 8.7 Hz, 1H), 7.59 (d, J= 8.7 Hz, 1H), 7.67 (d, J= 8.4 Hz, 2H), 7.90 (s, 1H), 8.00 (d, J= 8.4 Hz, 2H), 8.63 (s, 1H), 8.96 (s, 1H), 9.59 (s, 1H); MS (M+H) 507.3.

Example 12:

1-(4-([1 ,4'-bipiperidin]-1 '-yl)-3-cyanophenyl)-3-(1 -(4-chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)urea

The compound of example 12 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1 H-1 ,2,3-triazole-4-carbonyl azide with 2-([1 ,4'-bipiperidin]-1 '-yl)-5-aminobenzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.42-1 .73 (m, 4H), 2.1 5-2.27 (m, 4H), 2.79-3.49 (m, 11H), 6.81 (m, 1H), 7.20 (d, J = 8.7 Hz, 1H), 7.59-7.67 (m, 2H), 7.91 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 8.62 (s, 1H), 8.97 (s, 1H), 8.98-9.1 2 (m, 1H), 9.60 (s, 1H); MS: m/z 505.2 $(M+H)^+$.

Example 13:

2-(1-(4-(3-(1 -(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-2-cyanophenyl) piperidin-4-yl)ethyl diethyl phosphate

The compound of example 13 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazole-4-carbonyl azide with 2-(1 -(4-amino-2-cyanophenyl)piperidin-4-yl)ethyl diethyl phosphate in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.25 (t, J = 7.2 Hz, 6H), 1.32 (s, 9H), 1.53-1 .63 (m, 4H), 1.82 (d, J = 11.4 Hz, 2H), 2.71 (t, J = 11.1 Hz, 2H), 3.35-3.39 (m, 3H), 4.01 (qn, J = 7.2 Hz, 6H), 7.1 6 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 3H), 7.82 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H), 8.52 (s, 1H), 8.86 (s, 1H), 9.51 (s, 1H); MS: m/z 624.0 $(M+H)^+$.

Example 14:

1-(1 -(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(2-methoxyethyl) piperidin-1-yl)phenyl)urea

The compound of example 14 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(2-methoxyethyl)piperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.32 (s, 9H), 1.60-1 .63 (m, 2H), 1.90-1 .95 (m, 2H), 2.87 (t, J = 9.3 Hz, 2H), 3.26-3.56 (m, 10H), 7.1 5 (d, J = 8.7 Hz, 1H), 7.58 (d, J = 9.0 Hz, 3H), 7.83 (d, J = 8.4 Hz, 2H), 7.88 (s, 1H), 8.52 (s, 1H), 8.87 (s, 1H), 9.52 (s, 1H); MS: m/z 502.2 $(M+H)^+$.

Example 15:

1-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)-3-(4-(4-morpholinopiperidin-1-yl)-2-(trifluoromethyl)phenyl)urea

The compound of example 15 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 4-(4-morpholinopiperidin-1-yl)-2-(trifluoromethyl)aniline in step 3.

^{1}H NMR (DMSO-d6): δ 1.33 (s, 9H), 1.49 (q, J = 6.3 Hz, 2H), 1.88 **(d,** J = 7.2 Hz, 2H), 2.23-2.29 (m, 1H), 2.47 (s, 4H), 2.72 (t, J= 7.2 Hz, 2H), 3.57 (s, 4H), 3.77 (d, J = 7.2 Hz, 2H), 7.11 (s, 1H), 7.23 (d, J= 5.1 Hz, 1H), 7.59 (d, J = 4.4 Hz, 2H), 7.61 (s, 1H), 7.82 (d, J = 5.1 Hz, 2H), 8.04 (s, 1H), 8.43 (s, 1H), 9.86 (s, 1H); MS: m/z 572.6 $(M+H)^+$.

Example 16:

1-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-3-(1-(4-morpholinophenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 16 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-morpholinophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-morpholinopiperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.56-1.58 (m, 2H), 1.89-1.91 (m, 2H), 2.20-2.28 (m, 1H), 2.45 (s, 4H), 2.75 (t, J = 6.9 Hz, 2H), 3.20 (s, 4H), 3.43 (d, J = 6.6 Hz, 2H), 3.59 (s, 4H), 3.76 (s, 4H), 7.11 (d, J =5.1 Hz, 2H), 7.15 (d, J = 5.4 Hz, 1H), 7.57 (d, J = 5.1 Hz, 1H), 7.75 (d, J = 5.1 Hz, 2H), 7.88 (s, 1H), 8.43 (s, 1H), 8.86 (s, 1H), 9.45 (s, 1H); MS: m/z 558.4 $(M+H)^+$.

Example 17:

1-(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)-3-(1-(4-isopropylphenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 17 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-isopropylphenyl)-1H-1,2,3-triazole-4-carbonyl azide with 2-(4-aminophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.25 (d, J = 4.2 Hz, 6H), 2.97-3.00 (m, 1H), 7.46 (d, J = 4.8 Hz, 2H), 7.61 (s, 4H), 7.85 (d, J = 4.8 Hz, 2H), 8.53 (s, 1H), 8.59 (s, 1H), 9.03 (s, 1H), 9.47 (s, 1H); MS: m/z 488.1 $(M+H)^+$.

Example 18:

1-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1-yl)phenyl)urea

The compound of example 18 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-morpholinopiperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.21 (m, 2H), 1.50-1.53 (m, 2H), 2.16-2.20 (m, 4H), 2.69-2.76 (m, 2H), 3.37 (m, 3H), 3.56-3.57 (m, 7H), 7.14 (d, J= 8.7 Hz, 1H), 7.48-7.69 (m, 5H), 8.62 (s, 1H), 8.96 (s, 1H); MS: m/z 521.0 $(M+H)^+$.

Example 19:

3-(3-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)ureido)-N-(4-hydroxy-3-methoxy benzyl)benzamide

The compound of example 19 was prepared analogous to the procedure described in example 11 by reaction of 1 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 3-amino-N-(4-hydroxy-3-methoxybenzyl)benzamide in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.74 (s, 3H), 4.36 (d, J= 5.7 Hz, 2H), 6.71 (s, 2H), 6.90 (s, 1H), 7.37-7.40 (m, 1H), 7.48-7.50 (m, 1H), 7.61-7.66 (m, 3H), 7.96-8.01 (m, 3H), 8.64 (s, 1H), 8.84 (s, 1H), 8.91 (br s, 2H), 9.50 (s, 1H); MS: m/z 490.7 (M-H).

Example 20:

4-(1-(2-cyano-4-(3-(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)ureido) phenyl)piperidin-4-yl)butanoic acid

The compound of example 20 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 4-(1-(4-amino-2-cyanophenyl)piperidin-4-yl)butanoic acid in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.22-1.28 (m, 4H), 1.54-1.50 (m, 2H), 1.75-1.79 (m, 2H), 2.19-2.23 (m, 2H), 2.70 (t, J= 10.8 Hz, 2H), 3.26 (m, 3H), 7.14 (d, J= 9.00 Hz, 1H), 7.57 (d, J= 7.2 Hz, 1H), 7.88 (s, 1H), 7.96 (d, J= 8.4 Hz, 2H), 8.22 (d, J= 8.1 Hz, 2H), 8.74 (s, 1H), 8.90 (s, 1H), 9.61 (s, 1H), 12.03 (br s, 1H); MS: m/z 542.0 (M+H).

Example 21:

1-(3-cyano-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-3-(1-(4-(trifluoromethyl) phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 21 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(pyrimidin-2-yl)piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 3.19-3.24 (m, 4H), 3.91 (m, 4H), 6.74 (t, J= 4.5 Hz, 1H), 7.21 (d, J= 9.0 Hz, 1H), 7.62 (d, J= 6.9 Hz, 1H),7.97 (d, J= 8.4 Hz, 3H), 8.22 (d, J= 8.4 Hz, 2H), 8.40 (d, J= 4.5 Hz, 2H), 8.76 (s, 1H), 8.95 (s, 1H), 9.65 (s, 1H); MS: m/z 535.1 (M+H).

Example 22:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(piperazin-1-yl)phenyl) urea

The compound of example 22 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 3.27 (m, 8H), 7.25 (d, J= 8.7 Hz, 1H), 7.65 (d, J= 8.7 Hz, 3H), 7.94-7.99 (m, 3H), 8.61 (s, 1H), 8.89 (s, 1H), 9.22 (s, 1H), 9.67 (s, 1H); MS: m/z 423.1 (M+H).

Example 23:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(5-(4-morpholinopiperidin-1-yl) pyridin-2-yl)urea

The compound of example 23 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-(4-morpholinopiperidin-1-yl)pyridin-2-amine in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.17(bs, 2H), 1.34(m, 2H), 1.81 (d, J=1 1.4Hz, 2H), 2.46(bs, 3H), 2.74(t, J=1 2.0 Hz, 2H), 3.55(d, J=4.2Hz, 4H), 4.18(d, J=1 2.9 Hz, 2H), 6.81 (d, J=9.0 Hz, 1H), 7.63(d, J=8.7 Hz, 2H), 7.67(d, J=2.7 Hz, 1H), 7.96(d, J=8.7Hz, 2H), 8.16(d, J=2.4Hz, 1H), 8.48(s, 1H), 8.57(s, 1H), 9.40 (s, 1H); MS: m/z 483 (M+H).

Example 24:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(4-cyano-5-(4-morpholinopiperidin -1-yl)pyridin-2-yl)urea

The compound of example 24 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 2-amino-5-(4-morpholinopiperidin-1-yl)isonicotinonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.48(q, J=11.7 Hz, 2H), 1.86(d, J=11.4Hz, 2H), 2.38(d, J=11.4Hz, 1H), 2.95(t, J= 12.3Hz, 2H), 3.57(s, 4H), 4.04(d, J=12.6Hz, 2H), 7.63(d, J=8.7Hz, 2H), 7.97(d, J=8.7Hz, 2H), 8.20(d, J=2.7Hz, 1H), 8.44(d, J=2.4Hz, 1H), 8.61 (s, 1H), 8.86(s, 1H), 9.70 (bs, 1H); MS: m/z 508 (M+H).

Example 25:

1-(6-(4-morpholinopiperidin-1-yl)pyridin-3-yl)-3-(1-(3-(trifluoromethyl)pheny^)-1H-1,2,3-triazol-4-yl)urea

The compound of example 25 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 6-(4-morpholinopiperidin-1-yl)pyridin-3-amine in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.45 (s, 1H), 8.78 (s, 1H), 8.50 (s, 1H), 8.34 (m, 2H), 8.18 (d, J=2.4Hz, 1H), 7.84 (m, 2H), 7.69 (dd, J=2.7 & 6.3 Hz, 1H), 6.85 (d, J= 9.0 Hz, 1H), 4.22 (d, J=12.6 Hz, 2H), 3.56 (m, 4H), 2.78 (t, J=12.0 Hz, 2H), 2.46 (m, 4H), 2.34 (m, 1H), 1.84 (d, J= Hz, 2H), 1.37 (m, 2H); MS: m/z 517 (M+1).

Example 26:

1-(5-(3-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)ureido)pyridin-2-yl)piperidine-4-carboxylic acid

The compound of example 26 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 1-(5-aminopyridin-2-yl)piperidine-4-carboxylic acid in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 12.25 (bs, 1H), 9.72 (s, 1H), 9.21 (s, 1H), 8.51 (s, 1H), 8.28 (s, 1H), 7.84 (d, J=8.1 Hz, 3H), 7.58 (d, J=8.4 Hz, 2H), 7.26 (s, 1H), 4.11 (d, J=12.9 Hz, 2H), 3.18 (m, 2H), 2.57 (m, 1H), 1.94 (d, J=11.7 Hz, 2H), 1.62 (m, 2H), 1.31 (s, 9H); MS: m/z 464 (M+1).

Example 27:

1-(6-(4-(pyrimidin-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 27 was prepared analogous to the procedure described in example 11 by reaction of 1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 6-(4-(pyrimidin-2-yl)piperazin-1-yl)-5-(trifluoromethyl)pyridin-3-amine in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.79 (s, 1H), 9.17 (s, 1H), 8.88 (s, 1H), 8.55 (s, 1H), 8.47 (d, J=2.4 Hz, 1H), 8.38 (m, 4H), 7.83 (m, 2H), 6.66 (t, J=4.8 Hz, 1H), 3.85 (m, 4H), 3.18 (m, 4H); MS: m/z 579 (M+1).

Example 28:

1-(5-chloro-6-(4-morpholinopiperidin-1-yl)pyridin-3-yl)-3-(1-(4-chlorophenyl)-1 H-1,2,3-triazol-4-yl)urea

The compound of example 28 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1 H-1,2,3-triazole-4-carbonyl azide with 5-chloro-6-(4-morpholinopiperidin-1 -yl)pyridin-3-amine in step 3..

^{1}H NMR (DMSO-de, 300 MHz): δ 9.63 (s, 1H), 8.89 (s, 1H), 8.63 (s, 1H), 8.23 (s, 1H), 8.08 (s, 1H), 8.00 (d, J=8.4 Hz, 2H), 7.66 (d, J=8.1 Hz, 2H), 3.57 (m, 6H), 3.38 (m, 2H), 2.75 (m, 2H), 2.29 (m, 1H), 1.87 (m, 2H), 1.54 (m, 2H), **1.11** (m, 2H); MS: m/z 517 (M+1).

Example 29:

1-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)-3-(5-methyl-6-(4-morpholino piperidin-1-yl)pyridin-3-yl)urea

The compound of example 29 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1 H-1,2,3-triazole-4-carbonyl azide with 5-methyl-6-(4-morpholinopiperidin-1 -yl)pyridin-3-amine in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.45 (s, 1H), 8.66 (s, 1H), 8.51 (s, 1H), 8.16 (s, 1H), 7.85 (d, J=4.8 Hz, 2H), 7.70 (s, 1H), 7.59 **(d,** J=4.8 Hz, 2H), 3.58 (m, 6H), 3.32 (m, 2H), 2.68 (t, J=7.2 Hz, 2H), 2.29 (s, 3H), 1.87 (m, 2H), 1.54 (m, 2H), 1.33 (s, 9H); MS: m/z 519 (M+1).

Example 30:

1-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)-3-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1-yl)pyridin-3-yl)urea

The compound of example 30 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1 H-1,2,3-triazole-4-carbonyl azide with 5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1 -yl)pyridin-3-amine in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.47 (s, 1H), 8.71 (s, 1H), 8.39 (d, J=4.5 Hz, 3H), 8.19 (d, J=2.1 Hz, 1H), 7.85 (d, J=8.7 Hz, 2H), 7.76 (d, J=2.1 Hz, 1H), 7.59 **(d,** J=8.7 Hz,

2H), 6.66 (t, J=4.5 Hz, 1H), 3.86 (m, 4H), 3.04 (m, 4H), 2.30 (s, 3H), 1.32 (s, 9H); MS: m/z 513 (M+1).

