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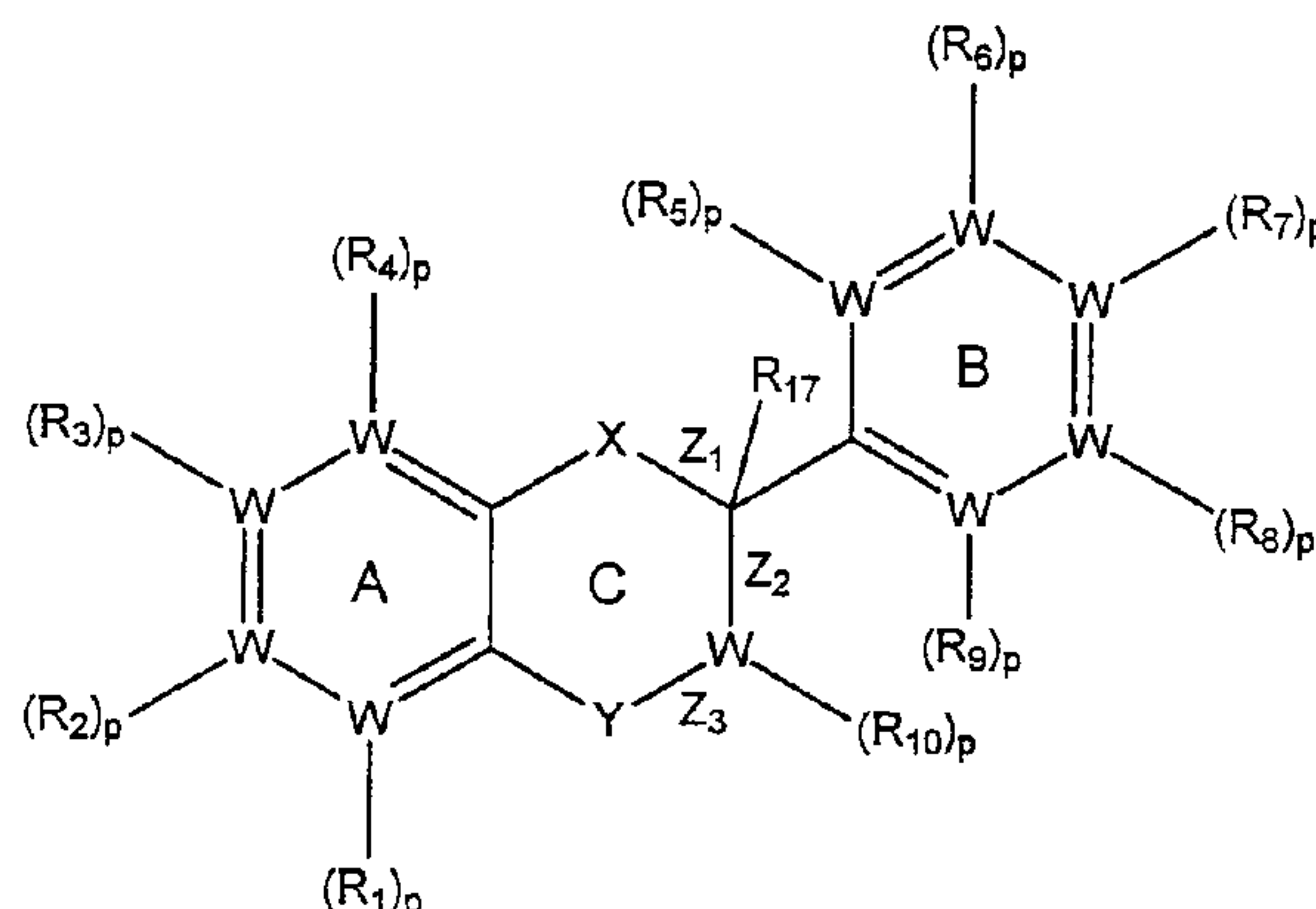
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(54) **Titre : FLAVANOIDES ET ISOFLAVANOIDES POUR LA PREVENTION ET LE TRAITEMENT DE MALADIES CARDIO-
VASCULAIRES**

(54) **Title: FLAVANOIDS AND ISOFLAVANOIDS FOR THE PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASES**



Formula I

(57) **Abrégé/Abstract:**

The present disclosure provides non-naturally occurring polyphenol compounds that upregulate the expression of Apolipoprotein A-I (ApoA-I), as shown in general formula I:

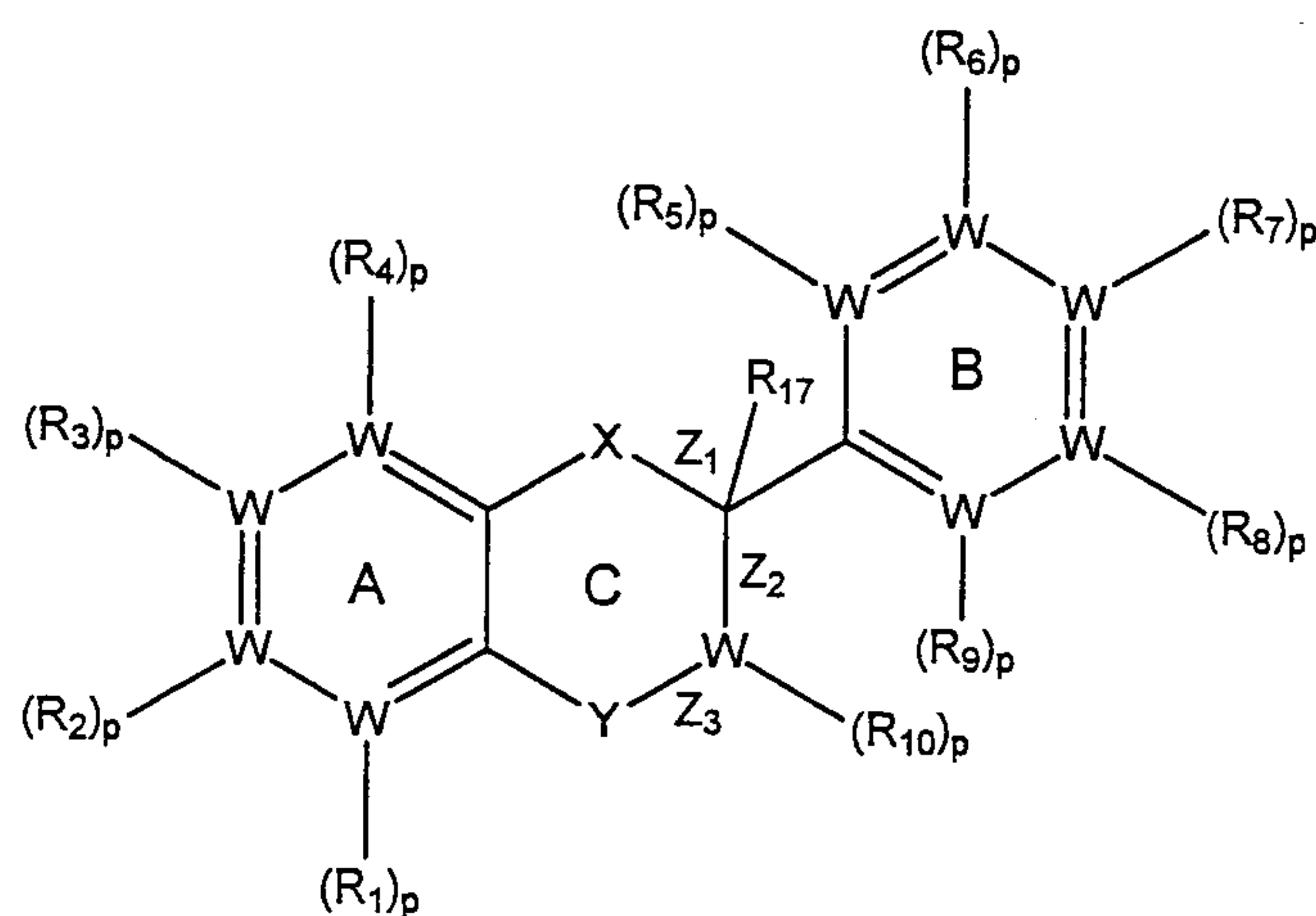
(see formula I)

The disclosed compositions and methods can be used for treatment and prevention of cardiovascular disease and related disease states, including cholesterol or lipid related disorders, such as, e.g., atherosclerosis.



ABSTRACT

The present disclosure provides non-naturally occurring polyphenol compounds that upregulate the expression of Apolipoprotein A-I (ApoA-I), as shown in general formula I:



Formula I

The disclosed compositions and methods can be used for treatment and prevention of cardiovascular disease and related disease states, including cholesterol or lipid related disorders, such as, e.g., atherosclerosis.

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
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THIS IS VOLUME __1__ OF __2__

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**FLAVANOIDS AND ISOFLAVANOIDS FOR THE PREVENTION AND
TREATMENT OF CARDIOVASCULAR DISEASES**

~~[001]~~

Technical Field

[002] The present disclosure relates to polyphenol compounds, which are useful for regulating the expression of apolipoprotein A-I (ApoA-I), and their use for treatment and prevention of cardiovascular disease and related disease states, including cholesterol or lipid related disorders, such as, e.g., atherosclerosis.

BACKGROUND

[003] Epidemiologic data demonstrate an inverse relationship between circulating levels of high density lipoprotein cholesterol (HDL-C) and the incidence of clinically significant atherosclerosis. Each 1 mg/dl increment in the HDL-C serum level is associated with a 2-3% decrement in cardiovascular risk; a 1% reduction in LDL-C reduces coronary heart disease (CHD) risk by 2%. Gordon et al., *Am. J. Med.* 62(5):707-14 (1997). Experimental evidence further supports the protective effect of HDL against cardiovascular disease. For example, in subjects with low HDL-C, administration of gemfibrozil results in a 6% increase in the HDL-C level and a corresponding 22% reduction of the CHD risk. Rubins et al., *N. Engl. J. Med.* 341(6):410-8 (1999). Observations in genetic disorders associated

with low HDL due to reduced ApoA-I expression, also indicate the link between elevated risk of CHD and low HDL-C.

[004] HDL appears to exert its antiatherogenic effect by mediating reverse cholesterol transport (RCT), in which cholesterol is recruited from peripheral tissues and transported to the liver. In addition, HDL also exerts anti-inflammatory, antioxidant effects and promotes fibrinolysis. HDL particles protect against oxidation of LDL, an important initial step in promoting cholesterol uptake by arterial macrophages. HDL exists in two main forms, one containing both apolipoprotein A-I (ApoA-I) and apolipoprotein A-II (ApoA-II), and the other containing ApoA-I without ApoA-II. Schultz et al., *Nature* 365(6448):762-4 (1993). The cardioprotective effect of HDL is mostly, but not exclusively, attributable to ApoA-I.

[005] Clinical and experimental data suggest that the production of ApoA-I is a critical determinant of circulating HDL. For example, persons with familial hyperalphalipoproteinemia (elevated ApoA-I) appear to be protected from atherosclerosis, while those deficient in ApoA-I (hypoalphalipoproteinemia) show accelerated cardiovascular disease. In addition, various experimental manipulations to increase production of ApoA-I are associated with reduced atherogenicity. For example, human ApoA-I is protective in transgenic animal models (Shah et al., *Circulation* 97(8):780-5 (1998); Rubin et al., *Nature* 353(6341):265-7 (1991), and treatment with ApoA-I_{Milano} prevents atherosclerotic lesions and leads to regression of atherosclerotic plaques in human patients (Nissen et al., *JAMA* 290(17):2292-300 (2003)). Further lines of research supporting an antiatherogenic role of ApoA-I include enhancement of reverse cholesterol transport, attenuation of oxidative stress, increased peroxonase

activity, enhanced anticoagulant activity, and anti-inflammatory activity.

Accordingly, ApoA-I is an attractive target for therapeutic intervention.

[006] Currently available therapeutic agents that increase the plasma concentration of ApoA-I, for example, recombinant ApoA-I or peptides that mimic ApoA-I, have potential drawbacks related to manufacturing and reproducibility, e.g., stability during storage, delivery of an active product, and *in vivo* half-life. Therefore, small molecule compounds that upregulate the production of endogenous ApoA-I, such as, e.g., transcriptional upregulators of ApoA-I expression, are very attractive as new therapeutic agents for cardiovascular disease.

[007] One class of compounds that are thought to contribute to the prevention of various diseases, including cancer and cardiovascular diseases, is polyphenols. Polyphenols are common constituents of the human diet, present in most food and beverages of plant origin, and are the most abundant dietary antioxidants. However, polyphenols protective properties are often minimized due to poor bioavailability, lack of clinical significance, and deleterious effects at high concentrations. For example, the most abundant and available source of resveratrol for consumers, red wine, cannot be consumed in therapeutically efficacious quantities on a daily basis due to the numerous well documented deleterious effects of excessive alcohol consumption. The actions of resveratrol may be better or safer in the absence of alcohol.

[008] Several human clinical studies, involving foods or beverages, have yet to demonstrate an unequivocal benefit on primary clinical endpoints, such as oxidative stress, lipemia, and inflammation. For example, out of 12 recent intervention studies with differing polyphenol sources, 6 showed no effect on lipid

parameters and the other 6 showed an improvement in the lipid parameters.

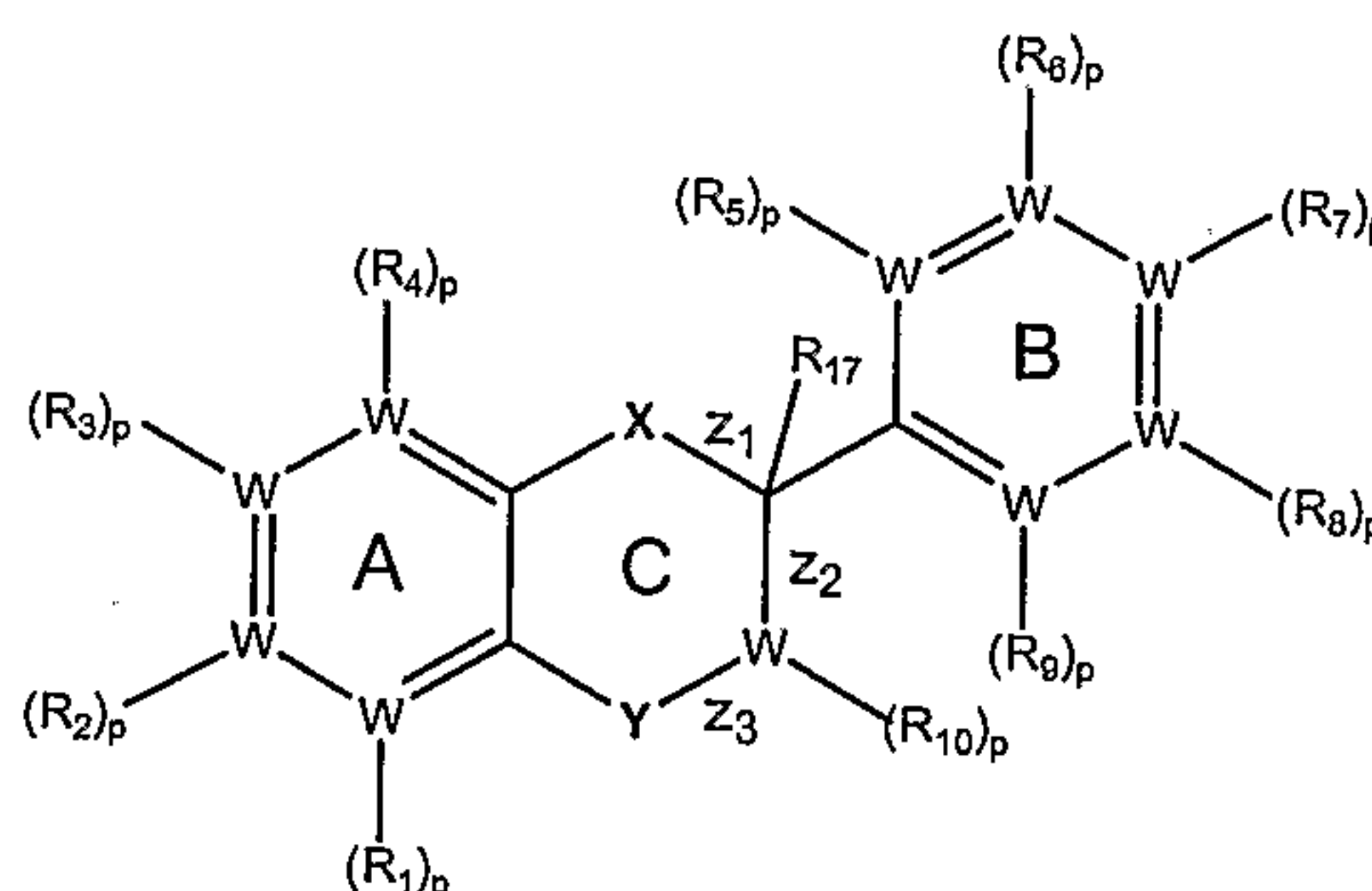
Manach, *Curr. Opin. Lipidol.* 16(1):77-84 (2005). Such contradictory data has limited the potential use of polyphenols, despite their many beneficial properties.

[009] The use of naturally occurring polyphenols as a potential therapy has also been impeded by the inability to achieve efficacious levels of bioavailability. The bioavailability of polyphenols in humans range from 1% to 26% and has a large inter-individual variability as well as variability between different polyphenols. Polyphenols differ in how they are absorbed, metabolized, and excreted. For example, polyphenol flavonoids, such as quercetin, have been reported to have less than 1% intestinal absorption following oral administration. Gugler et al., *Eur. J. Clin. Pharm.* 9:223 (1975). In addition, metabolites are known to negatively influence the biological activity of the parent compounds. Such metabolites often differ from the parent compound in terms of toxicity, efficacy, and length of residence in the plasma. Another limiting factor may be polyphenols' poor solubility in water which limits the routes of administration. These and other factors have made it difficult to determine appropriate dosages of the naturally occurring polyphenols, naringenin or resveratrol, for use in humans.

[010] Thus, there exists a need for synthetic polyphenols to be developed as therapeutic agents for the treatment and prevention of cardiovascular and related diseases, particularly, cholesterol or lipid related disorders, such as, e.g., atherosclerosis. It is therefore one of the objects of the present invention to provide compounds that upregulate the expression of ApoA-I, while having more favorable pharmacological properties than naturally occurring polyphenols.

SUMMARY

[011] The methods of invention include administering to a mammal (e.g., a human) in need thereof a therapeutically effective amount of a flavanoid compound of Formula I:



Formula I

wherein:

X is selected from CR_{11} , $CR_{11}R_{13}$, CO, CS, O, S, SO, SO_2 , N and NR_{11} , wherein R_{11} may be the same or different than R_{13} ;

Y is selected from CR_{12} , $CR_{12}R_{14}$, CO, CS, O, S, SO, SO_2 , N and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

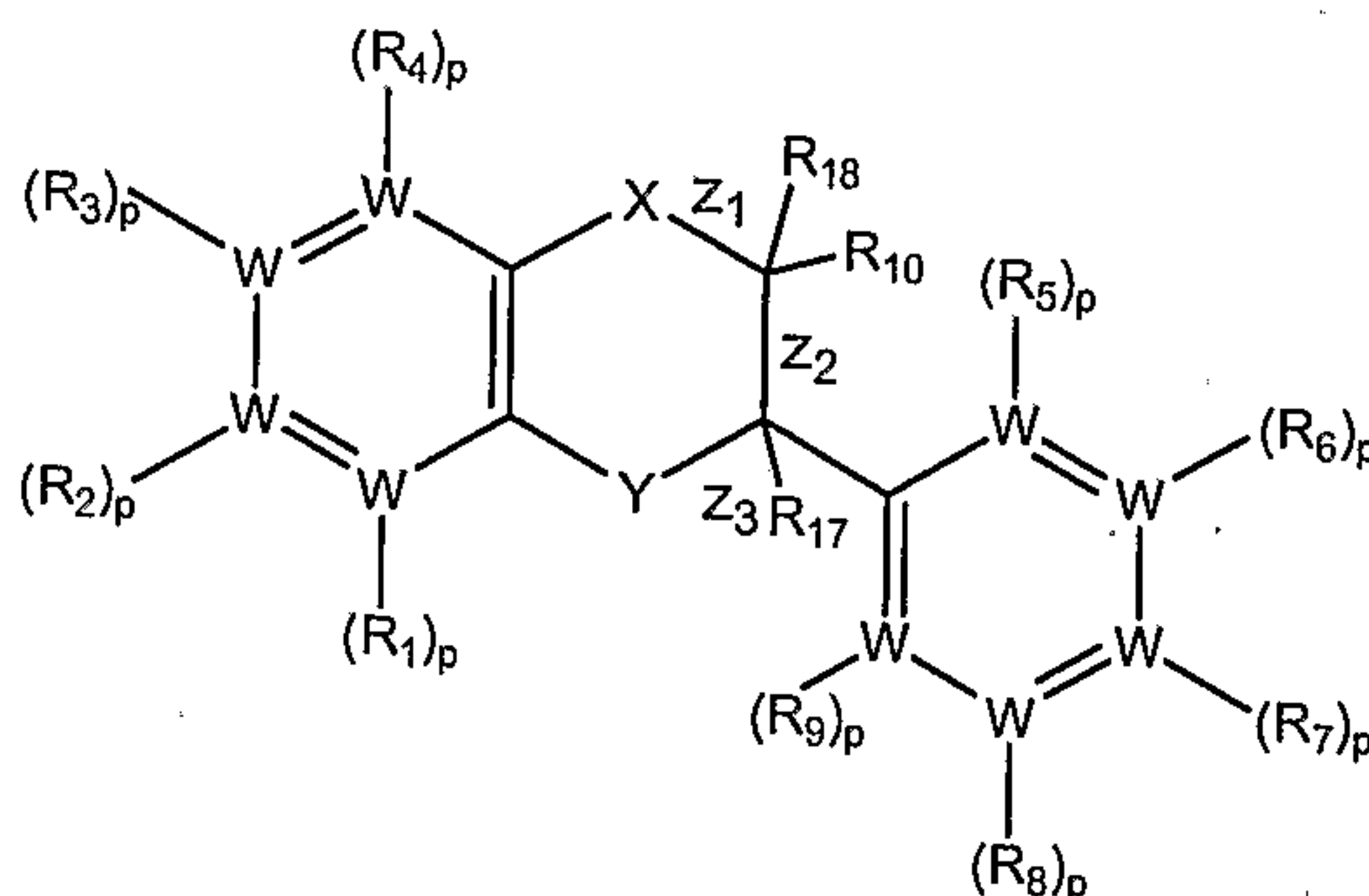
Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, the Z_1 is a single bond;

wherein if X is O and Z_2 is a single bond, then R_{10} is not hydroxyl or ester;
and pharmaceutically acceptable salts and hydrates thereof.

[012] Methods of invention also include administering to a mammal (e.g., a human) in need thereof a therapeutically effective amount of an isoflavanoid compound of Formula IV:



Formula IV

wherein:

X is selected from CR_{11} , $CR_{11}R_{13}$, CO, CS, O, S, SO, SO_2 , N and NR_{11} ,
wherein R_{11} may be the same or different than R_{13} ;

Y is selected from CR_{12} , $CR_{12}R_{14}$, CO, CS, O, S, SO, SO_2 , N and NR_{12} ,
wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{18} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, Y is CO and Z_2 is a double bond, then at least one of R_5 , R_6 , R_8 and R_9 is not hydrogen;

and pharmaceutically acceptable salts and hydrates thereof.

[013] In certain embodiments, the methods and compositions of the invention are useful for treatment of diseases characterized by reduced ApoA-I and/or HDL. The compounds and compositions of the invention can be used to increase expression of ApoA-I. Increasing expression of ApoA-I refers to transcriptionally modulating the expression of the ApoA-I gene thereby affecting the level of the ApoA-I protein expressed, i.e., synthesized and secreted, by the cell. An increase in ApoA-I protein expression leads to an increase in blood levels of HDL. Thus, the methods and compounds of the invention may further be used to reduce plasma cholesterol levels. Accordingly, the methods and compositions of the invention can be used for treatment and prevention of cardiovascular disease and related disease states, particularly, cholesterol or lipid related disorders, such as, atherosclerosis, dyslipidemias, dyslipoproteinemias, hypertension, coronary artery disease, cerebrovascular disease, and the like.

[014] In one aspect, the invention provides a method for prevention of arteriosclerosis lesion development in a mammal, including the development of new arteriosclerotic lesions. In another aspect, the present invention provides a method regressing arteriosclerosis lesions.

[015] The methods and compounds of the invention may further be used to lower blood levels of LDL and triglycerides and/or to increase free radical scavenging. In addition, these methods and compositions may also be used to inhibit HMG-CoA reductase, inhibit ACAT, and/or increase ABCA-I activity.

[016] In a further aspect, the invention provides methods and compositions for effecting an increase of HDL in a mammal comprising, wherein the compound is a flavonoid or a isoflavonoid, each derivatized with covalently bonded niacin. In certain embodiments, the covalent bond comprises a reverse ester linkage.

BRIEF DESCRIPTION OF THE FIGURES

[017] **FIGURE 1** shows results from an ELISA analysis to measure ApoA-I protein content of conditioned media from: (1) untreated HepG2 cells: (2) HepG2 cells treated with solvent: and (3) HepG2 cells treated with test compound, at 0, 6, and 24 hours after exposure.

[018] **FIGURE 2** shows permeability of Caco-2 cells to 4'-hydroxyflavone, 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one, and 2-(2-amino-4-hydroxy-phenyl)-chromen-4-one over time (expressed as percent transported Paap (cm/s)).

[019] **FIGURE 3(A)** shows the effect of 4'-hydroxyflavone, and 4-(4-oxo4H-chromen-2-yl)phenyl nicotinate on ApoA-I levels in hApoA-I transgenic

mice (expressed as net percent change in ApoA-I). **FIGURE 3(B)** shows the change in HDL-C, large HDL (HDL2), small HDL (HDL3) and total cholesterol (TC) levels in hApoA-I transgenic mice following administration of 4'-hydroxyflavone. **FIGURE 3(C)** graphically depicts the change in liver weight in hApoA-I transgenic mice following administration of 4'-hydroxyflavone, 4-(4-oxo4H-chromen-2-yl)phenyl nicotinate, and fenofibrate.

DETAILED DESCRIPTION

Definitions

[020] The term "aldehyde" or "formyl" as used herein refers to the radical -CHO.

[021] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-22, 2-8, or 2-6 carbon atoms, referred to herein as (C₂-C₂₂)alkenyl, (C₂-C₈)alkenyl, and (C₂-C₆)alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, etc.

[022] The term "alkoxy" as used herein refers to an alkyl group attached to an oxygen (-O-alkyl-). "Alkoxy" groups also include an alkenyl group attached to an oxygen ("alkenoxy") or an alkynyl group attached to an oxygen ("alkynoxy") groups. Exemplary alkoxy groups include, but are not limited to, groups with an alkyl, alkenyl or alkynyl group of 1-22, 1-8, or 1-6 carbon atoms, referred to herein as (C₁-C₂₂)alkoxy, (C₁-C₈)alkoxy, and (C₁-C₆)alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, etc.

[023] The term “alkyl” as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-22, 1-8, or 1-6 carbon atoms, referred to herein as (C₁-C₂₂)alkyl, (C₁-C₈)alkyl, and (C₁-C₆)alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[024] The term “alkynyl” as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-22, 2-8, or 2-6 carbon atoms, referred to herein as (C₂-C₂₂)alkynyl, (C₂-C₈)alkynyl, and (C₂-C₆)alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl, etc.

[025] The term “amide” as used herein refers to a radical of the form -R_aC(O)N(R_b)-, -R_aC(O)N(R_b)R_c-, or -C(O)NR_bR_c, wherein R_b and R_c are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. The amide can be attached to another group through the carbon, the nitrogen, R_b, R_c, or R_a. The amide also may be cyclic, for example R_b and R_c, R_a and R_b, or

R_a and R_c may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring. The term "amide" encompasses groups such as sulfonamide, urea, carbamate, carbamic acid, and cyclic versions thereof. The term "amide" also encompasses an amide group attached to a carboxy group, e.g., $-amide-COOH$ or salts such as $-amide-COONa$, etc, an amino group attached to a carboxy group, e.g., $-amino-COOH$ or salts such as $-amino-COONa$, etc.

[026] The term "amine" or "amino" as used herein refers to a radical of the form $-NR_dR_e$, $-N(R_d)R_e$, or $-R_eN(R_d)R_f$ where R_d , R_e , and R_f are independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. The amino can be attached to the parent molecular group through the nitrogen, R_d , R_e or R_f . The amino also may be cyclic, for example any two of R_a , R_b , and R_c may be joined together or with the N to form a 3- to 12-membered ring, e.g., morpholino or piperidiny. The term amino also includes the corresponding quaternary ammonium salt of any amino group, e.g., $-[N(R_d)(R_e)(R_f)]^+$. Exemplary amino groups include aminoalkyl groups, wherein at least one of R_d , R_e , or R_f is an alkyl group.

[027] The term "aryl" as used herein refers to a mono-, bi-, or other multi-carbocyclic, aromatic ring system. The aryl group can optionally be fused to one or more rings selected from aryls, cycloalkyls, and heterocyclyls. The aryl groups of this invention can be substituted with groups selected from alkoxy, aryloxy,

alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Exemplary aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Exemplary aryl groups also include, but are not limited to a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryl."

[028] The term "arylalkyl" as used herein refers to an aryl group having at least one alkyl substituent, e.g. -aryl-alkyl-. Exemplary arylalkyl groups include, but are not limited to, arylalkyls having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)arylalkyl."

[029] The term "aryloxy" as used herein refers to an aryl group attached to an oxygen atom. Exemplary aryloxy groups include, but are not limited to, aryloxys having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)aryloxy."

[030] The term "arylthio" as used herein refers to an aryl group attached to a sulfur atom. Exemplary arylthio groups include, but are not limited to, arylthios having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)arylthio."

[031] The term "arylsulfonyl" as used herein refers to an aryl group attached to a sulfonyl group, e.g., -S(O)₂-aryl-. Exemplary arylsulfonyl groups include, but are not limited to, arylsulfonyls having a monocyclic aromatic ring system, wherein the ring comprises 6 carbon atoms, referred to herein as "(C₆)arylsulfonyl."

[032] The term "benzyl" as used herein refers to the group -CH₂-phenyl.

[033] The term "bicyclic aryl" as used herein refers to an aryl group fused to another aromatic or non-aromatic carbocyclic or heterocyclic ring. Exemplary bicyclic aryl groups include, but are not limited to, naphthyl or partly reduced forms thereof, such as di-, tetra-, or hexahydronaphthyl.

[034] The term "bicyclic heteroaryl" as used herein refers to a heteroaryl group fused to another aromatic or non-aromatic carbocyclic or heterocyclic ring. Exemplary bicyclic heteroaryls include, but are not limited to, 5,6 or 6,6-fused systems wherein one or both rings contain heteroatoms. The term "bicyclic heteroaryl" also encompasses reduced or partly reduced forms of fused aromatic system wherein one or both rings contain ring heteroatoms. The ring system may contain up to three heteroatoms, independently selected from oxygen, nitrogen, or sulfur. The bicyclic system may be optionally substituted with one or more groups selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Exemplary bicyclic heteroaryl's include, but are not limited to, quinazolinyl, benzothiophenyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, benzofuranyl, indolyl, quinoliny, isoquinoliny, phthalazinyl, benzotriazolyl, benzopyridinyl, and benzofuranyl.

[035] The term "carbamate" as used herein refers to a radical of the form -R_gOC(O)N(R_h)-, -R_gOC(O)N(R_h)R_i-, or -OC(O)NR_hR_i, wherein R_g, R_h and R_i are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone,

nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Exemplary carbamates include, but are not limited to, arylcarbamates or heteroaryl carbamates, e.g. wherein at least one of R_g , R_h and R_i are independently selected from aryl or heteroaryl, such as pyridine, pyridazine, pyrimidine, and pyrazine.

[036] The term "carbonyl" as used herein refers to the radical $-C(O)-$.

[037] The term "carboxy" as used herein refers to the radical $-COOH$ or its corresponding salts, e.g. $-COONa$, etc. The term carboxy also includes "carboxycarbonyl," e.g. a carboxy group attached to a carbonyl group, e.g., $-C(O)-COOH$ or salts such as $-C(O)-COONa$, etc..

[038] The term "cyano" as used herein refers to the radical $-CN$.

[039] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen.

[040] The term "cycloalkyl" as used herein refers to a monovalent saturated or unsaturated cyclic, bicyclic, or bridged bicyclic hydrocarbon group of 3-12 carbons, or 3-8 carbons, referred to herein as " (C_3-C_8) cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclohexenes, cyclopentanes, and cyclopentenenes. Cycloalkyl groups may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Cycloalkyl groups can be fused to other cycloalkyl, aryl, or heterocyclyl groups.

[041] The term "dicarboxylic acid" as used herein refers to a group containing at least two carboxylic acid groups such as saturated and unsaturated

hydrocarbon dicarboxylic acids and salts thereof. Exemplary dicarboxylic acids include alkyl dicarboxylic acids. Dicarboxylic acids may be substituted with alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Dicarboxylic acids include, but are not limited to succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, maleic acid, phthalic acid, aspartic acid, glutamic acid, malonic acid, fumaric acid, (+)/(-)-malic acid, (+)/(-) tartaric acid, isophthalic acid, and terephthalic acid. Dicarboxylic acids further include carboxylic acid derivatives thereof, such as anhydrides, imides, hydrazides, etc., for example, succinic anhydride, succinimide, etc.

[042] The term "ester" refers to a radical having the structure $-C(O)O-$, $-C(O)O-R_j-$, $-R_kC(O)O-R_j-$, or $-R_kC(O)O-$, where O is not bound to hydrogen, and R_j and R_k can independently be selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, cycloalkyl, ether, formyl, haloalkyl, halogen, heteroaryl, heterocyclyl, ketone, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid and thioketone. R_k can be a hydrogen, but R_j cannot be hydrogen. The ester may be cyclic, for example the carbon atom and R_j , the oxygen atom and R_k , or R_j and R_k may be joined to form a 3- to 12-membered ring. Exemplary esters include, but are not limited to, alkyl esters wherein at least one of R_j or R_k is alkyl, such as $-alkyl-C(O)-O-$, $-C(O)-O-alkyl-$, $-alkyl-C(O)-O-alkyl-$, etc. Exemplary esters also include aryl or heteroaryl esters, e.g. wherein at least one of R_j or R_k is a heteroaryl group such as pyridine, pyridazine, pyrimidine and pyrazine, such

as a nicotinate ester. Exemplary esters also include reverse esters having the structure $-R_kC(O)O-$, where the oxygen is bound to the parent molecular group. Exemplary reverse esters include succinate, D-argininate, L-argininate, L-lysinate and D-lysinate. Esters also include carboxylic acid anhydrides and acid halides.

[043] The term "ether" refers to a radical having the structure $-R_lO-R_m-$, where R_l and R_m can independently be alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, or ether. The ether can be attached to the parent molecular group through R_l or R_m . Exemplary ethers include, but are not limited to, alkoxyalkyl and alkoxyaryl groups. Ethers also includes polyethers, e.g., where one or both of R_l and R_m are ethers.

[044] The terms "halo" or "halogen" or "Hal" as used herein refer to F, Cl, Br, or I.

[045] The term "haloalkyl" as used herein refers to an alkyl group substituted with one or more halogen atoms. "Haloalkyls" also encompass alkenyl or alkynyl groups substituted with one or more halogen atoms.

[046] The term "heteroaryl" as used herein refers to a mono-, bi-, or multi-cyclic, aromatic ring system containing one or more heteroatoms, for example 1 to 3 heteroatoms, such as nitrogen, oxygen, and sulfur. Heteroaryls can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. Heteroaryls can also be fused to non-aromatic rings. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl,

pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,-) and (1,2,4)-triazolyl, pyrazinyl, pyrimidyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, and oxazolyl. Exemplary heteroaryl groups include, but are not limited to, a monocyclic aromatic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as "(C₂-C₅)heteroaryl."

[047] The terms "heterocycle," "heterocyclyl," or "heterocyclic" as used herein refer to a saturated or unsaturated 3-, 4-, 5-, 6- or 7-membered ring containing one, two, or three heteroatoms independently selected from nitrogen, oxygen, and sulfur. Heterocycles can be aromatic (heteroaryls) or non-aromatic. Heterocycles can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone.

[048] Heterocycles also include bicyclic, tricyclic, and tetracyclic groups in which any of the above heterocyclic rings is fused to one or two rings independently selected from aryls, cycloalkyls, and heterocycles. Exemplary heterocycles include acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl,

tetrahydropyranyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, thiopyranyl, and triazolyl.

[049] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[050] The term "hydroxyalkyl" as used herein refers to a hydroxy radical attached to an alkyl group.

[051] The term "hydroxyaryl" as used herein refers to a hydroxy radical attached to an aryl group.

[052] The term "ketone" as used herein refers to a radical having the structure -C(O)-R_n (such as acetyl, -C(O)CH₃) or -R_n-C(O)-R_o-. The ketone can be attached to another group through R_n or R_o. R_n or R_o can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl or aryl, or R_n or R_o can be joined to form a 3- to 12-membered ring.

[053] The term "monoester" as used herein refers to an analogue of a dicarboxylic acid wherein one of the carboxylic acids is functionalized as an ester and the other carboxylic acid is a free carboxylic acid or salt of a carboxylic acid. Examples of monoesters include, but are not limited to, to monoesters of succinic acid, glutaric acid, adipic acid, suberic acid, sebacic acid, azelaic acid, oxalic and maleic acid.

[054] The term "nitro" as used herein refers to the radical -NO₂.

[055] The term "perfluoroalkoxy" as used herein refers to an alkoxy group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[056] The term "perfluoroalkyl" as used herein refers to an alkyl group in which all of the hydrogen atoms have been replaced by fluorine atoms.

Exemplary perfluoroalkyl groups include, but are not limited to, C₁₋₅ perfluoroalkyl, such as trifluoromethyl, etc.

[057] The term "perfluorocycloalkyl" as used herein refers to a cycloalkyl group in which all of the hydrogen atoms have been replaced by fluorine atoms.

[058] The term "phenyl" as used herein refers to a 6-membered carbocyclic aromatic ring. The phenyl group can also be fused to a cyclohexane or cyclopentane ring. Phenyl can be substituted with one or more substituents including alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone.

[059] The term "phosphate" as used herein refers to a radical having the structure $-OP(O)O_2^-$, $-R_xOP(O)O_2^-$, $-OP(O)O_2R_y^-$, or $-R_xOP(O)O_2R_y^-$, wherein R_x and R_y can be alkyl, alkenyl, alkynyl, alkoxy, amide, amino, aryl, aryloxy, carboxy, cyano, cycloalkyl, ester, ether, halogen, heterocyclyl, hydrogen, hydroxy, ketone, nitro, sulfonate, sulfonyl, and thio.

[060] The term "sulfide" as used herein refers to the radical having the structure R_ZS^- , where R_Z can be alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cycloalkyl, ester, ether, formyl, haloalkyl, heteroaryl, heterocyclyl, and ketone. The term "alkylsulfide" as used herein refers to an alkyl group attached to a sulfur atom.

[061] The term "sulfinyl" as used herein refers to a radical having the structure $-S(O)O^-$, $-R_pS(O)O^-$, $-R_pS(O)OR_q^-$, or $-S(O)OR_q^-$, wherein R_p and R_s can be alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone,

nitro, phosphate, sulfide, sulfonyl, sulfonic acid, sulfonamide and thioketone.

Exemplary sulfinyl groups include, but are not limited to, alkylsulfinyls wherein at least one of R_p or R_q is alkyl, alkenyl or alkynyl.

[062] The term “sulfonamide” as used herein refers to a radical having the structure $-(R_r)-N-S(O)_2-R_s-$ or $-R_t(R_r)-N-S(O)_2-R_s$, where R_t , R_r , and R_s can be, for example, hydrogen, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where R_s is alkyl), arylsulfonamides (e.g., where R_s is aryl), cycloalkyl sulfonamides (e.g., where R_s is cycloalkyl), and heterocyclyl sulfonamides (e.g., where R_s is heterocyclyl), etc.

[063] The term “sulfonate” as used herein refers to the radical $-OSO_3^-$. Sulfonate includes salts such as $-OSO_3Na$, $-OSO_3K$, etc. and the acid $-OSO_3H$.

[064] The term “sulfonic acid” refers to the radical $-SO_3H-$ and its corresponding salts, e.g. $-SO_3K-$, $-SO_3Na-$.

[065] The term “sulfonyl” as used herein refers to a radical having the structure R_uSO_2- , where R_u can be alkyl, alkenyl, alkynyl, amino, amide, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term “alkylsulfonyl” as used herein refers to an alkyl group attached to a sulfonyl group. “Alkylsulfonyl” groups can optionally contain alkenyl or alkynyl groups.

[066] The term “thioketone” refers to a radical having the structure $-R_v-C(S)-R_w-$. The ketone can be attached to another group through R_v or R_w . R_v or R_w can be alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl or aryl, or R_v or R_w can be joined to form a 3- to 12-membered ring.

[067] “Alkyl,” “alkenyl,” and “alkynyl” groups, collectively referred to as “saturated and unsaturated hydrocarbons,” can be substituted with or interrupted

by at least one group selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide, thioketone, and N.

[068] As used herein, a "suitable substituent" refers to a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to: C₁₋₂₂, C₁₋₈, and C₁₋₆ alkyl, alkenyl or alkynyl; C₁₋₆ aryl, C₂₋₅ heteroaryl; C₃₋₇ cycloalkyl; C₁₋₂₂, C₁₋₈, and C₁₋₆ alkoxy; C₆ aryloxy; -CN; -OH; oxo; halo, carboxy; amino, such as -NH(C₁₋₂₂, C₁₋₈, or C₁₋₆ alkyl), -N((C₁₋₂₂, C₁₋₈, and C₁₋₆ alkyl)₂), -NH((C₆)aryl), or -N((C₆)aryl)₂; formyl; ketones, such as -CO(C₁₋₂₂, C₁₋₈, and C₁₋₆ alkyl), --CO((C₆ aryl) esters, such as -CO₂(C₁₋₂₂, C₁₋₈, and C₁₋₆ alkyl) and -CO₂ (C₆ aryl). One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

[069] The term "pharmaceutically acceptable carrier" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[070] The term "pharmaceutically acceptable composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[071] The term "pharmaceutically acceptable prodrugs" as used herein represents those prodrugs of the compounds of the present invention that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, commensurate with a reasonable benefit / risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. A discussion is provided in Higuchi et al., "Pro-drugs as Novel Delivery Systems," *ACS Symposium Series*, Vol. 14, and in Roche, E.B., ed. *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

[072] The term "pharmaceutically acceptable salt(s)" refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to sulfate, citrate, malate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, 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. Compounds included in the present compositions that include an amino moiety may form

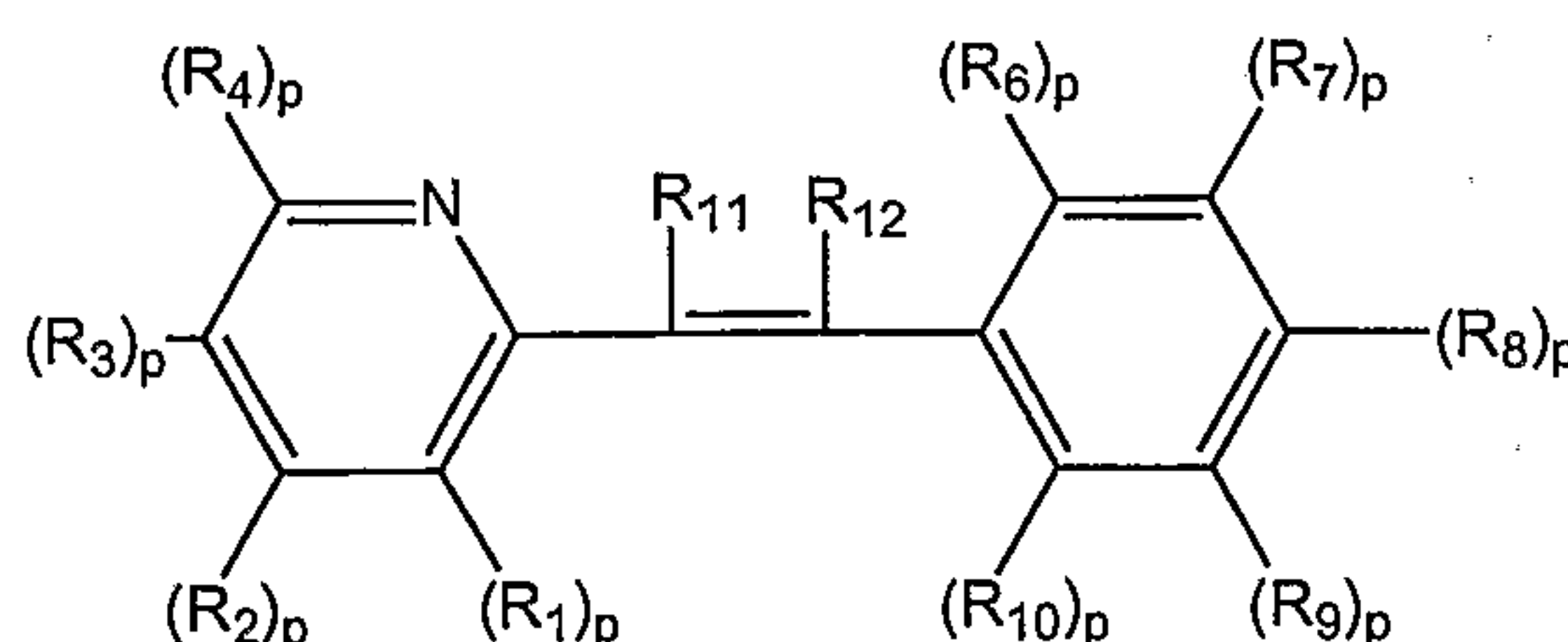
pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above. Compounds included in the present compositions, that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts.

[073] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[074] Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically

active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Stereoisomers can also be obtained from stereomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

[075] Geometric isomers can also exist in the compounds of the present invention. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the “*Z*” or “*E*” configuration wherein the terms “*Z*” and “*E*” are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the *E* and *Z* isomers. For example, the structure below represents a genus of alkenes in which the double bond is either an “*E*-double bond” or a “*Z*-double bond.”

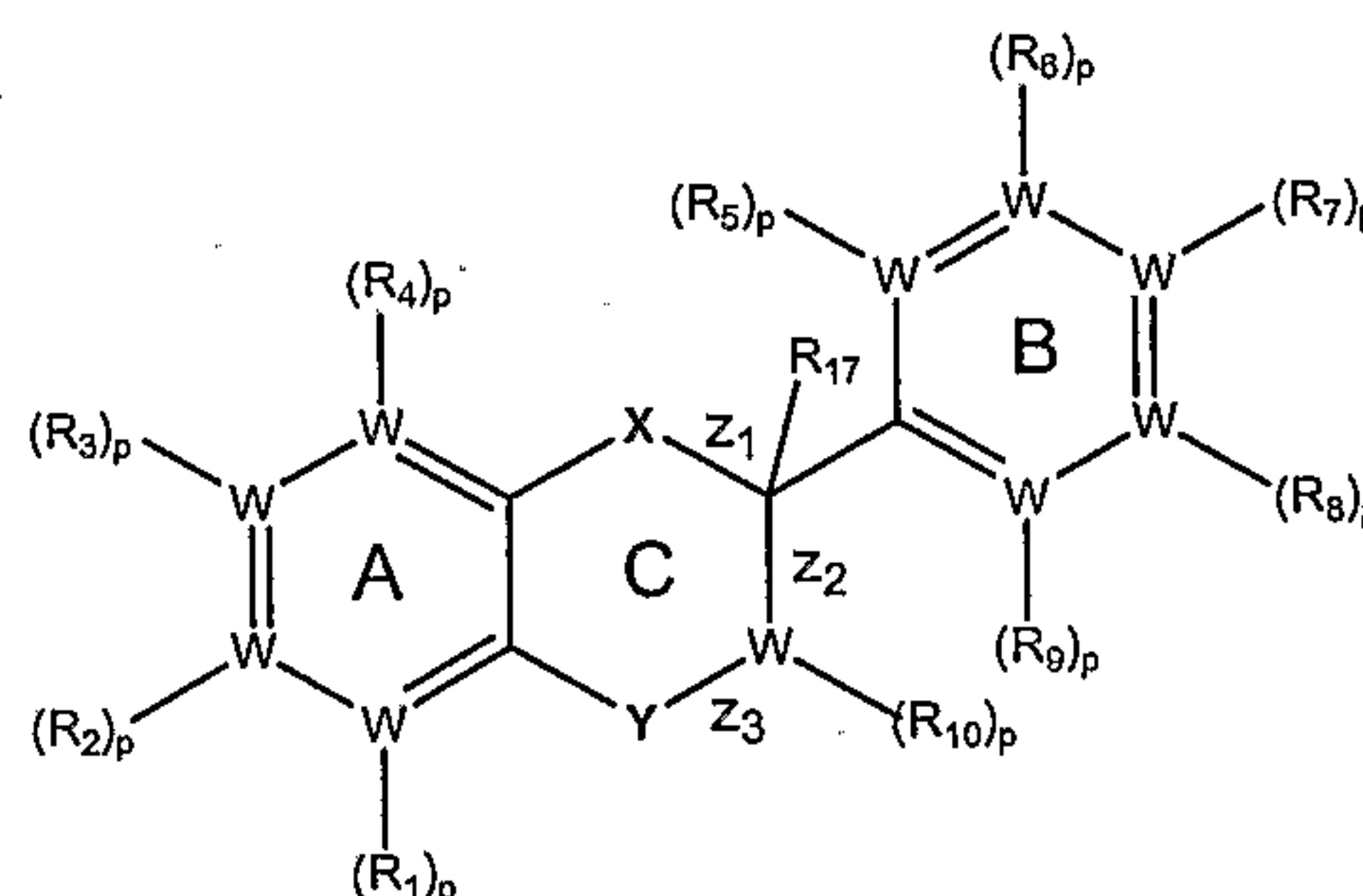


[076] Substituents around a carbon-carbon double bond alternatively can be referred to as “cis” or “trans,” where “cis” represents substituents on the same side of the double bond and “trans” represents substituents on opposite sides of

the double bond. The arrangement of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

Embodiments of the Invention

[077] Disclosed herein are methods for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

wherein:

X is selected from CR₁₁, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, N and NR₁₁, wherein R₁₁ may be the same or different than R₁₃;

Y is selected from CR₁₂, CR₁₂R₁₄, CO, CS, O, S, SO, SO₂, N and NR₁₂, wherein R₁₂ may be the same or different than R₁₄;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄ and R₁₇ are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl,

halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, and R₁₄ are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z₁, Z₂ and Z₃ are each independently selected from a single bond and a double bond;

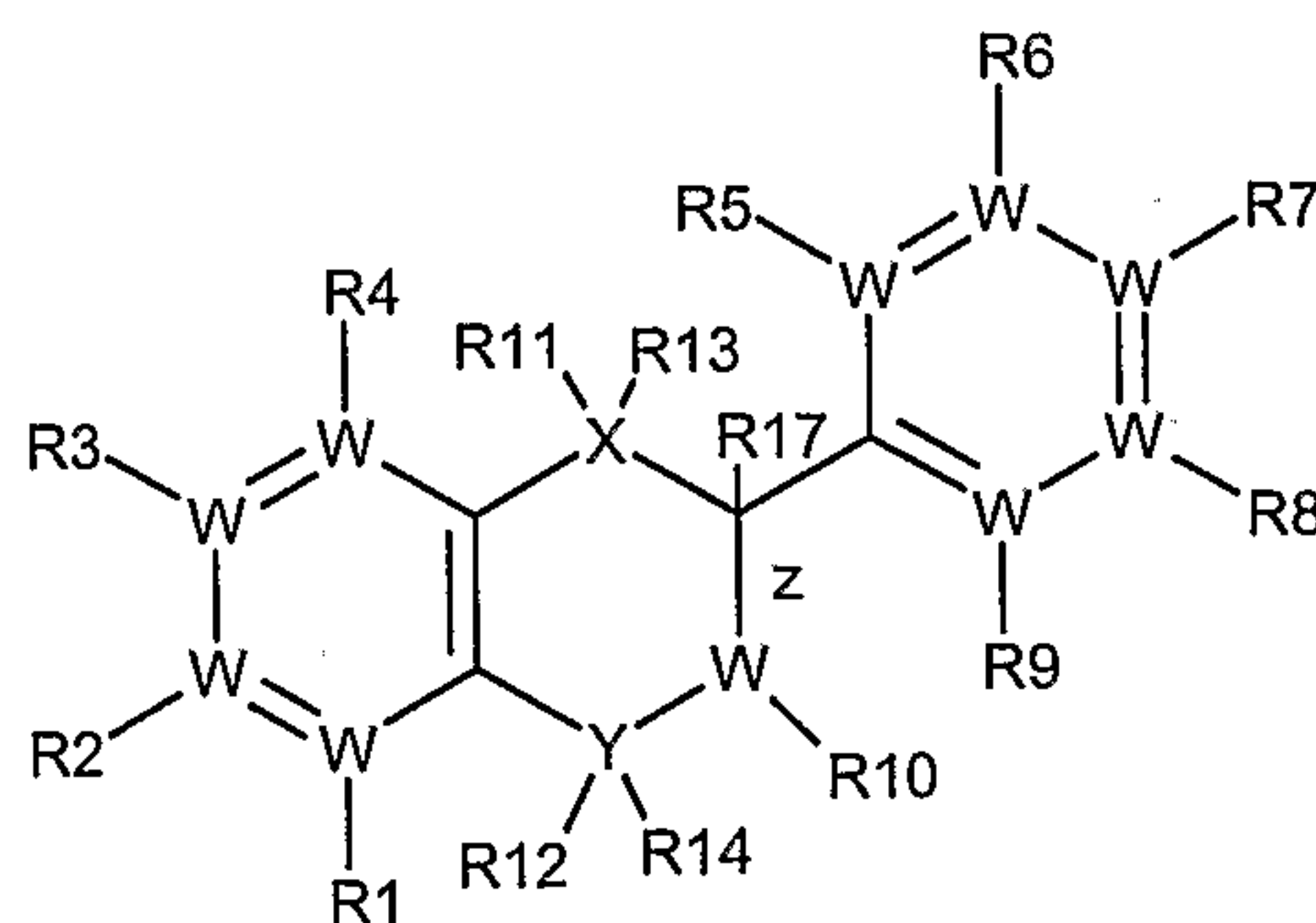
wherein if Y is O, then X is not CO;

wherein if X is O, the Z₁ is a single bond;

wherein if X is O and Z₂ is a single bond, then R₁₀ is not hydroxyl or ester;

and pharmaceutically acceptable salts and hydrates thereof.

[078] An alternative embodiment provides flavanoid compounds of Formula 1:



or a pharmaceutically acceptable salt thereof,

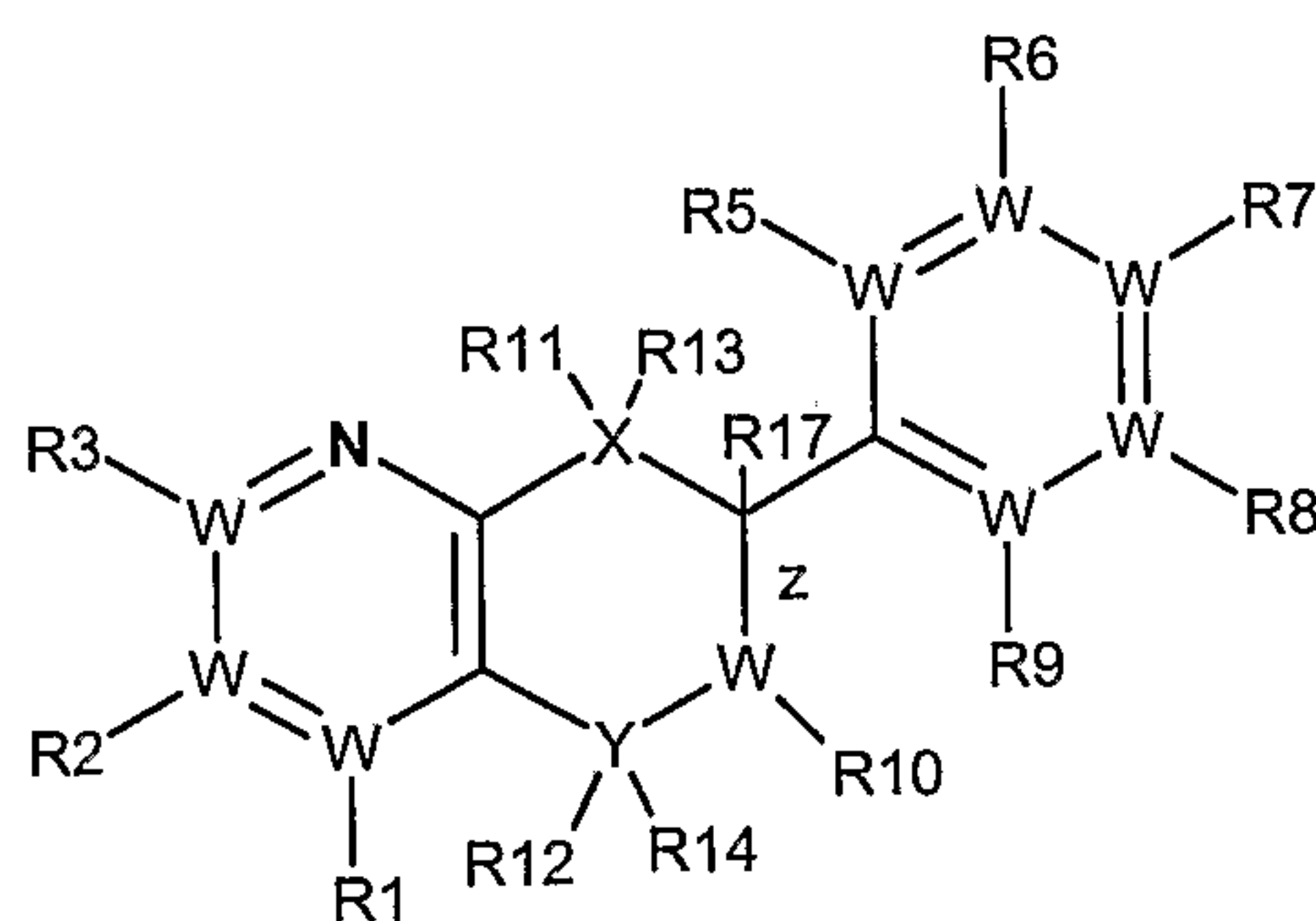
wherein

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, and R₁₇ are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl,

carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], monoesters, dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#, #STR100#,

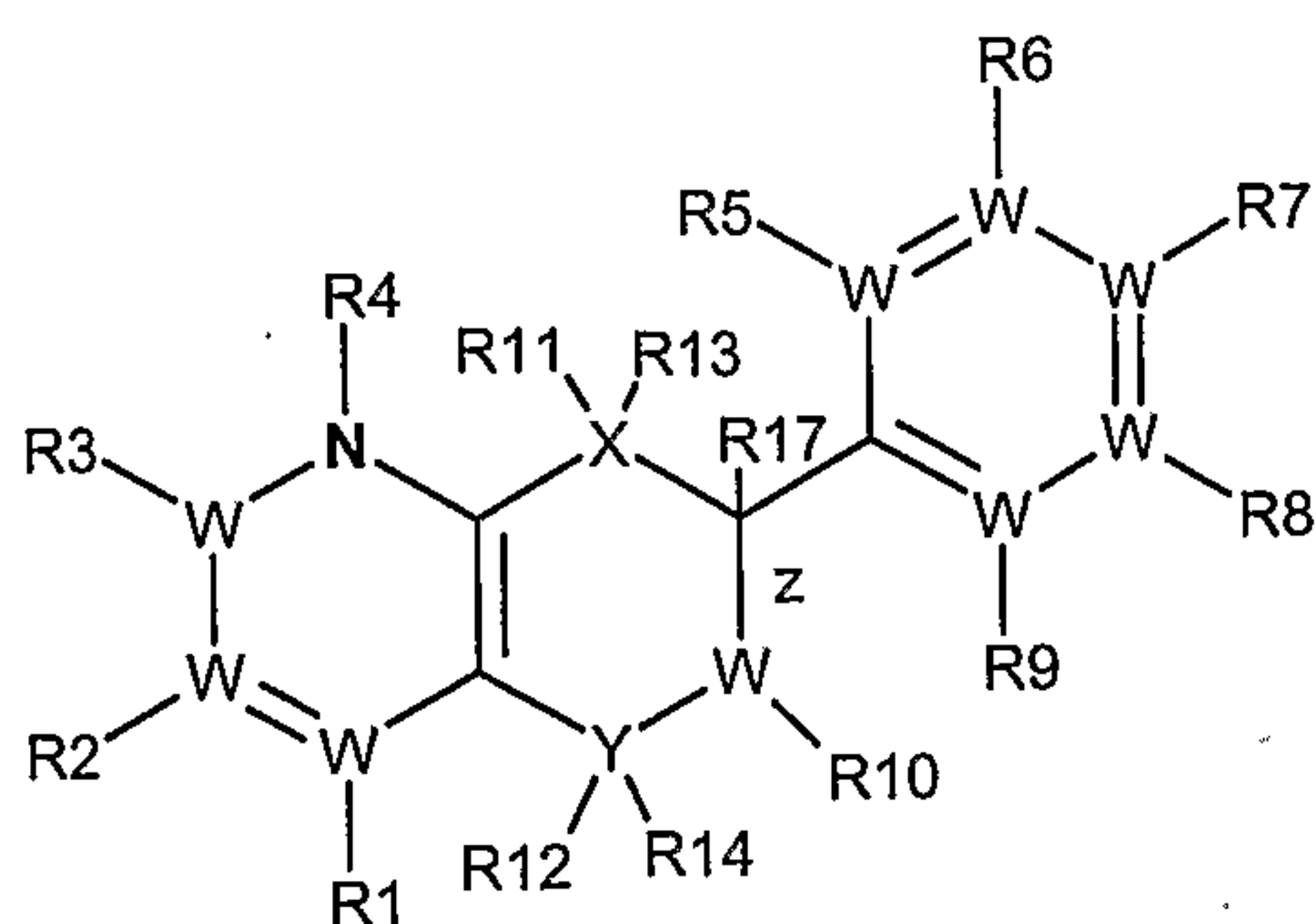
wherein W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 1:



wherein the same applies to any W;

or



wherein the same applies to any W:

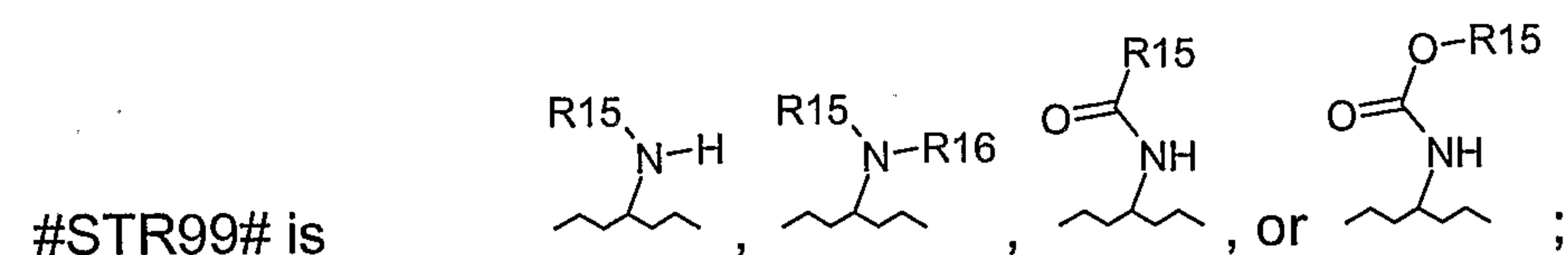
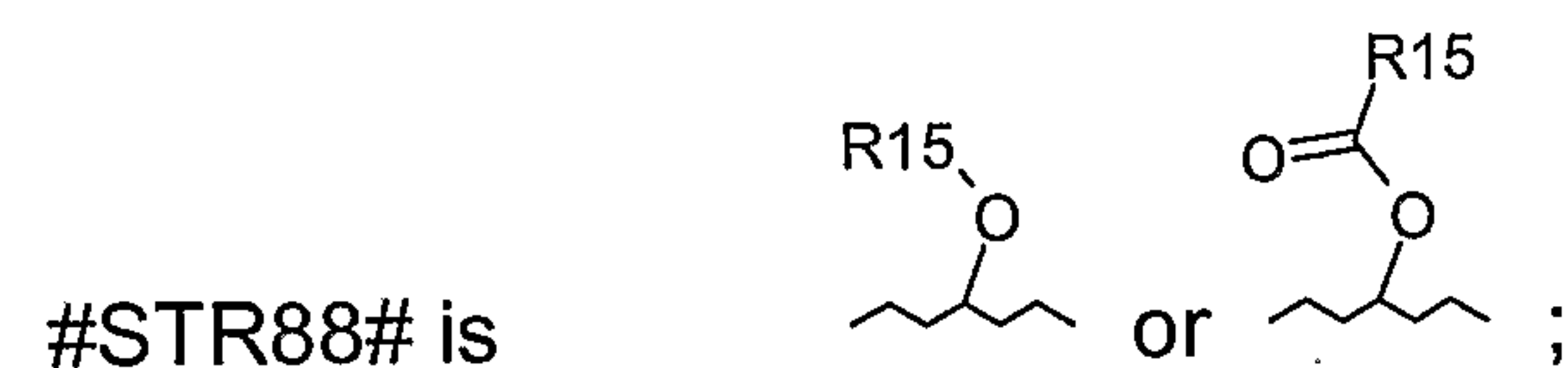
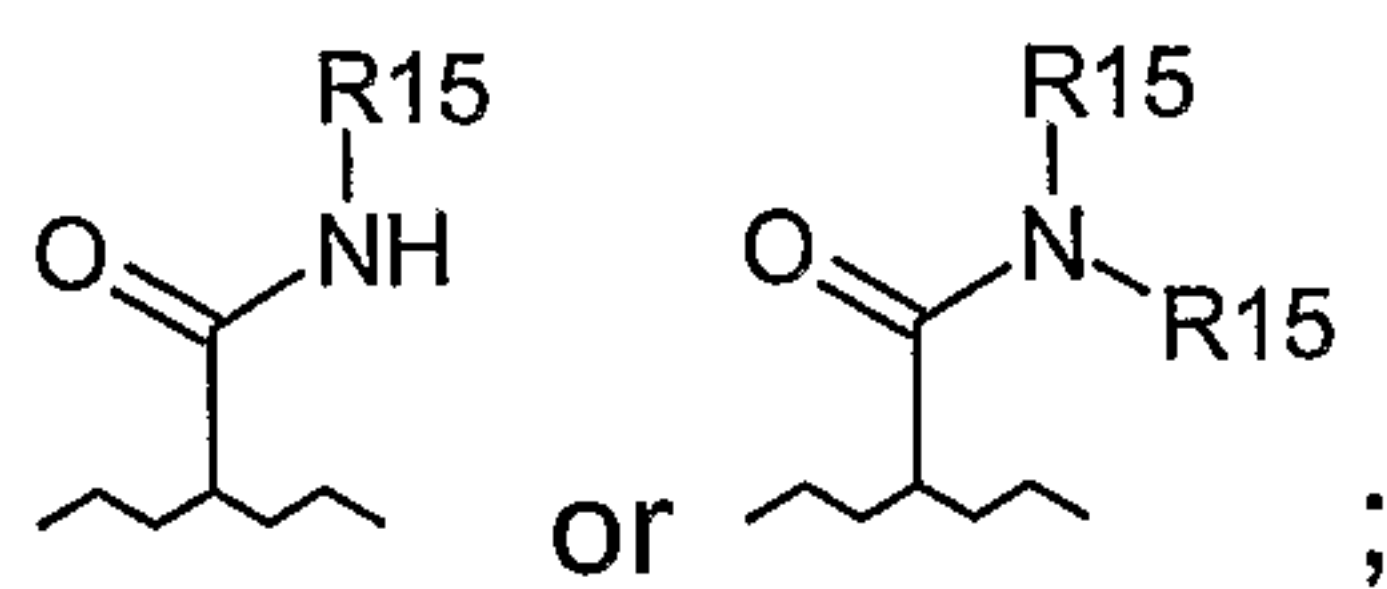
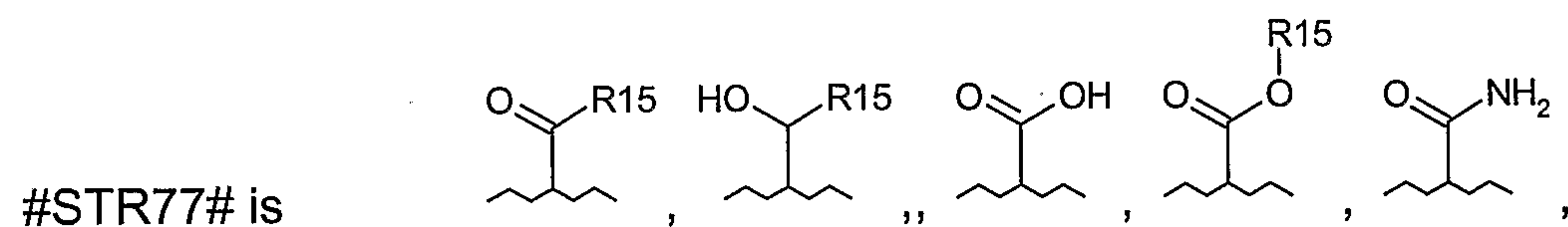
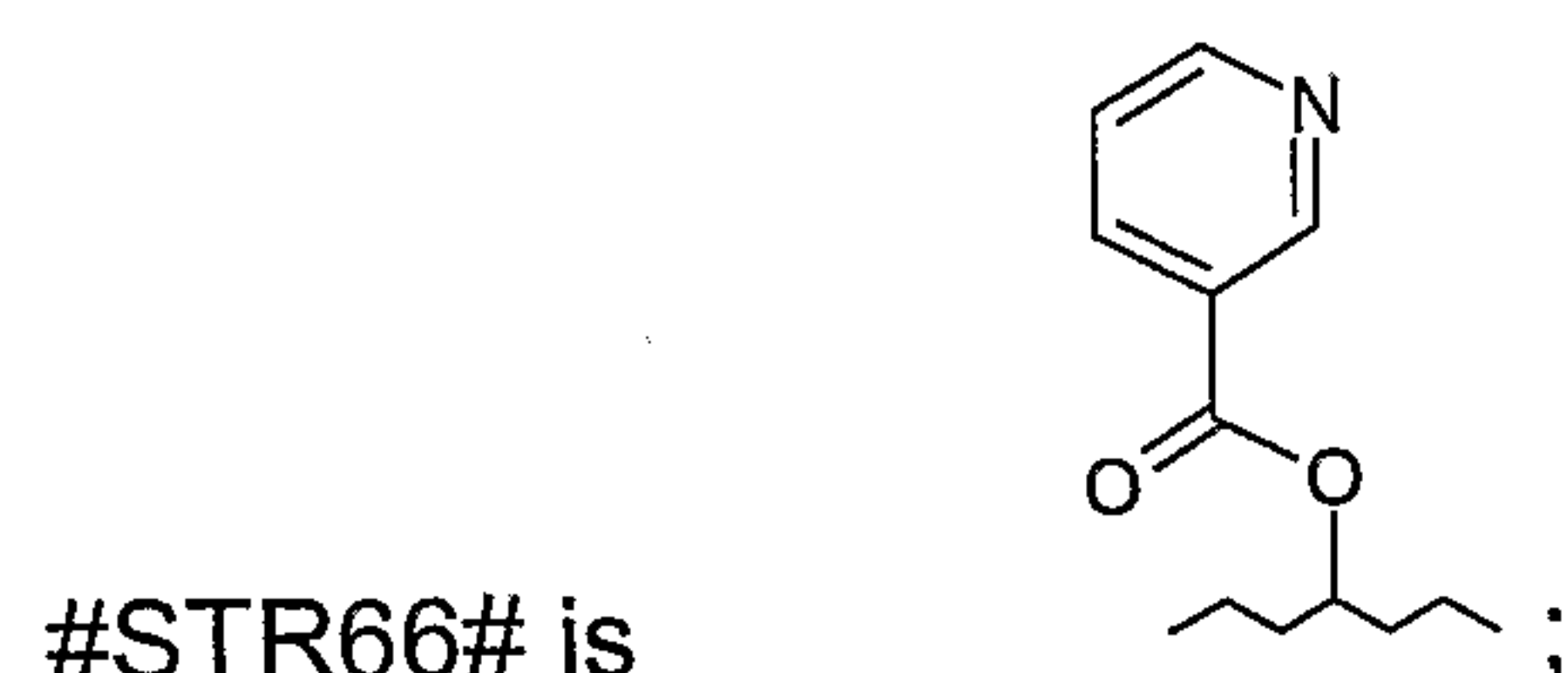
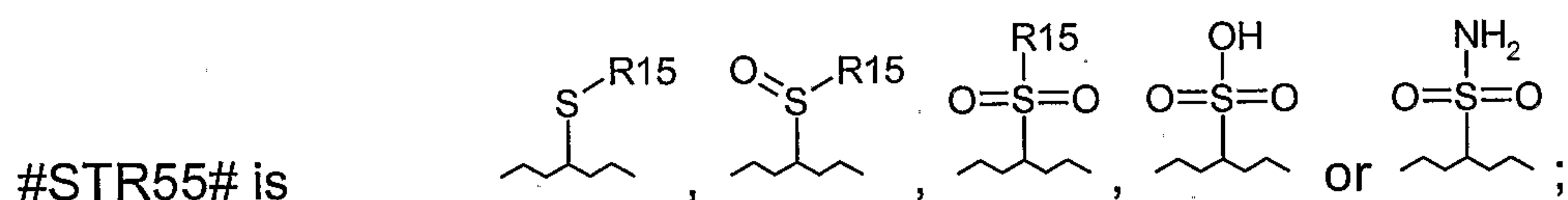
wherein

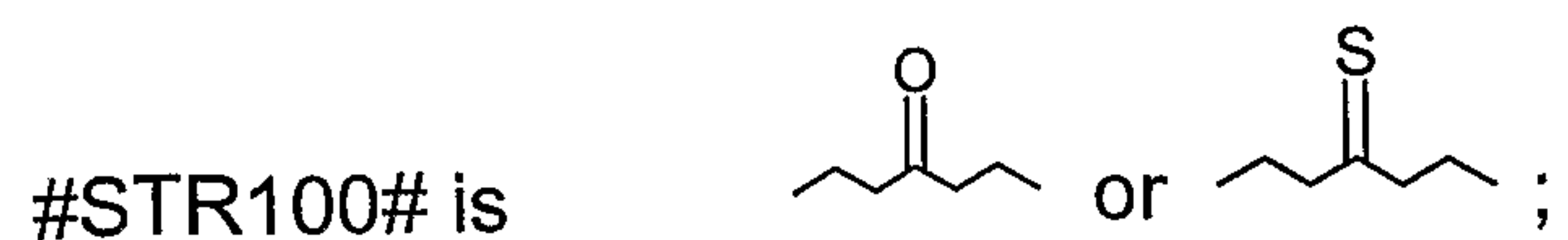
X can be CH, CH₂, CR₁₁, CR₁₃, CHR₁₁, CHR₁₃, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Y can be CH, CH₂, CR₁₂, CR₁₄, CHR₁₂, CHR₁₄, CR₁₁R₁₄, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Z can be a single, double bond or triple bond, with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Wherein





R15 and R16 are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 1 compounds have at least one proviso selected from the following

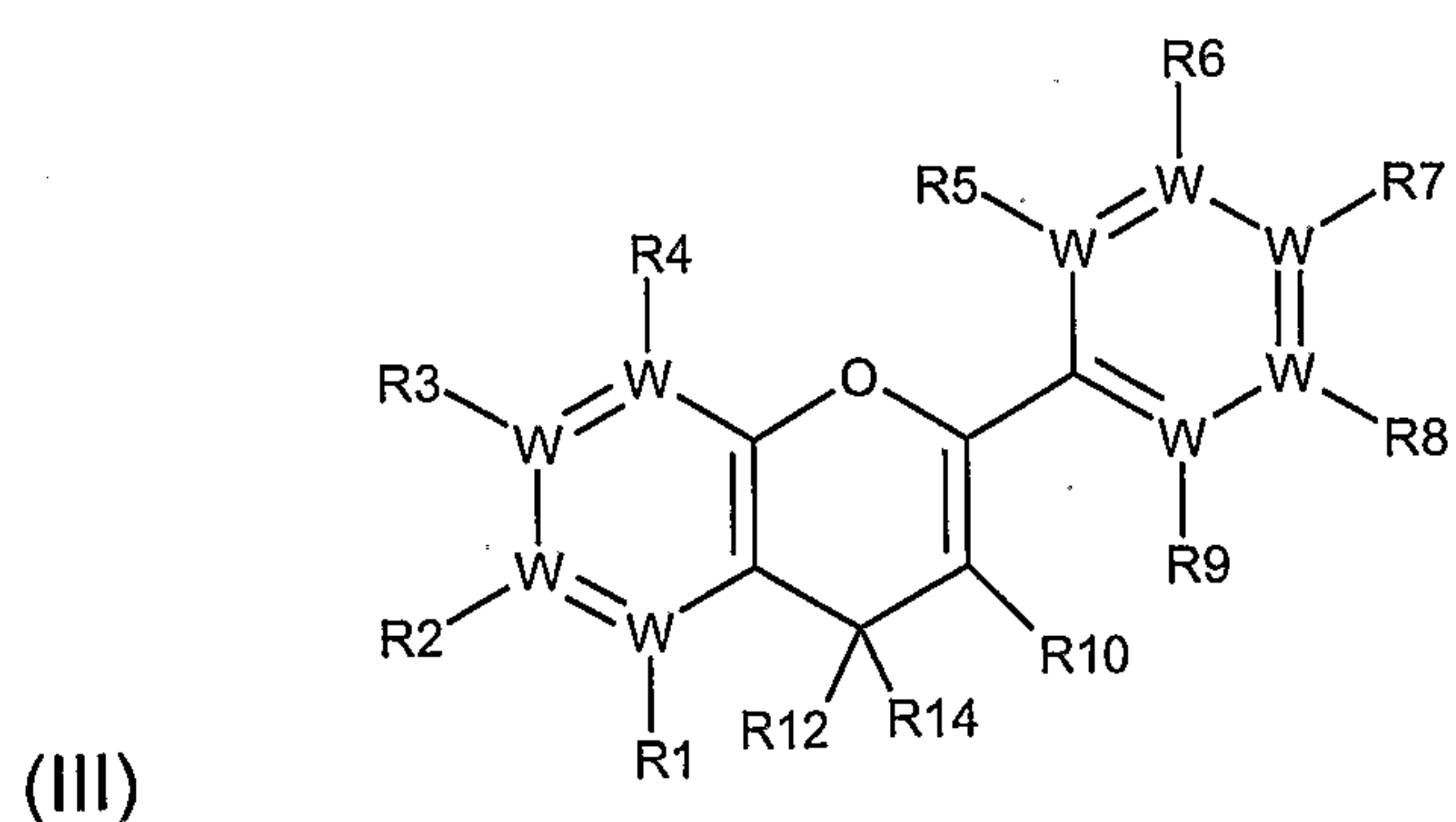
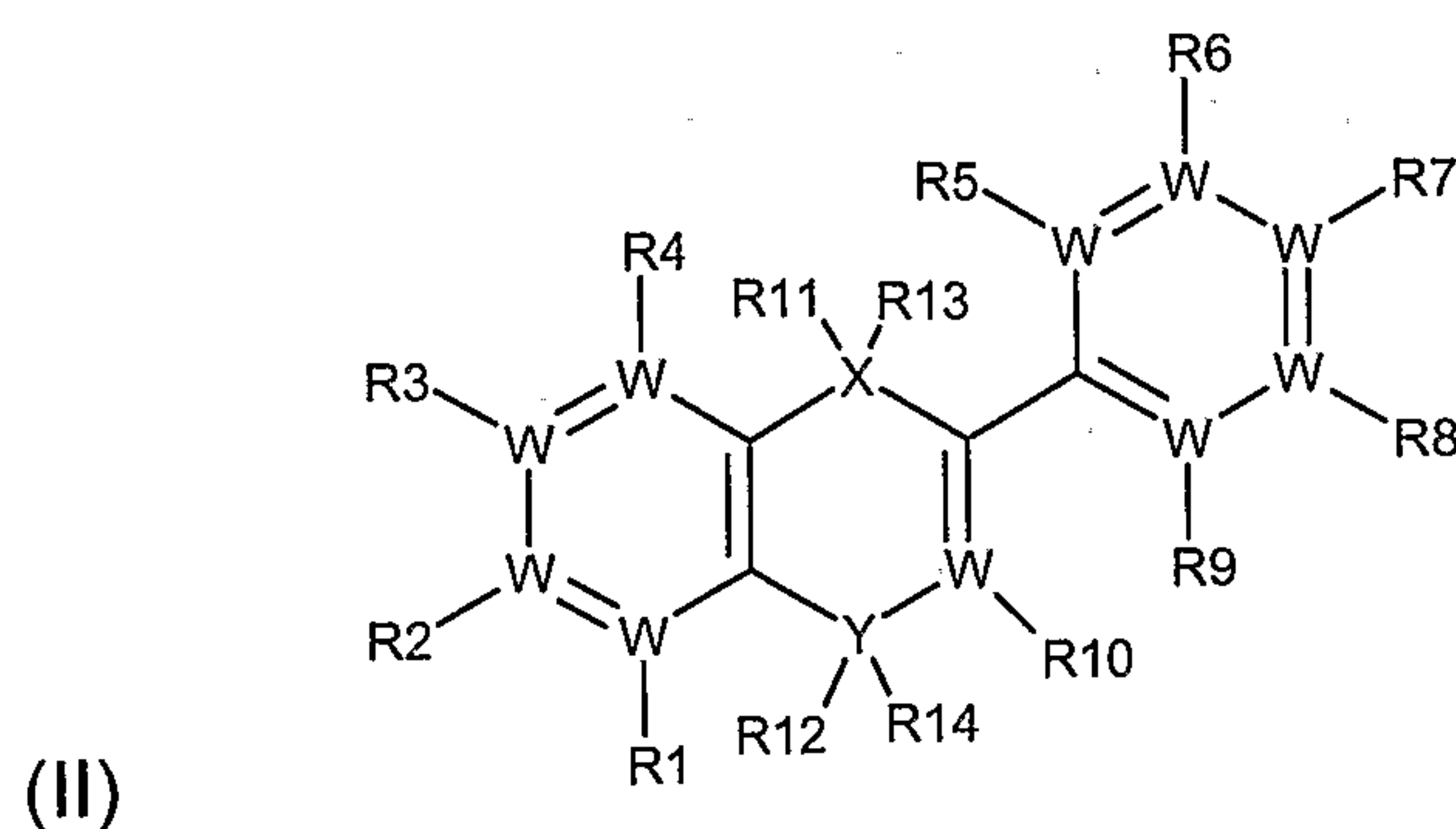
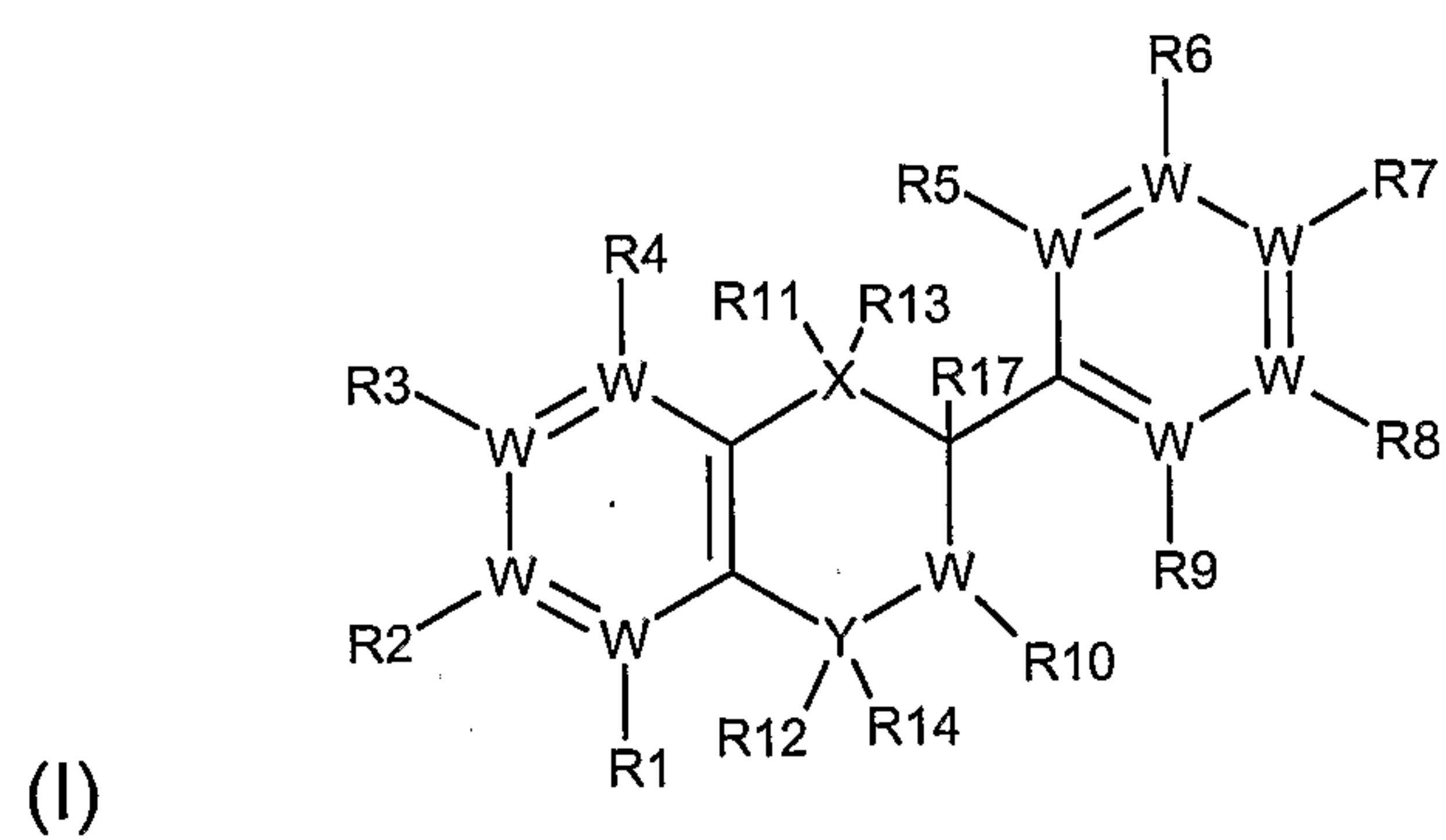
- a. R7 is a hydroxyl;
- b. at least one W is a N;
- c. at least one of R1-R10 is #STR77#, #STR88# or #STR99#;
- d. at least one of R1-R10 is #STR66#;
- e. one of R1-R10 is a monoester;
- f. one of R1-R10 is a dicarboxylic acid;
- g. one of R1-R10 is succinic acid;
- h. R7 is #STR55#;
- i. R7 and R2 are #STR55#;
- j. R7 and R2 are hydroxyls; and
- k. R7 is #STR66#.

[079] Non-limiting embodiments of Formula 1 include:

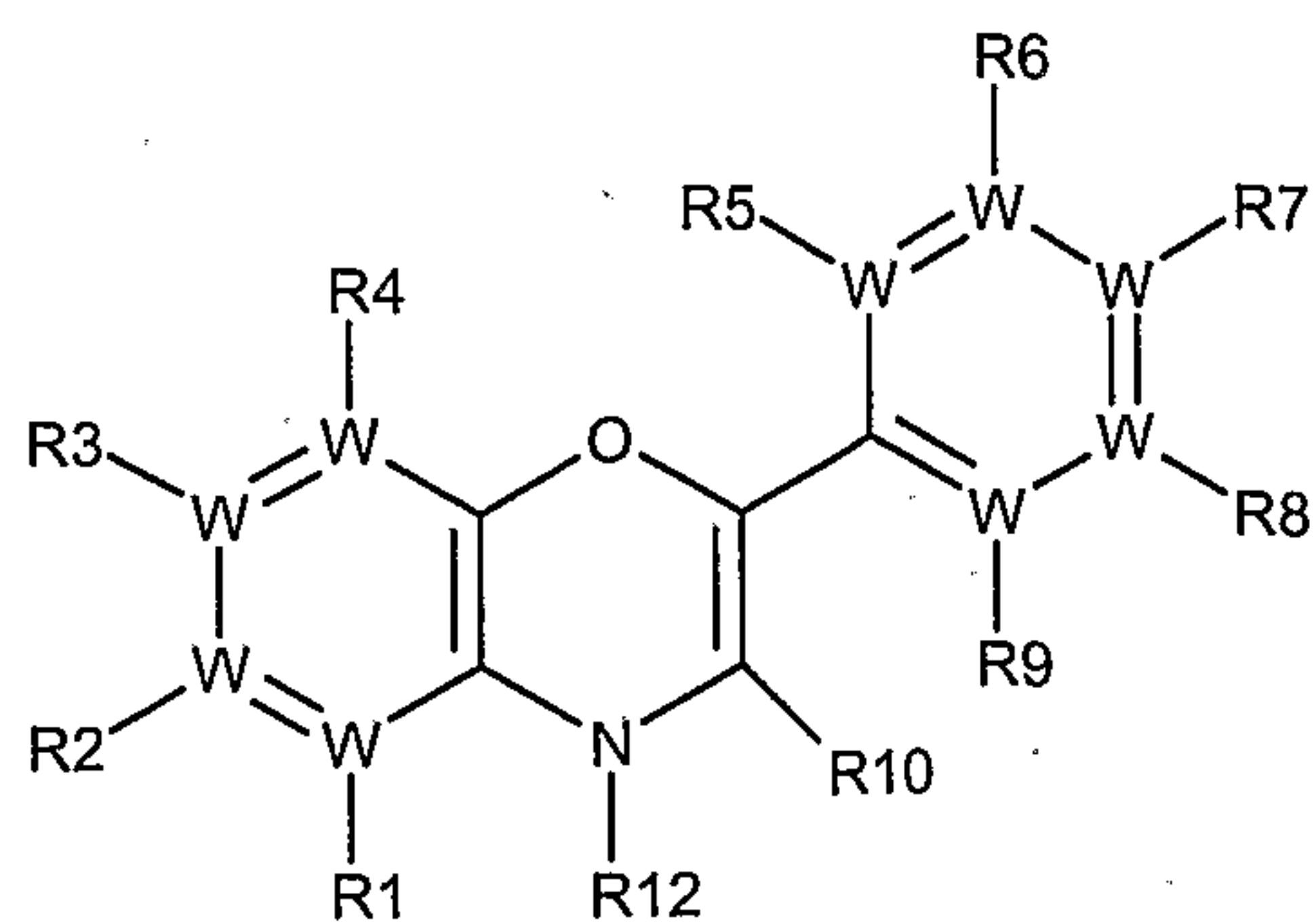
- i. R7 is a hydroxyl and at least one W is a N;

- ii. R7 is a hydroxyl and at least one of R1-R6 and R8-R10 is #STR66#;
- iii. R7 is a hydroxyl and at least one of R1-R6 and R8-R10 is #STR77#, #STR88# or #STR99#; and
- iv. R7 is #STR66# and at least one W is a N.

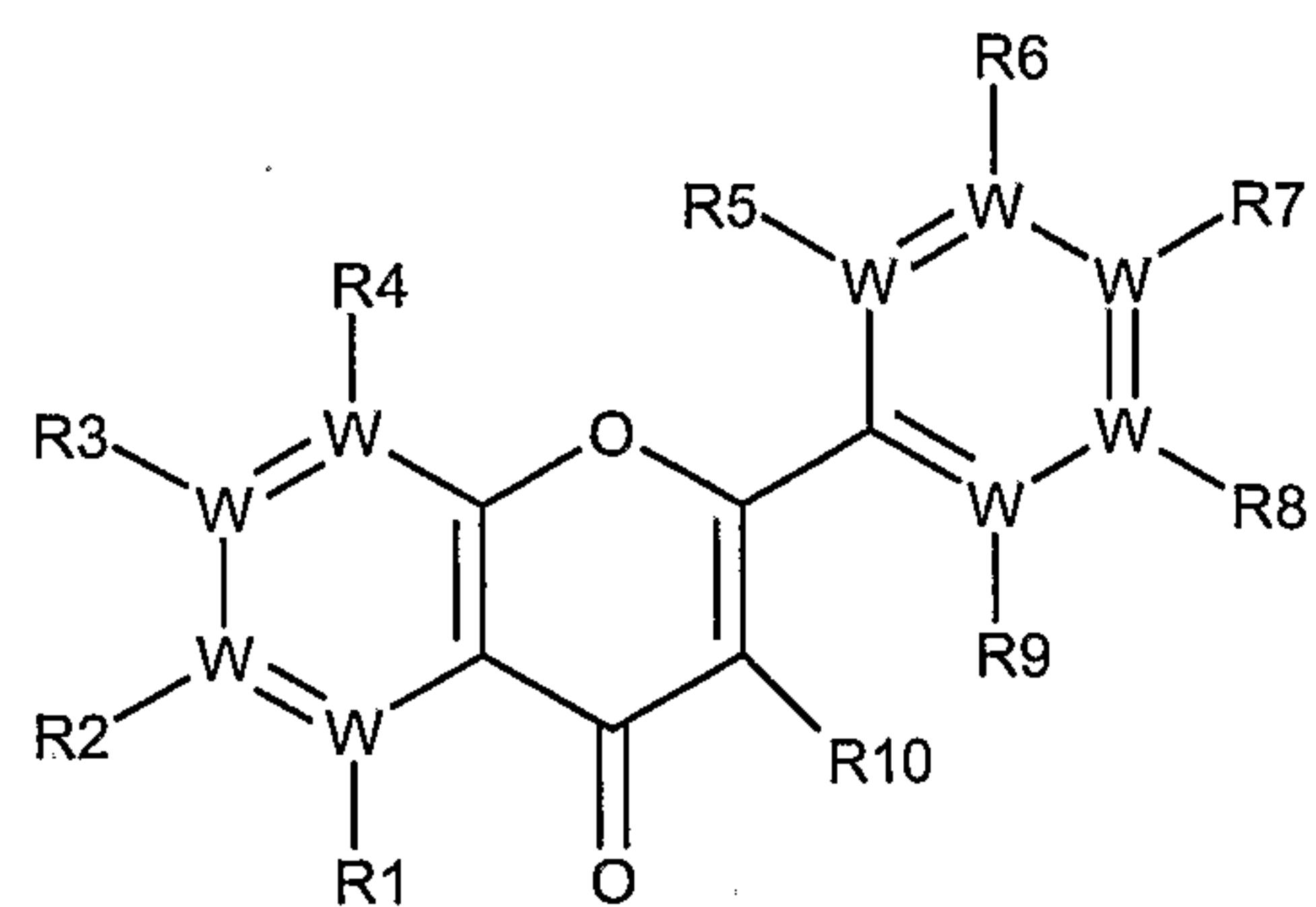
[080] Other alternative embodiments of Formula 1 include



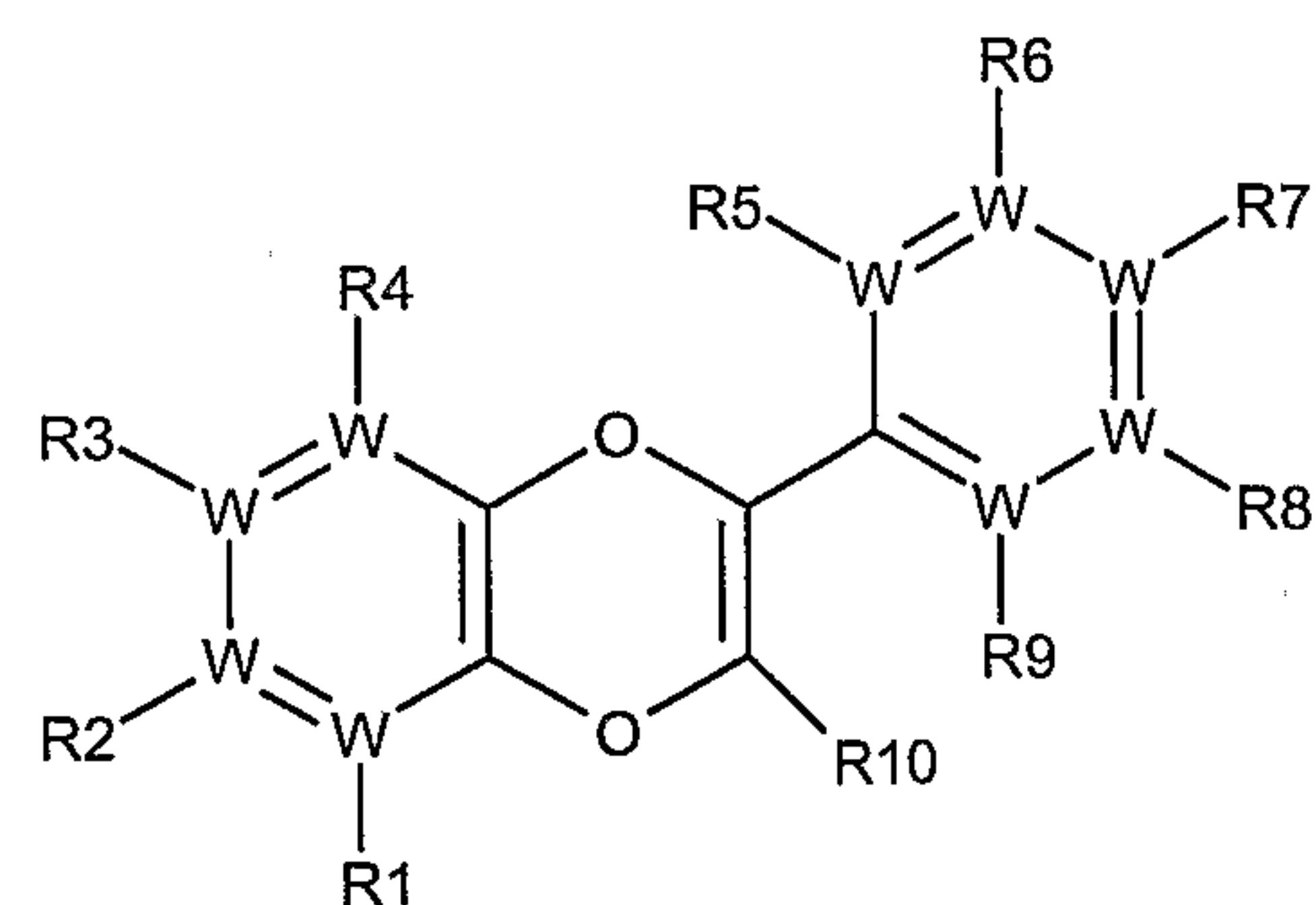
(IV)



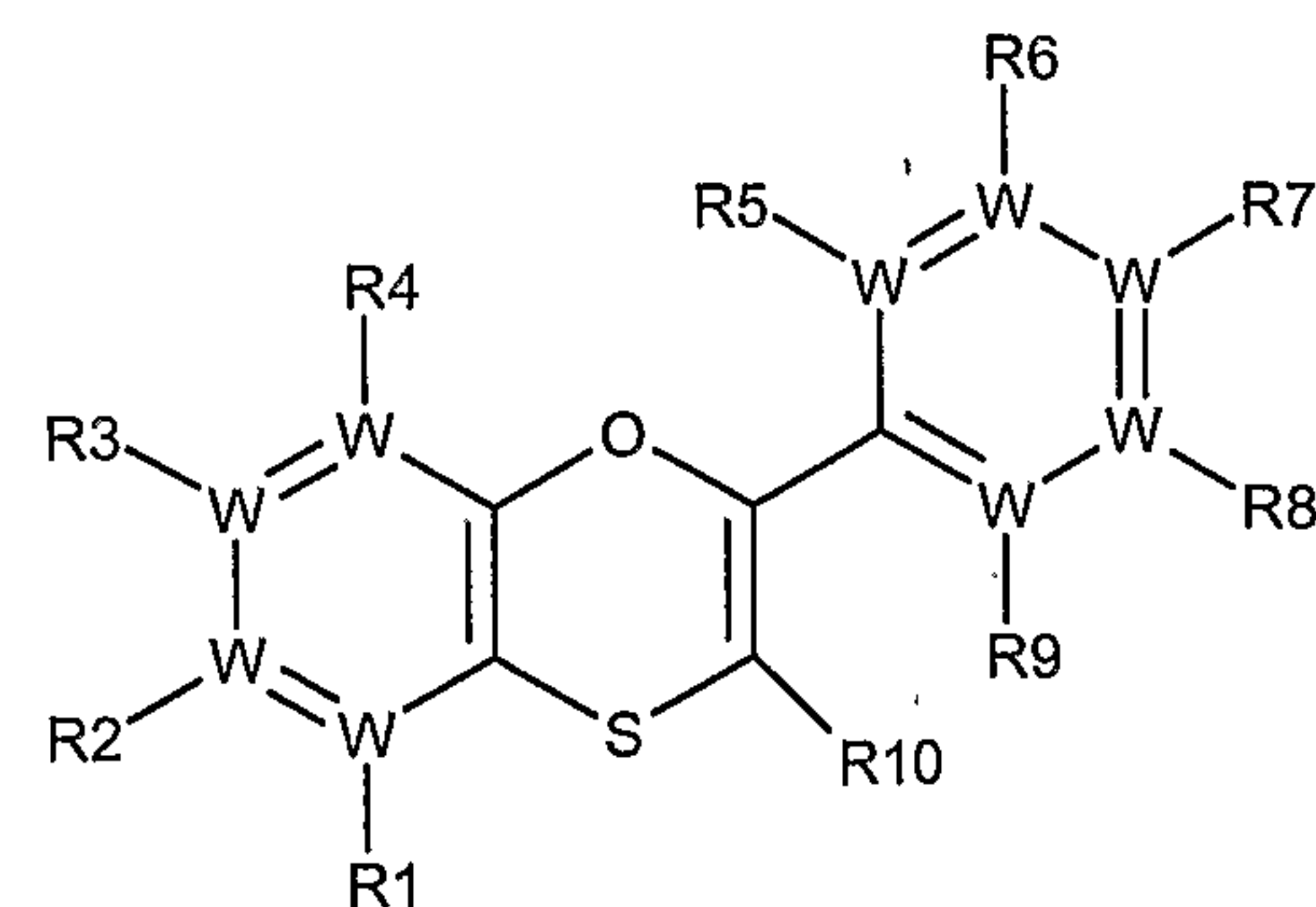
(V)



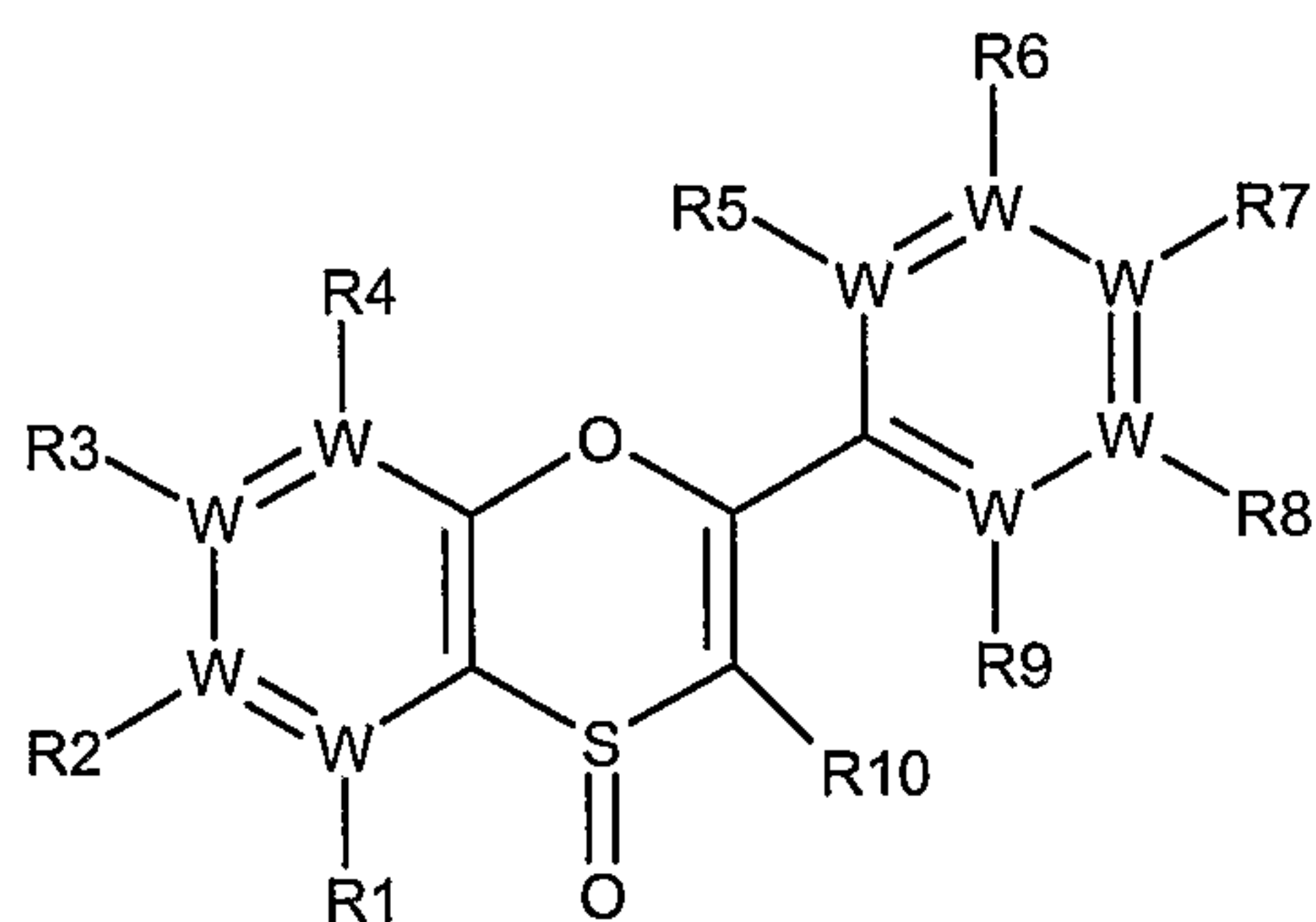
(VI)



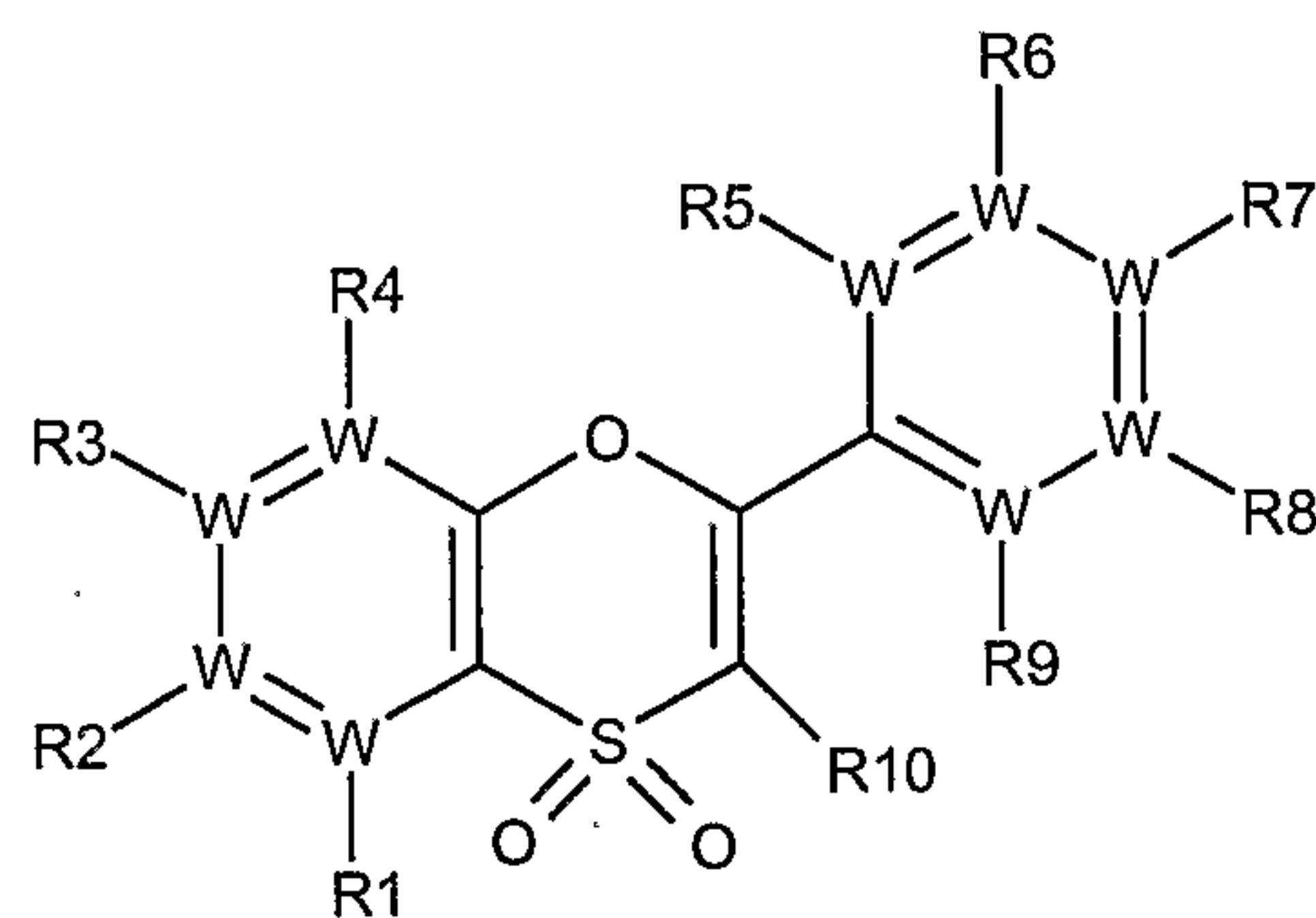
(VII)



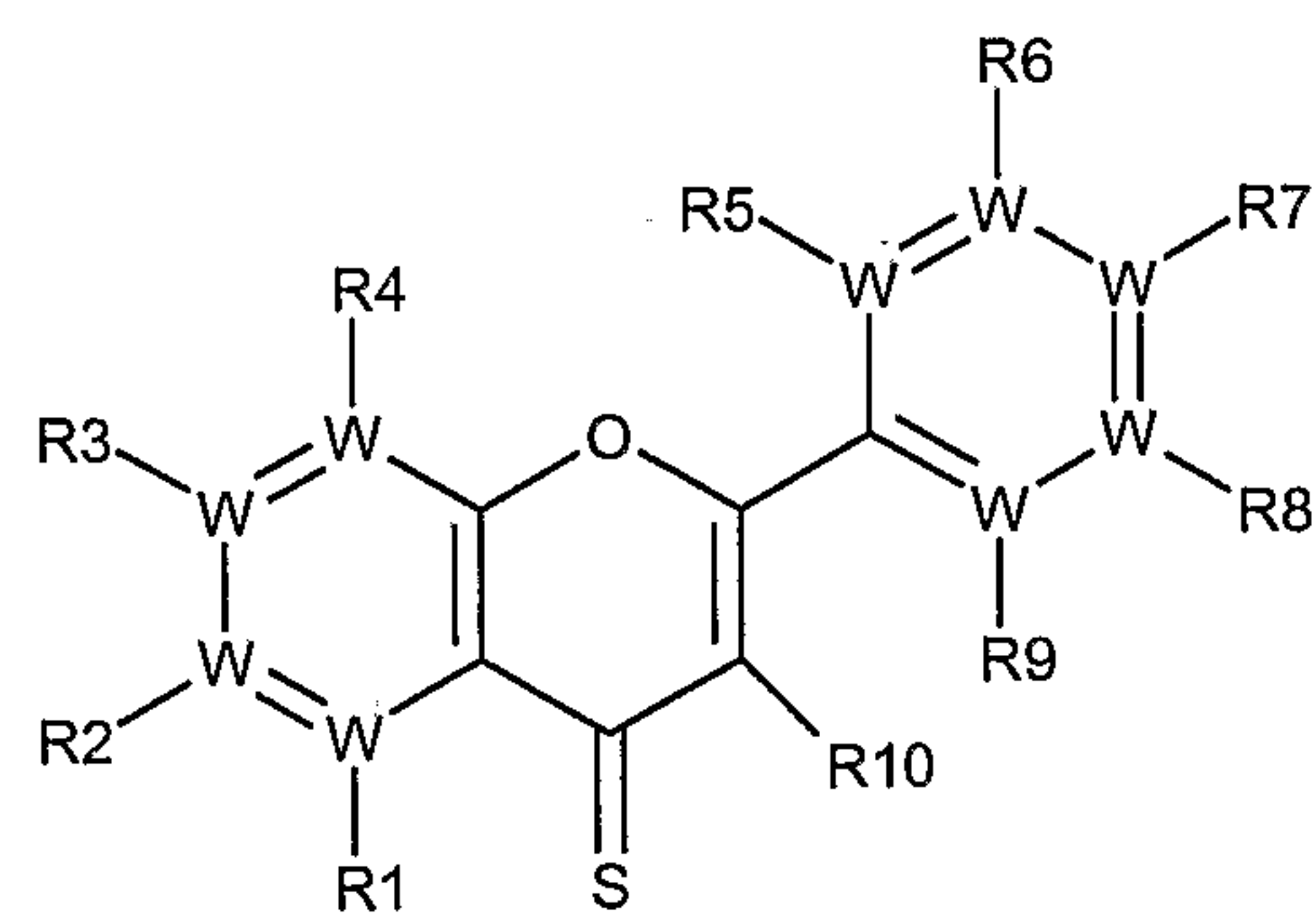
(VIII)



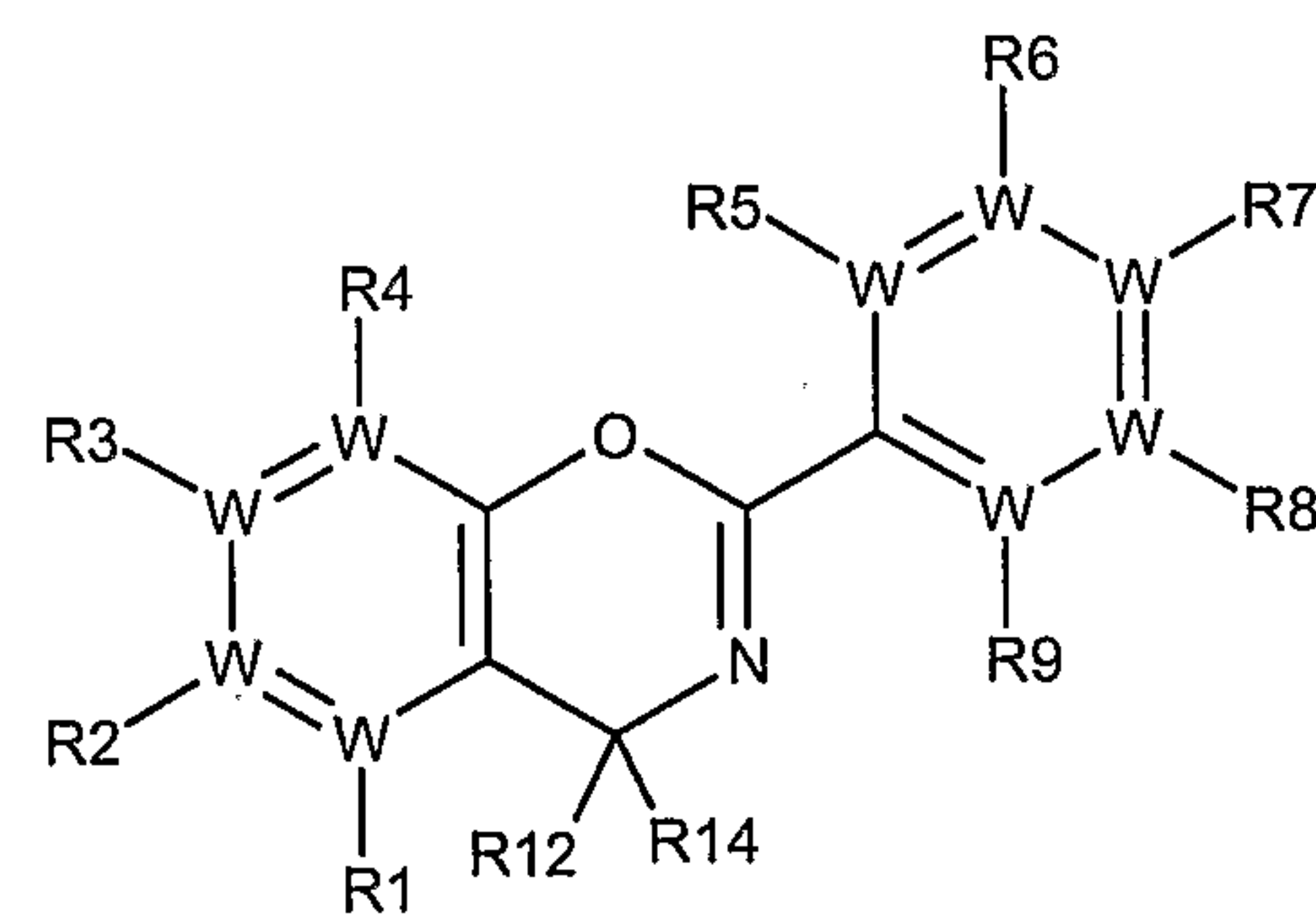
(IX)



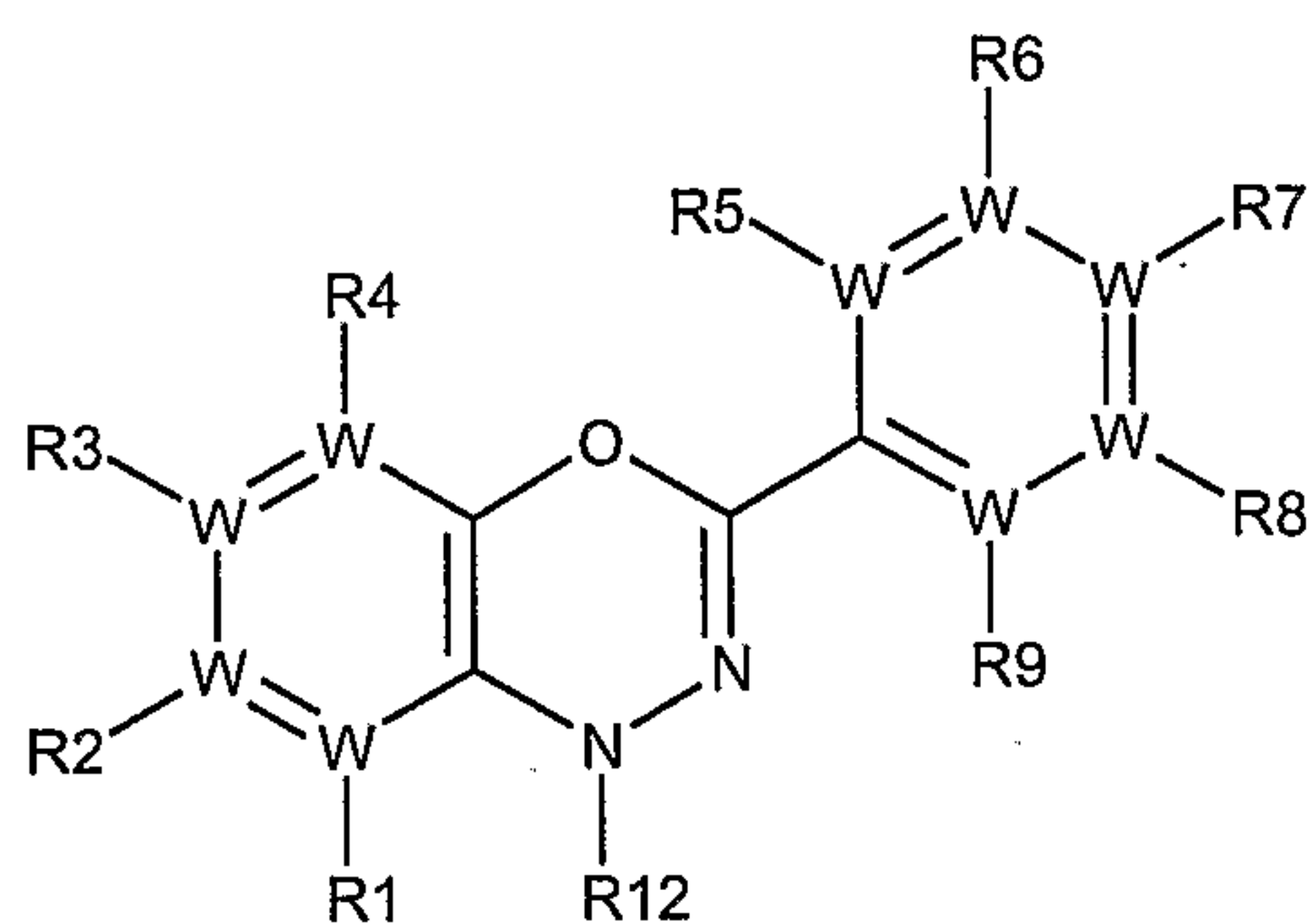
(X)



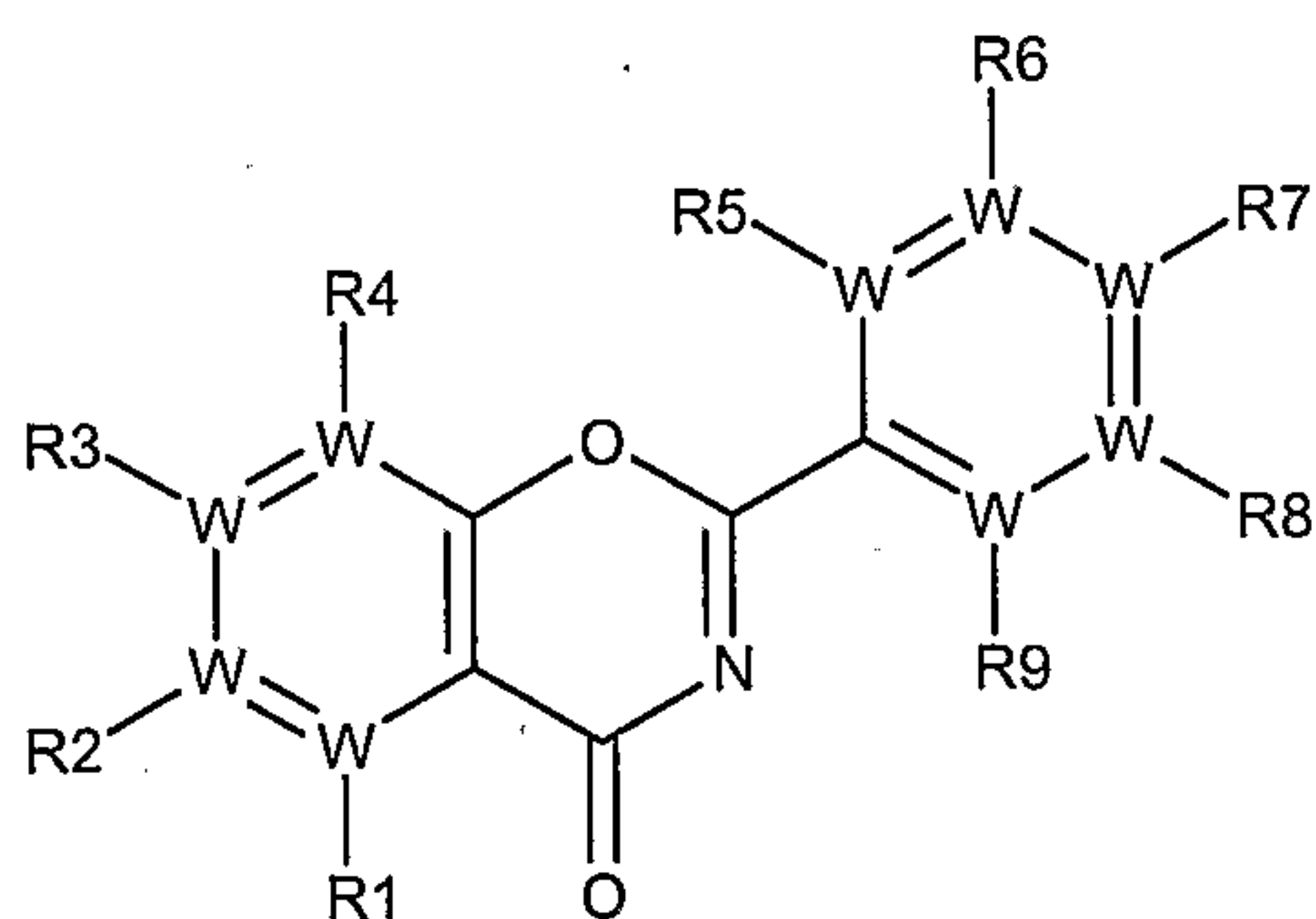
(XI)



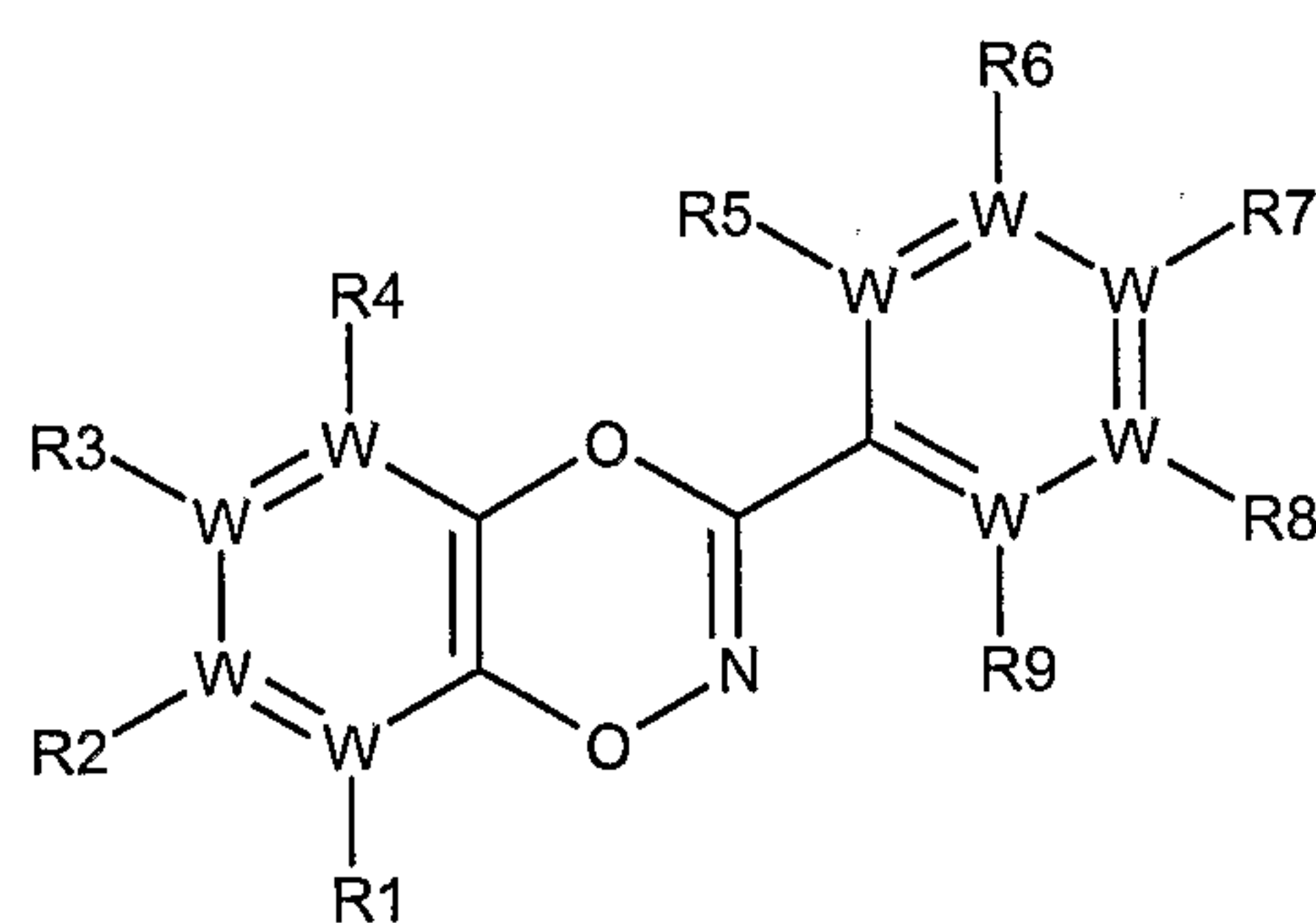
(XII)



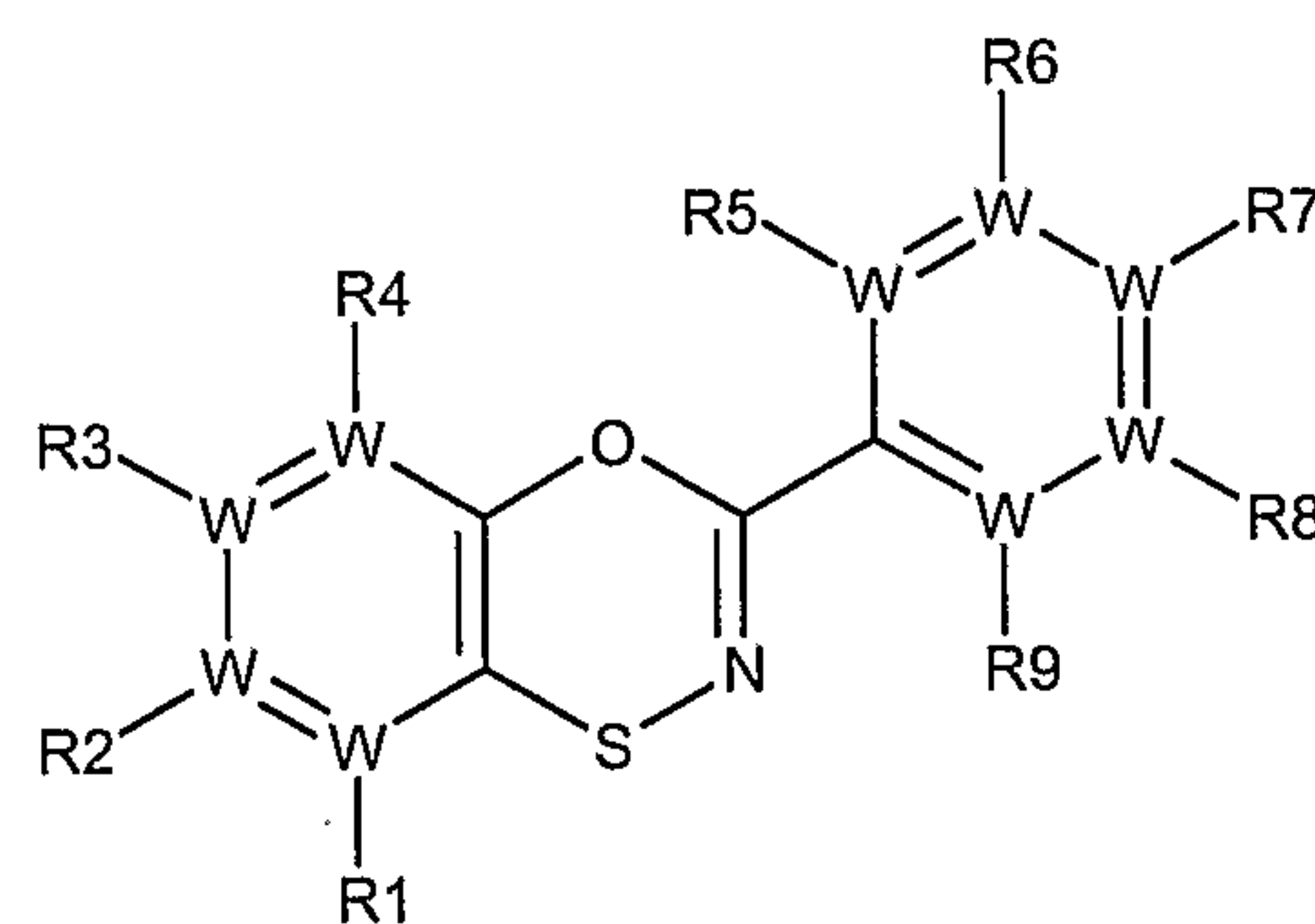
(XIII)



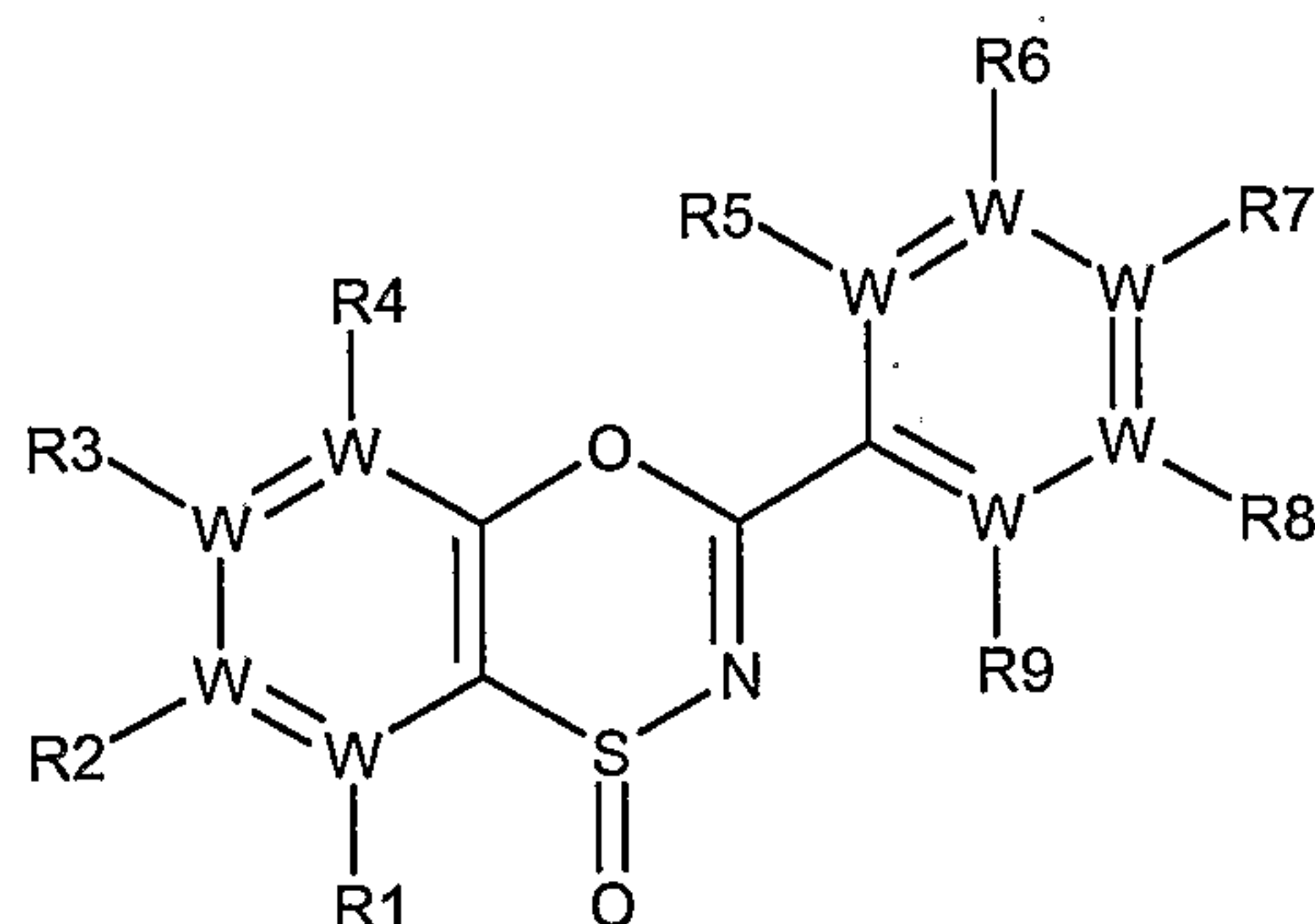
(XIV)



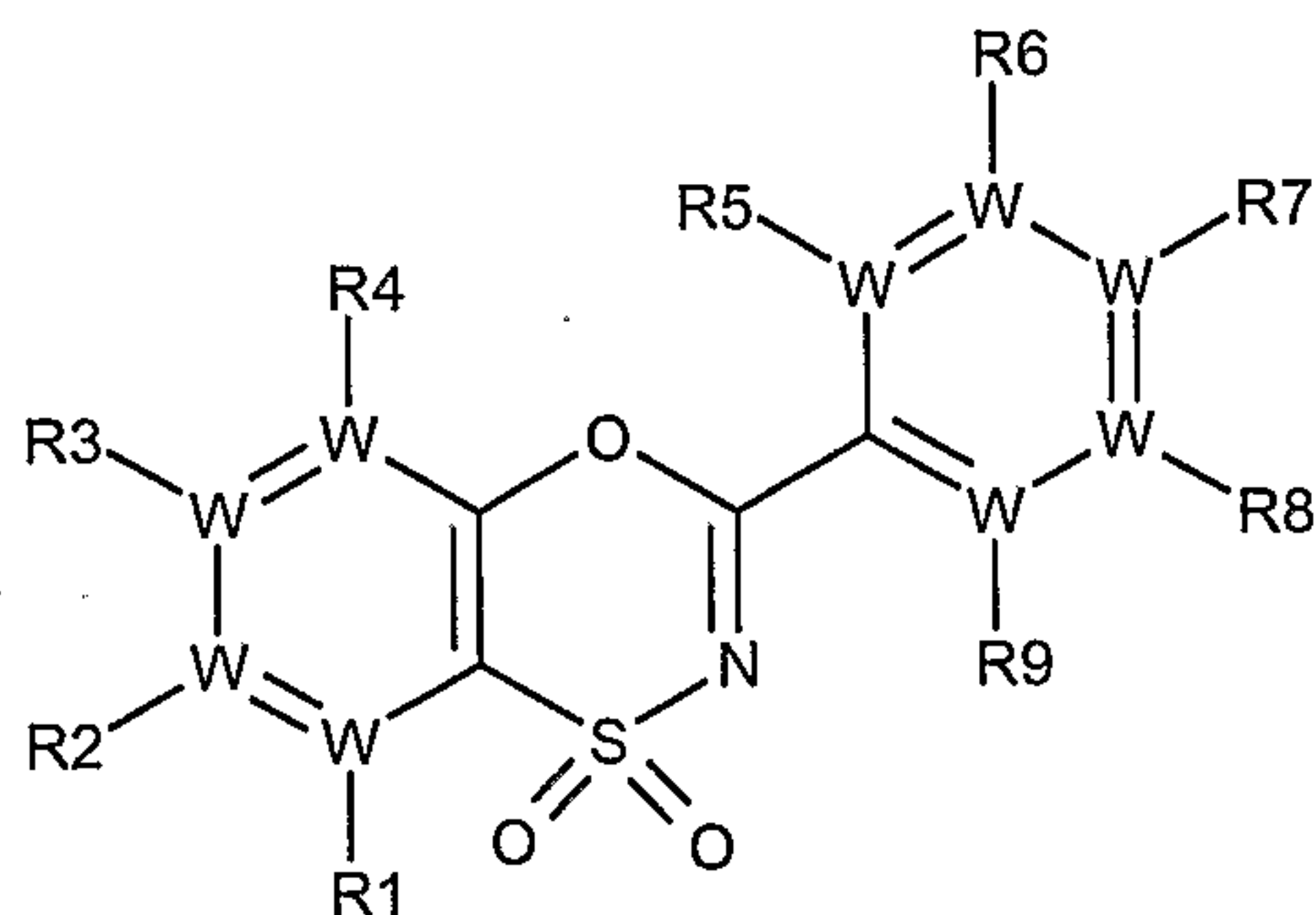
(XV)



