C3A ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREOF

Abstract: Aryl substituted pyrazole compounds according to the formula (I) or pharmaceutically acceptable salts thereof, are provided. These compounds are useful in pharmaceutical compositions as C3a antagonists for treating a variety of medical conditions associated with the Complement cascade. Methods for treating such conditions are also provided.
C3A ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREOF

Field of the Invention

The present invention provides novel pharmaceutically active compounds that act as antagonists of the mammalian C3a receptor, and methods of using these compounds to treat chronic inflammatory diseases, including, but not limited to inflammations in the central nervous system, peripheral nervous system, lungs, and bone joints. Additionally, disease states not classically categorized as inflammatory diseases, but which in fact have inflammatory components, can also be effectively treated according to the practice of the invention. Alzheimer's disease represents a particularly important example of this latter type of disease state, and its discussion usefully demonstrates that disease states not classically categorized as inflammatory share mechanistic linkages with disease states classically characterized as inflammations. The present invention relates to treatment of both such types of disease states via inhibition of binding of the C3a protein to its cellular receptors.

Background of the Invention

The pathological hallmark of Alzheimer's disease (AD) is the senile amyloid plaque; a proteinaceous extracellular deposit composed primarily of an amyloidogenic peptide termed A-beta protein, and which is surrounded by dystrophic neurites. Senile plaques are the focus of a robust and chronic inflammatory response mounted by microglia, the brain's endogenous macrophage cells. Macrophage cells are phagocytic immune system cells of monocytic origin that circulate in the tissues and participate both in first-line initial immunosurveillance, and acquired immunity processes.

Although inflammatory responses are designed to protect the body at sites of infection or tissue damage, chronic inflammation itself often causes tissue damage. As a further complication in regard of treatment of Alzheimer's disease, since many of the biochemical products of microglial cell activation are known to be very toxic to nerve cells, blocking the inflammatory response is very significant in the treatment of AD. In this regard, see generally, J. Rogers et al., Inflammation and Alzheimer's disease pathogenesis, Neurobiol. Aging, v. 17, pp. 425-432, 1996.


One of the key host defense mechanisms provided by macrophages involves use of complement, a phylogenetically old system of enzymes and other proteins that most likely evolved to protect organisms against microbial assault. Complement activation is a
prominent feature of the inflammatory response in Alzheimer's disease, and is apparently triggered by the presence of senile plaques. The triggering of the Complement system involves the sequential activation of numerous proteins by a cascade effect. The Complement cascade is best defined as a series of binding and cleavage events wherein active forms of Complement proteins are produced, which in turn act upon each other, often by proteolysis, to produce further active proteins and protein fragments, and complexes thereof, which then interact with immune system components, or with cellular debris, endogenous or foreign macromolecules, or invading cells which are then targeted for destruction.

During Complement activation, Complement protein C3 is proteolytically cleaved, resulting in a large fragment (C3b) and the smaller 77 residue peptide, C3a. C3a is known to regulate vasodilation increasing the permeability of small blood vessels, induce contraction of smooth muscles, induce oxidative burst, regulate cytokine release, and stimulate chemotaxis, depending on the involved cells, all inflammation related events. Target cells include macrophages, neutrophils, eosinophils, basophils, T-lymphocytes and mast cells, all having important immune and inflammation related functions.

Receptors for C3a are expressed on a variety of macrophages and macrophage cell lines. Functionally, C3a binding to C3a receptors in macrophages causes a mobilization of intracellular calcium ions, and leads to both chemotaxis and respiratory burst, which are both host defense mechanisms that generate high levels of cytotoxic superoxide. Again, although such mechanisms are useful in protecting against invading bacterial cells, for example, the triggering of such defense mechanism against normal cells (such as brain neurons that happen to be proximal to the site of plaque formation) is devastating to normal brain function. Similar disadvantageous results operate in regard of other inflammatory conditions.

In summary, substantial evidence indicates that a chronic inflammatory response to senile plaques contributes significantly to the neurotoxicity of Alzheimer's disease. A key step in this inflammatory response is the formation of C3a, which upon binding to microglial C3a receptors, causes recruitment of microglia to the plaque followed by activation of neurotoxin release. Blocking of C3a receptors would thus be expected to inhibit these deleterious microglial responses and slow the progression of Alzheimer's disease.

The C3a receptor (C3aR) belongs to the rhodopsin family of G protein-coupled receptors (see Embler et al. in The Human Complement System in Health and Disease, Marcel Dekker, New York, pp. 241-284, 1998). Traditionally, C3aR was thought to be present only on myeloid cells, such as macrophages, eosinophils and mast cells. However, the demonstration that C3aR receptor messenger RNA is expressed throughout the body (and in particular in the adrenal gland, pituitary gland, and the central nervous system) is consistent with participation of C3a in a wide variety of cellular processes and mediate numerous
disease states. Recently, C3a receptor-immunoreactivity has been detected in areas of inflammation in multiple sclerosis and bacterial meningitis patients. In the latter disorder, abundant C3a receptor expression on activated microglia and reactive astrocytes was noted.


It is also recognized that Complement activation plays a significant role in allergic lung damage caused by repeated inhalation of antigen, which is consistent with the etiology of asthma. (See Abe et al., Immunopharmacology, Volume 49, Issues 1-2, page 26 (August 2000)). Importantly, it is also recognized that controlling the Complement system can impact the treatment or prevention of disease states such as sepsis, adult respiratory distress syndrome, nephrites, graft rejection, myocardial ischemia/reperfusion injury, and intestinal ischemia/reperfusion injury. (See Kirshfink, M., (1997), Immunopharmacology, 38, 51-62; see also Lucchesi et al., (1997), Immunopharmacology, 38, 27-42).

Taken together, these observations strongly support the use of pharmaceutically active compounds, effective as C3a receptor antagonists, in the prevention and treatment of a wide range of disease states, whether or not the disease state is classically recognized to include an inflammatory component., and whether or not the activation of the Complement system is involved, in whole or part, in the pathology of the disease state. Such disease states include, but are not limited to: neurological diseases such as Alzheimer's disease, multiple sclerosis, Huntington's chorea, Pick's disease, Guillain Barre syndrome, encephalitis, meningitis, stroke; and hemorrhagic stroke; cancer generally and leukemia particularly; allergic and respiratory diseases including allergic dermatitis, anaphylaxis, asthma, eczema, rhinitis, and respiratory distress; cardiovascular or metabolic disease states including shock and hypertension, hyperlipidemia, hypercholesterolemia, edema, and obesity; and inflammatory conditions generally including without limitation, osteoarthritis, ischemia, lung inflammation and rheumatoid arthritis.
Summary of the Invention

Accordingly, there are provided compounds according to the formula I or pharmaceutically acceptable salts thereof

wherein,

A represents an optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

W represents hydrogen, -C(Rₛ)₂⁻, -NRₛ⁻, -O-, or -S(O)ₙ⁻ (wherein n is 0, 1, or 2), or a sing Rₛ is optionally substituted (C₆-C₁₀)aryl or optionally substituted 5-10-membered heteroaryl;

R₂ and R₃ independently for each occurrence represent one or more substituents selected from the group consisting of hydrogen, hydroxy, halo, amino, C(=O)Rₛ, -OC(=O)-Rₛ, -C(=O)O-Rₛ, -N(Rₛ)₂, -NRₛC(=O)-Rₛ, -C(=O)N(Rₛ)₂, -OC(=O)-N(Rₛ)₂, -NRₛC(=O)-N(Rₛ)₂, -NRₛ-C(NRₛ)₂-N(Rₛ)₂, -S(O)ₙ⁻Rₛ (wherein n is 0, 1, or 2), -S(O)ₙN(Rₛ)₂, (wherein n is 0, 1, or 2), (C₁-C₆)alkoxy⁻, (C₁-C₆)acyloxy⁻, (C₁-C₆)alkylamino⁻, ((C₁-C₆)alkyl)₂amino⁻, (C₁-C₆)acylamino⁻, cyano, nitro, optionally substituted (C₆-C₁₀)alkyl⁻, optionally substituted (C₆-C₁₀)aryl⁻optionally substituted C₆-C₁₀ alkyl, optionally substituted (C₆-C₁₀)cycloalkyl⁻, and optionally substituted 3-10-membered heterocycloalkyl⁻, or

when W represents NRₛ, Rₛ and R₃ taken together may form an optionally substituted 4-7 membered ring containing 2-3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; with the proviso that the group

may not be the group
\[ R_4 \text{ may be absent or represents hydrogen, } C(=O)R_5, -OC(=O)R_5, -C(=O)O-R_5, -N(R_5)_2, -NR_4C(=O)R_5, -C(=O)N(R_5)_2, -OC(=O)-N(R_5)_2, -NR_7-C(=O)-N(R_5)_2, -S(O)n-R_5 \]  
(wherein \( n = 0, 1, \text{ or } 2 \)),  
-\( S(O)_nN(R_5)_2 \) (wherein \( n = 0, 1, \text{ or } 2 \)),  
\( C_1-C_6 \)alkoxy-,  
\( C_1-C_6 \)acyloxy-,  
\( C_1-C_6 \)alkylamino-,  
\( ((C_1-C_6)alkyl)_2 \)amino-,  
\( (C_1-C_6)acylamino-, \) cyano, nitro, 
optionally substituted \( (C_1-C_{10}) \)alkyl with up to two of the \( (C_1-C_{10}) \)alkyl carbons each optionally replaced by an oxygen, \( (C_1-C_{10}) \) alkyl substituted with one \( R_5 \), optionally substituted \( (C_6-C_{10}) \)aryl, 
optionally substituted 5-10-membered heteroaryl, optionally substituted \( (C_3-C_{10}) \)cycloalkyl-, or optionally substituted 3-10-membered heterocycloalkyl; 

or when \( R_4 \) is \( N(R_5)_2 \), the two \( R_5 \) groups taken with the \( N \) may form a 5-7-membered heterocycloalkyl ring fused to a \( C_6 \) aromatic ring or to a 5-6-membered heteroaromatic ring; and

\[ R_6, \text{ independently for each occurrence, represents a hydrogen, optionally substituted } \]
\( (C_1-C_{10}) \)alkyl, optionally substituted \( (C_6-C_{10}) \)aryl, wherein the \( (C_6-C_{10}) \)aryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted 5-10-membered heteroaryl, wherein the 5-10-membered heteroaryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted \( (C_3-C_{10}) \)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl; 

with the proviso that 

(i) when \( R_7 \) is \( (NR_5)_2 \), \( R_5 \) is not \( H \) for each occurrence;  
(ii) \(-W-R_4 \) is not \( OH, NH-SO_2-\)optionally substituted \( C_1-C_6 \) alkyl-, \( NH-SO_2-\)optionally substituted \( C_6-C_{10} \) aryl, \( C_1-C_6 \) alkyl or \( S-\)optionally substituted \( C_1-C_6 \) alkyl;  
(iii) \( R_7 \) is not \( CONH-\)optionally substituted \( C_2-C_{10} \) cycloalkyl or \( CONH-\)optionally substituted \( C_6-C_{10} \) aryl;  
(iv) when \( R_3 \) is a substituted \( C_1-C_{10} \) alkyl, \( R_3 \) is not substituted with \( CO_2H \), with optionally substituted 5-10-membered heteroaryl, with \( O-\)optionally substituted \( C_6-C_{10} \) aryl, or with two or more optionally substituted \( C_6-C_{10} \) aryl groups on the same \( C_1-C_{10} \) alkyl carbon;  
(v) the compound of formula I does not contain an aliphatic or aromatic or heteroaromatic ring fused to two rings wherein the two rings are aliphatic rings, aromatic rings, heteroaromatic rings or a combination thereof; and  

(vi) the compound of formula I is not a compound or pharmaceutically acceptable salt thereof selected from the group consisting of  
3-\([1,1'-biphenyl]-4-yl-1,5-dimethyl-1H-pyrazole \)
3-\([1,1'-biphenyl]-4-yl-1-methyl-1H-pyrazol-5-amine \)
1H-pyrazole-1-ethanol, 3-[1,1'-biphenyl]-yl-5-methyl and
3-[4'-(dimethylamino)-2,5-dimethyl[1,1'-'biphenyl]-4-yl]-yl-1-methyl-1H-pyrazol-5-amine.

As an example, the compound of the present invention is a compound represented by formula (II)

\[
\text{(II)}
\]

wherein,

A and B, independently represent an optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

W represents \(-\text{C}-(\text{R₅})₂-, \text{NR₅}, -\text{O}, \text{or} -\text{S}-(\text{O})ₙ^-(\text{wherein} \ n \ \text{is} \ 0, \ 1, \ \text{or} \ 2);\)

R₁ is optionally substituted (C₆-C₁₀)aryl or optionally substituted 5-10-membered heteroaryl;

R₂, R₃ and R₇, independently for each occurrence, represent one or more substituents selected from hydrogen, hydroxy, halo, amino, C(=O)R₆, -OC(=O)-R₆, -C(=O)O-R₆, -N(R₅)₂-, -NR₅C(=O)-R₆, -C(=O)N(R₅)₂-, -OC(=O)-N(R₅)₂-, -NR₅C(=O)-N(R₅)₂-, -NR₅C(NR₅)₂-N(R₅)₂, -S(O)ₙN(R₅)₂, (wherein n is 0, 1, or 2), (C₃-C₆)alkoxy-, (C₁-C₆)acyloxy-, (C₁-C₆)alkylamino-, ((C₁-C₆)alkyl)₂amino-, (C₁-C₆)acylamino-, cyano, nitro, optionally substituted (C₁-C₁₀)alkyl-, (optionally substituted (C₆-C₁₀)aryl)optionally substituted C₁-C₆ alkyl, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

Or two R₇ groups may form an optionally substituted 3-10-membered heterocyclic ring fused to B;

Or when W represents NRS₅, R₃ and R₆ taken together may form a 4-7 membered ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur;

R₅, independently for each occurrence, represents a hydrogen, optionally substituted (C₁-C₁₀)alkyl, optionally substituted (C₆-C₁₀)aryl, wherein the (C₆-C₁₀)aryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted 5-10-membered heteroaryl, wherein the 5-9-membered heteroaryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl; and
R₆ᵣ, independently for each occurrence, represents hydrogen, halogen, -OR₆ᵣ, N(R₆)₂, -SR₆ᵣ; or two R₆ᵣ form =O with a double bond to the carbon attached to R₆ᵣ.

As an example, the compound of the present invention is a compound represented by Formula III

![Chemical Structure](image)

wherein,

A represents an optionally substituted (C₆₋C₁₀)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₃₋C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

D represents a 3-7 membered heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, a 5-7 heteroaromatic ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, or a C₆ aromatic ring;

R₁ is optionally substituted (C₆₋C₁₀)aryl or optionally substituted 5-10-membered heteroaryl;

· R₂, R₃ and R₇, independently for each occurrence, represent one or more substituents selected from hydrogen, hydroxy, halo, amino, C(=O)R₆ᵣ, -OC(=O)-R₆ᵣ, -C(=O)O-R₆ᵣ, -NR₆ᵣC(=O)-R₆ᵣ, -C(=O)N(R₆)₂₋₃₋₄₋₅₋₆₋₇₋₈₋₉₋₁₀₋₁₁₋₁₂₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋setFlash this text is an answer to a question about the chemical structure of a compound.

The chemical structure includes a heterocyclic ring with multiple substituents, including alkyl, aryl, heteroaryl, and cycloalkyl groups. The substituents are defined by their chemical nature and are optionally substituted with various functional groups.

The compound is part of a larger class of heterocyclic compounds, and its structure is represented by Formula III. The substituents R₁, R₂, R₃, and R₇ are defined in terms of their chemical nature and are optionally substituted with specific functional groups.

The compound is a representative example of the present invention, demonstrating the versatility and complexity of heterocyclic compounds in chemical design.
membered heterocyclic ring containing up to two oxygens, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl.

The present invention also relates to the pharmaceutically acceptable acid addition salts of compounds of the formula (I). Exemplary acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluencesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The present invention also relates to the pharmaceutically acceptable base addition salts of compounds of the formula (I). The bases which are used to prepare the pharmaceutically acceptable base addition salts of the aforementioned base compounds of this invention are those which form non-toxic base addition salts, i.e., salts containing pharmacologically acceptable cations. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (eq., potassium and sodium) and alkaline earth metal cations (eq., calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglimine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula (I), but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁶O, ¹⁷O, ³¹P, ³²P, ³⁵S, ³⁸F, and ³⁵Cl, respectively. Compounds of the present invention, produgs thereof, and pharmaceutically acceptable salts of said compounds or of said produgs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ³ H and ¹⁴ C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ³ H, and carbon ¹⁴, i.e., ¹⁴ C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ²H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.
Isotopically labelled compounds of Formula (I) of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples and Preparations below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The present invention provides for the treatment of a medical condition selected from the group consisting of Alzheimer's disease, multiple sclerosis, Huntington's chorea, Pick's disease, Guillain Barre syndrome, encephalitis, meningitis, stroke; and hemorrhagic stroke; cancer generally and leukemia particularly; allergic and respiratory diseases including allergic dermatitis, anaphylaxis, asthma, eczema, rhinitis, and adult respiratory distress syndrome; cardiovascular or metabolic disease states including ischemia and reperfusion injury, shock and hypertension, hyperlipidemia, hypercholesterolemia, edema, obesity; nephritis, graft rejection, and inflammatory conditions generally including without limitation, osteoarthritis, ischemia, lung inflammation and rheumatoid arthritis, comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. Exemplary conditions that may be treated by the compound of the invention are Alzheimer's disease, multiple sclerosis, Huntington's chorea, Pick's disease, Guillain Barre syndrome, encephalitis, meningitis, stroke, and hemorrhagic stroke.

Another aspect of the present invention is a method for preventing excessive Complement activation in a patient comprising administering to said patient, a therapeutically effective amount of a compound(s) of the present invention.

Another aspect of the present invention is a method for treating or preventing Complement-mediated tissue damage in a patient comprising administering to said patient, a therapeutically effective amount of a compound(s) of the present invention.

Another aspect of the present invention is a method for treating diseases characterized by chronic Complement activation comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention.

Another aspect of the present invention is a method for antagonizing the C3a receptor in a patient by administering an effective amount of a compound(s) of the present invention.

In connection with the practice of the invention, the following definitions will generally apply.

An "effective amount" or "therapeutically effective amount" of a subject compound, with respect to the subject method of treatment, refers to an amount of the therapeutic in a preparation which, when applied as part of a desired dosage regimen provides a benefit according to clinically acceptable standards for the treatment or prophylaxis of a particular disorder.
A "patient" or "subject" to be treated by the subject method can mean either a human or non-human subject.

The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof. Similarly, the terms "alkenyl" and "alkynyl" define hydrocarbon radicals having straight, branched or cyclic moieties wherein at least one double bond, or at least one triple bond, respectively, is present. Such definitions also apply when the alkyl, alkenyl or alkynyl group is present within another group, such as alkoxy or alkylamine.

The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is as defined above.

The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

A group or substituent "fused to C₆-C₁₀ arene" or "fused to an arene", as used herein, unless otherwise indicated, indicates, respectively, a group or substituent fused to a C₆-C₁₀ aromatic hydrocarbon and a group or substituent fused to a C₆-C₉₀ aromatic hydrocarbon.