Example 31:

1-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)-3-(5-cyano-6-(4-(pyrimidin-2-yl) piperazin-1-yl)pyridin-3-yl)urea

The compound of example 31 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(pyrimidin-2-yl)piperazin-1-yl)nicotinonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 9.45 (s, 1H), 8.92 (s, 1H), 8.53 (s, 1H), 8.50 (d, J=2.7 Hz, 1H), 8.40 (d, J=4.5 Hz, 2H), 8.28 (d, J=2.7 Hz, 1H), 7.85 (d, J=8.7 Hz, 2H), 7.60 (d, J=8.7 Hz, 2H), 6.69 (t, J=4.8 Hz, 1H), 3.90 (m, 4H), 3.57 (m, 4H), 1.32 (s, 9H); MS: m/z 524 (M+1).

Example 32:

1-(6-(4-cyano-4-phenylpiperidin-1-yl)pyridin-3-yl)-3-(1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 32 was prepared analogous to the procedure described in example 11 by reaction of 1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 1-(5-aminopyridin-2-yl)-4-phenylpiperidine-4-carbonitrile in step 3.

^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 9.49 (s, 1H), 8.78 (s, 1H), 8.60 (s, 1H), 8.32 (m, 2H), 8.25 (d, J=2.7 Hz, 1H), 7.85 (t, J=6.3 Hz, 2H), 7.76 (dd, J=2.4 Hz, 1H), 7.56 (d, J=7.5 Hz, 2H), 7.47 (t, J=7.2 Hz, 2H), 7.39 (m, 1H), 6.98 (d, J=9.0 Hz, 1H), 4.40 (d, J=13.8 Hz, 2H), 3.09 (t, J=12.3 Hz, 2H), 2.24 (d, J=13.2 Hz, 2H), 2.08 (t, J=12.3 Hz, 2H); MS: m/z 533 (M+1).

Example 33:

1-(3-cyano-4-(piperidin-1-yl)phenyl)-3-(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 33 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(piperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.53 (s, 2H), 1.67 (s, 4H), 3.02 (s, 4H), 7.15 (d, J=9.0 Hz, 1H), 7.59 (m, 1H), 7.88 (s, 1H), 7.97 (d, J=8.4 Hz, 2H), 8.22 (d, J=8.1 Hz, 2H), 8.75 (s, 1H), 8.88 (s, 1H), 9.61 (s, 1H); MS: m/z 454.2 (M-1).

Example 34:

1-(3-cyano-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)-3-(1-(4-(trifluoro methyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 34 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(2-oxa-6-azaspiro[3.3]heptan-6-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 4.23 (s, 4H), 4.72 (s, 4H), 6.61 (d, J=9.0 Hz, 1H), 7.47 (d, J=9.0 Hz, 1H), 7.70 (s, 1H), 7.97 (s, 1H), 7.97 (d, J=8.4 Hz, 1H), 8.22 (d, J=8.1 Hz, 2H), 8.72(d, J=12.3 Hz, 2H), 9.53 (s,1H); MS: m/z 470.0 (M+1).

Example 35:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(cyclopropylmethyl)pipera; 1-yl)phenyl)urea

The compound of example 35 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(cyclopropylmethyl)piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.37 (s, 2H), 0.66 (s, 2H), 0.85 (m, 1H), 1.08 (m, 2H), 3.14 (s, 4H), 3.50-3.68 (m, 4H), 7.27 (d, J=8.7 Hz, 1H), 7.67 (d, J=8.7 Hz, 3H), 8.00 (m, 3H), 8.62 (s, 1H), 9.00 (s, 1H), 9.62 (s, 1H); MS: m/z 475.9 (M-1).

Example 36:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-methoxypiperidin-1-yl)phenyl)urea

The compound of example 36 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-methoxypiperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.61-1.63 (m, 2H), 1.97 (s, 2H), 2.87-2.90 (m, 2H), 3.24-3.26 (m, 2H), 3.28 (s, 3H), 3.38 (m, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.57 (d, J = 5.4 Hz, 1H), 7.66(d, J = 5.1 Hz, 2H),7.88 (s, 1H), 8.00 (d, J = 5.1 Hz, 2H), 8.63 (s, 1H), 8.88 (s, 1H), 9.56 (s, 1H); MS: m/z 452.6 $(M+H)^+$.

Example 37:

1-(3-cyano-4-(4-(3-hydroxyphenyl)piperazin-1-yl)phenyl)-3-(1-(p-tolyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 37 was prepared analogous to the procedure described in example 11 by reaction of 1-(p-tolyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(3-hydroxyphenyl)piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 2.38 (s, 3H), 3.21 (s, 4H), 3.26 (m, 4H), 6.37 (s, 1H), 6.45 (d, J=4.8 Hz, 1H), 7.01 (m, 1H), 7.23 (d, J=5.4 Hz, 1H), 7.40(d, J=4.8 Hz, 2H), 7.64 (d, J=5.4 Hz, 1H), 7.82 (d, J=4.8 Hz, 2H), 7.93 (s, 1H), 8.53 (s, 1H), 8.92 (s, 1H), 9.17 (s, 1H), 9.53 (s, 1H); MS: m/z 495.3 (M+1).

Example 38:

1-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-3-(1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 38 was prepared analogous to the procedure described in example 11 by reaction of 1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-morpholinopiperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.58 (d, J=9.6 Hz, 2H), 1.80-2.00 (s, 2H), 2.20-2.30 (m, 1H), 2.38-2.60 (m, 4H), 2.74 (t, J=11.4 Hz, 2H),3.33-3.58 (m, 2H), 3.58 (s, 4H), 7.16 (d, J=9.0 Hz, 1H), 7.58 (d, J=7.2 Hz, 1H), 7.84-7.89 (m, 3H), 8.29-8.34(m, 2H), 8.83 (s, 1H), 8.90 (s, 1H), 9.60 (s, 1H); MS: m/z 541.0 (M+1).

Example 39:

1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-hydroxypiperidin-1-yl)phenyl)-1,3-dimethylurea

Step 1): Synthesis of 1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-hydroxypiperidin-1-yl)phenyl)urea

The compound of step 1 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-chlorophenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-hydroxypiperidin-1-yl)benzonitrile in step 3.

Step 2): Synthesis of 1-(1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)-3-(3-cyano-4-(4-hydroxypiperidin-1-yl)phenyl)-1,3-dimethylurea

To the compound of step 1 in DMF was added excess of methyl iodide and potassium carbonate (2 equivalents). The resulting reaction mixture was heated at 50-70 °C for 12-16 h to afford title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.32 (s, 2H), 1.33-1.46 (m, 2H), 1.70-1.73 (m, 2H), 1.63-1.72 (m, 3H), 3.10 (s, 3H), 3.12 (s, 3H), 4.70 (brs, 1H), 6.90 (d, J=9.0 Hz, 1H), 7.18 (dd, J=10.5, 1.8 Hz, 1H), 7.35 (d, J=2.1 Hz, 1H), 7.67 (d, J=8.7 Hz, 2H), 7.79 (d, J=8.7 Hz, 2H), 8.32 (s, 1H); MS: m/z 466.1 (M+1).

Example 40:

1-(4-(3-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)ureido)-2-cyanophenyl)-4-(2-hydroxypropan-2-yl)piperidine

The compound of example 40 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.06 (s, 6H), 1.30 (s, 9H), 1.32-1.40 (m, 2H), 1.77-1.81 (m, 2H), 2.25-2.30 (m, 2H), 2.31 (s, 3H), 2.63-2.65 (m, 2H), 3.35-3.46 (m, 3H), 7.12 (d, 1H, *J* = 9.0Hz), 7.56-7.59 (m, 3H), 7.81-7.87 (m, 3H), 8.51 (s, 1H), 8.87 (s, 1H), 9.50 (s, 1H); MS: m/z 502.2 $[M+1-(SO_3Me)]^+$.

Example 40A:

1-(4-(3-(1-(4-(tert-butyl)phenyl)-1H-1,2,3-triazol-4-yl)ureido)-2-cyanophenyl)-4-(2-hydroxypropan-2-yl)piperidin-1-ium methanesulfonate

The compound of example 40 (50 mg, 0.098 mmol) in dry ethyl acetate (2 ml.) was treated with methane sulphonic acid (9.4 mg, 0.098 mmol). The resulting reaction mixture was stirred for about 12-16 h at room temperature. Solvent was distilled off and residue was washed with ether and dried to afford methanesulfonate salt of example 40A.

Yield: 40 mg; 80 %.

Example 41:

1-(3-cyano-4-(piperazin-1-yl)phenyl)-3-(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea

The compound of example 41 was prepared analogous to the procedure described in example 11 by reaction of 1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carbonyl azide with 5-amino-2-(piperazin-1-yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.27-3.34 (m, 8H), 7.27 (d, J= 9.0 Hz, 1H), 7.67 (d, J= 8.7 Hz, 1H), 7.98-7.95 (m, 2H), 8.22 (d, J= 8.4 Hz, 2H), 8.74 (s, 1H), 8.87 (s, 2H), 9.23 (s, 1H), 9.74 (s, 1H); MS: m/z 493.2 (M-HCl).

Example 41A:

1-(3-cyano-4-(piperazin-1-yl)phenyl)-3-(1-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)urea hydrochloride

The compound of example 41 was further treated with hydrochloric acid to obtain hydrochloric salt of compound of example 41A.

Example 42:

1-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-3-(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)urea

Step 1) 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylic acid (intermediate 1)

To the stirred solution of ethyl 3-(4-fluorophenyl)-5-methylisoxazole-4-carboxylate (12.75 mmol) in THF: H_2O (1:1 vol, 20 mL) was added NaOH (25.50 mmol) and the resulting mixture was heated to reflux for 4 h. The reaction mixture was cooled to a room temperature and THF was removed. The aqueous layer was separated, washed with ethyl acetate and acidified with dilute HCl to afford the title compound.

Step 2): 3-(4-fluorophenyl)-5-methylisoxazole-4-carbonyl azide (intermediate 2)

Method A:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (3.90 mmol) in acetone (10 mL) in an ice bath, was added trichloroacetonitrile (7.81 mmol), triphenyl phosphine (7.81 mmol) and sodium azide (4.68 mmol). The reaction mixture was stirred for 2 h at room temperature. On completion of reaction, the reaction was quenched with water (10 mL). The reaction mixture was extracted with ethyl acetate (25 mL). The organic layer was separated, washed with brine (10 mL), dried with Na_2SO_4, concentrated and purified using column chromatography (silica gel, ethyl acetate and petroleum ether gradient) to afford the title compound.

Method B:

To a stirred solution of the compound obtained in step 1 [intermediate 1] (2.23 mmol) in dry acetone (5 mL) was added sodium azide (4.47 mmol), triethylamine (4.47 mmol) at 0 ^{0}C. Triphosgene (1.11 mmol) dissolved in dry acetone (5 mL) was added to the resulting reaction mixture drop wise over a period of 15 minutes. The resulting reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the

white precipitate was filtered out, and washed with acetone. The resulting organic layer was evaporated to afford a crude product, which was further purified using column chromatography (silica gel, ethyl acetate and petroleum ether gradient) to afford the title compound.

Step 3): 1-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-3-(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)urea (final compound)

The compound obtained in step 2 [intermediate 2] (0.339 mmol) and 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile (0.339 mmol) in toluene (3 mL) was refluxed for 5 h. The reaction mixture was allowed to cool to the room temperature. The precipitated compound was filtered, washed with petroleum ether and cold dichloromethane, and dried to afford the title compound.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.53-1 .57 (m, 2H), 1.91 (d, J= 11.4 Hz, 2H), 2.27(m,2H) 2.36 (s, 2H), 2.67-2.75 (m, 2H), 3.58 (br s, 4H), 7.1 2 (d, J = 9.0 Hz, 1H), 7.36 (t, J = 8.7 Hz, 2H), 7.55 **(d,** J = 8.7 Hz, 1H), 7.76-7.80 (m, 3H), 7.96 (s, 1H), 9.00 (s, 1H); MS: m/z $(M+H)^+$ 505.2.

Example 43:

1-(4-(tert-butyl) phenyl)-N-(3-cyano-4-(4-(2-hydroxyethyl) piperidin-1-yl) phenyl)-1H-1, 2, 3-triazole-4-carboxamide

To a stirred solution of 1-(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazole-4-carboxylic acid (0.21 4 mmol) in DMF (5 mL) was added EDC (45.1 mg, 0.235 mmol) and HOBt (36.0 mg, 0.235 mmol). The resulting reaction mixture was stirred for 30 min. 5-amino-2-(4-(2-hydroxyethyl)piperidin-1 -yl)benzonitrile (0.214 mmol) and triethylamine (0.1 19 mL, 0.855 mmol) was added to the reaction mixture. Resulting reaction mixture was stirred for 12-1 6 h at room temperature. After completion of the reaction, the solvent was evaporated and the crude product obtained was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.22-1 **.46** (m, 15H), 1.76-1 .80 (m, 2H), 2.73 (t, 2H, *J* = 11.4 Hz), 3.41 -3.50 (m, 4H), 4.38 (br s, 1H), 7.1 8 (d, 1H, *J* = 9.0 Hz), 7.63 (d, 2H, *J* = 8.4Hz), 7.90 (d, 2H, J = 8.7 Hz), 8.02 (d, 1H, J = 7.2 Hz), 8.1 6 (br s, 1H), 9.41 (s, 1H), 10.78 (s, 1H); MS: m/z 473.2 $[M + H]^+$.

Example 44:

1-(4-(tert-butyl) phenyl)-N-(3-cyano-4-(4-hydroxypiperidin-1-yl) phenyl)-1H-1, 2, 3-triazole-4-carboxamide

The compound of example 44 was prepared analogous to the procedure described in example 43 by reaction of 1-(4-(tert-butyl)phenyl)-1 H-1 ,2,3-triazole-4-carboxylic acid with 5-amino-2-(4-hydroxypiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.34 (s, 9H), 1.57-1 .59 (m, 2H), 1.87-1 .99 (m, 2H), 2.89 (t, 2H, *J* = 6.0 Hz), 3.31 -3.32 (m, 2H), 3.65 (br s, 1H), 4.72 (d, 1H, *J* = 2.4 Hz), 7.20 (d, 1H, J = 5.4Hz), 7.64 (d, 2H, J = 5.1 Hz), 7.92 (d, 2H, *J* = 5.1 Hz), 8.01 (d, 1H, J = 5.4 Hz), 8.1 7 (br s, 1H), 9.42 (s, 1H), 10.78 (s, 1H); MS: m/z 445.3 $[M+H]^+$.

Example 45:

1-(4-chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-1H-1,2,3-triazole-4-carboxamide

The compound of example 45 was prepared analogous to the procedure described in example 43 by reaction of 1-(4-chlorophenyl)-1 H-1 ,2,3-triazole-4-carboxylic acid with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.80-1 .84 (m, 2H), 1.98 (d, J = 12 Hz, 2H), 2.39 (m, 1H), 2.63 (s, 4H), 2.84 (t, J= 11.**4** Hz, 2H), 3.67 (d, J= 11.**4** Hz, 2H), 3.77 (s, 4H), 7.07 (d,J = 9.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 3H), 8.05 (s, 1H), 8.58 (s, 1H), 8.95 (s, 1H) MS: m/z 490.2 $(M-H)^+$.