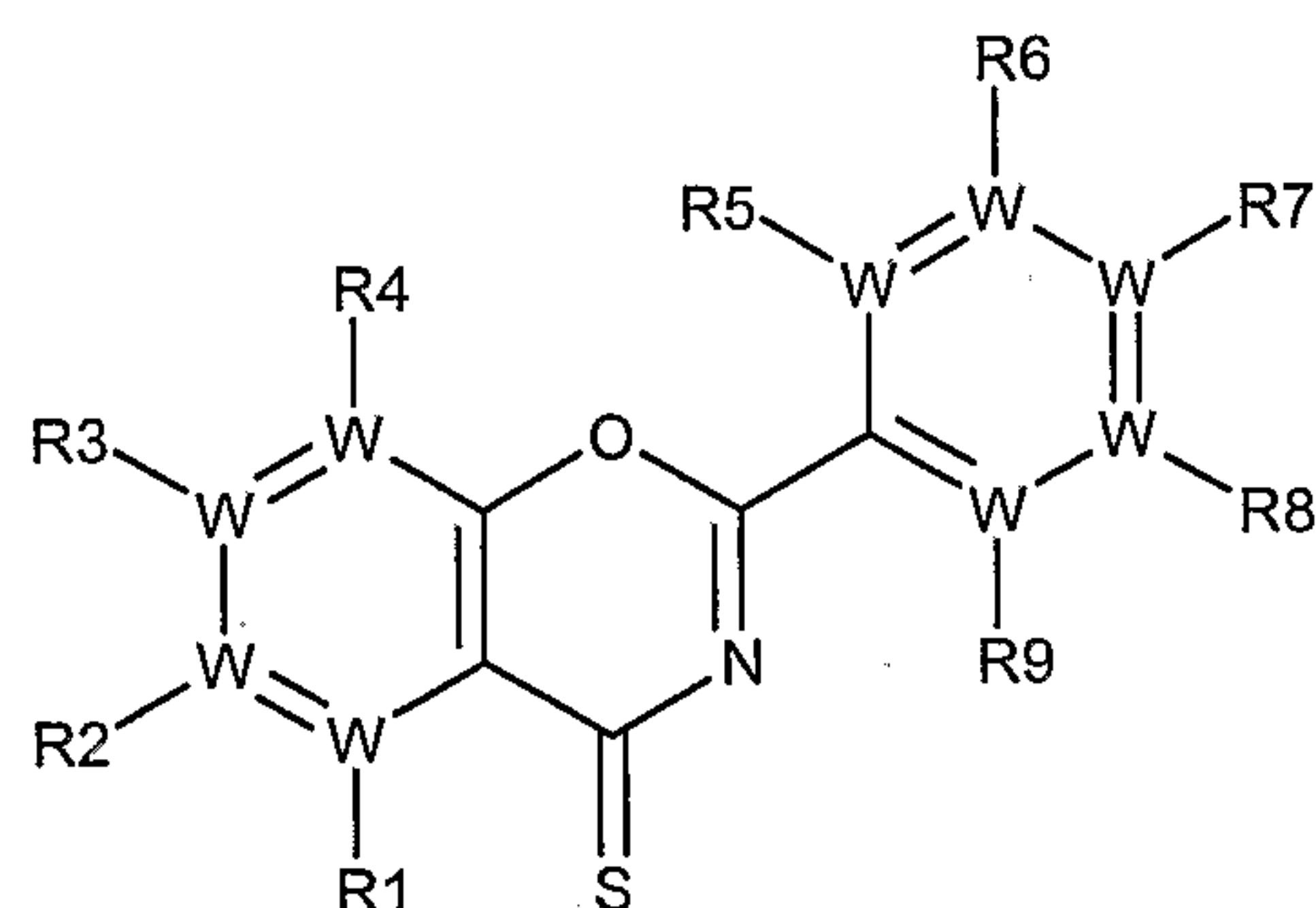
(XVI)



(XVII)



(XVIII)



or a pharmaceutically acceptable salt thereof,

wherein

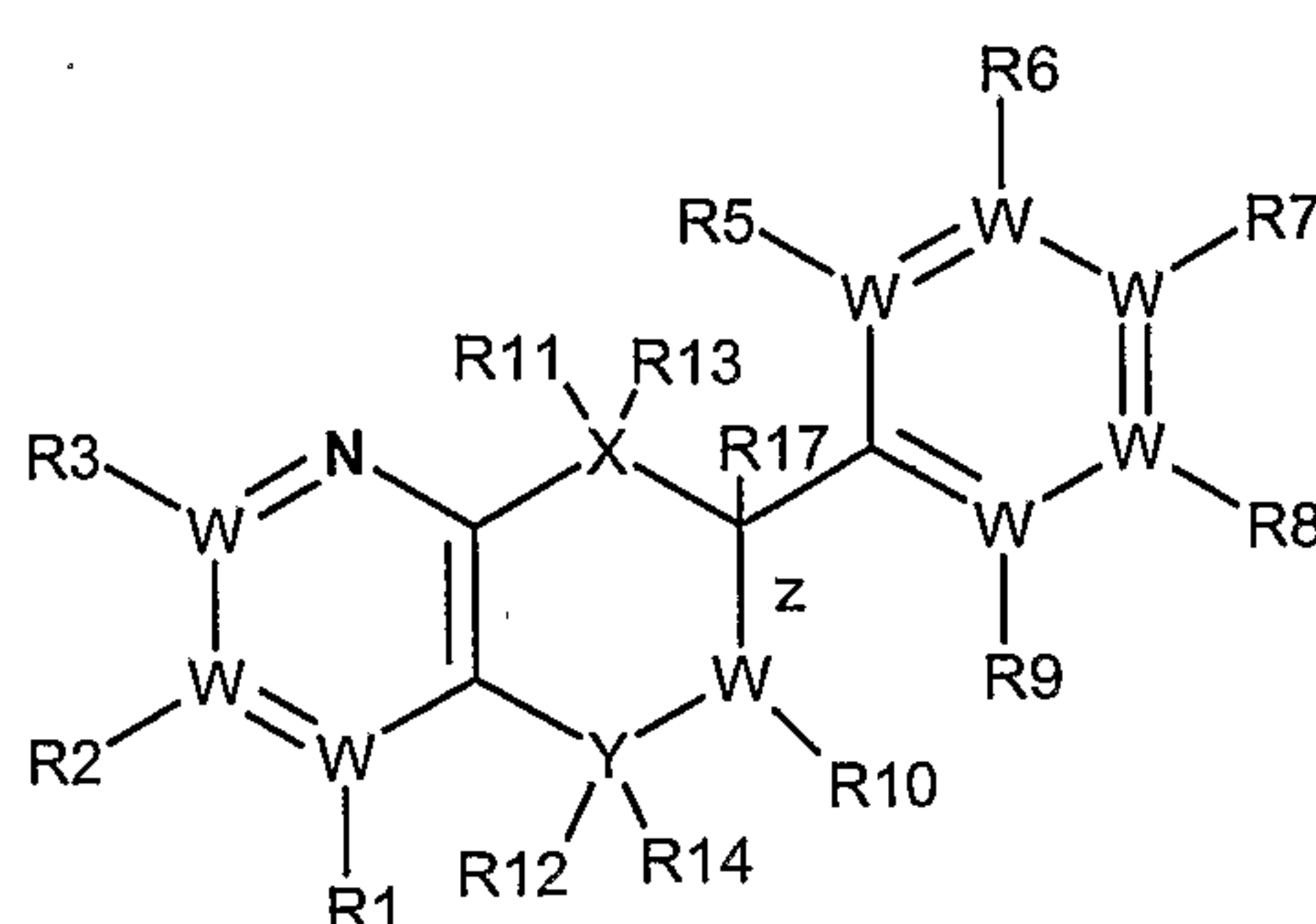
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, and R17 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₁-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, O-sulfate [the sulfate conjugate], O-glucuronidate [the glucuronic (AKA glucuronic) acid conjugates], monoesters,

dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#,
#STR100#,

wherein W can be C or N;

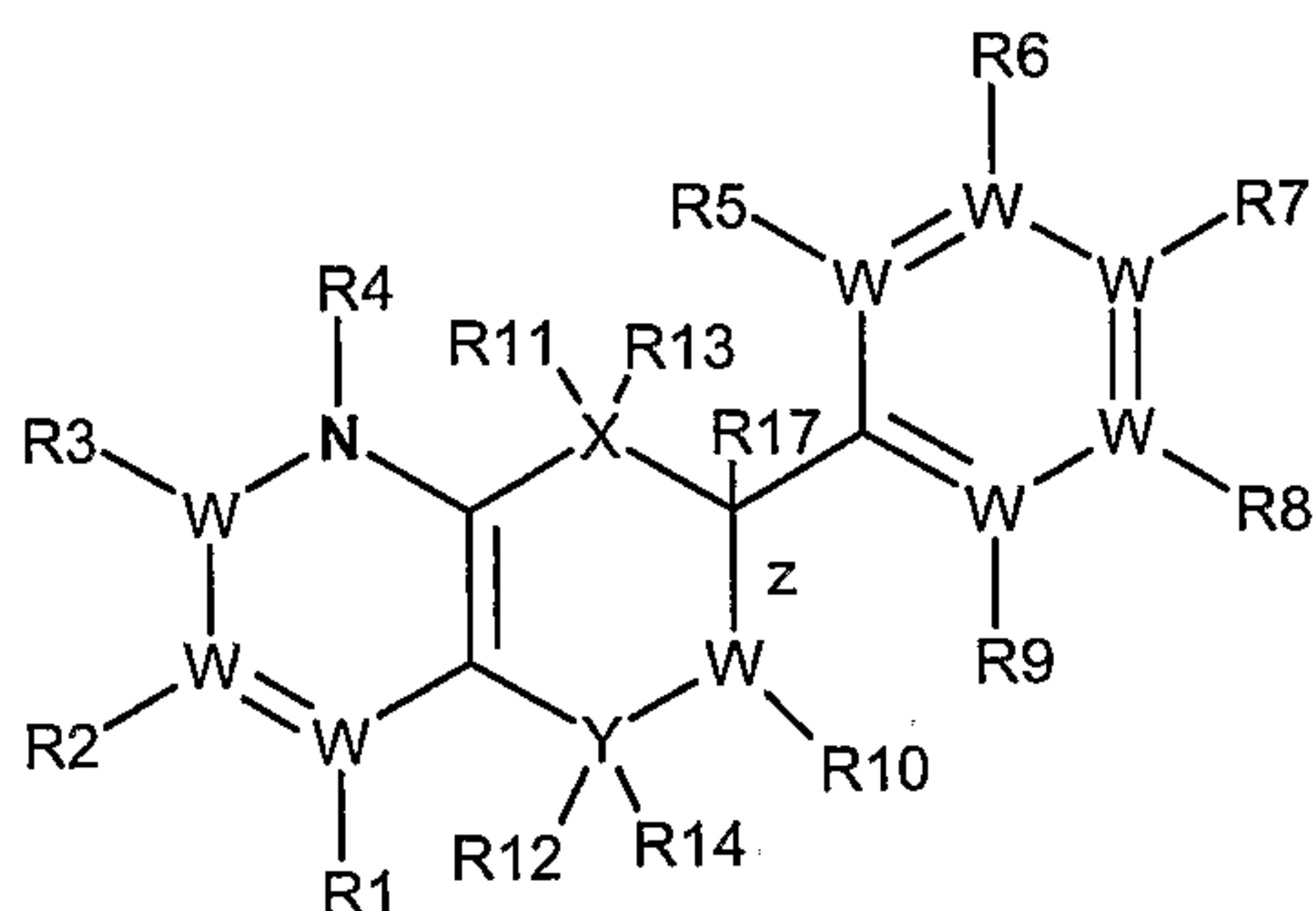
wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[081] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 1:



wherein the same applies to any W;

or



wherein the same applies to any W:

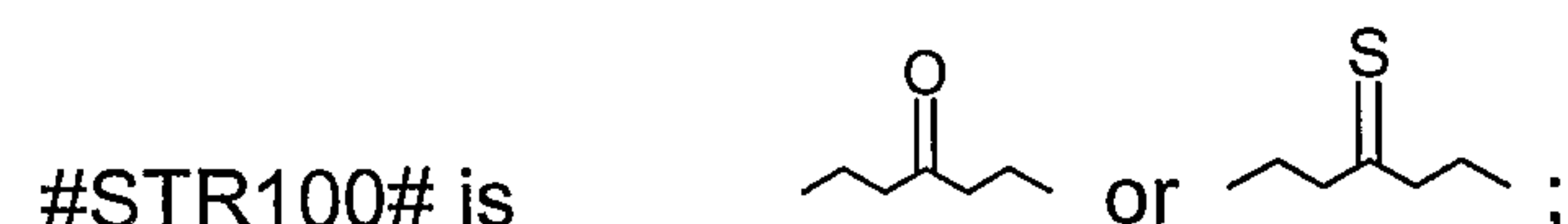
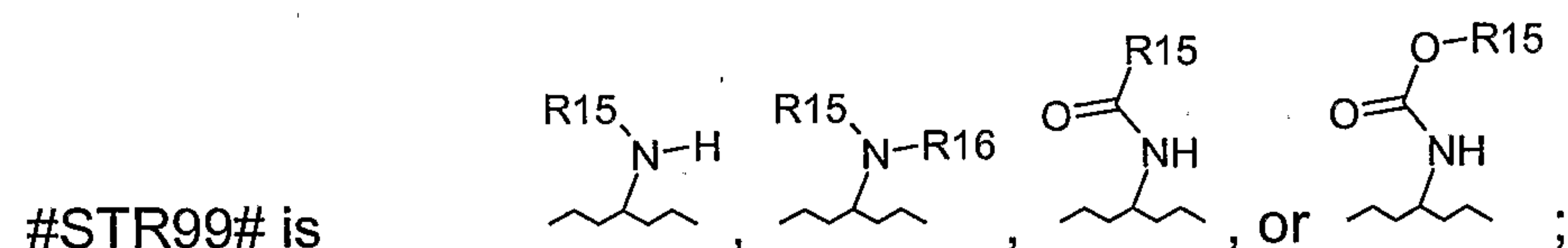
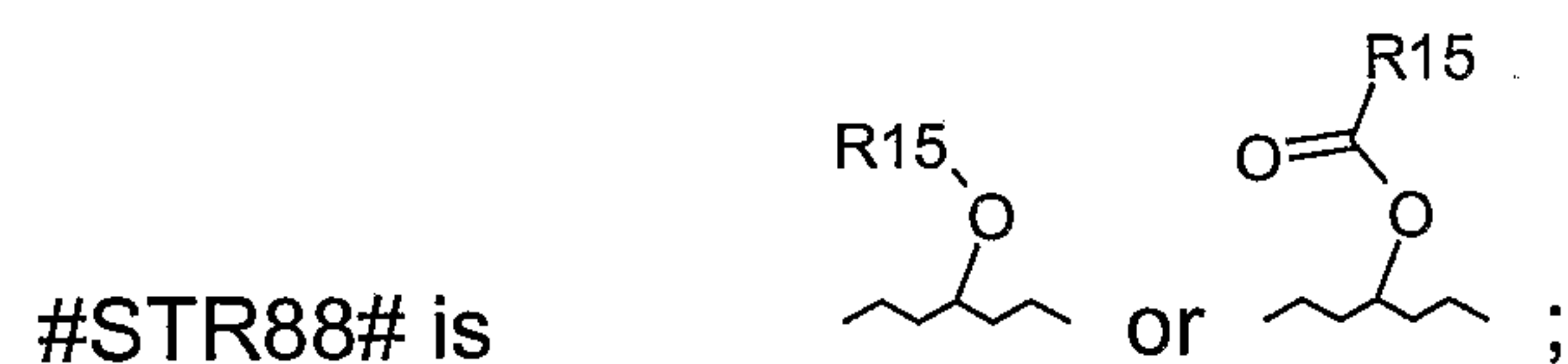
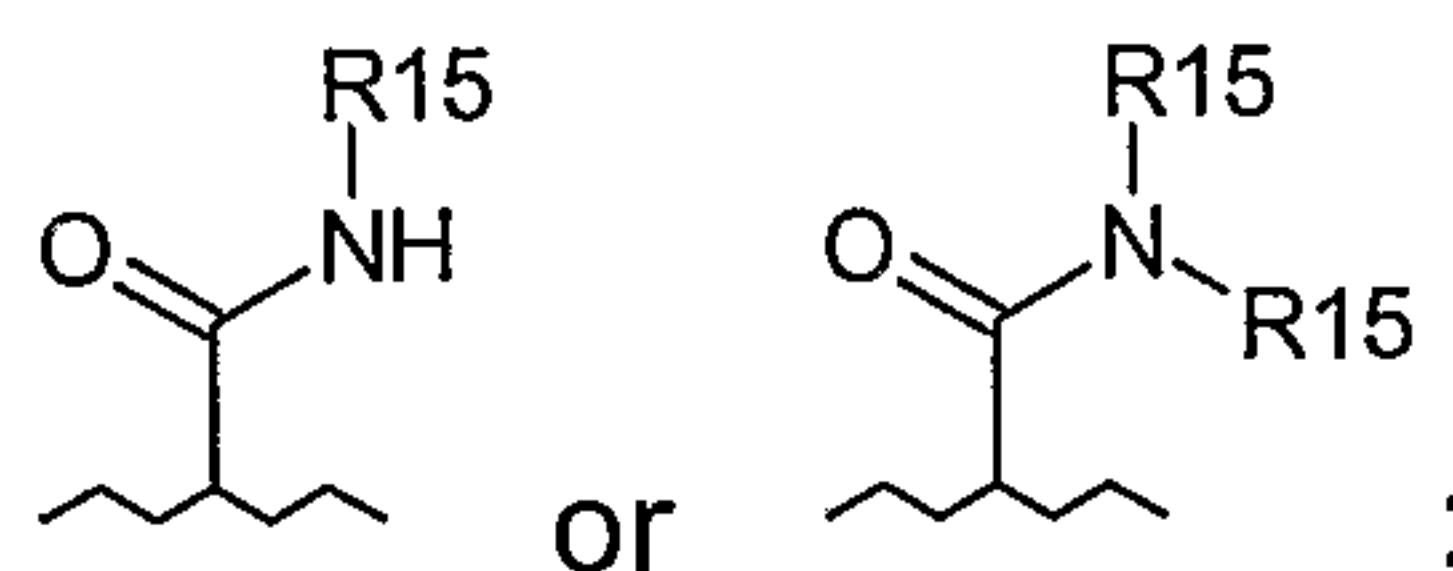
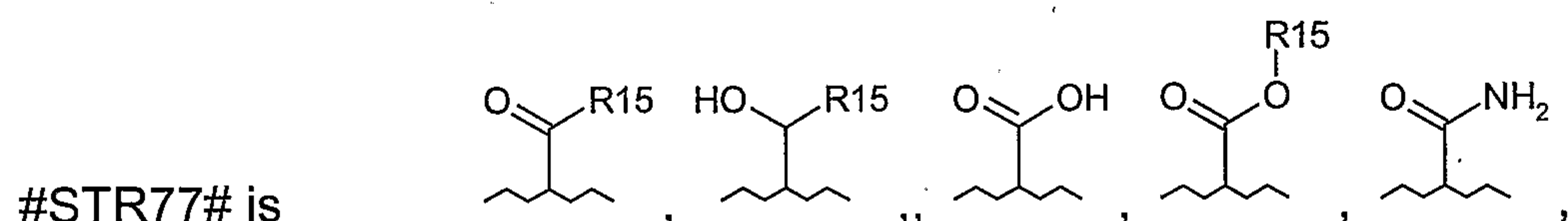
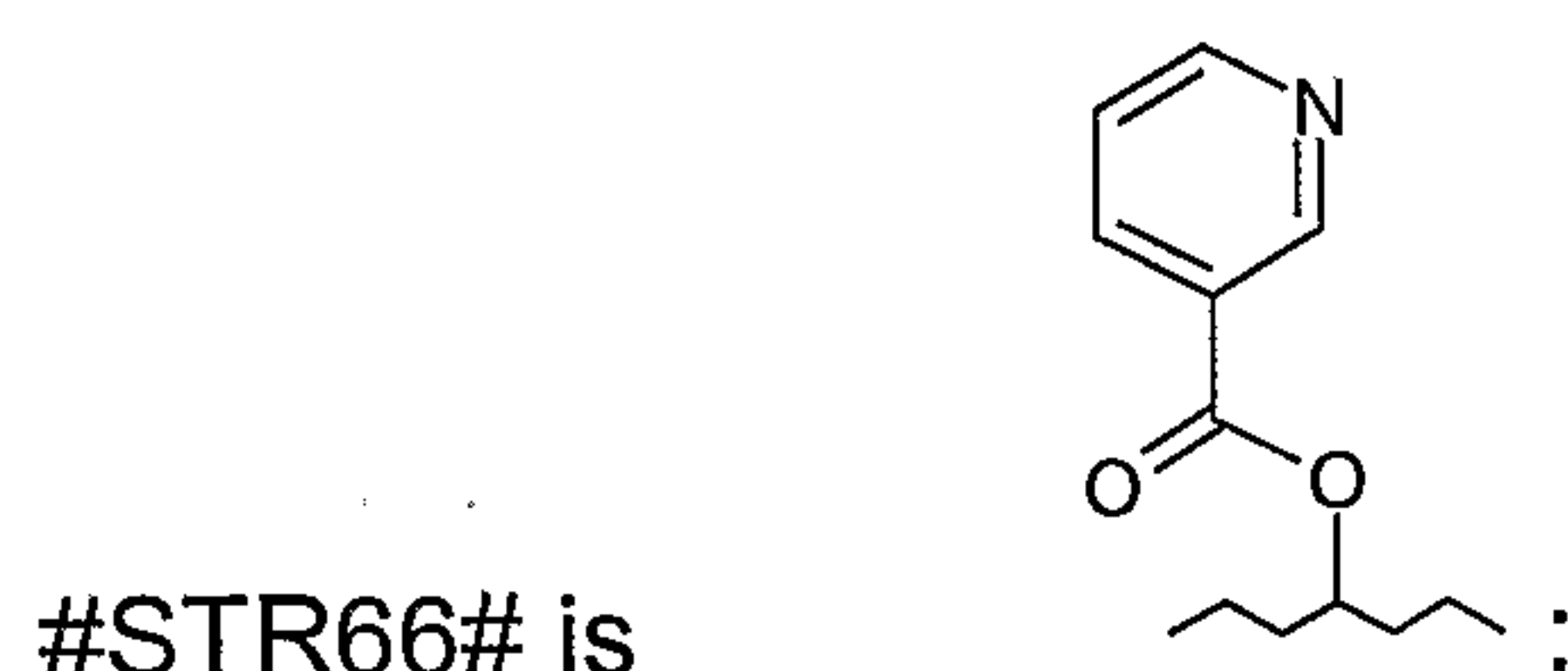
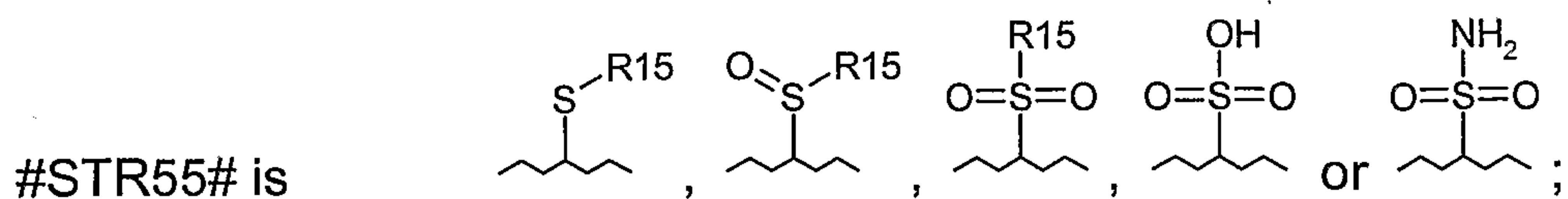
wherein

X can be CH, CH₂, CR₁₁, CR₁₃, CHR₁₁, CHR₁₃, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Y can be CH, CH₂, CR₁₂, CR₁₄, CHR₁₂, CHR₁₄, CR₁₁R₁₄, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Z can be a single, double bond or triple bond, with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

wherein



R15 and R16 are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₁-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, or a derivative thereof,

wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein non limiting examples of Formula 1 have at least one proviso selected from the following:

R7 is a hydroxyl;

at least one W is a N;

at least one of R1-R10 is #STR77#, #STR88# or #STR99#;

at least one of R1-R10 is #STR66#;

one of R1-R10 is a monoester;

one of R1-R10 is a dicarboxylic acid;

one of R1-R10 is succinic acid;

R7 is #STR55#;

R7 and R2 are #STR55#;

R7 and R2 are hydroxyls; and

R7 is #STR66#.

Non-limiting examples include compounds of Formula 1 where

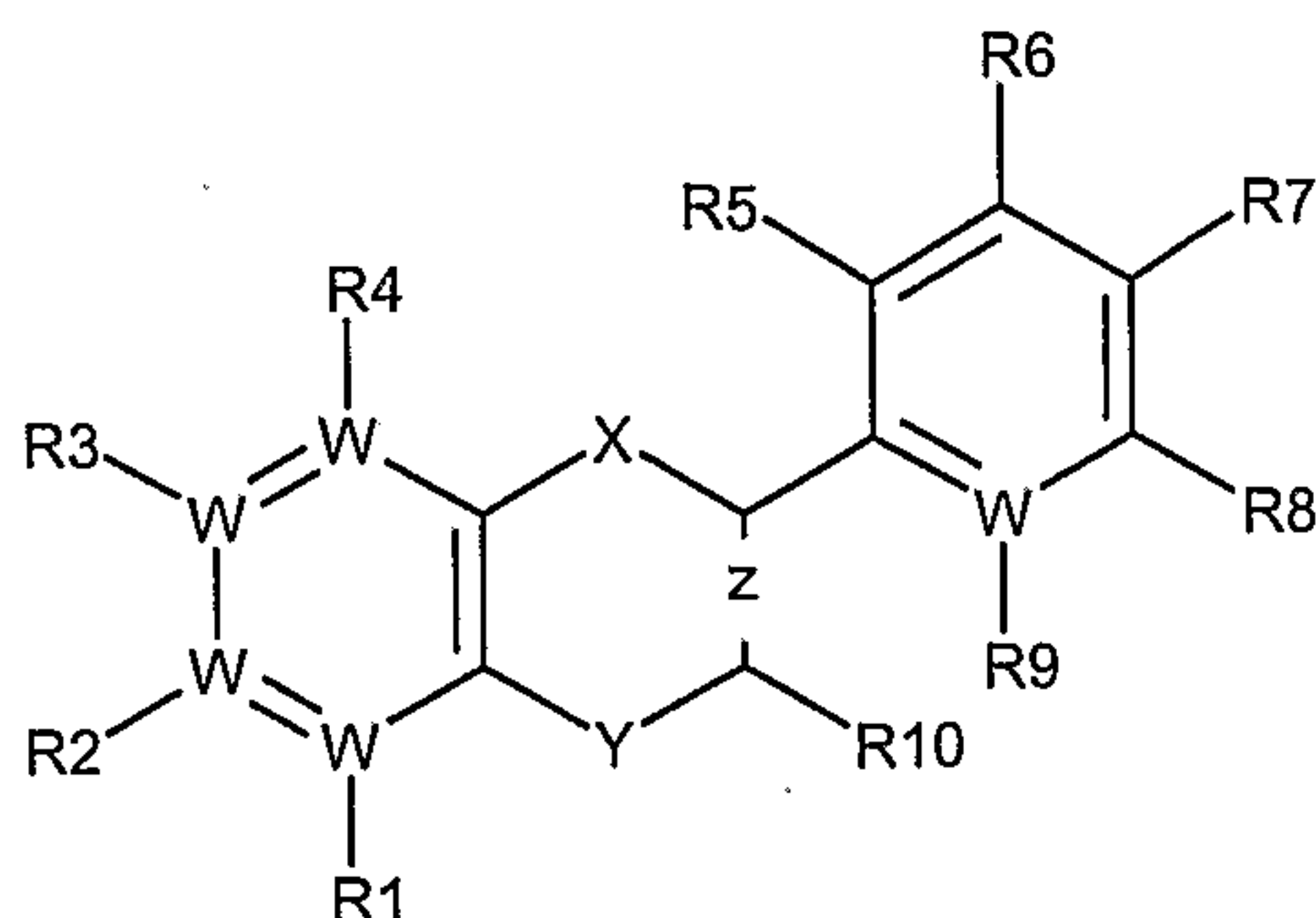
R7 is a hydroxyl and at least one W is a N;

R7 is a hydroxyl and at least one of R1-R6 and R8-R10 is #STR66#;

R7 is a hydroxyl and at least one of R1-R6 and R8-R10 is #STR77#, #STR88# or #STR99#; and

R7 is #STR66# and at least one W is a N.

[082] Another embodiment provides flavanoid compounds of Formula 2:



or a pharmaceutically acceptable salt thereof,

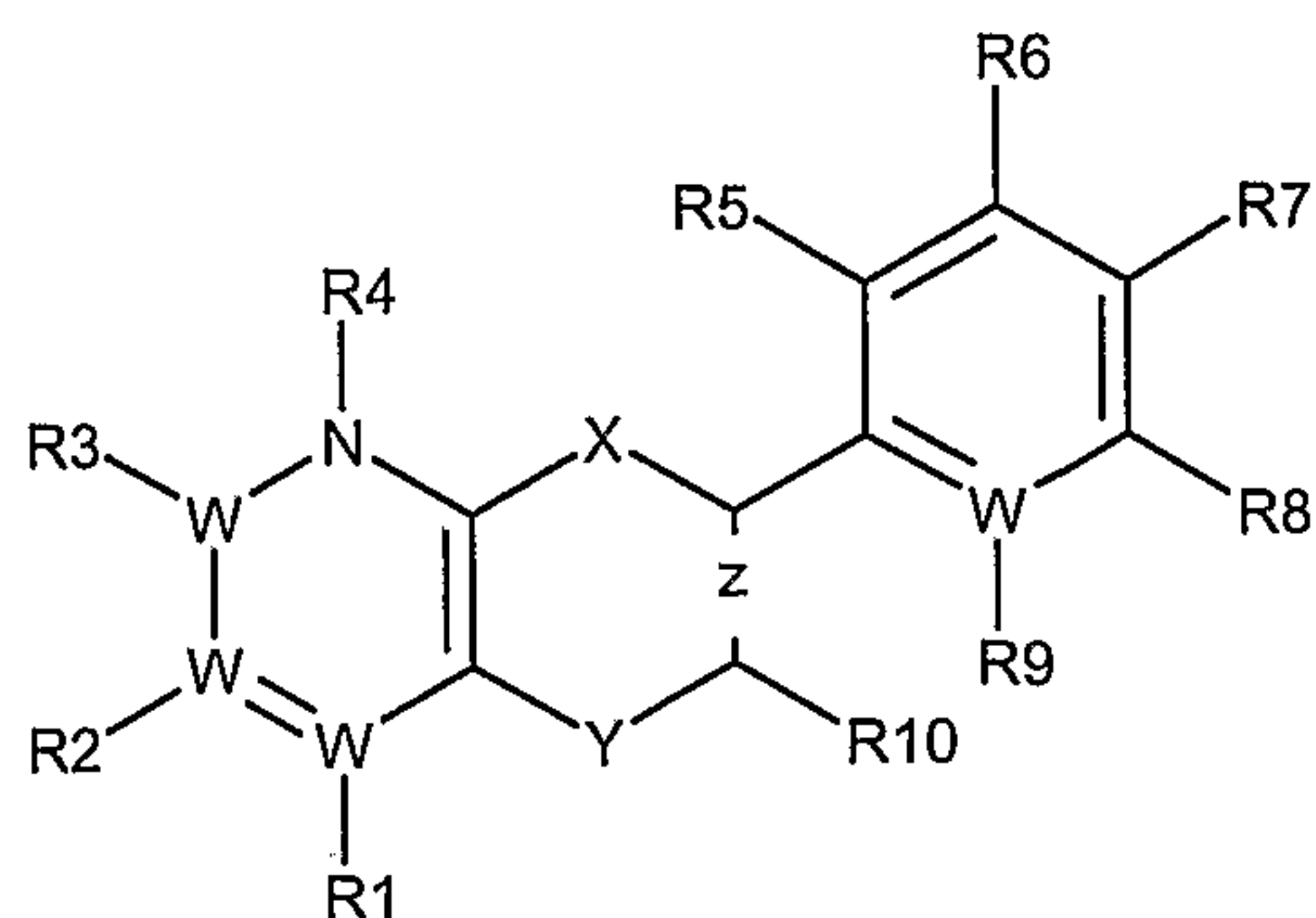
wherein

R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

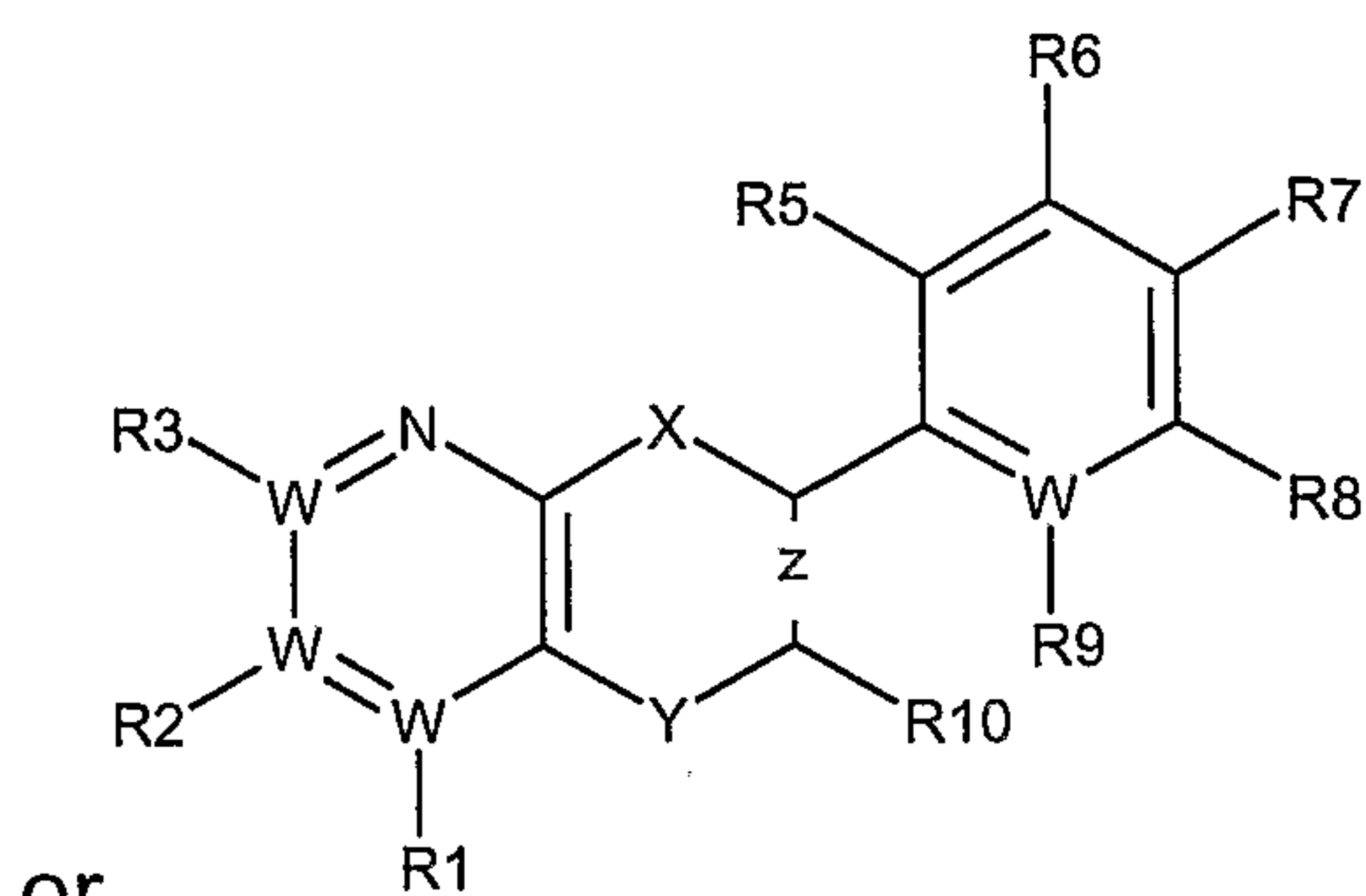
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 2:

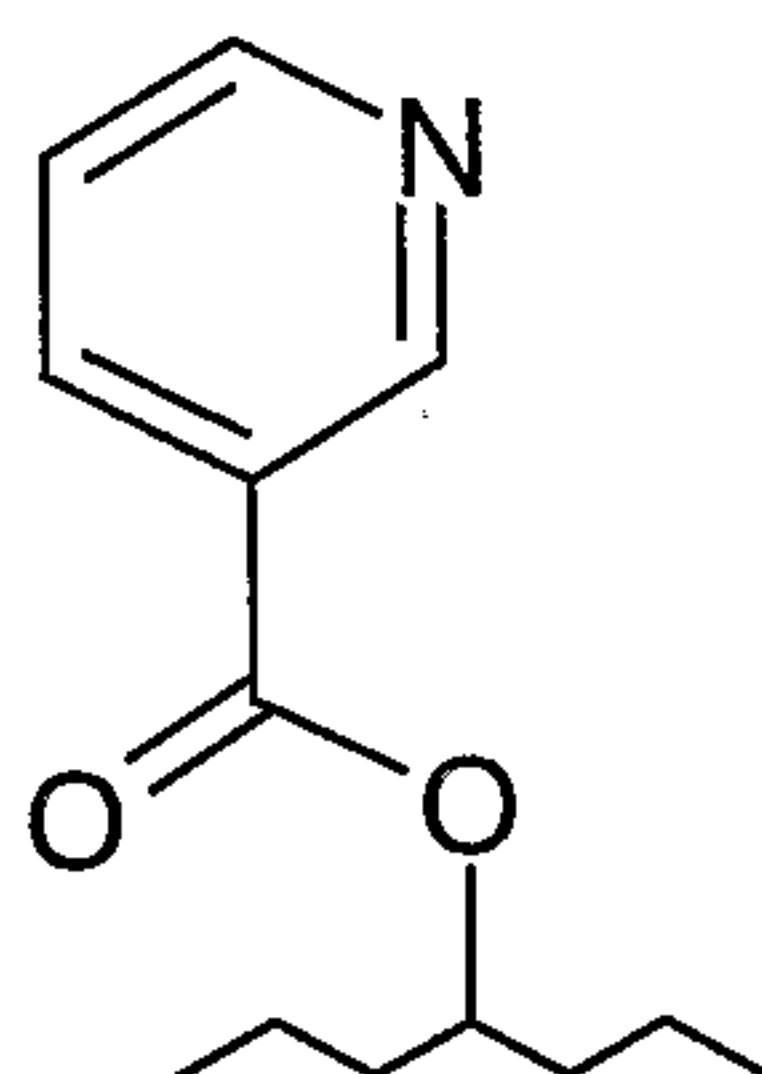


wherein the same applies to any W;



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

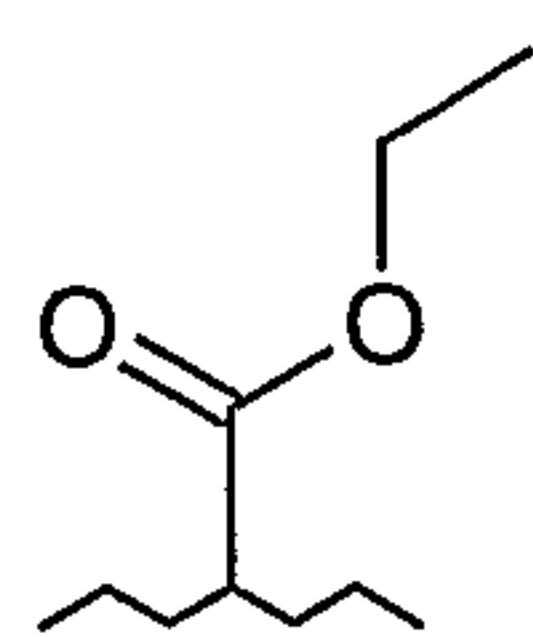
Z can be a single or a double bond

wherein

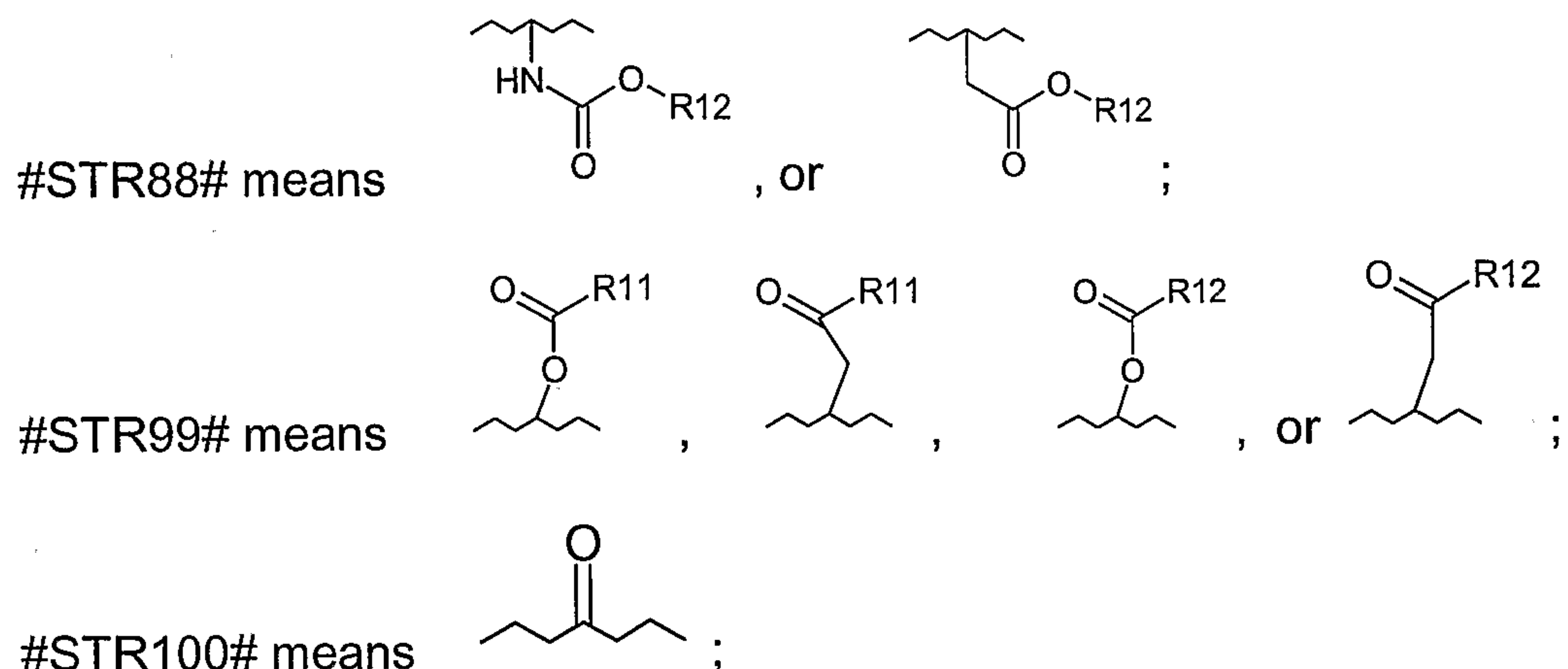
R₁₃ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein

#STR77# means



;



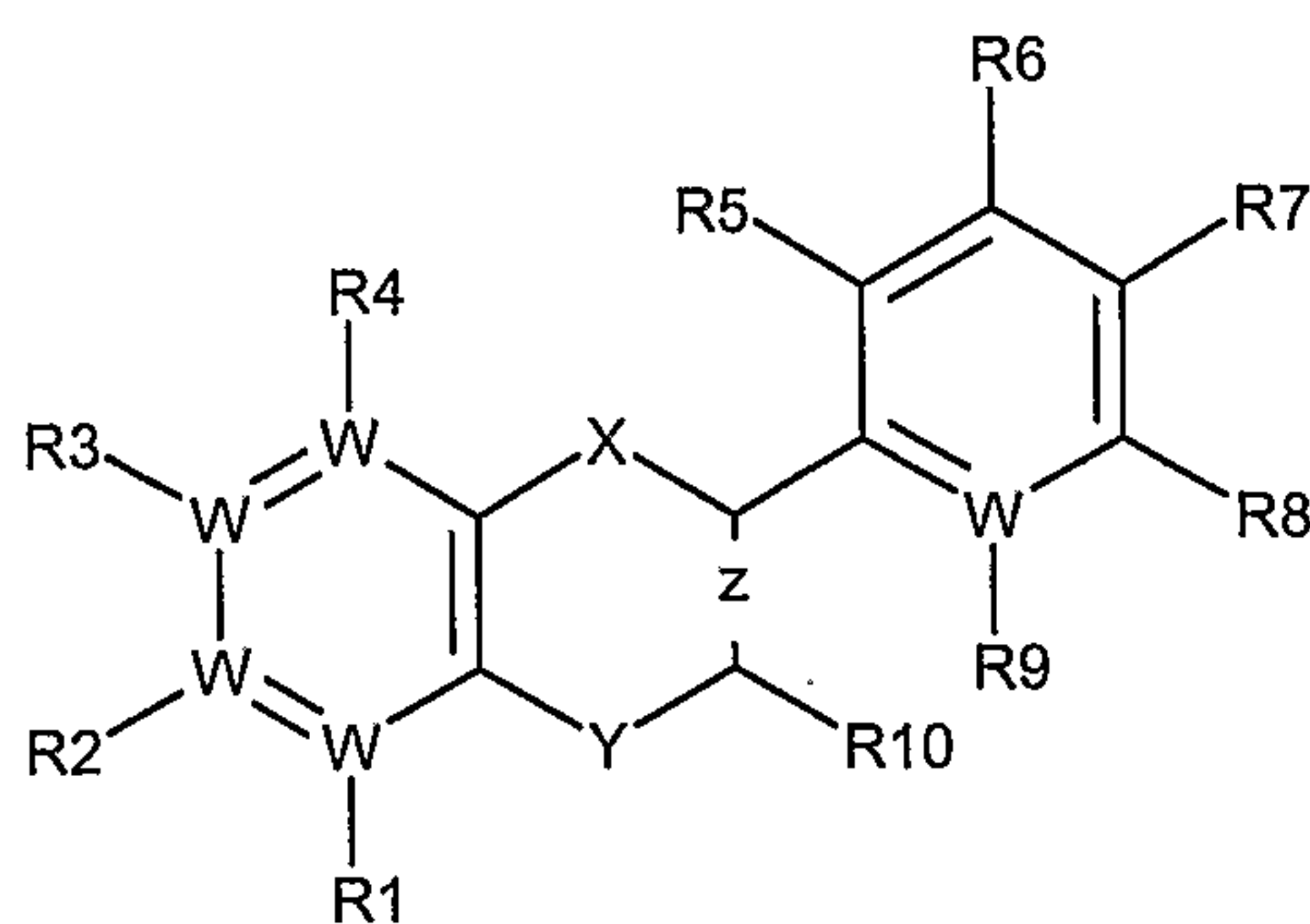
R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

- a) R7 is a hydroxyl; or
- b) R7 is a hydroxyl and optionally;
- c) at least one W is a N, and/or;
- d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;
- e) at least one of R1-R10 is #STR66#.

[083] Another embodiment provides compounds comprising the general flavonoid structure of Formula 2:



or a pharmaceutically acceptable salt thereof,

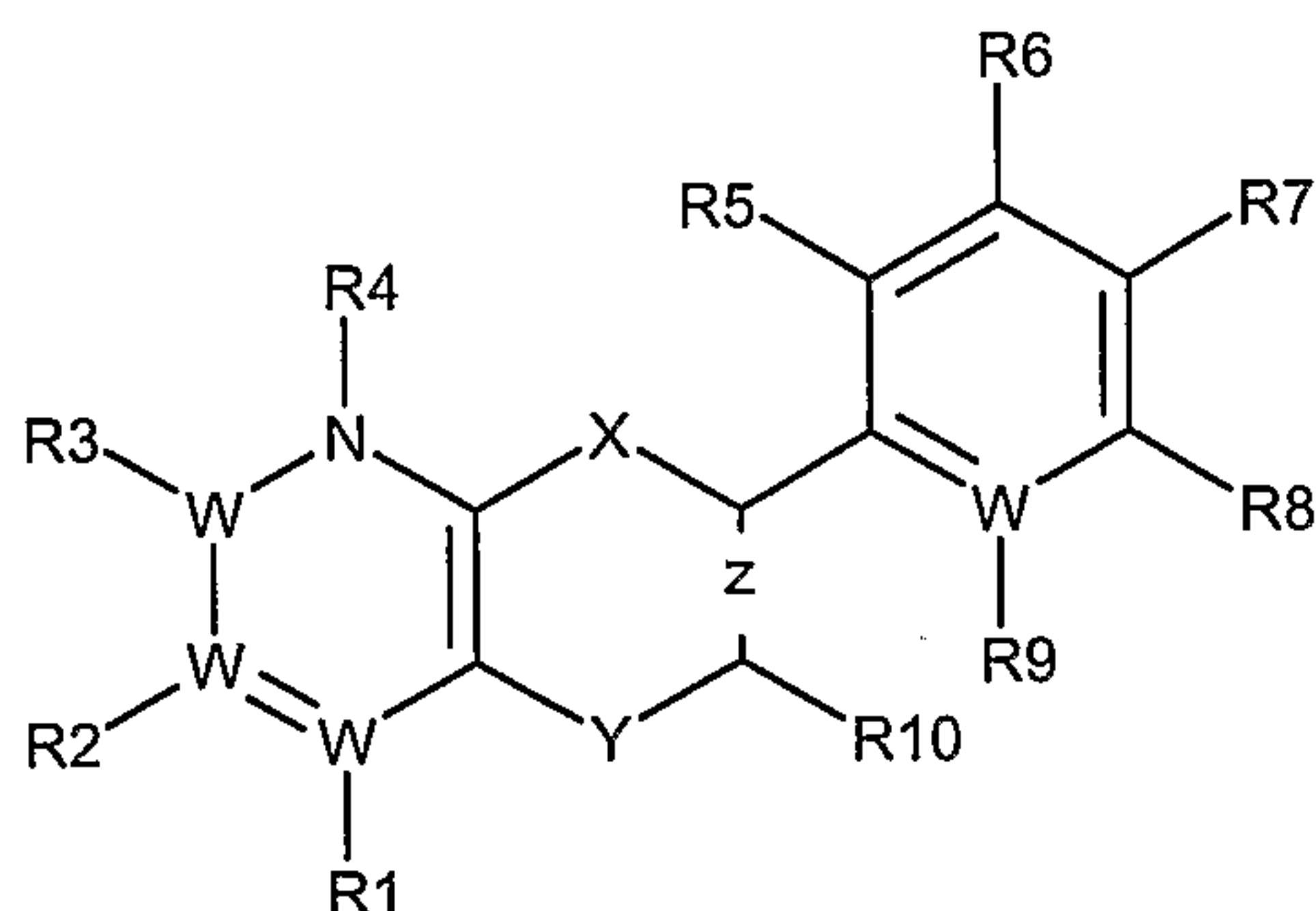
wherein

R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

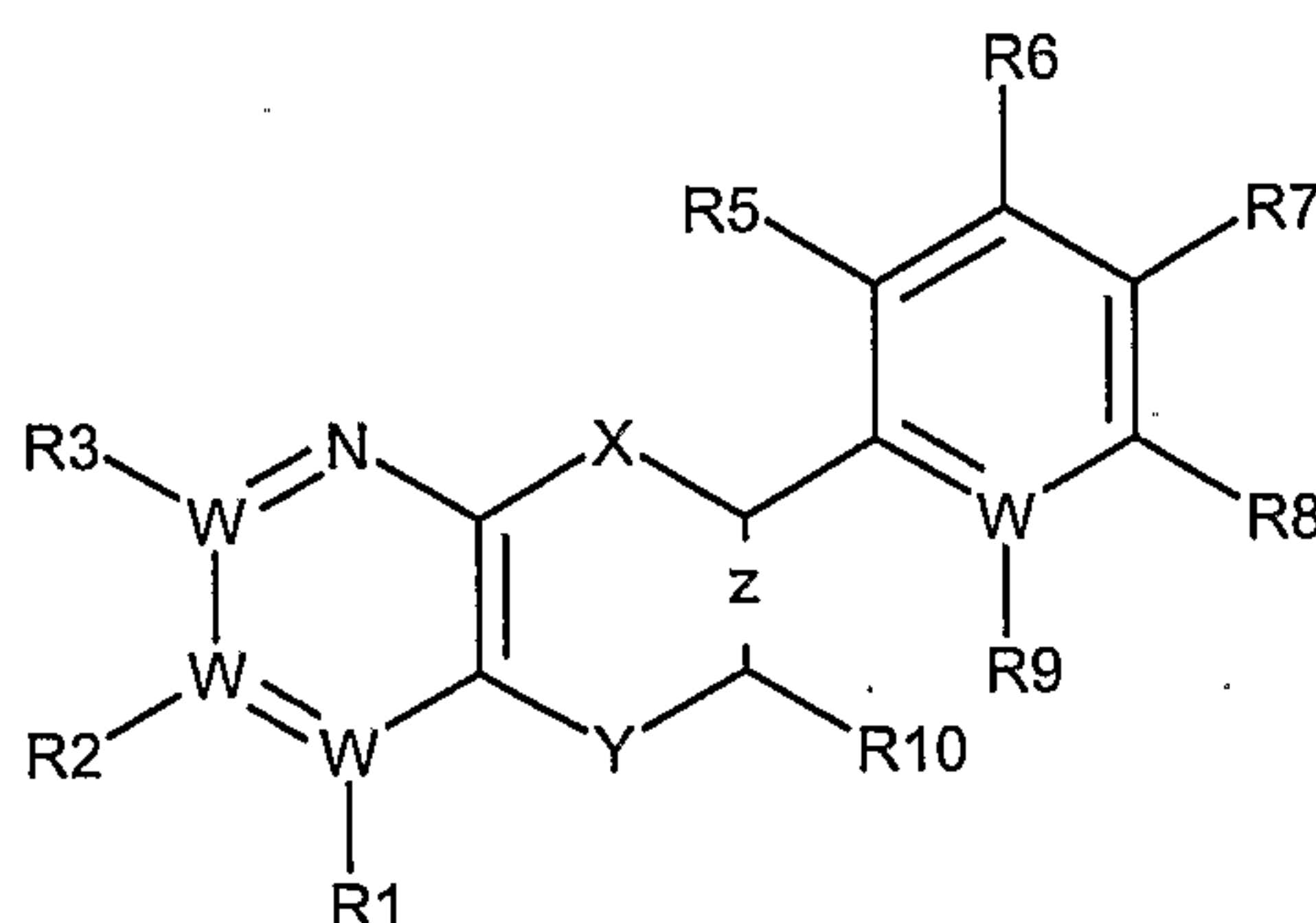
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 2:

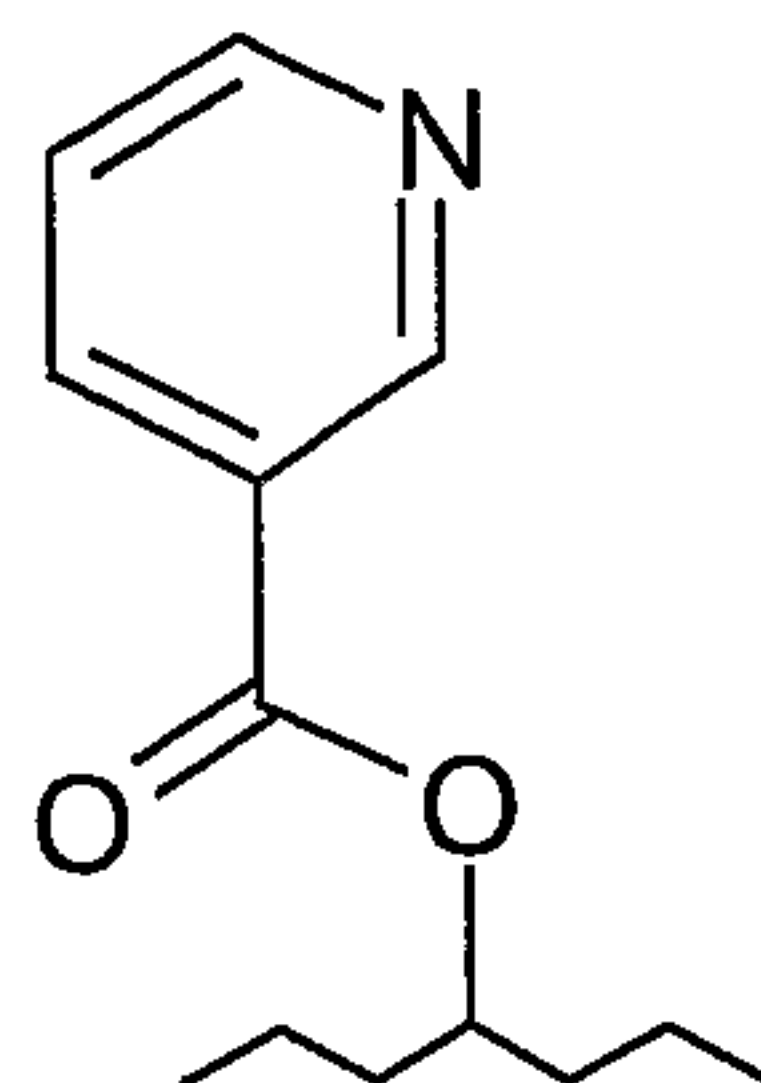


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

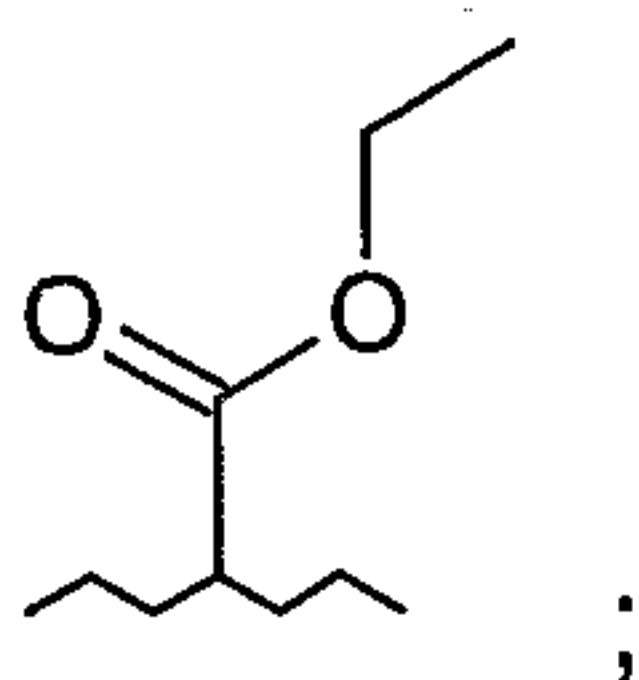
Z can be a single or a double bond

wherein

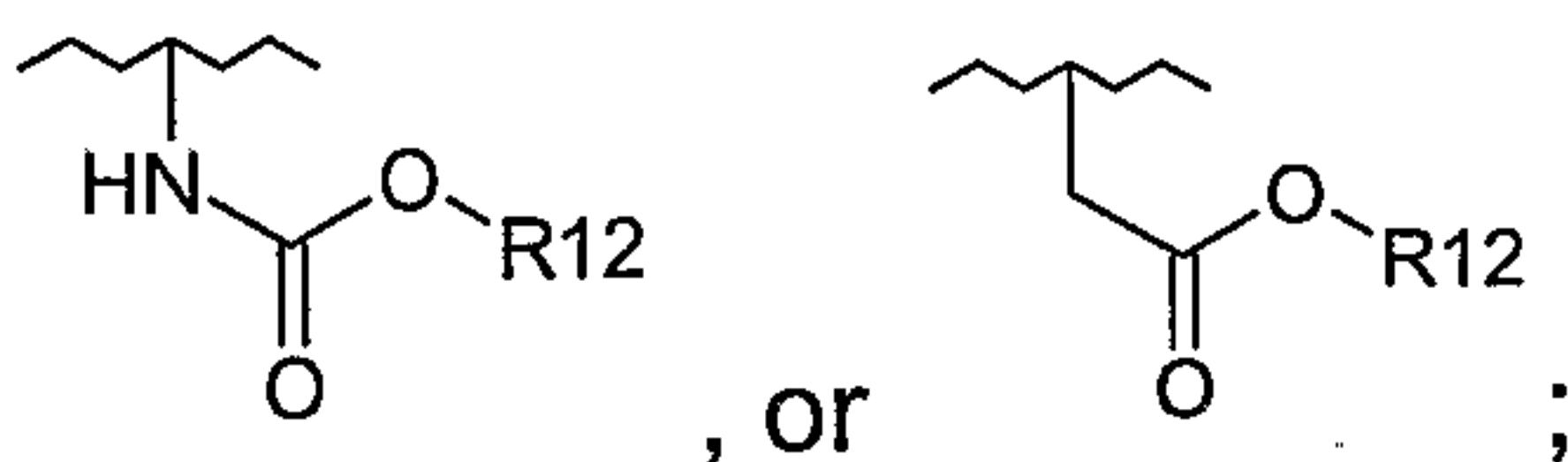
R₁₃ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein

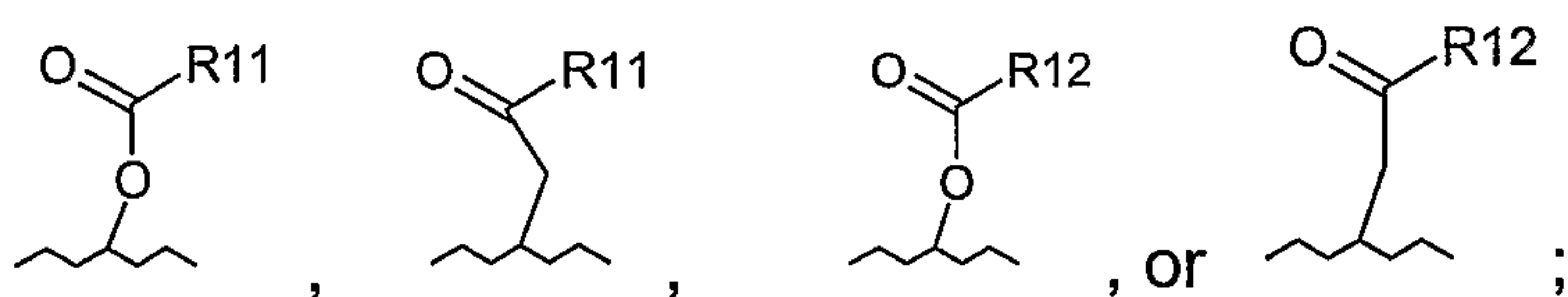
#STR77# means



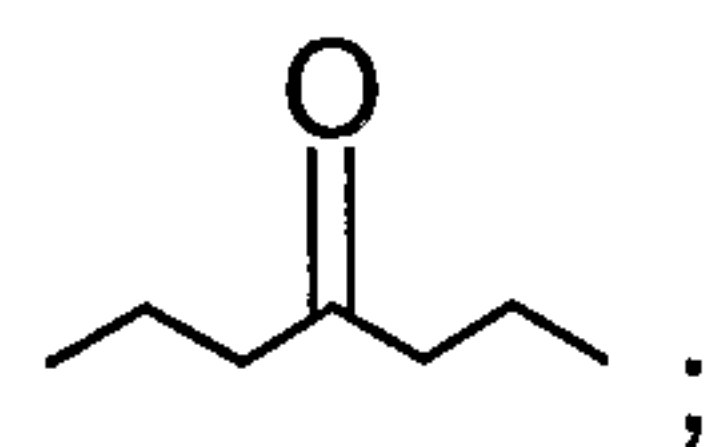
#STR88# means



#STR99# means



#STR100# means



R₁₁ is pyridine, pyridazine, pyrimidine, pyrazine; and

R₁₂ is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof,

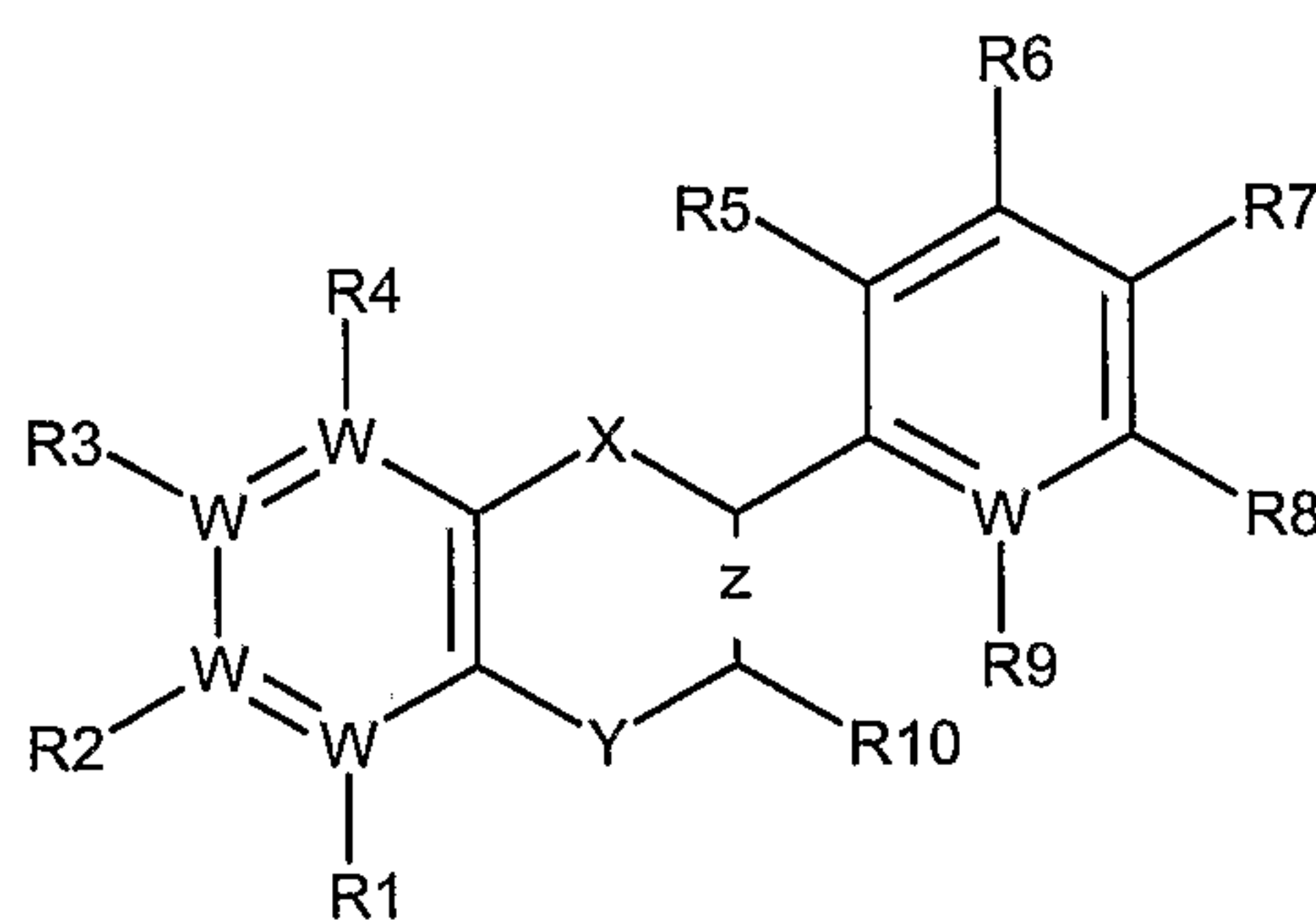
wherein said derivative is optionally substituted and optionally branched, and may

have one or more of the C atoms replaced by S, N or O;

with the proviso that;

- a) at least one W is a N and R7 is a hydroxyl; or
- b) at least one W is a N and R7 is a hydroxyl, and optionally;
- c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;
- d) at least one of R1-R10 is #STR66#.

[084] Another embodiment provides compounds comprising the general flavonoid structure of Formula 2:



or a pharmaceutically acceptable salt thereof,

wherein

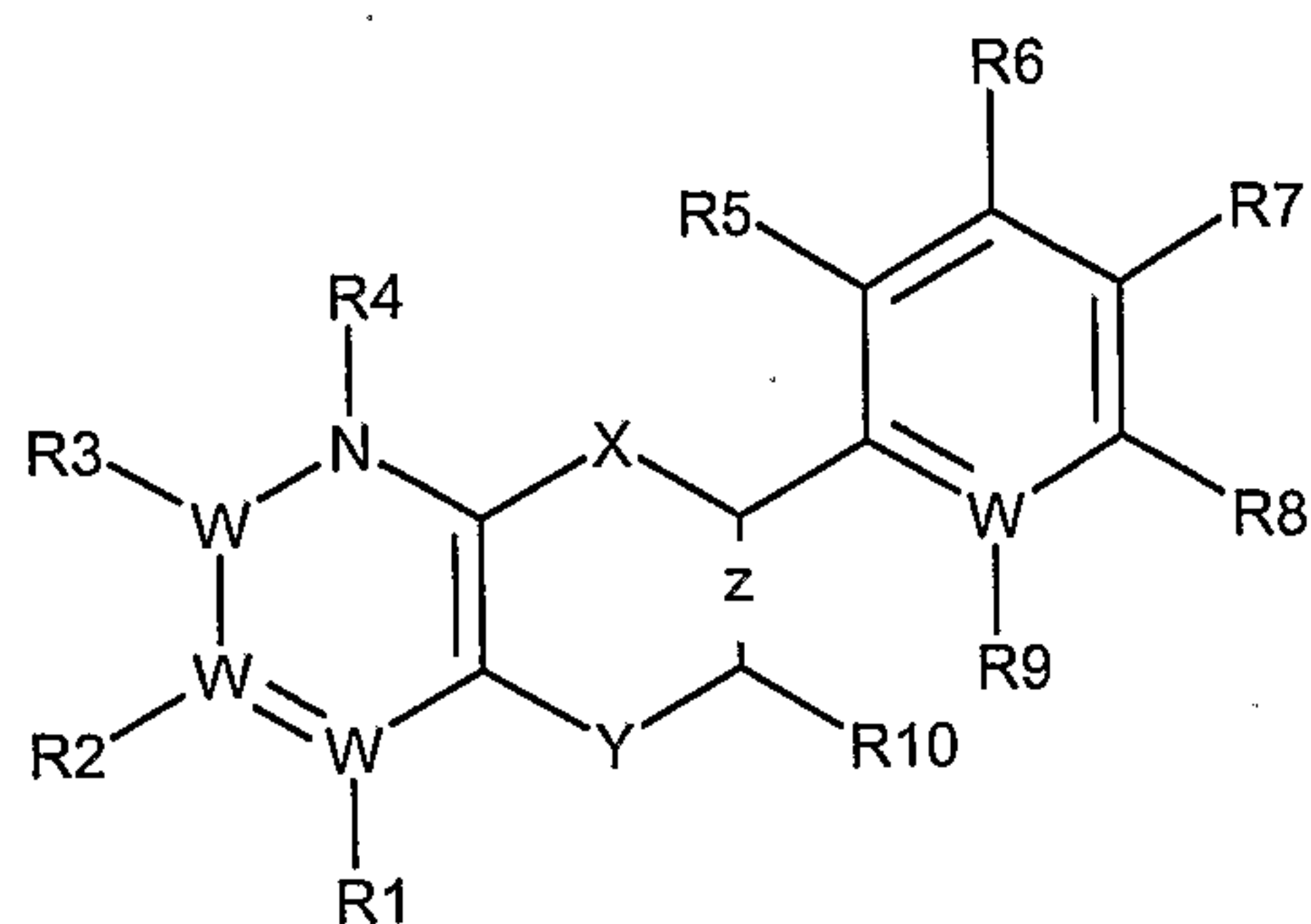
R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

wherein

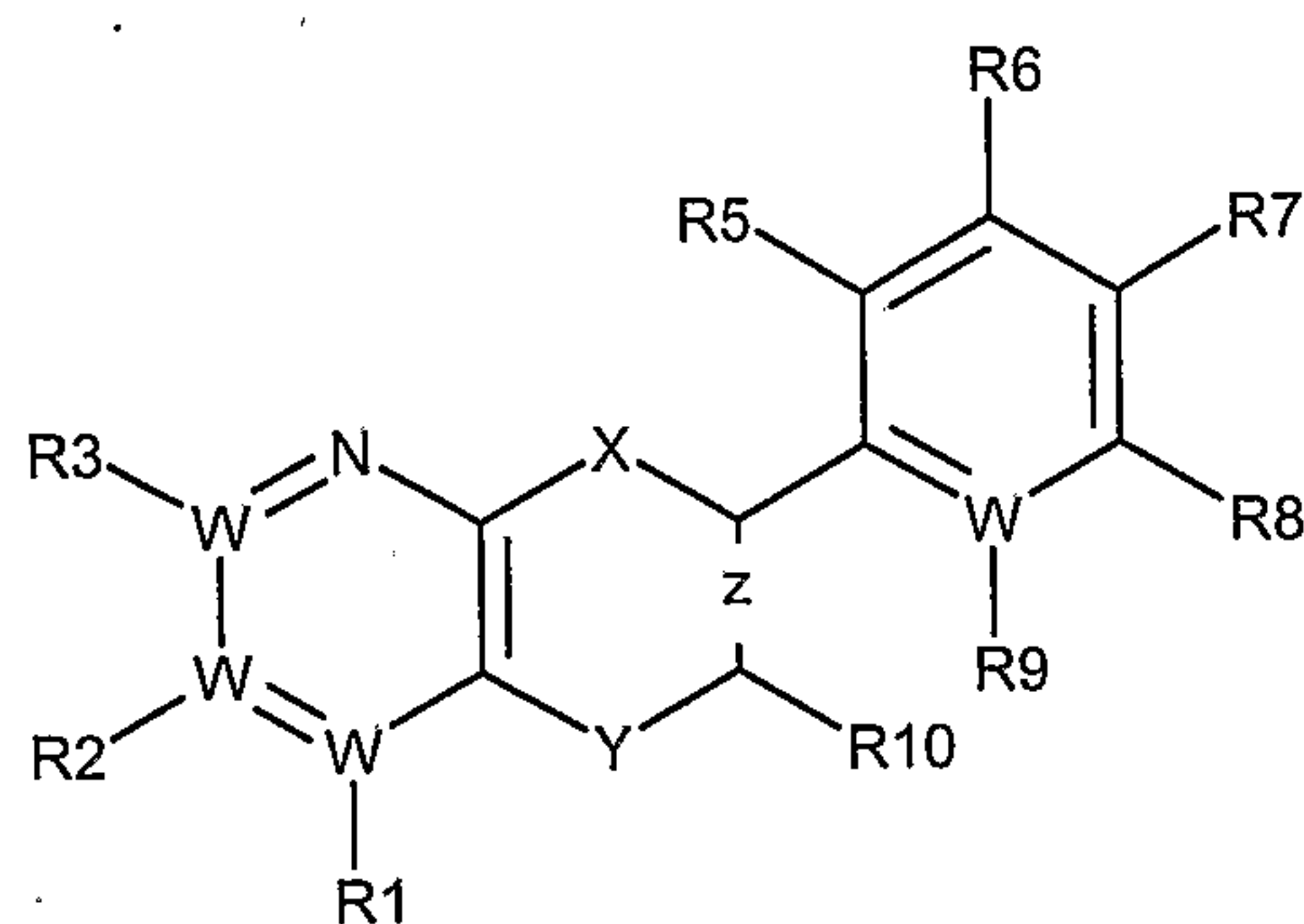
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below

demonstrate a nitrogen arrangement of one embodiment of the compounds of
Formula 2:

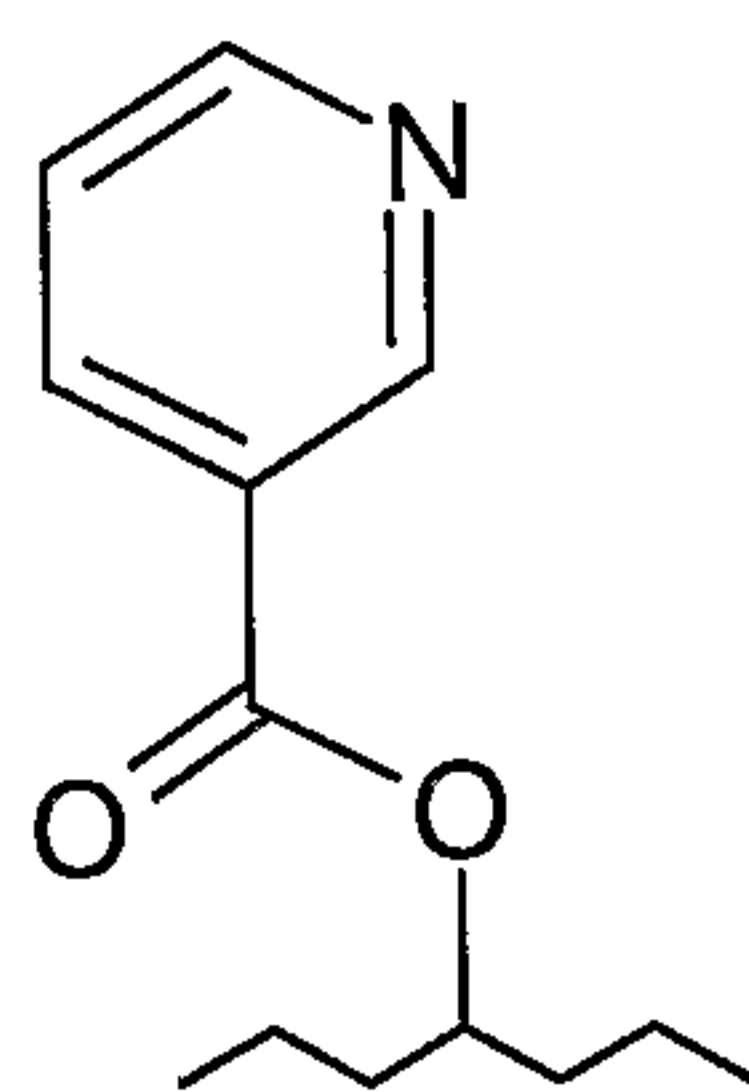


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR¹³, or NR¹³;

Y can be O, S, C, CR¹³, or NR¹³;

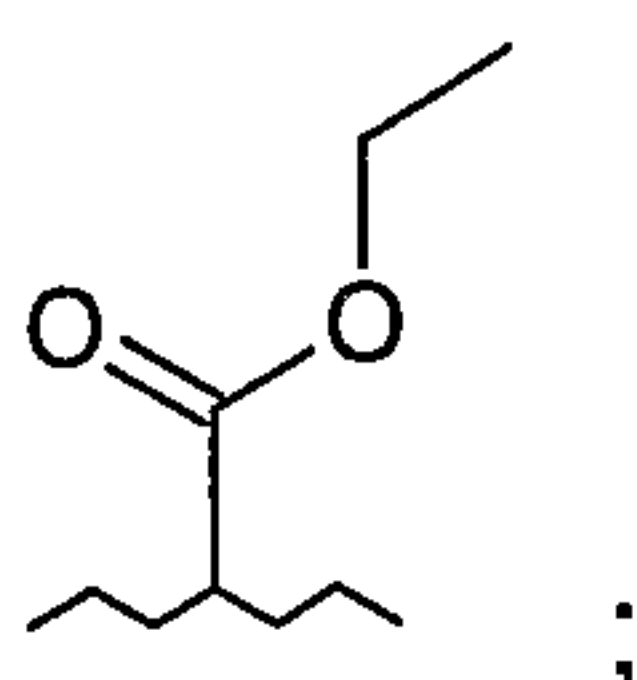
Z can be a single or a double bond

wherein

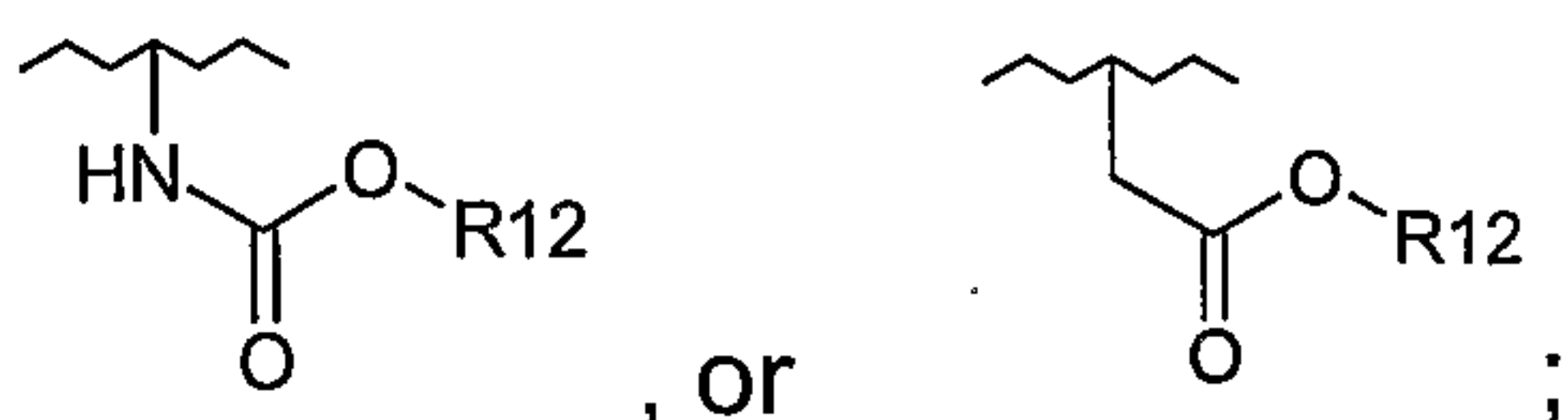
R¹³ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein

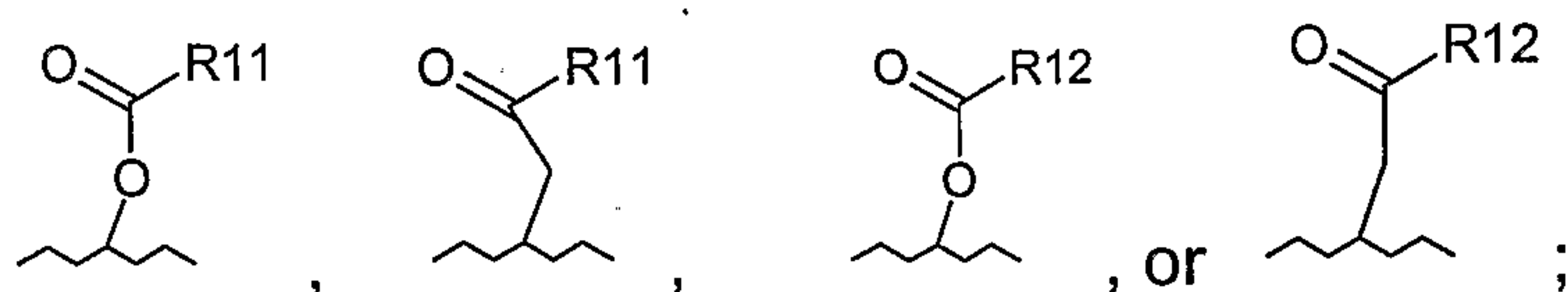
#STR77# means



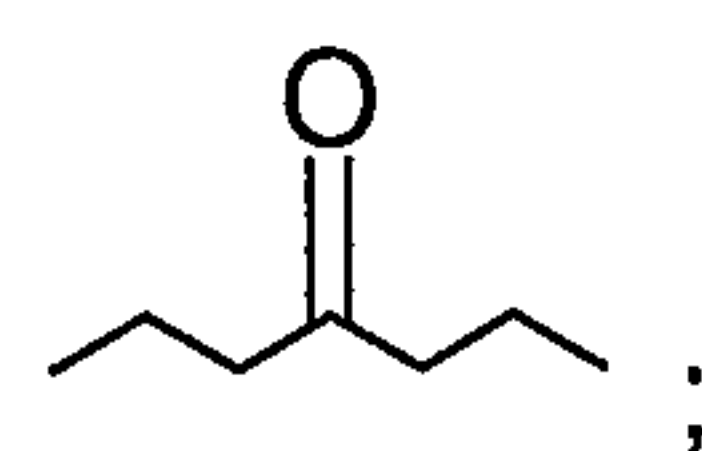
#STR88# means



#STR99# means



#STR100# means



R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

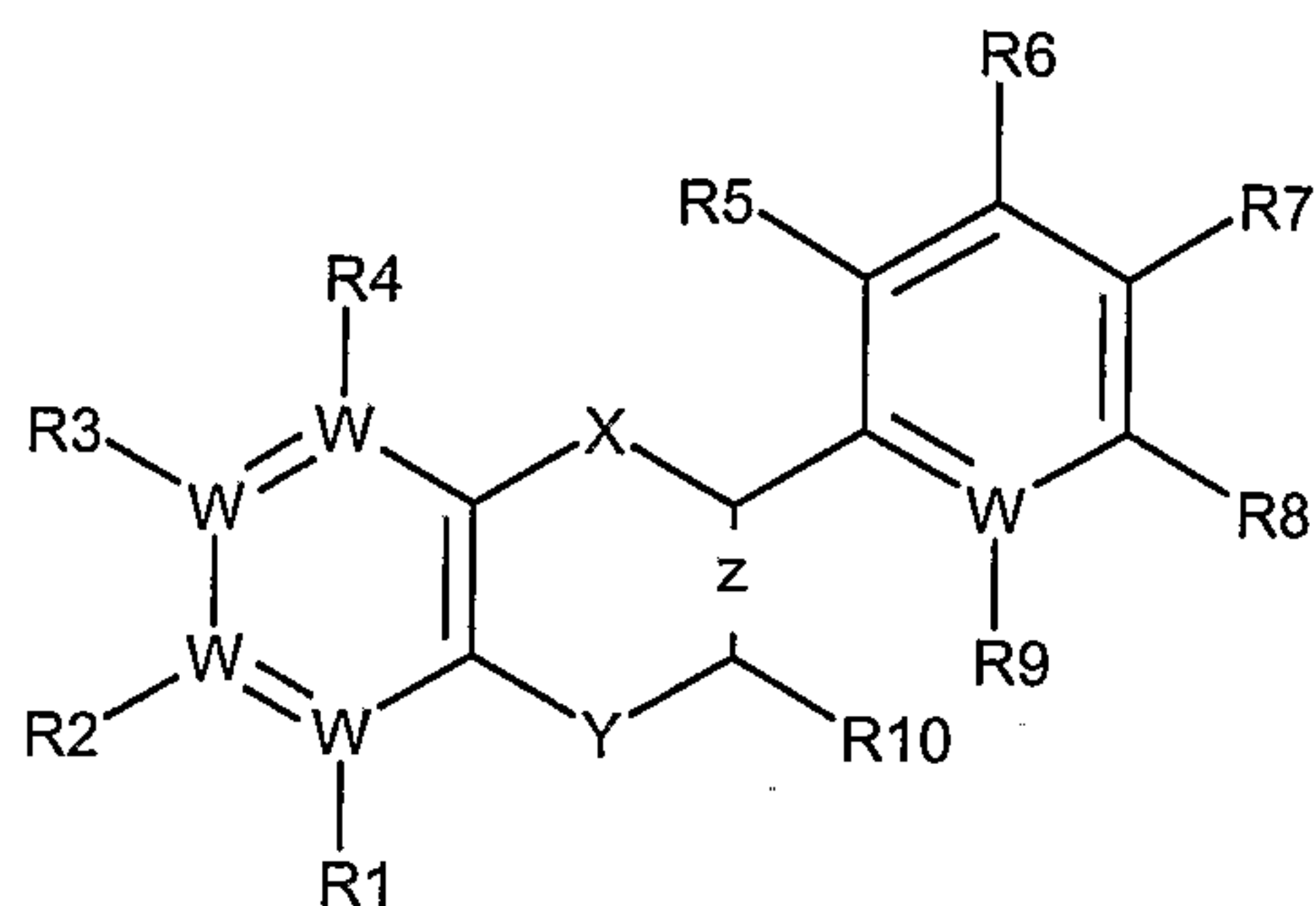
a) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R7 is a hydroxyl; or

b) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R7 is a hydroxyl, and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-R10 is #STR66#.

[085] Another embodiment provides compounds comprising the general flavonoid structure of Formula 2:



or a pharmaceutically acceptable salt thereof,

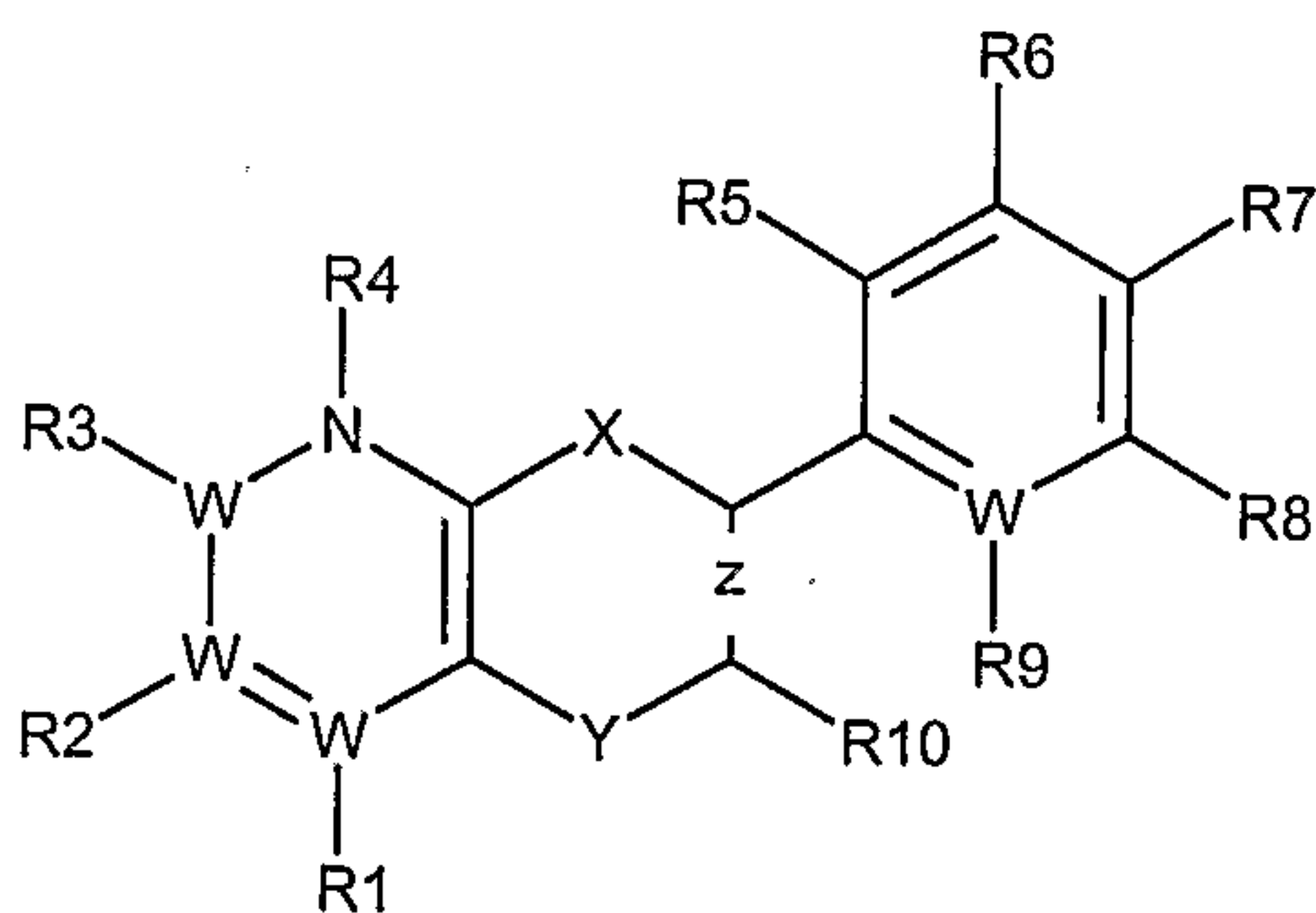
wherein

R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

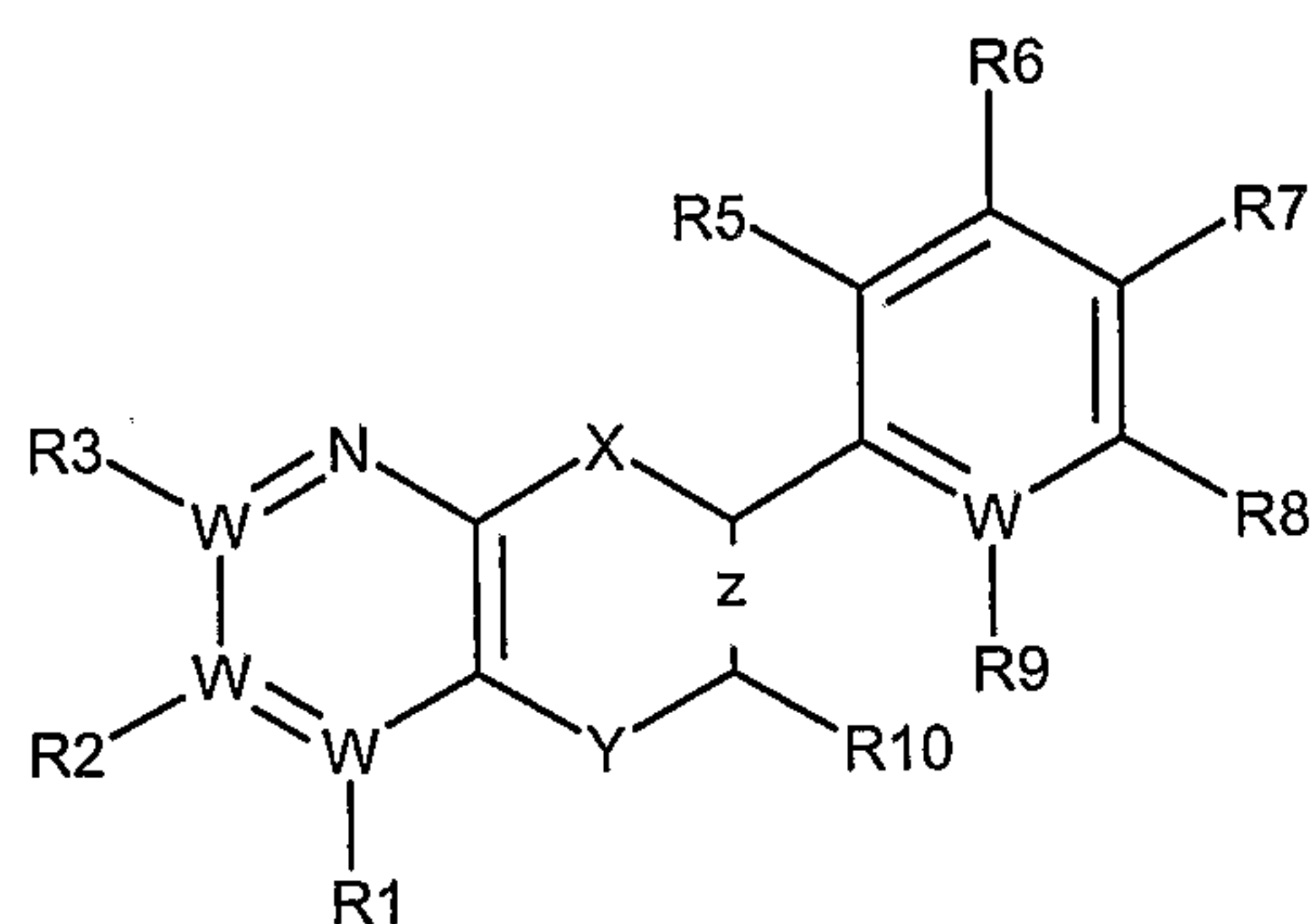
wherein

W can be C or N;

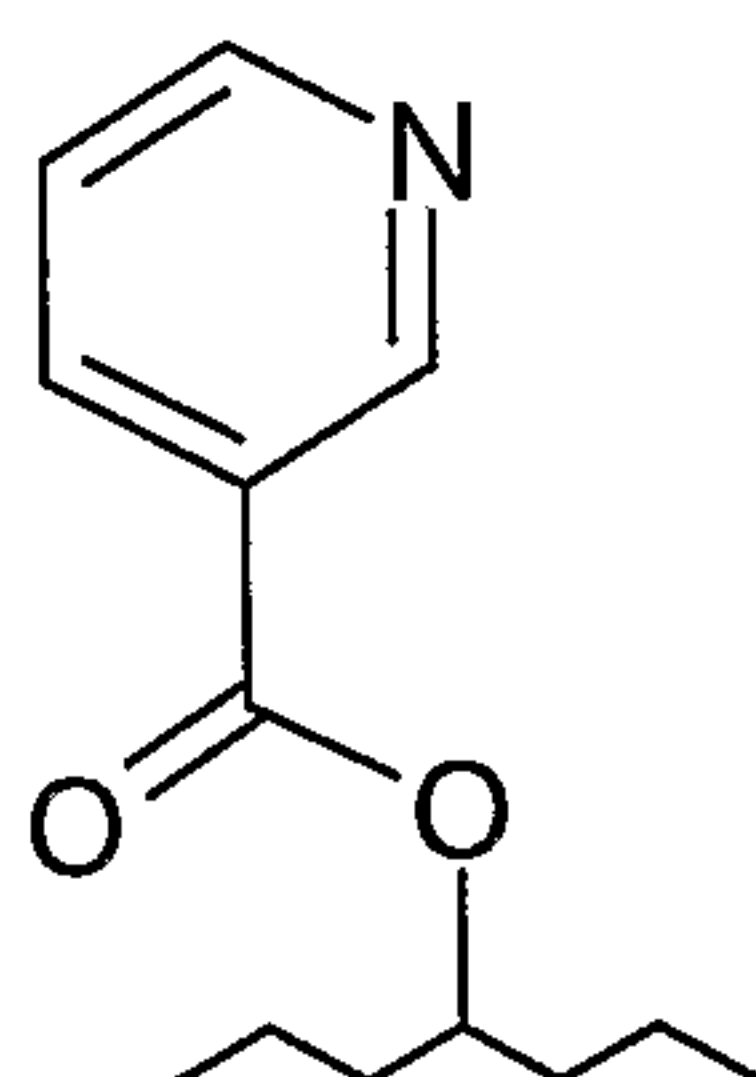
wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 2:



wherein the same applies to any W; or



wherein



wherein

X can be O, S, C, CR13, or NR13;

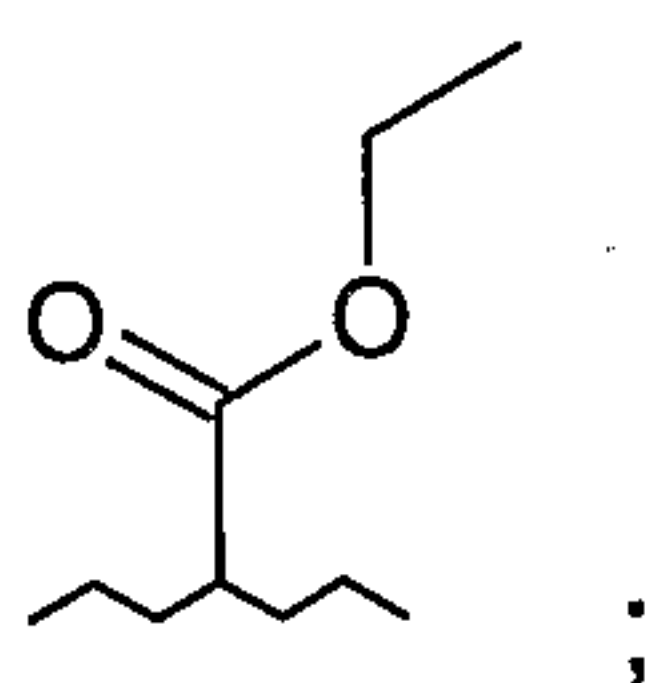
Y can be O, S, C, CR13, or NR13;

Z can be a single or a double bond

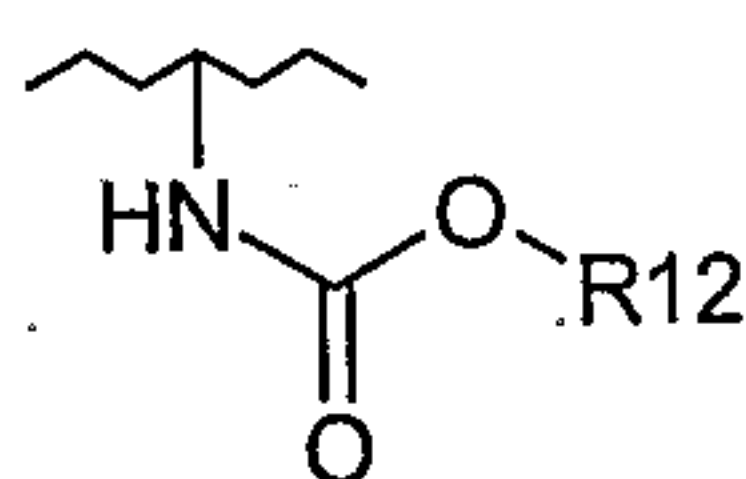
wherein

R13 is #STR77#, #STR88#, #STR99#, or #STR100#,

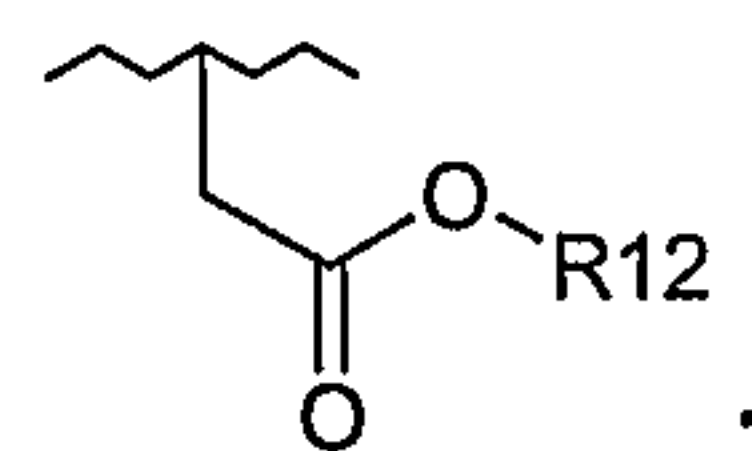
wherein



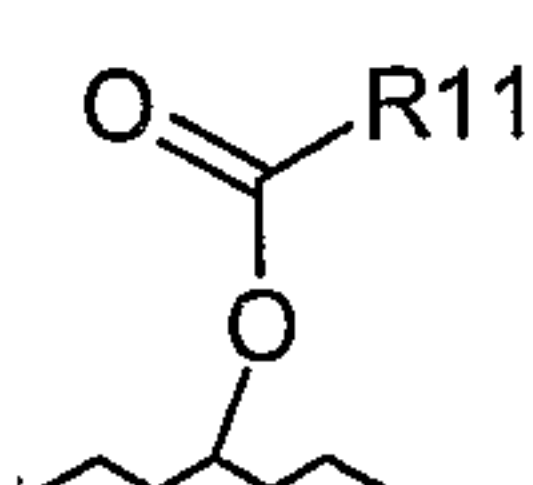
#STR77# means



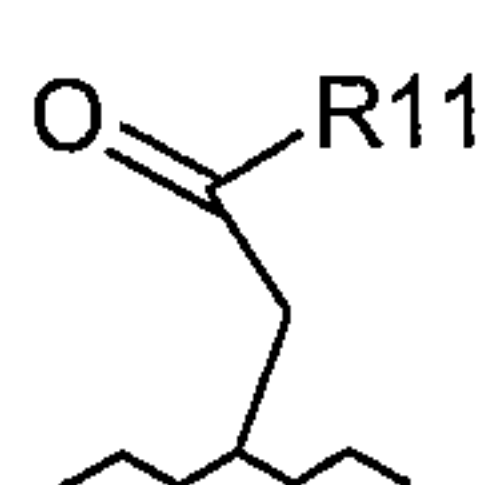
, or



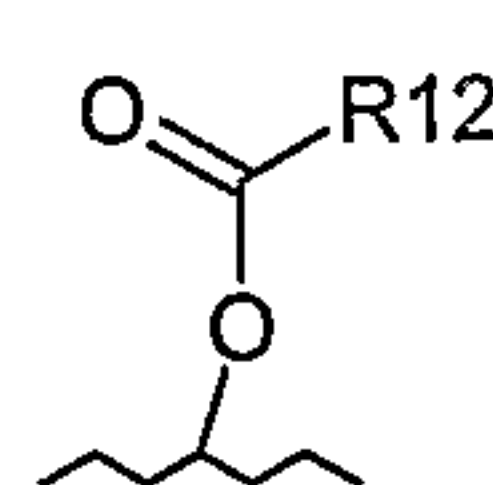
3



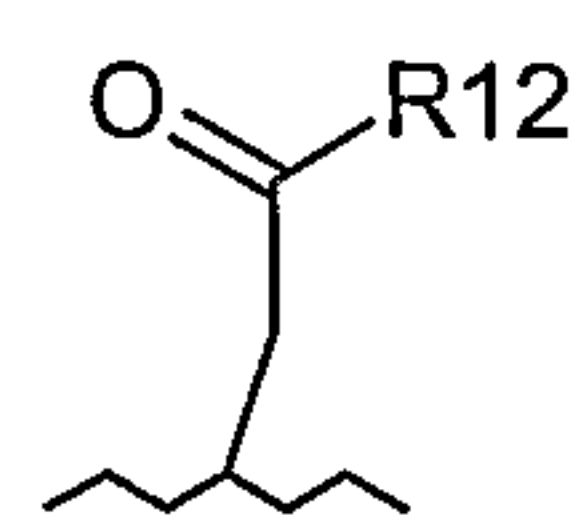
#STR99# means

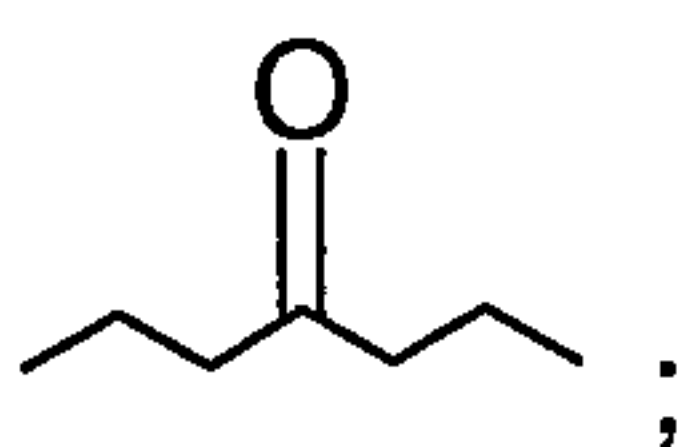


3



, or



#STR100# means  ;

R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

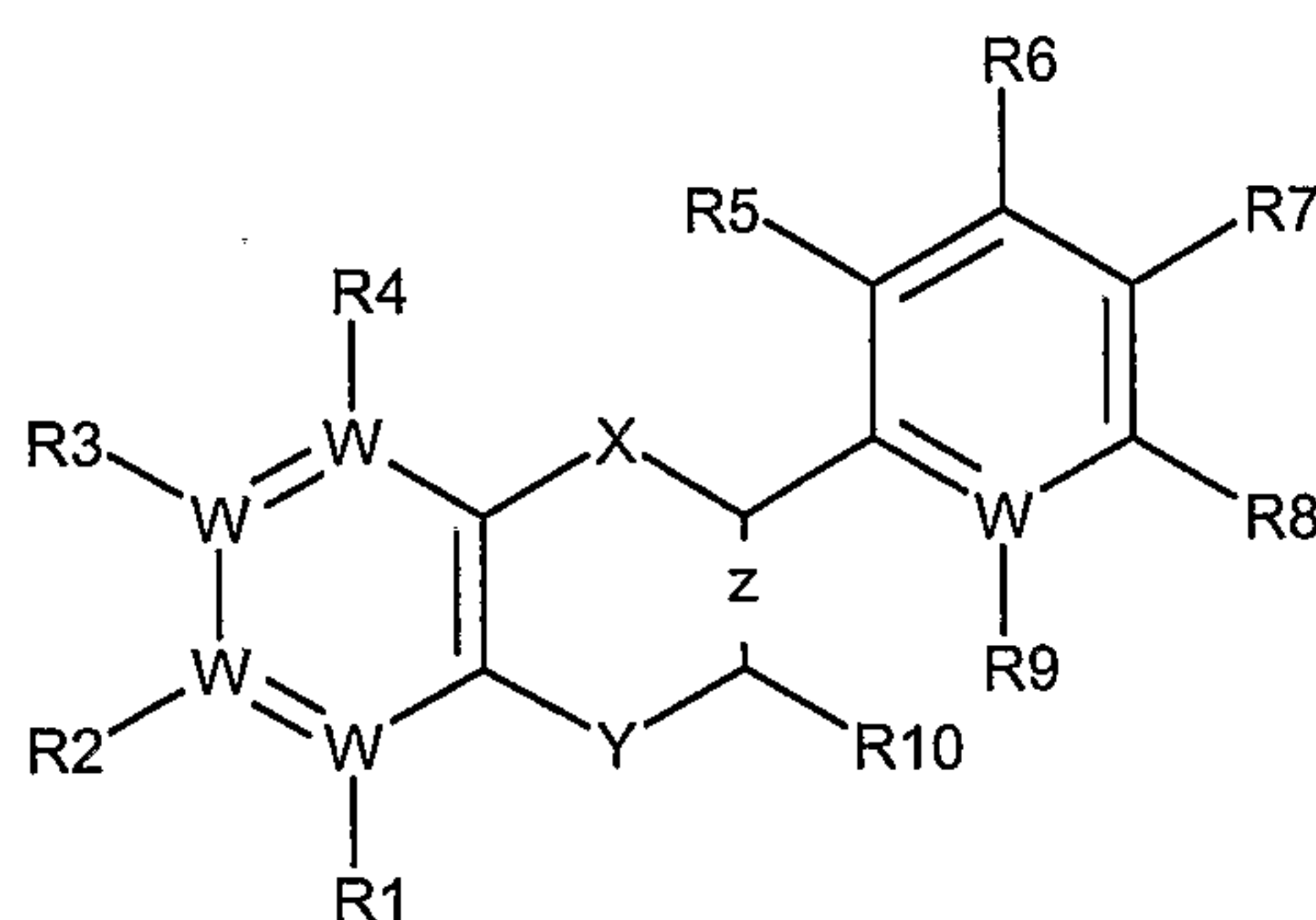
a) R7 is a hydroxyl or #STR66# and if R7 is a hydroxyl (R1-R6 and R8-R10) at least one of R1-R10 is #STR66#; or

b) R7 is a hydroxyl or #STR66# and if R7 is a hydroxyl (R1-R6 and R8-R10) at least one of R1-R10 is #STR66# and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#.

[086] Another embodiment provides compounds comprising the general flavonoid structure of Formula 2:



or a pharmaceutically acceptable salt thereof,

wherein

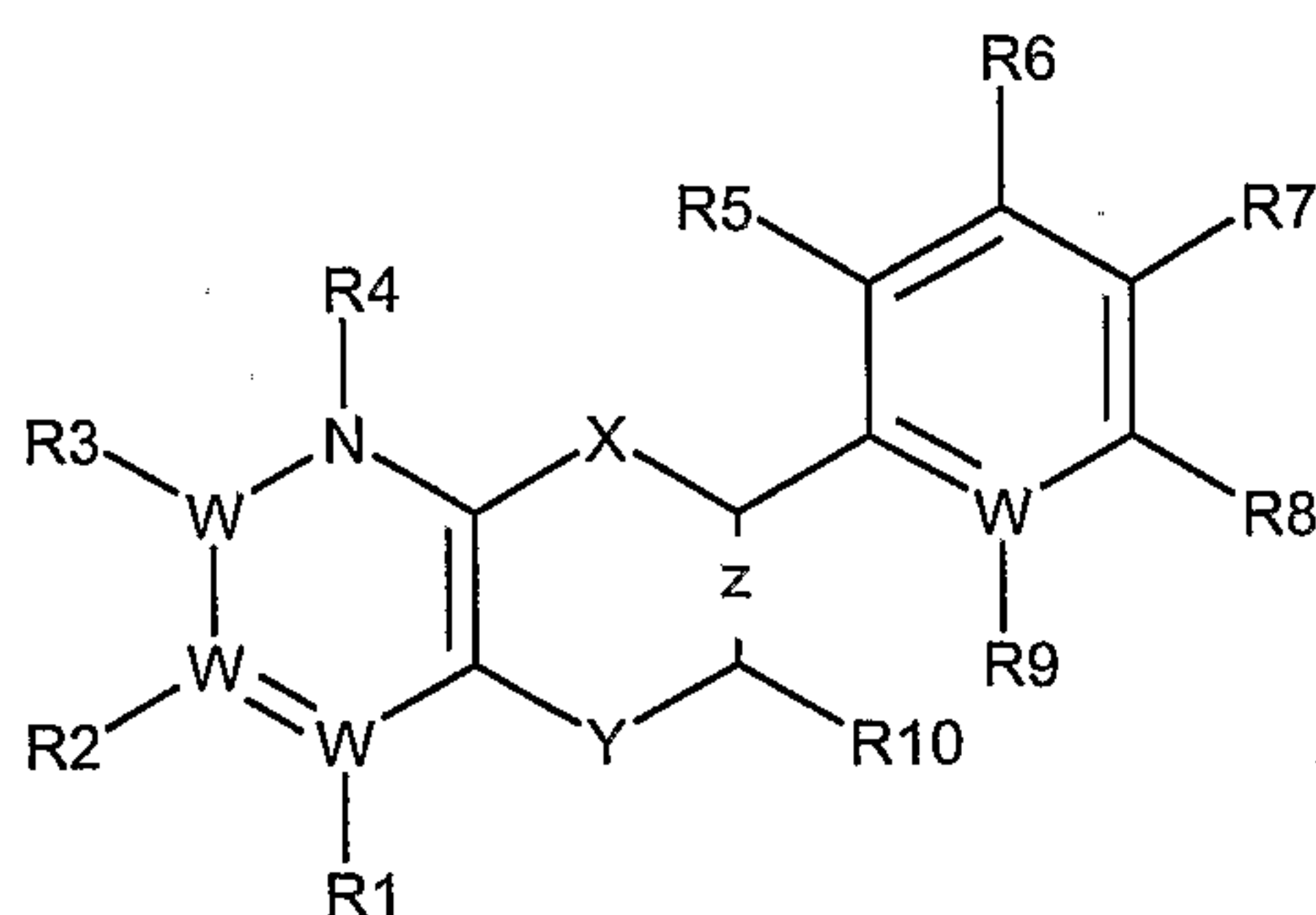
R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy

[OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

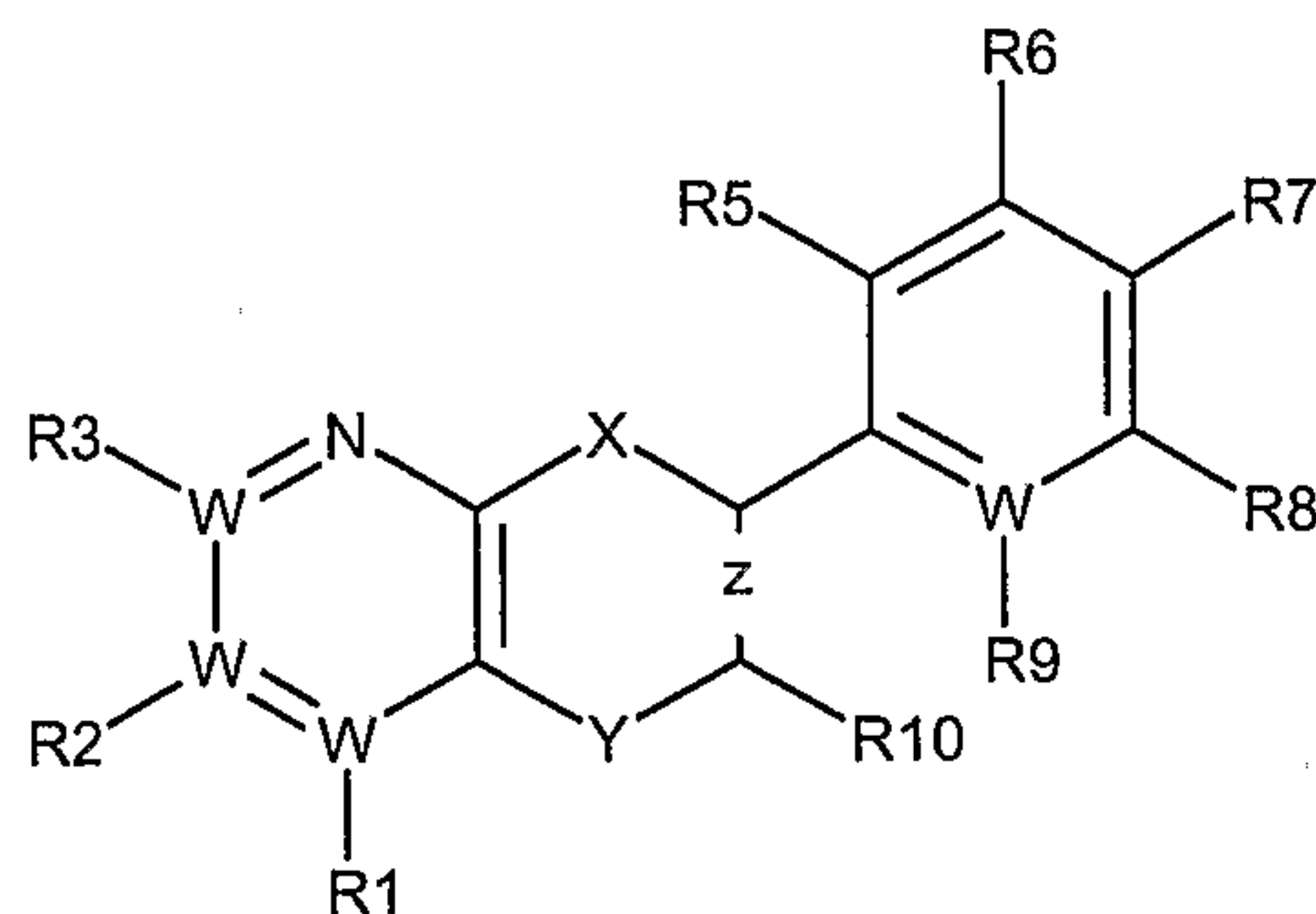
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 2:



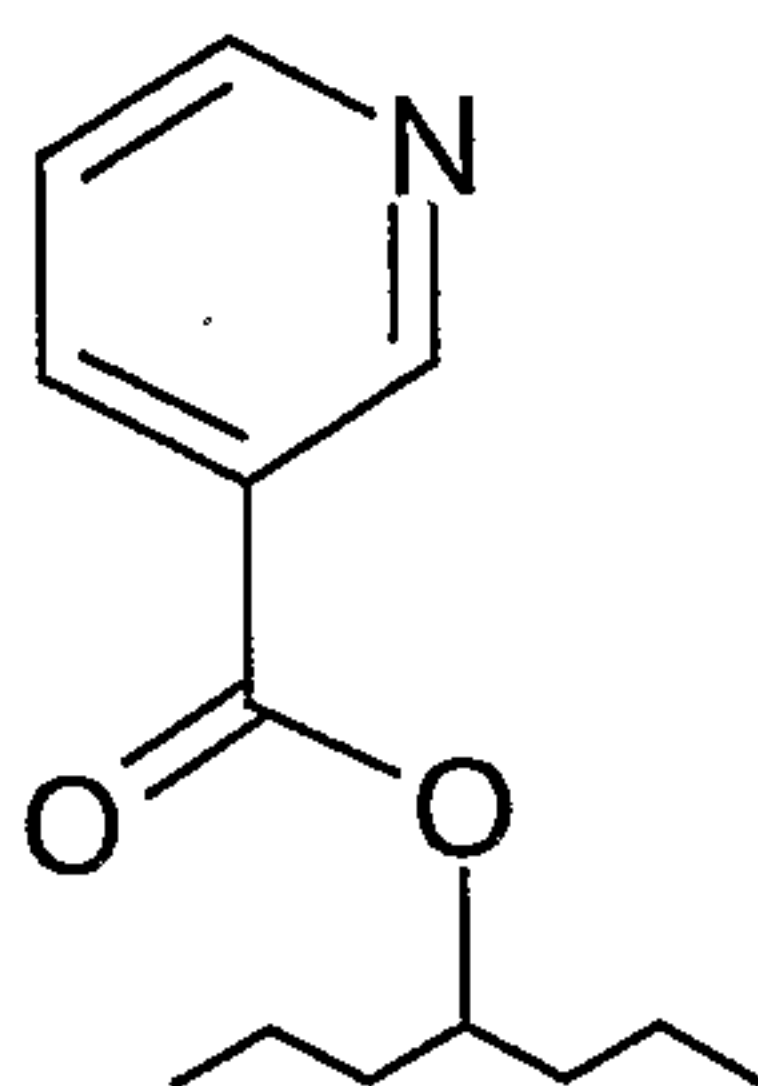
wherein the same applies to any W; or



wherein the same applies to any W:

wherein

#STR66# is



wherein

X can be O, S, C, CR¹³, or NR¹³;

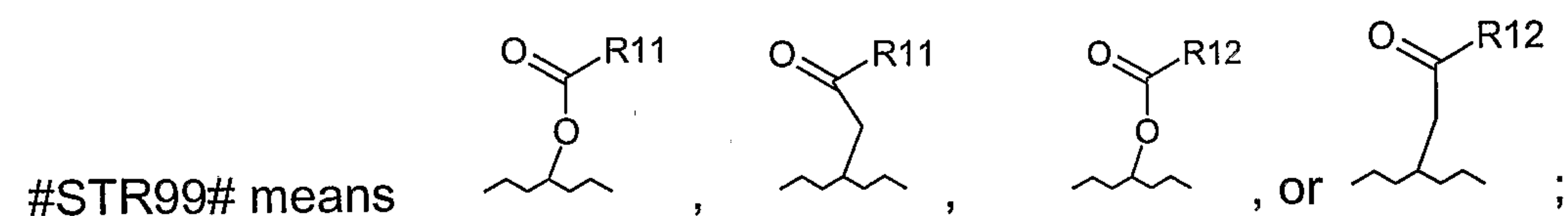
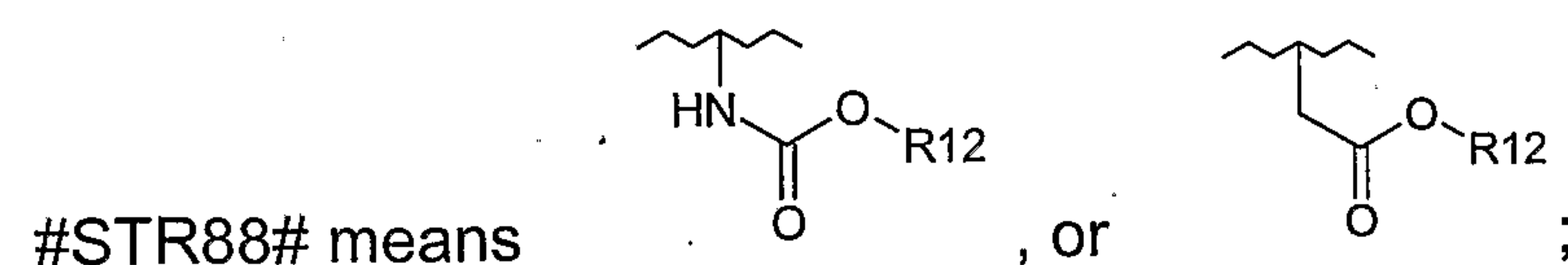
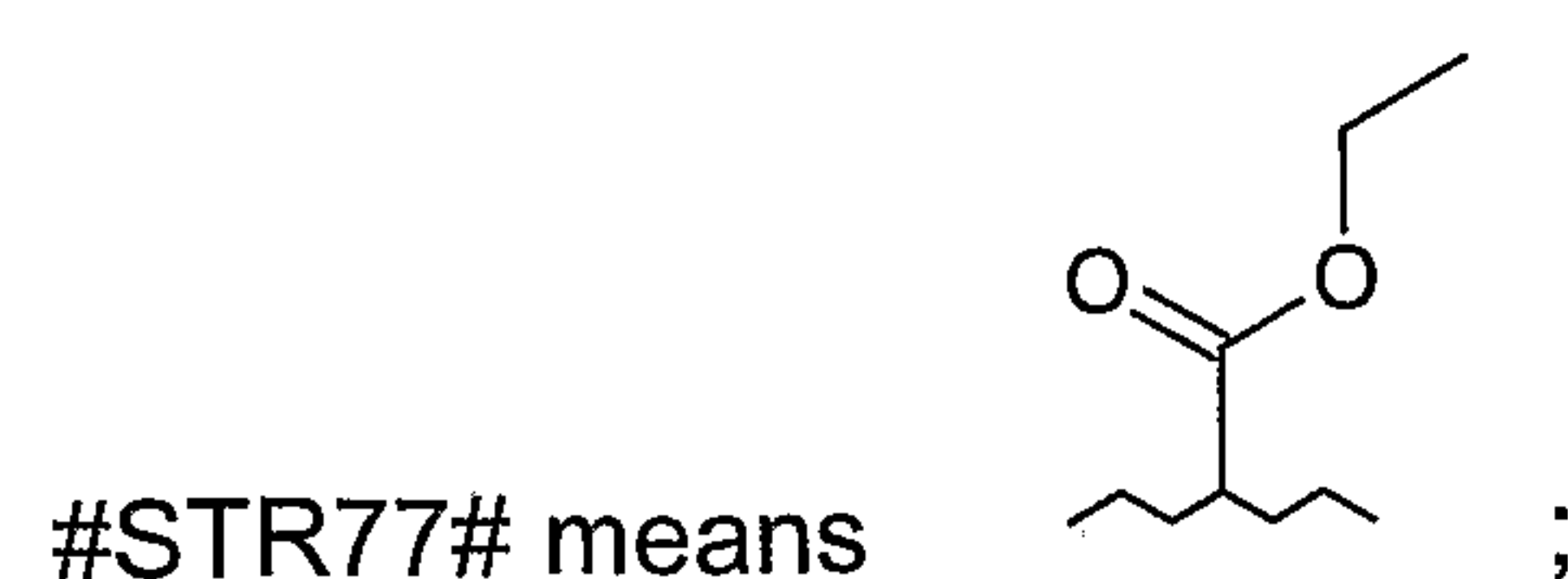
Y can be O, S, C, CR¹³, or NR¹³;

Z can be a single or a double bond

wherein

R¹³ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein



R¹¹ is pyridine, pyridazine, pyrimidine, pyrazine; and

R¹² is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof,

wherein said derivative is optionally substituted and optionally branched, and may

have one or more of the C atoms replaced by S, N or O;

with the proviso that;

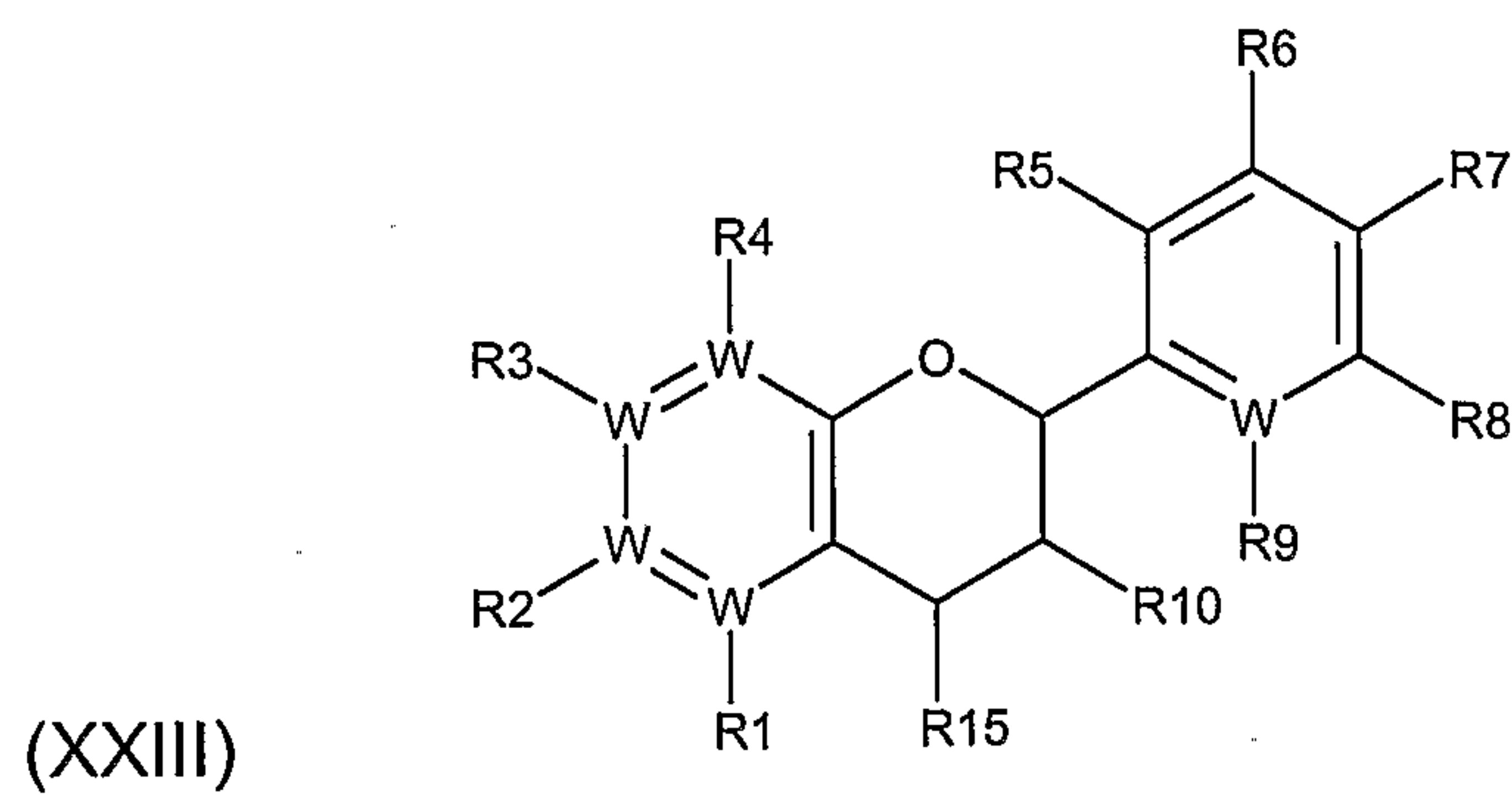
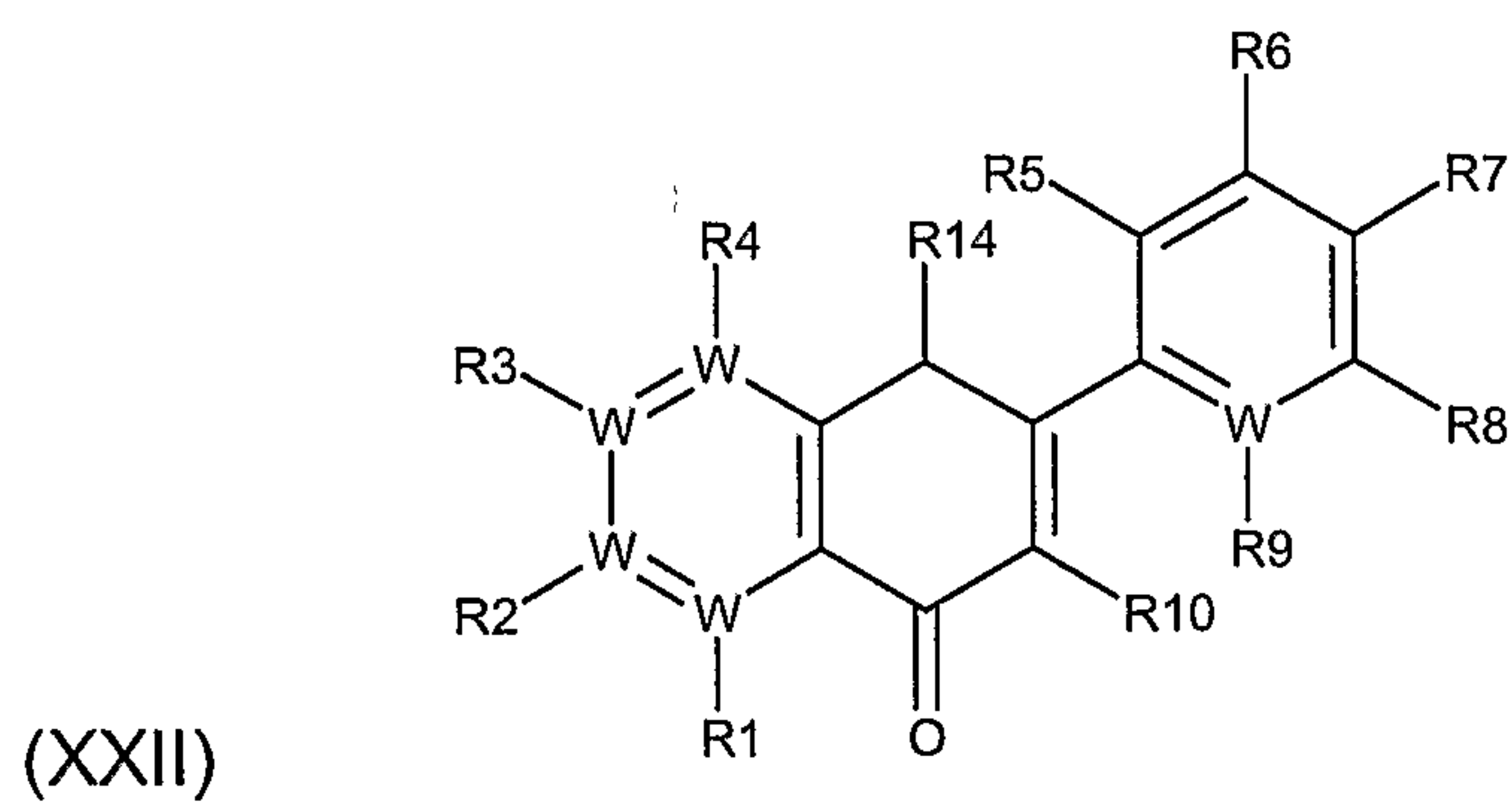
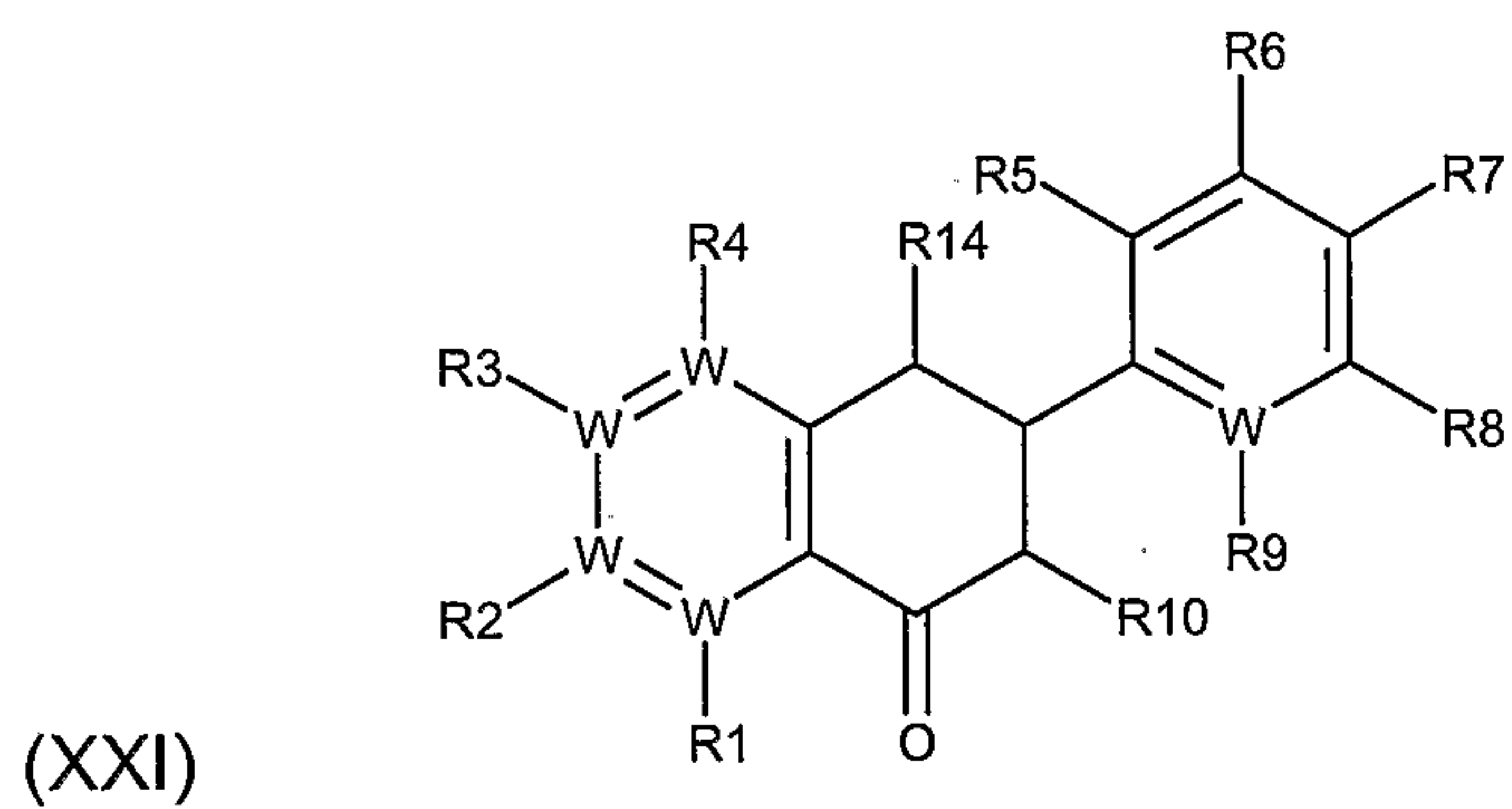
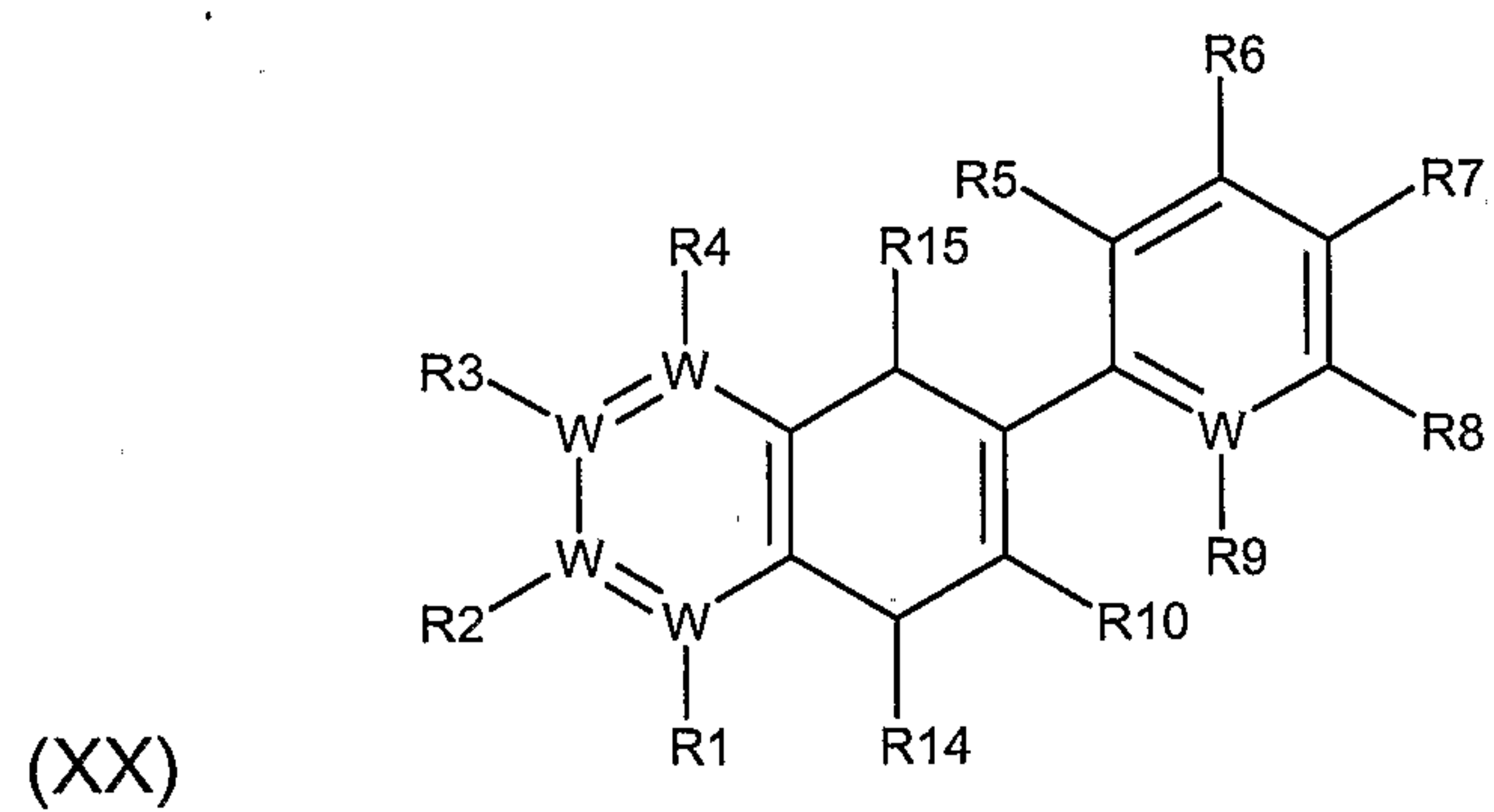
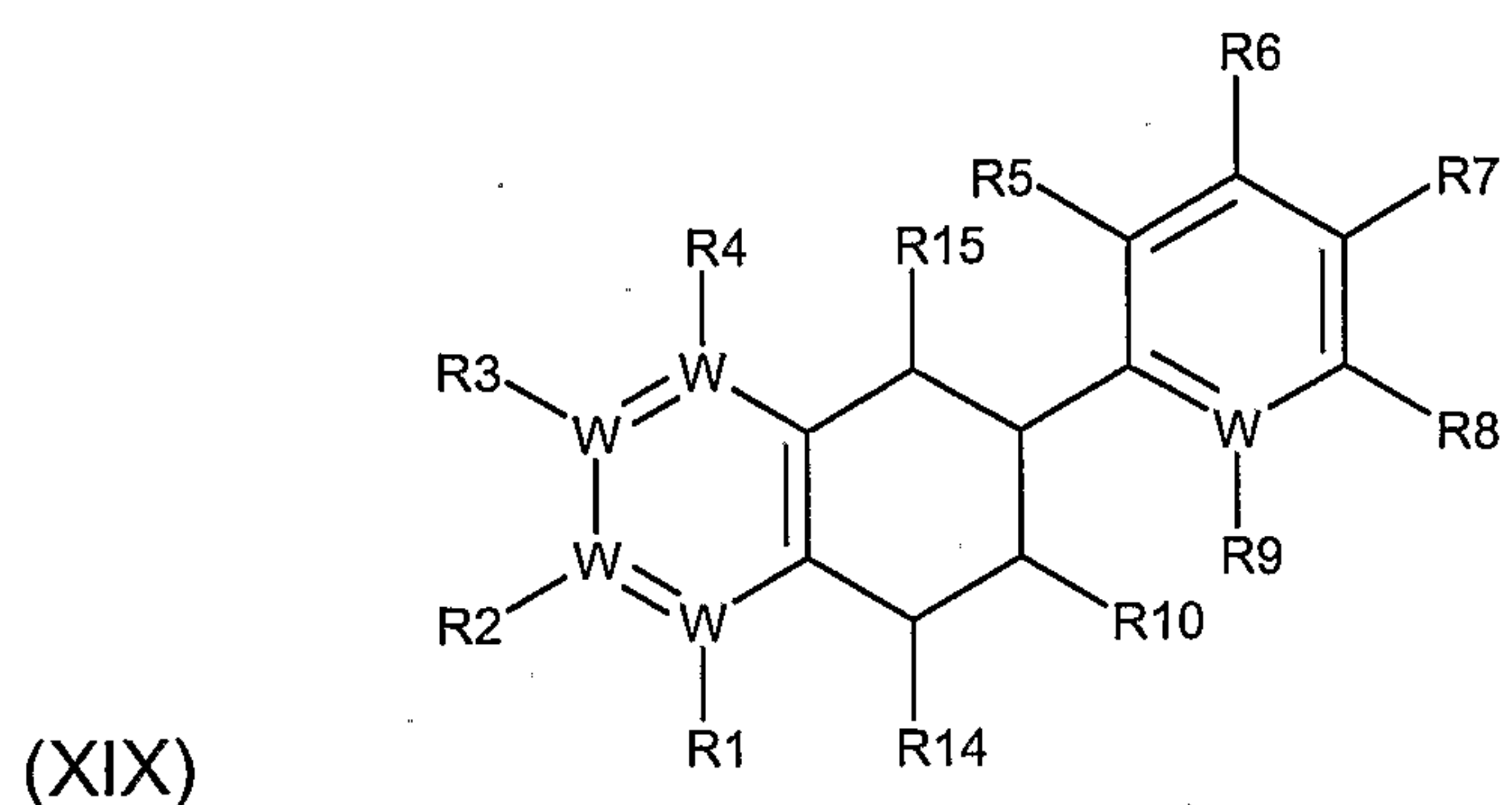
a) R⁷ is a hydroxyl or #STR66#, and

b) at least one W is a N, and

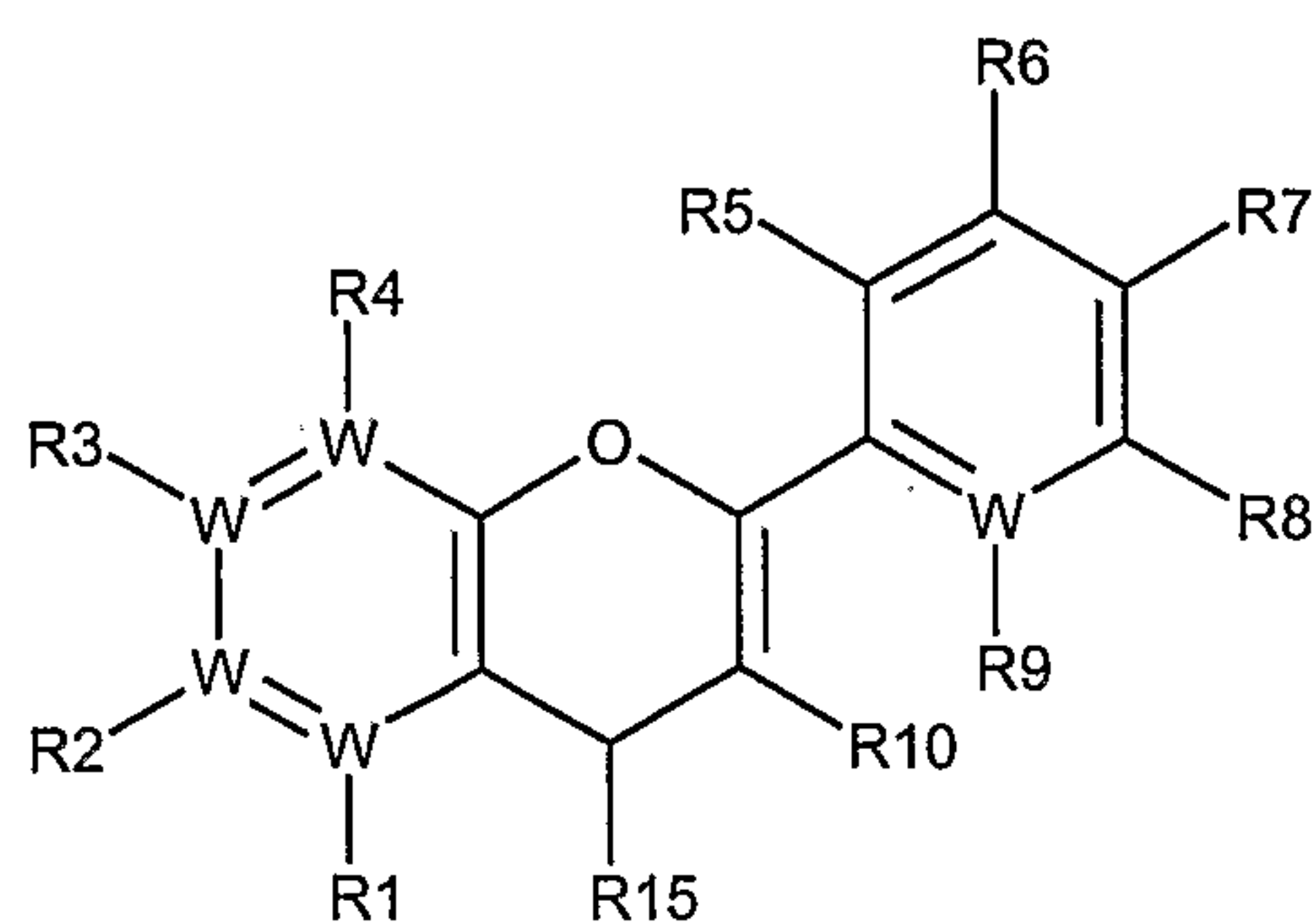
c) at least one of R¹-R¹⁰ is #STR77#, or #STR88#, or #STR99#, and

d) at least one of R¹-R¹⁰ is #STR66#.