The C₆-C₁₀ aromatic hydrocarbon, or the C₆-C₉₀ aromatic hydrocarbon, may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other substituents, and preferably the number of substituents is between 0 and 3, more preferably between 0 and 2. Representative aromatic hydrocarbon compounds are benzene and naphthalene.

An "aryl" group as used herein, unless otherwise indicated, includes an organic radical derived from a monocyclic or bicyclic (C₆-C₁₀) aromatic hydrocarbon compound by removal of a hydrogen radical from a ring carbon of the aryl compound. An aryl group may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other substituents, and preferably the number of substituents is between 0 and 3, more preferably between 0 and 2. It will be appreciated that the preferred number of substituents is determined in part by facility of synthesis. Representative aryl groups are phenyl and naphthyl.

An "arylene" group as used herein, unless otherwise indicated, includes an organic diradical derived from a monocyclic or bicyclic (C₆-C₁₀) aromatic hydrocarbon compound by removal of two hydrogen radicals from two ring carbons of the aryl compound. An arylene group may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other substituents, and
perferably the number of substituents is between 0 and 3, more preferably between 0 and 2. It will be appreciated that the preferred number of substituents is determined in part by facility of synthesis. Representative aryl groups are phenyl and naphthyl.

A "heteroaryl" group as used herein, unless otherwise indicated, includes an organic radical derived from a monocyclic or bicyclic 3-10-membered aromatic heterocyclic compound by removal of a hydrogen radical from a ring atom of the heteroaryl compound, said ring atom being uncharged in said compound. A heteroaryl group may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other substituents, and preferably the number of substituents is between 0 and 3, more preferably between 0 and 2. It will be appreciated that the preferred number of substituents is determined in part by facility of synthesis. Representative heteroaryl groups include furyl, thiethyl, thiazolyl, pyrazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrrolyl, triazolyl, tetrazolyl, imidazolyl, 1,3,5-oxadiazozy, 1,2,4-oxadiazozy, 1,2,3-oxadiazozy, 1,3,5-thiadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-triazinyl, pyrazolo[3,4-b]pyridinyl, cinnolinyl, pteridinyl, purinyl, 6,7-dihydro-5H-[1]pyrimidinyl, benzo[b]thiophenyl, 5, 6, 7, 8-tetrahydroquinolin-3-yl, benzoazazolyl, benzoazazolyl, benzothiazolyl, benzisothiazolyl, benzoxazolyl, benzimidazolyl, thianaphthenyl, isothianaphthenyl, benzofurananyl, isobenzofuranyl, isoindolyl, indolyl, indolizinyl, indazolyl, isoquinolyl, quinolyl, phthalazinyl, quinoxaliny, quinazoliny, and benzoazazinyl; and the like.

A "cycloalkyl" group as used herein, unless otherwise indicated, includes an organic radical derived from a monocyclic (C3-C10) cycloalkyl compound, by removal of a hydrogen radical from a ring carbon of the cycloalkyl compound. A cycloalkyl group may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other substituents, and preferably the number of substituents is between 0 and 3, more preferably between 0 and 2. It will be appreciated that the preferred number of substituents is determined in part by facility of synthesis. Representative cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, 1,3-cyclobutadienyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,4-cycloheptadienyl, 1,3,5-cycloheptatrienyl, bicyclo[3.2.1]octane, bicyclo [2.2.1] heptane, and the norborn-2-ene unsaturated form thereof. Thus, the term cycloalkyl also includes cycloalkeny groups having one or two double bonds.

A "heterocycloalkyl" group as used herein, unless otherwise indicated, includes an organic radical derived from a monocyclic 3-10-membered heterocycloalkyl compound by removal of a hydrogen radical from a ring atom of the heterocycloalkyl compound. A heterocycloalkyl group may be substituted by one or more substituents wherein, unless otherwise indicated, selection of each substituent is independent of selection of any other
substituents, and preferably the number of substituents is between 0 and 3, more preferably between 0 and 2. It will be appreciated that the preferred number of substituents is determined in part by facility of synthesis. Representative heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydropyranyl, piperidinyl, thiomorpholinyl, 1,2-dihydrothiazin-2-yl, 1,3-dihydrothiazin-3-yl, morpholinyl, 1,2-dihydrodiazin-2-yl, 1,3-dihydrodiazin-1-yl, tetrahydroazepinyl, piperezinyl, and chromanyl.

In connection with the terms "alkyl", "aryl", "heteroaryl", "cycloalkyl" and "heterocycloalkyl", as herein defined, the term "optionally substituted" means that at least one chemically and pharmaceutically acceptable functional group may be bonded thereto. Such a functional group is selected from the group consisting of hydroxy, halo, amino, trfluoromethyl, carboxy, (C₁₋₅)alkoxy-, (C₁₋₅)acyloxy-, (C₁₋₅)alkylamino-, (C₁₋₅)alkylamine-, (C₁₋₅)acylamino-, cyano, nitro, (C₁₋₅)alkyl-, (C₂₋₅)alkenyl-, (C₂₋₅)alkynyl-, cyano(C₁₋₅)alkyl-, trifluoromethyl(C₁₋₅)alkyl-, nitro(C₁₋₅)alkyl-, (C₁₋₅)alkyl(trifluoromethyl)alkyl-, (C₁₋₅)alkyl(nitroalkyl)alkyl-, (C₁₋₅)alkyl(polyfluoralkyl)alkyl-, (C₁₋₅)alkylamine(C₁₋₅)alkyl-, (C₁₋₅)acylamino(C₁₋₅)alkyl-, (C₁₋₅)alkoxy(C₁₋₅)alkyl-, (C₁₋₅)acylamino-, amino(C₁₋₅)alkyl-, amino(C₁₋₅)alkyl(C₁₋₅)alkyl-, (C₁₋₅)alkylamine(C₁₋₅)alkyl-, ((C₁₋₅)alkyl)₂amino(C₁₋₅)alkyl-, (C₅₋₁₀)cycloalkyl(C₁₋₅)alkyl-, (C₅₋₁₀)aryl(C₁₋₅)alkyl-, 5-10-membered heteroaryl(C₁₋₅)alkoxy(C₁₋₅)alkyl-, (C₆₋₁₀)arylsulfanyl-, (C₁₋₅)alkylsulfanyl(C₁₋₅)alkyl-, (C₆₋₁₀)arylsulfonyl-, (C₁₋₅)alkyl-(C₆₋₁₀)arylenesulfanyl-, (C₁₋₅)alkyl-(C₆₋₁₀)arylenesulfonyl-, amino(C₁₋₅)alkyl-, (C₁₋₅)alkylamine(C₁₋₅)alkyl-, (C₁₋₅)alkyl(difluoromethylene)₆-, (C₁₋₅)alkoxy(C₁₋₅)alkyl-, (C₆₋₁₀)aryl-, 5-10-membered heteroaryl-, (C₆₋₁₀)aryloxy(C₁₋₅)alkyl-, 5-10-membered heteroaryl(C₁₋₅)alkyl-, (C₆₋₁₀)aryloxy(C₅₋₁₀)aryl-, (C₆₋₁₀)aryloxy(C₅₋₁₀)aryloxy-, (C₅₋₁₀)cycloalkyl-, 3-10-membered heterocycloalkyl-, 3-10-membered heterocycloalkyl(C₁₋₅)alkyl-, hydroxy(C₂₋₅)alkyl-, (C₁₋₅)acyloxy(C₂₋₅)alkyl-, (C₁₋₅)alkoxy(C₂₋₅)alkyl-, (C₁₋₅)alkylthio(C₁₋₅)alkyl-, (C₂₋₁₀)arylothio(C₁₋₅)alkyl-, (C₁₋₅)alkylsulfanyl(C₁₋₅)alkyl-, (C₂₋₁₀)arylsulfanyl(C₁₋₅)alkyl-, (C₂₋₁₀)arylsulfonfyl(C₁₋₅)alkyl-, ((C₁₋₅)alkyl)₂amino(C₁₋₅)alkyl, (C₁₋₅)alkyl)₅-10-membered heteroaryl-, C₁₋₅ alkyl-CONH₂, wherein the C₁₋₅ alkyl may be substituted with a 5-10-membered heteroaryl or with a C₆₋₁₀ aryl that may be unsubstituted or substituted with one or more C₁₋₅ alkyl, halo, C₁₋₅ alkoxy, or a combination thereof, C₆₋₁₀ aryl-CONH₂, wherein the C₂₋₁₀ aryl may be unsubstituted or substituted with one or more C₁₋₅ alkyl, halo, C₁₋₅ alkoxy, or a combination thereof, wherein the 5-10-membered heteroaryl may be unsubstituted or substituted with one or more C₁₋₅ alkyl, halo, C₁₋₅ alkoxy, or a combination thereof, 5-10-membered heteroaryl-CONH₂, wherein the 5-10-membered heteroaryl may be unsubstituted or substituted with one or more C₁₋₅ alkyl, halo, C₁₋₅ alkoxy, or a combination thereof.
C_1-C_6 alkoxy, or a combination thereof, 3-10-membered heterocycloalkyl-CONH- wherein the
3-10-membered heterocycloalkyl may be unsubstituted or substituted with one or more C_1-C_6
alkyl, halo, C_1-C_6 alkoxy, or a combination thereof, and is optionally fused to a C_6-C_10 arene,
C_3-C_10 cycloalkyl-CONH- wherein the 3-10-membered heterocycloalkyl may be unsubstituted
or substituted with one or more C_1-C_6 alkyl, halo, C_1-C_6 alkoxy, or a combination thereof, and
is optionally fused to a C_6-C_10 arene, and a combination thereof.

Further aspects of the invention are described in accord with the Detailed Description
of the Invention which follows directly.

**Detailed Description of the Invention**

In certain embodiments of the compound of formula (I), W represents -C(R_6)_2-, or
-NR_6-, where R_6, independently for each occurrence, represents hydrogen, or optionally
substituted (C_1-C_10)alkyl.

In certain embodiments of the compound of formula (I), A represents an optionally
substituted (C_6-C_10)aryl, or an optionally substituted 5-10-membered heteroaryl.

In certain embodiments of the compound of formula (I), A represents a optionally
substituted phenyl ring or an optionally substituted pyrazolyl group.

In further embodiments of the compound of formula (I), A represents a phenyl group
substituted one or more times by a (C_1-C_6) alkyl (preferably methyl), or a 1-(C_1-C_6)alkyl-5-
trifluoromethyl-1H-pyrazol-3-yl group.

In certain embodiments of the compound of formula (I), R_2 and R_3, independently,
represent hydrogen or a (C_1-C_6) alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl,
n-hexyl).

In certain embodiments, R_4 represents a group selected from

![Diagram](attachment:image.png)

wherein
group C represents, an optionally substituted (C_6-C_10)aryl, optionally substituted 5-10-
membered heteroaryl, optionally substituted (C_3-C_10) cycloalkyl, or optionally substituted 3-10-
membered heterocycloalkyl;
R₆ independently for each occurrence represents, one or more substituents selected from hydrogen, hydroxy, halo, amino, C(=O)R₆, -OC(=O)-R₆, -C(=O)O-R₆, -N(R₆)₂,
-NR₆C(=O)-R₆, -C(=O)N(R₆)₂, -OC(=O)-N(R₆)₂, -NR₆-C(=O)-N(R₆)₂, -S(O)ₙ-R₆ (wherein n is 0, 1, or 2), -S(O)ₙ,N(R₆)₂ (wherein n is 0, 1, or 2), (C₆-C₆)alkoxy-,
(C₁-C₆)acylamino-, cyano, nitro, optionally substituted (C₁-C₁₀)alkyl-, optionally substituted (C₂-C₁₀)alkenyl-, optionally substituted (C₂-C₁₀)alkynyl-, optionally substituted (C₆-C₁₀)aryl,
optionally substituted 5-10-membered heteroaryl, optionally substituted (C₃-C₁₀)cycloalkyl-, 3-
10-membered heterocycloalkyl, or two R₆ groups taken together can form a 4-8 membered
ring containing 0-3 heteroatoms selected from N, O, and S; and n and m, in the groups −
(CH₂)ₙ and −[O-CH₂-CH₂-O]ₘ−, independently, represent 0, 1, 2, or 3.

In certain embodiments group C represents one of the following optionally substituted
groups: phenyl, furyl, thienyl, pyrazinyl, imidazolyl, pyridyl, cyclopropyl, cyclobutyl,
cyclopentyl, or a cyclohexyl group.

In certain embodiments, R₆, independently for each occurrence, represents one or
more moieties selected from the group consisting of hydrogen, methyl, ethyl, propyl, hydroxy,
methoxy, ethoxy, propoxy, fluoro, chloro, and bromo.

In certain embodiments,
the group

![](image)

may not be a group

In certain embodiments of the compound of formula (I), R₃ is not a C₁-C₁₀ alkyl
substituted with OH.

In certain embodiments of the compound of formula (II), W represents −C(R₆)₂−, or −
NR₆−, where R₆, independently for each occurrence, represents hydrogen, or optionally
substituted (C₁-C₁₀)alkyl.

In certain embodiments of the compound of formula (II), A represents an optionally
substituted (C₆-C₁₀)aryl, or an optionally substituted 5-10-membered heteroaryl.
In certain embodiments of the compound of formula (II), A represents an optionally substituted phenyl ring or an optionally substituted pyrazolyl group.

In further embodiments, A represents a phenyl group substituted one or more times by a (C₁₋₅alkyl) alkyl (preferably methyl), or a 1-(C₁₋₅alkyl)-5-trifluoromethyl-1H-pyrazol-3-yl group.

In certain embodiments of the compound of formula (II), B represents an optionally substituted (C₆₋₁₅)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₃₋₁₅)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

In still further embodiments, B represents one of the following optionally substituted groups: phenyl, furyl, thienyl, pyrazinyl, imidazolyl, pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, or a cyclohexyl group.

In certain embodiments of the compound of formula (II), R₂ and R₃ independently, represent hydrogen or a (C₁₋₅alkyl) alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl).

In certain embodiments of the compound of formula (III), A represents an optionally substituted (C₆₋₁₅)aryl, or an optionally substituted 5-10-membered heteroaryl.

In certain embodiments of the compound of formula (III), A represents an optionally substituted phenyl ring or an optionally substituted pyrazolyl group.

In further embodiments, A represents a phenyl group substituted one or more times by a (C₁₋₅alkyl) alkyl (preferably methyl), or a 1-(C₁₋₅alkyl)-5-trifluoromethyl-1H-pyrazol-3-yl group.

In certain embodiments of the compound of formula (III), R₂ and R₃, independently, represent hydrogen or a (C₁₋₅alkyl) alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl).

Another aspect of the present invention is a compound selected from the group consisting of 5-(3’, 4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine; 3-[5-amino-3-(3’,4’-dimethyl-biphenyl-4-yl)-pyrazol-1-ylmethyl]-phenol; cyclopropylmethyl-[5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3’, 4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-furan-2-ylmethyl-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-3H-imidazol-4-ylmethyl]-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-benzyl]-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[3-methyl-benzyl]-amine; [5-(3’,4’-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-(3-methyl-benzyl)-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-(3-methoxy-benzyl)-amine; (3-chloro-benzyl)-[5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; (2-chloro-benzyl)-[5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-thiophen-2-ylmethyl-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-thiophen-2-ylmethyl-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-thiophen-2-ylmethyl-amine; [5-(3’,4’-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-thiophen-2-ylmethyl-amine;
dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-2-ylmethyl-amine; 
(2,4-dichloro-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-pyridin-3-ylmethyl-amine; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-pyridin-4-ylmethyl-amine; 
benzo[1,3]dioxol-5-ylmethyl-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
(3,4-dimethoxy-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
(2,4-dimethoxy-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-nicotinamide; 
pyridine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amide; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-isonicotinamide; 
furan-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amide; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-4-fluorobenzamide; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-4-methoxybenzamide; 
benzo[1,3]dioxole-5-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amide; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-3,4-dimethoxy-benzamide; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-2,4-dimethoxy-benzamide; 
2-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-isoindole-1,3-dione; 
2-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-pyrrolo[3,4-c]pyridine-1,3-dione; 
6-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-pyrrolo[3,4-b]pyridine-5,7-dione; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-[4-fluorobenzyl]-amine; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-[4-methoxybenzyl]-amine; 
[4-chloro-benzyl]-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-[2-(2-methoxy-ethoxy)-ethyl]-amine; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-[2-(2-methyl-cyclopropylmethyl)]-amine; 
2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-4H-pyrazol-3-yl]-amine; 
3-(3',4'-dimethyl-biphenyl-4-yl)-1-methyl-1H-pyrazole; 
N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-acetamide; 
pyrazine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-amine; 
3-(3',4'-dimethyl-biphenyl-4-yl)-1,5-dimethyl-1H-pyrazole; 
6-(3',4'-dimethyl-biphenyl-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazole; 
pyridine-2-carboxylic acid (2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-yl]-amide; 
[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-methyl-amine; 
and 6-(3',4'-dimethyl-biphenyl-4-yl)-3-methyl-1H-pyrazolo[5,1-c][1,2,4]triazole, and pharmaceutically acceptable salts thereof.

The compounds of Formula (I), (II), and some of the intermediates in the present invention may contain one or more asymmetric carbons. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current
distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers.

Pure stereochemically isomeric forms of the compounds of Formula (I) or (II) may also be obtained from the pure stereochemical forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically. The pure and mixed stereochemically isomeric forms of the compounds of Formula (I) or (II) are intended to be embraced within the scope of the present invention.

The compounds of the invention may operate by more than one mechanism of action, including those unrelated to the Complement cascade, and the utility of the present compounds in the practice of the invention, including for use in treating other disease states not mentioned herein, is not limited by any particular theory of operation or mechanism of action as described herein, or by those theories or mechanisms generally recognized by those skilled in the art.

One aspect of the present invention is a method of synthesizing the C3a antagonists described herein. The following reaction schemes are intended to illustrate the preparation of the antagonists of the present invention.

