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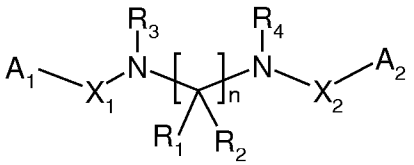
(54) Title: TUMOR NECROSIS FACTOR - ALPHA INHIBITORS



(I)

(57) Abstract: The present invention relates to small molecules that inhibit Tumor Necrosis Factor- alpha (TNF-α), for example, by interaction with TNF-α protein or its receptor, thereby lowering the overall TNF-α activity, and that are represented by formula (1) or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof; wherein: $A_1$, $A_2$, $X_1$, $X_2$, n, $R_1$, $R_2$, $R_3$ and $R_4$ are as defined in the specification. The present invention also relates to processes for the preparation of these small molecules and to pharmaceutical compositions containing them. The present invention further relates to a method of treatment of disorders characterized by increased TNF- α activity, such as inflammation.

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# TUMOR NECROSIS FACTOR - ALPHA INHIBITORS

## FIELD OF INVENTION

The present invention relates to small molecules that inhibit Tumor Necrosis Factor-alpha (TNF-α), for example, by interaction with TNF-α trimeric protein or its receptor, thereby lowering the overall TNF-α activity. The present invention also relates to processes for the preparation of such small molecules and to pharmaceutical compositions including them. The present invention further relates to the use of these small molecules in medicines for treatment or prevention of disorders characterized by increased TNF-α activity.

## BACKGROUND OF INVENTION

TNF-α is derived from mononuclear cells and macrophages and in turn induces the expression of a variety of genes that contribute to various disorders such as inflammation. TNF-α is initially synthesized and expressed as a 26 kDa transmembrane protein, the extracellular portion of which is subsequently cleaved by TNF-α converting enzyme (TACE), to release the soluble 17 kDa protein. TNF- α is found to be present in its membrane-bound and secreted form. TNF- α has a tendency to form a trimer.

An increase in TNF-α synthesis or release occurs in disorders such as inflammation. Inflammation is the response of a tissue to injury that can be caused by invading parasites, ischemia, antigen-antibody reactions or other forms of physical or chemical injury. It is characterized by increased blood flow to the tissue, causing pyrexia, redness, swelling, and pain. Several cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), and TNF-α, play an important role in the inflammatory process. Inflammation is an inherent part of various disease states like rheumatoid arthritis, Crohn's disease, septic shock syndrome, atherosclerosis and cancer, among other clinical conditions.

Rheumatoid arthritis (RA) - an autoimmune disorder, is a chronic, systemic, articular inflammatory disease of unknown etiology. Cartilage destruction in RA is linked to aberrant cytokines and growth factor expression in the affected joints. The most common rheumatoid arthritis therapy involves the use of nonsteroidal anti-

inflammatory drugs (NSAIDs) to alleviate symptoms. However, despite the widespread use of NSAIDs, many individuals cannot tolerate the doses necessary to treat the disorder over a prolonged period of time. In addition, NSAIDs merely treat the symptoms of disorder and not the cause.

When patients fail to respond to NSAIDs, other DMARDs (Disease Modifying Anti-Rheumatic Drugs) such as methotrexate, gold salts, D-penicillamine, cyclophosphamide and prednisone are used. These drugs have significant toxicities and their mechanism of action remains unknown.

The most convincing evidence to date that TNF- α is central in the pathogenesis of RA comes from clinical experience with either monoclonal antibodies against TNF-α or soluble TNF receptor–immunoglobulin constructs. Monoclonal antibody drugs such as Infliximab, Etanercept and Adalimumab are useful as anti-inflammatory agents, but have drawbacks such as route of administration (only parenteral), high cost, allergy induction, activation of latent tuberculosis, increased risk of cancer and congestive heart disease as mentioned in Semin Cutan Med Surg. 2007 Mar; 26(1):6-14.

There is a need for improved and alternative medicaments for the prevention and treatment of disorders characterized by increased TNF-α activity.

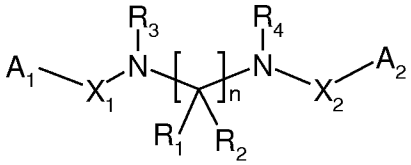
There is scope to develop small molecules as TNF-α inhibitors. The potential advantages of small molecule oral cytokine inhibitors include convenience of use because of oral efficacy and therefore greater patient compliance, better tissue penetration, specificity for defined signaling and synthesis pathway, non-immunogenicity, easier synthesis and lower manufacturing cost and that they can be used in combination with other drugs.

Science, 2005, Vol.310, 1022-1025; refers to small molecule interaction with proteins. The molecule described acts as TNF-α inhibitor by complexing with the TNF-α trimer and promoting the dissociation to form TNF-α dimer, leading to inactivation of cytokine. Besides this, not much information is available regarding detrimerization of TNF-α by small molecules.

Since TNF-α is one of the most important proinflammatory cytokines overexpressed in many disorders, the present invention includes small molecules that target this trimeric protein or its receptor.

## SUMMARY OF INVENTION

The present invention relates to small molecules represented by formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof;



Formula 1

in which $A_1$, $A_2$, $X_1$, $X_2$, n, $R_1$, $R_2$, $R_3$ and $R_4$ can be as described below.

Such compounds can bind to trimeric TNF-α protein or its receptor.

The small molecules of the present invention can be used for the prevention and treatment of disorders characterized by increased TNF-α activity, such as inflammation, rheumatoid arthritis, Crohn's disease, septic shock syndrome and atherosclerosis.

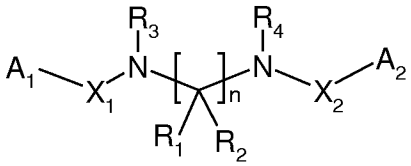
The present invention further relates to pharmaceutical compositions including the subject small molecules as active ingredient for the treatment and prevention of disorders characterized by increased TNF-α activity, such as inflammation, rheumatoid arthritis, Crohn's disease, septic shock syndrome and atherosclerosis.

The present invention further relates to processes for the preparation of such small molecules represented by formula 1.

## DETAILED DESCRIPTION OF INVENTION

The present invention includes small molecules that inhibit Tumor Necrosis Factor-alpha (TNF-α), for example, by interaction with TNF-α protein or its receptor, thereby lowering the overall TNF-α activity and that are represented by formula 1, or

a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof;



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group or a substituted or unsubstituted heterocyclic ring system, as defined herein below;

$X_1$ and $X_2$ are independently a carbonyl group or a methylene (-$CH_2$-) group;

n is an integer from 2-4;

$R_1$ and $R_2$ are independently hydrogen or ($C_1$-$C_4$)-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system;

with a proviso that when $A_1$ and $A_2$ are 1-(3-(trifluoromethyl)phenyl)-1H-indole and 6,7-dimethyl-4H-chromen-4-one respectively, and $X_1$ and $X_2$ are independently a methylene (-$CH_2$-) group, $R_3$ and $R_4$ form a ring system.

**Definitions**

As used herein, the term "alkyl" whether used alone or as part of a substituent group, refers to the radical of saturated aliphatic groups, including straight or branched-chain alkyl groups. An alkyl group can have a straight chain or branched chain with, for example, upto 4 carbon atoms in its backbone. Examples of alkyl residues containing from 1 to 4 carbon atoms include methyl, ethyl, propyl, isopropyl, n-propyl, t-butyl, n-butyl, sec-butyl and iso-butyl.

As used herein, the term “alkoxyl” or “alkoxy” refers to a ($C_1$-$C_4$)-alkyl group having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, and tert-butoxy.