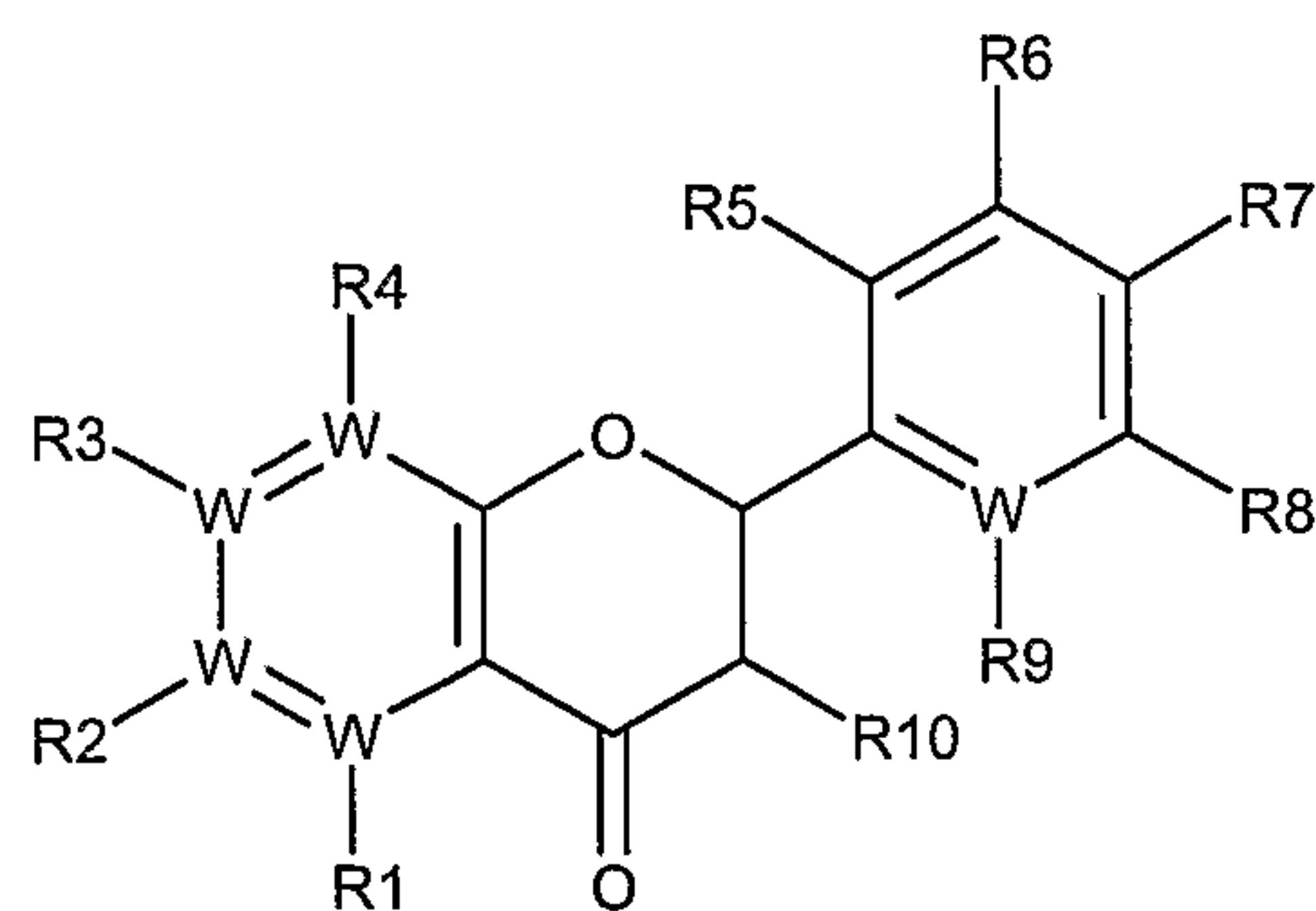
[087] Non-limiting examples of Formula 2 are provided below:



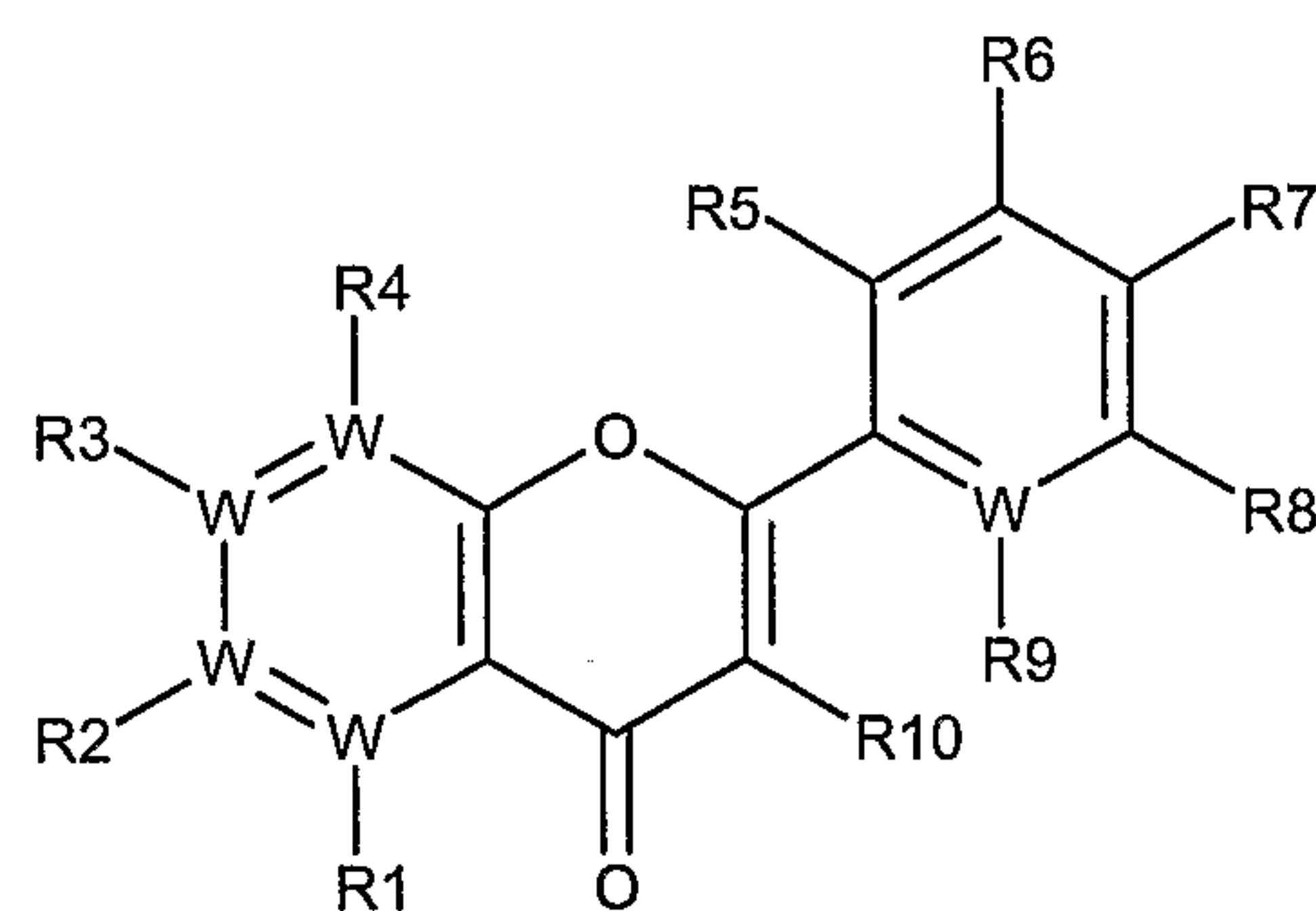
(XXIV)



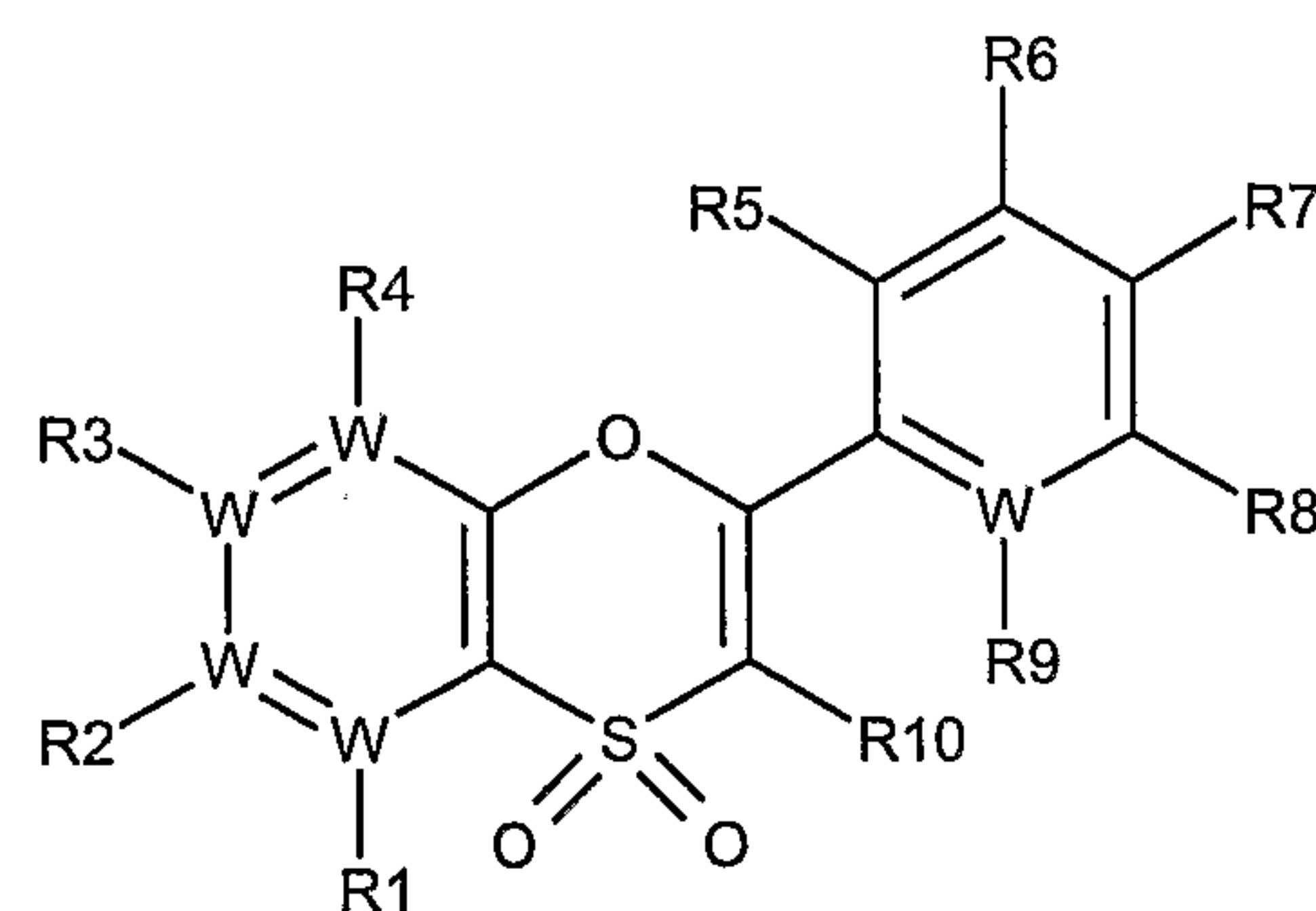
(XXV)



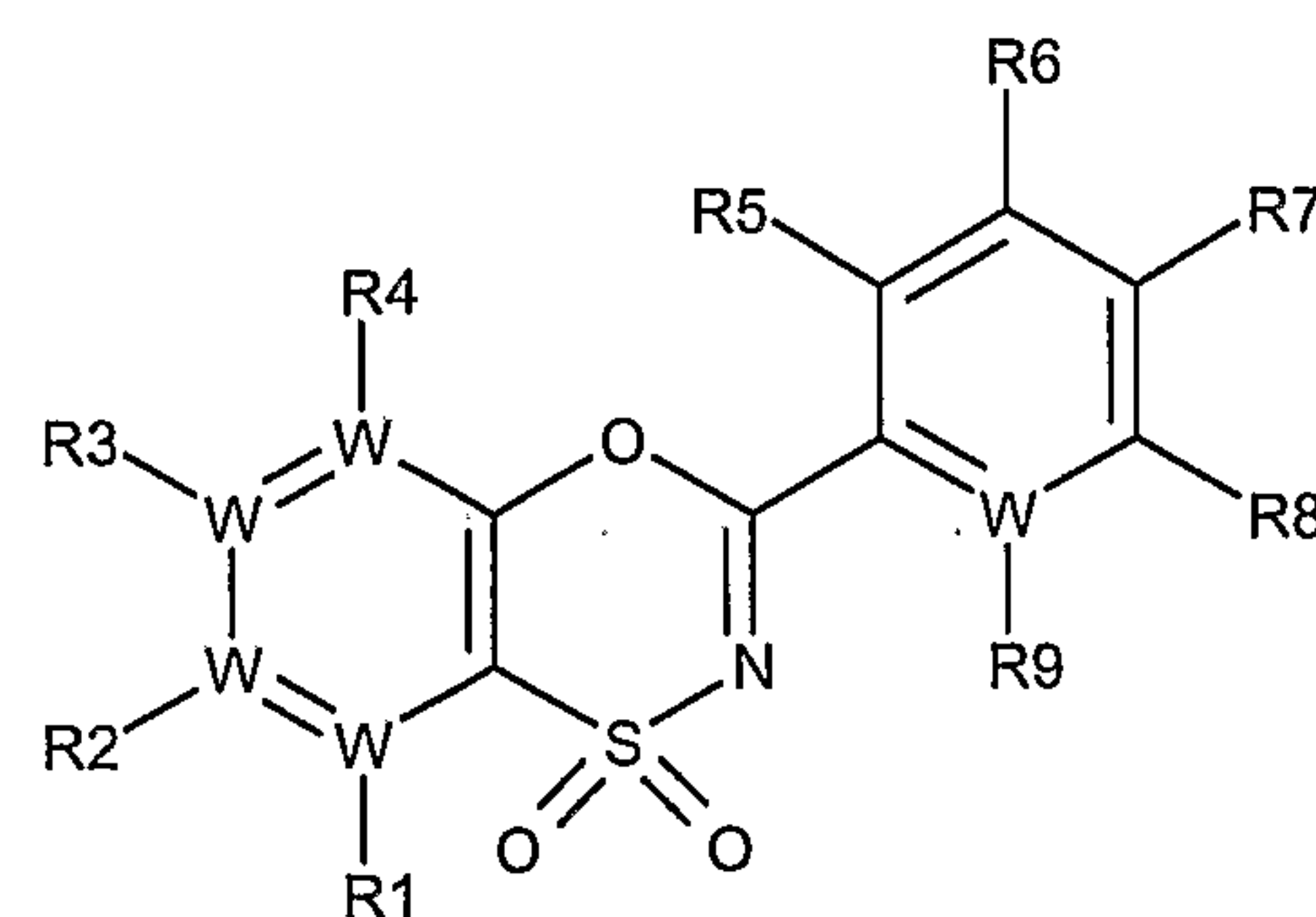
(XXVI)

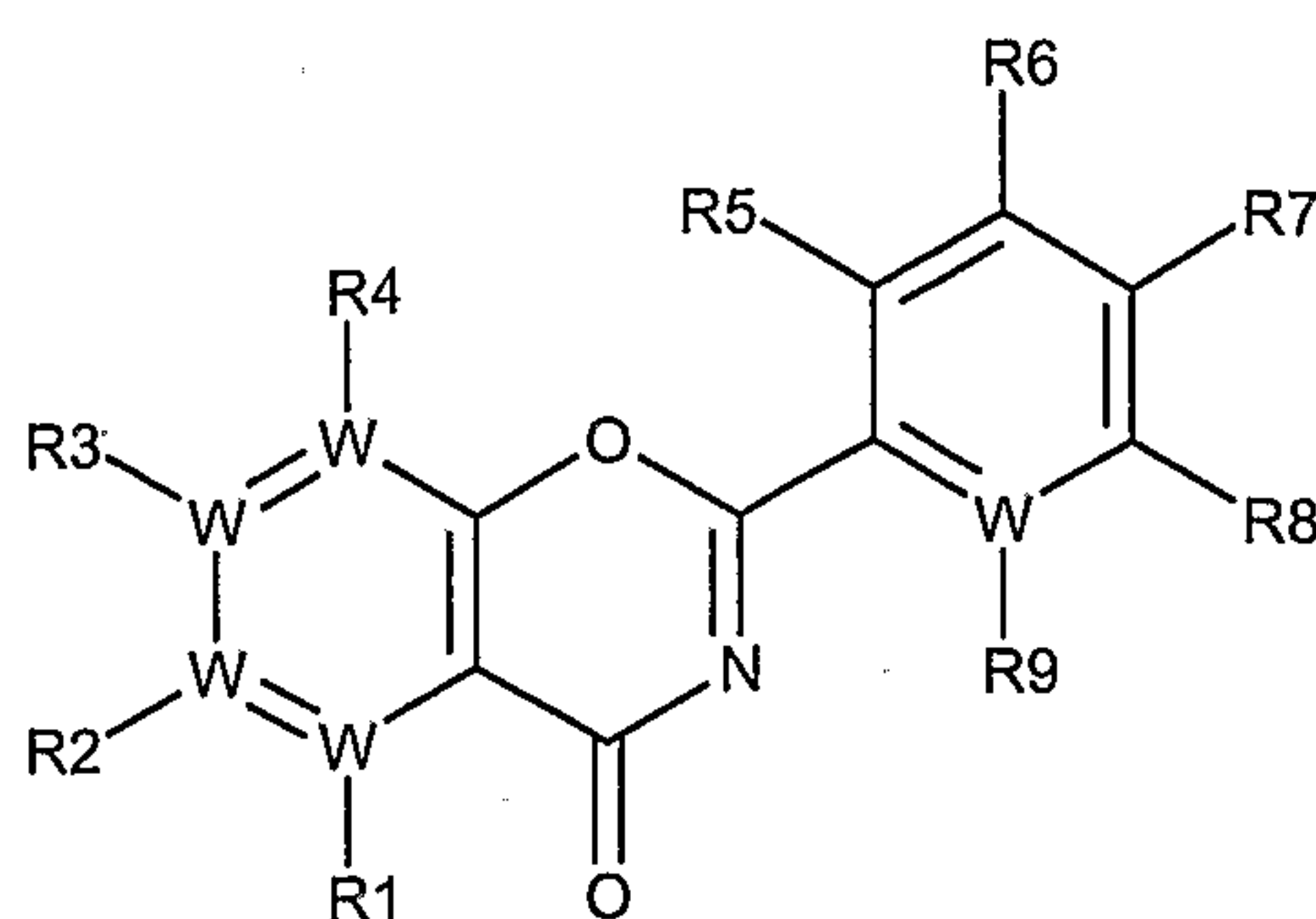


(XXVII)



(XXVIII)





(XXIX)

or pharmaceutically acceptable salts thereof,

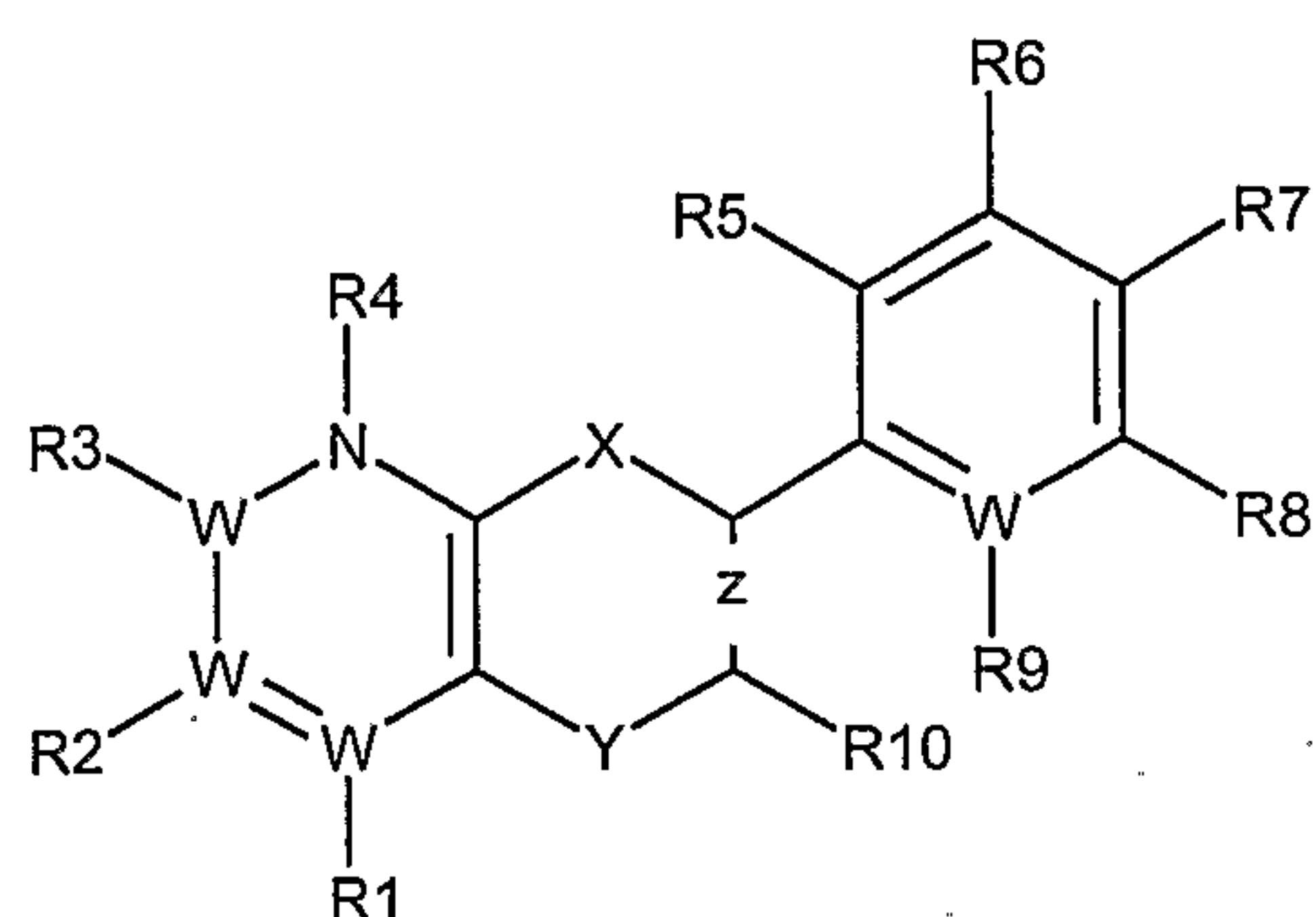
wherein

R1, R2, R3, R4, R5, R6, R8, R9, R10, R14 and R15 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

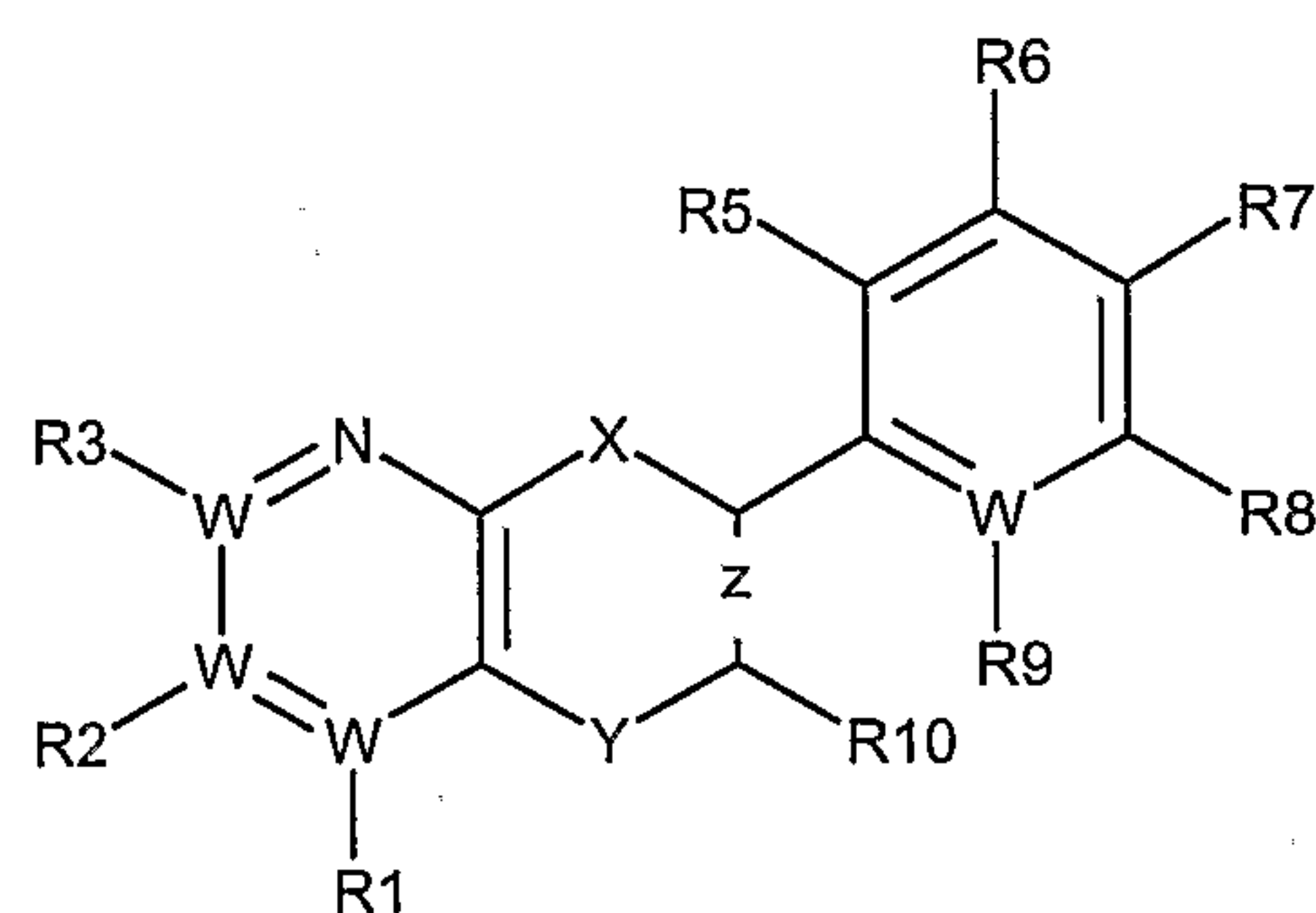
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 2:

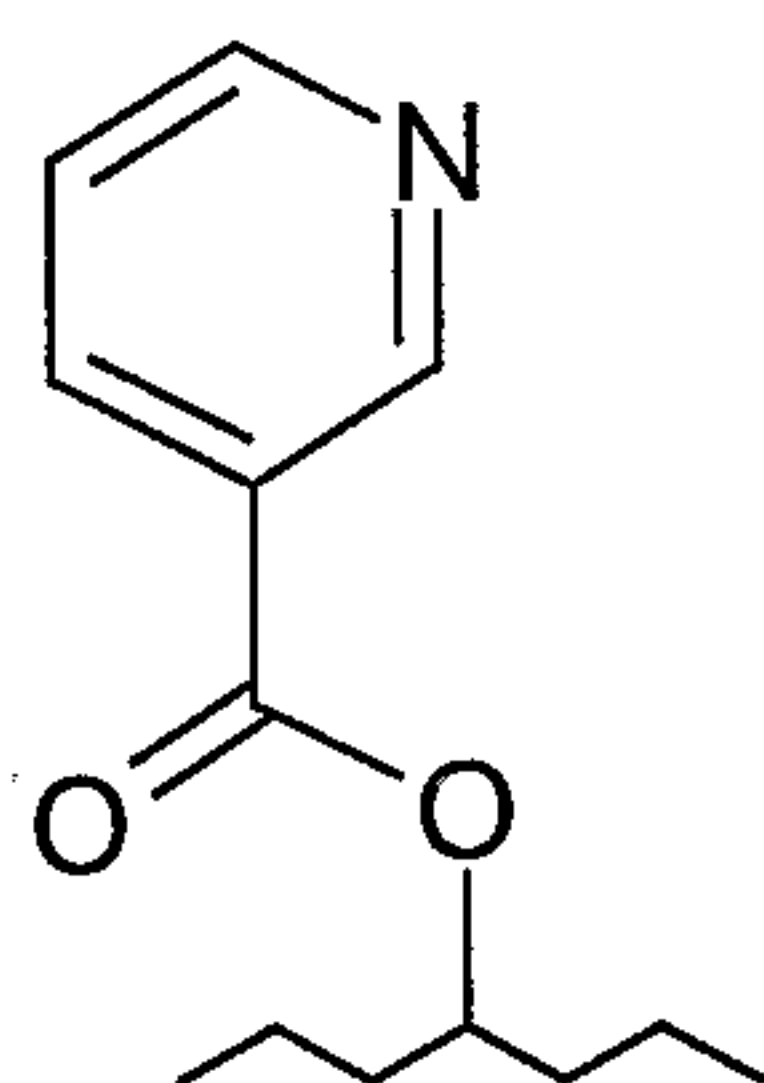


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

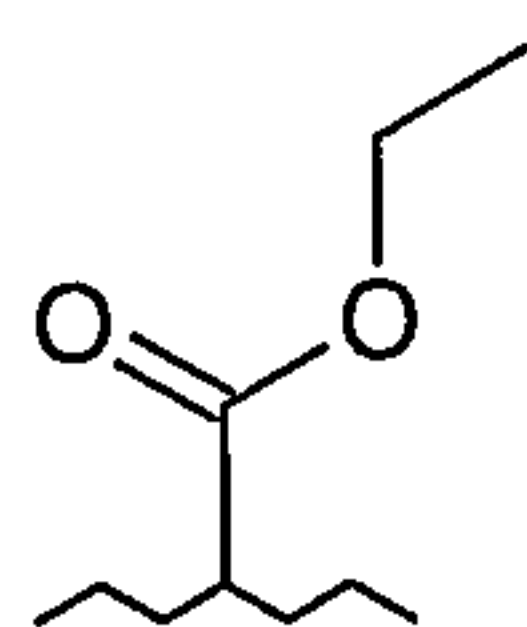
Z can be a single or a double bond

wherein

R₁₃ is #STR77#, #STR88#, #STR99#, or #STR100#,

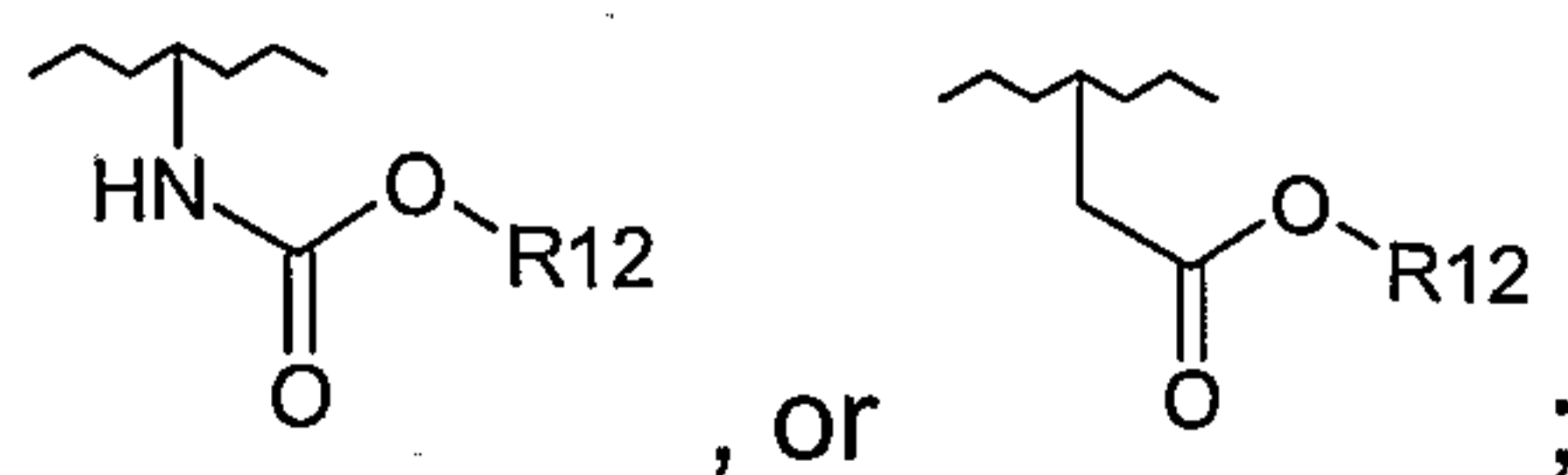
wherein

#STR77# means

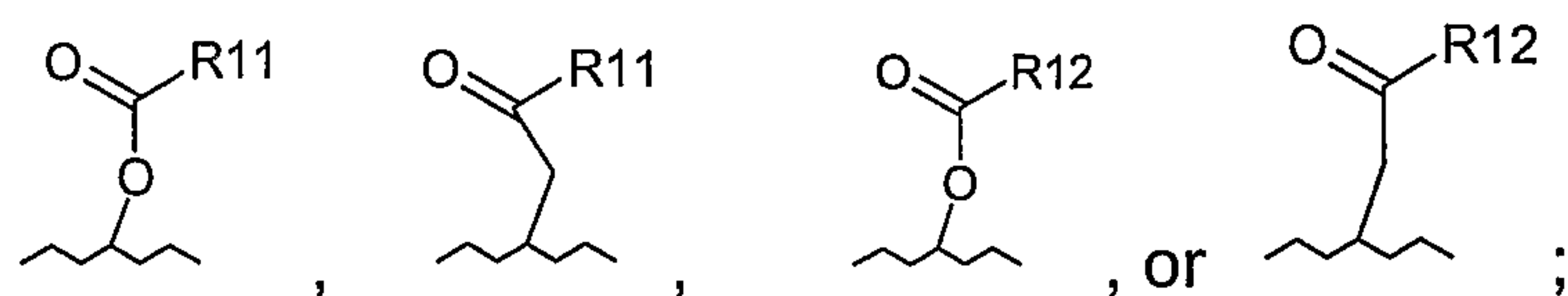


;

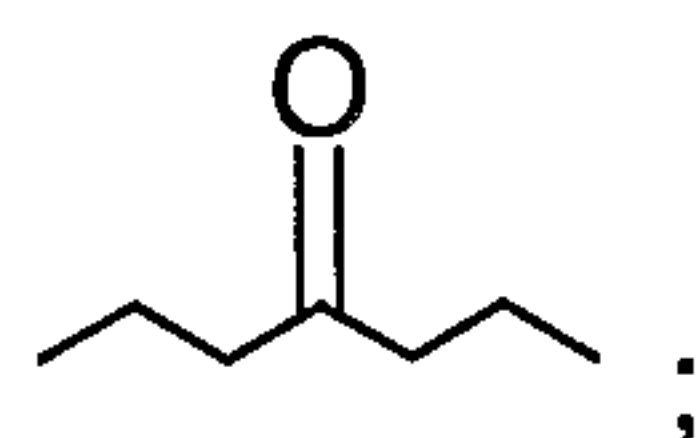
#STR88# means



#STR99# means



#STR100# means



R11 is pyridine, pyridazine, pyrimidine, pyrazine;

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 2 compounds have at least one of the following groups of provisos:

1) with the proviso that;

a) R7 is a hydroxyl; or

b) R7 is a hydroxyl and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;

e) at least one of R1-R10 is #STR66#.

2) with the proviso that;

a) at least one W is a N and R7 is a hydroxyl; or

b) at least one W is a N and R7 is a hydroxyl, and optionally;

c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;

d) at least one of R1-R10 is #STR66#.

3) with the proviso that;

- a) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R7 is a hydroxyl; or
- b) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R7 is a hydroxyl, and optionally;
- c) at least one W is a N, and/or;
- d) at least one of R1-R10 is #STR66#.

4) with the proviso that;

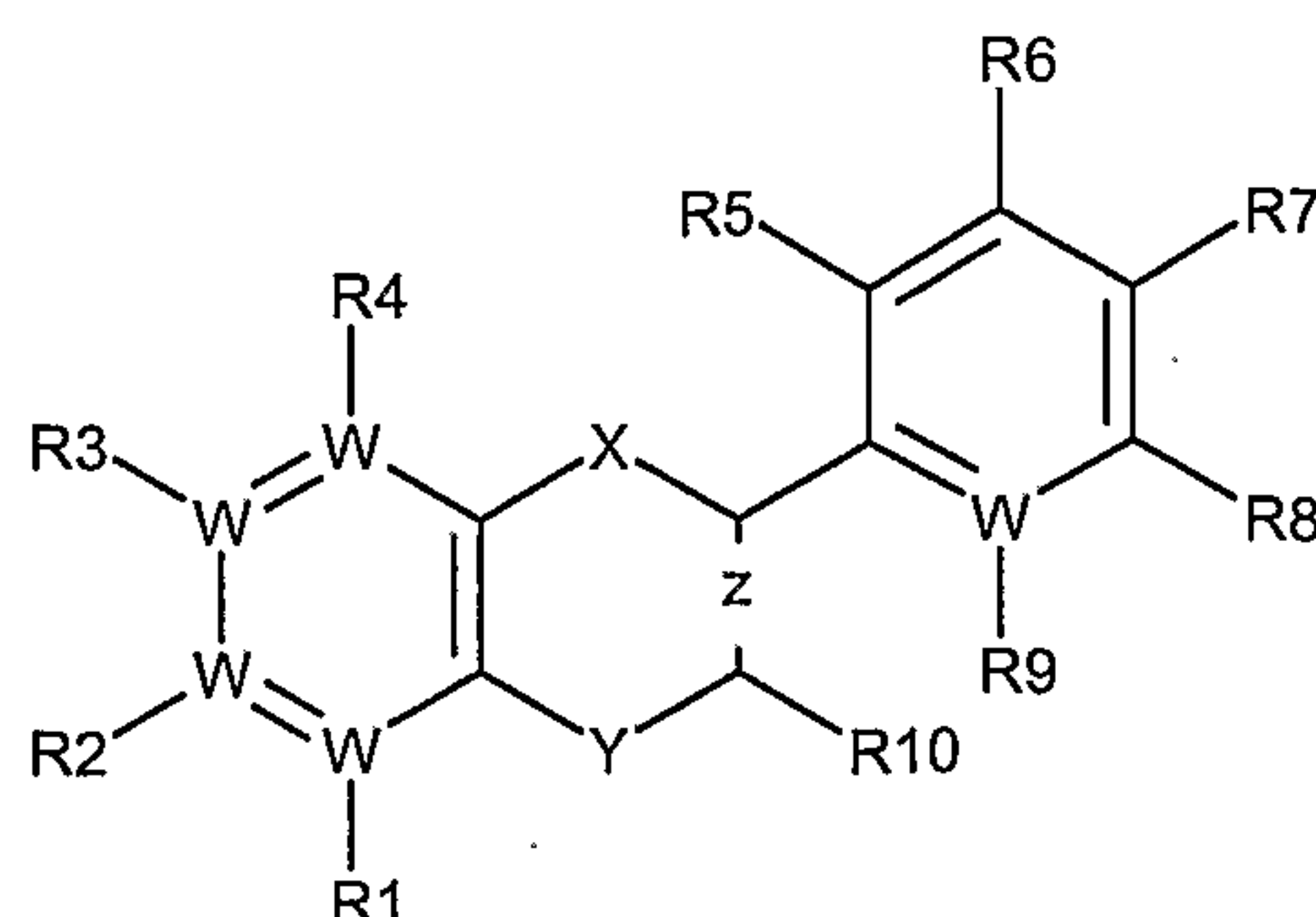
- a) R7 is a hydroxyl or #STR66# and if R7 is a hydroxyl at least one of (R1-R6 and R8-R10) is #STR66#; OR
- b) R7 is a hydroxyl or #STR66# and if R7 is a hydroxyl at least one of (R1-R6 and R8-R10) is #STR66# and optionally;
- c) at least one W is a N, and/or;
- d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#.

5) with the proviso that;

- a) R7 is a hydroxyl or #STR66#, and
- b) at least one W is a N, and
- c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and
- d) at least one of R1-R10 is #STR66#.

[088] Another alternative embodiment provides flavanoid compounds of

Formula 3:

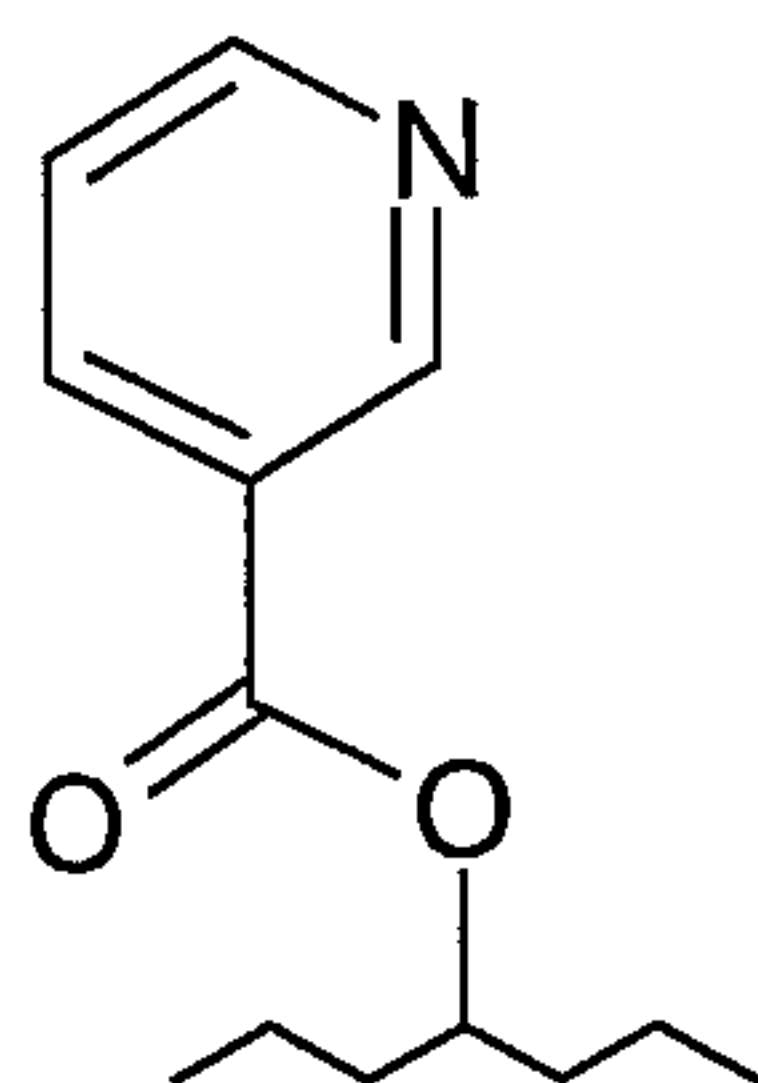


and a pharmaceutically acceptable salt thereof,

wherein

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucuronidate [the glucuronic (AKA glucuronic) acid conjugates],

wherein



#STR66# is

wherein

W can be C or N;

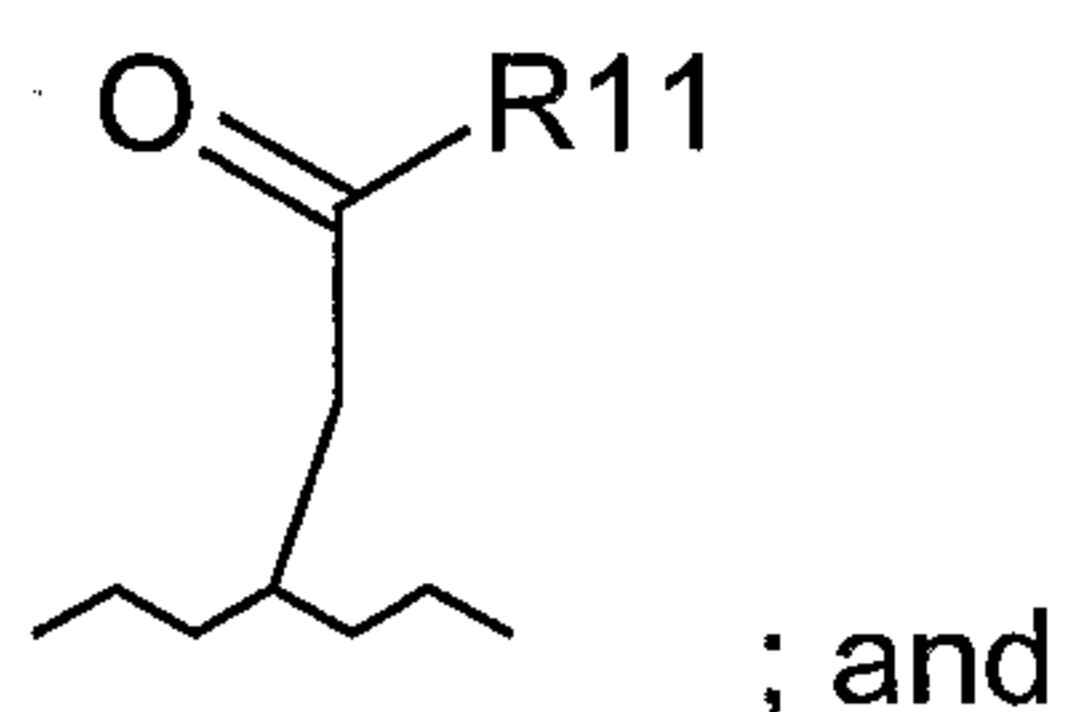
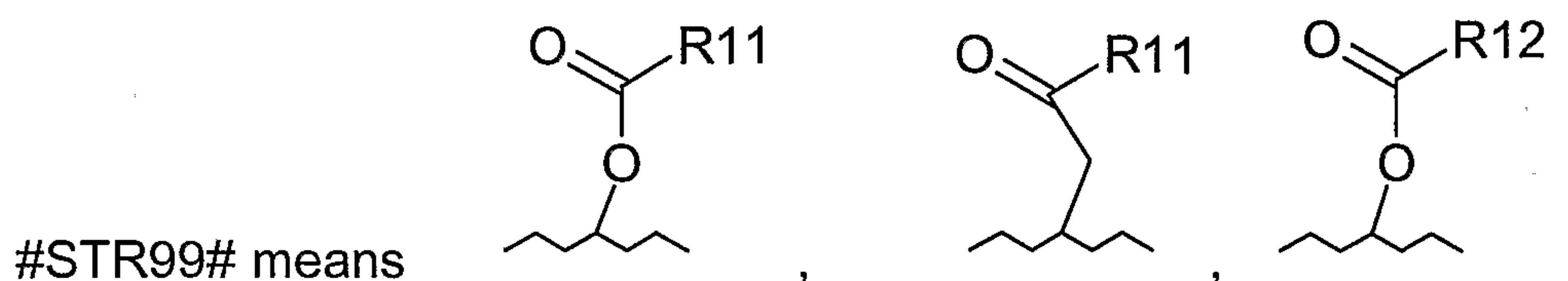
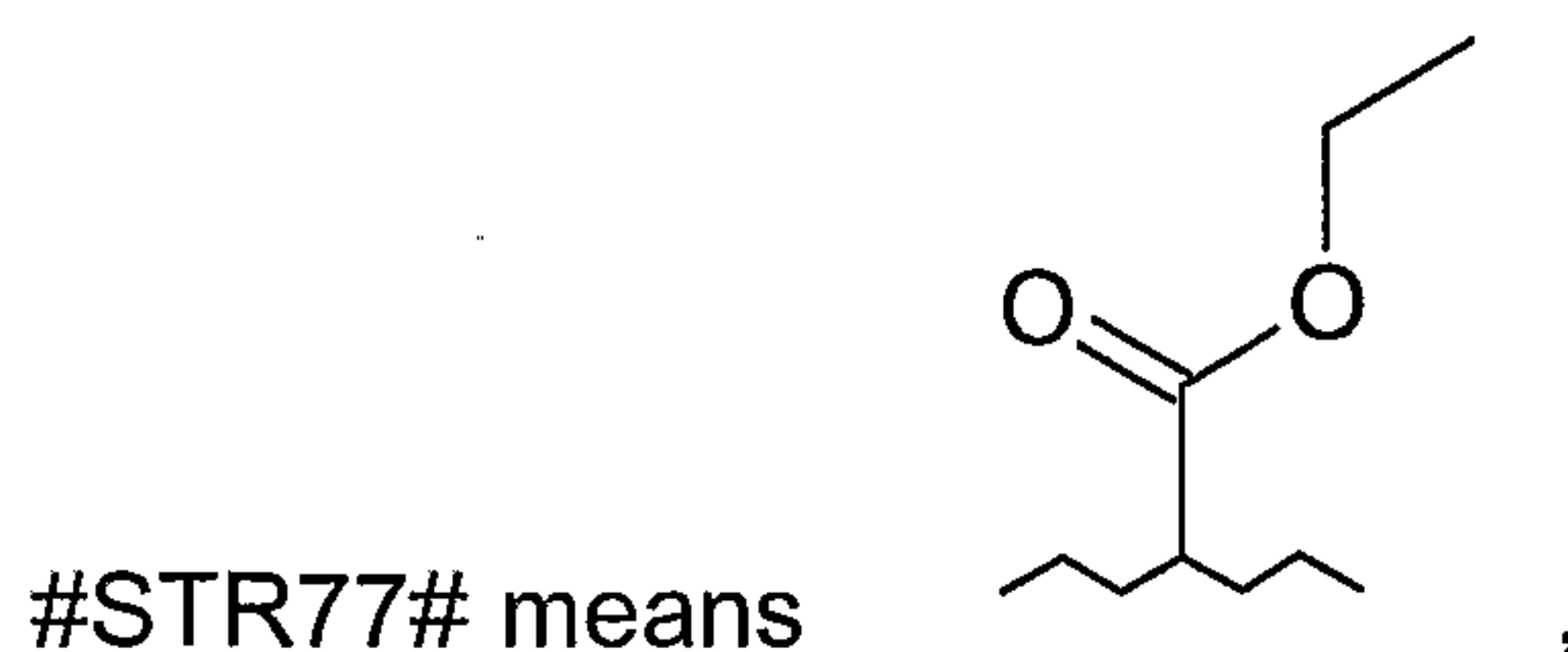
X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

Z can be a single or a double bond.

Wherein R₁₃ is #STR100#, #STR77# or #STR99#

Wherein



R11 is pyridine, pyridazine, pyrimidine, pyrazine;

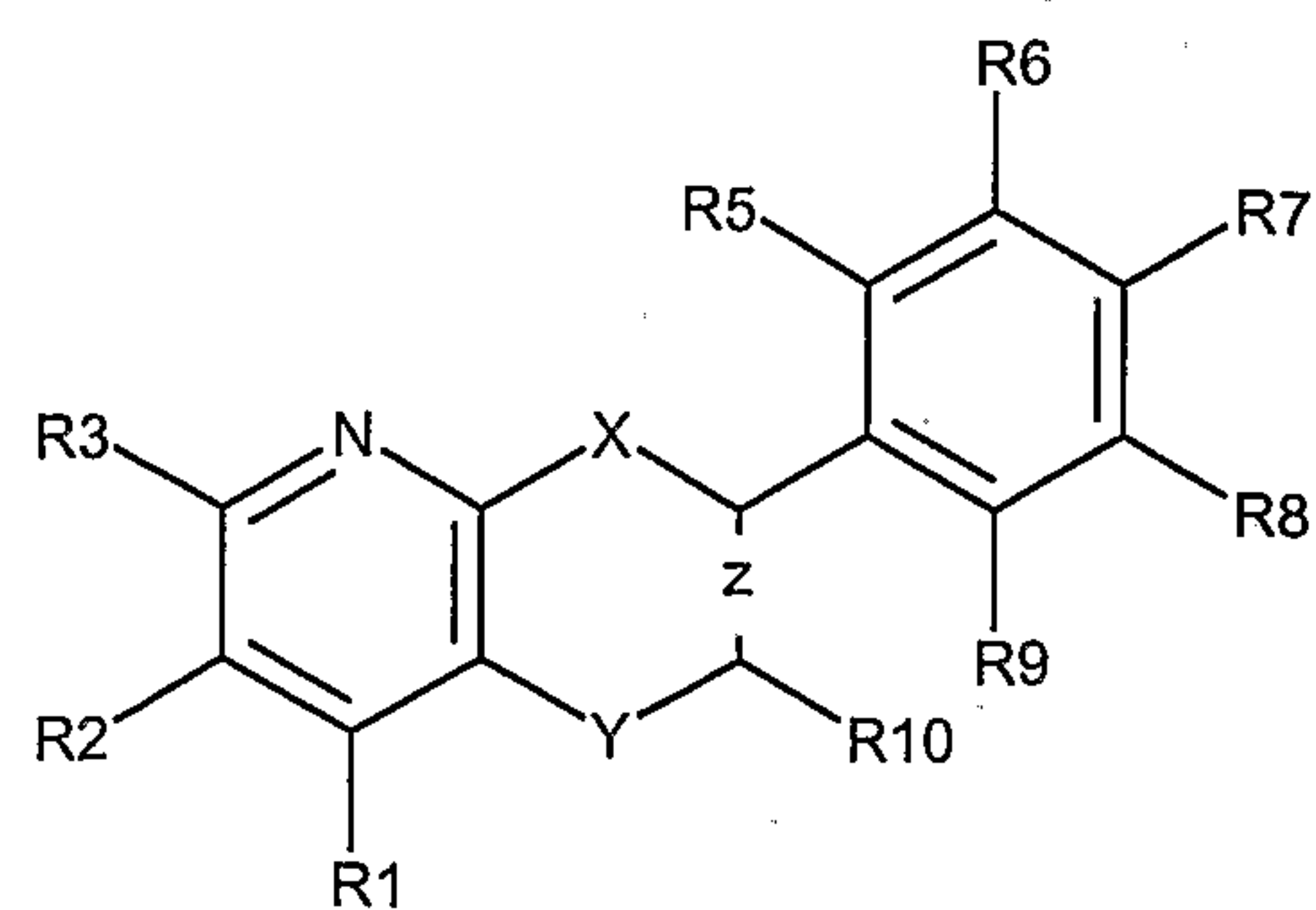
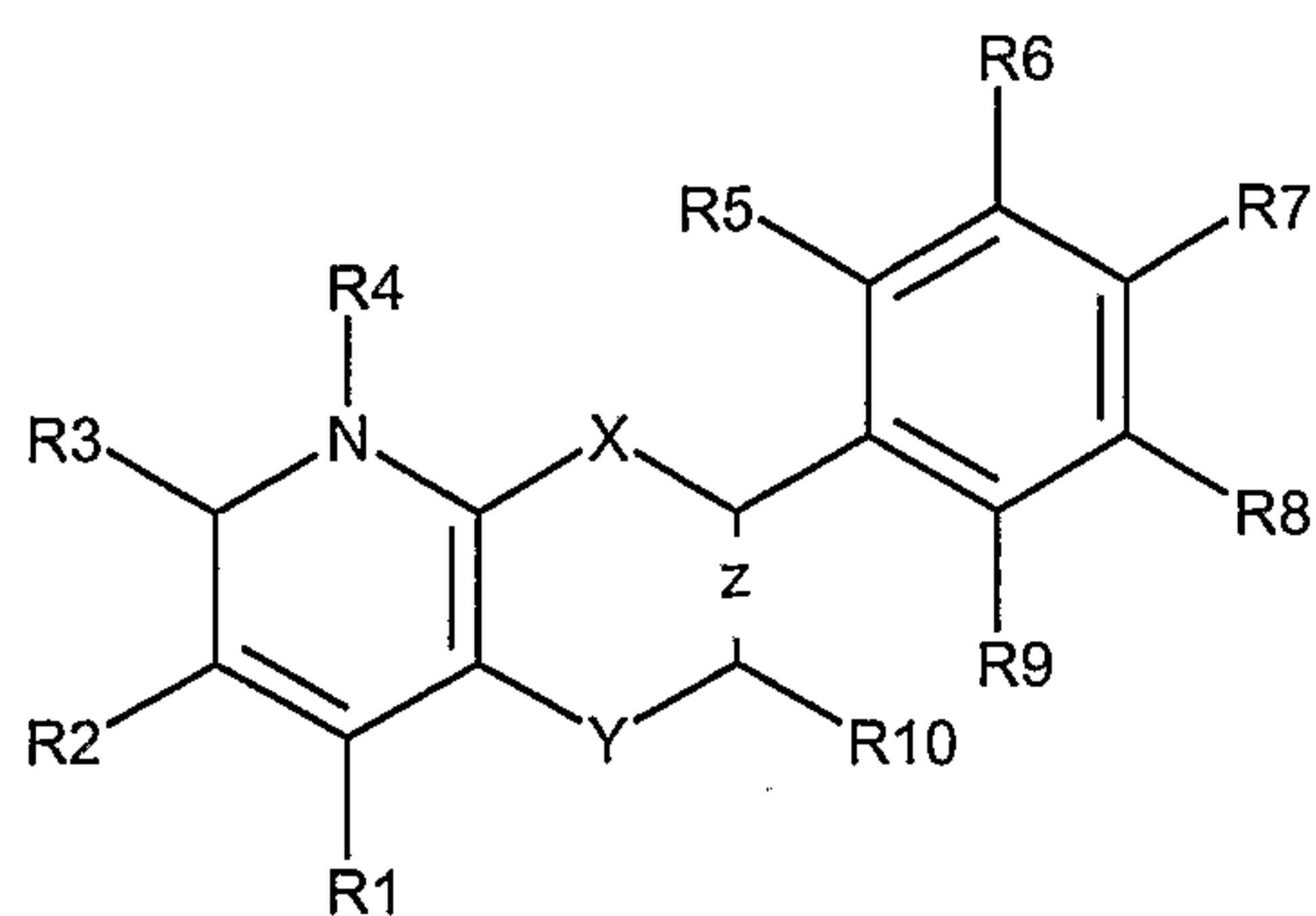
and R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

a) R7 is hydroxyl or #STR66# and at least one W is a N and optionally:

b) at least one of R1-R10 is #STR66#;

[089] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 3:

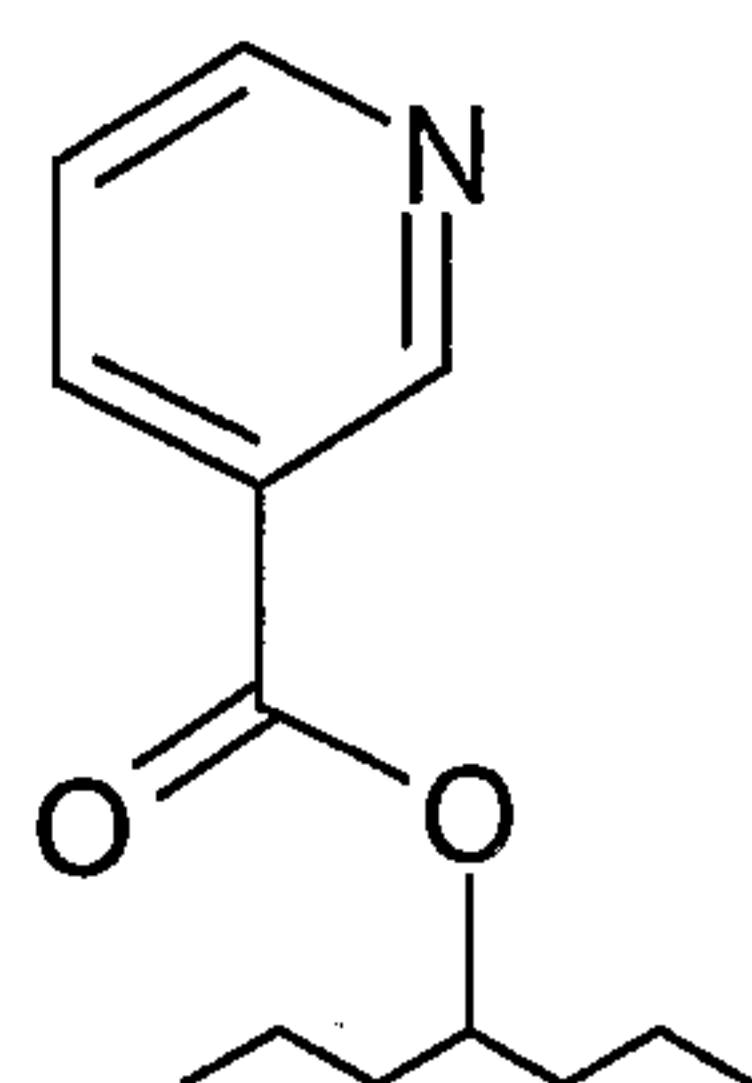


and a pharmaceutically acceptable salt thereof,

wherein

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates],

wherein



#STR66# means

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

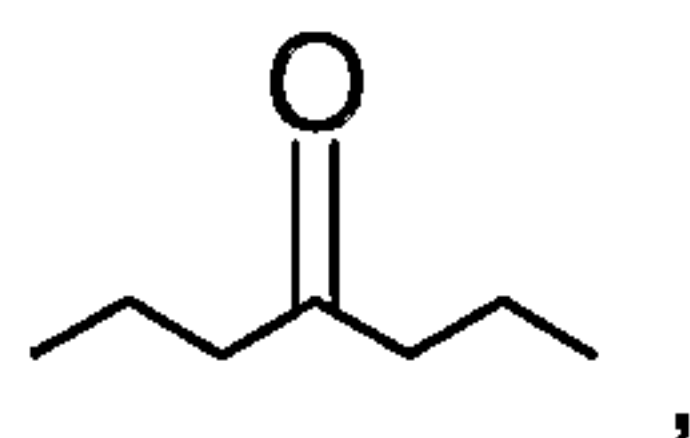
Y can be O, S, C, CR₁₃, or NR₁₃;

Z can be a single or a double bond

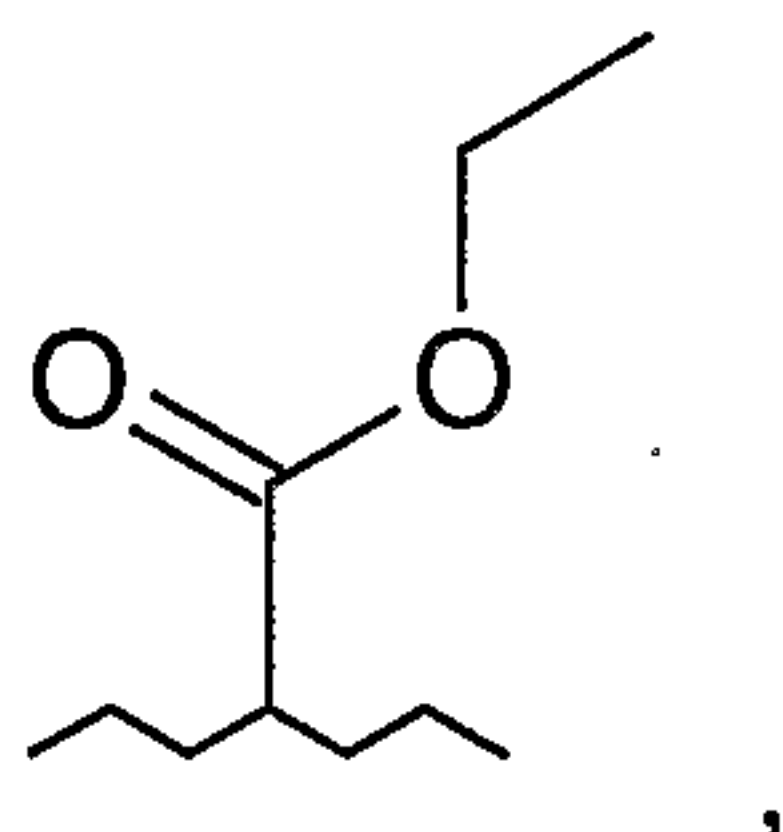
Wherein R₁₃ is #STR100#, #STR77# or #STR99#

Wherein:

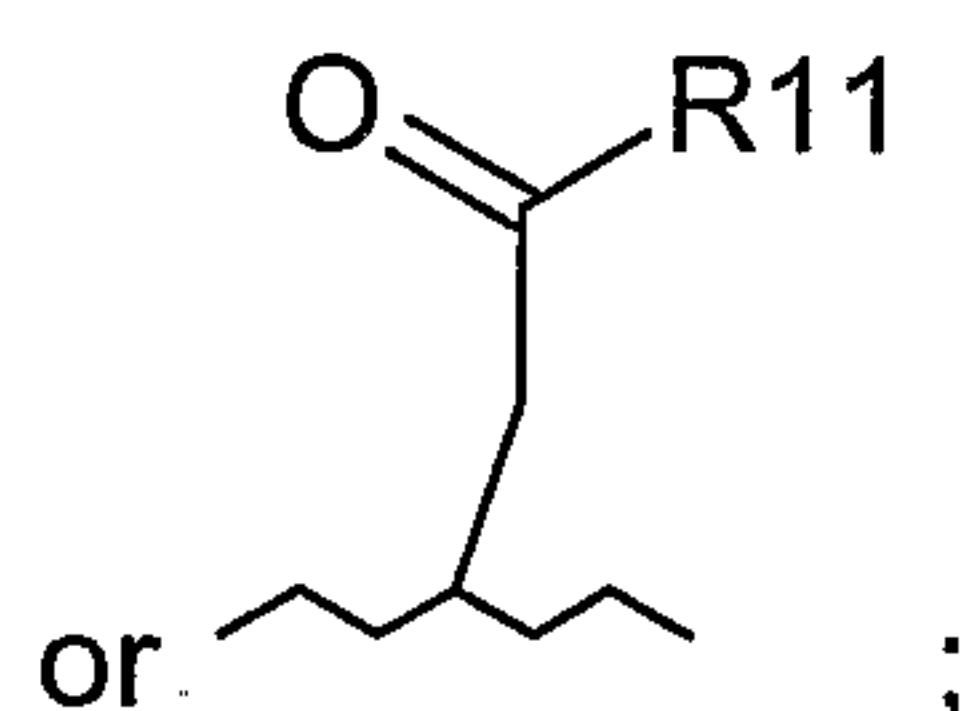
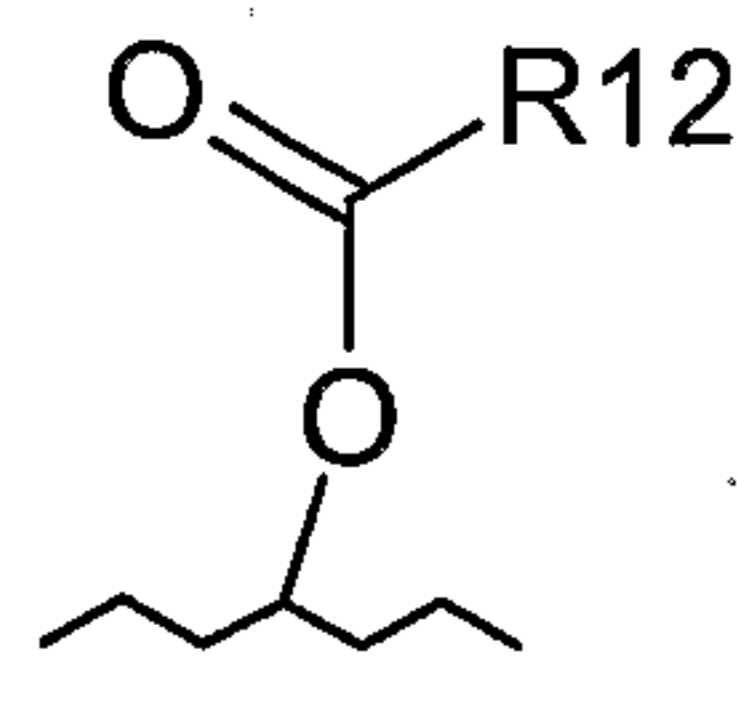
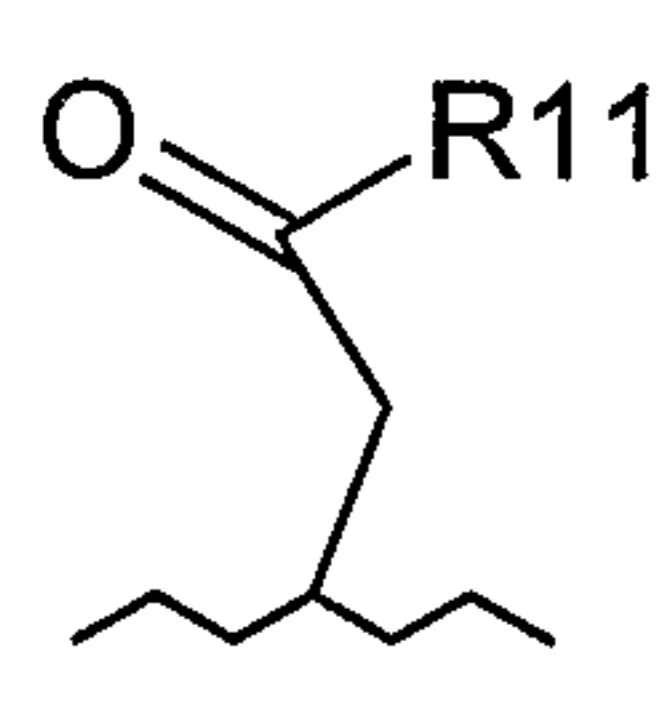
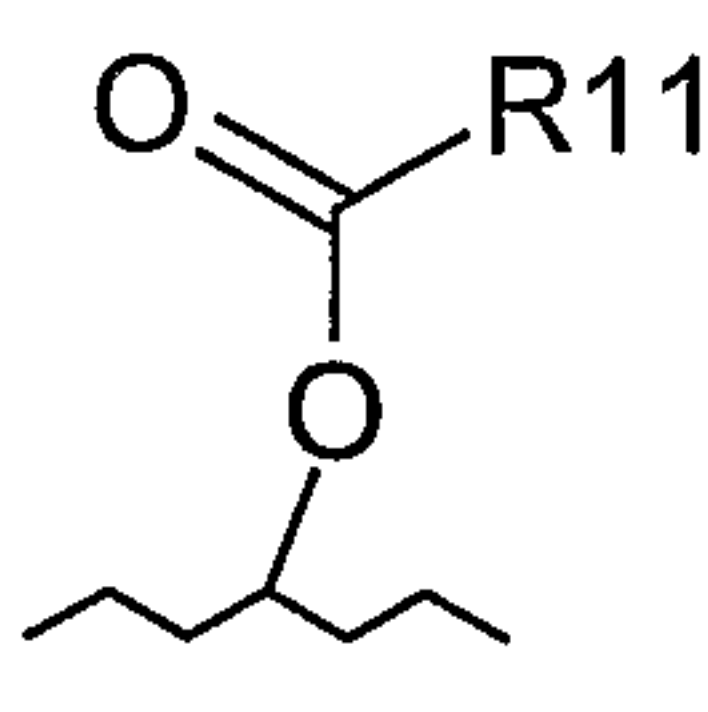
#STR100# means



#STR77# means



#STR99# means



R11 is pyridine, pyridazine, pyrimidine, pyrazine;

and R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

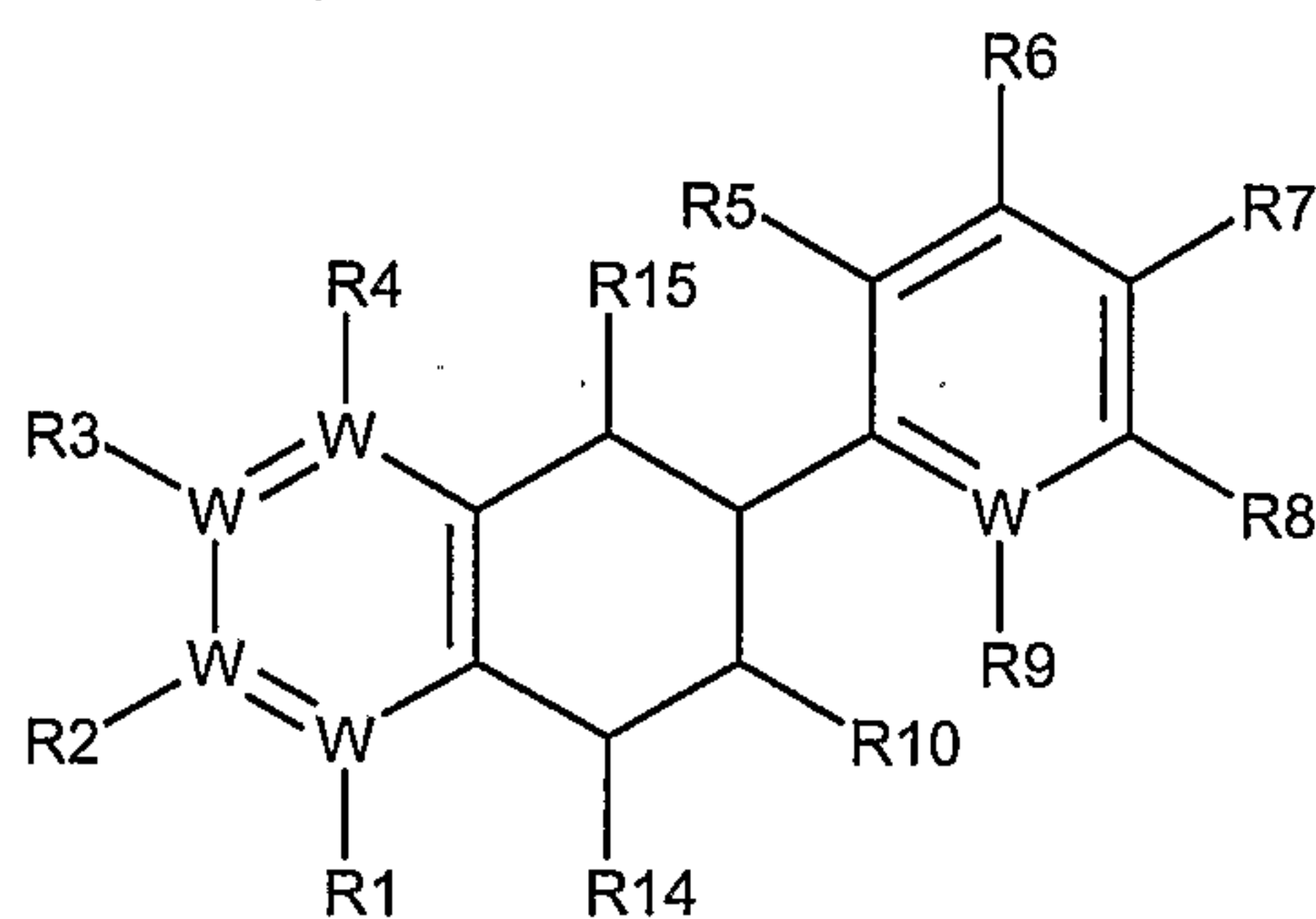
with the proviso that

a) R7 is a hydroxyl and at least one of R1-10 is #STR66#; and /or

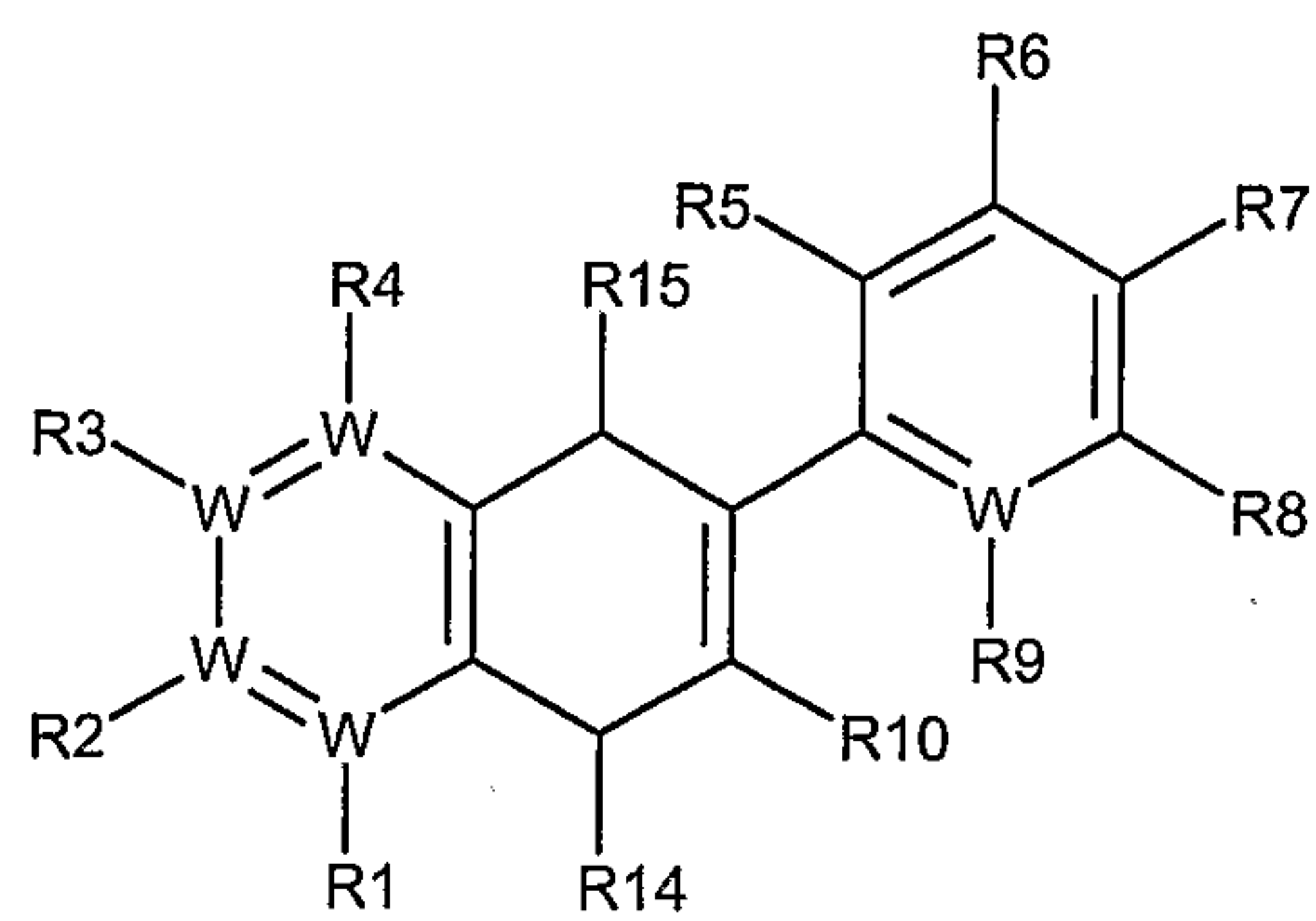
b) R7 is #STR66#.

[090] Non-limiting examples of Formula 3 include

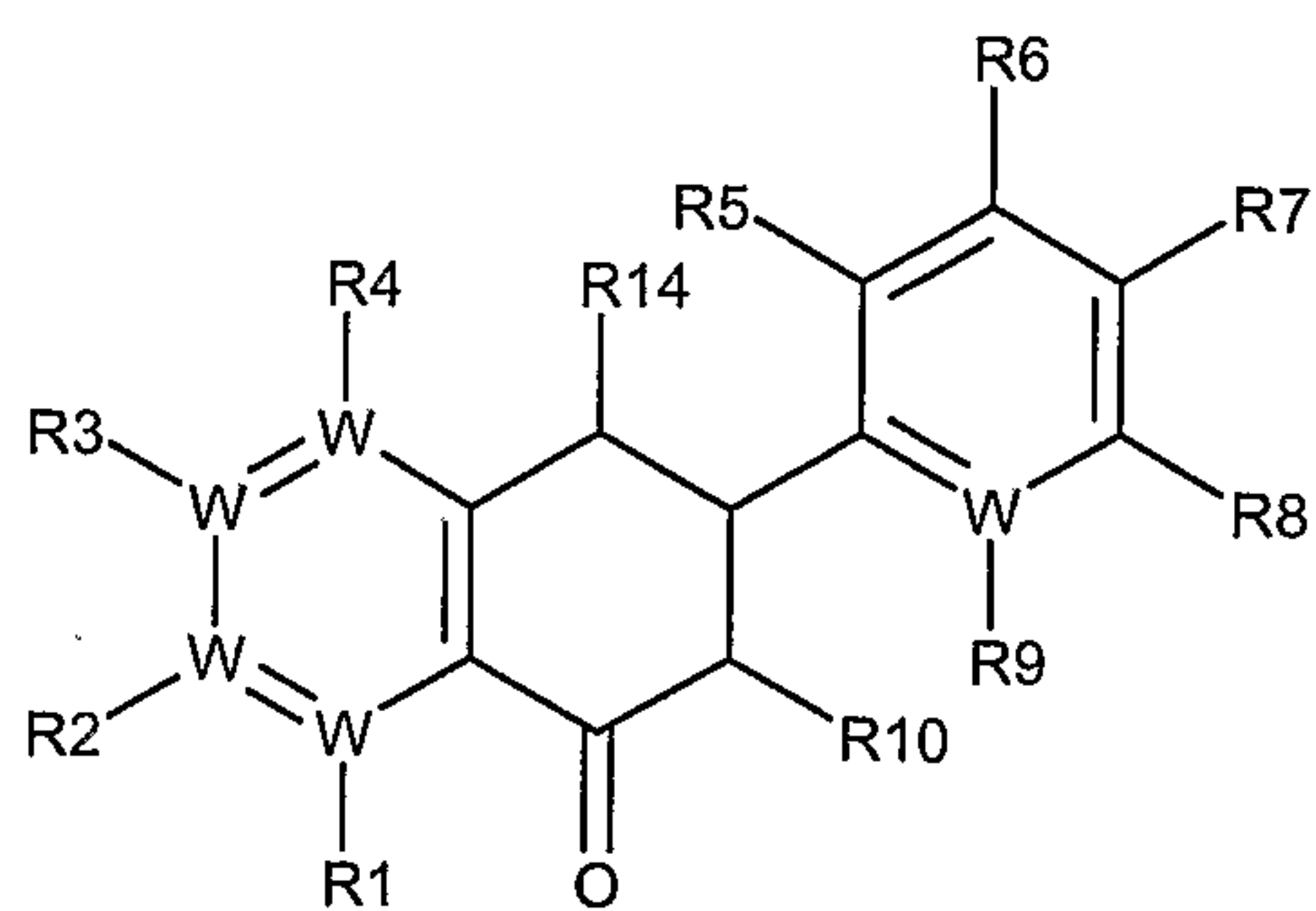
(XXX)



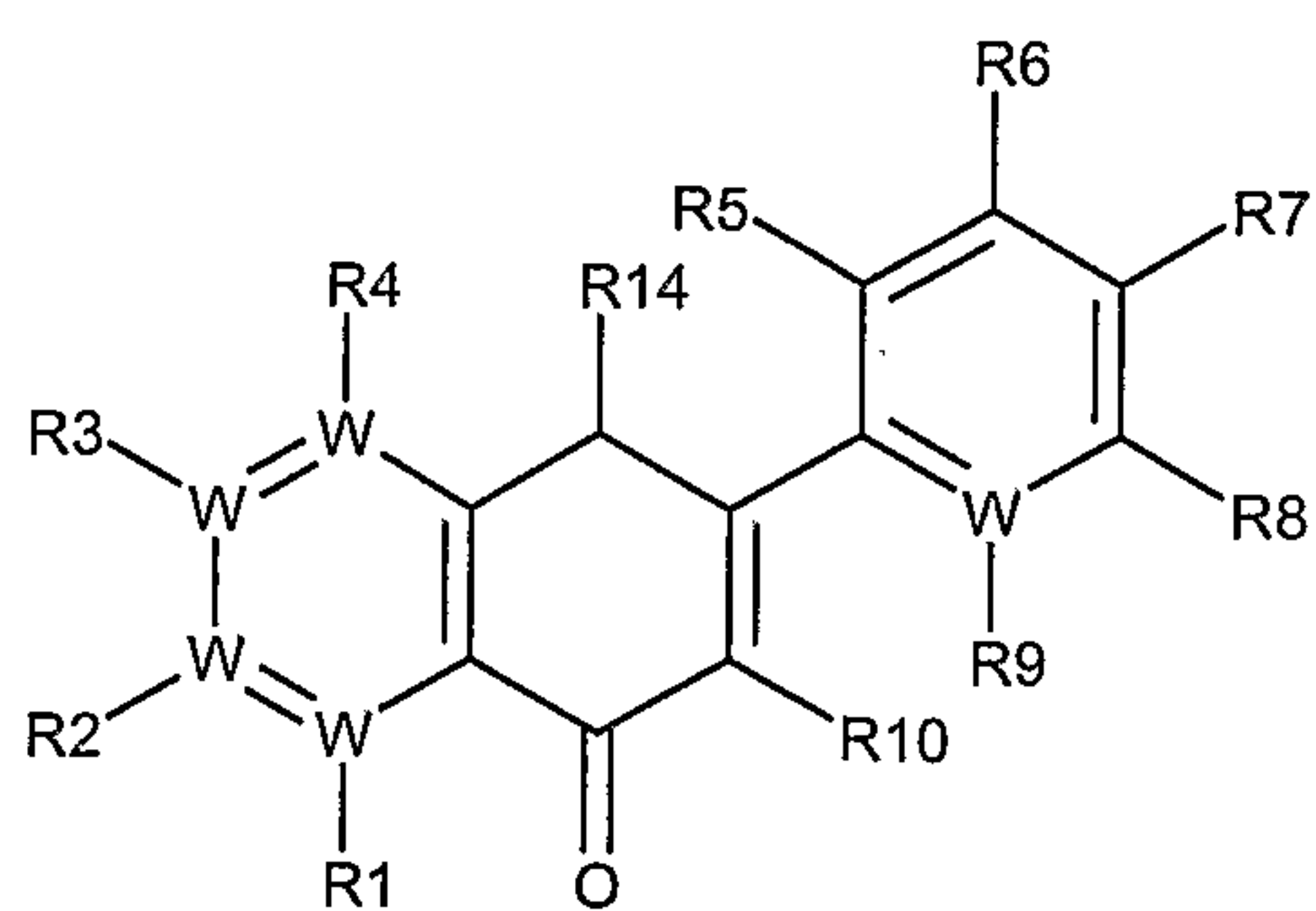
(XXXI)



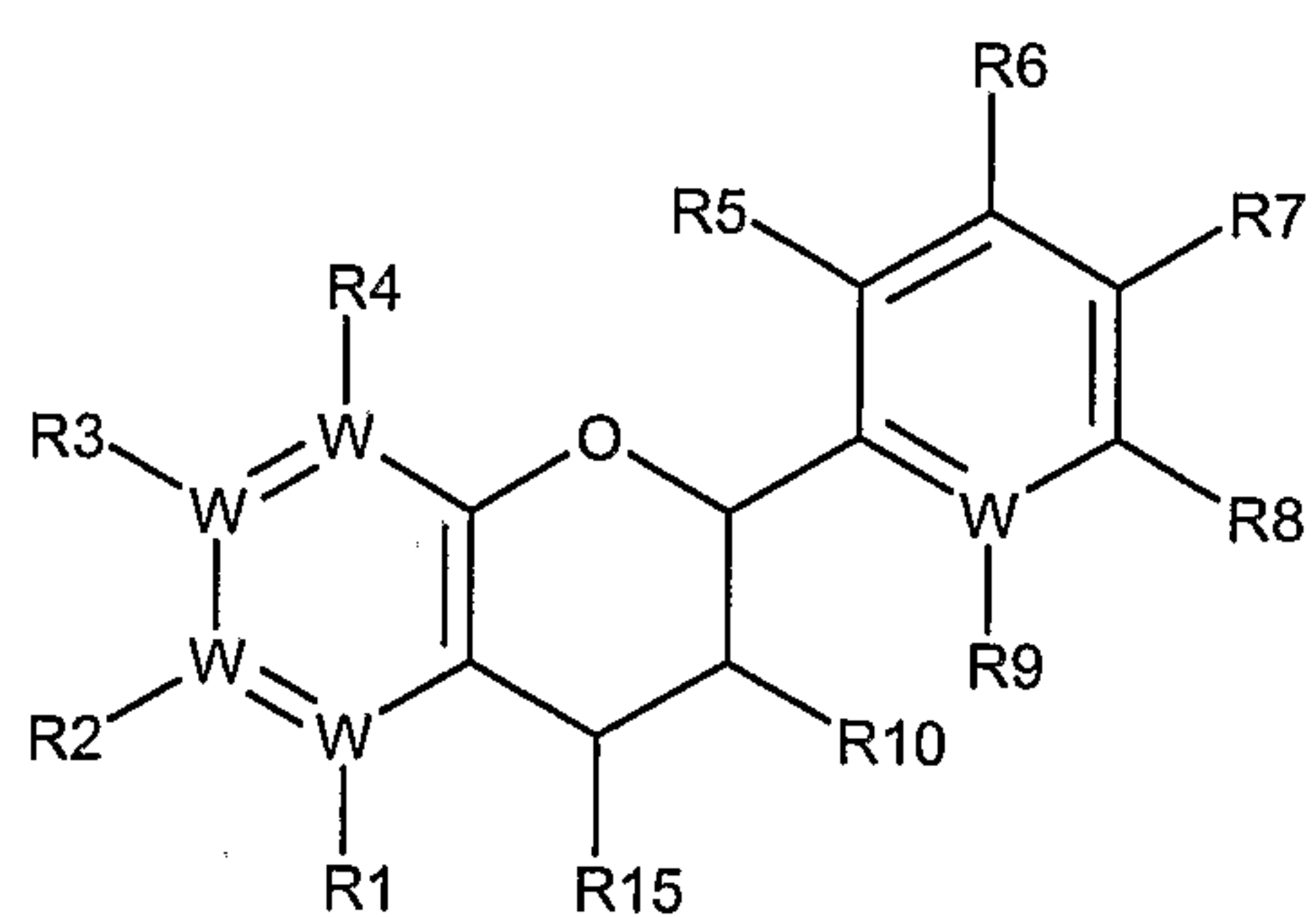
(XXXII)



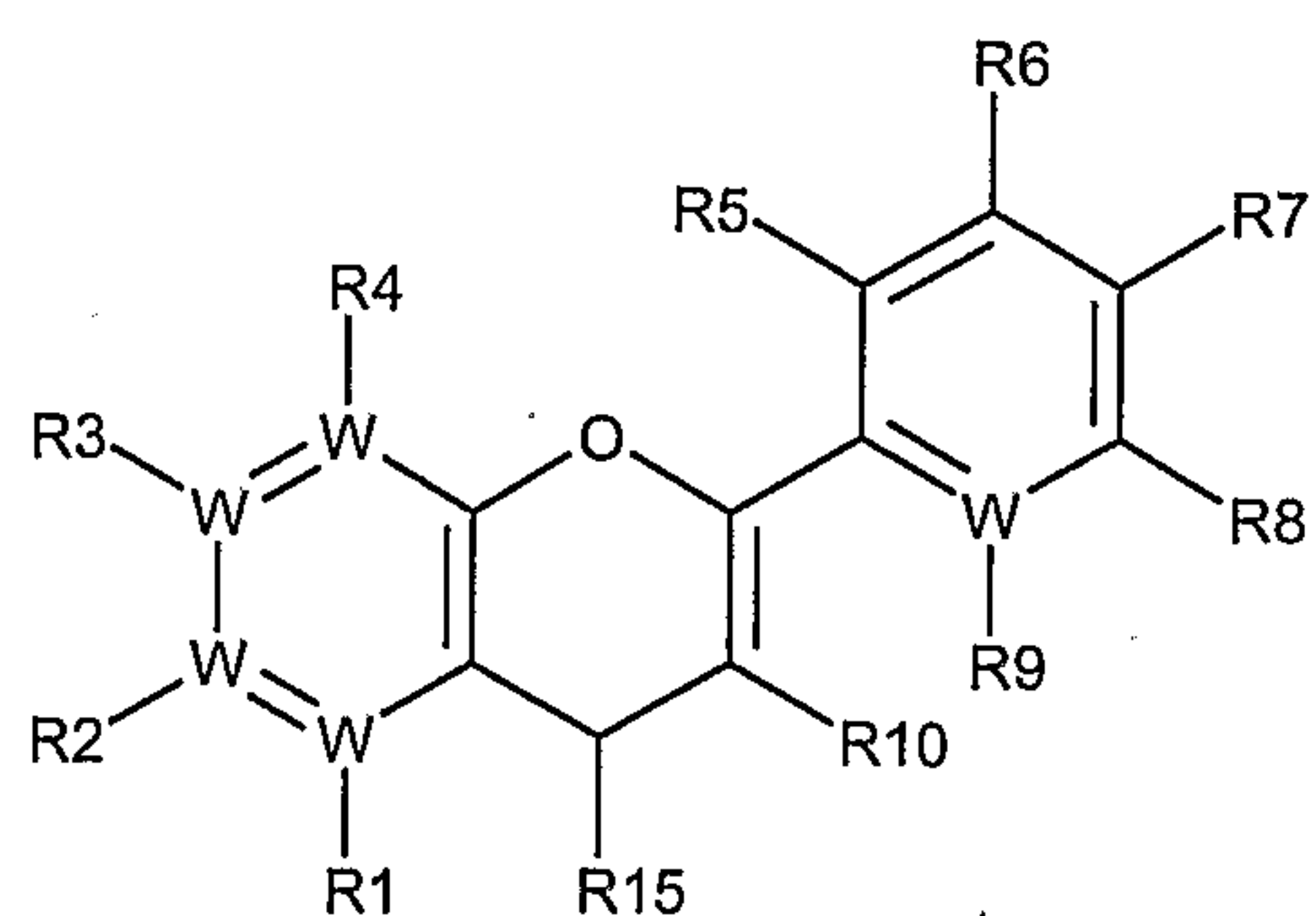
(XXXIII)



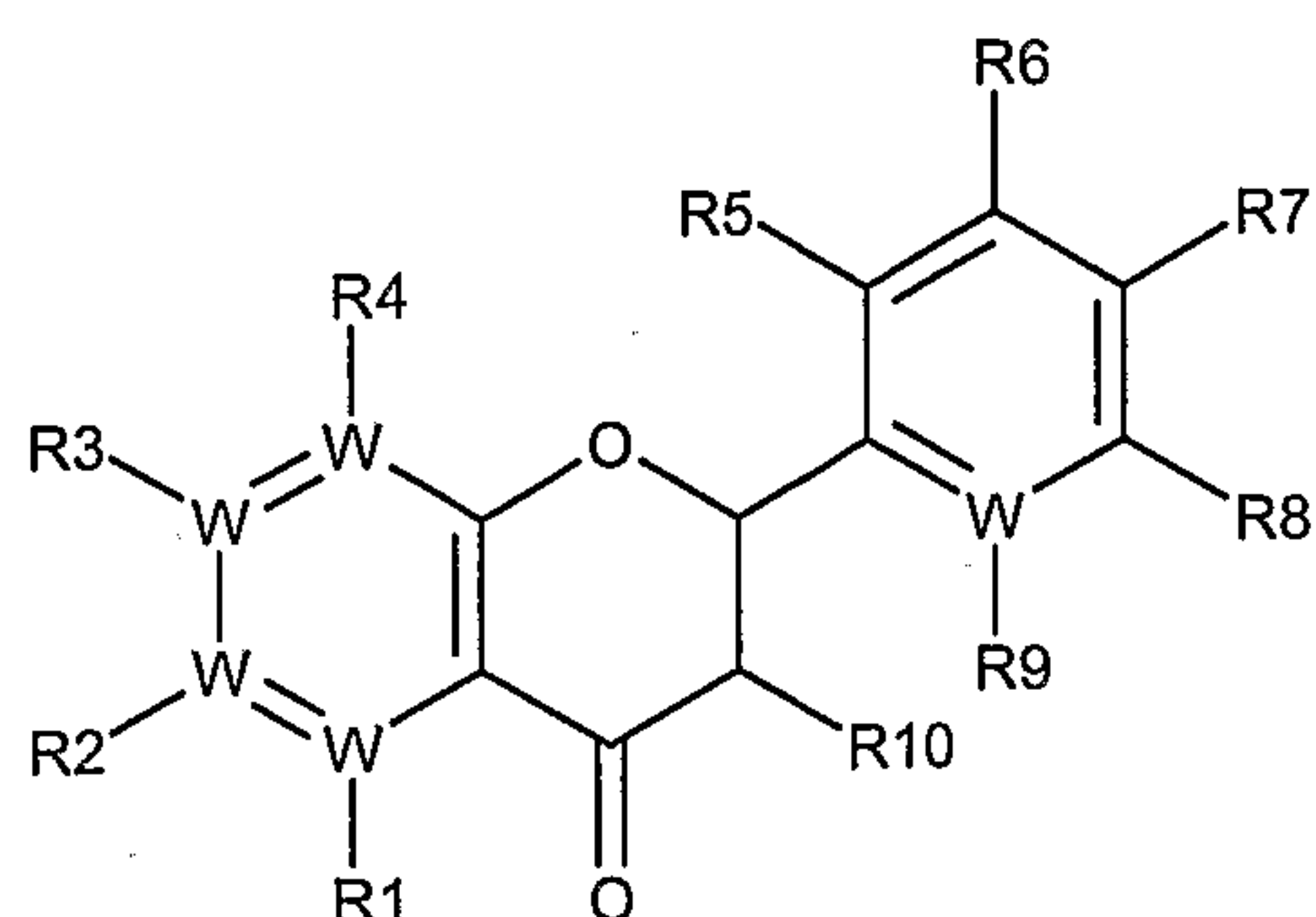
(XXXIV)



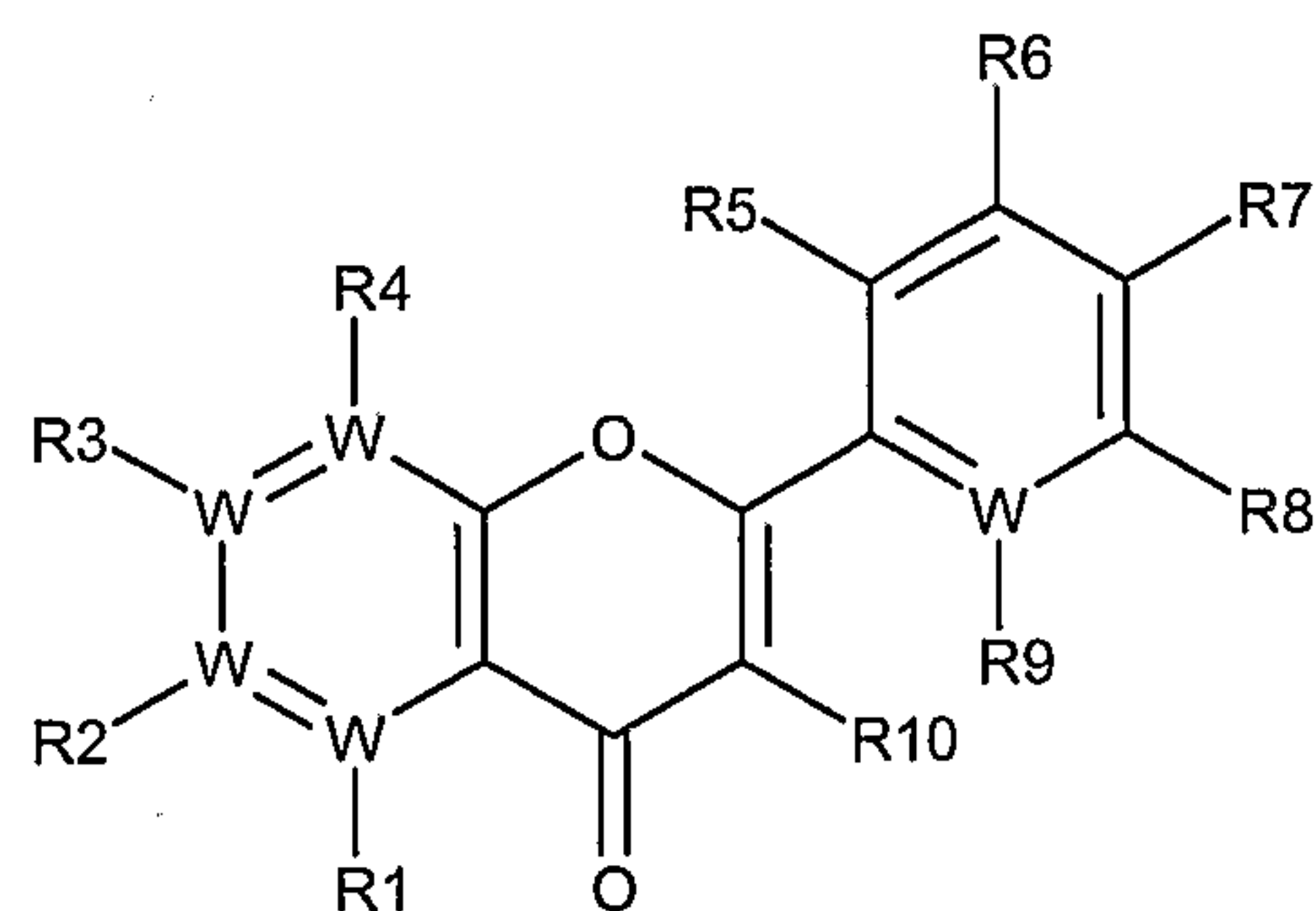
(XXXV)



(XXXVI)



(XXXVII)



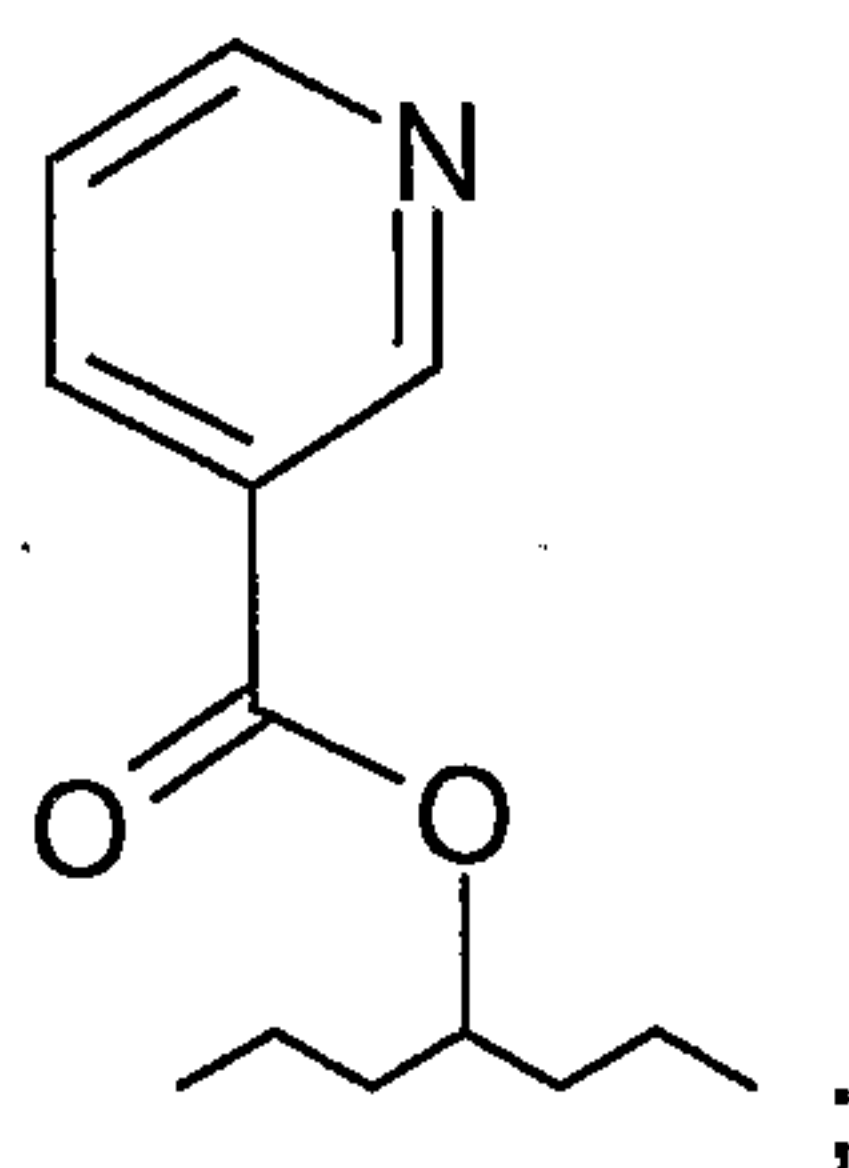
and a pharmaceutically acceptable salt thereof,

wherein

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates],

wherein

#STR66# means



wherein

W can be C or N;

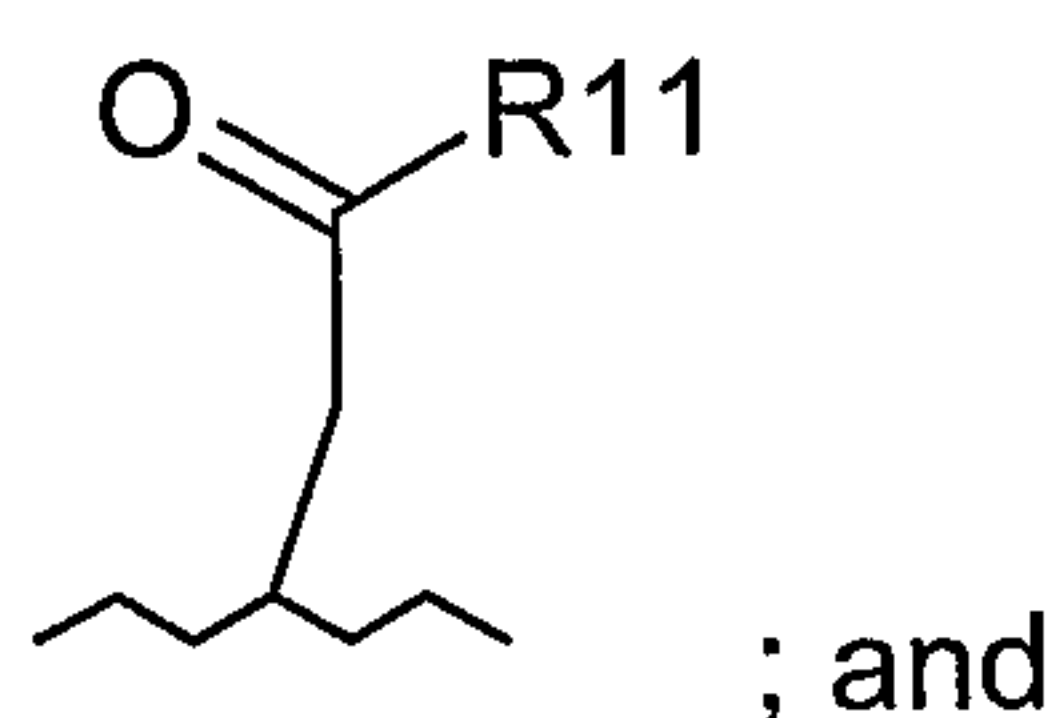
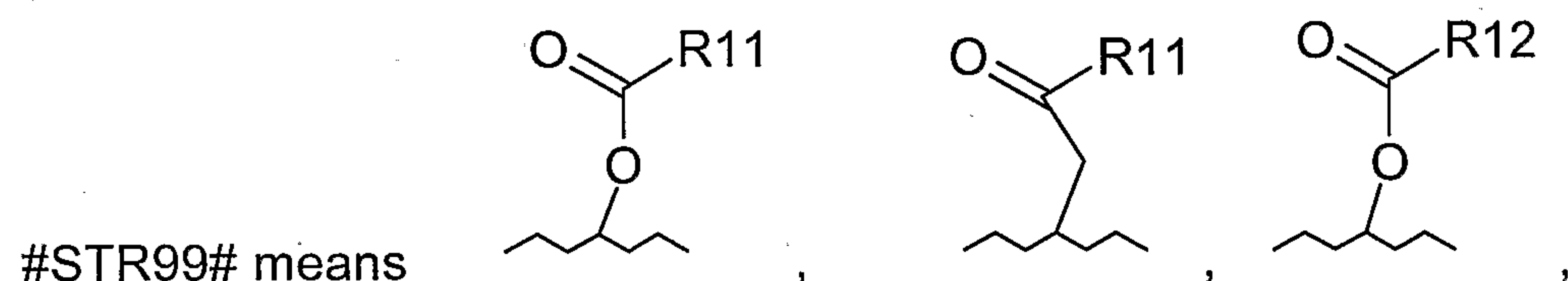
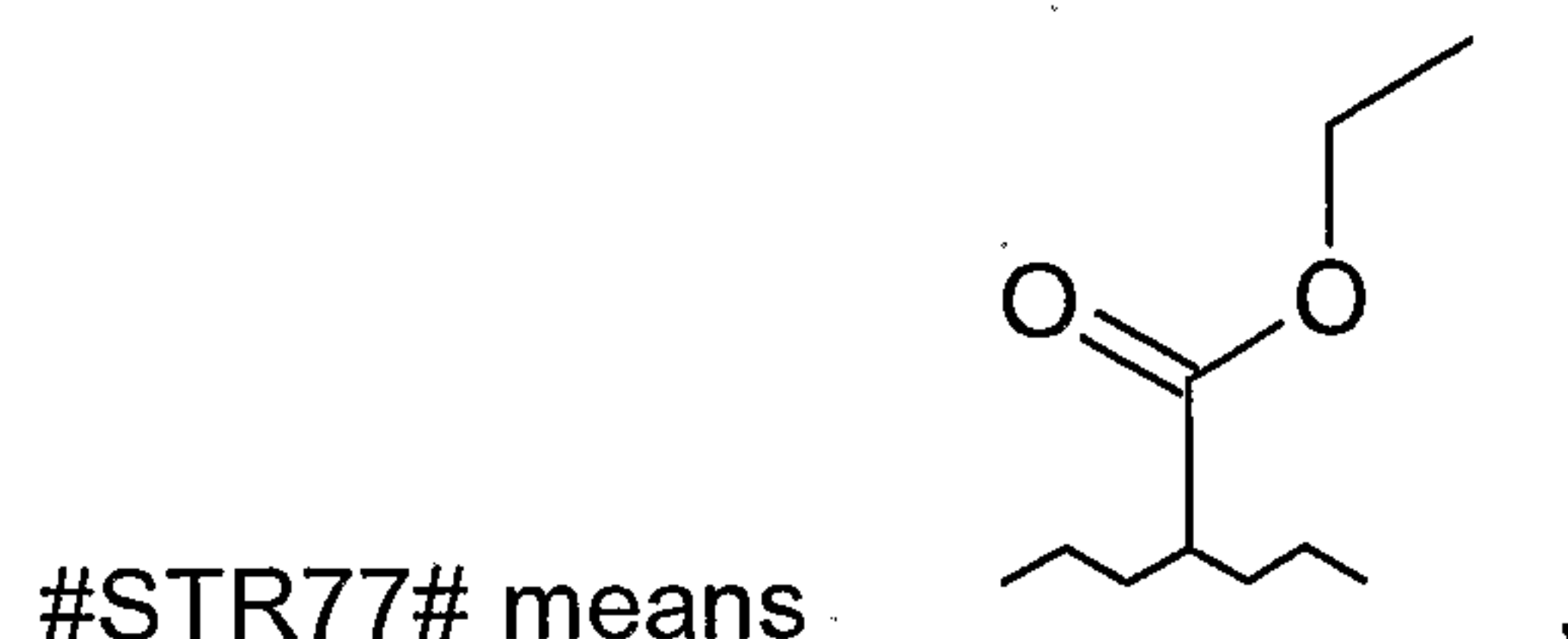
X can be O, S, C, CR¹³, or NR¹³;

Y can be O, S, C, CR¹³, or NR¹³;

Z can be a single or a double bond

Wherein R¹³ is #STR100#, #STR77# or #STR99#

Wherein



R¹¹ is pyridine, pyridazine, pyrimidine, pyrazine;

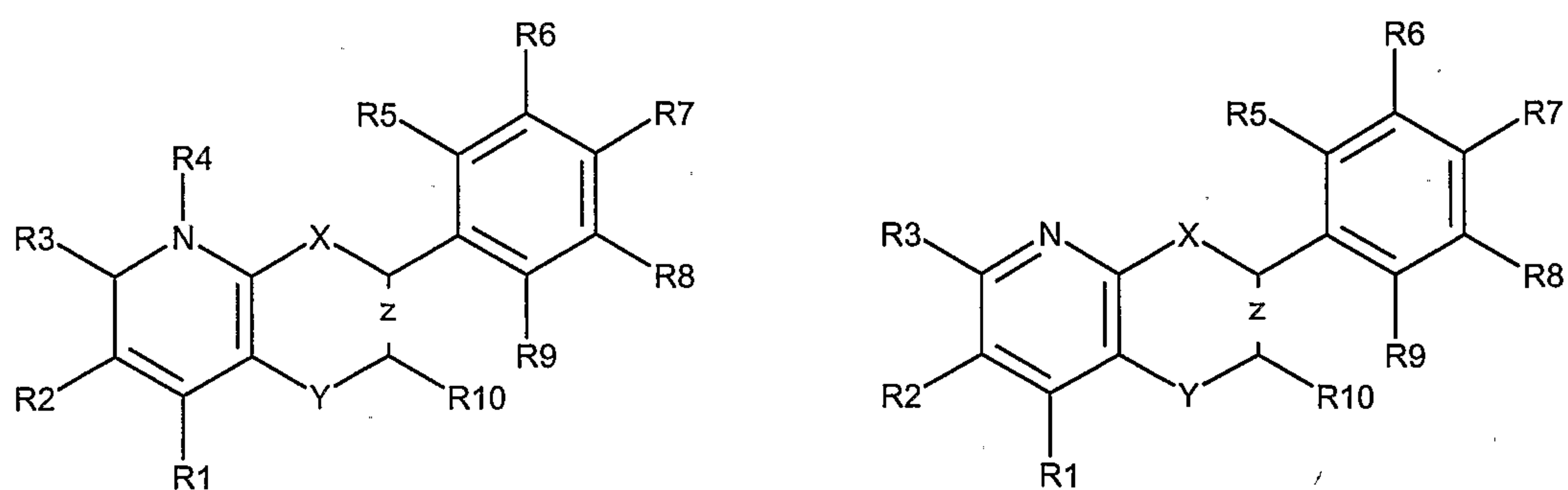
and R¹² is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

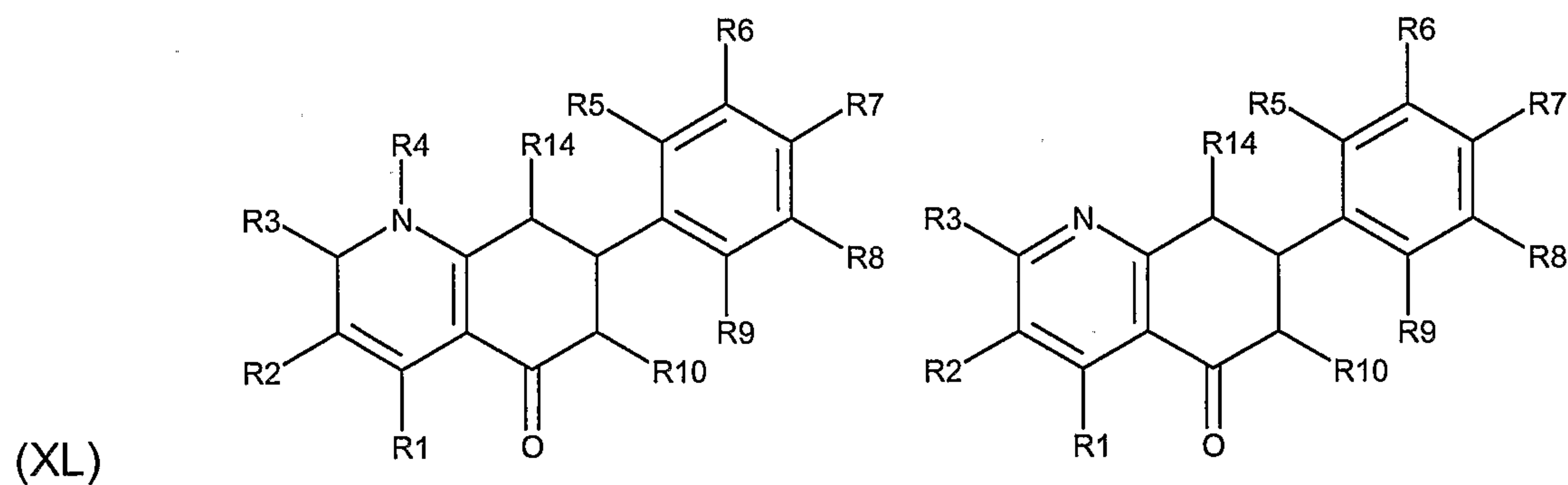
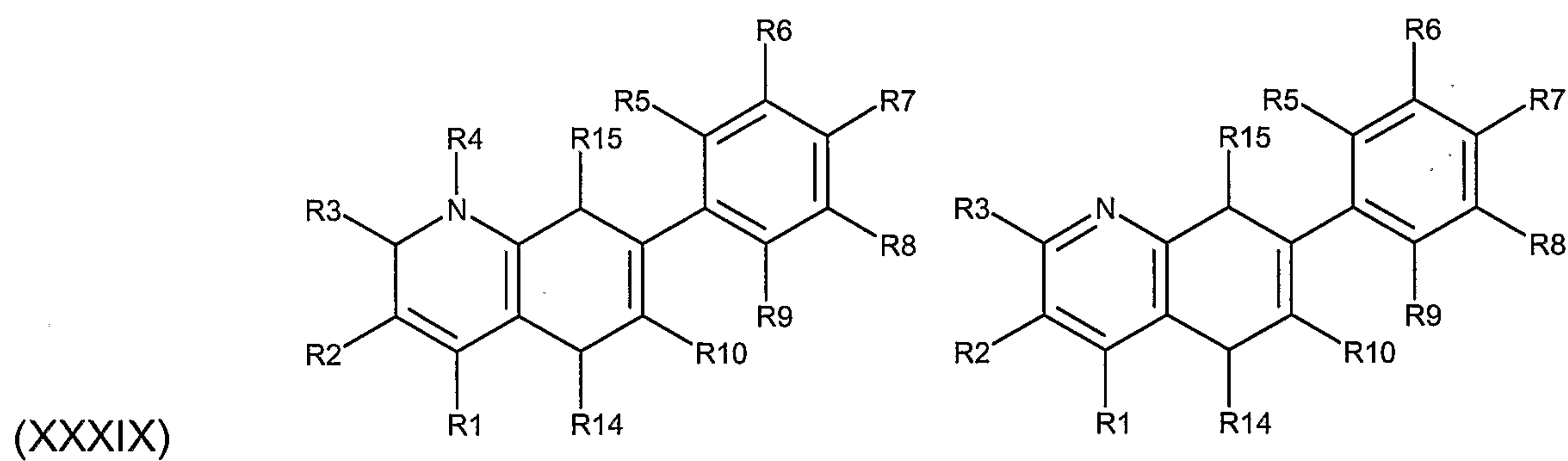
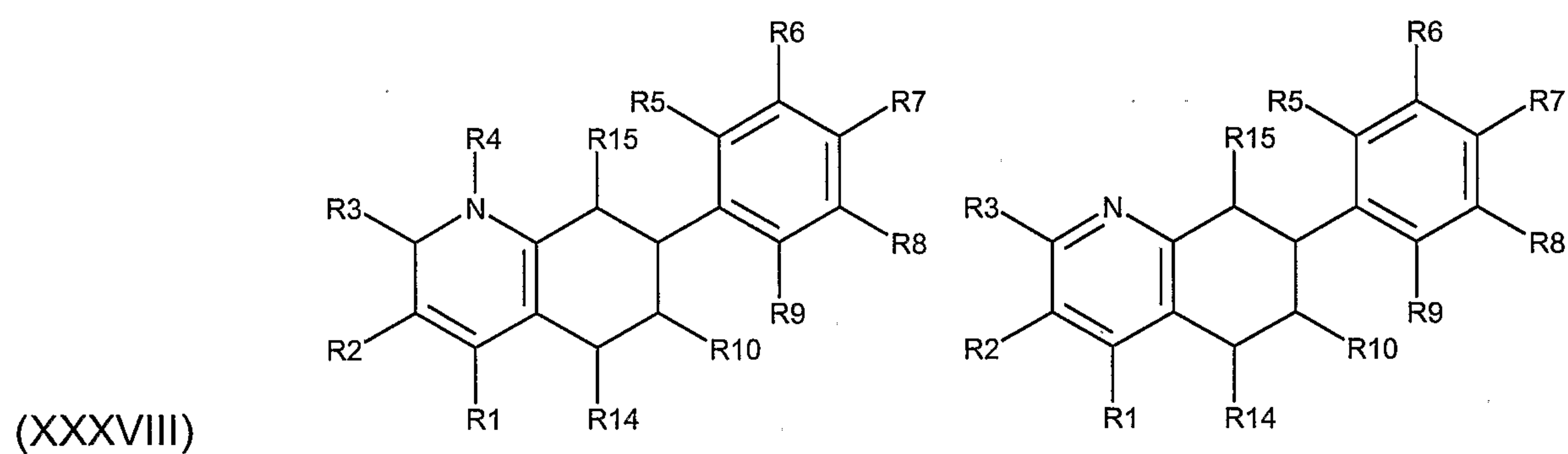
a) R⁷ is hydroxyl or #STR66# and at least one W is a N and optionally:

b) at least one of R¹-R¹⁰ is #STR66#;

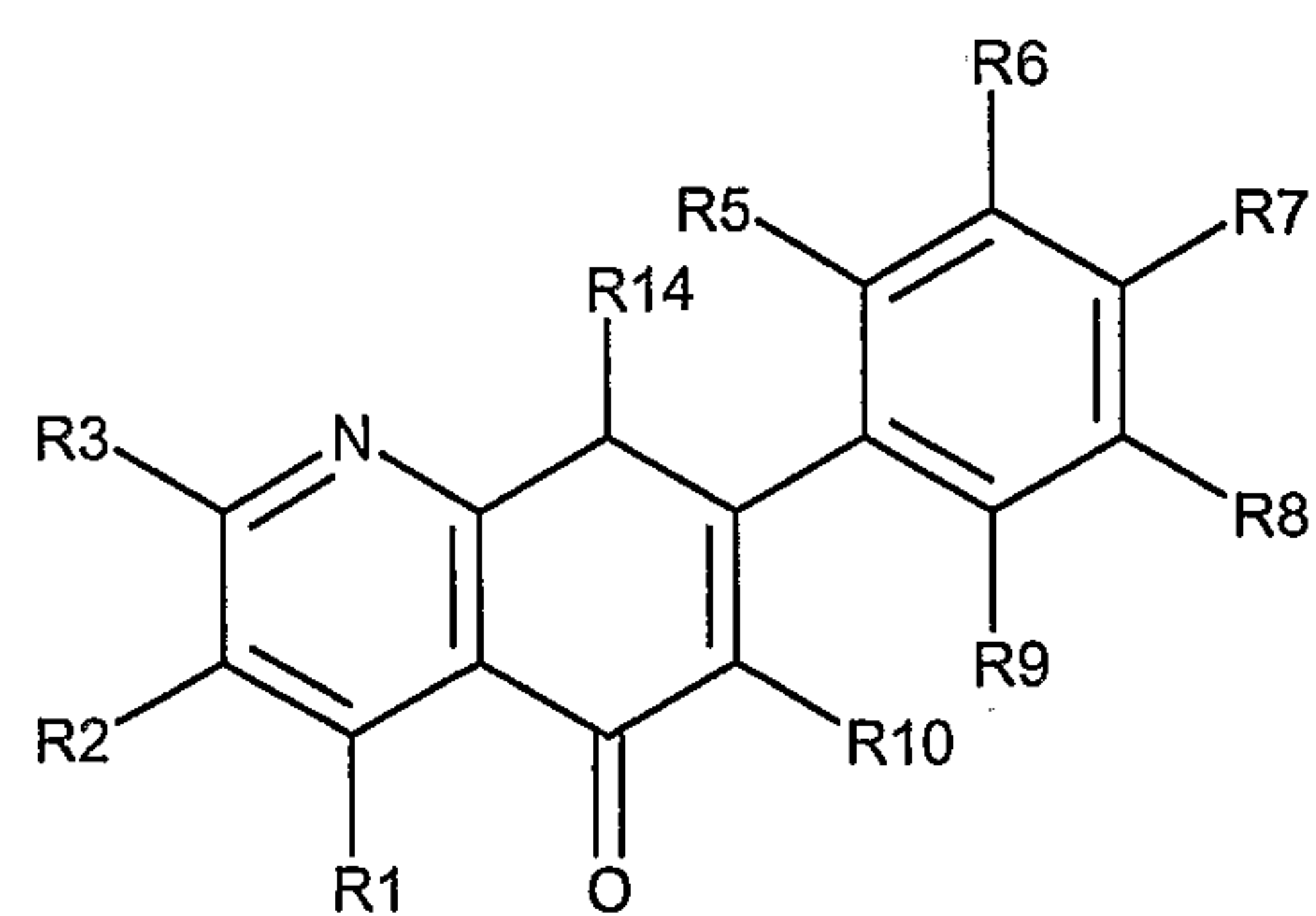
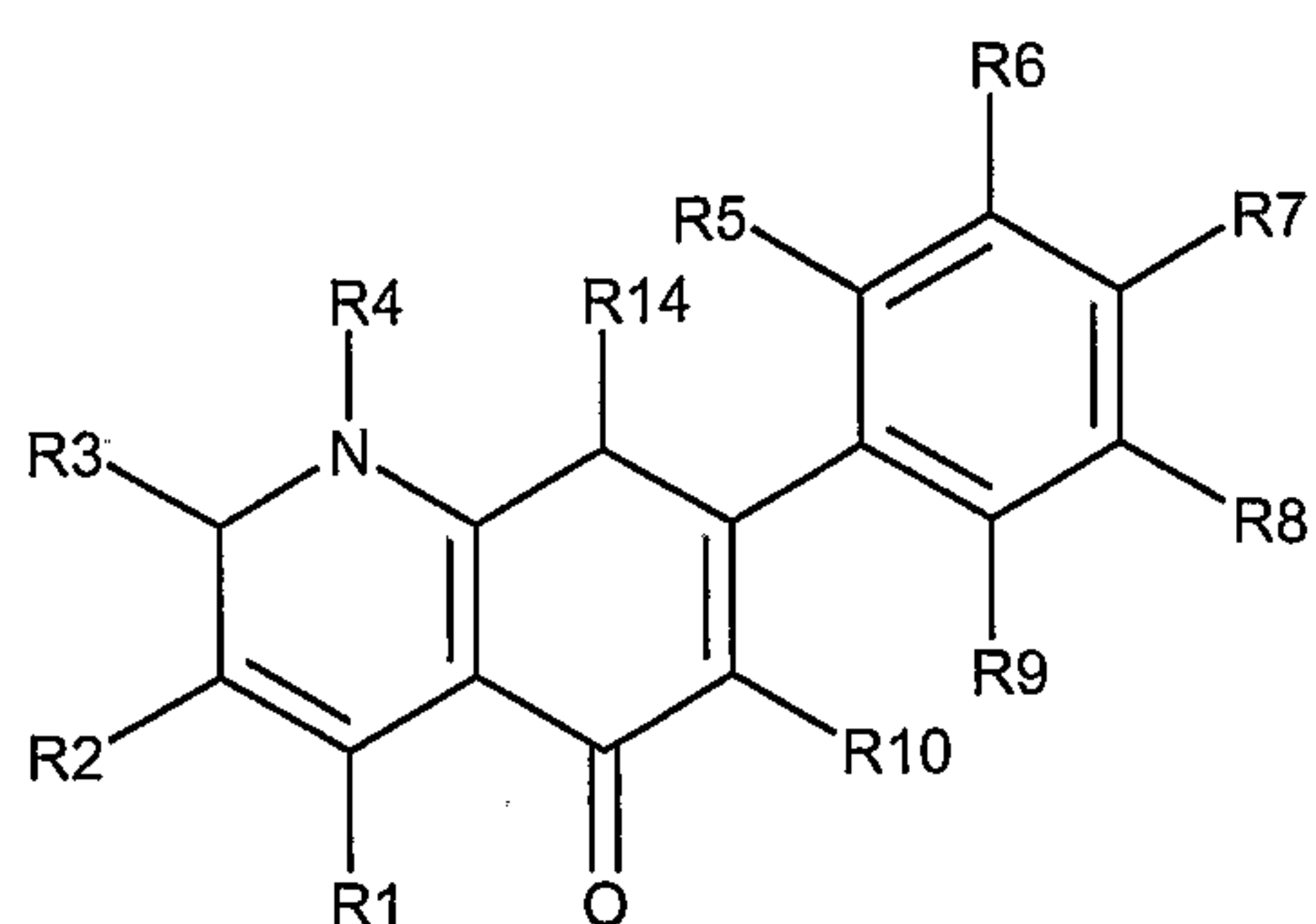
[091] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 3:



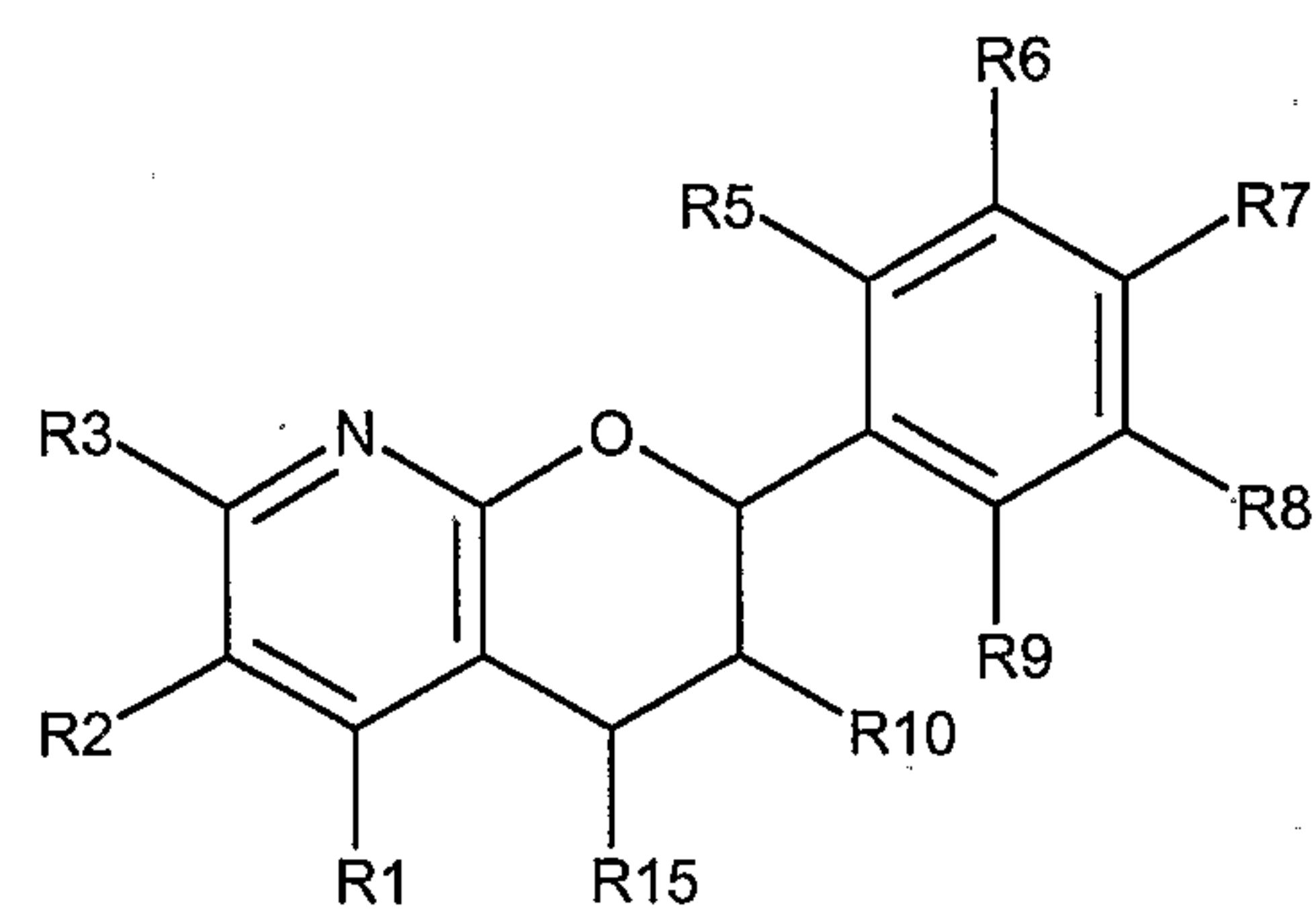
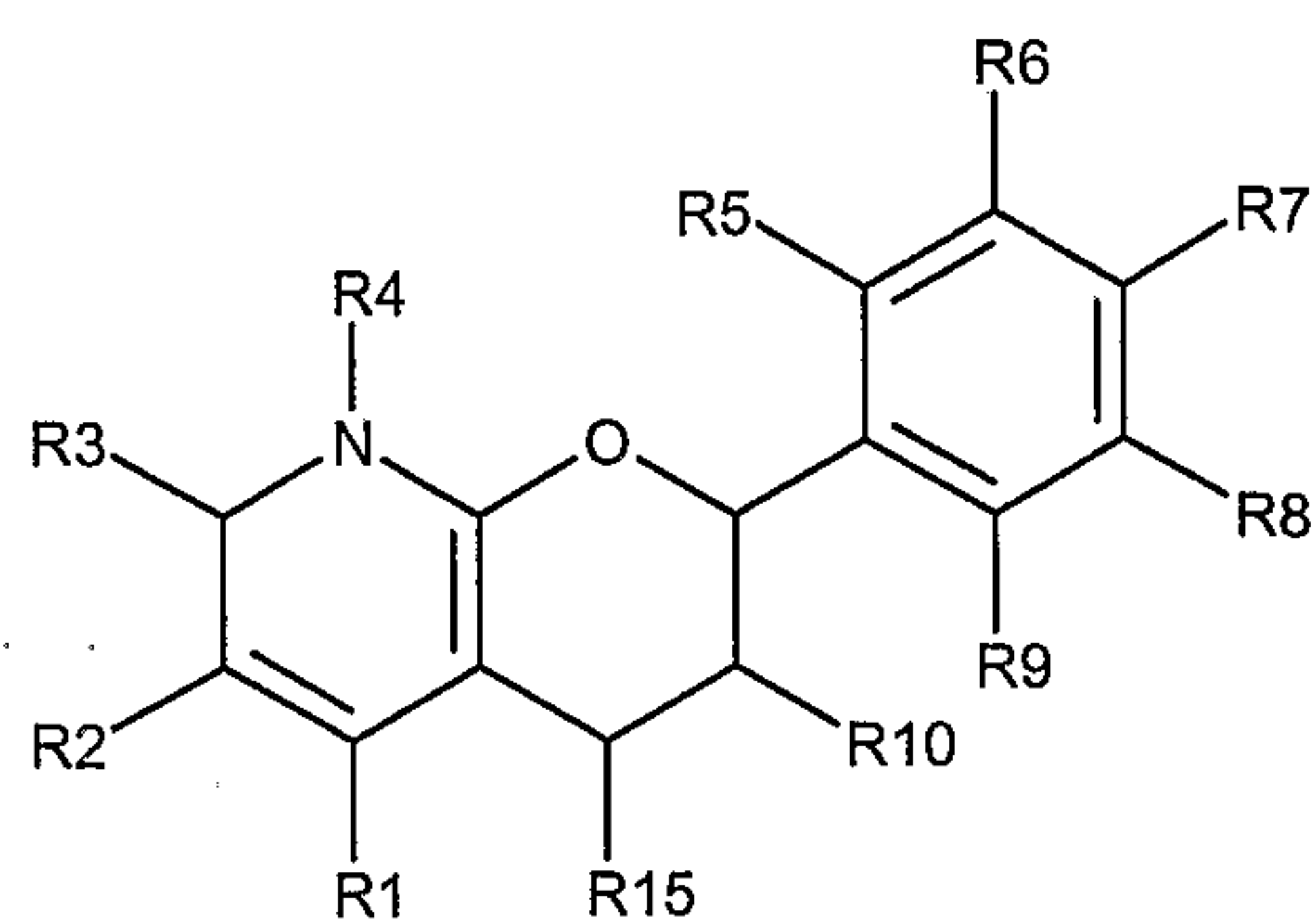
[092] Non-limiting examples of Formula 3 include:



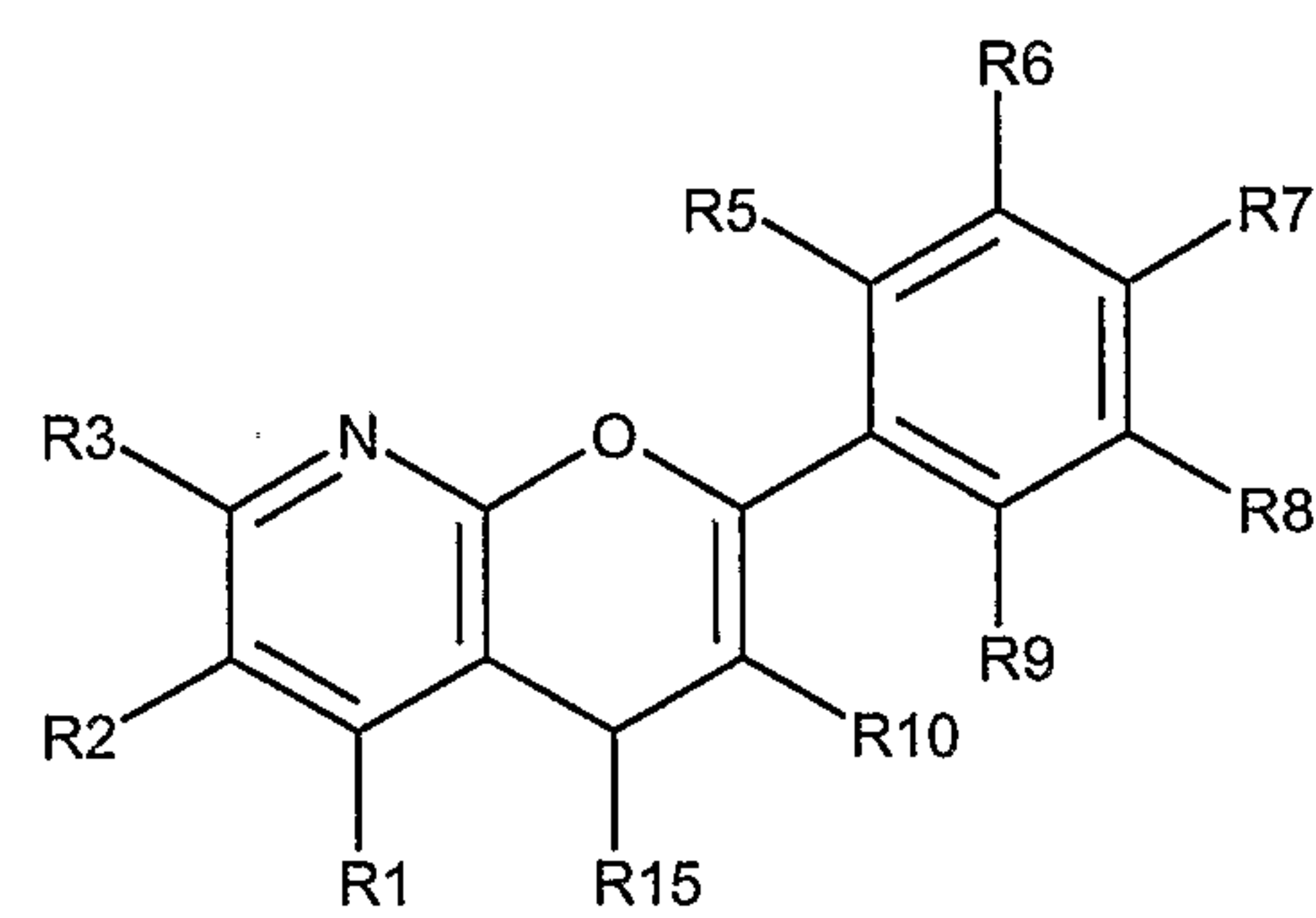
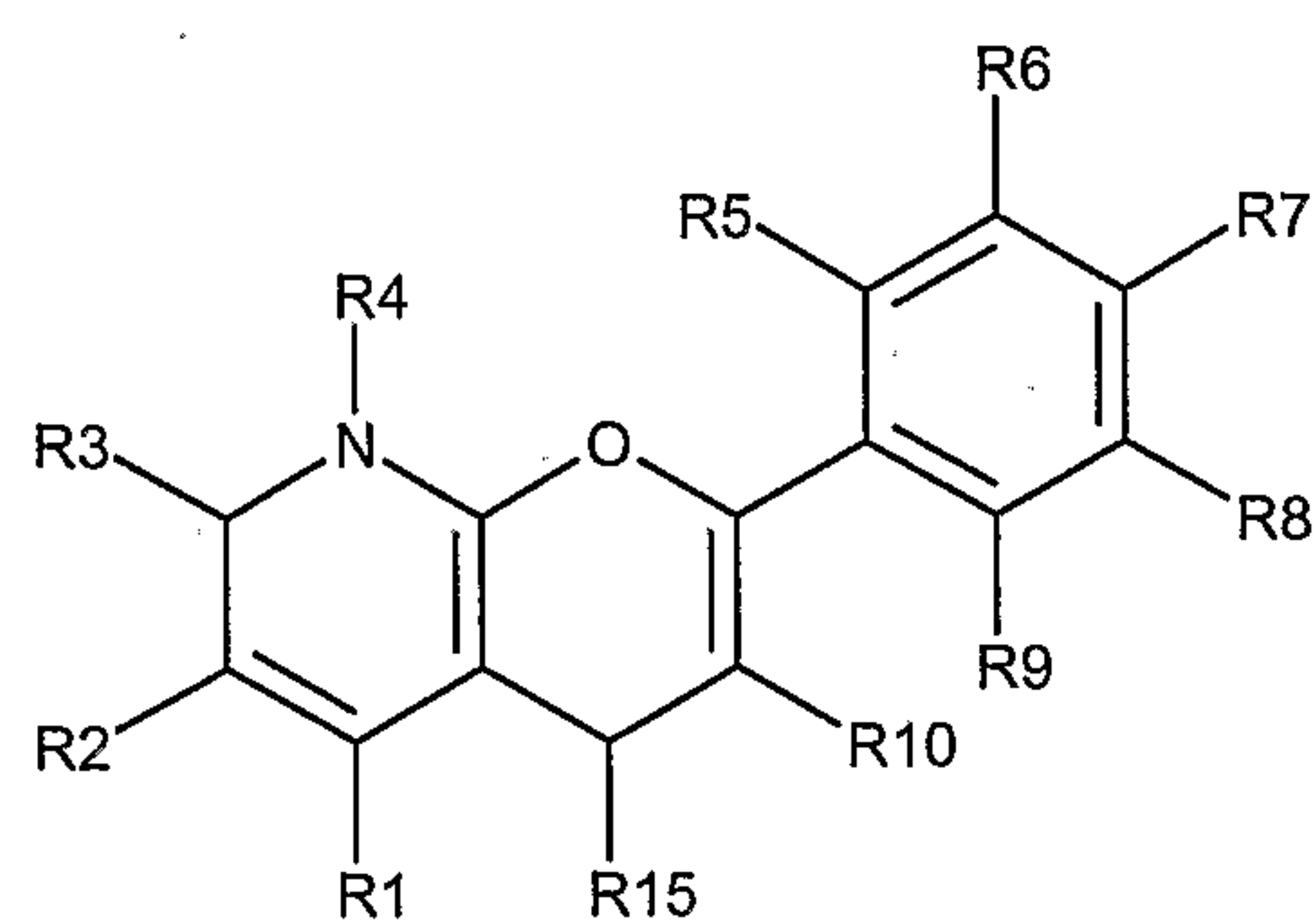
(XLI)



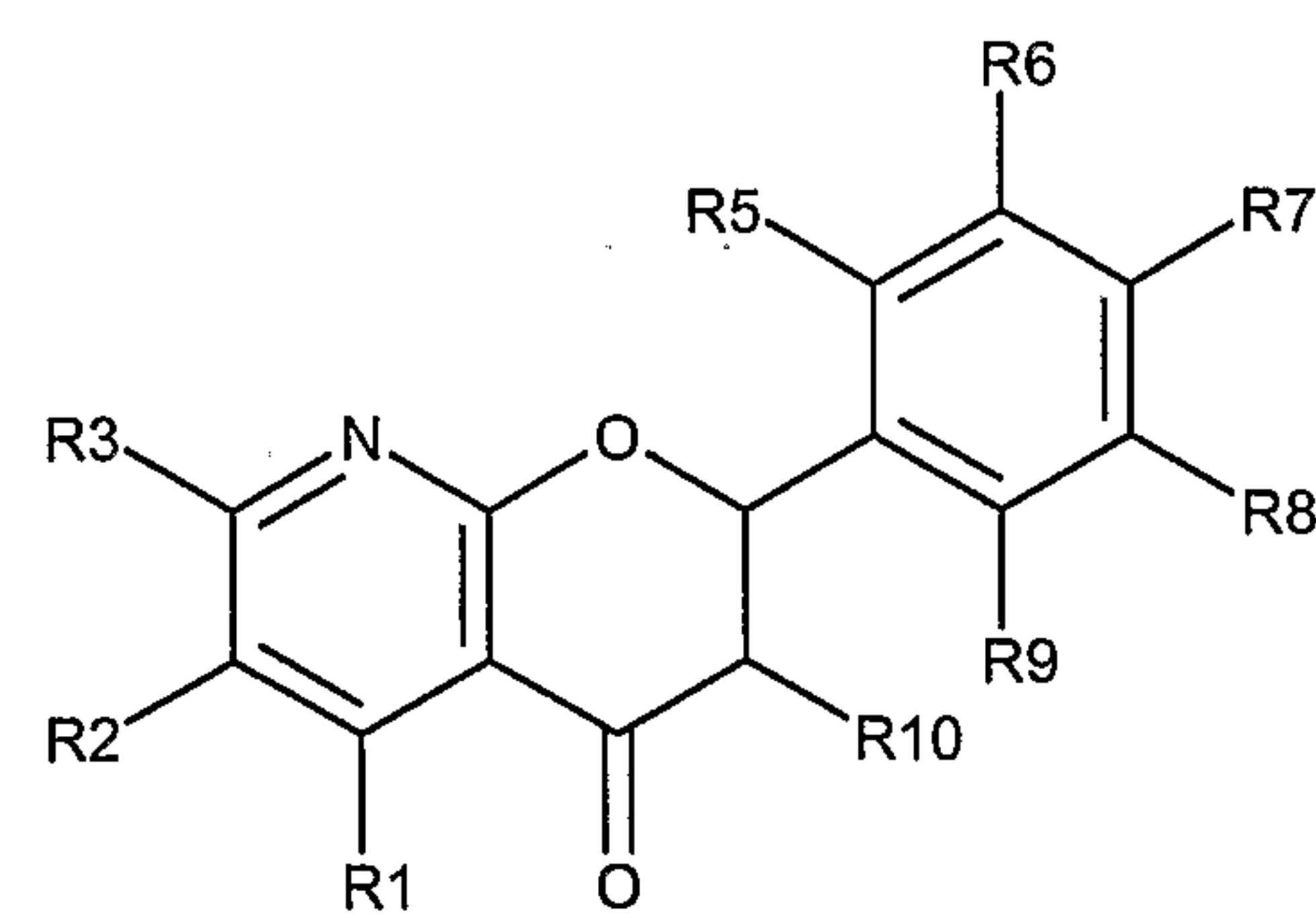
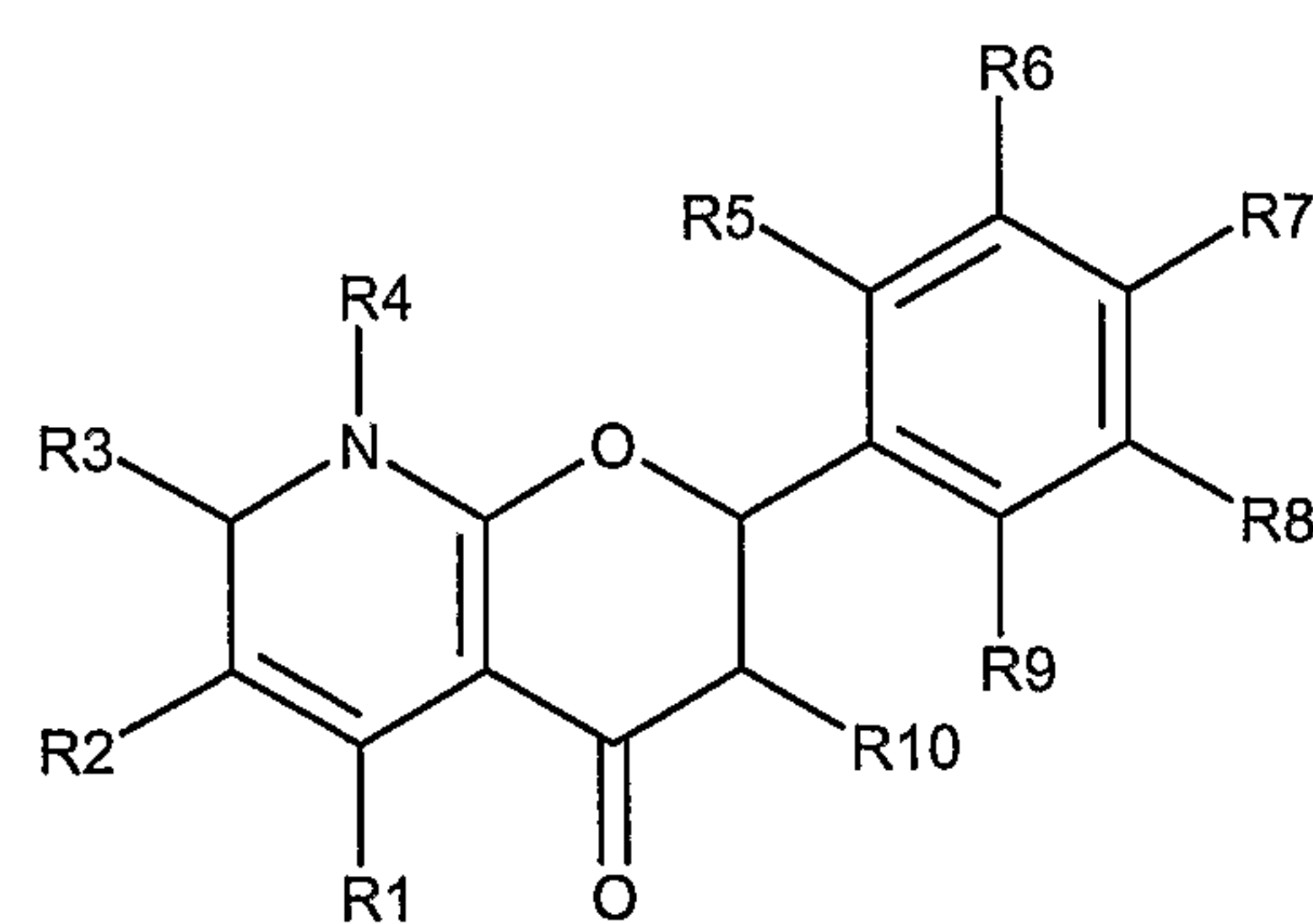
(XLII)



(XLIII)



(XLIV)



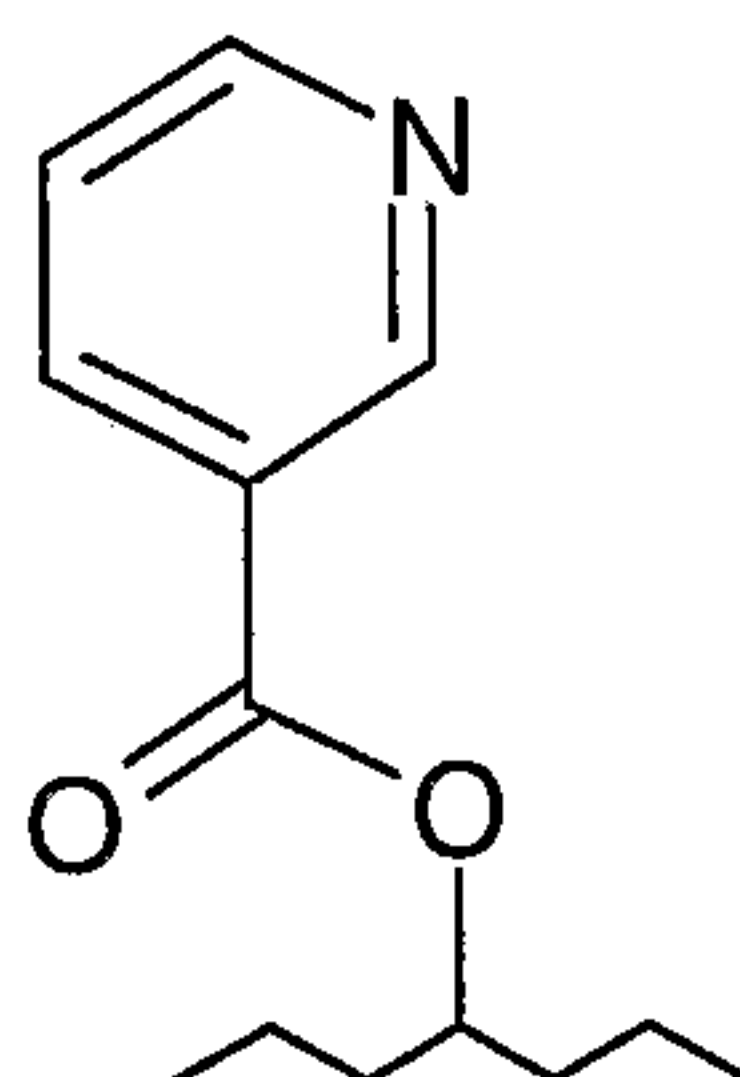
and a pharmaceutically acceptable salt thereof,

wherein

R1, R2, R3, R4, R5, R6, R7, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I],

methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates],

wherein



#STR66# means

wherein

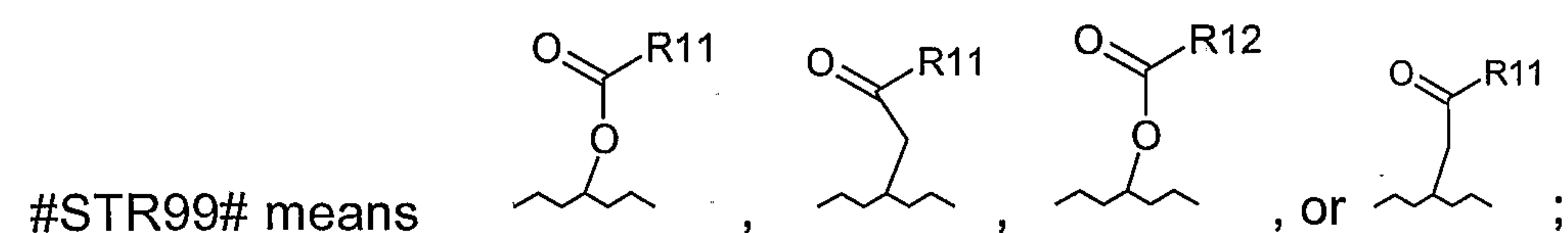
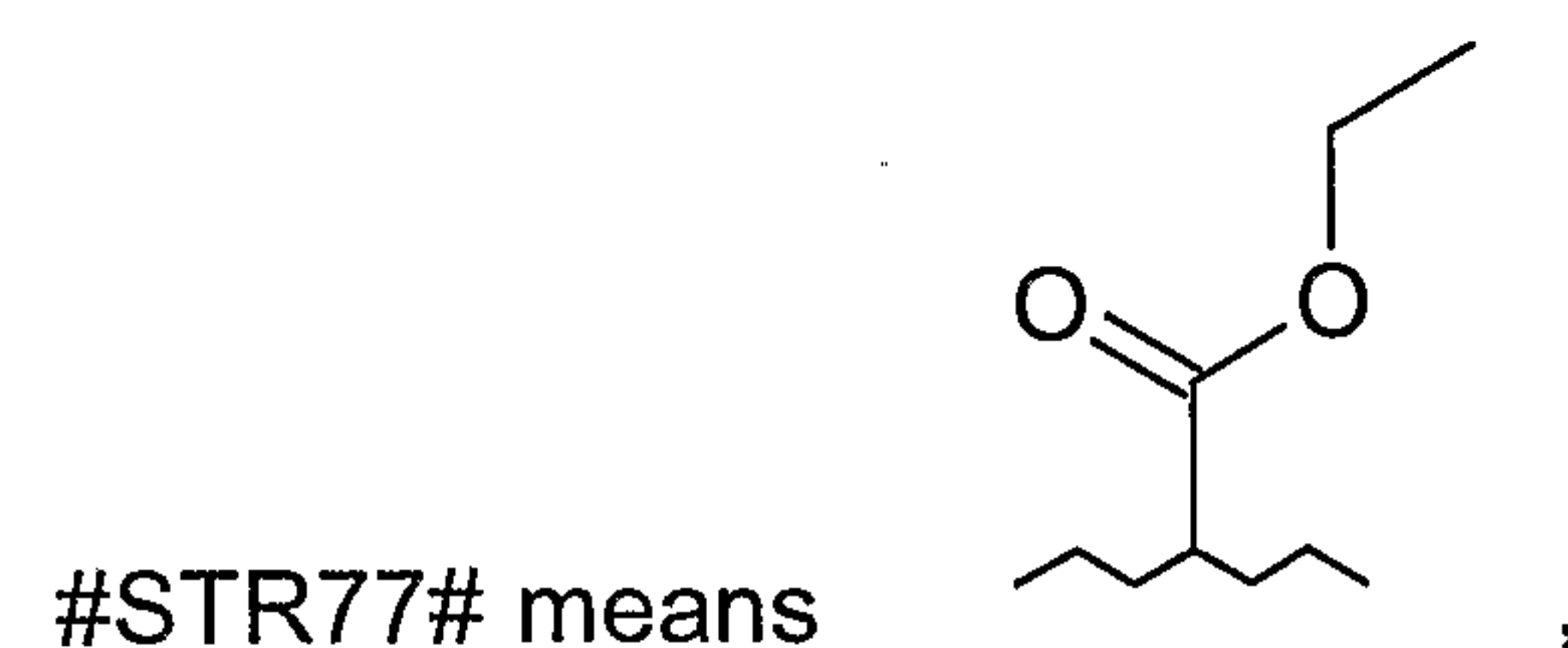
X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

Z can be a single or a double bond

Wherein R₁₃ is #STR100#, #STR77# or #STR99#

Wherein:



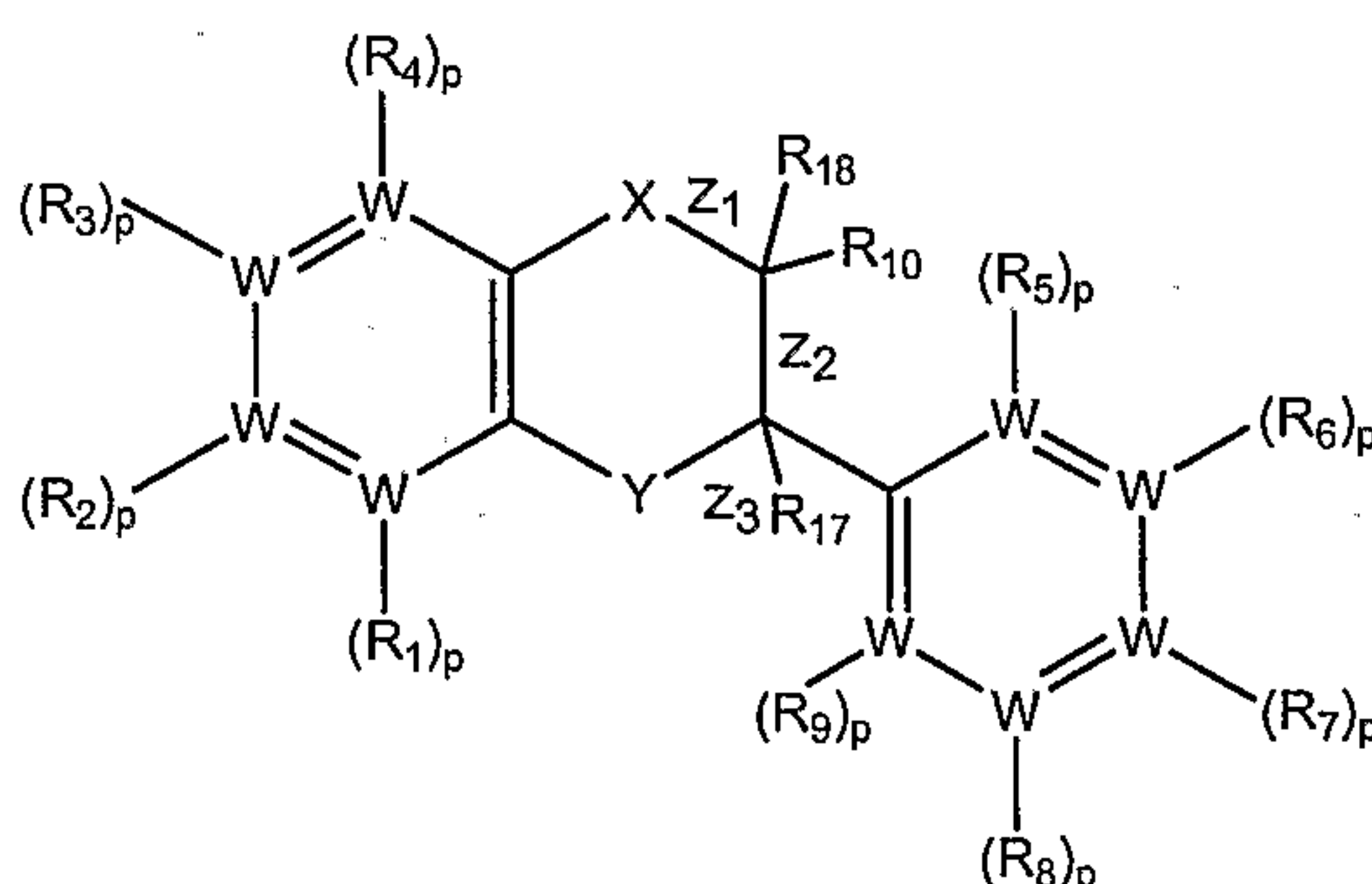
R₁₁ is pyridine, pyridazine, pyrimidine, pyrazine;

and R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that

- a) R7 is a hydroxyl and at least one of R1-10 is #STR66#; and /or
- b) R7 is #STR66#.

[093] Disclosed herein are methods for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

wherein:

X is selected from CR₁₁, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, N and NR₁₁, wherein R₁₁ may be the same or different than R₁₃;

Y is selected from CR₁₂, CR₁₂R₁₄, CO, CS, O, S, SO, SO₂, N and NR₁₂, wherein R₁₂ may be the same or different than R₁₄;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₇ and R₁₈ are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{18} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

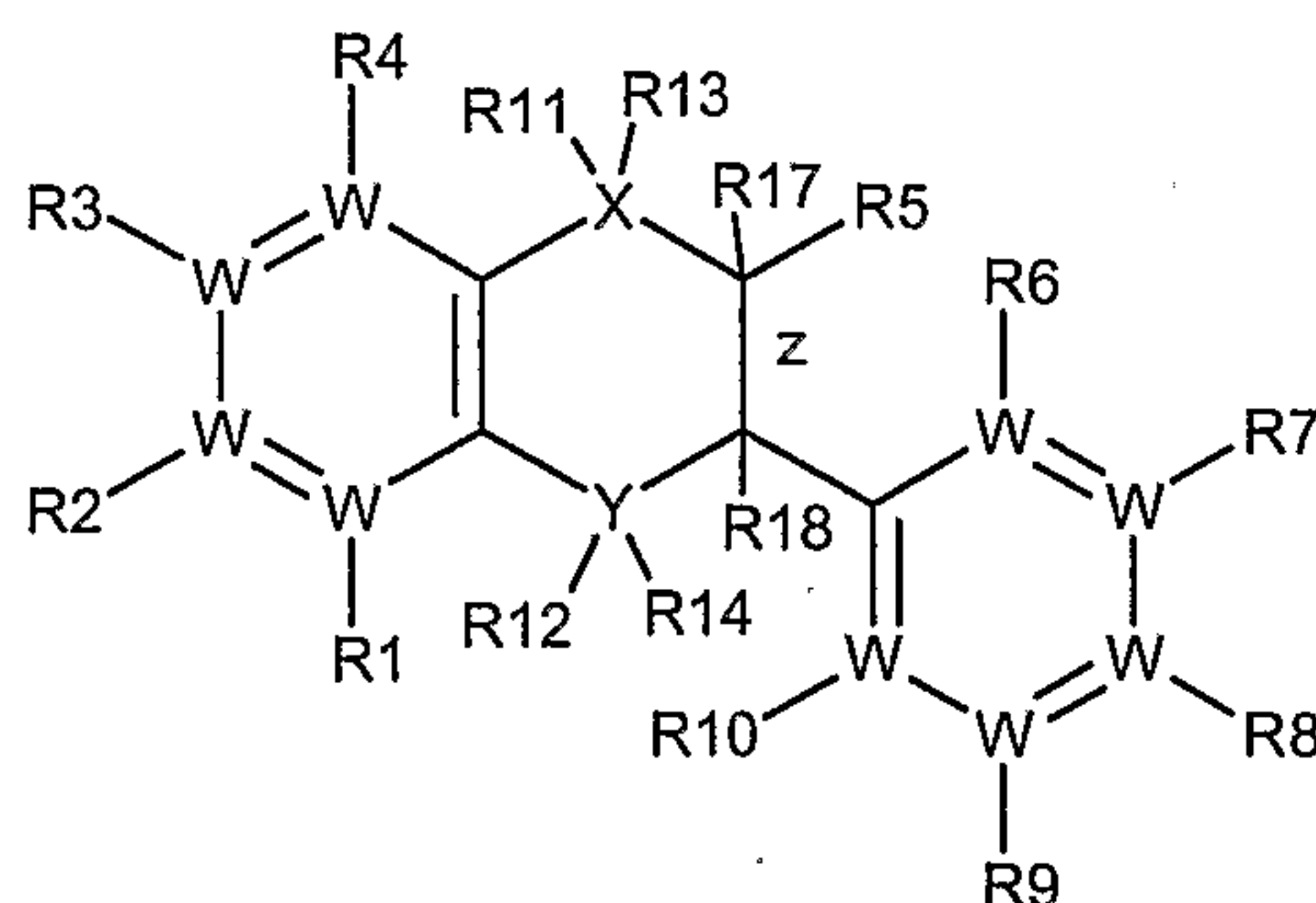
Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, Y is CO and Z_2 is a double bond, then at least one of R_5 , R_6 , R_8 and R_9 is not hydrogen;

and pharmaceutically acceptable salts and hydrates thereof.

[094] An alternative embodiment provides isoflavanoid compounds of Formula 4:



or a pharmaceutically acceptable salt thereof,

wherein

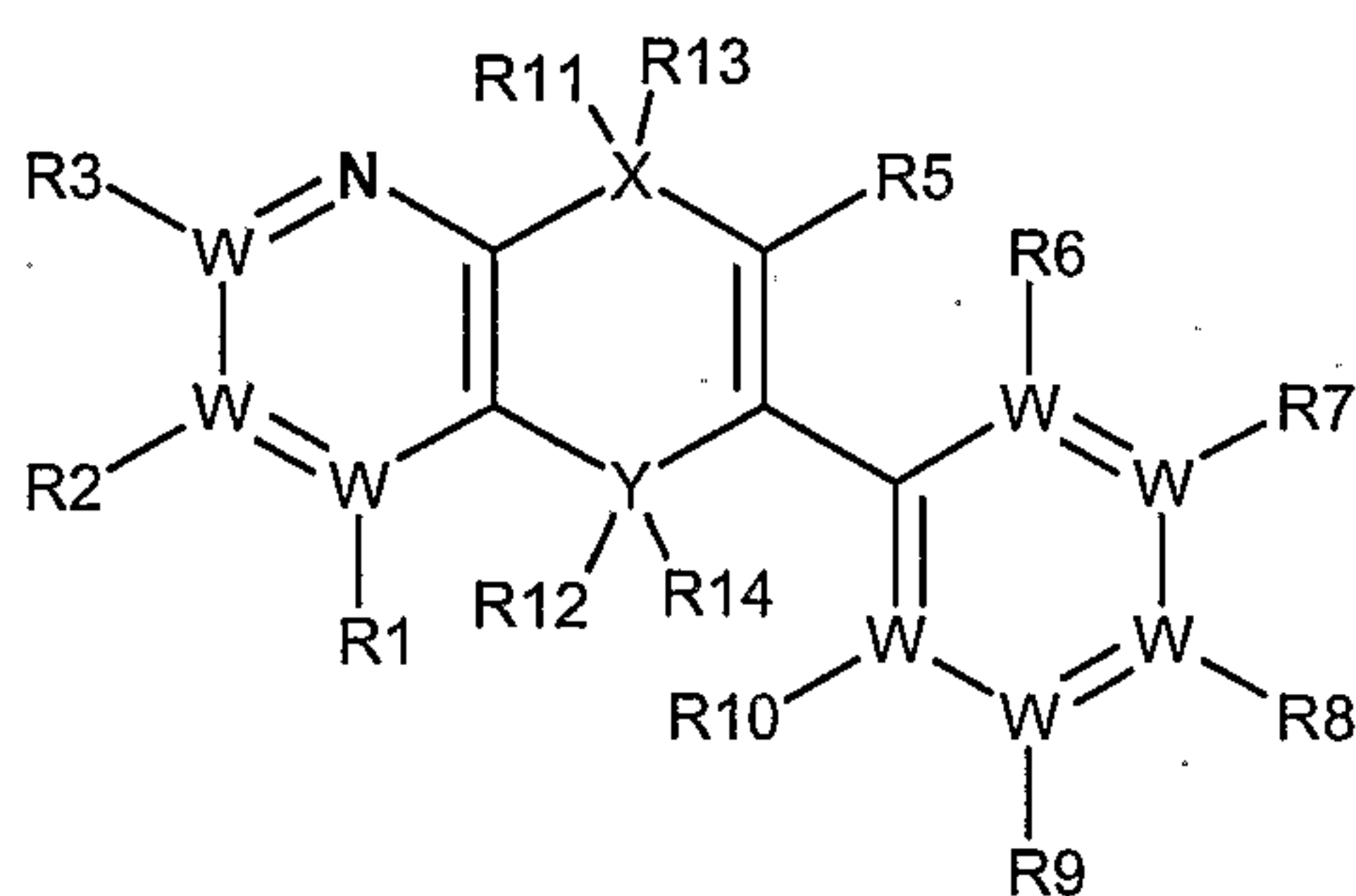
R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} are independently selected from the group consisting of (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, (C_1-C_{22}) alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl],

CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucronic (AKA glucuronic) acid conjugates], monoesters, dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#, #STR100#,

wherein

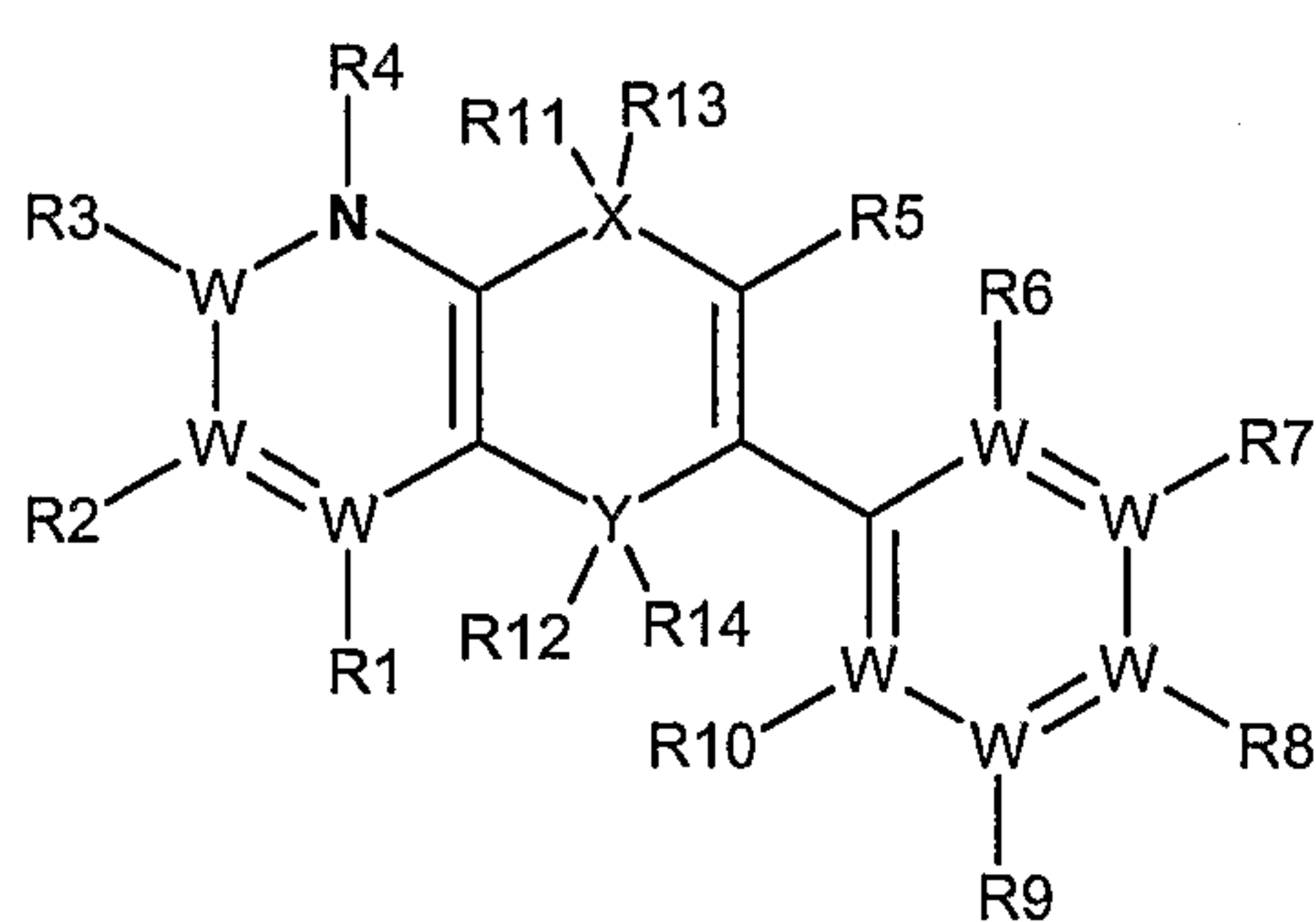
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 4:



wherein the same applies to any W;

or



wherein the same applies to any W:

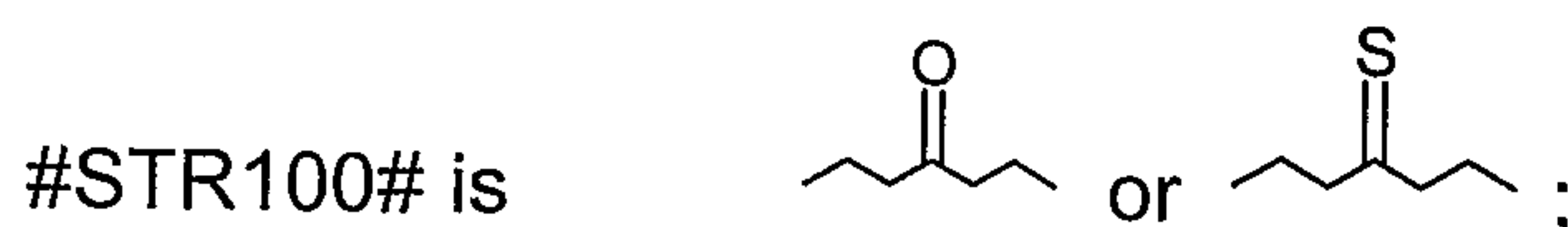
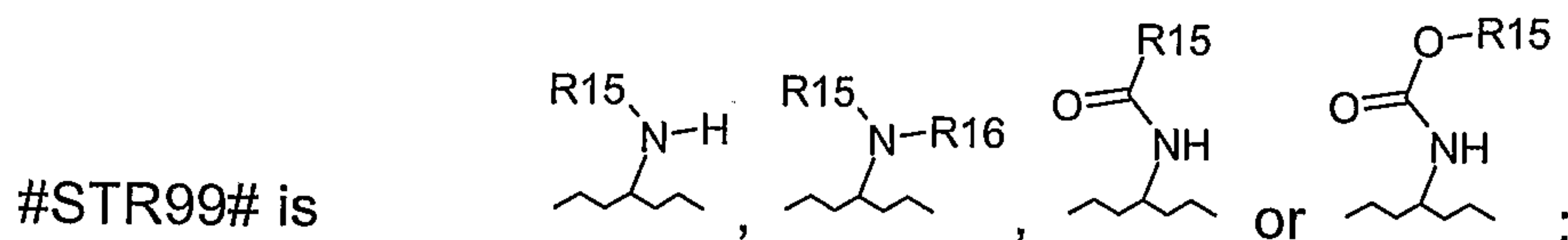
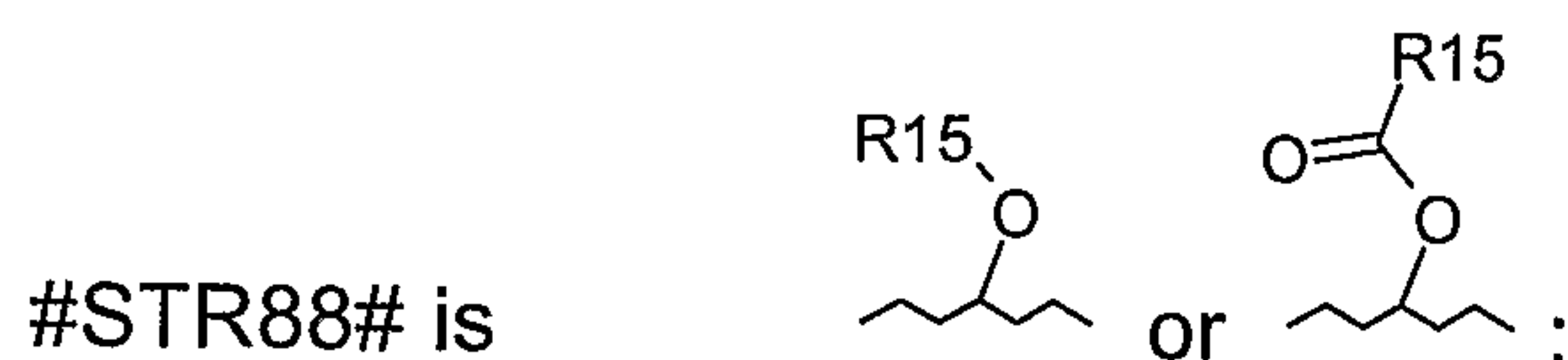
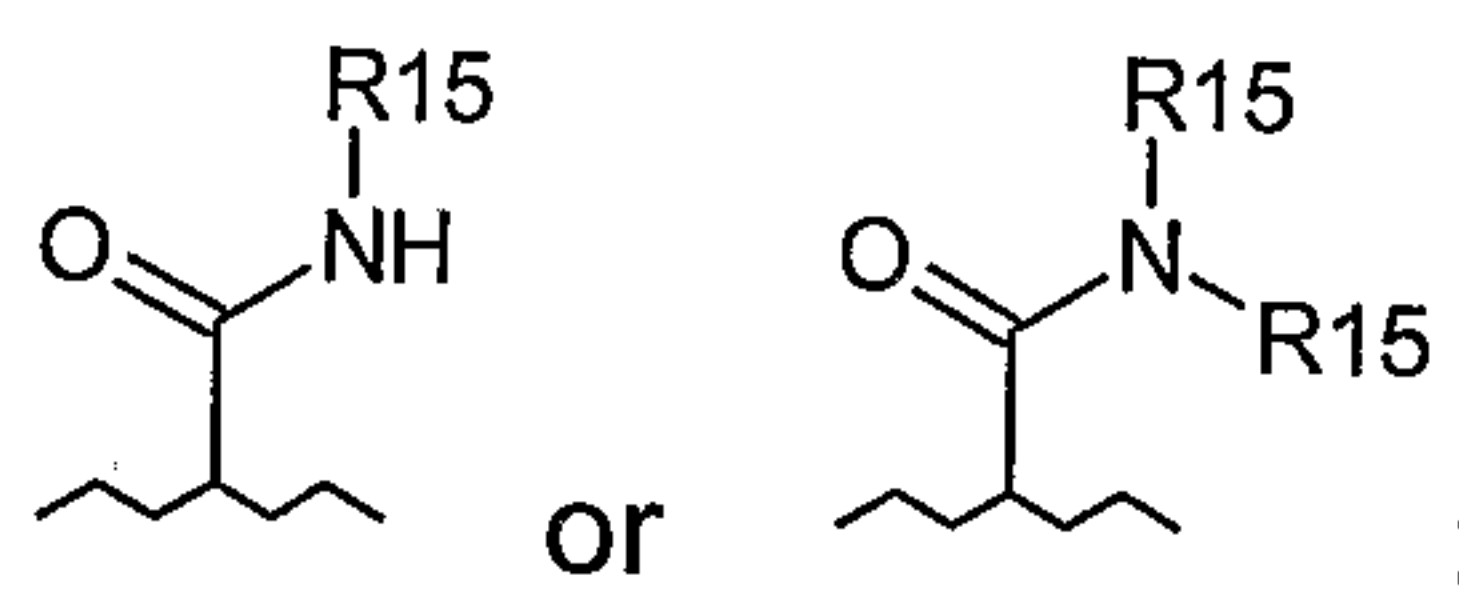
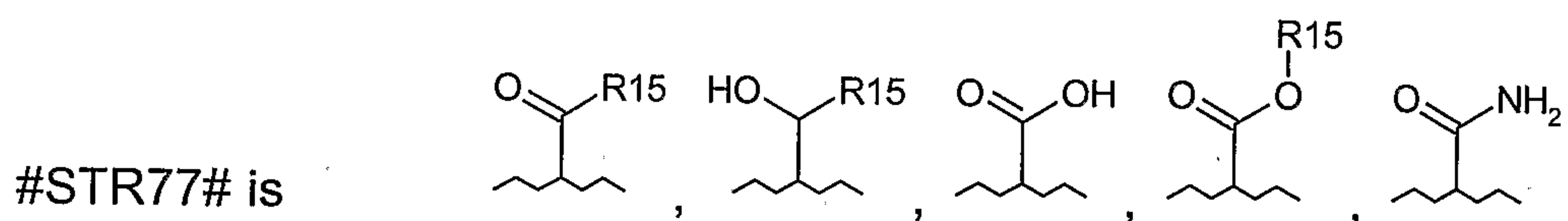
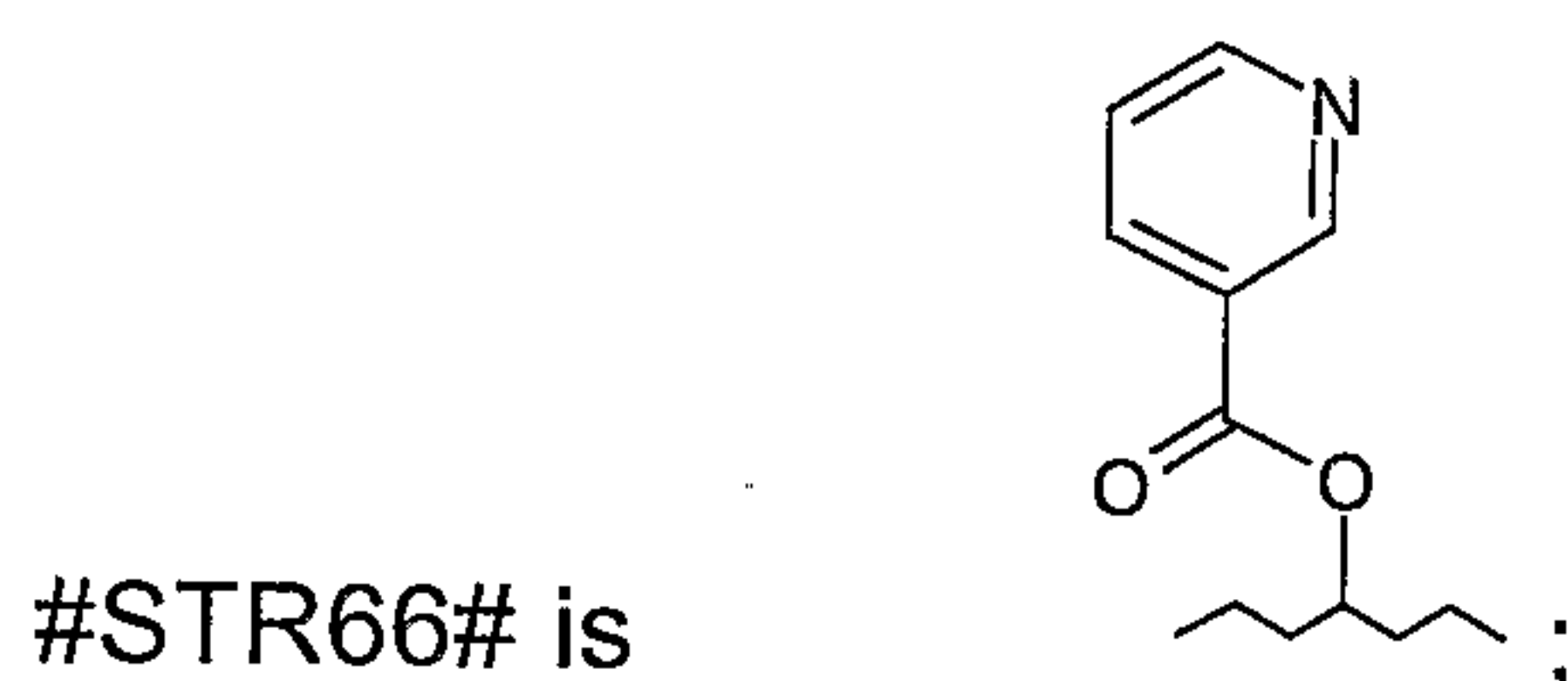
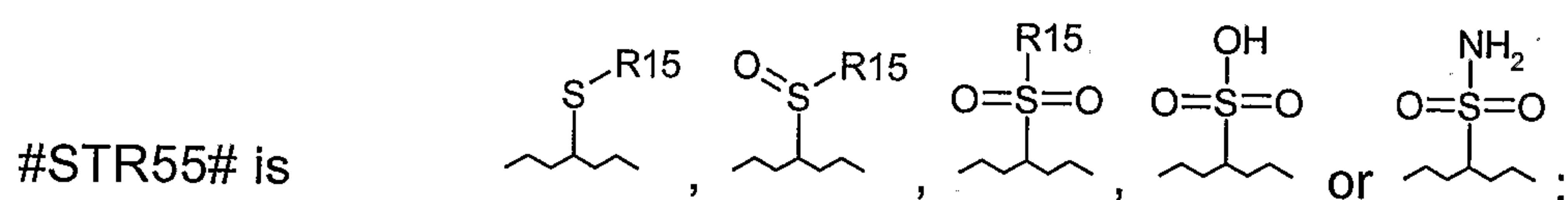
wherein

X can be CH, CH₂, CR₁₁, CR₁₃, CHR₁₁, CHR₁₃, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Y can be CH, CH₂, CR₁₂, CR₁₄, CHR₁₂, CHR₁₄, CR₁₁R₁₄, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Z can be a single, double bond or triple bond, with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

wherein



R₁₅ and R₁₆ are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₁-C₂₂)alkynyl, aryl, heteroaryl, alkoxy,

aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 4 compounds have at least one proviso selected from the following:

R8 is a hydroxyl;

at least one W is a N;

at least one of R1-R10 is #STR77#, #STR88# or #STR99#;

at least one of R1-R10 is #STR66#;

R8 is #STR66#;

one of R1-R10 is a monoester;

one of R1-R10 is a dicarboxylic acid;

R8 is #STR55#;

R8 and R3 are #STR55#;

R8 and R3 are hydroxyls; and

R8 is #STR66#.

[095] Another embodiment provides for compounds of Formula 4 wherein:

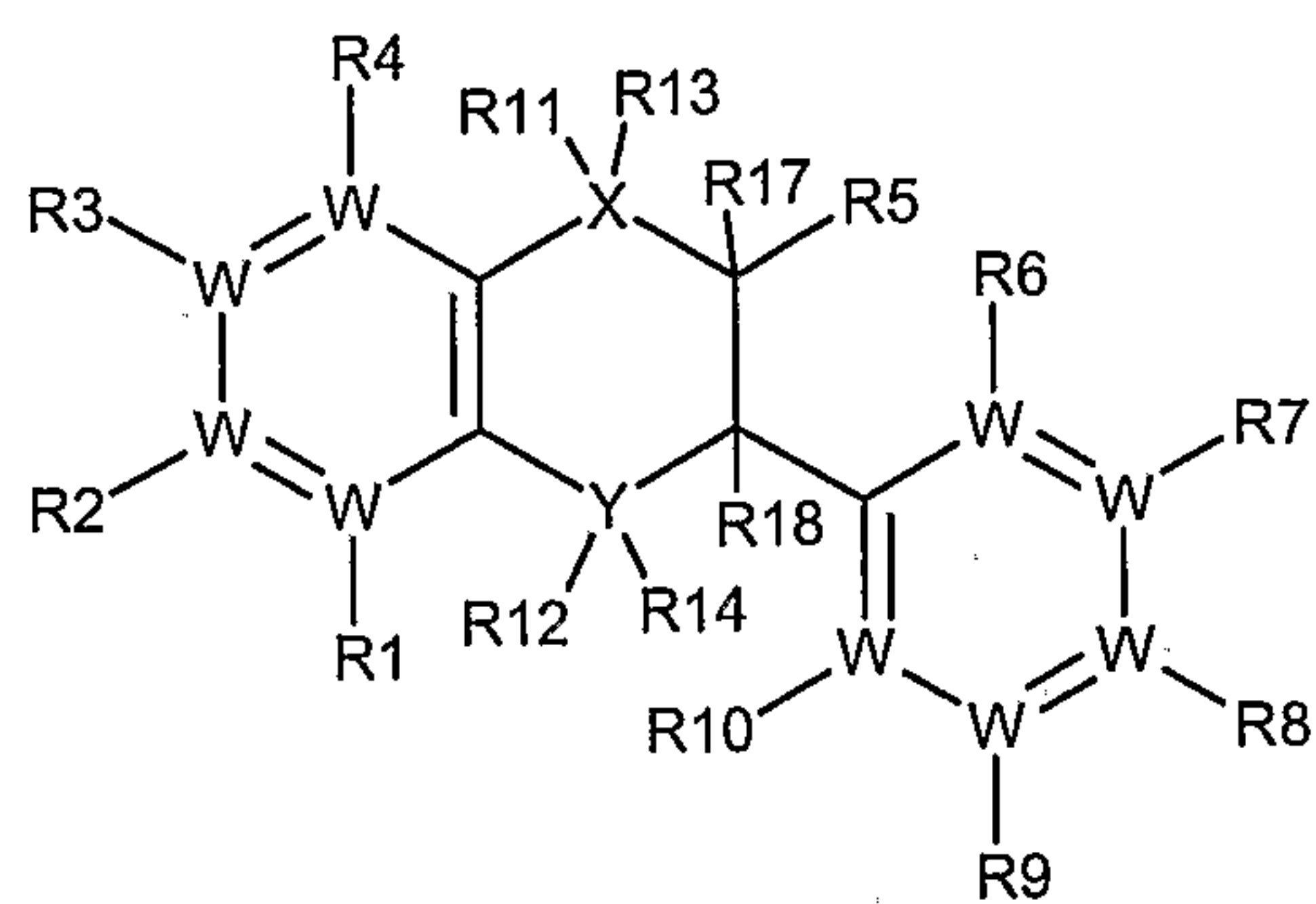
R8 is a hydroxyl and at least one W is a N;

R8 is a hydroxyl and at least one of R1-R7 and R9-R-10 is #STR66#;

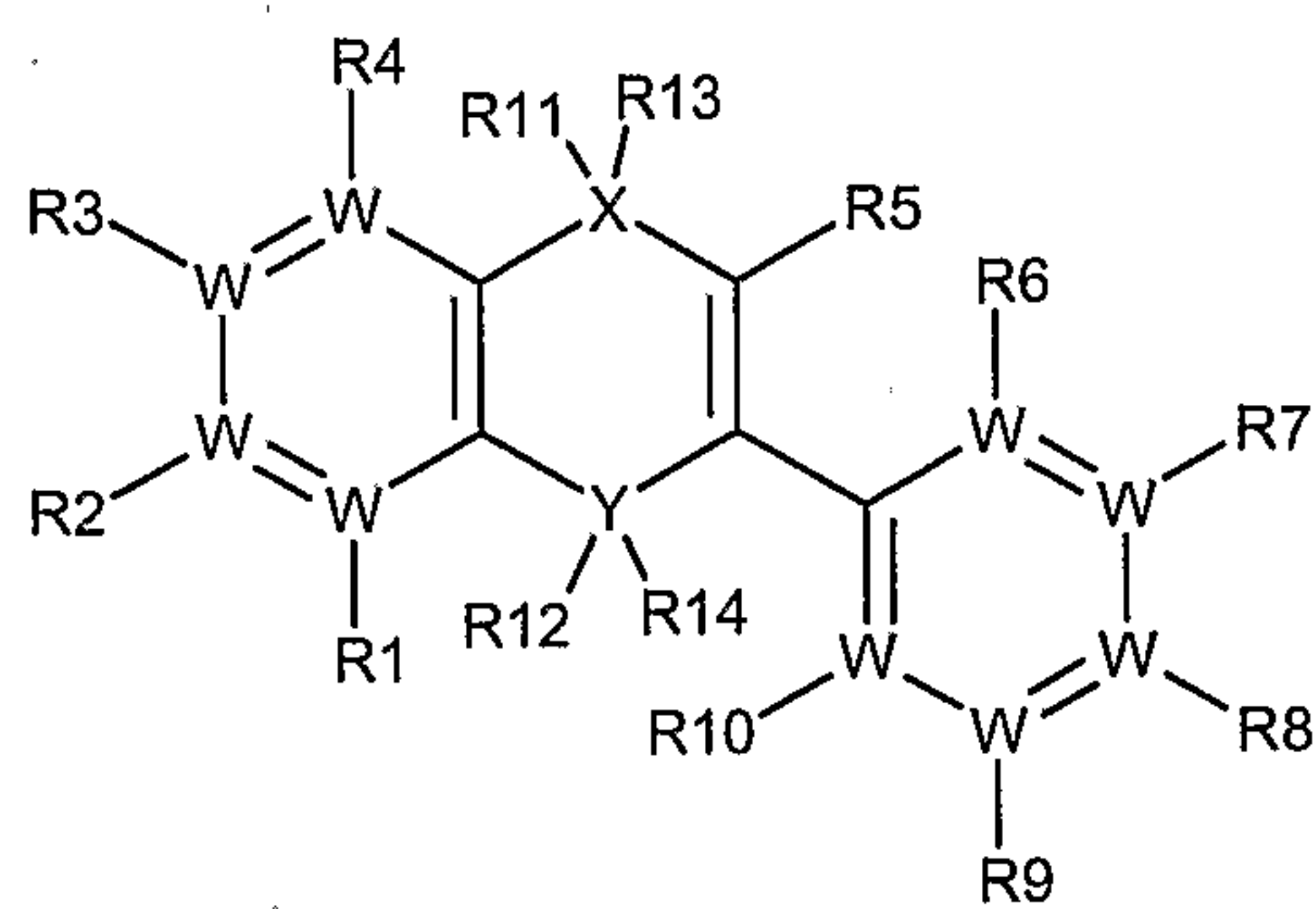
R8 is a hydroxyl and at least one of R1-R7 and R9-R10 is #STR77#, #STR88# or #STR99; and

R8 is #STR66# and at least one W is a N.

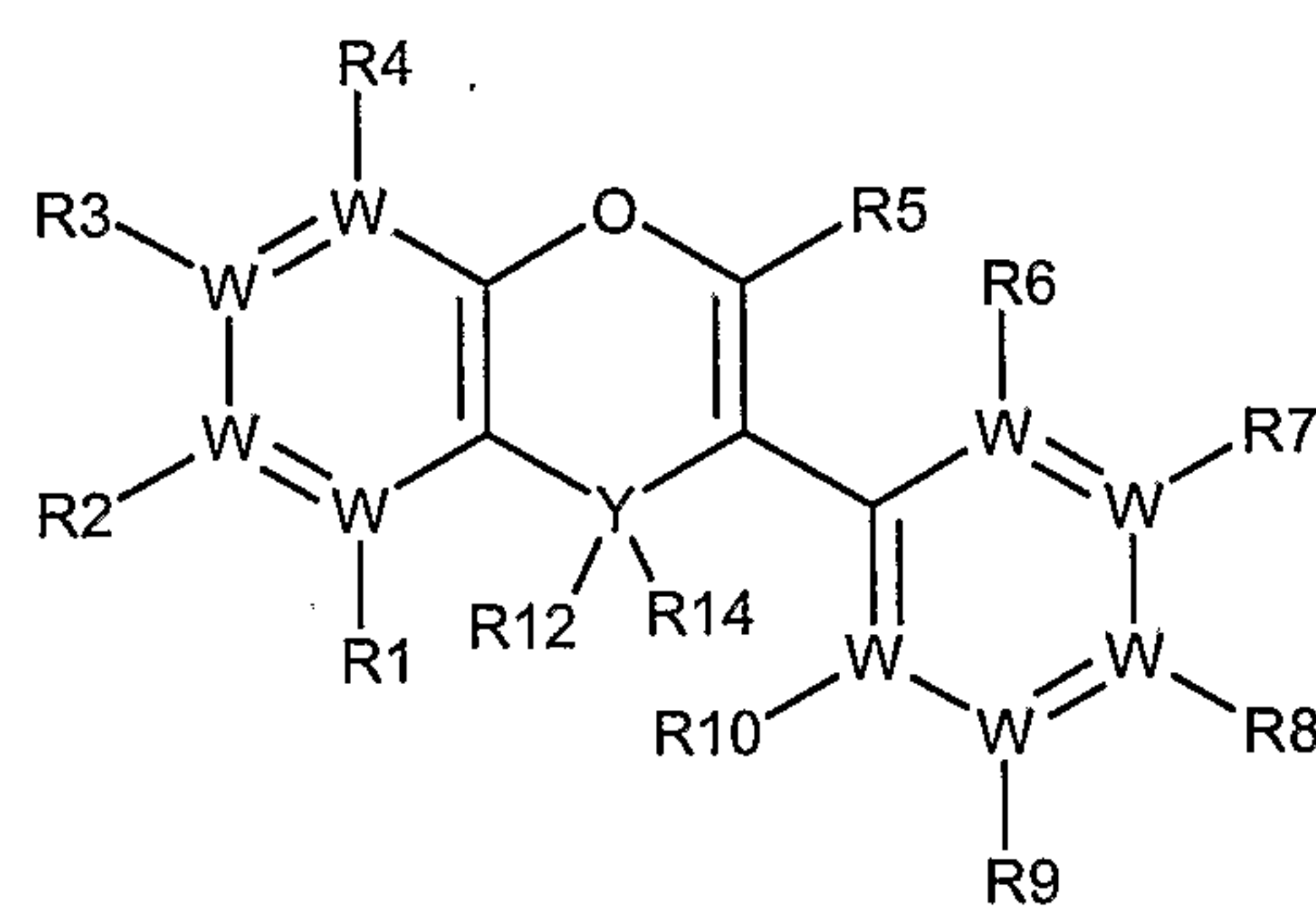
[096] Non-limiting examples of compounds of Formula 4 include:



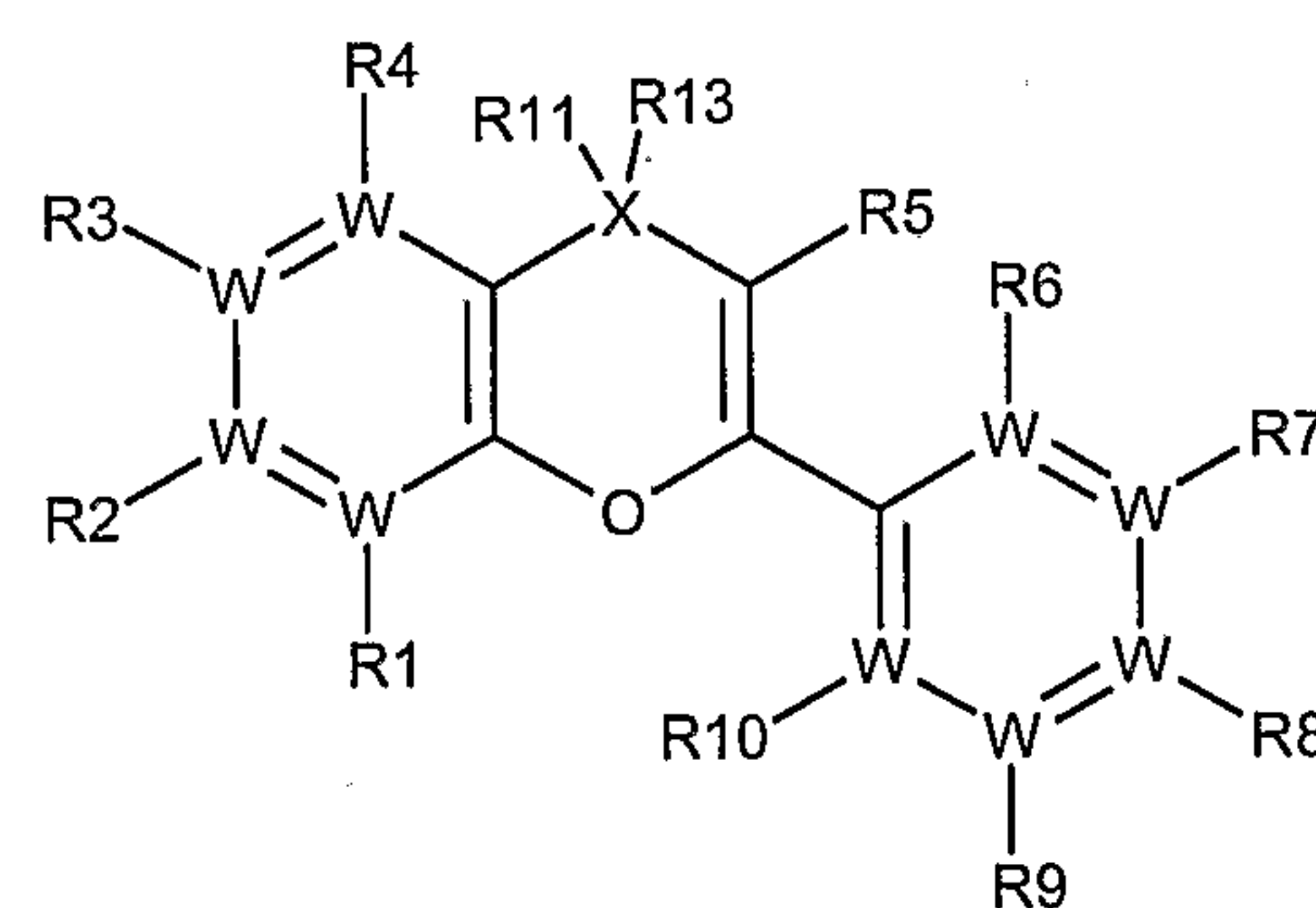
(XLV)



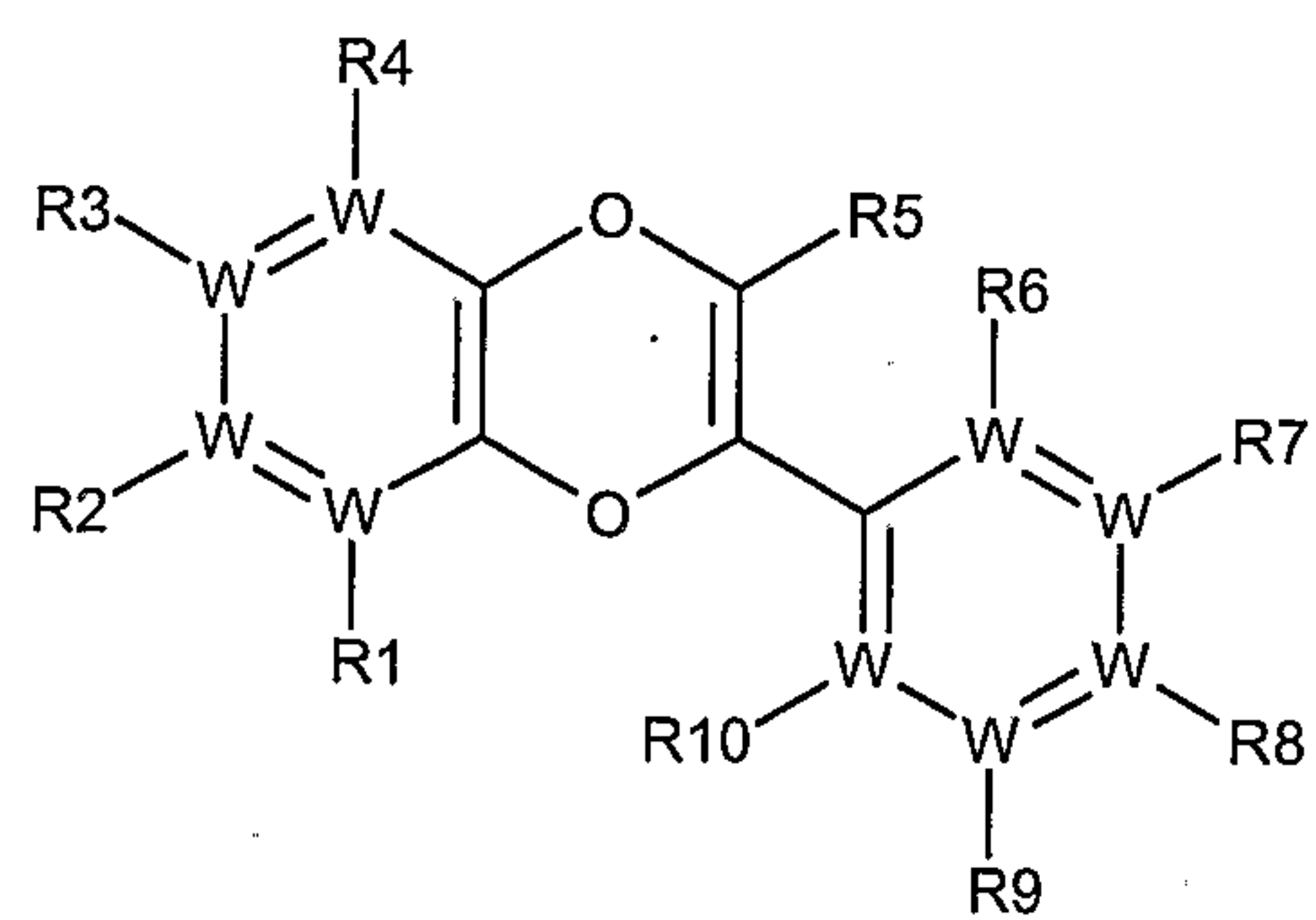
(XLVI)



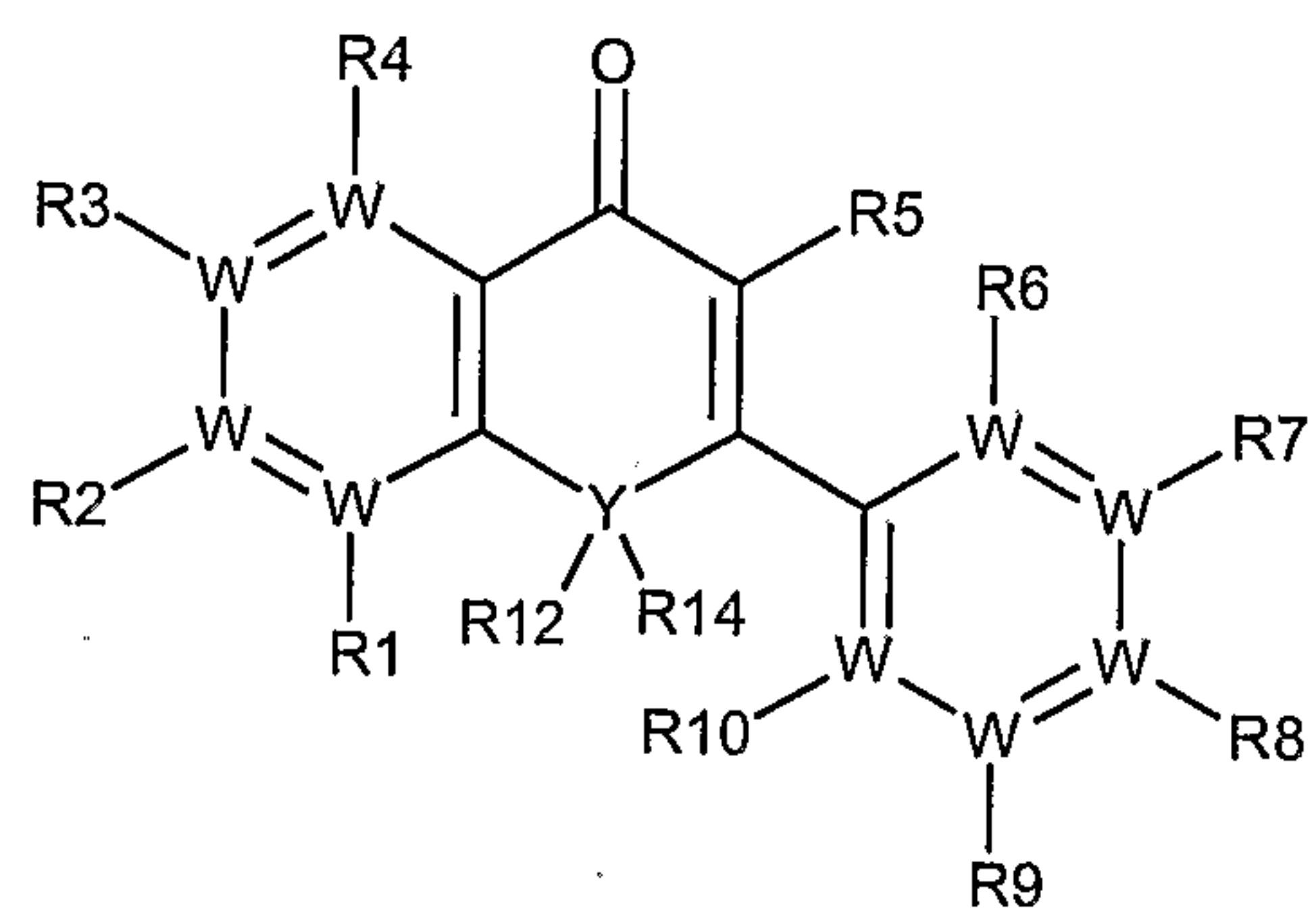
(XLVII)



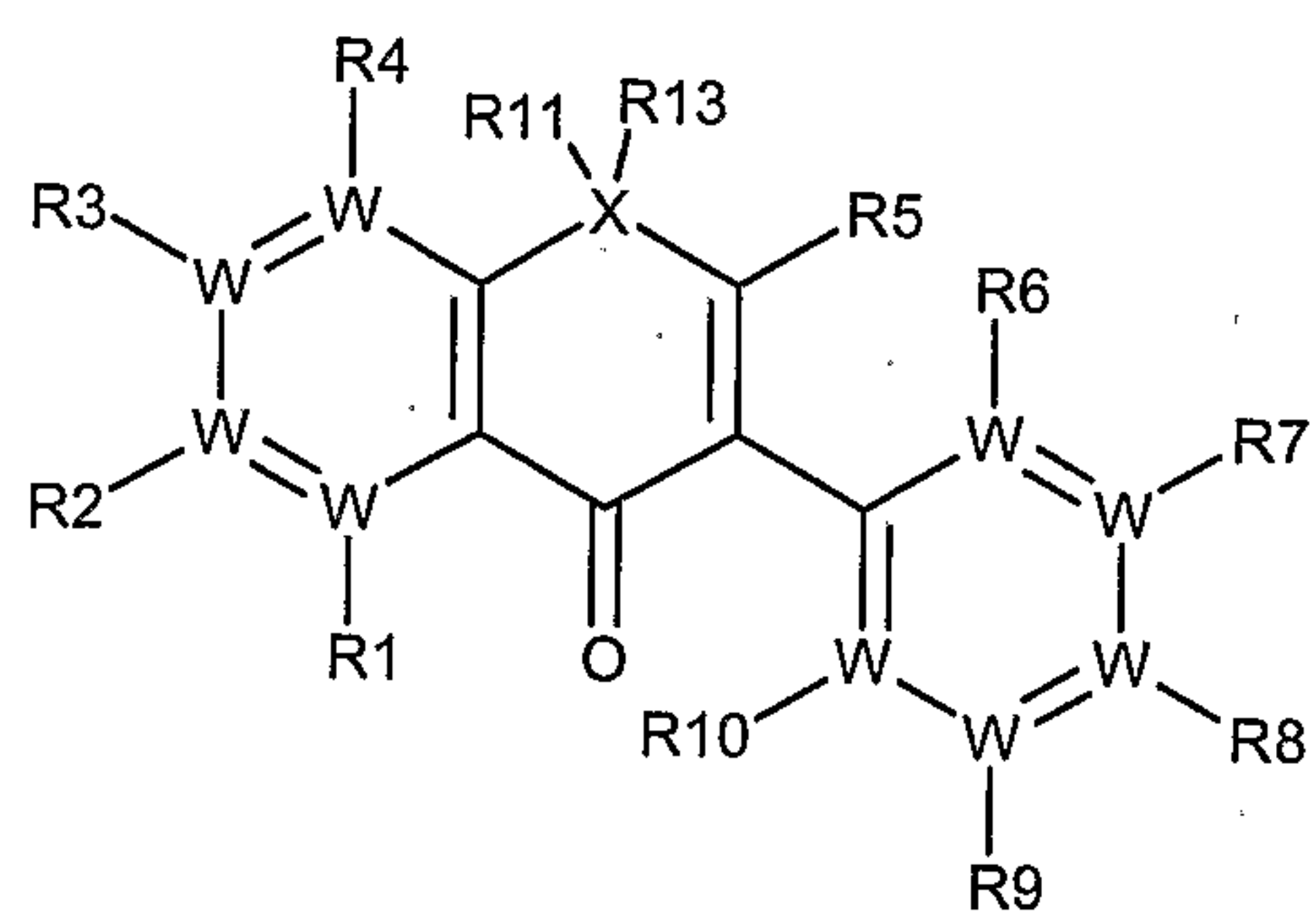
(XLVIII)



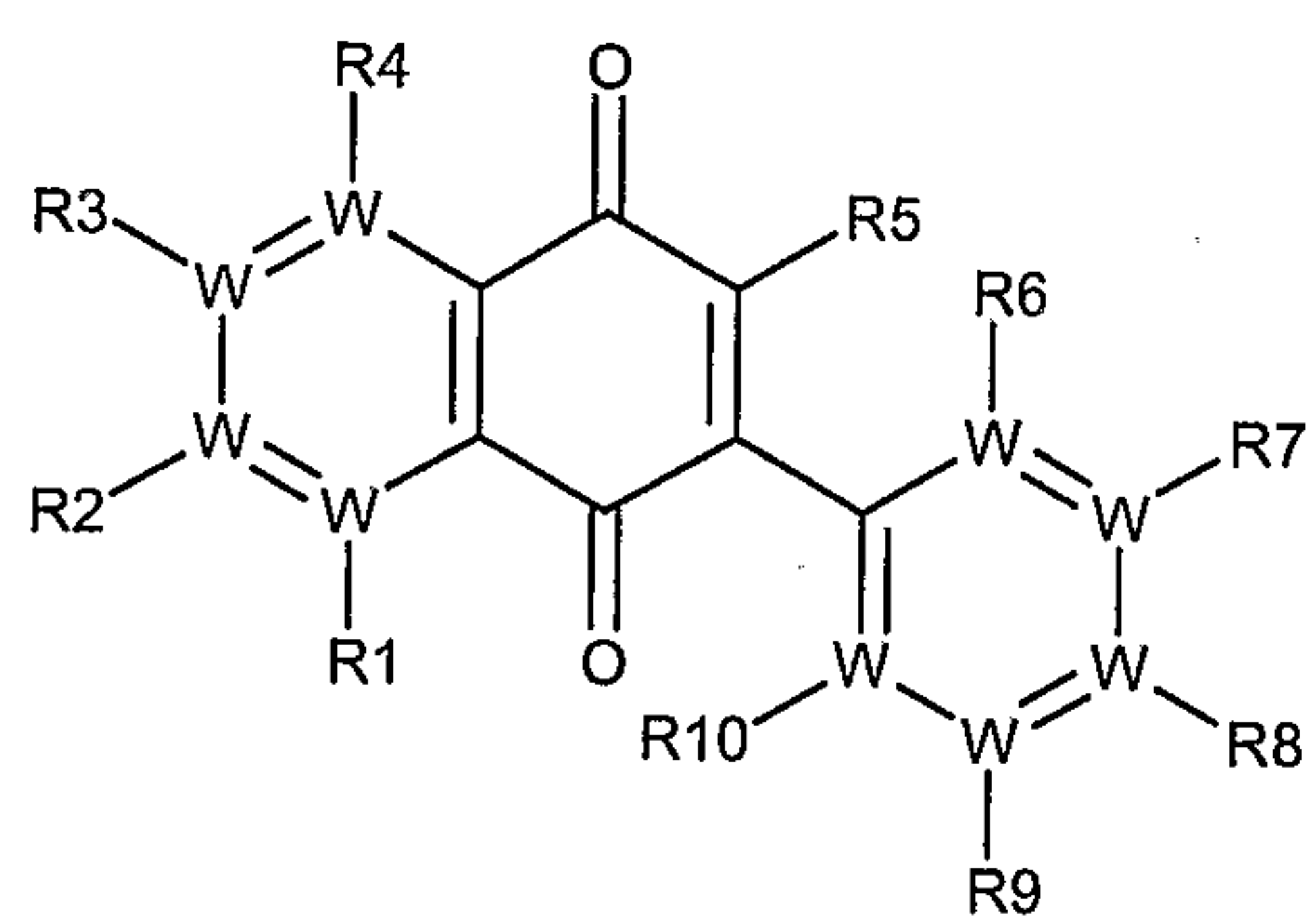
(XLIX)



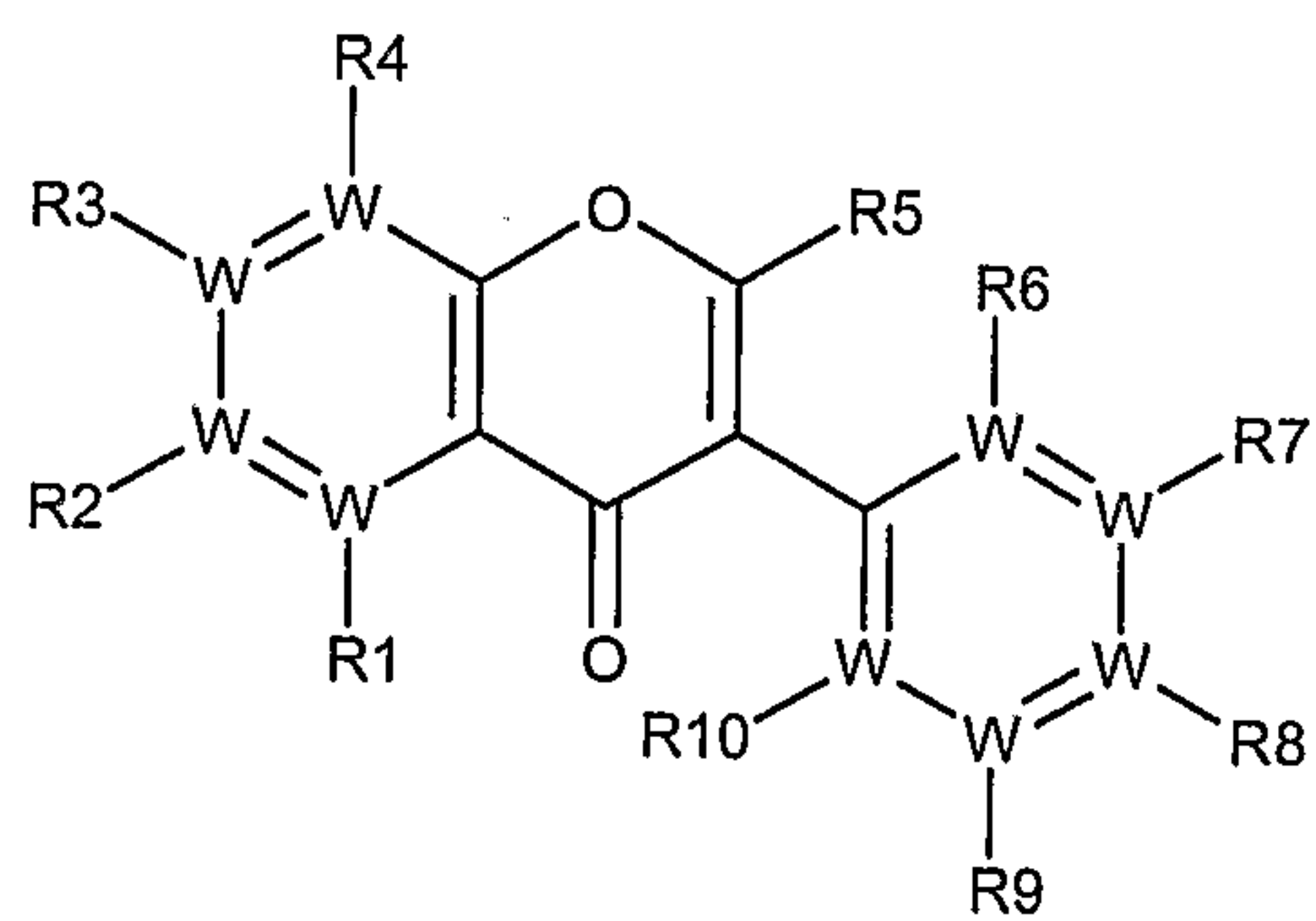
(L)



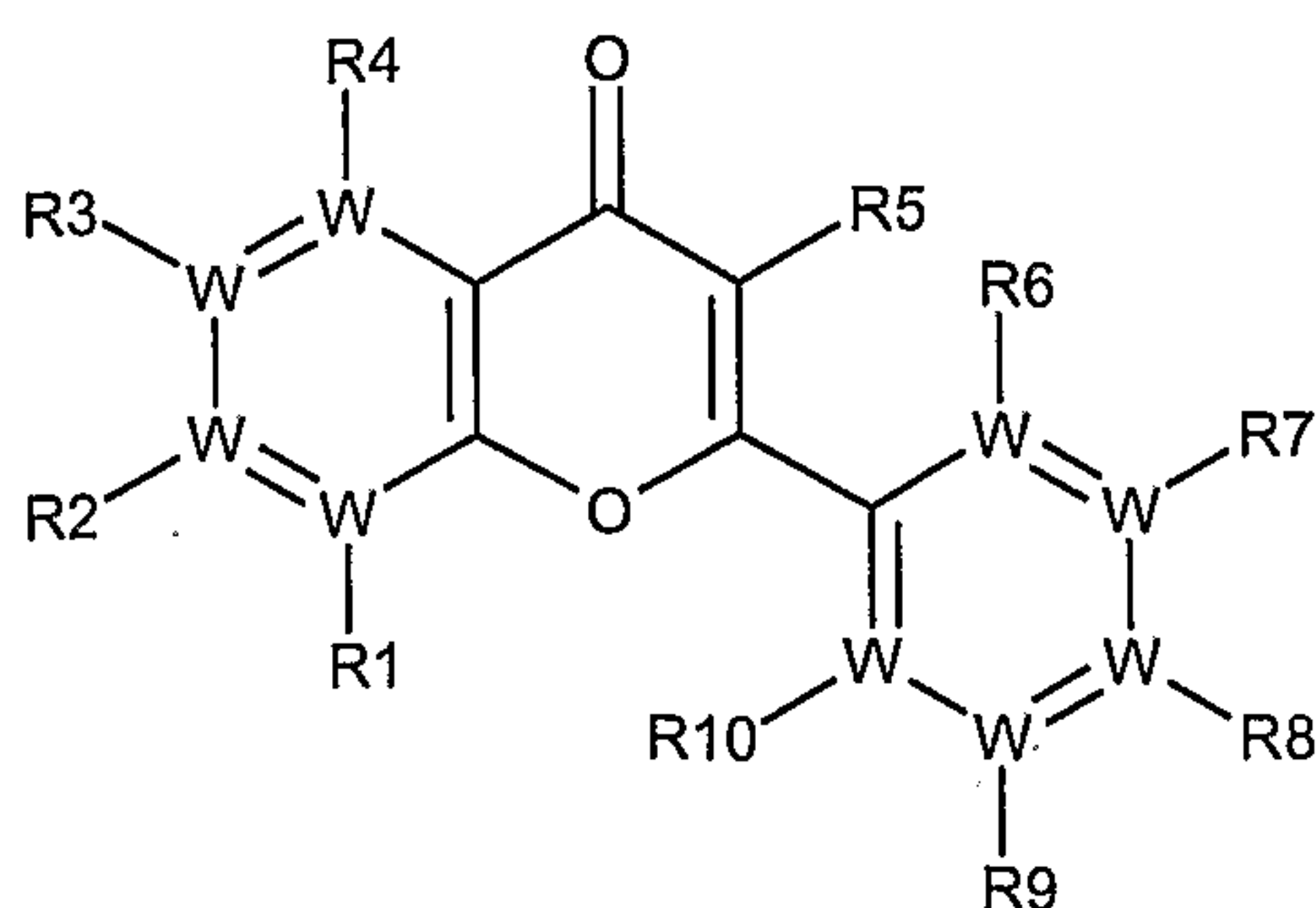
(LI)



(LII)



(LIII)



(LIV)

or a pharmaceutically acceptable salt thereof,

wherein

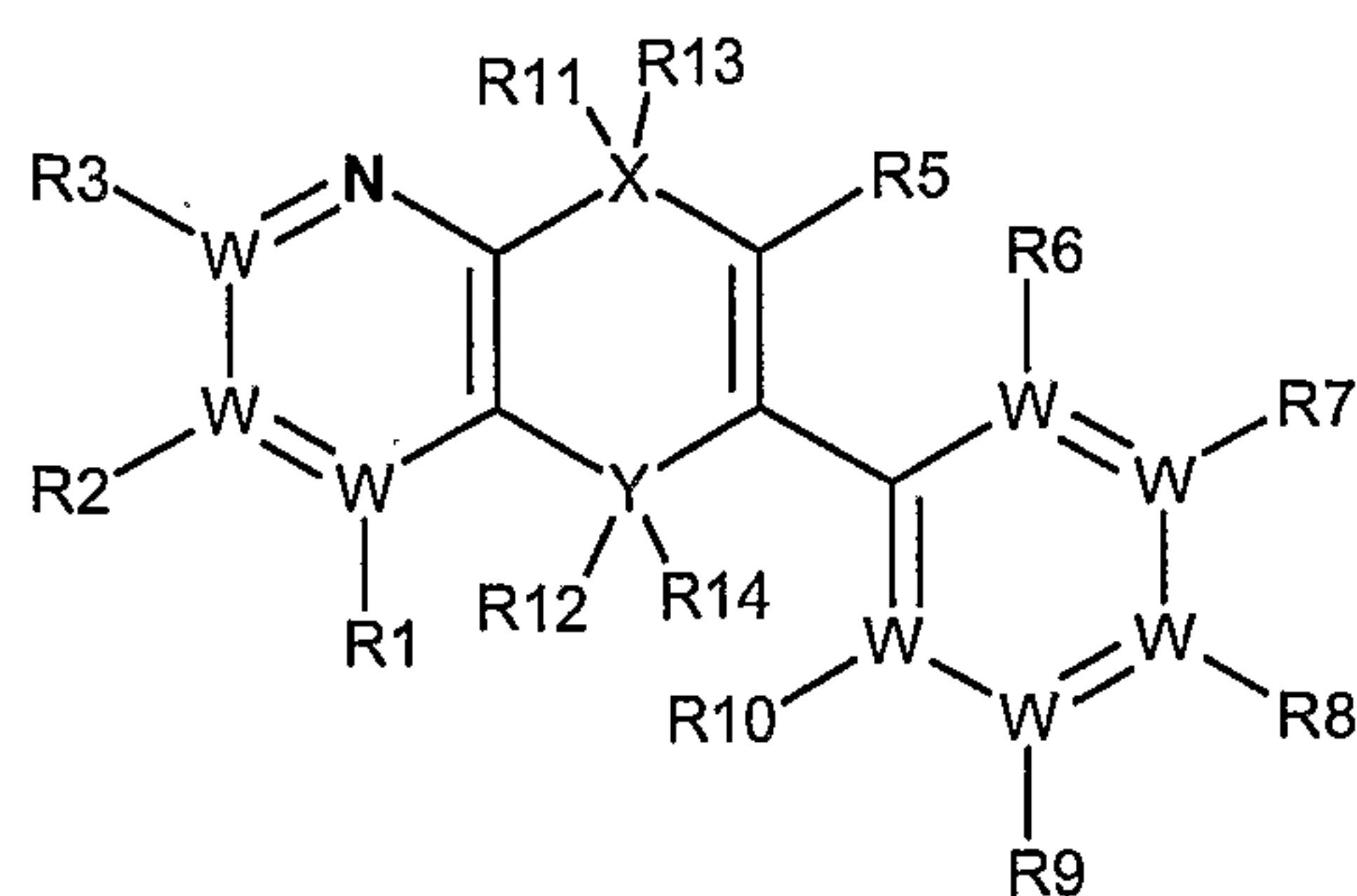
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R17 and R18 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₁-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], monoesters, dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#, #STR100#,

wherein

W can be C or N;

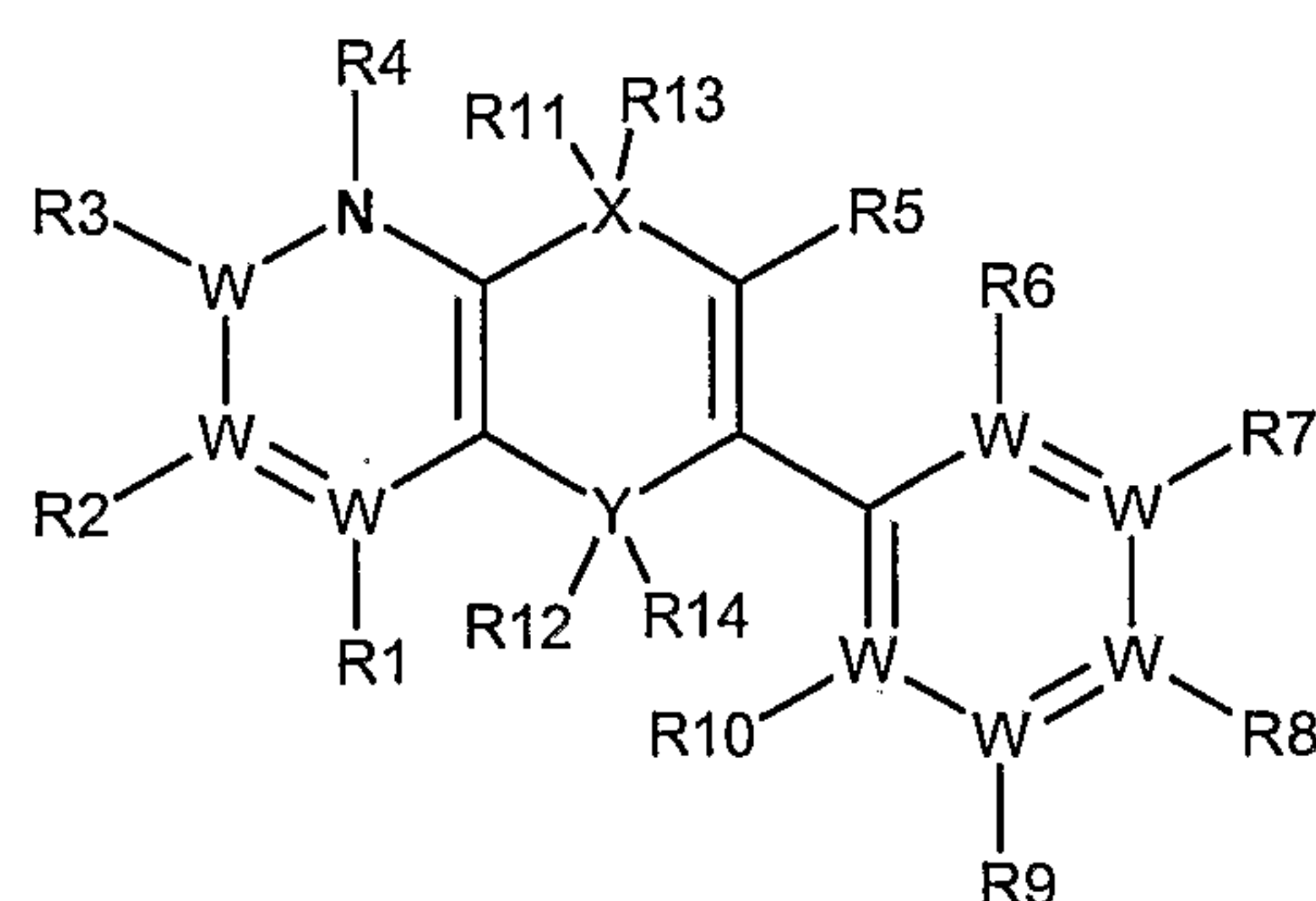
wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[097] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 4:



wherein the same applies to any W;

or



wherein the same applies to any W:

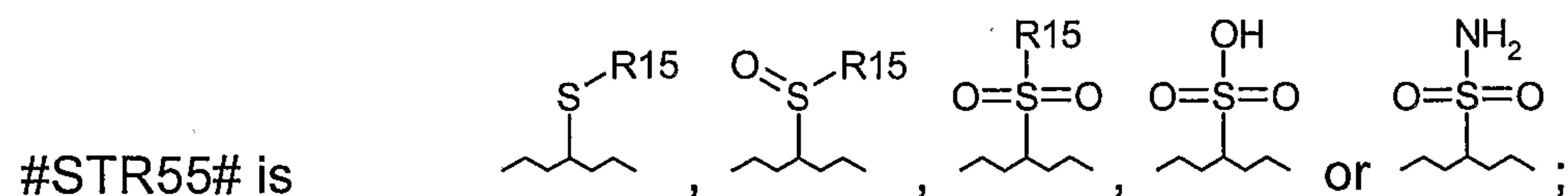
wherein

X can be CH, CH₂, CR₁₁, CR₁₃, CHR₁₁, CHR₁₃, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

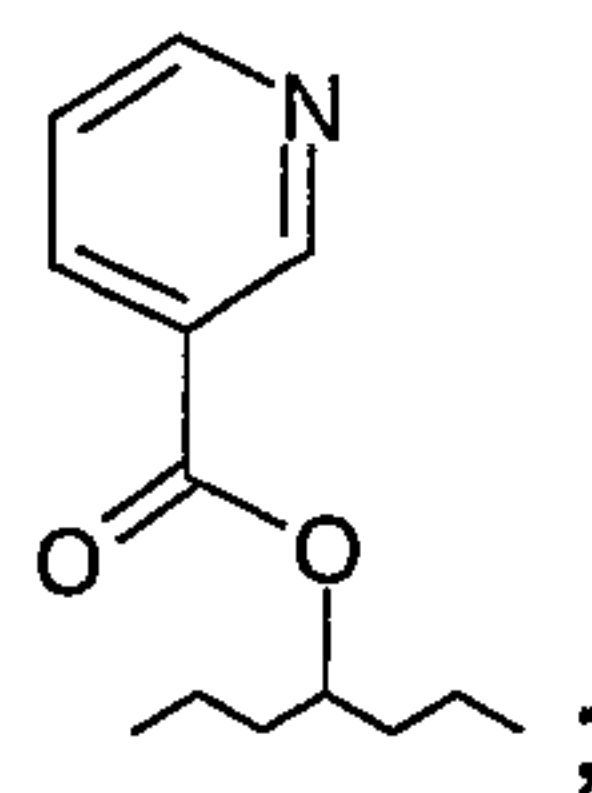
Y can be CH, CH₂, CR₁₂, CR₁₄, CHR₁₂, CHR₁₄, CR₁₁R₁₄, CO, CS, O, S, SO, SO₂, NH, NR₁₁ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Z can be a single, double bond or triple bond, with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

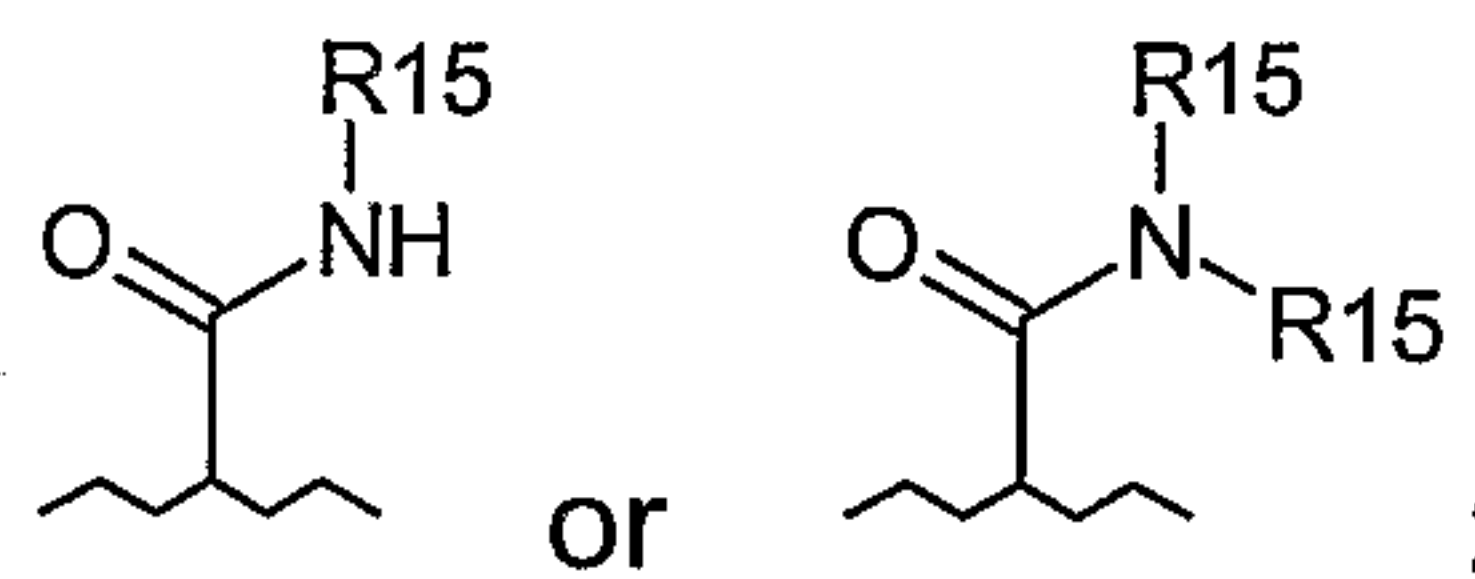
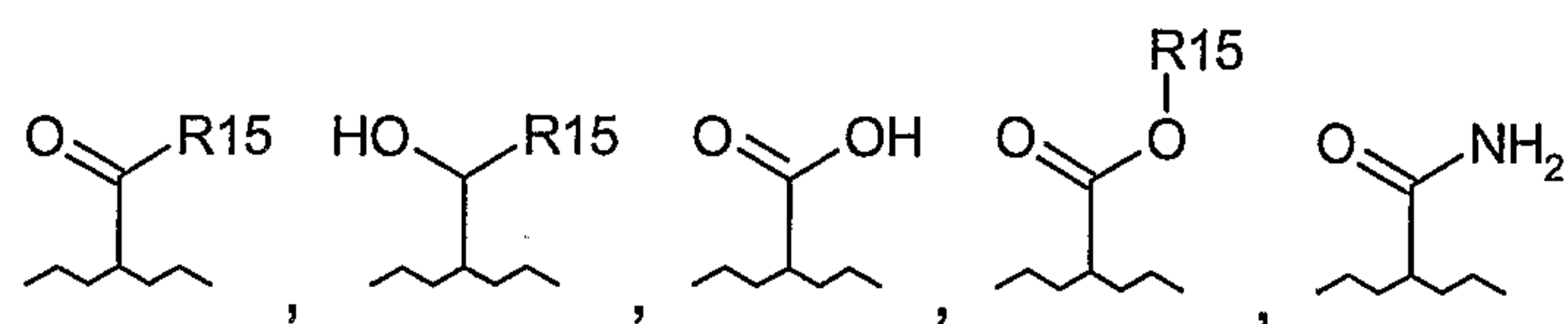
wherein



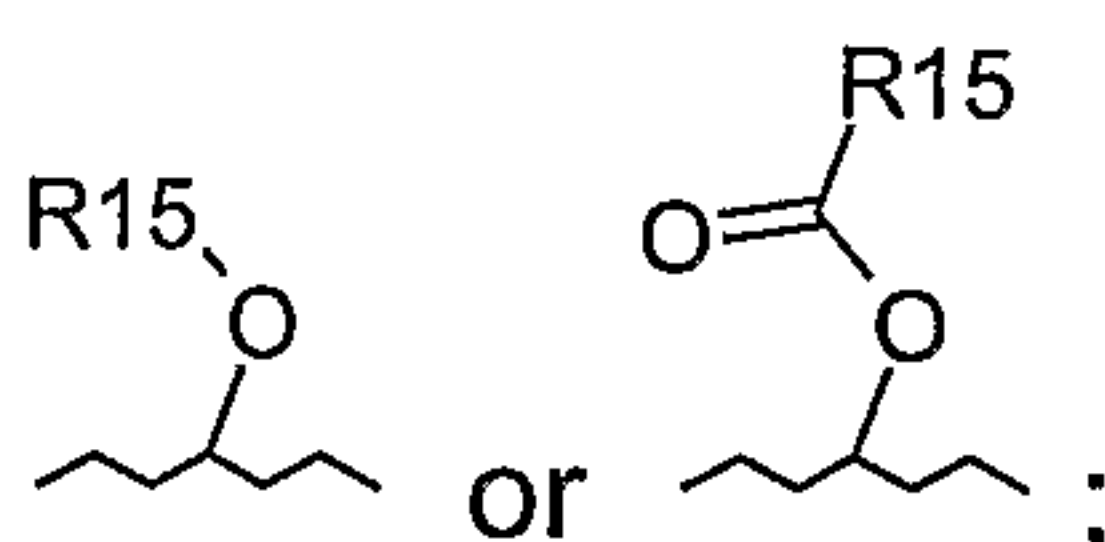
#STR66# is



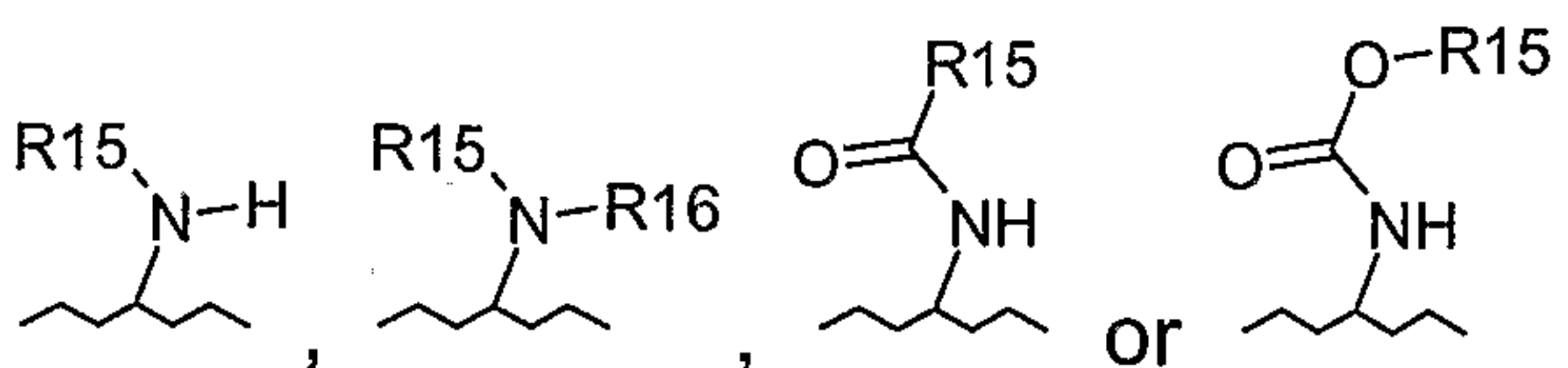
#STR77# is



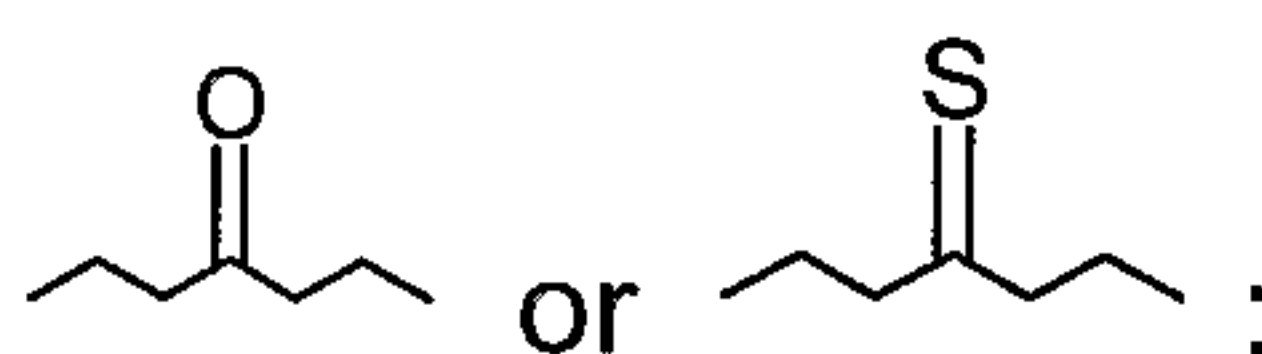
#STR88# is



#STR99# is



#STR100# is



R15 and R16 are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₁-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 4 compounds have at least one proviso selected from the following:

R8 is a hydroxyl;

at least one W is a N;

at least one of R1-R10 is #STR77#, #STR88# or #STR99#;

at least one of R1-R10 is #STR66#;

R8 is #STR66#;

one of R1-R10 is a monoester;

one of R1-R10 is a dicarboxylic acid;

R8 is #STR55#;

R8 and R3 are #STR55#;

R8 and R3 are hydroxyls; and

R8 is #STR66#.

[098] Another embodiment provides for compounds of Formula 4 wherein:

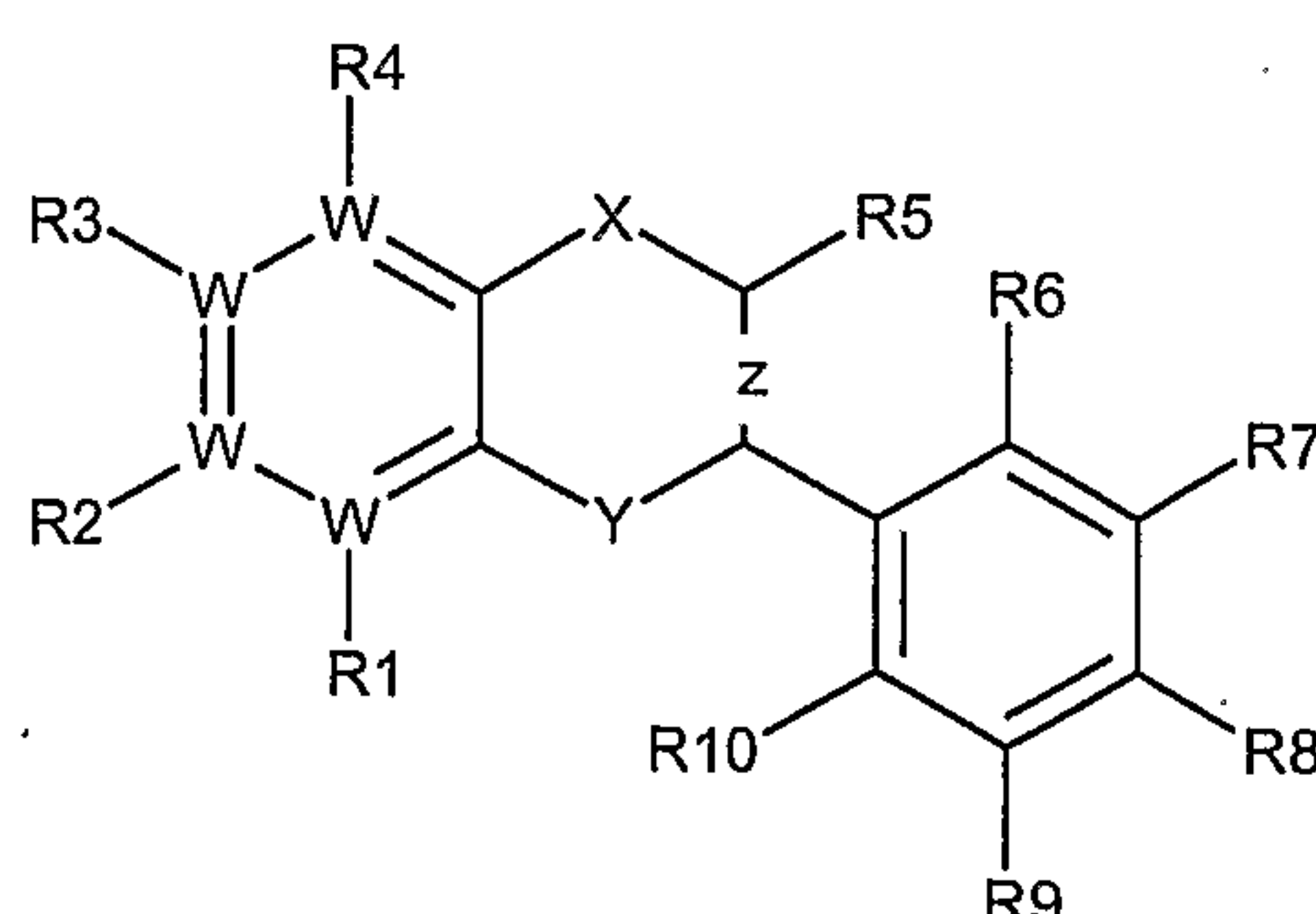
R8 is a hydroxyl and at least one W is a N;

R8 is a hydroxyl and at least one of R1-R7 and R9-R-10 is #STR66#;

R8 is a hydroxyl and at least one of R1-R7 and R9-R10 is #STR77#, #STR88# or #STR99; and

R8 is #STR66# and at least one W is a N.

[099] Another alternative embodiment provides isoflavanoid compounds of Formula 5:



or a pharmaceutically acceptable salt thereof,

wherein

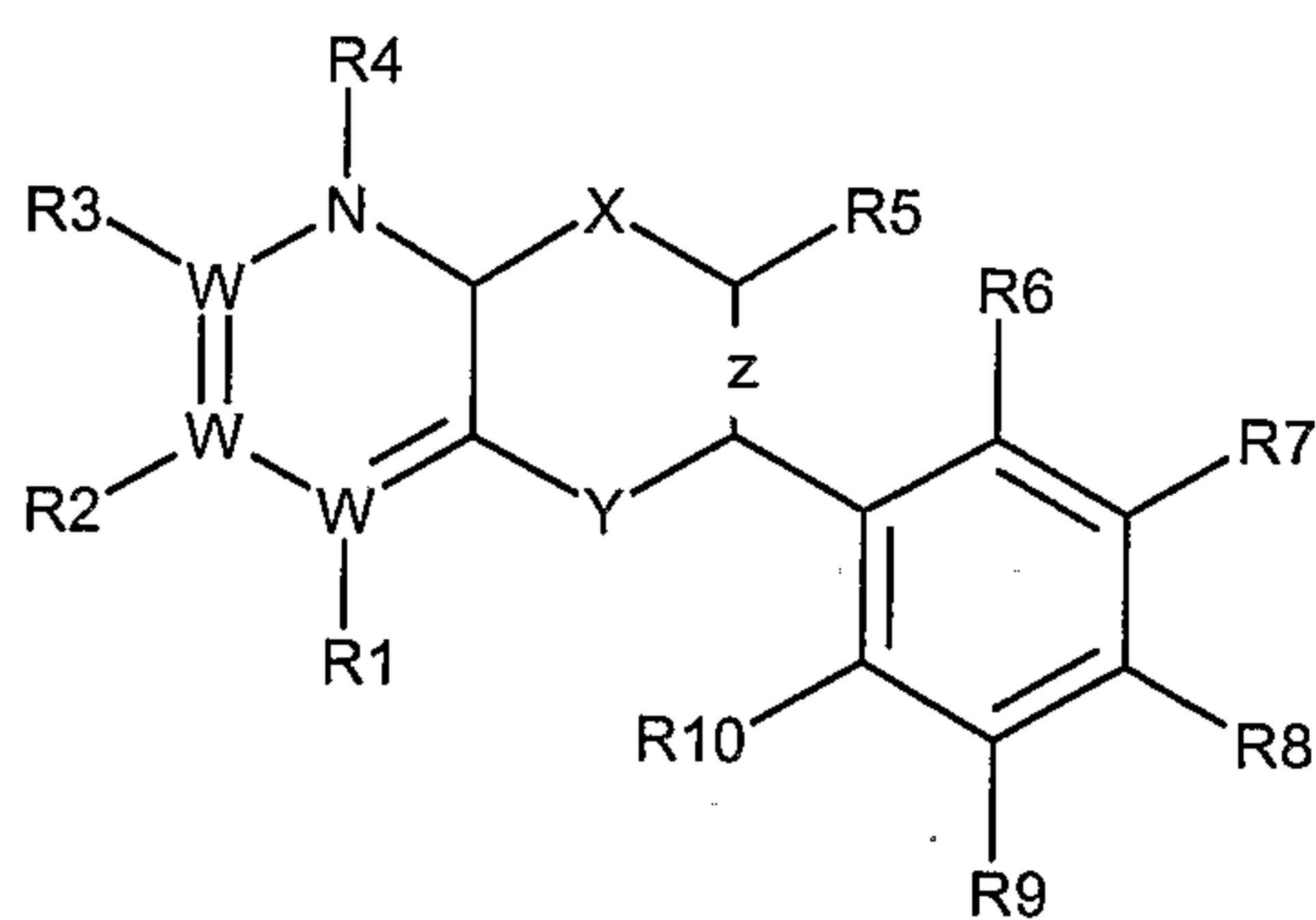
R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

wherein

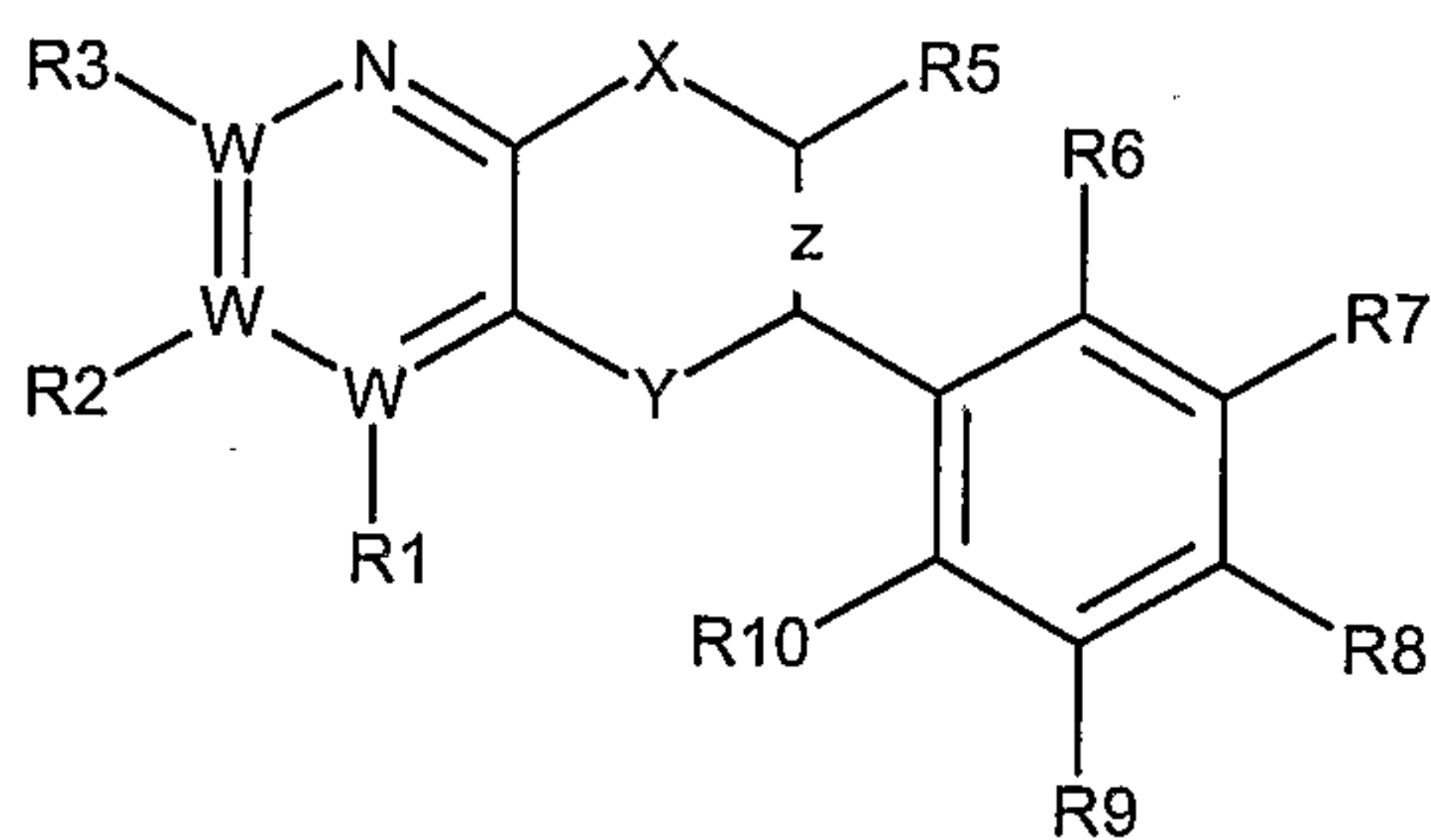
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0100] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5:

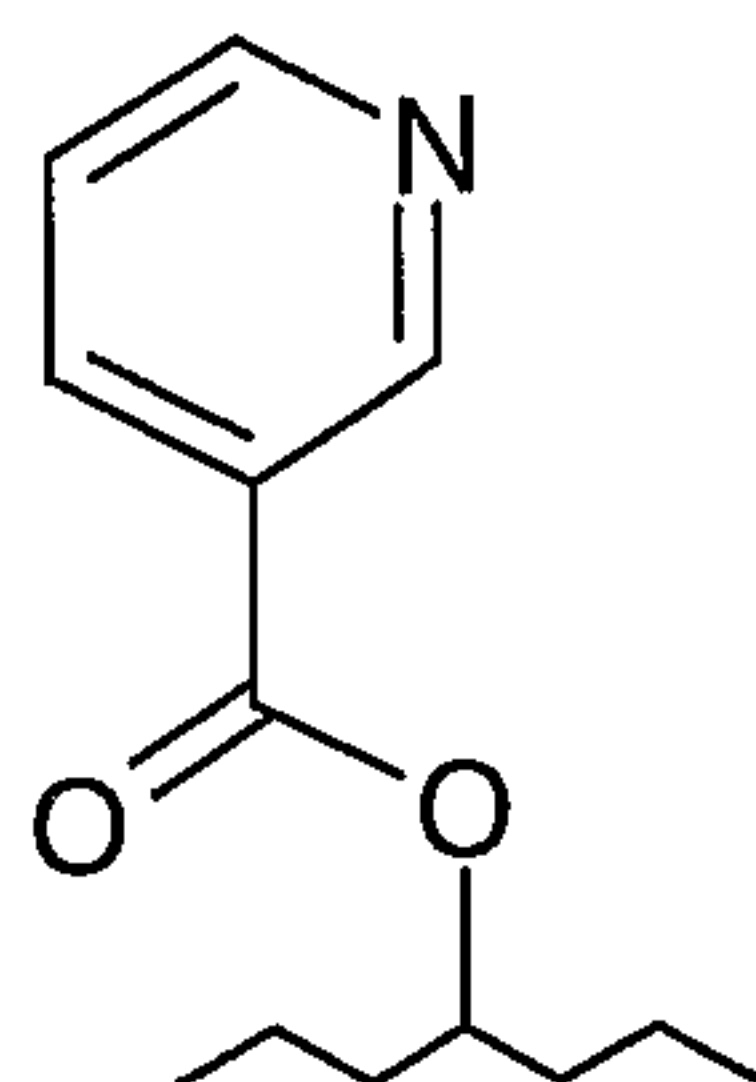


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

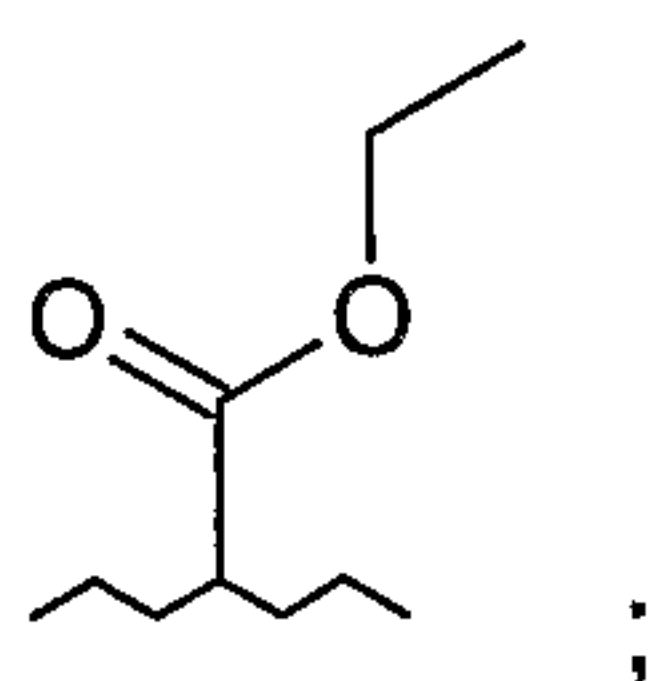
Z can be a single or a double bond

Wherein

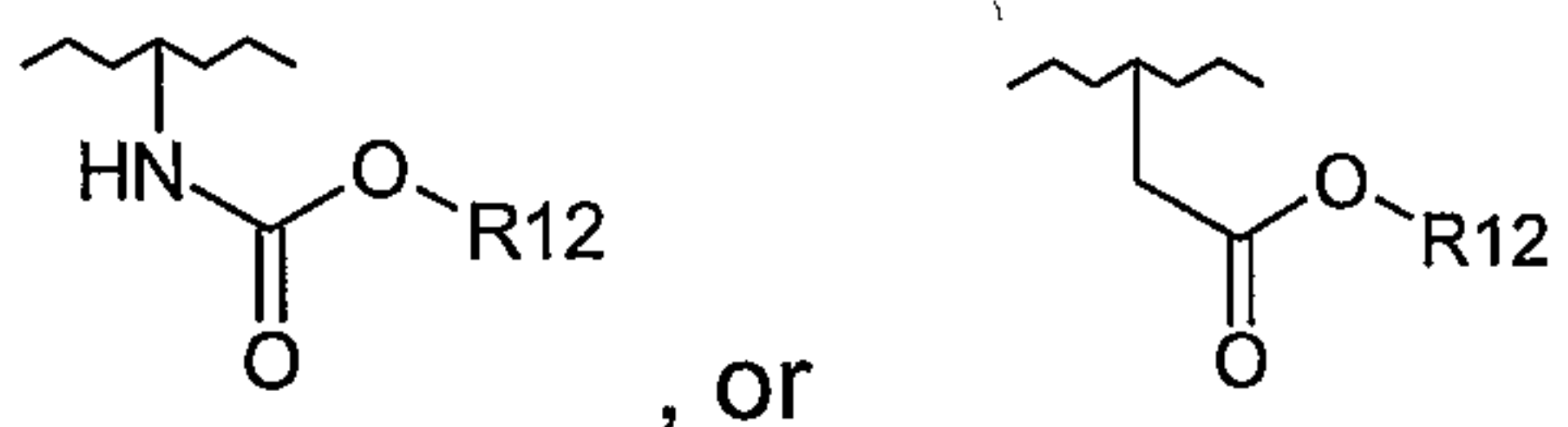
R₁₃ is #STR77#, #STR88#, #STR99#, or #STR100#,

Wherein

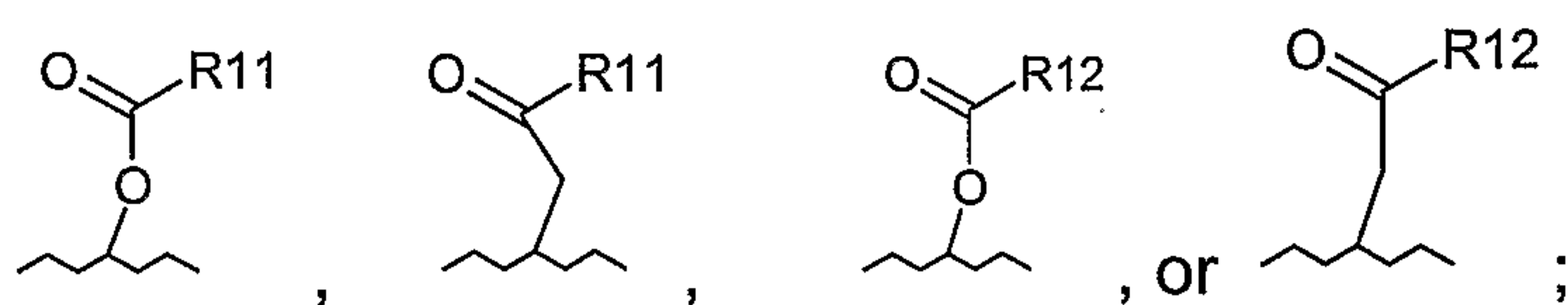
#STR77# means



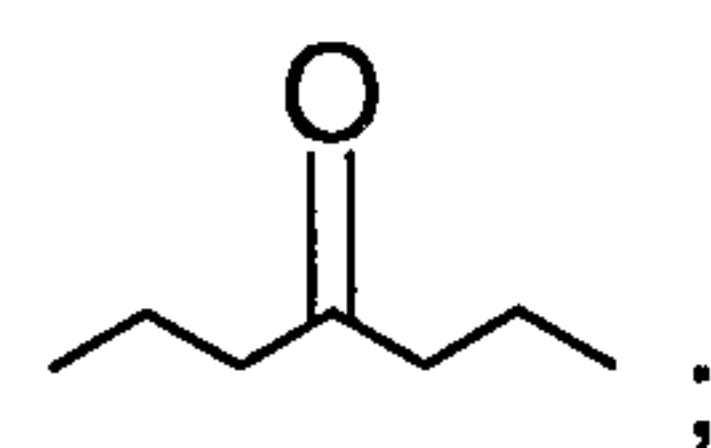
#STR88# means



#STR99# means



#STR100# means



R₁₁ is pyridine, pyridazine, pyrimidine, pyrazine; and

R₁₂ is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof,

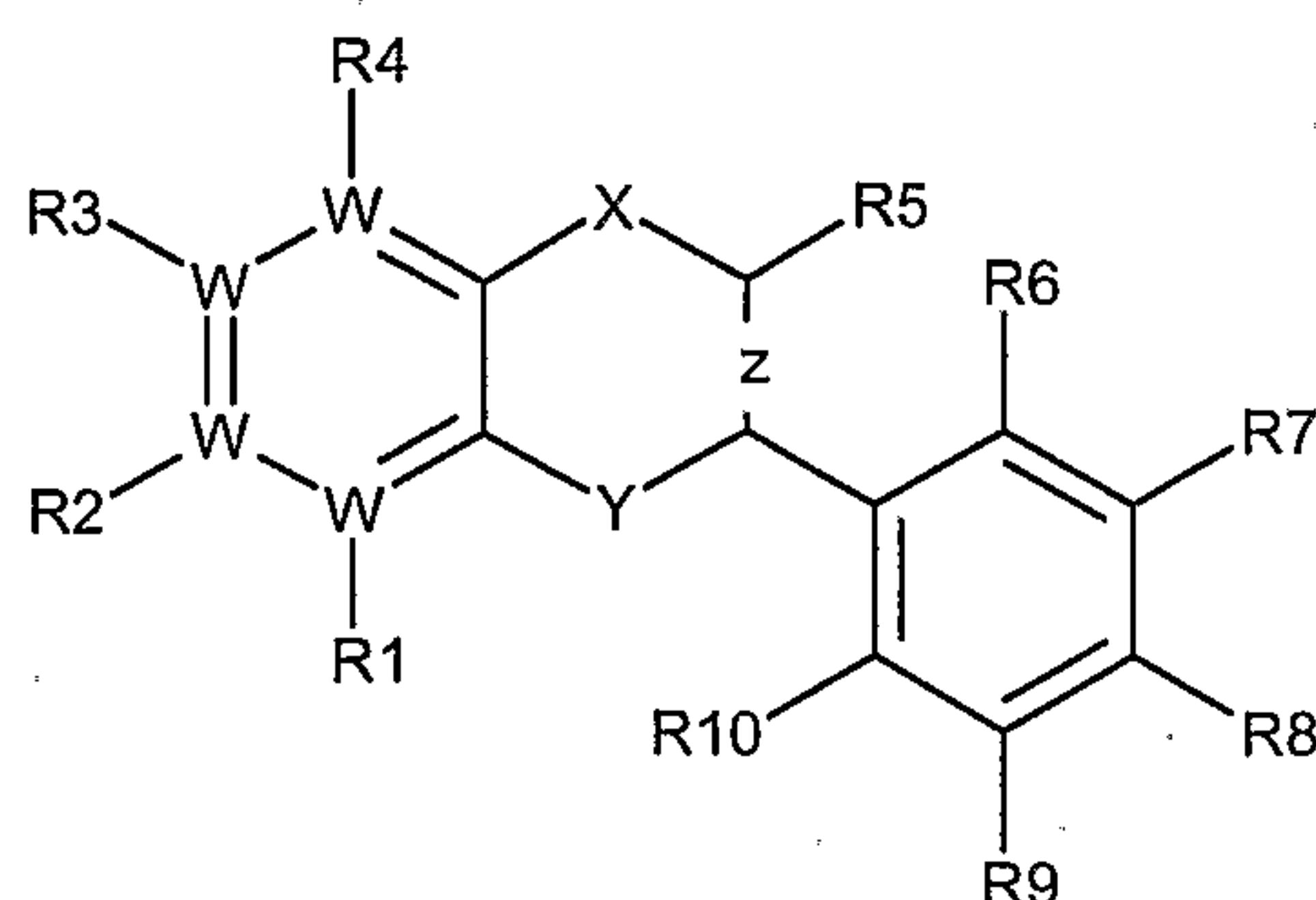
wherein said derivative is optionally substituted and optionally branched, and may

have one or more of the C atoms replaced by S, N or O;

with the proviso that;

- a) R8 is a hydroxyl; or
- b) R8 is a hydroxyl, and optionally;
- c) at least one W is a N, and/or;
- d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;
- e) at least one of R1-R10 is #STR66#.

