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(54) Benævnelse: **Indazol-, benzoxazol- og pyrozolopyridinderivater som P38-kinasehæmmere**

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DESCRIPTION

BACKGROUND OF THE INVENTION

Field of the Invention.

[0001] This invention relates to novel inhibitors of p38 MAP kinase and related kinases, pharmaceutical compositions containing the inhibitors, and methods for preparing these inhibitors. They are useful for the treatment of inflammation, osteoarthritis, rheumatoid arthritis, psoriasis, Crohn's disease, inflammatory bowel disease, cancer, autoimmune diseases, and for the treatment of other cytokine-mediated diseases.

Description of the state of the art.

[0002] A number of chronic and acute inflammatory conditions have been associated with the overproduction of pro-inflammatory cytokines. Such cytokines include but are not limited to tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 8 (IL-8) and interleukin 6 (IL-6). Rheumatoid Arthritis (RA) is a chronic disease where TNF-α and IL-1β are implicated in the onset of the diseases and in the progression of the bone and joint destruction seen with this debilitating condition. Recently approved therapeutic treatments for RA have included soluble TNF-α receptor (etanercept) and IL-1 receptor antagonist (anakinra). These treatments work by blocking the ability of their respective cytokines to bind to their natural receptors. Alternative methods to treat cytokine-mediated diseases are currently under investigation. One such method involves inhibition of the signaling pathway that regulates the synthesis and production of pro-inflammatory cytokines like p38.

[0003] P38 (also CSBP or RK) is a serine/threonine mitogen-activated proteinkinase (MAPK) that has been shown to regulate pro-inflammatory cytokines. P38 was first identified as a kinase which became tyrosine phosphorylated in mouse monocytes following treatment with lipopolysaccharide (LPS). A link between p38 and the response of cells to cytokines was first established by Saklatvala J., et al., Cell, 78: 1039-1049 (1994), who showed that IL-1 activates a protein kinase cascade that results in the phosphorylation of the small heat shock protein, Hsp27, probably by mitogen-activated protein activated protein kinase 2 (MAPKAP kinase-2). Analysis of peptide sequences derived from the purified kinase indicated that it was related to the p38 MAPK activated by LPS in mouse monocytes, Han, J., et al., Science, 265: 808-811 (1994). At the same time it was shown that p38 MAPK was itself activated by an upstream kinase in response to a variety of cellular stresses, including exposure to UV radiation and osmotic shock, and the identity of the kinase that directly phosphorylates Hsp27 was confirmed as MAPKAP kinase-2, Rouse, J., et al., Cell, 78: 1027-1037 (1994). Subsequently, workers at SmithKline Beecham showed that p38 MAPK was the molecular target of a series of pyridinylimidazole compounds that inhibited the production of TNF from LPS-challenged human monocytes, Lee, J., et al., Nature, 372: 739-746. This was a key discovery and has led to the development of a number of selective inhibitors of p38 MAPK and the elucidation of its role in cytokine signaling.

[0004] It is now known that multiple forms of p38 MAPK (α, β, γ, δ), each encoded by a separate gene, form part of a kinase cascade involved in the response of cells to a variety of stimuli, including osmotic stress, UV light and cytokine mediated events. These four isoforms of p38 are thought to regulate different aspects of intracellular signaling. Its activation is part of a cascade of signaling events that lead to the synthesis and production of pro-inflammatory cytokines like TNF-α. P38 functions by phosphorylating downstream substrates that include other kinases and transcription factors. Agents that inhibit p38 kinase have been shown to block the production of cytokines including but not limited to TNF-α, IL-6, IL-8 and IL-1β in vitro and in vivo models Adams, J. L., et al., Progress in Medicinal Chemistry, 38: 1-60 (2001).

[0005] Peripheral blood monocytes (PBMCs) have been shown to express and secrete pro-inflammatory cytokines when stimulated with lipopolysaccharide (LPS) in vitro. P38 inhibitors efficiently block this effect when PBMCs are pretreated with such compounds prior to stimulation with LPS. Lee, J.C., et al., Int. J. Immunopharmacol., 10: 835-843 (1988). The efficacy of p38 inhibitors in animal models of inflammatory disease has prompted an investigation of the underlying mechanism(s) which could account for the effect of these inhibitors. The role of p38 in the response of cells to IL-1 and TNF has been investigated in a number of cells systems relevant to the inflammatory response using a pyridinyl imidazole inhibitor: endothelial cells and IL-8, Hashimoto, S., et al., J. Pharmacol. Exp. Ther., 293: 370-375 (2001), fibroblasts and IL-6/GM-CSF/PGE2 Beyaert, R., et al., EMBO J., 15: 1914-1923 (1996), neutrophils and IL-8 Albanyan, E. A., et al., Infect. Immun., 68: 2053-2060 (2000) macrophages and IL-1 Caivano, M. and Cohen, P., J. Immunol., 164: 3018-3025 (2000), and smooth muscle cells and RANTES Maruoka, S., et

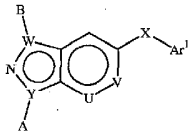
al., Am. J. Respir. Crit. Care Med., 161: 659-668 (1999). The destructive effects of many disease states are caused by the over production of pro-inflammatory cytokines. The ability of p38 inhibitors to regulate this overproduction makes them excellent candidates for disease modifying agents.

[0006] Inhibitors of p38 are active in a variety of widely recognized disease models and show positive effects in a number of standard animal models of inflammation including rat collagen-induced arthritis, Jackson, J.R., et al., J. Pharmacol. Exp. Ther., 284: 687-692 (1998); rat adjuvant-induced arthritis, Badger, A. M., et al., Arthritis Rheum., 43: 175-183 (2000); Badger, A. M., et al., J. Pharmacol. Exp. Ther., 279: 1453-1461 (1996); and carrageenan-induced paw edema in the mouse, Nishikori, T., et al., Eur. J. Pharm., 451: 327-333 (2002). Molecules that block p38's function have been shown to be effective in inhibiting bone resorption, inflammation, and other immune and inflammation-based pathologies in these animal models. Thus, a safe and effective p38 inhibitor would provide a means to treat debilitating diseases that can be regulated by modulation of p38 signaling like, but not limited to, RA.

[0007] P38 inhibitors are well known to those skilled in the art. Reviews of early inhibitors have helped establish the structure activity relationships important for enhanced activity both in vitro and in vivo. See, Salituro, E. G., et al., Current Medicinal Chemistry, 6: 807-823 (1999) and Foster, M. L., et al., Drug News Perspect., 13: 488-497 (2000). More contemporary reviews have focused on the structural diversity of new inhibitors being explored as p38 inhibitors Boehm, J. D. and Adams, J. L., Exp. Opin. Ther. Patents, 10: 25-37 (2000). Document WO 02100833A describes heterobicyclic compounds which are rho kinase inhibitors. This invention describes a novel series of substituted 2-aza-[4.3.0]-bicyclic hereroaromatic compounds as p38 inhibitors that are useful for the treatment of inflammation, osteoarthritis, rheumatoid arthritis, cancer, auto-immune diseases, and for the treatment of other cytokine mediated diseases.

SUMMARY OF THE DISCLOSURE

[0008] This document describes compounds, methods to produce these compounds, and pharmaceutical compositions containing them that inhibit p38 alpha and the associated p38 mediated events such as the inhibition of cytokine production. Such compounds, generally referred to as 2-aza-[4.3.0] bicyclic heteroaromatic rings, have utility as therapeutic agents for diseases that can be treated by the inhibition of the p38 signaling pathway. In general, the present document describes p38 inhibitors of the general Formula I:



I

wherein Y is C, N;

W is C, N, S, or O, provided that W is N, S, or O when Y is C, and W is C or N when Y is N;

U is CH or N; V is C-E or N;

X is O, S, SO, SO_2, NR^7, C=O, CHR^7, -C=NOR^1, -C=CHR^1, or CHOR^1;

R^1 is H, PO_3H_2 SO_3H_2 alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons, wherein said alkylene, alkenylene, or alkynylene may be substituted or unsubstituted;

R^7 is H or substituted or unsubstituted methyl;

Ar^1 is substituted or unsubstituted aryl or heteroaryl;

A is H, OH, an amine protecting group, Z_n-NR^2R^3, Z_n -NR^2(C=O)R^2, Z_n -SO_2R^2, Z_n-SOR^2, Z_n-SR^2, Z_n-OR^2, Z_n-(C=O)R^2, Z_n-(C=O)OR^2, Z_n-O-(C=O)R^2, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl,

heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

R^2 and R^3 are independently H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a thio protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted, or R^2 together with R^3 and N forms a saturated or partially unsaturated heterocycle having 1 or more heteroatoms, wherein said heterocycle may be substituted or unsubstituted and wherein said heterocycle may be fused to an aromatic ring;

B is H, NH_2, or substituted or unsubstituted methyl;

E is H, Z_n-NR^2R^3, Z_n-(C=O)R^4, Z_n-(C=O)R^5, Z_n-NR^5(C=O)R^5, Z_n-O(C=O)R^5, Z_n-OR^5, Z_n-SO_2R^5, Z_n -SOR^5, Z_n-SR^5, Z_n-NH(C=O)NHR^5, or R^5;

R^4 is a substituted or unsubstituted natural or unnatural amino acid, a protected natural or unnatural amino acid, NH(CHR^6)$(CH_2)_m$$OR^5$ where m is an integer from 1 to 4, or NR^2R^3;

R^5 is H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a thio protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

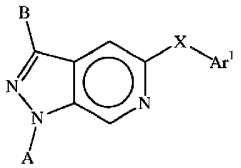
R^6 is a natural amino acid side chain, Z_n-NR^2R^3, Z_n-OR^5, Z_n-SO_2R^5, Z_n-SOR^5, or Z_n-SR^5; and

n is 0 or 1,

provided that when B is H and A is CH=CH-R^8 where R^8 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, then X-Ar^1 is a substituent where Ar^1 is other than substituted or unsubstituted aryl, heteroaryl, NH-alkyl, NH-cycloalkyl, NH-heterocycloalkyl, NH-aryl, NH-heteroaryl, NH-alkoxy, or NH-dialkylamide when X is O, S, C=O, S=O, C=CH_2, CO_2, NH, or N(C_1-C_8-alkyl).

[0009] The present document also describes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of the compound of Formula **I**. Methods of making the compounds of Formula **I** are also described.

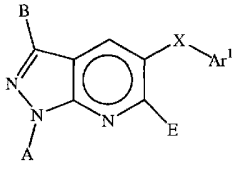
[0010] In another embodiment, this document describes compounds of the general Formula **II**:



II

where A, B, X and Ar^1 are as defined above.

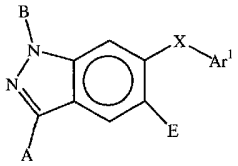
[0011] The present document describes compounds of the general Formula **III**:



III

where A, B, X, E and Ar^1 are as defined above.

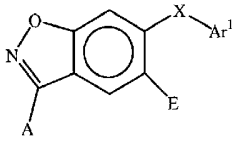
[0012] The present document describes compounds of the general Formula **IV**:



IV

where A, B, X, E and Ar^1 are as defined above, provided that when B is H and A is CH=CH-R^8 where R^8 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, then X-Ar^1 is a substituent where Ar^1 is other than substituted or unsubstituted aryl, heteroaryl, NH-alkyl, NH-cycloalkyl, NH-heterocycloalkyl, NH-aryl, NH-heteroaryl, NH-alkoxy, or NH-dialkylamide when X is O, S, C=O, S=O, C=CH_2, CO_2, NH, or N(C_1-C_8-alkyl) .

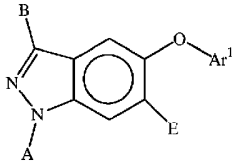
The present document describes compounds of the general Formula V:



V

where A, X, E and Ar^1 are as defined above.

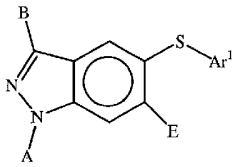
[0013] The present document describes compounds of the general Formula **VI:**



VI

where A, B, E and Ar^1 are as defined above.

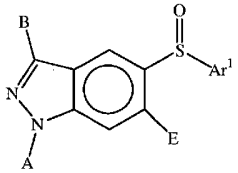
[0014] The present document describes compounds of the general Formula **VII:**



VII

where A, B, E and Ar^1 are as defined above.

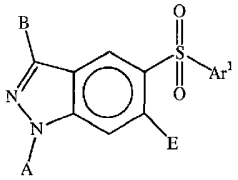
[0015] The present document describes compounds of the general Formula **VIII**:



VIII

where A, B, E and Ar^1 are as defined above.

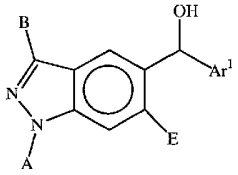
[0016] The present document describes compounds of the general Formula **IX:**



IX

where A, B, E and Ar^1 are defined as above.

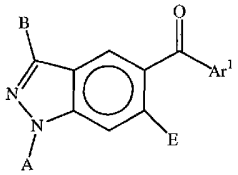
[0017] The present document describes compounds of the general Formula **X:**



X

where A, B, E and Ar^1 are defined as above.

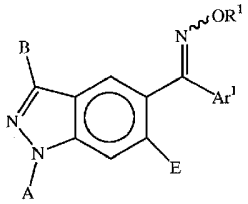
[0018] The present document describes compounds of the general Formula **XI**:



XI

where A, B, E and Ar^1 are defined as above.

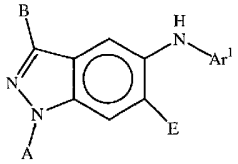
[0019] The present document describes compounds of the general Formula **XII**:



XII

where A, B, E, R^1 and Ar^1 are defined as above.

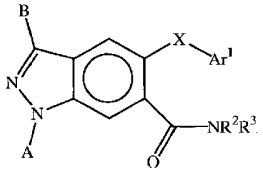
[0020] The present document describes compounds of the general Formula **XIII**:



XIII

where A, B, E and Ar^1 are defined as above.

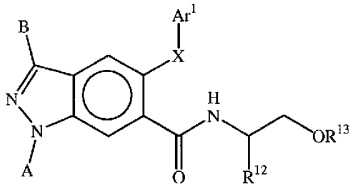
[0021] The present document describes ether compounds of the general Formula **XIV:**



XIV

where A, B, X, Ar^1, R^2 and R^3 are defined as above.

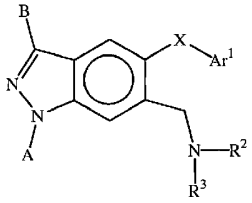
[0022] The present document describes compounds of the general Formula **XV**:



XV

where A, B, X, and Ar^1 are defined as above, and R^{12} and R^{13} are independently alkyl, allyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl ,or heteroaryl, wherein said alkyl, allyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl ,or heteroaryl may be substituted or unsubstituted.

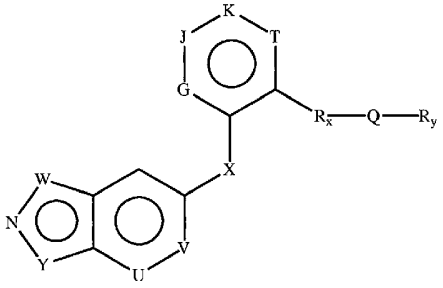
[0023] The present document describes compounds of the general Formula **XVI**:



XVI

where A, B, X, R^2, R^3, and Ar^1 are defined as above.

[0024] The invention provides compounds of the general Formula **XVII:**



XVII

where Y is O, or NR^2;

W is CR^3;

R^3 is H, NH_2, F, Cl, methyl or substituted methyl;

R^2 is H, OH, an amine protecting group, Z_n-NR^aR^b, Z_n-$NR^a(C=O)R^b$, Z_n-SO_2R^a, Z_n-SOR^a, Z_n-SR^a, Z_n-OR^a, Z_n-$(C=O)R^a$, Z_n-$(C=O)OR^a$, Z_n-O-$(C=O)R^a$, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, and Z_n-Ar^1 may be substituted or unsubstituted;

Ar^1 is aryl or heteroaryl, each of which may be substituted or unsubstituted;

R^a and R^b are independently H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a sulfur protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, and Z_n-Ar^1 may be substituted or unsubstituted,

or R^a and R^b together with the atoms to which they are both attached form a saturated or partially unsaturated heterocycle ring having 1 or more heteroatoms in said ring, wherein said heterocycle may be substituted or unsubstituted and wherein said heterocycle may be fused to an aromatic ring;

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons, wherein said alkylene, alkenylene, or alkynylene may be substituted or unsubstituted;

n is 0 or 1;

U is CR^c or N;

V is CR^c or N;

R^c is H, F, Cl, methyl or substituted methyl;

X is O, S, SO, SO_2, NR^5, C=O, CH_2, CH_2Z_n-OH, or C=NOR^d;

R^5 is H, methyl, or substituted methyl;

R^d is H, PO_3H_2 SO_3H_2 alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

G, H, J, and T independently are N or CR^z, provided that when any of said G, H, J, and T are N the total number of G, H, J, or T that is N does not exceed 2;

R^z is H, F, Cl, Br, CF_3, OR^6, SR^6, lower alkyl (C_1-C_4), CN, or NR^6R^7;

R^6 and R^7 are independently H, CF_3, lower alkyl (C_1-C_4) or lower heteroalkyl (C_1-C_4);

Q is -NR^8CONH-, -NHCO-, -NR^8SO_2NH-, -$NHSO_2$-, -$CONR^{11}$- ;

R^8 is H or lower (C_1-C_4) alkyl;

R^{11} is H or lower (C_1-C_4) alkyl;

R_x is -$(CR^9R^{10})_m$-, -O$(CR^9R^{10})_m$- , NH$(CR^9R^{10})_m$-, or -S$(CR^9R^{10})_m$-provided that Q is -$CONR^{11}$- when R^x is -O$(CR^9R^{10})_m$-, -NH$(CR^9R^{10})_m$-, or - S$(CR^9R^{10})_m$-;

R^9 and R^{10} are independently H, or lower alkyl, or R^9 and R^{10} together with the atoms to which they are both attached form a cycloalkyl ring which may be saturated or partially unsaturated;

m is 1-3;

R_y is H, PO_3H an amine protecting group, an oxygen protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^2, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-Ar^2 and Z_n-heterocycloalkyl may be substituted or unsubstituted;

Ar^2 is aryl or heteroaryl, each of which may be substituted or unsubstituted, wherein said substitution can be 1-3 substituents independently selected from F, Cl, Br, CF_3, CN, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, -OR^{12}, -SR^{12}, -SO_2R^{12}, -$SO_2NR^{13}R^{12}$, $NR^{13}SO^2R^{12}$, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl,

alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

R^{12} and R^{13} are independently H, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

wherein when Ar^2 is substituted with -$SO_2NR^{13}R^{12}$, R^{12} and R^{13} can form a cycloalkyl ring or heterocycloalkyl ring that may be substituted or unsubstituted wherein said substitution can be substituents selected from alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, -COR^{12}, -SO_2R^{12}, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

wherein when Q is -$CONR^{11}$, R_y in combination with R^{11} is additionally cycloalkyl ring or heterocycloalkyl ring that may be substituted or unsubstituted with groups selected from alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, Z_n-Ar^1, -COR^{14}, or -SO_2R^{14}, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-Ar^1, -COR^{14}, and -SO_2R^{14} may be substituted or unsubstituted; and

R^{14} is alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Zn-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Zn-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Zn-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Zn-cycloalkyl, Zn-heterocycloalkyl, and Zn-Ar^1 may be substituted or unsubstituted

and wherein the substituent(s) of each group is/are selected among: halo, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-OR, Z_n-NO_2, Z_n-CN, Z_n-CO_2R, Z_n-(C=O)R, Z_n-O(C=O)R, Z_n-O-alkyl, Z_n-OAr, Z_n-SH, Z_n-SR, Z_n-SOR, Z_n-SO_2R, Z_n-S-Ar, Z_n-SOAr, Z_n-SO_2Ar, aryl, heteroaryl, Z_n-Ar, Z_n-(C=O)NR'R", Z_n-NR'R", Z_n-NR(C=O)R, Z_n-$SO_2NR'R"$, PO_3H_2, SO_3H_2, amine protecting groups, alcohol protecting groups, sulfur protecting groups, or acid protecting groups, where:

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons,

n is zero or 1,

R, R' and R" are alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Zn-cycloalkyl or Zn-heterocycloalkyl, and

Ar is aryl or heteroaryl,

the resolved enantiomers, diastereoisomers, solvates and pharmaceutically acceptable salts thereof.

In a further aspect the present invention provides compounds that inhibit the production of cytokines such as TNF-α, IL-1, IL-6 and IL-8 comprising compounds of Formulas **XVII.**

The present document describes a method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of Formula **I-XVII,** or a pharmaceutically acceptable salt or in vivo cleavable prodrug thereof.

[0025] The present document describes a method of inhibiting the production of cytokines such as TNF-α, IL-1, IL-6 and IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of Formula **I-XVII,** or a pharmaceutically acceptable salt or in vivo cleavable prodrug thereof.

[0026] The present document describes a method of providing a p38 kinase inhibitory effect comprising administering to a warm-blooded animal an effective amount of a compound of Formula **I-XVII,** or a pharmaceutically-acceptable salt or in vivo cleavable prodrug thereof.

[0027] The present document describes treating or preventing a p38-mediated condition, comprising administering an amount of a compound effective to treat or prevent said p38-mediated condition or a pharmaceutical composition comprising said compound, to a human or animal in need thereof, wherein said compound is a compound of Formula **I-XVII,** or a pharmaceutically-acceptable salt or in vivo cleavable prodrug thereof. The p38-mediated condition that can be treated according to the methods of this invention includes inflammatory disease, autoimmune disease, destructive bone disorder, proliferative disorder, infectious disease, viral disease, or neurodegenerative disease

[0028] The compounds described are also useful in methods for preventing cell death and hyperplasia and therefore may be used to treat or prevent reperfusion/ischemia in stroke, heart attacks, and organ hypoxia. The compounds of this invention are also useful in methods for preventing thrombin-induced platelet aggregation.

[0029] The inventive compounds of formula XVII may be used advantageously in combination with other known therapeutic agents.

[0030] The invention also relates to pharmaceutical compositions comprising an effective amount of an agent selected from compounds of Formulas **XVII** or a resolved enantiomer, disatereoisomer, solvate, or pharmaceutically acceptable salt thereof.

[0031] The present invention relates to the compounds according to formula **XVII,** or resolved enantiomer, diastereoisomer, solvate, or a pharmaceutically acceptable salt thereof for use in therapy.

[0032] The present invention relates to the compounds according to formula **XVII,** or resolved enantiomer, diastereoisomer, solvate, or a pharmaceutically acceptable salt thereof for use in treating or preventing p-38 mediated condition.

[0033] The present invention relates to the compounds according to formula **XVII,** or resolved enantiomer, diastereoisomer, solvate, or a pharmaceutically acceptable salt thereof for use in treating or preventing inflammatory disease, autoimmune disease, destructive bone disorder, proliferative bone disorder, infectious disease, viral disease, or neurodegenerative disease.

[0034] The invention provides compounds of formula **XVII** which are selected from the group constituted by:

- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-methyl-1 H-indazol-5-yloxy)-pyridin-3-ylmethyl]-urea,
- 1-[5-cyclopropyl-2-(4-trifluoromethylphenyl)-2H-pyrazol-3yl]-3-[5-fluoro-2-(1-methyl-1H-indazol-5-ylamino)-benzyl]-urea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-cyclobutylmethyl-1 H-indazol-5-ylamino)-5-fluorobenzyl]-urea,
- 1-(5-tert-butyl-2-p-chlorophenyl-2H-pyrazol-3-yl)-3-[2-(1-methyl-1H-indazo-5-ylsulfanyl)-5-fluorobenzyl]-urea,
- 1-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-3-{2-[1-(3-isopropylamino-propyl)-1H-indazol-5-ylamino]-benzyl}-urea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]urea,
- 1-[5-tert-butyl-2-(4-chloro-phenyl)-2H-pyrazol-3-yl]-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]urea,
- 3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-1-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yloxy)-benzyl]-urea,
- 2-(5-{2-[3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-ureidomethyl]-4-fluorophenoxy}-indazol-1-yl)-N,N-di methylacetamide,
- 1-(5-tert-butyl-isoxazol-3-yl)-3-[5-fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzyl]-urea,
- 1-(3-tert-butyl-isoxazol-5-yl)-3-{5-fluoro-2-[1-(2-piperazin-1-yl-ethyl)-1H-indazol-5-yloxy]-benzyl}-urea,
- 1-(3-tert-butyl-isoxazol-5-yl)-3-{2-[1-(2-dimethylaminoethyl)-1H-indazol-5-yloxy]-5-fluoro-benzyl}-urea,
- 1-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-3-{5-fluoro-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzyl}-urea,

or resolved enantiomers, diastereoisomers, solvates and pharmaceutically acceptable salts thereof.