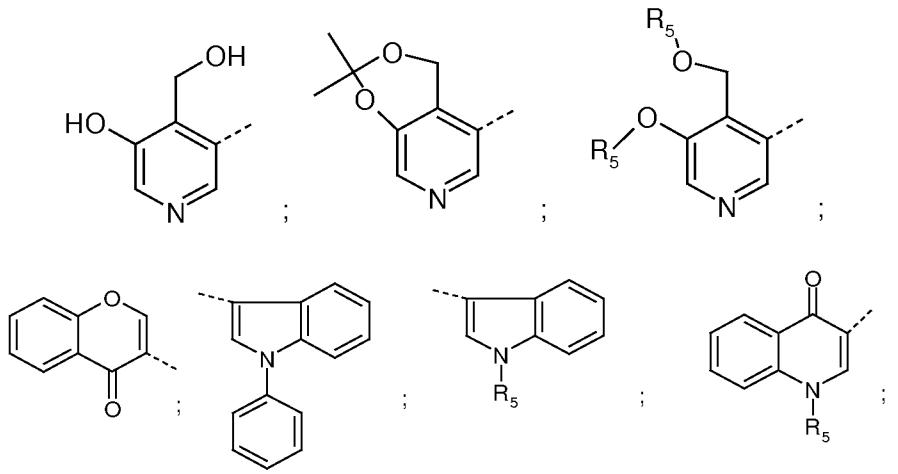
As used herein, a benzyloxy group refers to a benzyl group having an oxygen radical attached thereto.

As used herein, a ring system refers to a cyclic, saturated or unsaturated five or six membered system optionally containing 1-3 heteroatoms like O, N and/or S.

As used herein, a substituted phenyl group refers to a phenyl group substituted by substituents selected from ($C_1$-$C_4$)-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, ($C_1$-$C_4$)-alkoxy, benzyloxy and hydroxy-($C_1$-$C_4$)-alkyl. In substituted phenyl, the substituents can be located in any desired position. For example, in monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position, the 4-position or the 5-position. If the phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position.

The term "heteroatom" as used herein includes nitrogen, oxygen, and sulfur. Any heteroatom with unsatisfied valences is assumed to have a hydrogen atom to satisfy the valences.

As used herein, the term heterocyclic ring system refers to groups as exemplified herein below;



wherein the dotted line indicates the point of attachment and $R_5$ is hydrogen or ($C_1$-$C_4$)-alkyl group.

Substituted heterocyclic systems refer to the groups illustrated above wherein the rings are further substituted with 1-3 substituents from the groups selected from ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, hydroxyl, hydroxy-($C_1$-$C_4$)-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$). The substituents can be present at one or more positions provided that a stable molecule results.

It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the

substituted atom and the substituent, as well as represents a stable compound, which does not readily undergo undesired transformation such as by rearrangement, cyclization, or elimination.

The term 'small molecules' means molecules having a molecular weight upto 1200.

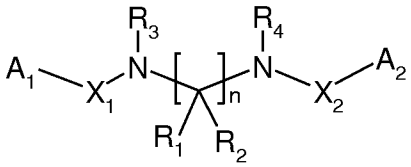
The term "treating", "treat" or "treatment" as used herein includes preventive (prophylactic) and palliative treatment.

By "pharmaceutically acceptable" is meant that the carrier, diluent, excipients, and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

As used herein, the term "compound of formula 1" or "small molecule of formula 1" includes a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof.

**Embodiments of Compounds of the Invention**

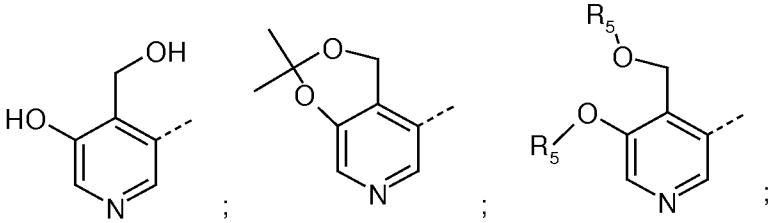
In an embodiment, the present invention provides compounds represented by formula 1:

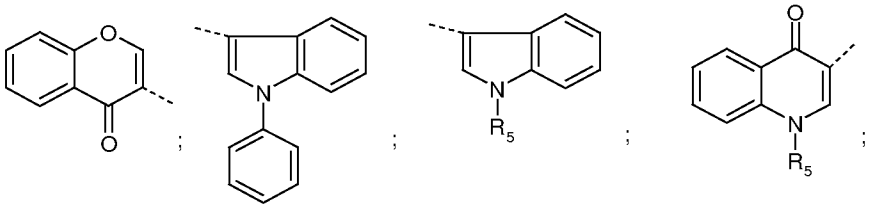


Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl group are selected from $(C_1$-$C_4)$-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, $(C_1$-$C_4)$-alkoxy, benzyloxy and hydroxy-$(C_1$-$C_4)$-alkyl;
or a substituted or unsubstituted heterocyclic system selected from:

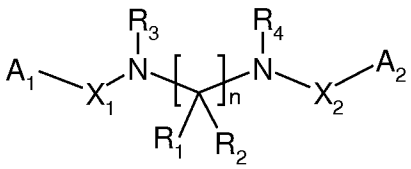




wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or ($C_1$-$C_4$)-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, hydroxyl, hydroxy-($C_1$-$C_4$)-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a carbonyl or a methylene (-$CH_2$-) group;
n is an integer from 2-4;
$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;
$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and
$R_3$ and $R_4$ can optionally form a ring system;
with a proviso that when $A_1$ and $A_2$ are 1-(3-(trifluoromethyl)phenyl)-1H-indole and 6,7-dimethyl-4H-chromen-4-one respectively and $X_1$ and $X_2$ are independently a methylene (-$CH_2$-) group, $R_3$ and $R_4$ form a ring system.

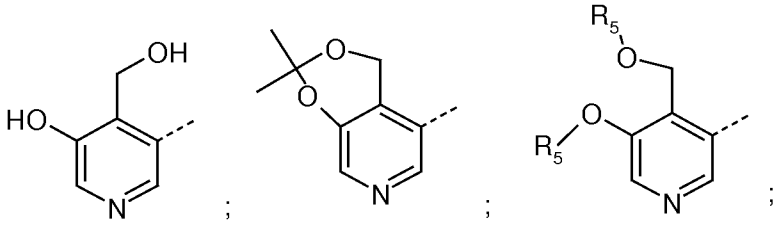
In another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted heterocyclic system selected from;



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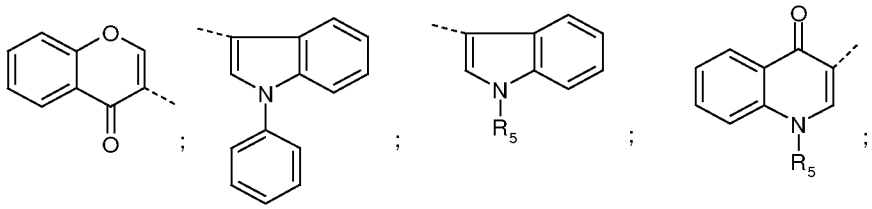


wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or $(C_1$-$C_4)$-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, hydroxyl, hydroxy-$(C_1$-$C_4)$-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a carbonyl group or a methylene ($-CH_2-$) group;

n is an integer from 2-4;

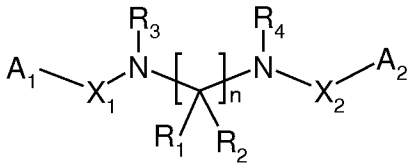
$R_1$ and $R_2$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system;

with a proviso that when $A_1$ and $A_2$ are 1-(3-(trifluoromethyl)phenyl)-1H-indole and 6,7-dimethyl-4H-chromen-4-one respectively and $X_1$ and $X_2$ are independently a methylene ($-CH_2-$) group, $R_3$ and $R_4$ form a ring system.

In yet another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl ring are selected from $(C_1$-$C_4)$-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, $(C_1$-$C_4)$-alkoxy, benzyloxy and hydroxy-$(C_1$-$C_4)$-alkyl;

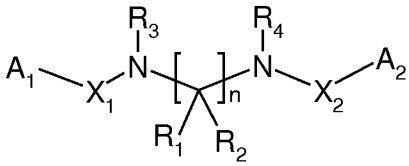
$X_1$ and $X_2$ are independently a carbonyl group or a methylene ($-CH_2-$) group;

n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group;

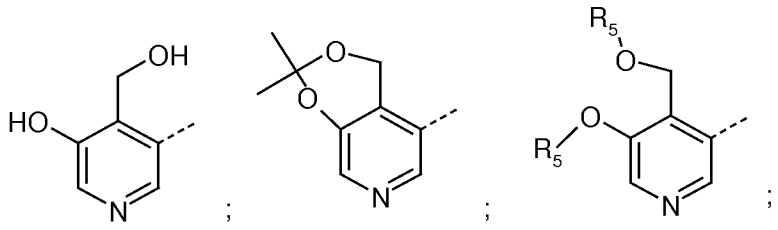
$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and
$R_3$ and $R_4$ can optionally form a ring system.