[0101] Another alternative embodiment provides compounds comprising the isoflavonoid structure of Formula 5:



or a pharmaceutically acceptable salt thereof,

wherein

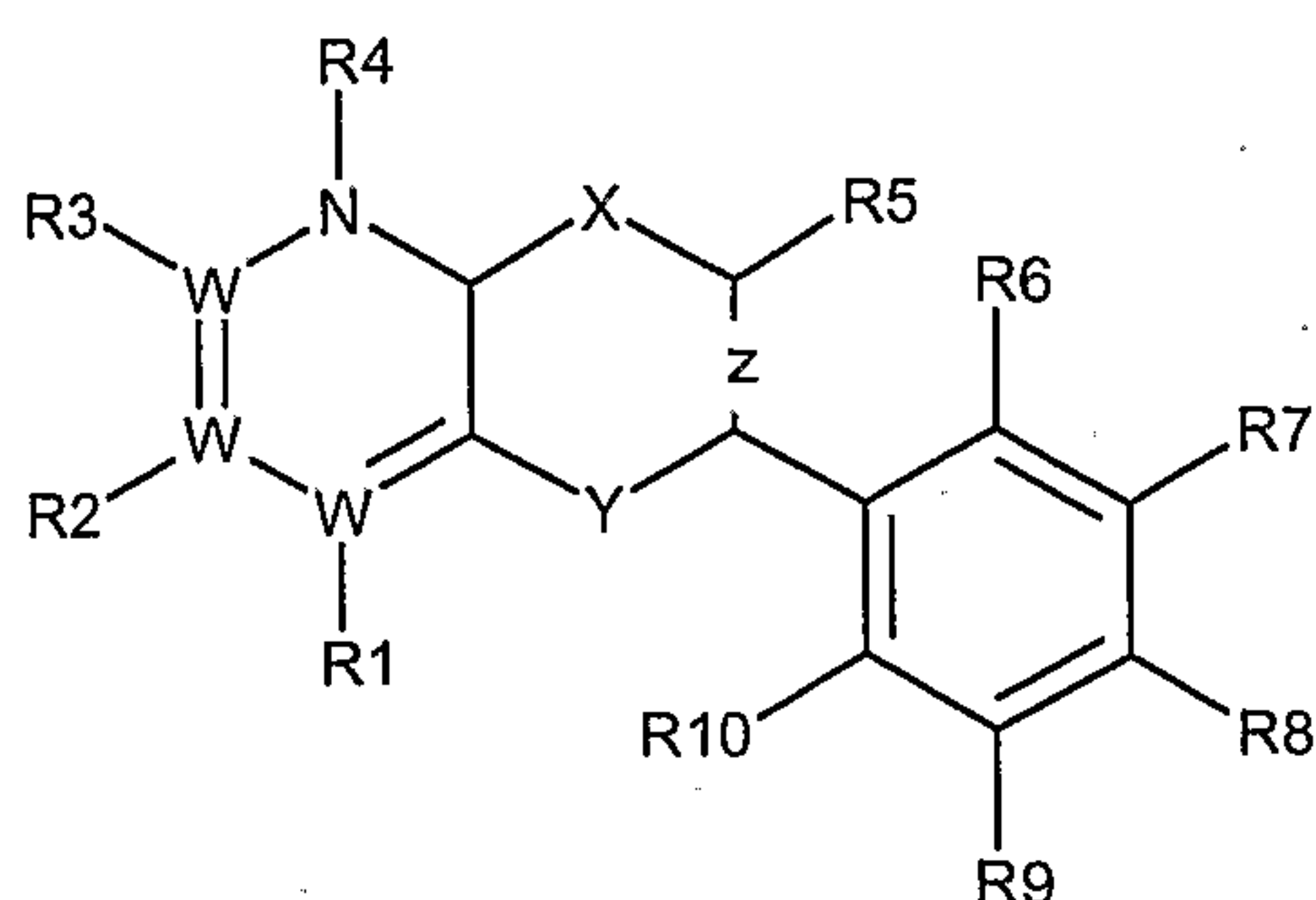
R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

wherein

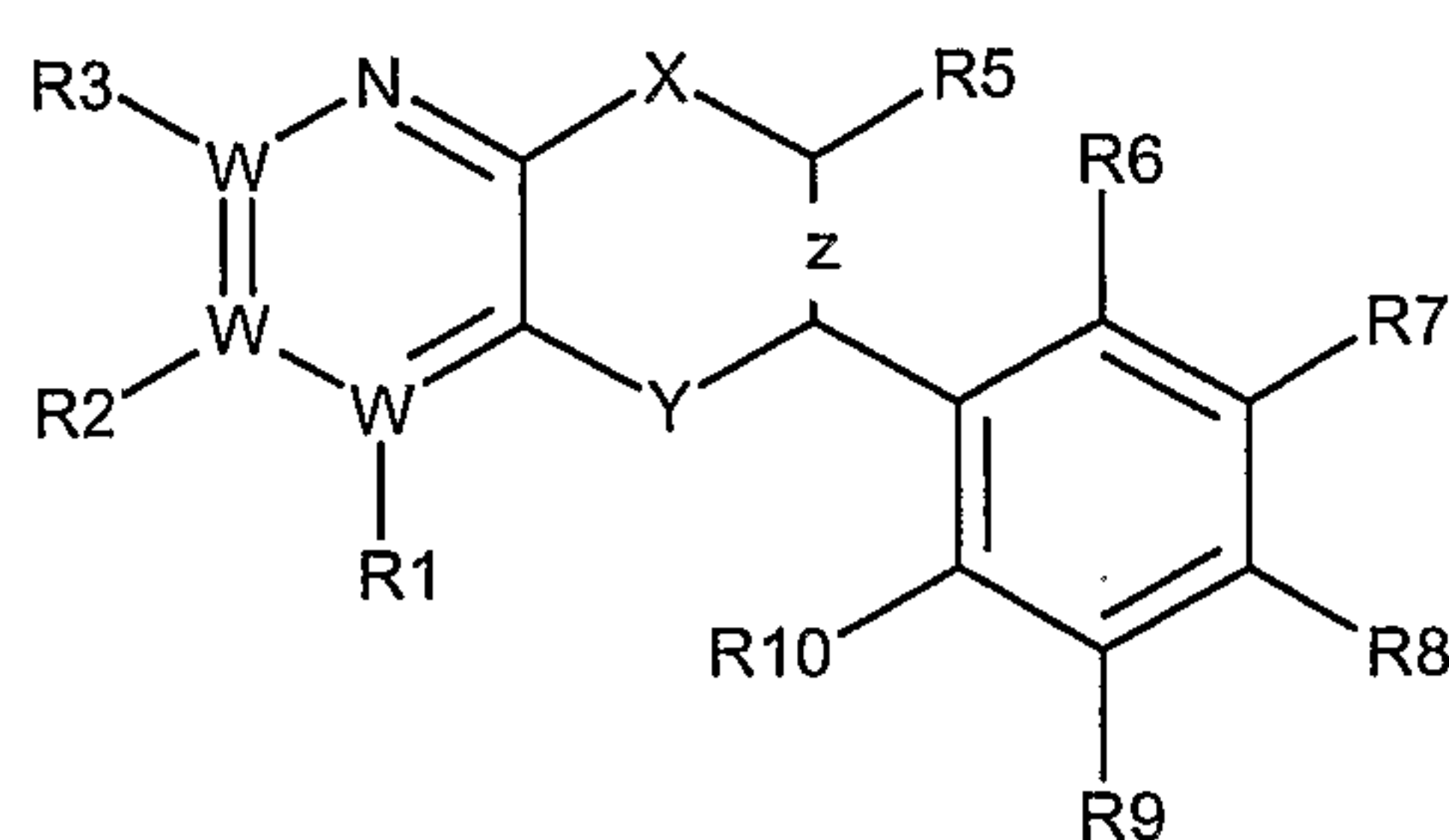
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0102] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5

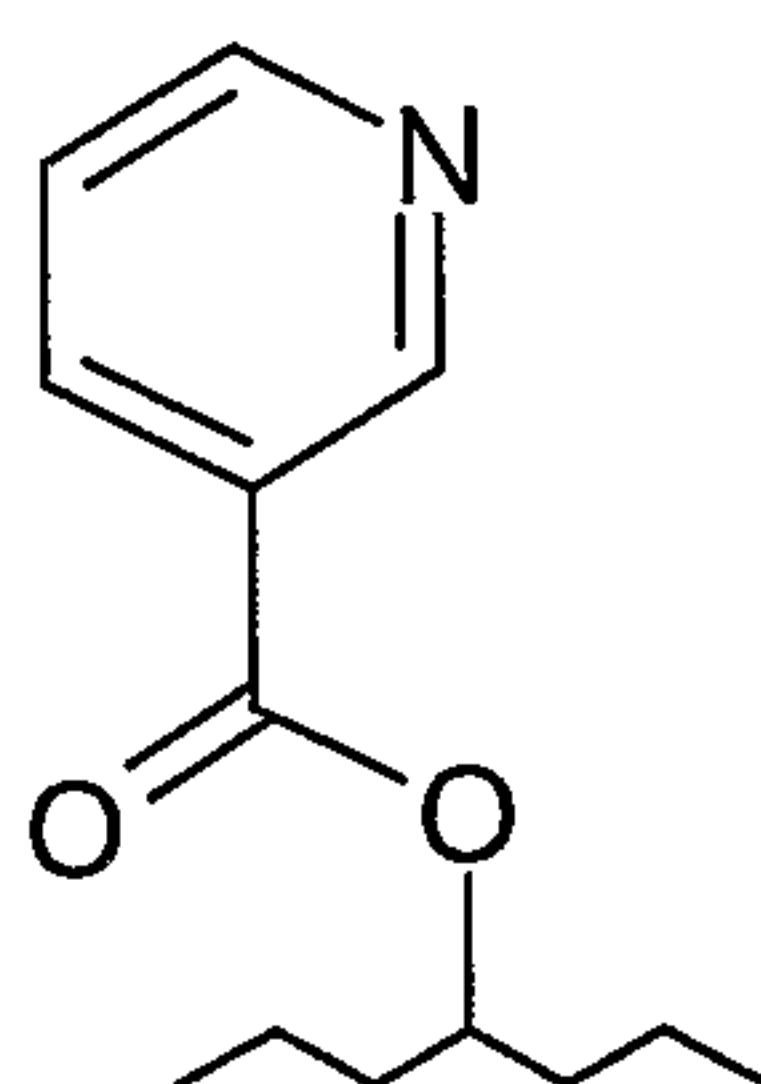


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR13, or NR13;

Y can be O, S, C, CR13, or NR13;

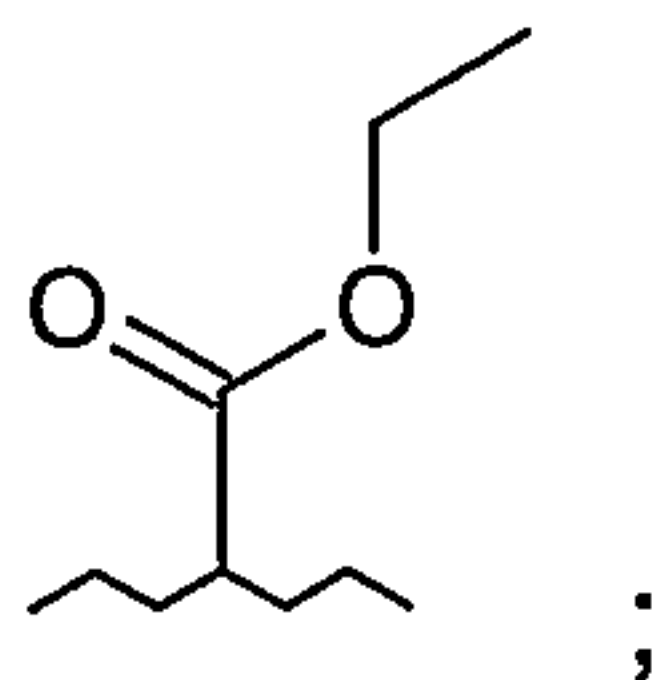
Z can be a single or a double bond

wherein

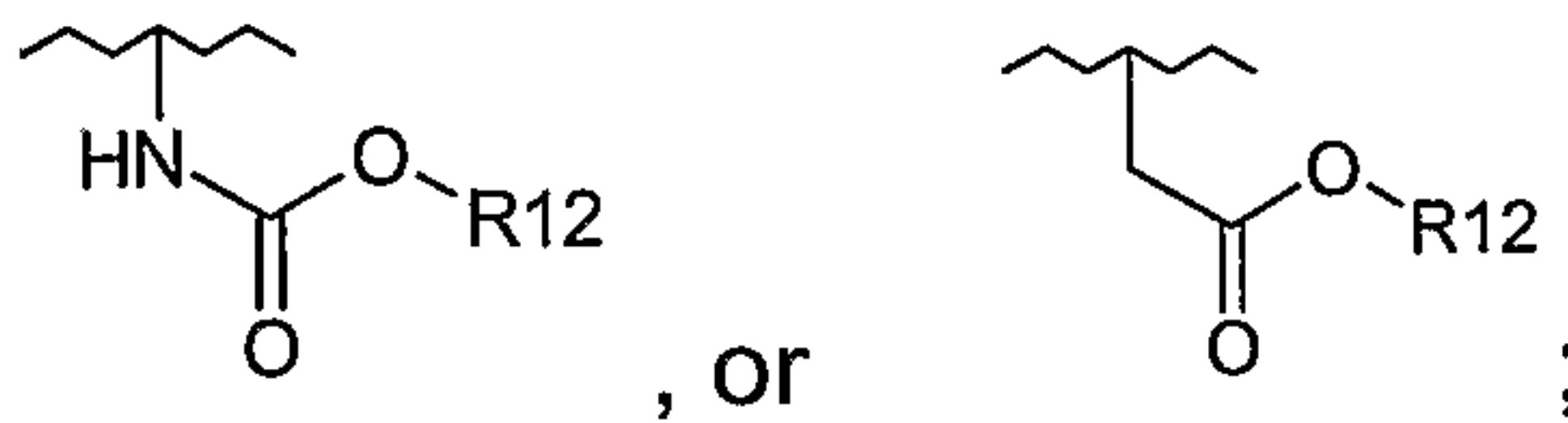
R13 is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein

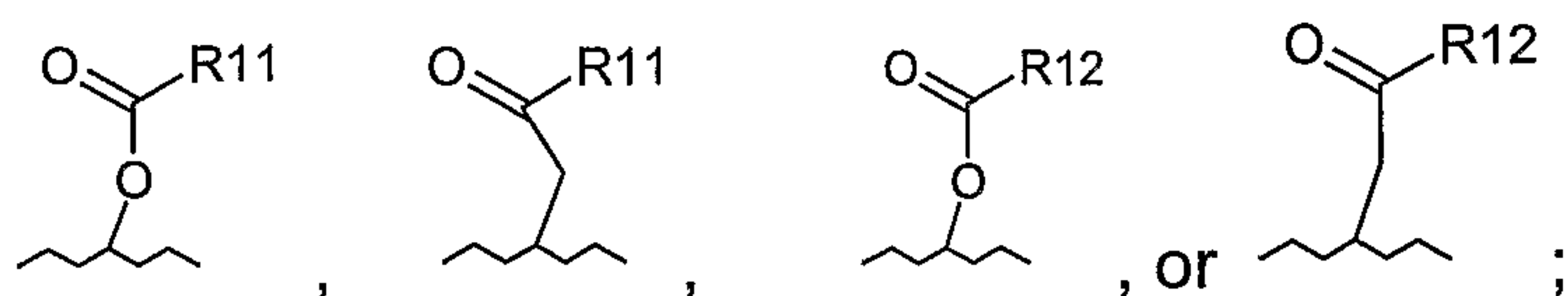
#STR77# means



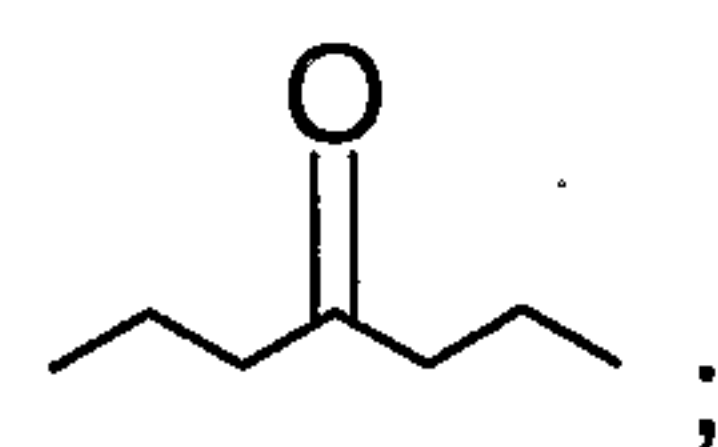
#STR88# means



#STR99# means



#STR100# means



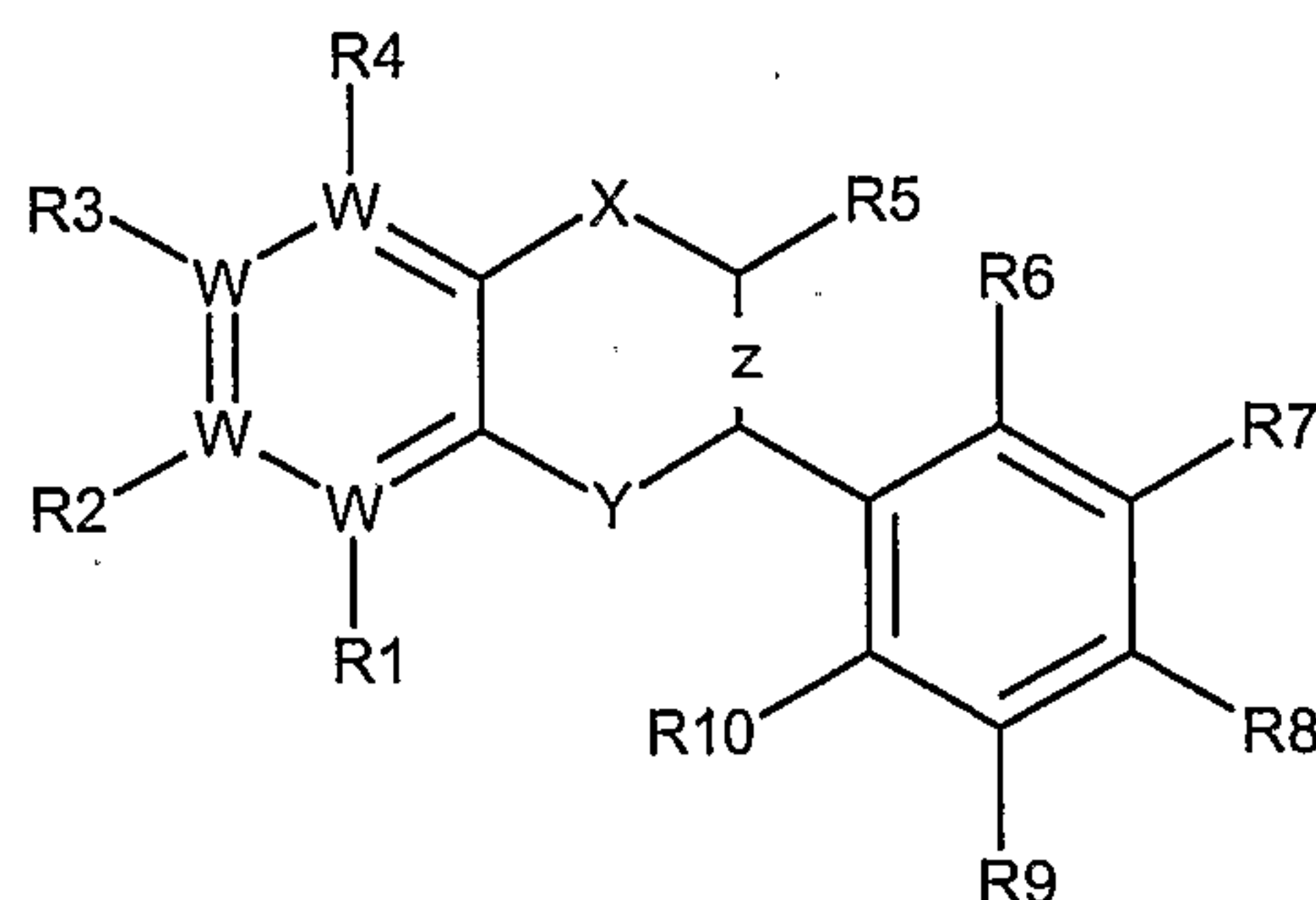
R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

- a) at least one W is a N and R8 is a hydroxyl; OR
- b) at least one W is a N and R8 is a hydroxyl, and optionally;
- c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;
- d) at least one of R1-R10 is #STR66#.

[0103] Another embodiment provides compounds comprising the isoflavonoid structure of Formula 5:



or a pharmaceutically acceptable salt thereof,

wherein

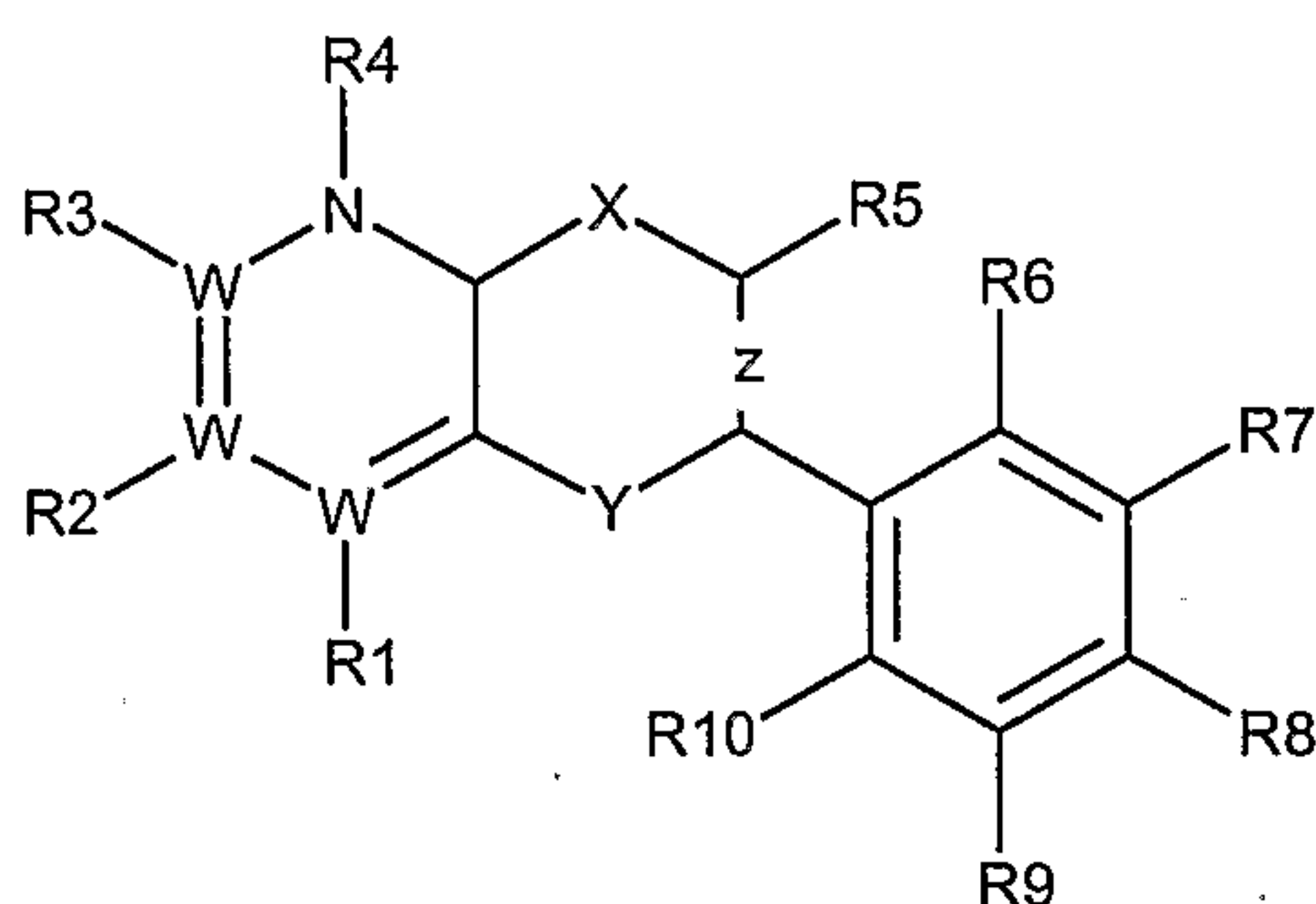
R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

wherein

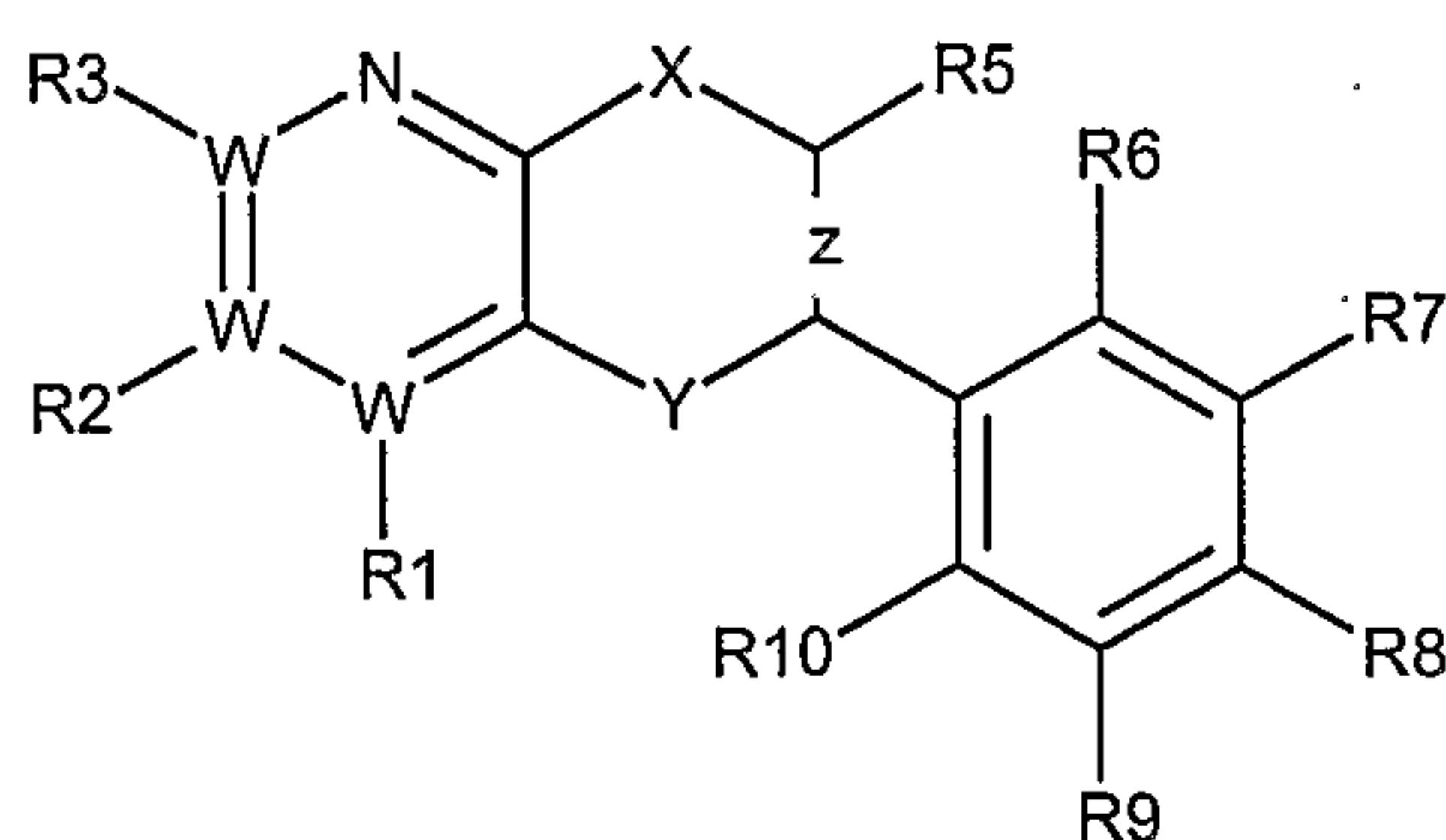
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0104] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5

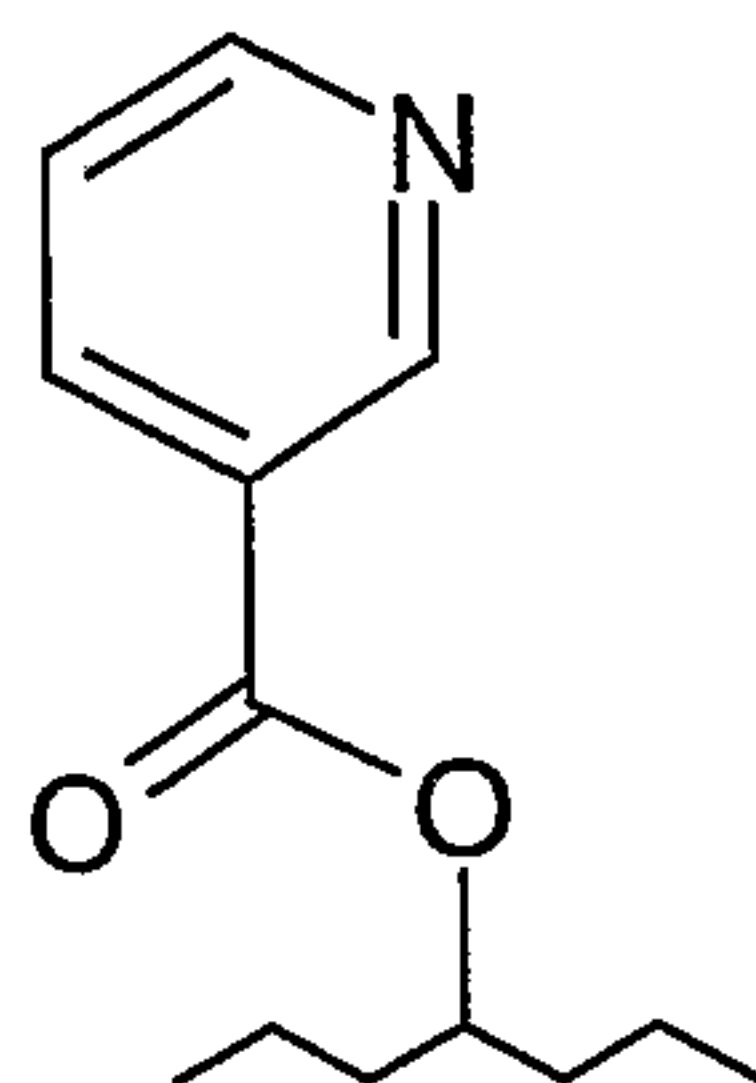


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR¹³, or NR¹³;

Y can be O, S, C, CR¹³, or NR¹³;

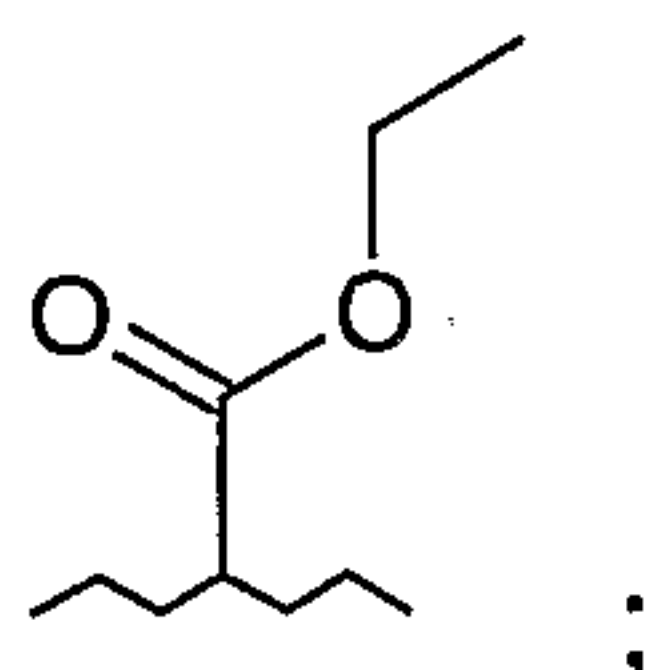
Z can be a single or a double bond

wherein

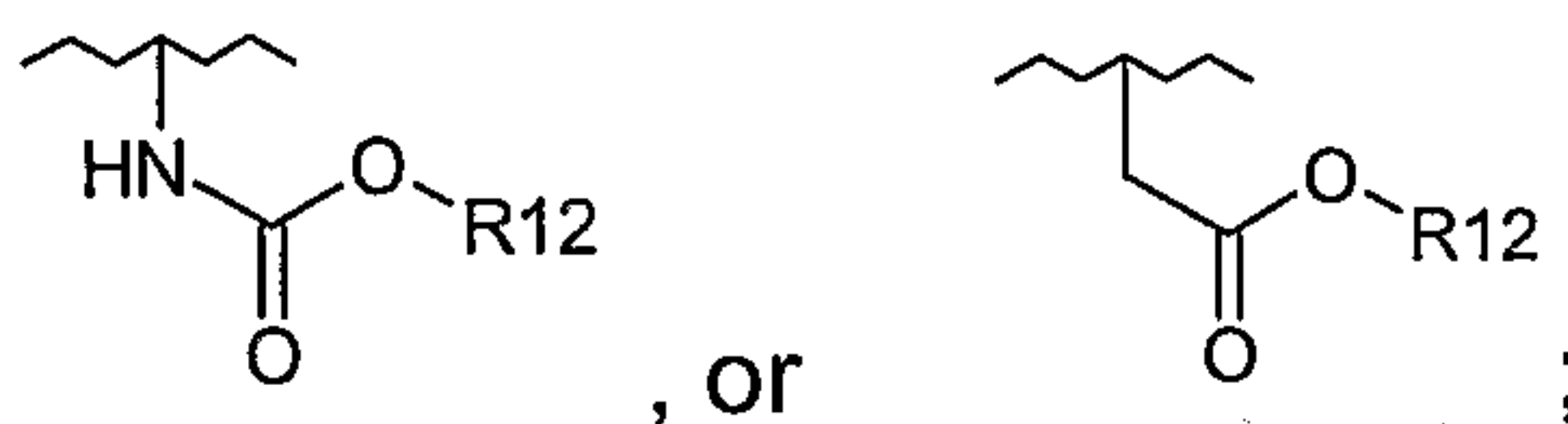
R¹³ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein

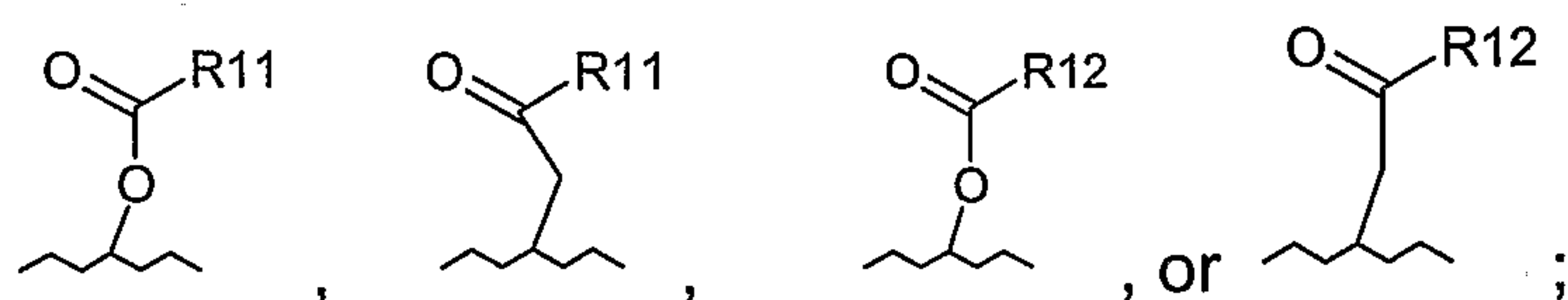
#STR77# means



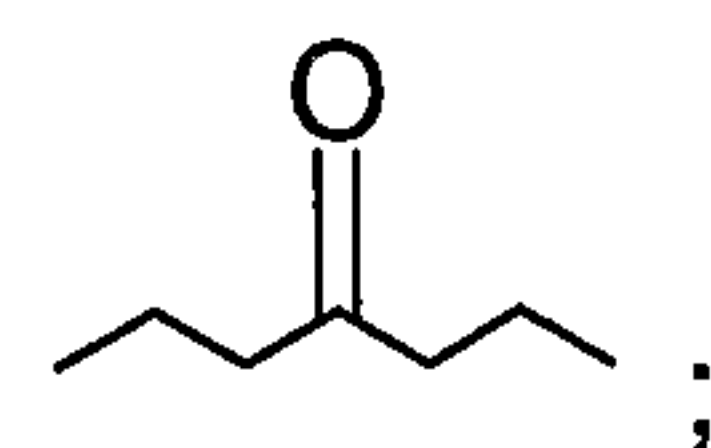
#STR88# means



#STR99# means



#STR100# means



R¹¹ is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

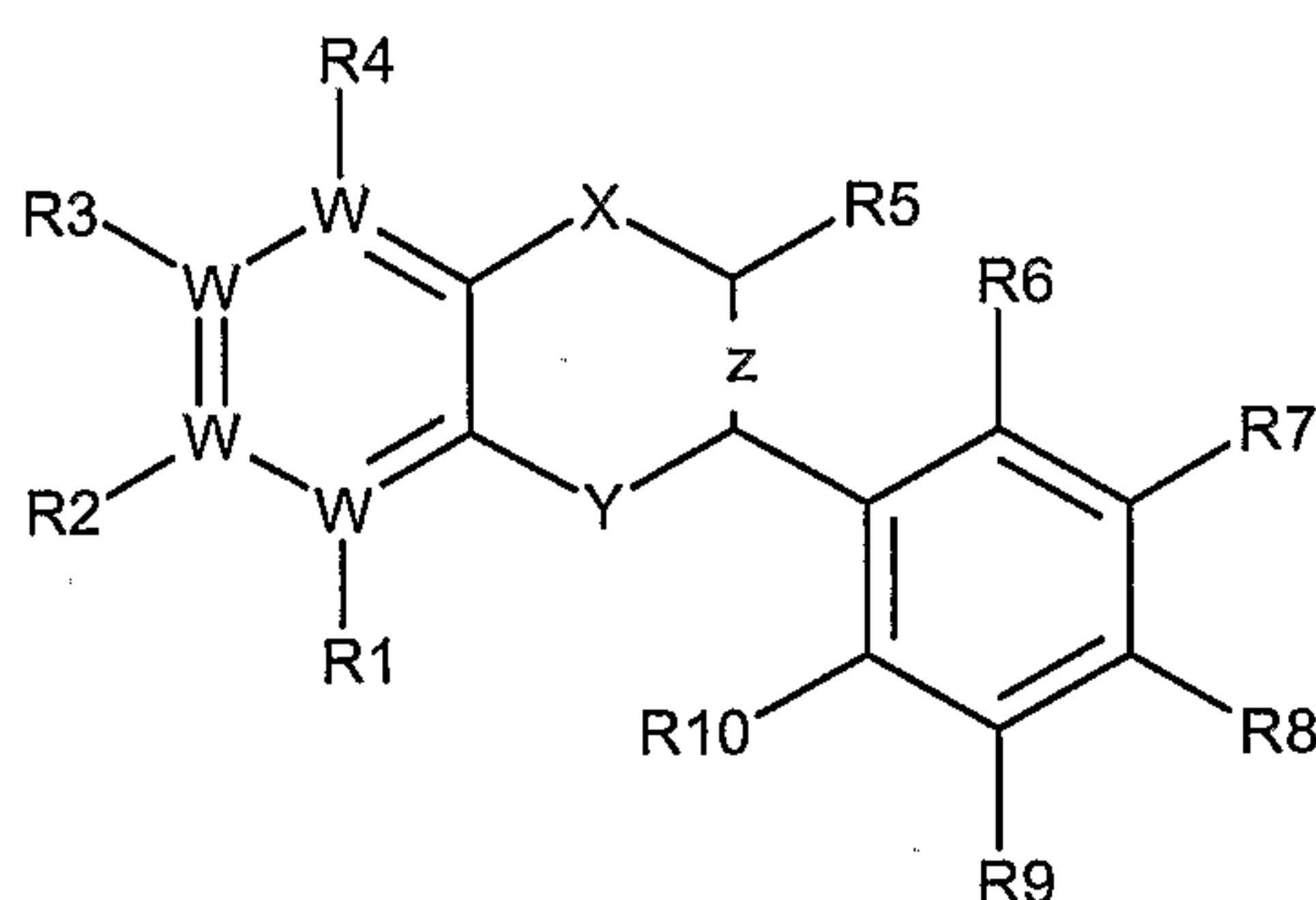
a) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R8 is a hydroxyl; or

b) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R8 is a hydroxyl, and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-R10 is #STR66#.

[0105] Another alternative embodiment provides compounds comprising the general isoflavonoid structure of Formula 5:



or a pharmaceutically acceptable salt thereof,

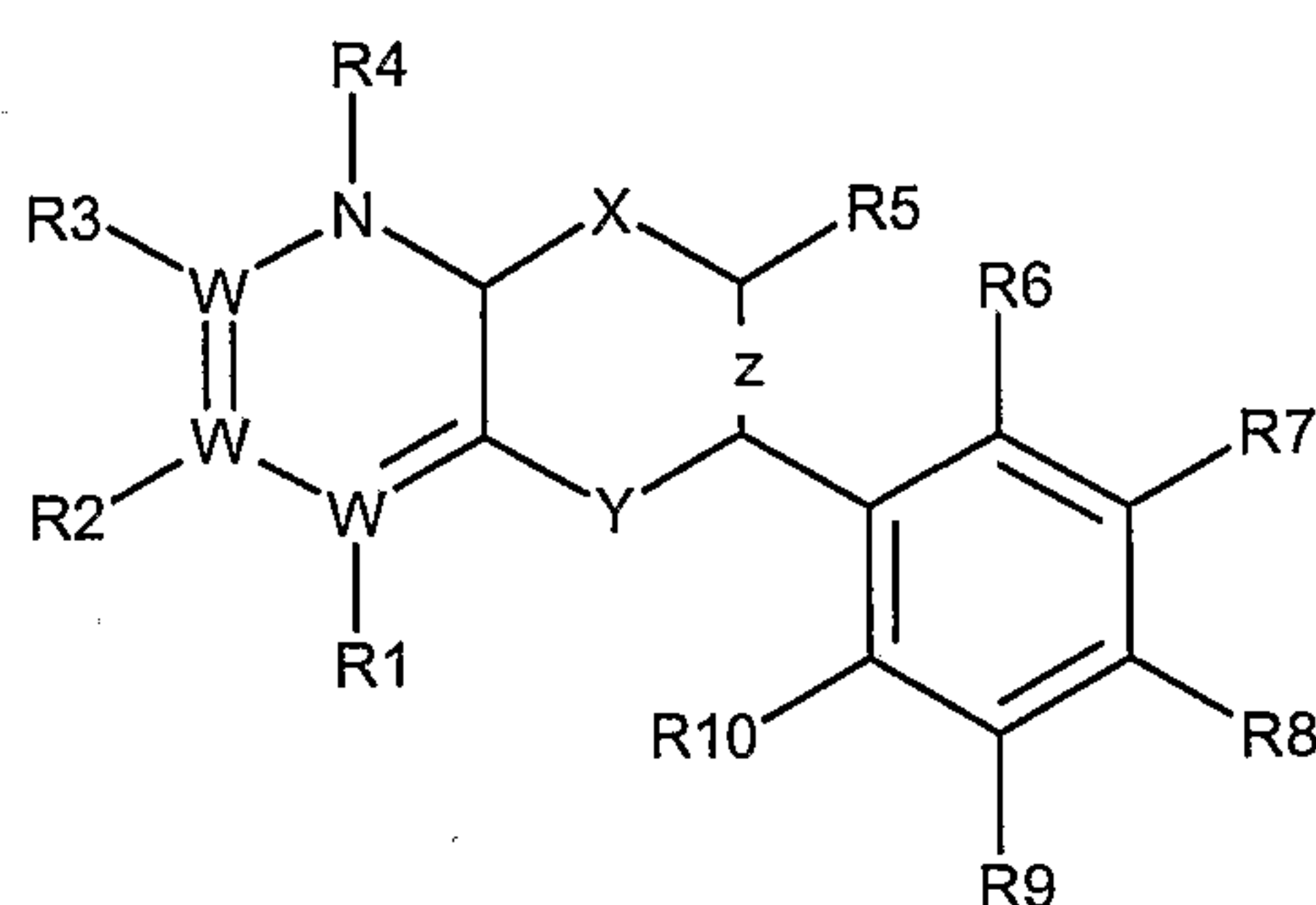
wherein

R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

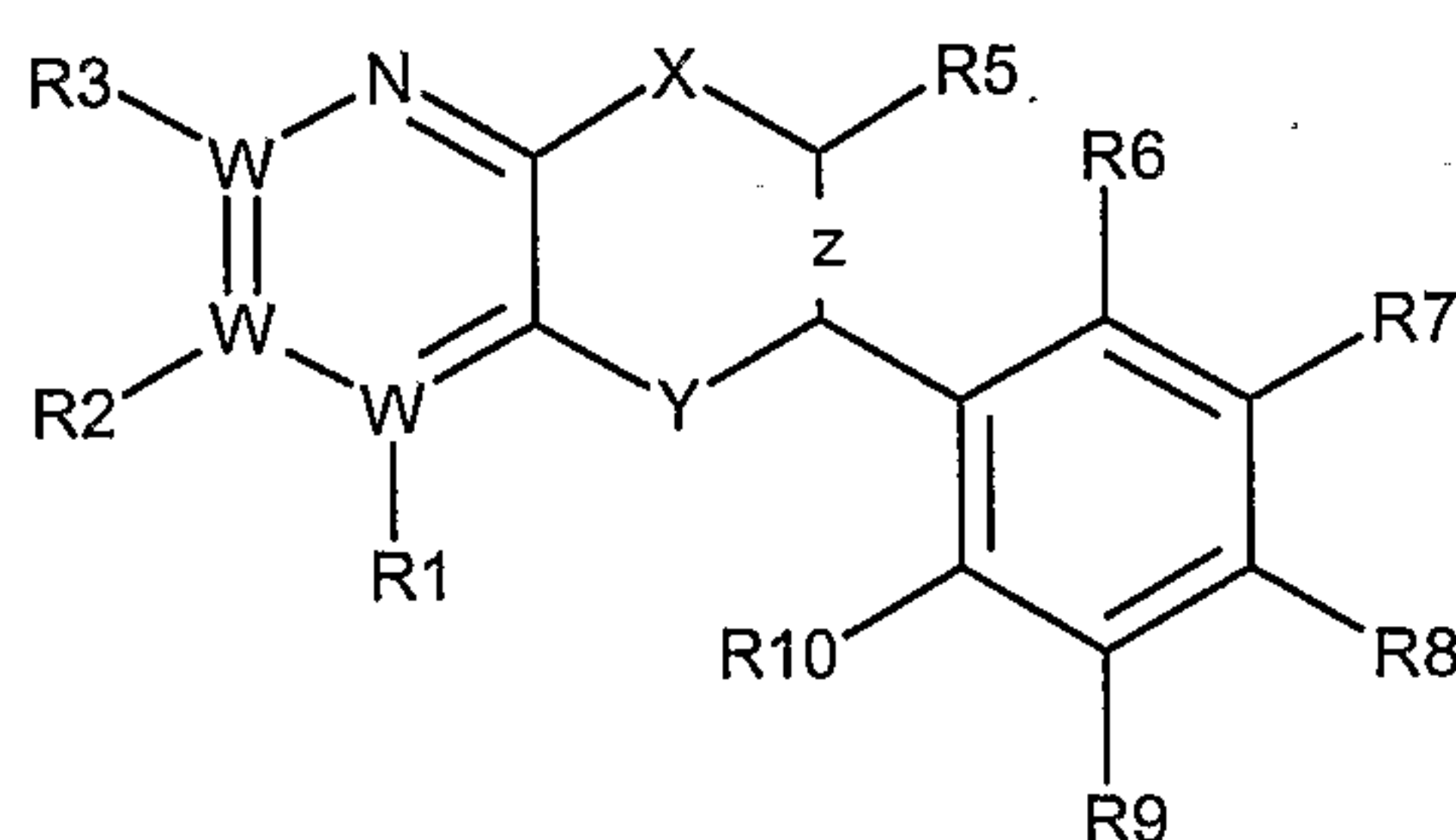
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5.

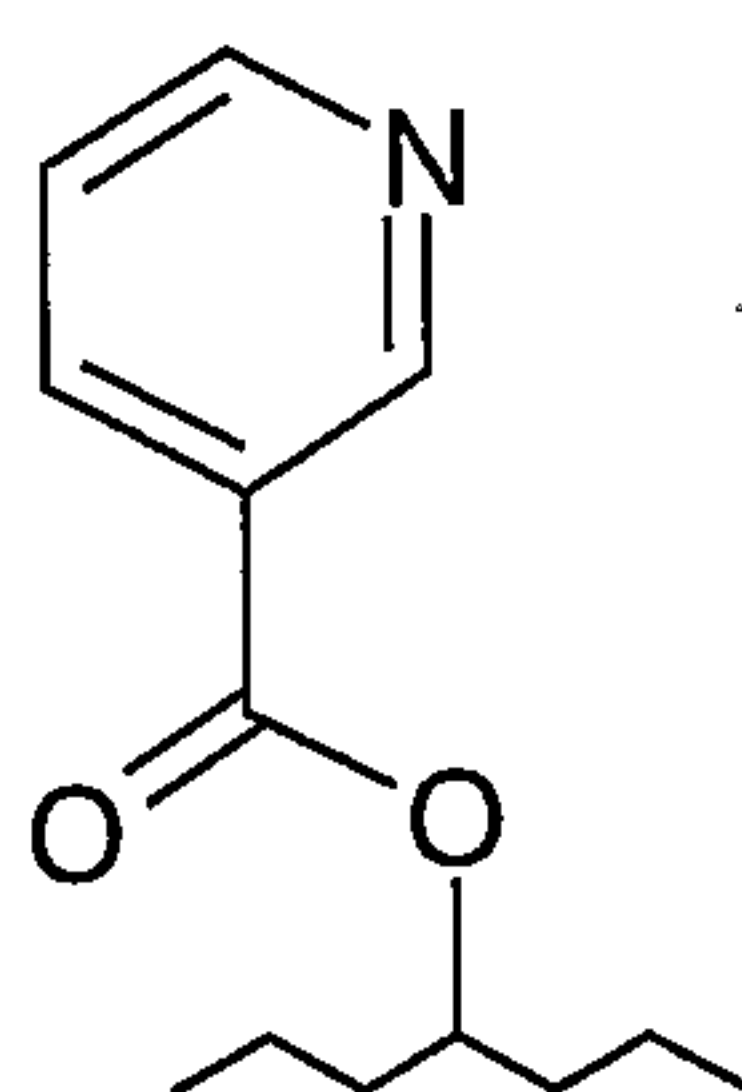


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR13, or NR13;

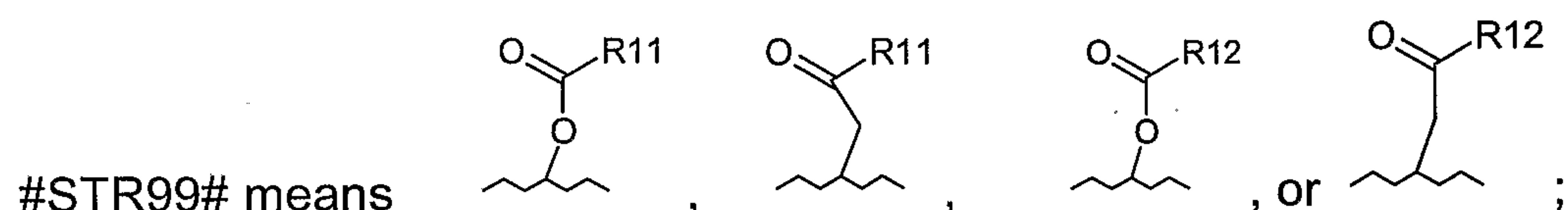
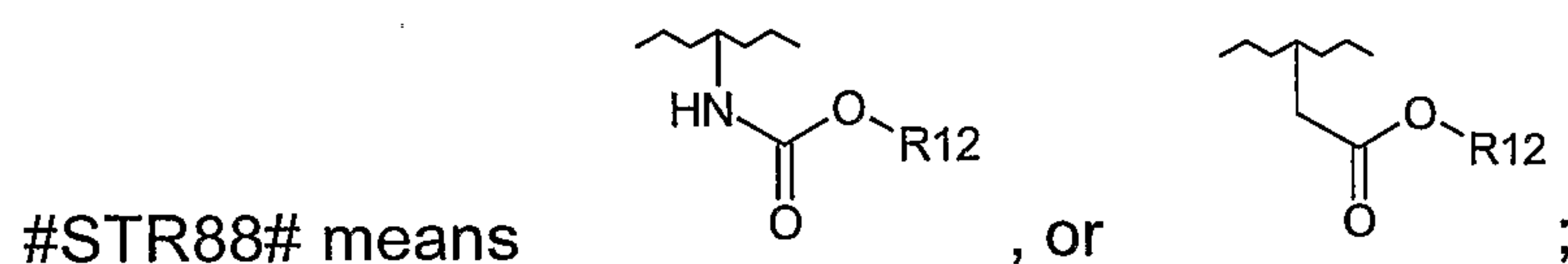
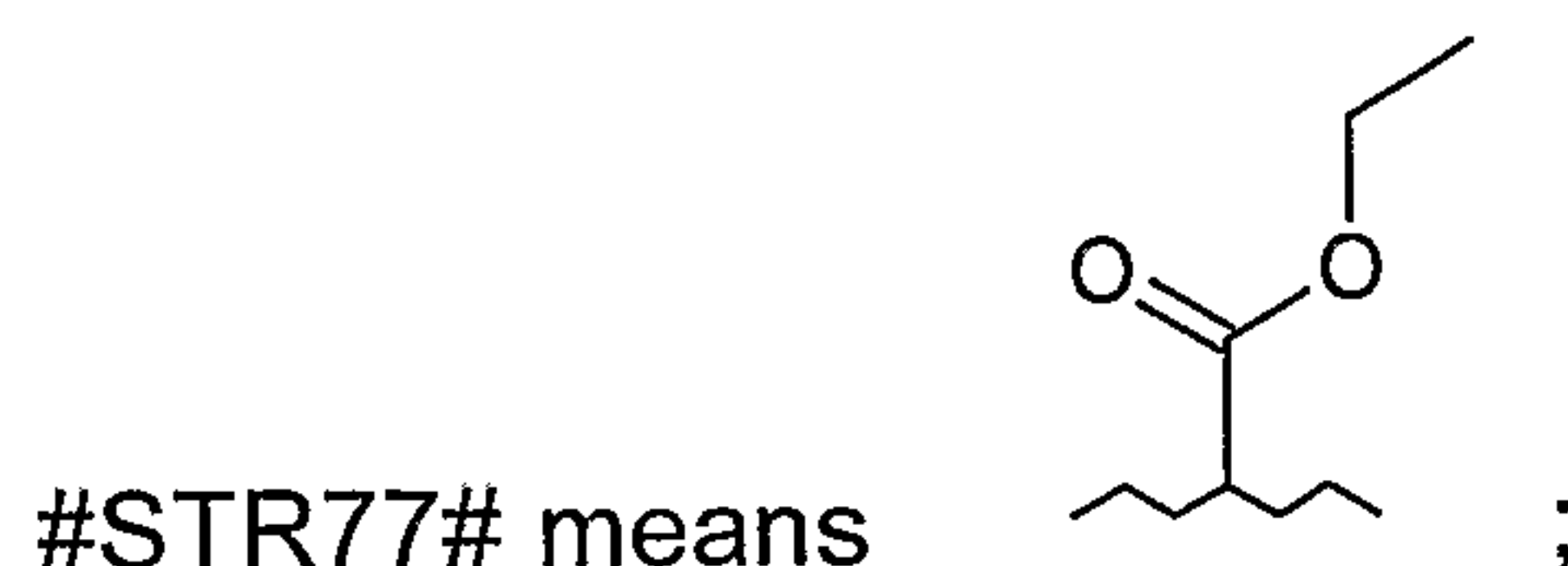
Y can be O, S, C, CR13, or NR13;

Z can be a single or a double bond

Wherein

R13 is #STR77#, #STR88#, #STR99#, or #STR100#,

Wherein



R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

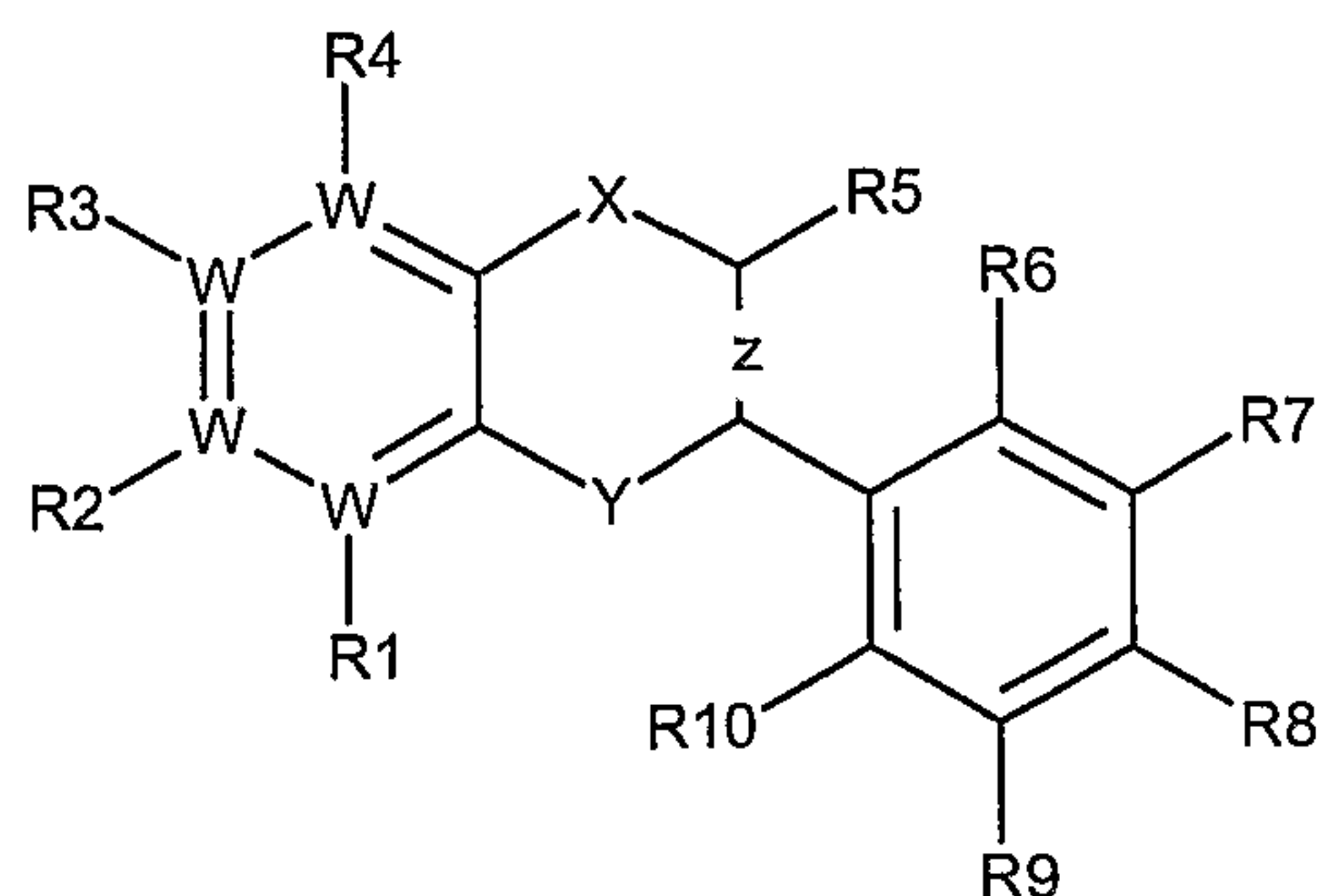
a) R8 is a hydroxyl or #STR66# and if R8 is a hydroxyl at least one of (R1-R7 and R9-R10) is #STR66#; or

b) R8 is a hydroxyl or #STR66# and if R8 is a hydroxyl at least one of (R1-R7 and R9-R10) is #STR66# and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#.

[0106] Another alternative embodiment provides compounds comprising the general isoflavonoid structure of Formula 5:



or a pharmaceutically acceptable salt thereof,

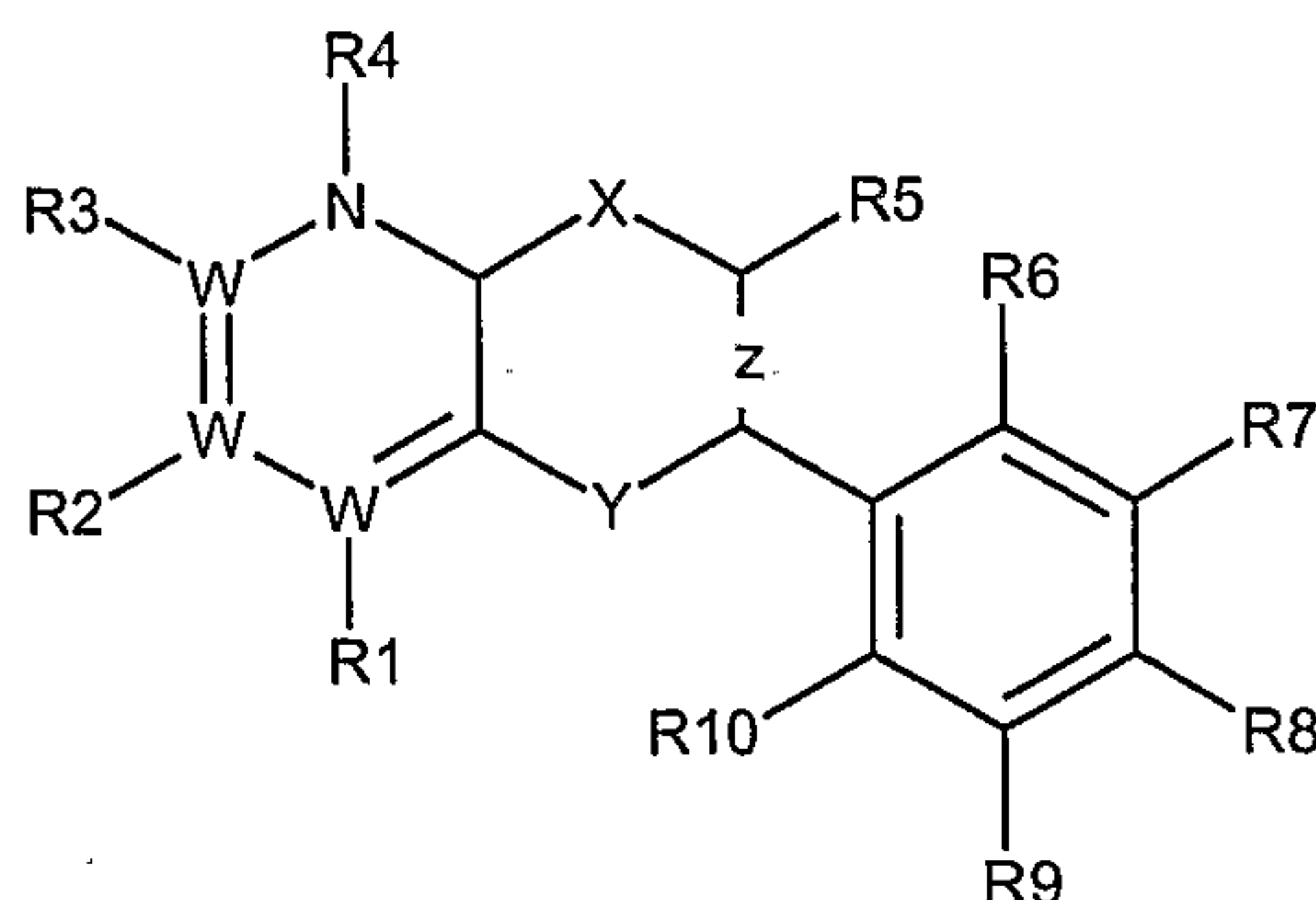
wherein

R1, R2, R3, R4, R5, R6, R8, R9, and R10 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

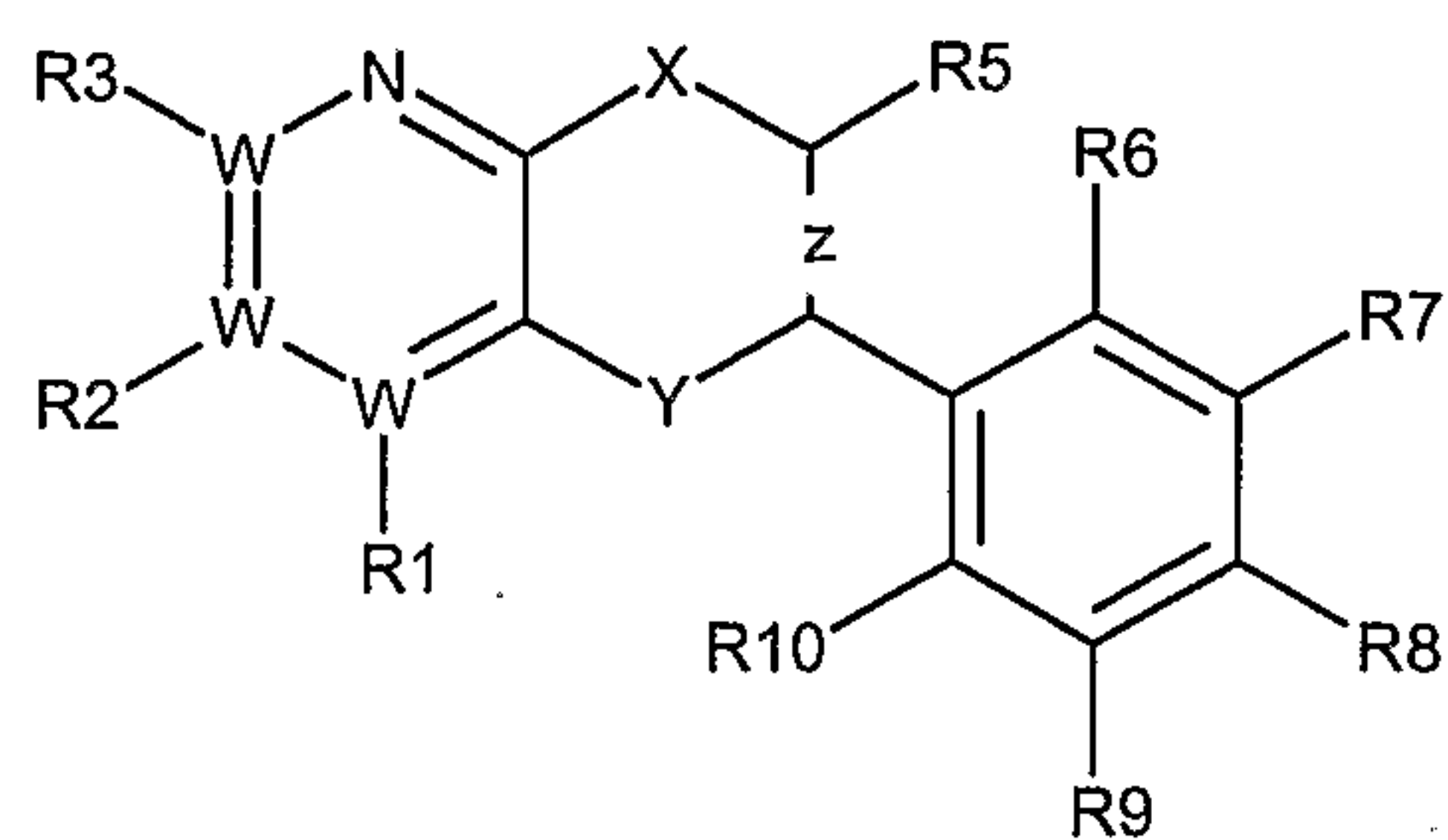
wherein

W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons. The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5.

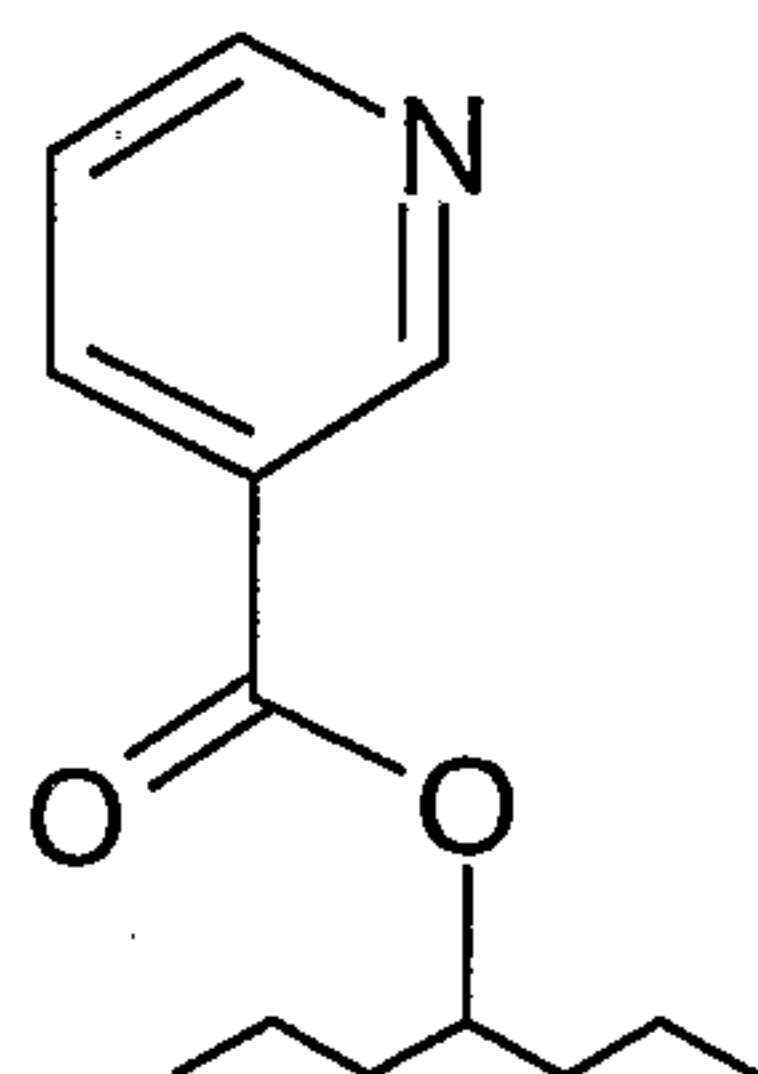


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR₁₃, or NR₁₃;

Y can be O, S, C, CR₁₃, or NR₁₃;

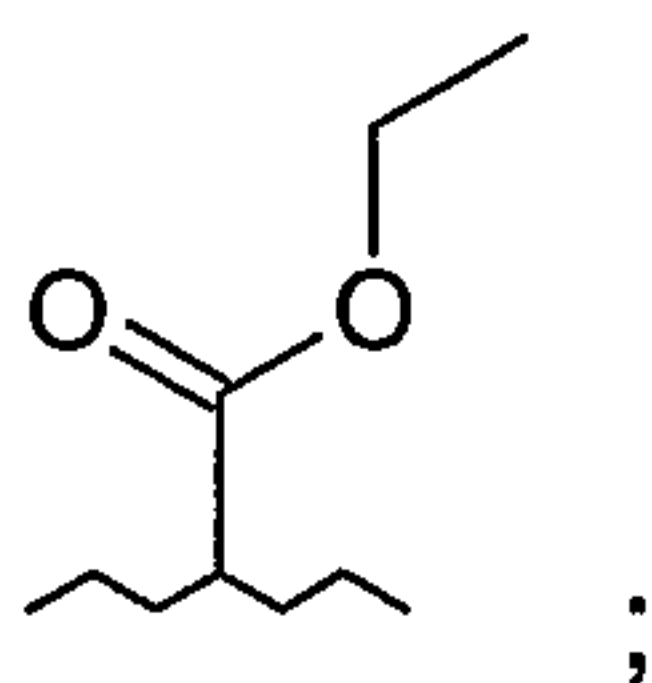
Z can be a single or a double bond

Wherein

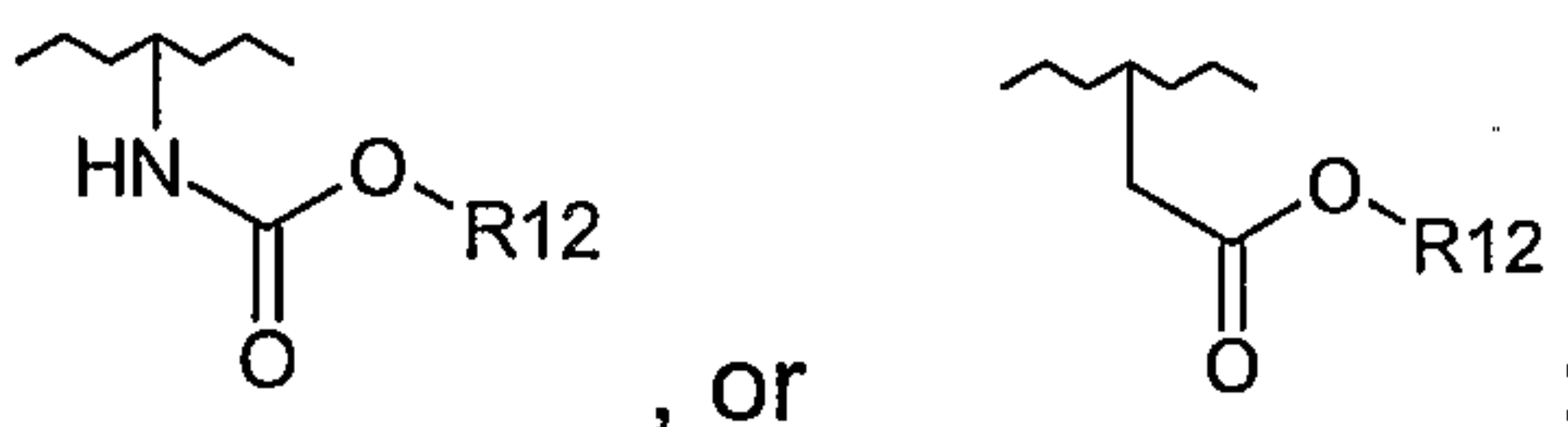
R₁₃ is #STR77#, #STR88#, #STR99#, or #STR100#,

Wherein

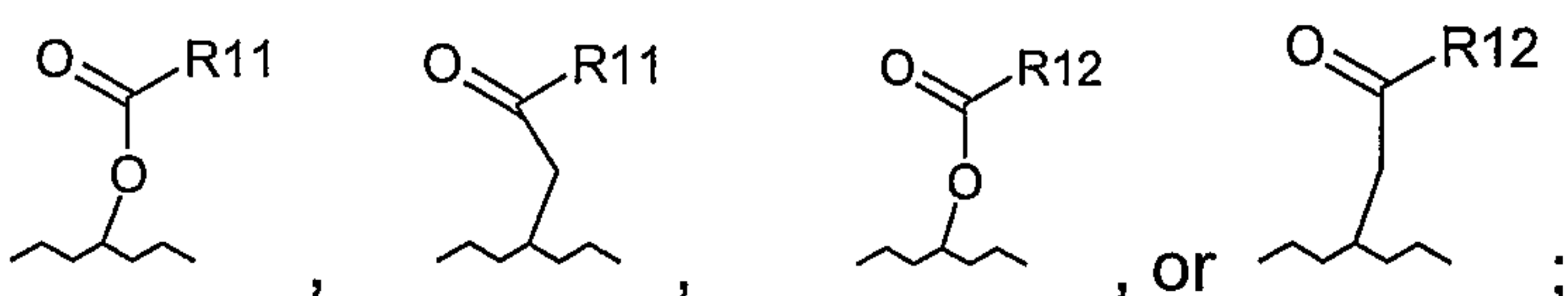
#STR77# means

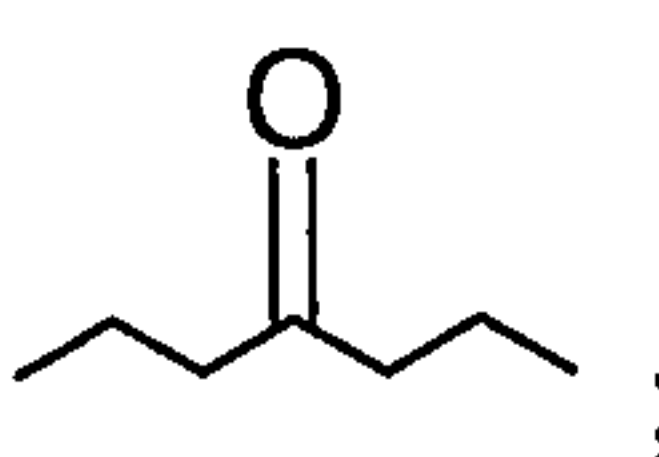


#STR88# means



#STR99# means



#STR100# means  ;

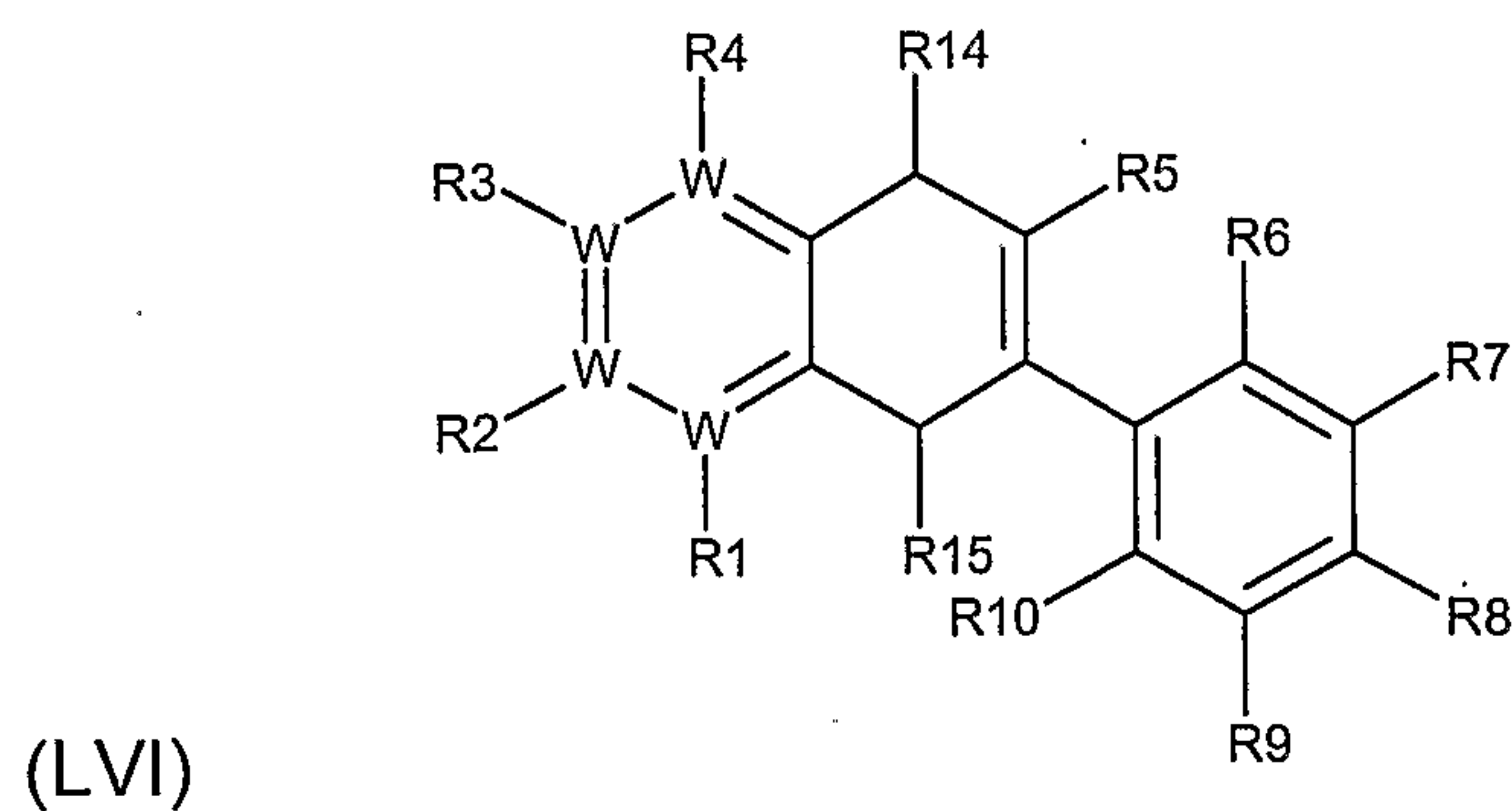
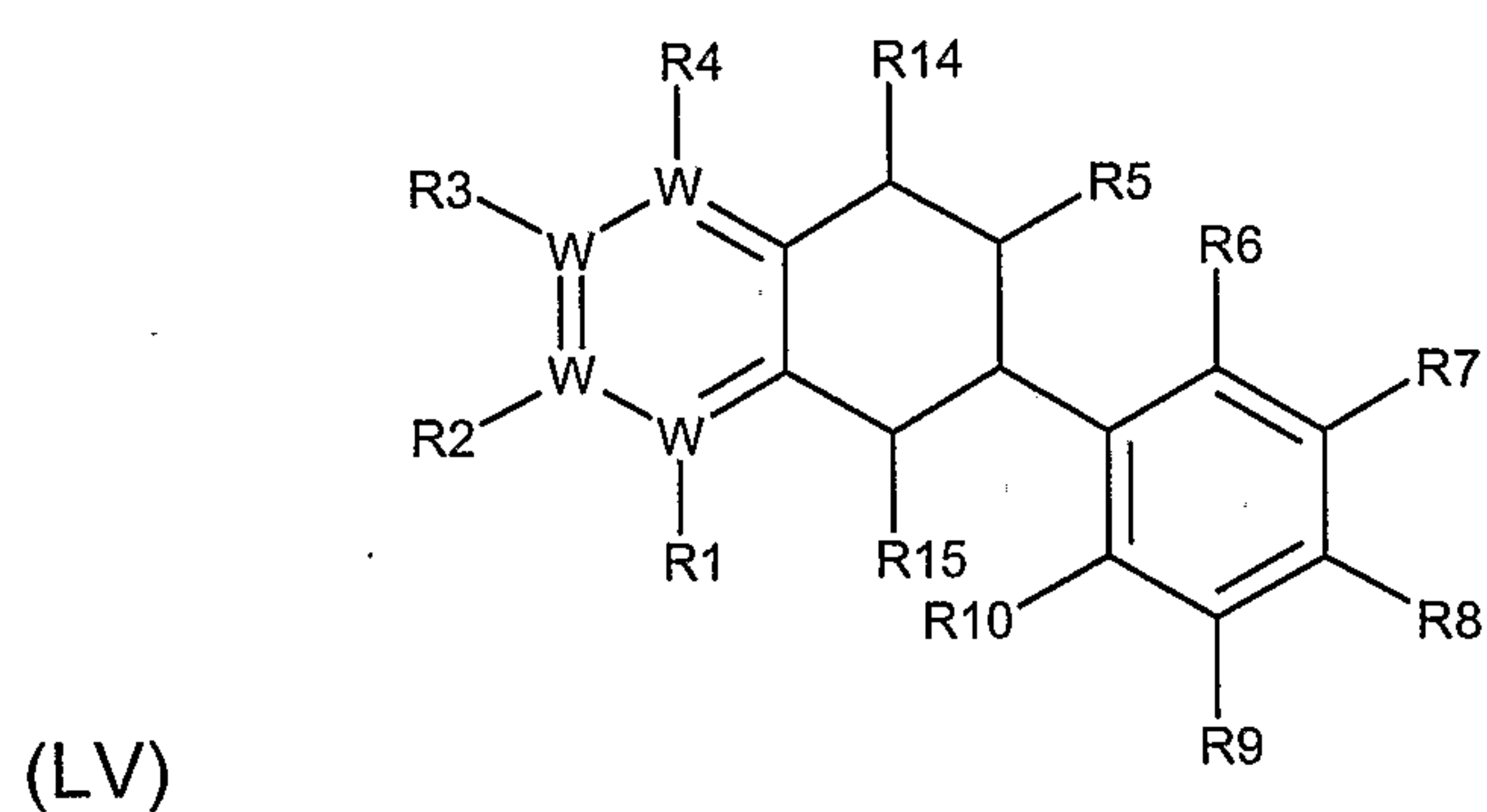
R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

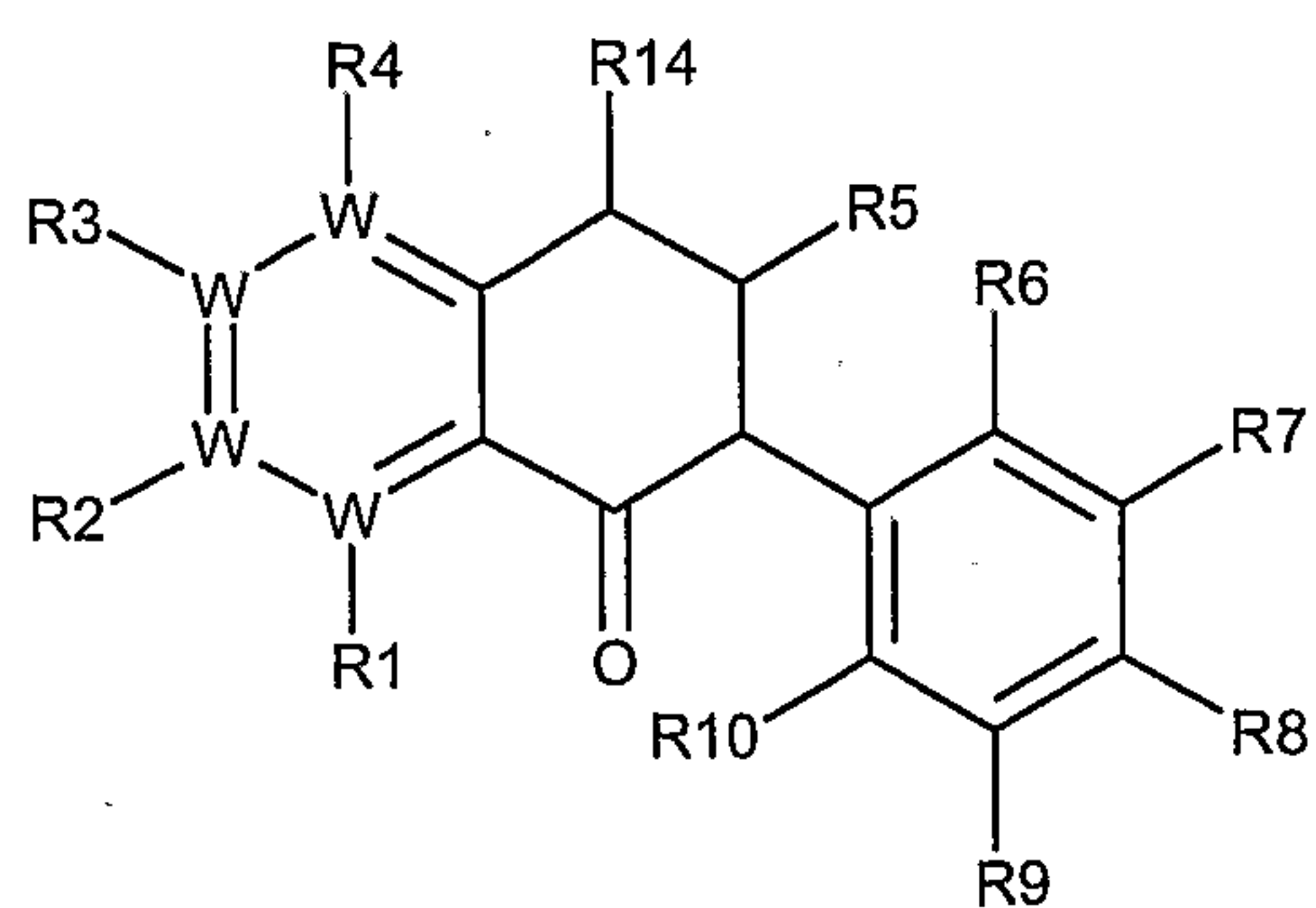
R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

with the proviso that;

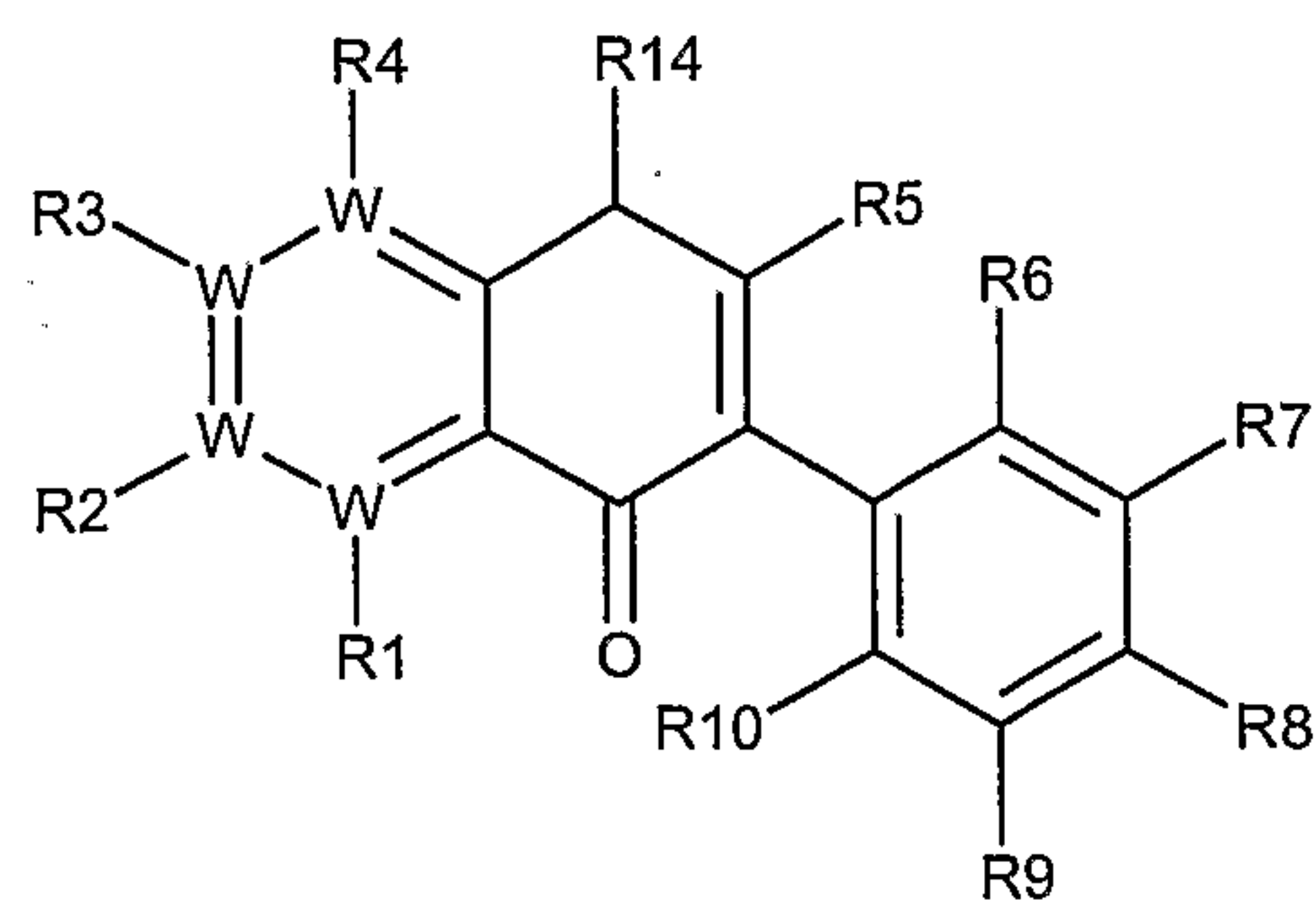
- a) R8 is a hydroxyl or #STR66#, and
- b) at least one W is a N, and
- c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and
- d) at least one of R1-R10 is #STR66#.

[0107] Non-limiting examples of compounds of Formula 5 include:

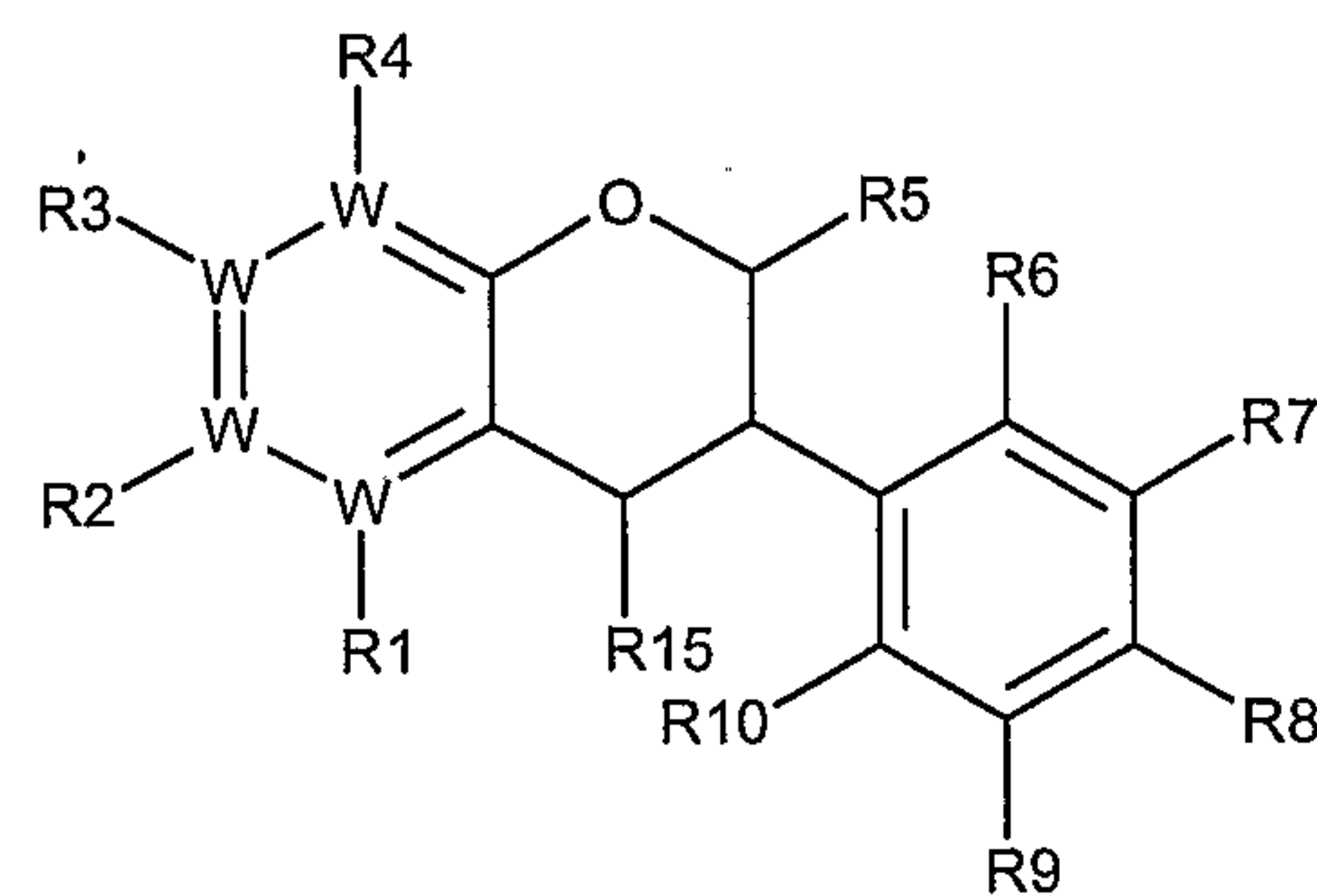




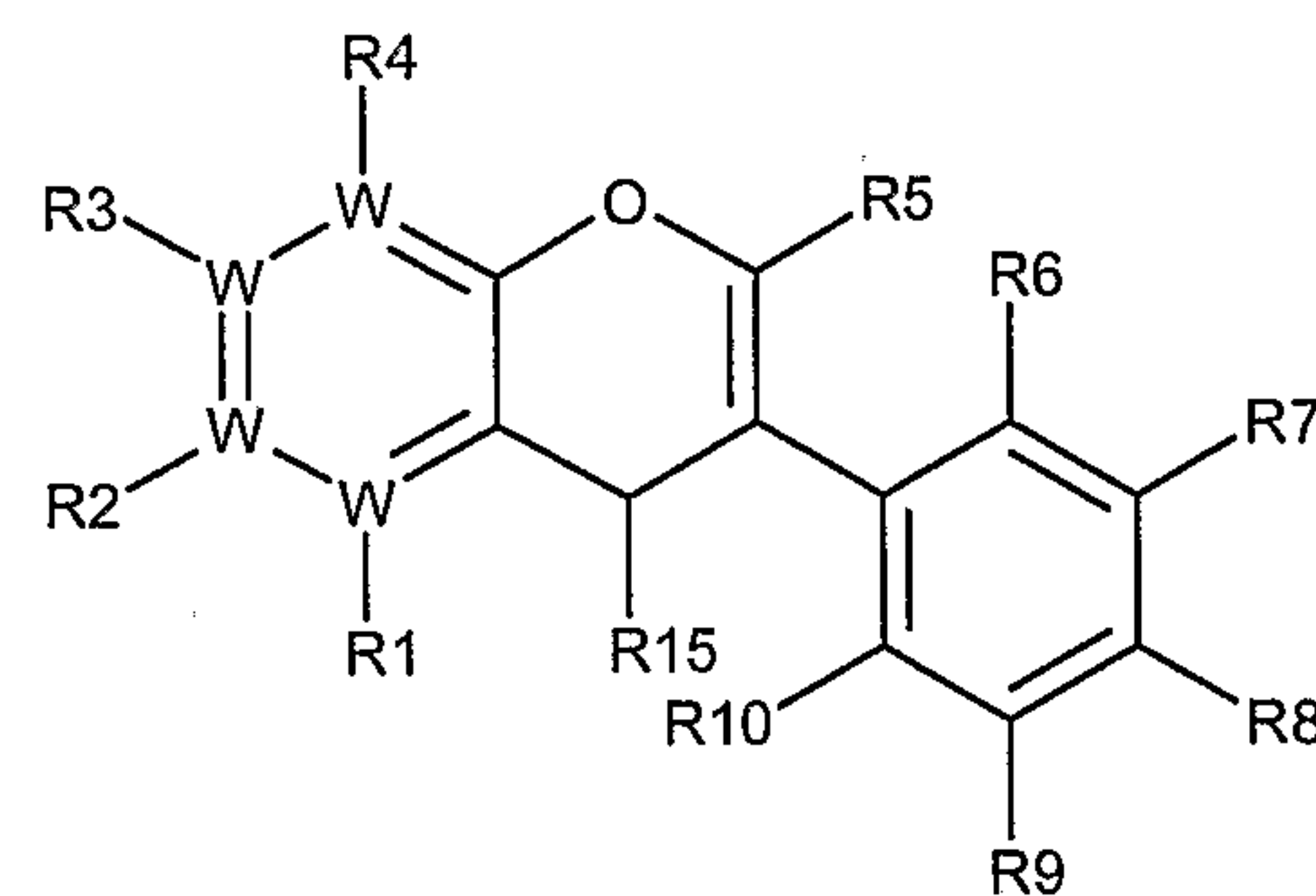
(LVII)



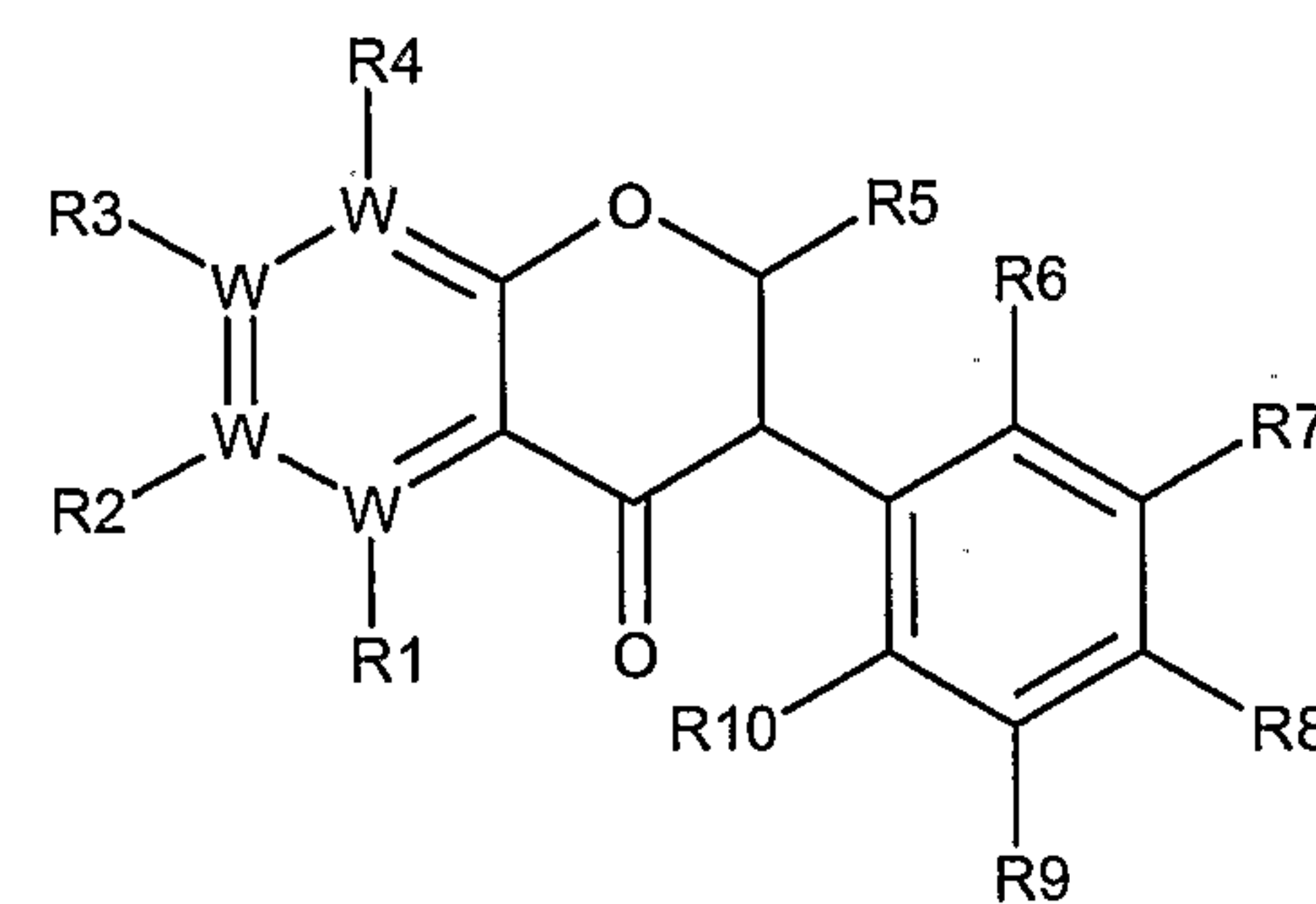
(LVIII)



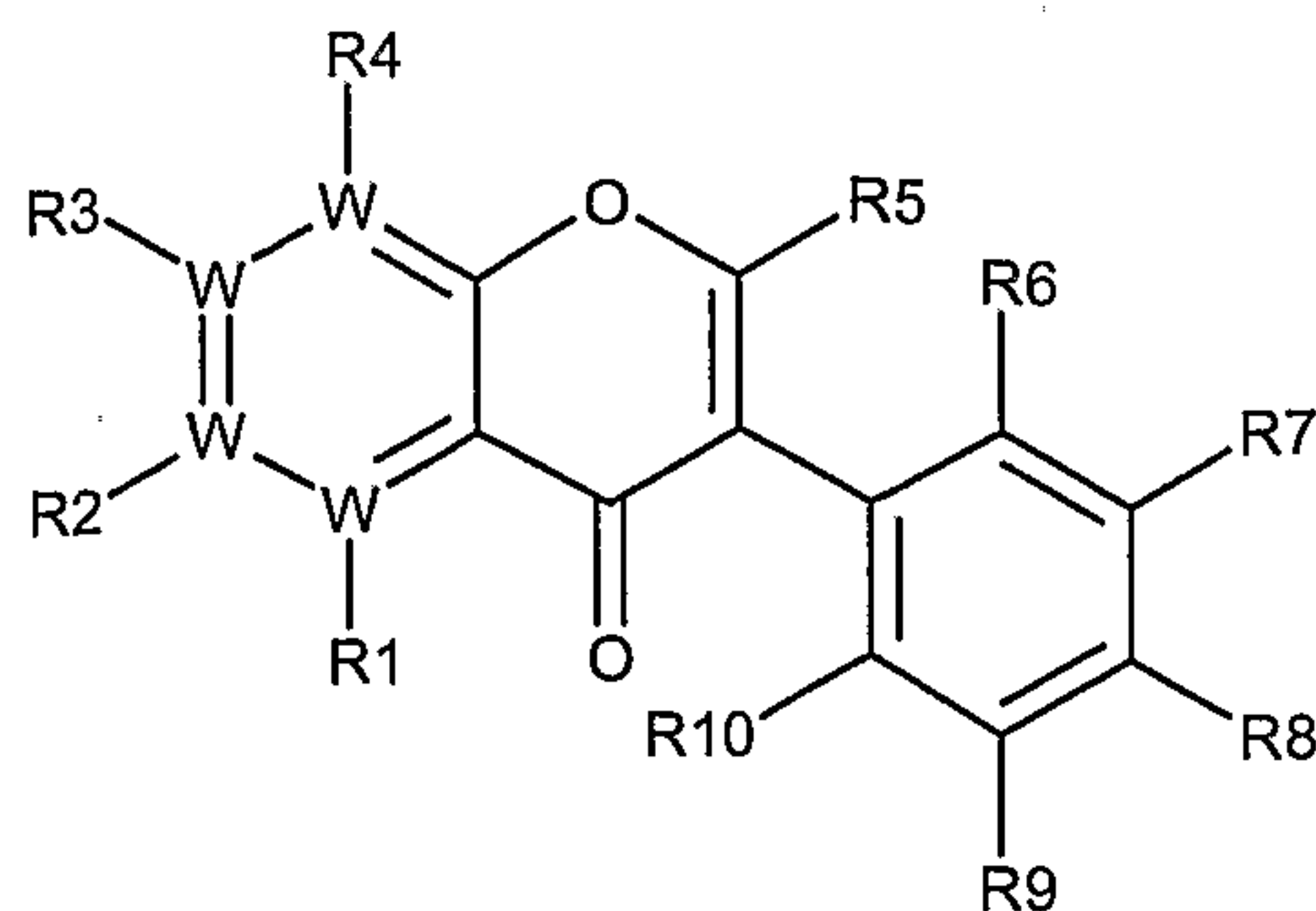
(LIX)



(LX)



(LXI)



(LXII)

or a pharmaceutically acceptable salts thereof,

wherein

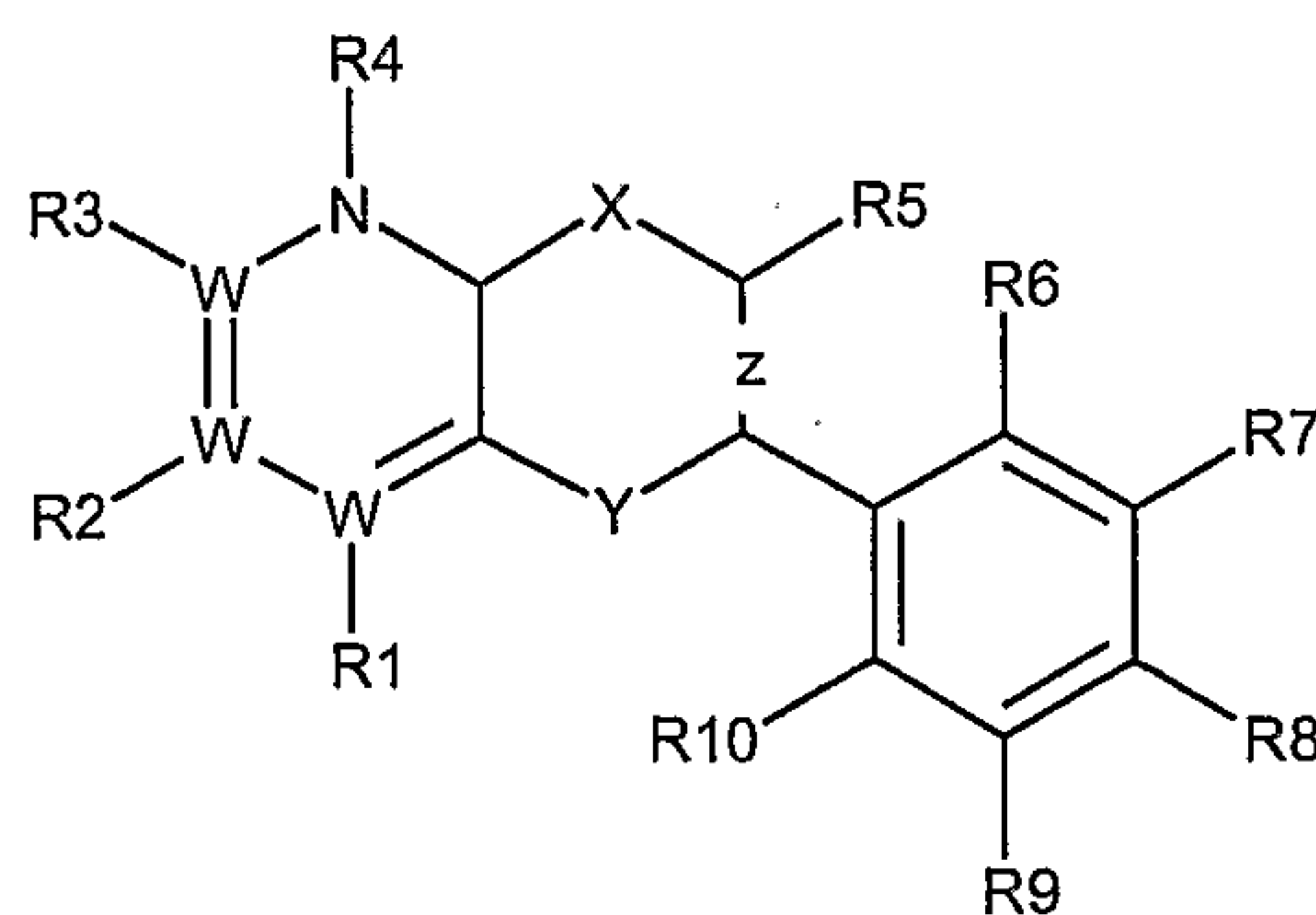
R1, R2, R3, R4, R5, R6, R8, R9, R10, R14 and R15 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, Bromide [Br], Iodide [I], methoxy [OCH₃], ethoxy [OCH₂CH₃], fluoride [F], chloride [Cl], CF₃, CCl₃, phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], #STR66#, #STR77#, #STR88#, #STR99#, #STR100#

wherein

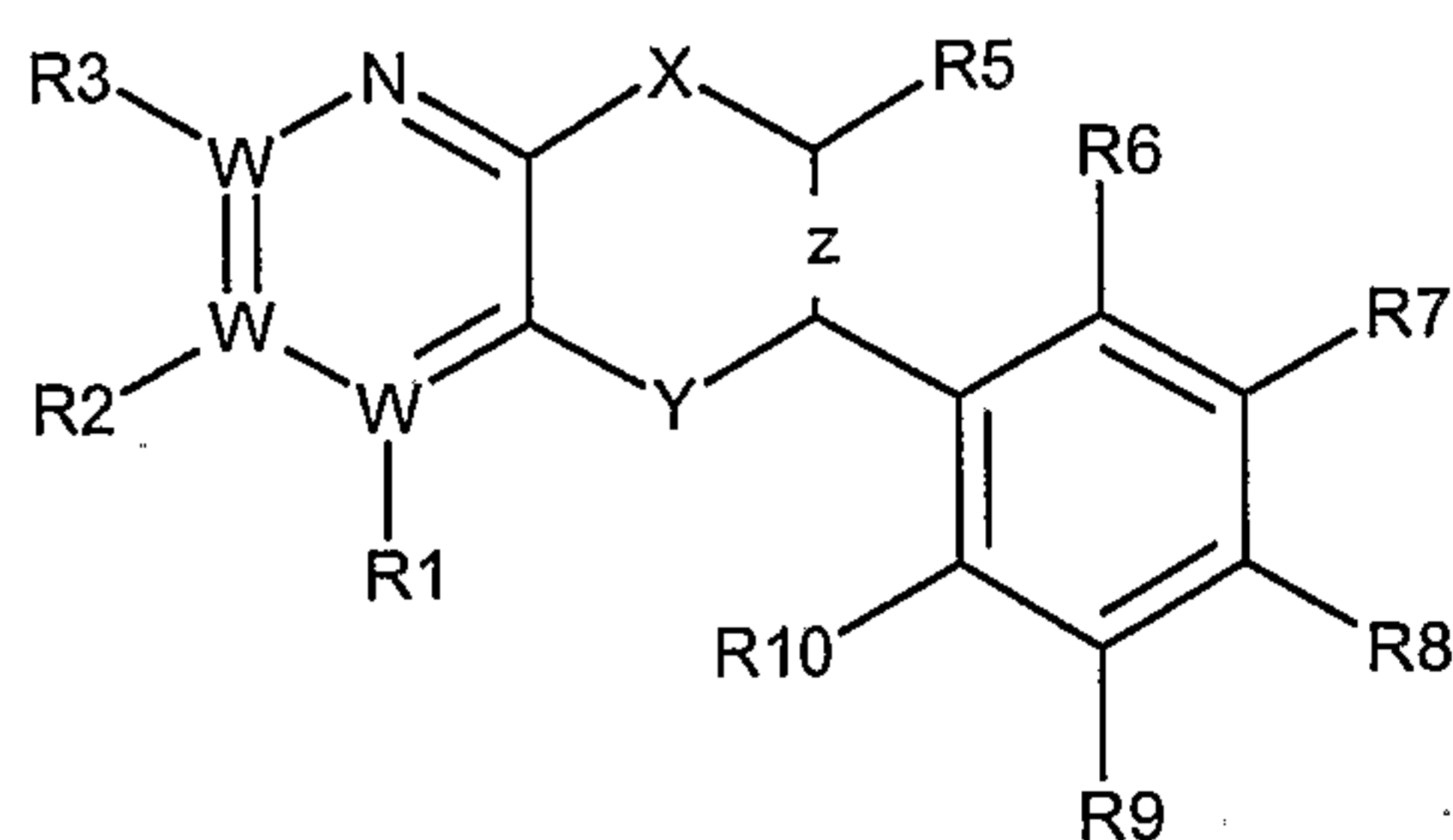
W can be C or N;

wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0108] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 5:

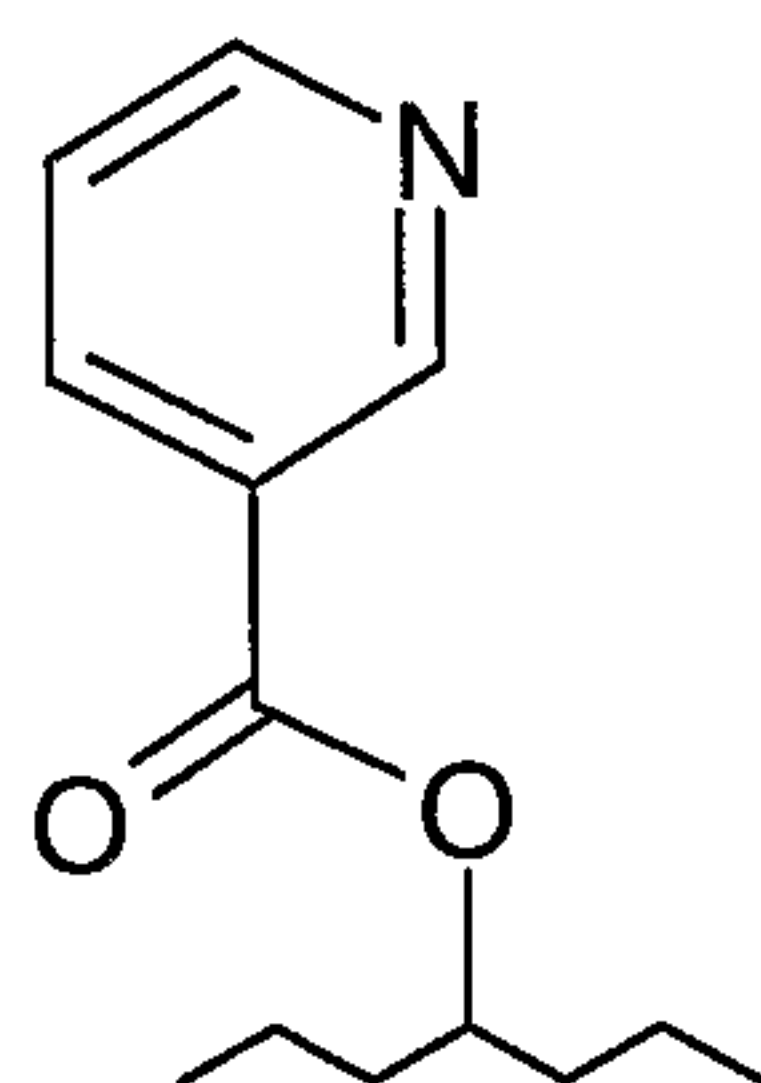


wherein the same applies to any W; or



wherein the same applies to any W:

wherein



#STR66# is

wherein

X can be O, S, C, CR¹³, or NR¹³;

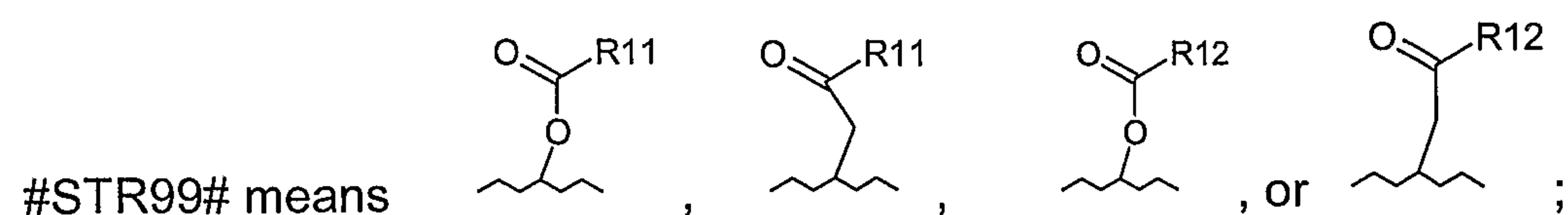
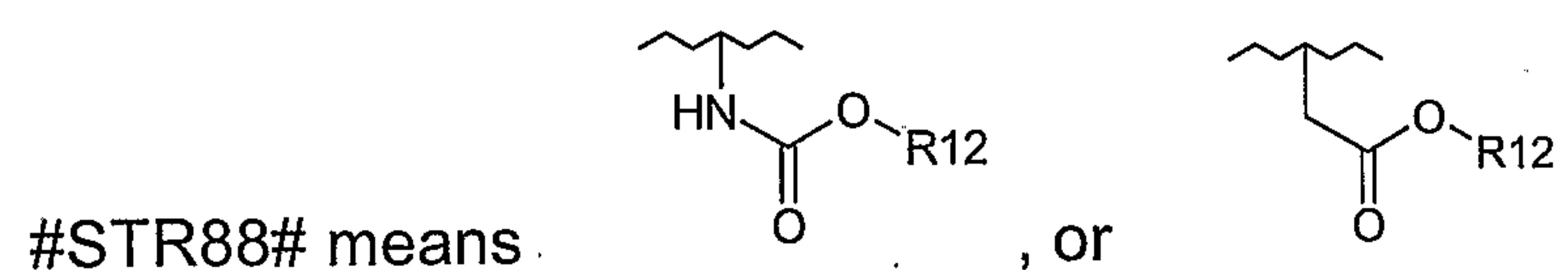
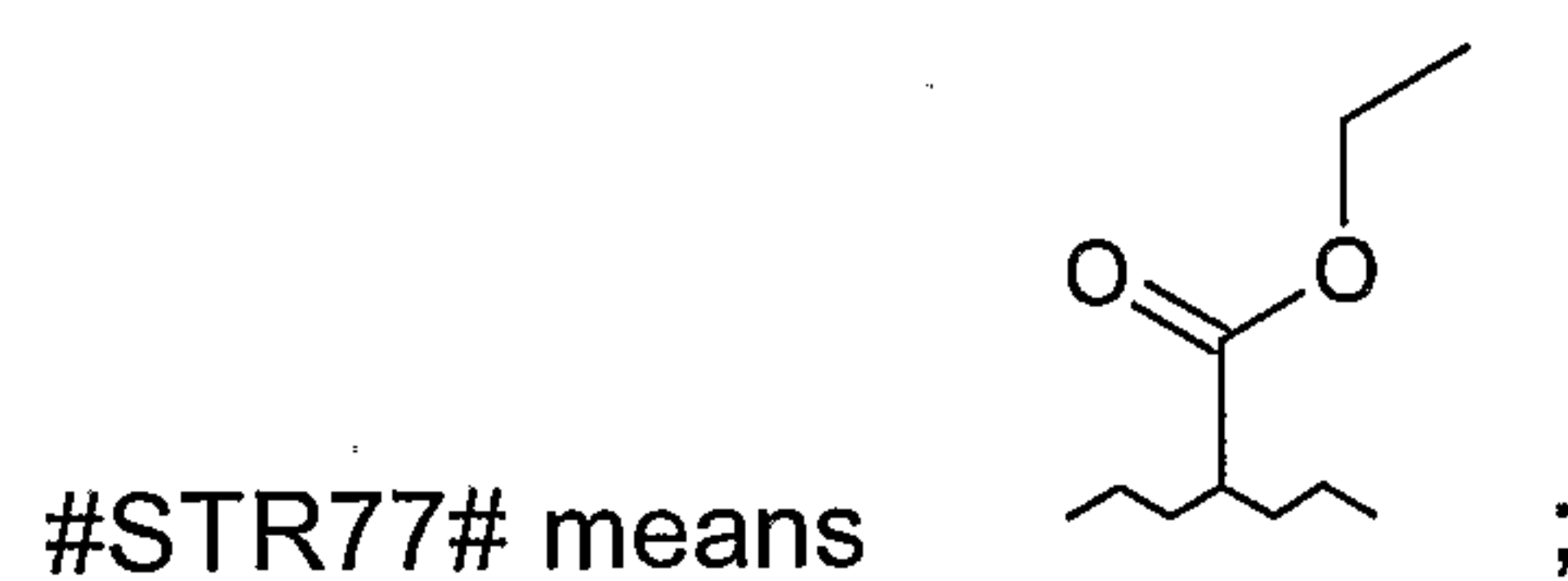
Y can be O, S, C, CR¹³, or NR¹³;

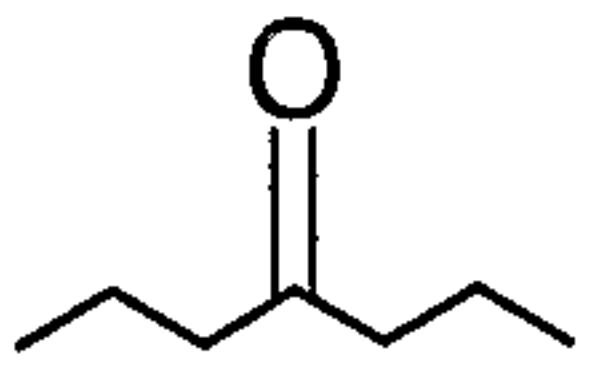
Z can be a single or a double bond

wherein

R¹³ is #STR77#, #STR88#, #STR99#, or #STR100#,

wherein



#STR100# means  ;

R11 is pyridine, pyridazine, pyrimidine, pyrazine; and

R12 is (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 5 compounds have one at least one of the following groups of provisos:

1) with the proviso that;

a) R8 is a hydroxyl; or

b) R8 is a hydroxyl, and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;

e) at least one of R1-R10 is #STR66#

2) with the proviso that;

a) at least one W is a N and R8 is a hydroxyl; or

b) at least one W is a N and R8 is a hydroxyl, and optionally;

c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and/or;

d) at least one of R1-R10 is #STR66#

3) with the proviso that;

a) at least one of R1-10 is selected from #STR77# or #STR88# or

#STR99#, and R8 is a hydroxyl; or

b) at least one of R1-10 is selected from #STR77# or #STR88# or #STR99#, and R8 is a hydroxyl, and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-R10 is #STR66#.

4) with the proviso that;

a) R8 is a hydroxyl or #STR66# and if R8 is a hydroxyl at least one of (R1-R7 and R9-R10) is #STR66#; or

b) R8 is a hydroxyl or #STR66# and if R8 is a hydroxyl at least one of (R1-R7 and R9-R10) is #STR66# and optionally;

c) at least one W is a N, and/or;

d) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#.

5) with the proviso that;

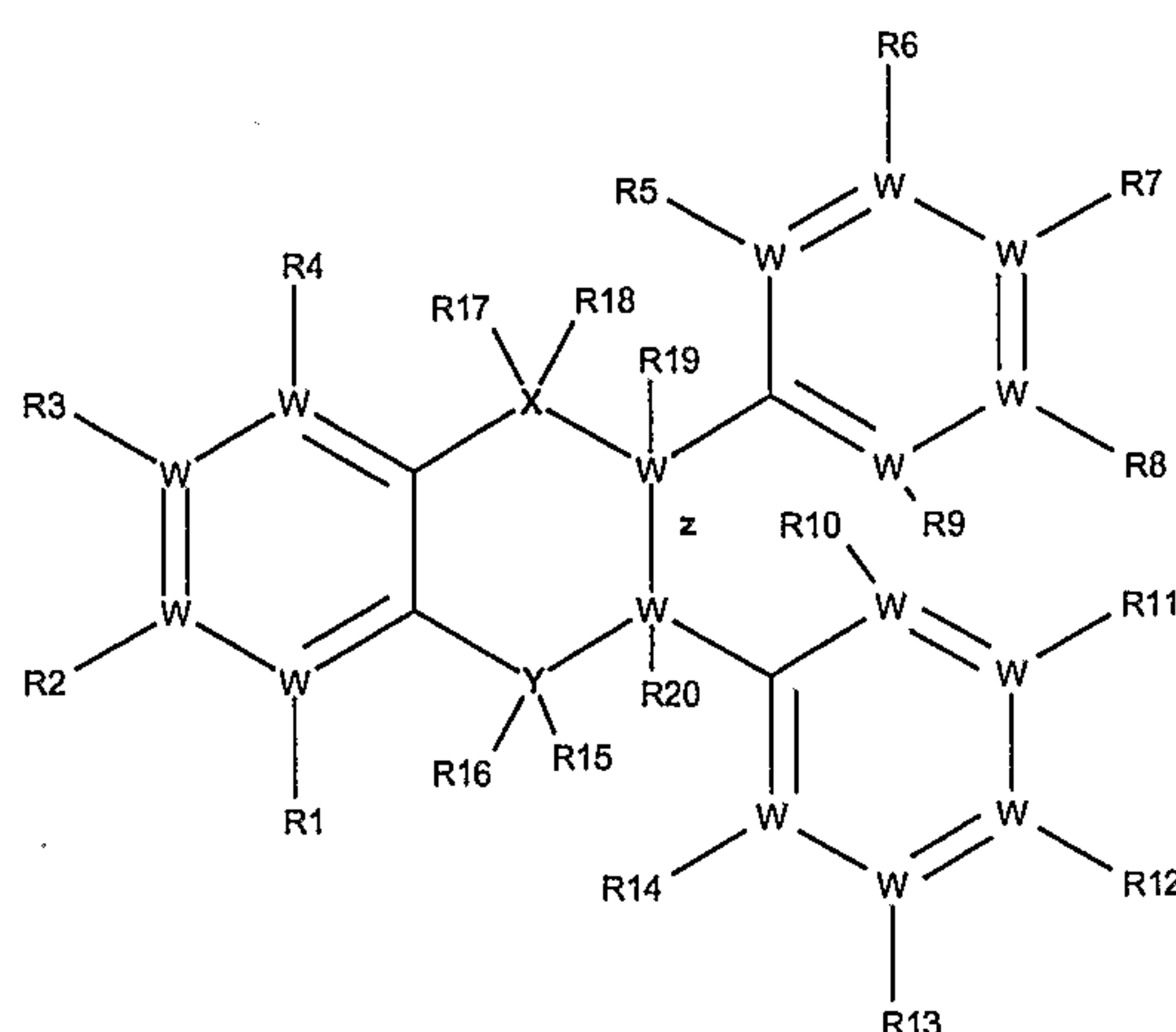
a) R8 is a hydroxyl or #STR66#, and

b) at least one W is a N, and

c) at least one of R1-10 is #STR77#, or #STR88#, or #STR99#, and

d) at least one of R1-R10 is #STR66#.