BRIEF DESCRIPTION OF THE FIGURES

[0035] The accompanying drawings, which are incorporated herein and form a part of the specification, illustrate embodiments of the present invention, and together with the description, serve to explain the principles of the invention. In the figures,

Figure 1 shows a reaction scheme for the synthesis of compound 6n;

Figure 2 shows a reaction scheme for the synthesis of compound 13p;

Figure 3 shows a reaction scheme for the synthesis of compound 16p;

Figures 4A-B show a reaction scheme for the synthesis of compounds 9q-1 and 9q-2;

Figure 5 shows a reaction scheme for the synthesis of compound 6r-2;

Figures 6A-B show a reaction scheme for the synthesis of compound 8s-2;

Figure 7 shows a reaction scheme for the synthesis of compound 7t-2;

Figure 8 shows a reaction scheme for the synthesis of compound 28t;

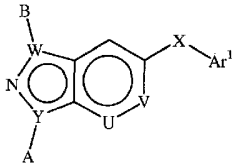
Figure 9 shows a reaction scheme for the synthesis of compound 32t;

Figure 10 shows a reaction scheme for the synthesis of compound 4u;

Figure 11 shows a reaction scheme for the synthesis of compound 47d.

DETAILED DESCRIPTION OF THE INVENTION

[0036] The present document describes compounds of the Formulas **I-XVI** (not included within the scope of the invention) and of Formula **XVII** (according to the invention) which are useful for inhibiting p38 alpha and associated p38 mediated events such as cytokine production. Such compounds have utility as therapeutic agents for diseases that can be treated by the inhibition of the p38 signaling pathway. In general, the present document describes compounds of the general Formula **I:**



I

wherein Y is C, N

W is C, N, S, or O, provided that W is N, S, or O when Y is C, and W is C or N when Y is N;

U is CH or N;

V is C-E or N;

X is O, S, SO, SO_2, NR^7, C=O, CHR^7, -C=NOR^1, -C=CHR^1, or $CHOR^1$;

R^1 is H, PO_3H_2 SO_3H_2, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons, wherein said alkylene, alkenylene, or alkynylene may be substituted or unsubstituted;

R^7 is H or substituted or unsubstituted methyl;

Ar^1 is substituted or unsubstituted aryl or heteroaryl;

A is H, OH, an amine protecting group, Z_n-NR^2R^3, Z_n -NR^2(C=O)R^2, Z_n -SO_2R^2, Z_n-SOR^2, Z_n-SR^2, Z_n-OR^2, Z_n-(C=O)R^2, Z_n-

$(C=O)OR^2$, Z_n-O-$(C=O)R^2$, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

R^2 and R^3 are independently H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a thio protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, $Z_n$cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted, or R^2 together with R^3 and N forms a saturated or partially unsaturated heterocycle having 1 or more heteroatoms, wherein said heterocycle may be substituted or unsubstituted and wherein said heterocycle may be fused to an aromatic ring;

B is H, NH_2, or substituted or unsubstituted methyl;

E is H, Z_n-NR^2R^3, Z_n-$(C=O)R^4$, Z_n-$(C=O)R^5$, Z_n-$NR^5(C=O)R^5$, Z_n-$O(C=O)R^5$, Z_n-OR^5, Z_n-SO_2R^5, Z_n-SOR^5, Z_n-SR^5, Z_n-$NH(C=O)NHR^5$, or R^5;

R^4 is a substituted or unsubstituted natural or unnatural amino acid, a protected natural or unnatural amino acid, $NH(CHR^6)(CH_2)_mOR^5$ where m is an integer from 1 to 4, or NR^2R^3;

R^5 is H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a thio protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, or Z_n-Ar^1 may be substituted or unsubstituted;

R^6 is a natural amino acid side chain, Z_n-NR^2R^3, Z_n-OR^5, Z_n-SO_2R^5, Z_n-SOR^5, or Z_n-SR^5; and

n is 0 or 1,

provided that when B is H and A is CH=CH-R^8 where R^8 is a substituted or unsubstituted alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, then X-Ar^1 is a substituent where Ar^1 is other than substituted or unsubstituted aryl, heteroaryl, NH-alkyl, NH-cycloalkyl, NH-heterocycloalkyl, NH-aryl, NH-heteroaryl, NH-alkoxy, or NH-dialkylamide when X is O, S, C=O, S=O, $C=CH_2$, CO_2, NH, or N(C_1-C_8-alkyl).

[0037] The term "alkyl" as used herein refers to a saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms, wherein the alkyl radical may be optionally substituted independently with one or more substituents described below. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

[0038] "Alkylene" means a linear or branched saturated divalent hydrocarbon radical of one to twelve carbon atoms, e.g., methylene, ethylene, propylene, 2-methylpropylene, pentylene, and the like.

[0039] The term "alkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0040] The term "alkenylene" refers to a linear or branched divalent hydrocarbon radical of two to twelve carbons containing at least one double bond, wherein the alkenylene radical may be optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, ethenylene, propenylene, and the like.

[0041] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to twelve carbon atoms containing at least one triple bond. Examples include, but are not limited to, ethynyl, propynyl, and the like, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein.

[0042] The term "alkynylene" to a linear or branched divalent hydrocarbon radical of two to twelve carbons containing at least one triple bond, wherein the alkynylene radical may be optionally substituted independently with one or more substituents described herein.

[0043] The term "allyl" refers to a radical having the formula RC=CHCHR, wherein R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or any substituent as defined herein, wherein the allyl may be optionally substituted independently with one or more substituents described herein.

[0044] The term "cycloalkyl" refers to saturated or partially unsaturated cyclic hydrocarbon radical having from three to twelve carbon atoms, wherein the cycloalkyl may be optionally substituted independently with one or more substituents described herein. The term "cycloalkyl" further includes bicyclic and tricyclic cycloalkyl structures, wherein the bicyclic and tricyclic structures may include a saturated or partially unsaturated cycloalkyl fused to a saturated or partially unsaturated cycloalkyl or heterocycloalkyl ring or an aryl or heteroaryl ring. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

[0045] The term "heteroalkyl" refers to saturated linear or branched-chain monovalent hydrocarbon radical of one to twelve carbon atoms, wherein at least one of the carbon atoms is replaced with a heteroatom selected from N, O, or S, and wherein the radical may be a carbon radical or heteroatom radical (i.e., the heteroatom may appear in the middle or at the end of the radical). The heteroalkyl radical may be optionally substituted independently with one or more substituents described herein. The term "heteroalkyl" encompasses alkoxy and heteroalkoxy radicals.

[0046] The term "heterocycloalkyl" refers to a saturated or partially unsaturated cyclic radical of 3 to 8 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen and sulfur, the remaining ring atoms being C where one or more ring atoms may be optionally substituted independently with one or more substituent described below and wherein the heterocycloalkyl ring can be saturated or partially unsaturated. The radical may be a carbon radical or heteroatom radical. "Heterocycloalkyl" also includes radicals where heterocycle radicals are fused with aromatic or heteroaromatic rings. Examples of heterocycloalkyl rings include, but are not limited to, pyrrolidine, piperidine, piperazine, tetrahydropyranyl, morpholine, thiomorpholine, homopiperazine, phthalimide, and derivatives thereof.

[0047] The term "heteroalkenyl" refers to linear or branched-chain monovalent hydrocarbon radical of two to twelve carbon atoms, containing at least one double bond, e.g., ethenyl, propenyl, and the like, wherein at least one of the carbon atoms is replaced with a heteroatom selected from N, O, or S, and wherein the radical may be a carbon radical or heteroatom radical (i.e., the heteroatom may appear in the middle or at the end of the radical). The heteroalkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

[0048] The term "heteroalkynyl" refers to a linear or branched monovalent hydrocarbon radical of two to twelve carbon atoms containing at least one triple bond. Examples include, but are not limited to, ethynyl, propynyl, and the like, wherein at least one of the carbon atoms is replaced with a heteroatom selected from N, O, or S, and wherein the radical may be a carbon radical or heteroatom radical (i.e., the heteroatom may appear in the middle or at the end of the radical). The heteroalkynyl radical may be optionally substituted independently with one or more substituents described herein.

[0049] The term "heteroallyl" refers to radicals having the formula RC=CHCHR, wherein R is alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or any substituent as defined herein, wherein at least one of the carbon atoms is replaced with a heteroatom selected from N, O, or S, and wherein the radical may be a carbon radical or heteroatom radical (i.e., the heteroatom may appear in the middle or at the end of the radical). The heteroallyl may be optionally substituted independently with one or more substituents described herein.

[0050] "Aryl" means a monovalent aromatic hydrocarbon monocyclic radical of 6 to 10 ring atoms or a polycyclic aromatic hydrocarbon, optionally substituted independently with one or more substituents described herein. More specifically the term aryl includes, but is not limited to, phenyl, 1-naphthyl, 2-naphthyl, and derivatives thereof.

[0051] "Heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 10 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, thiazolyl, and derivatives thereof.

[0052] The term "halo" represents fluoro, chloro, bromo or iodo.

[0053] "Amino protecting groups" refers to those organic groups intended to protect nitrogen atoms against undesirable reactions during synthetic procedures and include, but are not limited to, benzyl, benzyloxycarbonyl (CBZ), tert-butoxycarbonyl (Boc), trifluoroacetyl, and the like.

[0054] "Alcohol protecting groups" refers to those organic groups intended to protect alcohol groups or substituents against undesirable reactions during synthetic procedures and include, but are not limited to, (trimethylsilyl)ethoxymethyl (SEM), tert-butyl, methoxymethyl (MOM), and the like.

[0055] "Sulfur protecting groups" refers to those organic groups intended to protect sulfur groups or substituents against undesirable reactions during synthetic procedures and include, but are not limited to, benzyl, (trimethylsilyl)ethoxymethyl (SEM), tert-butyl, , trityl and the like.

[0056] "Acid protecting groups" refers to those organic groups intended to protect acid groups or substituents against undesirable reactions during synthetic procedures and include, but are not limited to, benzyl, (trimethylsilyl)-ethoxymethyl (SEM), methylethyl and tert-butyl esters, and the like.

[0057] In general, the various moieties or functional groups of the compounds of Formulas **I-XVII** described may be optionally substituted by one or more substituents. Examples of substituents suitable for purposes of this invention include, but are not limited to, halo, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n heterocycloalkyl, Z_n-OR, Z_n-NO_2, Z_n-CN, Z_n-CO_2R, Z_n -(C=O)R, Z_n-O(C=O)R, Z_n-O-alkyl, Z_n-OAr, Z_n-SH, Z_n-SR, Z_n-SOR, Z_n-SOsR, Z_n-S-Ar Z_n-SOAr, Z_n -SO_2Ar, aryl, heteroaryl, Z_n-Ar, Z_n-(C=O)NR^2R^3, Z_n-NR^2R^3, Zn-NR(C=O)R, Z_n-$SO_2NR^2R^3$, PO_3H_2, SO_3H_2, amine protecting groups, alcohol protecting groups, sulfur protecting groups, or acid protecting groups, where:

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons, wherein said alkylene, alkenylene, or alkynylene may be substituted or unsubstituted;

n is zero or 1,

R^1, R^2, and R^3 are alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, or Z_n-heterocycloalkyl, and

Ar is aryl or heteroaryl, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Ar, R^1, R^2, and R^3 may be further substituted or unsubstituted.

[0058] The compounds described may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)-stereoisomers or as mixtures thereof. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. Accordingly, the present document describes racemates and resolved enantiomers, and diastereomers compounds of the Formulas **I-XVII.** The methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (see discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

[0059] In addition to compounds of the Formulas **I-XVII,** the present document also describes solvates, pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds. The term "solvate" refers to an aggregate of a molecule with one or more solvent molecules. A "pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound (not included within the scope of the invention).

[0060] A "pharmaceutically active metabolite" is a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein (not included within the scope of the invention).

[0061] Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. Various forms of prodrugs are known in the art. For examples of such prodrug derivatives, see, for example, a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985); b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991); c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992); d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77:285 (1988); and e) N. Kakeya, et al., Chem. Pharm. Bull., 32: 692 (1984).

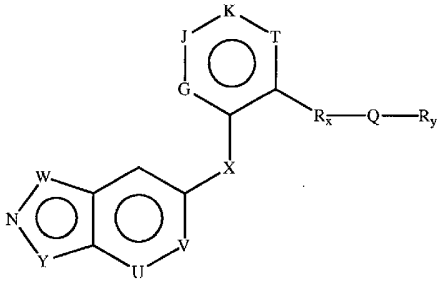
[0062] A "pharmaceutically acceptable salt" is a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable sale. Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, iso-butyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyn-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitro-menzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, pheylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycollates, tartrates, methanesulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

[0063] If the compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alphahydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid or ethanesulfonic acid, or the like.

[0064] If the compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include, but are not limited to, organic salts derived from amino acids, such as glycine and arginine, ammonia, primary, secondary, and tertiary amines, and cyclic amines, such as piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

[0065] The compounds may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available.

[0066] This present invention provides compounds of the general Formula **XVII:**



XVII

where Y is O or NR^2;

W is CR^3;

R^3 is H, NH_2, F, Cl, methyl or substituted methyl;

R^2 is H, OH, an amine protecting group, Z_n-NR^aR^b, Z_n-$NR^a(C=O)R^b$, Z_n-SO_2R^a, Z_n-SOR^a, Z_n-SR^a, Z_n-OR^a, Z_n-$(C=O)R^a$, Z_n-$(C=O)OR^a$, Z_n-O-$(C=O)R^a$, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, and Z_n-Ar^1 may be substituted or unsubstituted;

Ar^1 is aryl or heteroaryl, each of which may be substituted or unsubstituted;

R^a and R^b are independently H, OH, an amine protecting group, an alcohol protecting group, an acid protecting group, a sulfur protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, and Z_n-Ar^1 may be substituted or unsubstituted,

or R^a and R^b together with the atoms to which they are both attached form a saturated or partially unsaturated heterocycle ring having 1 or more heteroatoms in said ring, wherein said heterocycle may be substituted or unsubstituted and wherein said heterocycle may be fused to an aromatic ring;

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons, wherein said alkylene, alkenylene, or alkynylene may be substituted or unsubstituted;

n is 0 or 1;

U is CR^c or N;

V is CR^c or N;

R^c is H, F, Cl, methyl or substituted methyl;

X is O, S, SO, SO_2, NR^5, C=O, CH_2, CH_2Z_n-OH, or $C=NOR^d$;

R^5 is H, methyl, or substituted methyl;

R^d is H, PO_3H_2, SO_3H_2, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

G, H, J, and T independently are N or CR^z, provided that when any of said G, H, J, and T are N the total number of G, H, J, or T that is N does not exceed 2;

R^z is H, F, Cl, Br, CF_3, OR^6, SR^6, lower alkyl (C_1-C_4), CN, or NR^6R^7;

R^6 and R^7 are independently H, CF_3, lower alkyl (C_1-C_4) or lower heteroalkyl (C_1-C_4);

Q is -NR^8CONH-, -NHCO- , -NR^8SO_2NH-, -$NHSO_2$-, -$CONR^{11}$- ;

R^8 is H or lower (C_1-C_4) alkyl;

R^{11} is H or lower (C_1-C_4) alkyl;

R_x is -$(CR^9R^{10})_m$-, -O$(CR^9R^{10})_m$-, NH$(CR^9R^{10})_m$-, or -S$(CR^9R^{10})_m$- provided that Q is -$CONR^{11}$- when R^x is -O$(CR^9R^{10})_m$-, -NH$(CR^9R^{10})_m$-, or - S$(CR^9R^{10})_m$-;

R^9 and R^{10} are independently H, or lower alkyl, or R^9 and R^{10} together with the atoms to which they are both attached form a

cycloalkyl ring which may be saturated or partially unsaturated;

m is 1-3;

R_y is H, PO_3H, an amine protecting group, an oxygen protecting group, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^2, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-Ar^2 and Z_n-heterocycloalkyl may be substituted or unsubstituted;

Ar^2 is aryl or heteroaryl, each of which may be substituted or unsubstituted, wherein said substitution can be 1-3 substituents independently selected from F, Cl, Br, CF_3, CN, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, -OR^{12}, -SR^{12}, -SO_2R^{12}, -$SO_2NR^{13}R^{12}$, $NR^{13}SO_2R^{12}$, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

R^{12} and R^{13} are independently H, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

wherein when Ar^2 is substituted with -$SO_2NR^{13}R^{12}$, R^{12} and R^{13} can form a cycloalkyl ring or heterocycloalkyl ring that may be substituted or unsubstituted wherein said substitution can be substituents selected from alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, -COR^{12}, -SO_2R^{12}, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl and Z_n-Ar^1 may be substituted or unsubstituted;

wherein when Q is -$CONR^{11}$, R_y in combination with R^{11} is additionally cycloalkyl ring or heterocycloalkyl ring that may be substituted or unsubstituted with groups selected from alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, Z_n-Ar^1, -COR^{14}, or -SO_2R^{14}, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-Ar^1, -COR^{14}, and -SO_2R^{14} may be substituted or unsubstituted; and

R^{14} is alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Z_n-cycloalkyl wherein said cycloalkyl is saturated or partially unsaturated, Z_n-heterocycloalkyl wherein said heterocycloalkyl is saturated or partially unsaturated, or Z_n-Ar^1, wherein said alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, and Z_n-Ar^1 may be substituted or unsubstituted

and wherein the substituent(s) of each group is/are selected among: halo, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-OR, Z_n-NO_2, Z_n-CN, Z_n-CO_2R, Z_n-(C=O)R, Z_n-O(C=O)R, Z_n-O-alkyl, Z_n-OAr, Z_n-SH, Z_n-SR, Z_n-SOR, Z_n-SO_2R, Z_n-S-Ar, Z_n-SOAr, Z_n-SO_2Ar, aryl, heteroaryl, Z_n-Ar, Z_n-(C=O)NR'R", Z_n-NR'R", Z_n-NR(C=O)R, Z_n-SO_2NR'R", PO_3H_2, SO_3H_2, amine protecting groups, alcohol protecting groups, sulfur protecting groups, or acid protecting groups, where:

Z is alkylene having from 1 to 4 carbons, or alkenylene or alkynylene each having from 2 to 4 carbons,

n is zero or 1,

R, R' and R' are alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Zn-cycloalkyl or Zn-heterocycloalkyl, and

Ar is aryl or heteroaryl.

[0067] Figures 1-11 show examples of the synthesis of specific compounds having the general Formula **XVII.**

[0068] Therapeutically effective amounts of the compounds of the invention may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of compound that, when administered to a mammal in need of such treatment, is sufficient to effect treatment for a disease mediated by the activity of one or more protein kinases, such as that p38 alpha and the associated p38 mediated events such as cytokine production. Thus, for example, a therapeutically effective amount of a compound of Formula **XVII** or a salt, active metabolite or prodrug thereof, is a quantity sufficient to modulate, regulate, or inhibit the activity of one or more protein kinases such that a disease condition which is mediated by that activity is reduced or alleviated.

[0069] The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the mammal in need of treatment, but can nevertheless be routinely determined by one skilled in the art. "Treating" is intended to mean at least the mitigation of a disease condition in a mammal, such as a human, that is affected, at least in part, by the activity of one or more protein kinases, such as p38, and includes, but is not limited to, preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

[0070] In order to use a compound of the Formula **XVII,** or a pharmaceutically acceptable salt, for the therapeutic treatment (including prophylactic treatment) of mammals including humans, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition. According to this aspect of the invention there is provided a pharmaceutical composition that comprises a compound of the Formula **XVII,** or a pharmaceutically acceptable salt, as defined hereinbefore in association with a pharmaceutically acceptable diluent or carrier.

[0071] The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, or intramuscular dosing or as a suppository for rectal dosing). For example, compositions intended for oral use may contain, for example, one or more coloring, sweetening, flavoring and/or preservative agents.

[0072] Suitable pharmaceutically-acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

[0073] Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

[0074] Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), coloring agents, flavoring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

[0075] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0076] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavoring and coloring agents, may also be present.

[0077] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavoring and preservative agents.

[0078] Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavoring and/or coloring agent.

[0079] The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

[0080] Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

[0081] Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedures well known in the art.

[0082] Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30 μm or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50 mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

[0083] Compositions for administration by inhalation may be in the form of a conventional pressurized aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

[0084] For further information on formulations, see Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[0085] The amount of a compound of this invention that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will all may contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on routes of administration and dosage regimes, see Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

[0086] The size of the dose for therapeutic or prophylactic purposes of a compound of Formula **XVII** will naturally vary according

to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

[0087] In one aspect of this invention, the compounds of this invention or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans to treat or prevent a p38-mediated condition. The term "p38-mediated condition" as used herein means any disease or other deleterious condition in which p38 is known to play a role. This includes conditions which are known to be caused by IL-1, TNF, IL-6 or IL-8 overproduction. Such conditions include, without limitation, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, viral disease, and neurodegenerative diseases.

[0088] Inflammatory diseases which may be treated or prevented include, but are not limited to, acute pancreatitis, chronic pancreatitis, asthma, allergies, and adult respiratory distress syndrome.

[0089] Autoimmune diseases which may be treated or prevented include, but are not limited to, glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

[0090] Destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

[0091] Proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

[0092] Infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

[0093] Viral diseases which may be treated or prevented include, but are not limited to, acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

[0094] Degenerative conditions or diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia and other neurodegenerative diseases.

[0095] "p38-mediated conditions" also include ischemia/reperfusion in stroke, heart attacks, myocardial ischemia, organ hypoxia, vascular hyperplasia, cardiac hypertrophy and thrombin-induced platelet aggregation.

[0096] In addition, the p38 inhibitors of this invention are also capable of inhibiting the expression of inducible pro-inflammatory proteins such as prostaglandin endoperoxide synthase-2 (PGHS-2), also referred to as cyclooxygenase-2 (COX-2). Therefore, other "p38-mediated conditions" are edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain and arthritis pain.

[0097] The conditions and diseases that may be treated or prevented by the p38 inhibitors of this invention may also be conveniently grouped by the cytokine (e.g., IL-1, TNF, IL-6, IL-8) that is believed to be responsible for the disease.

[0098] Thus, an IL-1-mediated disease or condition includes rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, inflammatory bowel disease, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, diabetes, pancreatic ß-cell disease and Alzheimer's disease.

[0099] A TNF-mediated disease or condition includes rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, ARC or malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis or pyresis. TNF-mediated diseases also include viral infections, such as HIV, CMV, influenza and herpes; and veterinary viral infections, such as lentivirus infections, including, but not limited to equine infectious anaemia virus, caprine arthritis virus, visna

virus or maedi virus; or retrovirus infections, including feline immunodeficiency virus, bovine immunodeficiency virus, or canine immunodeficiency virus.

[0100] IL-8 mediated disease or condition includes diseases characterized by massive neutrophil infiltration, such as psoriasis, inflammatory bowel disease, asthma, cardiac and renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

[0101] In addition, the compounds of this infection may be used topically to treat or prevent conditions caused or exacerbated by IL-1 or TNF. Such conditions include inflamed joints, eczema, psoriasis, inflammatory skin conditions such as sunburn, inflammatory eye conditions such as conjunctivitis, pyresis, pain and other conditions associated with inflammation.

[0102] The compounds of this invention may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of cytokines, in particular IL-1, TNF, IL-6 or IL-8.