Example 45A:

1-(4-chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-1H-1,2,3-triazole-4-carboxamide hydrochloride

To the solution of compound of example 45 (0.01 5 g, 0.030 mmol) was added 10 mL ethyl acetate saturated in HCl and methanol (2 drops) with continuous stirring. The resulting reaction mixture was stirred for 10-1 2 h. The reaction solvent was decanted and triturated with hexane. The precipitate obtained was filtered and dried to afford the title compound.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.84 (m, 2H), 1.98-2.02 (m, 2H), 2.41 (m, 1H), 2.64 (s, 4H), 2.84 (t, J=1 1.4 Hz, 2H), 3.67 (d, J=1 1.4 Hz, 2H), 3.77(s, 4H), 7.07 (d, J=8.7 Hz, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.77 (d, J=8.4 Hz, 3H), 8.05 (s, 1H), 8.59 (s, 1H), 8.95 (s, 1H); MS: m/z 492.80 [M+1 -(HCl)].

Example 46:

1-(4-chlorophenyl)-N-(3-cyano-4-(4-(pyrimidin-2-yl)piperazin-1-yl)phenyl)-1H-1,2,3-triazole-4-carboxamide

The compound of example 46 was prepared analogous to the procedure described in example 43 by reaction of 1-(4-chlorophenyl)-1 H-1 ,2,3-triazole-4-carboxylic acid with 5-amino-2-(4-(pyrimidin-2-yl)piperazin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 3.1 8 (s, 4H), 3.93 (s, 4H), 6.68 (m, 1H), 7.28 (d, J= 7.5 Hz, 1H), 7.73-7.69 (m, 2H), 8.07 (d, J= 5.1 Hz, 3H), 8.24 (s, 1H), 8.41 (d, J = 3.0 Hz, 2H), 9.50 (s, 1H), 10.86 (s, 1H) MS: m/z 486.3 $[M+H]^+$.

Example 47:

N-(3-cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-5-pentyl-1 -(3-(trifluoromethyl) phenyl)-1 H-1 ,2,3-triazole-4-carboxamide

The compound of example 47 was prepared analogous to the procedure described in example 43 by reaction of 5-pentyl-1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazole-4-carboxylic acid with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.92 (s, 1H), 7.97(s, 1H), 7.95 (d, J=7.5Hz, 1H), 7.90 (d, J=8Hz, 1H), 7.84 (s, 1H), 7.83(d, J=8.5Hz, 1H), 7.72 (d, J=8.5Hz, 1H), 7.64 (d, J=8.5Hz, 1H), 7.20 (d, J= 9Hz, 1H), 3.2 (s, 4H), 3.50 (d, J= 9Hz, 2H), 2.86-2.75 (m, 4H), 2.63(s, 4H), 1.96-1 .94 (m, 2H), 1.68-1 .58 (m, 4H), 1.33-1 .23(m, 10H), 0.85 (t, J=7Hz, 3H); MS: m/z 596 $(M+1)^+$.

Example 48:

1-(4-chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-1H-1,2,3-triazole-5-carboxamide

The compound of example 48 was prepared analogous to the procedure described in example 43 by reaction of 1-(4-chlorophenyl)-1 H-1 ,2,3-triazole-5-carboxylic acid with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.85-1 .99 (m, 2H), 2.27 (d, J= 10.2 Hz, 2H), 2.79 (t, J= 11.2Hz, 2H), 3.08-3.32 (m, 3H), 3.45-3.60 (m, 4H), 3.84-3.99 (m, 4H), 7.24 (d, J= 9.0 Hz, 1H), 7.85 (d, J= 6.0 Hz, 1H), 8.03 (s, 1H), 8.62 (s, 1H), 11.1 1 (s, 1H), 11.26 (s, 1H); MS: m/z 492.0 (M-HCl).

Example 48 A:

1-(4-chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-1H-1,2,3-triazole-5-carboxamide hydrochloride

The compound of example 48 was further treated with hydrochloric acid to obtain hydrochloric salt of compound of example 48A.

Example 49:

N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)-3-(4-fluorophenyl)-4-methylisoxazole-5-carboxamide

To a stirred solution of 3-(4-fluorophenyl)-4-methylisoxazole-5-carboxylic acid (0.214 mmol) in DMF (5 mL) was added EDC (45.1 mg, 0.235 mmol) and HOBt (36.0 mg, 0.235 mmol). The resulting reaction mixture was stirred for 30 min. 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile (0.214 mmol) and triethylamine (0.119 mL, 0.855 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred 12-16 h at room temperature. After completion of the reaction, the solvent was evaporated and the crude product obtained was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70-7.63 (m, 3H), 7.31 -7.26 (m, 3H), 6.98-6.92 (m, 1H), 3.76 (brs, 4H), 3.61 **(d,** J=1 1**.4** Hz, 2H), 2.79-2.75 (m, 5H), 2.63 (brs, 4H), 2.39-2.40 (m, 1H), 2.20-1 .96 (m, 2H), 1.80-1 .77 (m, 2H); MS: m/z 490.2 $(M+1)^+$.

Example 50:

3-(4-chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1-yl)phenyl)isoxazole-5-carboxamide

The compound of example 50 was prepared analogous to the procedure described in example 49 by reaction of 3-(4-chlorophenyl)isoxazole-5-carboxylic acid with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (CDCl3, 300 MHz): δ 1.79-1 .86 (m, 2H), 1.98-2.02 (m, 2H), 2.36-2.39 (m, 1H), 2.62 (s, 4H), 2.86 (t, J = 11.4 Hz, 2H), 3.69 (d, J= 11.7 Hz, 2H), 3.76 (s, 4H), 7.05 (d, J = 9.0 Hz, 1H), 7.34 (s, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.7 Hz, 1H), 7.82 **(d,** J = 8.4 Hz, 2H), 7.97 (s, 1H), 8.22 (s, 1H);); MS: m/z 492.6 (M+H).

Example 51:

N-(1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-cyano-4-(4-morpholinopiperidin-1-yl)benzenesulfonamide

Step 1): Synthesis of 4-chloro-3-cyanobenzene-1-sulfonyl chloride (intermediate 1)

5-amino-2-chloro benzonitrile (0.59 g, 3.28 mmol) was added in one portion to the mixture of concentrated HCl (1.0 mL) and glacial acetic acid (0.4 mL) in a two neck flask. The resulting reaction mixture was cooled to a temperature 0 °C. A solution of sodium nitrite [0.226 g, 3.28 mmol in water (0.4 mL)] was added drop wise to the reaction mixture at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Acetic acid (3 mL) was added to the reaction mixture with continuous stirring. Sulphur dioxide was introduced into the reaction mixture by a bubler tube. Cuprous chloride (0.325 g, 3.28 mmol) was added to the reaction mixture. The reaction mixture was cooled to 0 °C. The solid precipitate was filtered and washed with hexane and dried to afford the title compound;

^{1}H NMR (DMSO-de, 300 MHz): δ 7.85 (d, J=8.7 Hz, 1H), 8.22 (m, 1H), 8.35 (s, 1H).

Step 2): Synthesis of_4-chloro-N-(1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-cyanobenzenesulfonamide (Intermediate 2)

To the stirred solution of compound obtained in step 1 [intermediate 1] (0.1 93 g, 0.81 9 mmol) in dichloromethane (10 mL) was added 1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-amine hydrochloride (0.200 g, 0.81 9 mmol) and triethylamine (0.1 66 g, 1.639 mmol) at room temperature. After completion of the reaction, the reaction was quenched with water. The crude compound obtained was extracted with dichloromethane, dried over anhydrous Na_2S0_4 and purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (CDCI3, 300 MHz): δ 2.28 (s, 3H), 5.32 (s, 1H), 6.13 (s, 1H), 7.40 (d, J= 8.4Hz, 2H), 7.50 **(d,** J= 8.4 Hz, 2H), 7.71 (d, J= 8.4 Hz, 1H), 7 .91 (m, 1H), 8.1 3 (s, 1H); MS: m/z 407.1 $(M+1)^+$.

Step 3): Synthesis of N-(1-(4-chlorophenyl)-5-methyl-1H-pyrazol-4-yl)-3-cyano-4-(4-morpholinopiperidin-1-yl)benzenesulfonamide (final compound)

To the stirred solution of compound obtained in step 2 [intermediate 2] (0.50 g, 1.228 mmol) in acetonitrile (10 mL) was added morpholinopiperidine (0.209 g, 1.228 mmol) and triethylamine (0.248 g, 2.455 mmol). The resulting reaction mixture was heated to 65-70 ºC for about 12-1 6 h. The solvent was removed, and the residue was diluted with ethylacetate and filtered through celite. The organic layers obtained were combined and

dried over anhydrous Na_2S0_4. The solvent was removed and the crude product obtained was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (CDCI3, 300 MHz): δ 1.27-1.31 (m, 2H), 1.77-1.81 (m, 2H), 2.00-2.04 (m, 2H), 2.29 (s, 3H), 2.58-2.66 (m, 4H), 3.03 (t, J= 11.7 Hz, 2H), 3.79 (br s, 3H), 3.93 (d, J = 12.3 Hz, 2H), 5.97 (s, 1H), 7.01 (d, J= 9.0 Hz, 2H), 7.14(s,1 H) 7.40 (d, J= 8.4 Hz, 2H, 7.49 (d, = J8.4 Hz, 2H), 7.77 (d, J=9.0 Hz,1 H) 7.97 (s, 1H); MS: m/z 541.1 $(M+1)^+$.

Example 52:

N-(4-(3-methoxyphenyl)pyrimidin-2-yl)-5-phenylthiazol-2-amine

To a stirred solution of 4-phenylthiazol-2-amine (0.453 mmol) in dioxane (10 mL) was added 2-chloro-4-(3-methoxyphenyl)pyrimidine (0.453 mmol), xantphos [4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene] (0.045 mmol), cesium carbonate (0.906 mmol) and Tris(dibenzylidineacetone)dipd(0) (0.023 mmol). The resulting reaction mixture was refluxed for about 12-16 h. The solvent was evaporated, residue was diluted with water, extracted with dichloromethane, dried over anhydrous Na_2S0_4 and purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.90 (s, 3H), 7.16-7.18 (m, 1H), 7.29-7.34 (m, 2H), 7.41-7.46 (m, 2H), 7.52 (t, J=8.1 Hz, 1H), 7.62 (s, 1H), 7.67 (d, J=5.4Hz, 1H), 7.87-7.95 (m, 3H), 8.72 **(d,** J=5.1 Hz, 1H), 11.9 (s, 1H); MS: m/z: 361.1 (M+1).

Example 53:

5-phenyl-N-(4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)thiazol-2-amine

The compound of example 53 was prepared analogous to the procedure described in example 52 by reaction of 4-phenylthiazol-2-amine with 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyrimidine.

^{1}H NMR (DMSO-de, 300 MHz): δ 7.32 (d, J=7.2Hz, 1H), 7.41 (t, J=7.5 Hz, 2H), 7.57-7.61 (m, 3H), 7.65 **(d,** J= 5.1 Hz, 1H), 7.93 (d, J= 7.2 Hz, 2H), 8.44 (d, J= 9.0 Hz, 2H), 8.73 (d, J=5.4 Hz, 1H), 11.96 (s, 1H); MS: m/z 415.1 (M+1).

Example 54:

N-(4-(2-methoxyphenyl)pyrimidin-2-yl)-5-phenylthiazol-2-amine

The compound of example 54 was prepared analogous to the procedure described in example 52 by reaction of 4-phenylthiazol-2-amine with 2-chloro-4-(2-methoxyphenyl)pyrimidine.

^{1}H NMR (DMSO-de, 300 MHz): δ 3.88 (s, 3H), 7.13-7.16 (m, 1H), 7.18-7.22(m, 1H), 7.28-7.31 (m, 1H), 7.40 (t, J= 7.5 Hz, 2H), 7.49-7.56 (m, 3H), 7.91 (d, J= 7.5 Hz, 2H), 8.14 (d, J=6.9 Hz, 1H), 11.79 (s, 1H); MS: m/z 361.2 (M+1).

Example 55:

5-((6-fluorobenzo[d]thiazol-2-yl) amino)-2-(4-morpholinopiperidin-1-yl) benzo nitrile

The compound of example 55 was prepared analogous to the procedure described in example 52 by reaction of 6-fluorobenzo[d]thiazol-2-amine with 5-chloro-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.73-1.84 (m, 2H), 2.22-2.28 (m, 2H), 2.76 (t, 2H, *J* = 11.7 Hz), 3.12-3.24 (m, 3H), 3.51-3.55 (m, 4H), 3.67 (t, 2H, *J* = 12.0 Hz), 4.03 (d, 2H, *J* = 12.6 Hz), 7.17-7.18 (m, 1H), 7.26 (d, 1H, *J* = 9.0 Hz), 7.60-7.64 (m, 1H), 7.74-7.78 (m, 1H), 7.81-7.84 (m, 1H), 8.22 (d, 1H, *J* = 2.4 Hz), 10.65 (s, 1H); MS: m/z 438.2 [M + H]$^+$.

Example 56:

5-((4-(3, 5-dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-morpholinopiperidin-1-yl) benzonitrile

To a stirred solution of 2-chloro-4-(3,5-dimethoxyphenyl)pyrimidine (0.199 mmol) and 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile (0.199 mmol) in N-methyl-2-pyrrolidinone (NMP, 1 mL) was added PTSA (0.199 mmol). The resulting reaction mixture was heated at 140 °C for 4 h. After completion of the reaction, the reaction mixture was cooled to the room temperature and quenched with ice water. The reaction mixture was extracted with ethyl acetate (10 mL). The organic layer was separated and washed with saturated $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL). The crude product was dried over anhydrous Na_2SO_4, purified using using column chromatography (silica gel, methanol and dichloromethane gradient) using methanol and dichloromethane as eluent to afford the title compound.

^{1}H NMR (DMSO- d_6, 300 MHz): δ 1.55-1.62 (m, 2H), 1.88-1.92 (m, 2H), 2.26-2.29 (m, 1H), 2.49-2.51 (m, 2H), 2.74 (t, J= 11.0 Hz, 2H), 3.32-3.44 (m, 4H), 3.58 (br s, 4H),

3.84 (s, 6H), 6.67 (s, 1H), 7.16 (d, J= 9.0 Hz, 1H), 7.31 (d, J= 2.1 Hz, 2H), 7.46 (d, J= 5.4 Hz, 1H), 7.84 (d, J= 9.0 Hz, 1H), 8.32 (br s, 1H), 8.56 (d, J= 2.1 Hz, 1H), 9.84 (s, 1H); MS: m/z 501.4 $[M+H]^+$.

