# 5-ARYLTETRAZOLE COMPOUNDS, COMPOSITIONS THEREOF, AND USES THEREFOR

This application is a continuation-in-part of U.S. application no. 10/197,609, filed July 18, 2002, which is currently pending, the entirety of which is incorporated herein by reference.

## GOVERNMENTAL SUPPORT

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## 1. FIELD OF THE INVENTION

The present invention relates to 5-Aryltetrazole Compounds, compositions comprising an effective amount of a 5-Aryltetrazole Compound, and methods for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia comprising administering to an animal in need thereof an effective amount of a 5-Aryltetrazole Compound.

## 2. BACKGROUND OF THE INVENTION

The level of xanthine oxidase ("XO") in an animal increases markedly (>400-fold in bronchoalveolar fluid in pneumonitis) during inflammation, ischemia-reperfusion injury, and atherosclerosis. Particularly, due to the spillover of tissue XO into the circulation, plasma levels of XO may be detected in an animal experiencing adult respiratory distress syndrome, ischemia-reperfusion injury, arthritis, sepsis, hemorrhagic shock, and other inflammatory conditions. Inflammation-induced histamine release by mast cells and basophils also enhances the activity of XO.

Superoxide radical ($O_2^-$) can be generated by xanthine oxidase and NADPH oxidase from the partial reduction of molecular oxygen. Neutrophils and macrophages are known to produce $O_2^-$ and hydrogen peroxide ($H_2O_2$), which normally are involved in the killing of ingested or invading microbes (T. Oda *et al.*, *Science*, 244:974-976). Under physiologic conditions XO is ubiquitously present in the form of a xanthine dehydrogenase (XDH). XDH is a molybdenum iron-sulfur flavin dehydrogenase that uses $NAD^+$ as an

electron acceptor to oxidize purines, pyrimidines, pteridins, and other heterocyclic nitrogen-containing compounds. In mammals, XDH is converted from the NAD-dependent dehydrogenase form to the oxygen-dependent oxidase form, either by reversible sulfhydryl oxidation or irreversible proteolytic modification (S. Tan *et al.*, *Free Radic. Biol. Med.* 15:407-414). Xanthine oxidase then no longer uses $NAD^+$ as an electron acceptor, but transfers electrons onto oxygen, generating $O^{2-}$, $H_2O_2$, and hydroxyl radical (OH) as purines are degraded to uric acid (J.M. McCord *et al.*, *New Engl. J. Med.* 312:159-163; R. Miesel *et al.*, *Inflammation*, 18:597-612). Inflammatory activation converts XDH to XO, mainly by oxidizing structurally important thiolates. Inflammation also markedly up-regulates the conversion of xanthine dehydrogenase (T.D. Engerson *et al.*, *J. Clin. Invest.* 79:1564-1570).

Inhibition of XO activity blocks the formation of $O_2^-$ and prevents loss of purine nucleotides, and is therefore salutary in a variety of shock and ischemia reperfusion disorders. Pharmacologic inhibition of XO can also be beneficial by blocking the pro-inflammatory effect of $O_2^-$ on gene expression (M.D. Schwartz *et al.*, *Am. J. Respir. Cell. Mol. Biol.*, 12:434-440). $O_2^-$ has been implicated in the nuclear translocation of NF-kappa B and the expression of NF-icB-dependent genes. In mice subjected to hemorrhagic shock, depletion of XO by a tungsten-enriched diet decreased mononuclear mRNA levels of IL-113 and TNF-a. Similar results were obtained after pharmacologic inhibition of XO by *in vivo* administration of allopurinol. A vicious cycle can be created by oxidant stress, in which $O_2^-$ induction of pro-inflammatory cytokines results in greater XDH to XO conversion, and thus more $O_2^-$ production. This suggests that XO inhibitors can exert important anti-inflammatory actions by interrupting this process at multiple points, in particular, by blocking pro-inflammatory gene expression.

Pharmacologic inhibition of XO can also be beneficial in hemorrhagic shock by preserving the intracellular nucleotide pool. Under conditions of energetic failure, induced by hypoxia or by oxidant-induced poly(ADP-ribose) synthetase activation, high energy phosphate nucleotides are sequentially degraded to inosine monophosphate, xanthine, and hypoxanthine. In the presence of XO and molecular oxygen, xanthine and hypoxanthine degrade to uric acid, thereby depleting the purine pool. The loss of available purines with which to form ATP accelerates the loss of intracellular energetics and contributes to cell necrosis and organ failure. XO inhibitors block this terminal degradative pathway and permit the cell to recover and reestablish adequate stores of high energy phosphate nucleotides. In a canine model of severe hemorrhagic shock, pre-treatment with allopurinol resulted in a 6-fold increase in survival (J.W. Crowell *et al.*, *Am. J. Phys.* 216:744-748). When the administration of allopurinol was delayed until after shock had

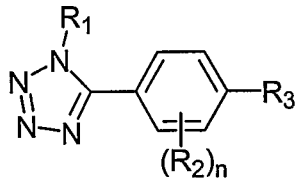
been produced, allopurinol exerted no benefit. Infusion of the purine base hypoxanthine after the onset of shock similarly provided no benefit. When allopurinol and hypoxanthine were co-infused, however, there was a dramatic increase in survival (no survival in control group at 16 hours post-shock vs. a 40 % survival in the treated group at 48 hours). Similar results were obtained in a canine model of hemorrhagic shock in which allopurinol significantly improved survival, whereas a cocktail of free-radical scavengers (superoxide dismutase, catalase, dimethylsulfoxide, and alpha tocopherol) had no effect (D. Mannion, *et al., Circ. Shock*, 42:39-43). Thus, XO blockade appears to be beneficial by three independent mechanisms: blockade of $O_2^-$ formation; inhibition of $O_2^-$ mediated pro-inflammatory gene expression; and preservation of the nucleotide pool available for ATP formation.

Accordingly, there is a clear need for compounds that inhibit the levels of xanthine oxidase in an animal and, accordingly, that are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia.

Citation of any reference in Section 2 of this application is not an admission that the reference is prior art to the application.

## 3. SUMMARY OF THE INVENTION

The invention encompasses compounds having the formula (Ia):



**(Ia)**

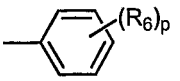
and pharmaceutically acceptable salts and hydrates thereof, wherein:

$R_1$ is $CO_2R_4$;

each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_3-C_{10})$heterocycle, -phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)N(R_5)(R_5)$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl,

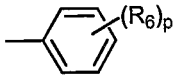
-($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -naphthyl, -($C_3$-$C_{10}$)heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-N(R_5)C(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



;

$R_4$ is -($C_5$)heteroaryl, -($C_6$)heteroaryl, phenyl, naphthyl, or benzyl;

each $R_5$ is independently -H, $-CF_3$, -($C_1$-$C_{10}$)alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_3$-$C_{10}$)heterocycle, or



;

each $R_6$ is independently -H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N((C_1$-$C_{10})alkyl(C_1$-$C_{10})alkyl)$, $-O(C_1$-$C_{10})alkyl$, $-C(O)(C_1$-$C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1$-$C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1$-$C_{10})alkyl(C_1$-$C_{10})alkyl)$, -C(O)H, $-CO_2(C_1$-$C_{10})alkyl$, -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_5$)heteroaryl, -($C_6$)heteroaryl, -phenyl, naphthyl, -($C_3$-$C_{10}$)heterocycle, $-CO_2(CH_2)_m(C_1$-$C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1$-$C_{10})alkyl$, $-NHC(O)NH(C_1$-$C_{10})alkyl$, $-OC(O)(C_1$-$C_{10})alkyl$, $-OC(O)O(C_1$-$C_{10})alkyl$, $-SO_2NHR_5$, or $-SO_2NH_2$;

n is an integer ranging from 0 to 4;

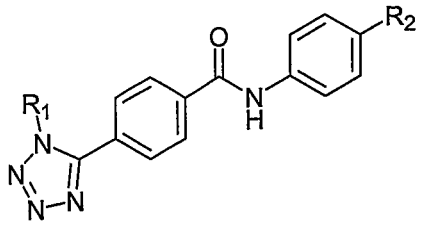
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

A compound of formula (Ia) or a pharmaceutically acceptable salt or hydrate thereof is useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia in an animal.

The invention also relates to pharmaceutical compositions comprising an effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia in an animal.

The invention also relates to compounds of formula (Ib):



**(Ib)**

and pharmaceutically acceptable salts and hydrates thereof, wherein:

$R_1$ is -H, $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

$R_2$ is $-(C_1\text{-}C_{10})$alkyl or $-O(C_1\text{-}C_{10})$alkyl;

$R_4$ is $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, naphthyl, or benzyl; and

each $R_5$ is independently -H, $-CF_3$, $-(C_1\text{-}C_{10})$alkyl, -benzyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_3\text{-}C_{10})$heterocycle.

A compound of formula (Ib) or a pharmaceutically acceptable salt or hydrate thereof is useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia in an animal.

The invention also relates to pharmaceutical compositions comprising an effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt or hydrate thereof; and a pharmaceutically acceptable carrier or vehicle. These compositions are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia in an animal.

The invention further relates to methods for treating or preventing an inflammation disease, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing a reperfusion disease, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

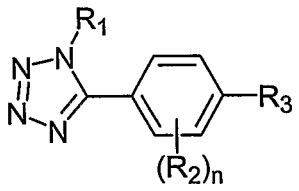
The invention further relates to methods for treating or preventing hyperuricemia, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing tumor-lysis syndrome, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing an inflammatory bowel disorder, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for inhibiting xanthine oxidase activity, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ia) or (Ib) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing an inflammation disease, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



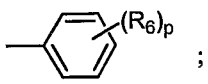
**(Ic)**

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

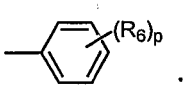
$R_1$ is -H, $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_3\text{-}C_{10})$heterocycle, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)N(R_5)(R_5)$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-N(R_5)C(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



$R_4$ is $-CF_3$, $-(C_1-C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_3-C_{10})$heterocycle, or



each $R_5$ is independently -H or $R_4$;

each $R_6$ is independently -H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, -C(O)H, $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, $-SO_2NHR_5$, or $-SO_2NH_2$;

n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

The invention further relates to methods for treating or preventing a reperfusion disease, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing hyperuricemia, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing tumor-lysis syndrome, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for treating or preventing an inflammatory bowel disorder, comprising administering to an animal in need thereof an

effective amount of a compound of formula (Ic) or a pharmaceutically acceptable salt or hydrate thereof.

The invention further relates to methods for inhibiting xanthine oxidase activity, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic) or a pharmaceutically acceptable salt or hydrate thereof.

The invention also relates to kits comprising a container containing a compound of formula (Ia), (Ib), or (Ic) or a pharmaceutically acceptable salt or hydrate thereof (each being a "5-Aryltetrazole Compound").

The invention can be understood more fully by reference to the following detailed description and illustrative examples, which are intended to exemplify non-limiting embodiments of the invention.

## 4. DETAILED DESCRIPTION OF THE INVENTION

### 4.1. DEFINITIONS

As used herein, the term "-($C_1$-$C_{10}$)alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl, -n-hexyl, -n-heptyl, -n-octyl, -n-nonyl and -n-decyl; while saturated branched alkyls include -isopropyl, -*sec*-butyl, -isobutyl, -*tert*-butyl, -isopentyl, -2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimtheylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. In addition, chemical nomenclature used to define alkyl groups has its standard meaning known to those of ordinary skill in the art, for example, "Me" means methyl or -$CH_3$, "Et" means ethyl or -$CH_2CH_3$, "n-Pr" means n-propyl or -$CH_2CH_2CH_3$, "i-Pr" means iso-propyl or -$CH(CH_3)_2$, "n-Bu" means n-butyl or -$CH_2(CH_2)_2CH_3$, "t-Bu" means tert-butyl or -$C(CH_3)_3$.

As used herein, the term "-($C_2$-$C_{10}$)alkenyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at least one carbon-carbon double bond. Representative straight chain and branched ($C_2$-$C_{10}$)alkenyls include -vinyl, -allyl, -1-butenyl, -2-butenyl, -isobutylenyl, -1-pentenyl, -2-pentenyl, -3-methyl-1-butenyl, -2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, -1-hexenyl, -2-hexenyl, -3-hexenyl, -1-heptenyl, -2-heptenyl, -3-heptenyl, -1-octenyl, -2-octenyl, -3-octenyl, -1-nonenyl, -2-nonenyl, -3-nonenyl, -1-decenyl, -2-decenyl, -3-decenyl and the like.

As used herein, the term "-($C_2$-$C_{10}$)alkynyl" means a straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and including at lease one carbon-carbon triple bond. Representative straight chain and branched -($C_2$-$C_{10}$)alkynyls include -acetylenyl, -propynyl, -1-butynyl, -2-butynyl, -1-pentynyl, -2-pentynyl, -3-methyl-1-butynyl, -4-pentynyl, -1-hexynyl, -2-hexynyl, -5-hexynyl, -1-heptynyl, -2-heptynyl, -6-heptynyl, -1-octynyl, -2-octynyl, -7-octynyl, -1-nonynyl, -2-nonynyl, -8-nonynyl, -1-decynyl, -2-decynyl, -9-decynyl and the like.

As used herein, the term "-($C_3$-$C_{10}$)cycloalkyl" means a saturated cyclic hydrocarbon having from 3 to 10 carbon atoms. Representative ($C_3$-$C_{10}$)cycloalkyls include -cyclopropyl, -cyclobutyl, -cyclopentyl, -cyclohexyl, -cycloheptyl, -cyclooctyl, -cyclononyl, and -cyclodecyl.

As used herein, the term "-($C_8$-$C_{14}$)bicycloalkyl" means a bi-cyclic hydrocarbon ring system having from 8 to 14 carbon atoms and at least one saturated cyclic alkyl ring. Representative -($C_8$-$C_{14}$)bicyclocycloalkyls include -indanyl, -1,2,3,4-tetrahydronaphthyl, -5,6,7,8-tetrahydronaphthyl, -perhydronaphthyl and the like.

As used herein, the term "-($C_5$-$C_{10}$)cycloalkenyl" means a cyclic non-aromatic hydrocarbon having at least one carbon-carbon double bond in the cyclic system and from 5 to 10 carbon atoms. Representative ($C_5$-$C_{10}$)cycloalkenyls include -cyclopentenyl, -cyclopentadienyl, -cyclohexenyl, -cyclohexadienyl,-cycloheptenyl, -cycloheptadienyl, -cycloheptatrienyl, -cyclooctenyl, -cyclooctadienyl, -cyclooctatrienyl, -cyclooctatetraenyl, -cyclononenyl, -cyclononadienyl, -cyclodecenyl, -cyclodecadienyl and the like.

As used herein, the term "-($C_3$-$C_{10}$)heterocycle" or "-($C_3$-$C_{10}$)heterocyclo" means a 3- to 10-membered monocyclic heterocyclic ring which is either saturated, unsaturated non-aromatic, or aromatic. A 3-membered -($C_3$-$C_7$)heterocycle can contain up to 3 heteroatoms, and a 4- to 10-membered -($C_3$-$C_{10}$)heterocycle can contain up to 4 heteroatoms. Each heteroatom is independently selected from nitrogen, which can be

quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The -($C_3$-$C_{10}$)heterocycle may be attached via any heteroatom or carbon atom. Representative -($C_3$-$C_{10}$)heterocycles include pyridyl, furyl, thiophenyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, morpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, benzo[1,3]dioxolyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group or the hydrogen on an oxygen may be substituted with a methoxymethyl.

As used herein, the term "-($C_5$)heteroaryl" means an aromatic heterocycle ring of 5 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, nitrogen. Representative -($C_5$)heteroaryls include furyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyrazinyl, triazolyl, thiadiazolyl, and the like.

As used herein, the term "-($C_6$)heteroaryl" means an aromatic heterocycle ring of 6 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, nitrogen. One of the -($C_6$)heteroaryl's rings contain at least one carbon atom. Representative ($C_6$)heteroaryls include pyridyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl, pyrimidyl, and the like.

As used herein, the term "-O($C_1$-$C_{10}$)alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include -methyoxy, -ethyoxy, -n-propyloxy, -n-butyloxy, -n-pentyloxy, -n-hexyloxy, -n-heptyloxy, -n-octyloxy, -n-nonyloxy and -n-decyloxy; while saturated branched alkyls include -isopropyloxy, -*sec*-butyloxy, -isobutyloxy, -*tert*-butyloxy, -isopentyloxy, -2-methylbutyloxy, -3-methylbutyloxy, -2-methylpentyloxy, -3-methylpentyloxy, -4-methylpentyloxy, -2-methylhexyloxy, -3-methylhexyloxy, -4-methylhexyloxy, -5-methylhexyloxy, -2,3-dimethylbutyloxy, -2,3-dimethylpentyloxy, -2,4-dimethylpentyloxy, -2,3-dimethylhexyloxy, -2,4-dimethylhexyloxy, -2,5-dimethylhexyloxy, 2,2-dimethylpentyloxy, -2,2-dimethylhexyloxy, -3,3-dimtheylpentyloxy, -3,3-dimethylhexyloxy, -4,4-dimethylhexyloxy, -2-ethylpentyloxy, -3-ethylpentyloxy, -2-ethylhexyloxy, -3-ethylhexyloxy, -4-ethylhexyloxy, -2-methyl-2-ethylpentyloxy, -2-methyl-3-ethylpentyloxy, -2-methyl-4-ethylpentyloxy, -2-methyl-2-ethylhexyloxy, -2-methyl-3-ethylhexyloxy,

-2-methyl-4-ethylhexyloxy, -2,2-diethylpentyloxy, -3,3-diethylhexyloxy, -2,2-diethylhexyloxy, -3,3-diethylhexyloxy and the like. In addition, chemical nomenclature used to define alkyloxy groups has its standard meaning known to those of ordinary skill in the art, for example, "OMe" means methoxy, methoxyl, or $-OCH_3$, "OEt" means ethoxy, ethoxyl, or $-OCH_2CH_3$, "n-OPr" means n-propyloxy or $-CH_2CH_2CH_3$, "i-OPr" means iso-propyloxy or $-OCH(CH_3)_2$, "n-OBu" means n-butyloxy or $-OCH_2(CH_2)_2CH_3$, "t-OBu" means tert-butyloxy or $-OC(CH_3)_3$.

As used herein, the term "-Halogen" or "-Halo" means -F, -Cl, -Br or -I.

As used herein, the term "animal," includes, but is not limited to, a cow, monkey, chimpanzee, baboon, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig and human.

As used herein, the term "adamantyl" includes 1-adamantyl, 2-adamantyl, and 3-adamantyl.

As used herein, the term "naphthyl" includes 1-naphthyl and 2-naphthyl.

As used herein, the term "morpholinyl" includes N-morpholinyl, 2-morpholinyl, and 3-morpholinyl.

As used herein, the term "pyrridyloxide" includes 2-pyrridyloxide, 3-pyrridyloxide, and 4-pyrridyloxide.

As used herein, the term "pyrrolidinyldione" includes N-pyrrolidinyl-2, 3-dione, N-pyrrolidinyl-2,4-dione, N-pyrrolidinyl-2,5-dione, N-pyrrolidinyl-3,5-dione, N-pyrrolidinyl-3,4-dione, 2-pyrrolidinyl-3,4-dione, or 3-pyrrolidinyldione-2,4-dione, and 3--pyrrolidinyl-2,5-dione.

As used herein, the term "piperdinyl" includes N-piperdinyl, 2-piperdinyl, and 3-piperdinyl.

As used herein, the term "pharmaceutically acceptable salt," is a salt formed from an acid and a basic nitrogen group of one of the 5-Aryltetrazole Compounds. Illustrative salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate, and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a 5-Aryltetrazole Compound having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but

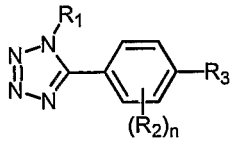
are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

As used herein, the term "pharmaceutically acceptable hydrate," is a hydrate formed from the association of one or more water molecules with a 5-Aryltetrazole Compound. The term "hydrate" includes a mono-hydrate, dihydrate, trihydrate, tetrahydrate, and the like.

As used herein in connection with a 5-Aryltetrazole Compound, the term "effective amount" means an amount effective for: (a) treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia; or (b) inhibiting xanthine oxidase activity.

## 4.2. COMPOUNDS OF FORMULA (Ia)

As stated above, the invention encompasses compounds of formula (Ia):




**(Ia)**

and pharmaceutically acceptable salts and hydrates thereof, wherein $R_1$, $R_2$, $R_3$, and n are defined above for the compounds of formula (Ia).

In one embodiment n is 0.

In another embodiment n is 0 and $R_3$ is -halo.

In another embodiment n is 0 and $R_3$ is $-C(O)R_5$,

In another embodiment n is 0 and $R_3$ is $-C(O)NHC(O)R_5$.

In another embodiment n is 0 and $R_3$ is $-C(O)N(R_5)(R_5)$.

In another embodiment n is 0 and $R_3$ is $-CO_2(CH_2)_m(R_5)$.

In another embodiment n is 0 and $R_3$ is -H.

In another embodiment n is 0 and $R_3$ is -NHC(O)N($R_5$)($R_5$).

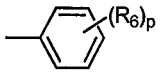
In another embodiment n is 0 and $R_3$ is -C(O)NH$R_5$.

In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; and $R_5$ is



.

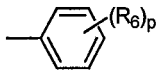
In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

and p is an integer from 1 to 3.

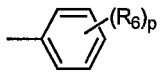
In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

and p is 1 or 2.

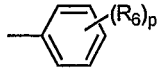
In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 1; and $R_6$ is in the para position.

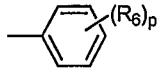
In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 1; and $R_6$ is in a meta position.

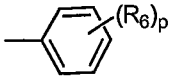
In another embodiment n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 1; and $R_6$ is in an ortho position.

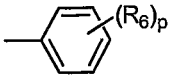
In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and each $R_6$ is independently -halo.

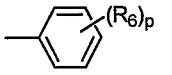
In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; and each $R_6$ is independently -halo.