[0103] For example, by virtue of their ability to inhibit cytokines, the compounds of Formula **XVII** are of value in the treatment of certain inflammatory and non-inflammatory diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin ketorolac, acetylsalicylic acid, ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the Formula **XVII** with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect, and thus the likelihood of adverse side-effects from the NSAID such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of Formula **XVII**, or a pharmaceutically-acceptable salt or in vivo cleavable ester thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

[0104] The compounds of Formula **XVII** may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

[0105] The compounds of the present invention may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Antril.

[0106] The compounds of Formula **XVII** may also be used in the treatment of asthma in combination with antiasthmatic agents such as bronchodilators and leukotriene antagonists.

[0107] Although the compounds of Formula **XVII** are primarily of value as therapeutic agents for use in warm-blooded animals (including man), they are also useful whenever it is required to inhibit the effects of cytokines. Thus, they are useful as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents.

[0108] The activity of the compounds of this invention may be assayed for p38 inhibition in vitro, in vivo, or in a cell line. In vitro assays include assays that determine inhibition of either the kinase activity or ATPase activity of activated p38. Alternate in vitro assays quantitate the ability of the inhibitor to bind to p38 and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/p38 complex and determining the amount of radiolabel bound, or by running a competition experiment where new inhibitors are incubated with p38 bound to known radioligands. These and other useful in vitro and cell culture assays are well known to those of skill in the art.

[0109] Cell culture assays of the inhibitory effect of the compounds of this invention may be used to determine the amounts of TNF-α, IL-1, IL-6 or IL-8 produced in whole blood or cell fractions thereof in cells treated with inhibitor as compared to cells treated with negative controls. Level of these cytokines may be determined through the use of commercially available ELISAs or as described in the Biological Examples section below.

BIOLOGICAL EXAMPLES

[0110] The biological activities of the compounds of the invention were demonstrated by the following in vitro assays.

p38 Biochemical Assay

[0111] P38 activity was assayed at room temperature in a 100 µl reaction containing 5 nM activated p38α enzyme and 1 uM ATF-2 (Activating Transcription Factor 2 fusion protein) as the substrate in 25mM HEPES (pH 7.4), 100 µM Vanadate, 1 mM DTT, 10 mM $MgCl_2$ and 10 µM [-^{33}P]-ATP (~0.1 µCi P^{33}/reaction). The reaction was terminated after 30-40 minutes by adding 25% TCA, let stand for 5 minutes and then transferred directly to a GF-B membrane filter plate. The filter was washed twice for 30 seconds with 0.5% phosphoric acid using a Tomtec Mach III Automated Harvestor. After washing, the vacuum was continued for 30 seconds to dry the filter. Approximately 30 µl of scintillant was added per well to the filter plate and then read in a Liquid Scintillation Counter (Packard TopCount HTS).

PBMC Assay

[0112] The ability of compounds of this invention to inhibit TNF-α production was assessed by using human peripheral blood mononuclear cells ("PBMC") which synthesize and secrete TNF-α when stimulated with lipopolysaccharide.

[0113] Compound test solutions were made by making 5 fold serial dilutions in DMSO, which dilutions were then diluted to 5x stocks by diluting with MEM, 2% heat inactivated fetal bovine serum ("FBS"), 20 mM HEPES, 2mM L-glutamine, and 1% penicillin/streptomycin.

[0114] PBMC's were isolated from human blood as follows. Whole blood samples were collected from human volunteers into Vacutainer™ CPT from Becton Dickinson. Tubes were mixed and centrifuged at room temperature (18 - 25°C) in a horizontal rotor for a minimum of 15 minutes at 1500 -1800 RCF (relative centrifugal force). For each donor, the buffy coat layers were pooled into a single tube and washed twice with phosphate buffered saline ("PBS"). The cell pellet was resuspended in MEM, 2% heat inactivated fetal bovine serum ("FBS"), 20 mM HEPES, 2mM L-glutamine, and 1% penicillin/streptomycin. Total cell number was determined using a hemocytometer and the cell suspension was adjusted to 2 X 106 cells/mL.

[0115] 0.1 mL of cell suspension was added to each well of a 96-well cell culture plate. 30 µL of a compound test solution was added, and the cells were incubated in a 37°C/5% CO2 incubator for 1 hour. 20 µL of 7.5 ng/mL lipopolysaccharide (LPS E. Coli K-235) was then added to each well, and the cells were returned to the 37°C/5% CO_2 incubator for 16-20 hours. The cells were centrifuged for 15 minutes at 1100 RCF. Approximately 0.12 mL of the supernatant was transferred into a clean 96 well polypropylene plate. The samples were either assayed immediately or were stored at -80°C until ready for assay. TNF-α levels were determined in each sample using a human TNF-α ELISA assay such as that described below.

[0116] TNF-α levels were determined using the following assay. TNF-alpha antibody coated plates were prepared by adding 150 µL of 2 µg/mL anti-TNF-α purified mouse monoclonal IgG in Carbonate-Bicarbonate buffer (BupH™ Carbonate-Bicarbonate Buffer Pack) to wells of a 96-well Immulon 4 plate (Immulon 4 ELISA Flat Bottom Plate; Dynex, catalog number 011-010-3855) and incubated overnight at 2 - 8 °C. Coating solution was removed and 200 µL of "blocking buffer" (20 mM HEPES pH 7.4, 150 mM NaCl, 2% BSA) was added and plates were stored 2 - 8 °C until ready to use. A ten-point recombinant human TNF-α standard curve was prepared by a 1:2 serial dilution in "sample diluent" (20 mM HEPES, pH 7.4, 150 mM NaCl, 2 mM $MgCl_2$, 1 % BSA) with a top concentration of 6000 pg/mL.

[0117] Blocking solution was removed from TNF-α ELISA plates by washing five times with 300 µL of "wash buffer" (20 mM HEPES, pH 7.4, 150 mM NaCl, 2 mM $MgCl_2$, 0.02% Tween-20). 50 µL of "sample diluent" was added to all wells, and then either 50 µL of a TNF-α standard curve solution or test compound supernatant was added to all wells. The plate was incubated at room temperature for one hour with shaking (300 rpm). The plate was washed wash five times with 300 µL "wash buffer". 100 µL of 0.2 µg/mL biotinylated goat anti-human TNF-α in "antibody diluent" (20 mM HEPES, pH 7.4, 150 mM NaCl, 2 mM $MgCl_2$, 1 % BSA, 0.02% Tween-20) was added per well, and the plate was incubated at room temperature for one hour with shaking (300 rpm). The plate was washed wash five times with 300 µL "wash buffer" per well. 100 µL of 0.02 µg/mL streptavidin alkaline phosphatase in "antibody diluent" was added per well, and the plate was incubated at room temperature for one hour with shaking (300 rpm). The plate was washed wash five times with 300 µL wash buffer per well. 200 µL of 1 mg/mL pNPP (p-nitrophenyl phosphate) in diethanolamine buffer with 0.5 mM $MgCl_2$ was added per well, and the plate was incubated for 30 to 45 minutes at room temperature with shaking (300 rpm). Reaction progress was monitored by determining optical density: when the top standard reached an OD between 2.0 and 3.0, 50 µL of 2N NaOH was added per well. The optical density of each well was determined within 30 minutes, using a microtiter plate reader set to 405 nm. The data was analyzed in XL fit using 4-parameter curve fitting.

[0118] The following reagents were used in the above-described assays. Dulbecco's Phosphate Buffered Saline without Calcium or Magnesium (Gibco Catalog No. 14190); Minimum essential medium Eagle (MEM; Gibco Catalog No. 11090); penicillin-streptomycin (Gibco Catalog No. 15140); L-glutamine, 200 mM (Gibco Catalog No. 25030); HEPES, 1 M (Gibco Catalog No. 15630); fetal bovine serum ("FBS "; HyClone Catalog No. SH30070.03); lipopolysaccharides from Escherichia coli K-235 ("LPS"; Sigma Catalog No. L2018); anti-TNF-α, Purified Mouse Monoclonal IgG (R&D Systems Catalog No. MAB21 0); BupH™ Carbonate-Bicarbonate Buffer Pack (Pierce Catalog No. 28382); HEPES (FW 238.3; Sigma Catalog No. H3575); NaCl (Sigma Catalog No. S7653); bovine serum albumin ("BSA"; Jackson ImmunoReseach Catalog No. 001-000-162); polyoxyethylene 20 sorbitan monolaurate (Sigma Catalog No. P2287); magnesium chloride, hexahydrate (Sigma Catalog No. M2670); recombinant human TNF-α (R&D Systems Catalog No. 210TA010); biotinylated TNF-α affinity purified goat IgG (R&D Systems Catalog No. BAF210); streptavidin alkaline phosphatase (Jackson ImmunoResearch Catalog No. 016-050-084); diethanolamine Substrate Buffer (Pierce Catalog No. 34064); p-nitrophenyl phosphate (Sigma Catalog No. N2765).

[0119] Table 3 shows the results of p38 inhibition and inhibition of LPS-induced TNF-α secretion from human peripheral blood mononuclear cells ("PBMC"). An "active" compound is defined as a compound having an IC_{50} below 500 nM.

TABLE 3

Compound	p38 Inhibition	PBMC
	IC_{50} (nM)	IC_{50} (nM)
28t	active	-
9q-2	active	-
7t-1	active	-
6n	active	-
16p	active	-

Mouse Assay

Mouse Model of LPS-Induced TNF-α Production

[0120] TNF-α was induced in male DBA-2J mice (from Jackson Laboratories) by tail vein injection with 2 mg/kg lipopolysaccharide (from Sigma, St. Louis). Ninety minutes later isoflurane anaesthetized mice were bled by cardiac puncture. The blood samples were then allowed to clot for two hours at 4°C and centrifuged. Serum was separated into eppendorf tubes for later TNF-α analysis. TNF-α analysis was performed using an ELISA kit (Quantikine, MN) and was performed according to the instructions that accompanied the kit.

[0121] Compound AR-00112190 (not included within the scope of the invention) was prepared with 10% DMSO plus 90% of 20% 2-hydroxyl-β-cyclodextrin (HPCD). The compound was then serially diluted with vehicle (10% DMSO, 90% 20% HPCD) to prepare concentrations required for the lower dose levels. The compound went into solution with the addition of DMSO, but then came out of solution on addition of 20% HPCD. Therefore, compounds were dosed as suspensions. Seven groups of male DBA-2J mice (seven/group) were dosed orally with AR-00112190 (10, 30 and 100 mg/kg) 30 minutes prior to LPS injection.

[0122] Treatment with compound AR-00112190 (10, 30 and 100 mg/kg) also significantly decreased TNF-α levels. AR-00112190 showed a similar inhibition (42%) seen with the 100 mg/kg dose (Table 4).

[0123] Results of this study demonstrated significant beneficial effects with 10, 30 and 100 mg/kg of AR-00112190 (29%, 44% and 42%).

TABLE 4

Group	Treatment	Animal	TNF Level pg/ml	Mean	SE	% inhibition
		1	3290			
		2	3545			
		3	3212			
	LPS + Vehicle	4	5604			
I				3825	390	0

Group	Treatment	Animal	TNF Level pg/ml	Mean	SE	% inhibition
		5	4978			
		6	2947			
		7	3196			
		1	3373			
		2	2047			
		3	2782			
II	LPS + AR-	4	2080	2706	206	29
	00112190	5	2365			
	10 mg/kg	6	3298			
		7	2967			
		1	2815			
		2	1826			
		3				
III	LPS + AR-	4	1464	2126	292	44
	00112190	5	3135			
	30 mg/kg	6	1393			
		7	2124			
		1	2074			
		2	1783			
		3	1832			
IV	LPS + AR-	4	2333	2216	224	42
	00112190	5	3257			
	100 mg/kg	6	1553			
		7	1683			

PREPARATIVE EXAMPLES

[0124] In order to illustrate the invention, the following examples are included.

EXAMPLES

[0125] In the examples described below, unless otherwise indicated all temperatures are set forth in degrees Celsius. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company, Lancaster, TCI or Maybridge, and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane (DCM), toluene, dioxane and 1,2-difluoroethane were purchased from Aldrich in Sure seal bottles and used as received.

[0126] The reactions set forth below were done generally under a positive pressure of nitrogen or argon or with a drying tube (unless otherwise stated) in anhydrous solvents, and the reaction flasks were typically fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried.

[0127] Column chromatography was done on a Biotage system (Manufacturer: Dyax Corporation) having a silica gel column or on a silica SepPak cartridge (Waters).

[0128] 1 H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz or on a Varian instrument operating at 400 MHz. ^{1}H-NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25

ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

[0129] Examples 1-23 describe the synthesis of aniline compounds of the general Formula **XVII.**

Example 1

Preparation of 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-methyl-1H-indazol-5-yloxy)-pyridin-3-ylmethyl]-urea (6n)

[0130] The reaction scheme for the synthesis of compound 6n is shown in Figure 1.

[0131] Step A: 2-(1-Methyl-1H-indazol-5-yloxy)-nicotinonitrile (3n): 1-Methyl-1 H-indazol-5-ol (1 n) (synthesized as described in Example 7) (0.10 g, 0.68 mmol) and 2-chloro-nicotinonitrile (2n) (0.11 g, 0.81 mmol) were suspended in DMSO (2 mL). The reaction mixture was heated to 110 °C for 18 hours. The reaction mixture was diluted with water and extracted into EtOAc. The combined organics were dried, Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification by flash column chromatography (20 - 100% EtOAc/Hexanes) furnished the desired product (3n), (0.152 g, 90% yield). ^{1}H NMR (400 mHz, CD_3OD) δ 8.27-8.25 (m, 1 H), 8.23-8.20 (m, 1H), 8.01 (s, 1 H), 7.62 (d, *J* = 8.6 Hz, 1 H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.28-7.26 (m, 1H), 7.23-7.20 (m, 1H), 4.10 (s, 3H); MS (ESI+) *m/z* 251 (M+H) detected.

[0132] Step B: C-[2-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-yl]-methylamine (4n): 2-(1-Methyl-1H-indazol-5-yloxy)-nicotinonitrile (3n) (0.132 g, 0.528 mmol) was suspended in MeOH (6 mL). $Pd(OH)_2$ (0.060 mg, 0.427 mmol) was added under a nitrogen atmosphere followed by concentrated aqueous HCl (0.6 mL). The system was purged with H_2 gas and the reaction stirred at room temperature for 3 hours under an H_2(g) atmosphere. The reaction mixture was filtered through a pad of celite, washed through with MeOH. The organics were concentrated under reduced pressure to afford the crude product, which was purified by flash column chromatography (MeOH/Et_3N/EtOAc) to provide the desired product (4n) (0.047 g, 35% yield). ^{1}H NMR (400 mHz, CD_3OD) δ 7.96 (s, 1H), 7.90 (d, *J* = 4.7 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1 H), 7.56 (d, *J* = 9.4 Hz, 1 H), 7.46 (d, *J* = 2.3 Hz, 1 H), 7.23-7.21 (m, 1 H), 7.09-7.06 (m, 1H), 4.07 (s, 3H), 3.95 (s, 2H).

[0133] Step C: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-methyl-1H-indazol-5-yloxy)-pyridin-3-ylmethyl]-urea (6n): C-[2-(1-Methyl-1H-indazol-5-yloxy)-pyridin-3-yl]-methylamine (4n) (0.017 g, 0.067 mmol) and (5-*tert*-butyl-2-p-tolyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trichloro-ethyl ester (5n) (0.035 g, 0.087 mmol) were placed in a 10 mL reactor vial and dissolved in DMF (5 mL). DIEA (0.058 mL, 0.334 mmol) was added to the reaction mixture and the system heated to 80 °C for 18 hours. The reaction mixture was concentrated under reduced pressure to afford the crude product. The crude material was purified by flash column chromatography using Sep-pak 10 g (35 cc) silica cartridge (50% EtOAc/Hexanes) to furnish the desired product (6n) (0.034 g, 100% yield). ^{1}H NMR (400 mHz, DMSO) δ 8.32 (s, 1H), 8.00 (s, 1 H), 7.94 (d, *J* = 4.7 Hz, 1 H), 7.65 (d, *J* = 8.6 Hz, 1 H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.46 (s, 1 H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.19-7.16 (m, 1H), 7.07-7.03 (m, 2H), 6.26 (s, 1H), 4.37 (d, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 2.36 (s, 3H), 1.25 (s, 9H); MS (ESI+) *m/z* 510 (M+H) detected.

Example 2

Preparation of 2-(4-{2-[2-(1-cyclobutylmethyl-1H-indazol-5-yloxy)-5-fluorophenyl]-acetyl}-piperazin-1-yl)-N-isopropylacetamide (13p)

[0134] The reaction scheme for the synthesis of compound 13p is shown in Figure 2.

[0135] Step A: 1-Allyloxy-4-fluorobenzene (3p): To a solution of 4-fluorophenol (1 p) (30 g, 268.0 mmol) in acetone (250 mL), anhydrous K_2CO_3 (65 g, 468.3 mmol) was added followed by 3-bromo-propene (2p) (28 mL, 321.1 mmol). The resulting mixture was refluxed for 16 hours, cooled to room temperature and then poured onto ice water (500 mL). The aqueous layer was extracted with ether (3 x 250 mL) and the combined organic layers were washed with 2 M NaOH (2 x 150 mL) and dried over a

mixture of anhydrous K_2CO_3 and Na_2SO_4. The solvent was removed under vacuum to afford the desired product (3p) (40.4 g, 99%) as light yellow oil. ^{1}HNMR (400 MHz, $CDCl_3$) δ7.01 - 6.92 (m, 2H), 6.89 - 6.82 (m, 2H), 6.10 - 6.82 (m, 1 H), 5.44 - 5.41 (m, 1 H), 5.39 - 5.37 (m, 1 H), 4.51 - 4.448 (m, 2H).

[0136] Step B: 2-Allyl-4-fluorophenol (4p): Intermediate (3p) (14.7 g, 96.6 mmol) was heated to 210 °C for 7 hours, cooled to room temperature and allowed to stand overnight. The reaction was checked by thin-layer chromatography. One new spot observed on TLC (Rf: -0.65 in hexane/ethyl acetate, 7:3). HPLC of crude mixture gave a major peak at retention time of 2.07 min and a minor peak at 2.36 min. The major product, crude (4p) was confirmed as desired product and carried on to the next step directly without purification. ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.88 - 6.78 (m, 2H), 6.78 - 6.72 (m, 1 H), 6.05 -5.93 (m, 1 H), 5.21 -5.13 (m, 2H), 4.8 (br s, OH), 3.38 (d, *J* = 6.26 Hz, 2H).

[0137] Step C: Acetic acid 2-allyl-4-fluorophenyl ester (5p): To crude (4p), acetic anhydride (36.5 mL, 386.4 mmol) and pyridine (37.5 mL, 463.7 mmol) were added. The resulting mixture was stirred at room temperature for 18 hours, checked by HPLC the next day (reaction appeared mostly complete). The mixture was then poured onto cold H_2O/Et_2O, the aqueous layer was extracted with Et_2O (2x), the combined organic layers were washed sequentially with 10% HCl (3x), saturated $NaHCO_3$ (2x), H_2O (2x) and brine, and then dried over anhydrous Na_2SO_4. After concentration, crude product purity was checked by thin-layer chromatography (hexane/ethyl acetate, 7:3) and HPLC. No mass ion was observed. The crude product (5p) was carried on to next step directly without subsequent purification. ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.04 - 6.91 (m, 3H), 6.09 - 5.65 (m, 1 H), 5.19 - 5.06 (m, 2H), 3.27 (d, *J* = 6.26 Hz, 2H), 2.30 (s, CH_3).

[0138] Step D: (2-Acetoxy-5-fluorophenyl)-acetic acid (6p-2): To a solution of (5p) (10 g, 51.5 mmol) in 100 mL of CCl_4/ acetonitrile (1:1), a solution of sodium metaperiodate ($NaIO_4$, 33.6 g, 154.5 mmol) in 500 mL of H_2O was added. After stirring for several minutes, ruthenium trichloride hydrate (0.93 g, 4.12 mmol) was added. The dark mixture was stirred at room temperature for 2 hours and DCM (600 mL) was added. The layers were separated, the aqueous phase was extracted with DCM (3x) and combined organic layers were washed with H_2O and dried over Na_2SO_4. Filtration through Celite 545 and evaporation gave a mixture of an aldehyde (6p-1) and an acid (6p-2) (9.1 g, 83%) as a brown oil that was carried onto the next step without purification.

[0139] Step E: (2-Acetoxy-5-fluoro-phenyl)-acetic acid (7p): A solution of sodium chlorite (52.16 g, 576.7 mmol) and sodium dihydrogen phosphate (44.5g, 371 mmol) in 225 mL of H_2O was added to a solution of acid (6p-2) and aldehyde (6p-1) in 100 mL of *i*-PrOH at 0 °C. The resulting solution was stirred at 0 °C for 3 hours, diluted with ether and then the layers were separated. The organic phase was washed with H_2O, 10% sodium thiosulfate (2x), H_2O and brine and dried over Na_2SO_4. After evaporation to a small volume, a few drops of hexane were added. Crystals formed gradually and were collected by filtration and washed with cold ether/hexane to give the desired compound (7p) (3.95 g, 36% isolated yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.12 - 6.98 (m, 3H), 3.57 (s, 2H), 2.29 (s, CH_3); MS (APCI-) *m/z* 422.7 (2M-H) was detected.

[0140] Step F: (5-Fluoro-2-hydroxyphenyl)-acetic acid (8p): Compound (7p) (3.5 g, 16.5 mmol) was dissolved in 65 mL of MeOH, and 7 mL of ammonium hydroxide (49.5 mmol) was added. The mixture was stirred at room temperature overnight and then checked by TLC (DCM/MeOH/AcOH (9:1:0.15)), HPLC and MS. No starting material was observed. The material was concentrated to dryness to give the desired product (8p) which was carried onto the next step directly. MS (APCI-) *m/z* 168.9 (M-H), 338.7 (2M-H) was detected.

[0141] Step G: [2-(1-Cyclobutylmethyl-1H-indazol-5-yloxy)-5-fluorophenyl]-acetic acid (10p): Cesium carbonate (24.2 g, 74.24 mmol) was added to a solution of (8p) (2.8 g, 16.5 mmol) in 6 mL of NMP, and the reaction mixture solidified. An additional 12 mL of NMP and cesium carbonate (6.29 g, 19.3 mmol) were added and the reaction mixture was purged with nitrogen. After vigorous stirring, compound (9p) (5.25 g, 19.8 mmol) and 2,2,6,6-tetramethylheptane-3.5-dione 90.86 mL, 4.12 mmol) were added. The reaction mixture was degassed and purged with nitrogen. Copper (I) chloride (0.82 g, 8.24 mmol) was added and the reaction mixture was degassed, purged with nitrogen and heated to 140 °C. After stirring for 18 hours, the reaction mixture was cooled to room temperature (about 23°C), diluted with Et_2O and filtered. The collected solids were washed several times with ether, dissolved in H_2O, acidified with 6 N HCl, and extracted with DCM (4x). The combined organic layers were washed with H_2O and brine and dried over Na_2SO_4. After concentration, the residue was purified by normal phase chromatography using hexane/EtOAc/AcOH (9:1:0.15) to give the desired product (10p) (1.01 g, 17% isolated yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1 H), 7.36 (d, *J* = 8.62 Hz, 1 H), 7.14 (d, *J* = 2.35 Hz, 1H), 7.11 (dd, *J* = 8.61, 2.35 Hz, 1 H), 7.05 (dd, *J* = 8.61, 3.13 Hz, 1 H), 6.92 (ddd, *J* = 8.61, 8.61, 3.13 Hz, 1 H), 6.79 (dd, *J* = 8.61, 4.70 Hz, 1 H), 4.35 (d, *J* = 7.04 Hz, 2H), 3.73 (s, 2H), 2.93 - 2.82 (m, 1

H), 2.06 - 1.97 (m, 2H), 1.94 - 1.76 (m, 4H); MS (ESI+) *m/z* 355 (M+H) was detected.