Example 57:

5-((4-(3, 5-dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-(hydroxymethyl) piperidin -1-yl) benzonitrile

The compound of example 57 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-(3,5-dimethoxyphenyl)pyrimidine with 5-amino-2-(4-(hydroxymethyl)piperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.22-1.38 (m, 2H), 1.71-1.80 (m, 2H), 1.84-1.94 (m, 1H), 2.69-2.74 (m, 2H), 3.29-3.41 (m, 4H), 3.84 (s, 6H), 4.48-4.53 (m, 1H), 6.67 (m, 1H), 7.16 (d, J= 9.0 Hz, 1H), 7.31 (d, J= 1.8 Hz, 2H), 7.46 (d, J= 5.1 Hz, 1H), 7.83 (d, J= 9.0 Hz, 1H), 8.32 (br s, 1H), 8.56 (d, J= 2.1 Hz, 1H), 9.83 (s, 1H); MS: 446.2 $[M+H]^+$.

Example 58:

4-(2-methoxyphenyl)-N-(4-(4-(pyrimidin-2-yl)piperazin-1-yl)-3-(trifluoromethyl) phenyl) pyrimidin-2-amine

The compound of example 58 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-(2-methoxyphenyl)pyrimidine with 3-(trifluoromethyl)-4-(4-(pyrimidin-2-yl)piperazin-1 -yl)benzenamine.

^{1}H NMR (DMSO-de, 300 MHz): δ 2.72-2.87 (m, 2H), 3.82 (m, 7H), 6.64 (t, J= 4.8 Hz, 1H), 7.10 (t, J= 7.5 Hz, 1H), 7.21 (d, J= 8.4Hz, 1H), 7.40 (d, J= 5.1 Hz, 1H), 7.55-7.48 (m, 2H), 7.92-7.97 (m, 2H), 8.37-8.39 (m, 3H), 8.53 (d, J= 5.1 Hz, 1H), 9.92 (s, 1H); MS: m/z 508.2 $[M+H]^+$.

Example 59:

1,1,1,3,3,3-hexafluoro-2-(4-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino)phenyl) propan-2-ol

The compound of example 59 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-(3-methoxyphenyl)pyrimidine with 2-(4-aminophenyl)-1 ,1,1,3,3,3-hexafluoropropan-2-ol.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.85 (s, 3H), 7.11-7.13 (m, 1H), 7.44-7.48 (m, 2H), 7.60 (d, J= 8.4 Hz, 2H), 7.76 (d, J= 8.1 Hz, 2H), 7.96 (d, J= 8.7 Hz, 2H), 8.52 (s, 1H), 8.58 (d, J= 5.4 Hz, 1H), 9.92 (s, 1H); MS: 444.1 $[M+H]^+$.

Example 60:

2-(4-hydroxypiperidin-1-yl)-5-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino) benzonitrile

The compound of example 60 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-(3-methoxyphenyl)pyrimidine with 5-amino-2-(4-hydroxypiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.59 (m, 2H), 1.89 (m, 2H), 2.87 (m, 2H), 3.33(m, 2H), 3.64 (m, 1H), 3.87 (s, 3H), 4.72 (d, J= 4.2 Hz, 1H), 7.10-7.19 (m, 2H), 7.43-7.48 (m, 2H), 7.71 -7.73 (m, 2H), 7.85-7.89 (m, 1H), 8.28 (d, J= 5.4 Hz, 1H), 9.84 (s, 1H); MS: m/z 402.2 $[M+H]^+$.

Example 61:

5-((4-morpholinopyrimidin-2-yl)amino)-2-(4-(pyridin-2-yl)piperazin-1-yl) benzonitrile

The compound of example 61 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-morpholinopyrimidine with 5-amino-2-(4-(pyridin-2-yl)piperazin-1 -yl)benzonitrile.

^{1}H NMR (CDCI3, 300 MHz): δ 9.25 (s, 1H), 8.13-8.11 (m, 2H), 8.01 (d, J=6Hz, 1H), 7.88 (dd, J=9.0, 2.7Hz, 1H) ,7.57-7.52 (m, 1H), 7.18 (d, J=9Hz,1 H), 6.89 (d, J=8.7Hz, 1H), 6.68-6.64 (m, 1H), 6.30 (d, J=6Hz, 1H), 3.66-3.55 (m, 12H), 3.17 (bs,4H), MS: m/z 443 (M+1).

Example 62:

2-morpholino-5-((4-morpholinopyrimidin-2-yl)amino)benzonitrile

The compound of example 62 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-4-morpholinopyrimidine with 5-amino-2-morpholinobenzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 8.82 (s, 1H), 7.95 (d, J=6Hz, 1H), 7.55 (d, J=8.5Hz, 2H), 6.86 (d, J=9Hz ,2H), 6.19 (d, J=6Hz, 1H), 3.72-3.73 (m, 4H), 3.66-3.65 (m, 4H), 3.54 (s, 4H), 3.00 (s, 4H).

Example 63:

5-((4-((2-morpholinoethyl)amino)pyrimidin-2-yl)amino)-2-(4-morpholinopiperidin-1-yl)benzonitrile

The compound of example 63 was prepared analogous to the procedure described in example 56 by reaction of 2-chloro-N-(2-morpholinoethyl)pyrimidin-4-amine with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 500 MHz): δ 9.08 (s, 1H), 8.18 (d, J=2.4Hz, 1H), 7.80-7.77 (m, 2H),7.06-7.03 (m, 2H), 5.95 (d, J=5.7Hz, 1H), 3.57 (bs, 8H), 3.36-3.30 (m, 3H), 2.71 (t, J=11.4Hz, 2H), 2.47-2.22 (m, 9H), 1.88-1.84 (m, 2H),1.54-1.51 (m,2H); MS: m/z 493 (M+1).

Example 64:

5-((2-chloro-6-methoxyquinolin-4-yl) amino)-2-(4-morpholinopiperidin-1-yl) benzonitrile

The compound of example 64 was prepared analogous to the procedure described in example 56 by reaction of 2,4-dichloro-6-methoxyquinoline with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.57-1.64 (m, 2H), 1.83-1.94 (m, 2H),2.27-2.34 (m, 2H), 2.83 (t, 2H, *J* = 11.4 Hz), 3.17-3.21 (m, 1H), 3.53-3.58 (m, 8H), 3.94 (s, 3H), 6.80 (br s, 1H), 7.26 (d, 1H, J = 9.0 Hz), 7.51-7.55 (m, 1H), 7.67 (d, 1H, *J* = 9.3 Hz), 7.90-7.96 (m, 2H), 8.05 (d, 1H, J = 2.4 Hz), 10.06(s, 1H); MS: m/z 478.2 $[M + H]^+$.

Example 65:

2-(4-morpholinopiperidin-1-yl)-5-(quinolin-2-ylamino) benzonitrile

The compound of example 65 was prepared analogous to the procedure described in example 56 by reaction of 2-chloroquinoline with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 300 MHz): δ 1.56-1.60 (m, 2H), 1.89-1.93 (m, 2H), 2.23-2.28 (m, 2H), 2.72-2.79 (m, 3H), 3.42-3.46 (m, 4H), 3.59 (br s, 4H), 7.00 (d, 1H, J = 8.7 Hz), 7.19 (d, 1H, *J* = 9.0 Hz), 7.30 (t, 1H, *J* = 6.6 Hz), 7.58 (t, 1H, *J* = 7.5 Hz), 7.66 (d, 1H, *J* = 8.1 Hz), 7.73 (d, 1H, J = 7.5 Hz), 7.98-8.02 (m, 1H), 8.06 (d, 1H, J = 9.0 Hz), 8.48 (d, 1H, *J* = 2.4 Hz), 9.56 (s, 1H); MS: m/z 414.2 $[M + H]^+$.

Example 66:

5-((cyano(1-(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)benzonitrile

Step 1): Synthesis of (1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methanol (intermediate 1)

To a solution of ethyl 1-(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazole-4-carboxylate (17.53 mmol) in tetrahydrofuran (25 ml.) was added LAH (26.3 mmol). The resulting reaction mixture was stirred at room temperature. On completion of the reaction, the reaction was quenched with saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate. The organic layer was separated and washed with brine and water, and dried over anhydrous Na_2SO_4 to afford the title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.89 (s, 1H), 8.29 (m, 2H), 5.39 (t, J= 5.4 Hz, 1H), 4.63 (d, J= 5.4 Hz, 2H).

Step-2: Synthesis of 1-(3-(trifluoromethyl) phenyl)-1H-1, 2, 3-triazole-4-carbaldehyde (intermediate 2)

To a stirred solution of the compound obtained in step 1 [intermediate 1] (11.10 mmol) in chloroform (30 mL) was added manganese dioxide (11.10 mmol). The resulting reaction mixture was heated at 70 °C for 3 h. On completion of the reaction, the reaction mixture was filtered through celite bed and residue was washed 2-3 times with chloroform. The combined filtrate was dried over anhydrous Na_2SO_4 to afford the title compound.

^{1}H NMR (DMSO-de, 300 MHz): δ 10.13 (s, 1H), 9.75 (s, 1H), 8.40-8.33 (m, 2H), 7.96-7.86 (m, 2H).

Step-3: Synthesis of 5-((cyano(1-(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(2-hydroxypropan-2-yl)piperidin-1-yl)benzonitrile (Final compound)

To a stirred solution of the compound obtained in step 2 [intermediate 2] (0.829 mmol) in tetrahydrofuran (20 mL) was added 5-amino-2-(4-(2-hydroxypropan-2-yl)piperidin-1 -yl)benzonitrile (0.829 mmol) and trifluoroacetic acid (0.035 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. After the formation of imine compound, trimethylsilanecarbonitrile (1.244 mmol) and tetrabutylammonium difluorotriphenylsilicate (1.244 mmol) was added to the reaction mixture. The resulting reaction mixture was stirred for about 12-16 h. The solvent was removed and the crude residue was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.24(s,1 H), 8.36 (s, 1H), 8.34(d, J=7.5Hz, 1H), 7.89-7.84 (m, 2H), 7.23(s, 1H), 7.13 (s, 2H), 6.94(d, J=9.3Hz, 1H), 6.36 (d, J=9.6Hz, 1H), 4.16 (s, 1H), 2.64 (t, J=10.8Hz, 2H), 2.28(s, 1H), 1.81 (d, J=11.7Hz, 2H), 1.42-1.23 (m, 4H), 1.07(s, 6H); MS: m/z 510 $(M+1)^+$.

Example 67:

5-((cyano(1-(3-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1-yl)benzonitrile

The compound of example 67 was prepared analogous to the procedure described in example 66 by reaction of 1-(3-(trifluoromethyl) phenyl)-1H-1, 2, 3-triazole-4-carbaldehyde with 5-amino-2-(4-(pyrimidin-2-yl)piperazin-1 -yl)benzonitrile in step 3.

^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.26(s, 1H), 8.40-8.31 (m, 4H), 7.93 (d, J=8.1 Hz, 2H), 7.29 (s, 1H), 7.18(s, 2H), 7.04 (d, J=9.6Hz, 1H), 6.68 (t, J=4.8Hz, 1H), 6.39 (d, J=6.3Hz, 1H), 3.90(brs, 4H), 3.07 (t, J=4.5Hz, 4H); MS: m/z 531 $(M+1)^+$.

Example 68:

2-chloro-5-(((1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino) benzonitrile

Step 1): Synthesis of (1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methanol (intermediate 1)

To a solution of ethyl 1-(4-chlorophenyl)-5-methyl-1 H-pyrazole-4-carboxylate (17.53 mmol) in tetrahydrofuran (25 ml.) was added LAH (26.3 mmol). The resulting reaction mixture was stirred at room temperature. On completion of the reaction, the reaction was quenched with saturated solution of ammonium chloride. The reaction mixture was extracted with ethyl acetate. The organic layer was separated and washed with brine and water, and dried over anhydrous Na_2SO_4 to afford the title compound.

Step-2: Synthesis of 1-(4-chlorophenyl)-5-methyl-1H-pyrazole-4-carbaldehyde (intermediate 2)

To a stirred solution of the compound obtained in step 1 [intermediate 1] (11.10 mmol) in chloroform (30 ml.) was added manganese dioxide (11.10 mmol). The resulting reaction mixture was heated at 70 °C for 3 h. On completion of the reaction, the reaction mixture was filtered through celite bed and residue was washed 2-3 times with chloroform. The combined filtrate was dried over anhydrous $Na2SO_4$ to afford the title compound.

Step-3: Synthesis of 2-chloro-5-(((1-(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino) benzonitrile (Final compound)

To a stirred solution of the compound obtained in step 2 [intermediate 2] (0.829 mmol) in tetrahydrofuran (20 ml_) was added 5-amino-2-chlorobenzonitrile (0.829 mmol) and trifluoroacetic acid (0.035 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. After the formation of imine compound, sodium borohydride was added to the reaction mixture. The resulting reaction mixture was stirred for about 12-16 h. The solvent was removed and the crude residue was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 3H), 3.99 (m, 1H), 4.15 (s, 2H), 6.79-6.82 (m, 1H), 6.88-6.92 (m, 1H), 7.30 (s, 1H), 7.42 (d, J= 8.7 Hz, 2H), 7.50(d, J= 8.7 Hz, 2H), 7.63 (s, 1H); MS: m/z 357.4 $[M+H]^+$.

Example 69:

5-(((1-(4-chlorophenyl)-5-methyl-1H-pyrazol-4-yl)methyl)amino)-2-(4-morpholino piperidin-1 -yl)benzonitrile

The compound of example 69 was prepared analogous to the procedure described in example 68 by reaction of 1-(4-chlorophenyl)-5-methyl-1 H-pyrazole-4-carbaldehyde with 5-amino-2-(4-morpholinopiperidin-1 -yl)benzonitrile in step 3.

^{1}H NMR (CDCI3): δ 1.77-1 .88 (m, 2H), 1.96-2.00 (m, 2H), 2.33 (s, 3H), 2.36-2.43 (m, 1H), 2.65-2.77 (m, 6H), 3.45 **(d,** J= 11.1 Hz, 2H), 3.79 (s, 4H), 4.12 (s, 2H), 6.81 -6.86 (m, 2H), 6.97 (d, J= 8.7 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.62 (s, 1H); MS: m/z 491 .6 $(M+H)^+$.

Example 70:

N-(4-(1 ,1 ,1 ,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxy-2-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide

To a stirred solution of 2-hydroxy-2-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)acetic acid (0.214 mmol) in DMF (5 imL) was added EDC (45.1 mg, 0.235 mmol) and HOBt (36.0 mg, 0.235 mmol). The resulting reaction mixture was stirred for 30 min. 2-(4-aminophenyl)-1 ,1 ,1 ,3,3,3-hexafluoropropan-2-ol (0.214 mmol) and triethylamine (0.119 ml_, 0.855 mmol) was added to the reaction mixture. Resulting reaction mixture was stirred for 12-16 h at room temperature. After completion of the reaction, the

solvent was evaporated and the crude product obtained was further purified using column chromatography (silica gel, methanol and dichloromethane gradient) to afford the title compound.