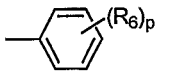
In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently halo; and one $R_6$ is in the para position and the other $R_6$ is in a meta position.

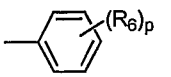
In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently halo; and one $R_6$ is in the para position and the other $R_6$ is in an ortho position.

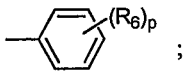
In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

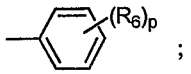
p is 2; each $R_6$ is independently halo; and one $R_6$ is in an ortho position and the other $R_6$ is in a meta position.

In another embodiment n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



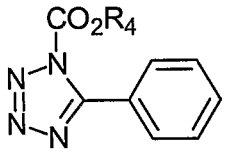
p is 2; each $R_6$ is independently halo; and each $R_6$ is in an ortho position.

In another embodiment n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is

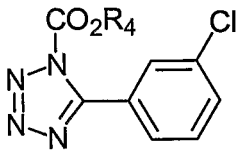


p is 2; each $R_6$ is independently halo; and each $R_6$ is in a meta position.

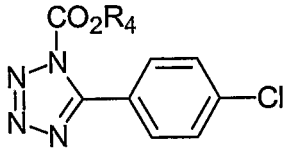
Illustrative subclasses of the compounds of formula (Ia) have the following formulas, wherein $R_4$ is -($C_5$)heteroaryl, -($C_6$)heteroaryl, phenyl, naphthyl, or benzyl:



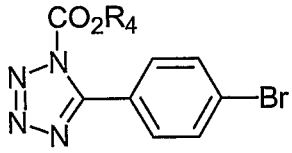
**Formula AA;**



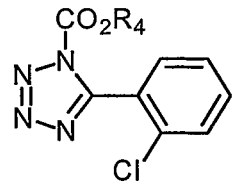
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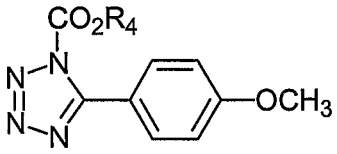
**Formula AC;**



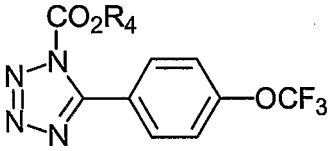
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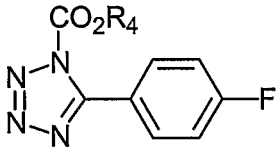
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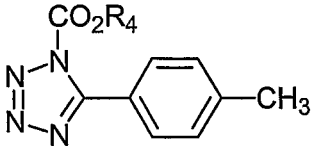
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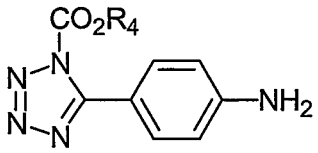
**Formula AG;**



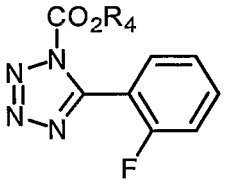
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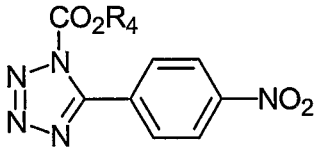
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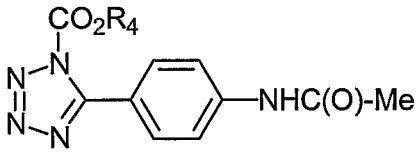
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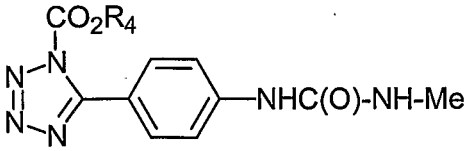
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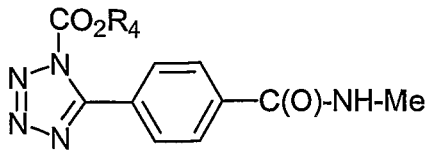
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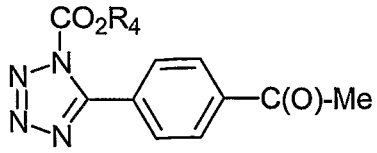
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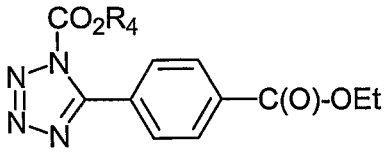
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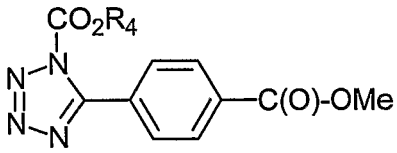

**Formula AO;**



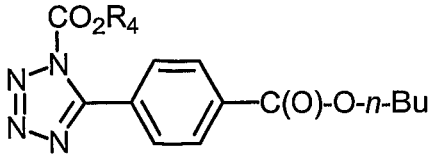

**Formula AP;**



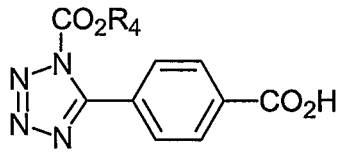

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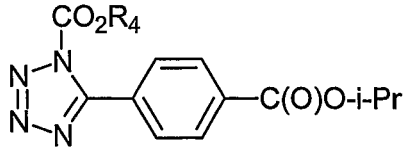

**Formula AR;**



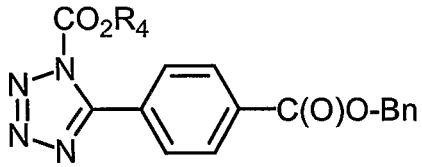

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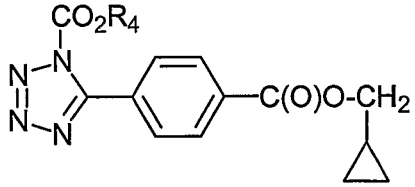
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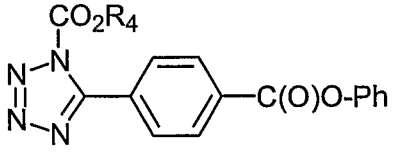
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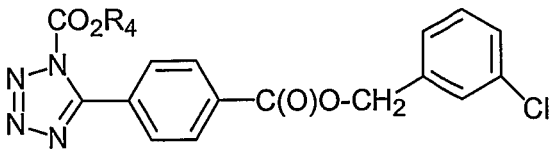
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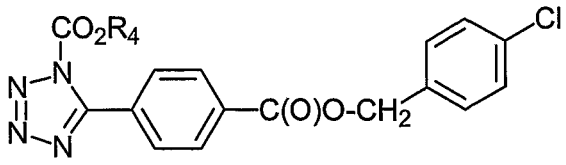
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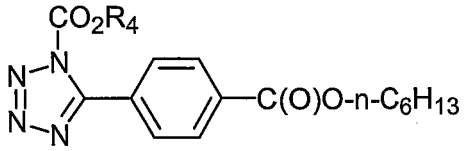
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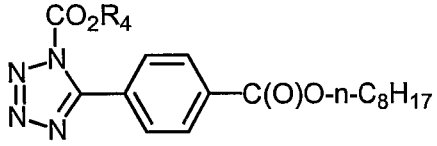
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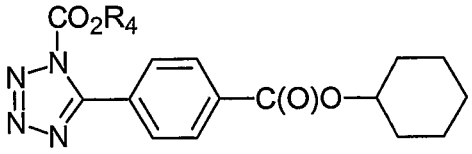

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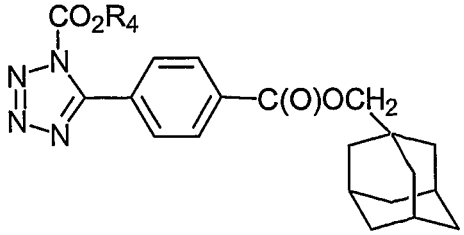

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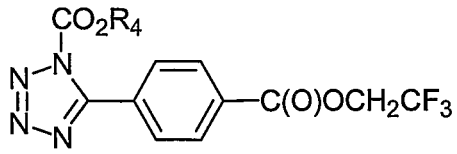

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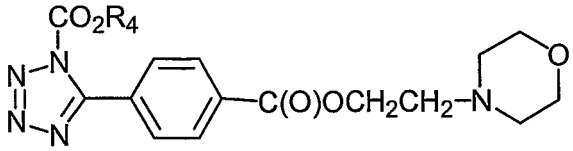

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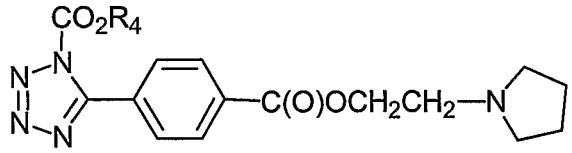

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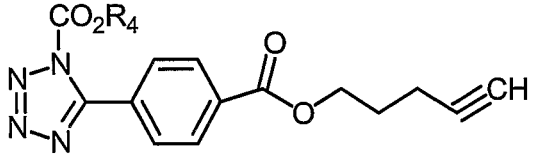
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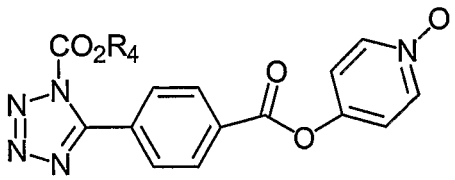
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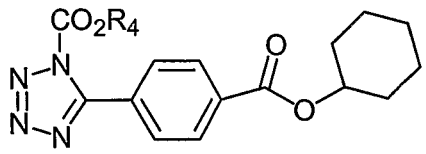
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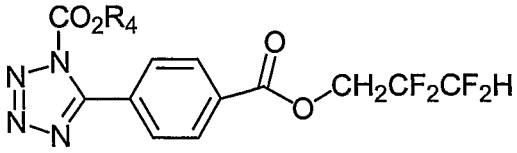
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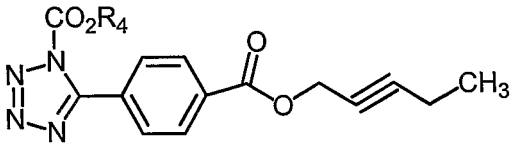
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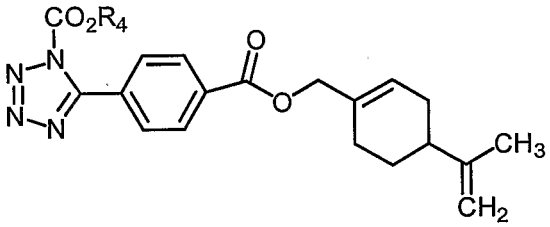
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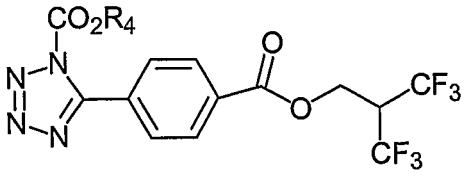
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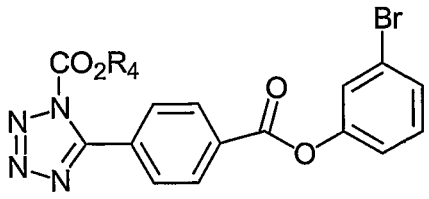
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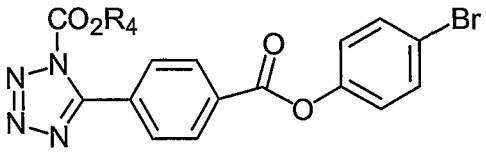
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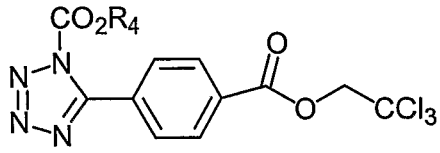
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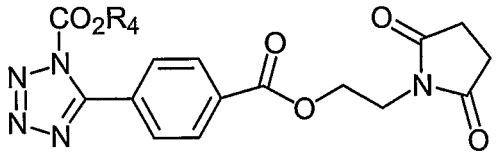
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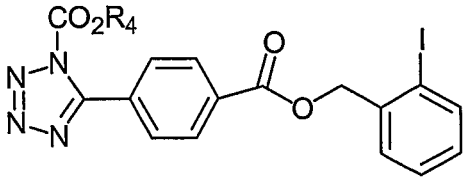
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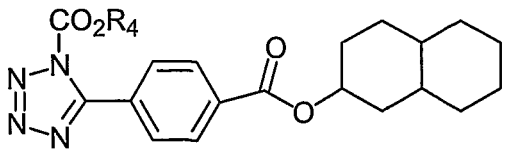
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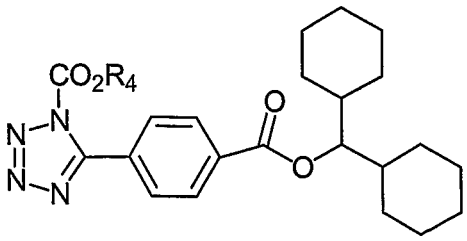
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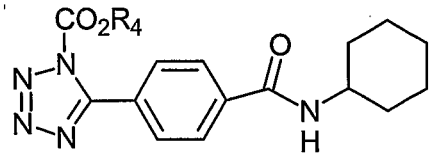
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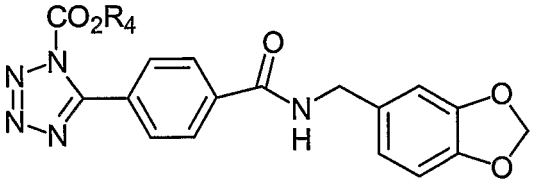
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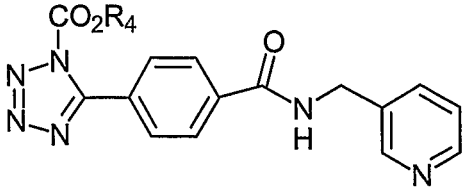
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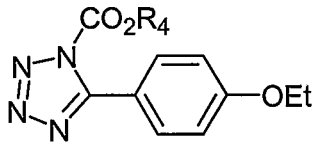
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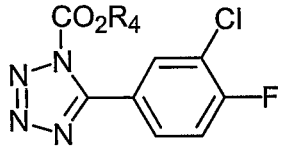
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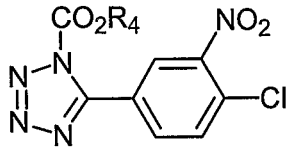
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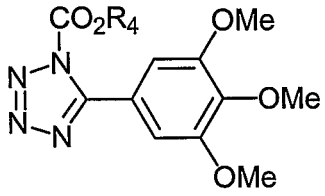

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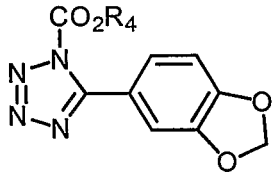

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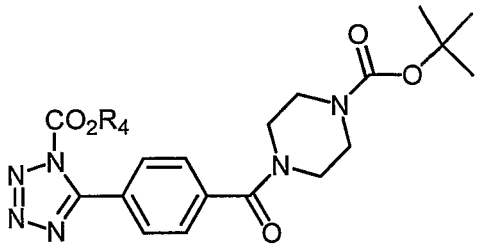

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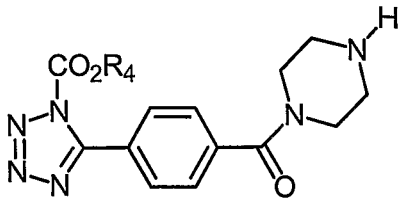

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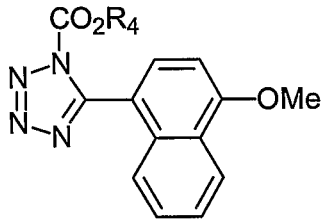

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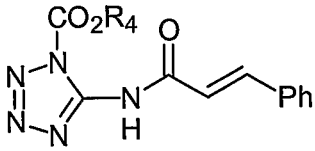
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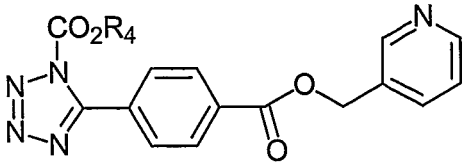
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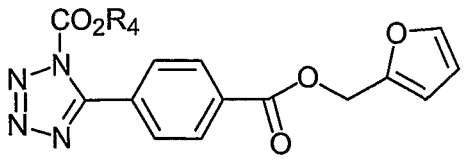
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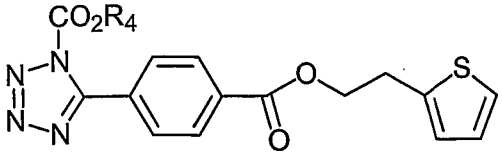
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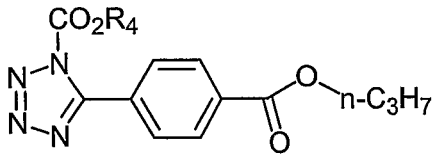
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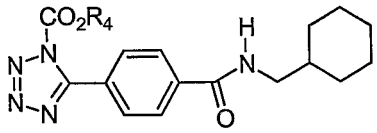
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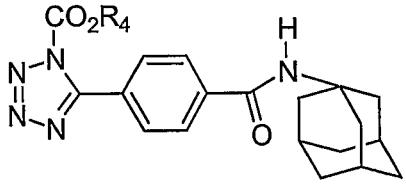
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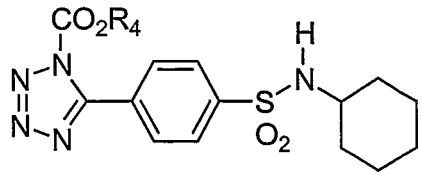
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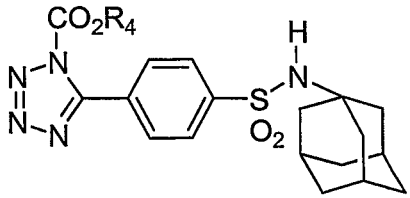
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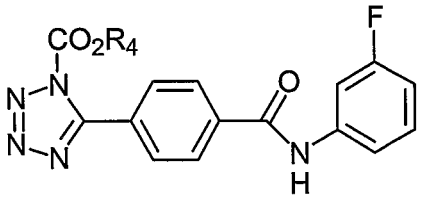
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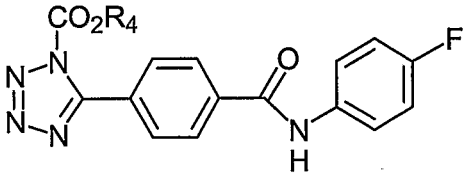
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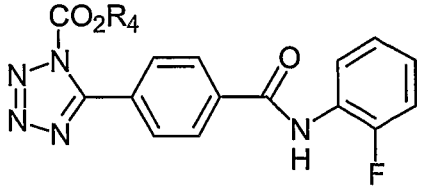
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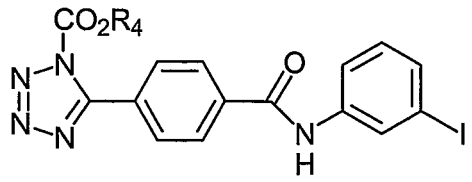
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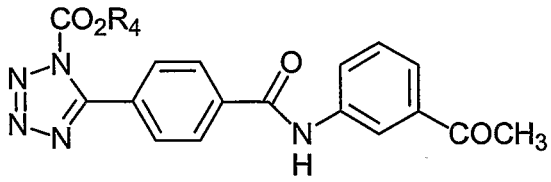
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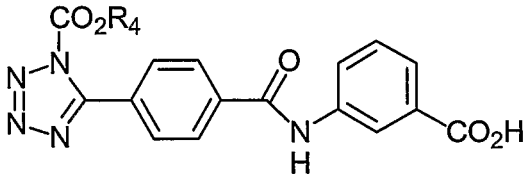
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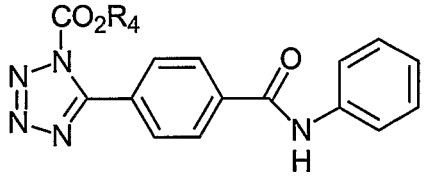
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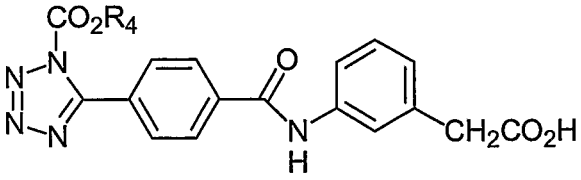
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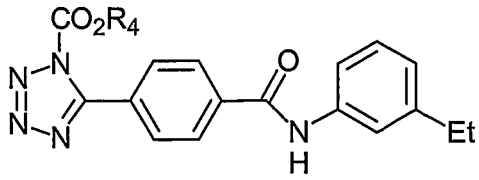
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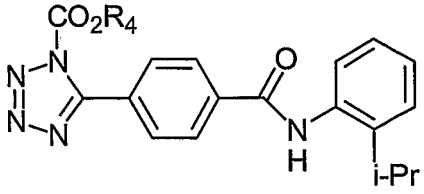
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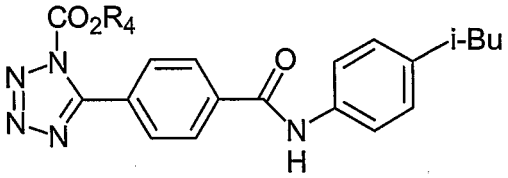
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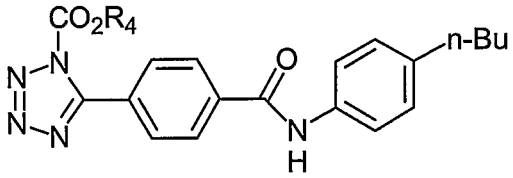

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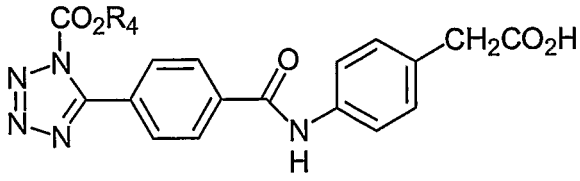