Other examples of specific embodiments of the present invention are depicted in the Examples.
Scheme 1 illustrates general methods suitable for the preparation of compounds of formula 1a, 1b, 1c, 1d, 1e, and 1f. Optionally substituted acetophenone 5 may be converted into dimethylaminopropenone 4 via treatment with t-butoxybis (dimethylamino)methane or an N, N-dimethylformamide dialkyl acetal, where N, N-dimethylformamide dimethyl acetal is preferred at temperatures ranging from 100° to 180°C, where 110°-140°C is preferred. Aryl substituted isoxazole 3 may be prepared by the in-situ formation of the corresponding oxime from the reaction of compound 4 and hydroxylamine hydrochloride in an alcoholic solvent, where methanol is preferred, and cyclization by heating in the range of 30°-100°C, where 50-80°C is preferred. 2-Cyanoacetophenone 2 may be prepared from isoxazole 4 and an alkoxide base, preferably sodium methoxide in alcohol solvent, where methanol is preferred, at temperatures ranging from 30°-120°C, where 50°-80°C is preferred. Aminopyrazole 1a may
be obtained by treating compound 2 with an optionally substituted hydrazine in an alcohol solvent, where methanol is preferred, at temperatures in the range of 30°-100°C, where 50-80°C is preferred. Amido compound 1b is prepared by treating aminopyrazole 1a with a substituted acid chloride and a non-nucleophilic base, such as triethylamine, diisopropylethylamine or preferably 2,6-lutidine, in a suitably inert solvent, such as THF, chloroform or preferably methylene chloride, at temperatures ranging from -30°-50°C, where 0° to 25°C is preferred. Amido compound 1b may also be prepared from aminopyrazole 1a and an optionally substituted carboxylic acid in the presence of a coupling reagent such as 1,3-dicyclohexylcarbodiimide, carbonyldimidazole, BOP reagent or preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1-hydroxybenzotriazole hydrate in a polar solvent, where DMF is preferred, at temperatures ranging from 0°-50°C, where 10°-35°C is preferred. Amide 1b may be converted to amine compound 1c by treatment with a metal hydride reducing agent, where lithium aluminum hydride is preferred. Compound 1c may also be prepared via reductive amination of compound 1a and an optionally substituted aldehyde in the presence of an acidic hydride reducing agent such as sodium cyanoborohydride/ acetic acid or preferably sodium triacetoxyborohydride in acetic acid at temperatures ranging from 0°-50°C, where 10°-35°C is preferred. Phthalamido compound 1d may be prepared from compound 1a and an optionally substituted phthalic anhydride by heating in the range of 100-200°C, where 130-160°C is preferred. Pyrazyl amide 1e may also be prepared from 2,3-pyrazinedicarboxylic anhydride using this method. Pyrazole 1f may be prepared by converting aminopyrazole 1a to the corresponding diazonium salt by treatment with sodium nitrite in aqueous acid, where hydrochloric acid is preferred, at preferably -10° to 5°C, and then adding this compound to aqueous hypophosphorous acid.

Scheme 2

Scheme 2 illustrates the general method for preparing compounds of the formula 1g. Optionally substituted acetophenone 5 is converted to dione 6 by Claisen condensation with ethyl acetate in the presence of dibenzo-18-crown-6 as described by Popic, et al., Synthesis, (3), 195-8, 1991. The dione is cyclized in the presence of an optionally substituted hydrazine in an alcohol solvent where methanol is preferred at temperatures ranging from 0° -120°C, where 40-70°C is preferred.
Scheme 3

\[ R_3 = \text{CH}_2\text{CH}_2\text{OH} \quad R_3 = \text{CH}_2\text{CH}_2\text{Cl} \]

Scheme 3 illustrates the procedure for preparing imidazopyrazole compound 1h. Compound 1a, wherein R3 is hydroxyethyl, is converted first to the chloride with a chlorinating agent, where thionyl chloride is preferred, in a halogenated solvent, where chloroform is preferred, at temperature in the range of 30°-120°C, where 50°-80°C is preferred. The in-situ conversion of the chloride to the iodide, and subsequent cyclization is accomplished in acetonitrile in the presence of sodium iodide and non-nucleophilic base where triethylamine is preferred at temperatures ranging from 50° to 100°C where 60°-90°C is preferred.

Scheme 4

Scheme 4 illustrates the procedure for preparing pyrazolo[1,5-a]pyrazole compound 1i. Ketonitrile 2 may be converted into the oxo-acetimidic acid ester 7 by treatment with ethanol and an acid, preferably hydrochloric acid, in a suitably inert solvent where dioxane is preferred at temperatures ranging from –10°–50°C, where 0°-30°C is preferred. Compound 1i may be prepared from compound 7 in a two step procedure: first treating it with acetylhydrazine and then hydrazine to form the intermediate 3-pyrazole,acetylyhydrazide, and then chlorinating and cyclizing with phosphorus oxychloride at temperatures ranging from 80° to 140°C, where 100°-120°C is preferred.

Scheme 5

Scheme 5 illustrates the general procedure for preparing trifluoromethyl pyrazole substituted acetophenone intermediates 5b. Compound 6a may be prepared by Claisen condensation of compound 5a with ethytrifluorooacetate, an alkoxide base such as sodium
methoxide, sodium ethoxide or preferably sodium t-butoxide in a non-protic solvent, where THF is preferred, in the presence of a cation chelating agent, where 18-crown-6 is preferred, at temperatures ranging from \(-10^\circ\text{C}\) to \(-50^\circ\text{C}\), where \(0^\circ\text{C}\) to \(-30^\circ\text{C}\) is preferred. Pyrazole 8 may be formed by treatment of compound 6a with hydrazine in a non-polar solvent, where toluene is preferred, at temperatures ranging from \(50^\circ\text{C}\) to \(-130^\circ\text{C}\), where \(80^\circ\text{C}\) to \(-120^\circ\text{C}\) is preferred. Compound 8 may be methylated with an alkylating agent, such as methyl iodide or preferably dimethylsulfate hydrazine, in a non-polar solvent, where toluene is preferred, at temperatures ranging from \(50^\circ\text{C}\) to \(-130^\circ\text{C}\), where \(80^\circ\text{C}\) to \(-120^\circ\text{C}\) is preferred, to afford compound 9. Synthesis of compound 5b may be accomplished by formation of the lithio species of compound 9 by halogen-metal exchange with an alkyl lithium reagent, such as t-butyl lithium or preferably n-butyl lithium, in a suitably inert solvent, such as diethyl ether or preferably THF, at temperatures ranging from \(-110^\circ\text{C}\) to \(-50^\circ\text{C}\), where \(-90^\circ\text{C}\) to \(-60^\circ\text{C}\) is preferred, followed by the addition of N-methoxy-N-methylacetamide.

Another aspect of the present invention is a pharmaceutical composition comprising substantially enriched enantiomeric forms of the compound(s) of the present invention; or pharmaceutically acceptable addition salts thereof, and a pharmaceutically acceptable carrier. In certain embodiments these compositions may be formulated in unit dosage forms.

The compositions of the present invention are preferably non-pyrogenic, e.g., do not trigger elevation of a patient's body temperature by more than a clinically acceptable amount.

Another aspect of the present invention is a pharmaceutical composition comprising a compound(s) of the present invention, or pharmaceutically acceptable addition salts thereof, and a pharmaceutically acceptable carrier. In certain embodiments these compositions may be formulated in unit dosage forms.

Plasticizers and stabilizing agents known in the art may be incorporated in the pharmaceutical compositions of the present invention. In certain embodiments, additives such as plasticizers and stabilizing agents are selected for their biocompatibility. In certain embodiments, the additives are lung surfactants, such as 1,2-dipalmitoylphosphatidylcholine (DPPC) and L-α-phosphatidylcholine (PC).

A composition of this invention may further contain one or more adjuvant substances, such as fillers, thickening agents or the like.

In certain embodiments, a subject composition includes an excipient. A particular excipient may be selected based on its melting point, solubility in a selected solvent (e.g., a solvent that dissolves the therapeutic agent), and the resulting characteristics of the microparticles.

Excipients may comprise a few percent, about 5%, 10%, 15%, 20%, 25%, 30%, 40%, 50%, or higher percentage of the subject compositions.
Buffers, acids and bases may be incorporated in the subject compositions to adjust their pH. Agents to increase the diffusion distance of therapeutic may also be included.

The pharmaceutical compositions as described herein can be administered in various pharmaceutical formulations, depending on the disorder to be treated and the age, condition and body weight of the patient, as is well known in the art. For example, where the compounds are to be administered orally, they may be formulated as tablets, capsules, granules, powders or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eye-drops or eye ointments. These formulations can be prepared by conventional means, and, if desired, the active ingredient may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses.

The precise time of administration and/or amount of therapeutic agent that will yield the most effective results in terms of efficacy of treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

The phrase "pharmacologically acceptable" is employed herein to refer to those therapeutic agents, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmacologically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other
ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the therapeutic agents. These salts can be prepared in situ during the final isolation and purification of the therapeutic agent, or by separately reacting a purified therapeutic agent in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, besylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic, inorganic or organic base addition salts of the compounds of the present invention. These salts can likewise be prepared in situ during the final isolation and purification of the therapeutic agent, or by separately reacting the purified therapeutic agent in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like (see, for example, Berge et al., supra).
When the therapeutic agent of the present invention is administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Another aspect of the present invention is a method for preventing excessive Complement activation in a patient comprising administering to said patient, a therapeutically effective amount of the compounds of the present invention.

Another aspect of the present invention is a method for treating or preventing Complement-mediated tissue damage in a patient comprising administering to said patient, a therapeutically effective amount of a compound(s) of the present invention.

Another aspect of the present invention is a method for treating diseases characterized by chronic Complement activation comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. In certain embodiments, these diseases are selected from neurodegenerative diseases and pulmonary diseases. The neurodegenerative diseases may be ones which affect the central nervous system (CNS) or the peripheral nervous system (PNS).

For example, the present compounds can be used in a method for treating Complement mediated nerve myeline loss (demyelination). Myelin provides the axonal “insulation” essential for efficient neural signal conduction in both the CNS and PNS. The cell which produces myelin in the CNS is the oligodendrocyte whereas the myelin-producing cell in the PNS is the Schwann cell. Diseases characterized by demyelination occur both in the CNS and the PNS. Accordingly, one aspect of the present invention is a method of treating Complement mediated demyelination of nerves in the CNS or in the PNS comprising administration of a therapeutically effective amount of a compound(s) of the present invention.

In the CNS, the most common demyelination disease is multiple sclerosis (MS). While it is now widely accepted that MS is an autoimmune disease of the nervous system driven by infiltrating T cells specific for CNS antigens (See Prineas et al., (1987), Lab. Invest., 38, 409-421), there is evidence to suggest that Complement and other inflammation-mediating substances might be involved in myelin damage in MS. (See Yam et al., (1980), Clin. Immunol. Immunopathol., 17, 492-505; Mollenes et al., (1987), J. Neurol. Sci., 78, 17-28; Compston et al., (1989), Neuropathol. Appl. Neurobiol., 15, 307-316) Accordingly, one aspect of the present invention is a method of treating MS comprising administration of a therapeutically effective amount of a compound(s) of the present invention.

In the PNS, several neuropathies, including, Guillain-Barre syndrome (GBS) and Miller-Fisher syndrome (MFS) are characterized by the presence of inflammation and extensive demyelination. The majority of GBS patients have serum IgM antibodies against Schwann cells and/or PNS myelin which can, in vitro, efficiently activate the Complement
cascade. (See Koski et al., (1986), Ann. Neurol., 19, 573-577; Koski et al., (1990), Ann. Neurol., 27, S44-S47) Nyland et al., have shown that GBS serum or purified antibody causes Complement-dependent demyelination in peripheral nerve cultures. (See Nyland et al., Acta Neurol. Scand., 58, 35-34) Moreover, it has been shown that C activation products (C3a, C5a, terminal C complex) are found in the CSF, plasma, and peripheral nerves of GBS patients. (See Hartung et al., (1987), 37, 1006-1009; Koski et al., (1987), J. Clin. Invest., 80, 1492-1497; Hays et al., (1988), J. Neuroimmunol. 18, 231-244). Accordingly, one aspect of the present invention is a method of treating GBS or MFS comprising administration of a therapeutically effective amount of a compound(s) of the present invention.

IgM monoclonal gammopathy and peripheral neuropathy constitute other instances of PNS diseases which are associated with (aberrant) Complement activation. (See Monaco et al., (1990), Peripheral neuropathy is a condition common in later stage (Type I, or Type II) diabetic patients. Accordingly, one aspect of the present invention is a method of treating IgM monoclonal gammopathy and peripheral neuropathy comprising administration of a therapeutically effective amount of a compound(s) of the present invention.

Another aspect of the present invention is a method of treating neuromuscular diseases wherein Complement is implicated, comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. An example of such neuromuscular disease is myasthenia gravis. (See Asghar SS. Pasch MC, Frontiers in Bioscience. 5:E63-81, 2000 Sep 1.)

Implication of Complement activation in Huntington's disease has been disclosed. (See Morgan, B.P., Gasque, P. et al., (1997), Immunopharmacology 38, 43-50, Morgan, B.P., Gasque, P., (1996), Immunology Today 17, 461-466, Morgan, B.P., Gasque, P., (1997), Clinical and Experimental Immunology 107, 1-7)

Another aspect of the present invention is a method for treating Huntington's disease (HD) comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disease characterized by the onset in mid-life of chorea, dementia, personality disturbance and inexorable progression to death. Singhrao et al. have reported significant presence of Complement factors C1q, C4, C3, iC3b-neopeptide and C9-neopeptide in HD striatum, neurons, myelin and astrocytes. (See Singhrao et al., (1999), Exper. Neurolo., 159, 362-376)

Another aspect of the present invention is a method for treating Pick's disease (PD) comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. PD is a neurodegenerative disorder, the histological hallmarks of which is the Pick body, a dense, amorphous body which is strongly stained for tau protein and ubiquitin. Neuronal loss and astrocyte proliferation occur in the areas of disease which appear to be restricted to the frontal and temporal lobes. Yasuhura et al. has shown that Complement is implicated in Pick's disease. (See Yasuhura et al., (1994), Brain Res., 652, 346-349).

Another aspect of the present invention is a method for treating asthma comprising administering to a patient a therapeutically effective amount of a compound(s) of the present invention. Asthma is a disease that affects approximately 10% of the population. The overall annual prevalence of cases has increased by 42% in the past decade, and despite the availability of more potent and selective therapy, the annual incidence of asthma mortality has risen by 40% over this same time period. Asthma is an allergenic reaction toward an inhaled antigen, characterized by a strong bronchoconstriction and edema formation with subsequent cell infiltration into the lung parenchyma and alveoli, mainly lymphocytes and eosinophils. Although IgE mediated histamine release is generally regarded as the major pathophysiological pathway for asthma, other non-IgE mediated mechanisms also contribute to the disease. A major candidate in that respect is the C3a anaphylatoxin. Other Complement mediated pulmonary disorders include hypersensitivity pneumonites, and anaphylaxis. (See Regal, J., (1997), Immunopharmacology, 38, 17-25)

Another aspect of the present invention is a method for treating or preventing a selected from sepsis, adult respiratory distress syndrome, nephrites, graft rejection, myocardial ischemia/reperfusion injury, and intestinal ischemia/reperfusion injury, comprising administering to a patient a therapeutically effective amount of a compound(s) of the present
invention. Lipton et al., in U.S. Patent No. 6,503,947 discloses attenuation of cerebral ischemia and reperfusion injury by administrating a Complement inhibitor.

Pharmaceutical Compositions and Their Use

The pharmaceutical compositions of the present invention comprise any one or more of the above-described compounds, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier in accordance with the properties and expected performance of such a carrier, as is well-known in the art.

The dosage and dose rate of the compounds identified in the present invention effective for treating or preventing a disease or condition exhibiting, caused by or relating to amyloid formation, or a disease or condition caused by, exhibiting or relating to the activities of microglia or cells of macrophage lineage, will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used, and the observations and conclusions of the treating physician.

For example, where the dosage form is oral, e.g., a tablet or capsule, suitable dosage levels may be between about 0.1 μg/kg and about 50.0 mg/kg body weight per day, preferably between about 1.0 μg/kg and about 5.0 mg/kg body weight per day, more preferably between about 10.0 μg/kg and about 1.0 mg/kg of body weight per day, and most preferably between about 20.0 μg/kg and about 0.5 mg/kg of body weight per day of the active ingredient.

Using representative body weights of 10 kg and 100 kg in order to illustrate the range of daily aerosolized topical dosages that might be used as described above, suitable dosage levels of a compound identified in the present invention will be between about 1.0-10.0 μg and 500.0-5000.0 mg per day, preferably between about 5.0-50.0 μg and 5.0-50.0 mg per day, more preferably between about 100.0-1000.0 μg and 10.0-100.0 mg per day, and most preferably between about 200.0-2000.0 μg and about 5.0-50.0 mg per day of the active ingredient. These ranges of dosage amounts represent total dosage amounts of the active ingredient per day for a given patient. The number of times per day that a dose is administered will depend upon such pharmacological and pharmacokinetic factors as the half-life of the active ingredient, which reflects its rate of catabolism and clearance, as well as the minimal and optimal blood plasma or other body fluid levels of said active ingredient attained in the patient that are required for therapeutic efficacy.

Numerous other factors must also be considered in deciding upon the number of doses per day and the amount of active ingredient per dose that will be administered. Not the least important of such other factors is the individual response of the patient being treated. Thus, for example, where the active ingredient is administered topically via aerosol inhalation into the lungs, from one to four doses consisting of aerosolizations of a dispensing device, i.e.,
"puffs" of an inhaler, will be administered each day, each dose containing from about 50.0 \( \mu g \) to about 10.0 mg of active ingredient.

Additional detailed information is as follows.

**The Drug Substance**

Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camyslate, citrate, cyclamate, edisylate, esylate, formate, fumarate, glucone, gluconate, glucuronic acid, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyrogallatate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* by Stahl and Wermuth (Wiley-VCH, 2002). Pharmaceutically acceptable salts of compounds of formula I, for example, may be prepared by one or more of three methods:

(i) by reacting the compound of formula I with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give
distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

The compounds of the invention may also exist in unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995). Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004). For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Halebian (August 1975).

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or
solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as -COO'Na⁺, -COO'K⁺, or -SO₃Na⁺) or non-ionic (such as -N³⁺(CH₃)₃) polar head group. For more information, see *Crystals and the Polarizing Microscope* by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

Hereinafter all references to compounds of formula I include references to salts, solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-component complexes and liquid crystals of salts thereof. The compounds of the invention include compounds of formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinbefore defined and isotopically-labeled compounds of formula I.

As indicated, so-called 'prodrugs' of the compounds of formula I are also within the scope of the invention. Thus certain derivatives of compounds of formula I which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of formula I having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in *Pro-drugs as Novel Delivery Systems*, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and *Bioreversible Carriers in Drug Design*, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).

Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of formula I with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in *Design of Prodrugs* by H. Bundgaard (Elsevier, 1985). Some examples of prodrugs in accordance with the invention include:

(i) where the compound of formula I contains a carboxylic acid functionality (-COOH), an ester thereof, for example, a compound wherein the hydrogen of the carboxylic acid functionality of the compound of formula I is replaced by (C₁-C₈)alkyl;

(ii) where the compound of formula I contains an alcohol functionality (-OH), an ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of the compound of formula I is replaced by (C₁-C₈)alkanoyloxymethyl; and

(iii) where the compound of formula I contains a primary or secondary amino functionality (-NH₂ or -NHR where R ≠ H), an amide thereof, for example, a compound wherein, as the case may be, one or both hydrogens of the amino functionality of the compound of formula I is/are replaced by (C₁-C₁₀)alkanoyl.
Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references. Moreover, certain compounds of formula I may themselves act as prodrugs of other compounds of formula I.

Also included within the scope of the invention are metabolites of compounds of formula I, that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites in accordance with the invention include:

(i) where the compound of formula I contains a methyl group, an hydroxymethyl derivative thereof (-CH₃ -> -CH₂OH);

(ii) where the compound of formula I contains an alkoxy group, an hydroxy derivative thereof (-OR -> -OH);

(iii) where the compound of formula I contains a tertiary amino group, a secondary amino derivative thereof (-NR¹R² -> -NHR¹ or -NHR²);

(iv) where the compound of formula I contains a secondary amino group, a primary derivative thereof (-NHR¹ -> -NH₂);

(v) where the compound of formula I contains a phenyl moiety, a phenol derivative thereof (-Ph -> -PhOH); and

(vi) where the compound of formula I contains an amide group, a carboxylic acid derivative thereof (-CONH₂ -> COOH).