^{1}H NMR (DMSO-de, 500 MHz): δ 10.31 (s, 1H), 9.01 (s, 1H), 8.64 (s, 1H), 8.32-8.28 (m, 2H)), 7.88-7.84 (m, 4H), 7.63 **(d,** J=3.8 Hz, 2H), 6.69 (d, J=5.5 Hz, 1H), 5.42 (d, J=5.5 Hz, 1H); MS: m/z 529.0 (M+1).

Example 71:

N-(3-cyano-4-(4-methoxypiperidin-1-yl)phenyl)-2-hydroxy-2-(1-(3 (trifluoromethyl) phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide

The compound of example 71 was prepared analogous to the procedure described example 70 by reaction of 2-hydroxy-2-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol yl)acetic acid with 5-amino-2-(4-methoxypiperidin-1 -yl)benzonitrile.

^{1}H NMR (DMSO-de, 500 MHz): δ 10.31 (s, 1H), 9.01 (s, 1H), 8.64 (s, 2H), 8.32-8.28 (m, 2H)) ,7.88-7.84 (m, 4H), 7.63 (d, J=8Hz, 2H), 6.89 (d, J=5.5Hz, 1H), 5.42 (d, J=5.5Hz, 1H), 3.27 (s, 3H), 2.92(t, J=9.5Hz, 2H), 1.96 (bs, 2H), 1.62(bs, 2H); MS: m/z 501 $(M+1)^+$.

Biological Assays

The biological activity of the compounds of the present invention as IL-1 7 and TNF-a inhibitor can be confirmed by a number of biological assays known in the art. The exemplified biological assays, given below, have been carried out with certain representative compounds of the formula I (referred to as the test compounds) synthesized in the above examples.

Materials:

Cell- based assays: RPMI-1 640 (AMIMED, Cat#1 -41 F50-1), MEM EBS (Amimed, Cat#1 -31 S22-I), Penicillin-Streptomycin Stabilized Solution (Sigma- Aldrich, Cat#P4333), FBS (Hyclone, Cat#SH30071 .03), Ficoll/Hypaque solution Histopaque-1077 (Sigma, Cat#1 0771), DMSO (Sigma, Cat#D4540), PMA (Sigma-Aldrich, Cat#79346), lonomycin (Sigma, Cat#l0634), Human-IL-1 7 duoset, economy Pack, 45 plates (R&D systems, Cat#DY31 7E), EGTA (Sigma, Cat#E3889), β glycerophosphate (Sigma, Cat#G5422), 96 well white flat bottom plate (Nunc, Cat#1 361 0 1), 96 flat bottom plates (NUNC, Cat#1 67008), Tritium (^{3}H) Thymidine (Methyl-T)(BRIT, Cat#LCT 3)

(Cat# = Catalogue number)

Dose Preparation

Test compounds are weighed and dissolved in required amount of DMSO to give a stock solution of 20 mg/mL and 20 mM respectively. Working stock of 200X was prepared for the test compounds according to procedure shown below.

Working stock	Assay Dilution	Assay concentration
20 mg/mL or mM	1 µL in 200 µL assay medium	100 µg/mL or µM
6 mg/mL or mM	1 µL in 200 µL assay medium	30 µg/mL or µM
2 mg/mL or mM	1 µL in 200 µL assay medium	10 µg/mL or µM
0.6 mg/mL or mM	1 µL in 200 µL assay medium	3 µg/mL or µM
0.2 mg/mL or mM	1 µL in 200 µL assay medium	1 µg/mL or µM
0.06 mg/mL or mM	1 µL in 200 µL assay medium	0.3 µg/mL or µM
0.02 mg/mL or mM	1 µL in 200 µL assay medium	0.1 µg/mL or µM
0.006 mg/mL or mM	1 µL in 200 µL assay medium	0.03 µg/mL or µM

Serial dilutions of 1:10 (10 µL of working stock and 90 µL of DMSO) were prepared from each concentration of 20 mg/mL (mM) or 6 mg/mL (mM) in a log dose to give the next log dose working stock concentration.

Test System: Human peripheral blood cells isolated from healthy volunteers.

Methods

***In vitro* screening method to identify inhibitors of IL-17 and TNF-α release**

Isolation of peripheral blood mononuclear cells (PBMC): PBMC were obtained from healthy donors by centrifugation of heparinized venous blood over Ficoll/Hypaque solution (Histopaque-1 077, Sigma). Mononuclear cells in the buffy layer were collected and washed three times in sterile PBS with 2 % FBS. Cells were suspended in RPMI-

1640 supplemented with 100 U/mL penicillin, 100 µg/mL streptomycin and 10 % fetal bovine serum (FBS).

Cytokine release assay: The cells were uniformly plated in 96-well tissue culture plates (Nunc 167008) at a concentration of 1x10^5 cells/well. After plating, different concentrations (0.003, 0.01 , 0.03, 0.1 , 0.3, 1, 3 and 10 µg/mL) of the test compounds dissolved in dimethylsulfoxide (DMSO) were added to the cells and incubated at 37 °C for 30 min in 5 % CO_2 atmosphere. The final concentration of DMSO was maintained at 0.5 %. The vehicle (0.5 % DMSO) was used as control. The cells were then stimulated with 25 ng/mL of PMA (P1585, SIGMA) and 1µM ionomycin (SIGMA, I0634). The plates were incubated in 5 % CO_2 air humidified atmosphere at 37 °C for 48 h. At the end of 48 h, the supernatant from the cells were collected and ELISA was performed to detect the level of IL-17 (R&D systems, DY317E) and TNF-a (BD Biosciences, 555212) in the supernatant.

Lymphocyte proliferation assay by ^{3}H thymidine uptake: The cells were uniformly plated in 96-well tissue culture plates (Nunc 167008) at a concentration of 1x10^5 cells/well. After plating, different concentrations (0.003, 0.01 , 0.03, 0.1 , 0.3, 1, 3 and 10 µg/mL) of the test compounds dissolved in DMSO were added to the cells and incubated at 37 °C for 30 min in 5 % CO_2 atmosphere. The final concentration of DMSO was maintained at 0.5 %. The vehicle (0.5 % DMSO) was used as control. The cells were then stimulated with 25 ng/mL of PMA (P1585, SIGMA) and 1 µM ionomycin (SIGMA, I0634). The plates were incubated in 5 % CO_2 air humidified atmosphere at 37 °C for 48 h. At the end of 24 h, cells are pulsed with 0.5 µci/ well of 3[H]-Thymidine (BRIT, LCT3). The cells were washed twice with PBS to remove excess radioactivity. Radioactivity in the incorporated cells was captured on lysis with Microscint-40, Perkin Elmer and measured by using a liquid scintillation counter (TopCount, Perkin Elmer). The anti-proliferative effect of the test compounds was measured using the following formula.

$$\% \text{ Anti-proliferation} = \frac{\text{Control (CPM)} - \text{Treated (CPM)}}{\text{Control (CPM)}} \times 100$$

Controls consisted of PBMC with PMA and ionomycin (Stimulated) and PBMC with RPMI (Un-stimulated)

The test compounds exhibited IL-17 and TNF-a inhibitory activity in the cytokine release assay in which the compounds were tested. The IC_{50} values for test compounds inhibiting IL-17 are given in Table 1, whereas the IC50 values for test compounds inhibiting TNF-a is given in Table 2.

Table 1: IC_{50} values of the test compounds (IL-17 inhibition)

Test compounds as per Example No.	IC_{50} in µM
2	++
3	+++
6	+++
7	+++
8	++
9	++
11	+++
12	++
18	++
21	+
22	++
34	++
35	+++
36	+++
37	++
38	+++
45 A	++
48	++
48A	++
49	++
50	+++
68	++

Symbol	IC_{50} range class
+++	≤ 0.1 µM but ≤ 1 µM
++	>1 µM but ≤ 10 µM
+	> 10 µM but < 1000 µM

Table 2: IC_{50} values of the test compounds (TNF-a inhibition)

Test compounds as per Example No.	IC_{50} in µM
2	++
6	+++
7	+++
8	++
9	++
11	+++
12	++
18	++
22	++
38	+++
45A	++
48	++
48A	++
49	++
50	+++
68	+

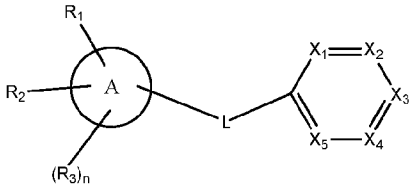
Symbol	IC50 range class
+++	≤ 0.1 µM but ≤ 1 µM
++	> 1 µM but ≤ 10 µM
+	> 10 µM but < 1000 µM

Conclusion:

The IC_{50} values determined for the test compounds are indicative of their IL17 and TNF-a inhibitory activity.

We claim:

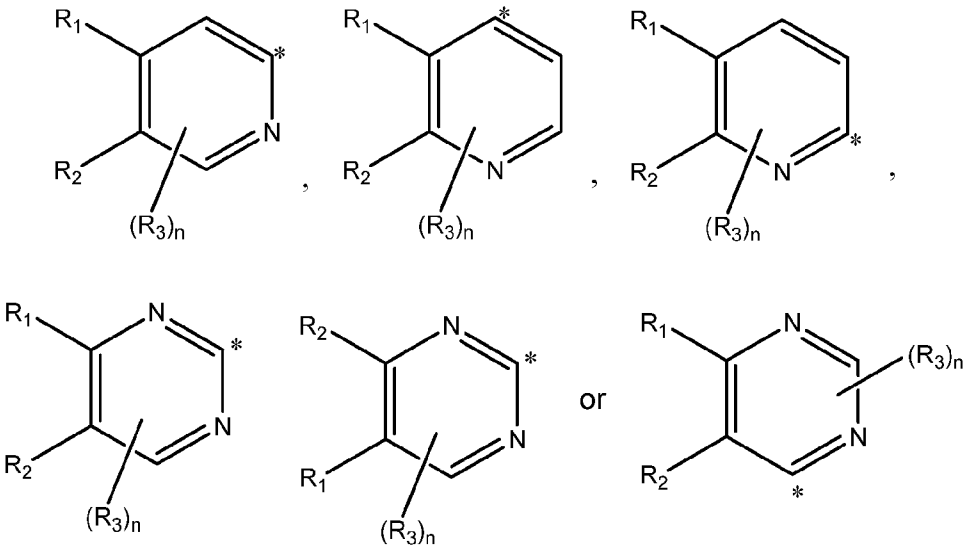
1. A compound of formula I;



Formula I

wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole, pyrrole, a 5- or 6-membered saturated heterocyclic ring system or a heteroaryl ring system selected from:



wherein * indicates the point of attachment to L;

R_1 and R_3 are independently selected from the group consisting of hydrogen, hydroxy, halogen, cyano, nitro, (C_1-C_6)-alkyl, (CrC $_6$)-alkoxy, (CrC $_6$)-alkoxyalkyl, (Ci-C $_6$)-alkylamino, (C_3-C_{12})-cycloalkyl, 0-(C_3-C_{12})-cycloalkyl, halo(C-|-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-Ci $_4$)-aryl, heterocyclyl, 0-(C $_6$-Ci $_4$)aryl, (C_6-Ci $_4$)ar(CrC $_6$)alkyl, (C_6-C_{14})ar(CrC $_6$)alkyloxy, heteroaryl, C(0)R $_a$, C(0)OR $_a$, S(0) $_n$R$_a$, NR$_a$R$_b$ and C(0)NR $_a$R$_b$;

n is an integer from 0 to 2;

R_2 is $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_6)$-alkoxy$(C_1\text{-}C_6)$-alkyl, $(C_3\text{-}C_{12})$-cycloalkyl, O-$(C_3\text{-}C_{12})$-cycloalkyl, $(C_6\text{-}Ci_4)$-aryl, 0-$(C_6\text{-}C_{14})$aryl, $(Ce\text{-}C_{14})ar(C_1\text{-}C_6)$alkyl, $(C_6\text{-}Ci_4)ar(C_1\text{-}Ce)$alkyloxy, heterocyclyl or heteroaryl;

R_2 together with $R\text{-}i$ can form a 5- or 6- membered saturated or unsaturated ring optionally containing 1 to 3 heteroatoms independently selected from the group consisting of O, N and S, which ring is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, $(C_1\text{-}C_6)$-alkyl, $(C_1\text{-}C_6)$-alkoxy, $(C_1\text{-}C_6)$-alkoxyalkyl, $(C_1\text{-}C_6)$-alkylamino, $(C_3\text{-}Ci_2)$-cycloalkyl, O-$(C_3\text{-}Ci_2)$-cycloalkyl, halo(CrC$_6$)alkyl, halo(CrC$_6$)alkoxy, $(C_6\text{-}Cu)$-aryl, 0-$(C_6\text{-}Cu)$aryl, $(C_6\text{-}Ci_4)ar(Ci\text{-}C_6)$alkyl, $(C_6\text{-}Ci_4)ar(Ci\text{-}C_6)$alkyloxy, heterocyclyl, heteroaryl, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, NR_aR_b and $C(0)NR_aR_b$;

L is $^*N(R_4)\text{-}C(0)\text{-}N(R_5)$, $^*C(0)N(R_5)$, $^*N(R_4)\text{-}C(0)$, $^*CH(R_6)\text{-}C(0)\text{-}N(R_5)$, $^*CH(R_6)N(R_5)$, $^*N(R_4)\text{-}S(0)_2$ or $^*NR_4$; wherein * indicates the point of attachment to A;

R_4, $R5$ and $R6$ are independently selected from the group consisting of hydrogen, hydroxy, cyano, (CrC$_6$)-alkyl, (CrC$_6$)-alkoxy, (CrC$_6$)-alkoxyalkyl, (CrC$_6$)-alkylamino, $(C_3\text{-}Ci_2)$-cycloalkyl, 0-$(C_3\text{-}Ci_2)$-cycloalkyl, halo(CrC$_6$)alkyl, halo$(C_1\text{-}C_6)$alkoxy, hydroxyld^-alkyl, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, $P(0)_n(0(Ci\text{-}C_6)alkyl)_2$, O-P(O) $(0(C_1\text{-}C_6)alkyl)_2$ and $C(0)NR_aR_b$;

Xi, X_2, X_4 and X_5 are independently selected from N and $C(R_7)$; wherein R_7 is hydrogen, halogen, hydroxy, nitro, cyano, (C-|-C$_6$)-alkyl, (CrC$_6$)-alkoxy, (C-|-C$_6$)-alkoxy(CrC$_6$)-alkyl, $(C_1\text{-}C_6)$-alkylamino, $(C_3\text{-}Ci_2)$-cycloalkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_2\text{-}C_6)$-alkenyl, $(C_2\text{-}C_6)$-alkynyl, $(C_6\text{-}Ci_4)$-aryl, 0-$(C_6\text{-}Ci_4)$aryl, $(C_6\text{-}Ci_4)ar(C_1\text{-}C_6)$alkyl, $(C_6\text{-}Ci_4)ar(Ci\text{-}C_6)$alkyloxy, heterocyclyl, O-heterocyclyl, heteroaryl, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, $P(0)_n(0(CrC_6)alkyl)_2$, 0-P(0)$(0(C_1\text{-}C_6)alkyl)_2$, NR_aR_b or $C(0)NR_aR_b$;