[0142] Step H: 2-(4-{2-[2-(1-Cyclobutylmethyl-1H-indazol-5-yloxy)-5-fluorophenyl]-acetyl}-piperazin-1-yl)-N-isopropylacetamide (12p): Compound (10p) (0.087 g, 0.247 mmol) was dissolved in $CHCl_3$ (1.6 mL), mixed with EDCI (0.072 g, 0.372 mmol) and stirred at room temperature for 30 minutes. *N*-Isopropyl-2-piperazin-1-yl-acetamide (12p) (0.069 g, 0.372 mmol) was added followed by an additional 0.8 mL of $CHCl_3$. The resulting solution was stirred at room temperature for 18 hours. PS-isocyanate (0.850 g, 1.6mmol/g) was added and the reaction mixture was shaken for 1 hour. After filtration, the filtrate was washed with H_2O (2x) and dried over Na_2SO_4, and concentrated. The residue was purified with by chromatography (Sep-Pak, 10 g) (DCM, EtOAc) to give the desired product (12p) (0.1 g, 77%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.40 (d, *J* = 8.61 Hz, 1 H), 7.13 - 7.06 (m, 3H), 6.91 (ddd, *J* = 8.61, 8.61, 3.13 Hz, 1H), 6.83 - 6.72 (m, 2H), 4.38 (d, *J* = 7.04 Hz, 2H), 4.15 - 4.02 (m, 1 H), 3.74 (s, 2H), 3.67 - 3.60 (m, 2H), 3.55 - 3.49 (m, 2H), 2.99 - 2.87 (m, 1 H), 2.91 (s, 2H), 2.44 - 2.33 (m, 4H), 2.10 - 2.00 (m, 2H), 1.97 - 1.79 (m, 4H), 1.16 (s, CH_3), 1.15 (s, CH_3); MS (APCI+) *m/z* 522.2 (M+H) was detected.

Example 3

Preparation of 2-[2-(1-isobutyl-1H-indazol-5-yloxy)-phenyl]-N-(4-morpholin-4-yl-phenyl)-acetamide (16p)

[0143] The reaction scheme for the synthesis of compound 16p is shown in Figure 3.

[0144] Step A: 5-Bromo-1-isobutyl-1H-indazole (14p): K_2CO_3 was added to a solution of 5-bromoindazole and in DMF. The mixture was heated to 105 °C. After disappearance of 5-bromoindazole the reaction mixture was poured onto DCM/brine. The two layers were separated and the aqueous layer was extracted with DCM (2x) and checked by TLC. The combined organics were washed with H_2O (2x) and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated and the resulting residue was purified by chromatography with 9.5:0.5 hexane/EtOAc to provide desired product (14p).

[0145] Step B: [2-(1-Isobutyl-1H-indazol-5-yloxy)-phenyl]-acetic acid (15p): To a degassed suspension of 2-hydroxybenzoic acid (2.4 g, 15.8 mmol) and Cs_2CO_3 (7.72 g, 23.7 mmol) in NMP (13 mL), 2,2,6,6-tetramethylheptane-3,5-dione (0.41 mL, 1.97 mmol) and compound 14p (2.0 g, 7.90 mmol) was added followed by small amount of NMP for rinsing. The resulting mixture was degassed again with nitrogen and then CuCl (0.39 g, 3.95 mmol) was added and reaction again degassed. The mixture was heated to 140-150 °C. After mixing for 22 hours, the reaction mixture was poured into ether/H_2O. The two layers were separated and the aqueous layer (pH ~11) was washed with ether. The aqueous layer was acidified to pH 7 and extracted with ether (4x) and the combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The precipitate was formed gradually in a small volume of a mixed solvent of ether/hexane/DCM and collected through filtration to obtain the desired compound (15p) (0.93 g, 36% isolation yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1 H), 7.38 -7.28 (m, 2H), 7.25 - 7.17 (m, 2H), 7.13 (d, J = 9.39Hz, 1 H), 7.10 - 7.03 (m, 1 H), 6.79 (d, J = 8.61 Hz, 1 H), 4.15 (br s, 2H), 3.79 (s, 2H), 2.40 - 2.27 (m, 1 H), 0.93 (s, 3H), 0.92 (s, 3H); MS (APCI+) *m/z* 325 (M+H), MS (APCI-) *m/z* 322.8 (M-H) and 646.8 (2M-H) detected.

[0146] Step C: 2-[2-(1-Isobutyl-1H-indazol-5-yloxy)-phenyl]-N-(4-morpholin-4-yl-phenyl)-acetamide (16p): To a solution of (15p) (0.04 g, 0.123 mmol), PyBOP (0.135 g, 0.26 mmol) and DIEA (0.02 mL, 0.12 mmol) in $CHCl_3$ (2ml), 4-morpholin-4-yl-phenylamine (0.044 g, 0.247 mmol) were added. The mixture was stirred at room temperature for 16 hours, treated with AP-trisamine resin (0.25 g, 2.49 mmol/g), and finally the solvent was removed under reduced pressure after filtration from the resin. The resulting residual was purified by chromatography (Sep-Pak, 10 g) with ether to provide the desired product (16p) (0.024 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1 H), 7.50 (br s, 1 H), 7.45 (dd, *J* = 7.83, 1.57 Hz, 1 H), 7.39 (d, *J* = 9.39 Hz, 2H), 7.31 - 7.26 (m, 3H), 7.23 (dd, *J* = 7.83, 1.57 Hz, 1 H), 7.15 - 7.09 (m, 2H), 6.86 - 6.79 (m, 3H), 4.17 (d, *J* = 7.04 Hz, 2H), 3.86 -3.82 (m, 4H), 3.80 (s, 2H), 3.11 - 3.06 (m, 4H), 2.41 - 2.29 (m, 1 H), 0.95 (s, CH3), 0.94 (s, CH_3); MS (APCI+) *m/z* 485.2 (M+H) was detected.

Example 4

Preparation of 1-[5-cyclopropyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazol-3yl]-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-ylamino-benzyl]-urea (9q-1) and 1-(5-tert-butyl-2-p-tolyl-2*H*-pyrazol-3-yl)-3-[2-(1-cyclobutylmethyl-1H-indazol-5-

ylamino)-5-fluorobenzyl]-urea (9q-2)

[0147] The reaction scheme for the synthesis of compounds 9q-1 and 9q-2 is shown in Figures 4A and B.

[0148] **Step A: 2-Azido-5-fluorobenzonitrile (1q):** A mixture of NaN_3 (1.17 g, 1.8 mmol) and difluorobenzonitrile (0.5 g, 3.6 mmol) in DMA (60 mL) was heated at 100 °C for 30 minutes. The mixture was next diluted with water (300 mL) and ether (300 mL). The organic layer was washed three times with water and brine. The organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography using ether:hexane (1:5) as eluent to give the desired product (1 q) as white crystals (0.3 g, 53% isolated yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 2H), 7.27-7.18 (m, 1H).

[0149] **Step B: 2-Amino-5-fluorobenzonitrile (2q):** To a solution of $CoBr_2$ (15 mg, 0.068 mmol) in ethanol (3 mL) was added 2,2'-dipyridyl (10 mg, 0.068 mmol) at room temperature followed by addition of $NaBH_4$ (40 mg, 1.02 mmol). The reaction mixture was cooled to -10 °C and then intermediate (2q) was added (0.22 g, 1.36 mmol) in ethanol (1 mL) dropwise over 10 minutes. The reaction mixture stirred for 15 minutes and was then quenched with acetic acid and methanol at -10 °C. The residue was then dissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine and dried ($MgSO_4$) and solvents were removed under reduced pressure. The crude product was purified by flash column chromatography using ether: hexane (1:2) as eluent to give compound (2q) as white crystals (0.16 g, 87% isolated yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.12-7.08 (m, 2H), 6.7 (dd, *J* = 10.4, 4.8 Hz, 1 H), 4.3 (br s, 2H).

[0150] **Step C: (2-Cyano-4-fluorophenyl)-bis(carbamic acid tert-butyl ester) (3q):** To a solution of (2q) (33 mg, 0.24 mmol) in THF (3 mL) was added Boc_2O (200 mg, 0.72 mmol) and DMAP (5.9 mg, 0.048 mmol) at room temperature. The reaction mixture refluxed for 2.5 hours and was then cooled to room temperature and the solvent evaporated at reduced pressure. The crude product was purified by flash column chromatography using ether: hexane (1:3) as eluent to give the product (3q) as white crystals (0.08 g, 98% isolated yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.4-7.26 (m, 3H), 1.45 (s, 18H).

[0151] **Step D: (2-Aminomethyl-4-fluorophenyl)-bis(carbamic acid tert-butyl ester) (4q):** To a solution of (3q) (1 g, 2.97 mmol) in ethanol (30 mL) was added $CoBr_2$ (27 mg, 0.12 mmol), 2,2'-dipyridyl (57 mg, 0.36 mmol) at room temperature followed by addition of $NaBH_4$ (350 mg, 9.2 mmol). The reaction mixture stirred at room temperature for 30 minutes and was quenched with acetic acid and methanol at 0 °C. The residue was then dissolved in ethyl acetate and washed with saturated sodium bicarbonate, brine and dried ($MgSO_4$) and solvents were removed under reduced pressure. The crude product (4q) was used directly in the next step (1 g, 100% isolated crude yield).

[0152] **Step E: 2-Aminomethyl-4-fluorophenylamine HCl salt (5q):** Crude intermediate (4q) (0.95 g, 2.8 mmol) was dissolved in MeOH/DCM (15 mL). Next, 4N HCl (10.5 mL, 42.0 mmol) in dioxane was added and stirred at room temperature for 1 hour. Solvent was removed under reduced pressure and the residue (5q) was carried on to next step without further purification or characterization.

[0153] **Step F: (2-Amino-5-fluorobenzyl)-carbamic acid *tert*-butyl ester (6q):** A solution of Boc anhydride (0.49 g, 2.5 mmol) in dioxane (5 mL) was added dropwise to an ice bath cooled solution of (5q) (2.8 mmol, 1 eq.) in 5.7 mL of 1 M $NaHCO_3$ (5.63 mmol) and dioxane (11.2 mL) (1:2). The reaction mixture was allowed to warm to room temperature and continued stirring at room temperature for 18 hours. The next day, the mixture was diluted with Et_2O and washed with brine. The layers were separated. The aqueous layer (brine) was extracted with Et_2O (3x) and the combined organic layers were extracted with 10% $KHSO_4$ (3x), and washed with H_2O and brine and dried over Na_2SO_4. After concentration, the obtained crude product was purified by chromatography (Sep-Pak) with hexane, hexane/EtOAc (9:1) to give the product (6q) (0.34 g, 50% isolated yield). ^1H NMR (400 MHz, CD_3OD) δ 6.85-6.75 (m, 2H), 6.6 (dd, *J* = 7.8, 4.7 Hz, 1 H), 4.82 (br s, NH), 4.21 (d, *J* = 6.2 Hz, 2H), 4.06 (br s, NH_2), 1.45 (s, 9H). LC-MS (ESI+) *m/z* 241 (M+H) was detected.

[0154] **Step G: [5-Fluoro-2-(1-cyclobutylmethyl-1*H*-indazol-5-ylamino)-benzyl]-carbamic acid *tert*-butyl ester (7q-2):** To a flask containing boronic acid (0.175 g, 0.76 mmol), amine (6q) (0.22 g, 0.915 mmol), $Cu(OAc)_2$ (0.135 g, 0.76 mmol) and 4 Å sieves (0.2 g) in DCM, Et_3N (0.52 mL, 3.7 mmol) was slowly added. The mixture was stirred at room temperature for 3 days. DCM was added to the reaction mixture and filtered. The filtrate was washed with H_2O (2x), brine and dried over Na_2SO_4. After concentration, the residue was purified by chromatography (Sep-Pak; 10 g) with hexane/Et_2O (3:1). The fractions containing the

product were combined to afford (7q-2) (0.12 g, 37% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.34 (d, *J* = 8.6Hz, 1 H), 7.24 (br s, 1 H), 7.13 (d, *J* = 8.6Hz, 1 H), 6.94 - 6.84 (m, 3H), 5.02 (br s, NH), 4.35 (d, *J* = 7.8 Hz, 2H), 4.29 (d, J = 6.2 Hz, 2H), 2.98 - 2.85 (m, 1H), 2.10-1.98 (m, 2H), 1.95-1.79 (m, 4H), 1.44 (s, 9H); MS (APCI+) *m/z* 425 (M+H) was detected.

[0155] Step H: (2-Aminomethyl-4-fluoro-phenyl)-(1-cyclobutylmethyl-1H-indazol-5-yl)-amine (8q-2): Intermediate (7q-2) (0.076 g, 0.18 mmol) was dissolved in DCM/i-PrOH (5 mL, 1:1), 0.5 mL of HCl (1.97 mmol) in dioxane were added and the reaction mixture was stirred for 3 days. The solvent was evaporated to give the product (8q-2) which was carried on to the next step. LC-MS (ESI+) *m/z* 308 (M- NH_2) was detected. Both (7q-1) and (8q-1) were carried forth to the final step using the protocol for analogues 7q-2 and 8q-2.

[0156] Step I: 1-[5-Cyclopropyl-2-(4-trifluoromethylphenyl)-2*H*-pyrazol-3yl]-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-ylamino)-benzyl]-urea (9q-1): A solution of (8q-1) (0.15 g, 0.54 mmol) in DMF (4.5 mL) was treated with carbamate 10q (0.26 g, 0.6 mmol) followed by DIEA (0.35 mL, 2.0 mmol) at room temperature. The mixture was heated at 80 °C for 18 hours and then the solvent was evaporated under reduced pressure. The residue was taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper and evaporated to dryness. The crude product was then purified by HPLC to provide the product (9q-1) (0.027 g, 9 % isolated yield). ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.59 (d, *J* = 7.96 Hz, 2H), 7.54 (d, *J* = 7.43 Hz, 2H), 7.57 (br s, NH), 7.37 (d, *J* = 8.49 Hz, 1 H), 7.22 - 7.16 (m, 2H), 7.15 (s, 1 H), 6.99 -6.91 (m, 2H), 6.21 (s, 1 H), 4.34 (s, 2H), 4.07 (s, 3H), 2.01 - 1.93 (m, 1H), 1.14 -0.98 (m, 2H), 0.90 - 0.83 (m, 2H); MS (APCI+) *m/z* 564 (M+H) was detected.

[0157] Step J: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-cyclobutylmethyl-1H-indazol-5-ylamino)-5-fluorobenzyl]-urea (9q-2): Compound (8q-2) (0.18 mmol) was dissolved in DMF (2.5 mL), carbamate 10q (0.08 g, 0.20 mmol) was added followed by DIEA (0.1 mL, 0.57 mmol). The reaction mixture was heated to 80 °C for 18 hours. The solvent was evaporated under reduced pressure and the residue was taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper and evaporated under reduce pressure to an oil. The crude product was then purified by HPLC to provide the product (9q-2) (0.045 g, 44 % isolated yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.7 (br s, NH), 7.32 (d, *J* = 9.39 Hz, 1 H), 7.18 - 7.06 (m, 7H), 6.94 - 6.85 (m, 2H), 6.50 (s, 1 H), 4.37 - 4.30 (m, 6H), 2.96 - 2.81 (m, 1 H), 2.27 (s, 3H), 2.09 - 1.96 (m, 2H), 1.94 - 1.76 (m, 4H), 1.34 (s, 9H); MS (APCI+) *m/z* 580 (M+H) was detected.

Example 5

Preparation of 1-(5-*tert*-butyl-2-p-chlorophenyl-2*H*-pyrazol-3-yl)-3-[2-(1-methyl-1*H*-indazo-5-ylsulfanyl)-5-fluorobenzyl]-urea (6r-2)

[0158] The reaction scheme for the synthesis of compound 6r-2 is shown in Figure 5.

[0159] Step A: 5-Bromo-1H-indazole (1r): 4-bromo-2-methyl aniline (20 g, 107 mmol), ammonium tetrafluoroborate (23 g, 215 mmol) and concentrated HCl (45 mL, 537 mmol) were added to AcOH/H_2O (350 mL, 2:1) and sonicated. Next, $NaNO_2$ (8.9 g, 129 mmol) was added slowly and the reaction mixture was sonicated for 10 additional minutes (reaction turned brown and a precipitate formed immediately). The reaction was allowed to stir overnight. No starting material was observed the next day. The mixture was evaporated on a speed vacuum at 65 °C, then azeotroped with toluene to dryness. The material was taken directly onto the next step without further purification. The above crude material, potassium acetate (42 g, 428 mmol) and 18-crown-6 (2.8 g, 11 mmol) were added to chloroform (300 mL) and sonicated for 10 minutes The reaction was stirred overnight at room temperature. The material was passed through a filter funnel with silica gel/celite/sand and washed through repeatedly with $CHCl_3$ (material not collected). Next, the column was washed with EtOAc, providing an orange material that was collected, pooled and evaporated to give about 16 g of material. The crude product was then flash chromatographed with silica gel using DCM:MeOH (5%) as eluent and dried on a high vacuum overnight to give the desired product (1 r) (8 g, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.9 (br s, 1 H), 8.05 (s, 1 H), 7.9 (s, 1 H), 7.46 (d, *J* = 8.8 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H); MS (ESI) *m/z* 197.1 (M+H) $^+$.

[0160] Step B: 5-Bromo-1-methyl-1H-indazole (2r): 5-Bromo-1H-indazole (1 r) (10 g, 51 mmol) in THF was added slowly to a cold solution of NaH (2.2 g, 60% wt in oil, 56 mmol) in THF under nitrogen. After 15 minutes, iodomethane (10.8 g, 76 mmol) was added to the dark solution at 0 °C. After 2 hours, the mixture was poured into 1 N HCl (30 mL) and extracted with EtOAc (2 x 50 mL), and the combined extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated. Column

chromatography (silica gel): hexane:EtOAc (10-40%) resulted in 8.2 g of final product (2r). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.9 (s, 1 H), 7.84 (s, 1 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 4.04 (s, 3H); MS (ESI) *m/z* 213 $(M+H)^+$.

[0161] Step C: 5-(Triisopropylsilylsulfanyl)-1-methyl-1*H*-indazole (3r): KH (1.3 g, 30% wt, 9.8 mmol) was washed with THF and then suspended in THF (10 mL) at 5 °C. Triisopropylsilylthiol (1.8 g, 9.3 mmol) was added over 15 minutes with vigorous evolution of hydrogen gas. The mixture was stirred at 5 °C for an hour and then at 25 °C for 1 hour. This solution was added to a solution of 1-methyl-5-bromoindazole (2r) (2 g, 9.5 mmol) and $(Ph_3P)_4Pd$ (1.1 g, 0.93 mmol) in THF (15 mL). The yellow suspension was stirred for 1 hour at 70 °C. After cooling, ether was added and the solution was washed with brine, dried (Na_2SO_2) and concentrated. The residue was chromatographed (silica gel, 3 % EtOAc in hexane) to give 5-(triisopropylsulfanyl)-1-methyl-1*H*-indazole (3r) (1.8 g, 59 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.86 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.25 (d, *J*= 8.4 Hz, 1H), 4.05 (s, 3H), 1.28-1.19 (m, 3H), 1.08 (d, *J* = 7.6 Hz, 18H).

[0162] Step D: 2-(1-methyl-1*H*-indazol-5-ylsulfanyl)-5-fluorobenzonitrile (4r): Compound (3r) (0.65 g, 2 mmol), potassium carbonate (0.34 g, 2.4 mmol), CsF (0.46 g, 3 mmol), 2,5-difluorobenzonitrile (0.56 g, 4.1 mmol) and DMF (5 mL) were placed in a 60 mL reaction vial and the vial was sealed. The mixture was heated to 100 °C for 16 hours. Excess DMF was removed under reduced pressure. This material was taken up in DCM (50 mL) and washed with water (20 mL). The aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine (2x) and dried over $MgSO_4$, filtered through a plug of celite/silica gel and concentrated under reduced pressure. The residue was purified by silica gel chromatography with hexane/EtOAc (20 %) to give the final product as a viscous liquid (4r) (0.43 g, 75% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.97 (s, 1H), 7.46 (dd, *J* = 16.8, 8.8 Hz, 2H), 7.35-7.32 (m, 1 H), 7.14-7.07 (m, 1H), 7.05-7.01 (m, 1H), 4.1 (s, 3H); MS (ESI) *m/z* 284.2 $(M+H)^+$.

[0163] Step E: 2-(1-Methyl-1H-indazol-5-ylsulfanyl)-5-fluorobenzylamine (5r): A solution of compound (4r), (0.43 g, 1.5 mmol) in MeOH (30 mL) was purged with nitrogen and treated with $Pd(OH)_2$/C catalyst (15% wt, 280 mg, 0.3 mmol) followed by concentrated HCl (0.38 mL, 4.6 mmol). After purging more with nitrogen, a hydrogen-filled balloon was placed on top of the flask. After stirring at room temperature for 18 hours, the LC showed no more starting material. Next, K_2CO_3 (0.5 g) was added. The catalyst was filtered through a plug of silicagel/celite/sand and washed with $CHCl_3$/Et_3N and the solvent was removed under reduced pressure. The resulting pale yellow foam (5r), (0.43 g, 87 % isolated yield) was stored under a nitrogen atmosphere. MS (ESI) *m/z* 287.9 $(M+H)^+$.

[0164] Step F: 1-(5-Cyclopropyl-2-p-chlorophenyl-2*H*-pyrazol-3-yl)-3-[2-(1-methyl-1*H*-indazo-5-ylsulfanyl)-5-fluorobenzyl]-urea (6r-1): A solution of compound (5r), (70 mg, 0.21 mmol) in DMF (1 mL) was treated with the corresponding carbamate (97 mg, 0.24 mmol) followed by DIEA (70 µL, 0.54 mmol). The mixture was heated at 80 °C for 18 hours under nitrogen atmosphere. The crude product was then purified by preparative thin layer chromatography using hexane/EtOAc (1:1) as eluent (R_f = 0.6) to give the final product (6r-1) (80 mg, 68% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.57 (s, 1 H), 7.34-7.26 (m, 5H), 7.2-7.14 (m, 2H), 6.97 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.92-6.84 (m, 2H), 5.99 (s, 1 H), 5.7 (t, *J* = 6.0 Hz, 1 H), 4.4 (d, *J* = 5.6 Hz, 2H), 1.89 (m, 1H), 0.95-0.9 (m, 2H), 0.75-0.71 (m, 2H); MS (ESI) *m/z* 547.1 $(M+H)^+$.

[0165] Step G: 1-(5-*tert*-Butyl-2-p-chlorophenyl-2*H*-pyrazol-3-yl)-3-[2-(1-methyl-1*H*-indazo-5-ylsulfanyl)-5-fluorobenzyl]-urea (6r-2): A solution of amine (5r), (70 mg, 0.21 mmol) in DMF (1 mL) was treated with the corresponding carbamate (100 mg, 0.24 mmol) followed by DIEA (70 µL, 0.54 mmol). The mixture was heated at 80 °C for 18 hours under nitrogen atmosphere. The crude product was then purified by preparative thin layer chromatography using hexane/EtOAc (1:1) as eluent (R_f = 0.6) to give the final product (6r-2) (80 mg, 66% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.58 (s, 1 H), 7.39-7.26 (m, 5H) 7.21-7.14 (m, 2H), 6.98 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.88 (d(t), *J* = 8.4, 2.4 Hz, 1H), 6.68 (s, 1H), 6.24 (s, 1H), 5.64 (t, *J* = 6.0 Hz, 1 H), 4.42(d, *J* = 6.4 Hz, 2H), 4.02 (s, 3H), 1.3 (s, 9H); MS (ESI) *m/z* 563.1 $(M+H)^+$.

Example 6

Preparation of 1-(5-*tert*-butyl-2-methyl-2*H*-pyrazol-3-yl)-3-{2-[1-(3-isopropylamino-propyl)-1H-indazol-5-ylamino]-benzyl}-urea (8s-2)

[0166] The reaction scheme for the synthesis of compound 8s-2 is shown in Figures 6A-B.