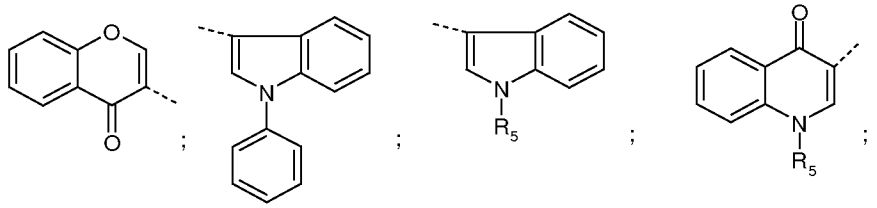
In a further embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:
$A_1$ and $A_2$ are independently a substituted or unsubstituted heterocyclic system selected from;

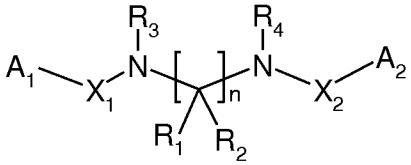




wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or ($C_1$-$C_4$)-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, hydroxyl, hydroxy-($C_1$-$C_4$)-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a carbonyl group;
n is an integer from 2-4;
$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;
$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and
$R_3$ and $R_4$ can optionally form a ring system.

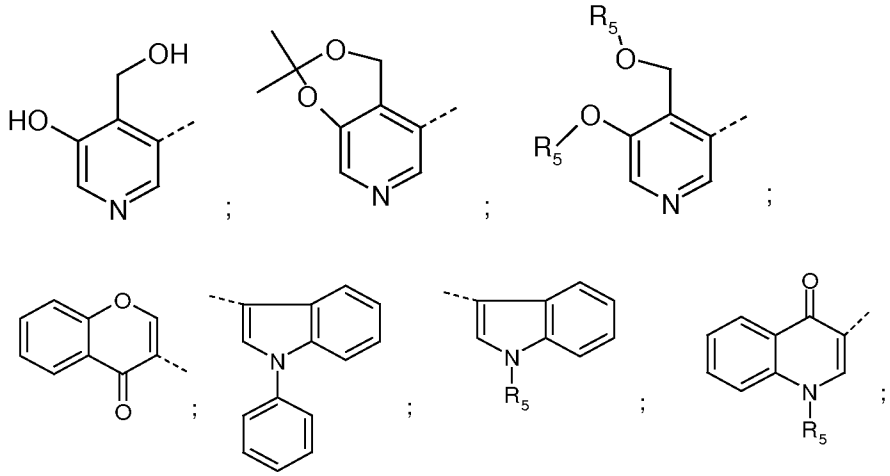
In another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted heterocyclic system selected from;



wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or $(C_1$-$C_4)$-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, hydroxyl, hydroxy-$(C_1$-$C_4)$-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a methylene ($-CH_2-$) group;

n is an integer from 2-4;

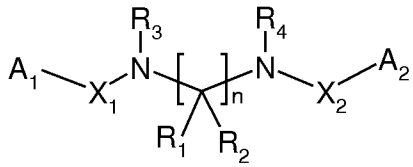
$R_1$ and $R_2$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system;

with a proviso that when $A_1$ and $A_2$ are 1-(3-(trifluoromethyl)phenyl)-1H-indole and 6,7-dimethyl-4H-chromen-4-one respectively, $R_3$ and $R_4$ form a ring system.

In yet another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl ring are selected from $(C_1\text{-}C_4)$-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, $(C_1\text{-}C_4)$-alkoxy, benzyloxy and hydroxy-$(C_1\text{-}C_4)$-alkyl;

$X_1$ and $X_2$ are independently a carbonyl group;

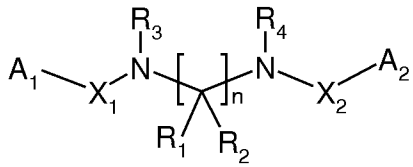
n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

In a further embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl ring are selected from $(C_1\text{-}C_4)$-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, $(C_1\text{-}C_4)$-alkoxy, benzyloxy and hydroxy-$(C_1\text{-}C_4)$-alkyl;

$X_1$ and $X_2$ are independently a methylene (-$CH_2$-) group;

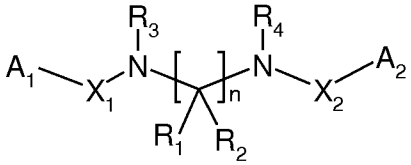
n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

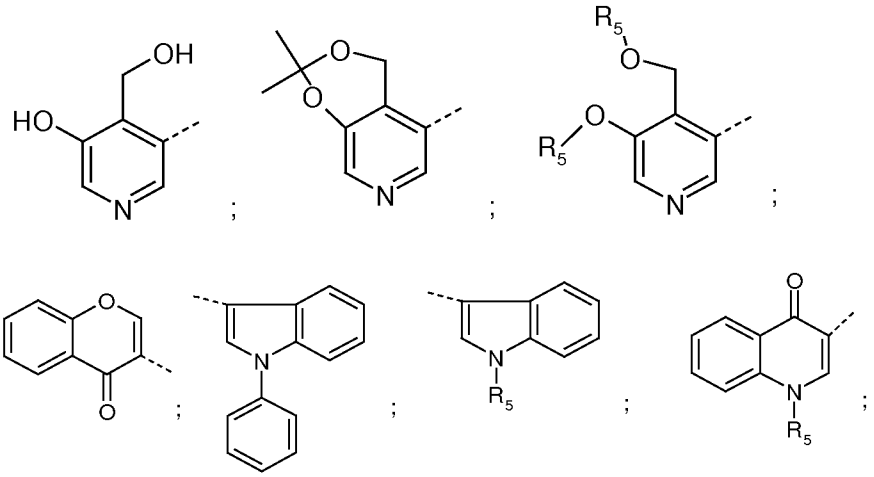
In another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted heterocyclic system selected from:



wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or $(C_1$-$C_4)$-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, hydroxyl, hydroxy-$(C_1$- $C_4)$-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a carbonyl group or a methylene ($-CH_2-$) group;

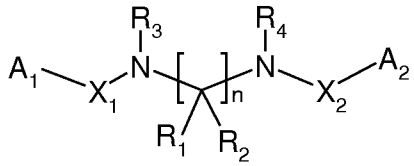
n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group; and

$R_3$ and $R_4$ form a ring system such as a piperazine ring system.

In yet another embodiment, the present invention provides compounds represented by formula 1:



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl ring are selected from ($C_1$-$C_4$)-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, ($C_1$-$C_4$)-alkoxy, benzyloxy and hydroxy-($C_1$-$C_4$)-alkyl;

$X_1$ and $X_2$ are independently a carbonyl group or a methylene (-$CH_2$-) group;

n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and

$R_3$ and $R_4$ form a ring system such as a piperazine ring system.

In a further embodiment, the compound of formula 1 is selected from:

3,3'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(6,7-dimethyl-4H-chromen-4-one) dihydrochloride;

5,5'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(4-(hydroxymethyl)-2-methylpyridin-3-ol) dihydrochloride;

6,7-Dimethyl-3-((methyl(2-(methyl((2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridin-5-yl)methyl)amino)ethyl)amino)methyl)-4H-chromen-4-one dihydrochloride;

1,4-Bis((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl)methyl)piperazine dihydrochloride; and

6,7-Dimethyl-3-((4-((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl) methyl)piperazin-1-yl)methyl)-4H-chromen-4-one dihydrochloride.

In yet another embodiment, the compound of formula 1 is selected from:

$N_1$,$N_2$-bis(4-(benzyloxy)-3-methoxybenzyl)ethane-1,2-diamine dihydrochloride;

N,N'-(ethane-1,2-diyl) bis (2-hydroxybenzamide) dihydrochloride;

N,N'-(propane-1,3-diyl) bis (2-hydroxybenzamide) dihydrochloride; and

4-Hydroxy-N-(2-(2-hydroxybenzamido)ethyl)-3-methoxybenzamide dihydrochloride.