Compounds of formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where a compound of formula I contains an alkenyl or alkenylene group, geometric cis/trans (or Z/E) isomers are possible. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ("tautomerism") can occur. This can take the form of proton tautomerism in compounds of formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartarate or dl-arginine.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallisation.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate
(or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula I contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomERICally-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the art - see, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel and S. H. Wilen (Wiley, 1994).

The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as $^2$H and $^3$H, carbon, such as $^{11}$C, $^{12}$C and $^{14}$C, chlorine, such as $^{35}$Cl, fluorine, such as $^{18}$F, iodine, such as $^{123}$I and $^{125}$I, nitrogen, such as $^{15}$N and $^{15}$N, oxygen, such as $^{15}$O, $^{17}$O and $^{18}$O, phosphorus, such as $^{30}$P, and sulphur, such as $^{35}$S.

Certain isotopically-labelled compounds of formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. $^3$H, and carbon-14, i.e. $^{14}$C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.
Substitution with heavier isotopes such as deuterium, i.e. $^2$H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as $^{11}$C, $^{18}$F, $^{15}$O and $^{13}$N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Similarly, substitution with $^{123}$I can be useful for Single Photon Emission Computed Tomography (SPECT) studies.

Isotopically-labeled compounds of formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Pharmaceutically acceptable solvents in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. $D_2$O, $d_6$-acetone, $d_6$-DMSO.

Also within the scope of the invention are intermediate compounds of formula II as hereinbefore defined, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for compounds of formula I. The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

When preparing compounds of formula I in accordance with the invention, it is open to a person skilled in the art to routinely select the form of compound of formula II which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

The Drug Product

The compounds of formula I should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, etc., in order to select the most appropriate dosage form and route of administration for treatment of the proposed indication. Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, or spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the
invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form. Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Oral Administration

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid, semi-solid and liquid systems such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches. Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or hydroxypropylmethylcellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet. The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form. Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.
Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet. Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticiser, a stabiliser or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of formula I may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a greater proportion of the composition, typically up to 88 weight % of the solutes. Alternatively, the compound of formula I may be in the form of multiparticulate beads. The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %. Other possible ingredients include anti-oxidants, colorants, flavourings and flavour enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.
Solid formulations for oral administration may be formulated to be immediate and/or modified controlled release. Controlled release formulations include Modified release formulations include delayed-, sustained-, pulsed-, controlled-, or targeted and programmed release. Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

**Additional Aspects of Drug Administration**

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

An example of a needle free injection is a powderjet to provide an example of suitable technologies). Formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as powdered a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art. The solubility of compounds of formula I used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for use with needle-free injection administration comprise a compound of the invention in powdered form in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

Formulations for parenteral administration may be formulated to be immediate and/or modified controlled release.. Controlled release formulations include Modified release formulations include delayed-, sustained-, pulsed-, controlled-, or targeted and programmed release. Thus compounds of the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(dl-lactic-coglycolic)acid (PGLA) microspheres.
The compounds of the invention may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. Typical formulations for this purpose to include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection. Topical administration may also be achieved using a patch, such as a transdermal iontophoretic patch. Formulations for topical administration may be formulated to be immediate and/or modified controlled release. Controlled release formulations include Modified release formulations include delayed-, sustained-, pulsed-, controlled-, or targeted release.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,2,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin. The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blister packs and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may
be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1μg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1μl to 100μl. A typical formulation may comprise a compound of formula I, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified controlled release using, for example, PGLA. Controlled release formulations include Modified release formulations include delayed-, sustained-, pulsed-, controlled-, or trargettedtargeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing the compound of formula I. The overall daily dose will typically be in the range 50 μg to 2000 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may also be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Inasmuch as it may desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula I in accordance with the invention, and means for separately retaining
said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 0.001 mg to 2000 mg depending, of course, on the mode of administration. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

In regard of the present specification, all patents and publications cited herein are incorporated by reference, as if fully set forth.

**EXAMPLES**

**General Procedures:**

All reactions were run under a nitrogen atmosphere for convenience and to maximize yields. Melting points are uncorrected. Chromatography refers to flash chromatography on silica gel. NMR refers to proton $[^1H]$ NMR. NMR spectra were obtained at 400 MHz and are reported in parts per million (δ) relative to the deuterium lock signal of the solvent of the specified solvent. $^{13}$C NMR spectra are referred to as such. Evaporation or concentration at reduced pressure implies the use of a rotary evaporation apparatus.

**Example 1:** Synthesis of 5-(3', 4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine, (1)

A mixture of 3-(3',4'-dimethyl-biphenyl-4-yl)-3-oxo-propionitrile (Example 28, 1.00g, 4.02 mmol), and methylhydrazine (0.74 ml, 12.06 mmol) in methanol (80 ml) was heated at reflux for 18h. After cooling to room temperature the mixture was concentrated to dryness. The residue was dissolved in ethyl acetate and washed once with water and once with brine. The organic phase was dried (MgSO$_4$) and concentrated to give 1.24 g of a yellow solid. The crude solid was chromatographed (hexane/ethyl acetate 7:3, followed by methylene chloride/methanol 95:5) to give 0.70 g of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine as an off-white solid which had: mp 171°C; MS: M$^+$ 278; NMR (acetone-d$_6$) δ 7.77 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.42 (s, 1H), 7.35 (dd, J = 1.7 Hz, 7.5 Hz, 1H), 7.17 (d, J = 7.0 Hz, 1H), 5.80 (s, 1H), 3.62 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H).
Example 2: Synthesis of 3-(5-Amino-3-(3',4''-dimethyl-biphenyl-4-yl)-pyrazol-1-ylmethyl)-phenol, (2)

The title compound was made by essentially the same procedure as exemplified in Example 1. 3-(3',4''-dimethyl-biphenyl-4-yl)-3-oxo-propionitrile (Example 39) was reacted with m-hydroxybenzylhydrazine dihydrochloride for a yield of 70%. Following titration with hot ethyl acetate, the resulting white solid had: mp 230°C (dec); MS: M⁺ 370; NMR (acetone-d₆) δ 8.30 (s, 1H), 7.79 (dd, J = 2.1 Hz, 6.6 Hz, 2H), 7.58 (dd, J = 2.1 Hz, 6.6 Hz, 2H), 7.42 (s, 1H), 7.36 (dd, J = 1.7, 7.8 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.11 (t, 1H), 6.66-6.71 (m, 3H), 5.88 (s, 1H), 5.59 (s, 2H), 4.71 (br s, 2H), 2.29 (s, 3H), 2.25 (s, 3H). Anal. calc. for C₁₇H₁₅NO·0.25H₂O: C 81.90; H 6.06; N 5.62. Found: C 81.82; H 6.18; N 5.56.

Example 3: Synthesis of Cyclopropylmethyl-[5-(3',4''-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine, (3)

A mixture of 5-(3',4''-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.075 g, 0.27 mmol) and cyclopropanecarboxaldehyde (0.022 ml, 0.30 mmol) in acetic acid (2 ml) was stirred at room temperature for 30 min. Sodium triacetoxoborohydride (0.092 g, 0.43 mmol) was added to the solution and the mixture was stirred at room temperature for 18 h. The mixture was concentrated and the residue was dissolved in ethyl acetate and basified with 1N NaOH to pH=10. The layers were separated and the aqueous phase was extracted twice with ethyl acetate. The combined organic extracts were washed with brine, dried (MgSO₄) and concentrated to give 0.102 g of an off-white solid. The crude solid was chromatographed (hexane/ethyl acetate 4:1) to give 0.018 g of cyclopropylmethyl-[5-(3',4''-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine as a white solid which had: MS: M⁺ 332; NMR (acetone-d₆) δ 7.81 (dd, J = 2.0 Hz, 6.63 Hz, 2H), 7.58 (dd, J = 2.1 Hz, 6.6Hz, 2H), 7.43 (s, 1H), 7.18 (d, J = 7.8 Hz, 1H), 5.85 (s, 1H), 3.62 (s, 3H) 2.97 (t, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 1.09-1.19 (m, 1H), 0.47-0.49 (m, 2H), 0.23-0.25 (m, 2H).

Example 4
The title compounds below were all made by essentially the same procedure as shown in Example 3.

A. Synthesis of [5-(3',4''-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-furan-2-ylmethyl-amine, (4)

The compound of Example 1 was reacted with 2-furaldehyde for a yield of 26%, as a clear oil which had: MS: M⁺ 358; NMR (acetone-d₆) δ 7.80 (dd, J = 2.0, 6.6 Hz, 2H), 7.58 (dd, J = 2.0, 6.6 Hz, 2H), 7.46 (s, 1H), 7.43 (s, 1H), 7.36 (dd, J = 2.0, 8.0 Hz, 1H), 7.19 (d, J = 7.9 Hz), 6.63 (m, 2H), 5.95 (s, 1H), 5.23 (t, 1H), 4.30 (d, J = 5.8 Hz, 2H), 3.64 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H).
B.  **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-3H-imidazole-4-carbaldehyde](5)  
The compound of Example 1 was reacted with 2-methyl-1-(toluene-4-sulfonyl)-1H-imidazole-4-carbaldehyde (Example 32) followed by HCl treatment to yield 8%, as a clear oil.  
The HCl salt had: MS: M⁺ 372; NMR (CD₂OD) δ 7.75 (q, 4H), 7.45 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.43 (s, 0.3H), 4.58 (s, 2H), 3.83 (s, 3H), 2.60 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H).

C.  **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-benzyl](6)  
The compound of Example 1 was reacted with o-tolualdehyde for a yield of 66%, the HCl salt of which had: mp 119° C; MS M⁺ 486; NMR (DMSO-d₆) δ 7.77 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.40 (dd, J = 1.7 Hz, J = 7.5 Hz, 1H), 7.35-7.33 (m, 1H), 7.21-7.14 (m, 4 H), 6.11 (s, 1H), 4.30 (s, 2H), 3.71 (s, 3H), 2.34 (s, 3H), 2.27 (s, 3H).  
Anal. calculated for C₂₆H₂₇N₃HClH₂O: C 71.63; H 6.93; N 9.64. Found C 71.46; H 6.78; N 9.41.

D.  **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[4-methyl-benzyl](7)  
The compound of Example 1 was reacted with p-tolualdehyde for a yield of 34% as a white solid. The HCl salt had: mp 120° C; MS M⁺ 382; NMR (DMSO-d₆) δ 7.77 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.41 (d, J = 7.47 Hz, 1H), 7.30 (d, J = 7.9 Hz, 2H), 7.20 (d, J = 7.9 Hz, 1H), 7.14 (d, J = 7.9 Hz, 2H), 6.15 (br s, 1H), 4.30 (s, 2H), 3.70 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H), 2.23 (s, 3H). Anal. calculated for C₂₆H₂₇N₃HCl 1.5H₂O: C 72.63; H 6.88; N 9.77. Found C 72.39; H 7.01; N 9.55.

E.  **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[3-methyl-benzyl](8)  
The compound of Example 1 was reacted with m-tolualdehyde for a yield of 25%. The HCl salt had: mp 108° C; MS M⁺ 382; NMR (DMSO-d₆) δ 7.73 (d, J = 8.71 Hz, 2H), 7.65 (d, J = 8.71, 2H), 7.45 (s, 1H), 7.38 (dd, J = 7.9, 2.1 Hz, 1H), 7.22-7.17 (m, 4 H), 7.04 (d, 1H), 6.06 (s, 1H) 4.27 (s, 2H), 3.67 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₆H₂₇N₃HCl0.25H₂O: C 73.57; H 7.24; N 9.90. Found: C 73.40; H 6.88; N 9.52.

F.  **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methoxy-benzyl](9)  
The compound of Example 1 was reacted with Using o-anisaldehyde for a yield of 22% as a white solid which had: mp 108° C; MS M⁺ 398; NMR (CDCl₃) δ 7.77 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 7.35-7.25 (m, 3H), 7.17 (d, J = 7.5 Hz, 1H), 5.86 (s, 1H), 4.29 (br s, 2H), 3.87 (s, 3H), 3.68 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H).
G. **Synthesis of** (3-Chloro-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine hydrochloride. (10)

The compound of Example 1 was reacted with 3-chlorobenzoic acid for a yield of 36%. The HCl salt had: mp 115-118°C; MS M⁺ 402; NMR (DMSO-d₆) δ 7.74 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 5.4 Hz, 2H), 7.39-7.33 (m, 3H), 7.29-7.27 (m, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.11 (br s, 1H), 4.33 (s, 2H), 3.69 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₅H₂₄N₃ClHClO.75H₂O: C 66.45; H 5.91; N 9.30. Found: C 66.44; H 5.87; N 9.21.

H. **Synthesis of** (2-Chlorobenzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine hydrochloride. (11)

The compound of Example 1 was reacted with 2-chlorobenzoic acid for a yield of 42%. The HCl salt had: mp 195°C; MS M⁺ 402; NMR (DMSO-d₆) δ 7.75 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.51-7.45 (m, 3H), 7.39 (dd, J = 7.9, 1.7 Hz, 1H), 7.35-7.28 (m, 2H), 7.20 (d, J = 8.3 Hz, 1H), 6.00 (s, 1H), 4.40 (br s, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C₂₅H₂₄N₃ClHClO.25H₂O: C 67.80; H 5.80; N 9.49. Found: C 67.59; H 5.81; N 9.35.

I. **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl][3-methoxy-benzyl]-amine hydrochloride. (12)

The compound of Example 1 was reacted with m-anisaldehyde for a yield of 34%. The HCl salt had: mp 112°C; MS M⁺ 398; NMR (DMSO-d₆) δ 7.75 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.47 (s, 1H), 7.40 (dd, J = 7.9, 1.7 Hz, 1H), 7.27-7.19 (m, 3H), 6.99-6.98 (m, 2H), 6.51 (dd, J = 2.5, 8.3 Hz, 1H), 6.07 (brs, 1H), 4.30 (s, 2H), 3.73 (s, 3H), 3.69 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C₂₆H₂₇N₃O.HClO.2H₂O: 69.09; H 6.69; N 9.30. Found: C 69.26; H 6.27; N 8.97.

J. **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl][2h-thiophen-2-ylmethyl-amine hydrochloride. (13)

The compound of Example 1 was reacted with 2-thiophene carboxaldehyde for a yield of 33%. The HCl salt had: mp 186°C; MS M⁺ 374; NMR (DMSO-d₆) δ 7.73(d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.39-7.36 (m, 2H), 7.18 (d, 1H), 7.11 (d, 1H), 6.96-6.94 (m, 1H), 6.11 (s, 1H), 4.47 (s, 2H), 3.62 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₆H₂₅N₃S.HClO.5H₂O: 65.93; H 6.01; N 10.03. Found: C 68.16; H 5.74; N 9.61.

K. **Synthesis of** [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl][2pyridin-2-ylmethyl-amine hydrochloride. (14)

The compound of Example 1 was reacted with 2-pyridine carboxaldehyde for a yield of 14%. The HCl salt had: mp 194°C (dec); MS M⁺ 369; NMR (DMSO-d₆) δ 8.76 (d, J = 5.0 Hz, 1H), 8.37-8.33 (m, 1H), 7.93 (d, J = 8.3 Hz, 1H), 7.78-7.75 (m, 1H), 7.70 (d, J = 8.7 Hz, 2
H), 7.61 (d, J = 8.7 Hz, 2H), 7.43 (s, 1H), 7.36 (dd, J = 7.9, 2.1 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 6.03 (s, 1H), 4.66 (s, 2H), 3.72 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H). Anal. calculated for C_{26}H_{26}N_{6}HClO.25H_{2}O: C 64.54; H 5.99; N 12.56. Found: C 64.41; H 5.93; N 12.40.

L. Synthesis of (2,4-Dichloro-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine hydrochloride, (15)

The compound of Example 1 was reacted with 2,4-dichlorobenzaldehyde for a yield of 31%. The HCl salt had: mp 217°C; MS M+ 436, 438; NMR (DMSO-d6) δ 7.76 (d, J = 8.3 Hz, 2H), 7.66-7.62 (m, 3H), 7.49-7.45 (m, 2H), 7.41-7.36 (m, 2H), 7.18 (d, J = 8.3 Hz, 1H), 6.07 (s, 1H), 4.37 (s, 2H), 3.71 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C_{25}H_{23}Cl_{2}N_{3}HClO.25H_{2}O: C 62.91; H 5.17; N 8.80. Found: C 63.01; H 4.97; N 8.53.

M. Synthesis of [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-3-ylmethyl-amine hydrochloride, (16)

The compound of Example 1 was reacted with 3-pyridine carboxaldehyde for a yield of 24%. The HCl salt had: mp 227°C; MS M+ 369; NMR (DMSO-d6) δ 8.96 (s, 1H), 8.79 (d, J = 5.0 Hz, 1H), 8.58 (d, J = 8.3 Hz, 1H), 8.02-7.99 (m, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.3 Hz, 2H), 7.44 (s, 1H), 7.37 (dd, J = 1.7, 7.9 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.11 (s, 1H), 4.53 (s, 2H), 3.72 (s, 3H), 2.24 (s, 3H), 2.21 (s, 3H). Anal. calculated for C_{24}H_{24}N_{4}HClO.2H_{2}O: C 62.73; H 6.14; N 12.19. Found: C 62.89; H 5.87; N 12.02.

N. Synthesis of [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-4-ylmethyl-amine hydrochloride, (17)

The compound of Example 1 was reacted with 4-pyridine carboxaldehyde for a yield of 7%. The HCl salt had: mp 182°C (dec); MS M+ 369; NMR (DMSO-d6) δ 8.85 (d, J = 6.6 Hz, 2H), 8.03 (d, J = 6.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 5.83 (s, 1H), 4.62 (s, 2H), 3.72 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H).

O. Synthesis of Benzol[1,3]dioxol-5-ylmethyl-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine, (18)

The compound of Example 1 was reacted with piperonal for a yield of 28%. The HCl salt had: mp 204°C; MS M+ 412; NMR (DMSO-d6) δ 7.76 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.30 Hz, 2H), 7.48 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 6.99 (s, 1H), 6.91-6.85 (m, 2H), 6.12 (br s, 1H), 5.96 (s, 2H), 4.23 (s, 2H), 3.68 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C_{28}H_{26}N_{5}O_{2}HClO.25H_{2}O: C 69.02; H 6.06; N 9.24. Found: C 69.12; H 6.06; N 9.24.

P. Synthesis of (3,4-Dimethoxy-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine, (19)

The compound of Example 1 was reacted with 3,4-dimethoxybenzaldehyde for a yield of 26%. The HCl salt had: mp 110°C; MS M+ 428; NMR (DMSO-d6) δ 7.81 (d, J = 8.3 Hz,
2H), 7.71 (d, J = 8.7 Hz, 2H), 7.49 (s, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.05 (s, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.25 (br s, 1H), 4.28 (s, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H). Anal. calculated for C_{27}H_{26}N_{3}O_{2}·HCl: C 68.56; H 6.61; N 8.88. Found: C 68.84; H 7.02; N 8.45.