[0167] Step A: 1-Allyl-5-bromo-1H-indazole (1s): 5-Bromoindazole (*Bioorg. Med. Chem. Lett.,* **11**:1153-1156 (2001)) (3.94 g, 20.0 mmol), allyl bromide (2.6 mL, 30 mmol) and potassium carbonate (4.15 g, 30.0 mmol) were heated in DMF (25 mL) at 100 °C for 18 hours. The reaction was cooled, filtered through celite, and the solids were washed with EtOAc. The solution was concentrated to near dryness and then partitioned between EtOAc and water. The organic phase was washed with $NaHCO_3$, dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel, 7% EtOAc/hexanes) to provide the *N*1 isomer (faster eluting) 1-allyl-5-bromo-1H-indazole (1 s) (1.7 g, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1 H), 7.88 (d, *J* = 2.3 Hz, 1 H), 7.44 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 6.06-5.97 (m, 1H), 5.24 (dd, *J* = 10.2, 1.6 Hz, 1H), 5.12 (d, *J* = 16.4 Hz, 1H), 5.01-5.00 (m, 2H); MS (ESI+) *m/z* 237, 239 (M+H, Br pattern) detected; HPLC (5 to 95%) 2.98 min.

[0168] Step B: 3-(5-Bromoindazol-1-yl)-propan-1-ol (2s): 1-Allyl-5-bromo-1*H*-indazole (1 s) (0.50 g, 2.1 mmol) was dissolved in 2 mL THF and cooled to 0 °C. A solution of 9-BBN in THF (0.5 M solution, 8.9 mL, 4.4 mmol) was then added slowly via syringe under nitrogen and stirring. The reaction was warmed to room temperature over 6.5 hours. Then, a solution of aqueous H_2O_2 (30% wt. solution; 1.4 mL) in 1 N NaOH (14 mL, 14 mmol) was added slowly to the solution. The reaction was stirred at room temperature overnight, resulting in the formation of a white precipitate. The reaction was diluted with H_2O and Et_2O. The layers were separated and the organic phase was washed with brine. The aqueous phases were extracted once with Et_2O. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material (2s) was carried on to the next step without characterization.

[0169] Step C: 5-Bromo-1-[3-(tert-butyl-diphenyl-silanyloxy)-propyl]-1 H-indazole (3s): Crude 3-(5-Bromoindazol-1-yl)-propan-1-ol (2s) (2.1 mmol) and imidzaole (0.22 g, 3.2 mmol) were dissolved in 10 mL CH_2Cl_2. *tert*-Butyldiphenylsilyl chloride (0.58 g, 2.1 mmol) was added to the solution and the reaction was stirred at room temperature for 4 hours. Additional amounts of imidazole (0.07 g, 1.0 mmol) and *tert*-butyldiphenylsilyl chloride (0.16 g, 0.63 mmol) were added and the reaction was stirred at room temperature overnight. The mixture was diluted with Et_2O and washed sequentially with an aqueous 3% HCl solution and brine. The aqueous phases were extracted once with Et_2O. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified on silica gel with 1:6 Et_2O/hexane to afford (3s) (1.0 g, 96% over two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.86 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 4H), 7.44-7.42 (m, 3H), 7.36-7.33 (m, 5H), 4.53 (t, *J* = 10.2 Hz, 2H), 3.63 (t, *J* = 9.0 Hz, 2H), 2.16-10 (m, 2H), 1.08 (s, 9H); HPLC (5 to 95%) 4.72 min.

[0170] Step D: 1-[3-(tert-Butyl-diphenylsilanyloxy)-propyl]-1H-indazole-5-boronic acid (4s): 5-Bromo-1-[3-(tert-butyl-diphenylsilanyloxy)-propyl]-1H-indazole (3s) (200 mg, 0.41 mmol) was dissolved in 4.0 mL THF and cooled to -78 °C. A solution of *n*-butyl lithium in hexanes (2.5M, 0.17 mL) was added slowly. The yellow solution was stirred for 30 minutes. Trimethyl borate (130 mg, 1.2 mmol) was added and the reaction was warmed to room temperature and stirred for 30 min. The reaction was quenched with 10 mL of a 0.3% aqueous HCl solution and the resulting mixture was stirred for 30 min. The reaction was diluted with Et_2O and the layers were separated. The organic phase was washed with brine. The aqueous phases were extracted once with Et_2O. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was partially purified on silica gel with 3% MeOH/CH_2Cl_2 to afford (4s) (97 mg, 52%). MS (ESI+) *m/z* 459 $(M+H)^+$. HPLC (5 to 95%) 3.74 min. This mixture was carried on to the next step without further purification.

[0171] Step E: 1-(2-Aminobenzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea (5s): 5-tert-Butyl-2-methyl-2H-pyrazol-3-ylamine (10s) (4.8 g, 31 mmol) and carbonyl diimidazole (4.6 g, 32 mmol) were partially dissolved in DCE (100 mL) and heated at 70 °C for 2 hours. The reaction was cooled and 2-aminomethyl-phenylamine (9s) (4.2 g, 34 mmol) was added and the reaction was stirred 14 hours. The reaction was concentrated to remove the solvent and then partitioned between EtOAc and 0.5N HCl (60 mL). The organic phase was washed with NH_4Cl and water and dried ($MgSO_4$). The solution was concentrated and recrystallized from EtOAc (200 mL) to provide the desired product (5s) (4.6 g, 49% yield). ^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1 H), 6.98 (d, *J* = 1.6 Hz, 1 H), 6.96 (dt, *J* = 7.8, 1.6 Hz, 1 H), 6.63 (t, *J* = 6.3 Hz, 1 H), 6.59 (d, *J* = 7.0 Hz, 1 H), 6.48 (t, *J* = 6.3 Hz, 1 H), 5.93 (s, 1 H), 5.07 (s, 2H), 4.12 (d, *J* = 6.3 Hz, 2H), 3.51 (s, 3H), 1.16 (s, 9H).

[0172] Step F: 1-(2-{1-[3-(tert-Butyldiphenylsilanyloxy)-propyl]-1H-indazol-5-ylamino}-benzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea (6s): Boronic acid 4 (240 mg, 0.52 mmol), 1-(2-amino-benzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea (5s) (170 mg, 0.58 mmol), copper (II) acetate (90 mg, 0.52 mmol), and 240 mg of 4 angstrom molecular sieves were suspended in 10 mL CH_2Cl_2. Triethylamine (0.36 mL, 2.6 mmol) was added and the mixture was stirred at room temperature overnight while exposed to air. An additional 3 mL of CH_2Cl_2 was added and the mixture was filtered through Celite and the

volatiles were removed *in vacuo*. The crude product was purified on silica gel with 2-4% MeOH/CH_2Cl_2 to afford (6s) (170 mg, 45% yield) as a brown tar. MS (ESI+) *m/z* 714 $(M+H)^+$; HPLC (5 to 95%) 4.32 min.

[0173] Step G: 1-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-3-{2-[1-(3-hydroxy-propyl)-1H-indazol-5-ylamino]-benzyl}-urea (7s): 1-(2-{1-[3-(tert-Butyldiphenyl-silanyloxy)-propyl]-1H-indazol-5-ylamino}-benzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea (6s) (40 mg, 0.056 mmol) was dissolved in 0.5 mL THF and treated with TBAF (1.0 M solution in THF, 0.11 mL, 0.11 mmol). The reaction was stirred at room temperature for 1 hour. Additional TBAF was added (0.3 mL, 0.3 mmol) and the reaction was stirred an additional 2 hours. The reaction was diluted with CH_2Cl_2 and washed with H_2O. The aqueous phase was extracted once with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The product was purified on silica gel with 5% MeOH/CH_2Cl_2 to afford the desired compound (7s) (8 mg, 30%, ~90% pure by ^1H NMR and HPLC). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.36-7.31 (m, 2H), 7.21-7.12 (m, 4H), 6.85 (s, 1 H), 6.81 (t, *J* = 10.6 Hz, 1 H), 5.93 (s, 1 H), 5.41-5.38 (m, 1 H), 4.49 (t, *J* = 9.0 Hz, 2H), 4.43 (d, *J* = 6.3 Hz, 2H), 3.57 (t, *J* = 8.2 Hz, 3H), 3.52 (s, 3H), 2.13- 2.07 (m, 2H), 1.25 (s, 9H); MS (APCI) *m/z* 476 $(M+H)^+$; HPLC (5 to 95%) 2.79 min.

[0174] Step H: 1-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-3-{2-[1-(3-dimethylamino-propyl)-1H-indazol-5-ylamino]-benzyl}-urea (8s-1): Methanesulfonic anhydride (12 mg, 0.070 mmol) was added to a solution of alcohol (7s) (24 mg, 0.050 mmol) and diisopropylethylamine (20 mg, 0.15 mmol) at room temperature. The solution was stirred for 1 hour. Dimethylamine (2.0 M in THF, 0.25 mL, 0.50 mmol) was added and the reaction was stirred overnight. Additional dimethylamine was added (2.0 M in THF, 0.25 mL, 0.50 mmol) and the reaction was stirred an additional 2 days. The mixture was then partitioned between $CHCl_3$ and water. The aqueous phase was extracted once with $CHCl_3$. The organic phases were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude product was purified on silica gel with 5% MeOH/CH_2Cl_2 containing 1 % Et_3N to provide the desired compound (8s-1) (11 mg, 43% yield) as a dark foam. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.42 (s, 1 H), 7.35-7.33 (m, 2H), 7.19-7.11 (m, 4H), 6.80-6.75 (m, 2H), 5.94 (s, 1 H), 5.55 (m, 1 H), 4.43 (d, *J* = 6.6 Hz, 2H), 4.38 (t, *J* = 10.5 Hz, 2H), 3.57 (s, 3H), 2.24 (t, *J* = 10.5 Hz, 2H), 2.19 (s, 6H), 2.08-2.01 (m, 2H), 1.24 (s, 9H); MS (ESI+) *m/z* 503 $(M+H)^+$; HPLC (5 to 95%) 2.59 min.

[0175] Step I: 1-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-3-{2-[1-(3-isopropylaminopropyl)-1H-indazol-5-ylamino]-benzyl}-urea (8s-2): Methanesulfonic anhydride (18 mg, 0.11 mmol) was added to a solution of alcohol (7s) (36 mg, 0.076 mmol) and diisopropylethylamine (29 mg, 0.23 mmol) at room temperature. The solution was stirred for 1 hour. Isopropylamine (0.13 mL, 1.50 mmol) was added and the reaction was stirred at room temperature for 60 hours. The volatiles were removed *in vacuo*. The crude product was purified on silica gel with 5% MeOH/CH_2Cl_2 containing 1% Et_3N and then on C_{18} silica with CH_3CN/H_2O to afford the desired compound (8s-2) (8 mg, 20% yield). ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1 H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.31-7.24 (m, 3H), 7.17-7.16 (m, 2H), 6.93-6.89 (m, 1H), 6.05 (s, 1 H), 4.52 (t, *J* = 10.2 Hz, 2H), 4.41 (s, 2H), 3.57 (s, 3H), 3.35-3.30 (m, 1 H), 3.03 (t, *J* = 11.7 Hz, 2H), 2.29-2.22 (m, 2H), 1.29 (d, *J* = 6.3 Hz, 6H), 1.26 (s, 9H); MS (ESI+) *m/z* 517 $(M+H)^+$; HPLC (5 to 95%) 2.61 min.

Example 7

Preparation of 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzyl]urea (7t-1) and 1-[5-*tert*-butyl-2-(4-chloro-phenyl)-2*H*-pyrazol-3-yl]-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzyl]urea (7t-2)

[0176] The reaction scheme for the synthesis of compound 7t-2 is shown in Figure 7.

[0177] Step A: 5-Methoxy-1-methyl-1*H*-indazole (2t): A solution of 6-methoxy indazole (1t) (5 g, 33.75 mmol; see *TetLett.*, **43**(15): 2695 (2002)) in DMF (200 mL) was treated with potassium carbonate (6.06 g, 43.87 mmol) at room temperature. After stirring at for 15 minutes, methyl iodide (2.33 mL, 37.12 mmol) was added. The resulting mixture was heated at 110 °C for 18 hours. LC showed minor starting material left. Additional methyl iodide was added (2.33 mL) and stirring continued for an additional 18 hours. LC showed a 2:1 mixture of the *N*1 to *N*2 alkylated isomers. The solvent was evaporated *in vacuo* and the residue taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper, evaporated *in vacuo* and purified on the Biotage eluting with 4:3, 3:1 hexane/Et_2O. The desired combined fractions (*N*1 isomer) were evaporated *in vacuo* to provide the desired product (2t) as a yellow oil (2.57 g; 47%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J*

= 7.8, 1.6 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1 H), 5.19-5.18 (m, 1 H), 4.51-4.44 (m, 1 H), 4.43-4.36 (m, 1 H), 2.53-2.45 (m, 1 H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 163 (M+H) detected.

[0178] Step B: 1-Methyl-1*H*-indazol-5-ol (3t): To a solution of (2t) (0.99 g, 6.1 mmol) in toluene (30 mL) was added $AlCl_3$ (2.44 g, 18.3 mmol) at room temperature, upon which a purple colored mixture formed. After refluxing for 20 minutes, an olive colored mixture formed. The mixture was refluxed for 2 hours, allowed to cool to room temperature and poured into an ice-water bath. The insoluble solids were collected by filtration (398 mg). The filtrate was extracted with DCM, filtered through 1 PS paper, evaporated *in vacuo* and purified on the Biotage eluting with (1:9) then (3:7) Et_2O/DCM and finally (1:1) DCM/Et_2O. The product fractions were evaporated *in vacuo* affording compound (3t) as a brown foam (122 mg). Total combined yield, 520 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.13 (d, *J* = 1.6 Hz, 1H), 5.19-5.18 (m, 1H), 4.51-4.44 (m, 1H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 149 (M+H) detected.

[0179] Step C: 5-Fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzonitrile (4t): A solution of (3t) (0.70 g, 4.74 mmol) in DMF (50 mL) was cooled to 0 °C and treated with 60% by weight sodium hydride (0.28 g, 7.11 mmol). After stirring at this temperature for 20 minutes, the aryl fluoride (0.79 g, 5.69 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 hour. The mixture was then cooled to 0 °C and treated with water (50 mL), extracted with Et_2O (3 x 150 mL) and the combined organic layers were washed with water (2 x 20 mL), brine (2 x 20 mL), dried over $MgSO_4$ and evaporated *in vacuo* to an oil. This material was purified by flash column chromatography (EtOAc/hexane = 2:3; loaded in warm toluene and DMF mixture). The desired fractions were evaporated *in vacuo* and azeotroped with toluene. The compound (4t) was obtained as white crystals, 1.09 g (86% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.13 (d, *J* = 1.6 Hz, 1 H), 5.19-5.18 (m, 1 H), 4.51-4.44 (m, 1 H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 268 (M+H) detected.

[0180] Step D: 5-Fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzylamine hydrochloride (5t): A solution of (4t) (0.32 g, 1.22 mmol) in MeOH (20 mL) was purged with nitrogen and treated with 20% $Pd(OH)_2$/C catalyst (15% wt, 180 mg) followed by concentrated HCl (0.3 mL, 3.6 mmol). After purging further with nitrogen, a balloon containing hydrogen was placed on top of the flask. After stirring at room temperature for 18 hours, the LC indicated no more starting material was present. The catalyst was filtered through a plug of silica gel/celite/sand and washed with MeOH. The solvent was evaporated *in vacuo* and the residue co-evaporated from ether. The resulting pale yellow foam (5t) was stored under N_2, 0.34 g (91 % isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.13 (d, *J* = 1.6Hz, 1 H), 5.19-5.18 (m, 1H), 4.51-4.44 (m, 1 H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 272 (M+H) detected.

[0181] Step E: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzyl]urea (7t-1): A solution of (5t) (70 mg, 0.23 mmol) in DMF (1 mL) was treated with the corresponding carbamate (6t-1) (100 mg, 0.25 mmol) followed by DIEA (99 µL, 0.57 mmol). The mixture was heated at 80°C for 18 hours under nitrogen purge. The solvent was evaporated *in vacuo* and the residue taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper and evaporated *in vacuo* to an oil that was purified on a silica gel SepPak cartridge eluting with 10:1 DCM/Et_2O. The desired fractions were evaporated *in vacuo* to provide the desired compound (7t-1) as a pale yellow oil (80 mg; 67% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.13 (d, *J* = 1.6 Hz, 1 H), 5.19-5.18 (m, 1 H), 4.51-4.44 (m, 1 H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 527 (M+H) detected.

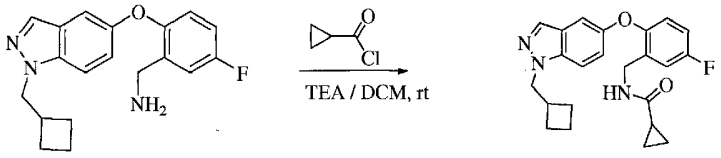
[0182] Step F: 1-[5-*tert*-Butyl-2-(4-chloro-phenyl)-2*H*-pyrazol-3-yl]-3-[5-fluoro-2-(1-methyl-1*H*-indazol-5-yloxy)-benzyl]urea (7t-2): A solution of (5t) (74 mg, 0.57 mmol) in DMF (1 mL) was treated with the corresponding carbamate (6t-2) (110 mg, 0.25 mmol) followed by DIEA (99 mL, 0.57 mmol). The mixture was heated at 80 °C for 18 hours, under nitrogen purge. The solvent was evaporated *in vacuo* and the residue taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper and evaporated *in vacuo* to an oil that was purified on a silica gel SepPak cartridge eluting with (10:1) DCM/Et_2O. Desired fractions were evaporated *in vacuo* to provide the desired compound (7t-2) as a pale yellow oil (80 mg; 64% isolated yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1 H), 7.17 (dd, *J* = 7.8,1.6 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 5.19-5.18 (m, 1H), 4.51-4.44 (m, 1H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1 H); MS (ESI+) *m/z* 547 (M+H) detected.

[0183] In a similar manner the following compounds were synthesized.

Example 8

Preparation of cyclopropanecarboxylic acid 2-(1-cyclobutylmethyl-1H-indazol)-5-fluorobenzylamide (9t)

[0184]



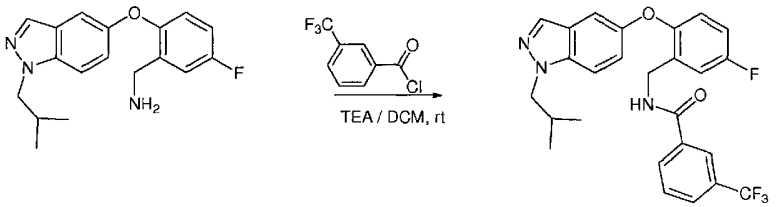
8t 9t

[0185] A solution of (8t) (20 mg, 0.06 mmol; prepared as in Example 7, Steps A-E) in DCM (0.5 mL) was treated with base (13 µL, 0.09 mmol) followed by cyclopropanecarbonyl chloride (6 µL, 0.07 mmol) at room temperature, under nitrogen purge. The mixture was stirred at room temperature for 18 hours and then purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. The desired fractions were evaporated *in vacuo* to afford the product (9t) as a pale yellow oil, 10.2 mg (42% isolated yield). MS (ESI+) *m/z* 394 (M+H) detected.

Example 9

Preparation of N-[5-fluoro-2-(1-isobutyl-1*H*-indazol-5-Yloxy)-benzyl]-3-trifluoromethyl benzamide (11t)

[0186]



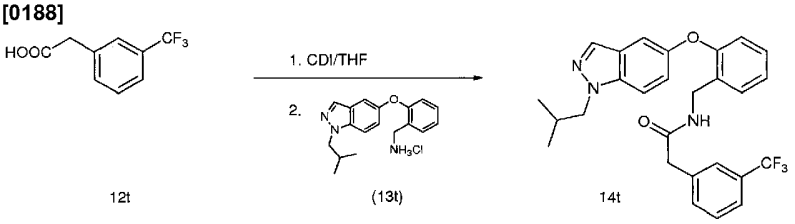
10t 11t

[0187] A solution of compound (10t) (14 mg, 0.05 mmol; prepared as in Example 7, Steps A-E) in DCM (0.5 mL) was treated with base (11 µL, 0.06 mmol) followed by 3-trifluoromethylbenzoyl chloride (12 mg, 0.075 mmol) at room temperature, under nitrogen purge. The mixture was stirred at room temperature for 18 hours and then purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. The desired fractions were evaporated *in vacuo* to afford the product (11t) as a yellow oil, 16.6 mg (53 % isolated yield ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 1H), 7.17 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.13 (d, *J* = 1.6 Hz, 1H), 5.19-5.18 (m, 1H), 4.51-4.44 (m, 1H), 4.43-4.36 (m, 1H), 2.53-2.45 (m, 1H), 2.36-2.30 (m, 1H); MS (ESI+) *m/z* 468 (M+H) detected.

Example 10

Preparation of N-[2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl]-2-(3-trifluoromethylphenyl)-acetamide (14t)

[0188]



12t (13t) 14t

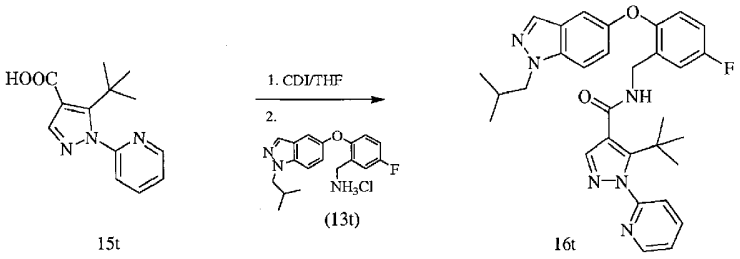
Preparation of N-[2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl]-2-(3-trifluoromethylphenyl)-acetamide (14t)

[0189] A solution of (3-trifluoromethylphenyl) acetic acid (12t) (10 mg, 0.051 mmol) in THF (0.5 mL) was treated with 1,1-carbonyldiimidazole (CDI, 9 mg, 0.055 mmol) at room temperature. After stirring at room temperature for 18 hours, under nitrogen purge, the benzylamine (13t) (17 mg, 0.05 mmol; prepared as in Example 7, Steps A-E) was added at room temperature. Stirring was continued for an additional 18 hours. The solvent was evaporated *in vacuo* and the residue taken up in DCM and purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. Desired fractions were evaporated *in vacuo* to afford the product (14t) as a pale yellow oil (10 mg; 42% isolated yield). MS (ESI+) *m/z* 482 (M+H) detected.

Example 11

Preparation of 5-tert-butyl-1-pyridin-2-yl-1*H*-pyrazole-4-carboxylic acid 5-fluoro-2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzylamide (16t)

[0190]

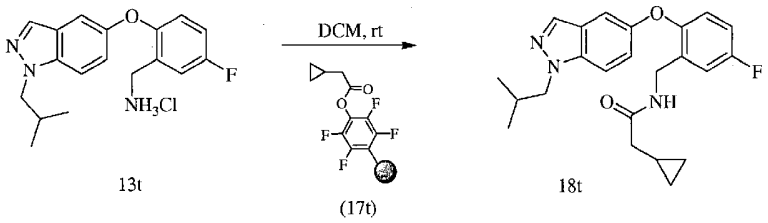


[0191] A solution of 5-tert-butyl-1-pyridin-2-yl-1*H*-pyrazole-4-carboxylic acid (15t) (12 mg, 0.05 mmol) in THF (0.5 mL) was treated with 1,1-carbonyldiimidazole (CDI, 9 mg, 0.05 mmol) at room temperature. After stirring at room temperature for 18 hours, under nitrogen purge, benzylamine (13t) (15 mg, 0.05 mmol; prepared as in Example 7, Steps A-E) was added at room temperature. Stirring was continued for an additional 18 hours. The solvent was evaporated *in vacuo* and the residue taken up in DCM and purified on a silica gel SepPak cartridge eluting with 2-10% MeOH in DCM. The desired fractions were *evaporated in vacuo* to afford the product (16t) as a yellow oil, 5.2 mg (23% isolated yield). MS (ESI+) *m/z* 541 (M+H) detected.