X_3 is N or $C(R_8)$, wherein R_8 is hydrogen, halogen, hydroxy, cyano, nitro, (CrC$_6$)-alkyl, (CrC$_6$)-alkoxy, $(Ci\text{-}C_6)$-alkoxy$(Ci\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$-alkylamino, $(C_3\text{-}Ci_2)$-cycloalkyl, O-$(C_3\text{-}Ci_2)$-cycloalkyl, halo$(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkoxy, $(C_6\text{-}Ci_4)$-aryl, 0-$(C_6\text{-}Ci_4)$aryl, $(C_6\text{-}Ci_4)ar(Ci\text{-}C_6)$alkyl, $(C6\text{-}Ci_4)ar(CrC_6)$alkyloxy, heterocyclyl, O-heterocyclyl, heteroaryl, $C(0)R_a$, $C(0)OR_a$, $S(0)_nR_a$, NR_aR_b or $C(0)NR_aR_b$;

provided that no more than three of the X_1 to X_5 positions can be simultaneously N;

when two or more of X_1, X_2, X_4 and X_5 represent $C(R_7)$ then R_7 groups on the two adjacent carbon atoms can form a 3-7 membered unsaturated or saturated fused ring optionally containing 1 to 3 heteroatoms independently selected from the group consisting of O, N and S; wherein the ring can be unsubstituted or substituted with 1-3 groups of R_c; or

when any one of X_2 and X_4 represent $C(R_7)$ and X_3 represents $C(R_8)$ then the R_7 group together with the R_8 group can form a 3-7 membered fused ring optionally containing 1 to 3 heteroatoms selected from O, N or S; wherein the ring can be unsubstituted or substituted with 1-3 groups of R_c;

R_a and R_b are independently selected from the group consisting of hydrogen, (C_1-C_6)-alkyl, (C_3-C_{12})-cycloalkyl, halo(C_1-C_6)alkyl, (C_6-C_{14})-aryl, (C_6-C_{14})ar(C_1-C_6)alkyl, heterocyclyl, heteroaryl, and $S(O)_nR_a$; or

R_a and R_b, can form a 3-7 membered saturated or unsaturated ring optionally containing one or more heteroatoms selected from N, O or S, which is unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, cyano, nitro, (C_1-C_6)-alkyl, (C_1-C_6)-alkoxy, (C_1-C_6)-alkylamino, (C_3-C_{12})-cycloalkyl, O-(C_3-C_{12})-cycloalkyl, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl, O-(C_6-C_{14})aryl, (C_6-C_{14})ar(C_1-C_6)alkyl, heterocyclyl, heteroaryl, $C(O)R_a$, $C(O)OR_a$, $S(O)_nR_a$, $P(O)_n(O(C_1-C_6)alkyl)_2$, O-P(O)(O$(C_1-C_6)$alkyl)$_2$, NR_aR_b and $C(O)NR_aR_b$;

wherein:

each of the (C_1-C_6)alkyl and (C_1-C_6)-alkoxy can be unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (C_1-C_6)-alkoxy-$(R_c)_{0-3}$, (C_3-C_{12})-cycloalkyl-$(R_c)_{0-3}$, O-(C_3-C_{12})-cycloalkyl-$(R_c)_{0-3}$, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl-$(R_c)_{0-3}$, O-(C_6-C_{14})aryl-$(R_c)_{0-3}$, (C_6-C_{14})ar(C_1-C_6)alkyl-$(R_c)_{0-3}$, heterocyclyl-$(R_c)_{0-3}$, heteroaryl-$(R_c)_{0-3}$, $C(O)R_a$, $C(O)OR_a$, $S(O)_nR_a$, $P(O)n(O(C_1-C_6)alkyl)_2$, O-P(O)(O(C_1-C_6)alkyl)$_2$, NR_aR_b and $C(O)NR_aR_b$;

heterocyclyl refers to a 3-12 membered saturated or partially unsaturated monocyclic or bicyclic ring system containing one to four identical or different heteroatoms independently selected from the group consisting of N, S and O;

heteroaryl refers to a 5-10 membered aromatic monocyclic or bicyclic ring system containing one to four identical or different heteroatoms independently selected from the group consisting of N, S and O;

each of the (C_2-C_6)-alkenyl, (C_2-C_6)-alkynyl, (C_3-C_{12})-cycloalkyl, (C_6-Ci_4)-aryl, (C_6-Ci_4)ar(CrC$_6$)alkyl, heterocyclyl and heteroaryl can be unsubstituted or substituted with one or more groups independently selected from the group consisting of halogen, hydroxy, nitro, cyano, (CrC6)alkyl-(R_c)o-3, (Ci-C_6)-alkoxy-(R_c)o-3, (C_3-C_{12})-cycloalkyl-(R_c)o-3, 0-(C_3-C_{12})-cycloalkyl-(R_c)o-3, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-Ci_4)-aryl-(Rc)o-3, 0-(C_6-Ci_4)aryl-(R_c)o-3, (C_6-Ci_4)ar(Ci-C_6)alkyl-(R_c)o-3, heterocyclyl-(R_c)o-3, heteroaryl-(R_c)o-3, C(0)R_a, C(0)OR_a, S(0)$_n$$R_a$, P(0)$_n$(0(Ci-$C_6$)alkyl)$_2$, O-P(O) (0($C_1$-$C_6$)alkyl)$_2$, N$R_a$$R_b$ and C(0)N$R_a$$R_b$; and

R_c is halogen, hydroxy, cyano, nitro, (Ci-C_6)-alkyl-(Rc)o-i, (Ci-C_6)-alkoxy-(Rc)o-i, (C_3-C_{12})-cycloalkyl-(R_c)o-i, O-(C_3-C_{12})-cycloalkyl-(R_c)$_0$-i, hydroxy(Ci-C_6)-alkyl-(R_c)$_0$-i, halo(C_1-C_6)alkyl, halo(C_1-C_6)alkoxy, (C_6-C_{14})-aryl-(R_c)$_0$-i, O-(C_6-C_{14})aryl-(R_c)$_0$-i, (C_6-Ci_4)ar(Ci-C_6)alkyl-(R_c)o-i, heterocyclyl-(R_c)$_0$-i, heteroaryl-(R_c)$_0$-i, C(0)R_a, C(0)OR_a, SR_a, S(0)$_n$$R_a$, P(0)n(0(Ci-$C_6$)alkyl)$_2$, 0-P(0)(0($C_1$-$C_6$)alkyl)$_2$, N$R_a$$R_b$ or C(0)N$R_a$$R_b$; and

with the provisos that:

(c) when A is pyrazole then L is a group other than *C(0)N(R_5) and *N(R_4)-C(0); and

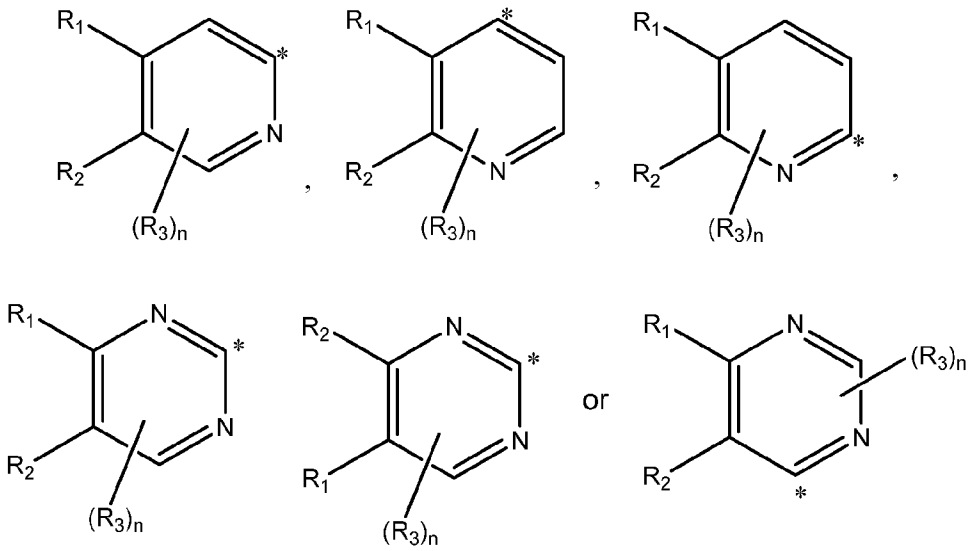
(d) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then the said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer or a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

2. The compound according to claim 1,

wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole, pyrrole or a heteroaryl ring system selected from:



wherein * indicates the point of attachment to L; with the provisos that:

(c) when A is pyrazole then L is a group other than *C(0)N(R_5) and *N(R_4)-C(0); and

(d) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

3. The compound according to claim 1 or claim 2,

wherein,

A is triazole, pyrazole, imidazole, oxazole, isoxazole, thiazole or pyrrole;

with the provisos that:

(a) when A is pyrazole then L is a group other than *C(0)N(R_5) and *N(R_4)-C(0); and

(b) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

4. The compound according to any one of the claims 1-3,

wherein,

A is triazole, pyrazole, isoxazole or thiazole;

L is $^*N(R_4)$-C(0)-N(R_5), $^*C(0)N(R_5)$, $^*N(R_4)$-C(0), $^*CH(R_6)$-C(0)-N(R_5), $^*CH(R_6)N(R_5)$, $^*N(R_4)$-$S(0)_2$ or $^*NR_4$; wherein * indicates the point of attachment to A;

with the provisos that:

(c) when A is pyrazole then L is a group other than $^*C(0)N(R_5)$ and $^*N(R_4)$-C(0); and

(d) when A is pyrazole and L is *$N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

5. The compound according to any one of the claims 1-4,

wherein,

A is triazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

6. The compound according to any one of the claims 1-4,

wherein,

A is pyrazole;

L is $^*N(R_4)$-C(0)-N(R_5); $^*CH(R_6)$-C(0)-N(R_5); $^*CH(R_6)N(R_5)$; $^*N(R_4)$-$S(0)_2$ or $^*NR_4$; wherein * indicates the point of attachment to A;

with the proviso that when L is $^*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

7. The compound according to any one of the claims 1-4,

wherein,

A is isoxazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

8. The compound according to any one of the claims 1-4,

wherein,

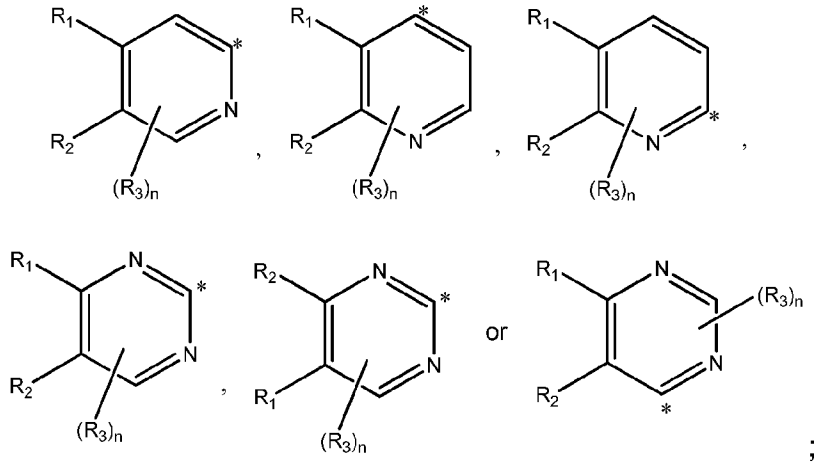
A is thiazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

9. The compound according to claim 1 or claim 2,

wherein,

A is



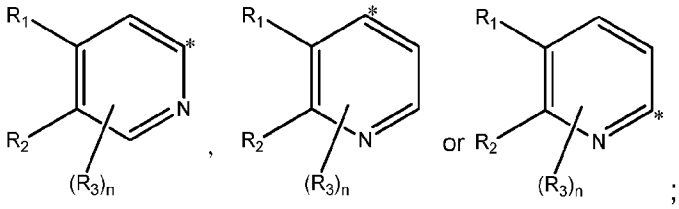
wherein * indicates the point of attachment to L;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

10. The compound according to any one of the claims 1, 2 and 9,

wherein,

A is



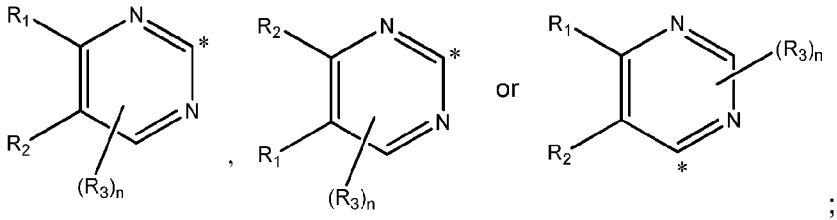
wherein * indicates the point of attachment to L;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

11. The compound according to any one of the claims 1, 2 and 9,

wherein,

A is



wherein * indicates the point of attachment to L;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

12. The compound according to claim 1 or claim 2,

wherein,

each of X_1, X_2, X_4 and X_5 is $C(R_7)$; and X_3 is $C(R_8)$;

with the provisos that:

(c) when A is pyrazole then L is a group other than $*C(0)N(R_5)$ or $*N(R_4)$-C(0); and

(d) when A is pyrazole and L is $*N(R_4)$-C(0)-$N(R_5)$, then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

13. The compound according to any one of the claims 1-4 and 12,

wherein,

A is triazole, pyrrazole, isoxazole or thiazole;

each of Xi, X_2, X_4 and X_5 is $C(R_7)$; and X_3 is $C(R_8)$;

with the provisos that:

(c) when A is pyrazole then L is a group other than $*C(0)N(R_5)$ or $*N(R_4)$-C(0); and

(d) when A is pyrazole and L is $*N(R_4)$-C(0)-$N(R_5)$, then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

14. The compound according to any one of the claims 1-4, 12 and 13,

wherein,

A is triazole or pyrazole;

L is $*N(R_4)$-C(0)-$N(R_5)$; wherein * indicates the point of attachment to A; and

each of Xi, X_2, X_4 and X_5 is $C(R_7)$; and X_3 is $C(R_8)$;

with the proviso that when A is pyrazole the said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

15. The compound according to any one of the claims 1-5 and 12-14, wherein,

A is triazole;

L is $^{*}N(R_4)$-C(0)-N(R_5); $^{*}C(0)N(R_5)$, $^{*}CH(R_6)$-C(0)-N(R_5); $^{*}CH(R_6)N(R_5)$ or $^{*}N(R_4)$-S(0)2 ;wherein * indicates the point of attachment to A;

each of Xi, X_2, X_4 and X_5 is $C(R_7)$; and X_3 is $C(R_8)$;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

16. The compound according to any one of the claims 1-4, 6 and 12-14, wherein,

A is pyrazole;

L is $*N(R_4)$-C(0)-N(R_5); $N(R_4)$-$S(0)_2$ or $*CH(R_6)N(R_5)$; wherein * indicates the point of attachment to A;