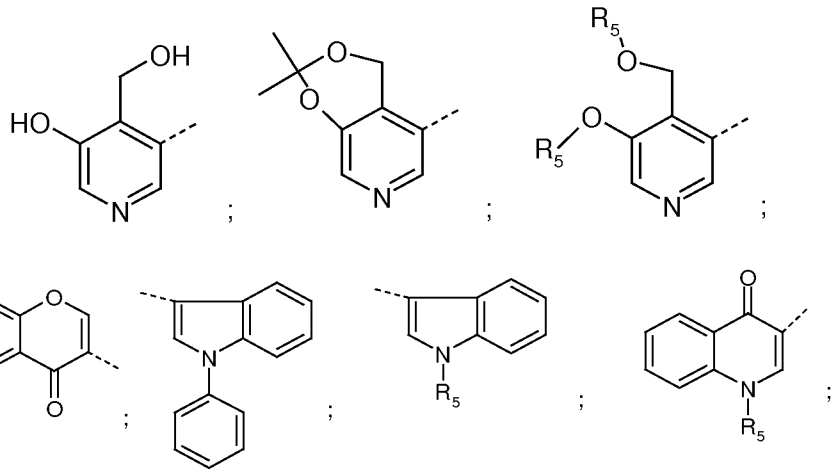
**Embodiments of Formula 1**

In certain embodiments, the present invention provides small molecules represented by formula 1, in which $A_1$, $A_2$, $X_1$, $X_2$, n, $R_1$, $R_2$, $R_3$ and $R_4$ can be as follows.

**$A_1$ and $A_2$**

In an embodiment, $A_1$ and $A_2$ are independently substituted or unsubstituted phenyl groups. In an embodiment, $A_1$ and/or $A_2$ is a substituted phenyl group, wherein the substituents may be selected from ($C_1$-$C_4$)-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, ($C_1$-$C_4$)-alkoxy, benzyloxy and hydroxy-($C_1$-$C_4$)-alkyl. In substituted phenyl, the substituents can be located in any desired position. For example, in monosubstituted phenyl residues the substituent can be located in the 2-position, the 3-position, the 4-position or the 5-position. If the phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position.

In an embodiment, $A_1$ is a heterocycle. In an embodiment, $A_2$ is a heterocycle. In an embodiment, $A_1$ and $A_2$ are independently a substituted heterocycle. In an embodiment, $A_1$ is a substituted heterocycle. In an embodiment, $A_2$ is a substituted heterocycle. In an embodiment, $A_1$ is a heterocycle and $A_2$ is a substituted heterocycle. In an embodiment, $A_1$ is a substituted heterocycle and $A_2$ is a heterocycle. In an embodiment, the heterocycle is selected from the groups:



wherein the dotted line indicates the point of attachment and $R_5$ is hydrogen or ($C_1$-$C_4$)-alkyl group.

In a yet further embodiment, the rings of the heterocycle systems herein above may be substituted with 1-3 substituents from the groups selected from ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, hydroxyl, hydroxy-($C_1$-$C_4$)-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$)

**$X_1$ and $X_2$**

In an embodiment, $X_1$ is a carbonyl group and $X_2$ is a carbonyl group. In an embodiment, $X_1$ is a methylene (-$CH_2$-) group and $X_2$ is a methylene (-$CH_2$-) group.

**n**

In an embodiment, n is an integer from 2-4, for example, 2, 3, or 4.

**$R_1$ and $R_2$**

In an embodiment, $R_1$ and/or $R_2$ is hydrogen.

In an embodiment, $R_1$ and/or $R_2$ is a ($C_1$-$C_4$)-alkyl group. For example, $R_1$ and $R_2$ can independently be a straight chain or branched chain alkyl having 1-4 carbon atoms in its backbone.

**$R_3$ and $R_4$**

In an embodiment, $R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl, group, or combination thereof. In an embodiment, $R_3$ and $R_4$ form a ring system. In an embodiment, the ring system is piperazine or a piperazinyl moiety.

In an embodiment, $R_3$ and/or $R_4$ is a ($C_1$-$C_4$)-alkyl group. For example, $R_3$ and $R_4$ can independently be a straight chain or branched chain alkyl having 1-4 carbon atoms in its backbone.

**Features of Formula 1**

In an embodiment, the compound of formula 1 includes two or more stereoisomers. In an embodiment, the compound of formula 1 includes one stereoisomer. Certain compounds exist as only a single stereoisomer. A compound that can be in the form

of two or more stereoisomers can be, for example, synthesized or purified as a single stereoisomer. The compound of formula 1 can include a mixture of stereoisomers with any of a variety of proportions of individual stereoisomers.

In an embodiment, the compound of formula 1 includes two or more tautomers. In an embodiment, the compound of formula 1 includes one tautomer. The compound of formula 1 can include a mixture of tautomers with any of a variety of proportions of individual tautomers.

In an embodiment, the compound of formula 1 is in the form of a pharmaceutically acceptable salt. In an embodiment, the compound of formula 1 is in the form of a pharmaceutically acceptable solvate. In an embodiment, the compound of formula 1 is in the form of a pharmaceutically acceptable polymorph.

Compounds of formula 1 are selected from:

3,3'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(6,7-dimethyl-4H-chromen-4-one) dihydrochloride;

$N_1$,$N_2$-bis(4-(benzyloxy)-3-methoxybenzyl)ethane-1,2-diamine dihydrochloride;

5,5'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(4-(hydroxymethyl)-2-methylpyridin-3-ol) dihydrochloride;

6,7-Dimethyl-3-((methyl(2-(methyl((2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridin-5-yl)methyl)amino)ethyl)amino)methyl)-4H-chromen-4-one dihydrochloride;

1,4-Bis((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl)methyl)piperazine dihydrochloride;

6,7-Dimethyl-3-((4-((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl) methyl)piperazin-1-yl)methyl)-4H-chromen-4-one dihydrochloride;

N,N'-(ethane-1,2-diyl) bis (2-hydroxybenzamide) dihydrochloride;

N,N'-(propane-1,3-diyl) bis (2-hydroxybenzamide) dihydrochloride; and

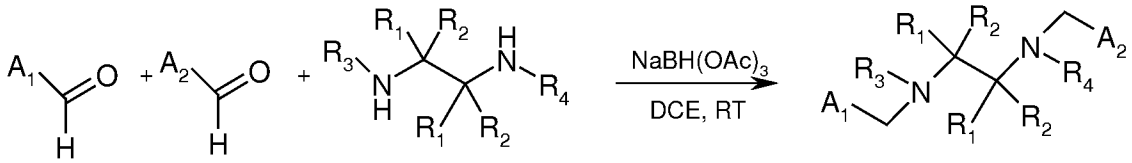
4-Hydroxy-N-(2-(2-hydroxybenzamido)ethyl)-3-methoxybenzamide dihydrochloride; or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof.

**Methods of Making the Present Small Molecules**

According to a further feature of the present invention there are provided processes for the synthesis of compounds of the present invention of formula 1 as illustrated in the schemes below.

The method of preparation includes reacting aldehydes or acids, which can be same or different, containing saturated or unsaturated ring systems, optionally substituted and optionally containing heteroatoms, with substituted or unsubstituted diamines to form amines or amides respectively. This can be accomplished in one pot or in several steps including, but not limited to, steps such as Schiff's base formation, reduction, and reductive amination, as shown in the schemes below.