Q. Synthesis of (2,4-Dimethoxybenzyl)-(5-(3',4'-dimethyl-biphenyl-4-y1)-2-methyl-2H-pyrazol-3-yl)-amine, (20)

The compound of Example 1 was reacted with 2,4-dimethoxybenzaldehyde for a yield of 11%. The HCl salt had: mp 177°C; MS M+ 428; NMR (DMSO-d6) δ 7.77 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.23-7.19 (m, 2H), 6.57 (d, J = 2.1 Hz, 1H), 6.48 (dd, J = 2.1 Hz, 8.3 Hz, 1H), 6.08 (s, 1H), 4.21 (s, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C_{27}H_{26}N_{3}O_{2}·HCl: C 68.56; H 6.61; N 8.88. Found: C 68.60; H 6.61; N 8.81.

R. Synthesis of (2,3-Dihydro-benzof[1,4]dioxin-6-ylmethyl)-(5-(3',4'-dimethyl-biphenyl-4-y1)-2-methyl-2H-pyrazol-3-yl)-amine hydrochloride, (21)

The compound of Example 1 was reacted with 1,4-benzodioxan-6-carboxaldehyde for a yield of 32%. The HCl salt had: mp 214°C; MS M+ 426; NMR (DMSO-d6) δ 7.79 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.47 (s, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.86 (dd, J = 2.1, J = 8.3 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.22 (s, 1H), 4.16 (s, 4H), 3.70 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Anal. calculated for C_{27}H_{26}N_{3}O_{2}·HCl: C 69.52; H 6.16; N 9.01. Found: C 69.79; H 6.38; N 8.86.

Example 5: Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-y1)-2-methyl-2H-pyrazol-3-yl]-nicotinamide hydrochloride, (22)

A mixture of nicotinic acid (0.025 g, 0.20 mmol) and 1-hydroxybenzotriazole hydrate (0.050 g, 0.33 mmol) in DMF (2 ml) was stirred for 5 min at room temperature. To the solution was added 5-(3',4'-dimethyl-biphenyl-4-y1)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.060 g, 0.21 mmol). After the mixture had stirred for 30 min, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.060 g, 0.21 mmol) was added and stirring was continued for 5 days at room temperature. The mixture was diluted with water (10 ml) and extracted with ethyl acetate. The organic phase was washed with water (5x), 1N NaOH, dried (MgSO4) and concentrated to give 80 mg of a yellow oil. The crude residue was chromatographed (methylene chloride:MeOH 98:2 to 95:5) to give 21 mg of an off-white solid that was triturated with methanol to give 15 mg of a white solid. This free base was dissolved in methylene chloride:methanol, and treated with 4M HCl in dioxane (2 eq.). After stirring for 5 min at room temperature, the solution was concentrated to dryness and reconverted from ethanol (2x) to give 16 mg of the title compound as a white solid which had: mp 215°C (dec); MS: M+ 383; NMR (DMSO-d6) δ 9.15 (s, 1H), 8.80 (dd, J = 1.6, 5.0 Hz, 1H), 8.37 (d, J = 8.7 Hz, 1H), 7.82
(d, J = 8.3 Hz, 2H), 7.61-7.65 (m, 3H), 7.45 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.76 (s, 1H), 3.52 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H).

Example 6

The title compounds below were all made by essentially the same procedure as shown in Example 5.

A. **Synthesis of Pyridine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide hydrochloride. (23)**

The compound of Example 1 was reacted with 2-picolinic acid for a yield of 53%. The HCl salt had: mp 176° C (dec); MS: M⁺ 383; NMR (CD3OD) δ 8.75 (d, 1H), 8.33 (d, 1H), 8.07 (t, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.65 (m, 3H), 7.41 (s, 1H), 7.37 (d, 1H), 7.18 (d, 1H), 6.89 (s, 1H), 5.45 (s, 0.75 H), 3.90 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H).

B. **Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-isonicotinamide. (24)**

The compound of Example 1 was reacted with isonicotinic acid for a yield of 13%. The HCl salt had: mp 240° C; MS: M⁺ 381; NMR (DMSO-d6) δ 8.81 (d, J = 6.2 Hz, 2H), 7.91 (d, J = 6.2 Hz, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.45 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.76 (s, 1H), 3.75 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H).

C. **Synthesis of Furan-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide. (25)**

The compound of Example 1 was reacted with 2-furoic acid for a yield of 26%. The HCl salt had: mp 167° C; MS: M⁺ 372; NMR (acetone-d6) δ 9.48 (br s, 0.5H), 7.87 (dt, J = 1.7, 8.7 Hz, 2H), 7.79 (m, 1H), 7.64 (dt, J = 1.7, 8.7 Hz, 2H), 7.45 (s, 1H), 7.38 (dd, J = 2.1, 5.8 Hz, 1H), 7.26 (d, J = 3.3 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 6.66-6.69 (m, 2H), 3.82 (s, 3H), 2.30 (s, 3H), 2.26 (s, 3H).

**Example 7: Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-4-fluoro-benzamide. (26)**

To a solution of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 111 mg, 0.400 mmol) and 2,6-lutidine (0.049 mL, 0.421 mmol) in methylene chloride (5 mL) at 0° C was added 4-fluorobenzyol chloride (0.05 mL, 0.421 mmol) and the mixture was allowed to warm to ambient temperature and stirred for 4 days. The reaction was quenched with saturated sodium bicarbonate solution and the aqueous mixture was extracted 3 times with CHCl₃. The combined organic phases were dried over MgSO₄, filtered and concentrated to give 116 mg of crude product. This material was washed with a minimum volume of EtOAc to give 81 mg (51%) of N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-4-fluoro-benzamide which had: mp > 250° C; MS M⁺ 400; NMR (DMSO-d6) δ 8.08-8.04 (m, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.47 (s, 1H), 7.41-7.36 (m, 3H), 7.20 (d, J = 7.8 Hz, 1H), 6.73 (s, 1H), 3.74 (s, 3H), 2.27 (s, 3H), 2.23
(s, 3H). Anal. calculated for C_{28}H_{22}N_{3}OF: 0.5 H_{2}O: C 73.51; H 5.68; N 10.29. Found: C 73.75; H 5.58; N 10.24.

**Example 8**

The title compounds below were all made by essentially the same procedure as shown in Example 7.

**A. Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-4-methoxy-benzamide.**

The compound of Example 1 was reacted with p-anisoyl chloride for a yield of 78%. Trituration with ethyl acetate gave a white solid which had: mp 205°C; MS M^+ 412; NMR (DMSO-d_6) δ 7.96 (dd, J = 9.1, J = 2.1 Hz, 2H), 7.81 (dd, J = 8.7, 2.1 Hz, 2H), 7.63 (dd, J = 8.3, 1.7 Hz, 2H), 7.45 (s, 1H), 7.38 (dd, J = 7.9, 1.7 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.05 (dd, J = 6.6, 1.7 Hz, 2H), 6.69 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Anal. calculated for C_{28}H_{22}N_{3}O_{2}.05 H_{2}O: C 75.07; H 6.18; N 10.10. Found: C 75.01; H 5.88; N 10.02.

**B. Synthesis of Benzo[1,3]dioxole-5-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide.**

The compound of Example 1 was reacted with piperonyl chloride and triethylamine in place of 2,6-lutidine for a yield of 45%. Material recrystallized from ethyl acetate/hexanes had: mp 199°C; MS M^+ 426; NMR (DMSO-d_6) δ 7.83 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.7 Hz, 2H), 7.61 (dd, J = 1.7, 7.8 Hz, 1H), 7.52 (s, 1H), 7.52 (d, J= 5.8 Hz, 1H), 7.44 (dd, J = 7.9, 1.7 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 6.72 (s, 1H), 6.14 (s, 2H), 3.73 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H). Anal. calculated for C_{28}H_{22}N_{3}O_{3}.25 H_{2}O: C 72.63; H 5.51; N 9.77. Found: C 72.48; H 5.27; N 9.57.

**C. Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-3,4-dimethoxy-benzamide.**

The compound of Example 1 was reacted with 3,4-dimethoxybenzoyl chloride for a yield of 41%. Recrystallization from ethyl acetate/hexane gave a white solid which had: mp 179°C; MS M^+ 442; NMR (DMSO-d_6) δ 7.81 (d, J = 8.3 Hz, 2H), 7.65-7.61 (m, 3H), 7.54 (d, J = 1.7 Hz, 1H), 7.46 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 3.81 (s, 6H), 3.71 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Anal. calculated for C_{27}H_{27}N_{3}O_{3} 2.5 H_{2}O: C 66.65; H 6.52; N 8.64. Found: C 66.29; H 6.15; N 8.55.

**D. Synthesis of N-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-3,4-dimethoxy-benzamide.**

The compound of Example 1 was reacted with 2,4-dimethoxybenzoyl chloride and 2,6-lutidine in methylene chloride for a yield of 44% as a white solid which had: mp 202°C; MS M^+ 442; NMR (DMSO-d_6) δ 9.97 (s, 1H), 7.85-7.79 (m, 3H), 7.63 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 6.77 (s, 1H), 6.71 (d, J = 2.1 Hz,
1H), 6.67 (dd, J = 2.1, 8.7 Hz, 1H), 3.96 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Anal. calculated for C_{72}H_{77}N_{3}O_{5}: C 73.45; H 6.16; N 9.52. Found: C 73.34; H 6.31; N 9.31.

**Example 9:** Synthesis of 2-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-isoindole-1,3-dione, (31)

A mixture of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.090 g, 0.32 mmol) and phthalic anhydride (0.047 g, 0.32 mmol) in DMF (3 ml) was heated at 143°C for 17 h. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic phase was washed with water (5x), dried (MgSO₄) and concentrated to give 0.124 g of an off-white solid. The solid was recrystallized first from ethyl acetate:hexane, and then ethyl acetate to give 41 mg (31%) of 2-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-isoindole-1,3-dione as a white solid which had: mp 183° C (dec.); MS: M⁺ 408; NMR (CDCl₃) δ 7.99-8.02 (m, 2H), 7.84-7.87 (m, 3H), 7.61 (dd, J = 2.1 Hz, 6.7 Hz, 2H), 7.39 (s, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.64 (s, 1H), 3.86 (s, 3H), 2.31 (s, 3H), 2.28 (s, 3H).

**Example 10**

The title compounds below were all made by essentially the same procedure as shown in Example 9.

A. Synthesis of 2-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyrrolo[3,4-c]pyridine-1,3-dione, (32)

The compound of Example 1 was reacted with 3,4-pyridinedicarboxylic anhydride for a yield of 53% as a yellow solid which had: mp 205-7° C; MS: M⁺ 409; ¹H NMR (DMSO-d₆) δ 9.29 (s, 1H), 9.20 (d, J = 5.0 Hz, 1H), 8.05 (d, J = 5.0Hz), 1H), 7.86 (d, J = 8.8Hz, 2H), 7.69 (d, J = 8.3Hz, 2H); 7.49 (s, 1H), 7.42 (d, J = 7.9Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 6.86 (s, 1H), 3.79 (s, 1H), 2.28 (s, 3H), 2.24 (s, 3H).

B. Synthesis of 6-[5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyrrolo[3,4-b]pyridine-5,7-dione, (33)

The compound of Example 1 was reacted with 2,3-pyridinedicarboxylic anhydride: product was a white solid which had: mp 178° C (dec); MS: M⁺ 409; ¹H NMR (DMSO-d₆) δ 9.05 (dd, J = 1.2Hz, 4.5Hz, 1H); 8.42 (dd, J = 1.2Hz, 7.4 Hz, 1H); 7.84 (m, 1H); 7.83 (d, J = 8.3Hz, 2H), 7.75 (d, J = 8.3Hz, 2H), 7.46 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H); 6.82 (s, 1H), 3.76 (s, 3H), 2.21 (s, 3H), 2.25 (s, 3H).

**Example 11:** Synthesis of 5-[3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-4-fluoro-benzamide hydrochloride, (34)

To a solution of N-[5-(3',4'-dimethyl-biphenyl-4-yl)]-2-methyl-2H-pyrazol-3-yl]-4-fluoro benzamide (Example 7) (54 mg, 0.135 mmol) in THF (5 mL) was added lithium aluminum hydride (1M THF solution, 0.135 mL, 0.135 mmol) at 0° C. After 30 minutes the solution was
warmed to room temperature and more LAH solution (0.135 mL, 0.135 mmol) was added. The reaction was gently refluxed for 5 h and became bright yellow. The reaction was cooled and carefully quenched by addition of sodium sulfate decahydrate. Anhydrous sodium sulfate was added and the mixture was stirred overnight, then filtered through Celite with CHCl₃ and methanol rinses. The filtrate was concentrated to afford 55 mg of a tan solid. The solid was chromatographed (hexane/ethyl acetate 4:1 and then 2:1) and the recovered free base product was treated with HCl to give 35 mg (61%) of the title product which had: mp > 210° C; MS M⁺ 386; NMR (DMSO-d₆) δ 7.73 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.47-7.44 (m, 3H), 7.39 (d, 1H), 7.21-7.14 (m, 3H), 5.99 (br s, 1H), 4.29 (s, 2H), 3.66 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C₂₅H₂₄N₃F⁻·HCl·0.25 H₂O: C 70.41; H 6.03; N 9.85. Found: C 70.18; H 6.16; N 9.50.

**Example 12**

The compounds below were all made by essentially the same procedure as shown in Example 11.

A. **Synthesis of [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-(4-methoxy-benzyl)-amine hydrochloride. (35)**

The compound of Example 1 was reacted with N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-4-methoxy-benzamide (Example 8A) for a yield of 48%. The HCl salt had: mp 183° C; MS M⁺ 398; NMR (DMSO-d₆) δ 7.75 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.46 (s, 1H), 7.38 (dd, J = 2.1, 7.9 Hz, 1H), 7.32 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 5.0, 2.9 Hz, 2H), 6.12 (br s, 1H), 4.24 (s, 2H), 3.69 (s, 3H), 3.66 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₅H₂₇N₃O·HCl: C 71.96; H 6.50; N 9.68. Found: C 71.85; H 6.57; N 9.63.

B. **Synthesis of (4-Chloro-benzyl)[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine hydrochloride. (36)**

The compound of Example 1 was reacted with 4-chloro-N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-benzamide for a yield of 28%. The salt had: mp > 200° C; MS M⁺ 400, 402; NMR (DMSO-d₆) δ 7.73 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.45-7.36 (m, 6H), 7.18 (d, J = 7.9 Hz, 1H), 6.05 (s, 1H), 4.31 (s, 2H), 3.67 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₅H₂₅N₂Cl·HCl: C 68.49; H 5.75; N 9.58. Found: C 68.24; H 5.92; N 9.17.

**Example 13:** **Synthesis of [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl][2-(2-methoxy-ethoxy)-ethyl]-amine hydrochloride. (37)**

2-(2-Methoxyethoxy) acetic acid (0.681 mmol) was dissolved in 5 mL THF. Oxalyl chloride (0.681 mmol) was added followed by catalytic dimethylformamide. After 20 minutes stirring at room temperature, 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.592 mmol) was added, followed by triethylamine (1.3 mmol). A white solid
formed and the reaction was stirred overnight. After 16 hours the reaction was quenched by addition of saturated sodium bicarbonate solution (15 mL). The aqueous phase was extracted with chloroform (3 x 15 mL). The combined organic layers were dried over magnesium sulfate, and concentrated to give 256 mg (92%) of [5-(3',4'-dimethyl-biphenyl-4-y1)-2-methyl-2H-pyrazol-3-yl]-[2-(2-methoxy-ethoxy)-ethyl]-amide as a white solid. To this material in THF (7 mL) at room temperature was added dropwise 1M (THF) lithium aluminum hydride (0.495 mmol). After 2h reflux the mixture was cooled to room temperature and sodium sulfate decahydrate was added to quench the excess lithium aluminum hydride. Anhydrous sodium sulfate was added as a drying agent and the mixture was diluted with ethyl acetate and methanol (5 mL each). This mixture was stirred overnight and then filtered through Celite and concentrated to give 189 mg of desired product as an orange oil. Silica gel chromatography with hexanes/ethyl acetate (2:1 followed by 1:1) and then straight ethyl acetate gave 119 mg (70%) of material which was dissolved in 5 mL methanol and treated with 4N HCL/dioxane solution (0.627 mmol). After stirring 15 minutes, the solution was concentrated and the resulting oil was crystallized from ethyl acetate to give 69 mg (53%) of [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-(2-methoxy-ethoxy)-ethyl]-amine hydrochloride which had: mp 115°C; MS M⁺ 380; NMR (DMSO-d₆) δ 7.82 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.41-7.39 (dd, J = 7.9, 1.7 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.3 (s, 1H) 3.66 (s, 3H), 3.56-3.51 (m, 4H), 3.42-3.39 (m, 2H), 3.30-3.27 (m, 2H), 3.19 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H). Anal. calculated for C₂₃H₂₀N₃O₂·HCl: C 66.41; H 7.27; N 10.10. Found: C 66.33; H 7.25; N 10.13.

Example 14: Synthesis of [5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[(2-methyl-cyclopropymethyl)-amine. (38)]

The title compound was prepared according to the method of Example 13 with 2-methylcyclopropane carboxylic acid for a yield of 50% as a white solid. The HCl salt had: mp 195°C; MS M⁺ 348; NMR (DMSO-d₆) δ 7.84 (d, J = 8.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.48 (s, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.39 (d, J = 2.1 Hz, 1H), 6.31 (br s, 1H) 3.68 (s, 3H), 3.05-2.95 (m, 2H), 2.25 (s, 3H), 2.21 (s, 3H), 0.98 (d, J = 5.8 Hz, 3H), 0.81-0.76 (m, 1H), 0.69-0.63 (m, 1H). Anal. calculated for C₂₃H₂₇N₃·HCl: C 72.33; H 7.39; N 11.00. Found: C 72.10; H 7.37; N 10.98.

Example 15: Synthesis of 2,3-Dihydro-benzo[1,4]dioxine-6-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-4H-pyrazol-3-yl]-amide. (39)

The title compound was prepared using the amide formation method described in Example 13 (without the final LAH reduction) using 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid for a yield of 66% as a white solid which had: mp 195°C; MS M⁺ 440; NMR (DMSO-d₆) δ 7.82 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.53 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.47 (s, 1H), 7.39 (d, J = 8.3 Hz, 1H) 7.20 (d, J = 7.9 Hz, 1H) 6.99 (d, J =
8.3 Hz, 1H) 6.70 (s, 1H) 4.32-4.28 (m, 4H), 3.71 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H). Anal. calculated for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>·0.25HCl: C 73.04; H 5.79; N 9.46. Found: C 72.98; H 5.59; N 9.42.

**Example 16:** Synthesis of 3-(3',4'-dimethyl-biphenyl-4-yl)-1-methyl-1H-pyrazole, (40)

To an ice cold slurry of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.150 g, 0.54 mmol) in 6N HCl (3 ml) was added a solution of sodium nitrite (0.048 g, 0.70 mmol) in water dropwise over 10 min. Water (2 x 0.1 ml) was used to complete the transfer. The solution turned deep orange in color as the nitrite was added, and the mixture did not become homogeneous. After stirring 15 min, the diazonium solution was then added dropwise to a beaker containing hypophosphorous acid (6 ml) at 0° C over 10 min. The transfer was completed with 6N HCl. The mixture was stirred for 2 h without replenishing the ice bath. The mixture was extracted with diethyl ether (3×). The combined organic extracts were washed with water and saturated aqueous sodium bicarbonate, dried (MgSO<sub>4</sub>) and concentrated to give 26 mg of a brown oil. The crude residue was chromatographed (hexane/ethyl acetate 3:1) to give 15 mg of an oily solid that was triturated with hexane to give 7 mg of 3-(3',4'-dimethyl-biphenyl-4-yl)-1-methyl-1H-pyrazole as a white solid which had: MS: M<sup>+</sup> 263; NMR (acetone-d<sub>6</sub>) δ 7.86 (d, J = 8.3 Hz, 2H), 7.59-7.63 (m, 3H), 7.44 (s, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 2.5 Hz, 1H), 3.90 (s, 3H), 2.29 (s, 3H).