[0109] Another alternative embodiment provides polyphenol compounds of Formula 6:



or a pharmaceutically acceptable salt thereof,

wherein

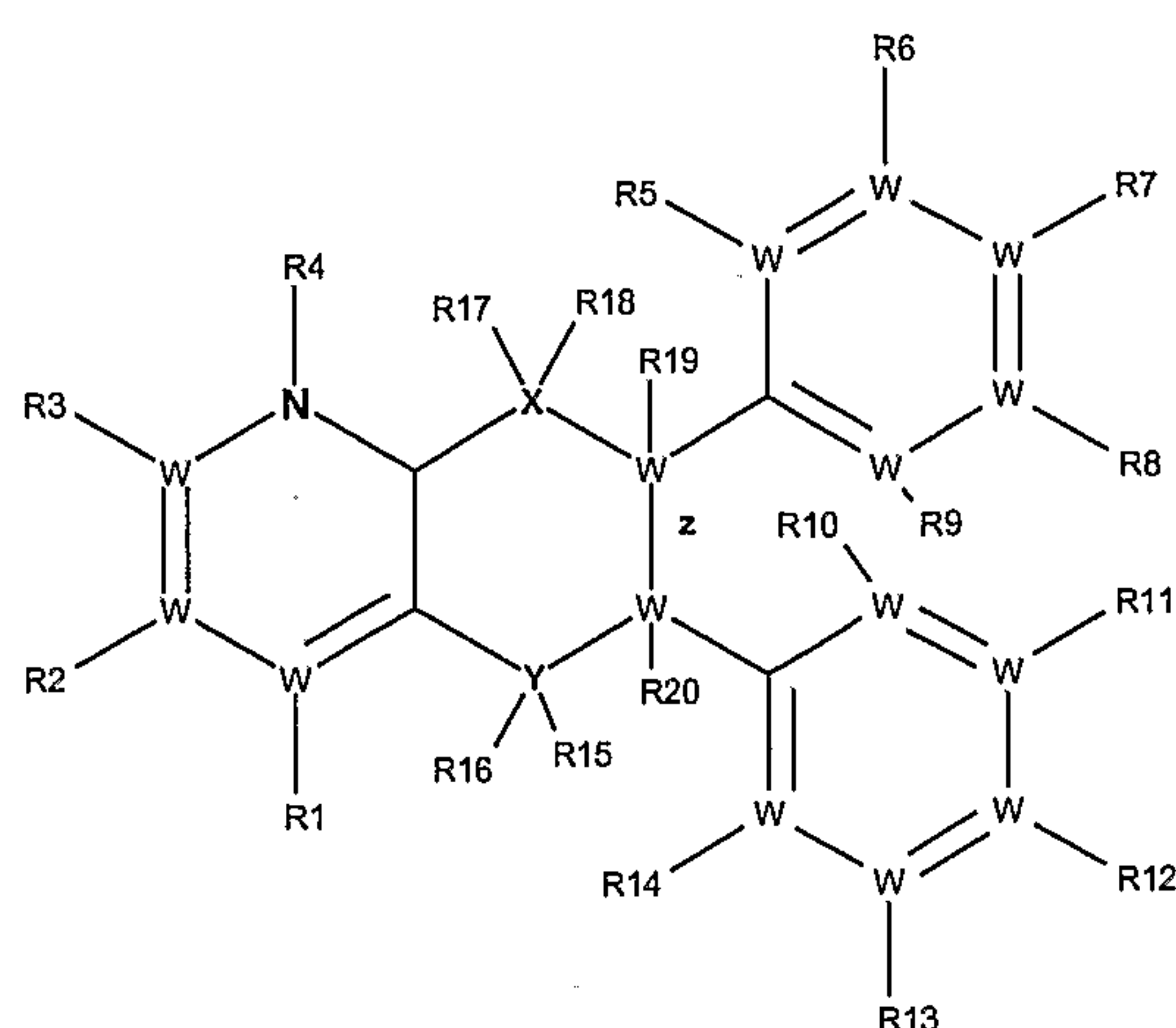
R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19 and R20 are independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I] fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid (-SO₃H), phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], monoesters, dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#, #STR100#,

wherein

W can be C or N;

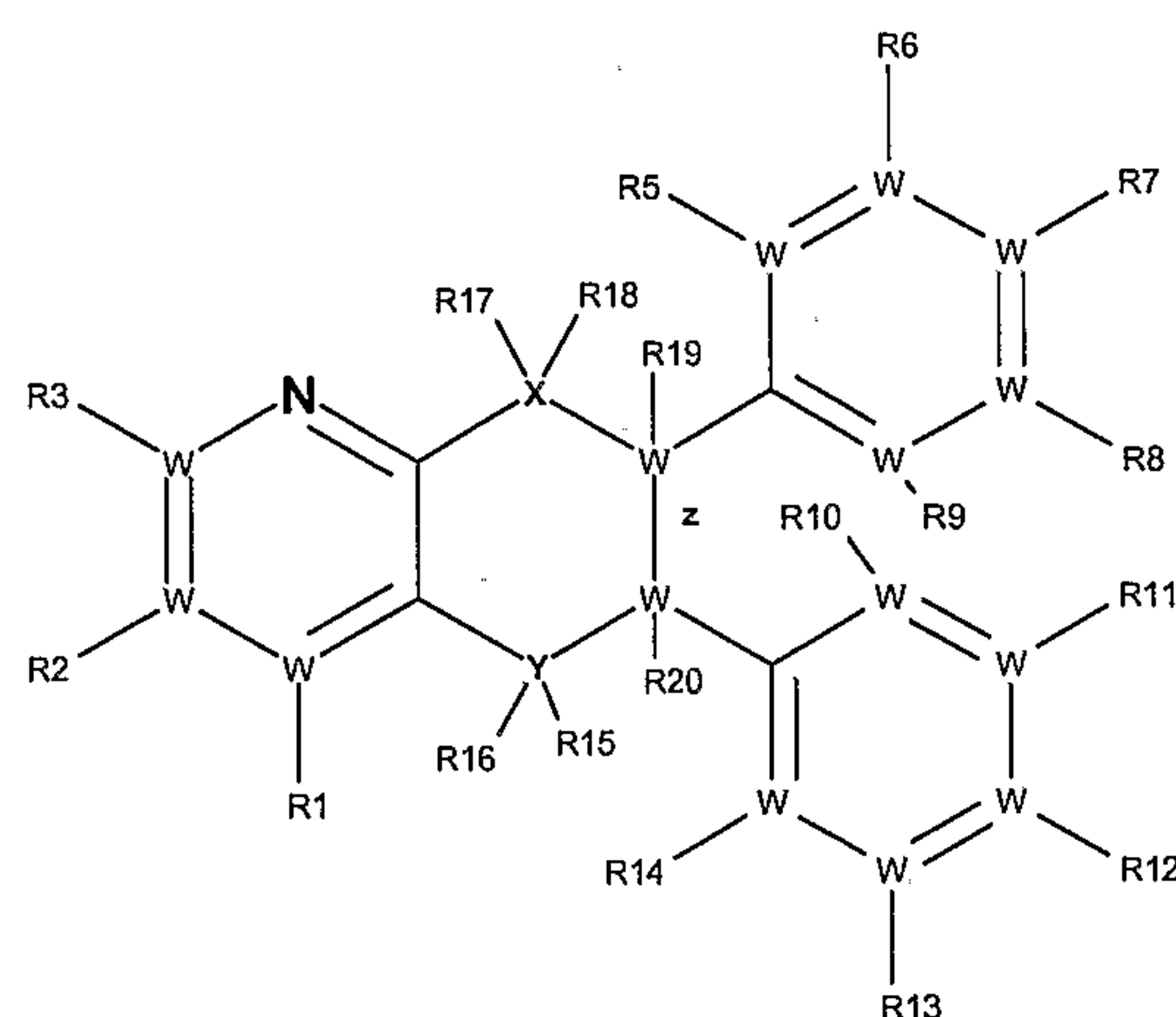
wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0110] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 6:



wherein the same applies to any W;

or



wherein the same applies to any W:

wherein

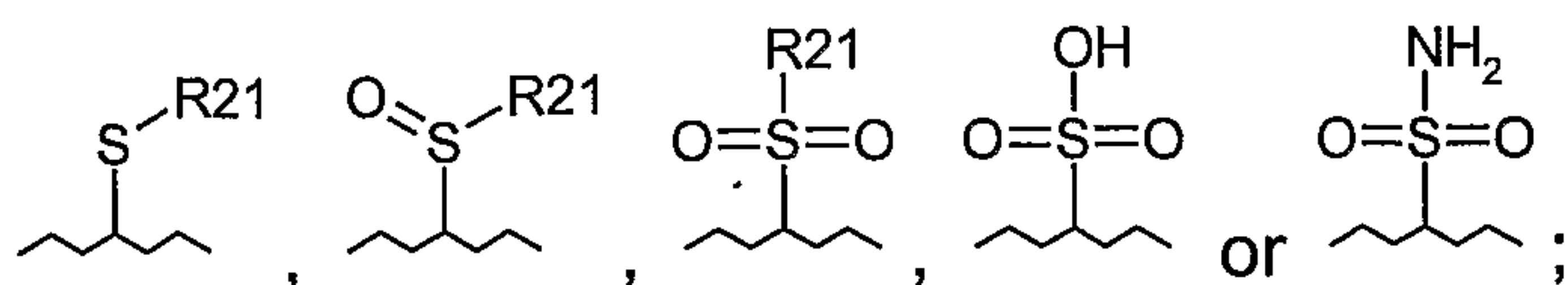
X can be CH, CH₂, CR₁₇, CR₁₈, CHR₁₇, CHR₁₈, CR₁₇R₁₈, CO, CS, O, S, SO, SO₂, NH, NR₁₇ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Y can be CH, CH₂, CR₁₅ CR₁₆, CHR₁₅, CHR₁₆, CR₁₅R₁₆, CO, CS, O, S, SO, SO₂, NH, NR₁₅ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

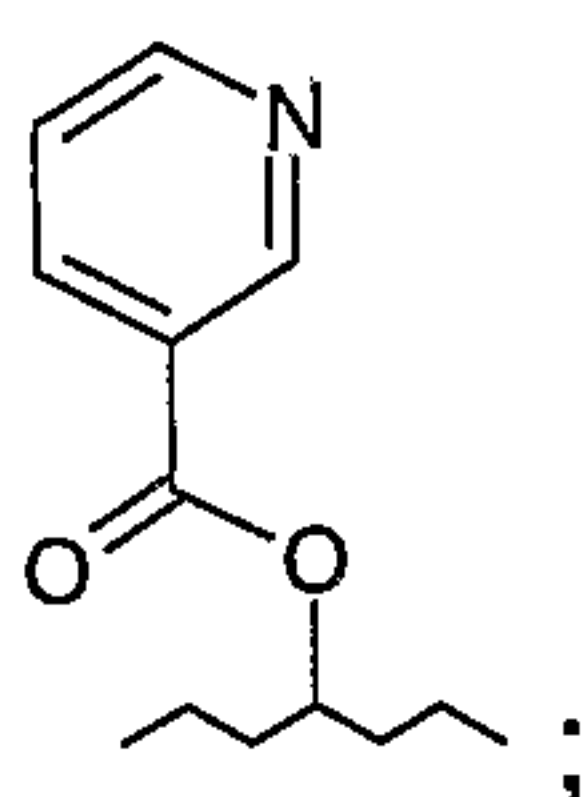
Z can be a single or double bond with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

wherein

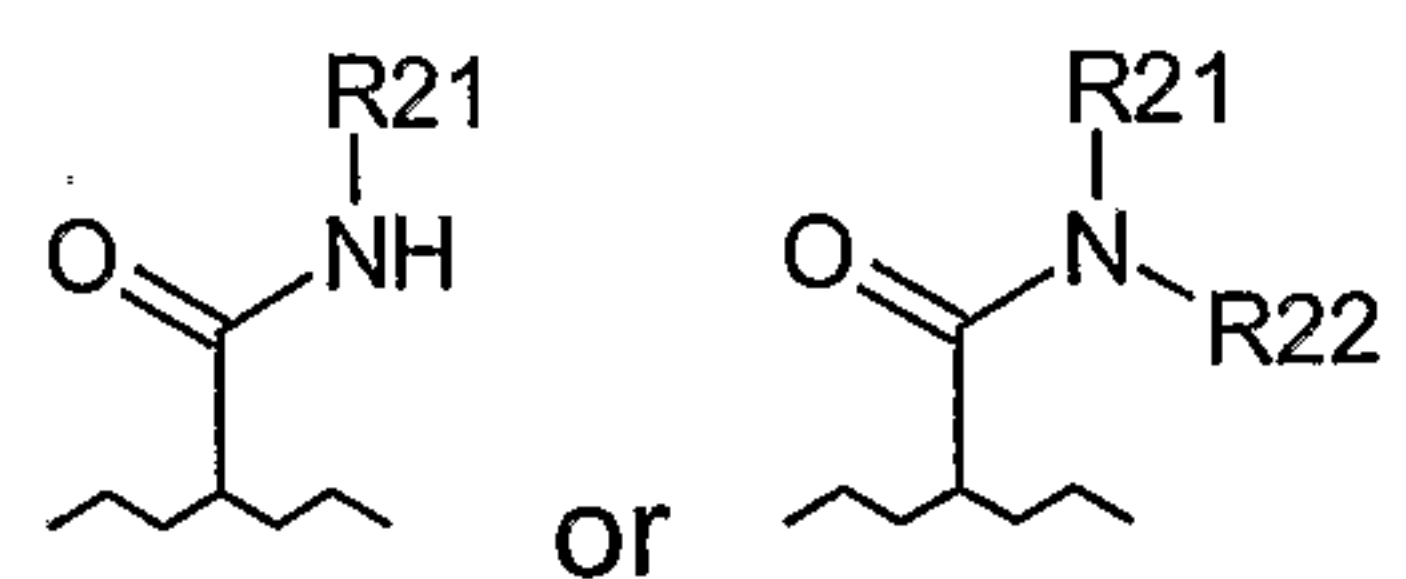
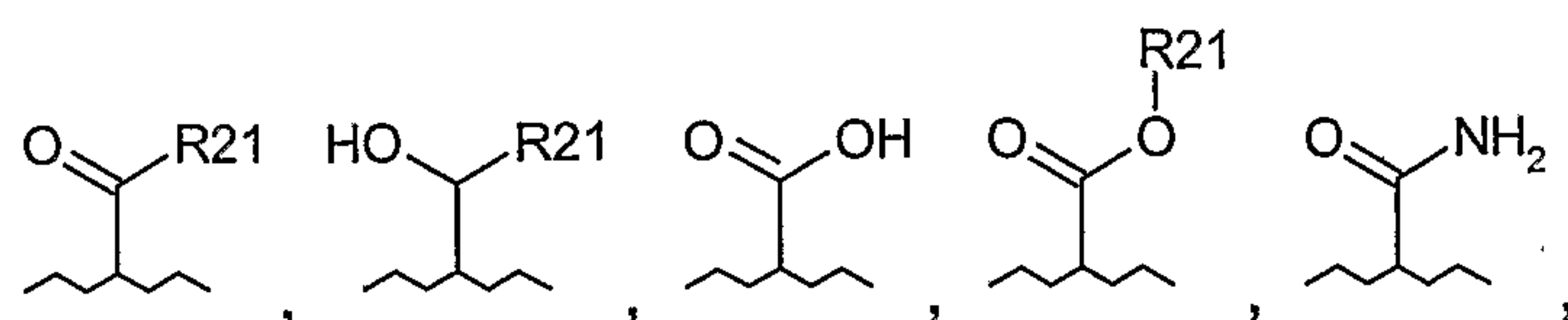
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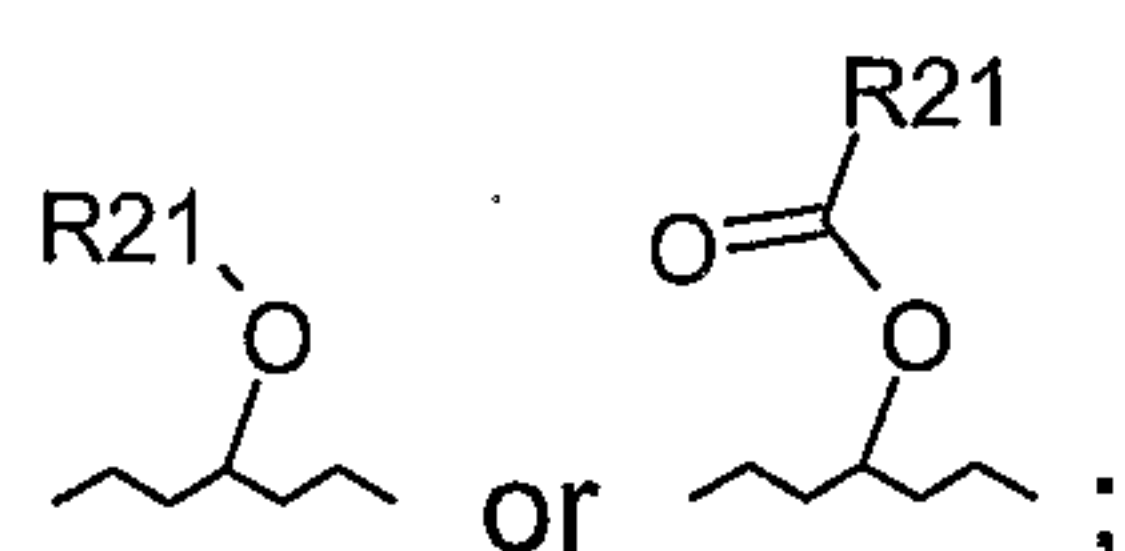
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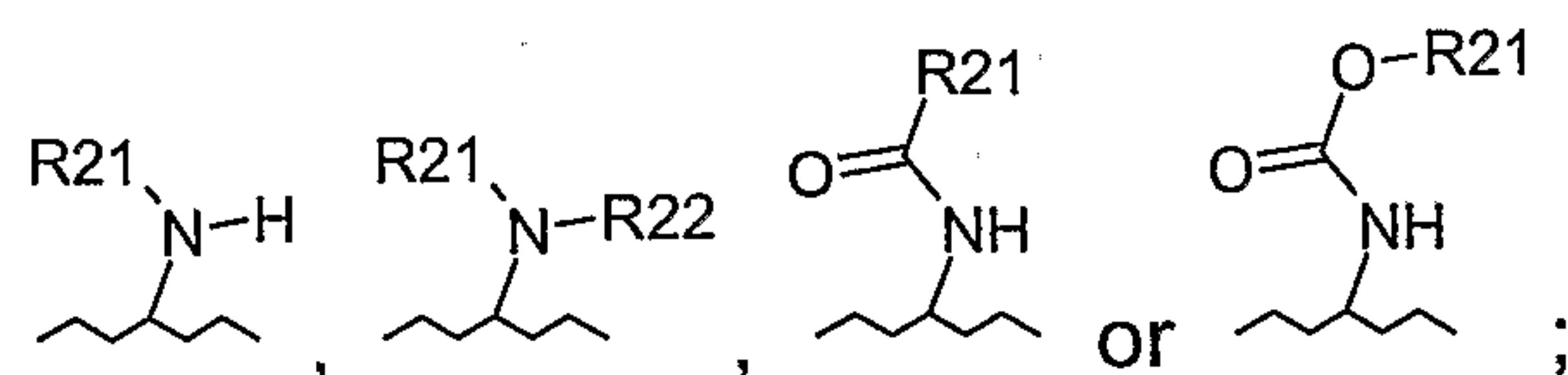
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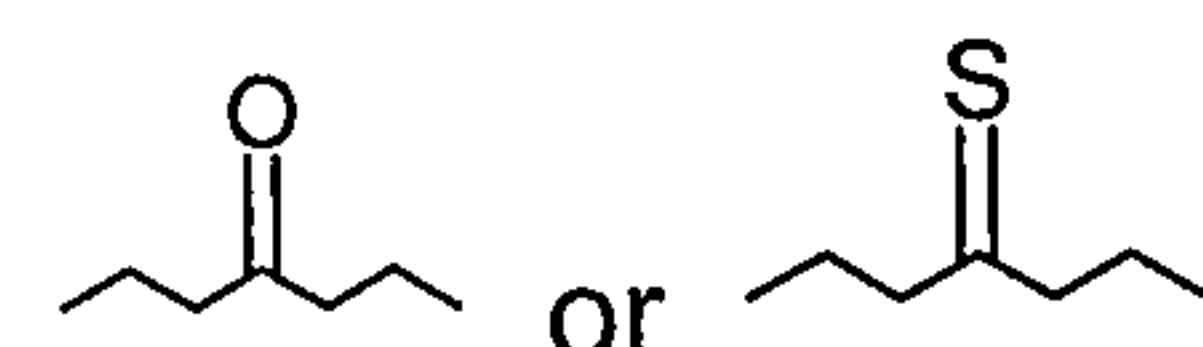
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#STR99# is



#STR100# is



R21 and R12 are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid (-SO₃H), phosphate, or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein Formula 6 compounds have at least one proviso selected from the following:

R7 and R12 are a hydroxyl;

at least one W is a N;

at least one of R1-R14 is #STR77#, #STR88# or #STR99#;

at least one of R1-R14 is #STR66#;

R7 is #STR66#;

R12 is #STR66#;

one of R1-R14 is a monoester;

one of R1-R14 is a succinic acid;

one of R1-R14 is a dicarboxylic acid;

R7 is #STR55#;

R12 is #STR55#;

R7 and R12 are #STR55#; and

[0111] Another embodiment provides for compounds of Formula 6 wherein:

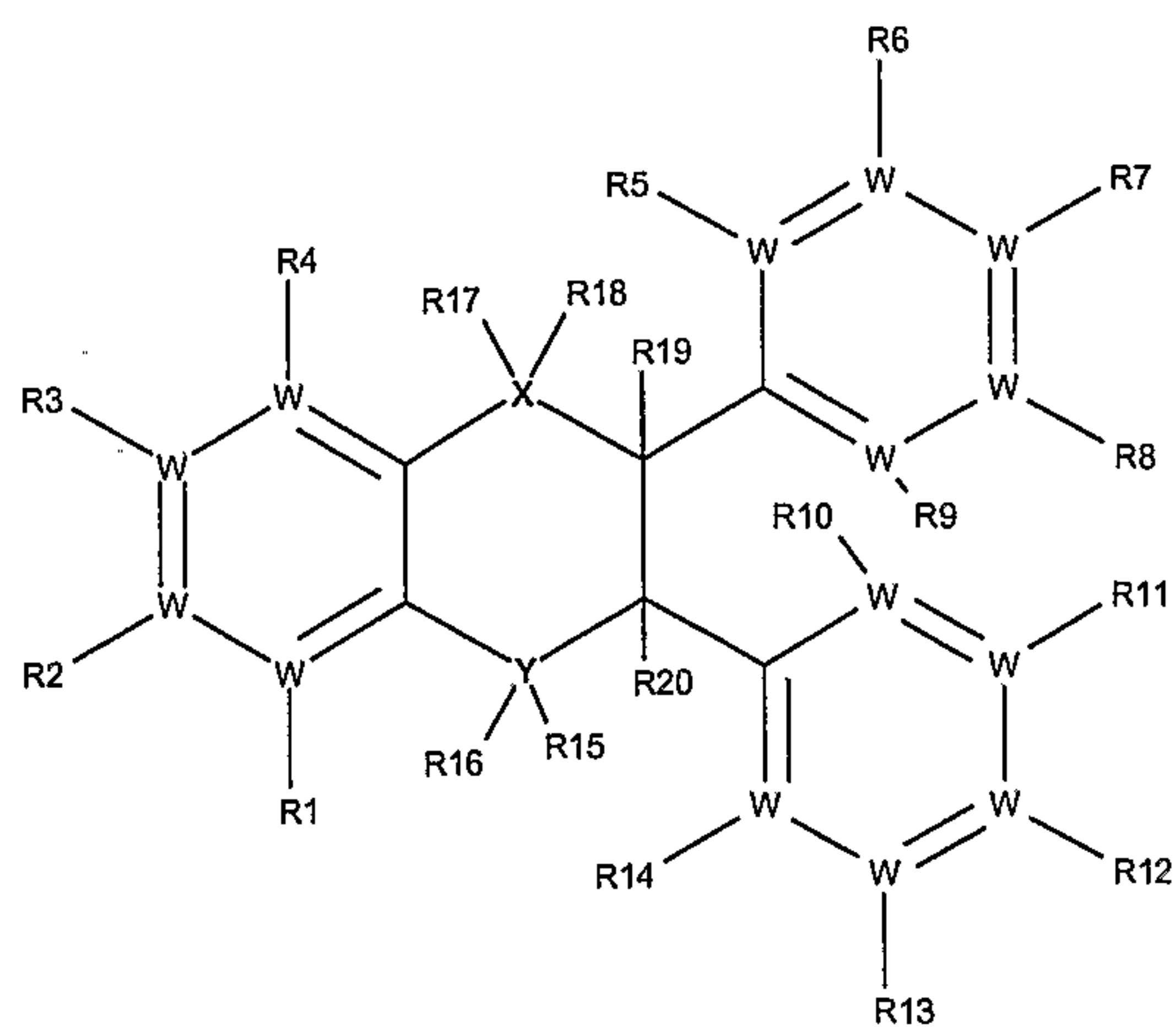
R7 is a hydroxyl and at least one W is a N;

R7 is a hydroxyl and at least one of R1-R6 and R8-R14 is #STR66#;

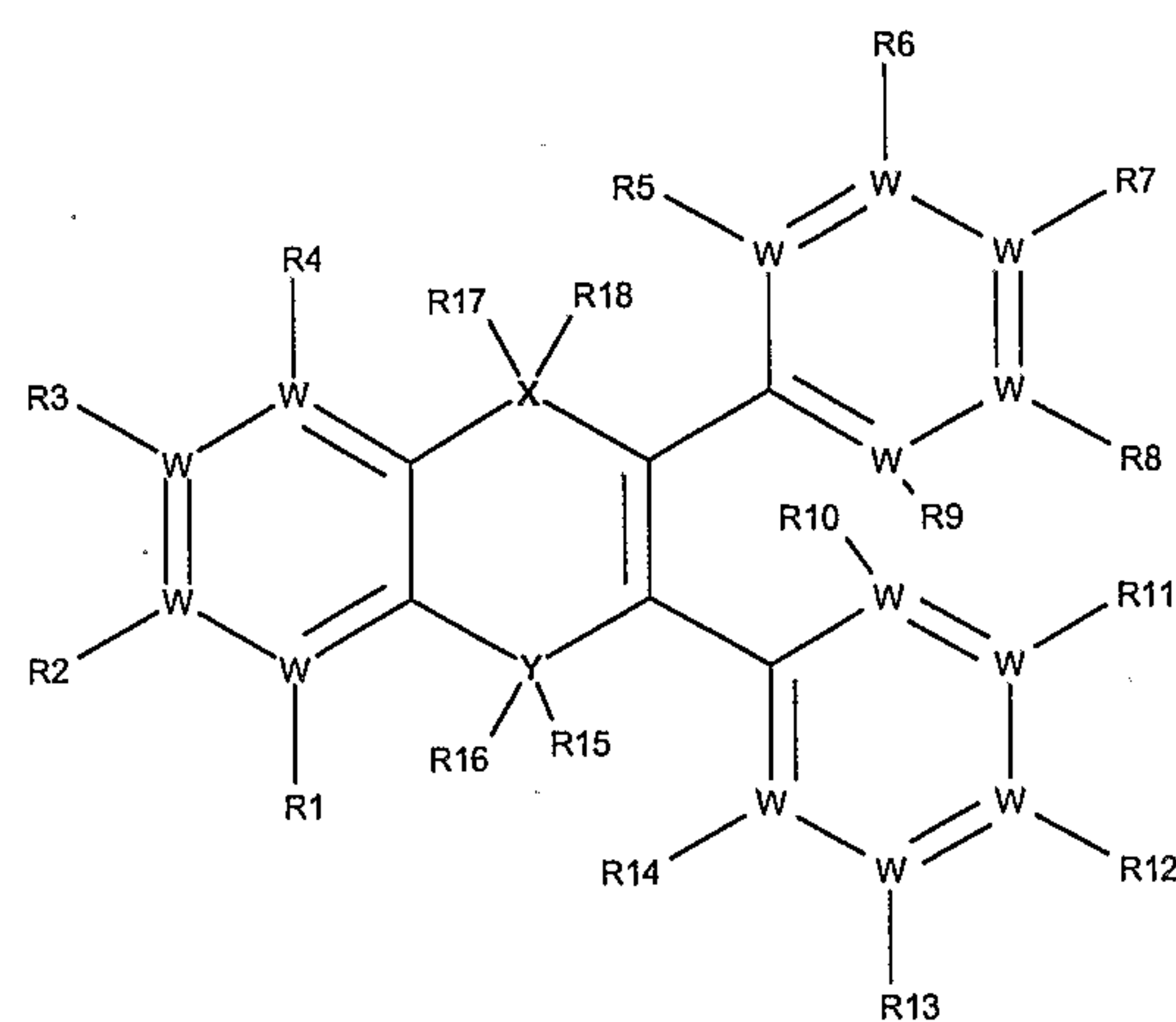
R7 is a hydroxyl and at least one of R1-R6 and R8-R14 is #STR77#, #STR88# and #STR99#;

R7 is #STR66# and at least one W is a N.

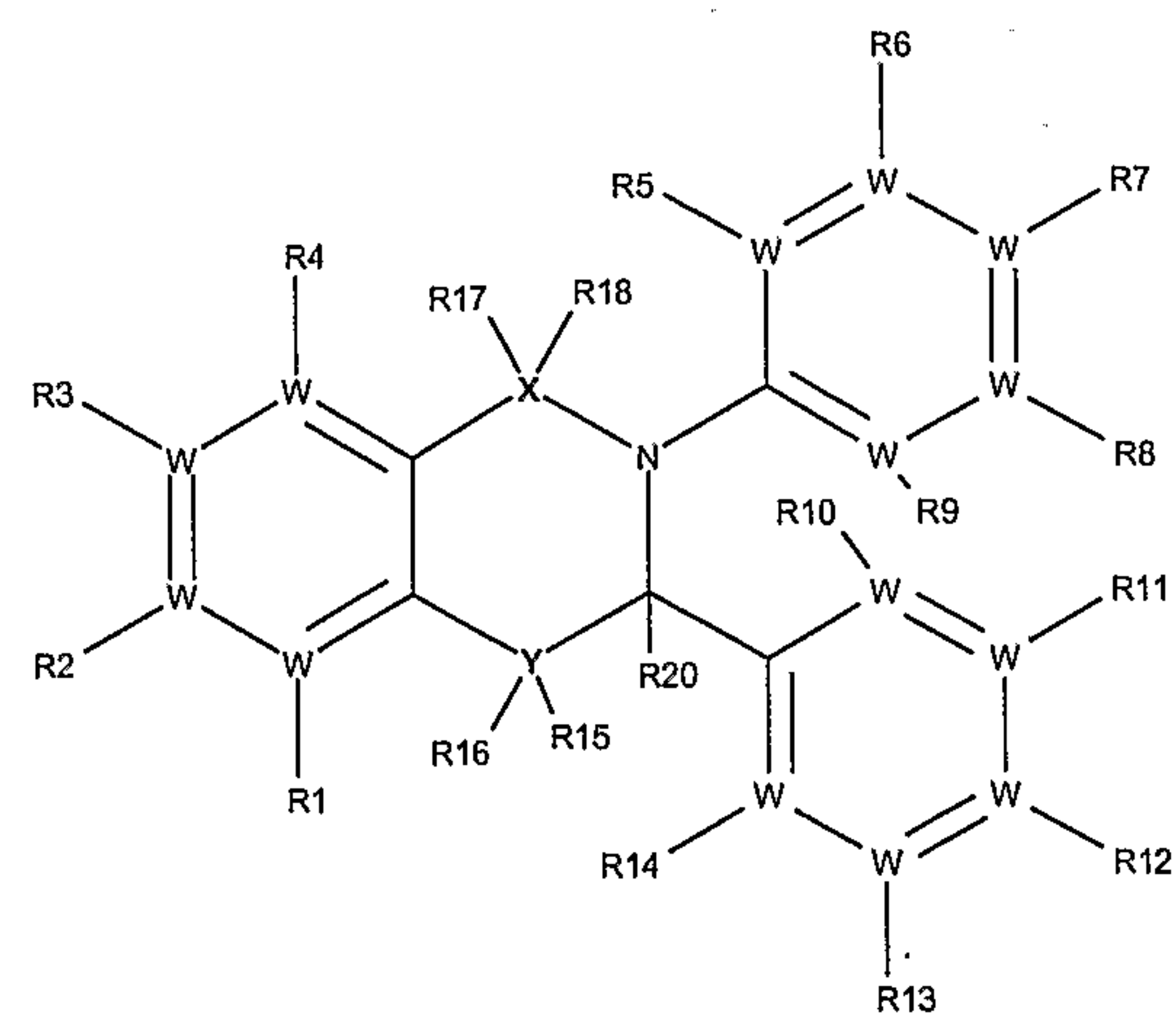
[0112] Non-limiting examples of compounds of Formula 6 include:



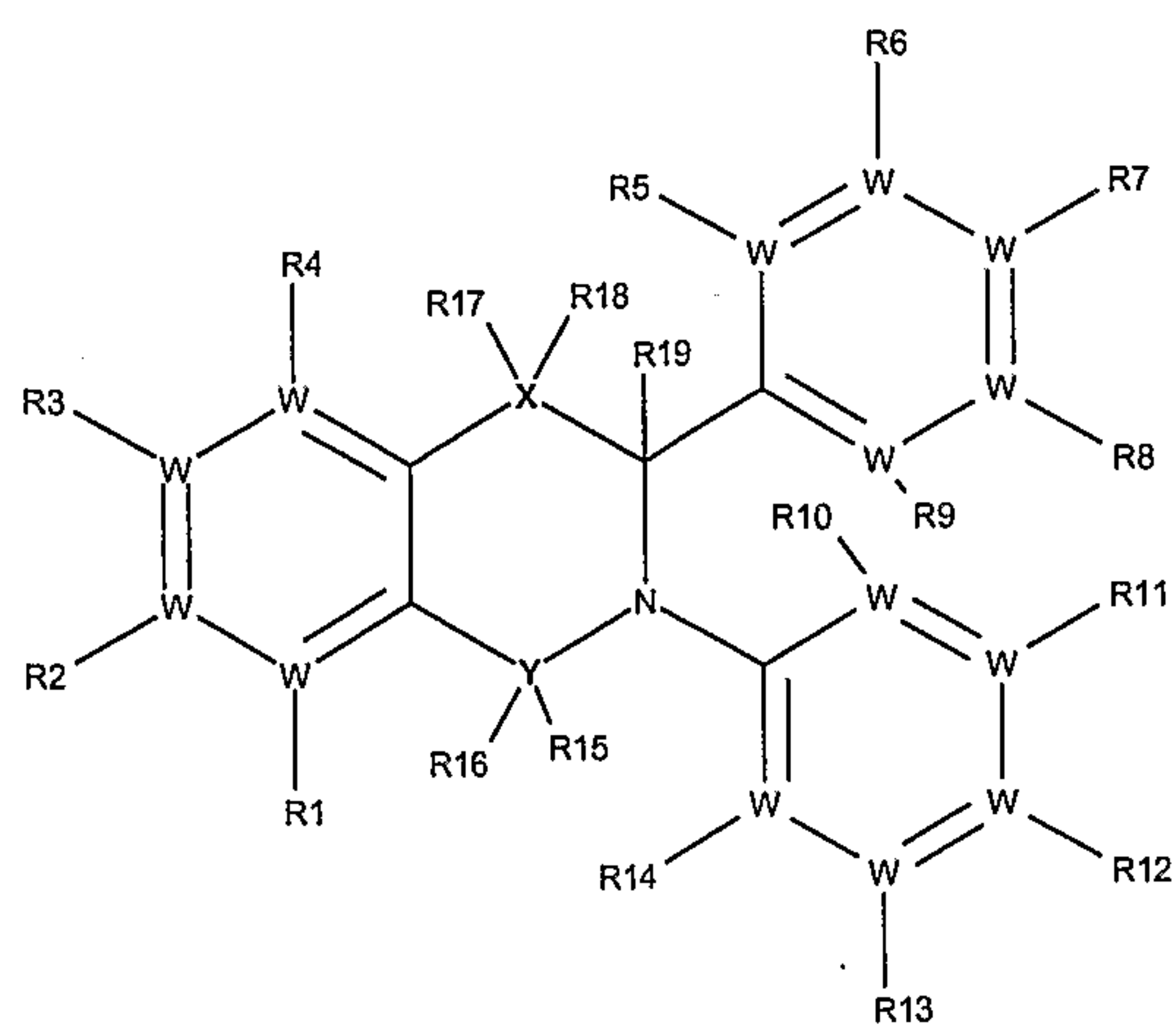
(LXIII)



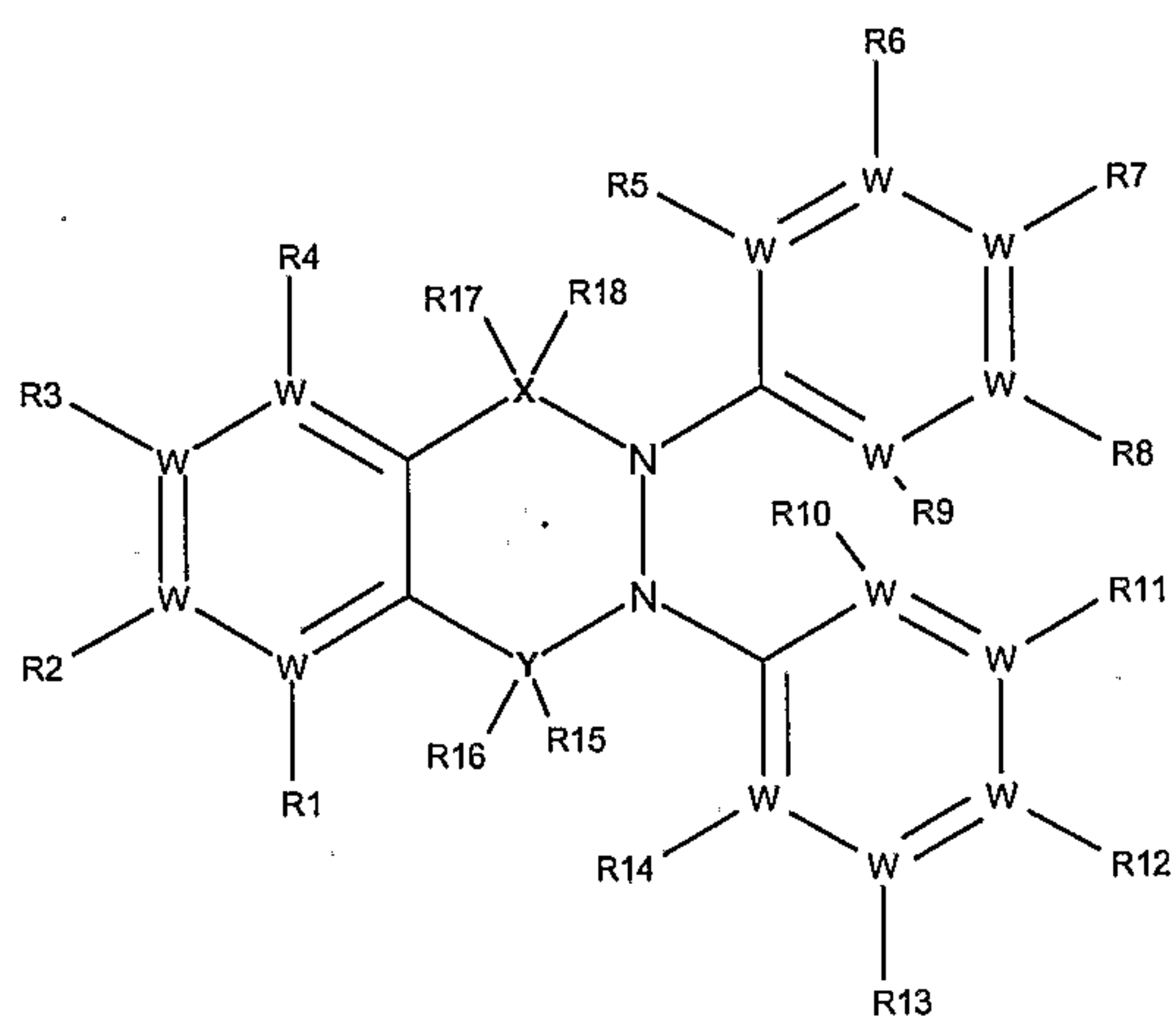
(LXIV)



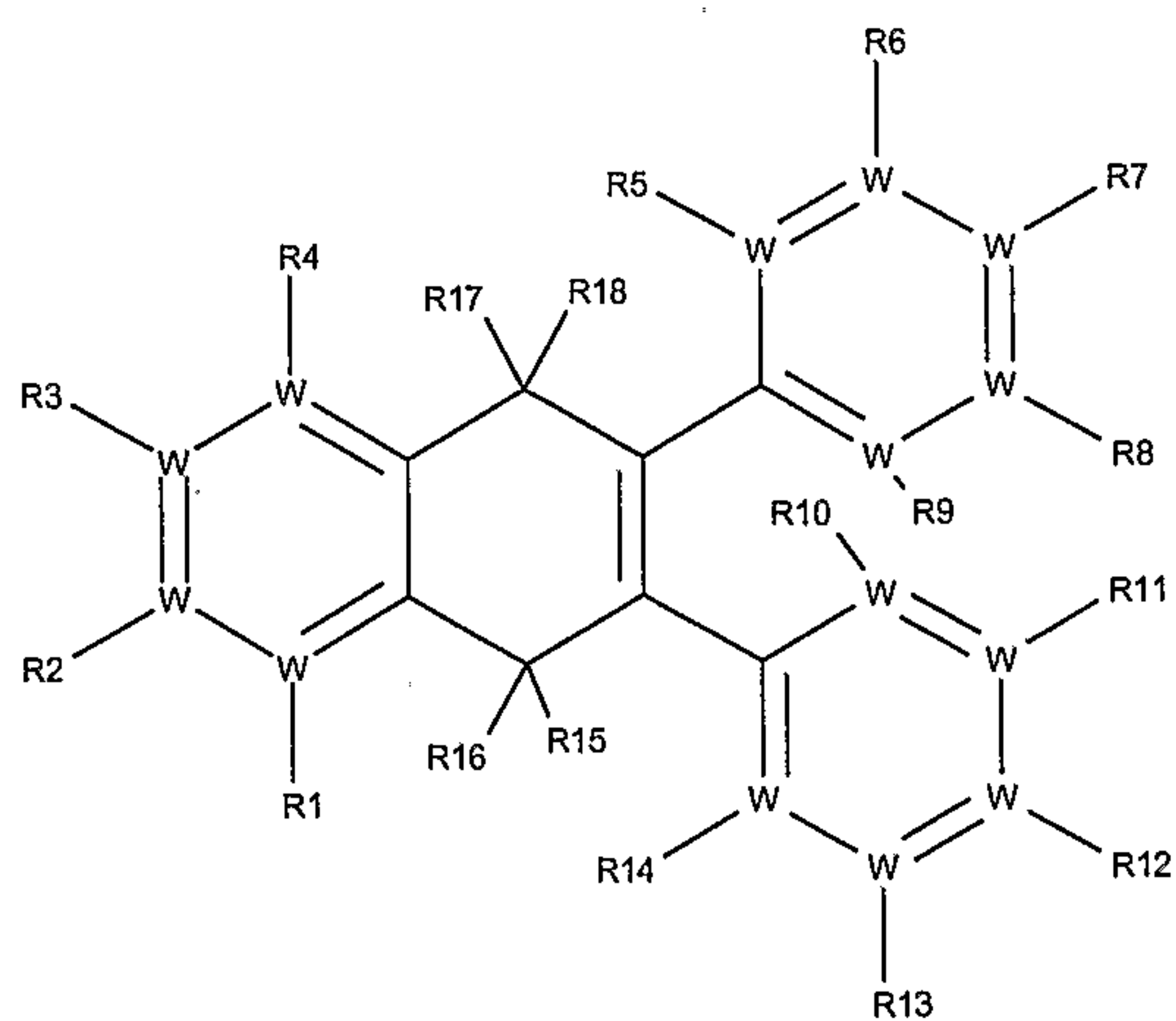
(LXV)



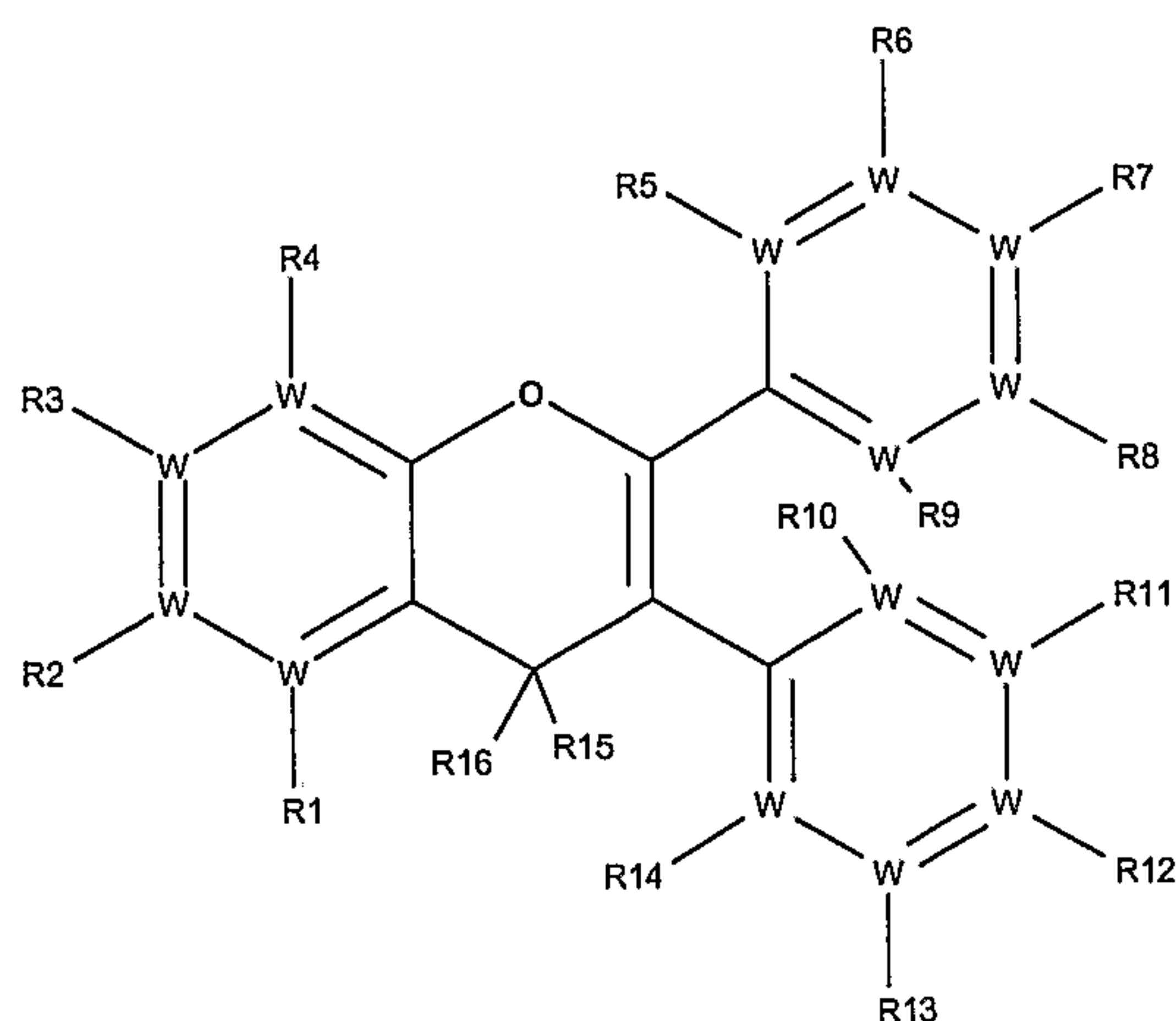
(LXVI)



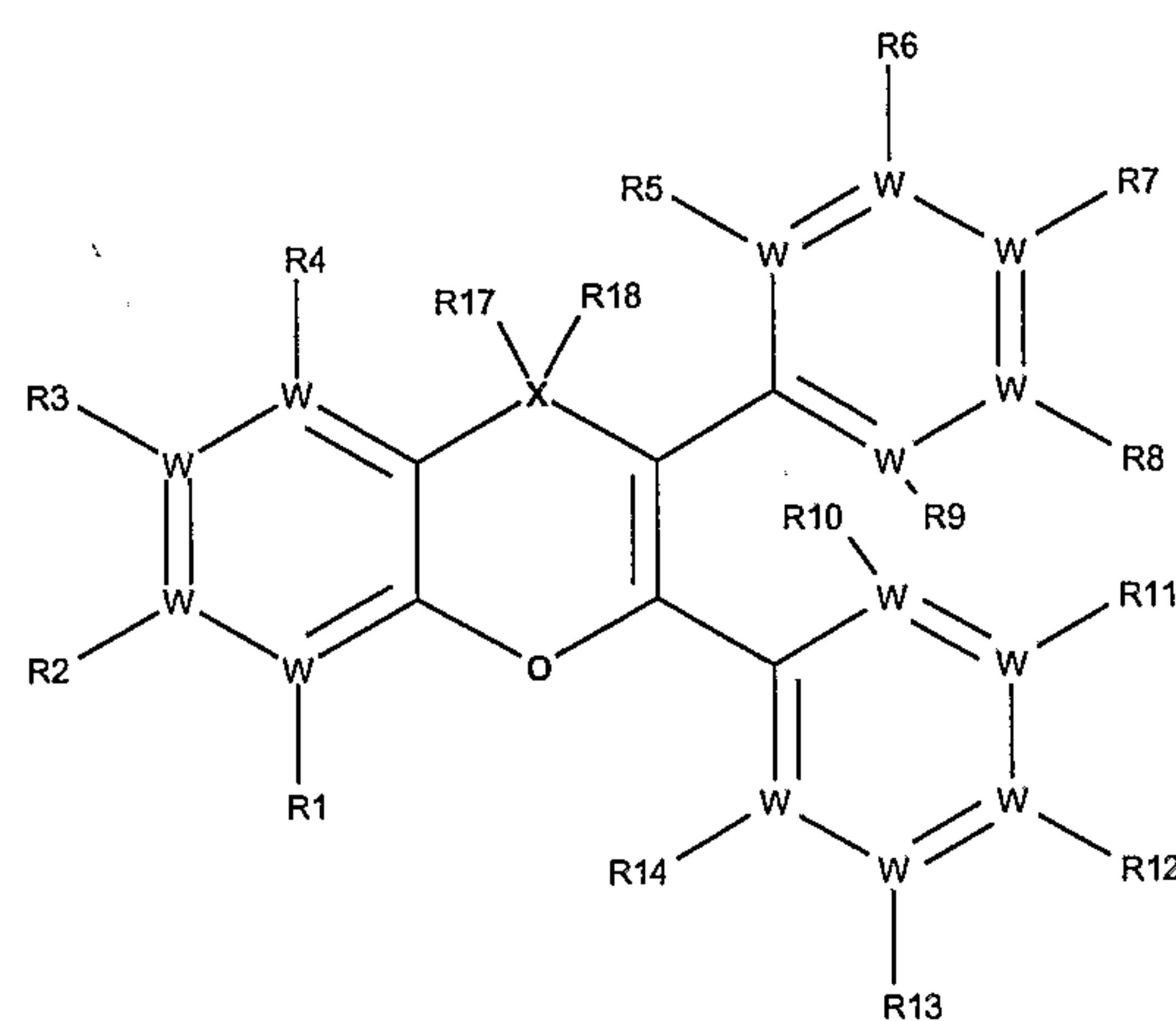
(LXVII)



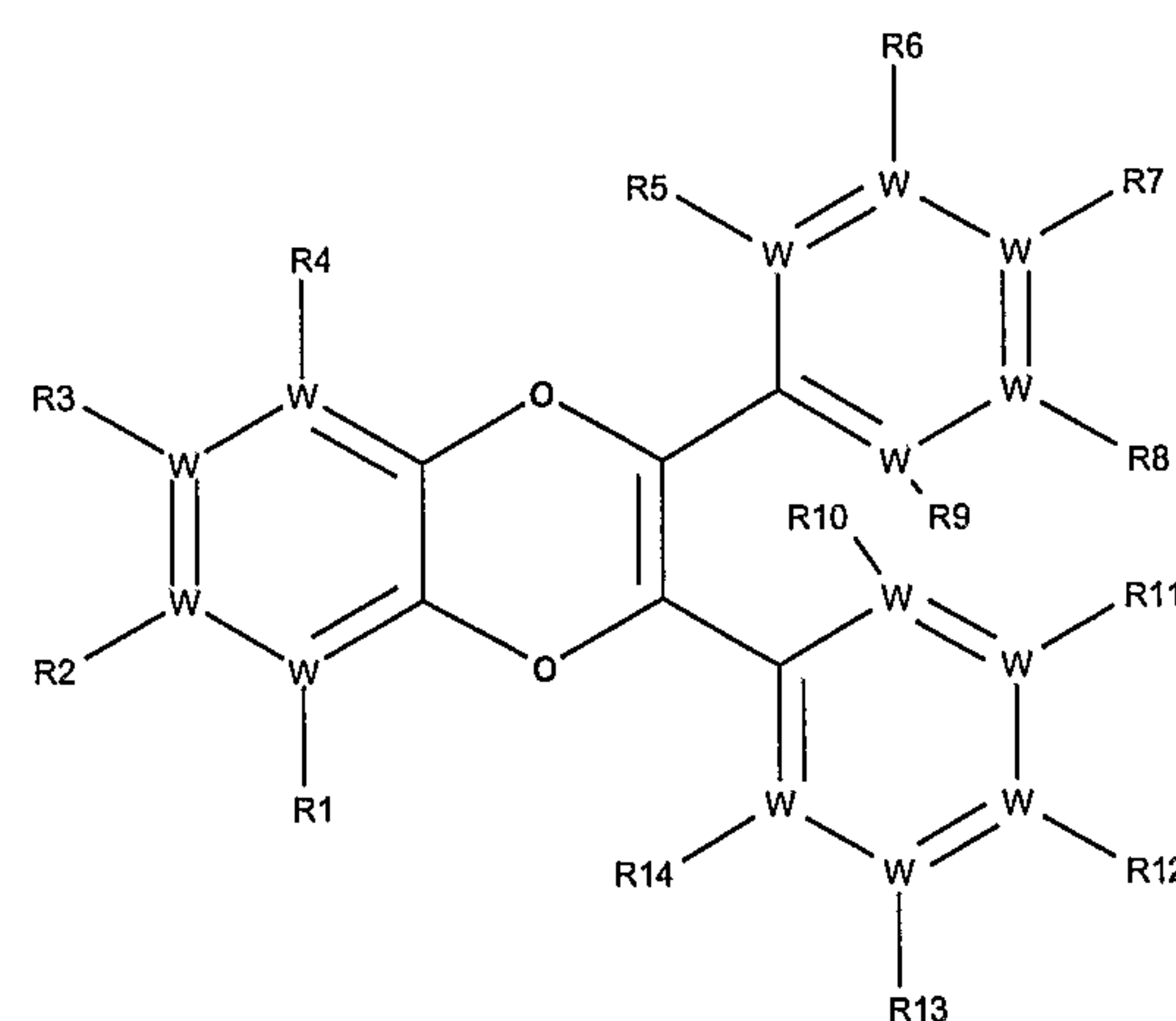
(LXVIII)



(LXIX)



(LXX)



(LXXI)

or a pharmaceutically acceptable salt thereof,

wherein

R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11, R12, R13, R14, R15, R16, R17, R18, R19 and R20 are independently selected from the group consisting of

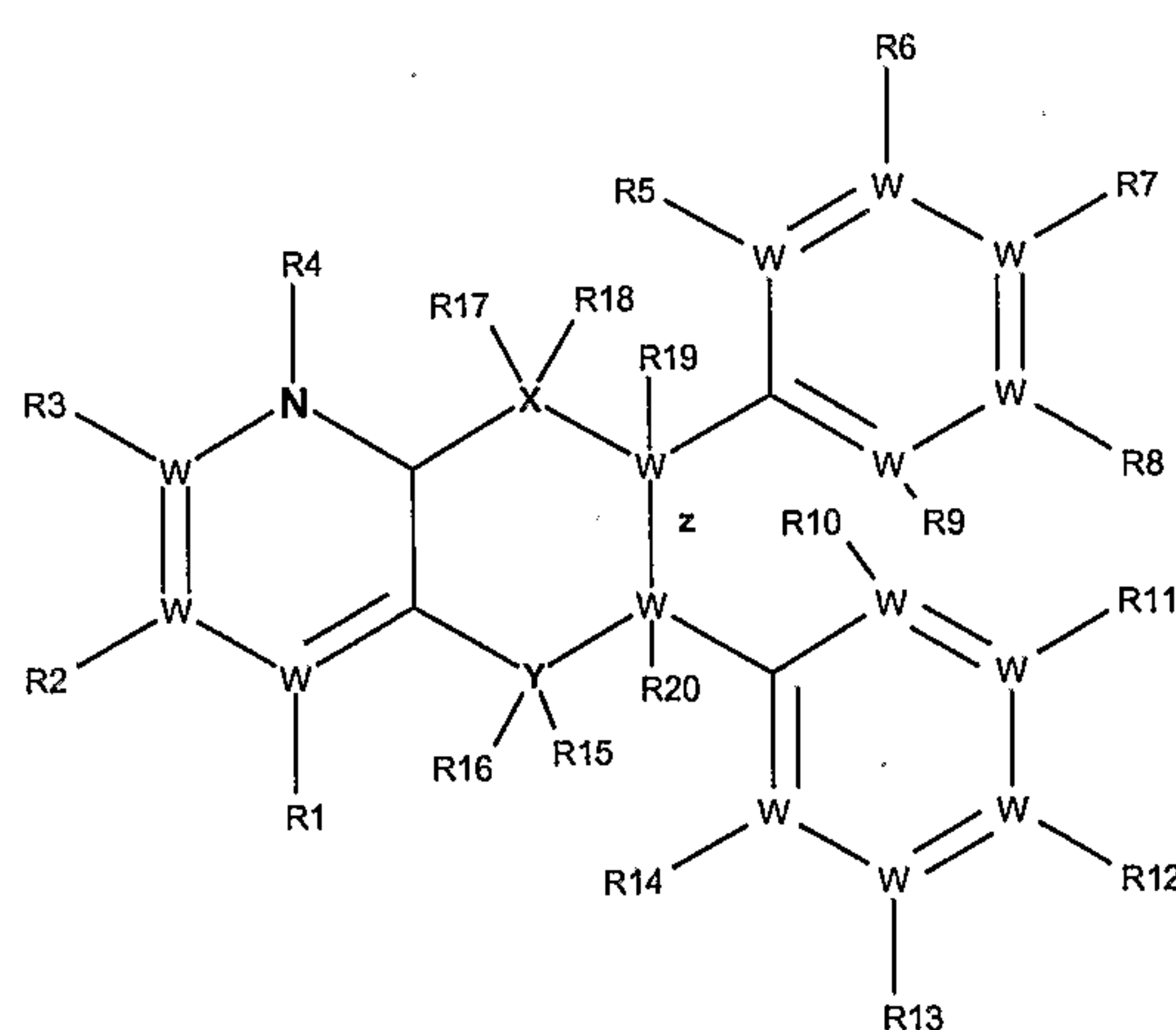
(C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid (-SO₃H), phosphate, O-sulfate [the sulfate conjugate], O-glucoronidate [the glucuronic (AKA glucuronic) acid conjugates], monoesters, dicarboxylic acid, #STR55#, #STR66#, #STR77#, #STR88#, #STR99#, #STR100#,

wherein

W can be C or N;

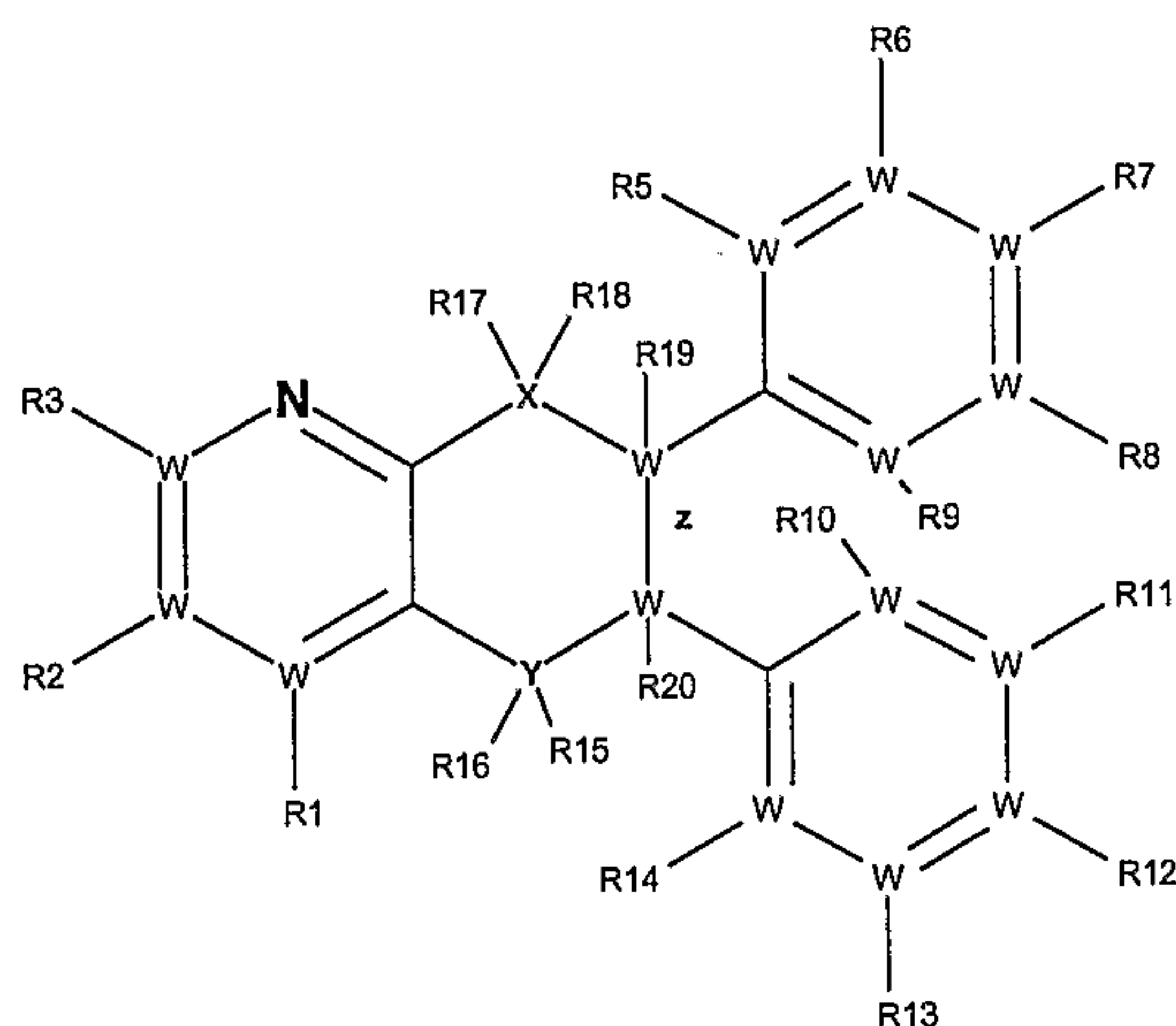
wherein when W is an nitrogen atom, the nitrogen atom will only bind to three covalent bonds due to available valence electrons.

[0113] The structures below demonstrate a nitrogen arrangement of one embodiment of the compounds of Formula 6:



wherein the same applies to any W;

or



wherein the same applies to any W:

wherein

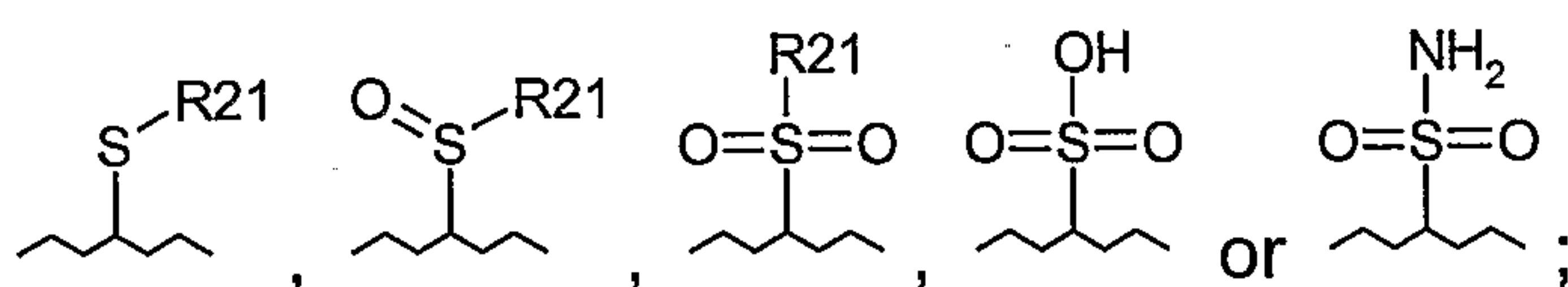
X can be CH, CH₂, CR₁₇, CR₁₈, CHR₁₇, CHR₁₈, CR₁₇R₁₈, CO, CS, O, S, SO, SO₂, NH, NR₁₇ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

Y can be CH, CH₂, CR₁₅ CR₁₆, CHR₁₅, CHR₁₆, CR₁₅R₁₆, CO, CS, O, S, SO, SO₂, NH, NR₁₅ with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

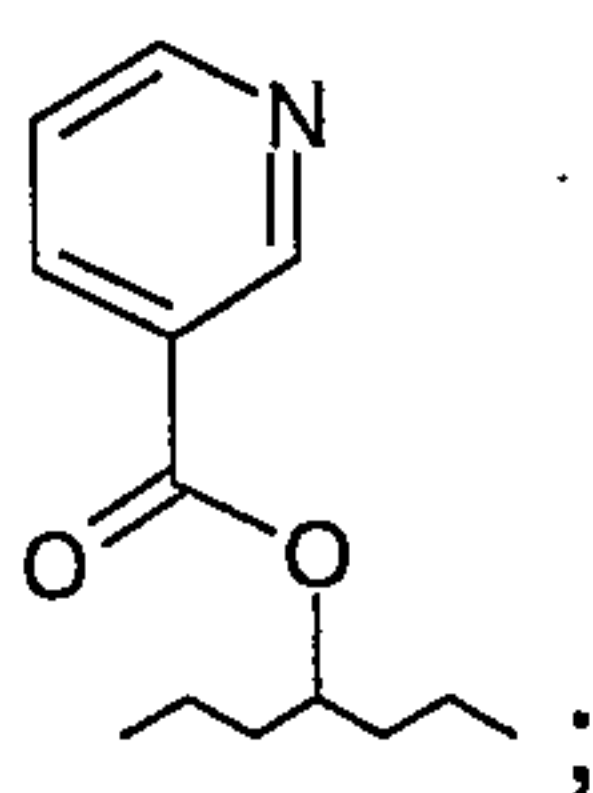
Z can be a single or double bond with the proviso that X and Y do not exceed the number of valence electrons available as per definitions of X and Y above

wherein

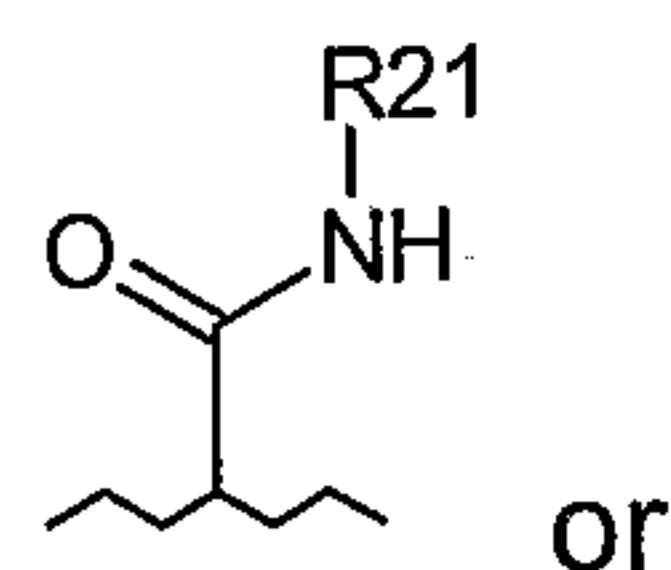
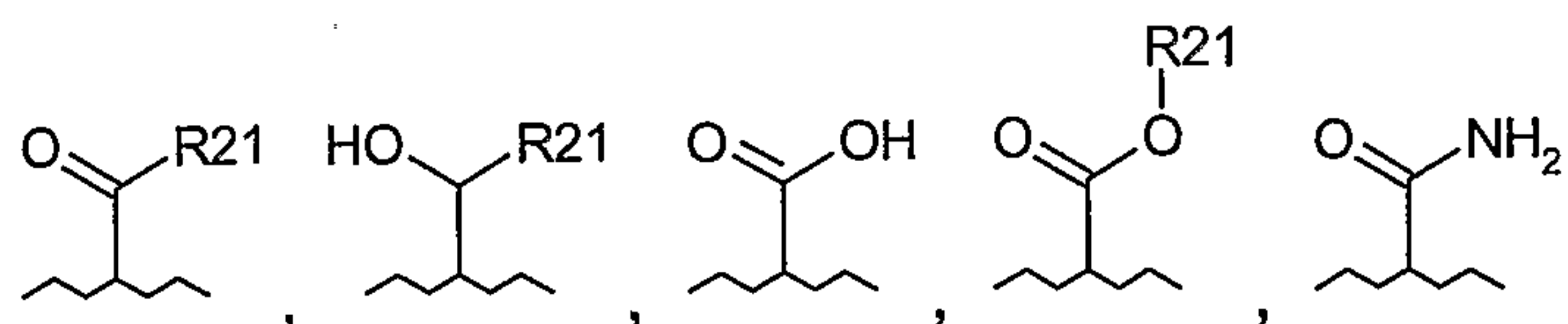
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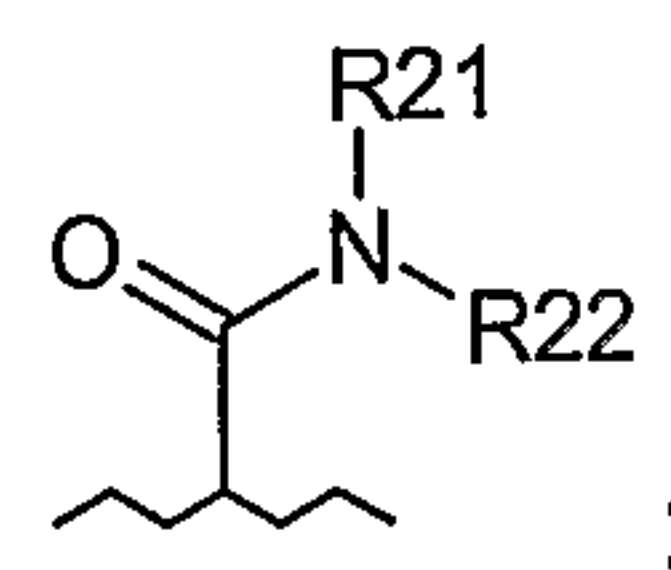
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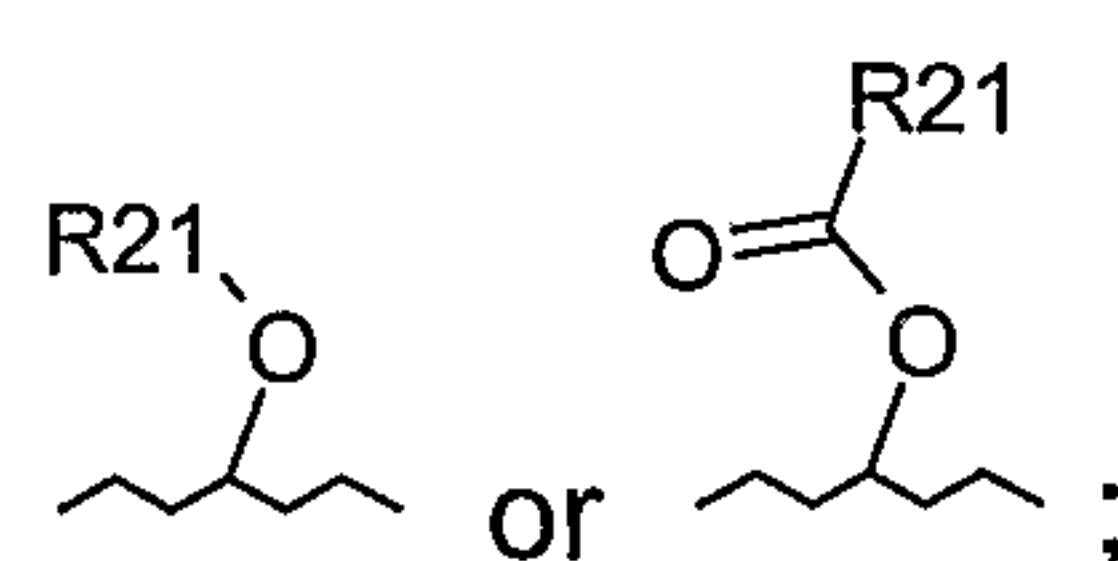


or



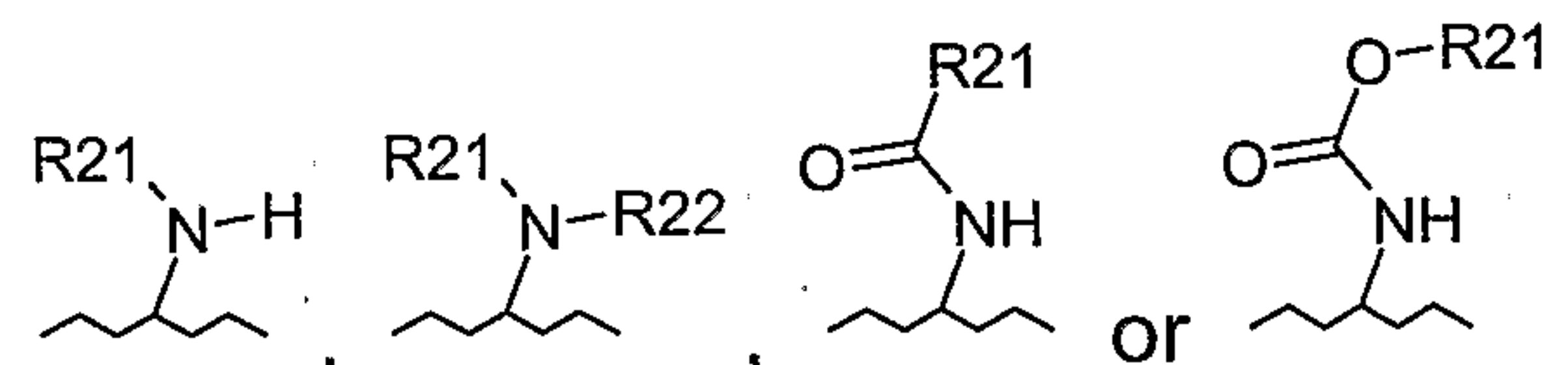
;

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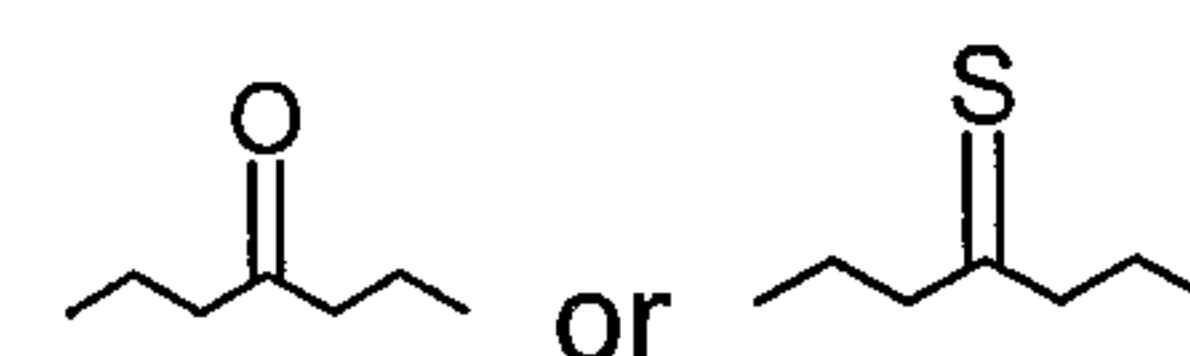
or

#STR99# is



or

#STR100# is



R21 and R12 are substituents independently selected from the group consisting of (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl [OH], acetyl, hydroxyalkyl, aminoalkyl, amides, carbamates, halogen, bromide [Br], iodide [I], fluoride [F], chloride [Cl], CF₃, CCl₃, sulfonic acid [-SO₃H], phosphate, or a derivative thereof, wherein said derivative is optionally substituted and optionally branched, and may have one or more of the C atoms replaced by S, N or O;

wherein compounds have at least one proviso selected from the following:

R7 and R12 are a hydroxyl;

at least one W is a N;

at least one of R1-R14 is #STR77#, #STR88# or #STR99#;

at least one of R1-R14 is #STR66#;

R7 is #STR66#;

R12 is #STR66#

one of R1-R14 is a monoester;

one of R1-R14 is a succinic acid;

one of R1-R14 is a dicarboxylic acid;

R7 is #STR55#;

R12 is #STR55#

R7 and R12 are #STR55#; and

[0114] Another embodiment provides for compounds of Formula 6 wherein:

R7 is a hydroxyl and at least one W is a N;

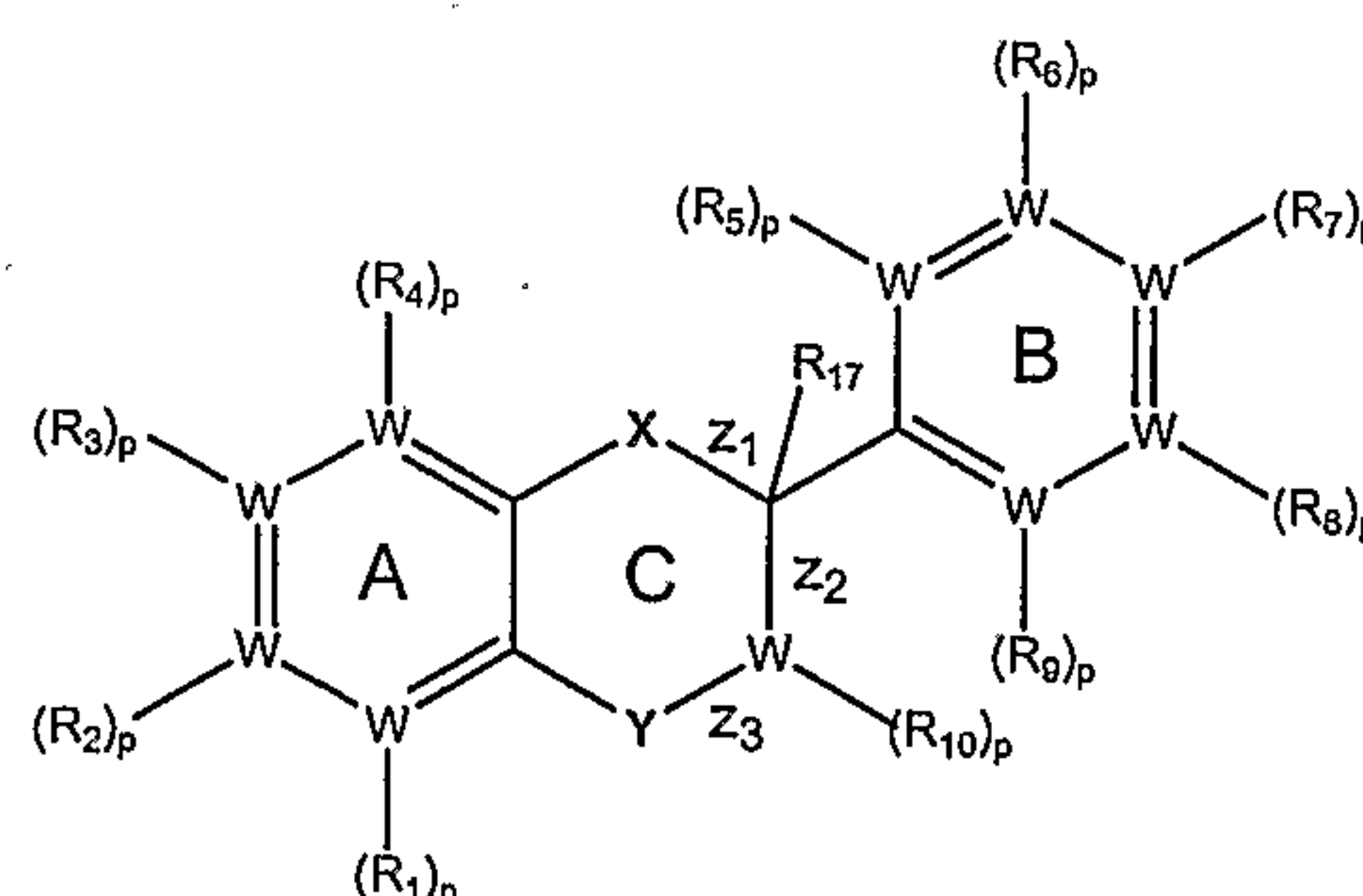
R7 is a hydroxyl and at least one of R1-R6 and R8-R14 is #STR66#;

R7 is a hydroxyl and at least one of R1-R6 and R8-R14 is #STR77#, #STR88# and #STR99#;

R7 is #STR66# and at least one W is a N.

[0115] The following is a list of specific exemplary embodiments are encompassed by the invention:

1. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

wherein:

X is selected from CR_{11} , $CR_{11}R_{13}$, CO, CS, O, S, SO, SO_2 , N and NR_{11} ,

wherein R_{11} may be the same or different than R_{13} ;

Y is selected from CR_{12} , $CR_{12}R_{14}$, CO, CS, O, S, SO, SO_2 , N and NR_{12} ,

wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, the Z_1 is a single bond;

wherein if X is O and Z_2 is a single bond, then R_{10} is not hydroxyl or ester;

and pharmaceutically acceptable salts and hydrates thereof.

2. The method of embodiment 1, wherein X is O and Y is CO.
3. The method of embodiment 1, wherein at least one W is N.
4. The method of embodiment 3, wherein X is O and Y is CO.

5. The method of embodiment 1, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from O-sulfate and O-glucuronidate.

6. The method of embodiment 1, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from succinate, D-argininate, L-argininate, L-lysinate and D-lysinate.

7. The method of embodiment 1, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from amide, amino, carbamate, carboxy, ester, ether, formyl, and ketone.

8. The method of embodiment 7, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is a nicotinate ester.

9. The method of embodiment 1, wherein at least one W in the A ring of Formula I is N.

10. The method of embodiment 1, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucuronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

11. The method of embodiment 10, wherein X is O and Y is CO.

12. The method of embodiment 10, wherein at least one W is N.

13. The method of embodiment 12, wherein X is O and Y is CO.

14. The method of embodiment 1, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

15. The method of embodiment 14, wherein X is O and Y is CO.

16. The method of embodiment 14, wherein at least one W is N.

17. The method of embodiment 16, wherein X is O and Y is CO.

18. The method of embodiment 14, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

19. The method of embodiment 18, wherein X is O and Y is CO.

20. The method of embodiment 18, wherein at least one W is N.

21. The method of embodiment 20, wherein X is O and Y is CO.

22. The method of embodiment 1, wherein

X is selected from CR_{11} , $CR_{11}R_{13}$, CO, CS, and O; and

Y is selected from CR_{12} , $CR_{12}R_{14}$, S, SO, SO_2 , and NR_{12} .

23. The method of embodiment 22, wherein at least one W is N.

24. The method of embodiment 22, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

25. The method of embodiment 24, wherein at least one W is N.

26. The method of embodiment 22, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

27. The method of embodiment 26, wherein at least one W is N.

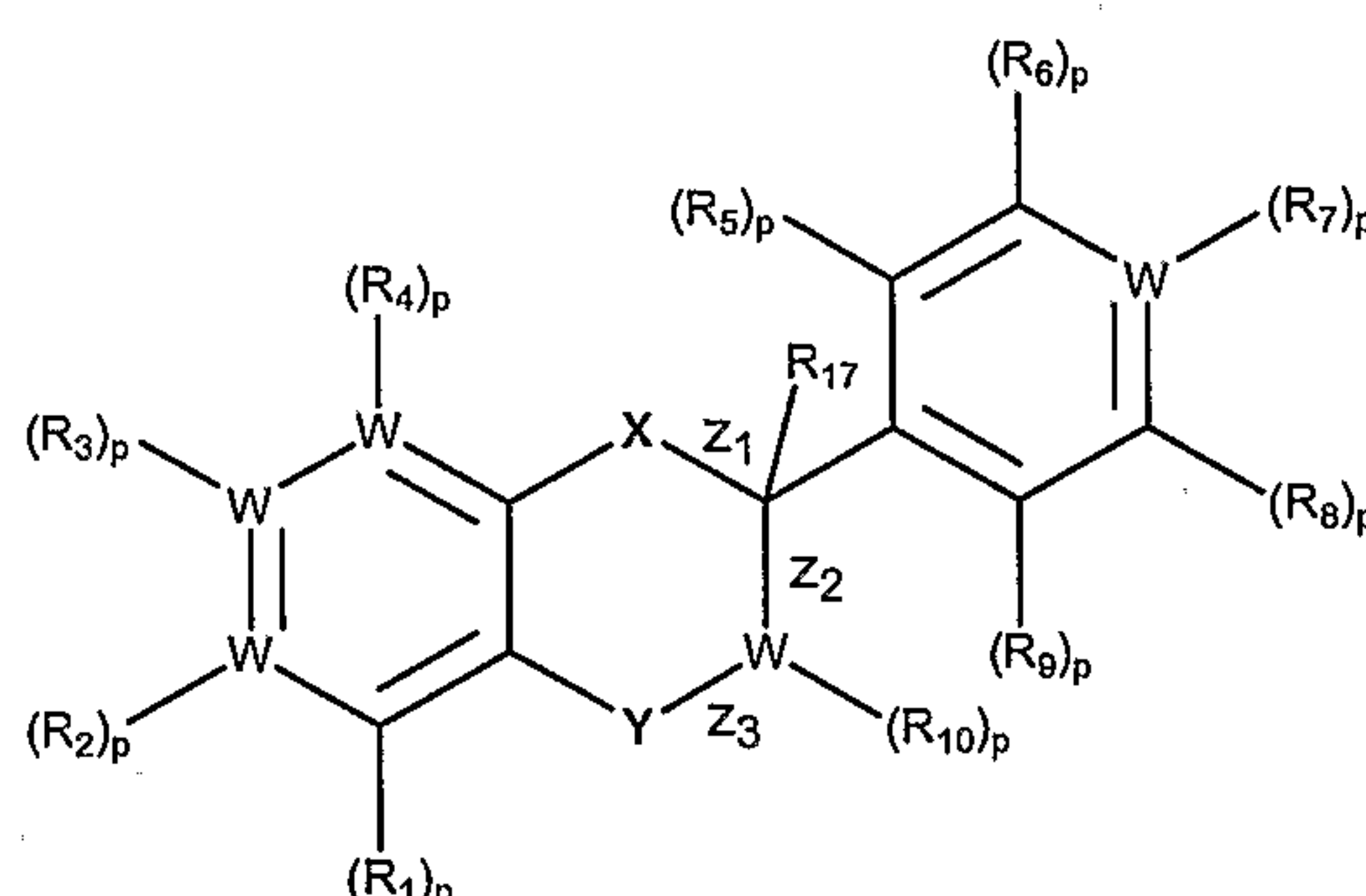
28. The method of embodiment 26, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

29. The method of embodiment 28, wherein at least one W is N.

30. The method of embodiment 1, wherein Formula I has the structure:



31. The method of embodiment 30, wherein X is O and Y is CO.

32. The method of embodiment 30, wherein at least one W is N.

33. The method of embodiment 32, wherein X is O and Y is CO.

34. The method of embodiment 30, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from O-sulfate and O-glucoronidate.

35. The method of embodiment 30, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from succinate, D-argininate, L-argininate, L-lysinate and D-lysinate.

36. The method of embodiment 30, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from amide, amino, carbamate, carboxy, ester, ether, formyl, and ketone.

37. The method of embodiment 36, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is a nicotinate ester.

38. The method of embodiment 30, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

39. The method of embodiment 38, wherein X is O and Y is CO.

40. The method of embodiment 38, wherein at least one W is N.

41. The method of embodiment 40, wherein X is O and Y is CO.

42. The method of embodiment 30, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

43. The method of embodiment 42, wherein X is O and Y is CO.

44. The method of embodiment 42, wherein at least one W is N.

45. The method of embodiment 44, wherein X is O and Y is CO.

46. The method of embodiment 42, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

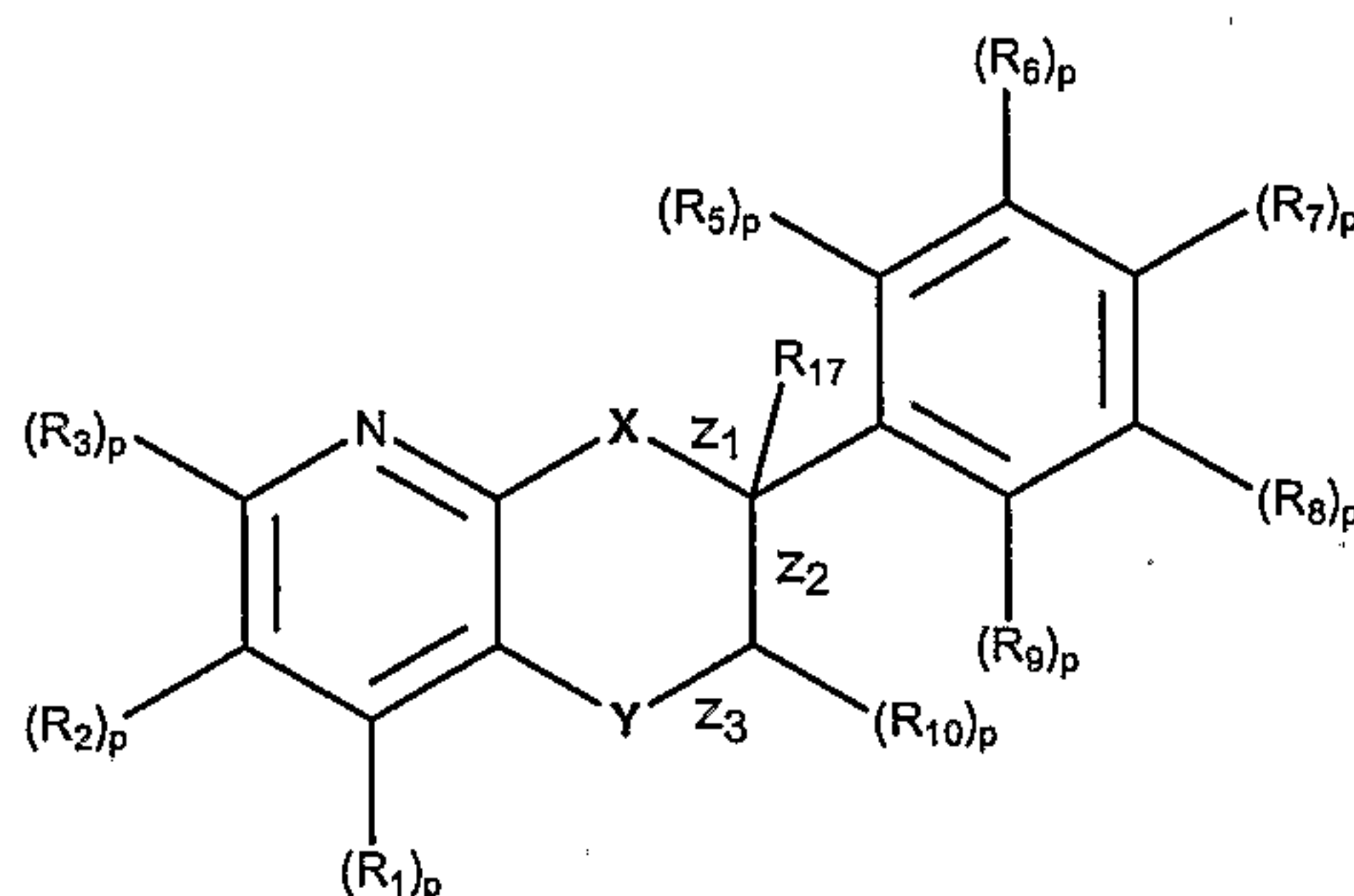
subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

47. The method of embodiment 46, wherein X is O and Y is CO.

48. The method of embodiment 46, wherein at least one W is N.

49. The method of embodiment 48, wherein X is O and Y is CO.

50. The method of embodiment 1, wherein Formula I has the structure:



51. The method of embodiment 50, wherein X is O and Y is CO.

52. The method of embodiment 50, wherein at least one W is N.

53. The method of embodiment 52, wherein X is O and Y is CO.

54. The method of embodiment 50, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from O-sulfate and O-glucoronidate.

55. The method of embodiment 50, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from succinate, D-argininate, L-argininate, L-lysinate and D-lysinate.

56. The method of embodiment 50, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from amide, amino, carbamate, carboxy, ester, ether, formyl, and ketone.

57. The method of embodiment 56, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is a nicotinate ester.

58. The method of embodiment 50, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

59. The method of embodiment 58, wherein X is O and Y is CO.

60. The method of embodiment 58, wherein at least one W is N.

61. The method of embodiment 60, wherein X is O and Y is CO.

62. The method of embodiment 50, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

63. The method of embodiment 62, wherein X is O and Y is CO.

64. The method of embodiment 62, wherein at least one W is N.

65. The method of embodiment 64, wherein X is O and Y is CO.

66. The method of embodiment 62, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone,

perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

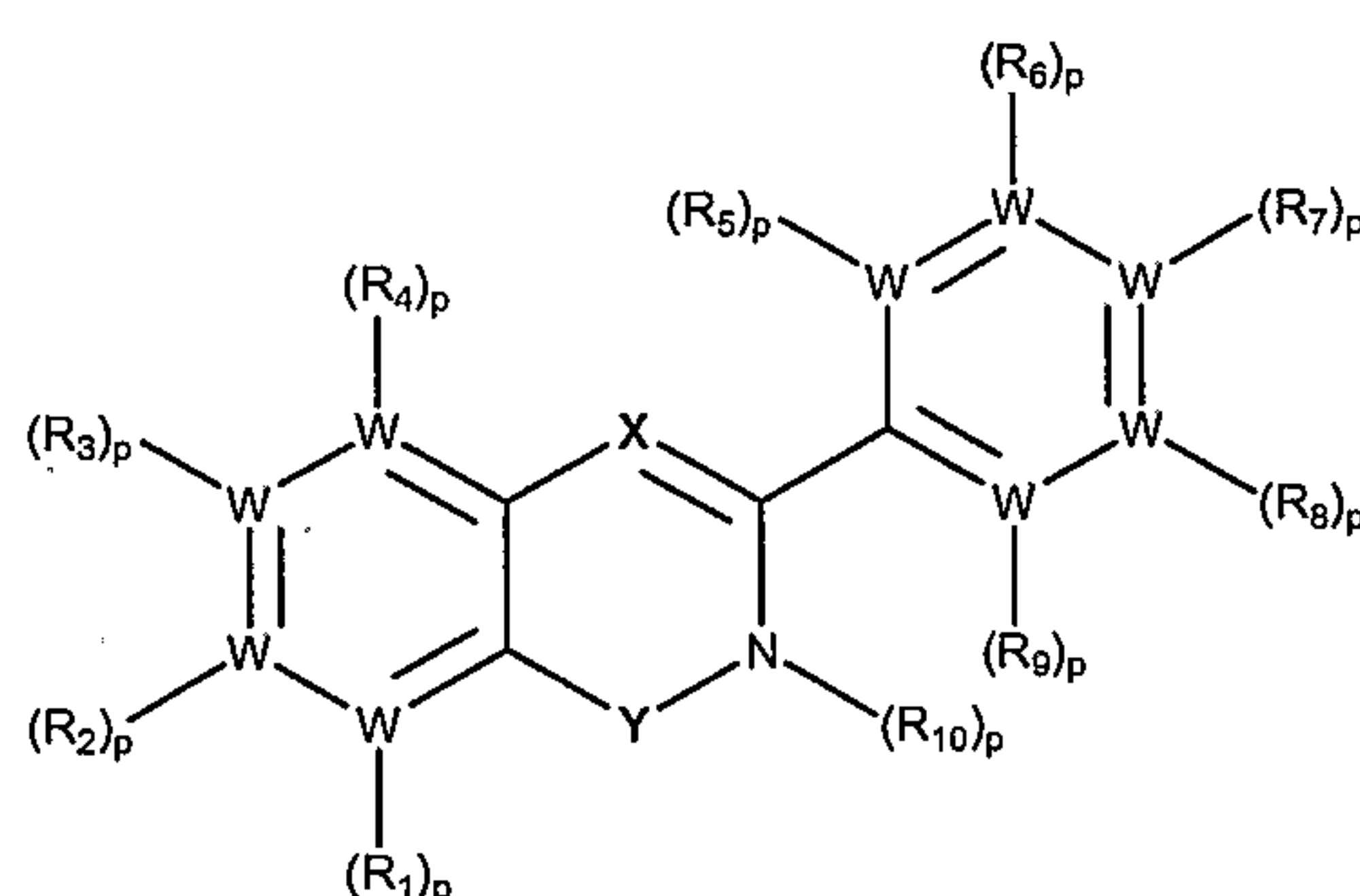
subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

67. The method of embodiment 66, wherein X is O and Y is CO.

68. The method of embodiment 66, wherein at least one W is N.

69. The method of embodiment 68, wherein X is O and Y is CO.

70. The method of embodiment 1, wherein Formula I has the structure:



71. The method of embodiment 70, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

72. The method of embodiment 70, wherein at least one W is N.

73. The method of embodiment 72, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

74. The method of embodiment 70, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from O-sulfate and O-glucoronidate.

75. The method of embodiment 70, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from succinate, D-argininate, L-argininate, L-lysinate and D-lysinate.

76. The method of embodiment 70, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is selected from amide, amino, carbamate, carboxy, ester, ether, formyl, and ketone.

77. The method of embodiment 76, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} is a nicotinate ester.

78. The method of embodiment 70, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

79. The method of embodiment 78, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

80. The method of embodiment 78, wherein at least one W is N.

81. The method of embodiment 80, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

82. The method of embodiment 70, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

83. The method of embodiment 84, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

84. The method of embodiment 84, wherein at least one W is N.

85. The method of embodiment 86, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

86. The method of embodiment 82, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, and O-glucoronidate,

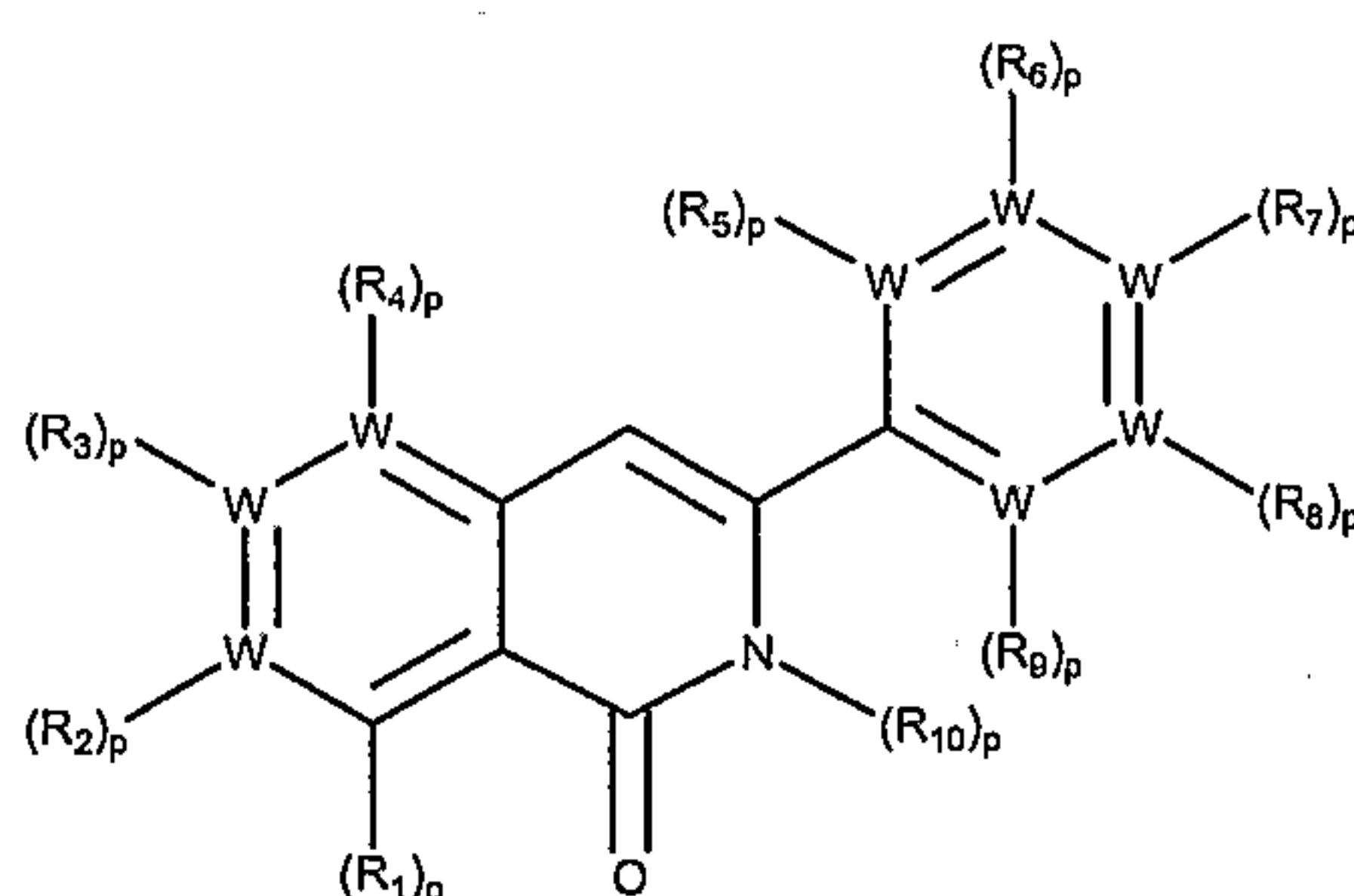
subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

87. The method of embodiment 86, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

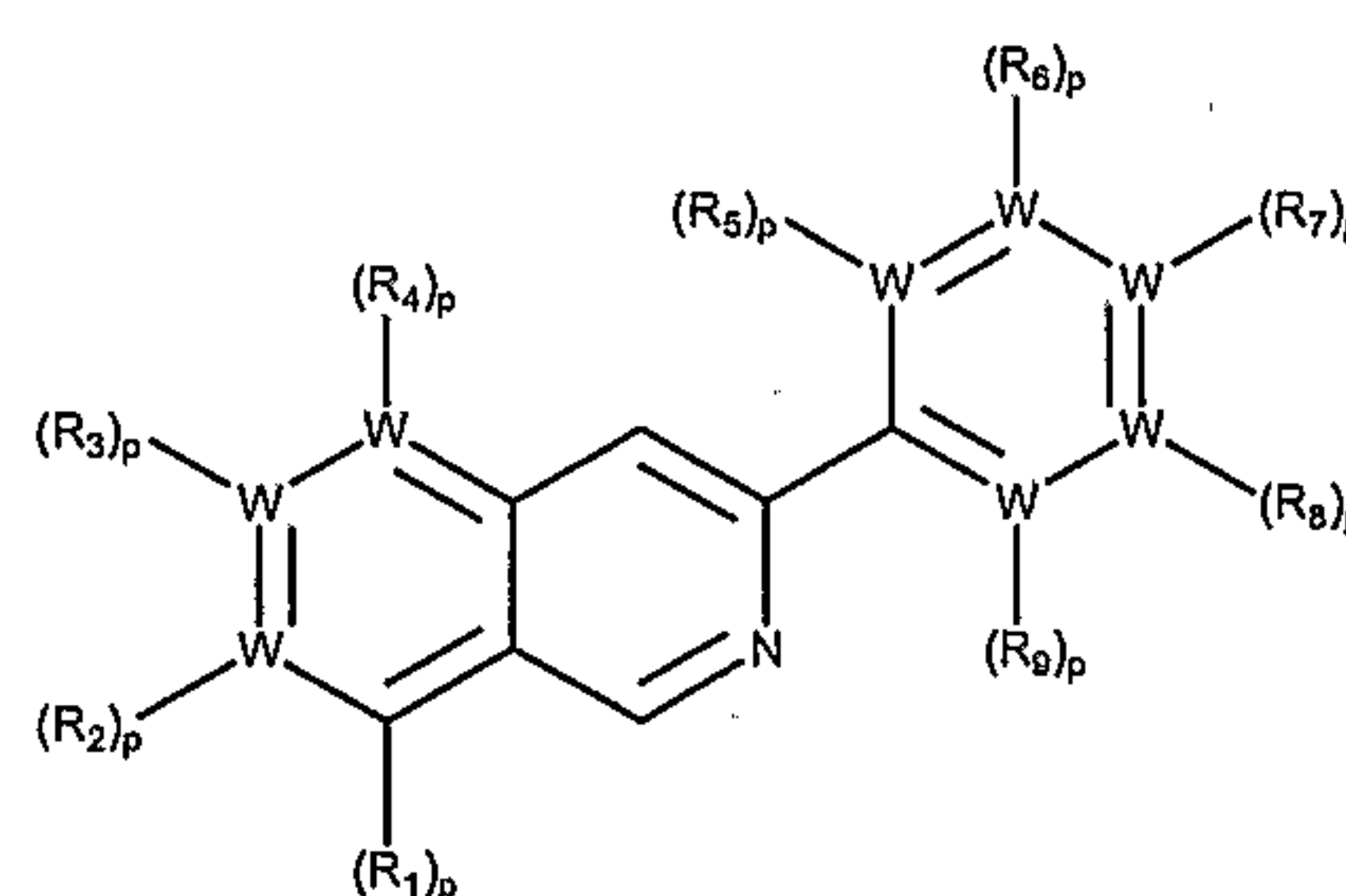
88. The method of embodiment 86, wherein at least one W is N.

89. The method of embodiment 88, wherein X is CR_{11} , R_{11} is hydrogen and Y is CO.

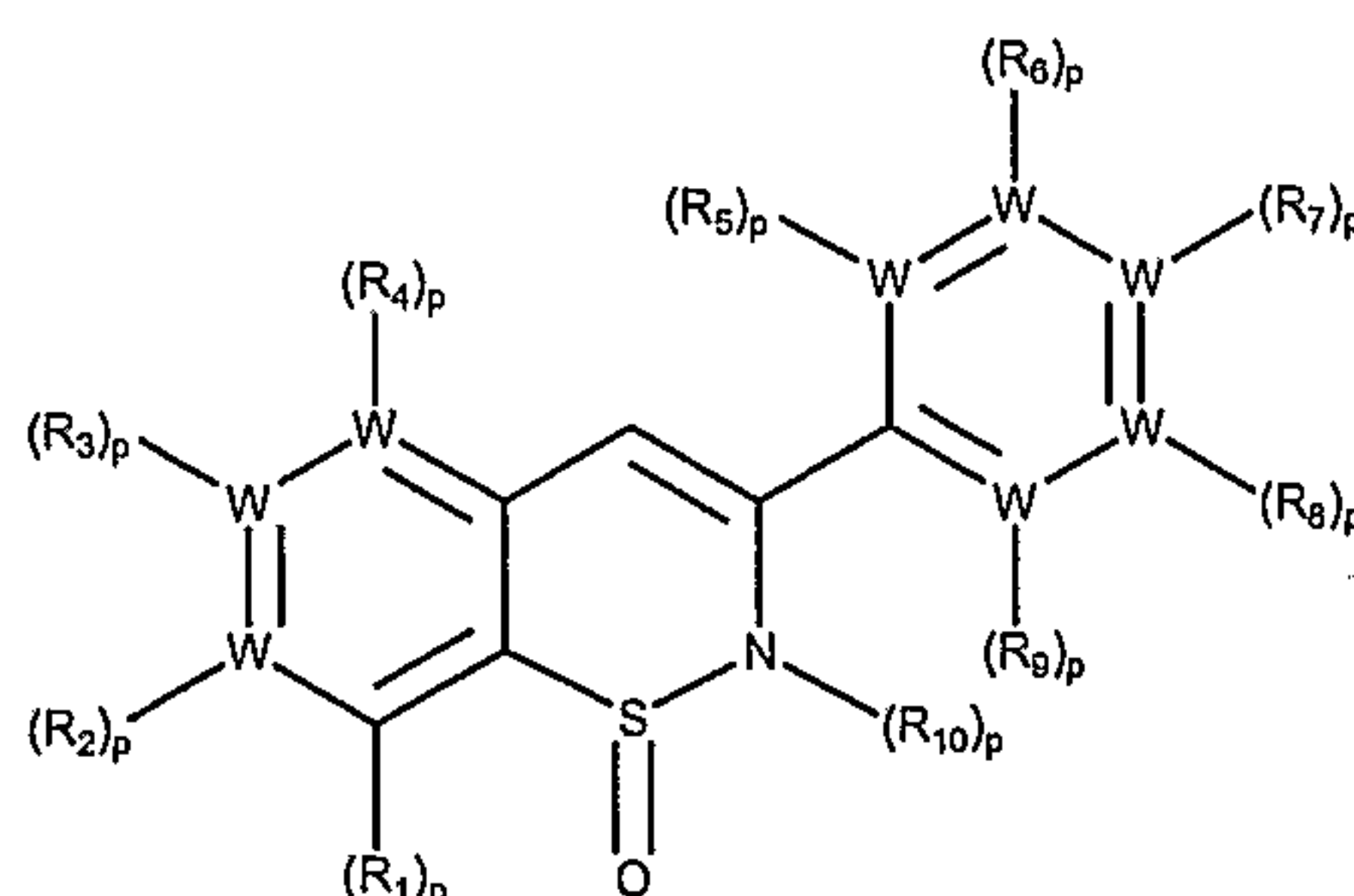
90. The method of embodiment 70, wherein Formula I is selected from Formulae IA-ID:



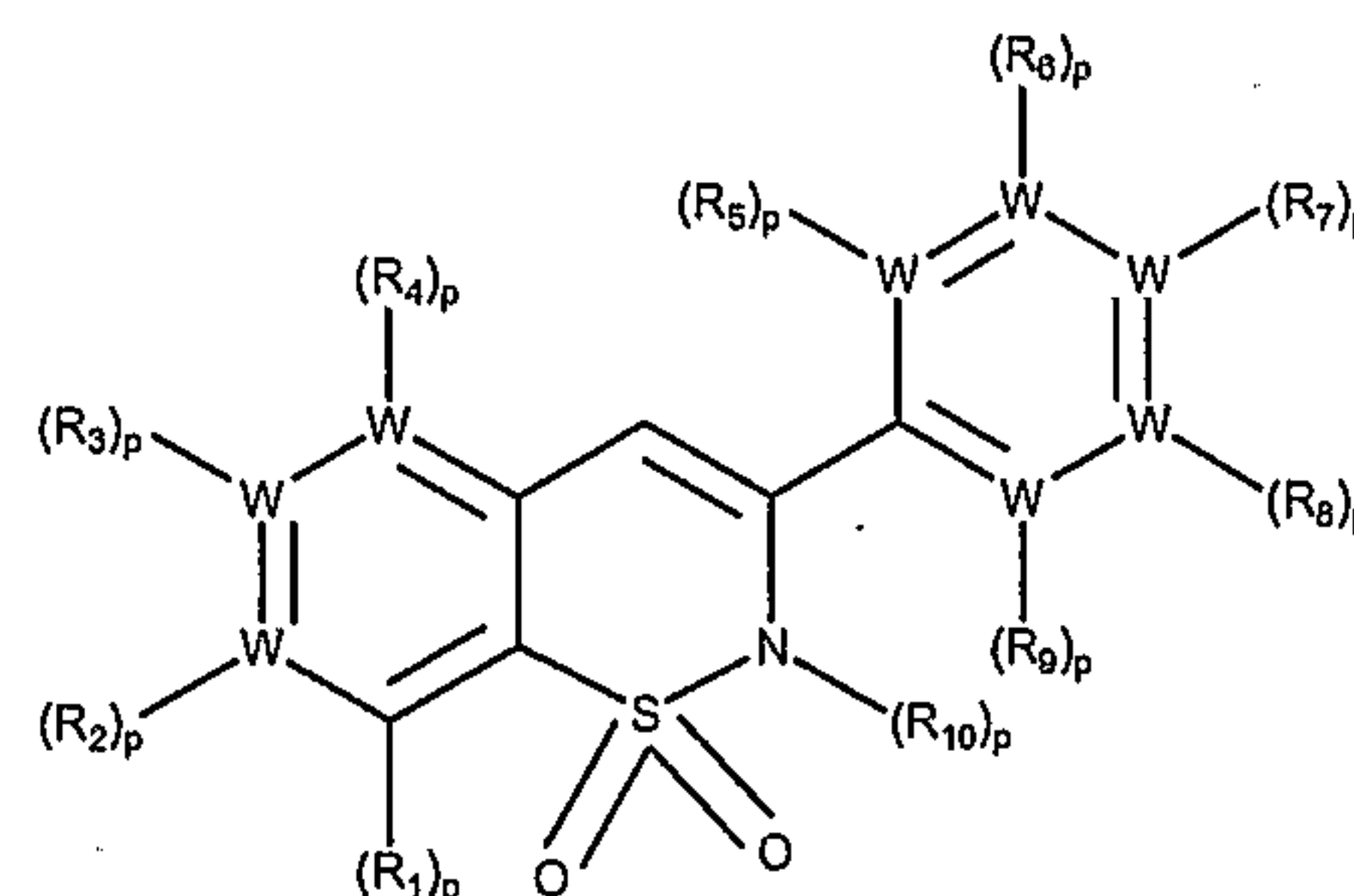
Formula IA



Formula IB



Formula IC



Formula ID.

91. The method of embodiment 1, wherein the therapeutically effective amount of the compound of Formula I is administered with a pharmaceutically acceptable carrier in a pharmaceutically acceptable composition.

92. The method of embodiment 1, wherein the therapeutically effective amount of the compound of Formula I is sufficient to establish a concentration ranging from about 0.001 μM to about 100 μM in the mammal.

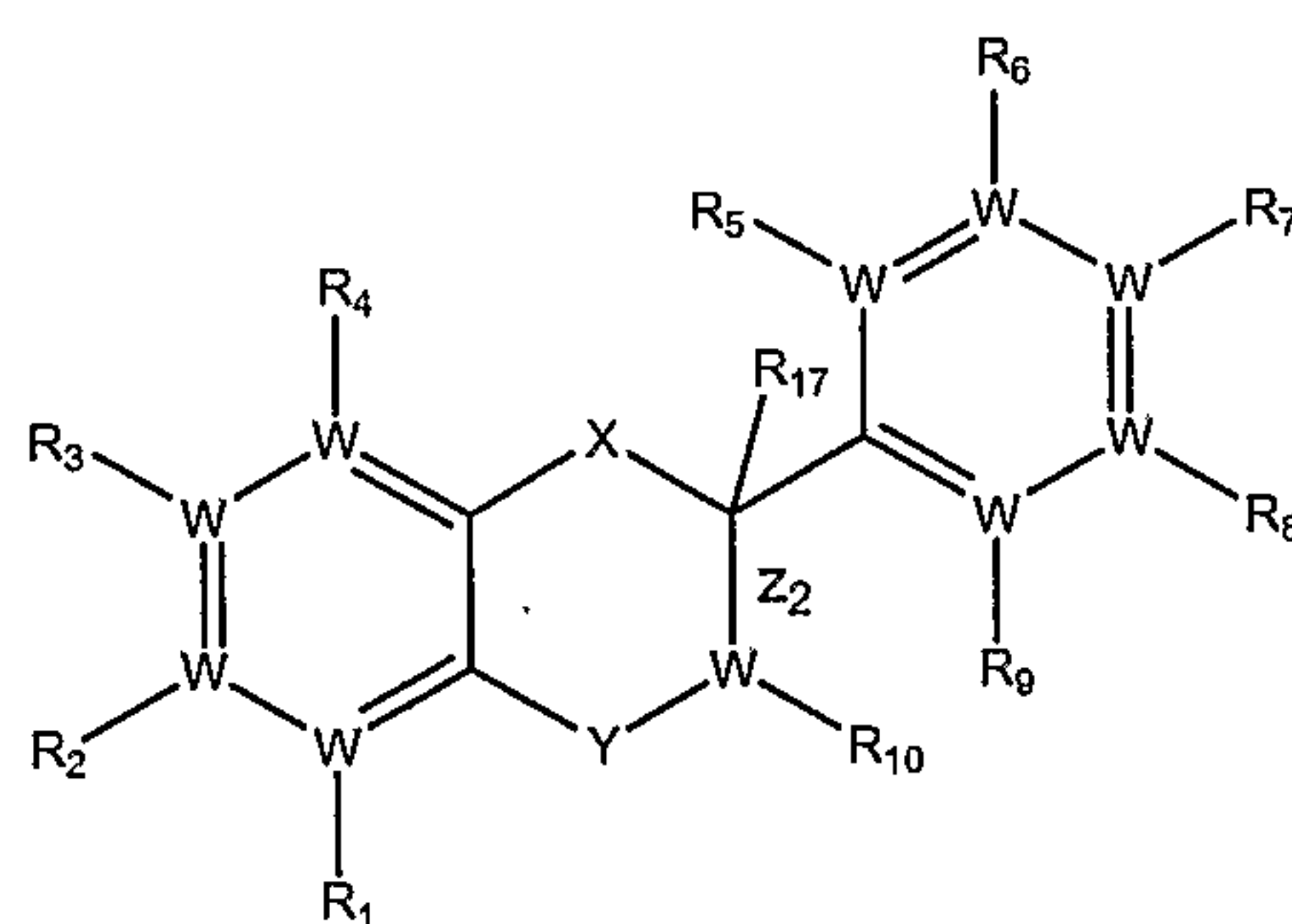
93. The method of embodiment 92, wherein the concentration ranges from about 1 μM to about 20 μM .

94. The method of embodiment 1, wherein the compound of Formula I is 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one.

95. The method of embodiment 1, wherein the compound is 3-(4-hydroxyphenyl)-2H-isoquinolin-1-one.

96. The method of embodiment 1, wherein the compound is 4-isoquinolin-3-yl-phenol.

97. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula II:



Formula II

wherein:

X is selected from CH_2 , CHR_{11} , CHR_{13} , $\text{CR}_{11}\text{R}_{13}$, CO, CS, O, S, SO, SO_2 , NH and NR_{11} , wherein R_{11} may be the same or different than R_{13} ;

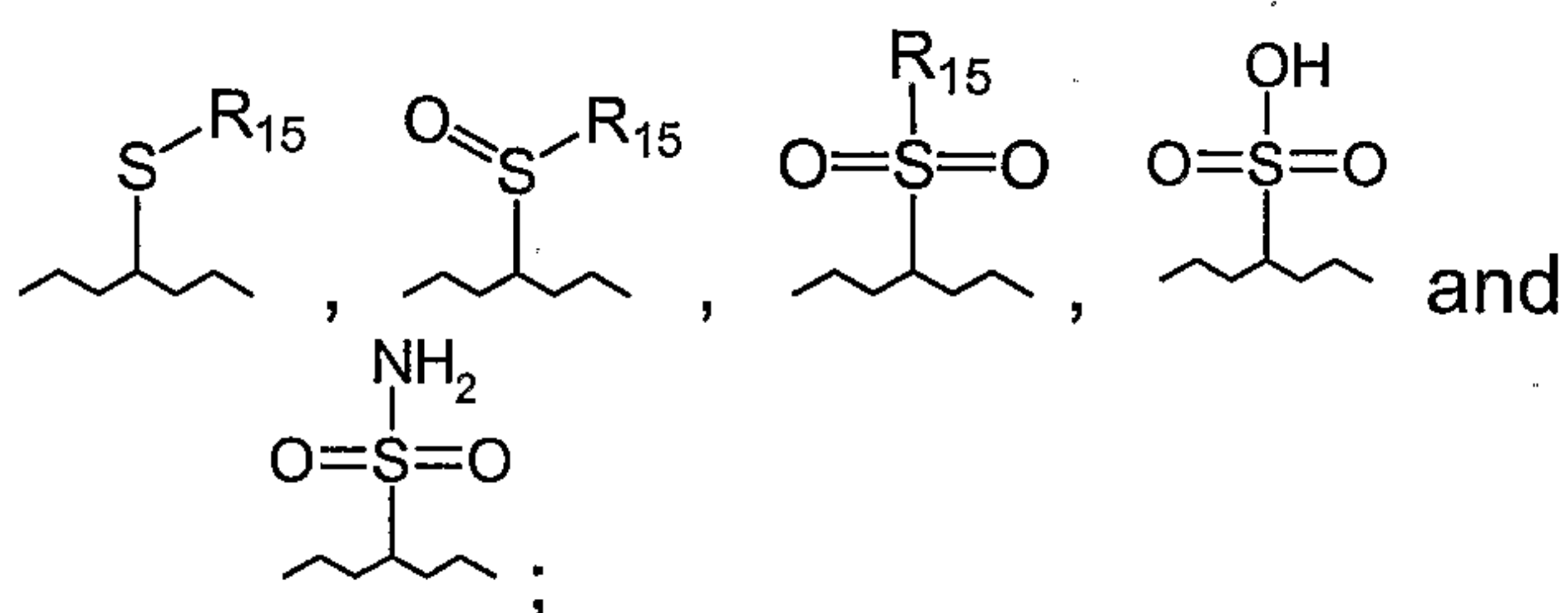
Y is selected from CH_2 , CHR_{12} , CHR_{14} , $\text{CR}_{12}\text{R}_{14}$, CO , CS , O , S , SO , SO_2 , NH and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} are each independently selected from $(\text{C}_1\text{-C}_{22})$ alkyl, $(\text{C}_2\text{-C}_{22})$ alkenyl, $(\text{C}_2\text{-C}_{22})$ alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, amide, carbamate, halogen, CF_3 , CCl_3 , sulfonic acid, phosphate, O-sulfate, O-glucoronidate, monoester, dicarboxylic acid, J, K, L, M, P and Q;

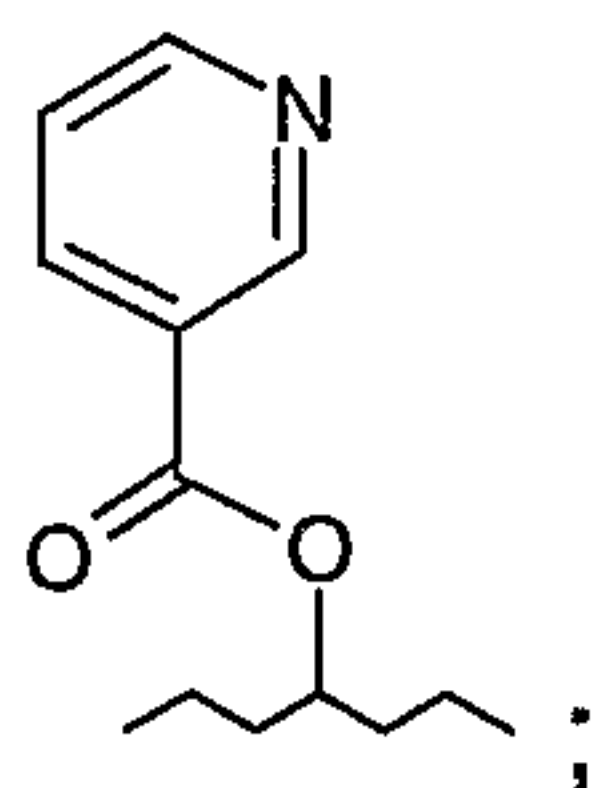
each W is independently selected from C and N;

Z_2 is selected from a single bond and a double bond;

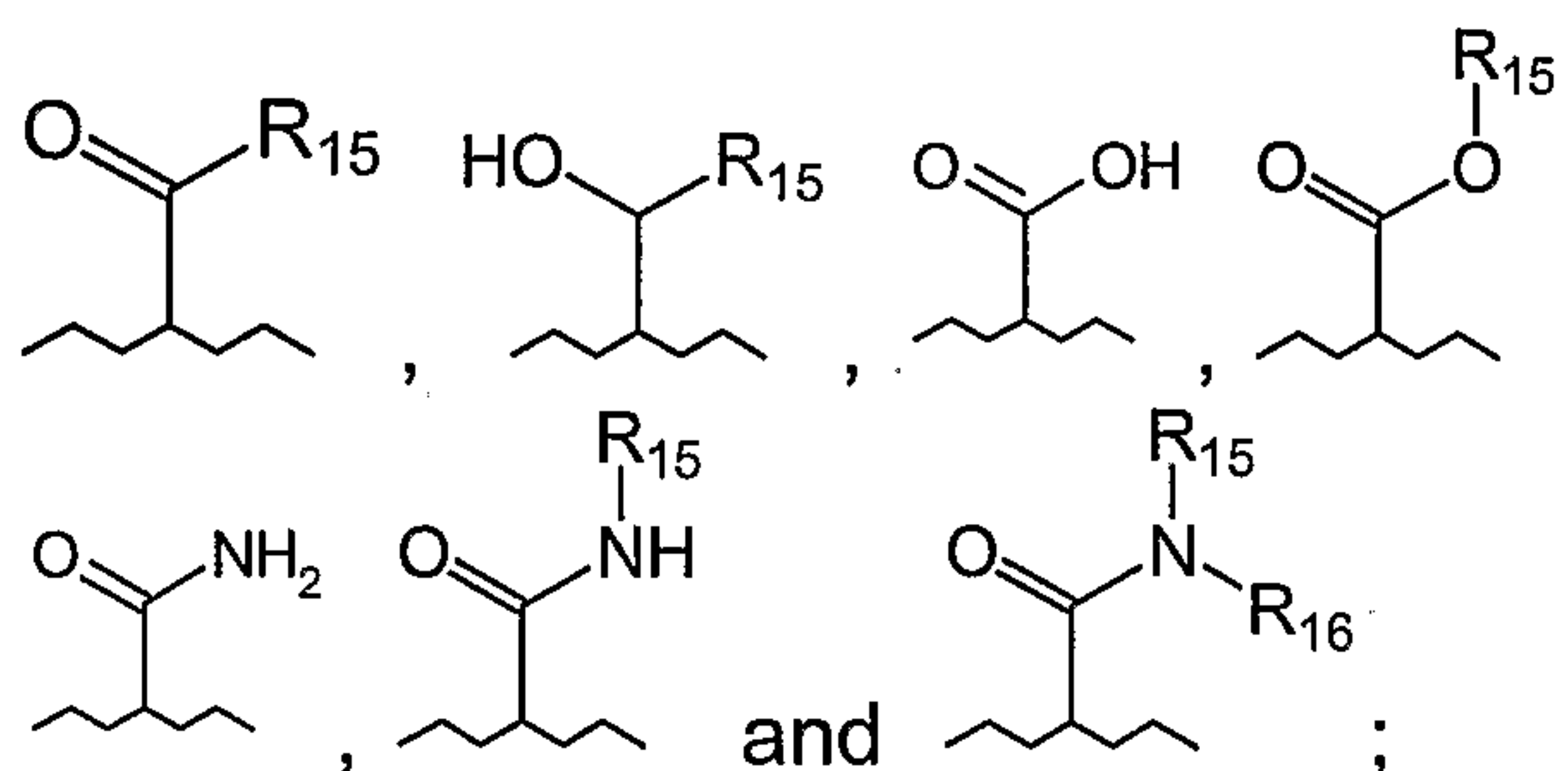
J is selected from



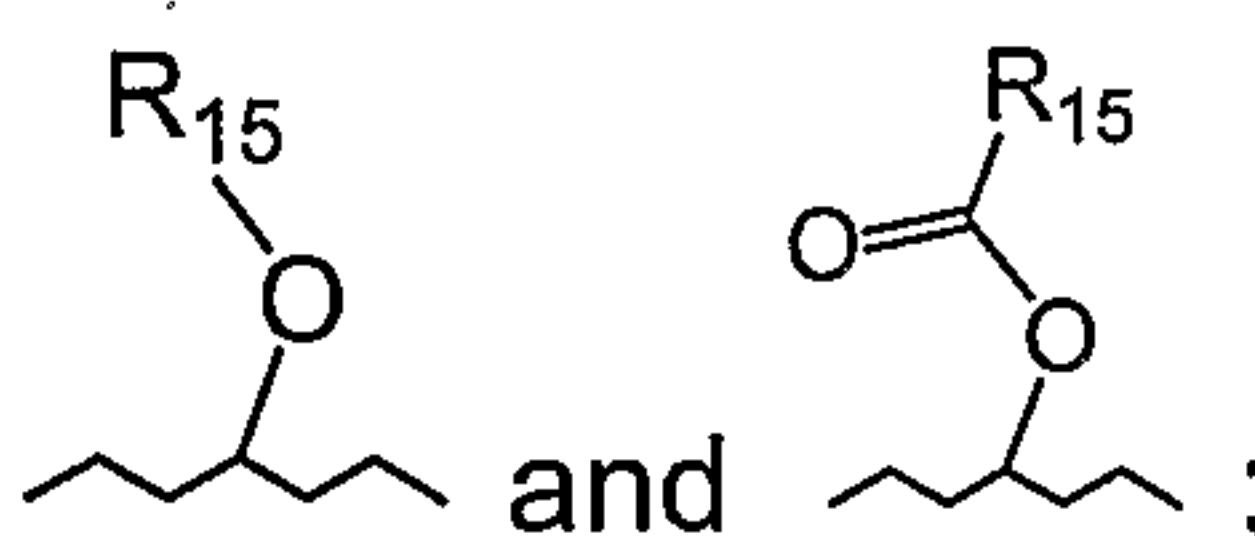
K is

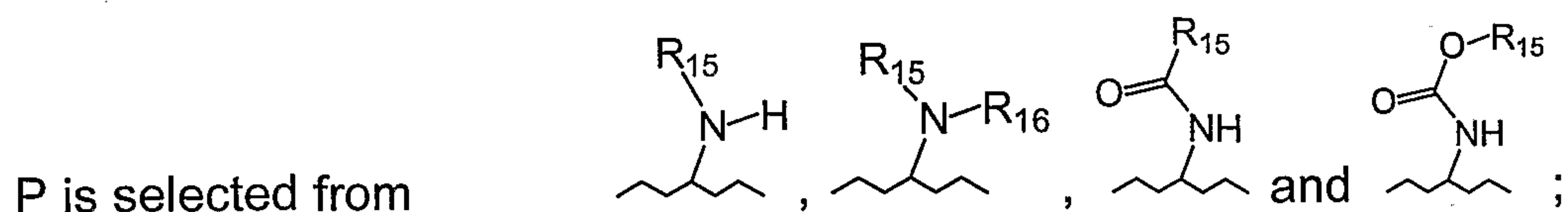


L is selected from



M is selected from





R_{15} and R_{16} are each independently selected from (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, (C₂-C₂₂)alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, amide, carbamate, halogen, CF₃, CCl₃, sulfonic acid and phosphate;

and pharmaceutically acceptable salts thereof;

subject to at least one proviso selected from:

- 1) R_7 is hydroxyl;
- 2) at least one W is N;
- 3) at least one of R_1 - R_{10} is selected from L, M and P;
- 4) at least one of R_1 - R_{10} is selected from K;
- 5) R_7 is K;
- 6) one of R_1 - R_{10} is a monoester;
- 7) one of R_1 - R_{10} is a dicarboxylic acid;
- 8) one of R_1 - R_{10} is succinic acid;
- 9) R_7 and R_2 are each hydroxyl;
- 10) R_7 is selected from J; and
- 11) R_7 and R_2 are each selected from J.

98. The method of embodiment 97, wherein if proviso 1 is selected, a second proviso is selected from provisos 2-4 and 6-9.

99. The method of embodiment 97, wherein R_7 is hydroxyl and at least one W is N.

100. The method of embodiment 97, wherein R_7 is hydroxyl and at least one of R_1 - R_6 and R_8 - R_{10} is K.

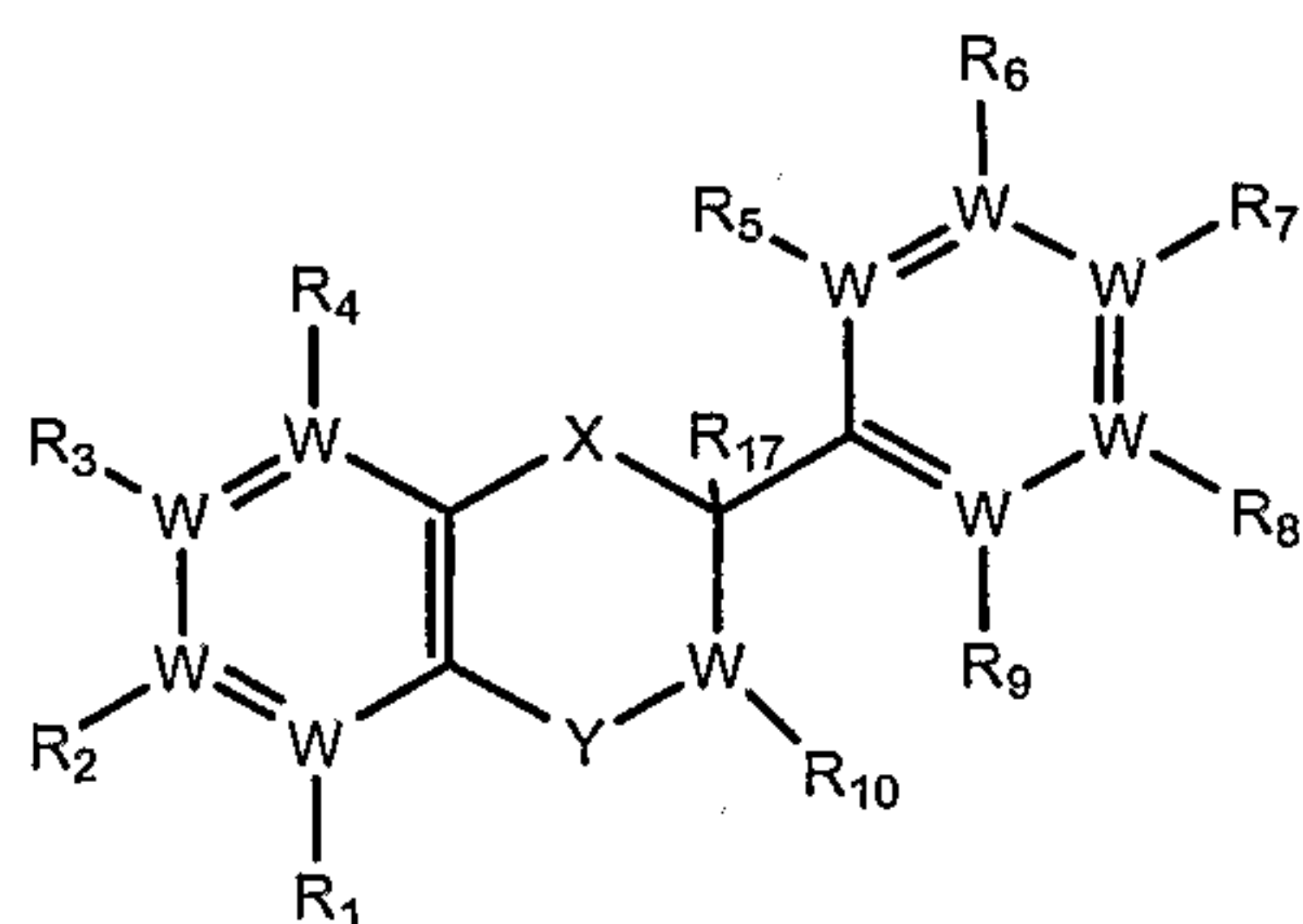
101. The method of embodiment 97, wherein R_7 is hydroxyl and at least one of R_1 - R_6 and R_8 - R_{10} is selected from L, M and P.

102. The method of embodiment 97, wherein R_7 is K and at least one W is N.

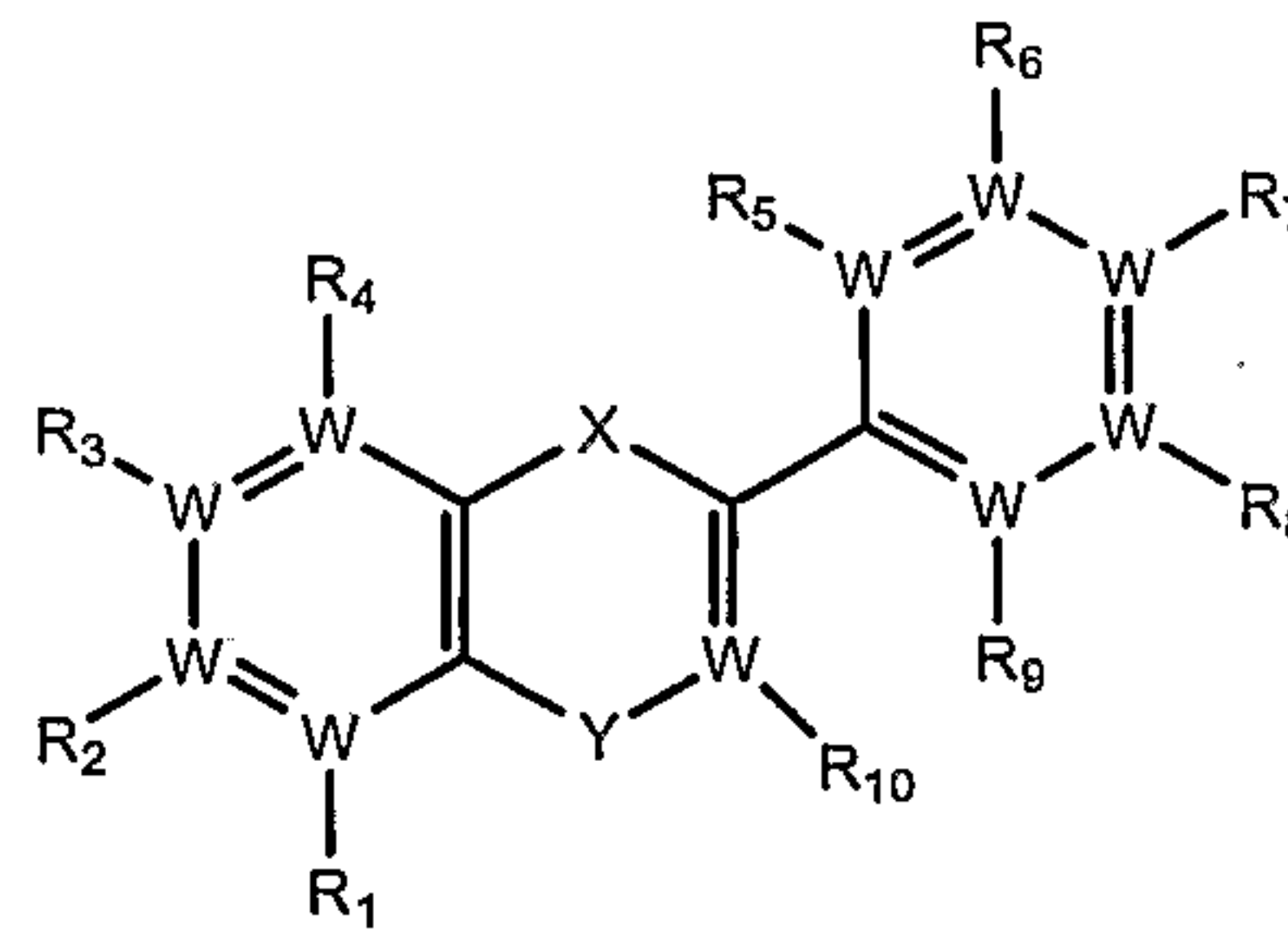
103. The method of embodiment 97, wherein Y is selected from CH_2 , CHR_{12} , CHR_{14} , $CR_{12}R_{14}$, CO, CS, S, SO, SO_2 , NH and NR_{12} , wherein R_{12} may be the same or different than R_{14} .

104. The method of embodiment 97, wherein the compound of Formula II is 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one.