**Scheme 1a :**




wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group or a substituted or unsubstituted heterocyclic system, as defined herein above;

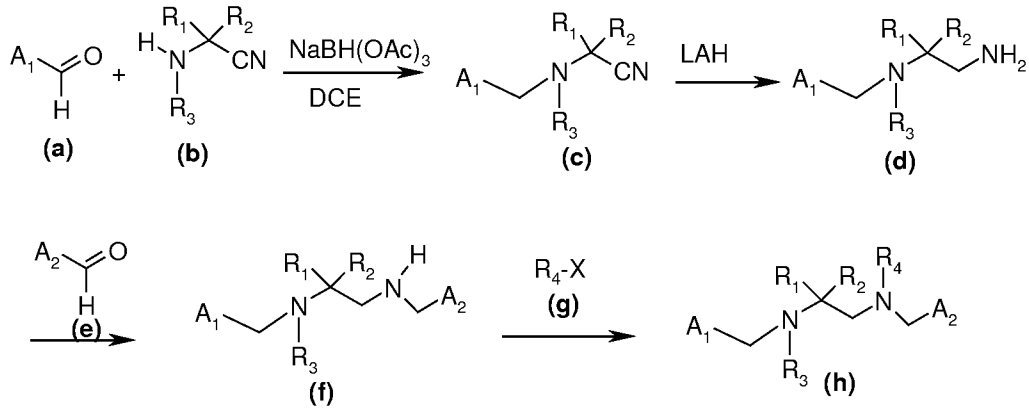
$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

The process of Scheme 1a is analogous to the process disclosed in U.S. Patent No. 6,344,334 and Tetrahedron Lett. 37:7193-7196 (1996).

**Scheme 1b :**




wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group or a substituted or unsubstituted heterocyclic system, as defined herein above;

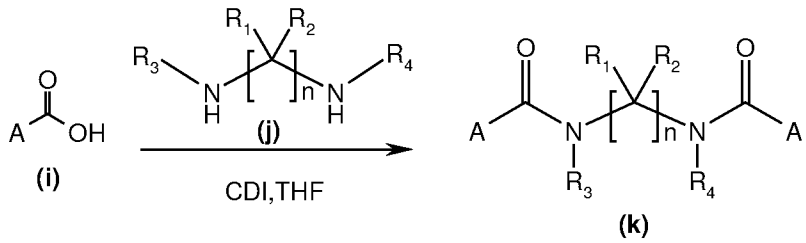
$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

In Scheme 1b, reductive amination of an aromatic aldehyde **(a)** with amino nitrile **(b)** compound provides a substituted nitrile intermediate **(c)**. The reducing agent used can be selected from, for example, sodium triacetoxy borohydride and sodium cyanoborohydride in solvents such as DCE, THF, acetonitrile and dioxane. In an embodiment, sodium triacetoxy borohydride is used as reducing agent in THF as solvent. The temperature used is 20-40 °C, for example, ambient temperature (25 °C). 1.0 equivalent of the intermediate **(c)** is taken in a suitable solvent such as ether, THF or dioxane at 0 °C and treated with LAH (Lithium aluminium hydride) (0.5 to 2.5 equivalent) to obtain an amino intermediate **(d)**. In an embodiment, the solvent used is THF. The amino intermediate **(d)** is then reacted with an aldehyde **(e)** to give a compound **(f)** (intermediate/product) by reductive amination, which can be N-alkylated using suitable alkyl halide **(g)** in solvent such as DMF or acetone, in presence of a base such as pyridine, triethylamine, sodium hydride, sodium carbonate or potassium carbonate to give the desired product **(h)**.

**Scheme 2 :**




wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group or a substituted or unsubstituted heterocyclic system, as defined herein above;

n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1\text{-}C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

In Scheme 2, an aromatic acid **(i)** is treated with a diamine **(j)** in presence of a coupling agent in a suitable solvent to obtain compound **(k)**. The coupling agent used can be, for example, CDI (1,1'-Carbonyldiimidazole), DCC (1,3-Dicyclohexylcarbodiimide), EDC (1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), chloro-dipyrrolidinocarbenium tetrafluoroborate, PyBOP (Benzotriazol-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate), HOBT (1-Hydroxybenzotriazole), or DIPEA (N,N-Diisopropylethylamine). In an embodiment, CDI is used as the coupling agent. The solvent used can be, for example, THF, ether, dioxane, or DMF. In an embodiment, the solvent used is THF. The temperature used is 20-40 °C, for example, ambient temperature (25 °C). The time required for the completion of the reaction is 3-10 h. In an embodiment, the reaction is mostly completed in 6 h. The resulting product is purified by various methods, which optionally include free base isolation or salt formation. Normal phase or reversed phase silica gel chromatography or precipitation techniques are used wherever required.

The compounds of the present invention can be prepared in a number of ways using methods well known to the skilled person. Examples of methods to prepare the present compounds are illustrated in Schemes 1 and 2 and exemplified herein. It will be appreciated by persons skilled in the art that within certain of the processes

described herein, the order of the synthetic steps employed can be varied and will depend inter alia on factors such as the nature of functional groups present in a particular substrate and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent to be used in the synthetic steps.

The reagents, reactants and intermediates used in the present processes are either commercially available or can be prepared according to standard literature procedures known in the art.

It will be appreciated by those skilled in the art that the compounds of the present invention can also be utilized in the form of their pharmaceutically acceptable salts or solvates thereof. The pharmaceutically acceptable salts of the compounds of the present invention are in particular salts which are non-toxic, or which can be used physiologically.

Thus, when the compounds of the present invention represented by the formula 1, contain one or more basic groups, i.e. groups which can be protonated, they can form an addition salt with an inorganic or organic acid. Examples of suitable inorganic acids include: boric acid, perchloric acid, hydrochloric acid, hydrobromic acid, hydrofluoric acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid and other inorganic acids known to the person skilled in the art. Examples of suitable organic acids include: acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, fumaric acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, toluenesulfonic acid, methanesulfonic acid, benzenesulfonic acid, ethane disulfonic acid, oxalic acid, isethionic acid, ketoglutaric acid, glycerophosphoric acid, aspartic acid, picric acid, lauric acid, palmitic acid, cholic acid, pantothenic acid, alginic acid, naphthoic acid, mandelic acid, tannic acid, camphoric acid and other organic acids known to the person skilled in the art.

Thus, when the compounds of the present invention represented by the formula 1 contain an acidic group they can form an addition salt with a suitable base. For example, such salts of the compounds of the present invention can include their alkali metal salts such as Li, Na, and K salts, or alkaline earth metal salts like Ca, Mg

salts, or aluminum salts, or salts with ammonia or salts of organic bases such as lysine, arginine, guanidine, diethanolamine, choline, and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from the subject compound, which contains a basic or an acidic moiety, by conventional chemical methods. Generally the salts are prepared by contacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base in a suitable solvent or dispersant or from another salt by cation or anion exchange. Suitable solvents are, for example, ethyl acetate, ether, alcohols, acetone, THF, dioxane or mixtures of these solvents.

The present invention furthermore includes all solvates of the compounds of formula 1, for example hydrates, and the solvates formed with other solvents of crystallization, such as alcohols, ethers, ethyl acetate, dioxane, DMF, or a lower alkyl ketone, such as acetone, or mixtures thereof.

Various polymorphs of compounds of formula 1, can be prepared by crystallization of the compounds under different conditions. The different conditions are, for example, using different commonly used solvents or their mixtures for crystallization; crystallization at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs can also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs can be determined by IR (Infra-red) spectroscopy, solid probe NMR (Nuclear Magnetic Resonance) spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

**Methods Employing and Compositions Including the Present Small Molecules**

Any reference to 'small molecules or compounds of formula 1' herein also includes a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof;

The present compounds can be employed in methods and compositions employed for treating disorders characterized by increased TNF-α activity. In an embodiment, the present compounds are TNF-α inhibitors. In an embodiment, the present invention includes a method of treating a disorder characterized by increased TNF-α

activity, by administering a small molecule according to the present invention to a human in need thereof. Such humans can be suffering from one or more disorders including: inflammatory bowel disease, inflammation, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, osteoarthritis, refractory rheumatoid arthritis, chronic non- rheumatoid arthritis, osteoporosis/bone resorption, Crohn's disease, septic shock, endotoxic shock, atherosclerosis, ischemia-reperfusion injury, coronary heart disease, vasculitis, amyloidosis, multiple sclerosis, sepsis, chronic recurrent uveitis, hepatitis C virus infection, malaria, ulcerative colitis, cachexia, psoriasis, plasmocytoma, endometriosis, Behcet's disease, Wegener's granulomatosis, meningitis, AIDS, HIV infection, autoimmune disease, immune deficiency, common variable immunodeficiency (CVID), chronic graft-versus-host disease, trauma and transplant rejection, adult respiratory distress syndrome, pulmonary fibrosis, recurrent ovarian cancer, lymphoproliferative disease, refractory multiple myeloma, myeloproliferative disorder, diabetes, juvenile diabetes, ankylosing spondylitis, and skin delayed-type hypersensitivity disorders, Alzheimer's disease, systemic lupus erythematosus, and allergic asthma.