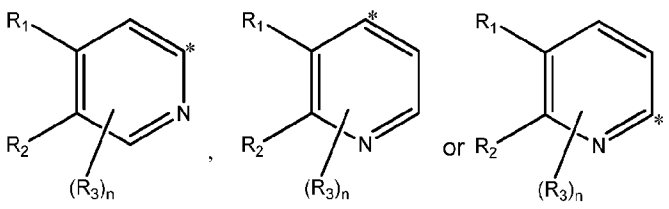
each of Xi, X_2, X_4 and X_5 is $C(R_7)$; and X_3 is $C(R_8)$;

with the proviso that when A is pyrazole and L is $*N(R_4)$-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

17. The compound according to any one of the claims 1, 2, 9, 10 and 12, wherein,

A is



;

wherein * indicates the point of attachment to L;

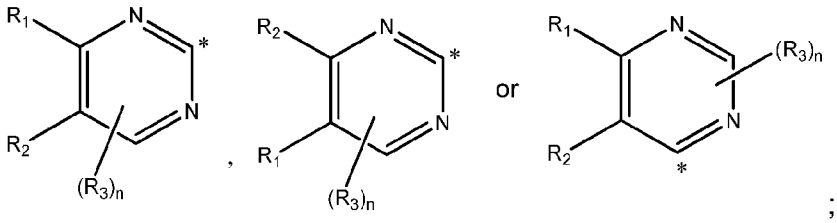
L is *N(R_4)-C(0)-N(R_5); *C(0)N(R_5); *N(R_4)-S(0)$_2$ or *NR_4; wherein * indicates the point of attachment to A;

each of Xi, X_2, X_4 and X_5 is C(R_7); and X_3 is C(R_8);

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

18. The compound according to any one of the claims 1, 2, 9, 11 and 12, wherein,

A is



;

wherein * indicates the point of attachment to L;

L is *N(R_4)-C(0)-N(R_5); *C(0)N(R_5); N(R_4)-S(0)$_2$ or *NR_4; wherein * indicates the point of attachment to A;

each of X_1, X_2, X_4 and X_5 is C(R_7); and X_3 is C(R_8);

or an isotopic form, a stereoisomer, a tautomer, a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

19. The compound according to claim 1 or claim 2, wherein,

one of X-i, X_2, X_4 or X_5 is N, while the remaining are C(R_7); X3 is N or C(Rs); or

any two of X-i, X_2, X_4 or X_5 are N, while the remaining are C(R_7); X_3 is N or C(R_8); with the provisos that:

(c) when A is pyrazole then L is a group other than *C(0)N(R_5) or *N(R_4)-C(0); and

(d) when A is pyrazole and L is *N(R_4)-C(0)-N(R_5), then said L group is not attached to 5-position of pyrazole;

or an isotopic form, stereoisomer or a tautomer or a pharmaceutically acceptable salt, a solvate, a polymorph, a prodrug, N-oxide or S-oxide thereof.

20. The compound according to any one of the claims 1 to 19, wherein said compound is selected from

1-(5-Methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)-3-(2-(trifluoromethyl)-1 H-benzo[d]imidazol-6-yl)urea;

1-(4-(4-(4-Chlorophenyl)-4-hydroxypiperidin-1 -yl)-3-cyanophenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(3-Cyano-4-(4-(2-hydroxyethyl)piperidin-1 -yl)phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(5-Methyl-1 -phenyl-1 H-pyrazol-4-yl)-3-(naphthalen-1 -yl)urea;

1-(1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1-yl) phenyl) urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(3-Cyano-4-(piperazin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(5-Chloro-6-morpholinopyridin-3-yl)-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(3-Cyano-4-(4-(4-fluoro-3-(trifluoromethyl) benzoyl) piperazin-1 -yl) phenyl)-3-(5-methyl-1 -(4-(trifluoromethyl)phenyl)-1 H-pyrazol-4-yl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-1 -methyl-3-(5-methyl-1 -(4-(trifluoromethyl) phenyl)-1 H-pyrazol-4-yl) urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholinopiperidin -1-yl)phenyl)urea;

1-(4-([1 ,4'-Bipiperidin]-1 '-yl)-3-cyanophenyl)-3-(1 -(4-chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

2-(1 -(4-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-2-cyanophenyl) piperidin-4-yl)ethyl diethyl phosphate;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(2-methoxyethyl) piperidin-1 -yl)phenyl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(4-(4-morpholinopiperidin-1 -yl)-2-(trifluoromethyl)phenyl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(1 -(4-morpholinophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(4-(1 ,1 ,1 ,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-3-(1 -(4-isopropylphenyl) -1H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-5-methyl-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-morpholino piperidin-1 -yl)phenyl)urea;

3-(3-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-N-(4-hydroxy-3-methoxy benzyl)benzamide;

4-(1-(2-Cyano-4-(3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido) phenyl)piperidin-4-yl)butanoic acid;

1-(3-Cyano-4-(4-(pyrimidin-2-yl)piperazin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl) phenyl)-1H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(piperazin-1 -yl)phenyl) urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-(4-morpholinopiperidin-1 -yl) pyridin-2-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(4-cyano-5-(4-morpholinopiperidin -1-yl)pyridin-2-yl)urea;

1-(6-(4-Morpholinopiperidin-1 -yl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(5-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)pyridin-2-yl)piperidine-4-carboxylic acid;

1-(6-(4-(Pyrimidin-2-yl)piperazin-1 -yl)-5-(trifluoromethyl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(5-Chloro-6-(4-morpholinopiperidin-1 -yl)pyridin-3-yl)-3-(1 -(4-chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-methyl-6-(4-morpholino piperidin-1-yl)pyridin-3-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-methyl-6-(4-(pyrimidin-2-yl)piperazin-1 -yl)pyridin-3-yl)urea;

1-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(5-cyano-6-(4-(pyrimidin-2-yl)piperazin-1 -yl)pyridin-3-yl)urea;

1-(6-(4-Cyano-4-phenylpiperidin-1 -yl)pyridin-3-yl)-3-(1 -(3-(trifluoromethyl) phenyl)-1 H-1,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(piperidin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)phenyl)-3-(1 -(4-(trifluoro methyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-(cyclopropylmethyl) piperazin-1 -yl)phenyl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-methoxypiperidin-1 -yl)phenyl)urea;

1-(3-Cyano-4-(4-(3-hydroxyphenyl)piperazin-1 -yl)phenyl)-3-(1 -(p-tolyl)-l H-1 ,2,3-triazol-4-yl)urea;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(1 -(3-(trifluoromethyl) phenyl)-1 H-1,2,3-triazol-4-yl)urea;

1-(1 -(4-Chlorophenyl)-1 H-1 ,2,3-triazol-4-yl)-3-(3-cyano-4-(4-hydroxypiperidin-1 -yl)phenyl)-1 ,3-dimethylurea;

1-(4-(3-(1 -(4-(Tert-butyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)ureido)-2-cyanophenyl)-4-(2-hydroxypropan-2-yl)piperidin-1 -ium methanesulfonate;

1-(3-Cyano-4-(piperazin-1 -yl)phenyl)-3-(1 -(4-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)urea hydrochloride;

1-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(3-(4-fluorophenyl)-5-methylisoxazol-4-yl)urea;

1-(4-(Tert-butyl) phenyl)-N-(3-cyano-4-(4-(2-hydroxyethyl) piperidin-1 -yl) phenyl)-1 H-1 , 2, 3-triazole-4-carboxamide;

1-(4-(Tert-butyl) phenyl)-N-(3-cyano-4-(4-hydroxypiperidin-1 -yl) phenyl)-1 H-1 , 2, 3-triazole-4-carboxamide;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide hydrochloride;

1-(4-Chlorophenyl)-N-(3-cyano-4-(4-(pyrimidin-2-yl)piperazin-1 -yl)phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

N-(3-Cyano-4-(4-morpholinopiperidin-1 -yl) phenyl)-5-pentyl-1 -(3-(trifluoromethyl) phenyl)-1 H-1 ,2,3-triazole-4-carboxamide;

N-(3-Cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)-3-(4-fluorophenyl)-4-rnethylisoxazole-5-carboxamide;

3-(4-Chlorophenyl)-N-(3-cyano-4-(4-morpholinopiperidin-1 -yl)phenyl)isoxazole-5-carboxamide;

N-(1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)-3-cyano-4-(4-morpholino piperidin-1 -yl)benzenesulfonamide;

N-(4-(3-Methoxyphenyl)pyrimidin-2-yl)-5-phenylthiazol-2-arnine;
5-Phenyl-N-(4-(4-(trifluoromethoxy)phenyl)pyrimidin-2-yl)thiazol-2-amine;
N-(4-(2-Methoxyphenyl)pyrimidin-2-yl)-5-phenylthiazol-2-arnine;
5-((6-Fluorobenzo[d]thiazol-2-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;
5-((4-(3, 5-Dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;
5-((4-(3, 5-Dimethoxyphenyl) pyrimidin-2-yl) amino)-2-(4-(hydroxymethyl) piperidin-1 -yl) benzonitrile;
4-(2-Methoxyphenyl)-N-(4-(4-(pyrimidin-2-yl)piperazin-1 -yl)-3-(trifluoromethyl) phenyl) pyrimidin-2-amine;
1,1,1,3,3,3-Hexafluoro-2-(4-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino)phenyl) propan-2-ol;
2-(4-Hydroxypiperidin-1 -yl)-5-((4-(3-methoxyphenyl)pyrimidin-2-yl)amino) benzonitrile;
5-((4-Morpholinopyrimidin-2-yl)amino)-2-(4-(pyridin-2-yl)piperazin-1 -yl)benzonitrile
2-morpholino-5-((4-morpholinopyrimidin-2-yl)amino)benzonitrile;
5-((4-((2-Morpholinoethyl)amino)pyrimidin-2-yl)amino)-2-(4-morpholino piperidin-1 -yl)benzonitrile;
5-((2-Chloro-6-methoxyquinolin-4-yl) amino)-2-(4-morpholinopiperidin-1 -yl) benzonitrile;
2-(4-Morpholinopiperidin-1 -yl)-5-(quinolin-2-ylamino) benzonitrile;
5-((Cyano(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(2-hydroxypropan-2-yl)piperidin-1 -yl)benzonitrile;
5-((Cyano(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)methyl)amino)-2-(4-(pyrimidin-2-yl)piperazin-1 -yl)benzonitrile;
2-Chloro-5-(((1 -(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino) benzonitrile;
5-(((1 -(4-Chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)amino)-2-(4-morpholino piperidin-1 -yl)benzonitrile;
Diethyl (((4-chloro-3-cyanophenyl)amino)(1 -(4-chlorophenyl)-5-methyl-1 H-pyrazol-4-yl)methyl)phosphonate;
N-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-2-hydroxy-2-(1 -(3-(trifluoromethyl)phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide; or
N-(3-Cyano-4-(4-methoxypiperidin-1 -yl)phenyl)-2-hydroxy-2-(1 -(3 (trifluoromethyl) phenyl)-1 H-1 ,2,3-triazol-4-yl)acetamide; or
a stereoisomer, a tautomer or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in any one of the claims 1-20, or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; and at least one pharmaceutically acceptable carrier or excipient.

22. A method for the treatment of a disease or disorder mediated by IL-17 or TNF-a, comprising administering to a subject in need thereof; a therapeutically effective amount of a compound as defined in any one of the claims 1-20, or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof.

23. The method according to claim 22, wherein the disease or disorder is selected from the group consisting of an autoimmune or inflammatory disease or disorder; and a metabolic disease or disorder.

24. The method according to claim 23, wherein the autoimmune or inflammatory disease or disorder is selected from the group consisting of inflammatory bowel disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, refractory rheumatoid arthritis, chronic non-rheumatoid arthritis, ankylosing spondylitis, osteoporosis/bone resorption, chronic graft-versus-host disease, acute graft-versus-host disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, asthma, bronchitis, epidermal hyperplasia, Crohn's disease, atherosclerosis, septic shock syndrome, coronary heart disease, vasculitis, ulcerative colitis, psoriasis, adult respiratory distress syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Type I diabetes, Graves' disease, Addison's disease, Raynaud's phenomenon, autoimmune hepatitis, psoriatic epidermal hyperplasia and delayed type hypersensitivity in skin disorders.

25. The method according to claim 23, wherein the metabolic disease or disorder is selected from the group consisting of obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, low adiponectin level, dyslipoproteinemia, impaired glucose

tolerance, insulin resistance, increase in HbA1 c (glycosylated haemoglobin) level, reduced metabolic activity and Type II diabetes.

26. A compound according to any one of the claims 1-20, or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as an IL-1 7 inhibitor.

27. A compound according to any one of the claims 1-20, or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; for use as a TNF-a inhibitor.

28. A compound as defined in any one of the claims 1-20, or a stereoisomer, a tautomer or a pharmaceutically acceptable salt or a solvate thereof; for use in the treatment of a disease or a disorder mediated by IL-1 7 or TNF-a.

29. The compound for the use according to claim 28, wherein the disease or disorder is selected from the group consisting of an autoimmune or inflammatory disease or disorder; and a metabolic disease or disorder.

30. The compound for the use according to claim 29, wherein the autoimmune or inflammatory disease or disorder is selected from the group consisting of inflammatory bowel disease, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, refractory rheumatoid arthritis, chronic non-rheumatoid arthritis, ankylosing spondylitis, osteoporosis/bone resorption, chronic graft-versus-host disease, acute graft-versus-host disease, multiple sclerosis, systemic lupus erythematosus, Celiac Sprue, idiopathic thrombocytopenic thrombotic purpura, myasthenia gravis, Sjogren's syndrome, scleroderma, asthma, bronchitis, epidermal hyperplasia, Crohn's disease, atherosclerosis, septic shock syndrome, coronary heart disease, vasculitis, ulcerative colitis, psoriasis, adult respiratory distress syndrome, myolitis, polymyolitis, dermatomyolitis, polyarteritis nodossa, Wegener's granulomatosis, arteritis, polymyalgia rheumatica, sarcoidosis, sclerosis, primary biliary sclerosis, sclerosing cholangitis, dermatitis, atopic dermatitis, Still's disease, chronic obstructive pulmonary disease, Guillain-Barre disease, Type I diabetes, Graves' disease, Addison's disease, Raynaud's

phenomenon, autoimmune hepatitis, psoriatic epidermal hyperplasia and delayed type hypersensitivity in skin disorders.

31. The compound for the use according to claim 29, wherein the metabolic disease or disorder is selected from the group consisting of obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, low adiponectin level, dyslipoproteinemia, impaired glucose tolerance, insulin resistance, increase in HbA1c (glycosylated haemoglobin) level, reduced metabolic activity and Type II diabetes.

32. Use of a compound as defined in any one of the claims 1-20 or a stereoisomer, a tautomer, a pharmaceutically acceptable salt or a solvate thereof; in combination with one further therapeutically active agent; for the treatment of a disease or a disorder mediated by IL-17 or TNF-a.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/061299

A. CLASSIFICATION OF SUBJECT MATTER

[See Supplemental Sheet]

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

Registry, CAplus: Substructure search (based on Formula I as limited to variables as defined in invention 1.