**Example 17:** Synthesis of N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-acetamide, (41)

To a solution of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.050 g, 0.18 mmol) and 2,6-lutidine (0.023 ml, 0.20 mmol) in methylene chloride (2 ml) at 0° C was added acetyl chloride (0.014 ml, 0.20 mmol). The mixture was stirred for 18 h, gradually warming to room temperature. Following concentration, the residue was dissolved in warm ethyl acetate and washed once each with water, 1N HCl and brine. The organic phase was dried (MgSO<sub>4</sub>) and concentrated to yield 58 mg of an off-white solid. Trituration with hot ethyl acetate gave 28 mg of N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-acetamide as an off-white solid which had: mp 163°C (dec); MS: M<sup>+</sup> 320; NMR (DMSO-d<sub>6</sub>) δ 9.92 (s, 1H), 7.76 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.44 (s, 1H), 7.36 (dd, J = 1.6, 7.5 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.61 (s, 1H), 3.67 (s, 3H), 2.25 (s, 3H).

**Example 18:** Synthesis of Pyrazine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide, (42)

A mixture of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.060 g, 0.21 mmol) and 2,3-pyrazinedicarboxylic anhydride (0.032 g, 0.21 mmol) in DMF (2 ml) was heated at 110° C for 17 h. After cooling to room temperature the reaction mixture
was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (5x), dried (MgSO₄) and concentrated to give 97 mg of a brown solid. The crude residue was triturated with ethyl acetate to give 23 mg of pyrazine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide as a tan solid which had: mp 183-5⁰ C; MS: M⁺ 372; NMR (DMSO-d₆) δ 9.28 (s, 1H), 8.89 (d, J = 2.5 Hz, 1H), 8.78 (dd, J = 1.6, 2.5 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.45 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.75 (s, 1H), 3.74 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H). Anal. calcd. for C₂₉H₂₅N₅O · 3/4H₂O: C 69.59; H 5.71; N 17.64. Found: C 69.65; H 5.46; N 17.22.

Examle 19: Synthesis of 3-(3',4'-Dimethyl-biphenyl-4-yl)-1,5-dimethyl-1H-pyrazole (43)

To a stirred mixture of ethyl acetate (0.399 ml, 4.46 mmol) and sodium hydride (60% oil dispersion, 0.178 g, 4.46 mmol) in THF (3 ml) was added 1 drop of ethanol, 1-(3,4-dimethyl-biphenyl-4-yl)-ethanone (see Example 28, 0.50 g, 2.23 mmol) in THF (2 ml) and dibenzo-18-crown-6 (0.013 g, 0.036 mmol) in THF (2 ml). The mixture was stirred for 35 min at room temperature and then heated at reflux for 2 h. The mixture was allowed to cool to room temperature, diluted with ethyl acetate and washed with water, dried (MgSO₄) and concentrated. The crude residue was chromatographed (hexane:ethyl acetate 4:1) to give 211 mg of a 1:1 mixture of 1-(3',4'-dimethyl-biphenyl-4-yl)-butane-1,3-dione and starting material which was used in the next step without further purification. MS: M⁺ 267.

A mixture of the crude 1-(3',4'-dimethyl-biphenyl-4-yl)-butane-1,3-dione (0.21 g, 0.79 mmol) and methylhydrazine (0.126ml, 2.36 mmol) in methanol (3 ml) were heated at reflux for 22 h. The mixture was concentrated and the residue was dissolved in ethyl acetate and washed with water (3x). The organic phase was dried (MgSO₄) and concentrated to give 0.27 g of amber oil. The crude residue was chromatographed (hexane:ethyl acetate 6:1) to give 100 mg of a 1:1 mixture of N-methyl regioisomers which were separated by preparative HPLC: (Chiralpak AD column 5cm x 25cm, heptane/ethanol (9:1), 50 ml/min).

Regioisomer 1 had a retention time of 12 min and was determined by NOE experiment to be 5-(3',4'-dimethyl-biphenyl-4-yl)-1,3-dimethyl-1H-pyrazole: mp 107-9⁰ C; MS: M⁺ 277 NMR (acetone-d₆) δ 7.72 (dd, J = 2.0, 6.2 Hz, 2H), 7.54 (dd, J=2.0, 6.3 Hz, 2H), 7.48 (s, 1H), 7.41 (dd, J = 2.0, 7.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.13 (s, 1H), 3.81 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H), 2.18 (s, 3H).

Regioisomer 2 had a retention time of 24 min and was determined by NOE experiment to be 3-(3',4'-dimethyl-biphenyl-4-yl)-1,5-dimethyl-1H-pyrazole: mp 132° C; MS: M⁺ 277; NMR (acetone-d₆) δ 7.82 (dd, J = 2.0, 6.2 Hz, 2H), 7.60 (dd, J = 2.0, 6.6 Hz, 2H), 7.44 (s, 1H), 7.37 (dd, J = 2.0, 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.41 (s, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H).
Example 20: Synthesis of 6-(3',4'-Dimethyl-biphenyl-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazole hydrochloride, (44)

A mixture of 3-(3',4'-dimethyl-biphenyl-4-yl)-3-oxo-propionitrile (Example 28, 1.00g, 4.01 mmol) and hydroxyethyldihydrazine (0.815 ml, 12.0 mmol) in methanol (40 ml) was heated at reflux for 18 h. After cooling to room temperature the precipitated solid was collected by filtration to give 0.602 g of 2-[5-amino-3-(3',4'-dimethyl-biphenyl-4-yl)-pyrazol-1-yl]-ethanol as a white solid which had: mp 214° C (dec.); MS: M⁺ 308; NMR (DMSO-d₆) δ 8 7.65 (dd, J = 2.0, 6.6 Hz, 2H), 7.55 (dd, J = 2.0, 6.6 Hz, 2H), 7.40 (s, 1H), 7.32 (dd, J = 1.6, 7.5 Hz, 2H), 7.15 (d, J = 7.8 Hz, 1H), 5.67 (s, 1H), 5.15 (s, 2H), 4.93 (t, 1H), 3.91 (t, 2H), 3.65 (q, 2H), 2.23 (s, 3H), 2.19 (s, 3H).

To a slurry of 2-[5-amino-3-(3',4'-dimethyl-biphenyl-4-yl)-pyrazol-1-yl]-ethanol (0.15 g, 0.49 mmol) in THF (6 ml) and methanol (2 ml) was added 4M HCl in dioxane (0.61 ml, 2.44 mmol) in one portion. The mixture became homogeneous and was stirred at room temperature for 5 min. The solution was concentrated to dryness and reconstituted from ethanol (2x) and methylene chloride (1x). The salt was dissolved in chloroform (3 ml) and thionyl chloride (0.107 ml, 1.46 mmol) was added to the stirring solution in one portion. The reaction mixture was heated at reflux for 18 h. The reaction mixture was concentrated to dryness and reconstituted from chloroform (3x) to give 0.176 g of a 1:1 mixture of starting material and 2-(2-chloro-ethyl)-5-(3',4'-dimethyl-biphenyl-4-yl)-2H-pyrazol-3-ylamine. The crude mixture was used in the next step without further purification.

To 2-(2-chloro-ethyl)-5-(3',4'-dimethyl-biphenyl-4-yl)-2H-pyrazol-3-ylamine (0.176 g, 0.54 mmol) in acetonitrile (6ml) and DMF (2 ml) was added sodium iodide (0.081 g, 0.54 mmol) and triethylamine (0.226 ml, 1.62 mmol) and the mixture was heated at 110° C for 18 h. The mixture became homogeneous during the course of reflux. The reaction mixture was concentrated and the residue was dissolved in ethyl acetate. The organic phase was washed with 1N NaOH. The aqueous phase was back-extracted with ethyl acetate (2x). The combined organic extracts were washed with water (5x), dried (MgSO₄) and concentrated to give 0.16 g of an oil. The crude residue was chromatographed (ethyl acetate hexane 4:1) to give 25 mg of 6-(3',4'-dimethyl-biphenyl-4-yl)-2,3-dihydro-1H-imidazo[1,2-b]pyrazole. The hydrochloride salt, a white solid, had: mp 197° C (dec.); MS: M⁺ 290; NMR (CD₂OD) δ 7.75-7.76 (m, 4H), 7.43 (s, 1H), 7.37 (dd, J = 2.0, 7.8 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 6.22 (s, 0.2H), 4.31 (m, 2H), 4.15 (m, 2H), 2.31 (s, 3H), 2.28 (s, 3H).

Example 21
To the acid (0.15 mmol) were added 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 20.8 mg, 0.075 mmol) dissolved in 0.375 ml of dimethyl acetamide (DMA), benzotriazole-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU, 0.1575 mmol, 59.07 mg, 1.05 equiv) in 0.3 ml of DMA, and 0.0627 ml of distilled triethylamine. The reaction was heated and shaken at 60°C for 10 hours and at room temperature overnight. The reaction was partitioned between 1.5 ml of 10% NaOH and 3 ml of CH₂Cl₂ (3 times). The combined organic layer was dried over Na₂SO₄ and concentrated to afford the crude coupled product which was purified by preparative HPLC (Column – Waters Symmetry C18, 5 μM, 30 x 150 mm; flow rate 20 mL/min; solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 10-100% B in 15 min then held at 100% B for 4 min). Collection of the product was triggered based on Mass Spectrometric sampling (MicroMass Platform LCMS system). Concentration of the sample afforded the product as a trifluoroacetate salt. The sample was re-analyzed for purity by HPLC (column: Waters Symmetry C18, 5 μM, 2.1 x 150 mm; flow rate: 0.5 mL/min; solvent: solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 20-100% B in 10 min then held at 100% B for 5 min; detection: UV at 220 nM).

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**Example 22**

![Chemical Structure](image)

The acids below (0.12 mmol) were charged into 1 dram vials with septa. 400 µl dry THF (containing 0.5 % DMF) was added and the vessels were shaken to dissolve acids. Oxalyl chloride as a solution in dry THF (10.1 µl per 100 µl total volume) was added, followed by agitating the vessels for 20 min. at ambient temperature. The vials were vented under a static nitrogen atmosphere to disperse any over-pressurization in reaction vials. The amine 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1) in THF/TEA (21.5 mg per 267 µl THF, 32 µl TEA) was added to each vial. The reactions were shaken at ambient temperature overnight. The reactions were concentrated to 1/2 their original volume under a nitrogen stream; then 2.5 ml CH₂Cl₂ and 1 ml 2 N NaOH were added and the vials were shaken (vortex). The organic layer was separated and passed through a 3 ml SPE cartridge with Na₂SO₄. The extraction/filtration/drying process was repeated twice with CH₂Cl₂. The filtrates were concentrated and the residues were purified by preparative HPLC (Column – Waters Symmetry C18, 5 µM, 30 x 150 mm; flow rate 20 mL/min; solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 10-100% B in 15 min then held at 100% B for 5 min). Collection of the product was triggered based on Mass Spectrometric sampling (MicroMass Platform LCMS system). Concentration of the sample afforded the product as a trifluoroacetate salt. The sample was re-analyzed for purity by HPLC (column: Waters Symmetry C18, 5 µM, 2.1 x 150 mm; flow rate: 0.5 mL/min; solvent: solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 20-100% B in 10 min then held at 100% B for 5 min; detection: UV at 220 nM).
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<td>9.14</td>
<td>358.07</td>
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<tr>
<td>3-Methoxy/cyclohexyl (two diastereomeric products)</td>
<td>440</td>
<td>9.24 and 9.52</td>
<td>418.13</td>
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</tbody>
</table>

**Example 23:**  Synthesis of Pyridine-2-carboxylic acid (2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-yl)-amide, (45)

To a flame-dried flask containing 3-(4-Bromo-phenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole (Example 31) (5.00 g, 16.3 mmol) was added toluene (200 ml). The flask was cooled to -78\(^\circ\) C and a solution of 2.5 M n-butyllithium in hexanes (6.66 ml, 16.65 mmol) was added over 6 min to the bromide with stirring. Tetrahydrofuran (6.3 ml) was added to the solution over 6 min and then stirring was continued for 15 min. A precooled solution of N-methoxy-N-methylacetamide (3.33 ml, 32.7 mmol) in toluene (25 ml) was added to the anion solution and the mixture was stirred for 15 min. The reaction mixture was poured into 1M HCl at 0\(^\circ\) C and stirred for 15 min. The aqueous phase was extracted with ethyl acetate (2x), dried (MgSO\textsubscript{4}) and concentrated to give 4.43 g of an off-white solid that was recrystallized from ethyl acetate/hexane to give 3.83 g of 1-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-ethanone as a white solid which had: MS: M\textsuperscript{+} 299; \(^1\)H NMR (CDCl\textsubscript{3}) \(\delta\) 7.98 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 6.94 (s, 1H), 4.03 (s, 3H), 2.60 (s, 3H).

A solution of 1-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-ethanone in dimethylformamide dimethyl acetal (10 ml) was heated at 120\(^\circ\) C for 17 h. A solid precipitated from the solution during heating. This solid was collected by filtration to give 1.67 g of an off-white solid, 3-dimethylamino-1-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-prop-2-en-1-one: MS: M\textsuperscript{+} 324; \(^1\)H NMR (acetone-d\textsubscript{6}) \(\delta\) 7.97 (d, J = 8.7 Hz, 2H), 7.89 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 12.0 Hz, 1H), 7.27 (s, 1H), 5.85 (d, J = 12.0 Hz, 1H), 4.05 (s, 3H), 3.20 (br s, 3H), 2.95 (br s, 3H).

A mixture of 3-dimethylamino-1-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-prop-2-en-1-one (2.05 g, 6.35 mmol) and hydroxyamine hydrochloride ((0.46 g, 6.66 mmol) in methanol (30 ml) was heated at reflux for 3 h. The reaction mixture was concentrated and the residue was partitioned between methylene chloride and water. The organic phase was dried (MgSO\textsubscript{4}) and concentrated to give 1.82 g of 5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-isoxazole as a white solid: MS: M\textsuperscript{+} 292; \(^1\)H NMR (acetone-d\textsubscript{6}) \(\delta\) 8.46 (d, J = 1.6 Hz, 1H), 8.02 (d, J = 6.6 Hz, 2H), 7.94 (d, J = 6.7 Hz, 2H), 7.32 (s, 1H), 6.90 (d, J = 1.7 Hz, 1H), 4.06 (s, 3H).
A mixture of 5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-isoxazole (1.20 g, 4.1 mmol) and sodium methoxide (0.44 g, 8.2 mmol) in methanol (20 ml) was refluxed for 18 h. After cooling to room temperature, the mixture was concentrated and the residue was partitioned between ethyl acetate and water. The aqueous phase was acidified to pH 2 with 1N HCl and the layers were separated. The aqueous phase was extracted with ethyl acetate (2x). The combined organics were dried (MgSO₄) and concentrated. The residue was triturated with hot ethyl acetate/hexane to give 0.94 g of 3-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-3-oxo-propionitrile: MS: M⁺ 292; ¹H NMR (CDCl₃) δ 7.87-7.97 (m, 4H), 6.96 (s, 1H), 4.07 (s, 2H), 4.05 (s, 3H).

A mixture of 3-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-3-oxo-propionitrile (0.218 g, 0.74 mmol) and methylhydrazine (0.118 ml, 2.23 mmol) in methanol (5 ml) was refluxed for 20 h. After concentration, the residue was chromatographed on silica gel (ethyl acetate: hexane 1:1) to (ethyl acetate: hexane 4:1) to yield 137 mg of an off-white solid that was recrystallized from ethyl acetate: hexane to give 0.11 g of 2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-ylamine as a white solid: mp 197-198.5°C; MS: M⁺ 322; ¹H NMR (acetone-d₆) δ 7.82 (dd, J = 1.7, 6.2 Hz, 2H), 7.76 (dd, J = 2.1, 6.6 Hz, 2H), 7.19 (s, 1H); 5.82 (s, 1H), 4.75 (br s, 2H), 4.03 (s, 3H), 3.63 (s, 3H); Anal. Calc. for C₁₅H₁₄F₃N₅: C 56.07%; H 4.39%; N 21.80%. Found: C 55.67%; H 4.35%; N 21.82%

To a slurry of 2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-ylamine (0.075 g, 0.23 mmol) in methylene chloride (3 ml) was added triethylamine (0.068ml, 0.49 mmol) followed by picolinoyl chloride hydrochloride (0.105 g, 0.49 mmol). The mixture was stirred for 18 h. then diluted with water and extracted with methylene chloride (3x). The combined organics were washed with 0.5 N NaOH, dried (MgSO₄) and concentrated. The residue was recrystallized from ethyl acetate: hexane to give 0.083 g of pyridine-2-carboxylic acid [2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-yl]-amide as a white solid which had: mp 152-4°C; MS: M⁺ 427; ¹H NMR (acetone-d₆) δ 8.70 (dd, J = 0.9, 2.9 Hz, 1H), 8.22 (dt, J = 0.9 Hz, 7.5 Hz, 1H), 8.08 (dt, J = 2.1, 7.9 Hz, 1H), 7.90 (s, 4H), 7.66-7.69 (m, 1H), 7.24 (s, 1H), 6.85 (s, 1H), 4.04 (s, 3H), 3.89 (s, 3H); Anal. Calc. for C₂₁H₁₇F₃N₅O: C 59.15%; H 4.02%; N 19.71% F 13.37%. Found: C 59.22%; H 4.06%; N 19.71% F 13.30%

Example 24: Synthesis of Pyrazine-2-carboxylic acid [2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-yl]-amide

Pyrazine-2-carboxylic acid (0.092 mmol) was charged into 1 dram vials with septa. 400 µl dry THF (containing 0.5 % DMF) was added and the vessels were shaken to dissolve the acid. Oxalyl chloride as a solution in dry THF (8 µl per 100 µl total volume) was added, followed by agitating the vessels for 20 min. at ambient temperature. The vial was vented
under a static nitrogen atmosphere to disperse any over-pressurization in the reaction vial. 2-Methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-ylamine in THF/TEA (19.71 mg per 267 µl THF, 25 µl TEA) was added to the vial. The reaction was shaken at ambient temperature overnight. The reaction was concentrated to 1/2 original volume under a nitrogen stream; then 2.5 ml CH₂Cl₂ and 1 ml 2 N NaOH were added and the vial was shaken (vortex). The organic layer was separated and passed through a 3 ml SPE cartridge with Na₂SO₄. The extraction/filtration/drying process was repeated two times with CH₂Cl₂. The filtrates were concentrated and the residues were purified by preparative HPLC (Column = Waters Symmetry C18, 5 µM, 30 x 150 mm; flow rate 20 mL/min; solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 10-100% B in 15 min then held at 100% B for 5 min). Collection of the product was triggered based on Mass Spectrometric sampling (MicroMass Platform LCMS system). Concentration of the sample afforded the product as a trifluoroacetate salt. The sample was re-analyzed for purity by HPLC (column: Waters Symmetry C18, 5 µM, 2.1 x 150 mm; flow rate: 0.5 mL/min; solvent: solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 20-100% B in 10 min then held at 100% B for 5 min; detection: UV at 220 nm). Potency IC₅₀ (nM) = 450. HPLC retention time (min) 7.73. MS M⁺ observed: 428.01.