Example 12

Preparation of 2-cyclopropyl-N-[5-fluoro-2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl]-acetamide (18t)

[0192]



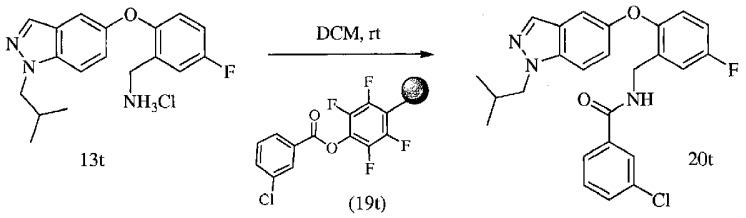
[0193] A solution of compound (13t) (15 mg, 0.05 mmol; prepared as in Example 7, Steps A-E) in DCM (0.5 mL) was added to the corresponding TFP acid (17t) (1 mmol/g) at room temperature. The mixture was shaken for 18 hours. The resin was washed with DCM. The combined filtrates were concentrated *in vacuo* and purified on a silica gel SepPak cartridge eluting with (10:1)

DCM-Et_2O. The desired fractions were evaporated *in vacuo* to afford the product (18t) as a yellow oil (12.6 mg; 66% isolated yield). MS (ESI+) *m/z* 400 (M+H) detected.

Example 13

Preparation of 3-chloro-N-[5-fluoro-2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl] benzamide (20t)

[0194]

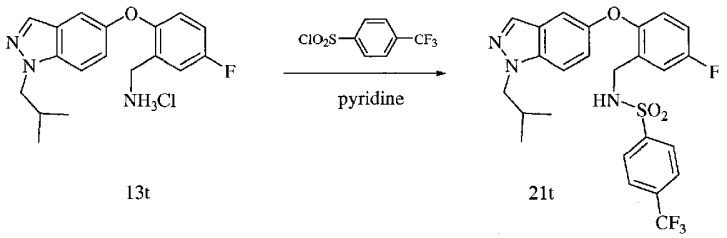


[0195] A solution of (13t) (15 mg, 0.05 mmol; prepared as in Example 7, Steps A-E) in DCM (0.5 mL) was added to the corresponding TFP acid (19t) (1 mmol/g) at room temperature. The mixture was shaken for 18 hours. The resin was washed with DCM. The combined filtrates were concentrated *in vacuo* and purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. The desired fractions were evaporated *in vacuo* to provide the product (20t) as a yellow oil (14.4 mg; 66% isolated yield). MS (ESI+) *m/z* 452 (M+H) detected.

Example 14

Preparation of N-[5-fluoro-2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl]-4-trifluoromethylbenzenesulfonamide (21t)

[0196]

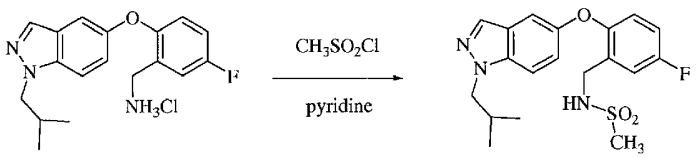


[0197] A solution of compound (13t) (15 mg, 0.04 mmol; prepared as in Example 7, Steps A-E) in pyridine (0.5 mL) was treated with 4-trifluoromethylbenzenesulfonyl chloride (13 mg, 0.05 mmol) at room temperature under nitrogen purge. The mixture was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo*, taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper, concentrated *in vacuo* and purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. The desired fractions were evaporated *in vacuo* to provide the product (21 t) as a yellow oil, 15.6 mg (70% isolated yield). MS (ESI+) *m/z* 522 (M+H) detected.

Example 15

Preparation of N-[5-fluoro-2-(1-isobutyl-1*H*-indazol-5-yloxy)-benzyl]-methanesulfonamide (22t)

[0198]



13t 14t

[0199] A solution of compound (13t) (15 mg, 0.043 mmol; prepared as in Example 7, Steps A-E) in pyridine (0.5 mL) was treated with methanenesulfonyl chloride (4 µL, 0.05 mmol) at room temperature, under nitrogen purge. The mixture was stirred at room temperature for 18 hours. The solvent was evaporated *in vacuo,* taken up in DCM and washed with 1 N HCl. The organic layer was filtered through 1 PS paper, concentrated *in vacuo* and purified on a silica gel SepPak cartridge eluting with (10:1) DCM-Et_2O. The desired fractions were evaporated *in vacuo* to a yellow oil (22t), 13.1 mg (78% isolated yield). MS (ESI+) *m/z* 392 (M+H) detected.

Example 16

Preparation of 3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-1-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea (28t)

[0200] The reaction scheme for the synthesis of compound 28t is shown in Figure 8.

[0201] Step A: 5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzylamine hydrochloride (5t): Intermediate (4t) (1.13 g, 4.23 mmol; prepared as in Example 7, Steps A-C) was dissolved in methanol (50 mL) and 20% palladium hydroxide on activated carbon (0.50 g, 0.71 mmol) was added to the solution under nitrogen atmosphere. After the addition of concentrated HCl (12 N, 5.0 mL, 60 mmol), the mixture was stirred under hydrogen atmosphere overnight (18 hours). The mixture was filtered and palladium hydroxide was washed with MeOH. After evaporation, the crude residue was azeotroped with a mixture of toluene and EtOH to dryness to compound (5t) as a white powder (1.29 g, 99 % yield) ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.72 (br, 3H), 8.01 (s, 1 H), 7.73 (d, *J* = 8.6 Hz, 1 H), 7.57 (dd, *J* = 9.4, 2.3 Hz, 1 H), 7.38 (s, 1 H), 7.19 (d, *J* = 3.1 Hz, 1 H), 7.04 (td, *J* = 74.8, 3.1 Hz, 1 H), 7.02 (dd, *J* = 195.1, 4.7 Hz, 1 H), 4.07 (s, 3H) ppm.

[0202] Step B: [5-Fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-carbamic acid tert-butyl ester (26t): Intermediate (5t) (134 mg, 0.43 mmol) was dissolved in CH_2Cl_2 (5 mL) and diisopropylethylamine (151 µL, 112 mg, 0.87 mmol) and di-*tert*-butyldi carbonate (94.7 mg, 0.43 mmol) were added to the solution. After overnight stirring (12 hours), the reaction mixture was diluted with ethyl acetate (100 mL), washed with 0.2N HCl (5 mL), saturated $NaHCO_3$ (5 mL) and brine, dried over $MgSO_4$ and concentrated under reduced pressure to obtain an yellow crude oil, which was purified on silica gel with EtOAc/hexane (1:2) to obtain the product (26t) as a colorless oil (150 mg, 93% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1 H), 7.35 (d, *J* = 9.4 Hz, 1 H), 7.15-7.08 (m, 3H), 6.87 (t, *J* = 9.4 Hz, 1 H), 6.75 (dd, *J* = 8.7, 4.7 Hz, 1 H), 5.09 (br, 1 H), 4.35 (d, *J* = 6.3 Hz, 2H), 4.06 (s, 3H), 1.42 (s, 9H) ppm.

[0203] Step C: [5-Fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-methylcarbamic acid tert-butyl ester (27t): Intermediate (26t) (50 mg, 0.135 mmol) was dissolved in DMF (2 mL) and cooled to 0 °C. Sodium hydride (60%, 8.1 mg, 0.20 mmol) and methyl iodide (42 µL, 95.5 mg, 0.67 mmol) were added to the solution at 0 °C and then the mixture was allowed to warm to room temperature. After 1 hour of stirring, the mixture was poured into saturated NH_4Cl solution and extracted 3 times with 30 mL of ether. The combined organic layer was washed with 5 mL of water twice and brine one, dried over $MgSO_4$ and evaporated under reduced pressure. The pale yellow residue was purified on silica gel with EtOAc/hexane (1:2) to obtain compound (27t) as a colorless oil (52 mg, quantitative). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.35 (s, 0.4H), 7.33 (s, 0.6H), 7.11 (s, 0.6H), 7.08 (s, 1.4H), 6.98 (d, *J* = 8.6 Hz, 1 H), 6.92-6.81 (m, 1), 6.81-6.73 (m, 1 H), 4.49 (s, 0.8H), 4.45 (s, 1.2H), 4.04 (s, 3H), 2.89 (s, 1.8H), 2.85 (s, 1.2H), 1.45 (s, 3.6H), 1.41 (s, 5.4H) ppm.

[0204] Step D: 3-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-1-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methyl-urea (28t): Intermediate (27t) (52 mg, 0.135 mmol) was dissolved in CH_2Cl_2 (2 mL) and TFA (1 mL) was added to the solution at room temperature. After 1 hour of stirring, the reaction solution was evaporated under reduced pressure. The residue was diluted

with EtOAc (50 mL) and neutralized with saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude pale yellow oil was dissolved in DMA (2 mL). The carbamate (6t-1) and diisopropylethyl amine were added to the solution and heated to 80 °C in a sealed tube. After 16 hours of stirring, reaction mixture was diluted with Et_2O (50 mL) and washed with 5 mL of water three times and brine once, dried over $MgSO_4$ and evaporated under the reduced pressure. The crude oil was purified by flash column chromatography (ethyl acetate/hexane 1:1) to obtain compound (28t) as a white foam (63.8 mg, 87% yield over 2 steps). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.32 (d, *J* = 9.4 Hz, 1 H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.02 (s, 1 H), 6.98 (d, *J* = 8.6 Hz, 1 H), 6.89 (t, *J* = 8.6 Hz, 1 H), 6.72 (dd, *J* = 7.7, 4.7 Hz, 1 H), 6.62 (s, 1 H), 6.39 (s, 1 H), 4.51 (s, 2H), 4.05 (s, 3H), 2.94 (s, 2H), 2.32 (s, 3H), 1.30 (s, 9H) ppm.

Example 17

Preparation of 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea (32t)

[0205] The reaction scheme for the synthesis of compound 32t is shown in Figure 9.

[0206] Step A: [5-Fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-(4-methoxybenzyl)-amine (29t): Intermediate (5t) (136 mg, 0.442 mmol; prepared as in Example 7, Step D) was dissolved in EtOAc (100 mL) and neutralized with saturated $NaHCO_3$ then washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to obtain the free amine. The free amine was dissolved in 1,2-dichloroethane (5 mL) and *p*-anisaldehyde was added to the solution at room temperature. After 2 hours of stirring, the solution was evaporated under reduced pressure. The residue was dissolved in MeOH (5 mL) and cooled to 0 °C. Sodium borohydride was added to the solution at 0 °C. After 40 minutes of stirring at 0 °C, the reaction mixture was quenched with several drops of acetic acid at 0 °C, then the reaction mixture was evaporated under reduced pressure. The residue was diluted with EtOAc (50 mL) and neutralized with saturated $NaHCO_3$ and washed with brine, dried over $MgSO_4$ and evaporated to obtain a crude oil, which was purified on silica gel with EtOAc/hexane (1:1) with 1 % Et_3N to afford compound (29t) as a color less oil (139 mg, 80% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.34 (d, *J* = 9.4 Hz, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.23-7.15 (m, 2H), 7.13-7.06 (m, 2H), 6.92-6.85 (m, 2H), 6.84-6.78 (m, 2H), 4.61 (s, 1 H), 4.06 (s, 3H), 3.82 (s, 2H), 3.77 (s, 3H), 3.72 (s, 2H) ppm.

[0207] Step B: 3-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-1-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-(4-methoxybenzyl)-urea (30t): Intermediate (29t) (135 mg, 0.354 mmol), trichloroethylcarbamate (6t-1) (154 mg, 0.379 mmol) and diisopropylamine (120 µL, 89mg, 0.69 mmol) were dissolved in DMA (5 mL) and heated to 80 °C. After 12 hours of stirring at 80 °C, the reaction mixture was cooled down to room temperature, diluted with ether (50 mL) and washed with 5 mL of water there times and with brine once, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude oil was purified on silica gel with EtOAc/hexane (2:3) to afford compound (30t) as a colorless oil (180 mg, 83% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.07-6.95 (m, 8H), 6.94-6.89 (m, 1H), 6.89-6.84 (m, 1 H), 7.29 (d, *J* = 9.0 Hz, 1 H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.69 (dd, *J* = 8.9, 4.7 Hz, 1H), 6.60 (s, 1 H), 6.41 (s, 1H), 4.57 (s, 2H), 4.44 (s, 2H), 4.04 (s, 3H), 3.78 (s, 1 H), 3.77 (s, 3H), 2.31 (s, 3H), 1.30 (s, 9H) ppm.

[0208] Step C: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-3-(4-methoxybenzyl)-1-methyl-urea (31t) : Intermediate (30t) (150 mg, 0.23 mmol) was dissolved in DMF (2 mL) and cooled to 0 °C. Sodium hydride (60% in oil, 14 mg, 0.36 mmol) and methyl iodide (73.8 µL, 168 mg, 1.19 mmol) were added to the solution at 0 °C and the reaction mixture was stirred at 0 °C for 1 hour. The reaction mixture was quenched by addition of 5 mL of water at 0 °C, and then extracted three times with 50 mL of Et_2O. The combined organic layer was washed with 5 mL of water twice and with brine once, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified on silica gel with EtOAc/hexane (1:2) to obtain compound (31 t) as a pale yellow amorphous (134 mg, 87% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.37 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 9.4 Hz, 1H), 7.15-7.02 (m, 2H), 7.00-6.81 (m, 6H), 6.80-6.60 (m, 3H), 5.85 (s, 1H), 4.21 (s, 2H), 4.20 (s, 2H), 4.05 (s, 3H), 3.76 (s, 3H), 2.98 (s, 3H), 2.29 (s, 3H), 1.23 (s, 9H) ppm.

[0209] Step D: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea (32t): Intermediate (31 t) (85 mg, 0.131 mmol) was dissolved in 5 mL of solution of 2 % (v/v) anisole in trifluoroacetic acid and stirred at room temperature for 1.5 hour. After evaporation the crude residue was dissolved in EtOAc (80 mL) and

neutralized with saturated $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The obtained crude oil was purified on silica gel with EtOAc/hexane (2:3) to obtain compound (32t) as a white amorphous (68.6 mg, 99% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.32 (d, *J* = 9.4 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.07 (t, *J* = 10.2 Hz, 1 H), 7.20-6.96 (m, 1 H), 6.93 (td, *J* = 8.6, 3.1 Hz, 1 H), 6.85 (td, *J* = 8.6, 3.1 Hz, 1 H), 6.68 (dd, *J* = 8.6, 4.7 Hz, 1 H), 6.11 (s, 1 H), 5.31 (t, *J*=6.3 Hz, 0.8 H), 5.17 (t, *J*=6.3 Hz, 0.2H), 4.48-4.26 (m, 2H), 4.05 (s, 3H), 3.00 (s, 3H), 2.33 (s, 2.4H), 2.32 (s, 0.6H), 1.36 (s, 1.8H), 1.29 (s, 7.2H) ppm.

Example 18

Preparation of 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluoro-2-(1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yloxy)-benzyl]-urea (4u)

[0210] The reaction scheme for the synthesis of compound 4u is shown in Figure 10.

[0211] Step A: 5-Fluoro-2-hydroxybenzonitrile (23t): 2,5-Difluorobenzonitrile (14.9 g, 107 mmol) and benzyl alcohol (11.1 mL, 11.6 g, 107 mmol) were dissolved in DMF (330 mL) and cooled to 0 °C. Sodium hydride (60% in oil, 6.40 g, 161 mmol) was added to the solution at 0 °C and the reaction mixture was allowed to warm to room temperature. After stirring for 1 hour at room temperature, the reaction solution was cooled to 0 °C and water (330 mL) was gradually added to the solution. The mixture was transferred to a separatory funnel and extracted three times with 500 mL of Et_2O. The combined organic layer was washed twice with 100 mL of water, brine once, then dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure to obtain a crude pale yellow solid. The crude solid was dissolved in MeOH (500 mL). To the solution was added 10% palladium on activated carbon under a nitrogen atmosphere. Replacing nitrogen gas with hydrogen gas, reaction mixture was stirred at room temperature (if the reaction did not proceed in 30 minutes, the Pd/C was filtered off and the reaction was set up again). After 2 hours of stirring, the palladium on carbon was filtrated off and washed with MeOH. The solution was concentrated under reduced pressure to obtain a pale yellow solid. The solid was recrystallized from hot toluene (100 mL) by addition of hexane (10 mL) followed by cooling to 0 °C. The obtained white needles were washed with 1:1 mixture of toluene and hexane (7.23 g, 49 % yield). Mother liquor was concentrated and purified on silica gel with Et_2O/hexane (2:3-1:1) to afford the desired compound (23t) (6.94 g, 47% yield). Total 14.2 g (96% yield) over 2 steps. ^{1}HNMR (400 MHz, d_6-DMSO) δ 11.09 (s, 1 H), 7.58 (dd, *J*= 8.4, 3.2 Hz, 1H), 7.40 (td, *J*=8.6, 3.2 Hz, 1H), 7.03 (dd, *J*=9.2, 4.4 Hz, 1H) ppm.

[0212] Step B: 5-Fluoro-2-(4-methyl-5-nitro-pyridin-2-yloxy)-benzonitrile (1u): Intermediate (23t) (1.78 g, 13.0 mmol), 2-chloro-4-methyl-5-nitropyridine (2.31 g, 13.0 mmol) and potassium carbonate (1.80 g, 13.0 mmol) were dissolved in DMF (120 mL). When the mixture was warmed to 60 °C, the colorless solution turned blue in 10 minutes. After 16 hours of stirring at 60 °C, the reaction mixture was allowed to cool down to room temperature and then diluted with 100 mL of Et_2O. The inorganic precipitate was removed by filtration and washed with Et_2O. The combined organic solution (600 mL total) was transferred to a separatory funnel and washed with 60 mL of water three times and with brine one time. The solution was dried over $MgSO_4$ and then concentrated under reduced pressure to obtain crude brown solid. The crude solid was dissolved in MeOH (240 mL). To the solution was added 10% palladium on activated carbon under nitrogen atmosphere. Replacing nitrogen gas with hydrogen gas, the reaction mixture was stirred at room temperature (if the reaction did not proceed in 30 minutes, filtrated the Pd/C was filtered off and the reaction was set up again. After 1.5 hours of stirring, palladium on carbon was filtered off and washed with MeOH. The solution was concentrated under reduced pressure to obtain a pale yellow solid. The crude compound was purified on silica gel with EtOAc/hexane (1/1-3/2) to afford (1 u) as a white solid (2.21 g, 70% yield over 2 steps). ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1 H), 7.33 (ddd, *J* = 7.8, 3.1, 1.6 Hz, 1 H), 7.29-7.22 (m, 1 H), 7.23 (s, 0H), 7.15 (ddd, *J* = 9.3, 4.7, 1.6 Hz, 1 H), 6.82 (s, 1 H), 2.22 (s, 3H) ppm.

[0213] Step C: 5-Fluoro-2-(1H-pyrazolo[3,4-c]pyridin-5-yloxy)-benzonitrile (2u): Intermediate (1 u) (0.25 g, 1.03 mmol) and NH_4BF_4 (0.22 g, 2.06 mmol) were dissolved in 10 mL of mixed solvent of AcOH/water (2:1) and cooled to 0 °C, and followed by addition of concentrated HCl (0.43 mL, 5.16 mmol) and $NaNO_2$ (0.078 g, 1.13 mmol) to the solution at 0 °C. The color of the solution immediately turned into yellow as sodium nitrate was added. The reaction mixture was then allowed to warm to room temperature. After stirring 2 hours, the solvent was removed under reduced pressure and azeotroped with toluene three times to removed the water, to give a pale yellow crude solid. The solid was dissolved in 10 mL of EtOAc and KOAc was added to the solution. The color of suspension turned into deep orange in 30 minutes and then stirred an additional hour. The white inorganic salt was removed by filtration and washed with EtOAc. The combined filtrate was diluted with EtOAc to 100 mL of total volume and

transferred to a separatory funnel, washed with sat. $NaHCO_3$ (10 mL) and brine, dried over $MgSO_4$, filtered and evaporated to obtain a deep orange colored solid. The crude solid was purified on silica gel with EtOAc/hexane (2:3) to afford an orange yellow colored solid (2u) (0.23 g, 88% yield over 2 steps). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.15 (s, 1H), 7.30-7.34 (m, 2H), 7.32-7.22 (m, 2H), 7.12 (dd, *J* = 9.4, 4.7 Hz, 1 H) ppm.

[0214] Step D: 5-Fluoro-2-(1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yloxy)-benzonitrile (3u): The intermediate (2u) (0.23 g) was dissolved in DMF (9 mL) and cooled to 0 °C. Sodium hydride (60% in oil, 0.054 g, 1.36 mmol) and methyl iodide (0.28 mL, 642 mg, 4.52 mmol) were added to the solution at 0 °C and then the reaction mixture was stirred for an hour at 0 °C. The mixture was quenched with 10 mL of water and extracted three times with 30 mL of ether. The combined organic layer was washed with 5 mL of water twice and brine once, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil residue was purified on silica gel with EtOAc/hexane (1:1) to afford colorless oil (3u) (0.124 g, 51% yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.02 (s, 1 H), 7.40-7.32 (m, 2H), 7.31-7.23 (m, 2H), 7.11-7.05 (m, 1H, 4.17 (s, 3H) ppm.

[0215] Step E: 1-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yi)-3-[5-fluoro-2-(1-methyl-1H-pyrazolo[3,4-c]pyridin-5-yloxy)-benzyl]-urea (4u): The intermediate (3u) was dissolved in 10 mL of MeOH, and then concentrated HCl (12N, 1.0 mL, 12 mmol) and 10% palladium on activated carbon were added to the solution. The mixture was stirred under hydrogen atmosphere. After 24 hours stirring, the palladium on activated carbon was filtered off and the filtrate was concentrated under reduced pressure. The obtained residue was azeotroped with a mixture of toluene and ethanol a couple of times to dryness to afford the crude hydrochloride salt of the amine. The crude salt was dissolved in 5 mL of DMF. Diisoproylethylamine and trichloroethylcarbamate were added to the solution and heated to 80 °C. After 16 hours of stirring, DMF was evaporated off under reduced pressure and the residue was diluted with 50 mL of EtOAc and washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The obtained crude oil was purified by preparative TLC with EtOAc/hexane (2:1) and then 100% of CH_2Cl_2 to afford a colorless oil (4u) (9.0 mg, 4 % yield). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.90 (s, 1 H), 7.24 (s, 1 H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.06-7.00 (m, 2H), 6.91 (td, *J* = 8.3, 3.1 Hz, 1 H), 6.82 (dd, *J* = 8.9, 4.7 Hz, 1 H), 6.46 (br, 1H), 6.18 (s, 1 H), 5.84 (t, *J* = 8.6 Hz, 1 H), 4.36 (s, 1 H), 4.34 (s, 2H), 4.05 (s, 3H), 2.28 (s, 3H), 1.28 (s, 9H) ppm.

Example 19

Preparation of 2-(5-{2-[3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-ureidomethyl]-4-fluorophenoxy}-indazol-1-yl)-N,N-dimethylacetamide (47d)

[0216] The reaction scheme for the synthesis of compound 47d according to this invention is shown in Figure 11.

[0217] Step A: 2-[5-(2-Cyano-4-fluorophenoxy)-indazol-1-yl]-N,N-dimethylacetamide (45d): To a solution of 5-fluoro-2-(1H-indazol-5-yloxy)-benzonitrile (44d) (0.200 g, 0.790 mmol) in DMF (6 mL) was added 2-chloro-N,N-dimethylacetamide (0.115 g, 0.948 mmol) and tetrabutyl ammonium iodide (0.088 g, 0.237 mmol), followed by K_2CO_3 (0.164 g, 1.19 mmol). The mixture was heated to 110°C for 48 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and dissolved in dichloromethane. The solution was washed with 1N HCl, filtered, and chromatographed on Biotage eluting with 5% MeOH in dichloromethane to afford 0.032 g of the product (12% yield).

[0218] Step B: 2-[5-(2-Aminomethyl-4-fluorophenoxy)-indazol-1-yl]-N,N-dimethylacetamide (46d): To a solution of 2-[5-(2-cyano-4-fluorophenoxy)-indazol-1-yl]-N,N-dimethylacetamide (0.090 g, 0.266 mmol) in EtOH (0.5 mL) was added $CoBr_2$ (27 µL, 0.005 mmol) followed by [2,2']bipyridinyl (81µL, 0.015 mmol). $NaBH_4$ (0.030 g, 0.798 mmol) was added to the mixture and it was stirred at room temperature for 18 hours. The mixture was treated with another portion each of $CoBr_2$, [2,2']bipyridinyl, and $NaBH_4$ and stirred for another 18 hours. The mixture was quenched with MeOH, followed by acetic acid and then concentrated under reduced pressure. The white residue was partitioned between saturated $NaHCO_3$ and ethyl acetate. The organic layer was filtered and concentrated under reduced pressure to afford 10 mg of white solid (11% yield).