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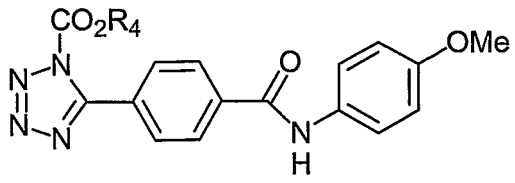

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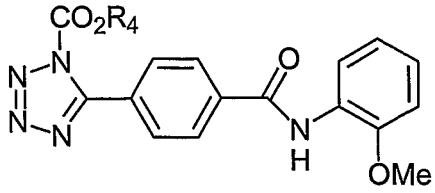

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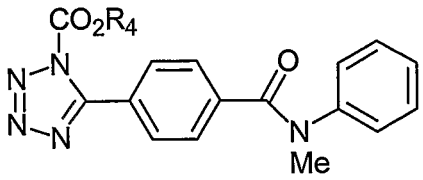

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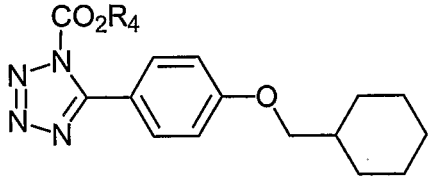
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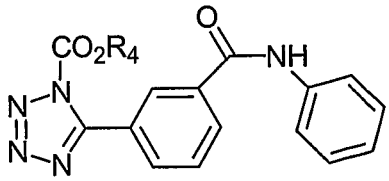
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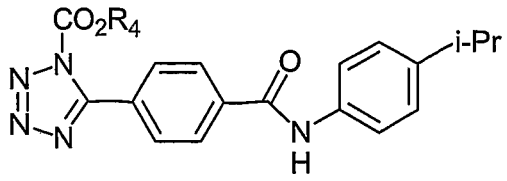
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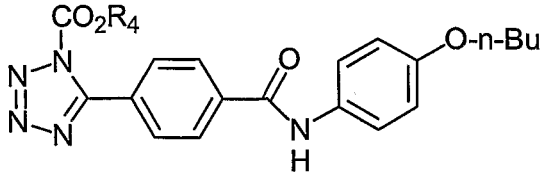
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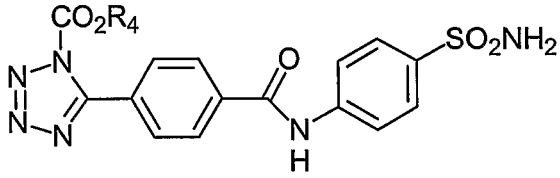
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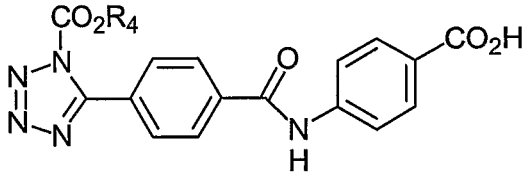
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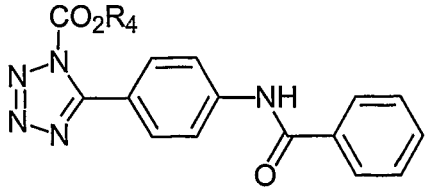
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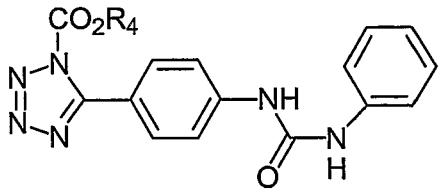
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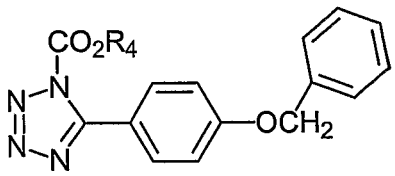
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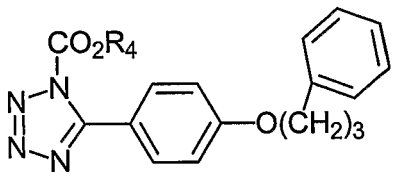
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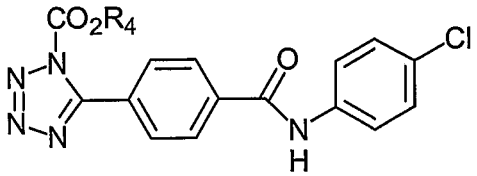
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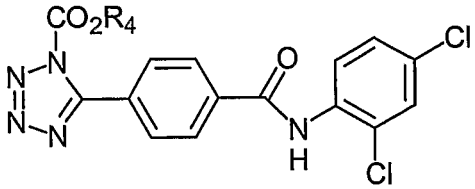
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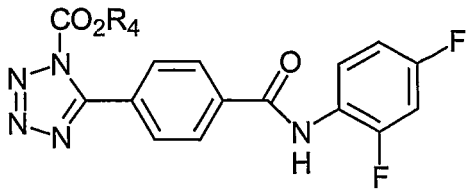
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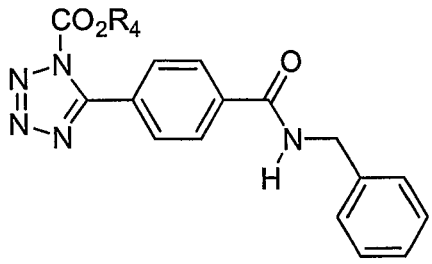
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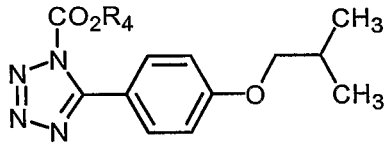
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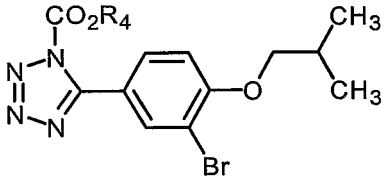
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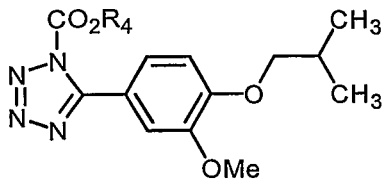
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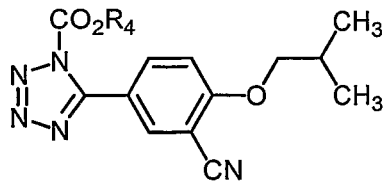
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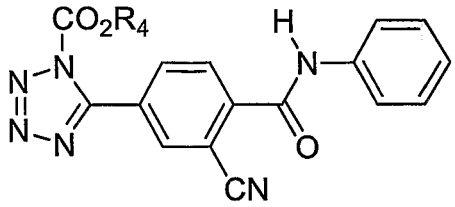
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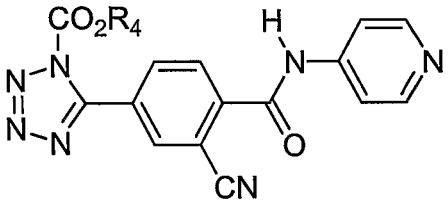
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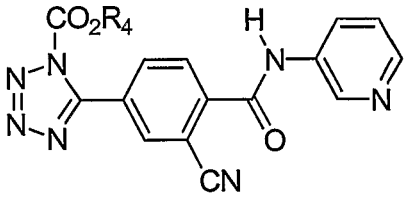
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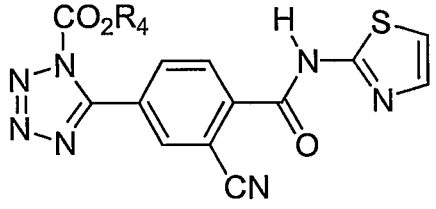
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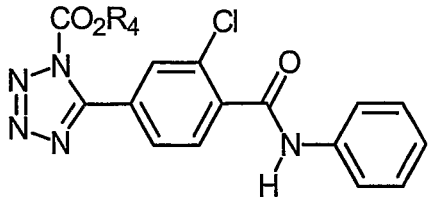
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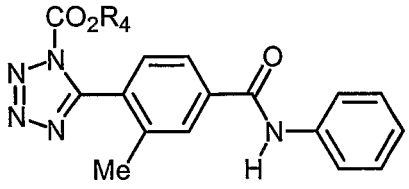
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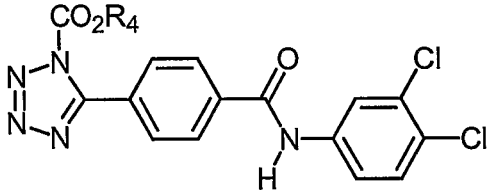
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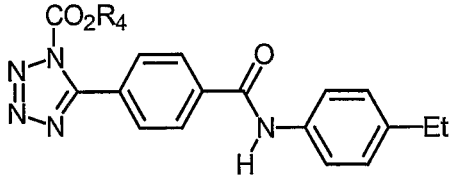
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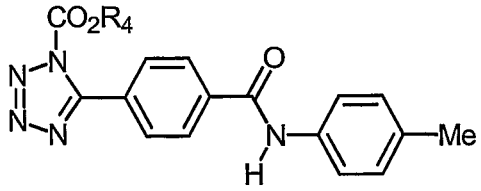
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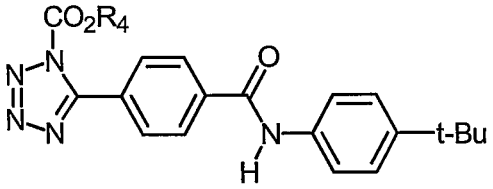
**Formula ED;**



**Formula EE;**




**Formula EF;**

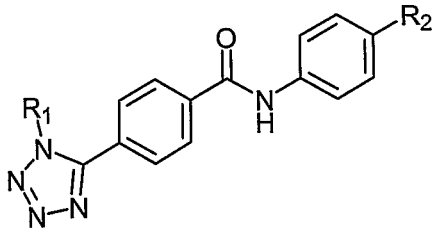



**Formula EG;**

and pharmaceutically acceptable salts or hydrates thereof.

## 4.3. COMPOUNDS OF FORMULA (Ib)

The invention also encompasses compounds of formula (Ib):




**(Ib)**

and pharmaceutically acceptable salts and hydrates thereof, wherein $R_1$ and $R_2$ are defined above for the compounds of formula (Ib).

In one embodiment $R_1$ is -H.

In another embodiment $R_1$ is -H and $R_2$ is -($C_1$-$C_{10}$)alkyl.

In another embodiment $R_1$ is -H and $R_2$ is -O($C_1$-$C_{10}$)alkyl.

In another embodiment, $R_1$ is -H and $R_2$ is methyl.

In another embodiment, $R_1$ is -H and $R_2$ is ethyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-propyl.

In another embodiment, $R_1$ is -H and $R_2$ is iso-propyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-butyl.

In another embodiment, $R_1$ is -H and $R_2$ is iso-butyl.

In another embodiment, $R_1$ is -H and $R_2$ is sec-butyl.

In another embodiment, $R_1$ is -H and $R_2$ is tert-butyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-pentyl.

In another embodiment, $R_1$ is -H and $R_2$ is isopentyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-hexyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-heptyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-octyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-nonyl.

In another embodiment, $R_1$ is -H and $R_2$ is n-decyl.

In another embodiment, $R_1$ is -H and $R_2$ is 2-methylbutyl.

In another embodiment, $R_1$ is -H and $R_2$ is 3-methylbutyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is methyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is ethyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-propyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is iso-propyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-butyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is iso-butyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is sec-butyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is tert-butyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-pentyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is isopentyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-hexyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-heptyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-octyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-nonyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-decyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is 2-methylbutyl.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is 3-methylbutyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is methyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is ethyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-propyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is iso-propyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-butyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is iso-butyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is sec-butyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is tert-butyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-pentyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is isopentyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-hexyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-heptyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-octyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-nonyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-decyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is 2-methylbutyl.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is 3-methylbutyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is methyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is ethyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-propyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is iso-propyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-butyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is iso-butyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is sec-butyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is tert-butyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-pentyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is isopentyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-hexyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-heptyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-octyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-nonyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-decyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is 2-methylbutyl.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is 3-methylbutyl.

In another embodiment, $R_1$ is -H and $R_2$ is methoxy.

In another embodiment, $R_1$ is -H and $R_2$ is ethoxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-propyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is iso-propyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-butyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is iso-butyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is sec-butyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is tert-butyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-pentyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is isopentyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-hexyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-heptyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-octyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-nonyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is n-decyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is 2-methylbutyloxy.

In another embodiment, $R_1$ is -H and $R_2$ is 3-methylbutyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is methoxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is ethoxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-propyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is iso-propyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-butyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is iso-butyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is sec-butyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is tert-butyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-pentyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is isopentyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-hexyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-heptyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-octyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-nonyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is n-decyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is 2-methylbutyloxy.

In another embodiment, $R_1$ is $-C(O)R_5$ and $R_2$ is 3-methylbutyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is methoxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is ethoxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-propyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is iso-propyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-butyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is iso-butyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is sec-butyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is tert-butyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-pentyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is isopentyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-hexyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-heptyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-octyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-nonyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is n-decyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is 2-methylbutyloxy.

In another embodiment, $R_1$ is $-CO_2R_4$ and $R_2$ is 3-methylbutyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is methyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is ethyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-propyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is iso-propyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-butyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is iso-butyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is sec-butyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is tert-butyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-pentyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is isopentyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-hexyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-heptyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-octyloxy.

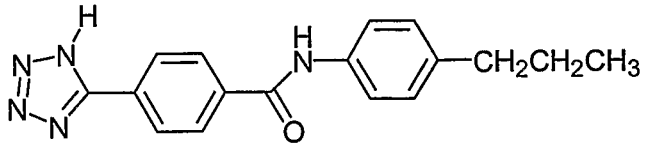
In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-nonyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is n-decyloxy.

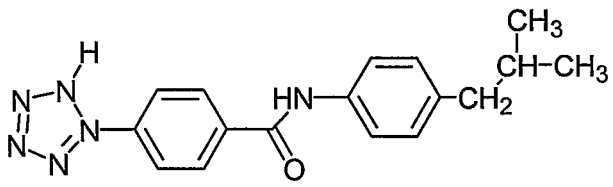
In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is 2-methylbutyloxy.

In another embodiment, $R_1$ is $-C(O)N(R_5)(R_5)$ and $R_2$ is 3-methylbutyloxy.

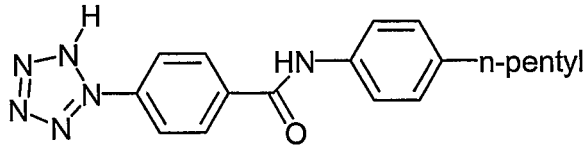
Illustrative compounds of formula (Ib) are:



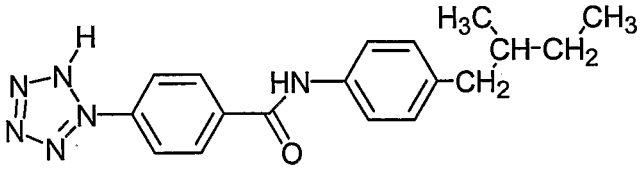

**Compound EH;**



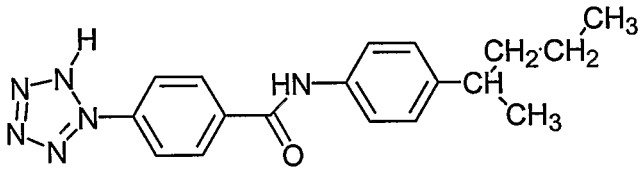
**Compound EI;**



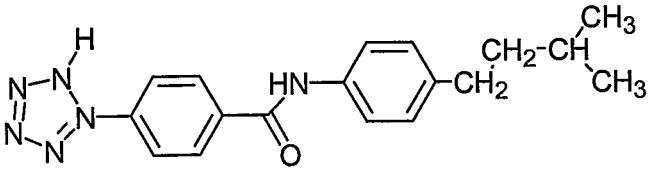
**Compound EJ;**



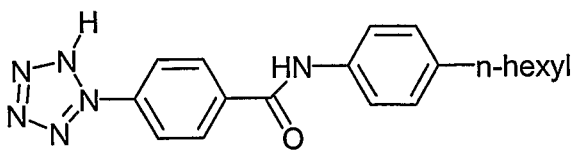
**Compound EK;**



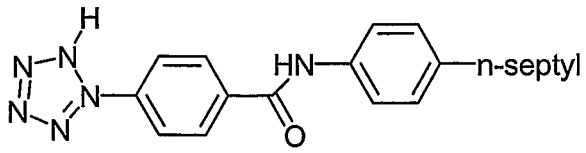
**Compound EL;**



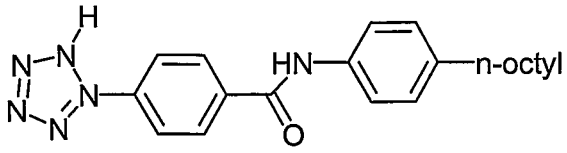
**Compound EM;**



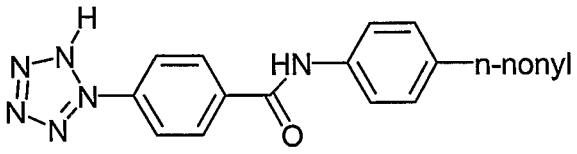
**Compound EN;**



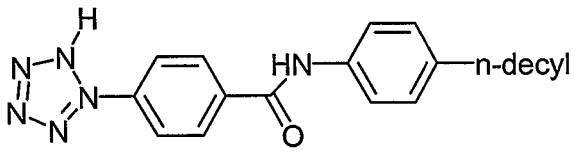

**Compound EO;**



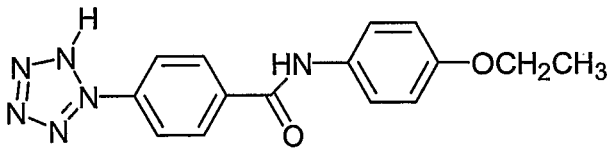

**Compound EP;**



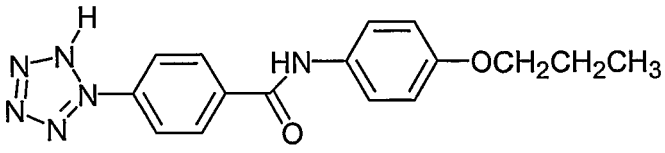

**Compound EQ;**



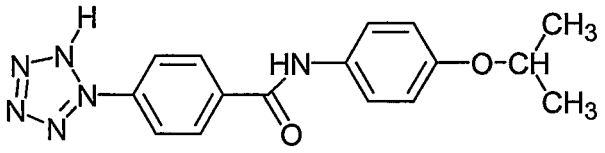

**Compound ER;**



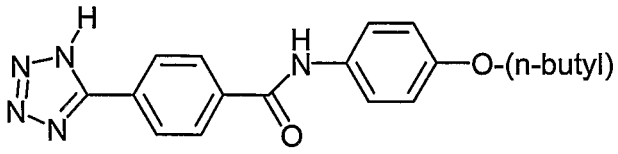

**Compound ES;**



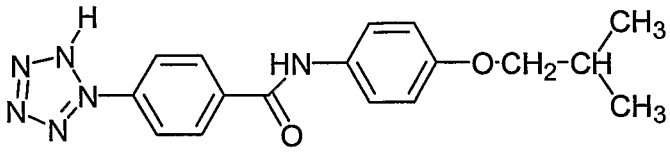

**Compound ET;**



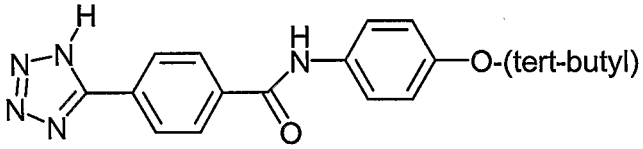
**Compound EU;**



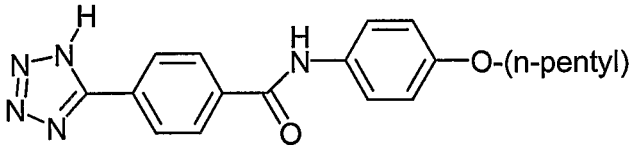
**Compound EV;**



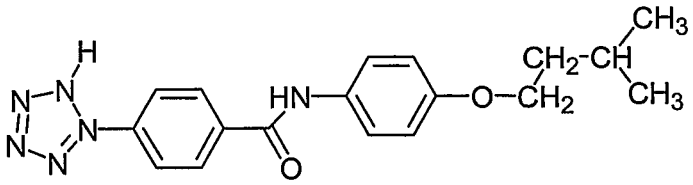
**Compound EW;**



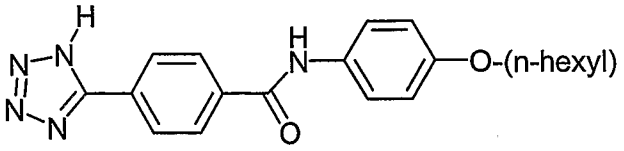
**Compound EX;**



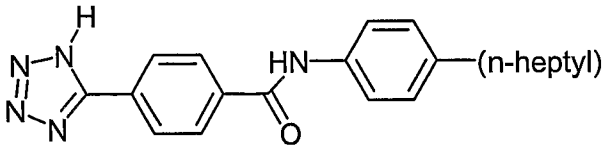
**Compound EY;**



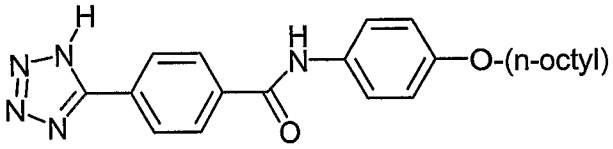
**Compound EZ;**



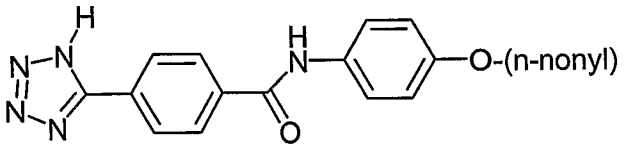

**Compound FA;**



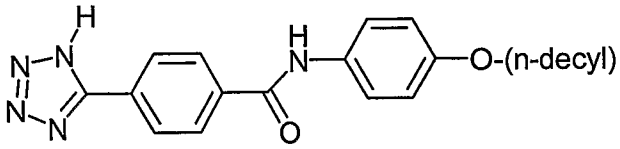

**Compound FB;**




**Compound FC;**




**Compound FD;**

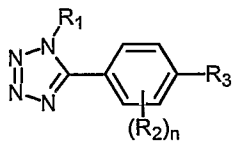



**Compound FE;**

and pharmaceutically acceptable salts and hydrates thereof.