Example 25  Synthesis of 5-(4'-Ethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine

DME was filtered through basic alumina. EtOH, DME and water were subjected to vacuum/N₂ cycles to remove O₂ from the solvents. 4-ethylphenyl boronic acid (0.1125 mmol) were charged into 2 dram vial with septa. To the vial was added 1.65 M cesium carbonate in water (0.091 mL, 0.15 mmol, 2.0 eq.), 0.107 M 5-(4-bromo-phenyl)-2-methyl-2H-pyrazol-3-ylamine (Example 30) in EtOH (0.7 mL, 0.075 mmol, 1.0 eq.) and 24 mM tetrakis(triphenylphosphine)palladium in DME (0.125 mL, 0.003 mmol, 0.04 eq.). The reaction was heated to 95°C for 16h in a sealed vial. To the vial was added 0.2 N NaOH (1.5 mL), and CH₂Cl₂ (2.4 mL). After agitation, the organic phase was added to a conditioned (1X MeOH, 2X CH₂Cl₂) 6mL/1g SCX cartridge. The cartridge was washed with CH₂Cl₂ (4 mL) and MeOH (5 mL) and then eluted with 5 mL 1.0N triethylamine in MeOH. The filtrates were concentrated and the residues were purified by preparative HPLC (Column = Waters Symmetry C18, 5 µM, 30 x 150 mm; flow rate 20 mL/min; solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear 10-100% B in 15 min then held at 100% B for 5 min). Collection of the product was triggered based on Mass Spectrometric sampling (MicroMass Platform LCMS system). Concentration of the sample afforded the product as a trifluoroacetate salt. The sample was re-analyzed for purity by HPLC (column: Waters Symmetry C18, 5 µM, 2.1 x 150 mm; flow rate: 0.5 mL/min; solvent: solvent: A = 0.1% aqueous TFA, B = ACN; gradient: linear
20-100% B in 10 min then held at 100% B for 5 min; detection: UV at 220 nM). Potency IC$_{50}$ (nM) = 207. HPLC retention time (min) 7.16. MS M$^+$ observed: 278.25.

**Example 26:** Synthesis of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-methyl-amine. (46)

To a solution of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine (Example 1, 0.30 g, 1.08 mmol) in THF (5ml) at 0$^\circ$ C was added pyridine (0.096 ml, 1.19 mmol), followed by ethyl chloroformate (0.114 ml, 1.19 mmol). The heterogeneous reaction mixture was allowed to stir for 1.25 h, diluted with water and extracted with ethyl acetate. The organic phase was washed with 0.5 N HCl (1x), saturated aqueous sodium bicarbonate (1x), dried and concentrated to give an oil which was recrystallized from ethyl acetate/hexane to give 225 mg of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]carbamic acid ethyl ester as a white solid. MS: M$^+$ 350; $^1$H NMR (CDCl$_3$) $\delta$ 7.78 (dd, J = 2.0, 6.6 Hz, 2H), 7.58 (dd, J = 2.0, 6.6 Hz, 2H), 7.37 (s, 1H), 7.33 (dd, J = 1.7 Hz, 6.5 Hz, 1H), 7.17 (d, J = 7.9 Hz, 1H), 6.51 (br s, 1H), 4.24 (q, 2H), 3.81 (s, 3H), 2.30 (s, 3H), 2.27 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H).

To a solution of 5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]carbamic acid ethyl ester (0.22 g, 0.63 mmol) in THF (5 ml) at 0$^\circ$ C was added a 1M (THF) solution of lithium aluminum hydride (0.69 ml, 0.69 mmol). The ice bath was removed and the reaction mixture was heated for 16 h at reflux. After cooling to room temperature, additional 1M (THF) lithium aluminum hydride (0.60 ml, 0.60 mmol) was added to the reaction mixture and refluxing was continued for 1h. The mixture was quenched with sodium sulfate decahydrate, then dried with sodium sulfate, filtered and concentrated to give an oil that solidified on standing. The solid was triturated with hot ethyl acetate/hexane to give 82 mg of 5-(3',4'-Dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-methyl-amine as an off-white solid: mp 153$^\circ$ C (dec); MS: M$^+$ 292; $^1$H NMR (CDCl$_3$) $\delta$ 7.86 (dd, J = 1.6, 6.2 Hz, 2H), 7.56 (dd, J = 2.1, 6.6 Hz, 2H), 7.37 (s, 1H), 7.33 (dd, J = 2.0, 7.8 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 5.79 (s, 0.7H, partially exchanged), 3.68 (s, 3H), 2.88 9s, 3H), 2.30 (s, 3H), 2.27 (s, 3H).

**Example 27:** Synthesis of 6-(3',4'-Dimethyl-biphenyl-4-yl)-3-methyl-1H-pyrazolo[5,1-c][1,2,4]triazole. (47)

A solution of 3-(3',4'-dimethyl-biphenyl-4-yl)-3-oxo-propionitrile (Example 28, 1.0 g, 4.02 mmol) in dioxane (20ml) at 0$^\circ$ C was saturated with HCl gas for 5 min. The reaction mixture was stirred for 1h and then resaturated with HCl. This sequence was repeated three times and then the mixture was allowed to warm to room temperature and stirred for 16h. Diethyl ether was added to the reaction mixture and the precipitated solid was collected by filtration to give 0.816 g of 2-(3',4'-dimethyl-biphenyl-4-yl)-2-oxo-acetimidic acid ethyl ester hydrochloride as a white solid. MS: M$^+$ 296. $^1$H NMR (CD$_3$OD) $\delta$ 8.04 (d, J = 8.7 Hz, 2H),
7.78 (d, J = 8.7 Hz, 2H), 7.45 (s, 1H), 7.41 (d, 1H), 7.22 (d, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 2.29 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H).

A suspension of 2-(3',4'-dimethyl-biphenyl-4-yl)-2-oxo-acetimidic acid ethyl ester hydrochloride (0.30 g, 0.90 mmol) and acetic hydrazide (0.067 g, 0.90 mmol) was stirred at room temperature for 2 h. To the suspension was added hydrazine, and stirring was continued for 4 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water (3x), dried (MgSO₄) and concentrated. The residue was treated with phosphorous oxychloride (0.084 ml, 0.99 mmol) and the reaction mixture was heated at reflux for 5 h. The mixture was poured over ice, ethyl acetate was added and the layers were separated. After washing with water (3x), triethylamine was added to the organic phase and the basic solution was allowed to stand overnight. The organic phase was washed with 0.5 N HCl dried (MgSO₄) and concentrated to give 220 mg of an oil. The crude residue was chromatographed on silica gel (hexane:ethyl acetate 7:3) to give 42 mg of an oil. Rechromatographed the residue by preparative TLC (2000u silica gel) using methylene chloride:MeOH (98:2) as eluent. Recovered 5mg of a solid which was triturated with ethyl acetate to give 2mg of 6-(3',4'-Dimethyl-biphenyl-4-yl)-3-methyl-1H-pyrazolo[5,1-c][1,2,4]triazole. MS: M⁺ 303. ¹H NMR (CD₃OD) δ 7.87 (dd, J = 1.7, 6.2 Hz, 2H), 7.66 (dd, J = 2.0, 6.6 Hz, 2H), 7.41 (s, 1H), 7.35 (dd, J = 1.6, 7.4 Hz, 1H), 7.17 (d, J = 7.5 Hz, 1H), 2.61 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H).

Example 28: Synthesis of 3-(3',4'-Dimethyl-biphenyl-4-yl)-3-oxo-propionitrile

A mixture of 3,4-dimethylbenzenecoboronic acid (15.0 g, 100.0 mmol), 4-bromoacetophenone (12.3 g, 83.3 mmol), sodium carbonate (35.3 g, 333.4 mmol), and tetrakis(triphenylphosphine)-palladium(0) (4.8 g, 4.2 mmol) in toluene (175 ml), 2-propanol (65 ml) and water (65 ml) was refluxed overnight. Excess alcohol was removed by evaporation and the resulting solution was poured into water and extracted with ethyl acetate. The organic layer was dried (MgSO₄) and concentrated. The residue was chromatographed (hexane/ethyl acetate 9:1) to give a white solid. The solid was recrystallized from iso-propyl ether to afford 15.51 g of 1-(3,4-dimethyl-biphenyl-4-yl)-ethanone as a white granular solid which had: mp 60°C (dec.); MS: M⁺ 225; NMR (CDCl₃) δ 7.98 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.38 (s, 1H), 7.34 (dd, J=1.7, 7.9 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 2.60 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H).

A solution of 1-(3,4-dimethyl-biphenyl-4-yl)-ethanone (14.40 g, 64.3 mmol) in N,N-dimethylformamide dimethyl acetal (30 ml) was heated at 120°C for 22 h. After cooling to room temperature the resulting precipitated solids were collected by filtration and washed with hexane:ethyl acetate 4:1. The solid was recrystallized from ethyl acetate to give 14.70 g of 3-dimethylamino-1-(3,4-dimethyl-biphenyl-4-yl)-prop-2-en-1-one as an off-white solid which had: m.p. 131°C. MS: M⁺ 280; NMR (acetone-d6) δ 7.97 (d, J = 8.3 Hz, 2H), 7.64-7.71 (m,
3H), 7.46 (s, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 5.88 (J = 12.4 Hz, 1H), 3.16 (br s, 3H), 2.94 (br s, 3H), 2.30 (s, 3H), 2.28 (s, 3H).

To a slurry of 3-dimethylamino-1-(3,4-dimethyl-biphenyl-4-yl)-prop-2-en-1-one (12.3 g, 44.0 mmol) in methanol (140 ml) was added of hydroxylamine hydrochloride (3.21 g, 46.2 mmol) in one portion. The mixture was refluxed for 1.5 h, never becoming completely homogeneous. After cooling to room temperature, the mixture was concentrated. The residue was dissolved in methylene chloride and this organic phase was washed with water and brine, dried (MgSO_4) and concentrated to give 10.77 g of 5-(3', 4'-dimethyl-biphenyl-4-yl)-isoxazole as a white solid which had: mp 107°C; MS: M^+ 250; NMR (CDCl_3) δ 8.27 (d, J = 2.1 Hz, 1H), 7.82 (dd, J = 2.0, 6.6 Hz, 2H), 7.65 (dd, J = 2.0, 7.0 Hz, 7.38 (s, 1H), 7.34 (dd, J = 2.0, 7.9 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 6.51 (d, J = 2.0 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

To a slurry of 5-(3', 4'-dimethyl-biphenyl-4-yl)-isoxazole (10.67 g, 42.8 mmol) in methanol (210 ml) was added sodium methoxide (2.31 g, 42.85 mmol) and the mixture was refluxed for 5 h. The solution was cooled to room temperature and additional sodium methoxide (0.96 g, 17.8 mmol) was added and refluxing was continued for an additional 8 h. The mixture was concentrated and the residue was partitioned between water and ethyl acetate. The aqueous phase was acidified to pH 2 with 1N HCl and the phases were separated. The aqueous phase was extracted twice with ethyl acetate and the combined organic extracts were dried (MgSO_4) and concentrated to give 10.70 g of an orange solid. The solid was recrystallized from ethyl acetate/hexane to give 8.88 g of 3-(3', 4'-dimethyl-biphenyl-4-yl)-3-oxo-propionitrile as a yellow solid which had: mp 110-112°C; MS: M^+ 250; NMR (CDCl_3) δ 7.94 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 4.06 (s, 2H), 2.32 (s, 3H), 2.29 (s, 3H). Anal. calc. for C_{17}H_{18}NO: C 81.90; H 6.06; N 5.62. Found: C 81.82; H 6.18; N 5.56.

**Example 29:** Synthesis of 3-(4-Bromo-phenyl)-3-oxo-propionitrile

This compound described above was made by essentially the same procedure as exemplified in Example 28 starting with 4-bromoacetophenone without the initial Suzuki coupling: mp 110-112°C; NMR (DMSO-d_6) δ 7.81 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 4.71 (s, 2H); ^13C NMR (DMSO-d_6) δ 189.69, 134.31, 132.62, 130.99, 129.12, 116.38, 30.76.

**Example 30:** Synthesis of 5-(Bromo-phenyl)-2-methyl-2H-pyrazol-3-ylamine

This compound was made by essentially the same procedure as described in Example 1 starting with (4-bromo-phenyl)-3-oxo-propionitrile (Example 29): mp 155°C; NMR (DMSO-d_6) δ 7.58 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 5.67 (s, 1H), 5.28 (s, 2H), 3.53 (s, 3H); Anal. calc. for C_{16}H_{16}N_3Br: C 47.64; H 3.40; N 16.67. Found: C 47.39; H 3.94; N 16.34.
Example 31: Synthesis of 3-(4-Bromo-phenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole

Potassium t-butoxide (84.6 g, 753.5 mmol) was added in 3 portions over 5 min to a solution of 4-bromoacetophenone (30.0 g, 150.7 mmol) in THF (500 mL). The mixture was cooled in a water bath and ethyl trifluoroacetate (89.7 mL, 753.5 mmol) was added dropwise over 5 min. 18-Crown-6 (7.97 g, 30.1 mmol) was added and the resulting mixture was stirred at rt for 4.5 hrs. The mixture was poured into water (1L), extracted with ethyl acetate (3 x 500 mL), dried over sodium sulfate and concentrated. An additional re concentration from toluene to remove residual water gave 1-(4-bromo-phenyl)-4,4,4-trifluoro-3-hydroxy-but-2-en-1-one as a yellow oil which had: NMR (CDCl₃) δ 7.81 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 9.1 Hz, 2H), 6.55-6.54 (m, 1H). This was dissolved in toluene (500 mL) and hydrazine monohydrate (50 mL) was added dropwise over 5 min. The mixture was heated to 95°C for 14 hr, cooled and concentrated to a yellow-orange solid. Hot hexane (300 mL) was added and the mixture allowed to recol in room temperature. The resulting white precipitate was collected to afford 27.5 g of 3-(4-3-bromo-phenyl)-5-trifluoromethyl-1H-pyrazole. Concentration of the mother liquors and trituration with hexane yielded another 9.4 g of material (total yield = 84%). NMR (CDCl₃) δ 7.61 (d, J = 8.3 Hz, 2H) 7.44 (d, J = 8.7 Hz, 2H), 6.79 (s, 1H).

A mixture of dimethylsulfate (35.7 mL, 377.5 mmol) and 3-(4-3-bromo-phenyl)-5-trifluoromethyl-1H-pyrazole (27.47 g, 94.38 mmol) in toluene (700 mL) was heated for 12.5 h at 100°C, then cooled and poured into 1N NaOH (1L). This was extracted with ethyl acetate (3 x 500 mL) and the extracts were concentrated. Flash chromatography on silica gel using 5-10% ethyl acetate/hexane as eluent followed by evaporation on a vacuum pump for ~60 hrs to remove the residual dimethyl sulfate gave 27.56 g (96%) of 3-(4-bromo-phenyl)-1-methyl-5-trifluoromethyl-1H-pyrazole as a white solid which had: NMR (CDCl₃) δ 7.63 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 6.87 (s, 1H), 4.02 (s, 3H).

Example 32: Synthesis of 2-Methyl-1-(toluene-4-sulfonil)-1H-imidazole-4-carbaldehyde

2-Methyl-3H-imidazole-4-carbaldehyde (2.00 g, 18.16 mmol), triethylamine (3.0 mL, 21.5 mmol) and p-toluenesufonylchloride (3.5 g, 18.36 mmol) were combined in methylene chloride (50 mL) and stirred at rt for 16 h. The reaction was concentrated and the residue partitioned between ethyl acetate and water, the organics were then washed with brine, dried (MgSO₄) and concentrated to give 4.1 g (85%) of 2-methyl-1-(toluene-4-sulfonil)-1H-imidazole-4-carbaldehyde as a yellow solid which had :NMR (CDCl₃) δ 9.79 (s, 1H), 8.04 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.38 (d, J = 8.7 Hz, 2H), 2.53 (s, 3H), 2.44 (s, 3H).
Example 33:

C3a Receptor Binding Assay

The present assay utilizes $^{125}\text{I}$ labeled human C3a peptide (50 pM, New England Nuclear) with detection of binding to a human B-cell line (L1.2) that has been stably transfected with a human C3a receptor construct. The C3aR transfected cell line was generated in the laboratory of Dr. Craig Gerard (Harvard Univ.).

In the assay, approximately 375,000 cells are plated per well in a 96-well plate format (200 µL total volume). In a 96-well plate format, 200 cells and C3a ligand are incubated in assay buffer (20mM HEPES, 125 mM NaCl, 5 mM KCl, 0.5 mM glucose, 0.2% BSA, 1 mM CaCl$_2$, 1 mM MgCl$_2$, pH=7.4) for 45 minutes while shaking on a titer plate shaker at room temperature. Non-specific binding is defined as binding measured following quenching with a 250-fold excess of unlabelled human C3a peptide. The reaction is pelleted by centrifugation (3500 rpm) and terminated by filtration over glass fiber A filters (1% PEI soaked) with ice-cold wash buffer (50 mM HEPES, 1 mM CaCl$_2$, 5 mM MgCl$_2$, 0.5 M NaCl, 0.03% CHAPS). Activity is counted on a Wallac beta scintillation counter. The inhibitor compounds are tested for IC50 potency from 10 µM to 10 pM.

C3a Binding Protocol – Detailed Steps

<table>
<thead>
<tr>
<th>Assay Buffer:</th>
<th>1L</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mM Hepes pH 7.4</td>
<td>4.80g</td>
</tr>
<tr>
<td>125 mM NaCl</td>
<td>7.40g</td>
</tr>
<tr>
<td>5 mM KCl</td>
<td>1.02g</td>
</tr>
<tr>
<td>0.5 mM Glucose</td>
<td>90.10mg</td>
</tr>
<tr>
<td>0.2% BSA (SigmaA7906)</td>
<td>2.00g</td>
</tr>
<tr>
<td>1 mM CaCl$_2$</td>
<td>111mg</td>
</tr>
<tr>
<td>1 mM MgCl$_2$ (hexahydrate)</td>
<td>203.32mg</td>
</tr>
</tbody>
</table>

Wash Buffer:

| 4L |
| 50 mM Hepes pH 7.4 | 47.6g |
| 1 mM CaCl$_2$ | 440mg |
| 5 mM MgCl$_2$ (hexahydrate) | 4.08g |

Filtermats:

Soak Printed Filtermat A Glass Fiber Filters (Wallac; 1205-401) in 1% (20g/L) polyethylenimine (PEI, Sigma; P3143) for 60 min. Air dry overnight. Store until used.

Hot Cocktail:

| 0.2 nM stock $^{125}\text{I}$-C3a (NEN; NEX-356) in L. |

C3a cold peptide:
50 µg C3a (Advanced Research Technologies; A118) in 5.4 mL assay buffer.
55 ug in 0.61 mls AB.
Aliquot into 15 uL and store at -20 C.
Daily stock is 1 uM - dilute 15 µL + 135 µL AB.