In an embodiment, the present invention includes a method for treating a human having a disorder characterized by increased TNF-α activity such as inflammatory disorder, including administering to the human a therapeutically effective amount of a compound of formula 1. In an embodiment, the present invention includes the use of a compound of formula 1 for treating a human having disorders characterized by increased TNF-α activity. In an embodiment, the present invention includes the use of a compound of formula 1 for preparing a medicament for treating a human having disorders characterized by increased TNF-α activity.

In an embodiment, the present invention includes a method of treating a disorder with underlying TNF- α involvement including administering to the human suffering from or exhibiting a symptom or risk factor for the disorder, a therapeutically effective amount of a compound of formula 1. In an embodiment, the present invention includes the use of a compound of formula 1 for treating a human having a disease or condition with underlying TNF-α involvement. In an embodiment, the present invention includes the use of a compound of formula 1 for preparing a medicament for treating a human having a disease or condition with underlying TNF-α involvement.

Another aspect of this invention is directed to a method for preventing and/or reducing damage resulting from a disorder characterized by increased TNF-α activity such as inflammatory disorder, including administering to an affected human, a therapeutically effective amount of a compound of formula 1. In an embodiment, the present invention includes the use of a compound of formula 1 for preventing and/or reducing damage resulting from disorder. In an embodiment, the present invention includes the use of a compound of formula 1 for preparing a medicament for preventing and/or reducing damage resulting from a disorder characterized by increased TNF-α activity such as inflammatory disorder.

The present invention also envisages the use of a compound of formula 1 in combination with other pharmaceutically active compounds. For instance, a pharmaceutical composition, including a compound of the formula 1 can be administered to a human, with another TNF-α inhibitor or any other pharmaceutically active compound known to be useful in treating an inflammatory disorder, such as one of the above mentioned disorders, in mixtures with one another or in the form of pharmaceutical preparations.

The present invention furthermore relates to pharmaceutical compositions that contain a therapeutically effective amount of at least one compound of the formula 1, in addition to a pharmaceutically acceptable carrier or diluent, and to a process for the production of a pharmaceutical, which includes bringing at least one compound of formula 1, into a suitable administration form using a pharmaceutically suitable and physiologically tolerable excipient and, if appropriate, further suitable active compounds, additives or auxiliaries.

The present invention also relates to pharmaceutical compositions adapted for the treatment of disorders associated with increased TNF-α activity such as inflammatory disorders, comprising a therapeutically effective amount of at least one compound of the formula 1, along with pharmaceutically acceptable carrier.

The present invention also relates to a method for the preparation of a medicament for the treatment or prevention of disorders associated with increased TNF-α activity characterized in that at least one compound of the formula 1 is used as the pharmaceutically active substance.

In another aspect of this invention, a compound of the present invention is

administered locally. In the methods of treatment using the pharmaceutical compositions described above, the following are preferred administration routes, modes, etc.

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

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art. Pharmaceutically acceptable inert inorganic and/or organic carriers and/or additives can be used in addition to the compound(s) of the formula 1. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, cornstarch or derivatives thereof, gum arabica, magnesia or glucose, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, natural or hardened oils, etc. Suitable carriers for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological sodium chloride solution or alcohols, for example, ethanol, propanol or glycerol, sugar solutions, such as glucose solutions or mannitol solutions, or a mixture of the various solvents which have been mentioned.

The pharmaceutical preparations normally contain about 1 to 99%, for example, about 5 to 70%, or about 10 to about 30% by weight of the compound of formula 1.. The amount of the active ingredient, i.e. the compound of formula 1 in the pharmaceutical preparations can, for example, be from about 5 to 500 mg. The dose of the compounds of this invention, which is to be administered, can cover a wide range. The dose to be administered daily is to be selected to suit the desired effect. About 20 to 1,000 mg are preferably administered daily per patient. If required, higher or lower daily doses can also be administered. Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention can be varied so as to obtain an amount of the active ingredient, which is effective to achieve the

desired therapeutic response for a particular patient, composition, and mode of administration without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

In addition to the compound of formula 1 and carrier substances, the pharmaceutical preparations can contain additives such as, for example, fillers, antioxidants, dispersants, emulsifiers, defoamers, flavors, preservatives, solubilizers or colorants. They can also contain two or more compounds of the formula 1. Furthermore, in addition to at least one compound of the formula 1, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not to limit the present invention.

The following abbreviations are used herein:

| | | |
|---|---|---|
| ATCC | : | American Type Culture Collection |
| $CO_2$ | : | Carbon dioxide |
| DCE | : | Dichloroethane |
| DMF | : | N,N-dimethylformamide |
| DMSO | : | Dimethylsulfoxide |
| HCl | : | Hydrochloric acid |
| PDE4 | : | Phosphodiesterase 4 |
| RT | : | Room temperature |
| THF | : | Tetrahydrofuran |
| TLC | : | Thin layer chromatography |

## EXAMPLES

**Procedure according to Scheme 1a:**

To a mixture of two aldehydes (1 equivalent each) in a suitable solvent such as DCE, was added 1 equivalent of diamine and the reaction mixture was stirred at ambient temperature (25 °C). To this reaction mixture, sodium triacetoxy borohydride (3 equivalents) was added and it was stirred until the reaction was complete (4-5 h). The solvent was removed under reduced pressure. After addition of water and extraction with dichloromethane, the combined organic layers were dried over anhydrous sodium sulfate and concentrated. The crude product obtained was subjected to purification by silica gel column chromatography.

The following compounds were prepared using the procedure according to Scheme 1a:

**Example 1:**

**3,3'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(6,7-dimethyl-4H-chromen-4-one) dihydrochloride**

6,7-dimethyl-4-oxo-4H-chromene-3-carbaldehyde (150 mg, 0.73 mmol) was reacted with $N_1$, $N_2$-dimethylethane-1, 2-diamine (0.040 mL, 0.36 mmol) in presence of sodium triacetoxy borohydride (0.236 mg, 1.11 mmol), according to the procedure corresponding to Scheme 1a, to afford the title compound.

Yield: 60 mg (17.6 %).

$^1$H NMR ($CD_3OD$, 300MHz): δ 8.49(s, 2H), 7.67(s, 2H), 7.36(s, 2H), 4.26(bs, 4H), 3.79 (bs, 4H), 2.91(s, 6H), 2.33(s, 6H), 2.25(s, 6H);

MS: m/e (ES+) 460.96 (M+1).

**Example 2:**

**$N_1$,$N_2$-bis(4-(benzyloxy)-3-methoxybenzyl)ethane-1,2-diamine dihydrochloride**

4-(benzyloxy)-3-methoxybenzaldehyde (0.5 g, 2 mmol) was reacted with ethylene diamine (0.0690 mL, 1 mmol) in methanol (15 mL) in presence of sodium borohydride (119 mg, 3 mmol), according to the procedure corresponding to Scheme 1a, to afford the title compound.

Yield : 500 mg (82.78 %)

$^1$H NMR (DMSO-$d_6$, 300MHz): δ 7.3 – 7.4(m, 12 H), 6.99(dd, 4H, J=8.5Hz, 8Hz), 5.07(s, 4H), 4.07(t, 4H), 3.78(s, 6H), 3.30(m, 4H);
MS: m/e (ES+) 513 (M+1).

**Example 3:**
**5,5'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(4-(hydroxymethyl)-2-methylpyridin-3-ol) dihydrochloride**
2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridine-5-carbaldehyde(0.5 g, 2.41 mmol) was reacted with $N_1$, $N_2$-dimethylethane -1, 2-diamine (0.132 mL, 1.20 mmol) in dry DCE (10 mL) in presence of sodium triacetoxy borohydride (1.5 g, 7 mmol), according to the procedure corresponding to Scheme 1a, to afford the title compound.
Yield: - 22 mg (2 %)
$^1$H NMR ($CD_3OD$, 300MHz): δ 8.56(s, 2H), 4.88(s, 4H), 4.55 (b, 4H), 3.46 (bs 4H), 2.61(s, 6H), 2.48 (s, 6H);
MS: m/e (ES+) 391 (M+1).