## 4.4. COMPOUNDS OF FORMULA (Ic)

As stated above, the invention further relates to methods for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



**(Ic)**

or a pharmaceutically acceptable salt or hydrate thereof, wherein $R_1$, $R_2$, $R_3$ and n are defined above for the compounds of formula (Ic).

In one embodiment $R_1$ is -H.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is -($C_1$-$C_{10}$)alkyl.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-O(CH_2)_mR_5$.

In another embodiment $R_1$ is -H; n is 0; $R_3$ is $-O(CH_2)_mR_5$; and $R_5$ is -H.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is -halo.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-C(O)R_5$.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-C(O)NHC(O)R_5$.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-C(O)N(R_5)(R_5)$.

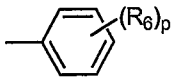
In another embodiment $R_1$ is -H; n is 0; and $R_3$ is -H.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-CO_2(CH_2)_m(R_5)$.

In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-NHC(O)N(R_5)(R_5)$.

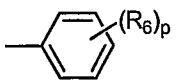
In another embodiment $R_1$ is -H; n is 0; and $R_3$ is $-C(O)NHR_5$.

In another embodiment $R_1$ is -H; n is 0; $R_3$ is $-C(O)NHR_5$; and $R_5$ is



.

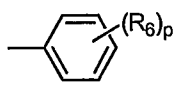
In another embodiment $R_1$ is -H; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is an integer from 1 to 3.

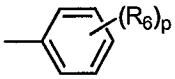
In another embodiment $R_1$ is -H; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is 1 or 2.

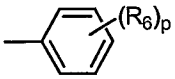
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in the para position.

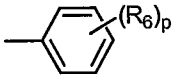
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in a meta position.

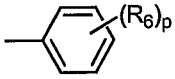
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in an ortho position.

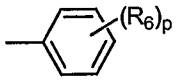
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 2; and each $R_6$ is independently -halo.

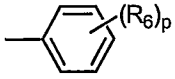
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in a meta position.

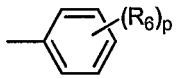
In another embodiment $R_1$ is -H; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in an ortho position.

In another embodiment $R_1$ is -H; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; and one $R_6$ is in an ortho position and the other $R_6$ is in a meta position.

In another embodiment, $R_1$ is $-CO_2R_4$.

In another embodiment $R_1$ is $-CO_2R_4$ and n is 0.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is -halo.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-C(O)R_5$.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-C(O)NHC(O)R_5$.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is -H.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-CO_2(CH_2)_m(R_5)$.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-NHC(O)N(R_5)(R_5)$.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-C(O)N(R_5)(R_5)$.

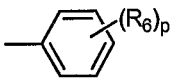
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; and $R_3$ is $-C(O)NHR_5$.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; and $R_5$ is



.

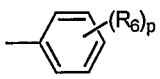
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is an integer from 1 to 3.

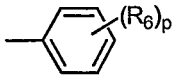
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is 1 or 2.

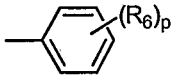
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in the para position.

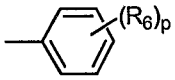
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 1, and $R_6$ is halo and is in a meta position.

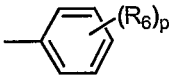
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 1, and $R_6$ is halo and is in an ortho position.

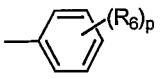
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; and each $R_6$ is independently -halo.

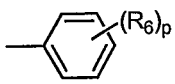
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently halo; and one $R_6$ is in the para position and the other $R_6$ is in a meta position.

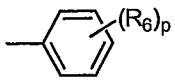
In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently halo; and one $R_6$ is in the para position and the other $R_6$ is in an ortho position.

In another embodiment $R_1$ is $-CO_2R_4$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently halo; and one $R_6$ is in the ortho position and the other $R_6$ is in a meta position.

In another embodiment, $R_1$ is -C(O)$R_5$.

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -halo.

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -C(O)$R_5$,

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -C(O)NHC(O)$R_5$,

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -H.

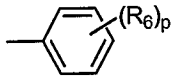
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -$CO_2(CH_2)_m(R_5)$.

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -NHC(O)N($R_5$)($R_5$).

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is C(O)N($R_5$)($R_5$).

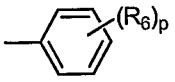
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; and $R_3$ is -C(O)NHR$_5$.

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NHR$_5$; and $R_5$ is



.

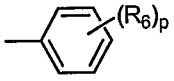
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

and p is an integer from 1 to 3.

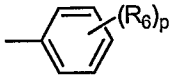
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

and p is 1 or 2.

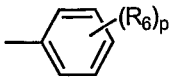
In another embodiment $R_1$ is -C(O)R5; n is 0; $R_3$ is -C(O)NHR$_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in the para position.

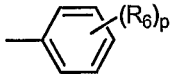
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in a meta position.

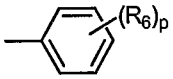
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in an ortho position.

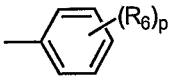
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 2; and each $R_6$ is independently -halo.

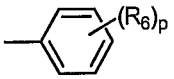
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in a meta position.

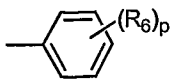
In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in an ortho position.

In another embodiment $R_1$ is -C(O)$R_5$; n is 0; $R_3$ is -C(O)NH$R_5$; $R_5$ is



;

p is 2; and one $R_6$ is in an ortho position and the other $R_6$ is in a meta position.

In another embodiment, $R_1$ is $-C(O)NR_5R_5$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is -halo.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-C(O)R_5$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-C(O)NHC(O)R_5$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is -H.

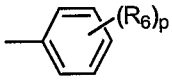
In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-CO_2(CH_2)_m(R_5)$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-NHC(O)N(R_5)(R_5)$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-C(O)N(R_5)(R_5)$.

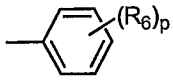
In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; and $R_3$ is $-C(O)NHR_5$.

In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; $R_3$ is $-C(O)NHR_5$; and $R_5$ is



.

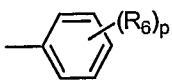
In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is an integer from 1 to 3.

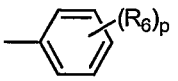
In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

and p is 1 or 2.

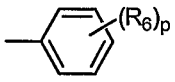
In another embodiment $R_1$ is $-C(O)NR_5R_5$; n is 0; $R_3$ is $-C(O)NHR_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in the para position.

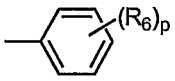
In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in a meta position.

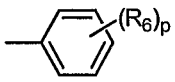
In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



;

p is 1; and $R_6$ is halo and is in an ortho position.

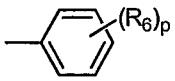
In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



;

p is 2; and each $R_6$ is independently -halo.

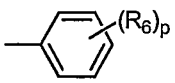
In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in a meta position.

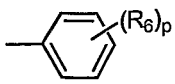
In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



;

p is 2; each $R_6$ is independently -halo; and one $R_6$ is in the para position and the other $R_6$ is in an ortho position.

In another embodiment $R_1$ is -C(O)$NR_5R_5$; n is 0; $R_3$ is -C(O)$NHR_5$; $R_5$ is



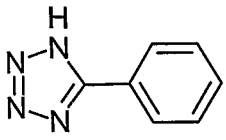
;

p is 2; and one $R_6$ is in an ortho position and the other $R_6$ is in a meta position.

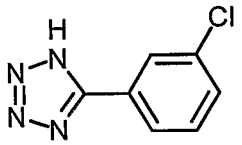
In another embodiment, the compounds of formula (Ic) are the compounds of formula (Ia) and pharmaceutically acceptable salts and hydrates thereof, above.

In another embodiment, the compounds of formula (Ic) are the compounds of formula (Ib) and pharmaceutically acceptable salts and hydrates thereof, above.

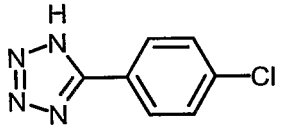
Illustrative compounds of formula (Ic) are:



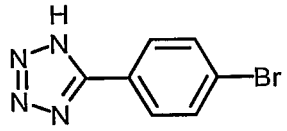
**Compound FF;**



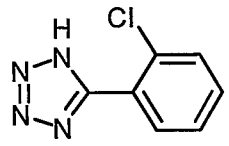
**Compound FG;**



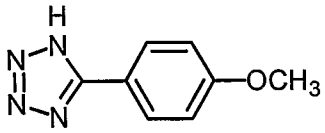
**Compound FH;**



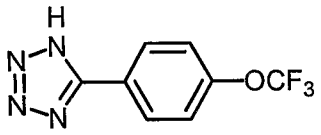
**Compound FI;**



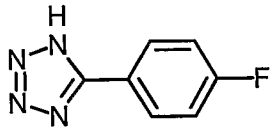
**Compound FJ;**



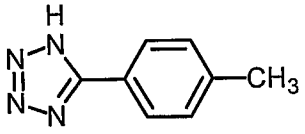
**Compound FK;**



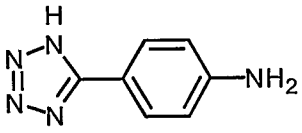
**Compound FL;**



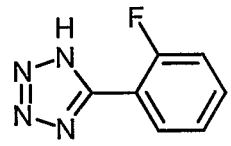
**Compound FM;**



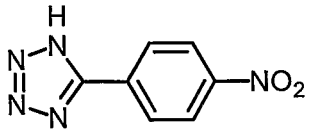
**Compound FN;**



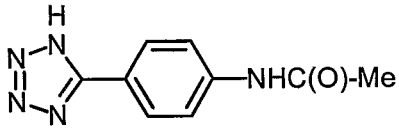
**Compound FO;**



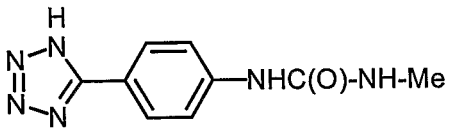

**Compound FP;**



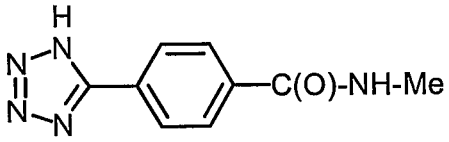

**Compound FQ;**



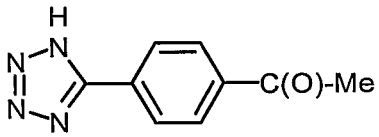

**Compound FR;**



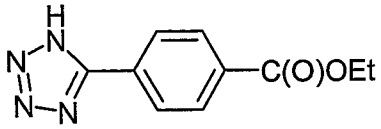

**Compound FS;**



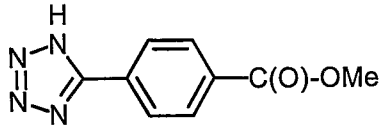

**Compound FT;**



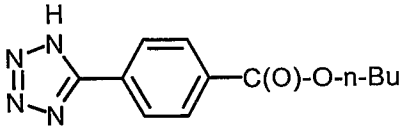

**Compound FU;**



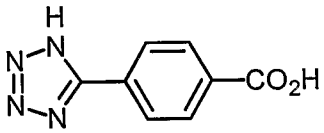

**Compound FV;**



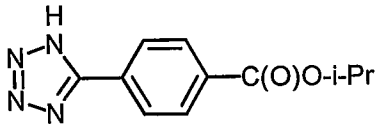

**Compound FW;**



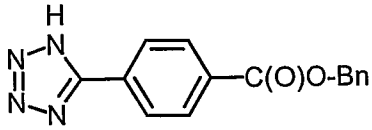

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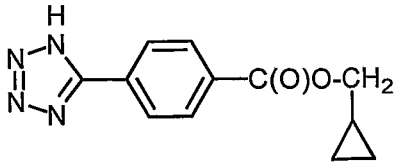

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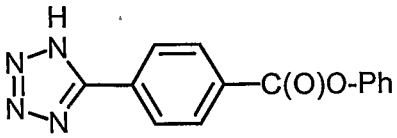

**Compound FZ;**



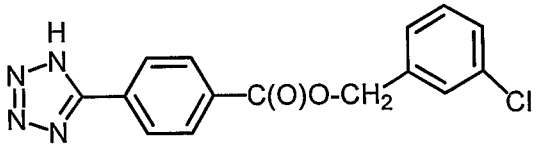

**Compound GA;**



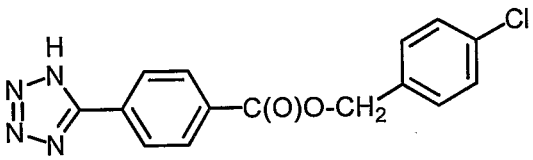

**Compound GB;**



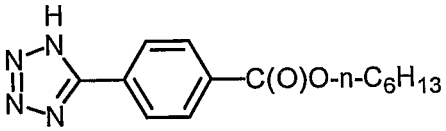

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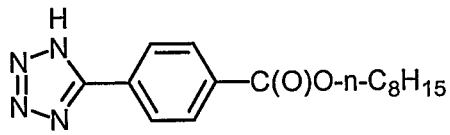

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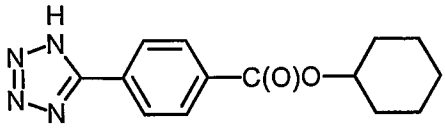

**Compound GE;**



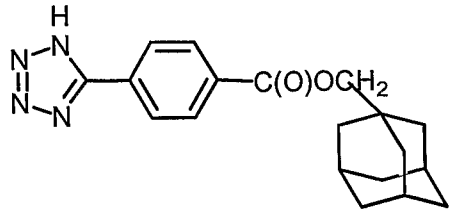

**Compound GF;**



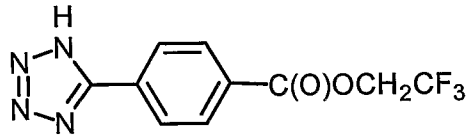

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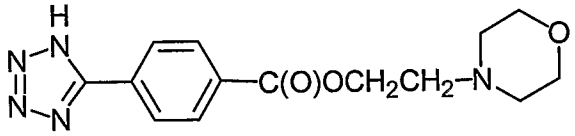
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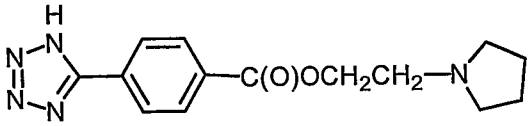
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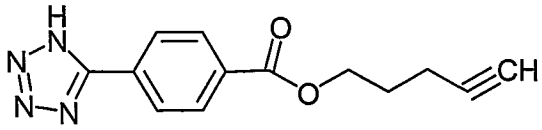
**Compound GJ;**



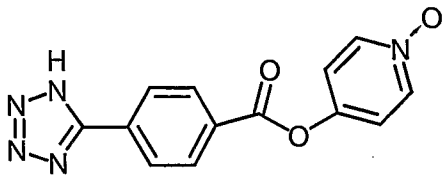
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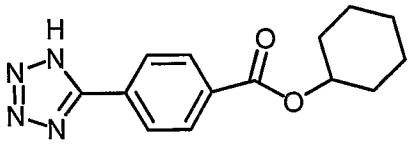
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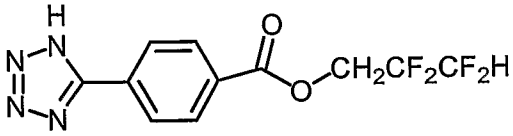
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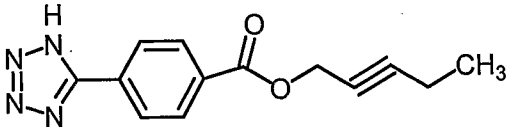
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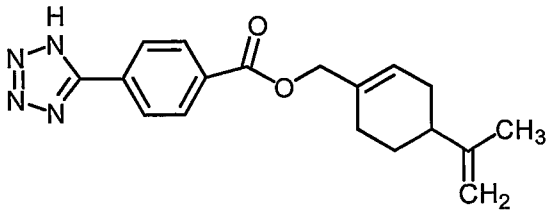
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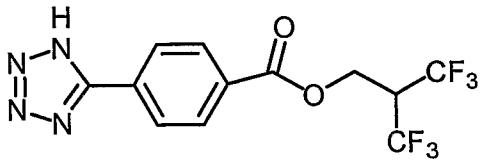
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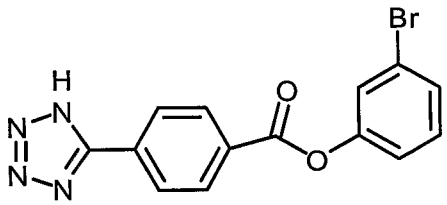
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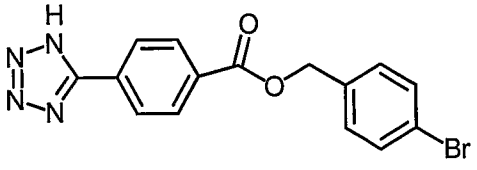
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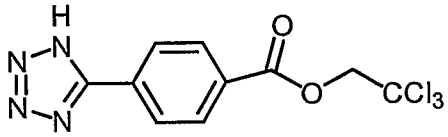
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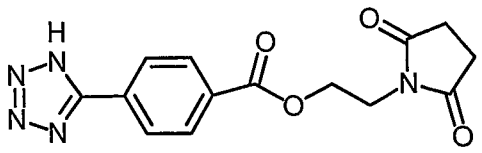
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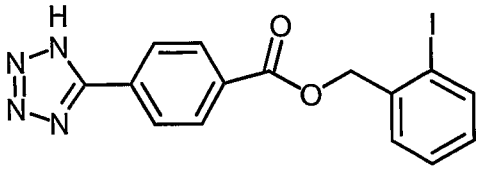
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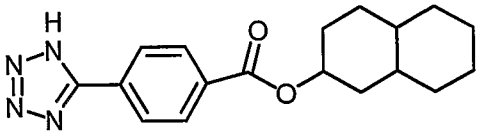
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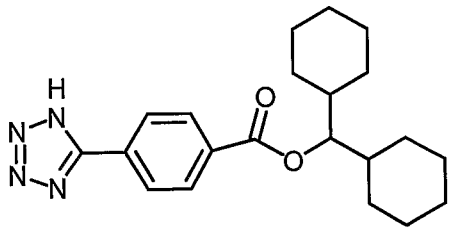
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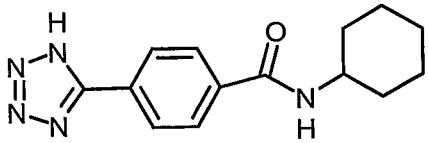
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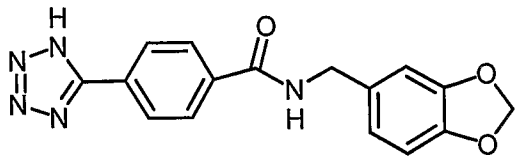
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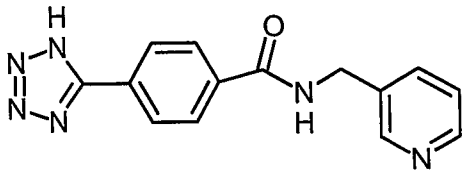
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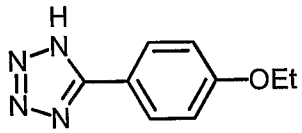
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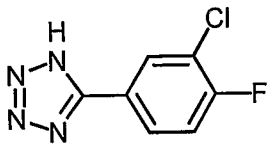
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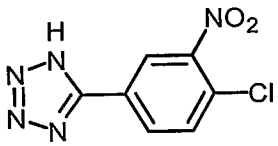
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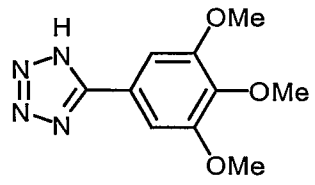
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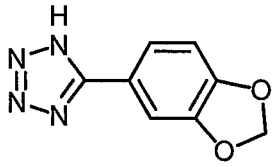
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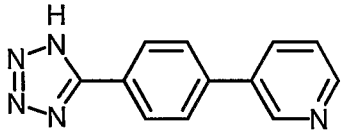
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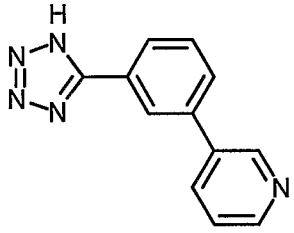
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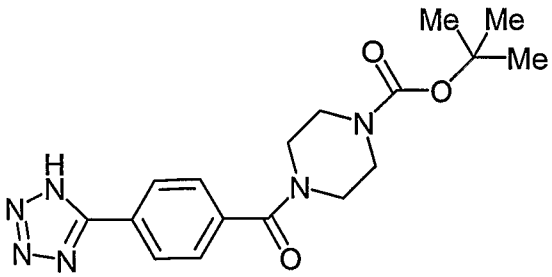
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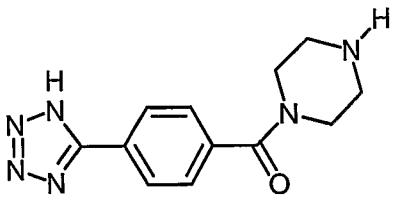
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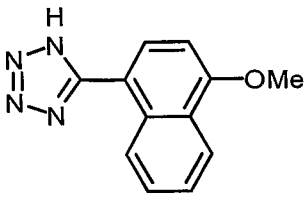
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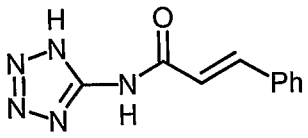
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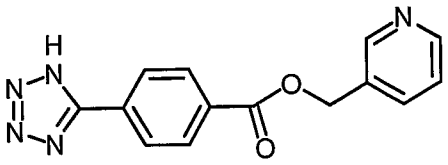
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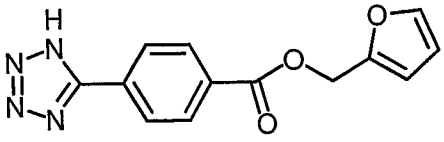
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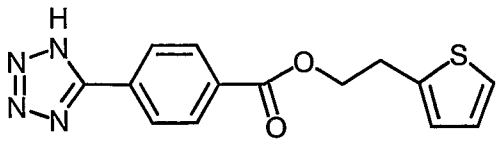
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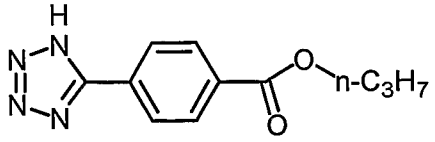
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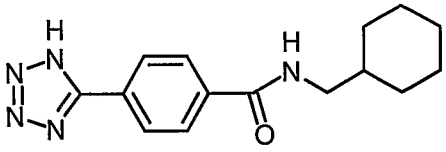
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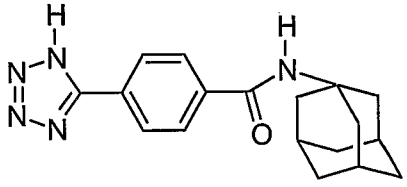
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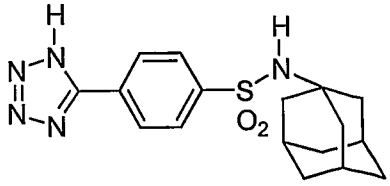
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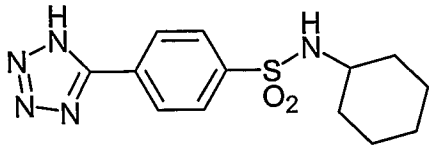
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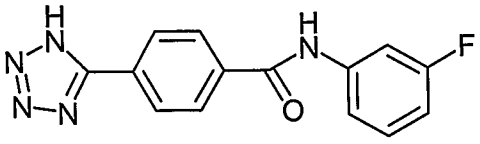
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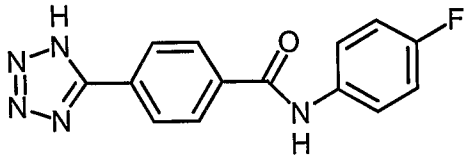
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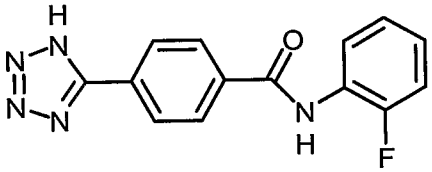
**Compound HV;**