[0219] Step C: 5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-ylamine: A solution of p-tolyl-hydrazine hydrochloride (15.86 g, 100 mmol) and pivaloylacetonitrile (17.9 g, 143 mmol) dissolved in MeOH (65 mL) was heated to reflux for 18 hours under N_2 atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was triturated with ether and collected by filtration. The solid was dried under high vacuum to provide 26.6 g of white solid (99% yield).

[0220] Step D: (5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trichloroethyl ester: A cooled (0°C) biphasic solution of 5-tert-butyl-2-p-tolyl-2H-pyrazol-3-ylamine (26.6 g, 100 mmol) in water (80 mL) and ethyl acetate (180 mL) was treated with NaOH (10 g, 250 mmol) followed by trichloroethylchloroformate (29.7 g, 140 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. The layers were separated and the organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to provide 40.3 g of pale yellow solid (99% yield).

[0221] Step E: 2-(5-{2-[3-(5-tert-Butyl-2-p-tolyl-2H-pyrazol-3-yl)-ureidomethyl]-4-fluorophenoxy}-indazol-1-yl)-N,N-dimethylacetamide (47d): To a solution of 2-[5-(2-aminomethyl-4-fluoro-phenoxy)-indazol-1-yl]-N,N-dimethylacetamide (46d) (0.010 g, 0.029 mmol) and (5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trichloroethyl ester (0.013 g, 0.032 mmol) in DMF (1 mL) was added DIEA (0.01 mL, 0.058 mmol). The mixture was heated to 80°C for 18 hours under N_2 atmosphere. The mixture was concentrated under reduced pressure and dissolved in dichloromethane. The solution was washed with 1 N HCl, filtered, and concentrated under reduced pressure. The oil was chromatographed eluting with dichloromethane/ether (10:1) and then 5% MeOH in dichloromethane to afford 6.3 mg of pale yellow oil (36% yield). MS (APCI +) *m/z* 598 (M+1) detected; ^1H NMR (400 mHz, DMSO-D_6) δ 8.29 (s, 1 H), 7.97 (s, 1 H), 7.58 (d, 1 H), 7.36 (d, 2H), 7.28 (d, 2H), 7.19 (d, 1H), 7.12 (d, 1H), 7.07 (m, 2H), 6.99 (m, 1 H), 6.84 (m, 1H), 6.24 (s, 1H), 5.40 (s, 2H), 4.28 (d, 2H), 3.10 (s, 3H), 2.84 (s, 3H), 2.35 (s, 3H), 1.25 (s, 9H).

Example 20

Preparation of 1-(5-tert-butyl-isoxazol-3-yl)-3-[5-fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzyl]-urea (48d)

[0222] Step A: 1-Isobutyl-5-methoxy-1H-indazole: A solution of 5-methoxy-1H-indazole (5.00 g, 33.7 mmol) in DMF (100 mL) was treated with K_2CO_3 (5.83 g, 42.2 mmol) and stirred at room temperature for 15 minutes. To this solution was added 1-bromo-2-methylpropane (5.09 g, 37.1 mmol) and the .resulting mixture was heated to 110°C for 18 hours. Another equivalent of 1-bromo-2-methyl-propane was added and the mixture continued to heat for 48 hours more. The mixture was concentrated under reduced pressure and dissolved in dichloromethane. The solution was washed with 1 N HCl, filtered, and concentrated under reduced pressure. The residue was chromatographed on Biotage eluting with hexanes/ether (5:1) to afford 2.51 g of orange oil (36% yield).

[0223] Step B: 1-Isobutyl-1H-indazol-5-ol: To a cooled (-78°C) solution of 1-isobutyl-5-methoxy-1 H-indazole (2.57 g, 12.6 mmol) in dichloromethane (100 mL) was added BBr_3 (25 mL of 1 M solution in dichloromethane). The mixture was stirred at -78°C for 2 hours and then warmed to room temperature and stirred for 18 hours. The reaction mixture was poured into ice water and extracted with dichloromethane. The organic extract was filtered and concentrated under reduced pressure to afford 2.3 g of solid (96% yield).

[0224] Step C: 5-Fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzonitrile: To a solution of 1-isobutyl-1H-indazol-5-ol (2.33 g, 12.2 mmol) and K_2CO_3 (2.03 g, 14.7 mmol) in DMF (75 mL) was added 2,5-difluorobenzonitrile (1.87 g. 13.5 mmol). The mixture was heated to 110°C for 18 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in dichloromethane. The solution was washed with 1 N HCl, filtered, and concentrated under reduced pressure. The residue was chromatographed on Biotage eluting with hexanes/ether (5:2) to afford 3.05 g of pale yellow oil (81 % yield).

[0225] Step D: 5-Fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzylamine: To a solution of 5-fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzonitrile (3.05 g, 9.86 mmol) purged with N_2 in MeOH (50 mL) was added concentrated HCl (1.6 mL) and $Pd(OH)_2/C$ (15% wt, 0.457 g). The mixture was stirred at room temperature for 18 hours under H_2 atmosphere. The catalyst was removed by filtration and the solution was concentrated under reduced pressure to afford 3.32 g of pale yellow foam (96% yield).

[0226] Step E: 1-(5-tert-Butyl-isoxazol-3-yl)-3-[5-fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzyl]-urea: To a cooled (0°C) solution of 5-fluoro-2-(1-isobutyl-1H-indazol-5-yloxy)-benzylamine (0.364 g, 1.04 mmol) and DIEA (0.5 mL, 2.08 mmol) in dichloromethane (10 mL) was added triphosgene (0.131 g, 0.374 mmol). The mixture was stirred at 0°C for 1 hour and then stirred at room temperature for 18 hours under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure and suspended in dichloromethane (10 mL) making a 0.123 M solution. 0.4 mL of this solution (0.015 g, 0.048 mmol) was treated with 5-tert-butyl-isoxazol-3-ylamine (0.008 g, 0.053 mmol). The product was obtained in 44% yield. MS (APCI +) *m/z* 480 (M+1)

detected.

Example 21

Preparation of 1-(3-tert-butyl-isoxazol-5-yl)-3-{5-fluoro-2-[1-(2-piperazin-1-yl-ethyl)-1H-indazol-5-yloxy]-benzyl}-urea (49d)

[0227] Step A: 2-[1-(2,2-Dimethoxyethyl)-1H-indazol-5-yloxy]-5-fluorobenzonitrile: To a cooled (0°C) solution of 5-fluoro-2-(1H-indazol-5-yloxy)-benzonitrile (0.100 g, 0.395 mmol) and 2-bromo-1,1-dimethoxyethane (0.114 g, 0.671 mmol) in DMF (4 mL) was added NaH (0.024 g of 60%, 0.59 mmol). The reaction mixture was warmed to room temperature and stirred for 1 hour. Tetrabutyl ammonium iodide (0.029 g, 0.079 mmol) was added to the mixture and it was heated to 60°C for 3 hours. The mixture was cooled to room temperature, diluted with water (4 mL), and extracted with ether (3 X 30 mL). The combined extracts were washed with water (2 X 5 mL) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with ethyl acetate/hexanes (1:2) to afford 0.066 g of product (49% yield).

[0228] Step B: 5-Fluoro-2-[1-(2-oxoethyl)-1H-indazol-5-yloxy]-benzonitrile: To a solution of 2-[1-(2,2-dimethoxyethyl)-1H-indazol-5-yloxy]-5-fluorobenzonitrile (1.42 g, 4.16 mmol) in dichloromethane (62 mL) was added iodotrimethylsilane (3.33 g, 16.64 mmol) portion-wise over 3 hours. The mixture was stirred at room temperature for 2 hours. Aqueous $NaHCO_3$ (60 mL) was added to the mixture and it was extracted with ethyl acetate (2 X 50 mL). The combined extracts were washed with $Na_2S_2O_4$, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used in the next reaction without further purification.

[0229] Step C: 4-{2-[5-(2-Cyano-4-fluorophenoxy)-indazol-1-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester: To a solution of 5-fluoro-2-[1-(2-oxo-ethyl)-1H-indazol-5-yloxy]-benzonitrile (0.307 g, 1.04 mmol) and triacetoxyborohydride (0.66 g, 3.1 mmol) in dichloroethane (10 mL) was added piperazine-1-carboxylic acid tert-butyl ester (0.65 g, 3.49 mmol). The mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with MeOH (2 mL) and diluted with ethyl acetate (100 mL). The solution was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with ethyl acetate/hexanes (2:3, with 1% triethylamine) to afford 0.29 g of product (60% yield).

[0230] Step D: 4-{2-[5-(2-Aminomethyl-4-fluorophenoxy)-indazol-1-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester: To a solution of 4-{2-[5-(2-cyano-4-fluorophenoxy)-indazol-1-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (0.160 g, 0.344 mmol), $CoBr_2$ (0.008 g, 0.034 mmol), [2,2']bipyridinyl (0.016 g, 0.010 mmol) in EtOH (6 mL) was added $NaBH_4$ (0.039 g, 1.0 mmol). The mixture was stirred for 3 hours at room temperature. The reaction was quenched with MeOH (3 mL) and acetic acid (10 drops). The solution was concentrated under reduced pressure and diluted with ethyl acetate. The mixture was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was chromatographed eluting with 1% triethylamine in ethyl acetate, MeOH/ CH_2Cl_2/hexanes (1:15:15, 1 % triethylamine), then MeOH/CH_2Cl_2/hexanes (1:10:10, 1 % triethylamine). The pure product was obtained in 86% yield.

[0231] Step E: (3-tert-Butyl-isoxazol-5-yl)-carbamic acid 4-nitrophenyl ester: A solution of 3-tert-butyl-isoxazol-5-ylamine (2.50 g, 17.83 mmol) in dichloromethane was treated with pyridine (2 mL, 26.7 mmol) followed by p-nitrophenyl chloroformate (3.77 g, 18.73 mmol). The mixture was stirred at room temperature for 2 hours. The reaction mixture was washed with 1 N HCl, filtered, and concentrated under reduced pressure. The residue was triturated with ether and collected by filtration to afford 2.2 g of product (41 % yield).

[0232] Step F: 4-[2-(5-{2-[3-(3-tert-Butyl-isoxazol-5-yl)-ureidomethyl]-4-fluorophenoxy}-indazol-1-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester: A solution of 4-{2-[5-(2-aminomethyl-4-fluorophenoxy)-indazol-1-yl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (0.050 g, 0.107 mmol) dissolved in dichloromethane (2 mL) was treated with (3-tert-butyl-isoxazol-5-yl)-carbamic acid 4-nitrophenyl ester (0.081 g, 0.266 mmol) and stirred at room temperature for 24 hours. The mixture was diluted with ethyl acetate (60 mL), washed with 1 N NaOH (5 mL), water (2 X 10 mL), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with acetone/hexanes (2:3, then 1:1) to afford 0.056 g of product (83% yield).

[0233] Step G: 1-(3-tert-Butyl-isoxazol-5-yl)-3-{5-fluoro-2-[1-(2-piperazin-1-yl-ethyl)-1H-indazol-5-yloxy]-benzyl}-urea: 4-

[2-(5-{2-[3-(3-tert-Butyl-isoxazol-5-yl)-ureidomethyl]-4-fluorophenoxy}-indazol-1-yl)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester (0.056 g, 0.088 mmol) was treated with TFA/ CH_2Cl_2 (1:1, 2 mL) and stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure and azeotroped with toluene. The residue was diluted with ethyl acetate (40 mL) and washed with 1 N NaOH and brine. The solution was concentrated under reduced pressure to afford 0.038 g of the product (80% yield). MS (ESI +) *m/z* 536 (M+1) detected; ^{1}H NMR (400 mHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.35 (d, 1 H), 7.15 (dd, 1 H), 7.08 (s, 1 H), 7.05 (d, 1H), 6.88 (m, 1 H), 6.76 (m, 1H), 6.28 (m, 1H), 5.99 (s, 1H), 4.46 (m, 4H), 2.86 (m, 2H), 2.79 (m, 4H), 2.43 (m, 4H), 1.26 (s, 9H).

Example 22

Preparation of 1-3-tert-butyl-isoxazol-5-yl)-3-{2-1-(2-dimethylaminoethyl)-1H-indazol-5-yloxy]-5-fluoro-benzyl}-urea (50d)

[0234] Step A: 2-[1-(2-Dimethylaminoethyl)-1H-indazol-5-yloxy]-5-fluorobenzonitrile: A solution of 5-fluoro-2-[1-(2-oxoethyl)-1H-indazol-5-yloxy]-benzonitrile (0.110 g, 0.372 mmol) (prepared according to the procedure in Example 21, Steps A-B) and sodium triacetoxyborohydride (0.39 g, 1.9 mmol) in dichloroethane (3 mL) was treated with dimethylamine (0.17 g, 3.7 mmol) and stirred at room temperature for 3 hours. The reaction was quenched with MeOH (1 mL) and diluted with ethyl acetate (30 mL). The solution was washed with aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with ethyl acetate and then acetone/ hexanes (2:3 with 1% triethylamine) to afford 0.115 g of product (95% yield).

[0235] Step B: {2-[5-(2-Aminomethyl-4-fluorophenoxy)-indazol-1-yl]-ethyl}-dimethylamine: To a cooled (0ºC) solution of 2-[1-(2-dimethylaminoethyl)-1H-indazol-5-yloxy]-5-fluorobenzonitrile (0.115 g, 0.303 mmol) in THF (3 mL) was added LAH (0.61 mL of 1 M in THF). The mixture was warmed to room temperature and stirred for 1.5 hours. The mixture was quenched with water (23 µL), 3N NaOH (23 µL) and water (69 µL). The salts were removed by filtration and the filtrate was concentrated under reduced pressure to afford 0.113 g of product (97% yield).

[0236] Step C: 1-(3-tert-Butyl-isoxazol-5-yi)-3-{2-[1-(2-dimethylamino-ethyl)-1H-indazol-5-yloxy]-5-fluoro-benzyl}-urea: A solution of {2-[5-(2-Aminomethyl-4-fluorophenoxy)-indazol-1-yl]-ethyl}-dimethylamine (0.020 g, 0.061 mmol) in DMF (1 mL) was treated with (3-tert-buylisoxazol-5-yl)-carbamic acid 4-nitrophenyl ester (0.020 g, 0.067 mmol) (prepared according to Example 21, Step E). The mixture stirred at room temperature for 18 hours under a N_2 atmosphere. The reaction mixture was chromatographed eluting with dichloromethane/ether (10:1) and then 5% MeOH in dichloromethane to afford 5.3 mg of pale yellow oil (18% yield). MS (APCI +) *m/z* 495 (M+1) detected; ^{1}H NMR (400 mHz, DMSO - D_6) δ 10.14 (s, 1 H), 7.98 (s, 1 H), 7.74 (d, 1H), 7.22 (d, 1H), 7.16 (m, 2H), 7.08 (m, 1 H), 6.88 (m, 2H), 5.93 (s, 1H), 4.48 (t, 2H), 4.35 (d, 2H), 2.70 (t, 2H), 2.17 (s, 6H), 1.23 (s, 9H).

Example 23

Preparation of 1-(5-tert-butyl-2-methyl-2H-pyrrazol-3-yl)-3-{5-fluoro-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzyl}-urea (51d)

[0237] Step A: 5-Fluoro-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzonitrile: A solution of 5-fluoro-2-(1H-indazol-5-yloxy)-benzonitrile (0.100 g, 0.395 mmol) in DMF (4 mL) was treated with NaH (0.022 g, 60%, 056 mmol) and stirred for 5 minutes. 2,2-Dimethyloxirane (0.035 g, 0.48 mmol) was added and the solution was stirred at room temperature for 1 hour. The reaction mixture was then heated to 80ºC. for 1.5 hours. The solution was cooled to room temperature, diluted with ether (50 mL), washed with water (3 X 5 mL), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with ethyl acetate/ hexanes (1:1) to afford 0.070 g of product (47% yield).

[0238] Step B: 2-{1-[2-(tert-Butyl-dimethylsilanyloxy)-2-methyl-propyl]-1H-indazol-5-yloxy}-5-fluorobenzonitrile: To a cooled (0ºC) solution of 5-Fluoro-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzonitrile (0.070 g, 0.215 mmol) and 2,6-lutidine (0.030 g, 0.284 mmol) in dichloromethane (2 mL) was added TBSOTf (0.063 g, 0.240 mmol). The reaction mixture was

warmed to room temperature and stirred for 1 hour. The mixture was diluted with ether (50 mL) and washed with 0.2N HCl, $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed eluting with ether/hexanes (1:3) to afford 0.071 g of pale yellow oil (94% yield).

[0239] Step C: 2-{1-[2-(tert-Butyldimethylsilanyloxy)-2-methylpropyl]-1H-indazol-5-yloxy}-5-fluorobenzylamine: To a cooled (0°C) solution of 2-{1-[2-(tert-butyldimethylsilanyloxy)-2-methyl-propyl]-1H-indazol-5-yloxy}-5-fluorobenzonitrile (0.071 g, 0.162 mmol) in THF (2 mL) was added LAH (0.32 mL of 1M in THF). The solution was warmed to room temperature and stirred for 1 hour. The reaction mixture was cooled to 0°C and quenched with water (12 µL), 3N NaOH (12 µL) and water (36 µL). The salts were removed by filtration and the filtrate was concentrated under reduced pressure and used in the next reaction without further purification.

[0240] Step D: (5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trichloroethyl ester: To a cooled (10°C) solution of 5-tert-butyl-2-methyl-2H-pyrazol-3-ylamine (3.75 g, 24.5 mmol) and NaOH (1.5 g in 20 mL water) in ethyl acetate (45 mL) was added 2,2,2-trichloroethyl chloroformate (7.52 g, 35.5 mmol) over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 2 hours. The mixture was diluted with ethyl acetate and the layers separated. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was diluted with ethyl acetate/dichloromethane and treated with aminomethyl silica (10 g) for 1 hour. The mixture was filtered and the filtrated concentrated under reduced pressure to provide the product.

[0241] Step E: 1-(2-{1-[2-(tert-Butyldimethylsilanyloxy)-2-methyl-propyl]-1H-indazol-5-yloxy}-5-fluorobenzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea: A mixture of 2-{1-[2-(tert-butyldimethylsilanyloxy)-2-methyl-propyl]-1H-indazol-5-yloxy}-5-fluorobenzylamine (0.072 g, 0.162 mmol), (5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid 2,2,2-trichloroethyl ester (0.080 g, 0.24 mmol) and DIEA (0.06 mL, 0.324 mmol) in DMA (3 mL) was heated to 80°C for 16 hours. The mixture was diluted with ether (60 mL) and washed with water (3 X 5 mL), brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica eluting with ethyl acetate/ hexanes (3:1) to afford 0.084 g of product (83% yield).

[0242] Step F: 1-(5-tert-Butyl-2-methyl-2H-pyrazol-3-yl)-3-{5-fluoro-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzyl}-urea: To a solution of -(2-{1-[2-(tert-butyldimethylsilanyloxy)-2-methyl-propyl]-1H-indazol-5-yloxy}-5-fluorobenzyl)-3-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-urea (0.084 g, 0.135 mmol) in dichloromethane (3 mL) was added TBAF (0.70 mL of 1 M in THF). The mixture was stirred at room temperature for 5 days. The reaction mixture was poured into NH_4Cl and extracted with ethyl acetate (3 X 30 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica eluting with acetone/ hexanes (2:1) to afford 0.060 g of product (87% yield). MS (ESI +) *m/z* 509 (M+1) detected; ^1H NMR (400 mHz, DMSO- D_6) δ 8.45 (s, 1 H), 7.98 (s, 1 H), 7.74 (d, 1 H), 7.17 (m, 3H), 7.08 (m, 1 H), 6.85 (m, 2H), 5.95 (s, 1H), 4.66 (s, 1H), 4.33 (d, 2H), 4.30 (s, 2H), 2.50 (s, 3H), 1.18 (s, 9H), 1.12 (s, 6H).

[0243] The words "comprise," "comprising," "include," "including," and "includes" when used in this specification and in the following claims are intended to specify the presence of stated features, integers, components, or steps, but they do not preclude the presence or addition of one or more other features, integers, components, steps, or groups thereof.

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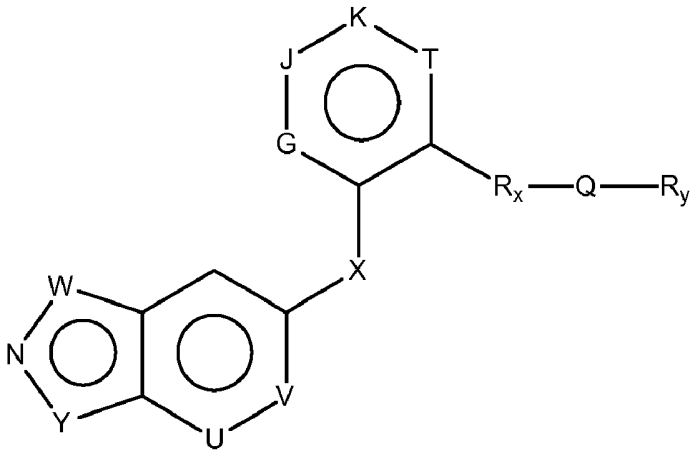
Patentkrav

1. Forbindelse, der indbefatter opløste enantiomerer, diastereomerer, solvater og farmaceutisk acceptable salte deraf, hvilken forbindelse har formlen XVII:



XVII

hvor

Y er O, NR^2;

W er CR^3;

R^3 er H, NH_2, F, Cl, methyl eller substitueret methyl;

R^2 er H, OH, en aminbeskyttelsesgruppe, Z_n-NR^aR^b, Z_n-$NR^a(C=O)R^b$, z_n-SO_2R^a, Z_n-SOR^a, Z_n-SR^a, Z_n-OR^a, Z_n-$(C=O)R^a$, Z_n-$(C=O)OR^a$, Z_n-O-$(C=O)R^a$, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret;

Ar^1 er aryl eller heteroaryl, der begge kan være substitueret eller ikke-substitueret;

R^a og R^b uafhængigt er H, OH, en aminbeskyttelsesgruppe, en alkoholbeskyttelsesgruppe, en syrebeskyttelsesgruppe, en svovlbeskyttelsesgruppe, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller

Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret,

eller R^a og R^b sammen med de atomer, hvortil de begge er bundet, danner en mættet eller delvist umættet heterocyklusring med 1 eller flere heteroatomer i ringen, hvor heterocyklussen kan være substitueret eller ikke-substitueret, og hvor heterocyklussen kan være kondenseret til en aromatisk ring;

Z er alkylen, der har fra 1 til 4 carboner, eller alkenylen eller alkynylen, der hver har fra 2 til 4 carboner, hvor alkylen, alkenylen eller alkynylen kan være substitueret eller ikke-substitueret;

n er 0 eller 1;

U er CR^c eller N;

V er CR^c eller N;

R^c er H, F, Cl, methyl eller substitueret methyl;

X er O, S, SO, SO_2, NR^5, C=O, CH_2, CH_2Z_n-OH eller C=NOR^d;

R^5 er H, methyl eller substitueret methyl;

R^d er H, PO_3H_2, SO_3H_2, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Zn-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Zn-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret;

G, K, J, og T uafhængigt er N eller CR^Z, forudsat, når en hvilken som helst af G, K, J og T er N, at det totale antal af G, K, J, eller T, der er N, ikke overstiger 2;

R^z er H, F, Cl, Br, CF_3, OR^6, SR^6, lavere alkyl (C_1-C_4), CN, eller NR^6R^7;

R^6 og R^7 uafhængigt er H, CF_3, lavere alkyl (C_1-C_4) eller lavere heteroalkyl (C_1-C_4);

Q er -NR^8CONH-, -NHCO-, -NR^8SO_2NH-, -$NHSO_2$-, -$CONR^{11}$-;

R^8 er H eller (C_1-C_4) alkyl;

R^{11} er H eller (C_1-C_4) alkyl;