**Example 4:**
**6,7-Dimethyl-3-((methyl(2-(methyl((2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridin-5-yl)methyl)amino)ethyl)amino)methyl)-4H-chromen-4-one dihydrochloride**
2,2,8-trimethyl-4H- [1,3] dioxino [4,5-c] pyridine-5-carbaldehyde (207 mg, 1 mmol) and 6,7-dimethyl-4-oxo-4H-chromene-3-carbaldehyde (202 mg, 1 mmol) were reacted with $N_1$, $N_2$-dimethylethane-1, 2-diamine (0.11 mL, 1 mmol) in presence of sodium triacetoxy borohydride (316 mg, 1.5 mmol), according to the procedure corresponding to Scheme 1a, to afford the title compound.
Yield: - 350 mg (63 %)
$^1$H NMR ($CD_3OD$, 300MHz): δ 8.67(s, 1H), 8.54(s, 1H), 7.89(s, 1H), 7.47(s, 1H), 5.39(s, 2H), 4.33(bs, 4H), 3.80(bm, 4H), 2.96(s, 3H), 2.64(s, 6H), 2.45(s, 3H), 2.41(s, 3H), 1.64 (s, 6H);
MS: m/e (ES+) 466.22 (M+1).

**Example 5:**
**1,4-Bis((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl)methyl)piperazine dihydrochloride**

1-(3-(trifluoromethyl) phenyl)-1H-indole-3-carbaldehyde (580 mg, 2 mmol) was reacted with piperazine (88 mg, 1 mmol) in DCE (3 mL), in presence of sodium triacetoxy borohydride (632 mg, 3 mmol), to afford the title compound.

Yield: 150 mg ( 21 %)

$^1$H NMR ($CD_3OD$, 300MHz): δ 7.91(s, 2H), 7.88(br s, 6H), 7.84-7.75(m, 4H), 7.57(d, 2H, *J*=7.5), 7.36-7.28(m, 4H), 4.75(s, 4H), 3.84 (br s, 4H), 3.63(br s, 4H);

MS: m/e (ES+) 633.32 (M+1).

**Example 6:**

**6,7-Dimethyl-3-((4-((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl) methyl)piperazin-1-yl)methyl)-4H-chromen-4-one dihydrochloride**

1-(3-(trifluoromethyl) phenyl)-1H-indole-3-carbaldehyde (290 mg, 1 mmol) and 6,7-dimethyl-4-oxo-4H-chromene-3-carbaldehyde (203 mg, 1 mmol) were reacted with piperazine (88 mg, 1 mmol) in DCE (3 mL), in presence of sodium triacetoxy borohydride (632 mg, 3 mmol), to afford the title compound.

Yield: 120 mg (19 %)

$^1$H NMR ($CD_3OD$, 300MHz): δ 8.39(s, 1H), 7.82(s, 1H), 7.79(br s, 4H), 7.74-7.65(m, 2H), 7.47(d, 1H), 7.33(s, 1H), 7.27-7.20(m, 2H), 4.65(s, 2H), 4.17(s, 2H), 3.62(bs, 8H) 2.32(s, 3H) 2.27(s, 3H);

MS: m/e (ES+) 546.22 (M+1).

**Procedure According to Scheme 2 :**

To an aromatic acid (1 equivalent) in a suitable solvent such as THF, was added CDI (1.2 equivalent) and the reaction mixture was stirred at ambient temperature (25 °C) for about 2 h. On formation of an intermediate ester, as indicated by TLC, diamine (0.5 equivalent) was taken in the solvent used such as THF and added to the reaction mixture. Stirring was continued for about 4 h at 25 °C. On completion of the reaction, THF was evaporated from the reaction mixture. To the crude oily mass, was added water and ethyl acetate. The separated aqueous layer was again extracted with ethyl acetate. The organic layers were combined and washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated to afford a crude product. The crude product was purified by silica gel column chromatography to give the pure product as a free base. This free base was treated

with saturated ethereal HCl to give the hydrochloride salt as a solid precipitate, which was filtered and dried.

The following compounds were prepared using the procedure according to Scheme 2:

**Example 7:**

**N,N'-(ethane-1,2-diyl) bis (2-hydroxybenzamide) dihydrochloride**

Salicylic acid (1 g, 7.2 mmol) in THF (20 mL) was reacted with CDI (1.4 g, 8.7 mmol), followed by ethylene diamine (0.24 mL, 3.5 mmol), according to the procedure corresponding to Scheme 2, to afford the title compound.

Yield: 280 mg (20.74 %)

$^1$H NMR ($CD_3OD$, 300MHz): δ 7.74(dd, 2H, J=1.8Hz, 8.7Hz), 7.36(m, 2H, J=1.5Hz, 7.8Hz, 9.3Hz), 6.84 (m, 4H, J=1.2Hz, 7.8Hz, 6.6Hz), 3.62 (s, 4H);

MS: m/e (ES-) 299 (M-1).

**Example 8:**

**N, N'-(propane-1,3-diyl) bis (2-hydroxybenzamide) dihydrochloride**

Salicylic acid (1 g, 7.2 mmol) in THF (20 mL) was reacted with CDI (1.4 g, 8.7 mmol), followed by 1,3-diaminopropane (0.31 mL, 3.5 mmol), according to the procedure corresponding to Scheme 2, to afford the title compound.

Yield: - 180 mg (12.85 %)

$^1$HNMR ($CD_3OD$, 300MHz): δ 7.73(d, 2H, J=8.1Hz), 7.36(t, 2H, J=7.2Hz, 15.3Hz), 8.1Hz), 6.89(m, 4H,J=7.5Hz, 3Hz, 12.3Hz, 4.8Hz), 3.48(t, 4H), 1.90(m, 2H),

MS: m/e (ES+) 315 (M+1).

**Example 9:**

**4-Hydroxy-N-(2-(2-hydroxybenzamido)ethyl)-3-methoxybenzamide dihydrochloride**

Salicylic acid (0.690 g, 5 mmol) and vanillic acid (0.840 g, 5 mmol) was reacted with CDI (2.2 g, 13.5 mmol), followed by ethylene diamine (0.33 mL, 5 mmol), according to the procedure corresponding to Scheme 2, to afford the title compound.

Yield:- 130 mg (6.52%)

$^1$HNMR (DMSO-$d^6$, 300MHz): δ 9.53,12.60(bs, 2-OH), 8.41, 8.94(bs, 2 N-H); 7.82(d, 1H, J=8.1Hz), 7.30-7.39(m, 3H), 6.85(m, 2H,), 6.76(d, 1H,J=8.4Hz), 3.77(s, 3H), 3.41 (s, 4H);

MS: m/e (ES+) 331 (M+1).

**Biological Screening of Compounds:**

The efficacy of the present compounds in inhibiting the activity of TNF-α can be determined by a number of pharmacological assays well known in the art and described below. The exemplified pharmacological assays, which follow, have been carried out with the compounds of the present invention and their salts.

**Example 10:**

***In vitro* bioassay**

NCTC clone 929 (L-929), a murine fibroblast cell line was procured from The American Type Culture Collection, (ATCC, USA). The cells were maintained in Minimum Essential Medium (MEM) supplemented with 100 U/mL penicillin, 100 µg/mL streptomycin and 10% horse serum. 50 µL of the cells were seeded into 96-well plates at a concentration of $4x10^5$ cells/mL and left to acclimatize for at least 16 h before being treated. The viability, as determined by trypan blue dye exclusion, was uniformly ≥ 98%.

Preliminary experiments indicated that a concentration of 100 pg/mL TNF-α was required to achieve 70% cell death as compared to untreated control and subsequently this concentration was used in all ensuing experiments to identify compounds that will have the ability to block the interaction of TNF-α with its receptor.