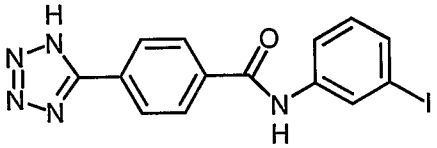
**Compound HW;**



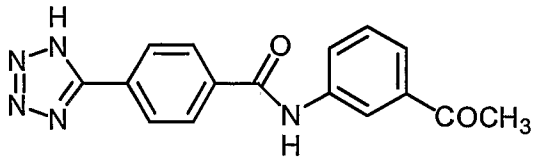
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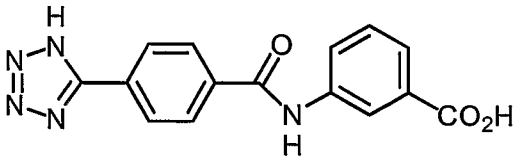
**Compound HY;**



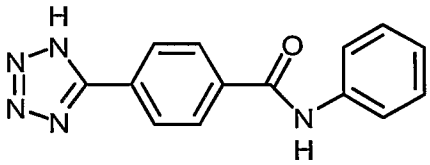
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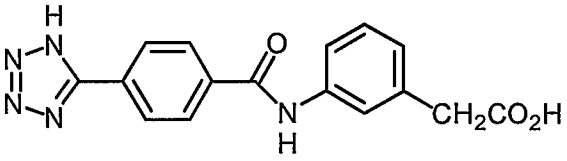
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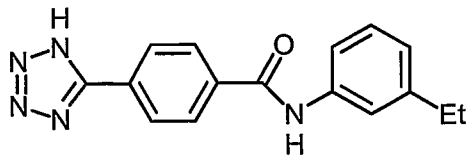
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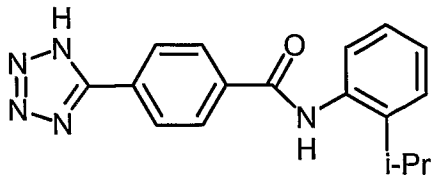
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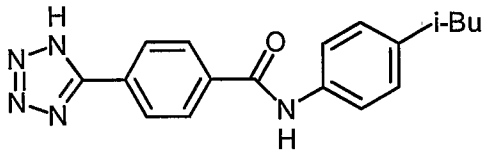
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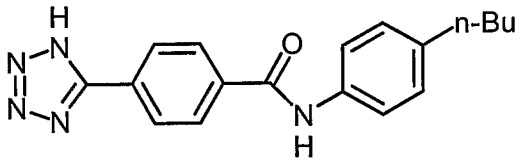

**Compound IE;**



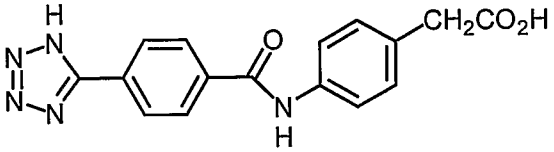

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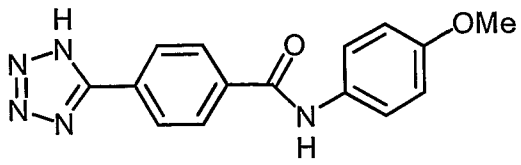

**Compound IG;**



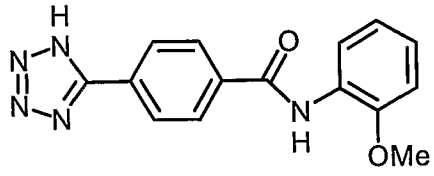

**Compound IH;**



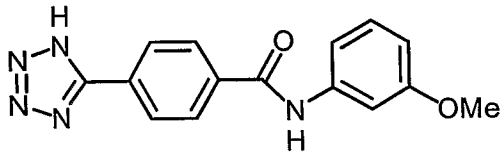

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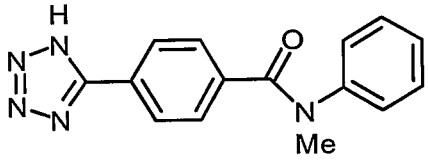
**Compound IJ;**



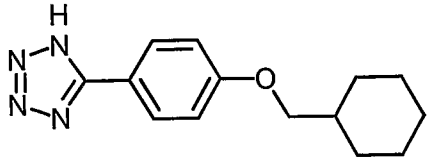
**Compound IK;**



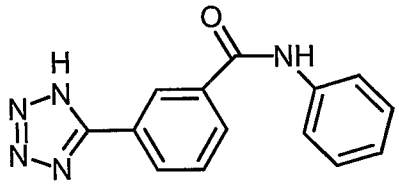
**Compound IL;**



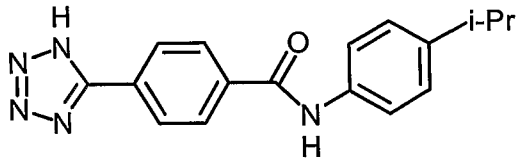
**Compound IM;**



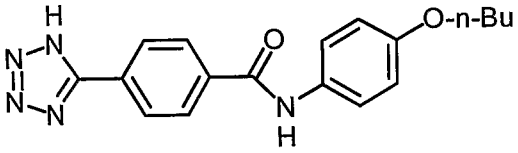
**Compound IN;**



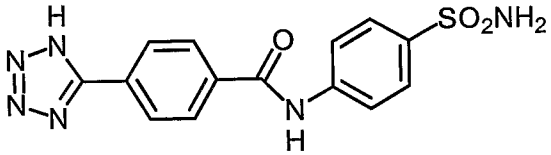
**Compound IO;**



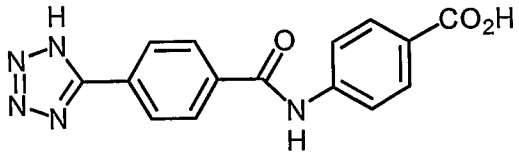
**Compound IP;**



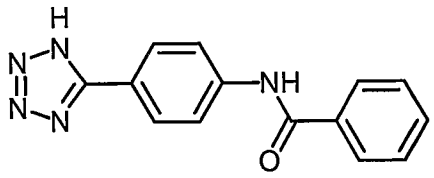
**Compound IQ;**



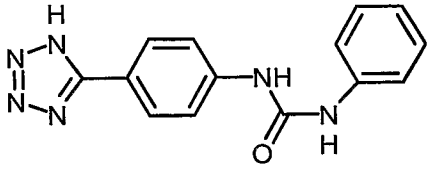
**Compound IR;**



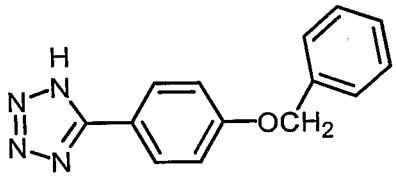
**Compound IS;**



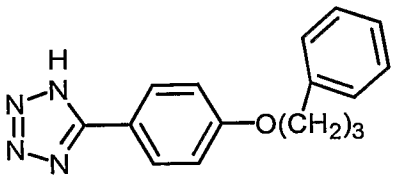
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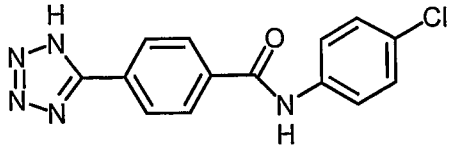
**Compound IU;**



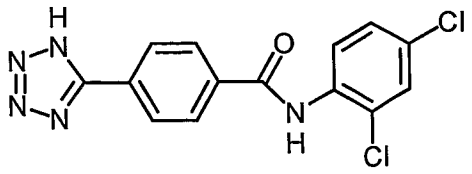
**Compound IV;**



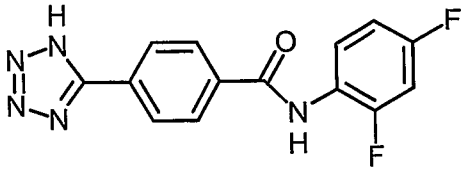
**Compound IW;**



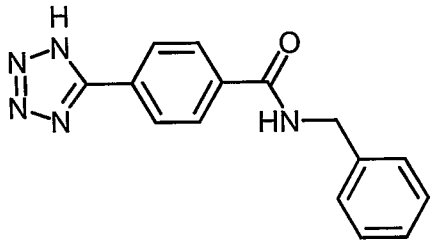
**Compound IX;**



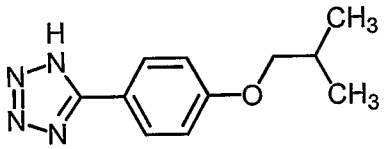
**Compound IY;**



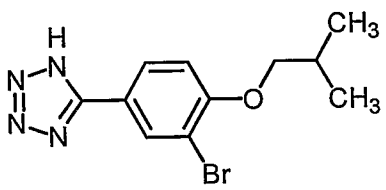
**Compound IZ;**



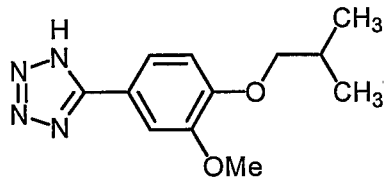
**Compound JA;**



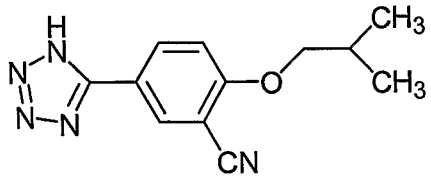
**Compound JB;**



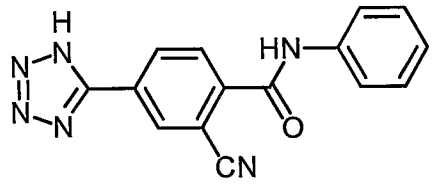
**Compound JC;**



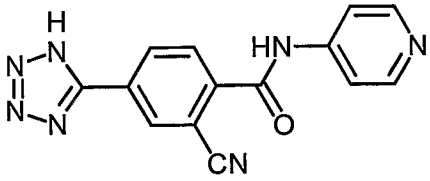
**Compound JD;**



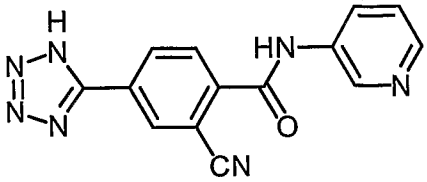
**Compound JE;**



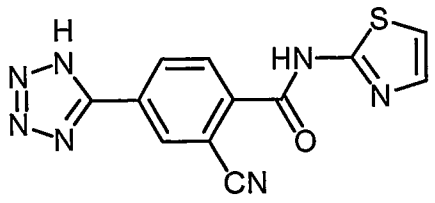
**Compound JF;**



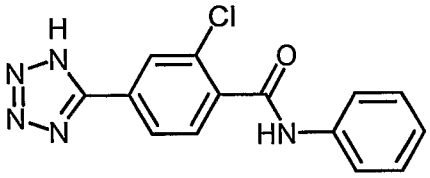
**Compound JG;**



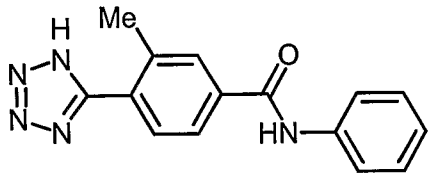
**Compound JH;**



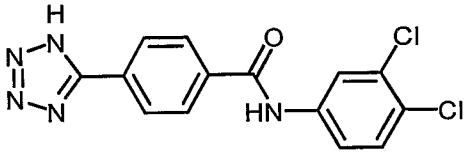
**Compound JI;**



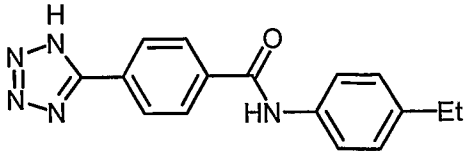
**Compound JJ;**



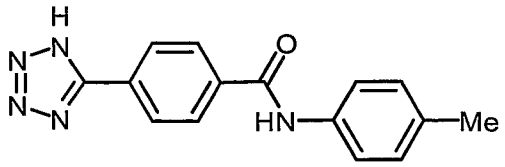
**Compound JK;**



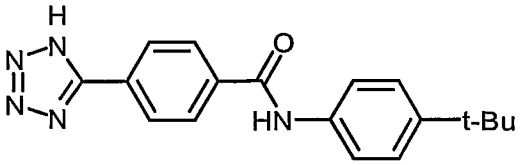
**Compound JL;**



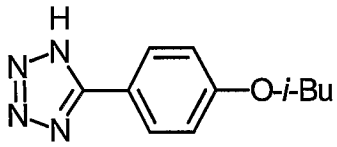
**Compound JM;**



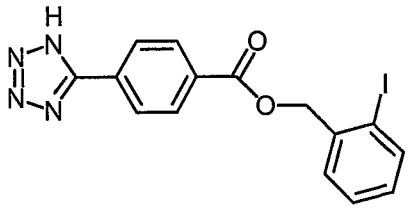

**Compound JN;**



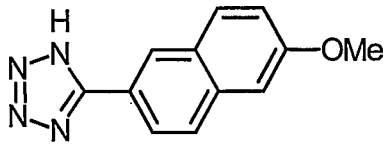

**Compound JO;**




**Compound JP;**




**Compound JQ;**




**Compound JR;**

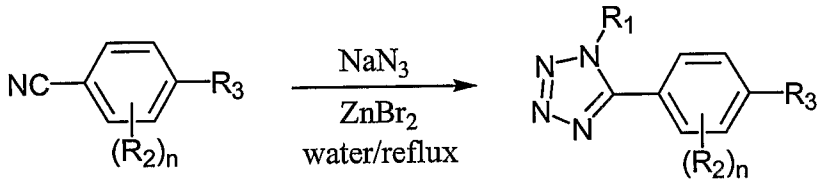
and pharmaceutically acceptable salts or hydrates thereof.

## 4.4. METHODS FOR MAKING THE 5-ARYLTETRAZOLE COMPOUNDS

The 5-Aryltetrazole Compounds can be made using conventional organic synthesis and/or by the following illustrative methods. General procedures for the synthesis of aryl tetrazoles are provided in, Butler, R.N., *Comprehensive Heterocyclic Chemistry Vol. IV*, pp. 664-668 (Katritzky *et al.* eds., 1996).

### 4.4.1. METHOD A

The 5-Aryltetrazole Compounds of formula (Ic) wherein $R_1$ is -H can be obtained by contacting a compound of formula A with an with an azide (*e.g.*, sodium azide ("$NaN_3$")) at reflux, (*e.g.*, about 100 °C), in the presence of zinc bromide ("$ZnBr_2$") using water as a solvent as shown below in Scheme A. Compounds of formula A can be obtained commercially (*e.g.*, commercially available from Sigma-Aldrich Co., http://www.sigmaaldrich.com) or made readily by those skilled in the art. A representative procedure for obtaining a 5-Aryltetrazole Compounds of formula (Ic) from a substituted phenyl nitrile in the presence of sodium azide is provided in Sharpless *et al.*, *J. Org. Chem.* 7945-7950 (2001).




**A** **Formula Ic**

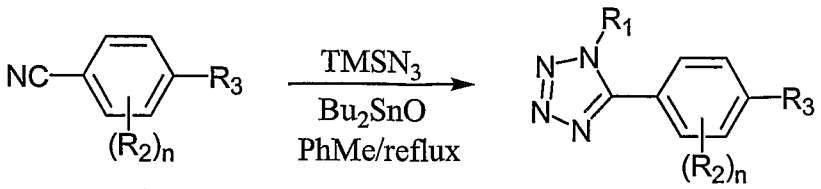
**Scheme A**

A 5-Aryltetrazole Compound of formula (Ic) wherein $R_1$ is $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$ can be obtained by contacting a 5-Aryltetrazole Compound of formula (Ic), wherein $R_1$ is -H with an acyl compound (*e.g.*, $XCO_2R_4$, $XC(O)R_5$, or $XC(O)N(R_5)(R_5)$, wherein X is Br or Cl) in triethylamine ($NEt_3$).

### 4.4.2. METHOD B

In another embodiment, a 5-Aryltetrazole Compounds of formula (Ic) wherein $R_1$ is H can be obtained by contacting a compound of formula A with an azide, (*e.g.*, azidotrimethylsilane ("$TMSN_3$")) and a catalytic amount of dibutyl tin oxide ("n-$Bu_2SnO$") in refluxing toluene as a solvent as shown below in Scheme B. Methods for

obtaining tetrazoles from nitriles and $TMSN_3$ are provided in, for example, Curran *et al.*, *Tetrahedron*, **1999**, *55*, 8997-9006.



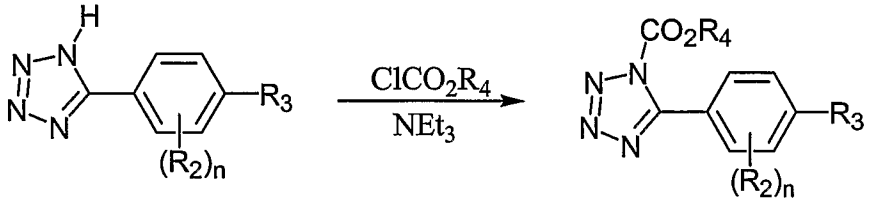

**A** **Formula Ic**

**Scheme B**

A 5-Aryltetrazole Compound of formula (Ic) wherein $R_1$ is $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$ can be obtained by contacting a 5-Aryltetrazole Compound of formula (Ic), wherein $R_1$ is -H with an acyl compound (*e.g.*, $XCO_2R_4$, $XC(O)R_5$, or $XC(O)N(R_5)(R_5)$, wherein X is Br or Cl) in triethylamine ($NEt_3$). Where $R_5$ is -H, protecting group chemistry can be used.

### 4.4.3. METHOD C

The 5-Aryltetrazole Compounds of formula (Ic) wherein $R_1$ is -H can be converted to 5-Aryltetrazole compounds of formula (Ia) by contacting the compound of formula (Ic) wherein $R_1$ is -H with an alkyl chlorocarbonate or carbonic acid anhydride under conditions suitable for the formation of a carbamate as shown in Scheme C. Methods for obtaining carbamates from amines and carbonates are provided in, for example, Raucher *et al.*, *Synthetic Commun.* **1985**, *15*, 1025. For example, illustrative compounds **AA-AZ**, **BA-BZ**, **CA-CZ**, **DA-DZ**, **EA-EG** can be made using this method.