L12 C3a Cells:
Spin down cells in 50 ml tubes by 3500 rpm for 5 min at RT in the Sorvall RT6000D.
Decant supernatant and resuspend at 5 x 10^5 cells/mL in assay buffer. Assume 1 flask for 4 plates.

Drug Dilutions
Run in triplicate at ½ log concentrations in the standard HTS format.
Prepare dilutions in 100% DMSO on the BIOMEK robot (LFL 60 µL all plates).
Begin at 3.2 µM final (40 X would then be 128 µM, prepare 1:0 ml).
Procedure:
Add 75 µL assay buffer to 96 well plate (polypropylene; Costar. VWR #29445-112).
Add 5 µL compound via BIOMEK 5 uL transfer program
Add 10 µL cold C3a (1 uM) to wells D7, D8, and D9. Final 50 nM in assay.
Add 50 µL (0.2 nM) hot cocktail. Final ~0.05 nM = 50 pM (with 33,000 cpm).
Then prepare cells as described above.
Add 75 µL C3a cells (3.75e5 cells per well = 5x10^6 cells/mL).
Incubate with shaking for 45 min, room temperature at speed 4 on the titer plate shaker.
Collect cells by centrifugation, 3500 rpm for 5 min at RT on the Sorvall.
Decant the supernatant (hot) for disposal.
Harvest plate onto filtermat with Skatron Micro 96 Harvester with cold wash buffer.
Dry filtermat in microwave (4 min).
Transfer filtermat to bag (Wallac; 1205-411).
Add 10 mL Wallac beta scintillation cocktail.
Seal bag. Let filters set 10 minutes to equilibrate.
Count on 1205 Betaplate liquid scintillation counter with disk for electronic storage,
protocol 23.
Precipitation has been observed with ^125I C3a. To counteract or minimize this it is recommended that fresh batches of radioactivity be thawed, thoroughly mixed and then aliquoted by 5 x 200 µL.
IC_{50} values are provided in Table 1 below.
<table>
<thead>
<tr>
<th>Compound</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>100 nM</td>
</tr>
<tr>
<td>2</td>
<td>460 nM</td>
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<tr>
<td>3</td>
<td>220 nM</td>
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<td>4</td>
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<td>5</td>
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<tr>
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<tr>
<td>46</td>
<td>64 nM</td>
</tr>
<tr>
<td>47</td>
<td>71 nM</td>
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</table>

All of the references, patents, and publications cited herein are hereby incorporated by reference in their entirety.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the compounds and methods of use thereof described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.
CLAIMS

1. A compound according to the formula I or pharmaceutically acceptable salts thereof

![Chemical Structure](image)

wherein,

A represents an optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₃-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

W represents hydrogen, -C(R₅)₂-, -NR₅, -O-, or -S(O)ₙ- (wherein n is 0, 1, or 2), or a single bond;

R₁ is optionally substituted (C₆-C₁₀)aryl or optionally substituted 5-10-membered heteroaryl;

R₂, and R₃ independently for each occurrence represent one or more substituents selected from the group consisting of hydrogen, hydroxy, halo, amino, C(=O)R₆, -OC(=O)-R₆, -C(=O)O-R₆, -N(R₅)₂, -NR₅C(=O)-R₆, -C(=O)N(R₆)₂, -OC(=O)-N(R₆)₂, -NR₅-C(=O)-N(R₆)₂, -NR₅-C(NR₅)-N(R₆)₂, -S(O)ₙ-R₆ (wherein n is 0, 1, or 2), -S(O)ₙ-N(R₆)₂, (wherein n is 0, 1, or 2), (C₁-C₆)alkoxy-, (C₁-C₆)acyloxy-, (C₁-C₆)alkylamino-, ((C₁-C₆)alkyl)₂amino-, (C₁-C₆)acylamino-, cyano, nitro, optionally substituted (C₁-C₁₀)alkyl-, optionally substituted (C₆-C₁₀)aryl optionally substituted C₁-C₆ alkyl, optionally substituted (C₅-C₁₀)cycloalkyl-, and optionally substituted 3-10-membered heterocycloalkyl-, or

when W represents NR₅, R₃ and R₅ taken together may form an optionally substituted 4-7 membered ring containing 2-3 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; with the proviso that the group

![Additional Chemical Structure](image)

may not be the group
R₄ may be absent or represents hydrogen, C(=O)R₅, -OC(=O)-R₅, -C(=O)O-R₅, -N(R₆)₂, -NR₃C(=O)-R₅, -C(=O)N(R₇)₂, -OC(=O)-N(R₇)₂, -NR₇C(=O)-N(R₇)₂, -S(O)ₙN-R₅ (wherein n is 0, 1, or 2), -S(O)ₙN(R₇)₂, (wherein n is 0, 1, or 2), (C₃-C₆)alkoxy-, (C₃-C₆)alkylamino-, ((C₁-C₆)alkyl)amino-, (C₃-C₆)acylamino-, cyano, nitro, optionally substituted (C₃-C₆)alkyl with up to two of the (C₃-C₆)alkyl carbons each optionally replaced by an oxygen, (C₃-C₆)alkyl substituted with one R₆, optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10-membered heteroaryl, optionally substituted (C₃-C₆)cycloalkyl-, or optionally substituted 3-10-membered heterocycloalkyl;

or when R₄ is N(R₆)₂, the two R₅ groups taken with the N may form a 5-7-membered heterocycloalkyl ring fused to a C₆ aromatic ring or to a 5-6-membered heteroaromatic ring;

and

R₅, independently for each occurrence, represents a hydrogen, optionally substituted (C₃-C₆)alkyl, optionally substituted (C₆-C₁₀)aryl, wherein the (C₆-C₁₀)aryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted 5-10-membered heteroaryl, wherein the 5-10-membered heteroaryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted (C₃-C₆)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

with the proviso that

(i) when R₂ is (NR₃)₂, R₅ is not H for each occurrence;

(ii) W-R₄ is not OH, NH-SΟ₂-optionally substituted C₃-C₆ alkyl-, NH-SΟ₂-optionally substituted C₆-C₁₀ aryl, C₃-C₆ alkyl or S-optionally substituted C₃-C₆ alkyl;

(iii) R₅ is not CONH-optionally substituted C₃-C₆ cycloalkyl or CONH-optionally substituted C₆-C₁₀ aryl;

(iv) when R₅ is a substituted C₃-C₆ alkyl, R₅ is not substituted with CO₂H, with optionally substituted 5-10-membered heteroaryl, with O- (optionally substituted C₆-C₁₀ aryl), or with two or more optionally substituted C₆-C₁₀ aryl groups on the same C₃-C₆ alkyl carbon;

(v) the compound of formula I does not contain an aliphatic or aromatic or heteroaromatic ring fused to two rings wherein the two rings are aliphatic rings, aromatic rings, heteroaromatic rings or a combination thereof; and

(vi) the compound of formula I is not a compound or pharmaceutically acceptable salt thereof selected from the group consisting of

3-[1,1′-biphenyl]-4-yl-1,5-dimethyl-1H-pyrazole;
3-[1,1′-biphenyl]-4-yl-1-methyl-1H-pyrazol-5-amine;
1H-pyrazole-1-ethanol, 3-[1,1'-bipheyl]4-yl-5-methyl; and
3-[4'-dimethylamino]-2,5-dimethyl[1,1'-bipheyl]-4-yl]-1-methyl-1H-pyrazol-5-amine.

2. The compound of claim 1, wherein the compound has the formula (II)

![Diagram](attachment:image.png)

(II)

wherein,

A and B, independently represent an optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10 membered heteroaryl, optionally substituted (C₅-C₁₀)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

W represents -C(R₅)₂₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋_-
3. A compound of claim 1, wherein the compound has the Formula III

\[
\text{(III)}
\]

wherein,

A represents an optionally substituted \((C_6-C_{10})\)aryl, optionally substituted \((C_3-C_{10})\)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl;

D represents a 3-7 membered heterocyclic ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, a 5-7 heteroaromatic ring containing one or more heteroatoms selected from nitrogen, oxygen, and sulfur, or a \(C_6\) aromatic ring;

\(R_1\) is optionally substituted \((C_6-C_{10})\)aryl or optionally substituted 5-10-membered heteroaryl;

\(R_2, R_3\) and \(R_7\), independently for each occurrence, represent one or more substituents selected from hydrogen, hydroxy, halo, amino, \(C(=O)R_5\), \(-OC(=O)R_5\), \(-C(=O)OR_5\), \(-N(R_5)\), \(-NR_5C(=O)R_5\), \(-C(=O)N(R_5)\), \(-OC(=O)N(R_5)\), \(-NR_5C(=O)N(R_5)\), \(-NR_5C(NR_5)\), \(-OR_5\), \(-S(O)\), \(-N(R_5)\), \(-S(O)\), \(-N(R_5)\), \(-S(O)\), \(-N(R_5)\), \(-S(O)\), \(-N(R_5)\), \(-NO_{2}\), \((-C_{1-6})\)alkoxy-, \((-C_{1-6})\)acyloxy-, \((-C_{1-6})\)alkylamino-, \((-C_{1-6})\)alkylamino-, \((-C_{1-6})\)aclylamino-, cyano, nitro, optionally substituted \((C_1-C_{10})\)alkyl-, optionally substituted \((C_1-C_{10})\)alkyl-, or optionally substituted \((C_1-C_{10})\)alkyl-

or two \(R_7\) groups may form an optionally substituted 3-10-membered heterocyclic ring fused to \(B\); and

\(R_5\), independently for each occurrence, represents a hydrogen, optionally substituted \((C_1-C_{10})\)alkyl, optionally substituted \((C_6-C_{10})\)aryl, wherein the \((C_6-C_{10})\)aryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted 5-10-membered heteroaryl, wherein the 5-10-membered heteroaryl is optionally fused to a 5-7-membered heterocyclic ring containing up to two oxygens, optionally substituted \((C_3-C_{10})\)cycloalkyl, or optionally substituted 3-10-membered heterocycloalkyl.

4. A compound of claim 1, wherein \(W\) represents \(-C(R_5)\), or \(-NR_5\), and \(R_5\), independently for each occurrence, represents hydrogen, or optionally substituted \((C_1-C_{10})\)alkyl.
5. A compound of claim 1, wherein A represents an optionally substituted (C₆-C₁₀)aryl, or an optionally substituted 5-10-membered heteroaryl.

6. A compound of claim 1, wherein A represents a optionally substituted phenyl ring or an optionally substituted pyrazolyl group.

7. A compound of claim 1, wherein A represents a phenyl group substituted one or more times by a (C₁-C₆) alkyl, or a 1-(C₁-C₆)alkyl-5-trifluoromethyl-1H-pyrazol-3-yl group.

8. A compound of claim 1, wherein R₈ and R₉, independently, represent hydrogen or a (C₁-C₆) alkyl.

9. A compound of claim 1, wherein R₈ represents a group selected from

\[
\text{a. } \begin{array}{c}
\text{O} \\
\text{C} \\
\text{R₈}
\end{array} \quad \text{b. } \begin{array}{c}
(\text{CH}_2)_n \\
\text{C} \\
\text{R₈}
\end{array}
\]

\[
\text{c. } \begin{array}{c}
\text{O} \\
\text{C} \\
\text{m}
\end{array}
\]

10. A compound of claim 9, wherein C represents one of the following optionally substituted groups: phenyl, furyl, thieryl, pyrazinyl, imidazolyl, pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, or a cyclohexyl group.

15. R₈ independently for each occurrence represents, one or more substituents selected from hydrogen, hydroxy, halo, amino, C(=O)R₈, -OC(=O)-R₈, -C(=O)O-R₈, -N(R₈)₂, -NR₆C(=O)-R₈, -C(=O)N(R₈)₂, -OC(=O)-N(R₈)₂, -NR₆-C(=O)-N(R₈)₂, -S(O)ₙ-R₈ (wherein n is 0, 1, or 2), -S(O)ₙN(R₈)₂ , (wherein n is 0, 1, or 2), (C₁-C₆)alkoxy-, (C₁-C₆)acyloxy-, (C₁-C₆)acylamino-, cyano, nitro, optionally substituted (C₁-C₁₀)alkyl-, optionally substituted (C₂-C₁₀)alkenyl-, optionally substituted (C₂-C₁₀)alkynyl-, optionally substituted (C₆-C₁₀)aryl, optionally substituted 5-10-membered heteroaryl, optionally substituted (C₆-C₁₀)cycloalkyl, 3-10-membered heterocycloalkyl, or two R₈ groups taken together can form a 4-8 membered ring containing 0-3 heteroatoms selected from N, O, and S; and n and m, in the groups \(-(\text{CH}_2)_n\) and \(-[\text{O-CH}_2-\text{CH}_2-O])_m\), independently, represent 0, 1, 2, or 3.

20. A compound of claim 9, wherein C represents one of the following optionally substituted groups: phenyl, furyl, thieryl, pyrazinyl, imidazolyl, pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, or a cyclohexyl group.
11. A compound of claim 9, wherein \( R_8 \), independently for each occurrence, represents one or more moieties selected from the group consisting of hydrogen, methyl, ethyl, propyl, hydroxy, methoxy, ethoxy, propoxy, fluoro, chloro, and bromo.

12. A compound of claim 1, wherein the group

\[
\begin{align*}
\text{N} & \quad \text{N} \\
R_3 & \quad R_4 \\
R_2 & \quad R_2
\end{align*}
\]

is not

13. A compound of claim 1, wherein \( R_3 \) is not a \( C_1-C_{10} \) alkyl substituted with OH.

14. A compound of claim 2, wherein \( W \) represents \(-C(R_6)_{2-}\), or \(-NR_5\), and \( R_5 \), independently for each occurrence, represents hydrogen, or optionally substituted \( (C_1-C_{10})\text{alkyl} \).

15. A compound of claim 2, wherein \( A \) represents an optionally substituted \( (C_6-C_{10})\text{aryl} \), or an optionally substituted 5-10-membered heteroaryl.

16. A compound of claim 2, wherein \( A \) represents an optionally substituted phenyl ring or an optionally substituted pyrazolyl group.

17. A compound of claim 2, wherein \( A \) represents a phenyl group substituted one or more times by a \( (C_1-C_6) \) alkyl, or a \( 1-(C_1-C_6)\text{alkyl}-5\text{-trifluoromethyl-1H-pyrazol-3-yl} \) group.

18. A compound of claim 2, wherein \( B \) represents an optionally substituted \( (C_6-C_{10})\text{aryl} \), optionally substituted 5-10 membered heteroaryl, optionally substituted \( (C_3-C_{10})\text{cycloalkyl} \), or optionally substituted 3-10-membered heterocycloalkyl.

19. A compound of claim 2, wherein \( B \) represents one of the following optionally substituted groups: phenyl, furyl, thieryl, pyrazinyl, imidazolyl, pyridyl, cyclopropyl, cyclobutyl, cyclopentyl, or a cyclohexyl group.

20. A compound of claim 2, wherein \( R_2 \) and \( R_3 \), independently, represent hydrogen or a \( (C_1-C_6) \) alkyl.

21. A compound of claim 3, wherein \( A \) represents an optionally substituted \( (C_6-C_{10})\text{aryl} \), or an optionally substituted 5-10-membered heteroaryl.
22. A compound of claim 3, wherein A represents an optionally substituted phenyl or an optionally substituted pyrazolyl group.

23. A compound of claim 3, wherein A represents a phenyl group substituted one or more times by a (C₅₋₇) alkyl, or a 1-(C₅₋₇)alkyl-5-trifluoromethyl-1H-pyrazol-3-yl group.

24. A compound of claim 3, wherein R₂ and R₃, independently, represent hydrogen or a (C₅₋₇) alkyl.

25. A compound selected from the group consisting of 5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-ylamine; 3-[5-amino-3-(3', 4'-dimethyl-biphenyl-4-yl)-pyrazol-1-ylmethyl]-phenol; cyclopropylmethyl-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-furan-2-ylmethyl-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-3H-imidazol-4-ylmethyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-benzyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[4-methyl-benzyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[3-methyl-benzyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methoxy-benzyl]-amine; [3-chloro-benzyl]-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [2-chloro-benzyl]-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[3-methoxy-benzyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[3-thiophen-2-ylmethyl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-2-ylmethyl-amine; (2, 4-dichloro-benzyl)]-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-3-ylmethyl-amine; [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyridin-4-ylmethyl-amine; benzol[1, 3]dioxol-5-ylmethyl-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; (3, 4-dimethoxy-benzyl)]-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; N-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-nicotinamide; pyridine-2-carboxylic acid [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide; N-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-isonicotinamide; furan-2-carboxylic acid [5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide; N-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-isoindole-1, 3-dione; 2-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-pyrrole[3, 4-c]pyridine-1, 3-dione; 6-[5-(3', 4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-
pyrrolo[3,4-b]pyridine-5,7-dione; [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-(4-fluoro-benzyl)-amine; [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-(4-methoxy-benzyl)-amine; (4-chloro-benzyl)-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amine; [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-(2-methoxy-ethoxy-ethyl)]-amine; [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-[2-methyl-cyclopropylmethyl]-amine; 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-4H-pyrazol-3-yl]-amide; 3-(3',4'-dimethyl-biphenyl-4-yl)-1-methyl-1H-pyrazole; N-[5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-acetamide; pyrazine-2-carboxylic acid [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-amide; 3-(3',4'-dimethyl-biphenyl-4-yl)-1,5-dimethyl-1H-pyrazole; 6-(3',4'-dimethyl-biphenyl-4-yl)-2,3-dihydro-1H-imidazol[1,2-b]pyrazole; pyridine-2-carboxylic acid [2-methyl-5-[4-(1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl)-phenyl]-2H-pyrazol-3-yl]-amide; [5-(3',4'-dimethyl-biphenyl-4-yl)-2-methyl-2H-pyrazol-3-yl]-methyl-amine; and 6-(3',4'-dimethyl-biphenyl-4-yl)-3-methyl-1H-pyrazolo[5,1-c][1,2,4]triazole, and pharmaceutically acceptable salts thereof.

26. A composition comprising a compound of claim 1 and optionally a pharmaceutically acceptable carrier.

27. A method for treating the excessive Complement activation in a patient comprising administering to said patient, a therapeutically effective amount of a compound of claim 1.

28. A method for treating a condition selected from the group consisting of Alzheimer's disease, multiple sclerosis, Huntington's chorea, Pick's disease, Guillain Barre syndrome, encephalitis, meningitis, stroke, hemorrhagic stroke, cancer, allergic diseases, respiratory diseases, cardiovascular or metabolic disease states, shock, hypertension, hyperlipidemia, hypercholesterolemia, edema, obesity; nephritis, graft rejection, and inflammatory conditions, comprising administering to a patient a therapeutically effective amount of a compound of claim 1.

29. A method for treating a condition selected from the group consisting of Alzheimer's disease, multiple sclerosis, Huntington's chorea, Pick's disease, Guillain Barre syndrome, encephalitis, meningitis, stroke, and hemorrhagic stroke, comprising administering to a patient a therapeutically effective amount of a compound of claim 1.

30. A method for antagonizing the C3a receptor in a patient by administering an effective amount of a composition of claim 26.