Various concentrations (10, 30, and 100 µM) of the compounds dissolved in dimethylsulfoxide (DMSO) were incubated with 1000 pg/mL. TNF-α prepared in complete medium supplemented with 10 µg/mL of actinomycin D for 1 h at 37 $^oC$ in 5% $CO_2$ atmosphere. Enbrel (Etanercept; Soluble TNFR2 coupled to Fc portion of IgG (Immunoglobulin)) (5,000, 10,000 and 50,000 pg/mL) and a small molecule, 6,7-dimethyl-3-((methyl(2-(methyl((1-(3-(trifluoromethyl)phenyl)-1H-indol-3-

yl)methyl)amino) ethyl) amino) methyl)-4H-chromen-4-one (10, 30 and 100 µM) were used as positive controls. Subsequently, 10 µL of this pre-incubated mixture was added to the formerly plated cells, to give a final concentration of 100 pg/mL TNF-α and 1µg/mL actinomycin D. The final concentration of DMSO is maintained at 0.05%. The vehicle (0.05% DMSO) was used as a carrier control. The positive control should contain 200 ng/mL TNF-α and 1µg/mL actinomycin D. The negative control should contain no TNF-α. Cell viability was determined after 20 h using MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxy methoxyphenyl)-2-(4-sulfonyl)-2H-tetrazolium) staining. Toxicity of the compound was assessed in a parallel set of plates. Absorbance was measured at 490 nm.

When certain small molecules of the present invention were screened by the above assay, they showed TNF-α inhibitory activity as indicated in Table 1.

**Table 1:**

| Compound | Anti-inflammatory Assay, L929, % Protection | | |
|---|---|---|---|
| | 10 µM | 30 µM | 100 µM |
| Compound of Example 1 | - | 60 | 63 |
| Compound of Example 2 | 17 | 26 | 50 |
| Compound of Example 3 | - | 26 | 24 |
| Compound of Example 4 | - | 02 | 23 |
| Compound of Example 5 | - | 25 | 12 |
| Compound of Example 6 | - | - | 26 |
| Compound of Example 7 | - | 08 | 00 |
| Compound of Example 8 | - | 00 | 00 |
| Compound of Example 9 | - | - | 20 |

It should be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the content clearly

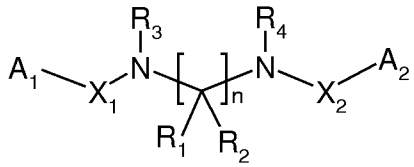
dictates otherwise. Thus, for example, reference to a composition containing "a compound" includes a mixture of two or more compounds. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

All publications and patent applications in this specification are indicative of the level of ordinary skill in the art to which this invention pertains.

The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

We claim :

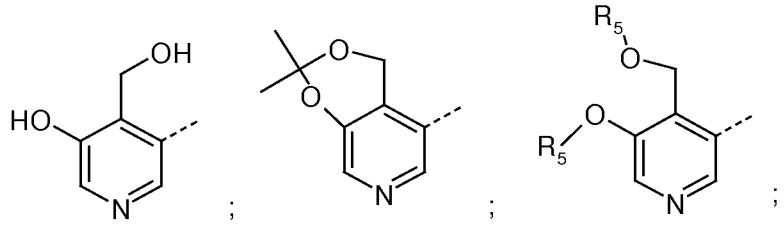
1. A compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof;

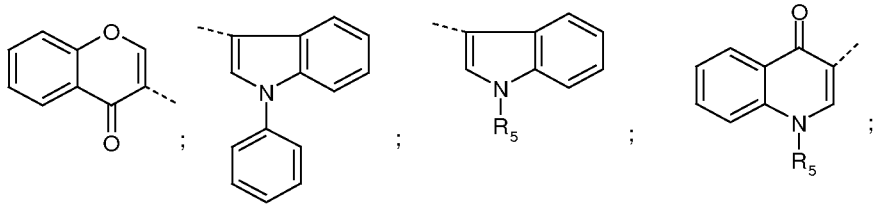


Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted heterocyclic system selected from;





wherein the dotted line indicates the point of attachment, $R_5$ is hydrogen or $(C_1$-$C_4)$-alkyl group and the rings of the heterocyclic systems herein above may be substituted with groups selected from $(C_1$-$C_4)$-alkyl, $(C_1$-$C_4)$-alkoxy, hydroxyl, hydroxy-$(C_1$-$C_4)$-alkyl (e.g., hydroxymethyl or 1-hydroxyethyl or 2-hydroxyethyl), and fluoroalkyl (e.g., $CF_3$);

$X_1$ and $X_2$ are independently a carbonyl group or a methylene ($-CH_2-$) group;

n is an integer from 2-4;

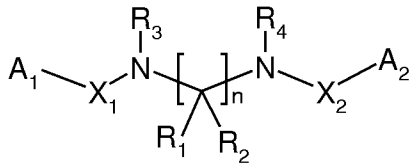
$R_1$ and $R_2$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or $(C_1$-$C_4)$-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system;

with a proviso that when $A_1$ and $A_2$ are 1-(3-(trifluoromethyl)phenyl)-1H-indole and 6,7-dimethyl-4H-chromen-4-one respectively and $X_1$ and $X_2$ are independently a methylene (-$CH_2$-) group, $R_3$ and $R_4$ form a ring system.

2. A compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof;



Formula 1

wherein:

$A_1$ and $A_2$ are independently a substituted or unsubstituted phenyl group wherein the substituents on the phenyl ring are selected from ($C_1$-$C_4$)-alkyl, fluoroalkyl such as $CF_3$, hydroxyl, ($C_1$-$C_4$)-alkoxy, benzyloxy and hydroxy-($C_1$-$C_4$)-alkyl;

$X_1$ and $X_2$ are independently a carbonyl group or a methylene (-$CH_2$-) group;

n is an integer from 2-4;

$R_1$ and $R_2$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group;

$R_3$ and $R_4$ are independently, hydrogen or ($C_1$-$C_4$)-alkyl group; and

$R_3$ and $R_4$ can optionally form a ring system.

3. The compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to claim 1, is selected from:

3,3'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(6,7-dimethyl-4H-chromen-4-one) dihydrochloride;

5,5'-(ethane-1,2-diylbis(methylazanediyl))bis(methylene)bis(4-(hydroxymethyl)-2-methylpyridin-3-ol) dihydrochloride;

6,7-Dimethyl-3-((methyl(2-(methyl((2,2,8-trimethyl-4H-[1,3]dioxino[4,5-c]pyridin-5-yl)methyl)amino)ethyl)amino)methyl)-4H-chromen-4-one dihydrochloride;

1,4-Bis((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl)methyl)piperazine dihydrochloride; and
6,7-Dimethyl-3-((4-((1-(3-(trifluoromethyl) phenyl)-1H-indol-3-yl) methyl)piperazin-1-yl)methyl)-4H-chromen-4-one dihydrochloride.

4. The compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to claim 2, is selected from:
$N_1$,$N_2$-bis(4-(benzyloxy)-3-methoxybenzyl)ethane-1,2-diamine dihydrochloride;
N,N'-(ethane-1,2-diyl) bis (2-hydroxybenzamide) dihydrochloride;
N,N'-(propane-1,3-diyl) bis (2-hydroxybenzamide) dihydrochloride; and
4-Hydroxy-N-(2-(2-hydroxybenzamido)ethyl)-3-methoxybenzamide dihydrochloride.

5. The compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-4, wherein the compound inhibits Tumor Necrosis Factor-alpha (TNF-α).

6. A pharmaceutical composition comprising a therapeutically effective amount of the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, and a pharmaceutically acceptable carrier or diluent.

7. A method of inhibition of Tumor Necrosis Factor- alpha (TNF-α), comprising administering the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, to a human in need thereof.

8. A method of treating a disorder with underlying TNF-α involvement, comprising administering the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, to a human suffering from or exhibiting a symptom or risk factor for the disorder.

9. The method according to claim 8, wherein the disorder is an inflammatory disorder.

10. Use of the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, for the inhibition of Tumor Necrosis Factor- alpha (TNF-α).

11. Use of the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, for the treatment of disorders characterised by increased Tumor Necrosis Factor- alpha (TNF-α) activity.

12. Use of the compound of formula 1, or a stereoisomer thereof, tautomer thereof, or mixture thereof in any ratio; a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable polymorph thereof, according to any one of the claims 1-5, for the preparation of a medicament for the treatment of disorders characterised by increased Tumor Necrosis Factor- alpha (TNF-α) activity.

13. The use according to claim 11 or claim 12, wherein the disorder is an inflammatory disorder.