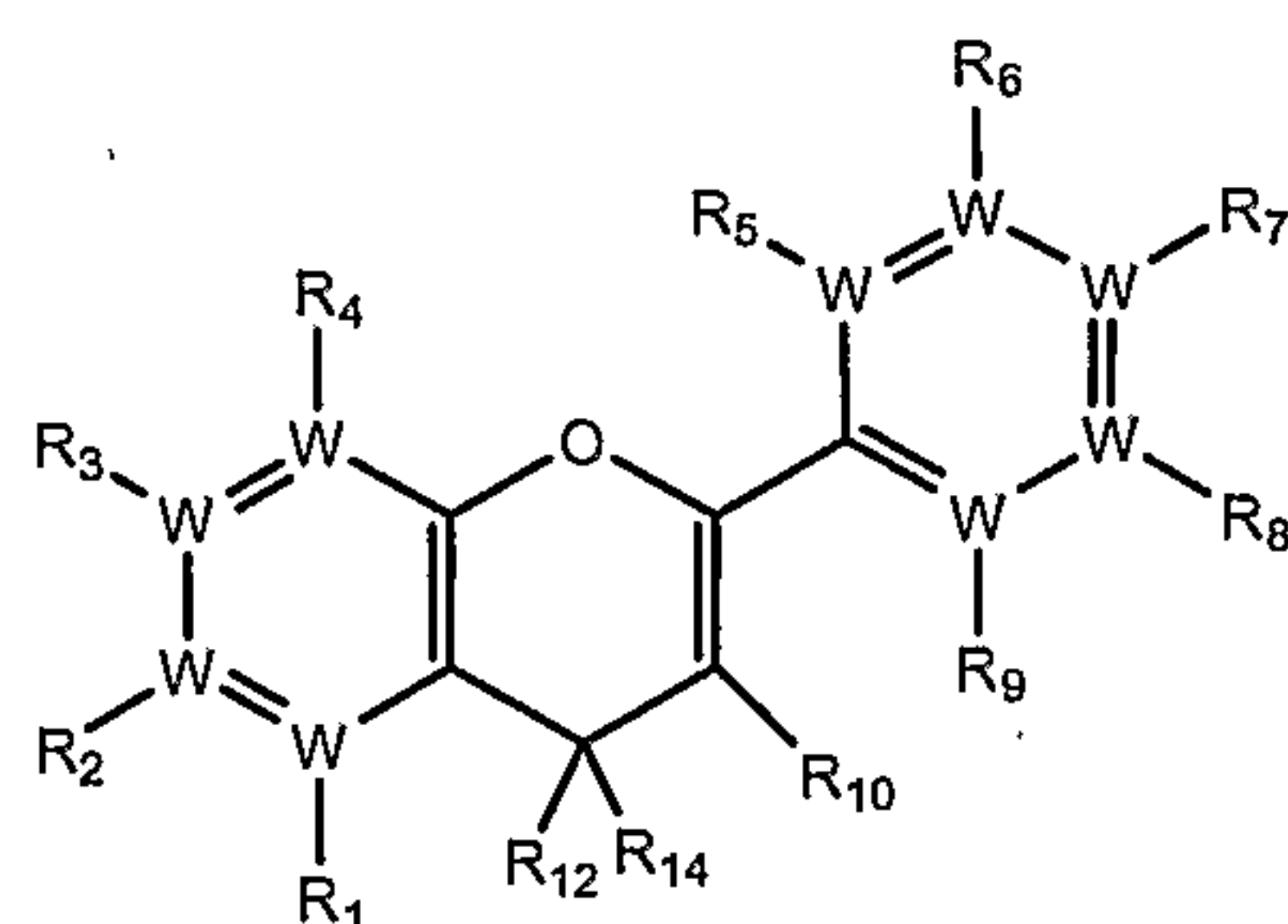
105. The method of embodiment 97, wherein Formula II is selected from Formulae IIA-IIS:



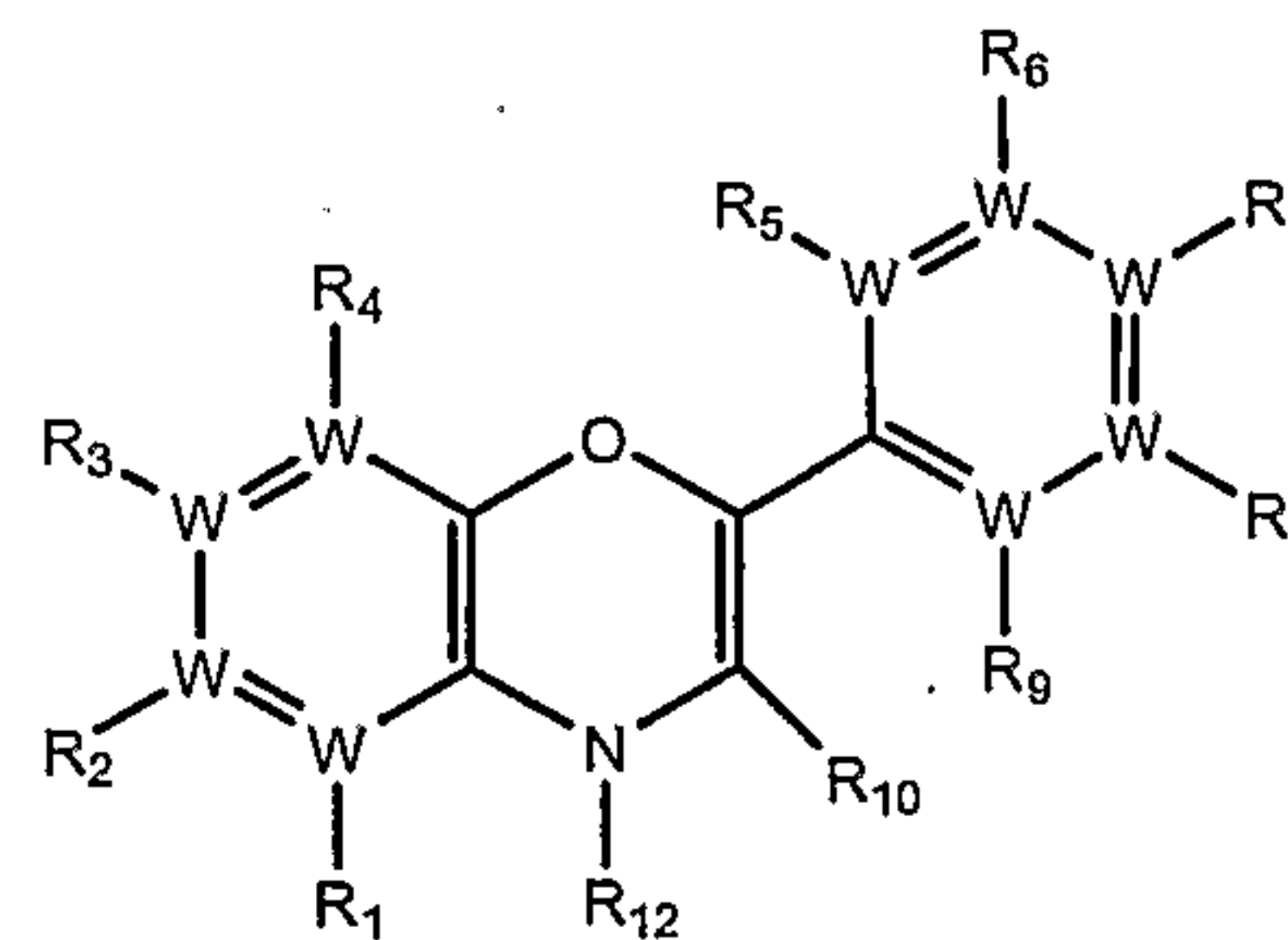
Formula IIA



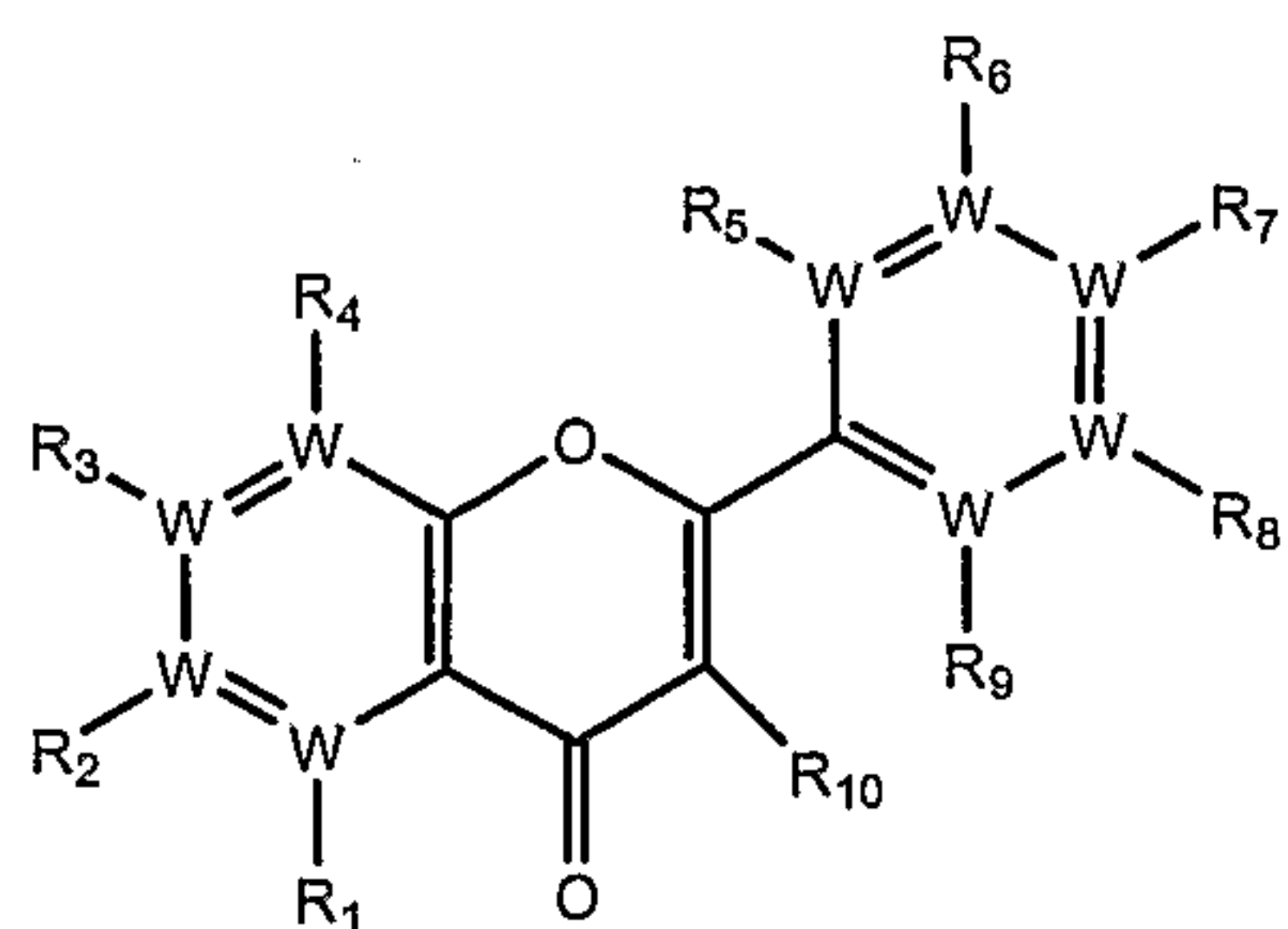
Formula IIB



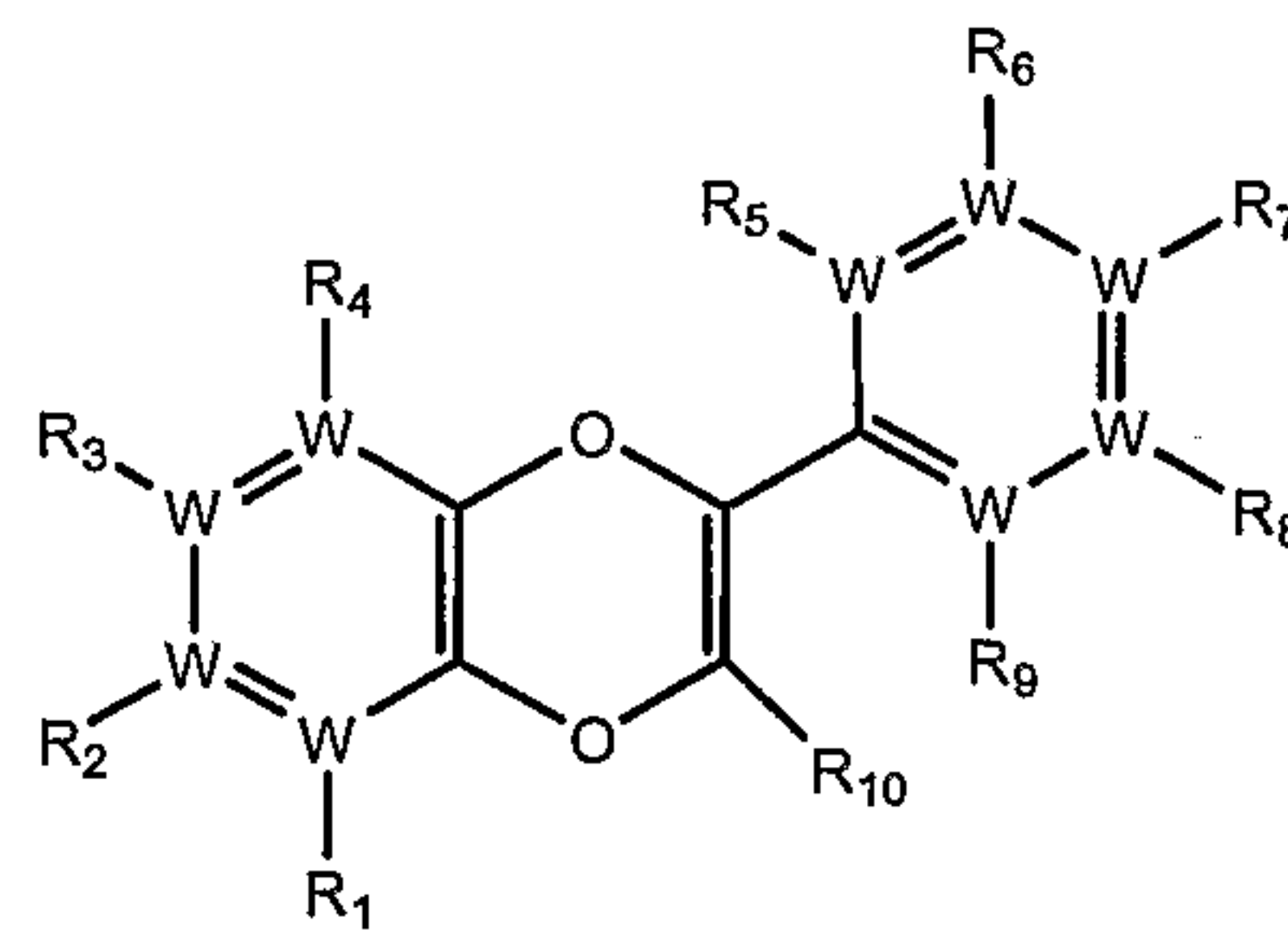
Formula IIC



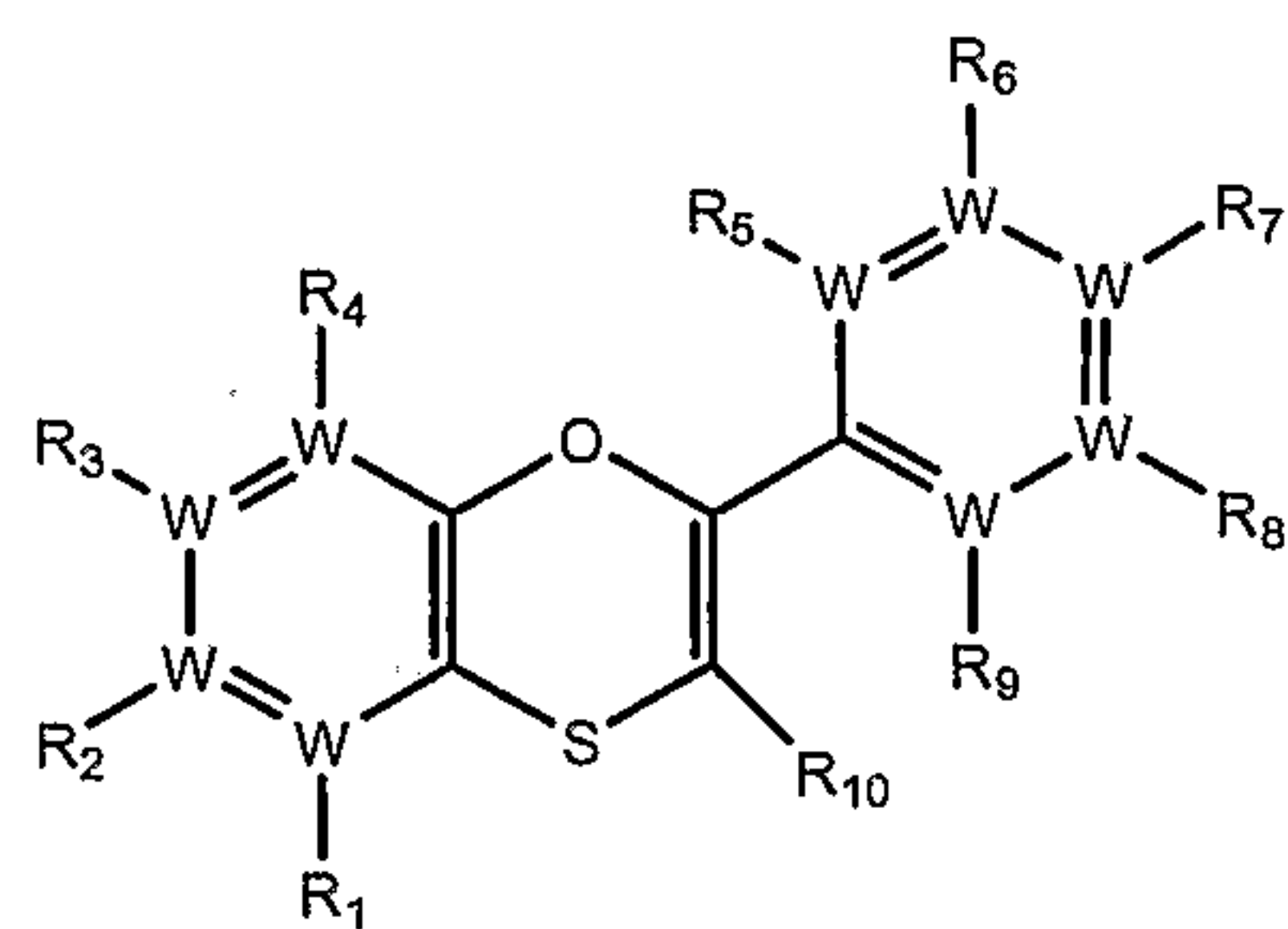
Formula IID



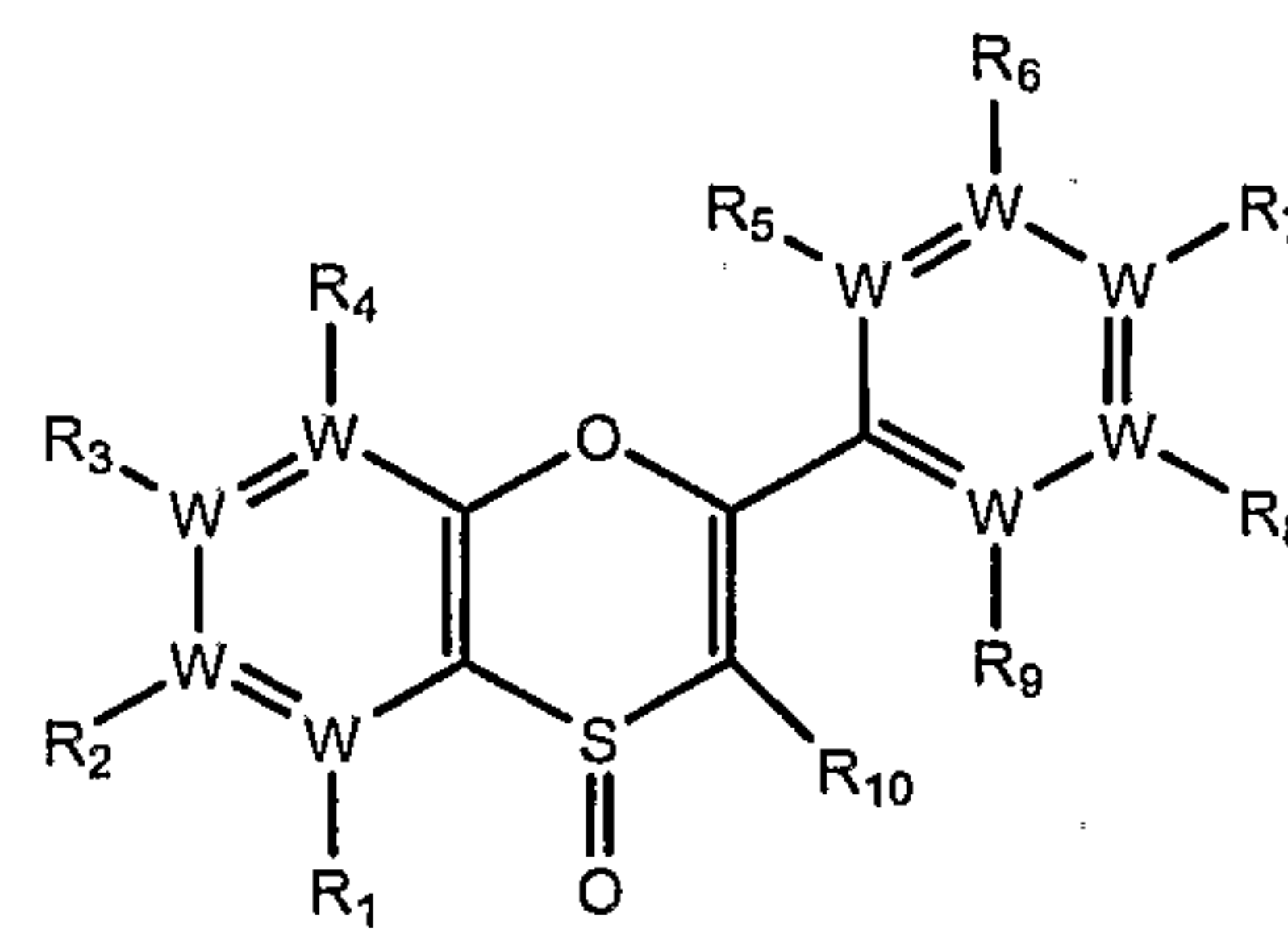
Formula IIE



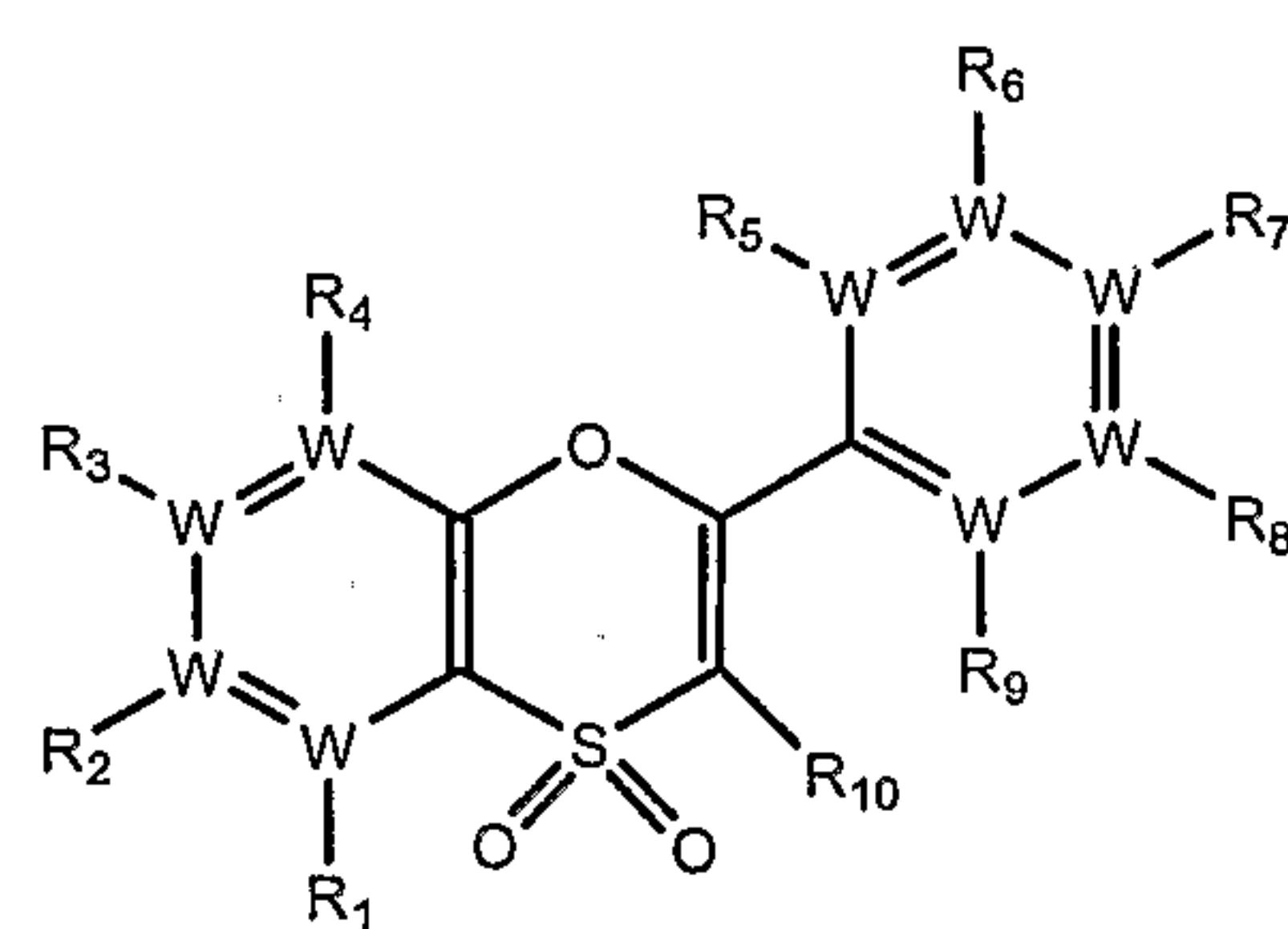
Formula IIF



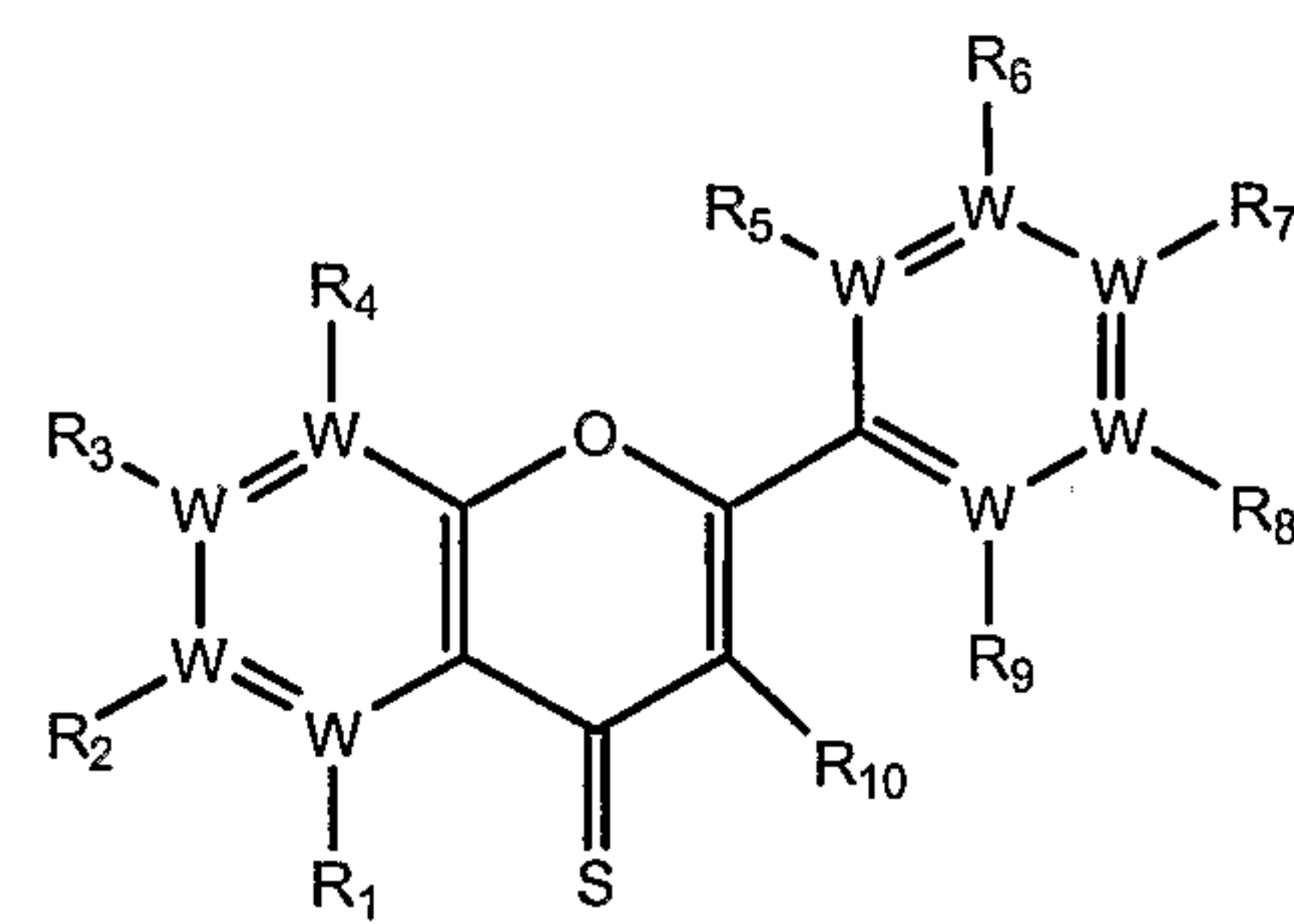
Formula IIG



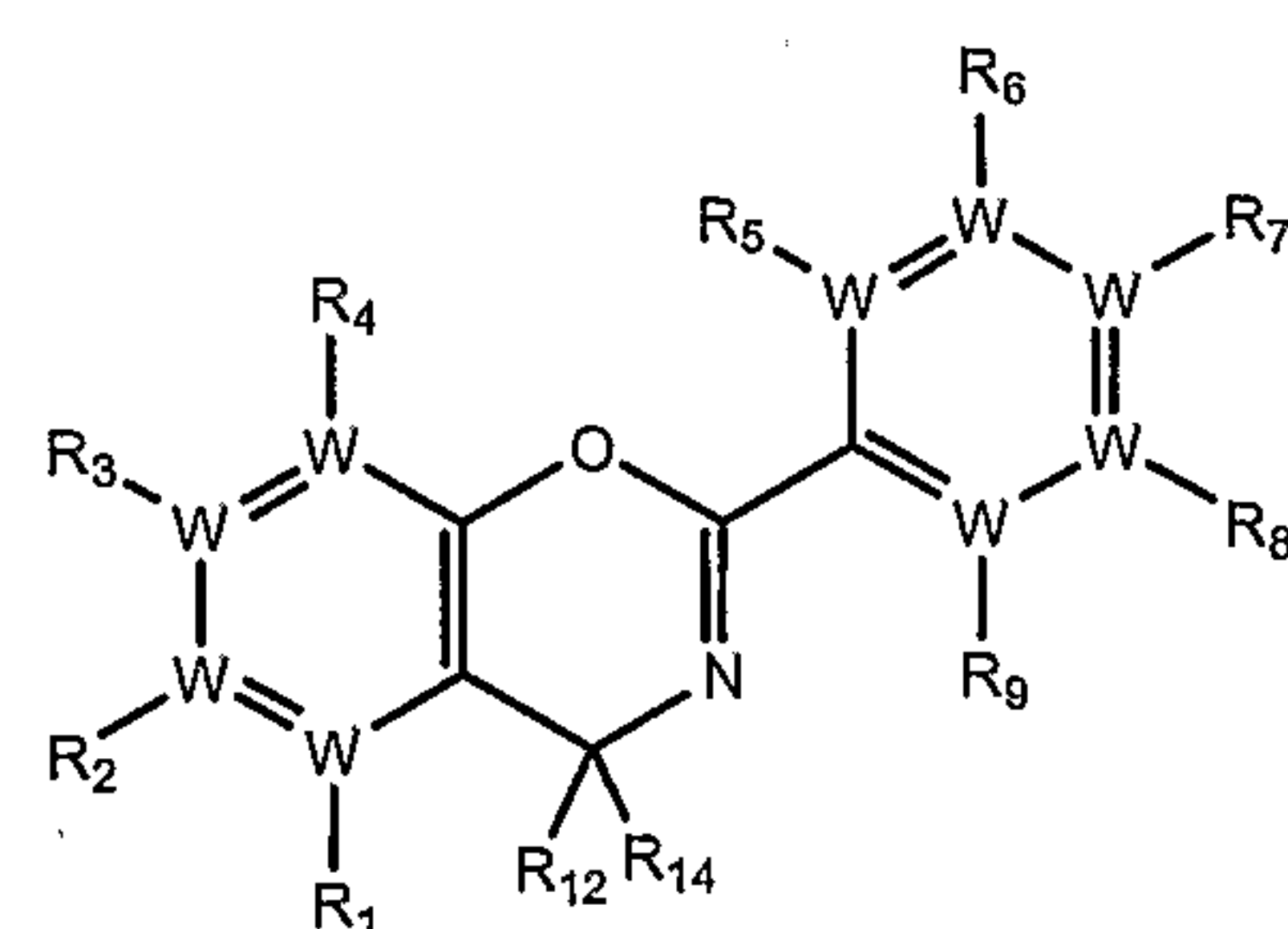
Formula IIH



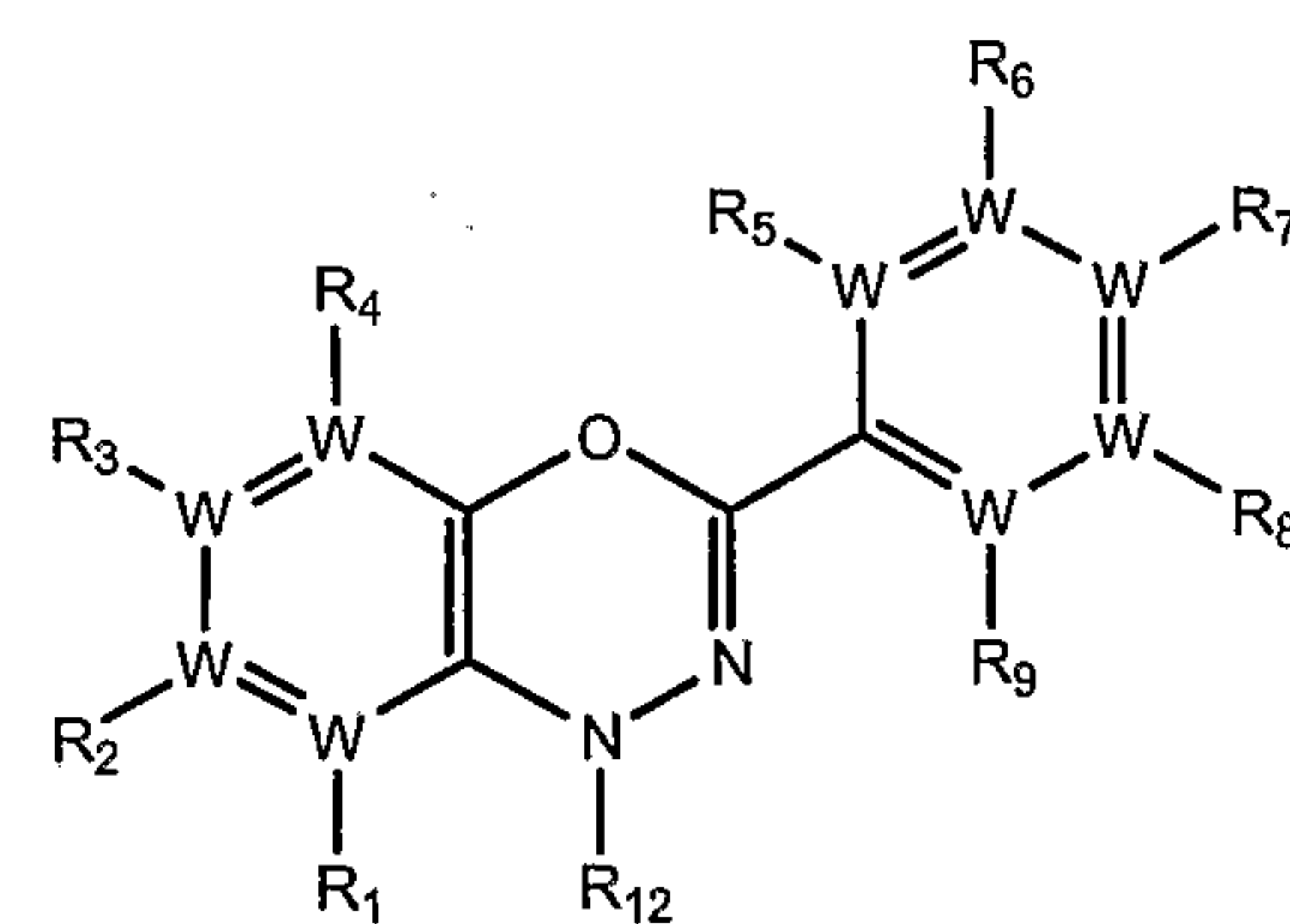
Formula IIJ



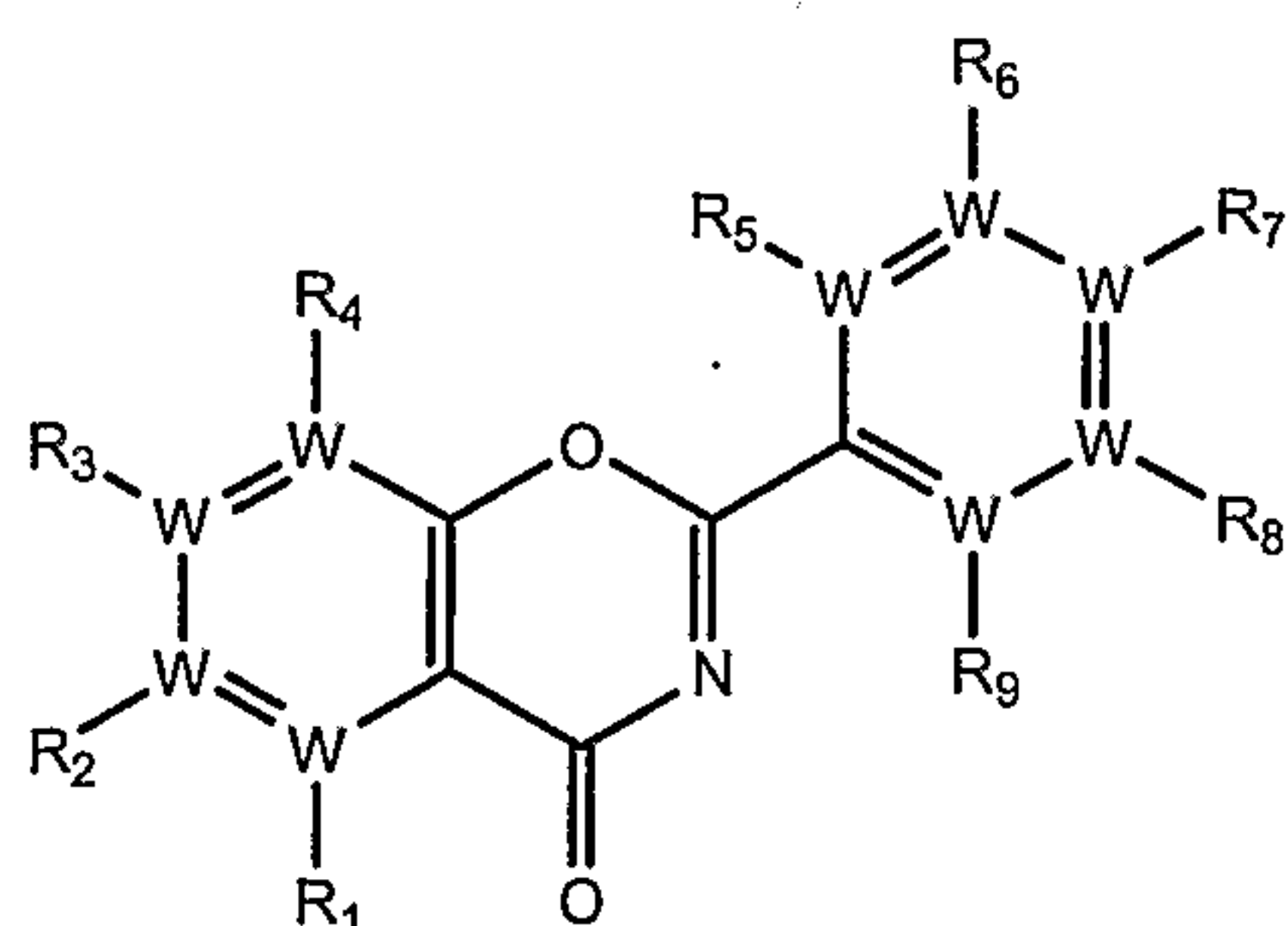
Formula IIK



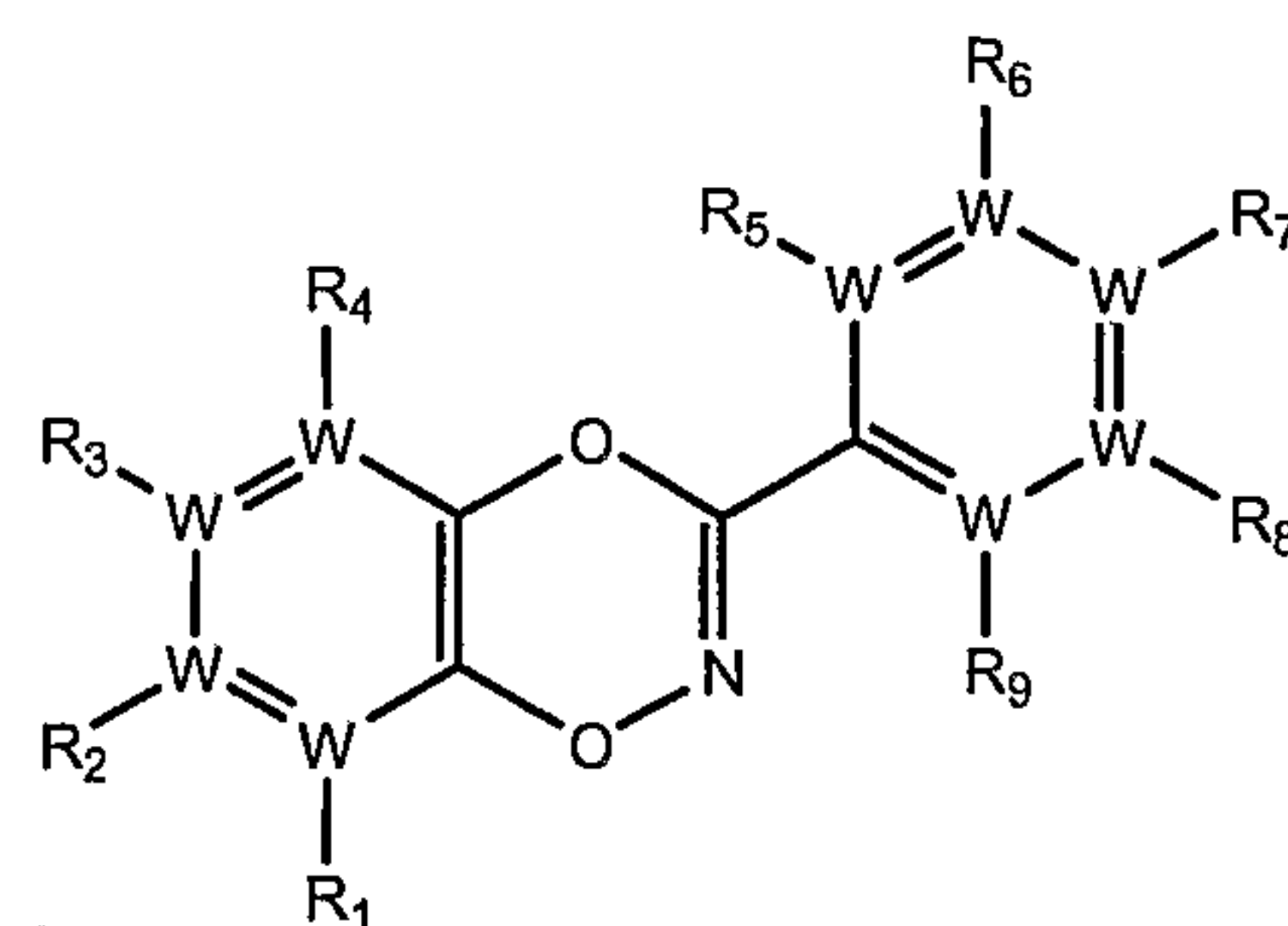
Formula III



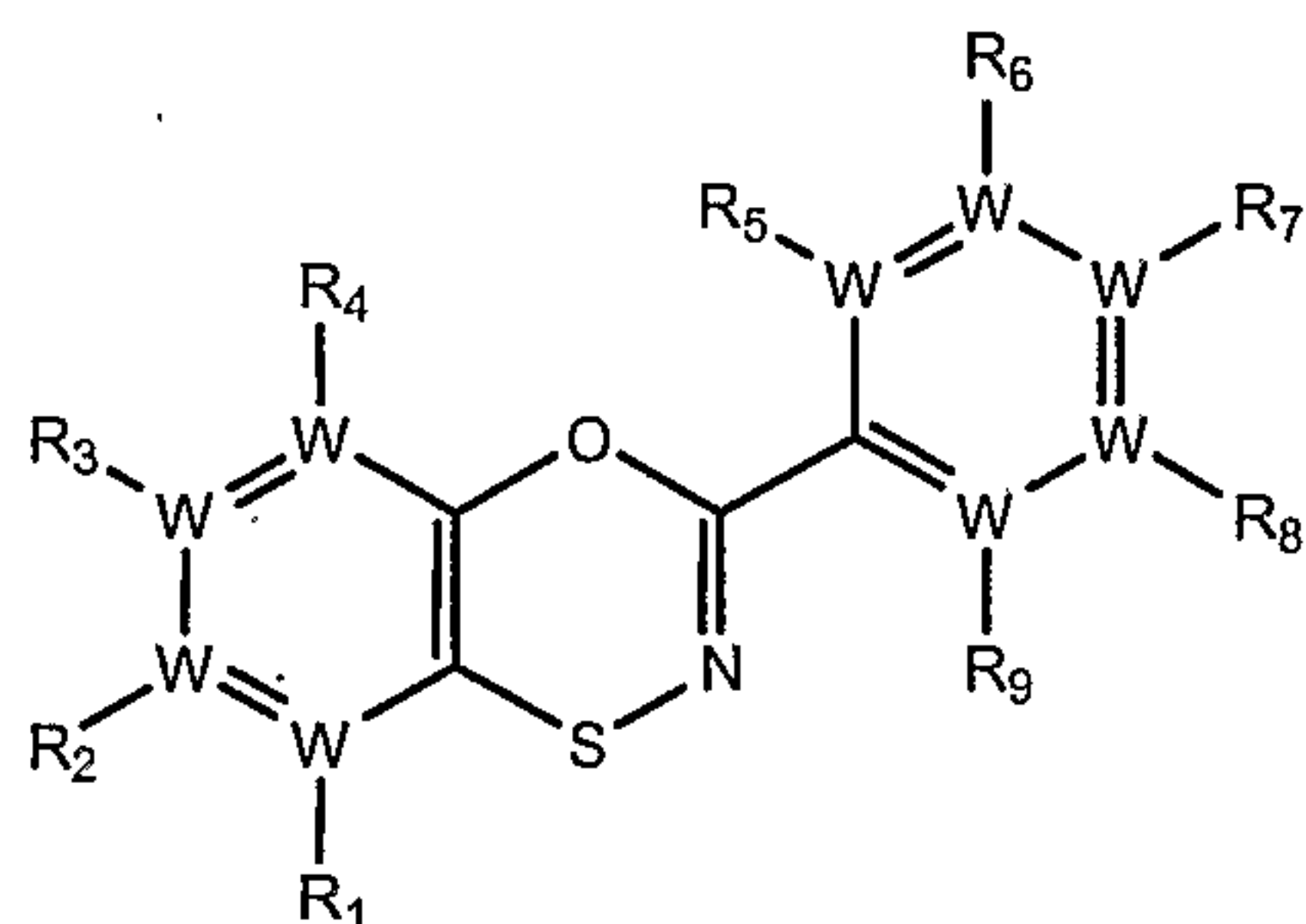
Formula IIM



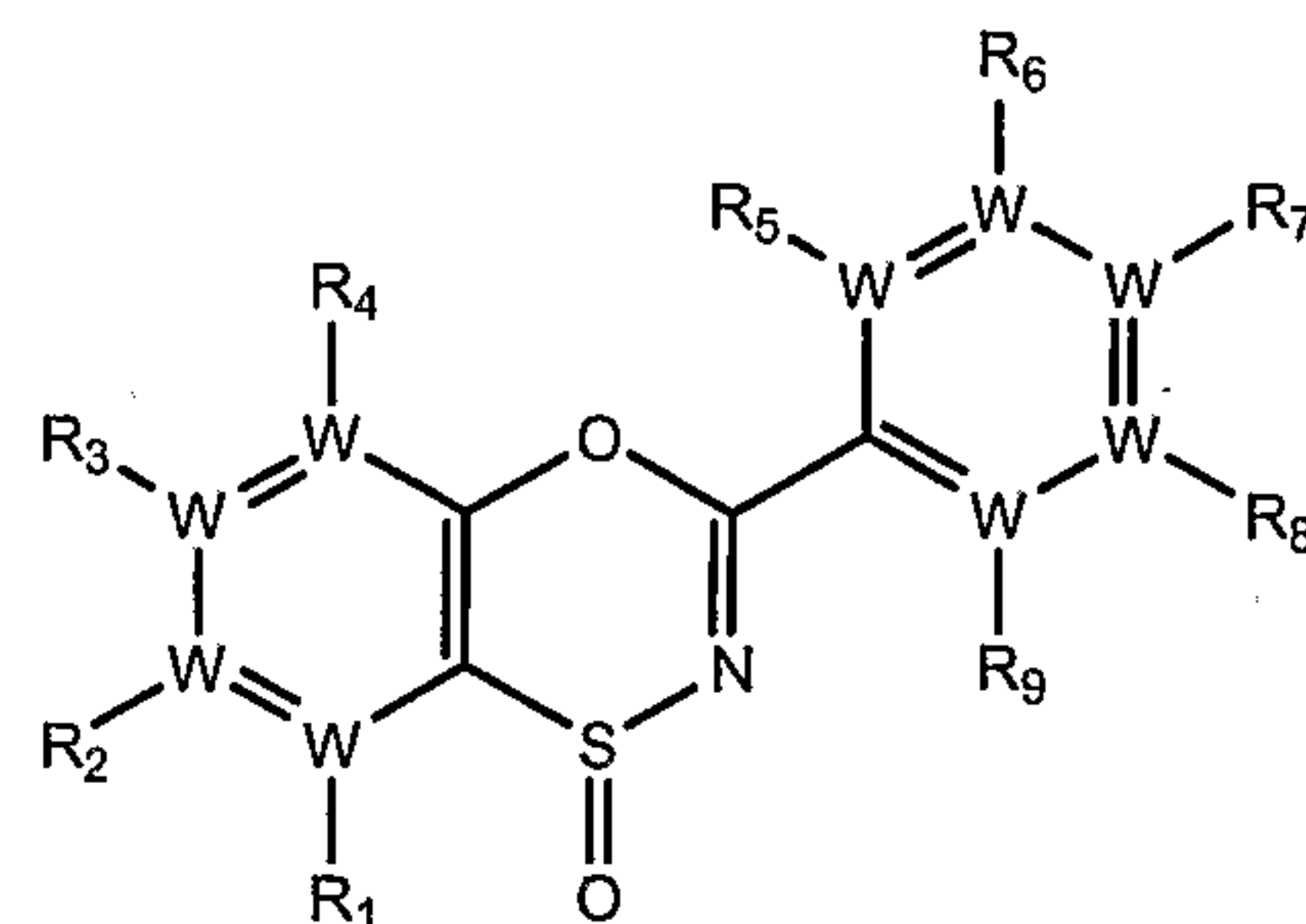
Formula IIN



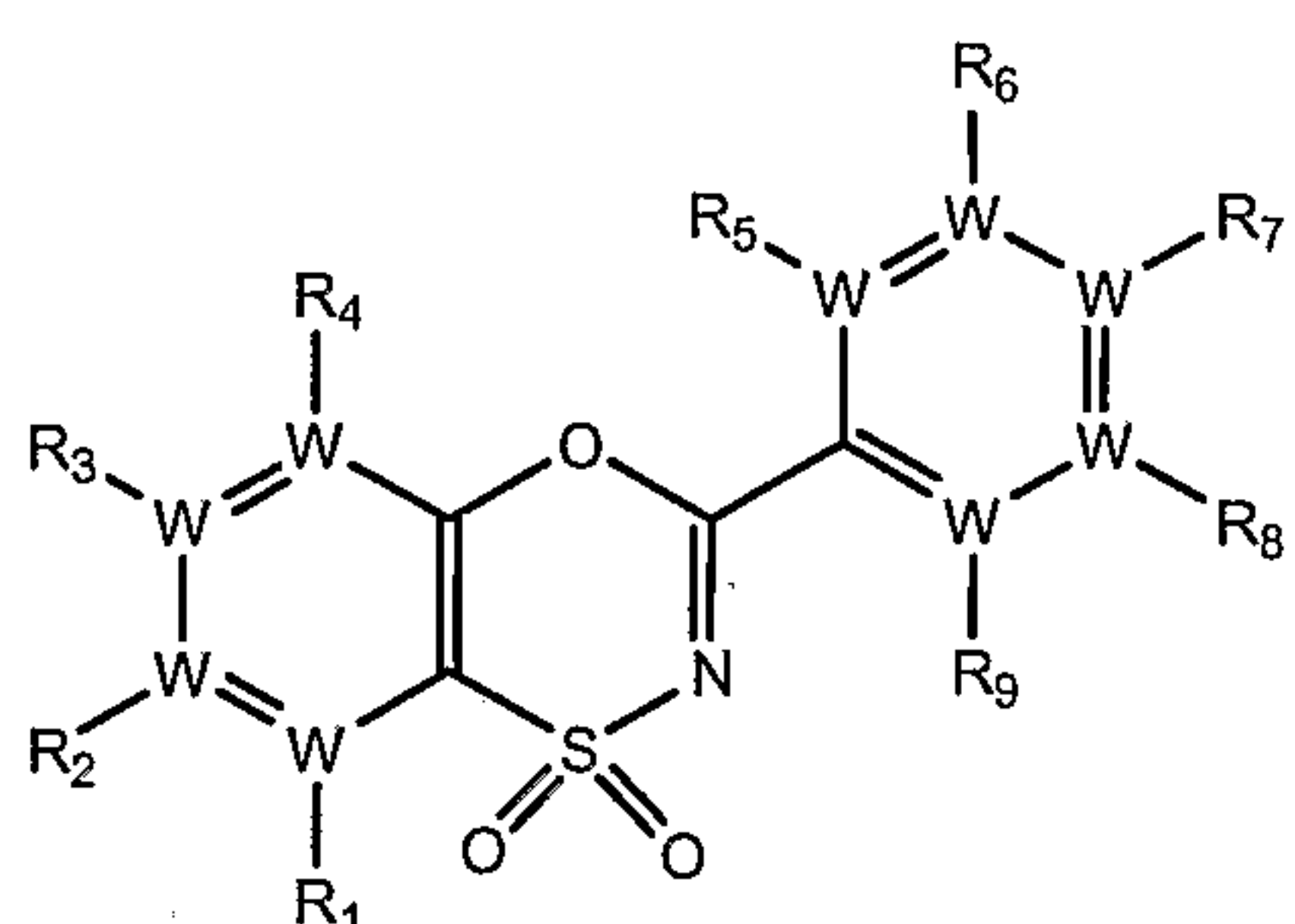
Formula IIO



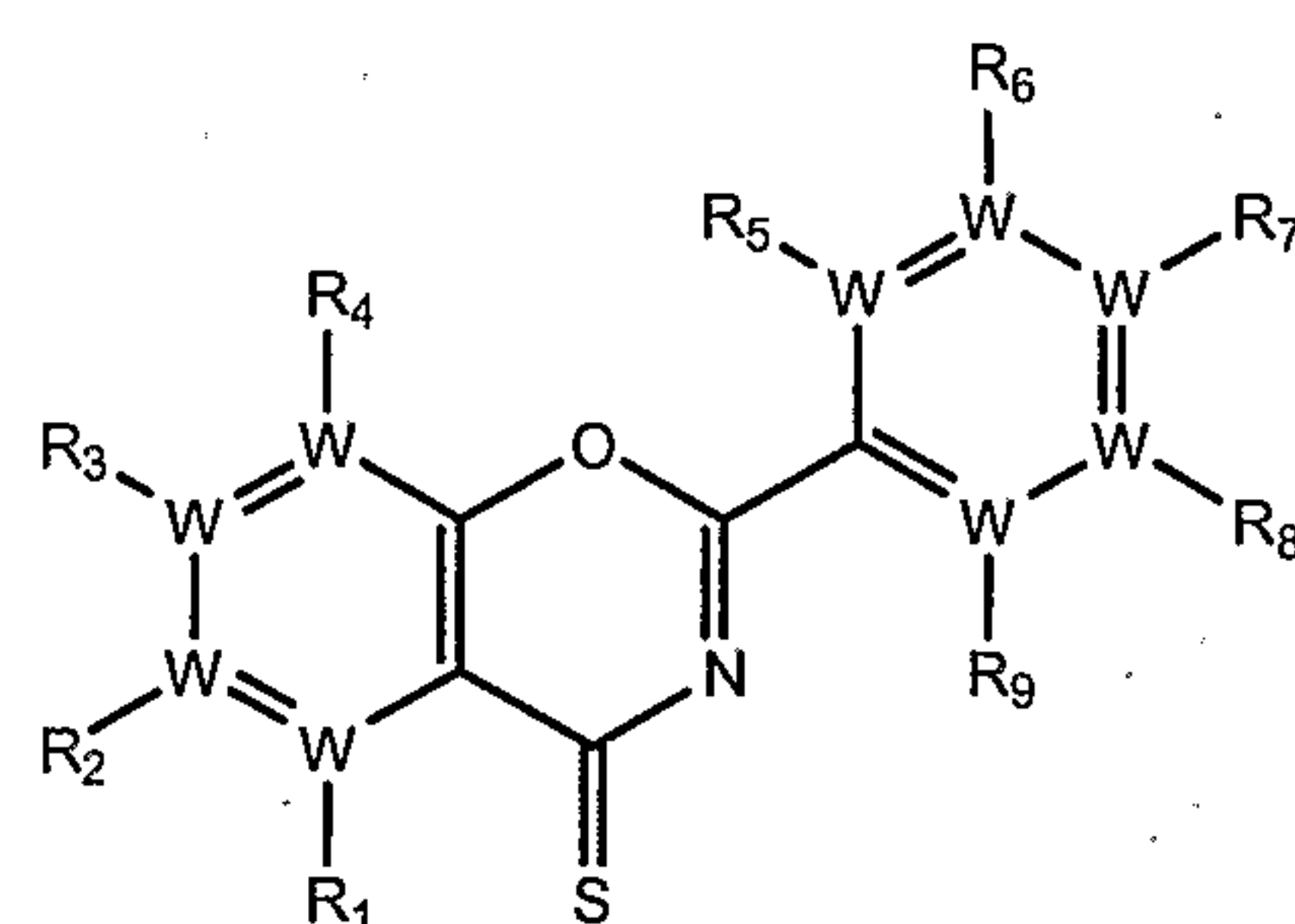
Formula IIP



Formula IIQ

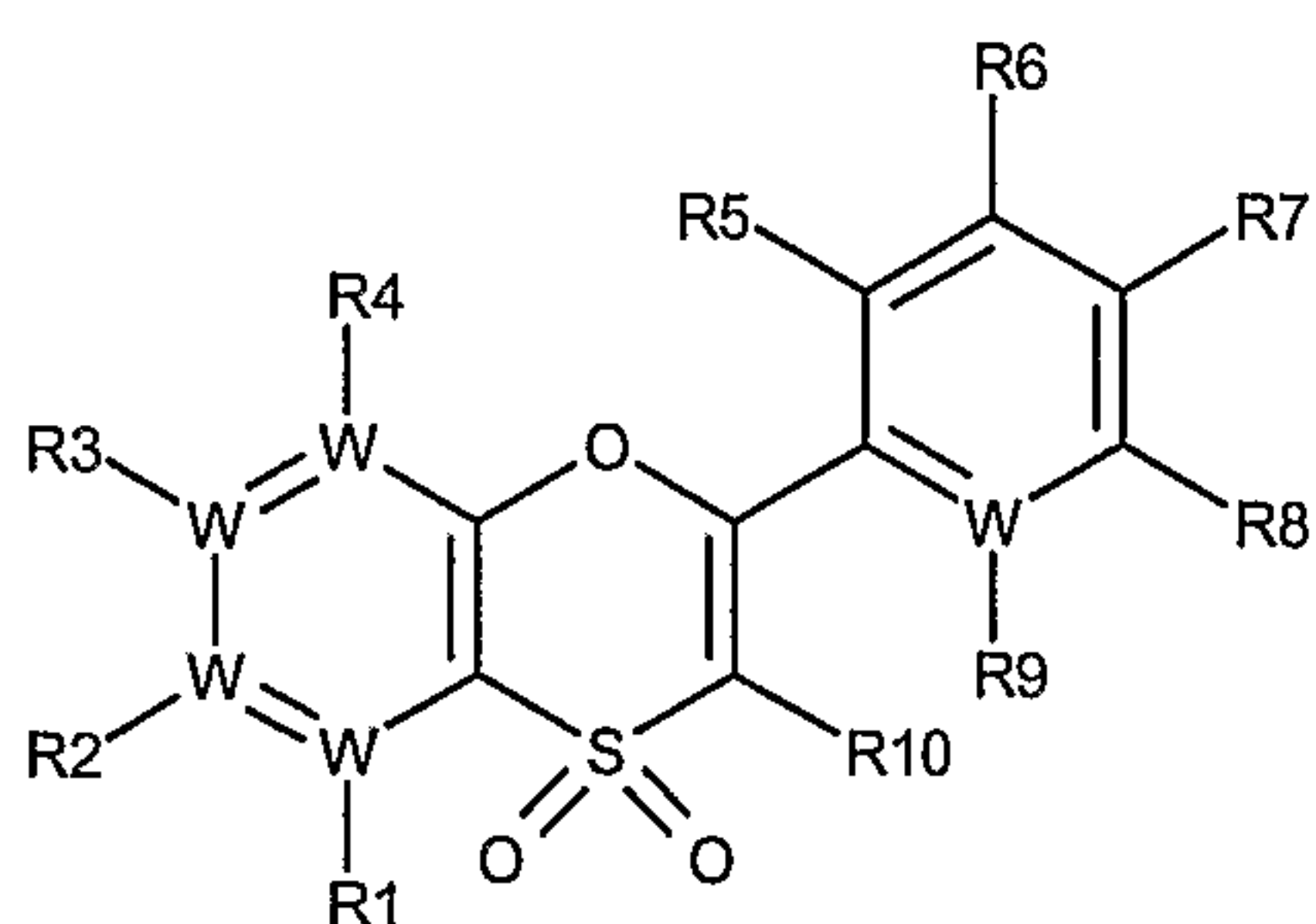


Formula IIR

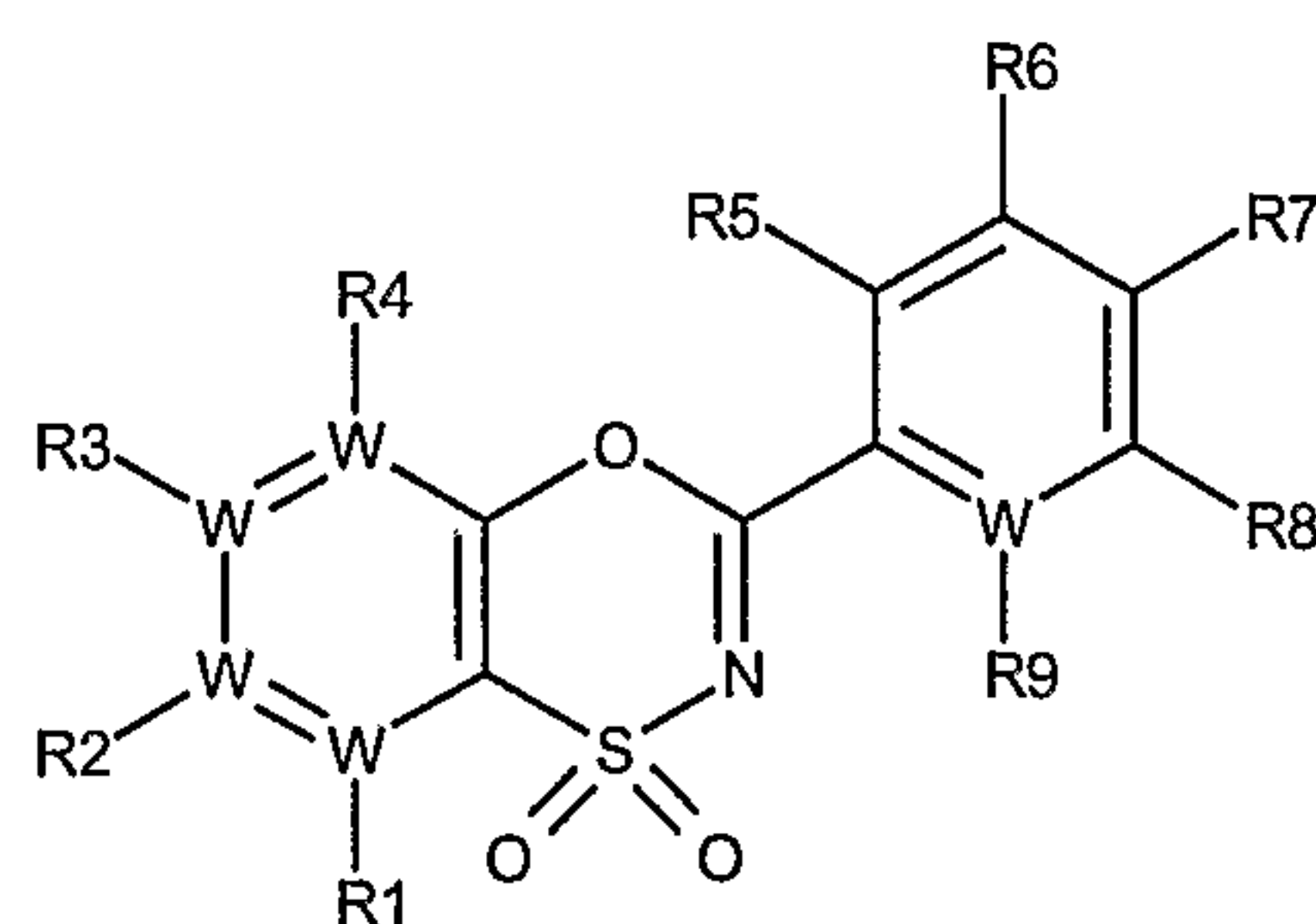


Formula IIS.

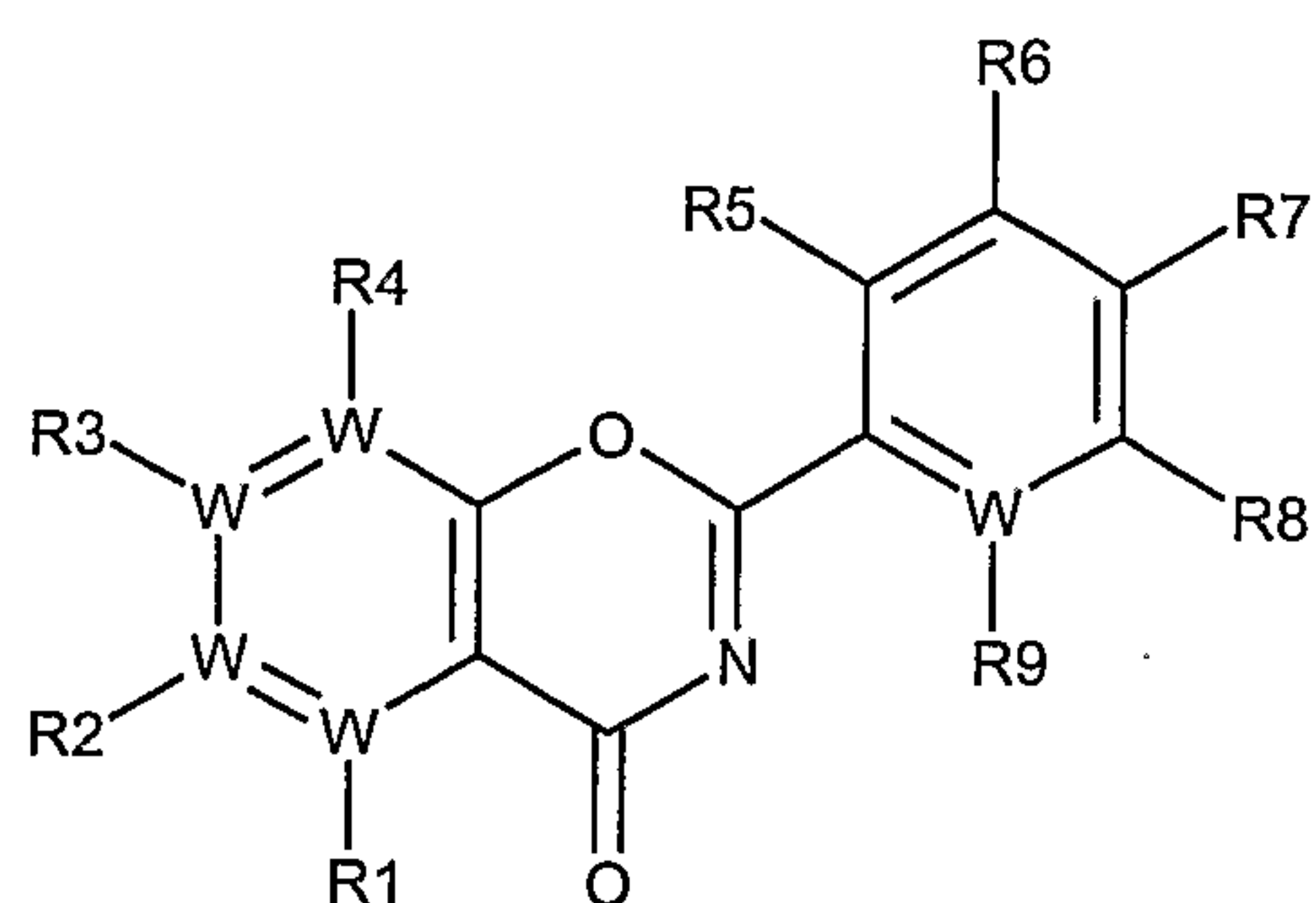
106. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound selected from Formulae IIT to IIW:



Formula IIT



Formula IIU



Formula IIW

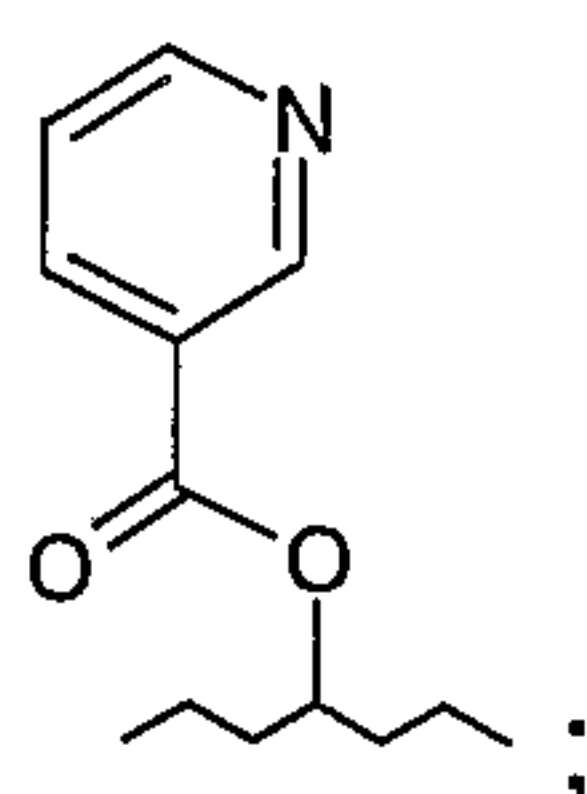
wherein:

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_8 , R_9 , and R_{10} are independently selected from (C_1 - C_{22})alkyl, (C_2 - C_{22})alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF_3 , CCl_3 , phosphate, O-sulfate, O-glucoronidate, K, D, E, F, and G;

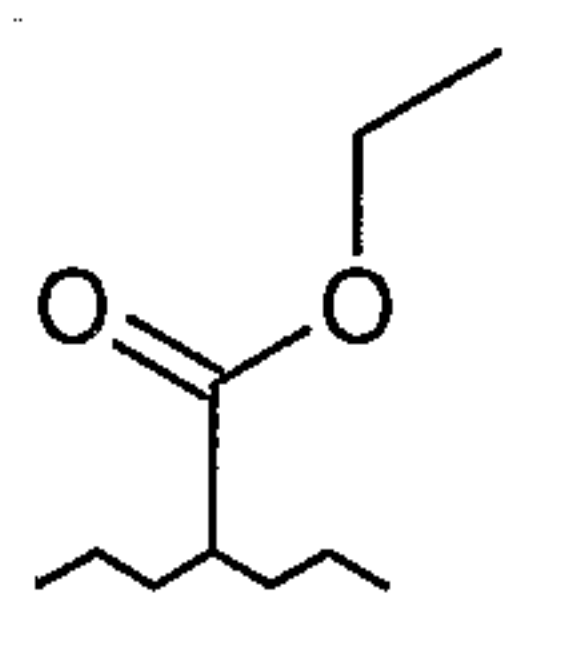
R_7 is selected from hydroxyl and K;

each W is independently selected from C and N;

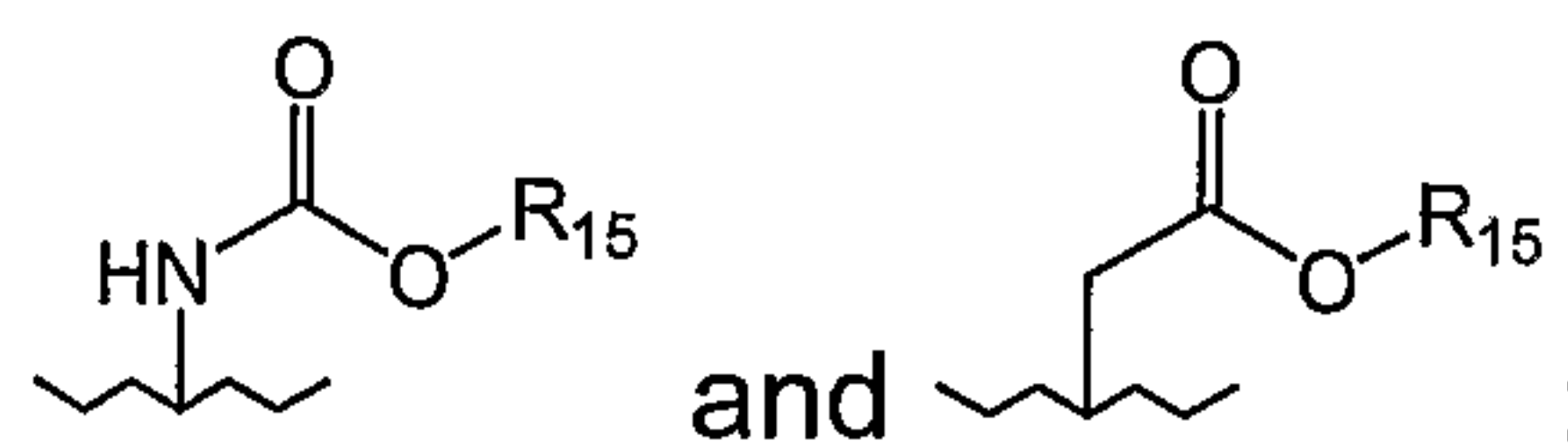
K is



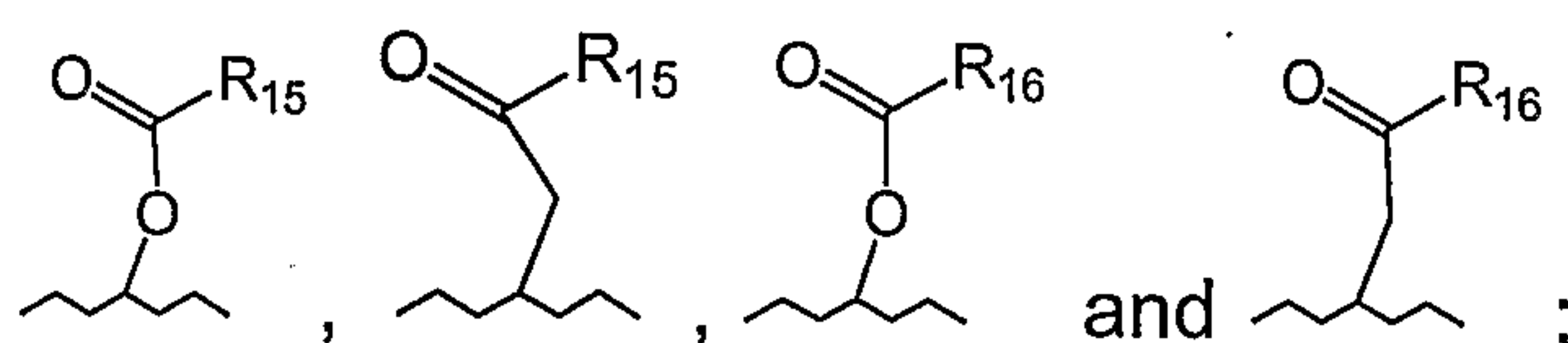
D is



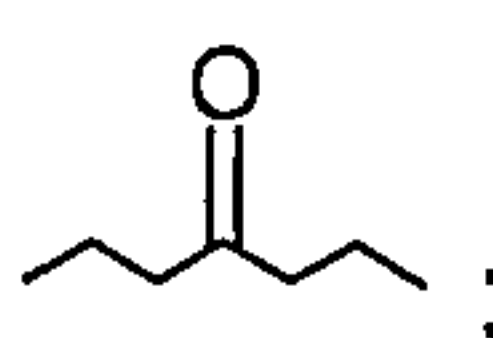
E is selected from



F is selected from



G is

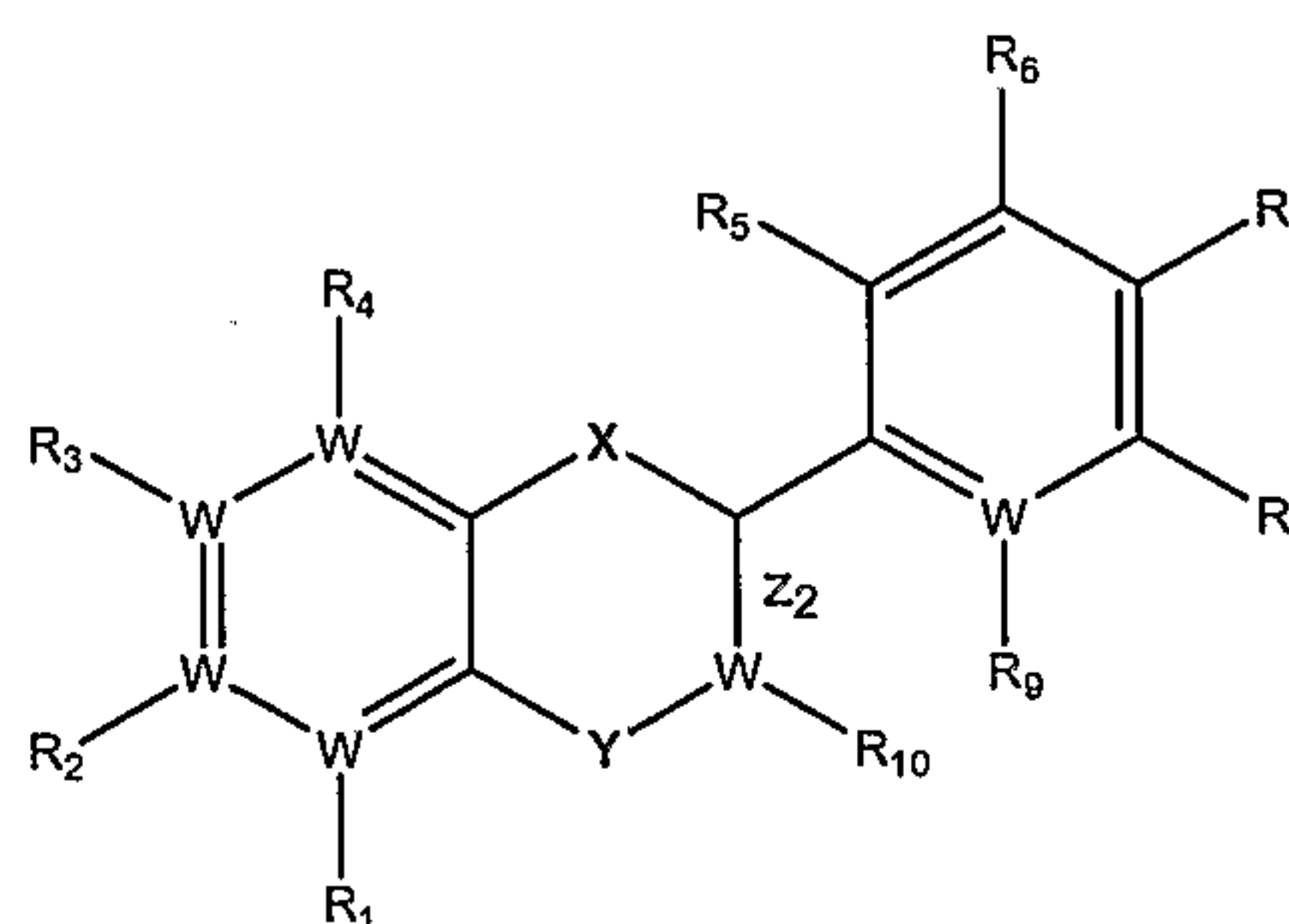


and pharmaceutically acceptable salts thereof;

subject to at least one proviso selected from

- 1) at least one W is N;
- 2) at least one of R₁₋₆ and R₈₋₁₀ is selected from D, E and F; and
- 3) at least one of R₁₋₆ and R₈₋₁₀ is selected from K.

107. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula III:



Formula III

wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₉, and R₁₀ are each independently selected from (C₁-C₂₂)alkyl, (C₂-C₂₂)alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF₃, CCl₃, phosphate, O-sulfate, O-glucoronidate, K, D, E, F and G;

R₇ is selected from hydroxyl and K;

each W is independently selected from C and N;

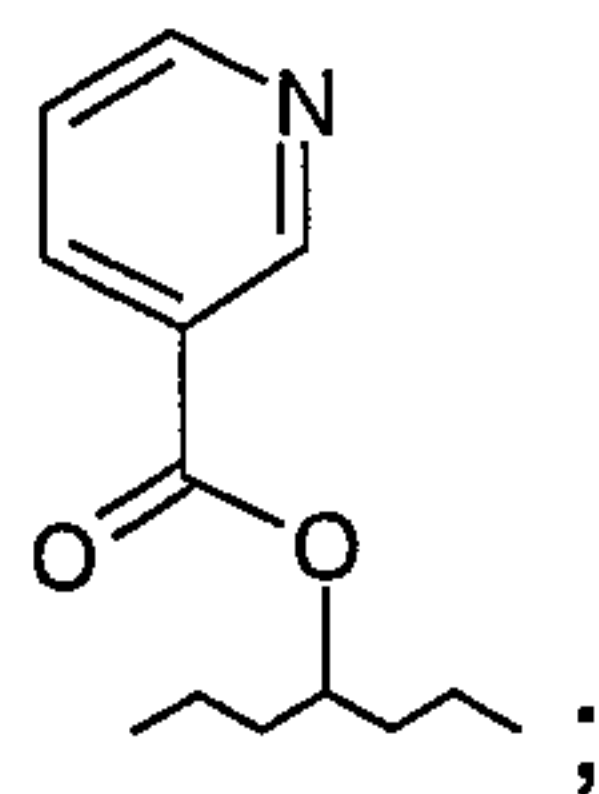
Z₂ is selected from a single bond and a double bond;

X is selected from O, S, C, CR₁₁ and NR₁₁;

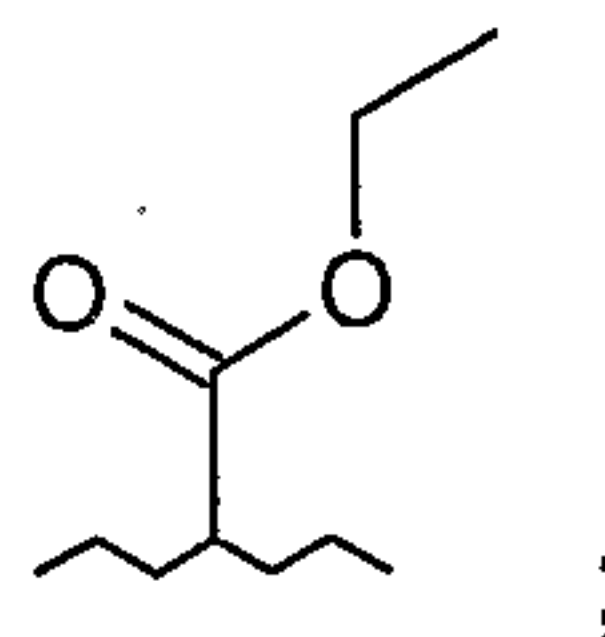
Y is selected from O, S, C, CR₁₂ and NR₁₂;

R₁₁ and R₁₂ are each independently selected from D, E, F, and G;

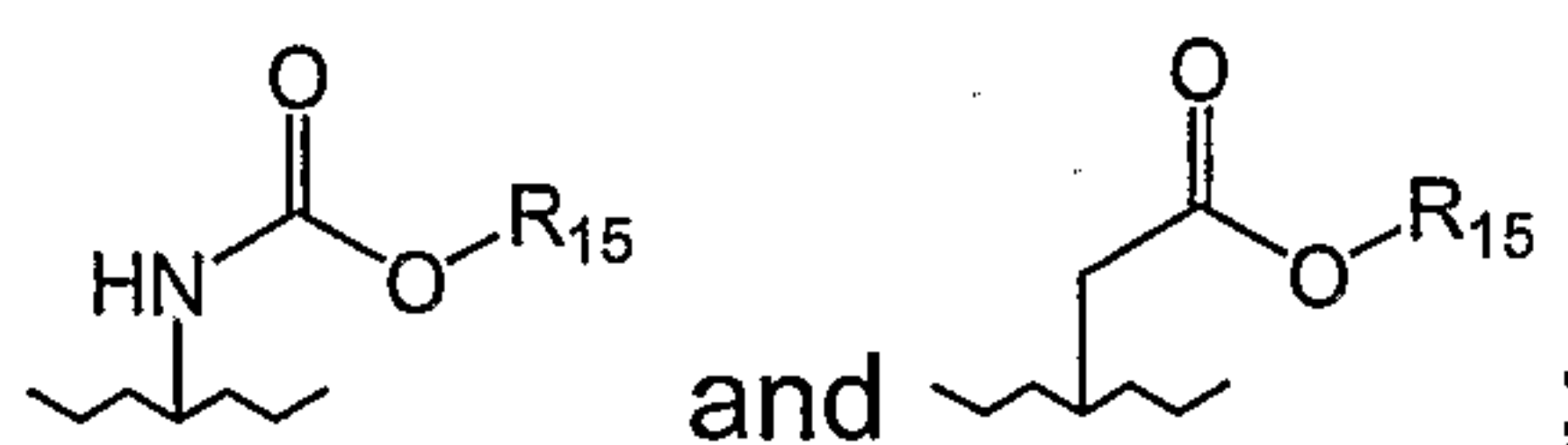
K is



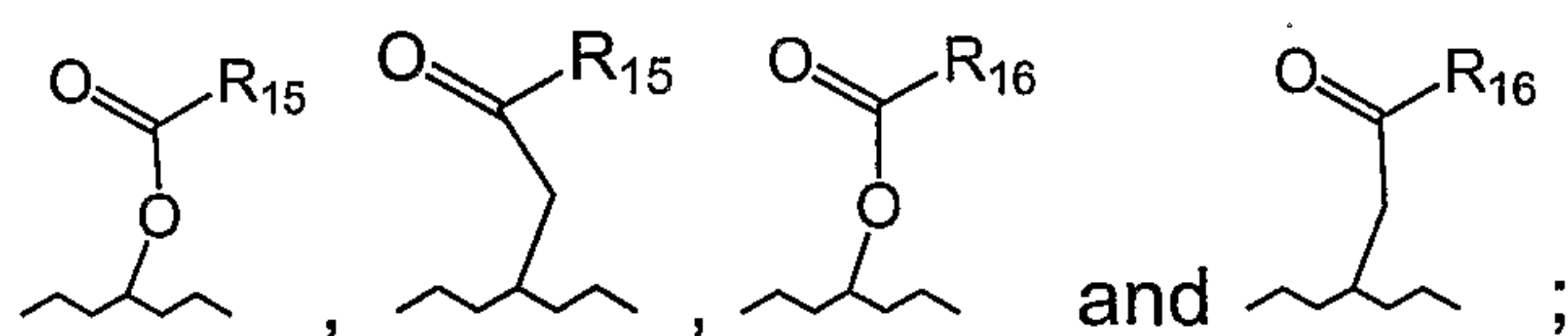
D is



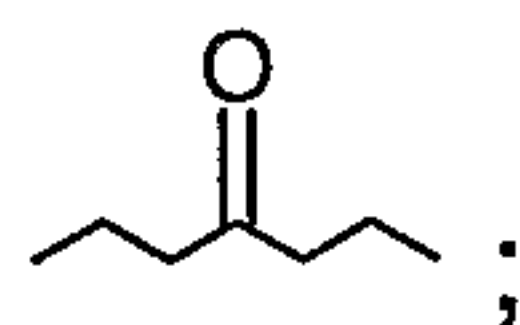
E is selected from



F is selected from



G is



R_{15} is selected from pyridine, pyridazine, pyrimidine, and pyrazine;

R_{16} is selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, aryl and heteroaryl;

and pharmaceutically acceptable salts thereof;

subject to at least one proviso selected from

- 1) at least one W is N;
- 2) at least one of R_{1-6} and R_{8-10} is selected from D, E and F; and
- 3) at least one of R_{1-6} and R_{8-10} is selected from K.

108. The method of embodiment 107, wherein R_7 is hydroxyl and at least one of R_{1-6} and R_{8-10} is selected from K.

109. The method of embodiment 108, subject to at least one proviso selected from

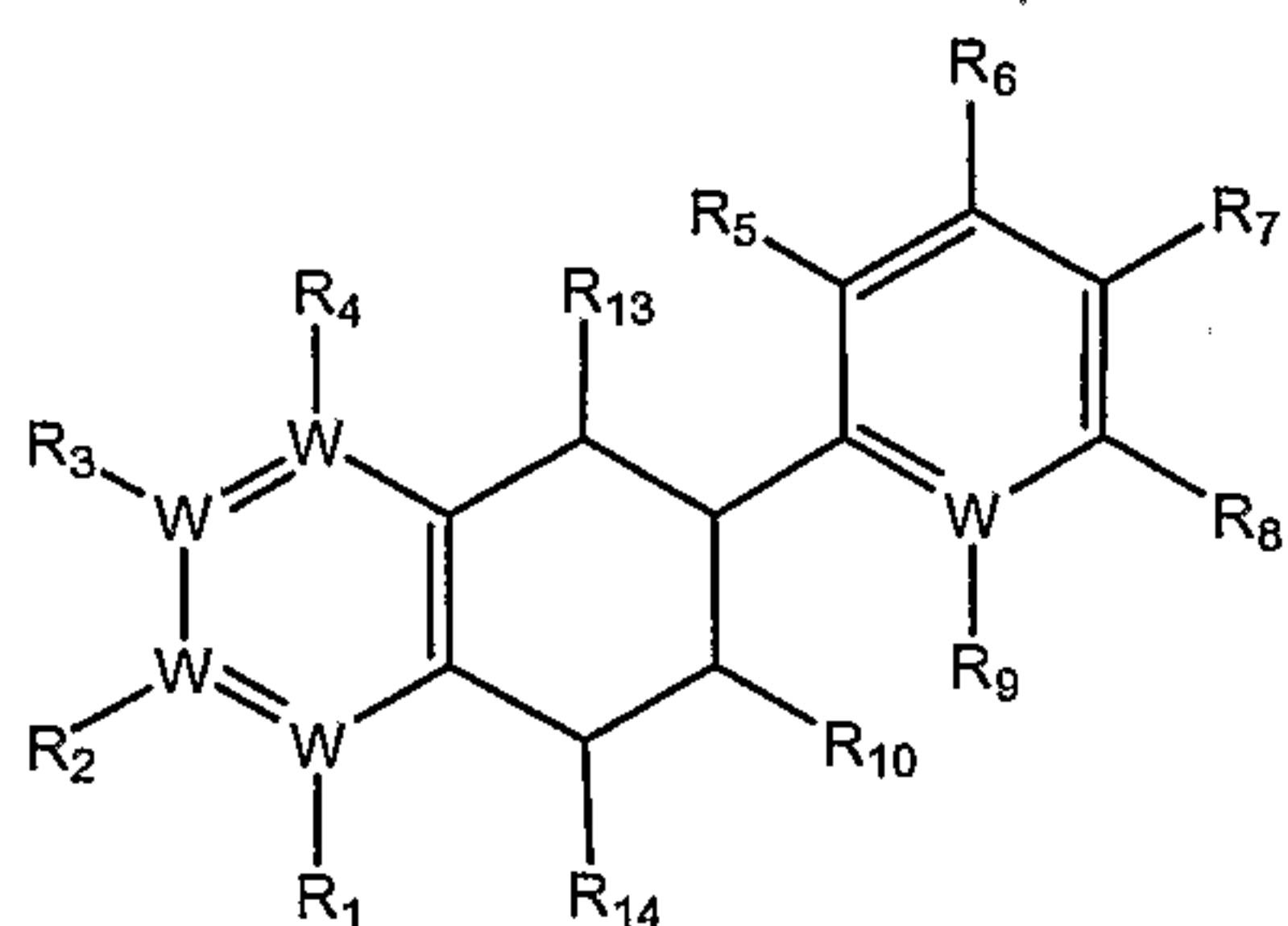
- 1) at least one W is N; and
- 2) at least one of R_{1-6} and R_{8-10} is selected from D, E and F.

110. The method of embodiment 107, wherein at least one W is N, at least one of R₁₋₆ and R₈₋₁₀ is selected from D, E and F, and at least one of R₁₋₆ and R₈₋₁₀ is selected from K.

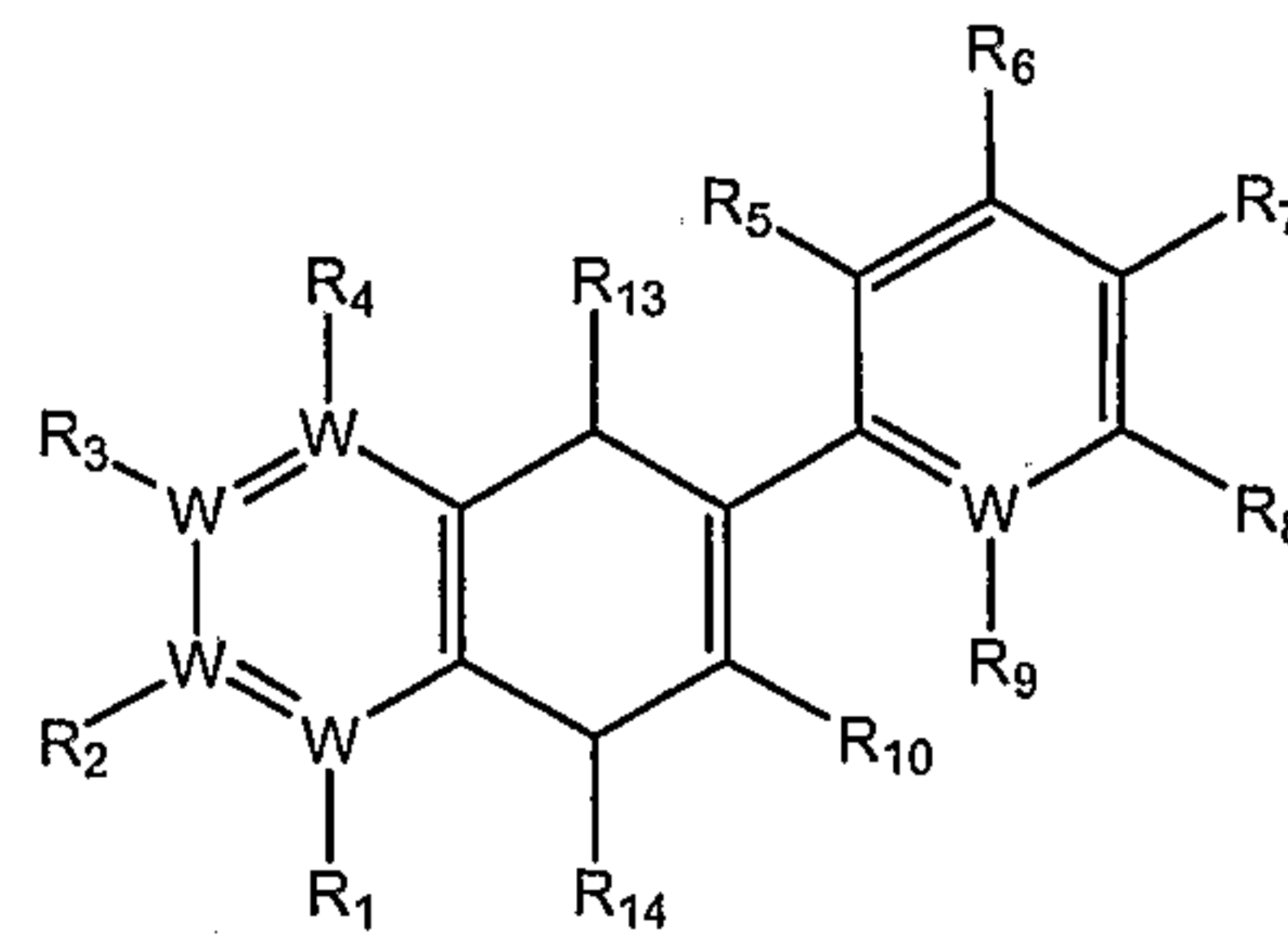
111. The method of embodiment 107, wherein X is O, Y is CR₁₂, and R₁₂ is G.

112. The method of embodiment 107, wherein the compound of Formula III is 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one.

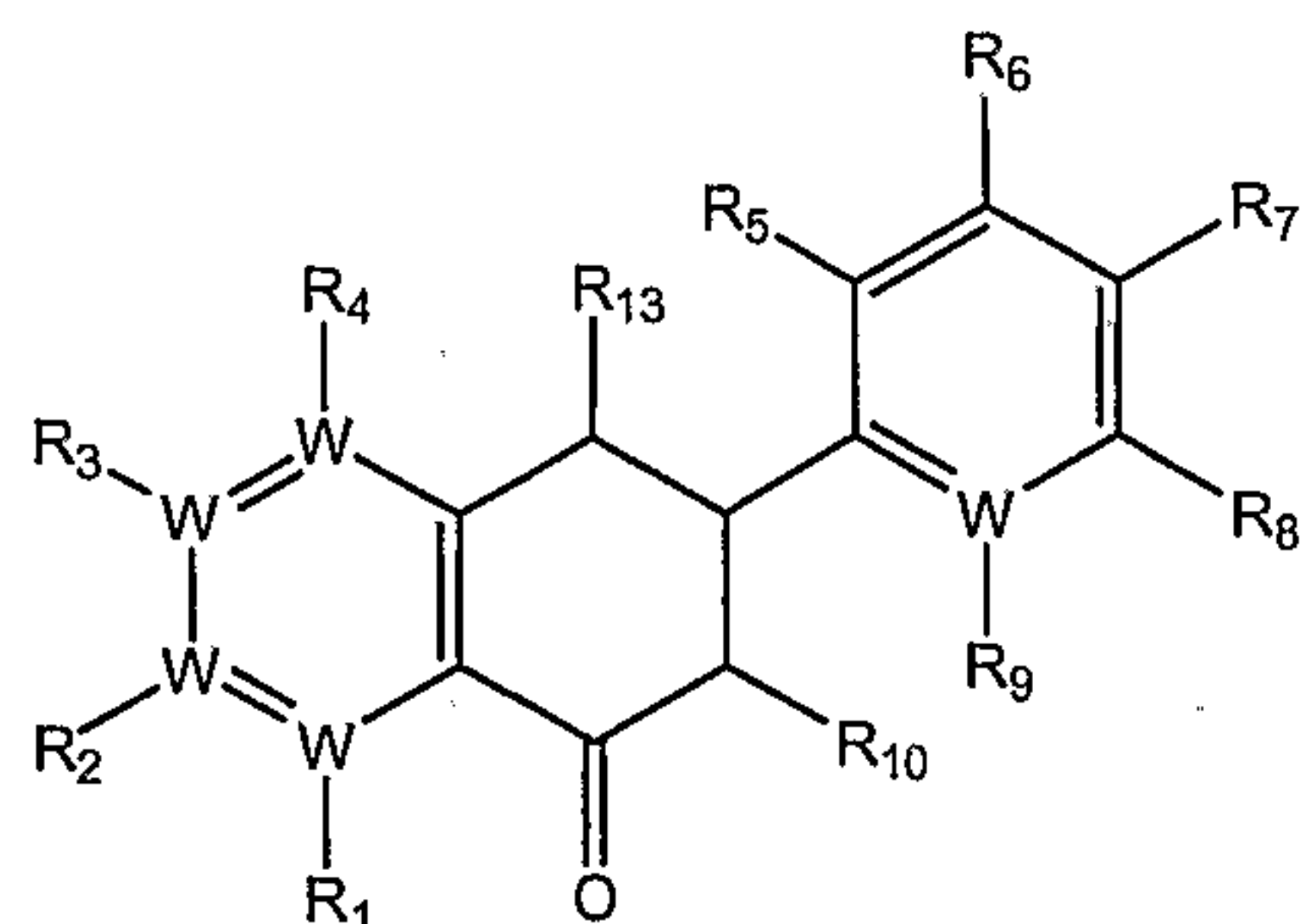
113. The method of embodiment 107, wherein Formula III is selected from Formulae IIIA-IIIH:



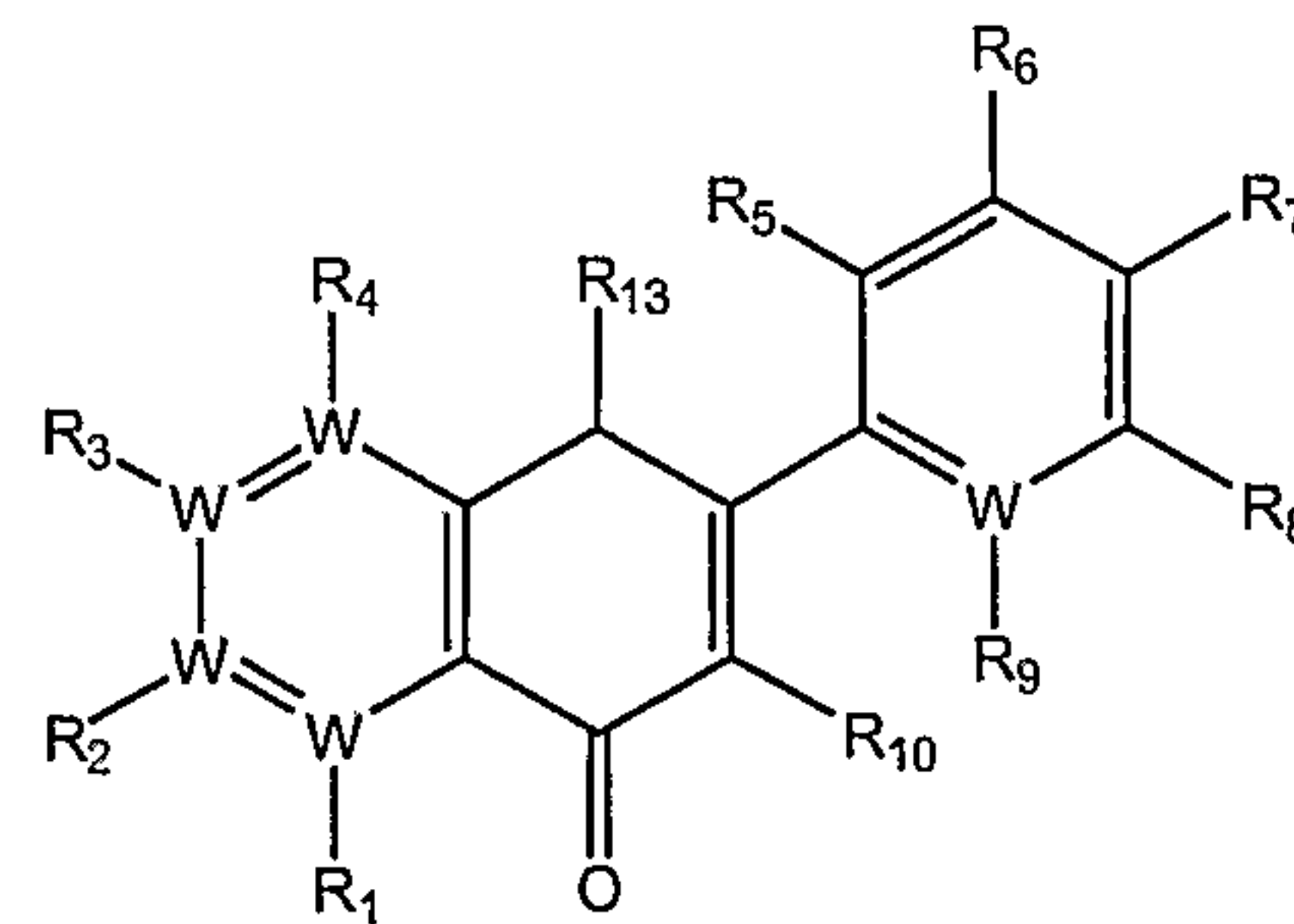
Formula IIIA



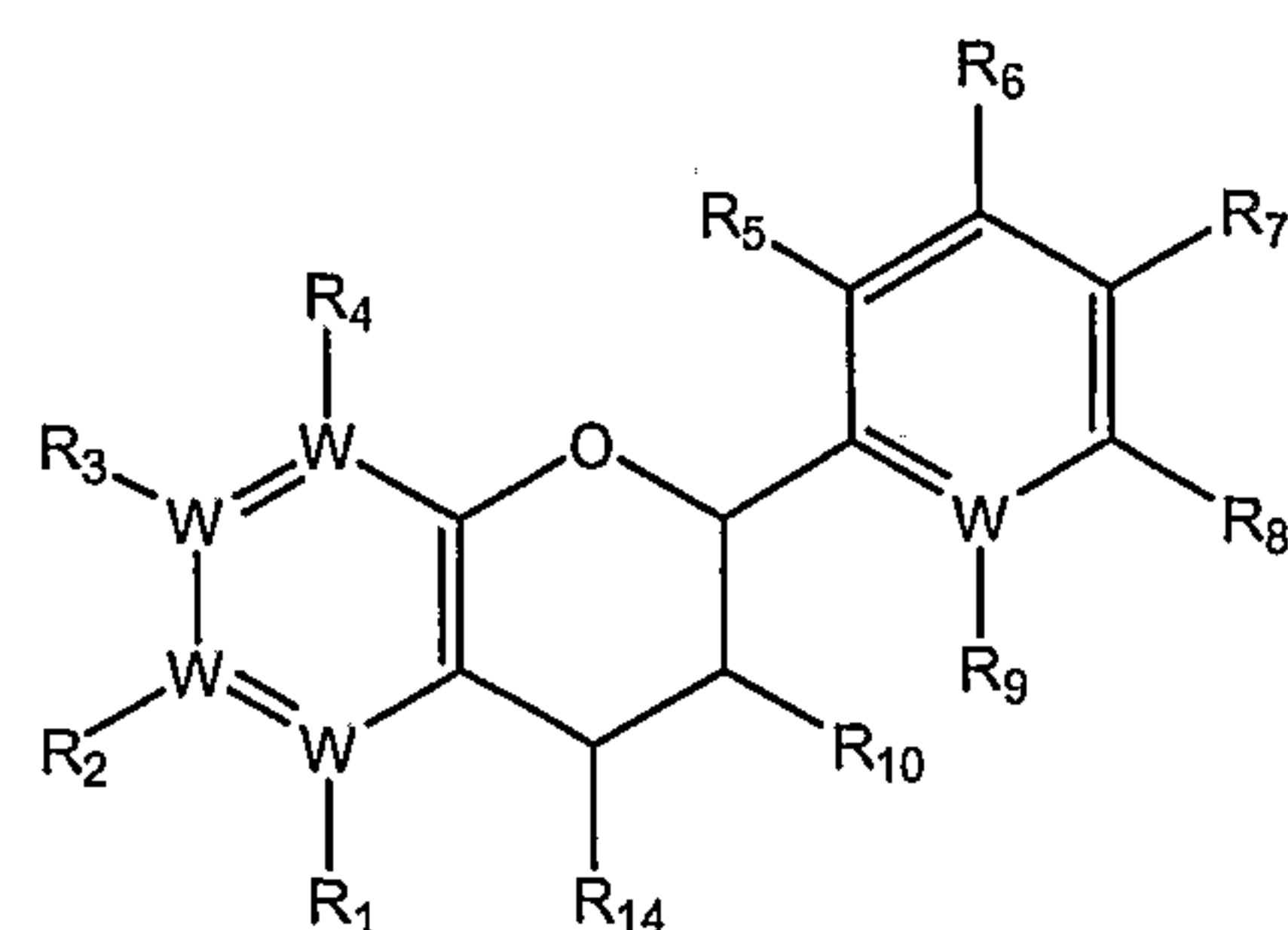
Formula IIIB



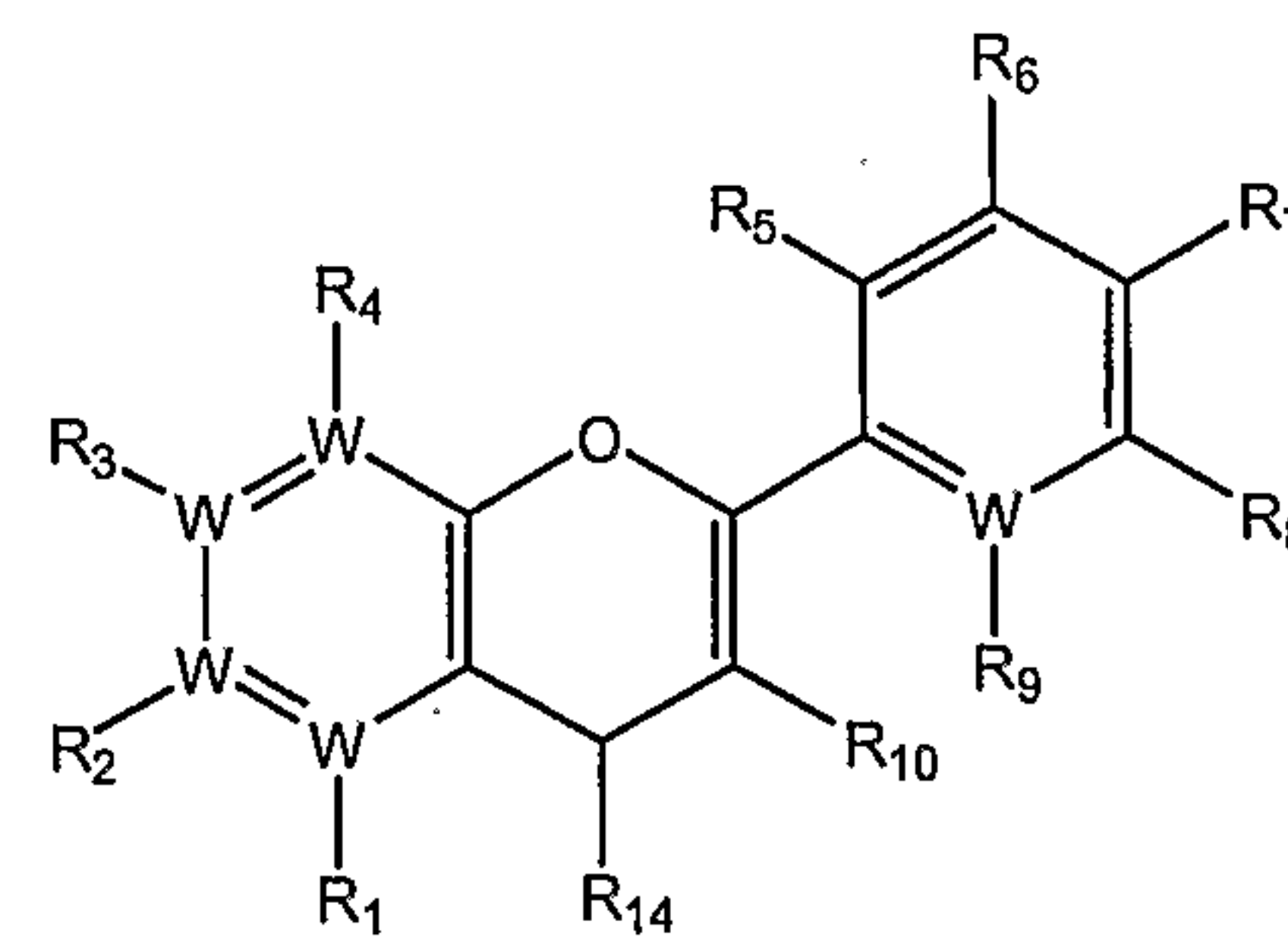
Formula IIIC



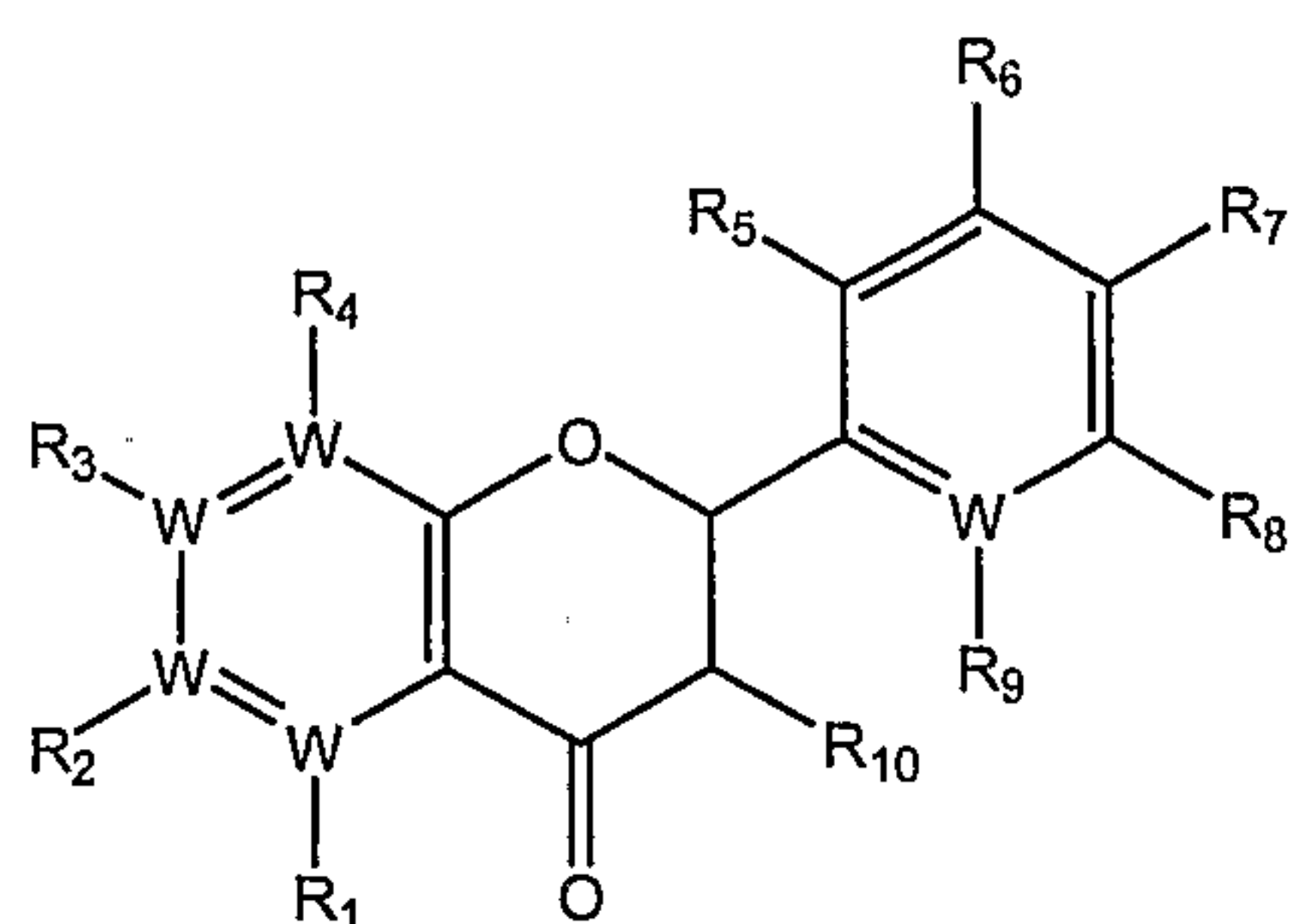
Formula IIID



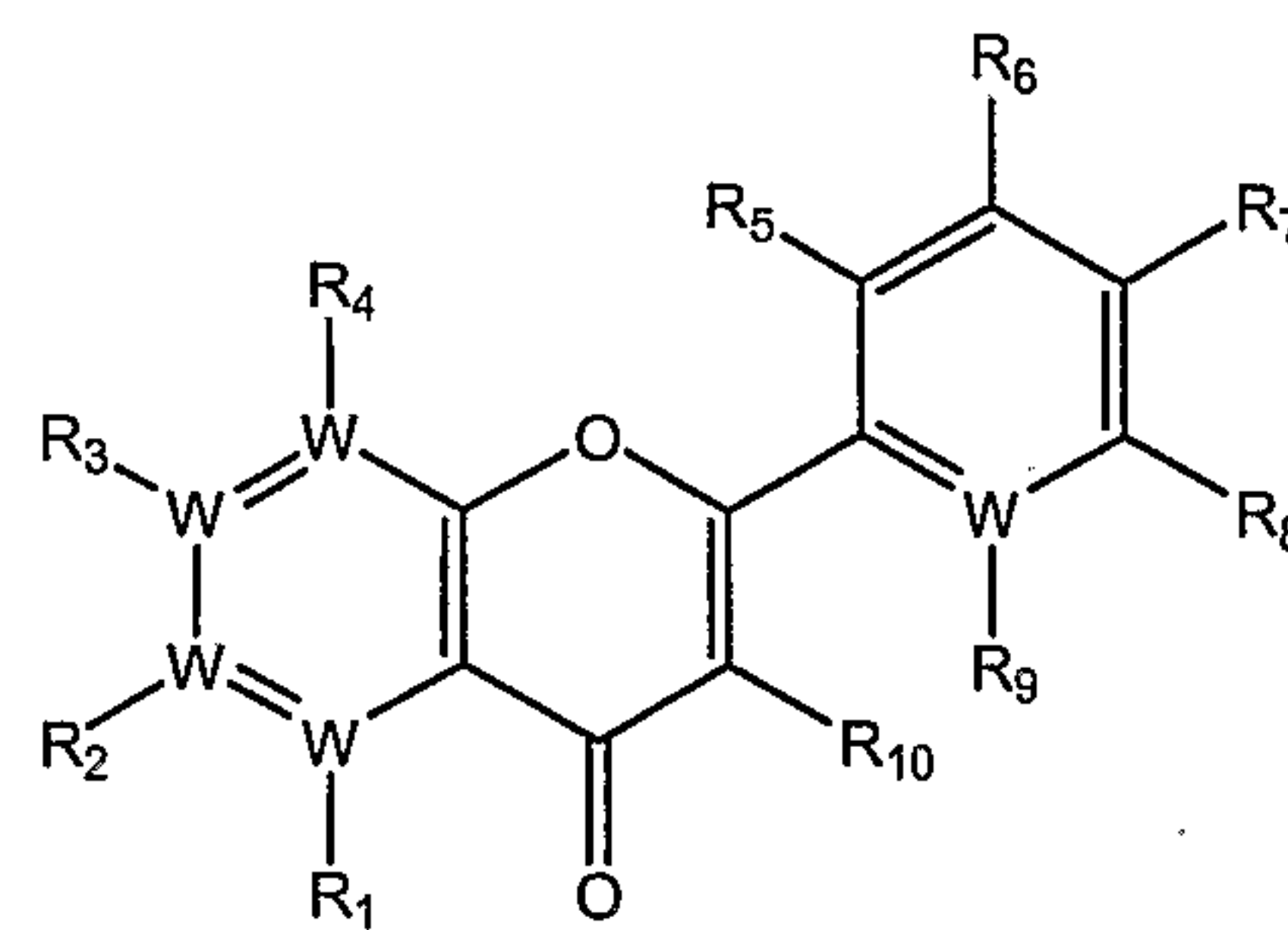
Formula IIIE



Formula IIIF



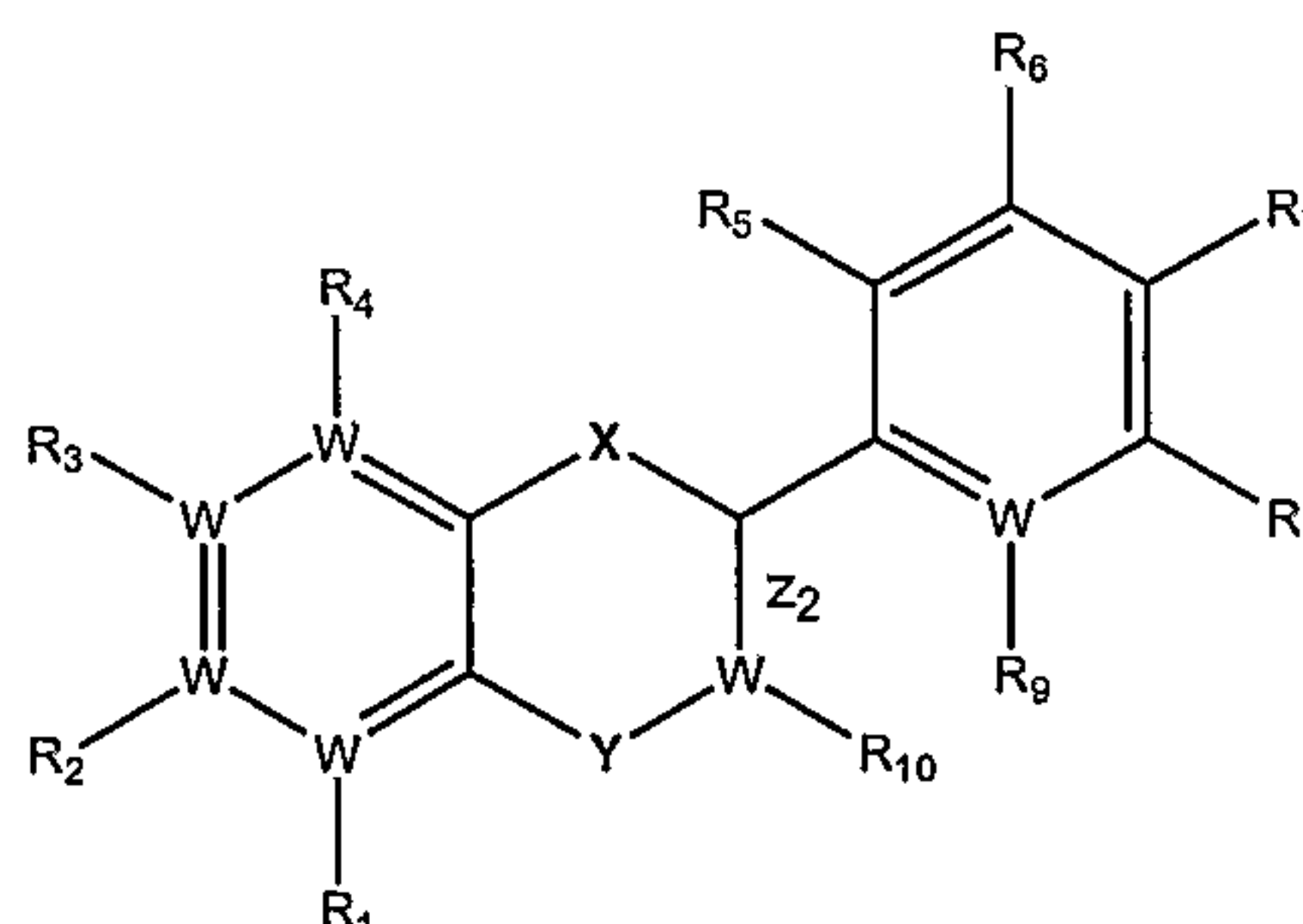
Formula IIIG



Formula IIIH

wherein R_{13} and R_{14} are each independently selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF_3 , CCl_3 , phosphate, O-sulfate, O-glucoronidate, K, D, E, F and G.

114. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula III:



Formula III

wherein

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_8 , R_9 and R_{10} are each independently selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF_3 , CCl_3 , phosphate, O-sulfate, and O-glucoronidate;

R_7 is selected from hydroxyl and K;

each W is independently selected from C and N;

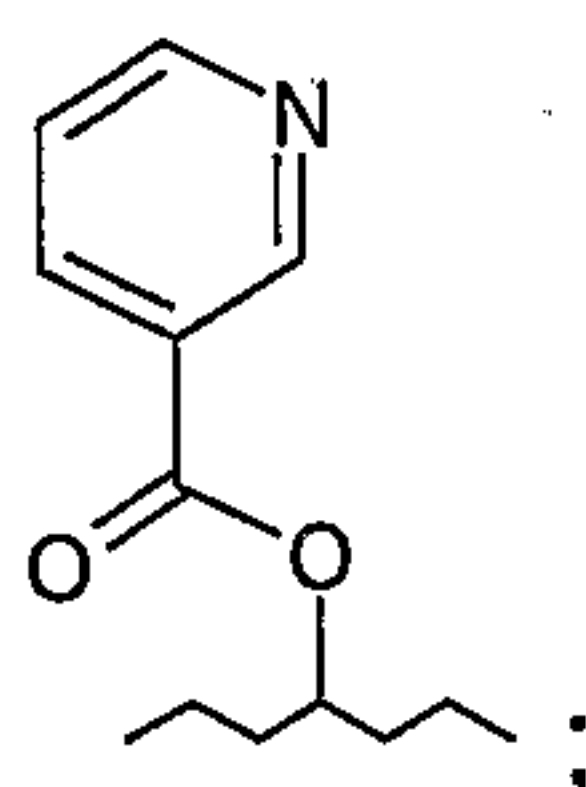
Z_2 is selected from a single bond and a double bond;

X is selected from O, S, C, CR_{11} and NR_{11} ;

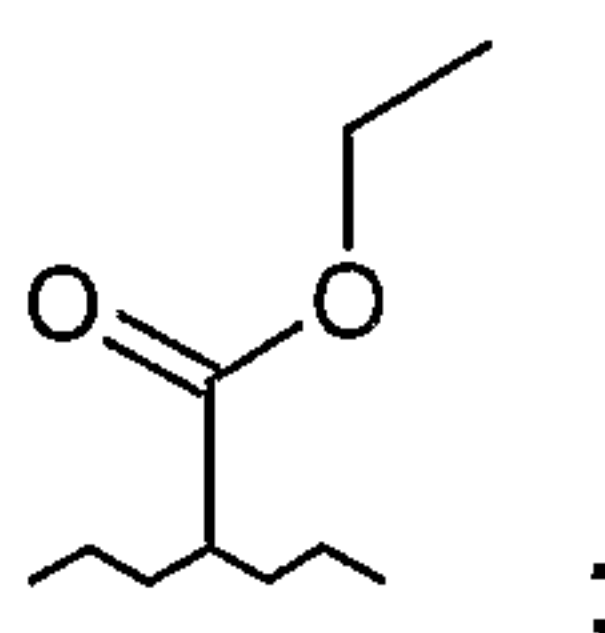
Y is selected from O, S, C, CR_{12} and NR_{12} ;

R_{11} and R_{12} are each independently selected from D, F and G;

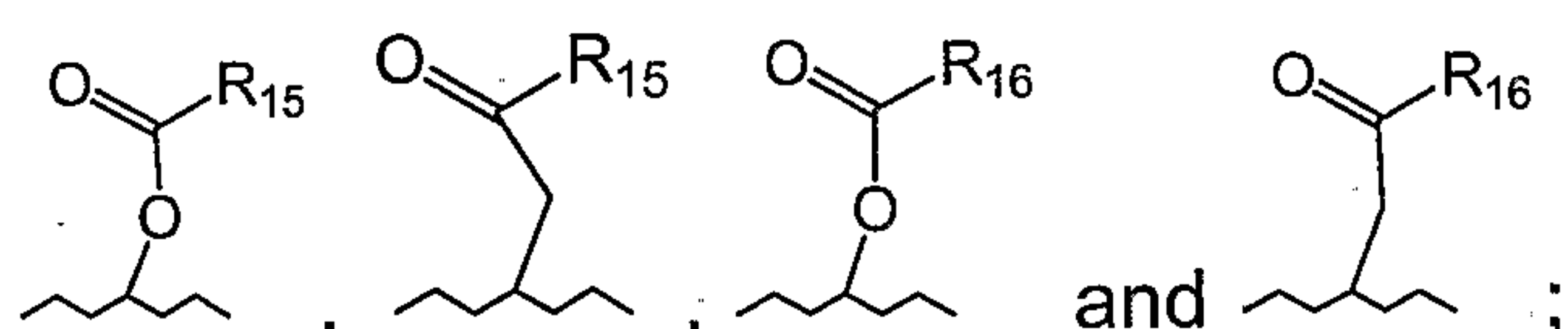
K is



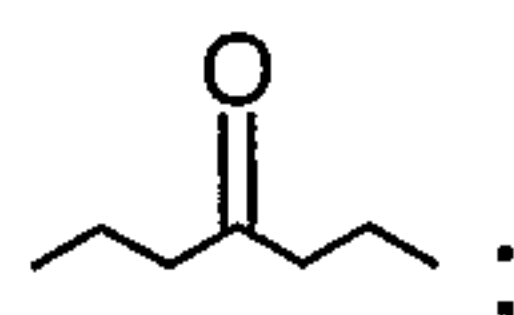
D is



F is selected from



G is

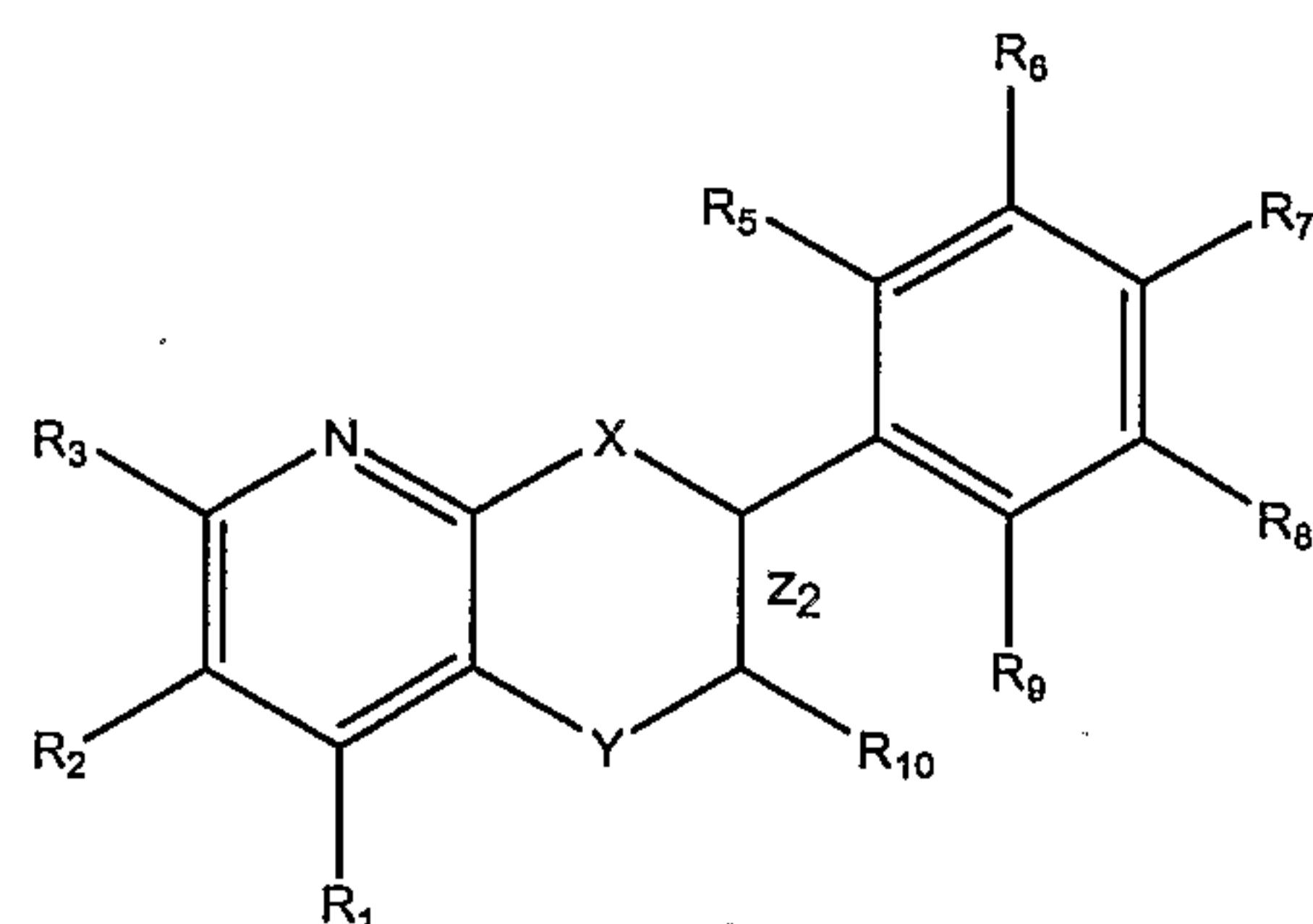


wherein if R_7 is hydroxyl, then at least one W is N and at least one of R_{1-6} and R_{8-10} is selected from K, and

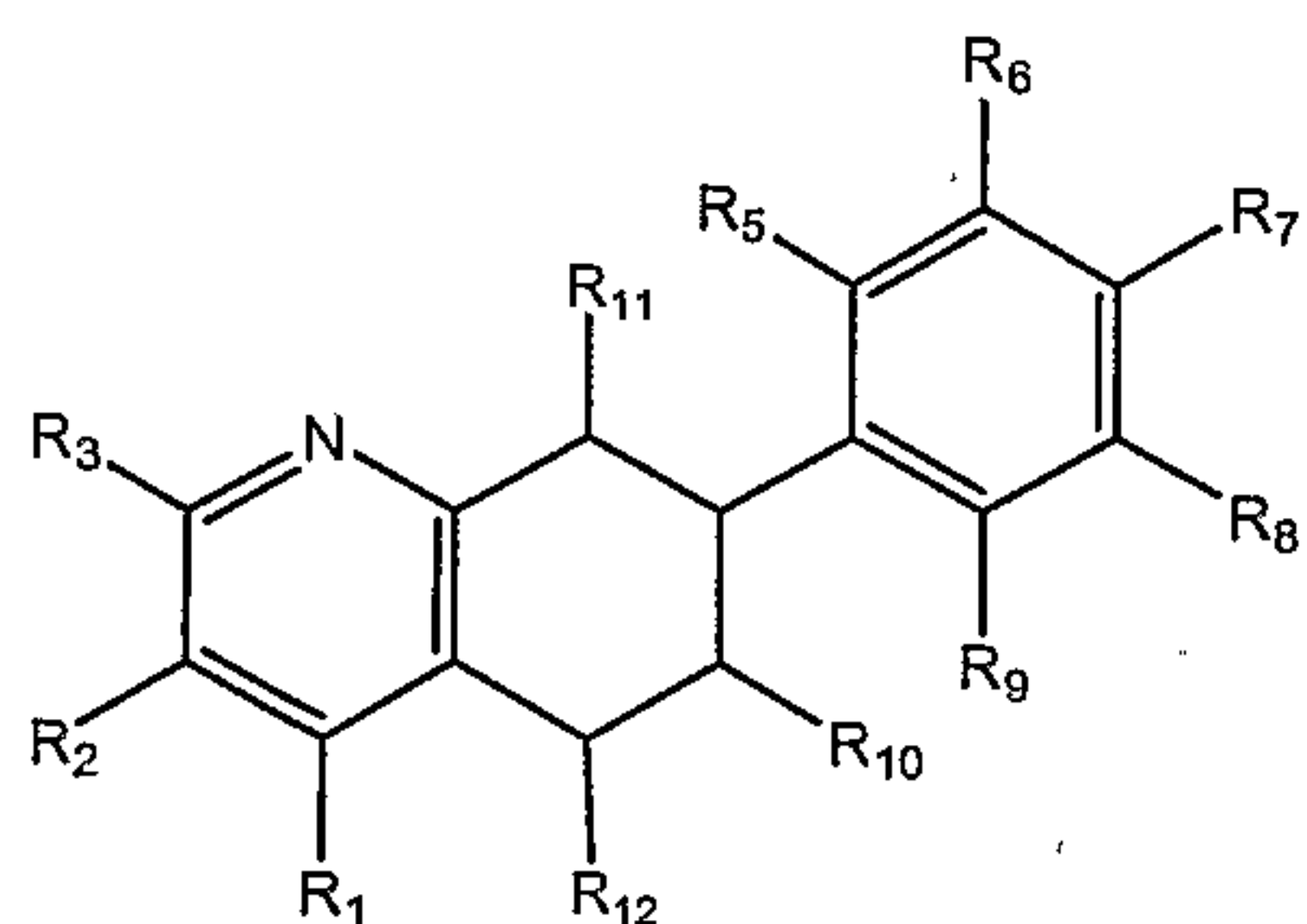
wherein if R_7 is K, then at least one W is N.

115. The method of embodiment 114, wherein X is O, Y is CR_{12} , and R_{12} is G.

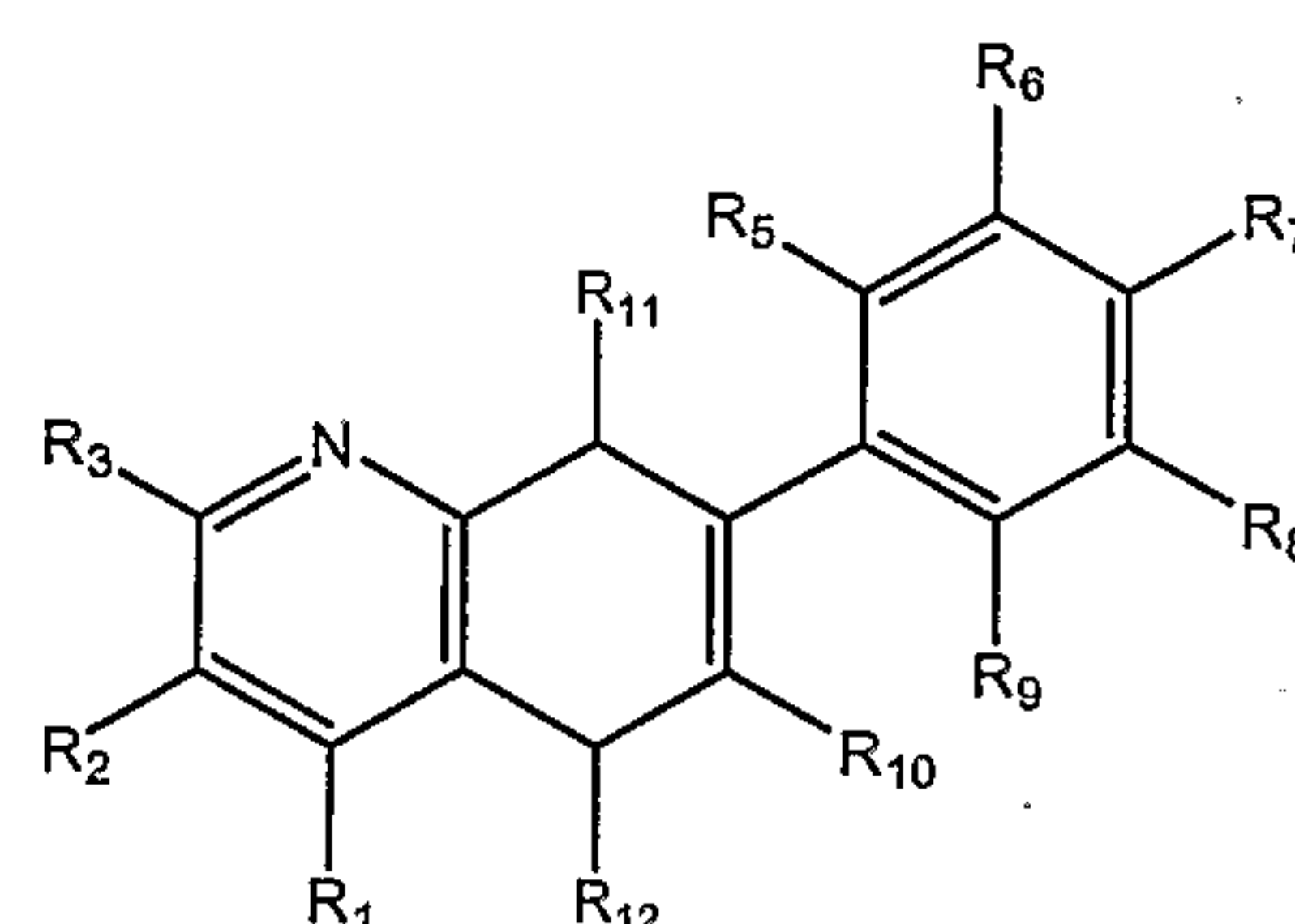
116. The method of embodiment 114, wherein Formula III has the structure:



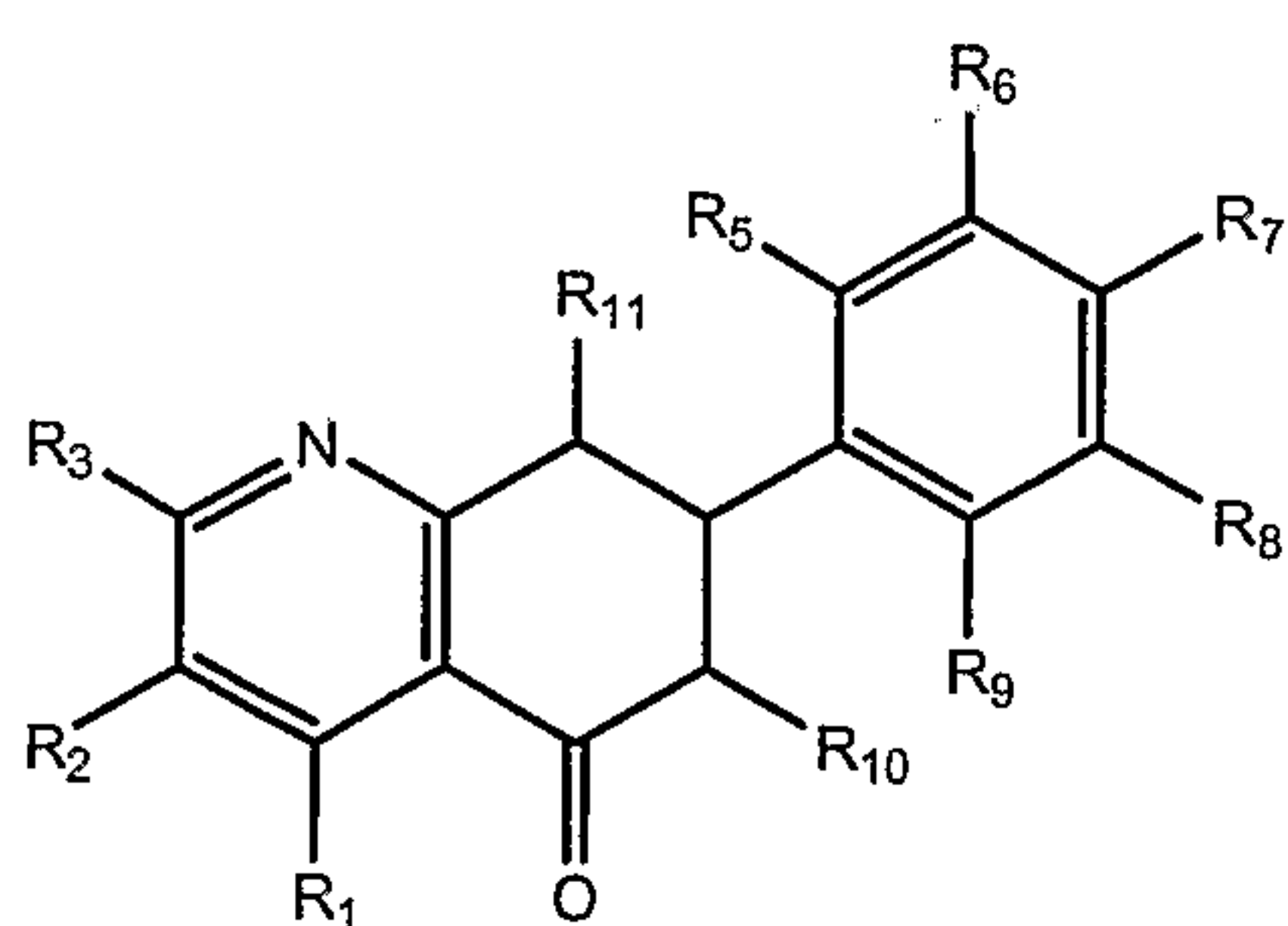
117. The method of embodiment 114, wherein Formula III is selected from Formulae IIIJ to IIIP:



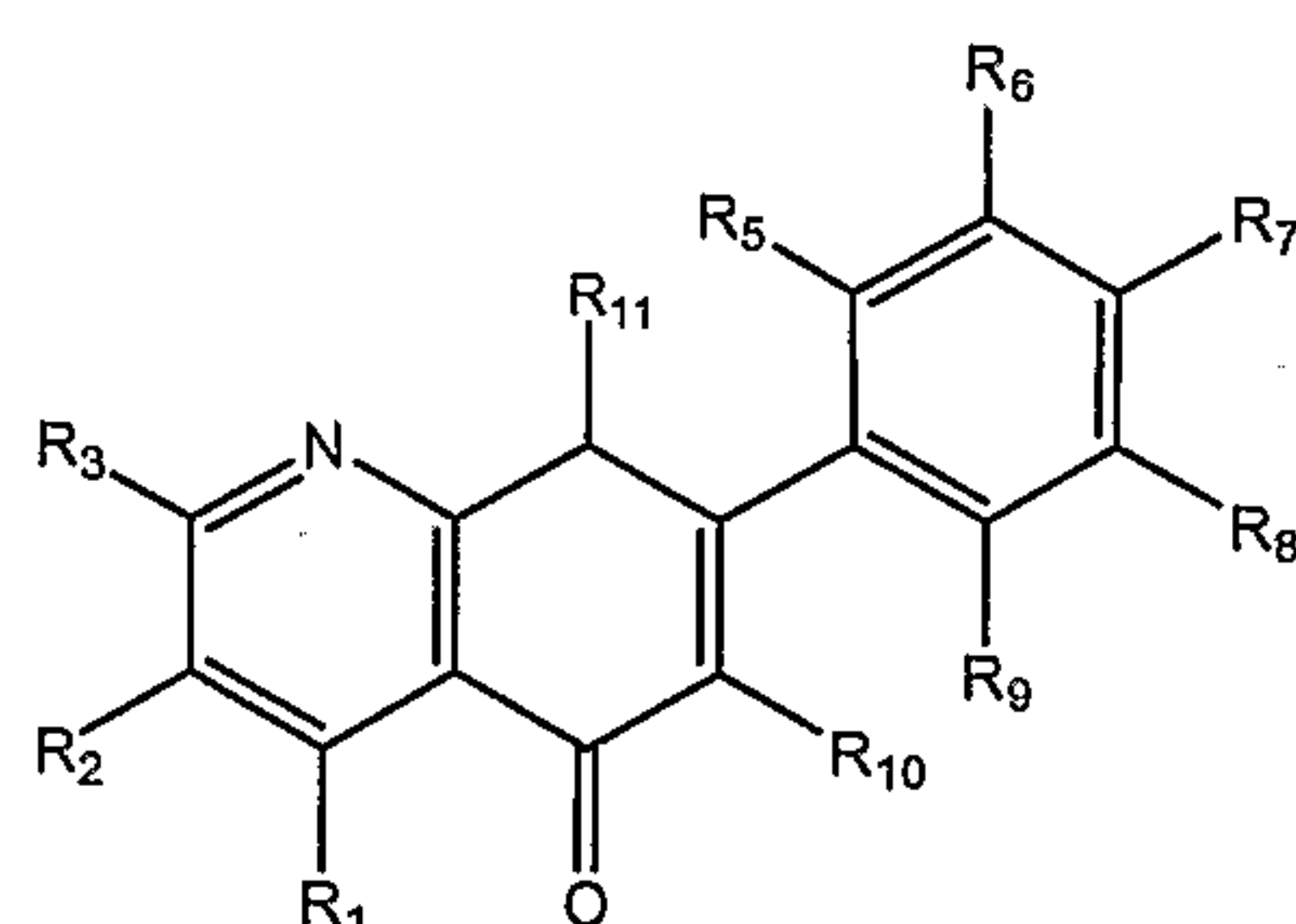
Formula IIIJ



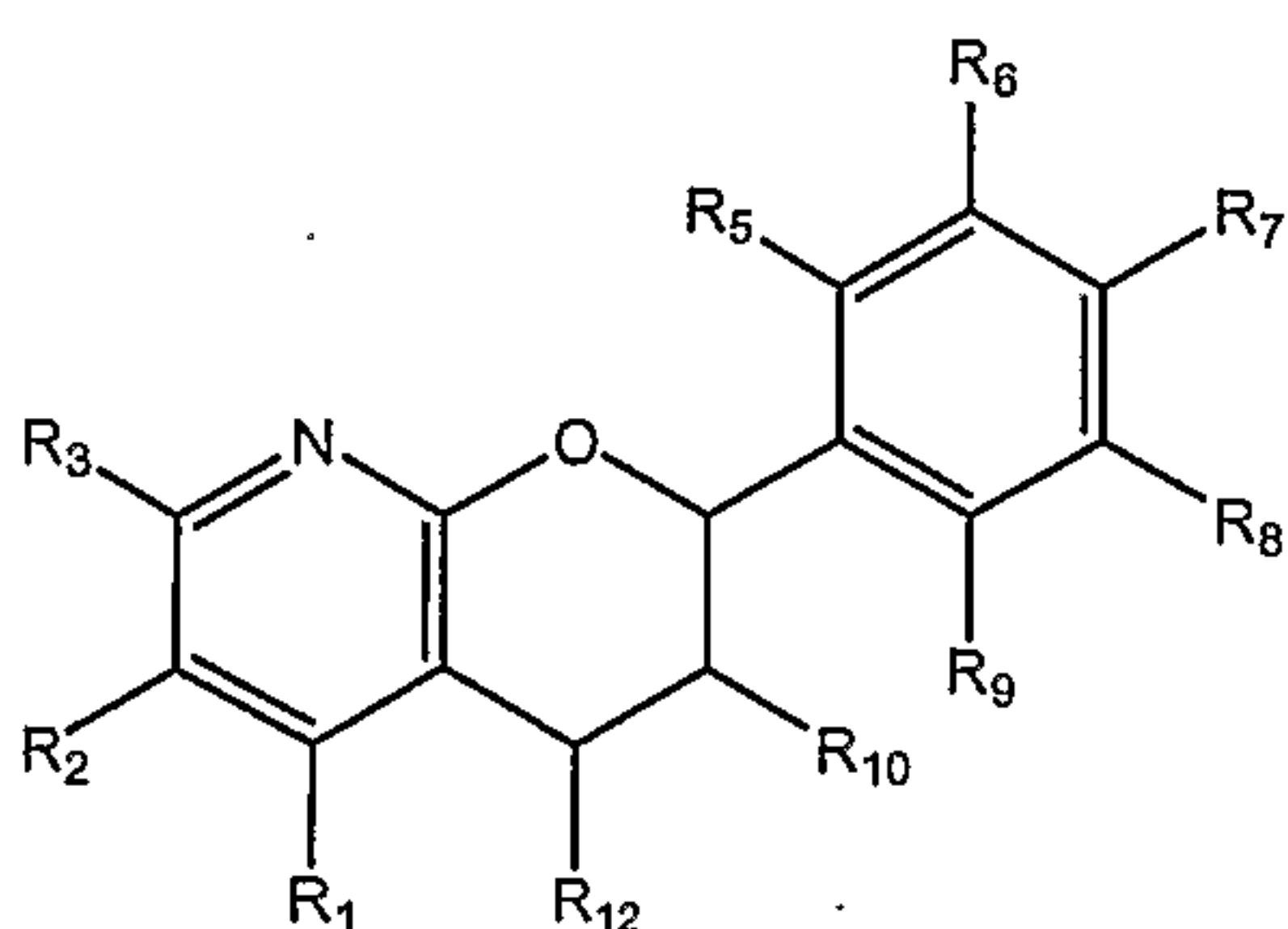
Formula IIIK



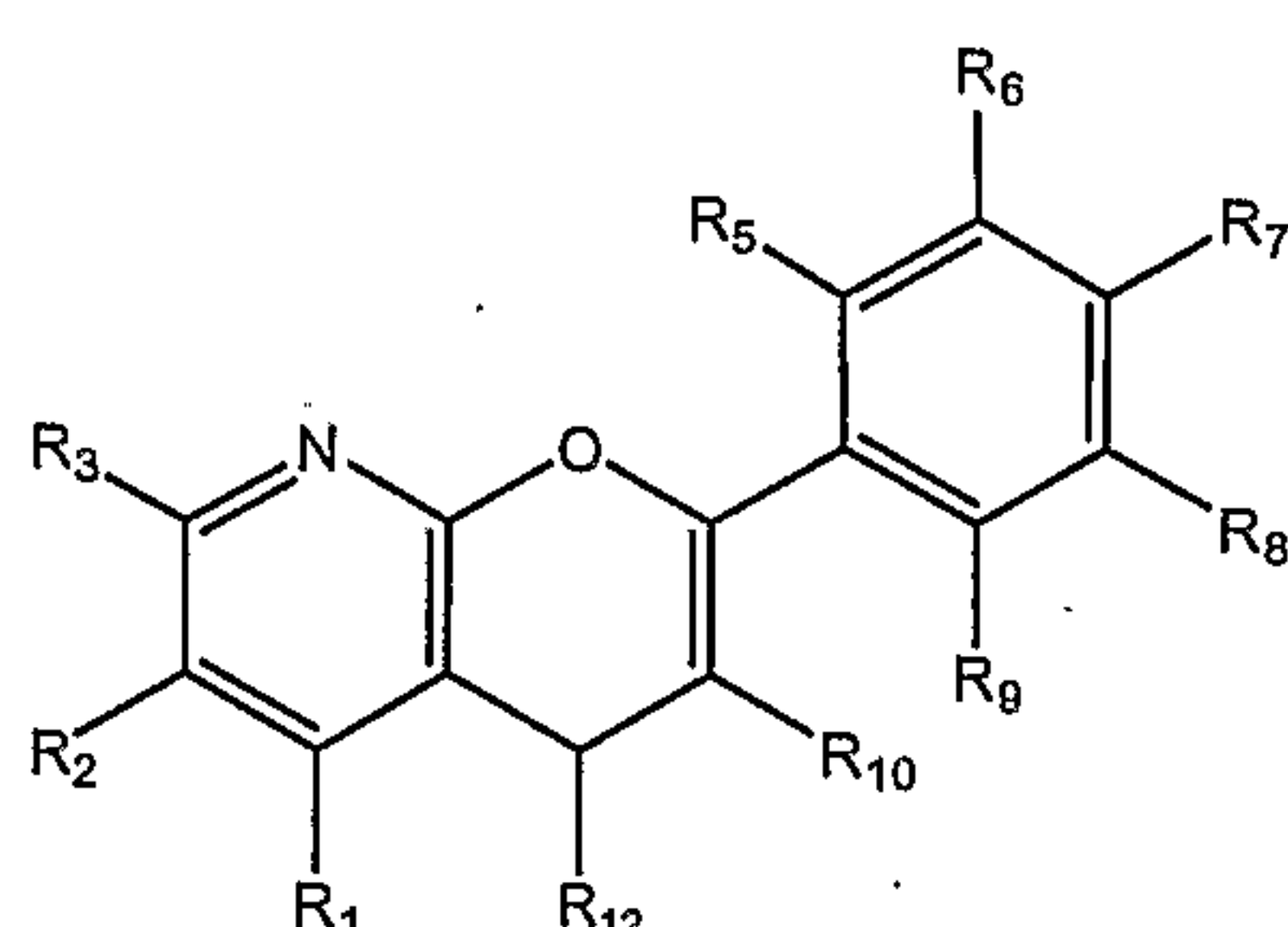
Formula IIIL



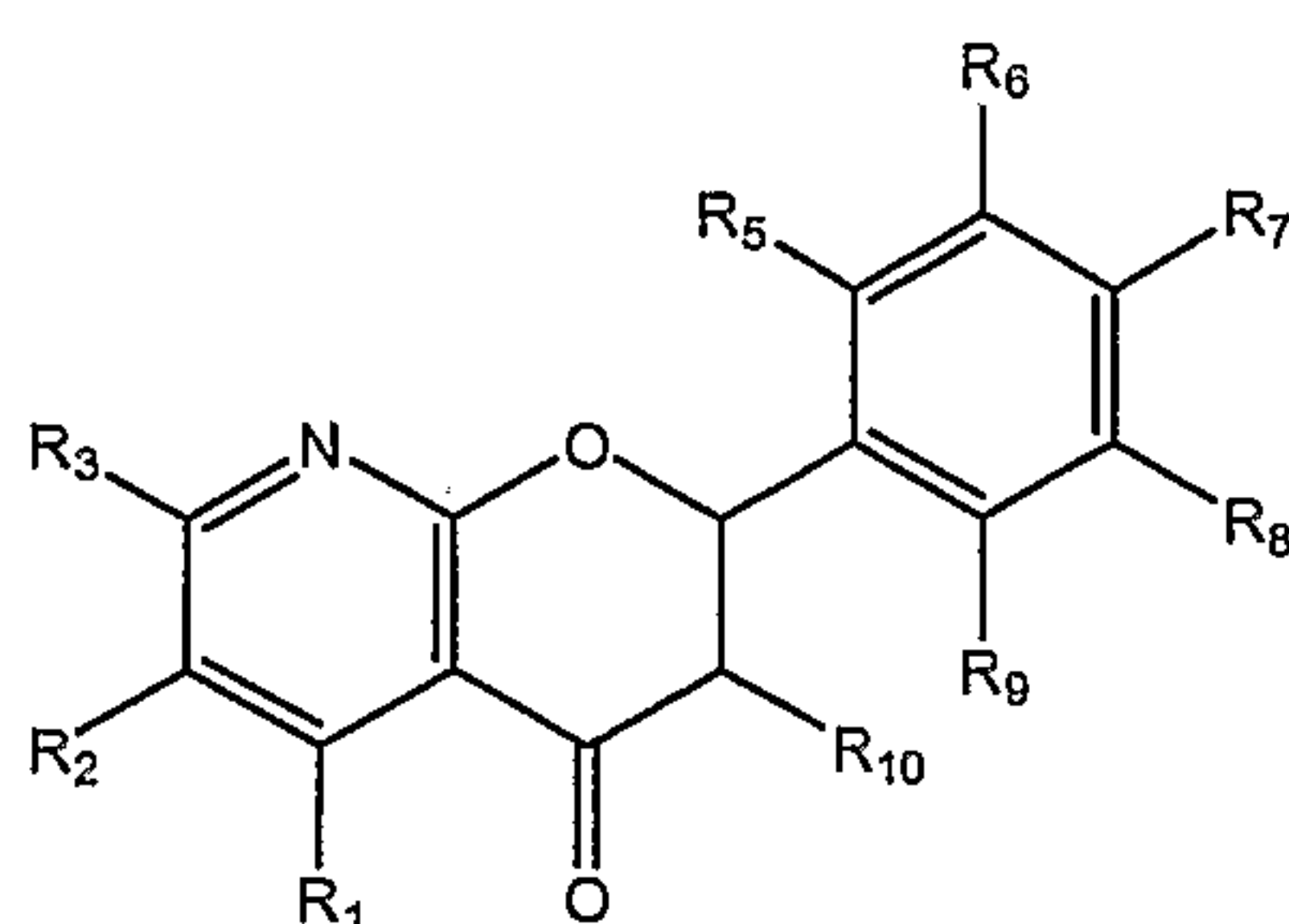
Formula IIIM



Formula IIIN



Formula IIIO



Formula III P.