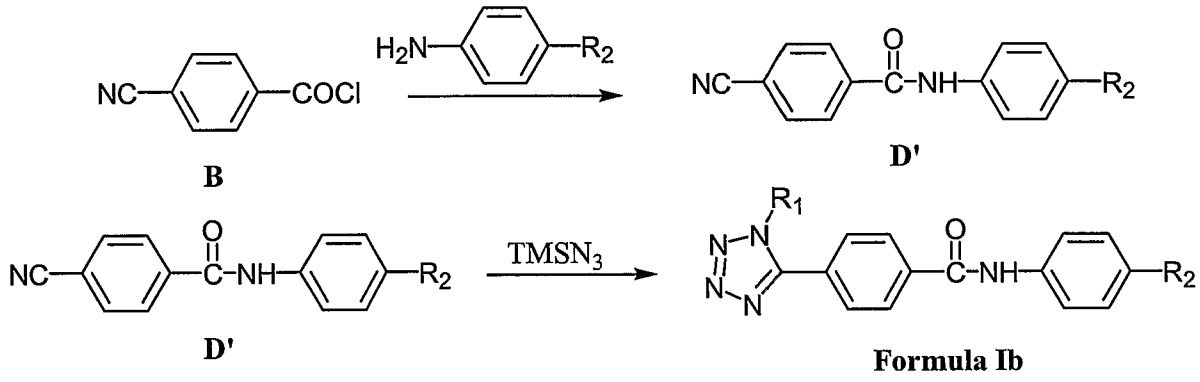



**Formula Ic** **Formula Ia**

**Scheme C**

#### 4.4.4. METHOD D

In another embodiment, a 5-Aryltetrazole Compound of formula (Ib) wherein $R_1$ is -H can be obtained by contacting a compound of formula B with a 4-substituted aniline (*e.g.*, 4-methylaniline or 4-methoxyaniline) to obtain a compound of formula D'. The compound of formula D' is then contacted with azide, (*e.g.*, azidotrimethylsilane ("$TMSN_3$")) and a catalytic amount of dibutyl tin oxide ("n-$Bu_2SnO$") in refluxing toluene as a solvent as shown below in Scheme B. Methods for obtaining tetrazoles from nitriles and $TMSN_3$ are provided in, for example, Curran *et al.* (*see, e.g.*, section 4.4.2, above).




**Scheme D**

To obtain a 5-Aryltetrazole Compound of formula (Ib) wherein $R_1$ is $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$, a 5-Aryltetrazole Compound of formula (Ib) wherein $R_1$ is -H is contacted with an acyl derivative (*e.g.*, $XCO_2R_4$, $XC(O)R_5$, or $XC(O)N(R_5)(R_5)$, wherein X is Br or Cl) in triethylamine ($NEt_3$) to provide a 5-Aryltetrazole Compound of formula (Ib). Where $R_5$ is -H, protecting group chemistry can be used. For example, illustrative compounds **EH-FE** can be made using this method.

5-Aryltetrazole Compounds can have asymmetric centers and therefore can exist in particular enantiomeric and/or diastereomeric forms. A 5-Aryltetrazole Compound can be in the form of an optical isomer or a diastereomer. Accordingly, the invention encompasses 5-Aryltetrazole Compounds and their uses as described herein in the form of their optical isomers, diastereomers, and mixtures thereof, including a racemic mixture.

In addition, one or more hydrogen, carbon or other atoms of a 5-Aryltetrazole Compound can be replaced by an isotope of the hydrogen, carbon, or other atom. Such compounds, which are encompassed by the present invention, are useful as research and diagnostic tools in metabolism pharmokinetic studies and binding assays.

## 4.5. PROPHYLACTIC AND/OR THERAPEUTIC USES OF THE 5-ARYLTETRAZOLE COMPOUNDS

In accordance with the invention, an effective amount of a 5-Aryltetrazole Compound, or a pharmaceutical composition comprising an effective amount of a 5-Aryltetrazole Compound, is administered to an animal in need of treatment or prevention of an inflammation disease, a reperfusion disease, or hyperuricemia. In one embodiment, an effective amount of a 5-Aryltetrazole Compound can be used to treat or prevent any condition that is treatable or preventable by inhibiting xanthine oxidase. Examples of cells that express xanthine oxidase include, but are not limited to, lung, liver, and intestinal cells. Examples of conditions that are treatable or preventable by inhibiting xanthine oxidase include, but are not limited to, an inflammation disease, a reperfusion disease, or hyperuricemia. In another embodiment, an effective amount of a 5-Aryltetrazole Compound can be used to treat or prevent an inflammation disease, a reperfusion disease, or hyperuricemia.

Examples of inflammation diseases include, but are not limited to, chronic inflammatory disorders of the joints including arthritis, *e.g.,* rheumatoid arthritis and osteoarthritis; respiratory distress syndrome; inflammatory bowel disorders; and inflammatory lung disorders such as asthma and chronic obstructive airway disease, inflammatory disorders of the eye such as corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis, and endophthalmitis; inflammatory disorders of the gum, *e.g.,* periodontitis and gingivitis; tuberculosis; leprosy; inflammatory diseases of the kidney including glomerulonephritis and nephrosis; inflammatory disorders of the skin including acne, sclerodermatitis, psoriasis, eczema, photoaging and wrinkles; inflammatory diseases of the central nervous system, including AIDS-related neurodegeneration, stroke, neurotrauma, Alzheimer's disease, encephalomyelitis and viral or autoimmune encephalitis; autoimmune diseases including immune-complex vasculitis, systemic lupus and erythematodes; systemic lupus erythematosus (SLE); and inflammatory diseases of the heart such as cardiomyopathy.

Examples of inflammatory bowel disorders include, but are not limited to, ileitis, including, but not limited to, regional ileitis; colitis, including, but not limited to, ulcerative colitis, collagenous/microscopic colitis, and enterocolitis; Crohn's disease; and pouchitis.

Examples of reperfusion diseases include, but are not limited to, shock and sepsis. Shock can be septic shock, *e.g.*, gram positive bacteria-mediated circulatory shock, gram negative bacteria-mediated circulatory shock, hemorrhagic shock, anaphylactic shock, shock associated with systemic inflammation, shock associated with pro-inflammatory cytokines, and shock associated with systemic inflammatory response syndrome (SIRS). The 5-Aryltetrazole Compounds can also be used to prevent or treat circulatory shock, such as shock occurring as a result of gram negative and gram positive sepsis, trauma, hemorrhage, burn injury, anaphylaxis, cytokine immunotherapy, organ failure (particularly kidney or liver failure), or systemic inflammatory response syndrome. Other examples of reperfusion disease are disease arising from cell or solid-organ transplantation, cardiopulmonary bypass surgery, compartment syndrome, crush injury, splanchnic ischemia-reperfusion, myocardial infarction and stroke.

Examples of hyperuricemia include, but are not limited to, gout; tumor-lysis syndrome; idiopathic hyperuricemia; hyperuricemia inherited including, but not limited to, hyperuricemia due to PP-ribose-P synthetase overactivity; hypoxanthine-gaunine phosphoribosyltransferase deficiency; glucose-6-phosphate deficiency; Gierke's glycogen storage disease; chronic hemolytic hyperuricemia including, but not limited to, erythroid, myeloid, and lymphoid proliferative hyperuricemia; renal mechanistic hyperuricemia including, but not limited to, familial progressive renal insufficiency, acquired chronic renal insufficiency, drug related renal insufficiency, and endogenous renal production disorders.

Examples of tumor-lysis syndrome include, but are not limited to, tumor-lysis syndrome resulting from chemotherapy treatment in patients with cancer, including but not limited to, leukemias, lymphomas, small cell lung cancer, and breast cancer. In one embodiment, the tumor-lysis syndrome is that which results from chemotherapy, particularly for treating cancer.

## 4.6. METHODS FOR ADMINISTRATION

Due to their activity, the 5-Aryltetrazole Compounds are advantageously useful in veterinary and human medicine. As described above, the 5-Aryltetrazole Compounds are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia.

When administered to an animal, an effective amount of a 5-Aryltetrazole Compound can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present compositions, which comprise a 5-Aryltetrazole Compound, are in one embodiment administered orally. The

compositions of the invention can also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal, and intestinal mucosa, *etc.*) and may be administered together with another therapeutic agent. Administration can be systemic or local. Various delivery systems are known, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, capsules, *etc.*, and can be used to administer the 5-Aryltetrazole Compounds.

Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of the 5-Aryltetrazole Compounds into the bloodstream.

In specific embodiments, it may be desirable to administer the 5-Aryltetrazole Compounds locally. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, *e.g.*, in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it may be desirable to introduce the 5-Aryltetrazole Compounds into the central nervous system by any suitable route, including intraventricular, intrathecal, and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, *e.g.*, by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the 5-Aryltetrazole Compounds can be formulated as a suppository, with traditional binders and excipients such as triglycerides.

In another embodiment, the 5-Aryltetrazole Compounds can be delivered in a vesicle, in particular a liposome (*see* Langer, *Science* 249:1527-1533 (1990) and Treat et al., *Liposomes in the Therapy of Infectious Disease and Cancer* 317-327 and 353-365 (1989).

In yet another embodiment, the 5-Aryltetrazole Compounds can be delivered in a controlled-release system (*see, e.g.*, Goodson, in Medical Applications of Controlled

Release, *supra*, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, *Science* 249:1527-1533 (1990) may be used. In one embodiment, a pump may be used (Langer, *Science* 249:1527-1533 (1990); Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); and Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (*see Medical Applications of Controlled Release* (Langer and Wise eds., 1974); *Controlled Drug Bioavailability, Drug Product Design and Performance* (Smolen and Ball eds., 1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); and Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled-release system can be placed in proximity of a target of the 5-Aryltetrazole Compound, *e.g.*, the spinal column or brain, thus requiring only a fraction of the systemic dose.

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable carrier or vehicle so as to provide the form for proper administration to the animal.

Such pharmaceutical carriers or vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable, or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, and coloring agents may be used. When administered to an animal, the pharmaceutically acceptable carriers or vehicle s are preferably sterile. Water is a particularly useful vehicle when the 5-Aryltetrazole Compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid excipients, particularly for injectable solutions. Suitable pharmaceutical excipients also include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol, and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the composition is in the form of a capsule (see *e.g.*, U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical

excipients are described in *Remington's Pharmaceutical Sciences* 1447-1676 (Alfonso R. Gennaro ed., 19th ed. 1995), incorporated herein by reference.

In one embodiment, the 5-Aryltetrazole Compounds are formulated in accordance with routine procedures as a composition adapted for oral administration to human beings. Compositions for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs, for example. Orally administered compositions may contain one or more agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or pill form, the compositions can be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compositions. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard excipients such as mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose and magnesium carbonate. Such excipients are preferably of pharmaceutical grade.

In another embodiment, the 5-Aryltetrazole Compounds can be formulated for intravenous administration. Typically, compositions for intravenous administration comprise sterile isotonic aqueous buffer. Where necessary, the compositions may also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to lessen pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the 5-Aryltetrazole Compounds are to be administered by infusion, they can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the 5-Aryltetrazole Compounds are administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The 5-Aryltetrazole Compounds of the invention can be administered by controlled-release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

The amount of the 5-Aryltetrazole Compound that is effective in the treatment or prevention of an inflammation disease, a reperfusion disease, or hyperuricemia and/or for inhibiting xanthine oxidase activity can depend on the nature of the disorder or condition causing the inflammation disease, reperfusion disease, or hyperuricemia, or the need for inhibiting xanthine oxidase activity and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify dosage ranges. The effective amount to be employed will also depend on the route of administration, and the seriousness of the inflammation disease, reperfusion disease, or hyperuricemia and/or need for inhibiting xanthine oxidase activity and can be decided according to the judgment of the practitioner and each patient's circumstances. Administration can be at an effective amount ranging from about 0.1 to about 500 mg/kg/day of the 5-Aryltetrazole Compound to animal in need thereof. Suitable effective amounts can range from about 0.1 milligrams to about 500 milligrams about every 4 h, although typically about 100 mg or less. In one embodiment the effective amounts range from about 0.01 milligrams to about 500 milligrams of a 5-Aryltetrazole Compound about every 4 h, in another embodiment about 0.020 milligrams to about 50 milligrams about every 4 h, and in another embodiment about 0.025 milligrams to about 20 milligrams about every 4 h. The effective amounts described herein refer to total amounts administered; that is, if more than one 5-Aryltetrazole Compound is administered, the effective amounts correspond to the total amount administered.

The 5-Aryltetrazole Compounds can be assayed *in vitro* or *in vivo*, for the desired therapeutic or prophylactic activity, prior to use in humans. Animal model systems can be used to demonstrate safety and efficacy.

The present methods for treating or preventing inflammation disease, a reperfusion disease, or hyperuricemia in an animal in need thereof can further comprise administering to the animal being administered a 5-Aryltetrazole Compound an effective amount of another therapeutic agent.

Effective amounts of the other therapeutic agents are well known to those skilled in the art. However, it is well within the skilled artisan's purview to determine the other therapeutic agent's optimal effective-amount range. In one embodiment of the invention where another therapeutic agent is administered to an animal, the effective amount of the 5-Aryltetrazole Compound is less than its effective amount would be where the other therapeutic agent is not administered. In another embodiment, the 5-Aryltetrazole Compound and the other therapeutic agent act synergistically to treat an inflammation disease, a reperfusion disease, or hyperuricemia. It is to be understood that where the methods comprise administering an effecitve amount of a 5-Aryltetrazole Compound and another therapeutic agent, the 5-Aryltetrazole Compound is adminstered when the other therapeutic agent exerts its therapeutic effect, or the other therapeutic agent is administered when the 5-Aryltetrazole Compound exerts its therapeutic or prophylactic effect.

The other therapeutic agent can be a non-steroidal anti-inflammatory agent. Useful non-steroidal anti-inflammatory agents, include, but are not limited to, aspirin, ibuprofen, diclofenac, naproxen, benoxaprofen, flurbiprofen, fenoprofen, flubufen, ketoprofen, indoprofen, piroprofen, carprofen, oxaprozin, pramoprofen, muroprofen, trioxaprofen, suprofen, aminoprofen, tiaprofenic acid, fluprofen, bucloxic acid, indomethacin, sulindac, tolmetin, zomepirac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac, oxpinac, mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid, tolfenamic acid, diflurisal, flufenisal, piroxicam, sudoxicam, isoxicam; salicylic acid derivatives, including aspirin, sodium salicylate, choline magnesium trisalicylate, salsalate, diflunisal, salicylsalicylic acid, sulfasalazine, and olsalazin; para-aminophennol derivatives including acetaminophen and phenacetin; indole and indene acetic acids, including indomethacin, sulindac, and etodolac; heteroaryl acetic acids, including tolmetin, diclofenac, and ketorolac; anthranilic acids (fenamates), including mefenamic acid, and meclofenamic acid; enolic acids, including oxicams (piroxicam, tenoxicam), and pyrazolidinediones (phenylbutazone, oxyphenthartazone); and alkanones, including nabumetone and pharmaceutically acceptable salts thereof and mixtures thereof. For a more

detailed description of the NSAIDs, *see Paul A. Insel, Analgesic-Antipyretic and Antiinflammatory Agents and Drugs Employed in the Treatment of Gout, in Goodman & Gilman's The Pharmacological Basis of Therapeutics* 617-57 (Perry B. Molinhoff and Raymond W. Ruddon eds., 9th ed 1996) and Glen R. Hanson, *Analgesic, Antipyretic and Anti-Inflammatory Drugs in Remington: The Science and Practice of Pharmacy Vol II* 1196-1221 (A.R. Gennaro ed. 19th ed. 1995) which are hereby incorporated by reference in their entireties.

The other therapeutic agent can be an anticonvulsant. Useful anticonvulsants include, but are not limited to, acetylpheneturide, albutoin, aloxidone, aminoglutethimide, 4-amino-3-hydroxybutyric acid, atrolactamide, beclamide, buramate, calcium bromide, carbamazepine, cinromide, clomethiazole, clonazepam, decimemide, diethadione, dimethadione, doxenitroin, eterobarb, ethadione, ethosuximide, ethotoin, felbamate, fluoresone, gabapentin, 5-hydroxytryptophan, lamotrigine, magnesium bromide, magnesium sulfate, mephenytoin, mephobarbital, metharbital, methetoin, methsuximide, 5-methyl-5-(3-phenanthryl)-hydantoin, 3-methyl-5-phenylhydantoin, narcobarbital, nimetazepam, nitrazepam, oxcarbazepine, paramethadione, phenacemide, phenetharbital, pheneturide, phenobarbital, phensuximide, phenylmethylbarbituric acid, phenytoin, phethenylate sodium, potassium bromide, pregabaline, primidone, progabide, sodium bromide, solanum, strontium bromide, suclofenide, sulthiame, tetrantoin, tiagabine, topiramate, trimethadione, valproic acid, valpromide, vigabatrin, and zonisamide.

The other therapeutic agent can be an anti-depressant. Useful antidepressants include, but are not limited to, binedaline, caroxazone, citalopram, dimethazan, fencamine, indalpine, indeloxazine hydrocholoride, nefopam, nomifensine, oxitriptan, oxypertine, paroxetine, sertraline, thiazesim, trazodone, benmoxine, iproclozide, iproniazid, isocarboxazid, nialamide, octamoxin, phenelzine, cotinine, rolicyprine, rolipram, maprotiline, metralindole, mianserin, mirtazepine, adinazolam, amitriptyline, amitriptylinoxide, amoxapine, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dothiepin, doxepin, fluacizine, imipramine, imipramine N-oxide, iprindole, lofepramine, melitracen, metapramine, nortriptyline, noxiptilin, opipramol, pizotyline, propizepine, protriptyline, quinupramine, tianeptine, trimipramine, adrafinil, benactyzine, bupropion, butacetin, dioxadrol, duloxetine, etoperidone, febarbamate, femoxetine, fenpentadiol, fluoxetine, fluvoxamine, hematoporphyrin, hypericin, levophacetoperane, medifoxamine, milnacipran, minaprine, moclobemide, nefazodone, oxaflozane, piberaline, prolintane, pyrisuccideanol, ritanserin, roxindole, rubidium chloride,

sulpiride, tandospirone, thozalinone, tofenacin, toloxatone, tranylcypromine, L-tryptophan, venlafaxine, viloxazine, and zimeldine.

The other therapeutic agent can be an anti-hyperuricemic agent. Useful anti-hyperuricemic agents also include, but are not limited to, allopurinol.

The other therapeutic agent can be an agent useful in treating or preventing tumor-lysis syndrome. Therapeutic agents useful for treating or preventing tumor-lysis syndrome also include, but are not limited to, Lasix or Zyloprim.

The other therapeutic agent can be an agent useful in treating or preventing an inflammatory bowel disorder. Therapeutic agents useful for treating or preventing an inflammatory bowel disorder include, but are not limited to, sulfasalazine, olsalazine, and mesalamine.

A 5-Aryltetrazole Compound and the other therapeutic agent can act additively or, more preferably, synergistically. In one embodiment, a 5-Aryltetrazole Compound is administered concurrently with another therapeutic agent. In one embodiment, a composition comprising an effective amount of a 5-Aryltetrazole Compound and an effective amount of another therapeutic agent can be administered. Alternatively, a composition comprising an effective amount of a 5-Aryltetrazole Compound and a different composition comprising an effective amount of another therapeutic agent can be concurrently administered. In another embodiment, an effective amount of a 5-Aryltetrazole Compound is administered prior or subsequent to administration of an effective amount of another therapeutic agent.

## 4.7. KITS

The invention encompasses kits that can simplify the administration of a 5-Aryltetrazole Compound to an animal.

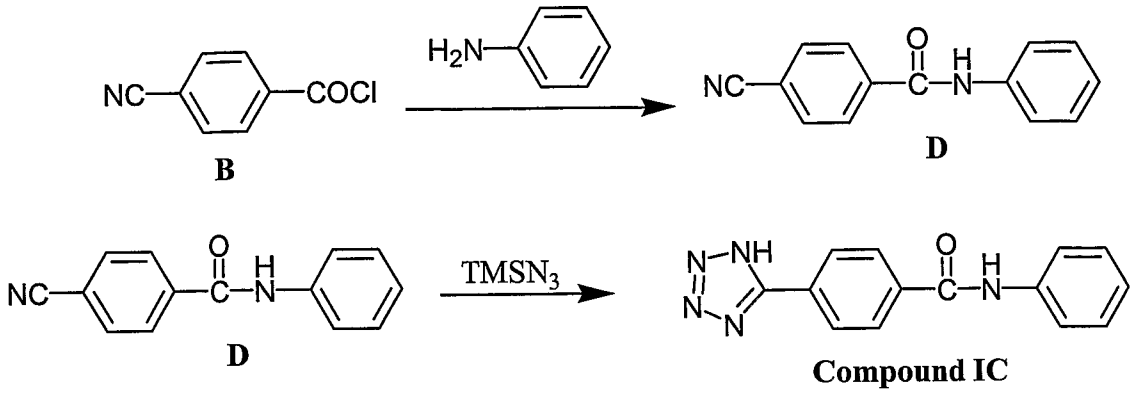
A typical kit of the invention comprises a unit dosage form of a 5-Aryltetrazole Compound. In one embodiment, the unit dosage form is a container, which can be sterile, containing an effective amount of a 5-Aryltetrazole Compound and a pharmaceutically acceptable carrier or excipient. The kit can further comprise a label or printed instructions instructing the use of the 5-Aryltetrazole Compound to treat or prevent inflammation disease, reperfusion disease, or hyperuricemia. The kit can also further comprise a unit dosage form of another therapeutic agent, for example, a container containing an effective amount of the other therapeutic agent. In one embodiment, the kit comprises a container containing an effective amount of a 5-Aryltetrazole Compound and an effective amount of another therapeutic agent. Examples of other therapeutic agents include, but are not limited to, those listed above.

Kits of the invention can further comprise devices that are useful for administering the unit dosage forms. Examples of such devices include, but are not limited to, syringes, drip bags, patches, enema bags, and inhalers.

The following examples are set forth to assist in understanding the invention and should not, of course, be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, which would be within the purview of those skilled in the art, and changes in formulation or minor changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

## 5. EXAMPLES

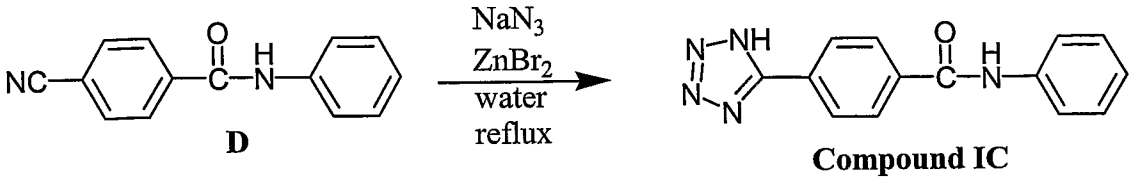
### 5.1. EXAMPLE 1: SYNTHESIS OF COMPOUND IC




A solution of 4-cyanobenzoylchloride **B** (0.82 g, 5 mmol) (commercially available from Sigma-Aldrich Co., http://www.sigmaaldrich.com) was stirred in dry toluene (20 mL). Aniline (0.5 mL, 0.55 mmol) was added dropwise, and following the initial exothermic reaction, the suspension was refluxed for 2 h. After cooling to room temperature, hexane (100 mL) was added to the reaction mixture and the precipitate was filtered and washed with hexane to afford Compound **D**: Yield 2.0 g (90 %), $^1$H NMR (DMSO-$D_6$): δ 7.1 (t, 1H, *p*-H- NHPh) 7.35 (t, 2H, m-H, NHPh) , 7.75 (d, 2H, *o*-H, NHPh); 8.15 (AA'BB', Δ=27 Hz, 4H, C(O)Ar), 10.45 (s, 1H, C(O)NH).