R_x er -$(CR^9R^{10})_m$-, -O$(CR^9R^{10})_m$-, NH$(CR^9R^{10})_m$- eller -S$(CR^9R^{10})_m$- forudsat at Q er -$CONR^{11}$-, når R^x er -O$(CR^9R^{10})_{m-}$, -NH$(CR^9R^{10})_m$ eller -S$(CR^9R^{10})_m$-;

R^9 og R^{10} uafhængigt er H eller lavere alkyl, eller R^9 og R^{10} sammen med de atomer, hvortil de begge er bundet, danner en cycloalkylring, der kan være mættet eller delvist umættet;

m er 1-3;

R_y er H, PO_3H, en aminbeskyttelsesgruppe, en oxygenbeskyttelsesgruppe, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^2, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-Ar^2 og Z_n-heterocycloalkyl kan være substitueret eller ikke-substitueret;

Ar^2 er aryl eller heteroaryl, der begge kan være substitueret eller ikke-substitueret, hvor substitutionen kan være 1-3 substituenter uafhængigt udvalgt fra F, Cl, Br, CF^3, CN, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, $-OR^{12}$, $-SR^{12}$, $-SO_2R^{12}$, $-SO_2NR^{13}R^{12}$, $NR^{13}SO_2R^{12}$, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret;

R^{12} og R^{13} uafhængigt er H, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret;

Hvor, når Ar^2 er substitueret med $-SO_2NR^{13}R^{12}$, R^{12} og R^{13} kan danne en cycloalkylring eller heterocycloalkylring, der kan være substitueret eller ikke-substitueret, hvor substitutionen kan være substituenter udvalgt fra alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, $-COR^{12}$, $-SO_2R^{12}$, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl,

alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret;

hvor, når Q er -$CONR^{11}$, R_y i kombination med R^{11} endvidere er en cycloalkylring eller heterocycloalkylring, der kan være substitueret eller ikke-substitueret med grupper udvalgt fra alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, Z_n-Ar^1, -COR^{14}, eller -SO_2R^{14}, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-Ar^1, -COR^{14}, og -SO_2R^{14} kan være substitueret eller ikke-substitueret; og

R^{14} er alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, Z_n-cycloalkyl, hvor cycloalkyl er mættet eller delvist umættet, Z_n-heterocycloalkyl, hvor heterocycloalkyl er mættet eller delvist umættet, eller Z_n-Ar^1, hvor alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl og Z_n-Ar^1 kan være substitueret eller ikke-substitueret, og

hvor hver gruppes substituent(er) er udvalgt blandt: halo, alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl, Z_n-heterocycloalkyl, Z_n-OR, Z_n-NO_2, Z_n-CN, Z_n-CO_2R, Z_n-(C=O)R, Z_n-O(O=O)R, Z_n-O-alkyl, Z_n-OAr, Z_n-SH, Z_n-SR, Z_n-SOR, Z_n-SO_2R, Z_n-S-Ar, Z_n-SOAr, Z_n-SO_2Ar, aryl, heteroaryl, Z_n-Ar, Z_n-(C=O)NR'R'', Z_n-NR'R'', Z_n-NR(C=O)R, Z_n-$SO_2NR'R''$, PO_3H_2, SO_3H_2, aminbeskyttelsesgrupper, alkoholbeskyttelsesgrupper, svovlbeskyttelsesgrupper eller syrebeskyttelsesgrupper, hvor:

Z er alkylen der har fra 1 til 4 carboner, eller alkenylen eller alkynylen, der hver har fra 2 til 4 carboner,

n er nul eller 1,

R, R' og R'' er alkyl, allyl, alkenyl, alkynyl, heteroalkyl, heteroallyl, heteroalkenyl, heteroalkynyl, alkoxy, heteroalkoxy, Z_n-cycloalkyl eller Z_n-heterocycloalkyl, og

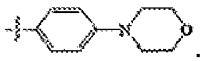
Ar er aryl eller heteroaryl.

2. Forbindelse ifølge krav 1, hvor W er CH og Y er NR^2.

3. Forbindelse ifølge krav 1, hvor G, J, K og T er CR^z.

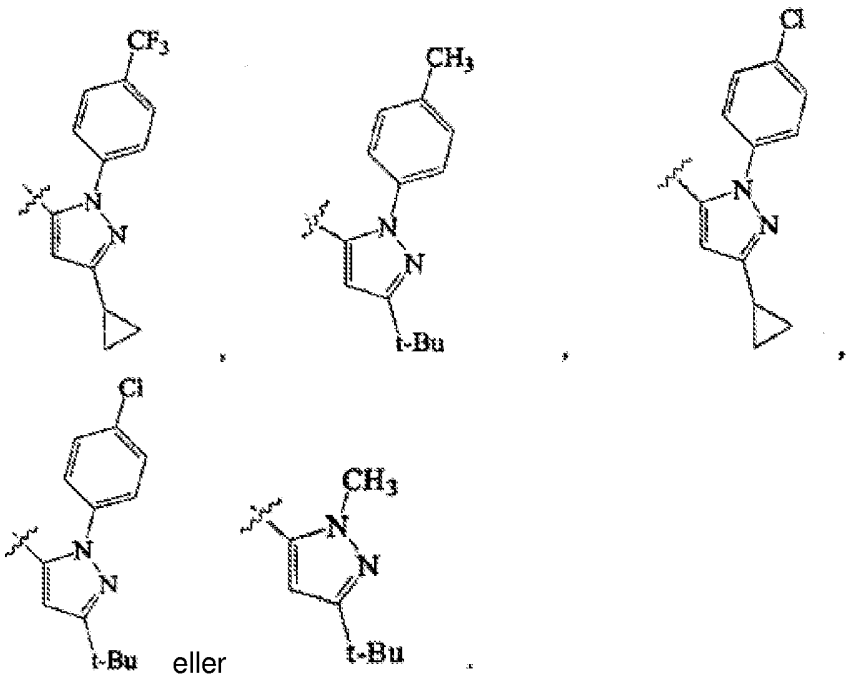
4. Forbindelse ifølge krav 1, hvor X er NH, S eller O.

5. Forbindelse ifølge krav 1, hvor R_x er CH_2 og Q er -NHCO-.

6. Forbindelse ifølge krav 5, hvor R_y er isopropyl eller  .

7. Forbindelse ifølge krav 1, hvor R_x er CH_2 og Q er $-NR^8CONH-$.

8. Forbindelse ifølge krav 7, hvor R_y er



eller .

9. Forbindelse ifølge et hvilket som helst af kravene 1 til 8, hvilken forbindelse er udvalgt fra gruppen bestående af:

- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3[2-(1-methyl-1H-indazol-5-yloxy)-pyridin-3-ylmethyl]-urea,
- 1-[5-cyclopropyl-2-(4-trifluormethylphenyl)-2H-pyrazol-3yl]-3-(5-fluor-2-(1-methyl-1H-indazol-5-ylamino)-benzyl]-urea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[2-(1-cyclobutylmethyl-1H-indazol-5-ylamino)-5-fluorbenzyl]-urea,
- 1-(5-tert-butyl-2-p-chlorphenyl-2H-pyrazol-3-yl)-3[2-(1-methyl-1H-indazo-5-ylsulfanyl)-5-fluorbenzyl]-urea,

- 1-(5-tert-butyl-2-methy1-2H-pyrazol-3-yl)-3-{2-[1-(3-isopropylamino-propyl)-1H-indazol-5-ylamino]-benzyl}-urea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluor-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]urea,
- 1[5-tert-butyl-2-(4-chlorphenyl)-2H-pyrazol-3-yl]-3-[5-fluor-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]urea,
- 3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-1-[5-fluor-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluor-2-(1-methyl-1H-indazol-5-yloxy)-benzyl]-1-methylurea,
- 1-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl)-3-[5-fluor-2-(1-methyl-1H-pyrazol[3,4-c]pyridin-5-yloxy)-benzyl]-urea,
- 2-(5-{2-[3-(5-tert-butyl-2-p-tolyl-2H-pyrazol-3-yl}-ureidomethyl]-4-fluorphenoxy)-indazol-1-yl)-N,N-dimethylacetamid,
- 1-(5-tert-butyl-isoxazol-3-yl)-3[5-fluor-2-(1-isobutyl-1H-indazol-5-yloxy)-benzyl]-urea,
- 1-(3-tert-butyl-isoxazol-5-yl)-3-{5-fluor-2[1-(2-piperazin-1-yl-ethyl)-1H-indazol-5-yloxy]-benzyl}urea,
- 1-(3-tert-butyl-isoxazol-5-yl)-3-{2[1-(2-dimethylaminoethyl)-1H-indazol-5-yloxyl-5-fluor-benzyl)-urea,
- 1-(5-tert-butyl-2-methyl-2H-pyrazol-3-yl)-3-{5-fluor-2-[1-(2-hydroxy-2-methylpropyl)-1H-indazol-5-yloxy]-benzyl}-urea

og et farmaceutisk acceptabelt salt deraf.

10. Sammensætning omfattende en forbindelse ifølge krav 1 og et farmaceutisk acceptabelt bærestof.

11. Forbindelse ifølge et hvilket som helst af kravene 1 til 9 til anvendelse i terapi.

12. Forbindelse ifølge et hvilket som helst af kravene 1 til 9 til anvendelse ved behandling eller forebyggelse af en p-38-medieret tilstand.

13. Forbindelse ifølge krav 12, hvor den p-38-medierede tilstand er en inflammatorisk sygdom, autoimmun sygdom, destruktiv knogleforstyrrelse, proliferativ knogleforstyrrelse, infektionssygdom, virussygdom eller neurodegenerativ sygdom.

DRAWINGS

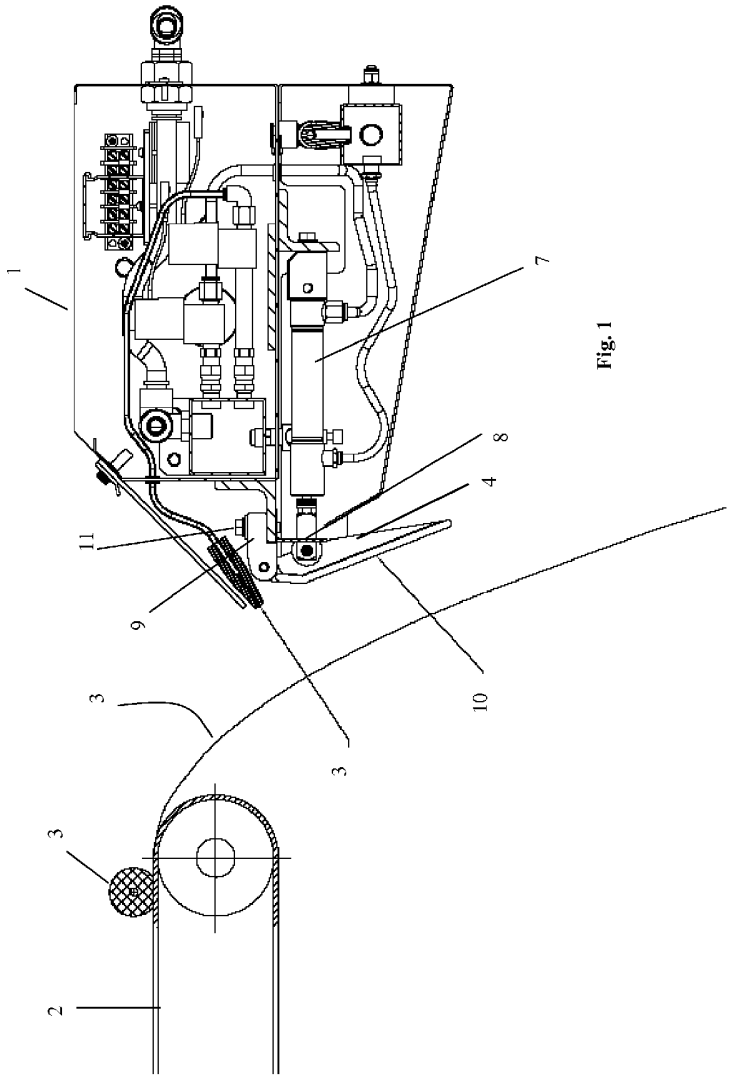


Fig. 1

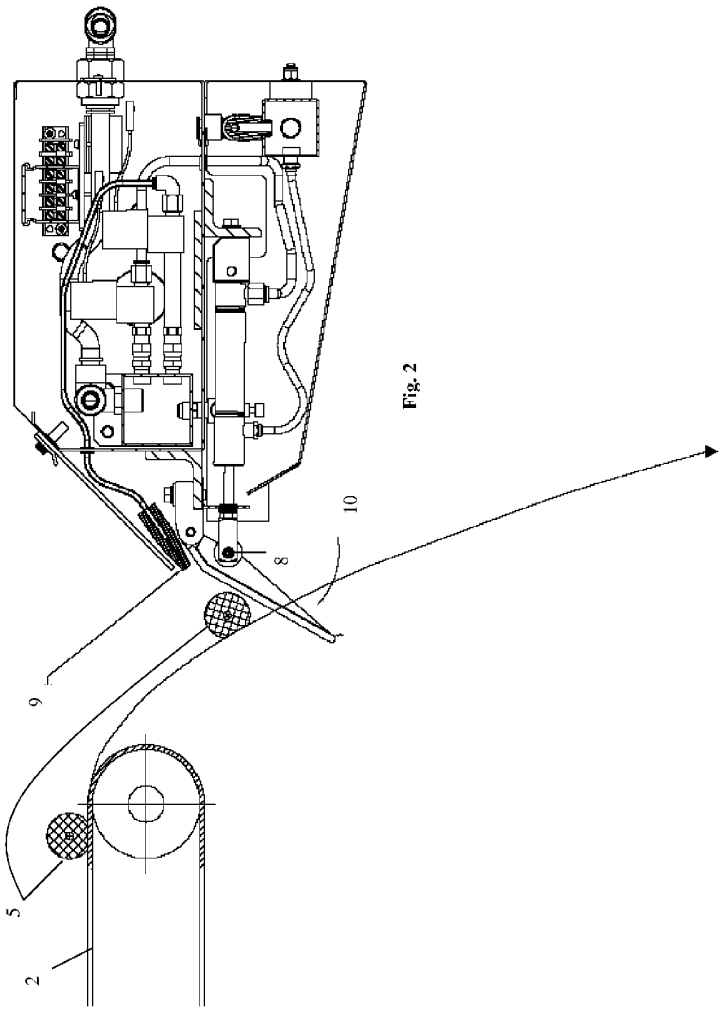


Fig. 2

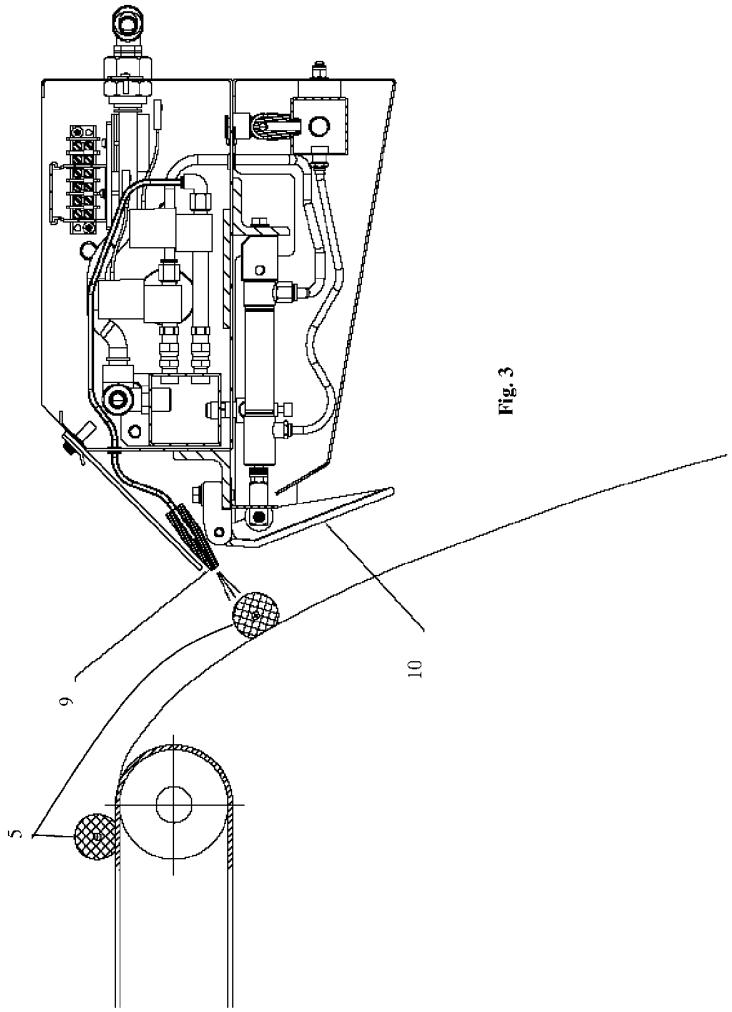


Fig. 3

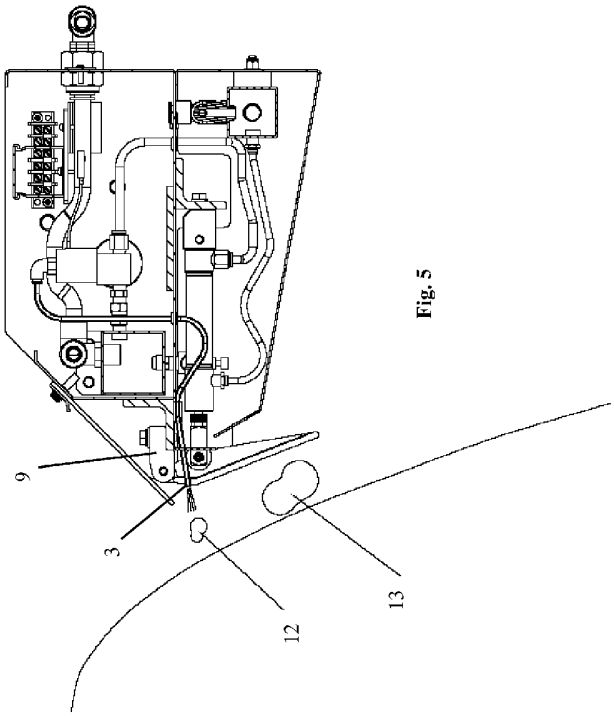


Fig. 5

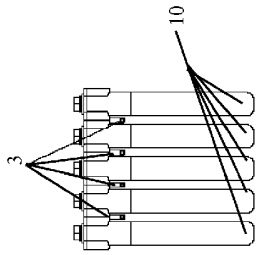
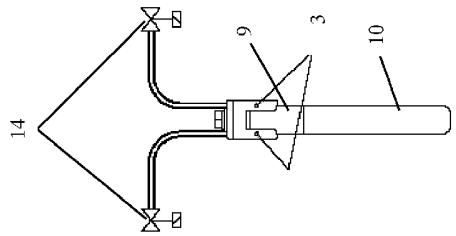


Fig. 4

Fig. 6



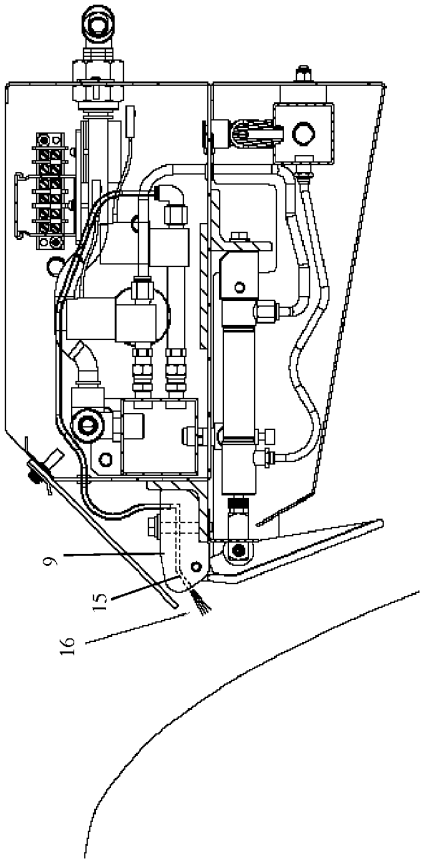


Fig. 7

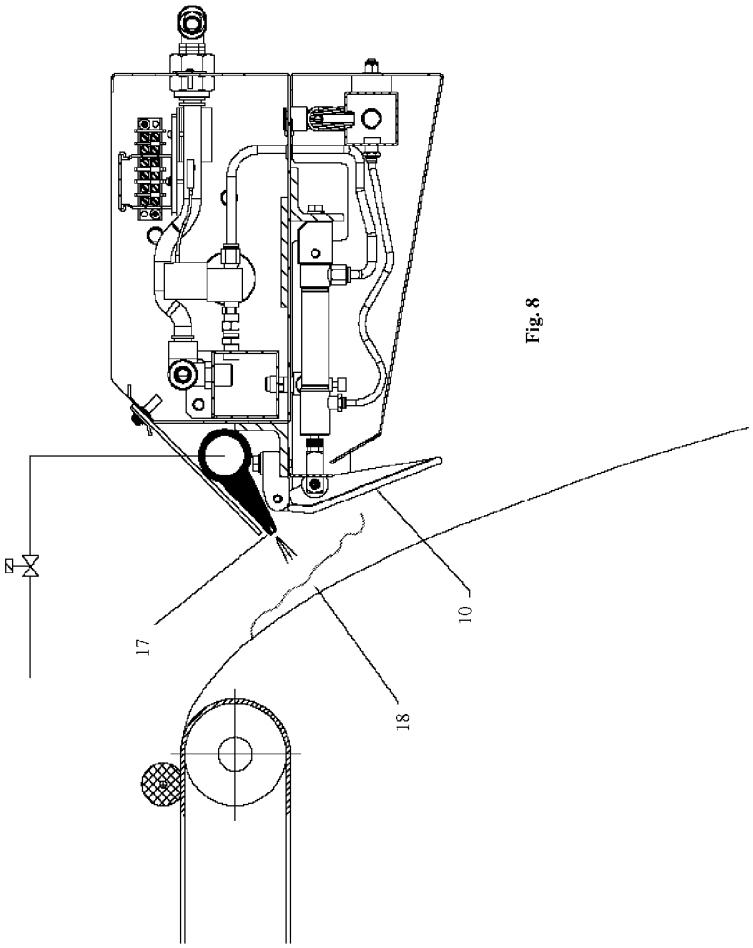


Fig. 8

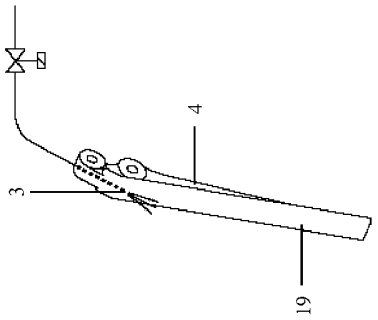


Fig. 10

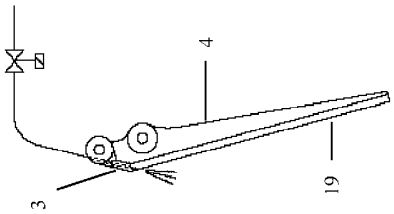


Fig. 9

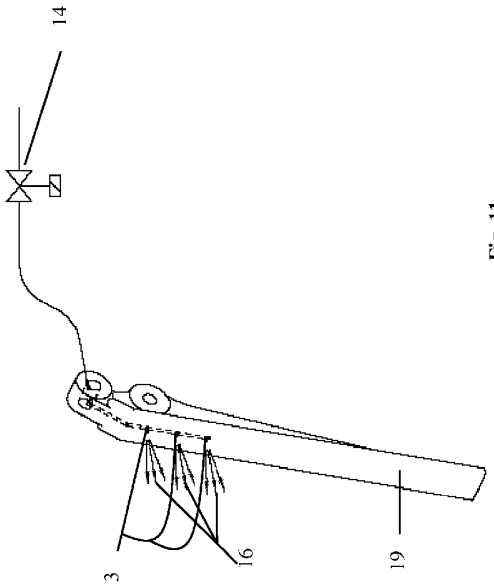


Fig. 11