Applicant in Patentscope: PTRAMAL ENTERPRISES LIMITED

Inventors in Google: SHARMA, Rajiv; JAIN, Arunkumar; SAHU, Bichismita; SINGH, Deepak; MALT, Sunil.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

Ψ Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 October 2014	14 October 2014
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Pina Potenza AUSTRALIAN PATENT OFFTCE (ISO 9001 Quality Certified Service) Telephone No. 0399359614

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/IB201 4/061 299**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/061923 A2 (TAKEDA SAN DIEGO, INC.) 31 May 2007 Abstract; page 67 specifically the 12th, 13th and 14th listed compounds; claim 1 for a generic definition; claim 96, page 253, specifically the 17th, 18th and 19th listed compounds; claim 119	1-5, 12-15, 19-32
X	WO 2006/124692 A2 (WYETH [US/US]) 23 November 2006 Abstract, compounds associated with CAS Registry Numbers RN 915361-49-8, RN 915361-50-1, RN 915361-83-0, RN 915362-00-4, RN 915363-19-8, RN 915363-40-5; Claims 1-2, 6-7, 9-15, 17-18, 22-24, 26 and 30-33	1-5, 12-15, 19-32
X	WO 2006/024034 A1 (TARGEGEN, INC.) 02 March 2006 Abstract; general structure (B), page 32-33; Examples 30, 42, 47, 54, 56, 68; Claims 18, 69, 72-74	1-5, 12-15, 19-32
X	WO 2005/000298 A2 (TRIAD THERAPEUTICS, INC.) 06 January 2005 Abstract; Example 7, page 78; Claims 1, 14, 17, 50, 52, 55-56, 77 and 79	1-5, 12-15, 19-32
X	WO 2004/052280 A2 (IMCLONE SYSTEMS INCORPORATED) 24 June 2004 Abstract; page 22 Formula (la"); Table 3, Cmpd. Nos. 161-167, 176-182, 184, 185, 212 and 213; Claim 6	1-5, 12-15, 19-32
X	WO 2000/025780 A1 (BRISTOL-MYERS SQUIBB COMPANY) 11 May 2000 Abstract; page 14 formula (II) and (III); Examples 1, 4-15, 17-21, 25-28; Claims 3, 7-10	1-5, 12-15, 19-32

Supplemental Box - IPC **Marks**

C07D 413/02 (2006.01)

C07D 413/14 (2006.01)

C07D 417/12 (2006.01)

C07D 207/30 (2006.01)

C07D 213/02 (2006.01)

C07D 231/10 (2006.01)

C07D 239/20 (2006.01)

C07D 247/02 (2006.01)

C07D 249/06 (2006.01)

C07D 261/02 (2006.01)

C07D 263/02 (2006.01)

C07D 275/02 (2006.01)

C07D 277/20 (2006.01)

A61K 31/4192 (2006.01)

A61K 31/4196 (2006.01)

A61K 31/4164 (2006.01)

A61K 31/422 (2006.01)

A61K 31/426 (2006.01)

A61K 31/44 (2006.01)

A61K 31/495 (2006.01)

A61K 31/506 (2006.01)

A61P 3/08 (2006.01)

A61P 9/00 (2006.01)

A61P 11/00 (2006.01)

A61P 17/00 (2006.01)

A61P 31/12 (2006.01)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/061299

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

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

1. ☐ Claims Nos.:

because they relate to subject matter not required to be searched by this Authority, namely:

the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☐ Claims Nos.:

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

3. ☐ Claims Nos:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

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

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

See Supplemental Box for Details

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. :
1-4, 12-14, 19-32 (in part) and 5, 15 (in full)

Remark **on Protest**

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

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

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of: Box III
This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

For Markush claims, the requirement of a technical interrelationship and the same corresponding special technical features defined by PCT Rule 13.2 is considered to be met when all alternatives are of a similar nature. When the Markush grouping is for alternatives of chemical compounds, they are regarded as being of a similar nature where the following criteria are fulfilled:

a) All alternatives have a common property or activity; and

b) A common structure is present, that is, a significant structural element is shared by all of the alternatives.

As noted in the PCT Guidelines, the words *'significant structural element is shared by all of the alternatives'* refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity.

The present invention *prima facie* resides in the treatment of conditions associated with an autoimmune or inflammatory disease or disorder; and/or a metabolic disease or disorder, using a compound of Formula (I) as set out in claims 21-32.

In order to provide a meaningful search and examination for the applicant, the International Searching Authority (ISA) has attempted to identify distinct groups or classes of compounds from the claims and examples provided in the specification. To this end, the ISA has found that there are at least eleven different inventions based on the following features that separate the claims into distinct groups:

INVENTION **1:**

Claims 1-4, 12-14, 19-32 (in part) and 5, 15 (in full).

Compounds of formula I wherein:

A=triazole,

$X_1 = X_2 = X4 = X5$ = C(R_7) or N,

X3 = C(Rg) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R_4)-C(0), *CH(Rg)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)$_2$ or ¾NR4, wherein R_4=R_5=H or **CH3,** R_6=H, OH or C≡N.

INVENTION 2:

Claims 1-4, 12-14, 19-32 (in part) and 6, 16 (in full).

Compounds of formula I wherein:

A=pyrazole

Supplemental Box

$X_1 = X_2 = X_4 = X_5 = C(R_7)$ or N,

$X_3 = C(R_8)$ or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R_4)-C(0), *CH(R_6)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)2 or *NR_4, wherein R_4=R5=H or **CH3,** R_6=H, OH or C≡N.

INVENTION 3:

Claims 1-3, 12, 19, 21-32 (all in part)

Compounds of formula I wherein:

A=imidazole

$X_1 = X_2 = X_4 = X_5 = C(R_7)$ or N,

$X_3 = C(R_8)$ or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R4)-C(0), *CH(R6)-C(0)-N(R_5), *CH(R6)N(R_5), *N(R4)-S(0)$_2$ or *NR4, wherein R_4=R5=H or **CH3,** R_6=H, OH or C≡N.

INVENTION 4:

Claims 1-3, 12, 19, 21-32 (all in part)

Compounds of formula I wherein:

A=pyrrole

$X_1 = X_2 = X_4 = X_5 = C(R_7)$ or N,

X_3 = C(R8) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R_4)-C(0), *CH(R6)-C(0)-N(R_5), *CH(Rg)N(R_5), *N(R4)-S(0)$_2$ or *NR4, wherein R_4=R_5=H or CH_3, R_6=H, OH or C≡N.

INVENTION 5:

Claims 1-3, 12, 19, 21-32 (all in part)

Compounds of formula I wherein:

A=oxazole

$X_1 = X_2 = X_4 = X_5$ = C(R_7) or N,

X_3 = C(Rg)

L = *N(R4)-C(0)-N(R5), *C(0)N(R5), *N(R4)-C(0), *CH(R^)-C(0)-N(R5), *CH(R5)N(R5), *N(R4)-S(0)2 or *NR4, wherein R4=R_5=H or CH_3, R6=H, OH or C≡N.

INVENTION 6:

Claims 1-4, 12-13, 19-32 (in part) and 7 (in full)

Compounds of formula I wherein:

A=isoxazole

Xl= X_2 =X_4= **X5** = C(R7) or N,

X_3 = C(Rg) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R4)-C(0), *CH(R_6)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)$_2$ or *NR4, wherein R_4=R_5=H or CH_3, R6=H, OH or C≡N.

INVENTION 7:

Claims 1-4, 12-13, 19-32 (in part) and 8 (in full)

Compounds of formula I wherein:

A=thiazole

Xl= X_2 =X_4= **X5** = C(R_7) or N,

X_3 = C(R8) or N,

L = *N(R4)-C(0)-N(R_5), *C(0)N(R_5), *N(R4)-C(0), *CH(R6)-C(0)-N(R_5), *CH(R<5)N(R_5), *N(R4)-S(0)$_2$ or *NR4, wherein R_4=R_5=H or **CH3,** R_6=H, OH or C≡N.

INVENTION 8:

Claims 1, 12, 19, 21-32 (all in part)

Compounds of formula I wherein:

A=5-membered saturated heterocyclic ring system

Xl= X_2 =X_4= **X5** = C(R_7) or N,

X_3 = C(R8) or N,

L = *N(R4)-C(0)-N(R5), *C(0)N(R5), *N(R4)-C(0), *CH(R^)-C(0)-N(R5), *CH(R_6)N(Rs), *N(R4)-S(0)2 or *NR_4, wherein R_4=R_5=H or CH_3, R_6=H, OH or **C**≡N.

INVENTION 9:

Claims 1, 12, 19, 21-32 (all in part)

Compounds of formula I wherein:

A=6-membered saturated heterocyclic ring system

Xl= X_2 =X_4 = X5 = C(R_7) or N,

X3 = C(Rg) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R_4)-C(0), *CH(R_6)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)2 or *NR4, wherein R_4=R_5=H or CH3, R_6=H, OH or ON.

INVENTION 10:

Claims 1-2, 9, 12, 19-32 (in part) and 11. 18 (in full)

Compounds of formula I wherein:

A=pyrimidine

X_1= X_2 =X_4 = X5 = C(R7) or N,

X3 = C(Rg) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R4)-C(0), *CH(R_6)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)$_2$ or *N¾4, wherein R_4=R_5=H or CH3, R_6=H, OH or ON.

INVENTION 11:

Claims 1-2, 9, 12, 19-32 (in part) and 10, 17 (in full)

Compounds of formula I wherein:

A=pyridme

X_1= X2 =X_4 = X5 = C(R_7) or N,

X3 = C(Rg) or N,

L = *N(R_4)-C(0)-N(R_5), *C(0)N(R_5), *N(R_4)-C(0), *CH(R_6)-C(0)-N(R_5), *CH(R_6)N(R_5), *N(R4)-S(0)$_2$ or *N¾4, wherein R_4=R5=H or CH3, R_6=H, OH or ON.

INTERNATIONAL SEARCH REPORT	International application No. PCT/IB201 4/061 299

Supplemental Box

PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art. When there is no special technical feature common to all the claimed inventions there is no unity of invention.

In the above groups of claims, the identified features may have the potential to make a contribution over the prior art but are not common to all the claimed inventions and therefore cannot provide the required technical relationship. The only feature common to all of the claimed inventions and which provides a technical relationship among them is a compound of formula I comprising an aryl or heteroaryl group linked to a cyclic group A via a nitrogen containing linker.

However this feature does not make a contribution over the prior art because it is disclosed in:

WO 2007/061923 A2 (TAKEDA SAN DIEGO, INC.) 31 May 2007 (see Abstract; page 67 specifically the 12th, 13th and 14th listed compounds; claim 1 for a generic definition; and claim 96, page 253, specifically the 17th, 18th and 19th listed compounds).

Therefore in light of this document this common feature cannot be a special technical feature. Therefore there is no special technical feature common to all the claimed inventions and the requirements for unity of invention are consequently not satisfied *a posteriori.*

As the search and examination for the additional inventions will each require more than negligible additional search and examination effort over that for the first invention and each other invention, additional search fees are warranted.

Because no additional search fees were paid, the International Search Report and the Written Opinion of the International Searching Authority is established and restricted to Invention 1 only, in present claims 1-5, 12-15 and 19-32.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2014/061299**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2007/061923 A2	31 May 2007	EP 1948614 A2	30 Jul 2008
		JP 2009515997 A	16 Apr 2009
		US 2007197532 A1	23 Aug 2007
		US 2011070297 A1	24 Mar 2011
WO 2006/124692 A2	23 November 2006	AU 2006247520 A1	23 Nov 2006
		BR PI0609928 A2	11 May 2010
		CA 2608540 A1	23 Nov 2006
		CN 101223143 A	16 Jul 2008
		EP 1888529 A2	20 Feb 2008
		JP 2008540656 A	20 Nov 2008
		MX 2007014261 A	22 Jan 2008
		US 2006264460 A1	23 Nov 2006
WO 2006/024034 A1	02 March 2006	AU 2005276974 A1	02 Mar 2006
		AU 2005276974 B2	02 Aug 2012
		CA 2578283 A1	02 Mar 2006
		CN 101044125 A	26 Sep 2007
		CN 101654452 A	24 Feb 2010
		EP 1799656 A1	27 Jun 2007
		EP 2532653 A1	12 Dec 2012
		IL 181524 A	30 Apr 2013
		JP 2008510839 A	10 Apr 2008
		JP 5275628 B2	28 Aug 2013
		JP 2012167111 A	06 Sep 2012
		MX 2007002208 A	08 May 2007
		NZ 553492 A	26 Nov 2010
		NZ 588896 A	25 May 2012
		PL 382308 A1	20 Aug 2007
		RU 2007110934 A	10 Oct 2008
		US 2006079526 A1	13 Apr 2006
		US 7652051 B2	26 Jan 2010
		US 2010330069 A1	30 Dec 2010
		US 8084618 B2	27 Dec 2011
		US 2012220584 A1	30 Aug 2012
		US 8372971 B2	12 Feb 2013
		US 2013243754 A1	19 Sep 2013

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2014/061299**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2005/000298 A2	06 January 2005	AU 2004251668 A1	06 Jan 2005
		AU 200425 1668 B2	20 Mar 2008
		BR PI0410905 A	27 Jun 2006
		CA 2528438 A1	06 Jan 2005
		CN 1829513 A	06 Sep 2006
		EP 1635824 A2	22 Mar 2006
		EP 1635824 B1	19 Aug 2009
		JP 2006526656 A	24 Nov 2006
		MX PA05013075 A	17 Mar 2006
		US 2004254236 A1	16 Dec 2004
		US 7652044 B2	26 Jan 2010
		US 2010004298 A1	07 Jan 2010
WO 2004/052280 A2	24 June 2004	AU 2003293376 A1	30 Jun 2004
WO 2000/025780 A1	11 May 2000	AR 021033 A1	12 Jun 2002
		AR 021034 A1	12 Jun 2002
		AU 764479 B2	21 Aug 2003
		AU 1131500 A	22 May 2000
		AU 1707700 A	22 May 2000
		AU 2002352950 A1	17 Jun 2003
		CA 2348234 A1	11 May 2000
		CA 2348267 A1	11 May 2000
		EP 1126843 A1	29 Aug 2001
		EP 1127054 A1	29 Aug 2001
		EP 1448187 A2	25 Aug 2004
		JP 2002528499 A	03 Sep 2002
		JP 2002528533 A	03 Sep 2002
		US 6399773 B1	04 Jun 2002
		US 2002143 176 A1	03 Oct 2002
		US 6596747 B2	22 Jul 2003
		US 6624184 B1	23 Sep 2003
		US 2004082562 A1	29 Apr 2004
		US 70531 11 B2	30 May 2006
		US 2004102497 A1	27 May 2004
		US 7060720 B2	13 Jun 2006
		US 2006122245 A1	08 Jun 2006

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2014/061299**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
		US 7205324 B2	17 Apr 2007
		WO 0026197 A1	11 May 2000
		WO 03047512 A2	12 Jun 2003

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.