A mixture of Compound **D** (2.2 g, 10 mmol), azidotrimethylsilane (2 mL, 15 mmol) and dibutyltin oxide (0.5 g, 2 mmol) in anhydrous toluene (40 mL) was heated at 100 °C for 5 h. The progress of the reaction was monitored by Thin-Layer Chromatography. After completion of the reaction the organic phase was extracted with 1 M NaOH (20 mL). The aqueous layer was washed with ethyl acetate (2 x 20 mL) and acidified to pH 2 using 2 M HCl. The separated white solid was collected by filtration to provide Compound **IC**: Yield 1.95 g (75 %). $^1$H NMR (DMSO-$D_6$): δ 5 7.1 (t, 1H, *p*-H, NHPh) 7.35 (t, 2H, *m*-H, NHPh), 7.8 (d, 2H, *o*-H, NHPh); 8.15 (AA'BB', Δ=12 Hz, 4H, C(O)Ar), 10.4 (s, 1H, C(O)NH). ES/MS: m/z$^+$ 263 ($M^+$ + 1, 100 %).

## 5.2. EXAMPLE 2: ALTERNATIVE SYNTHESIS OF COMPOUND IC




**D** **Compound IC**

A mixture of Compound **D** (2.2 g, 10 mmol), sodium azide (1.3 g, 20 mmol), zinc bromide (1.15 g, 10 mmol) and isopropanol (5 mL) in water (20 mL) was stirred at reflux for 48 h. After the mixture was cooled to 60 °C, 50 mL of 2 M NaOH was added and the suspension was stirred for additional 30 min at this temperature. The precipitate was filtered and the aqueous solution was extracted with ethyl acetate (2 x 50 mL). The aqueous layer was separated and acidified to pH 2 using 2 M HCl. The precipitate was filtered and washed thoroughly with water to provide Compound **IC**. Yield 1.3 g (50 %).

Experimental data for illustrative 5-Aryltetrazoles Compounds prepared using the methods analogous to those above are given below.

## 5.3. EXAMPLE 3: COMPOUNDS FT, HA-HC, HK, HL, HS, HT, HW-IM, IO, IP, IS, IX-JA, JG-JI, AND JK-JO

Compounds **FT, HA-HC, HK, HL, HS, HT, HW-IF, IH-IM, IO, IS, IX-JA, JG-JI,** and **JK-JN** were prepared according to the method of example 1 using the corresponding amine in place of aniline. Compounds **JO, IP,** and **IG** were prepared according to the method of examples 1 and 2 using the corresponding amine in place of aniline.

Experimental data for illustrative 5-Aryltetrazoles Compounds prepared using the method in Section 5.1 are given below.

**5.3.1. Compound HX:** $^1$H NMR (DMSO-$D_6$): δ 7.2 (t, 2H, *m*-H, NHAr), 7.8 (q, 2H, *o*-H, NHAr), 8.05 (AA'BB', Δ=10 Hz, 4H, C(O)Ar), 10.4 (s, 1H, C(O)NH).

**5.3.2. Compound IA:** $^1$H NMR (DMSO-$D_6$): δ 2.6 (S, 3H, $CH_3$), 7.5 (d, 1H 3-H, NHAr), 7.7 (d, 1H, 4-H, NHAr), 8.1 (m, 5H, 2-H NAr+C(O)Ar), 8.4 (s, 1H, 6-H, NHAr), 10.6 (s, 1H, C(O)NH).

**5.3.3. Compound IP**: $^1$H NMR (DMSO-$D_6$): δ 1.2 (d, 6H, $2CH_3$), 2.8 (m, 1H, $CH(CH_3)_2$), 7.4 (AA'BB', Δ = 140 Hz, 4H, C(O)Ar), 8.05 (AA'BB', m, 4H, C(O)Ar), 10.6 (s, 1H, C(O)NH).

**5.3.4. Compound IS:** $^1$H NMR (DMSO-$D_6$): δ 6 7.9 (s, 4H, NHAr), 8.1 (AA'BB', Δ = 34 Hz, 4H, C(O)Ar), 10.6 (s, 1H, C(O)NH).

**5.3.5. Compound JN**: $^1$H NMR (DMSO-$D_6$): δ 2.2 (s, 3H, $CH_3$), 7.4 (AA'BB', Δ = 154 Hz, 4H, NHAr), 8.05 (AA'BB', Δ = 14 Hz, 4H, C(O)Ar), 10.3 (s, 1H, C(O)NH).

## 5.4. EXAMPLE 4: SYNTHESIS OF COMPOUNDS FV-FX, FZ-GZ, HO-HR, AND JQ

Compounds **FV-FX, FZ-GZ, HO-HR, AND JQ** were prepared according to Method B (described in Section 4.4 above) from the corresponding esters of 4-cyanobenzoic acid. These esters were obtained from 4-cyanobenzoyl chloride and an alcohol or a halide as described in *Vogel's Textbook of Practical Organic Chemistry 5th Ed.*, p. 695. Such alcohols and halides are commercially available.

## 5.5. EXAMPLE 5: SYNTHESIS OF COMPOUNDS IN, IR, IV, IW, AND JB-JE

To a solution of 4-cyanophenol (1.2 g, 10 mmol) in dry DMF (20 mL) was added triethylamine (20 mmol) followed by *i*-butyl bromide (2.7 g, 20 mmol). The resulting reaction mixture was stirred at 100 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2x40 mL). The organic layer was washed with 4 M KOH (3x30 mL) and then with water, dried over $Na_2SO_4$ and concentrated under vacuum to provide 1.5 g (85%) 4-iso-butoxybenzonitrile that was used for the next step without further purification. $^1$H NMR (DMSO-$D_6$): δ 0.95 (d, 6H, $2CH_3$), 2.0 (m, 1H, $CH(CH_3)_2$), 3.8 (d, 2H, $CH_2$), 7.4 (AA'BB', Δ = 270 Hz, 4H, Ar).

A mixture of 4-*iso*-butoxybenzonitrile (1.75 g, 10 mmol), azidotrimethylsilane (2 mL, 15 mmol) and dibutyltinoxide (0.5 g, 2 mmol) in anhydrous toluene (40 mL)

was heated at 100 °C for 18 h. While still hot, the organic phase was extracted with 20 mL 1 M NaOH, aqueous layer was washed with ethyl acetate (2x20 mL) and acidified to pH 2 using 2 M HCl. The resulting white solid was collected by filtration to provide Compound **IR**: Yield 1.2 g (55 %). $^1$H NMR (DMSO-$D_6$): δ 0.95 (d, 6H, $2CH_3$), 2.0 (m, 1H, $CH(CH_3)_2$), 3.8 (d, 2H, $CH_2$), 7.5 (AA'BB', Δ = 295 Hz, 4H, Ar).

Compounds **IN**, **IV**, **IW**, **JB**, **JC**, and **JD** were prepared analogously starting from the commercially available substituted 4-cyanophenols. 3-Bromocyanophenol used in the synthesis of the compound **JC** was prepared by bromination of 4-cyanophenol in acetic acid using bromine as described in Minoshima *et. al.*, JP 10139770 (1998). Compound **JE** was prepared be reacting Compound **JC** with potassium cyanide in the presence of catalytic amount of $Ni[(PPh_3)_4]$ in N-methylpyrrolidone as described in Minoshima *et. al.*, JP 10139770 (1998).

## 5.6. EXAMPLE 6: COMPOUNDS FF-FQ, FU, FY, HE, HF, HG-HJ, HM, JP, AND JR

These compounds were obtained from the commercially available substituted benzonitriles using the Method B.

## 5.7. EXAMPLE 7: COMPOUNDS OF FORMULA DL

Compounds of the Formula **DL** ($R_4$ = Bzl, Et, *tert*-Bu) were obtained from Compound **HE** using Method C (described in Section 4.4), using commercially available CbzCl, $ClCO_2Et$, and $Boc_2O$, respectively.

## 5.8. EXAMPLE 8: COMPOUND FR

Compound **FR** was synthesized by reacting a commercially available 4-aminobenzonitrile with acetic anhydride as described in *Vogel's Textbook of Practical Organic Chemistry* 5th Ed., p. 917 and then converting a resulting 4-acetylaminobenzonitrile to Compound **FR** following the Method B.

## 5.9. EXAMPLE 9: COMPOUNDS FS AND IU

Compounds **FS** and **IU** were synthesized by reacting 4-aminobenzonitrile with methylisocyanate or phenylisocyanate, respectively, as described in Vishnyakova *et al.*, *Russ. Chem. Rev.*, 1985, 54, 249 and then converting the resulting urea derivative to the respective 5-Aryltetrazole Compound following Method B.

### 5.10. EXAMPLE 10: COMPOUND HN

Compound **HN** was prepared by reacting commercially available 5-aminotetrazole with cinnamoyl chloride as described in *Vogel's Textbook of Practical Organic Chemistry 5th Ed.*, p. 917.

### 5.11. EXAMPLE 11: COMPOUNDS HU AND HV

Compounds **HU** and **HV** were prepared by reacting commercially available 4-cyanobenzoylsulfonyl chloride with adamantyl amine and cyclohexylamine, respectively, and then converting a resulting amide to a tetrazole as described in Example 5.1. above.

### 5.12. EXAMPLE 12: COMPOUND IT

Compound **IT** was prepared by benzoylation of 4-aminobenzonitrile as described in *Vogel's Textbook of Practical Organic Chemistry* 5th Ed., p. 917 and then converting a resulting N-benzoyl-4-cyanoaniline to Compound **IT** following the Method B (Sect. 4.4).

### 5.13. EXAMPLE 13: XANTHINE OXIDASE INHIBITORY ACTIVITY OF ILLUSTRATIVE 5-ARYL TETRAZOLE COMPOUNDS

A typical assay showing of xanthine oxidase inhibitory activity of illustrative 5-Aryltetrazole Compounds involved the use of a 96 well plate setup. Analysis of the sample utilized a Spectrophotometer with a SoftMax Pro Program set at a kinetic reading at a wavelength of 295 nm with a runtime of 10 minutes taking a reading at 12 second intervals. Before the first reading the sample was mixed using an automixer for five seconds and between readings the sample was mixed for three seconds.

Sample Preparation: Approximately 1-2 mg of a 5-Aryltetrazole Compound was placed in a 5 mL vial and dissolved in about 1 mL of DMSO resulting in a 2.5 mM solution.

Well Plate Preparation: Four to eight wells were used for each 5-Aryltetrazole Compound. In each well was added 200 mL of Phosphate-buffered saline (50 mM), 20 mL of xanthine (0.5 mg/mL in water), 10 mL of the 2.5 mM solution of 5-Aryltetrazole Compound (prepared as described above), and 20 mL of xanthine oxidase (1/100 x 40 mL PBS). The xanthine oxidase was kept on ice and was added immediately before the plate was run on the spectrophotometer. A control well was also prepared using only DMSO.

The following table shows concentrations of illustrative 5-Aryltetrazole Compounds providing xanthine-oxidase inhibition. Without being limited by theory, compounds that inhibit xanthine oxidase are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia.

5

**PERCENT XANTHINE OXIDASE INHIBITION**

**5-Aryltetrazole Compound Concentration (μM)**

| Compound | 100 | 10 | 1 | 0.1 | 0.05 | 0.03 | 0.01 |
|---|---|---|---|---|---|---|---|
| **FF** | 10 | NT | NT | NT | NT | NT | NT |
| **FG** | 34 | NT | NT | NT | NT | NT | NT |
| **FH** | 69 | 27 | NT | NT | NT | NT | NT |
| **FI** | 67 | 21 | NT | NT | NT | NT | NT |
| **FJ** | 7 | 5 | NT | NT | NT | NT | NT |
| **FK** | 71 | 30 | NT | NT | NT | NT | NT |
| **FL** | 55 | 14 | NT | NT | NT | NT | NT |
| **FM** | 78 | 19 | NT | NT | NT | NT | NT |
| **FN** | 32 | 3 | NT | NT | NT | NT | NT |
| **FO** | 30 | 3 | NT | NT | NT | NT | NT |
| **FP** | 21 | 3 | NT | NT | NT | NT | NT |
| **FQ** | 99 | 81 | 34 | NT | NT | NT | NT |
| **FR** | 40 | NT | NT | NT | NT | NT | NT |
| **FS** | 10 | NT | NT | NT | NT | NT | NT |
| **FT** | 67 | 70 | 15 | NT | NT | NT | NT |
| **FU** | 92 | 54 | 9 | NT | NT | NT | NT |
| **FV** | 100 | 92 | 64 | NT | NT | NT | NT |
| **FW** | 100 | 82 | 39 | NT | NT | NT | NT |
| **FX** | 95 | 95 | 73 | NT | NT | NT | NT |
| **FY** | 91 | 56 | 11 | NT | NT | NT | NT |
| **FZ** | 100 | 97 | 88 | NT | NT | NT | NT |
| **GA** | 100 | 100 | 78 | NT | NT | NT | NT |
| **GB** | 100 | 97 | 82 | NT | NT | NT | NT |
| **GC** | NT | NT | 100 | 97 | 52 | NT | NT |
| **GD** | 100 | 82 | 79 | NT | NT | NT | NT |
| **GE** | NT | NT | 100 | 100 | 59 | NT | NT |

## PERCENT XANTHINE OXIDASE INHIBITION

### 5-Aryltetrazole Compound Concentration (μM)

| Compound | 100 | 10 | 1 | 0.1 | 0.05 | 0.03 | 0.01 |
|---|---|---|---|---|---|---|---|
| GF | 97 | 79 | 28 | NT | NT | NT | NT |
| GG | 89 | 97 | 90 | NT | NT | NT | NT |
| GH | NT | NT | 100 | 91 | NT | 65 | NT |
| GI | NT | NT | 100 | 95 | NT | 75 | NT |
| GJ | NT | NT | 99 | 59 | NT | NT | 12 |
| GK | NT | NT | 46 | 12 | NT | NT | 3 |
| GL | NT | NT | 4 | NT | NT | NT | NT |
| GM | NT | NT | 76 | 28 | NT | NT | 8 |
| GN | NT | NT | 9 | NT | NT | NT | NT |
| GO | NT | NT | 82 | 18 | NT | NT | 6 |
| GP | NT | NT | 92 | 65 | NT | NT | 9 |
| GQ | NT | NT | 78 | 35 | NT | NT | 0 |
| GR | NT | NT | 48 | 8 | NT | NT | 0 |
| GS | NT | NT | 95 | 68 | NT | NT | 13 |
| GT | NT | NT | 94 | 53 | NT | NT | 8 |
| GU | NT | NT | 94 | 69 | NT | NT | 17 |
| GV | NT | NT | 95 | 73 | NT | NT | 14 |
| GW | NT | NT | 39 | 9 | NT | NT | 5 |
| GX | NT | NT | 100 | 84 | NT | NT | 19 |
| GY | NT | NT | 76 | 11 | NT | NT | 19 |
| GZ | NT | NT | 8 | NT | NT | NT | NT |
| HA | NT | NT | 61 | 10 | NT | NT | NT |
| HB | NT | NT | 25 | NT | NT | NT | NT |
| HC | NT | NT | 25 | NT | NT | NT | NT |
| HD | 60 | NT | NT | NT | NT | NT | NT |
| HE | 33 | NT | NT | NT | NT | NT | NT |
| HF | 80 | NT | NT | NT | NT | NT | NT |
| HG | 22 | NT | NT | NT | NT | NT | NT |
| HH | 48 | NT | NT | NT | NT | NT | NT |
| HI | 70 | 24 | 14 | NT | NT | NT | NT |
| HJ | 2 | NT | NT | NT | NT | NT | NT |

## PERCENT XANTHINE OXIDASE INHIBITION

### 5-Aryltetrazole Compound Concentration (μM)

| Compound | 100 | 10 | 1 | 0.1 | 0.05 | 0.03 | 0.01 |
|---|---|---|---|---|---|---|---|
| HK | 43 | NT | NT | NT | NT | NT | NT |
| HL | 0 | NT | NT | NT | NT | NT | NT |
| HM | 27 | NT | NT | NT | NT | NT | NT |
| HN | 42 | 13 | 10 | NT | NT | NT | NT |
| HO | NT | NT | 98 | 95 | 46 | NT | NT |
| HP | NT | NT | 100 | 91 | 41 | NT | NT |
| HQ | NT | NT | 95 | 97 | 53 | NT | NT |
| HR | NT | NT | 95 | 95 | 34 | NT | NT |
| HS | NT | NT | 55 | 16 | NT | 8 | NT |
| HT | NT | NT | 62 | 23 | NT | 15 | NT |
| HU | NT | NT | 0 | NT | NT | NT | NT |
| HV | NT | NT | 0 | NT | NT | NT | NT |
| HW | NT | NT | 89 | 62 | NT | 32 | NT |
| HX | NT | NT | 92 | 59 | NT | 37 | NT |
| HY | NT | NT | 86 | 45 | NT | 20 | NT |
| HZ | NT | NT | 88 | 41 | NT | 20 | NT |
| IA | NT | NT | 90 | 54 | NT | 31 | NT |
| IB | NT | NT | 94 | 64 | NT | 38 | NT |
| IC | NT | NT | 100 | 81 | NT | 60 | NT |
| ID | NT | NT | 72 | 37 | NT | 13 | NT |
| IE | NT | NT | 87 | 38 | NT | 22 | NT |
| IF | NT | NT | 16 | NT | NT | NT | NT |
| IG | NT | NT | 93 | 59 | NT | 33 | NT |
| IH | NT | NT | 95 | 63 | NT | 33 | NT |
| II | NT | NT | 90 | 45 | NT | 20 | NT |
| IJ | NT | NT | 93 | 58 | NT | 27 | NT |
| IK | NT | NT | 55 | 17 | NT | 9 | NT |
| IL | NT | NT | 86 | 46 | NT | 21 | NT |
| IM | NT | NT | 0 | NT | NT | NT | NT |
| IN | NT | NT | 68 | 21 | NT | NT | NT |
| IO | NT | NT | 0 | NT | NT | NT | NT |

## PERCENT XANTHINE OXIDASE INHIBITION

### 5-Aryltetrazole Compound Concentration (μM)

| Compound | 100 | 10 | 1 | 0.1 | 0.05 | 0.03 | 0.01 |
|---|---|---|---|---|---|---|---|
| **IP** | NT | NT | 92 | 52 | NT | 28 | NT |
| **IQ** | NT | NT | 64 | 33 | NT | 36 | NT |
| **IR** | NT | NT | 88 | 47 | NT | 28 | NT |
| **IS** | NT | NT | 97 | 68 | NT | 44 | NT |
| **IT** | NT | NT | 56 | 15 | NT | 7 | NT |
| **IU** | NT | NT | 42 | 9 | NT | 3 | NT |
| **IV** | NT | NT | 35 | 10 | NT | NT | NT |
| **IW** | NT | NT | 22 | 9 | NT | NT | NT |
| **IX** | NT | NT | 98 | 74 | NT | 46 | NT |
| **IY** | NT | NT | 86 | 47 | NT | 26 | NT |
| **IZ** | NT | NT | 89 | 52 | NT | 23 | NT |
| **JA** | NT | NT | NT | 0 | NT | NT | NT |
| **JB** | NT | NT | 32 | 15 | NT | NT | NT |
| **JC** | NT | NT | 31 | 6 | NT | NT | NT |
| **JD** | NT | NT | 28 | 0 | NT | NT | NT |
| **JE** | NT | NT | 82 | 32 | NT | 12 | NT |
| **JF** | NT | NT | 34 | 6 | NT | NT | NT |
| **JG** | NT | NT | 93 | 61 | NT | 33 | NT |
| **JH** | NT | NT | 86 | 41 | NT | 23 | NT |
| **JI** | NT | NT | 79 | 30 | NT | 19 | NT |
| **JJ** | NT | NT | 0 | NT | NT | NT | NT |
| **JK** | NT | NT | 0 | NT | NT | NT | NT |
| **JL** | NT | NT | 95 | 68 | NT | 34 | NT |
| **JM** | NT | NT | 89 | 38 | NT | 16 | NT |
| **JN** | NT | NT | 88 | 41 | NT | 20 | NT |
| **JO** | NT | NT | 83 | 36 | NT | 18 | NT |
| **JP** | NT | NT | 98 | 74 | NT | 46 | NT |
| **JQ** | NT | NT | 100 | 89 | NT | NT | 18 |
| **JR** | 85 | 56 | 14 | NT | NT | NT | NT |

The term "NT" means that the compound was not tested at the indicated concentration.

The above example demonstrates that Compounds **FF-HK, HM-HT, HW-IL, IN, IP-IZ, JB-JI,** and **JL-JR**, illustrative 5-Aryltetrazole Compounds, inhibit xanthine oxidase activity and, accordingly are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia. In addition, Applicants believe that Compounds **HL, HU, HV, IM, IO, JA, JJ,** and **JK,** illustrative 5-Aryltetrazole Compounds, are useful for treating or preventing an inflammation disease, a reperfusion disease, or hyperuricemia.

## 5.14. EXAMPLE 14: TOXIC LIVER INJURY MODEL

Illustrative 5-Aryltetrazole Compounds exert hepatoprotective effects in a thioacetamide model of hepatic failure. The table below shows the efficacy of various illustrative 5-Aryltetrazole Compounds for their hepatoprotective activity in mice. Illustrated are percent inhibition of the increased serum AST levels resulting from an intraperitoneal injection of thioacetamide (400mg/kg) following a single oral dose (3 mL/kg or 10 mL/kg) of various doses of 5-Aryltetrazole Compounds. Results are expressed as percent inhibtion, mean ±SEM (n = 7-10). Studies were conducted as described in *Biochim. Biophys. Acta.* 1536(1):21-30 (2001).

| TOXIC LIVER INJURY MODEL | | |
|---|---|---|
| | Percent Inhibition of Serum AST Levels | |
| **Compound** | **3 mg/kg** | **10 mg/kg** |
| **IC** | 3±8 | 20±5 |
| **IG** | 25±4 | 46±8 |
| **IP** | 23±8 | 41±8 |
| **IS** | NT | 33±5 |
| **JM** | 12±7 | 31±7 |
| **JN** | 11±7 | 31±7 |
| **JO** | 24±9 | 36±12 |
| **IX** | NT | 31±1 |

Accordingly, the above example demonstrates that Compounds **IC**, **IG**, **IP**, **IS**, **JM-JO**, and **IX**, illustrative 5-Aryltetrazole Compounds, inhibit serum AST levels and, accordingly, are useful for treating or preventing organ failure.

## 5.15. EXAMPLE 15: COLLAGEN-INDUCED ARTHRITIS

An illustrative 5-Aryltetrazole Compound exerts protective effects in a model of collagen-induced arthritis in mice. Results are expressed as incidence and severity over time. Studies were conducted as described in *Inflamm. Res.* 50(11):561-569 (2001). The results illustrate that the administration of Compound **JO**, an illustrative 5-Aryltetrazole Compound, reduced incidence of collagen-induced arthritis in mice. Specifically, after 33 days 100 % of the untreated mice exhibited arthritis; however, mice that were administered Compound **JO** showed a significant decrease in the incidence of collagen-induced arthritis.

| **Time (days)** | 25 | 27 | 29 | 31 | 33 |
|---|---|---|---|---|---|
| **% Incidence** | 35 | 45 | 55 | 90 | 100 |
| **Vehicle** | | | | | |
| **Compound JO** | 20 | 35 | 45 | 75 | 85 |

| **Time (days)** | 25 | 27 | 29 | 31 | 33 |
|---|---|---|---|---|---|
| **Mean Severity** | 0 | 0 | 8 | 10 | 12 |
| **Vehicle** | | | | | |
| **Compound JO** | 0 | 0 | 3 | 8 | 8 |

The above example demonstrates that Compound **JO**, an illustrative 5-Aryltetrazole Compound, inhibits collagen-induced arthritis and accordingly, is useful for treating or preventing arthritis.

## 5.16. EXAMPLE 16: REPERFUSION INJURY

Illustrative 5-Aryltetrazole Compounds exert protective effects in various models of organ ischemia and reperfusion. For example, intraperitoneal administration of illustrative 5-Aryltetrazole Compounds retards the progression of gut ischemia reperfusion-induced hyperpermeability and mortality in mice. Results are expressed as % decrease in gut hyperpermeability and as mortality as observed after 6 hours and 2 days of reperfusion. Studies were conducted as described in *Shock*, 14(2):134-141 (2000). There was a notable

dose-dependent effect on gut hyperpermeability and there was an improvement in survival rate, as tested at the highest dose of both levels.

| **Dose** | | **3mg/kg** | **10 mg/kg** | **30 mg/kg** | **30 mg/kg** |
|---|---|---|---|---|---|
| **Compound** | Control | **IG** | **IG** | **IG** | **JO** |
| **Gut Permeability** | 100% | 73% | 69% | 47% | 39% |

| **Dose** | | **30 mg/kg** | **30 mg/kg** |
|---|---|---|---|
| **Compound** | Control | **IG** | **JO** |
| **Survival % (6h)** | 60 | 87 | 87 |
| **Survival % (2days)** | 0 | 20 | 13 |

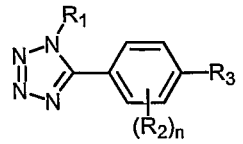
The above example demonstrates that Compound **IG** and **JO**, illustrative 5-Aryltetrazole Compounds, are useful for treating or preventing a reperfusion disease in an animal.

The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited, the entire disclosures of which have been incorporated herein in their entirety.

What is claimed is:

1. A compound of formula Ia:



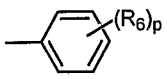
(Ia)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is $CO_2R_4$;

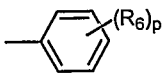
each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_3\text{-}C_{10})$heterocycle, -phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-N(R_5)C(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



$R_4$ is $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, naphthyl, or benzyl;

each $R_5$ is independently -H, $-CF_3$, $-(C_1\text{-}C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_3\text{-}C_{10})$heterocycle, or



each $R_6$ is independently -H, -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), -C(O)H,

-$CO_2(C_1$-$C_{10})$alkyl, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_5)$heteroaryl, -$(C_6)$heteroaryl, -phenyl, naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_m(C_1$-$C_{10})$alkyl, -$CO_2(CH_2)_mH$, -NHC(O)$(C_1$-$C_{10})$alkyl, -NHC(O)NH$(C_1$-$C_{10})$alkyl, -OC(O)$(C_1$-$C_{10})$alkyl, -OC(O)O$(C_1$-$C_{10})$alkyl, -$SO_2NHR_5$, or -$SO_2NH_2$;

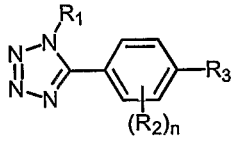
n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

2. A pharmaceutical composition comprising an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt or hydrate thereof and a pharmaceutically acceptable carrier or excipient.

3. A method for treating an inflammation disease in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



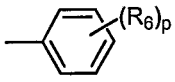
(Ic)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

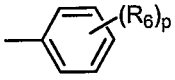
$R_1$ is -H, -$CO_2R_4$; -C(O)$R_5$, or -C(O)N$(R_5)(R_5)$;

each $R_2$ is independently -halo, -$NO_2$, -CN, -OH, -N$(R_5)(R_5)$, -$OR_5$, -C(O)$R_5$, -C(O)NHC(O)$(R_5)$, -OC(O)$R_5$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl,-$(C_3$-$C_7)$heterocycle, -$(C_5)$heteroaryl, -$(C_6)$heteroaryl, phenyl, -naphthyl, -benzyl, -$CO_2R_5$, -C(O)OCH$(R_5)(R_5)$, -NHC(O)$R_5$, -NHC(O)N$HR_5$, -C(O)N$HR_5$, -OC(O)$R_5$, -OC(O)O$R_5$, -$SR_5$, -S(O)$R_5$, or -$S(O)_2R_5$;

$R_3$ is -H, -halo, -$NO_2$, -CN, -OH, -N$(R_5)(R_5)$, -$O(CH_2)_mR_5$, -C(O)$R_5$, -C(O)N$R_5R_5$, -C(O)N$H(CH_2)_m(R_5)$, -$OCF_3$, -benzyl, -$CO_2CH(R_5)(R_5)$, -$(C_1$-$C_{10})$alkyl, -$(C_2$-$C_{10})$alkenyl, -$(C_2$-$C_{10})$alkynyl, -$(C_3$-$C_{10})$cycloalkyl, -$(C_8$-$C_{14})$bicycloalkyl, -$(C_5$-$C_{10})$cycloalkenyl, -$(C_5)$heteroaryl, -$(C_6)$heteroaryl, -naphthyl, -$(C_3$-$C_{10})$heterocycle, -$CO_2(CH_2)_mR_5$, -NHC(O)$R_5$, -NHC(O)$R_5$, -NHC(O)N$HR_5$, -OC(O)$(CH_2)_mCHR_5R_5$, -$CO_2(CH_2)_mCHR_5R_5$,-OC(O)O$R_5$, -$SR_5$, -S(O)$R_5$, -$S(O)_2R_5$, -$S(O)_2NHR_5$, or



$R_4$ is $-CF_3$, $-(C_1-C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_3-C_{10})$heterocycle, or



each $R_5$ is independently H or $R_4$;

each $R_6$ is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$,-benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), -C(O)H, $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl,$-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

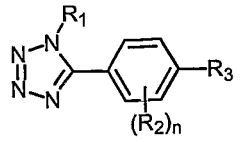
n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

4. The method of claim 3, wherein the inflammation disease is arthritis, psoriasis, gingivitis, colitis, uveitis, diabetes, adult respiratory distress syndrome, autoimmune disease, lupus erythematosus, ileitis, ulcerative colitis, Crohn's disease, asthma, periodontitis, ophthalmitis, endophthalmitis, nephrosis, AIDS-related eurodegeneration, stroke, neurotrauma, Alzheimer's disease, encephalomyelitis, cardio-myopathy, or transplant rejection.

5. A method for treating a reperfusion disease in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



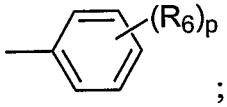
(Ic)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, $-CO_2R_4$; $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

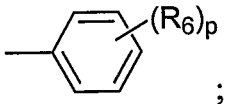
each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_3\text{-}C_7)$heterocycle, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, -NHC(O)$R_5$, -NHC(O)$R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



;

$R_4$ is $-CF_3$, $-(C_1\text{-}C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_3\text{-}C_{10})$heterocycle, or



;

each $R_5$ is independently H or $R_4$;

each $R_6$ is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl, $-O(C_1\text{-}C_{10})$alkyl, $-C(O)(C_1\text{-}C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1\text{-}C_{10})$alkyl$(C_1\text{-}C_{10})$alkyl), -C(O)H, $-CO_2(C_1\text{-}C_{10})$alkyl, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl,$-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1\text{-}C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1\text{-}C_{10})$alkyl, $-NHC(O)NH(C_1\text{-}C_{10})$alkyl, $-OC(O)(C_1\text{-}C_{10})$alkyl, $-OC(O)O(C_1\text{-}C_{10})$alkyl, or $-SO_2NH_2$;

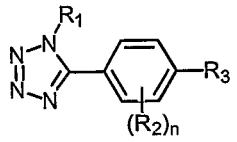
n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

6. The method of claim 5, wherein the reperfusion disease is hemorrhagic shock, sepsis, septic shock, myocardial infarction, or stroke.

7. A method for inhibiting xanthine oxidase activity in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



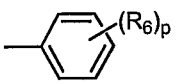
(Ic)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, $-CO_2R_4$; $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

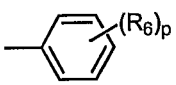
each $R_2$ is indepedently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl,$-(C_3\text{-}C_7)$heterocycle, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1\text{-}C_{10})$alkyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_5\text{-}C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3\text{-}C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



;

$R_4$ is $-CF_3$, $-(C_1\text{-}C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, $-(C_3\text{-}C_{10})$heterocycle, or



;

each $R_5$ is independently H or $R_4$;

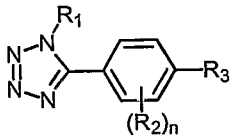
each $R_6$ is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})alkyl(C_1-C_{10})alkyl$, $-O(C_1-C_{10})alkyl$, $-C(O)(C_1-C_{10})alkyl$, $-C(O)NH(CH_2)_m(C_1-C_{10})alkyl$, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})alkyl(C_1-C_{10})alkyl)$, -C(O)H, $-CO_2(C_1-C_{10})alkyl$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -phenyl, naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_m(C_1-C_{10})alkyl$, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})alkyl$, $-NHC(O)NH(C_1-C_{10})alkyl$, $-OC(O)(C_1-C_{10})alkyl$, $-OC(O)O(C_1-C_{10})alkyl$, or $-SO_2NH_2$;

n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

8. A method for treating hyperuricemia in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



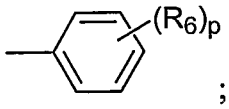
(Ic)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, $-CO_2R_4$; $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_3-C_7)heterocycle$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

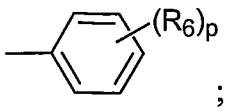
$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})alkyl$, $-(C_2-C_{10})alkenyl$, $-(C_2-C_{10})alkynyl$, $-(C_3-C_{10})cycloalkyl$, $-(C_8-C_{14})bicycloalkyl$, $-(C_5-C_{10})cycloalkenyl$, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$, -naphthyl, $-(C_3-C_{10})heterocycle$, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



;

$R_4$ is $-CF_3$, $-(C_1-C_{10})alkyl$, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)heteroaryl$, $-(C_6)heteroaryl$,

-($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_3$-$C_{10}$)heterocycle, or



;

each $R_5$ is independently H or $R_4$;

each $R_6$ is independently -halo, -$NO_2$, -CN, -OH, -$CO_2$H, -N($C_1$-$C_{10}$)alkyl($C_1$-$C_{10}$)alkyl, -O($C_1$-$C_{10}$)alkyl, -C(O)($C_1$-$C_{10}$)alkyl, -C(O)NH$(CH_2)_m$($C_1$-$C_{10}$)alkyl, -$OCF_3$, -benzyl, -$CO_2(CH_2)_m$CH(($C_1$-$C_{10}$)alkyl($C_1$-$C_{10}$)alkyl), -C(O)H, -$CO_2$($C_1$-$C_{10}$)alkyl, -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_5$)heteroaryl, -($C_6$)heteroaryl, -phenyl, naphthyl, -($C_3$-$C_{10}$)heterocycle, -$CO_2(CH_2)_m$($C_1$-$C_{10}$)alkyl, -$CO_2(CH_2)_m$H, -NHC(O)($C_1$-$C_{10}$)alkyl, -NHC(O)NH($C_1$-$C_{10}$)alkyl, -OC(O)($C_1$-$C_{10}$)alkyl, -OC(O)O($C_1$-$C_{10}$)alkyl, or -$SO_2NH_2$;

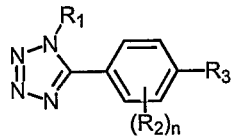
n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

9. The method of claim 8, wherein the hyperuricemia is gout.

10. A method for treating tumor-lysis syndrome in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



(Ic)

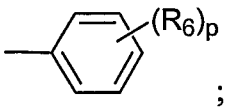
or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, -$CO_2R_4$; -C(O)$R_5$, or -C(O)N($R_5$)($R_5$);

each $R_2$ is independently -halo, -$NO_2$, -CN, -OH, -N($R_5$)($R_5$), -O$R_5$, -C(O)$R_5$, -OC(O)$R_5$, -C(O)NHC(O)$R_5$, -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_3$-$C_7$)heterocycle, -($C_5$)heteroaryl, -($C_6$)heteroaryl, phenyl, -naphthyl, -benzyl, -$CO_2R_5$, -C(O)OCH($R_5$)($R_5$), -NHC(O)$R_5$, -NHC(O)NH$R_5$, -C(O)NH$R_5$, -OC(O)$R_5$, -OC(O)O$R_5$, -S$R_5$, -S(O)$R_5$, or -$S(O)_2R_5$;

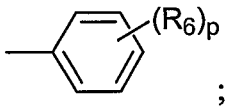
$R_3$ is -H, -halo, -$NO_2$, -CN, -OH, -N($R_5$)($R_5$), -O$(CH_2)_m$$R_5$, -C(O)$R_5$, -C(O)N$R_5R_5$, -C(O)NH$(CH_2)_m$($R_5$), -$OCF_3$, -benzyl, -$CO_2$CH($R_5$)($R_5$), -($C_1$-$C_{10}$)alkyl, -($C_2$-$C_{10}$)alkenyl, -($C_2$-$C_{10}$)alkynyl, -($C_3$-$C_{10}$)cycloalkyl, -($C_8$-$C_{14}$)bicycloalkyl, -($C_5$-$C_{10}$)cycloalkenyl, -($C_5$)heteroaryl, -($C_6$)heteroaryl, -naphthyl, -($C_3$-$C_{10}$)heterocycle,

$-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or



;

$R_4$ is $-CF_3$, $-(C_1-C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_3-C_{10})$heterocycle, or



;

each $R_5$ is independently H or $R_4$;

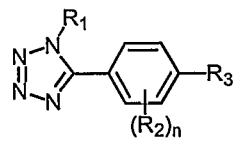
each $R_6$ is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), -C(O)H, $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

n is an integer ranging from 0 to 4;

each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

11. A method for treating an inflammatory bowel disorder in an animal, comprising administering to an animal in need thereof an effective amount of a compound of formula (Ic):



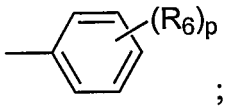
(Ic)

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, $-CO_2R_4$; $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

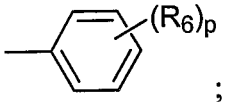
each $R_2$ is independently -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-OR_5$, $-C(O)R_5$, $-OC(O)R_5$, $-C(O)NHC(O)R_5$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_3-C_7)$heterocycle, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, -naphthyl, -benzyl, $-CO_2R_5$, $-C(O)OCH(R_5)(R_5)$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-C(O)NHR_5$, $-OC(O)R_5$, $-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, or $-S(O)_2R_5$;

$R_3$ is -H, -halo, $-NO_2$, -CN, -OH, $-N(R_5)(R_5)$, $-O(CH_2)_mR_5$, $-C(O)R_5$, $-C(O)NR_5R_5$, $-C(O)NH(CH_2)_m(R_5)$, $-OCF_3$, -benzyl, $-CO_2CH(R_5)(R_5)$, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_mR_5$, $-NHC(O)R_5$, $-NHC(O)R_5$, $-NHC(O)NHR_5$, $-OC(O)(CH_2)_mCHR_5R_5$, $-CO_2(CH_2)_mCHR_5R_5$,$-OC(O)OR_5$, $-SR_5$, $-S(O)R_5$, $-S(O)_2R_5$, $-S(O)_2NHR_5$, or




;

$R_4$ is $-CF_3$, $-(C_1-C_{10})$alkyl, -benzyl, -adamantyl, -morpholinyl, -pyrrolidyl, -pyrridyloxide, -pyrrolidinyldione, -piperdidyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_3-C_{10})$heterocycle, or




;

each $R_5$ is independently H or $R_4$;

each $R_6$ is independently -halo, $-NO_2$, -CN, -OH, $-CO_2H$, $-N(C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl, $-O(C_1-C_{10})$alkyl, $-C(O)(C_1-C_{10})$alkyl, $-C(O)NH(CH_2)_m(C_1-C_{10})$alkyl, $-OCF_3$, -benzyl, $-CO_2(CH_2)_mCH((C_1-C_{10})$alkyl$(C_1-C_{10})$alkyl), -C(O)H, $-CO_2(C_1-C_{10})$alkyl, $-(C_1-C_{10})$alkyl, $-(C_2-C_{10})$alkenyl, $-(C_2-C_{10})$alkynyl, $-(C_3-C_{10})$cycloalkyl, $-(C_8-C_{14})$bicycloalkyl, $-(C_5-C_{10})$cycloalkenyl, $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, -phenyl, naphthyl, $-(C_3-C_{10})$heterocycle, $-CO_2(CH_2)_m(C_1-C_{10})$alkyl, $-CO_2(CH_2)_mH$, $-NHC(O)(C_1-C_{10})$alkyl, $-NHC(O)NH(C_1-C_{10})$alkyl, $-OC(O)(C_1-C_{10})$alkyl, $-OC(O)O(C_1-C_{10})$alkyl, or $-SO_2NH_2$;

n is an integer ranging from 0 to 4;

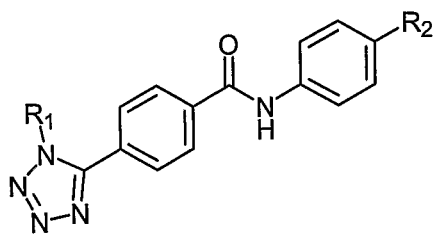
each m is independently an integer ranging from 0 to 8; and

each p is independently an integer ranging from 0 to 5.

12. The method of claim 11, wherein the inflammatory bowel disorder is regional ileitis, colitis, Crohn's disease, or pouchitis.

13. The method of claim 12, wherein the colitis is collagenous or microscopic colitis, ulcerative colitis, or enterocolitis.

14. A compound of formula (Ib):



**(Ib)**

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

$R_1$ is -H, $-CO_2R_4$, $-C(O)R_5$, or $-C(O)N(R_5)(R_5)$;

$R_2$ is $-(C_1\text{-}C_{10})$alkyl or $-O(C_1\text{-}C_{10})$alkyl;

$R_4$ is $-(C_5)$heteroaryl, $-(C_6)$heteroaryl, phenyl, naphthyl, or benzyl; and

each $R_5$ is independently -H, $-CF_3$, $-(C_1\text{-}C_{10})$alkyl, -benzyl, $-(C_2\text{-}C_{10})$alkenyl, $-(C_2\text{-}C_{10})$alkynyl, $-(C_3\text{-}C_{10})$cycloalkyl, $-(C_8\text{-}C_{14})$bicycloalkyl, or $-(C_3\text{-}C_{10})$heterocycle.

15. The compound or pharmaceutically acceptable salt or hydrate of claim 13, wherein $R_1$ is -H.

16. A method for treating an inflammation disease in an animal, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.

17. The method of claim 15, wherein the inflammation disease is arthritis, psoriasis, gingivitis, colitis, uveitis, diabetes, adult respiratory distress syndrome, autoimmune disease, lupus erythematosus, ileitis, ulcerative colitis, Crohn's disease, asthma, periodontitis, ophthalmitis, endophthalmitis, nephrosis, AIDS-related eurodegeneration, stroke, neurotrauma, Alzheimer's disease, encephalomyelitis, cardio-myopathy, or transplant rejection.

18. A method for treating a reperfusion disease in an animal, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.

19. The method of claim 17, wherein the reperfusion disease is hemorrhagic shock, sepsis, septic shock, myocardial infarction, or stroke.

20. The compound of claim 13, wherein the animal is human.

21. A method for inhibiting xanthine oxidase activity in an animal, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.

22. A method for treating hyperuricemia in an animal, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.

23. The method of claim 22, wherein the hyperuricemia is gout.

24. A method for treating tumor-lysis syndrome in an animal, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.

25. A method for treating an inflammatory bowel disorder in an animal, comprising administering to an animal in need thereof an effective amount of a compound. or a pharmaceutically acceptable salt or hydrate of the compound of claim 13.