118. The method of embodiment 1, wherein the compound of Formula I is selected from

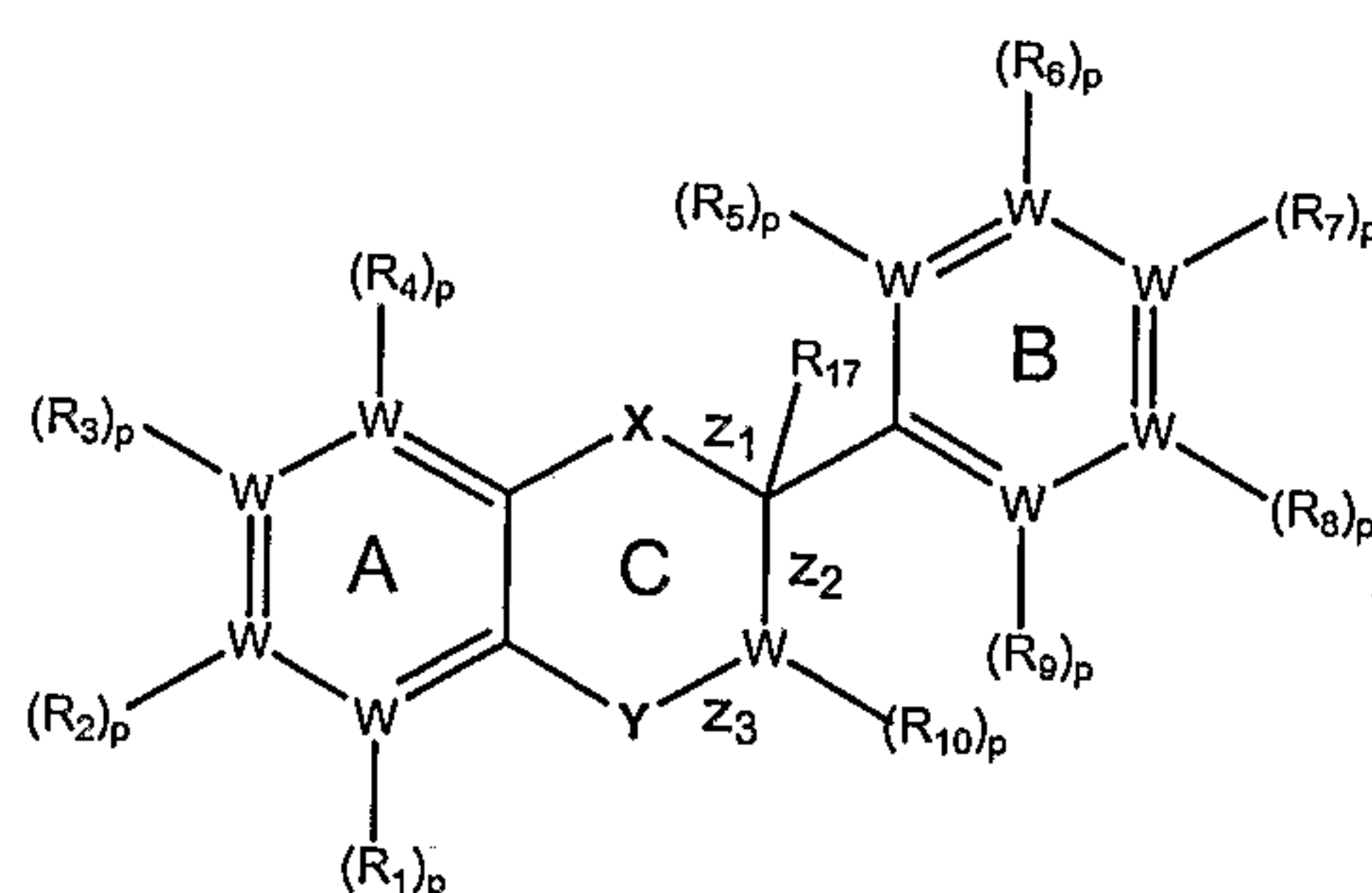
5,7-Difluoro-2-(4-methoxy-phenyl)-chromen-4-one,
 5,7-Difluoro-2-(4-hydroxy-phenyl)-chromen-4-one,
 2-(3,5-Difluoro-4-hydroxyphenyl)chromen-4-one,
 2-(4-Hydroxy-3,5-dimethylphenyl)chromen-4-one,
 2-(5-Methoxy-pyridin-2-yl)-chromen-4-one,
 2-(5-Hydroxy-pyridin-2-yl)-chromen-4-one,
 2-(6-Hydroxy-pyridin-3-yl)-chromen-4-one,
 2-Pyridin-4-yl-chromen-4-one,
 2-(4-Methoxy-phenyl)-thiochromen-4-one,
 2-(4-Hydroxy-phenyl)-thiochromen-4-one,
 2-(4-Hydroxyphenyl)-3-methyl-4H-chromen-4-one,
 4-(6-Bromo-4-oxo-4H-chromen-2-yl)-2-fluorophenyl acetate,
 1-(2-Nitro-4-methoxy-phenyl)-chromen-4-one,
 2-(4-Hydroxy-2-nitrophenyl)chromen-4-one,
 2-(2-Amino-4-methoxy-phenyl)-chromen-4-one,
 2-(2-Amino-4-hydroxy-phenyl)-chromen-4-one,
 N-[5-Hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]acetamide,
 6-Hydroxy-2-(4-hydroxymethylphenyl)chromen-4-one,
 2-(2-Fluoro-4-hydroxyphenyl)chromen-4-one,

2-(4-Hydroxyphenyl)-8-nitro-4H-chromen-4-one,
2-(4-Hydroxyphenyl)-8-methoxy-4H-chromen-4-one,
2-(4-Hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one,
2-(3-Bromo-4-hydroxyphenyl)-4H-chromen-4-one,
2-(4-Hydroxyphenyl)-4-oxo-4H-chromene-6-carbonitrile,
2-(4-Methoxy-phenyl)-chromen-4-one,
2-(3-Fluoro-4-hydroxyphenyl)chromen-4-one,
2-(4-Hydroxyphenyl)-4-oxo-4H-chromene-6-sulfonic acid,
6-Hydroxymethyl-2-(4-hydroxyphenyl)chromen-4-one,
6-((Dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one,
8-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one,
2-(4-Hydroxy-phenyl)-chromen-4-one,
7-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one,
5-Hydroxy-2-(4-hydroxy-phenyl)-chromen-4-one,
5,7-Dihydroxy-2-(4-hydroxy-phenyl)-chromen-4-one,
5,7-Dihydroxy-2-phenyl-chromen-4-one,
5-Hydroxy-2-phenyl-chromen-4-one,
2-(4-Acetoxy-phenyl)-thiochromen-4-one,
2-(4-Acetoxy-phenyl)-1,1-dioxo-1H-1 λ ⁶-thiochromen-4-one,
2-(4-Hydroxy-phenyl)-1,1-dioxo-1H-1 λ ⁶-thiochromen-4-one,
5,7-Dimethoxy-2-(4'-hydroxy-phenyl)-quinolin-4-one,
5,7-Dihydroxy-2-(4-hydroxy-phenyl)-quinolin-4-one,
2-(4-Hydroxy-phenyl)-1H-quinolin-4-one,
2-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one,
2-(4-Methoxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one,
2-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one,

2-(4-(2-Hydroxyethoxy)phenyl)-4H-pyrano[2,3-b]pyridine-4-one,
2-(3-Fluoro-4-hydroxyphenyl)pyrano[2,3-b]pyridine-4-one,
2-(4-Hydroxy-3-methylphenyl)-4H-pyrano[2,3-b]pyridine-4-one,
4-(4-Oxo-4H-pyrano[2,3-b]pyridine-2-yl)benzonitrile,
2-(3-Chloro-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one,
2-(3-Bromo-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one,
2-(4-Hydroxy-3-methoxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one,
2-(4-Hydroxy-phenyl)-pyrano[2,3-c]pyridine-4-one,
2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-c]pyridine 7-oxide,
2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-b]pyridine 8-oxide,
2-(4-Hydroxy-phenyl)-pyrano[3,2-c]pyridine-4-one,
2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[3,2-c]pyridine-6-oxide,
3-((Dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one,
2-(2-(4-Hydroxyphenyl)-4-oxo-4H-chromen-3-yl)acetonitrile,
3-(Hydroxymethyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one,
2-(4-Hydroxyphenyl)-3-(methoxymethyl)-4H-chromen-4-one,
3-(4-Hydroxyphenyl)-2H-isoquinolin-1-one,
7-(3-Fluoro-4-hydroxyphenyl)-6-methyl-1,6-naphthyridin-5(6H)-one,
3-(3-Fluoro-4-hydroxyphenyl)-5-methoxyisoquinolin-1(2H)-one,
2-Fluoro-4-(5-methoxy-1-(methylamino)isoquinolin-3-yl)phenol,
4-Naphthalen-2-yl-phenol,
6-Naphthalen-2-yl-pyridin-3-ol,
3-(4-Hydroxyphenyl)naphthalene-1-ol,
4-Isoquinolin-3-yl-phenol,
4-(1,6-Naphthyridin-7-yl)phenol,
2-(4-Hydroxy-phenyl)-[1,4]naphthoquinone,

4-(Benzo[b][1,4]dioxin-2-yl)phenyl acetate,
 4-(Benzo[b][1,4]dioxin-2-yl)phenol,
 4-(4H-Chromen-2-yl)-phenol,
 2-(4-Hydroxyphenyl)benzo[e][1,3]oxazin-4-one,
 6-Naphthalen-2-yl-pyridin-3-ol,
 2-(4-Ethoxycarbonyloxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester,
 nicotinic acid 4-(4-oxo-4H-chromen-2-yl)-phenyl ester,
 Acetic acid 4-(4-oxo-4H-chromen-2-yl)-phenyl ester,
 4-(4-Oxo-4H-pyrano[2,3-b]pyridine-2-yl)phenyl acetate,
 2-Amino-5-guanidino-pentanoic acid 4-(4-oxo-4H-chromen-2-yl)phenyl ester,
 4-(Isoquinolin-3-yl)phenyl 2-amino-5-guanidinopentanoate,
 4-(1-Oxo-1,2-dihydroisoquinolin-3-yl)phenyl 2-amino-5-guanidinopentanoate,
 2-(4-(Nicotinoyloxy)phenyl)-4-oxochroman-5,7-diyl dinicotinate, and
 2-(4-(Nicotinoyloxy)phenyl)-4-oxo-4H-chromene-5,7-diyl dinicotinate.

119. A method of treating or preventing cardiovascular, cholesterol or lipid related disorders comprising administering a therapeutically effective amount of a compound of Formula I:



Formula I

wherein:

X is selected from CR₁₁, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, N and NR₁₁,

wherein R₁₁ may be the same or different than R₁₃;

Y is selected from CR_{12} , $CR_{12}R_{14}$, CO, CS, O, S, SO, SO_2 , N and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, the Z_1 is a single bond;

wherein if X is O and Z_2 is a single bond, then R_{10} is not hydroxyl or ester; and pharmaceutically acceptable salts and hydrates thereof.

120. The method of embodiment 119, wherein the cardiovascular, cholesterol or lipid related disorder is selected from

acute coronary syndrome, angina pectoris, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia,

familial combined hyperlipidemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, multi-infarct dementia, myocardial infarction, peripheral vascular disease, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X and impotence.

121. The method of embodiment 118, wherein treating or preventing a cholesterol disorder comprises decreasing blood cholesterol levels.

122. The method of embodiment 118, wherein treating or preventing a cholesterol disorder comprises increasing blood ApoA-I levels.

123. The method of embodiment 118, wherein the therapeutically effective amount of the compound of Formula I is administered with a pharmaceutically acceptable carrier in a pharmaceutically acceptable composition.

124. The method of embodiment 118, wherein the therapeutically effective amount of the compound of Formula I is sufficient to establish a concentration ranging from about 0.001 μM to about 100 μM in the mammal.

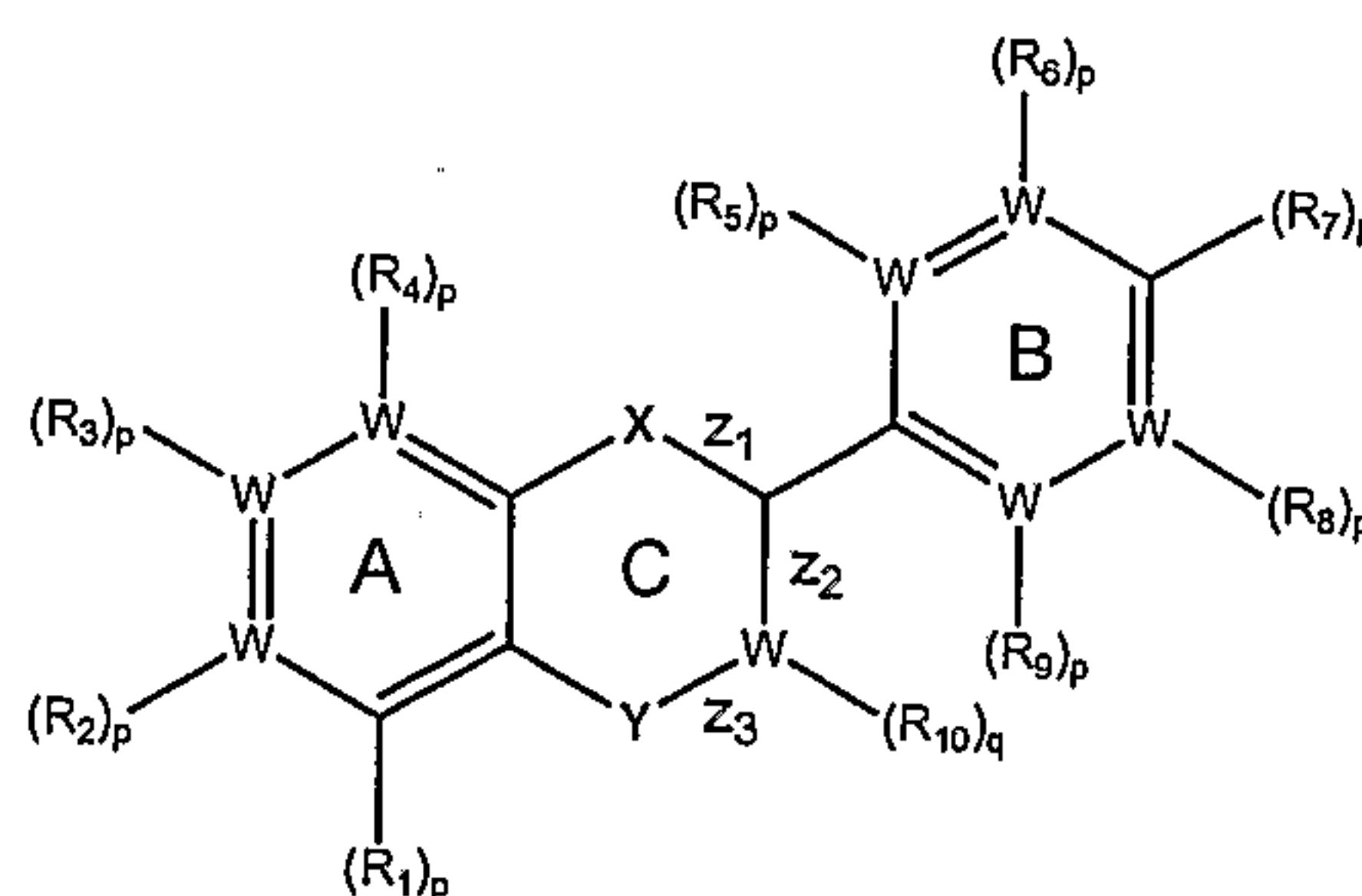
125. The method of embodiment 124, wherein the concentration ranges from about 1 μM to about 20 μM .

126. The method of embodiment 118, wherein the compound of Formula I is 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one.

127. The method of embodiment 118, wherein the compound is 3-(4-hydroxyphenyl)-2H-isoquinolin-1-one.

128. The method of embodiment 118, wherein the compound is 4-isoquinolin-3-yl-phenol.

129. A compound of Formula I:



Formula I

wherein

X is selected from CR_{11} , $CR_{11}R_{13}$, CO, O, N and NR_{11} , wherein R_{11} may be the same or different than R_{13} ;

Y is selected from CR_{12} , $CR_{12}R_{14}$, CO, O, N and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{17} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , and R_{14} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

at least one W is N;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if X is O and Z_2 is a single bond, then R_{10} is not hydroxyl or ester;

wherein if

a W in the C ring is selected from N and NR_{10} ,

Z_1 is a double bond, and

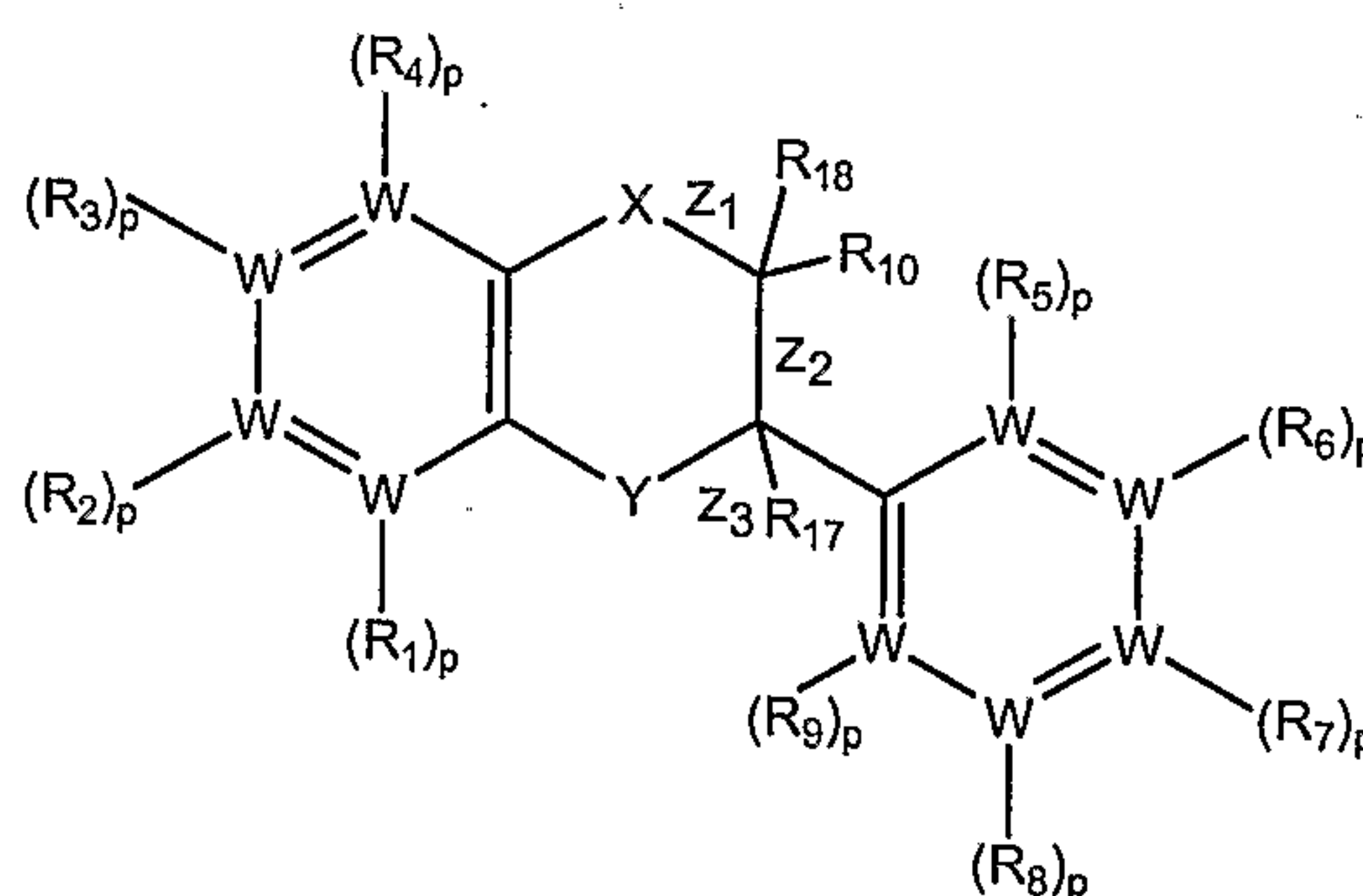
R_5 , R_6 , R_8 , and R_9 are each hydrogen,

then R_7 is not hydroxyl or alkoxy;

and pharmaceutically acceptable salts or hydrates thereof.

130. The compound of embodiment 129, wherein R_7 is hydroxyl.
131. The compound of embodiment 129, wherein at least one W in the A ring is N.
132. The compound of embodiment 131, wherein X is O, Y is CO and Z_2 is a double bond.
133. The compound of embodiment 132, wherein R_5 , R_6 , R_8 , R_9 and R_{10} are each hydrogen.
134. The compound of embodiment 129, wherein at least one W in the B ring is N.
135. The compound of embodiment 129, wherein the W in the C ring is selected from N and NR_{10} , where R_{10} is selected from hydrogen and methyl.
136. The compound of embodiment 135, wherein Z_1 is a double bond.
137. The compound of embodiment 136, wherein Z_3 is a double bond and the W in the A ring is N.
138. The compound of embodiment 135, wherein R_8 is halogen.
139. The compound of embodiment 129, wherein at least one of R_1 , R_2 , R_3 and R_4 is alkoxy.
140. The compound of embodiment 129, wherein Y is CR_{12} and R_{12} is amino.

141. A pharmaceutical composition comprising a compound of embodiment 129 and a pharmaceutically acceptable carrier.
142. A method of increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of embodiment 129.
143. A method of treating or preventing cardiovascular, cholesterol or lipid related disorders comprising administering a therapeutically effective amount of a compound of embodiment 129.
144. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

wherein:

X is selected from CR₁₁, CR₁₁R₁₃, CO, CS, O, S, SO, SO₂, N and NR₁₁, wherein R₁₁ may be the same or different than R₁₃;

Y is selected from CR₁₂, CR₁₂R₁₄, CO, CS, O, S, SO, SO₂, N and NR₁₂, wherein R₁₂ may be the same or different than R₁₄;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₇ and R₁₈ are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl,

halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or

two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{18} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, then X is not CO;

wherein if X is O, Y is CO and Z_2 is a double bond, then at least one of R_5 , R_6 , R_8 and R_9 is not hydrogen;

and pharmaceutically acceptable salts and hydrates thereof.

145. The method of embodiment 14, wherein X is O and Y is CO.

146. The method of embodiment 14, wherein at least one W is N.

147. The method of embodiment 146, wherein X is O and Y is CO.

148. The method of embodiment 146, wherein at least one W in the A ring of Formula IV is N.

149. The method of embodiment 14, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate and O-glucoronidate, subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

150. The method of embodiment 149, wherein X is O and Y is CO.
151. The method of embodiment 149, wherein at least one W is N.
152. The method of embodiment 151, wherein X is O and Y is CO.
153. The method of embodiment 14, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.
154. The method of embodiment 153, wherein X is O and Y is CO.
155. The method of embodiment 153, wherein at least one W is N.
156. The method of embodiment 155, wherein X is O and Y is CO.
157. The method of embodiment 153, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from
 arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate and O-glucoronidate, subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.
158. The method of embodiment 157, wherein X is O and Y is CO.
159. The method of embodiment 157, wherein at least one W is N.
160. The method of embodiment 159, wherein X is O and Y is CO.
161. The method of embodiment 14, wherein
 X is selected from CR_{11} , $CR_{11}R_{13}$, CO, CS, and O; and
 Y is selected from CR_{12} , $CR_{12}R_{14}$, S, SO, SO_2 , and NR_{12} .
162. The method of embodiment 161, wherein at least one W is N.
163. The method of embodiment 161, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate and O-glucoronidate, subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

164. The method of embodiment 163, wherein at least one W is N.

165. The method of embodiment 161, wherein Z_1 and Z_3 are single bonds, and Z_2 is a double bond.

166. The method of embodiment 165, wherein at least one W is N.

167. The method of embodiment 165, wherein R_7 is hydroxyl, and R_6 and R_8 are independently selected from

arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate and O-glucoronidate, subject to the proviso that R_6 and R_8 are not both simultaneously hydrogen.

168. The method of embodiment 167, wherein at least one W is N.

169. The method of embodiment 14, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} is selected from O-sulfate and O-glucoronidate.

170. The method of embodiment 14, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} is selected from succinate, D-argininate, L-argininate, L-lysinate and D-lysinate.

171. The method of embodiment 14, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} is selected from amide, amino, carbamate, carboxy, ester, ether, formyl, and ketone.

172. The method of embodiment 171, wherein at least one of R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} is a nicotinate ester.

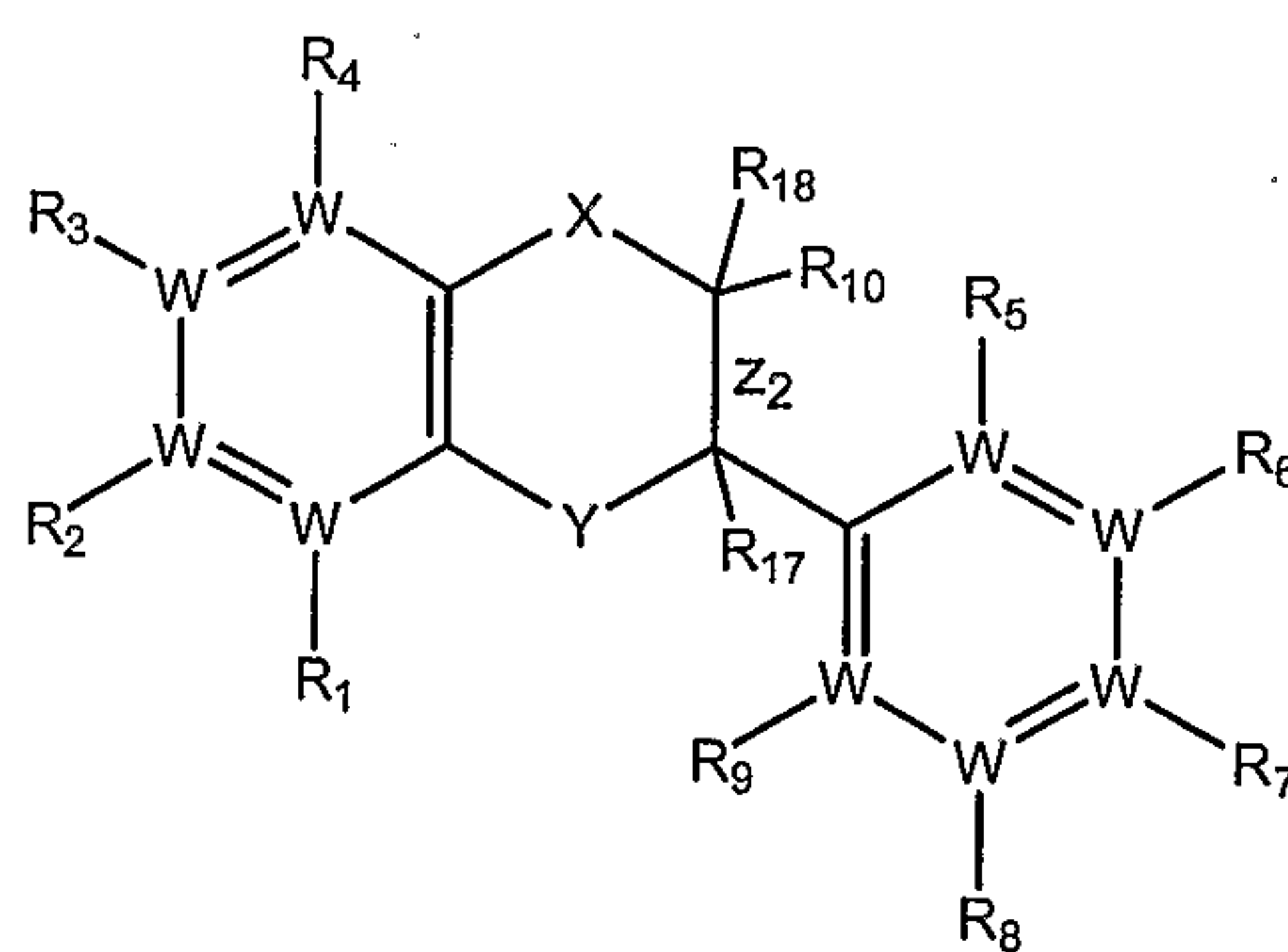
173. The method of embodiment 14, wherein the therapeutically effective amount of the compound of Formula I is administered with a pharmaceutically acceptable carrier in a pharmaceutically acceptable composition.

174. The method of embodiment 14, wherein the therapeutically effective amount of the compound of Formula IV is sufficient to establish a concentration ranging from about 0.001 μM to about 100 μM in the mammal.

175. The method of embodiment 16, wherein the concentration ranges from about 1 μM to about 20 μM .

176. The method of embodiment 14, wherein the compound of Formula IV is 3-(4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one.

177. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula V:



Formula V

wherein

X is selected from CH_2 , CHR_{11} , CHR_{13} , $\text{CR}_{11}\text{R}_{13}$, CO , CS , O , S , SO , SO_2 , NH and NR_{11} , wherein R_{11} may be the same or different than R_{13} ;

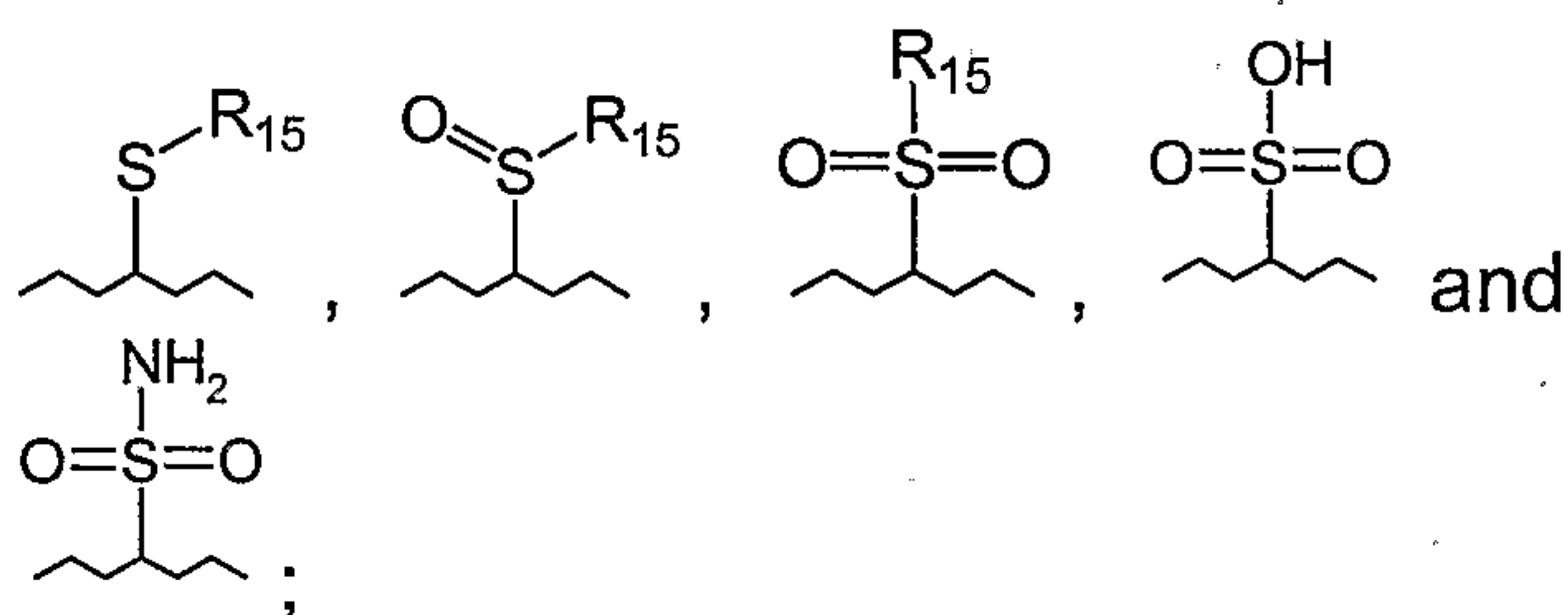
Y is selected from CH_2 , CHR_{12} , CHR_{14} , $\text{CR}_{12}\text{R}_{14}$, CO , CS , O , S , SO , SO_2 , NH and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} are each independently selected from $(\text{C}_1\text{-C}_{22})$ alkyl, $(\text{C}_2\text{-C}_{22})$ alkenyl, $(\text{C}_2\text{-C}_{22})$ alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, thioketone, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, amide, carbamate, halogen, CF_3 , CCl_3 , sulfonic acid, phosphate, O-sulfate, O-glucoronidate, monoester, dicarboxylic acid, J, K, L, M, P and Q;

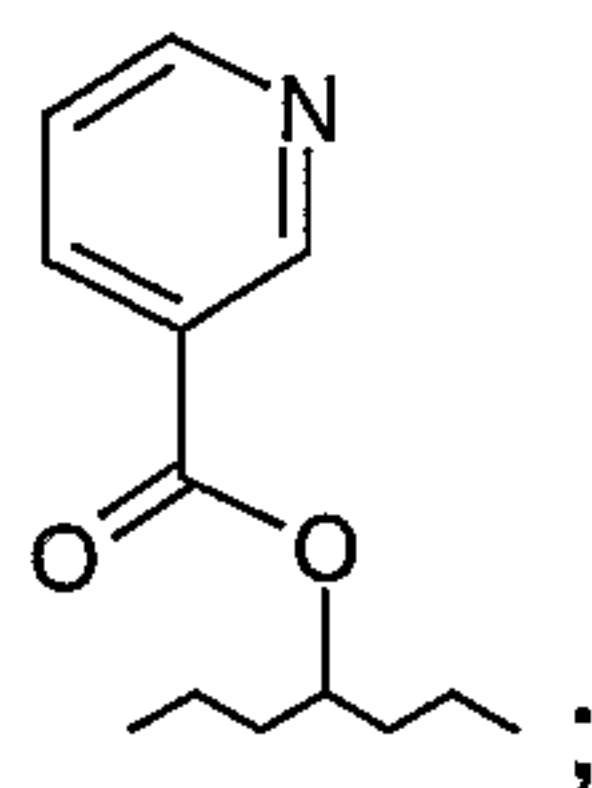
each W is independently selected from C and N;

Z_2 is selected from a single bond and a double bond;

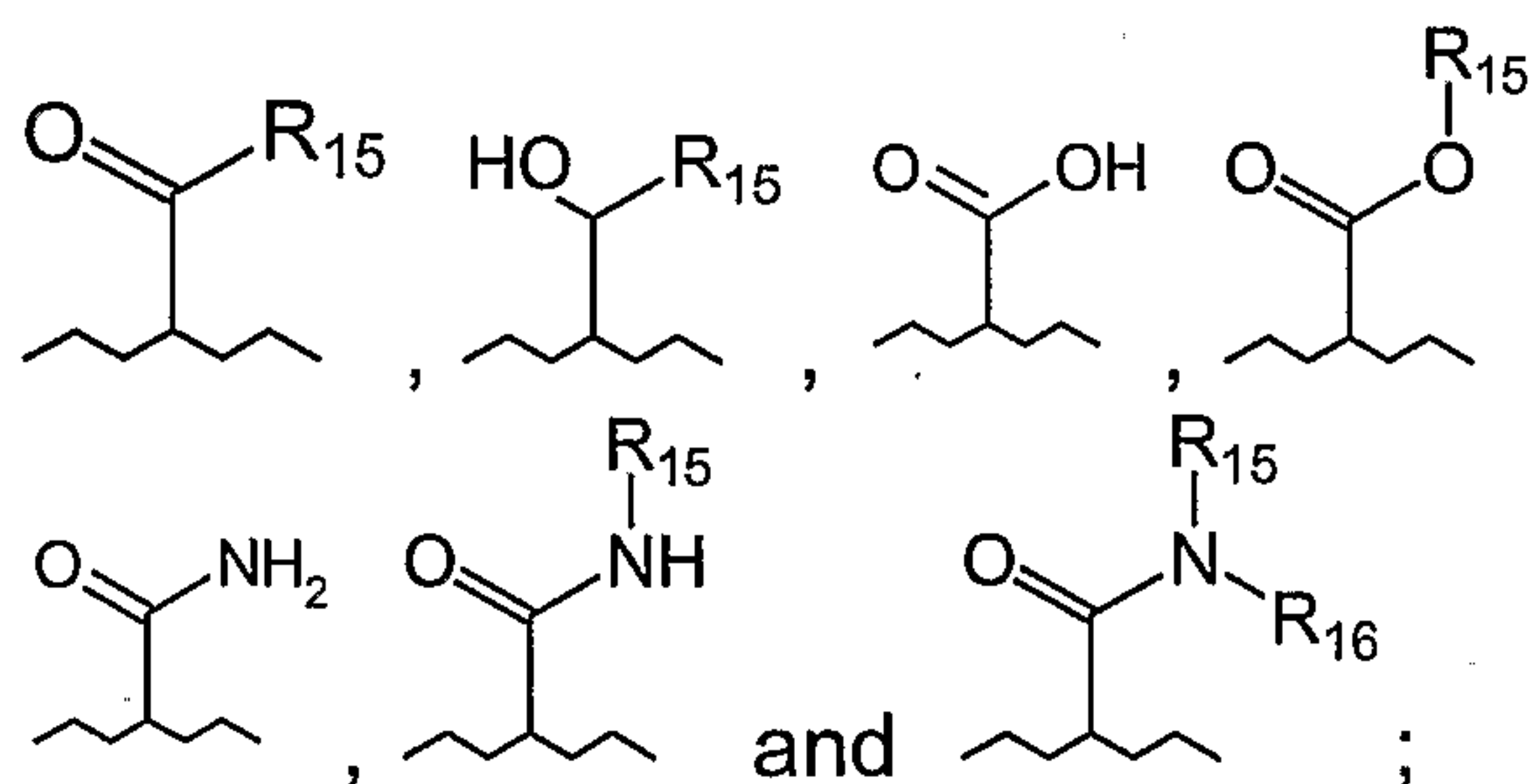
J is selected from



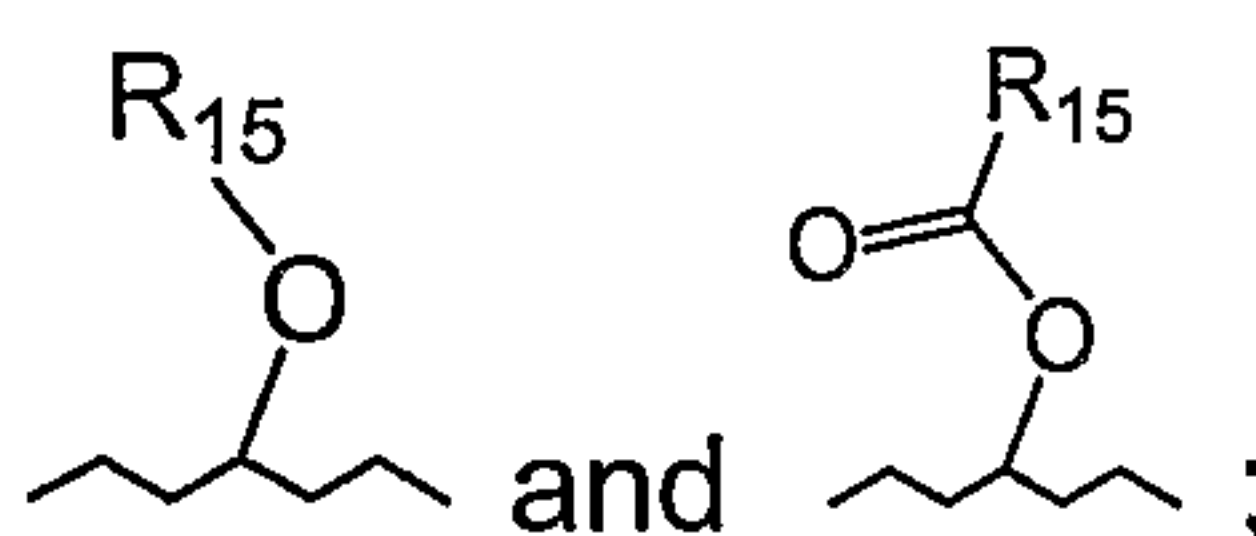
K is



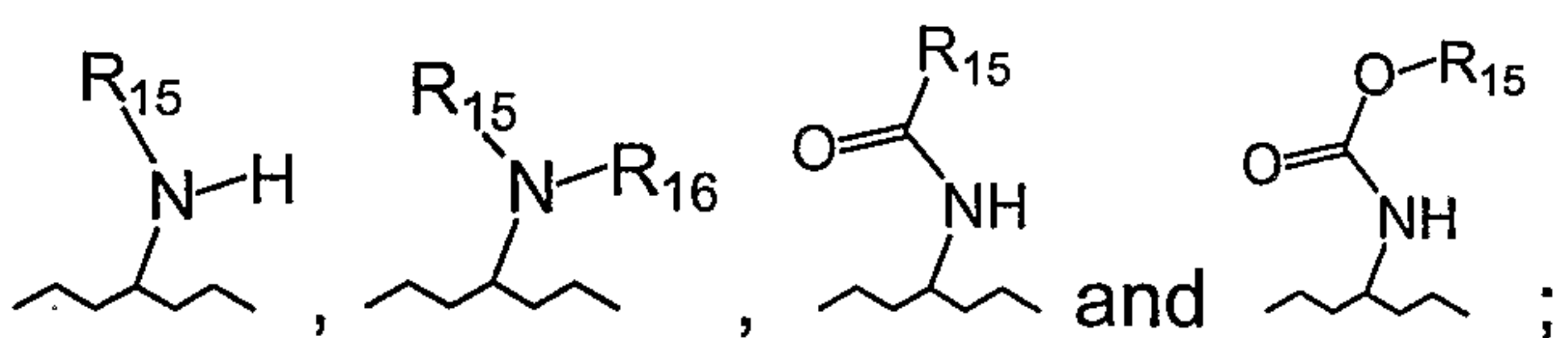
L is selected from



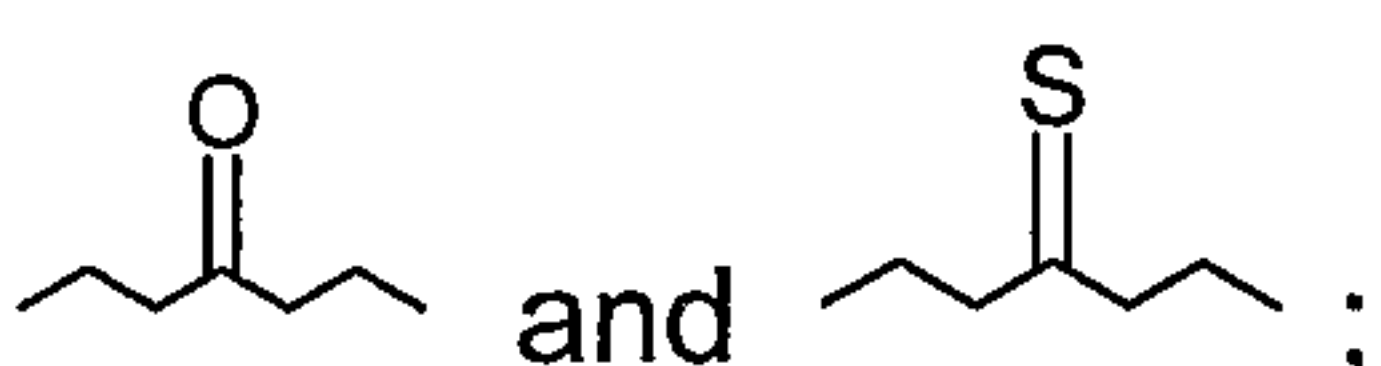
M is selected from



P is selected from



Q is selected from



R_{15} and R_{16} are each independently selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, (C_2-C_{22}) alkynyl, aryl, heteroaryl, alkoxy, aryloxy, benzyl, phenyl, carbonyl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, amide, carbamate, halogen, CF_3 , CCl_3 , sulfonic acid and phosphate;

and pharmaceutically acceptable salts thereof;

subject to at least one proviso selected from:

- 1) R_7 is hydroxyl;
- 2) at least one W is N;
- 3) at least one of R_1-R_{10} is selected from L, M and P;
- 4) at least one of R_1-R_{10} is selected from K;
- 5) R_7 is K;
- 6) one of R_1-R_{10} is a monoester;
- 7) one of R_1-R_{10} is a dicarboxylic acid;
- 8) one of R_1-R_{10} is succinic acid;
- 9) R_7 and R_2 are each hydroxyl; and
- 10) R_7 is selected from J.

178. The method of embodiment 177, wherein if proviso 1 is selected, a second proviso is selected from provisos 2-4 and 6-9.

179. The method of embodiment 177, wherein R_7 is hydroxyl and at least one W is N.

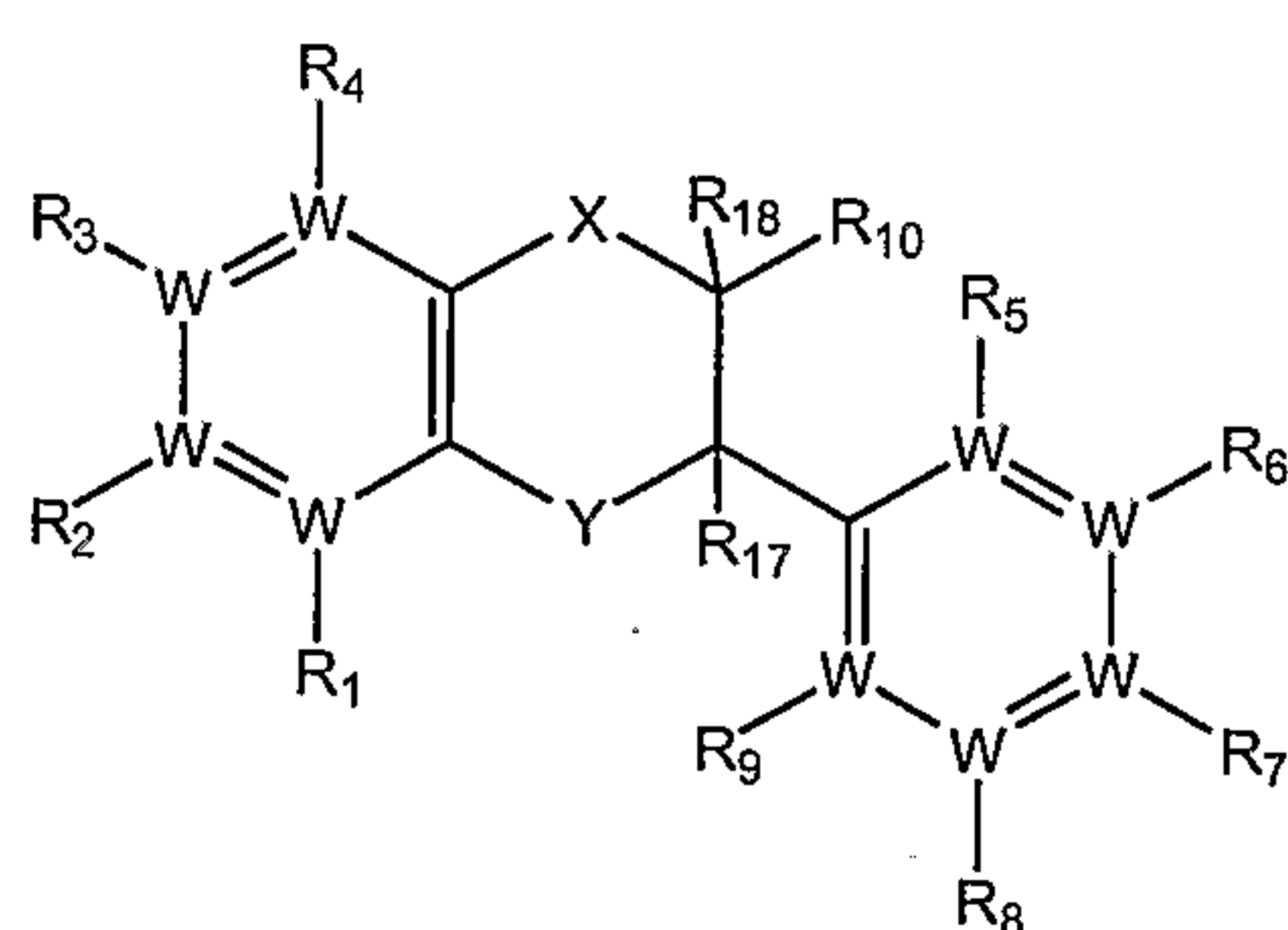
180. The method of embodiment 177, wherein R_7 is hydroxyl and at least one of R_1 - R_6 and R_8 - R_{10} is K.

181. The method of embodiment 177, wherein R_7 is hydroxyl and at least one of R_1 - R_6 and R_8 - R_{10} is selected from L, M and P.

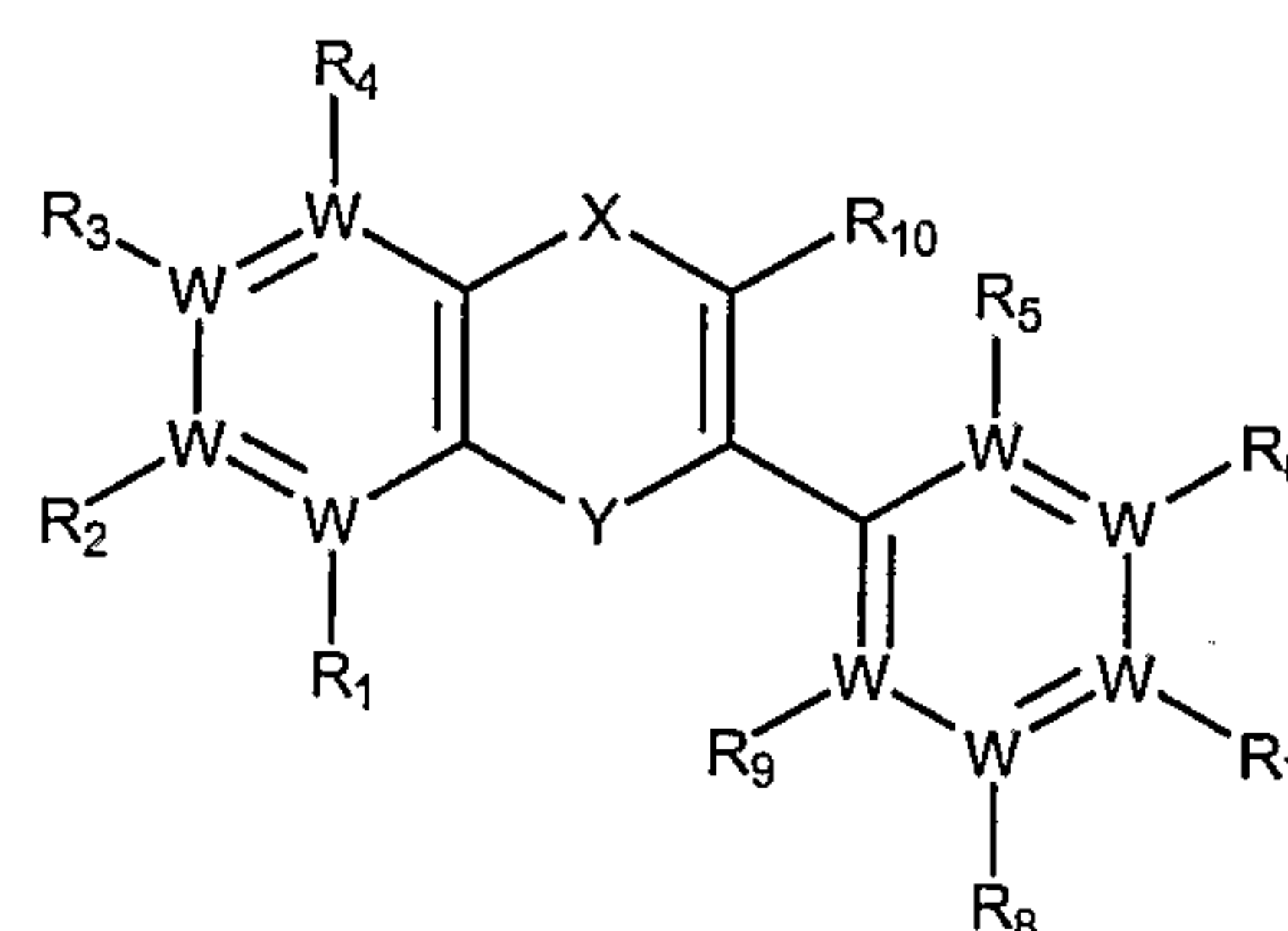
182. The method of embodiment 177, wherein R_7 is K and at least one W is N.

183. The method of embodiment 177, wherein Y is selected from CH_2 , CHR_{12} , CHR_{14} , $CR_{12}R_{14}$, CO, CS, S, SO, SO_2 , NH and NR_{12} , wherein R_{12} may be the same or different than R_{14} .

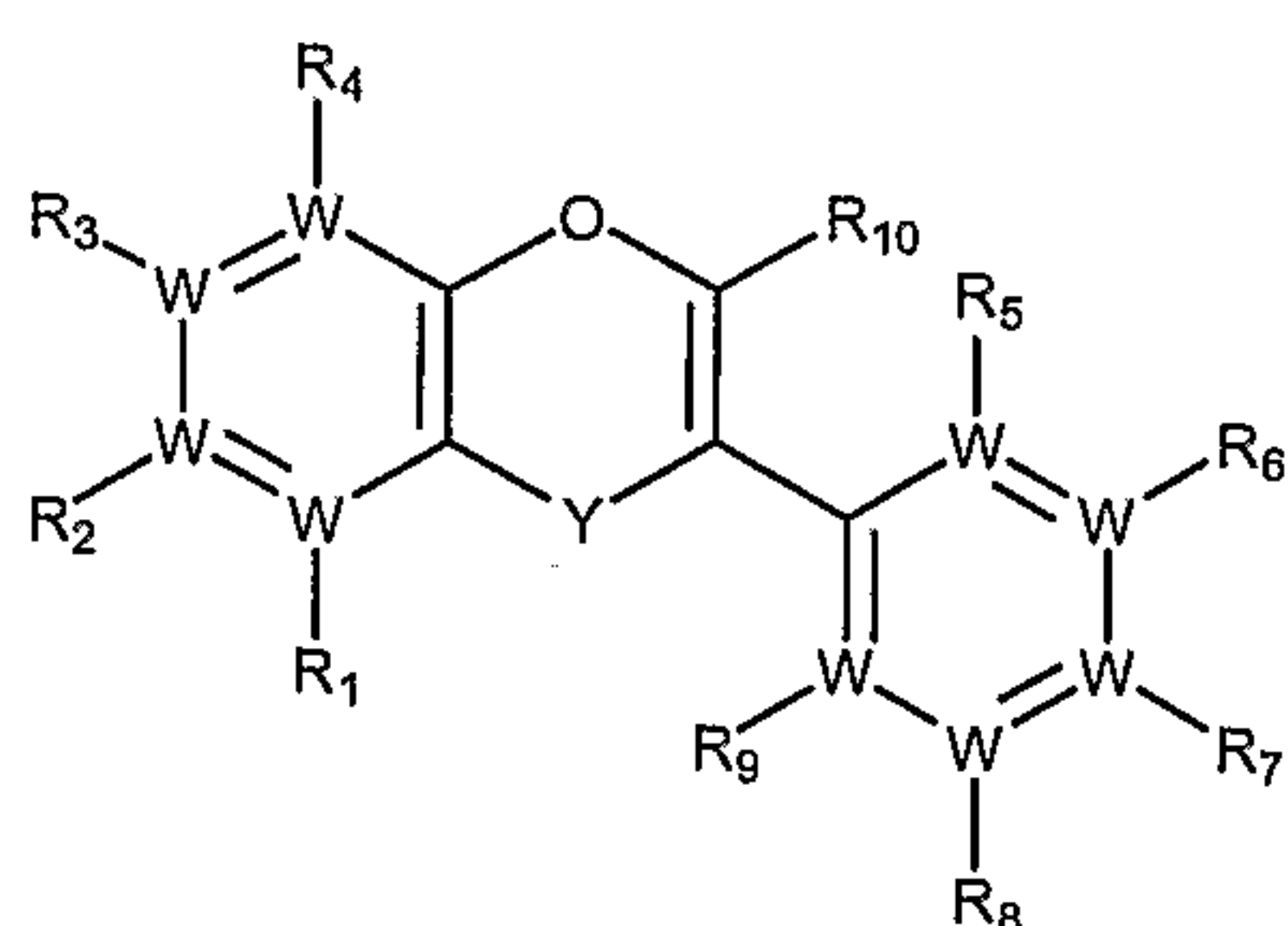
184. The method of embodiment 177, wherein Formula V is selected from Formulae VA to VK:



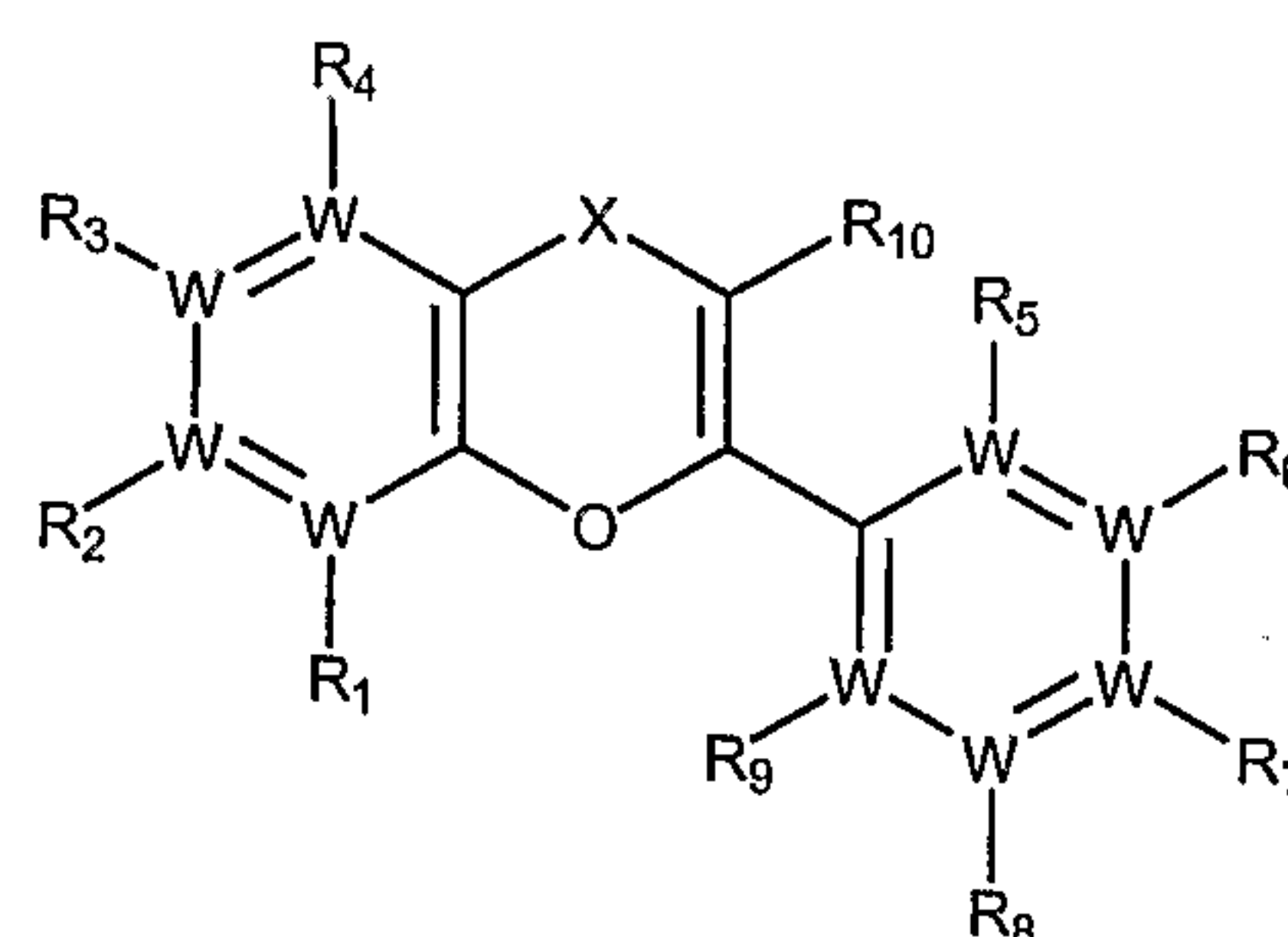
Formula VA



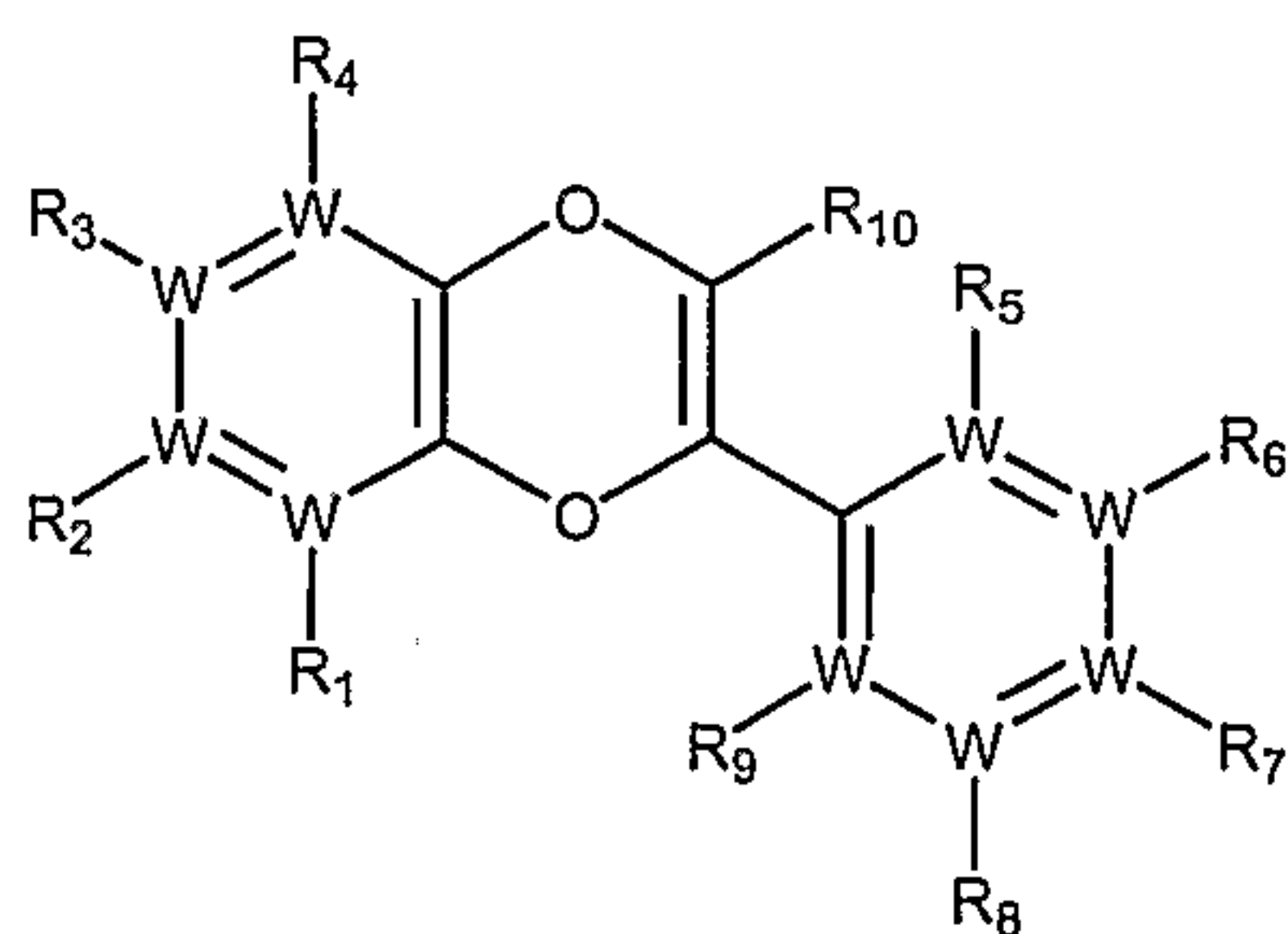
Formula VB



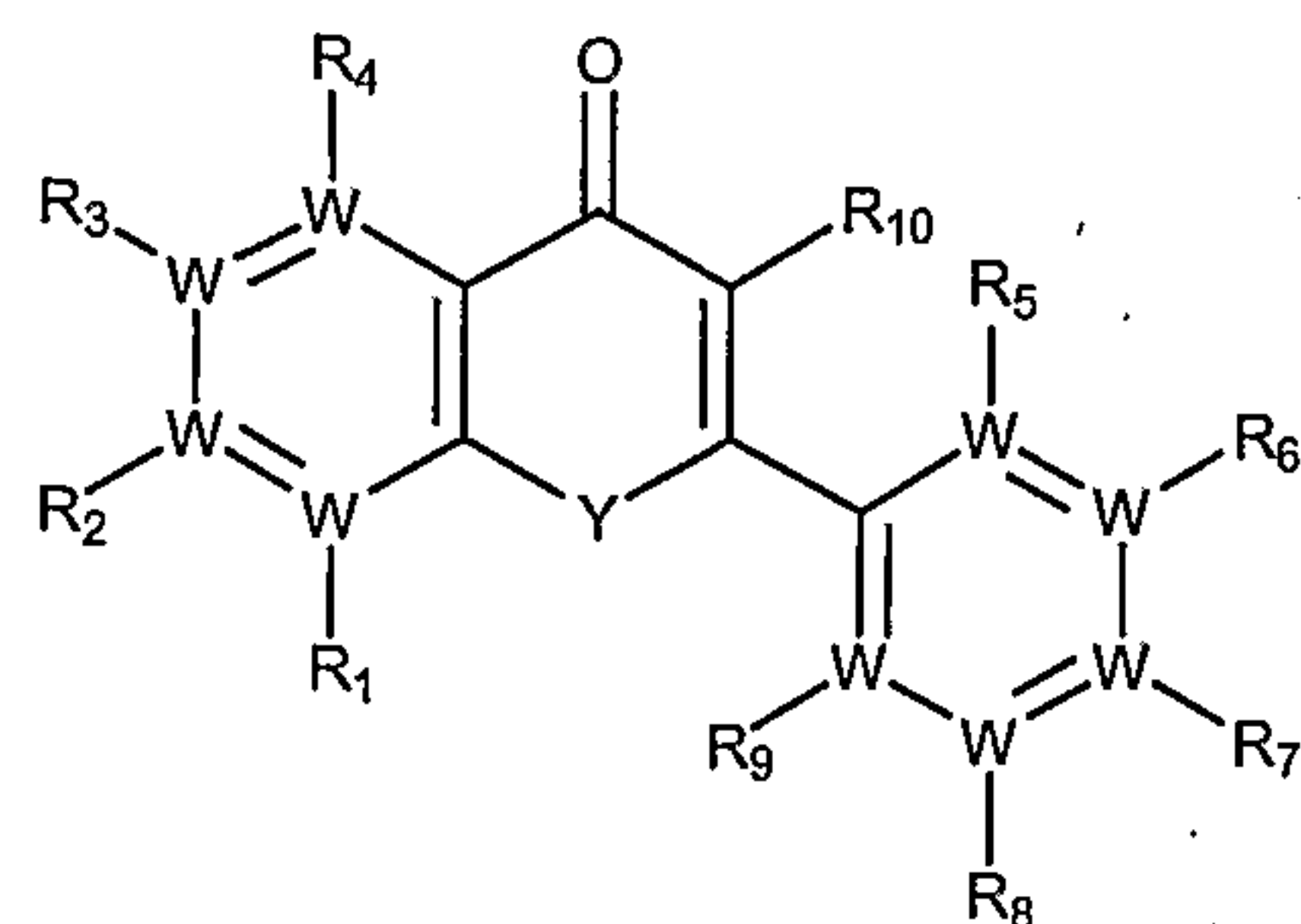
Formula VC



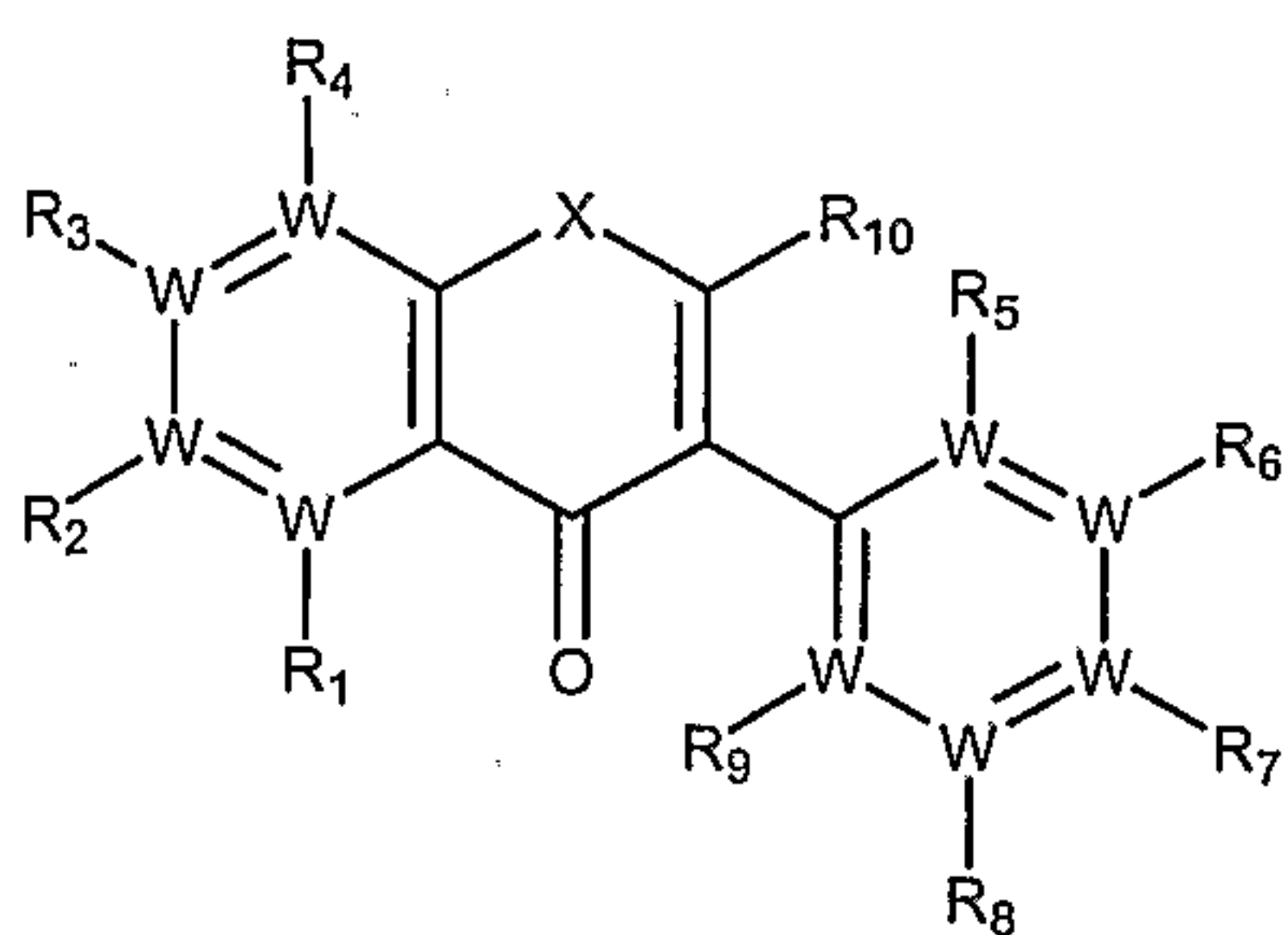
Formula VD



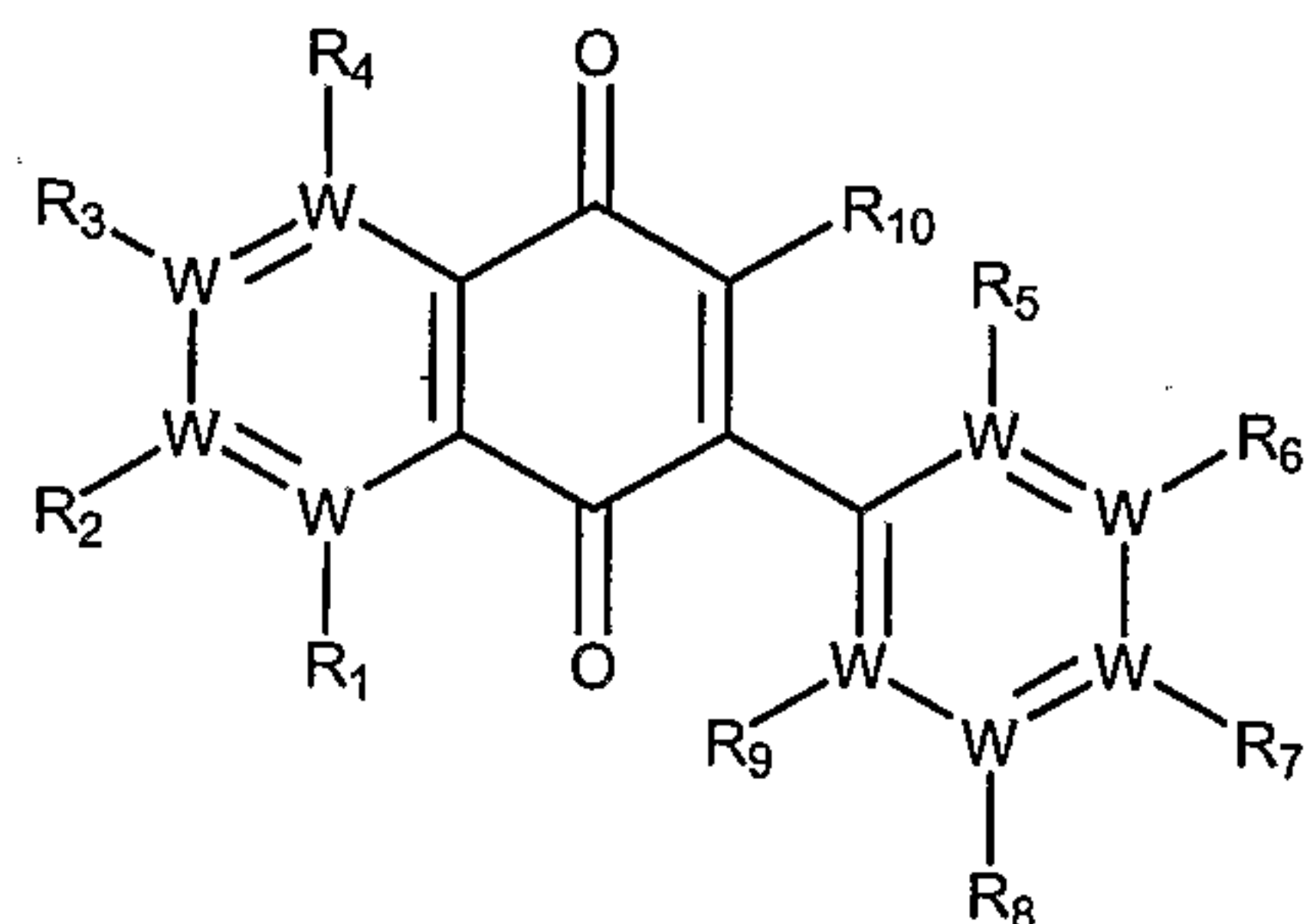
Formula VE



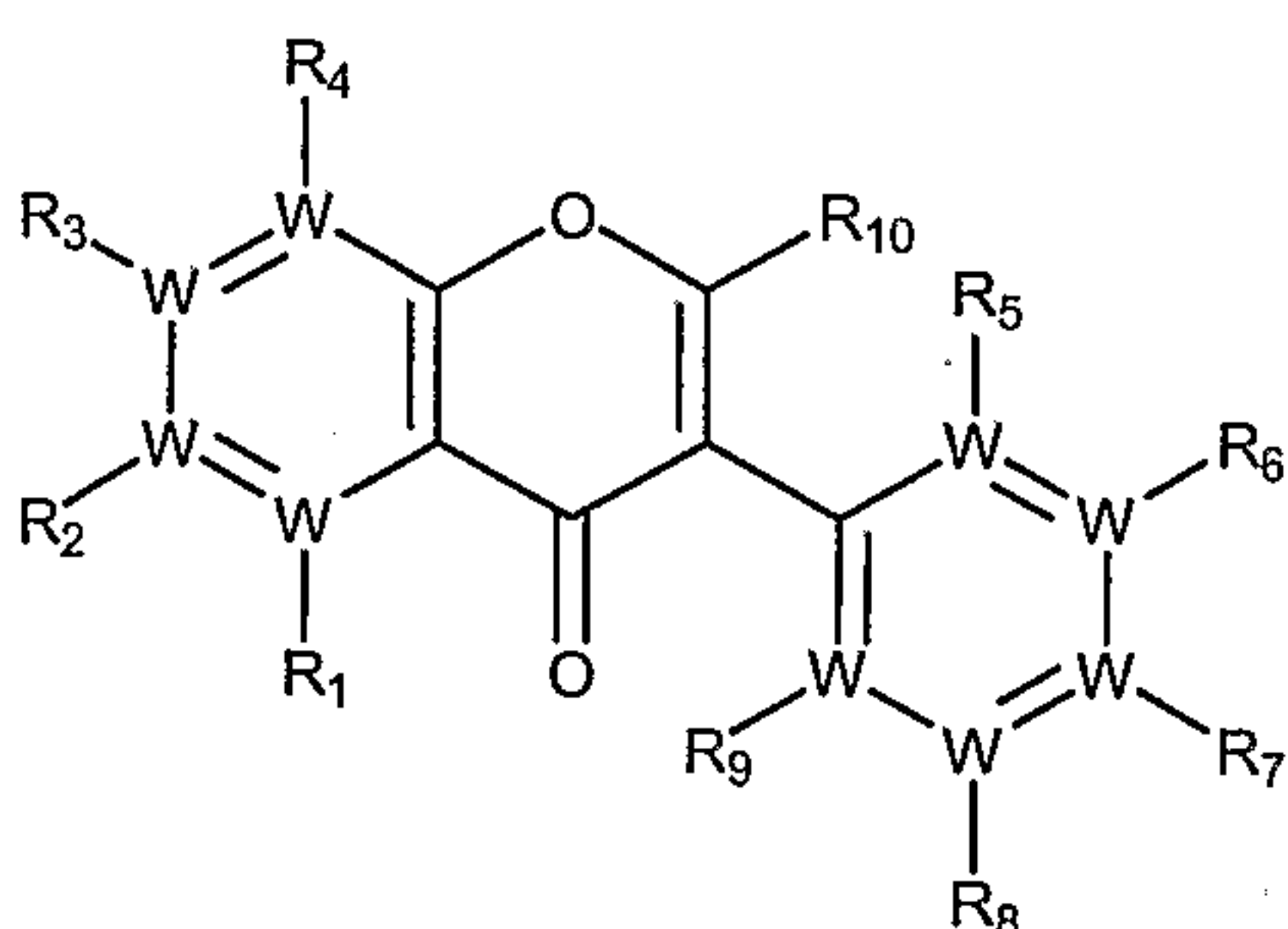
Formula VF



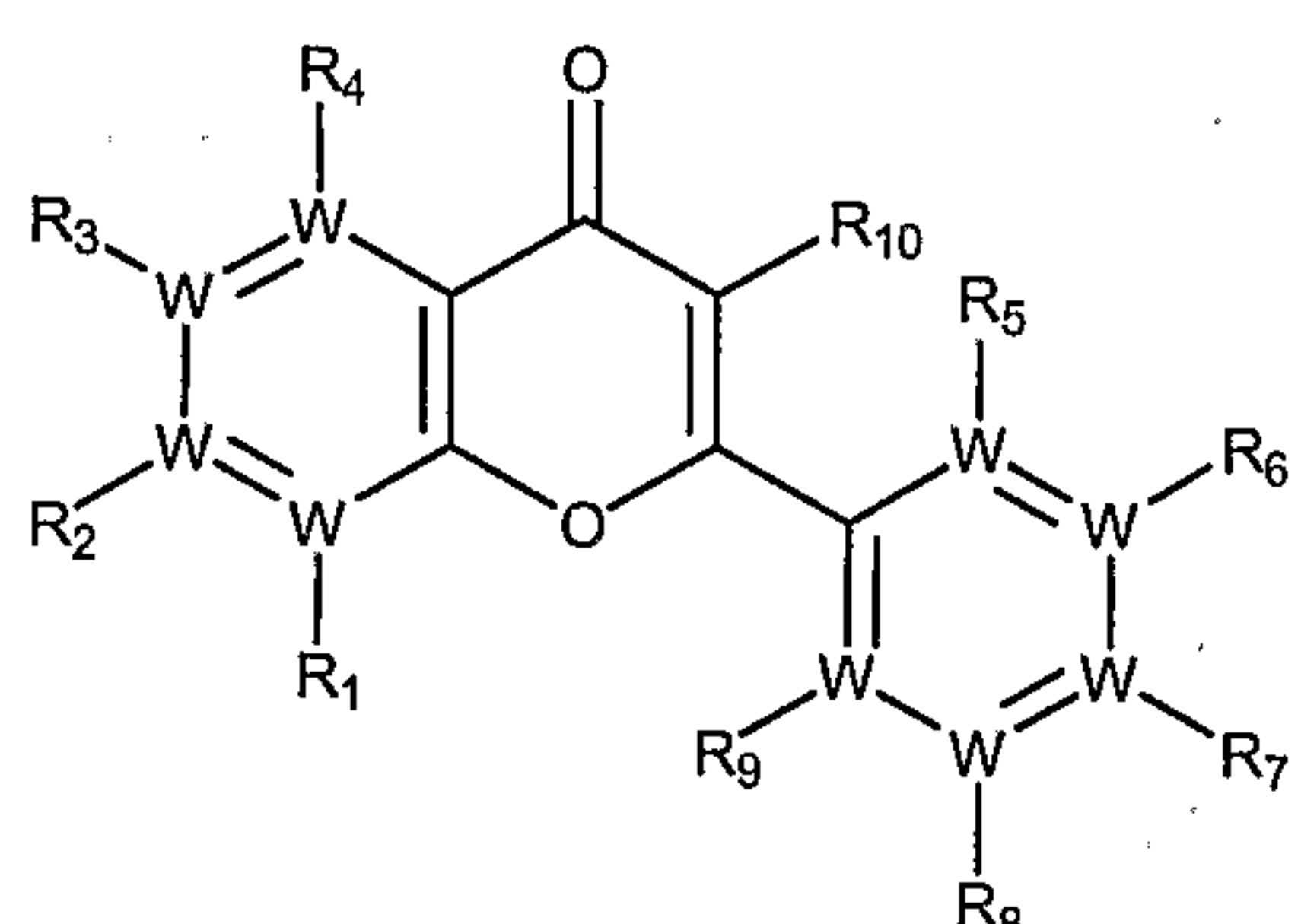
Formula VG



Formula VH

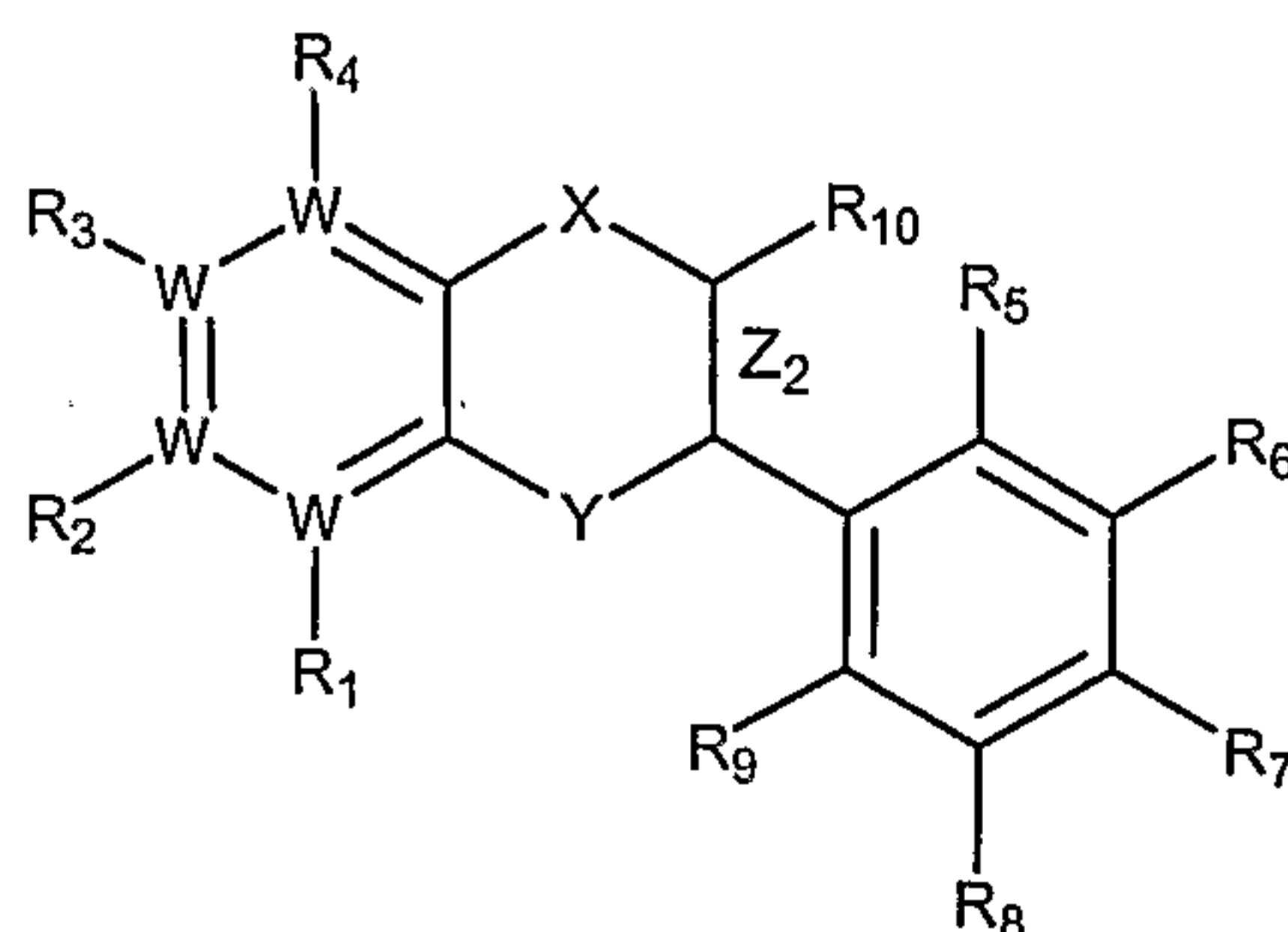


Formula VJ



Formula VK.

185. A method for increasing expression of ApoA-I in a mammal comprising administering a therapeutically effective amount of a compound of Formula VI:



Formula VI

wherein:

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_8 , R_9 , and R_{10} are independently selected from (C_1 - C_{22})alkyl, (C_2 - C_{22})alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF_3 , CCl_3 , phosphate, O-sulfate, O-glucoronidate, K, D, E, F, and G;

R_7 is selected from hydroxyl and K;

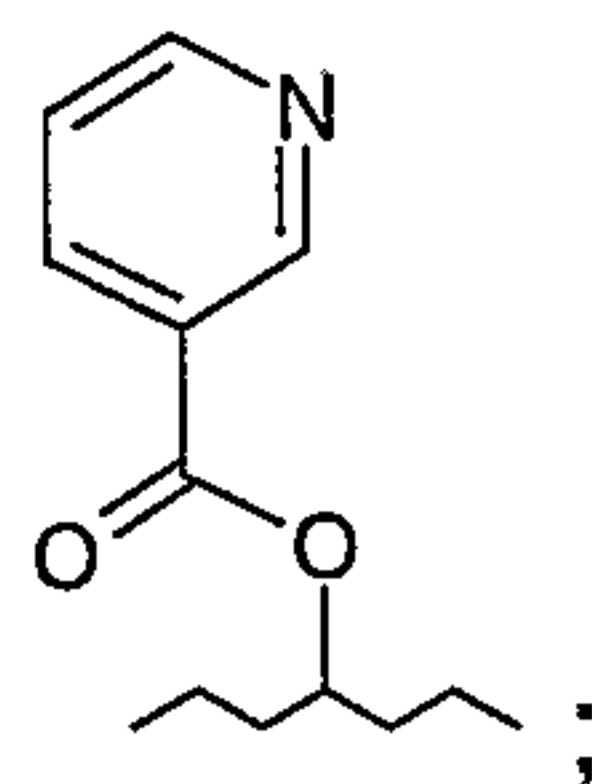
each W is independently selected from C and N;

X is selected from O, S, C, CR_{11} and NR_{11} ;

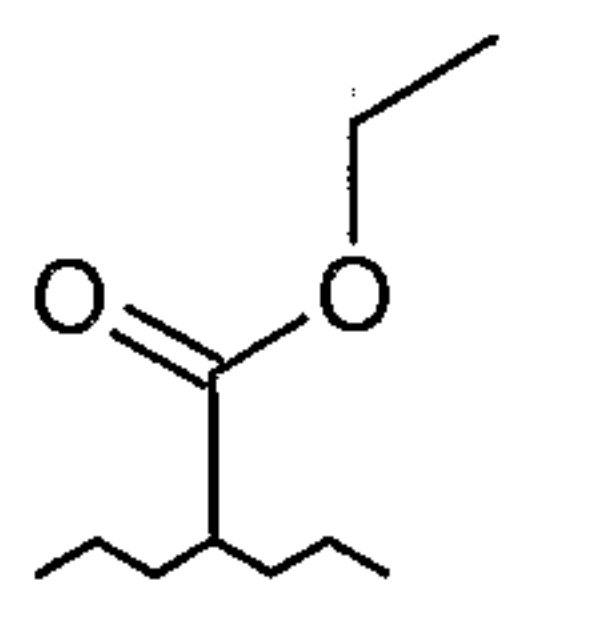
Y is selected from O, S, C, CR_{12} and NR_{12} ;

R_{11} and R_{12} are each independently selected from D, E, F, and G;

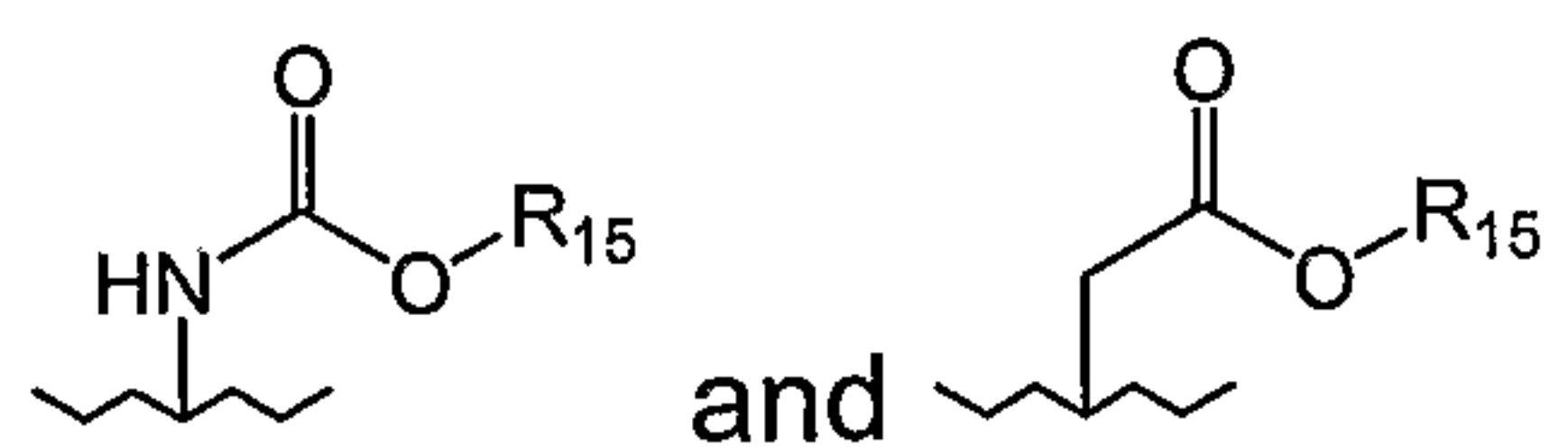
K is



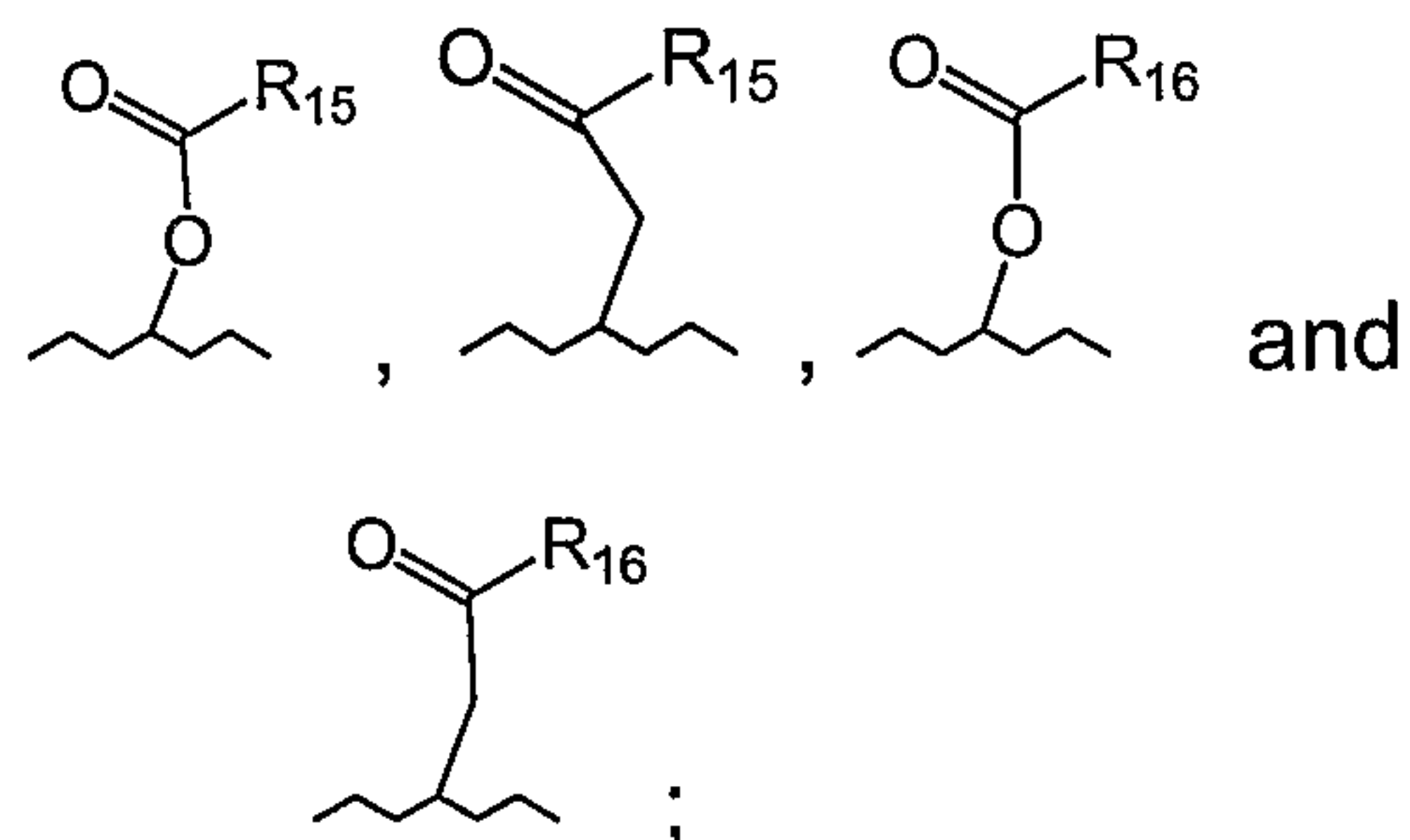
D is



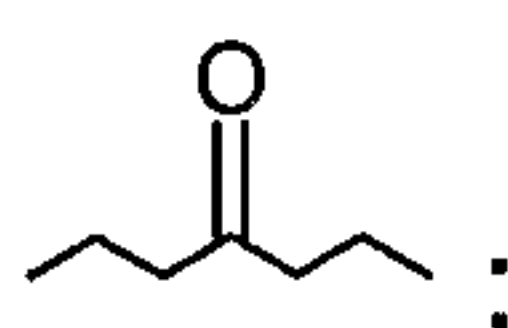
E is selected from



F is selected from



G is



R_{15} is selected from pyridine, pyridazine, pyrimidine, and pyrazine;

R_{16} is selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, aryl and heteroaryl;
and pharmaceutically acceptable salts thereof;

subject to at least one proviso selected from

- 1) at least one W is N;
- 2) at least one of R_{1-6} and R_{8-10} is selected from D, E and F; and
- 3) at least one of R_{1-6} and R_{8-10} is selected from K.

186. The method of embodiment 185, wherein R_7 is hydroxyl and at least one of R_{1-6} and R_{8-10} is selected from K.

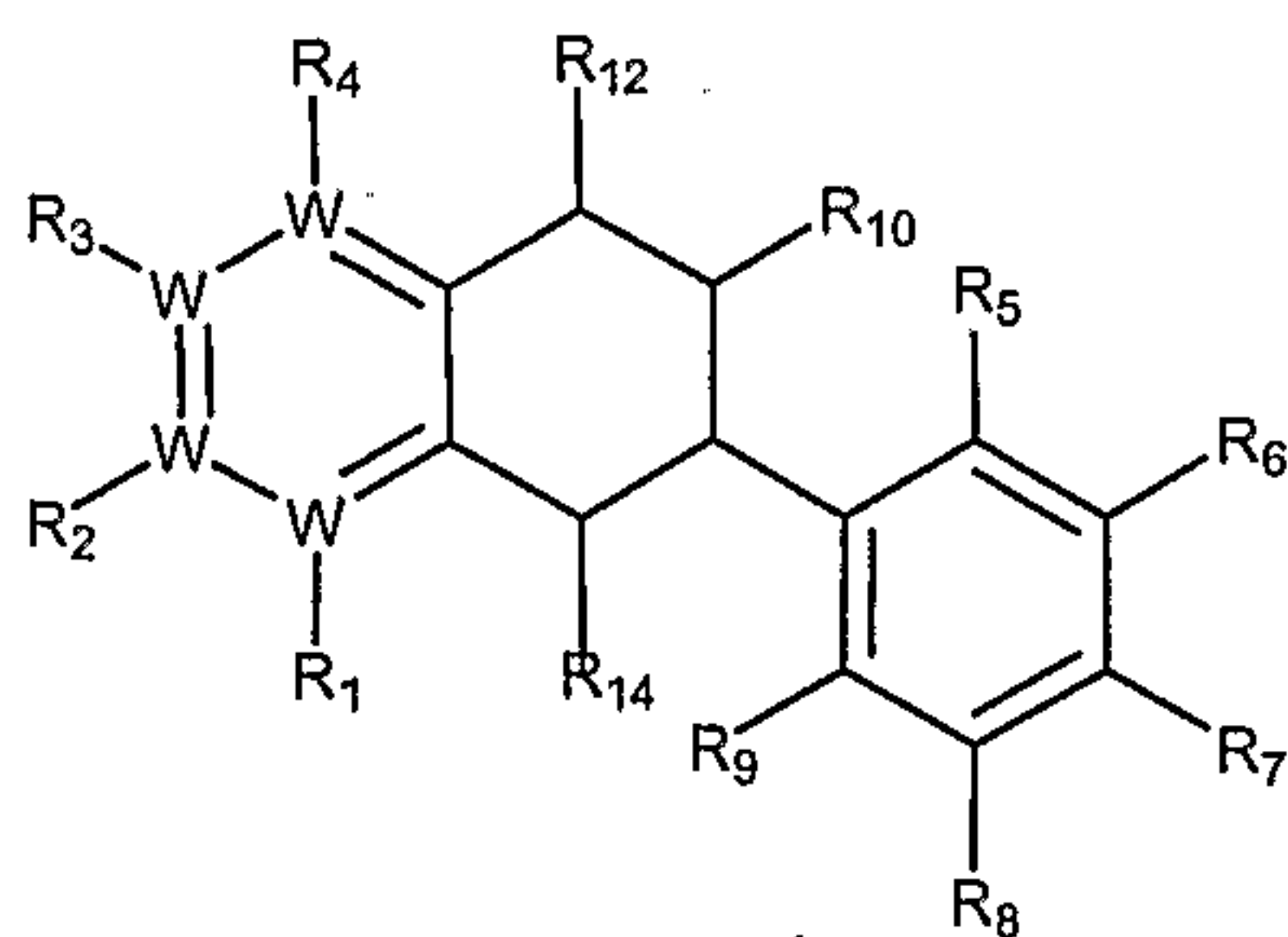
187. The method of embodiment 186, subject to at least one proviso selected from

- 1) at least one W is N; and
- 2) at least one of R_{1-6} and R_{8-10} is selected from D, E and F.

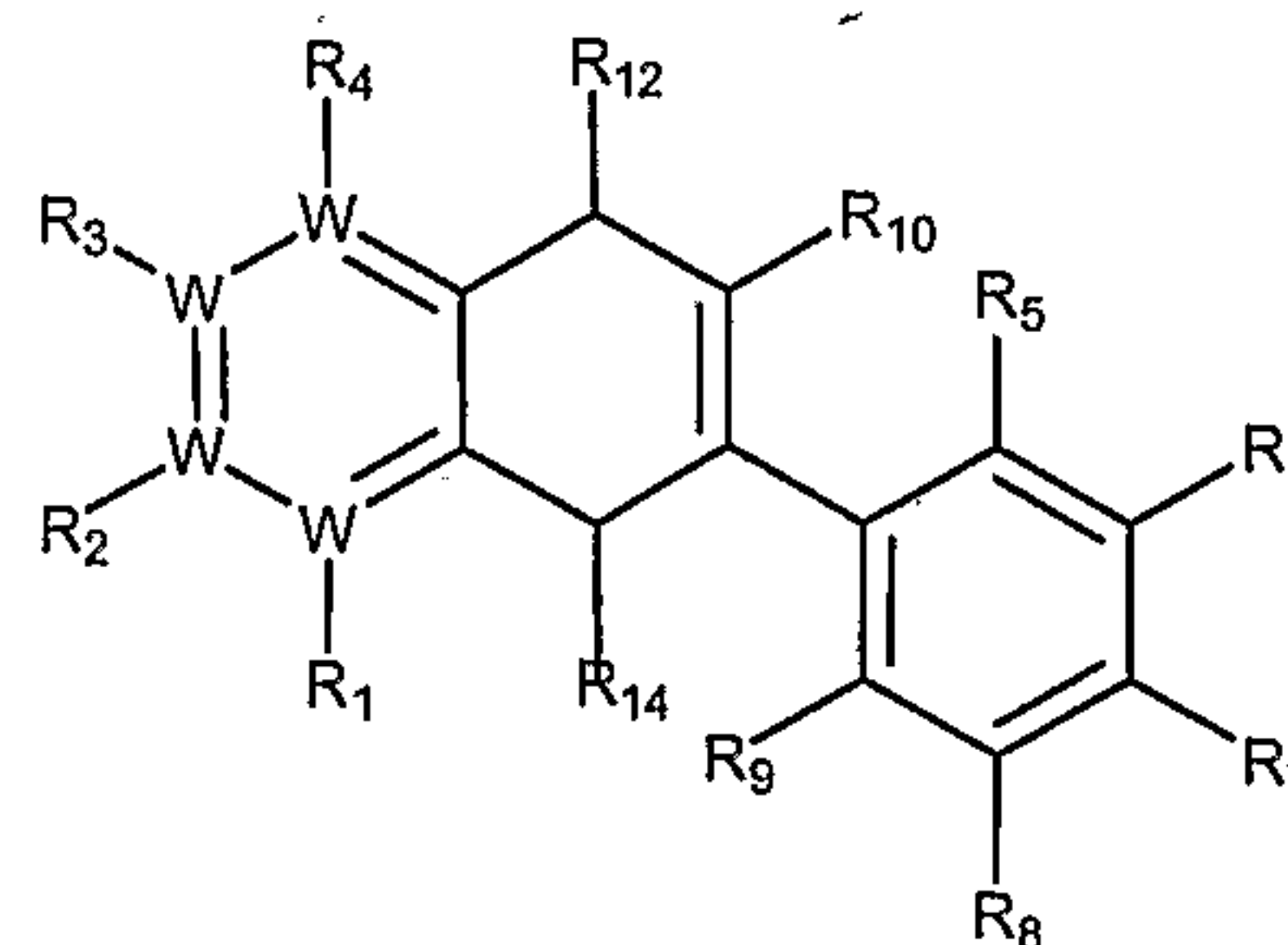
188. The method of embodiment 185, wherein at least one W is N, at least one of R_{1-6} and R_{8-10} is selected from D, E and F, and at least one of R_{1-6} and R_{8-10} is selected from K.

189. The method of embodiment 185, wherein X is O, Y is CR_{12} , and R_{12} is G.

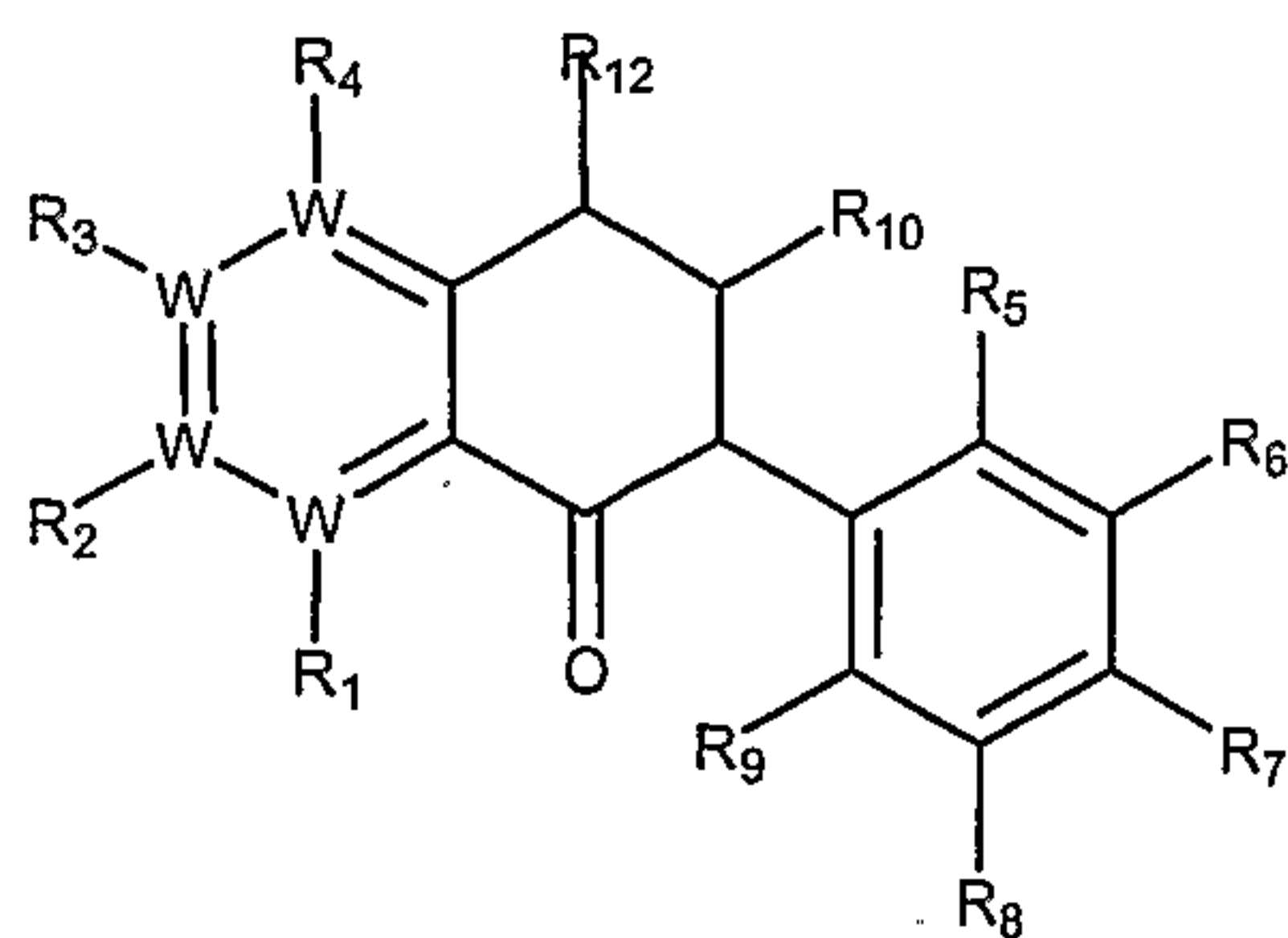
190. The method of embodiment 185, wherein Formula VI is selected from Formulae VIA-VIH:



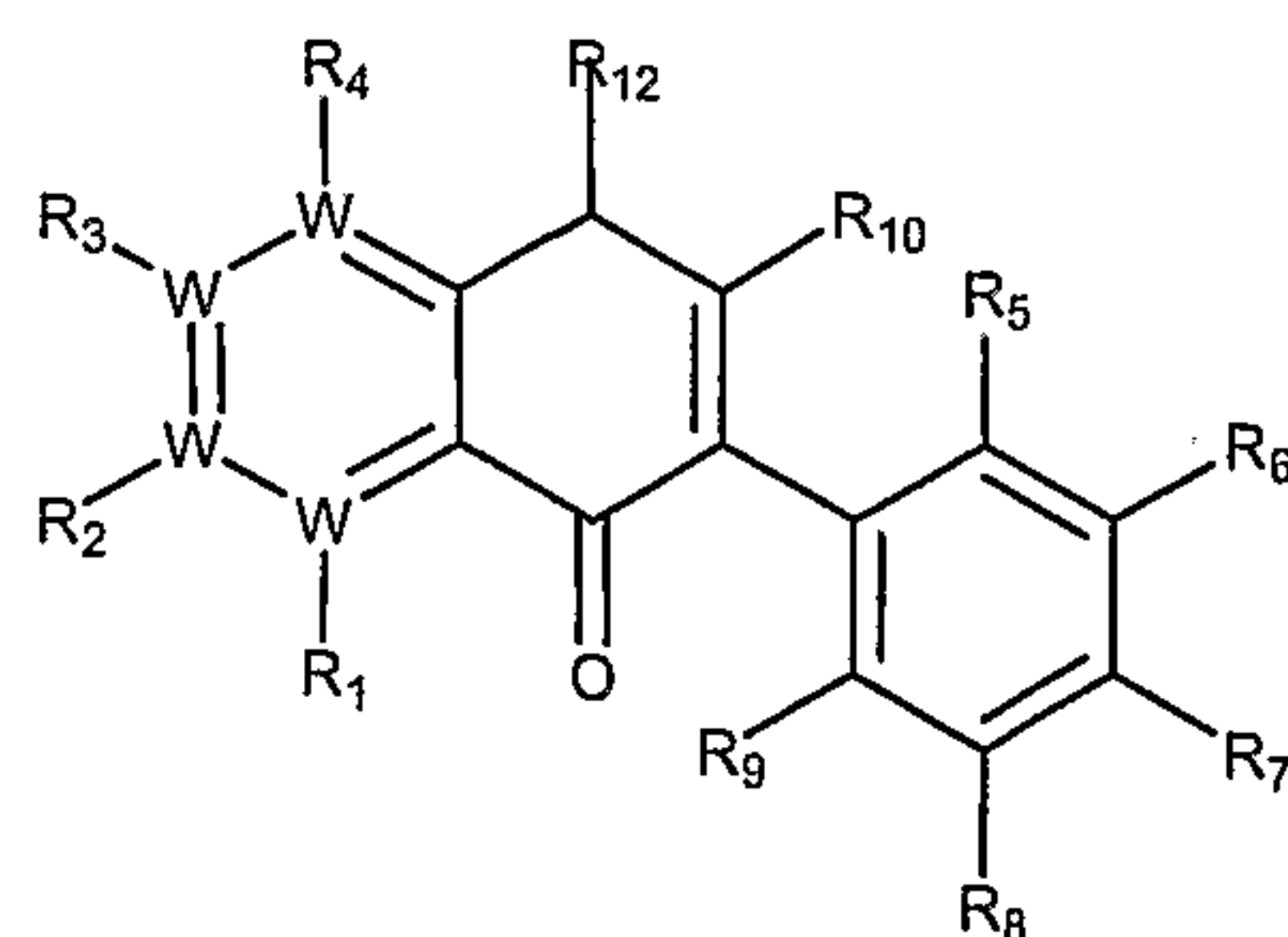
Formula VIA



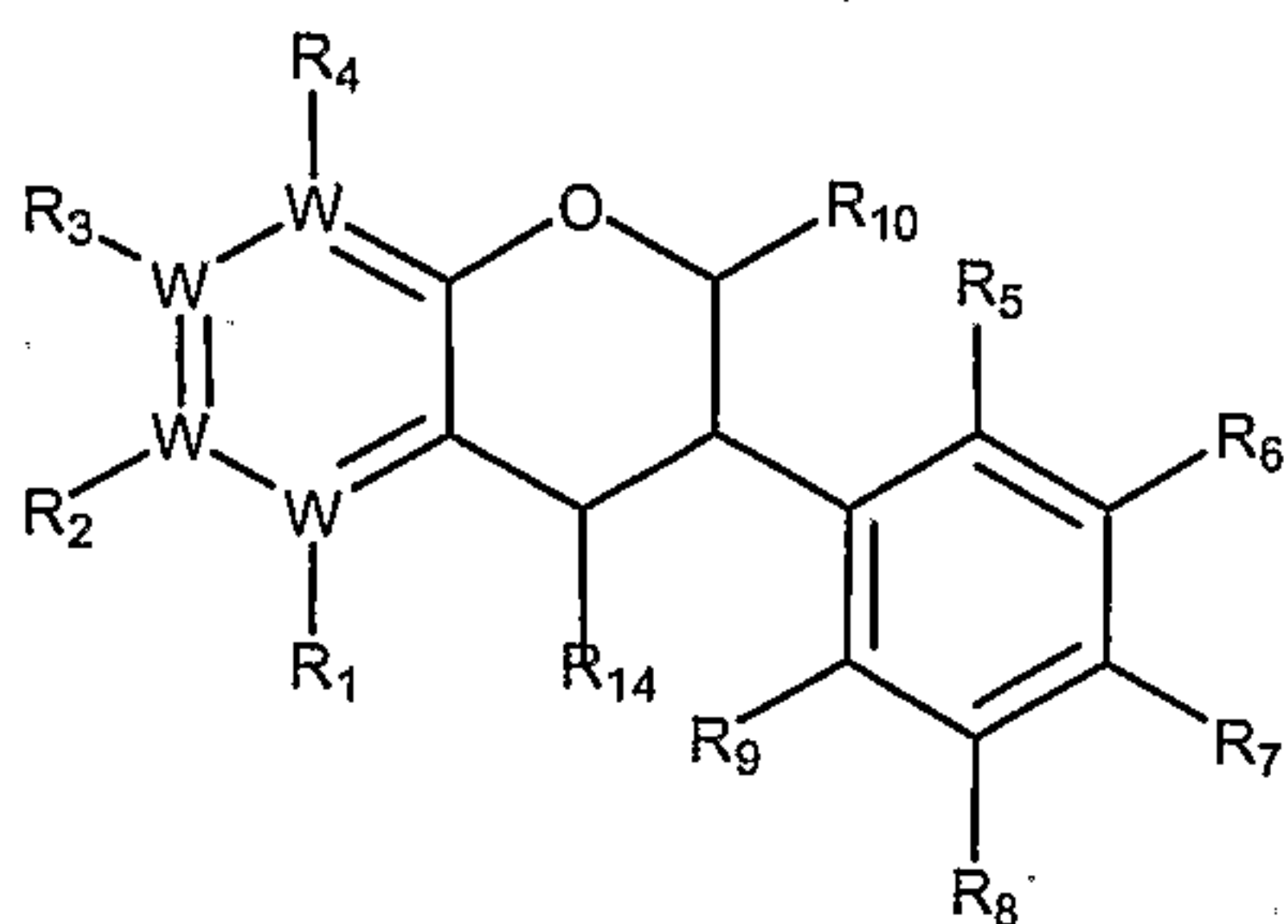
Formula VIB



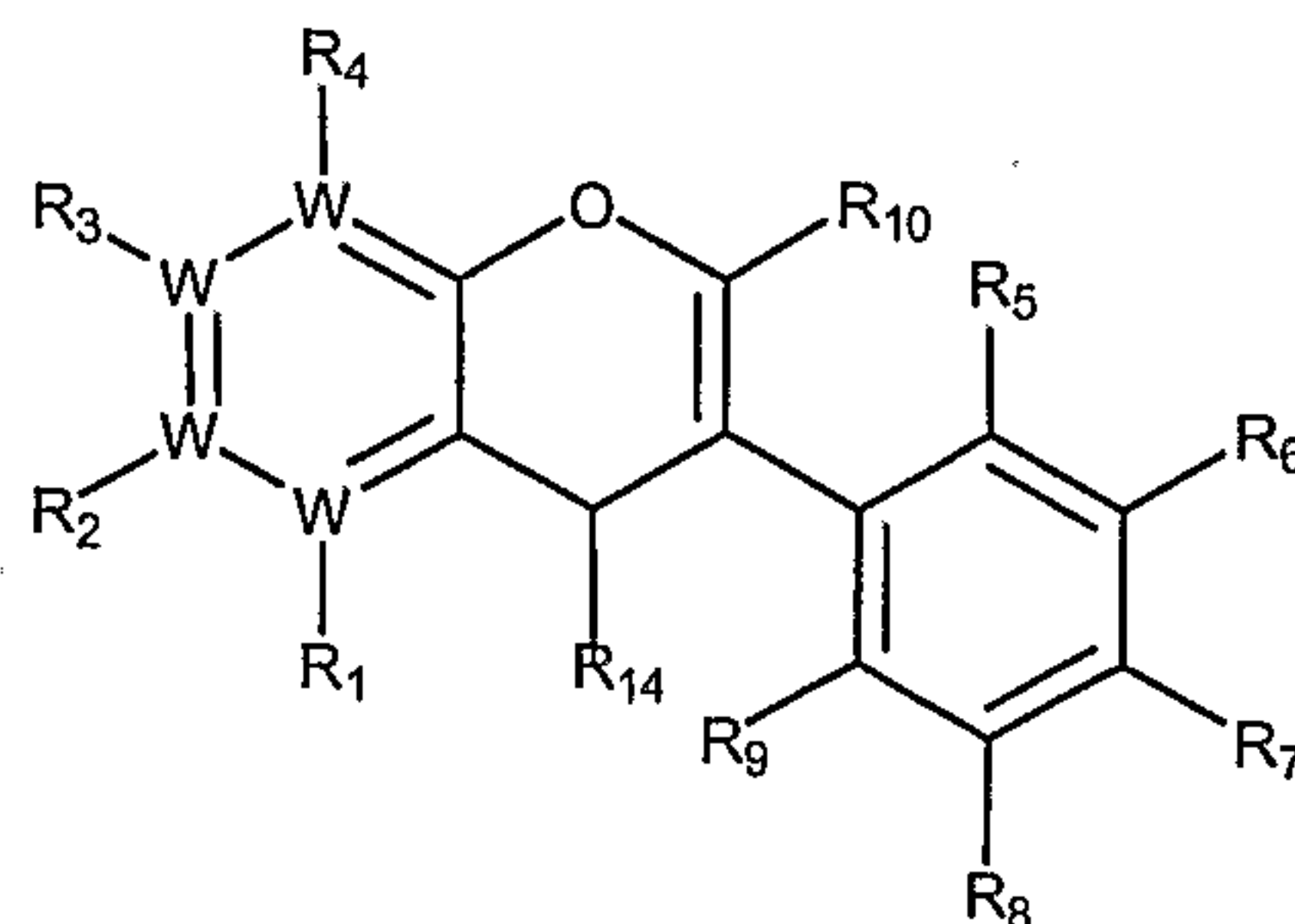
Formula VIC



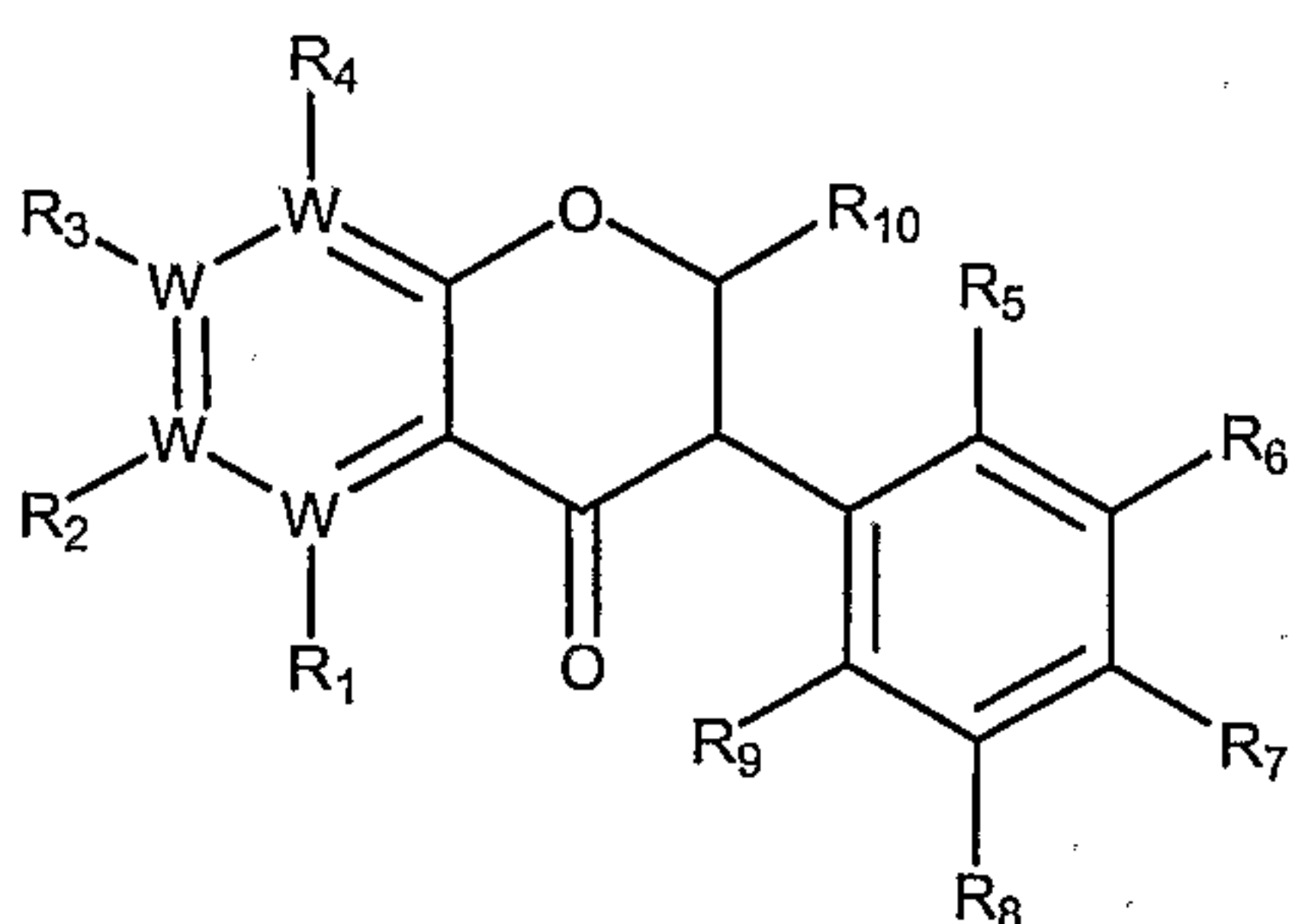
Formula VID



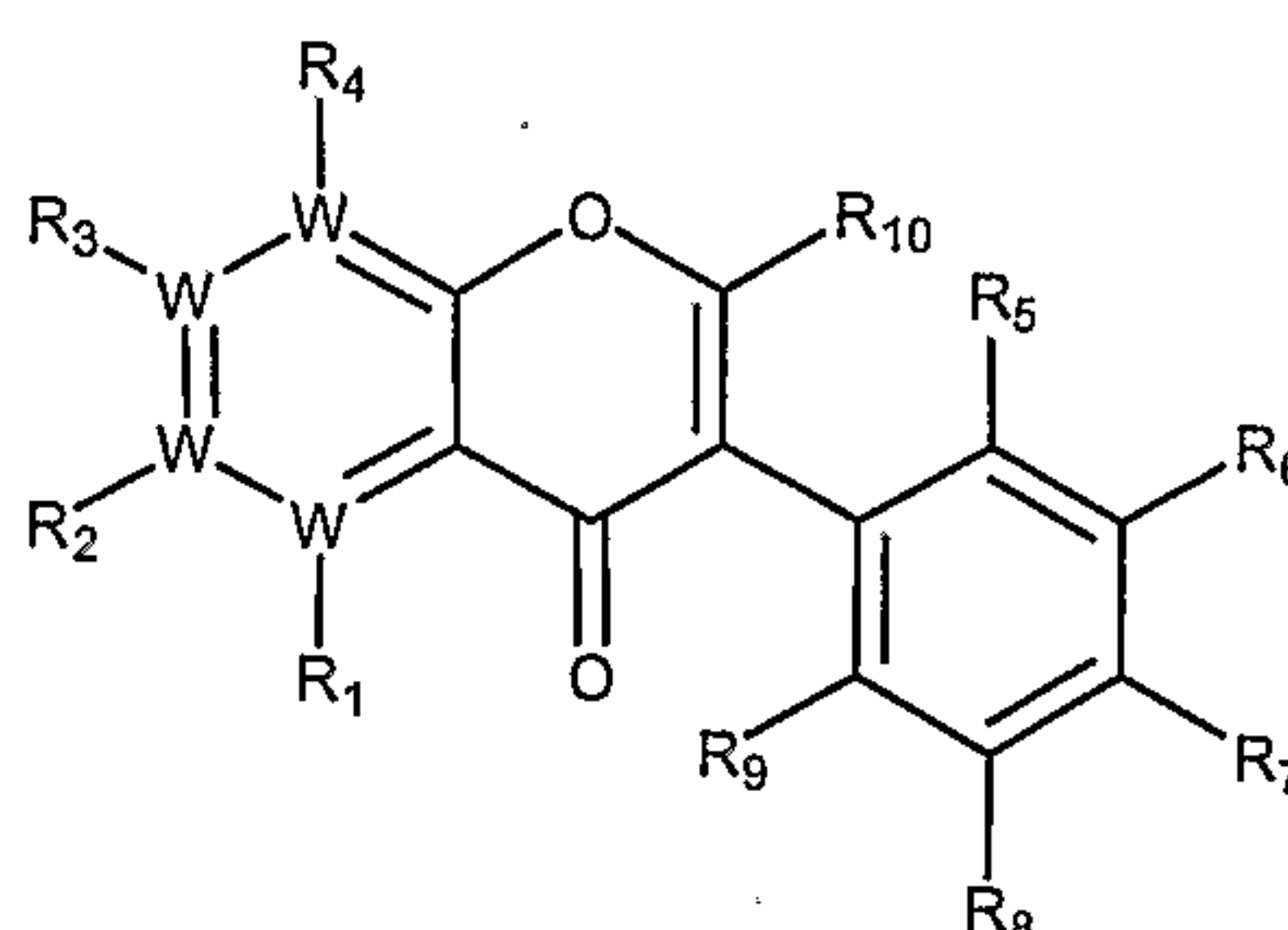
Formula VIE



Formula VIF



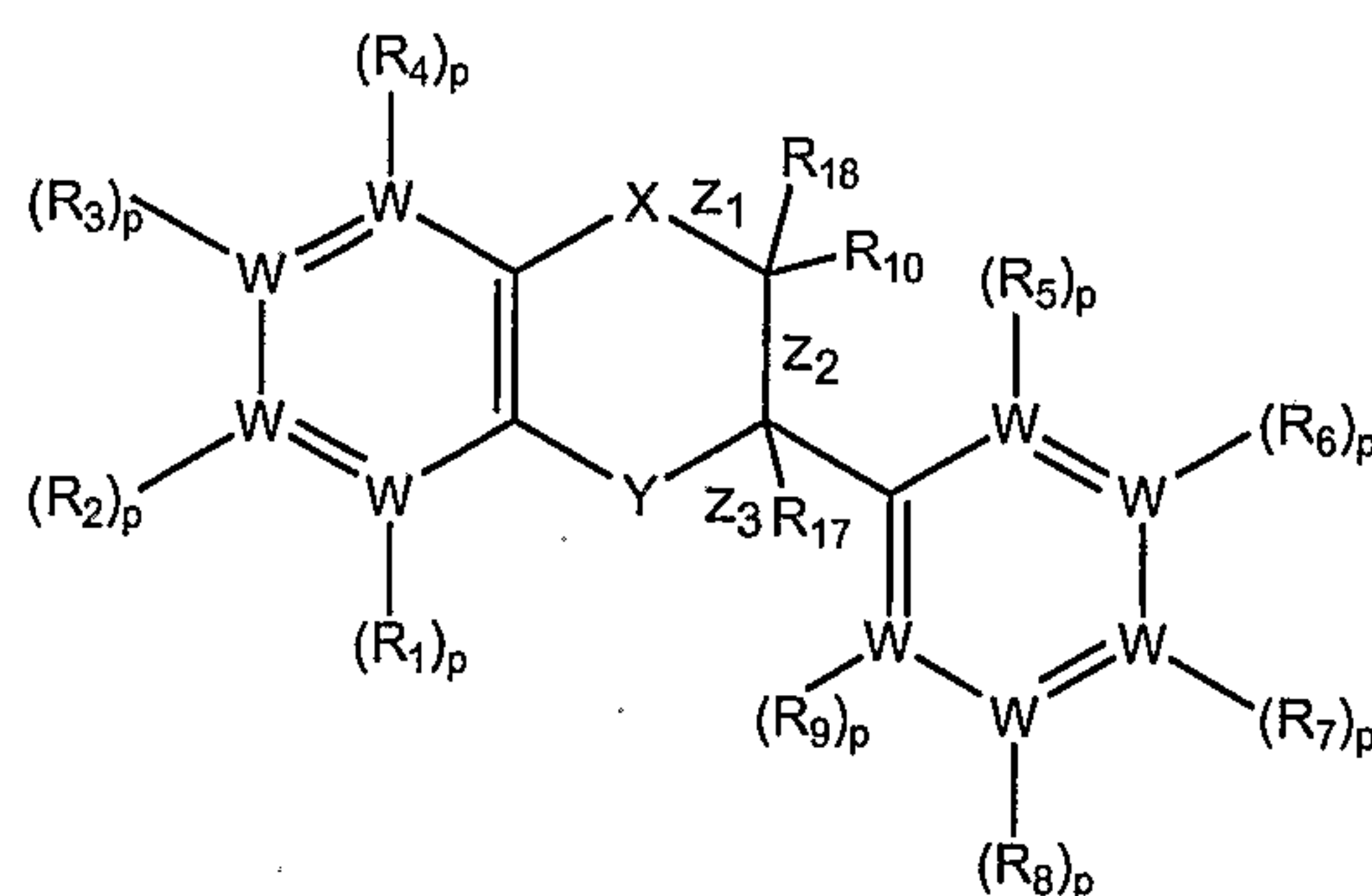
Formula VIG



Formula VIH

wherein R_{13} and R_{14} are each independently selected from (C_1-C_{22}) alkyl, (C_2-C_{22}) alkenyl, aryl, heteroaryl, hydrogen, hydroxyl, acetyl, hydroxyalkyl, aminoalkyl, bromide, iodide, methoxy, ethoxy, fluoride, chloride, CF_3 , CCl_3 , phosphate, O-sulfate, O-glucoronidate, K, D, E, F and G.

191. A method of treating or preventing cardiovascular, cholesterol or lipid related disorders comprising administering a therapeutically effective amount of a compound of Formula IV:



Formula IV

wherein:

X is selected from CR_{11} , $\text{CR}_{11}\text{R}_{13}$, CO, CS, O, S, SO, SO_2 , N and NR_{11} , wherein R_{11} may be the same or different than R_{13} ;

Y is selected from CR_{12} , $\text{CR}_{12}\text{R}_{14}$, CO, CS, O, S, SO, SO_2 , N and NR_{12} , wherein R_{12} may be the same or different than R_{14} ;

R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{17} and R_{18} are each independently selected from alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone, or two adjacent substituents selected from R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} and R_{18} are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

each W is independently selected from C and N, wherein if W is N, then p is 0 and if W is C, then p is 1;

Z_1 , Z_2 and Z_3 are each independently selected from a single bond and a double bond;

wherein if Y is O, X is not CO;

wherein if X is O, Y is CO and Z₂ is a double bond, then at least one of R₅, R₆, R₈ and R₉ is not hydrogen;

and pharmaceutically acceptable salts and hydrates thereof.

192. The method of embodiment 191, wherein the cardiovascular, cholesterol or lipid related disorder is selected from

acute coronary syndrome, angina pectoris, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, familial combined hyperlipidemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, multi-infarct dementia, myocardial infarction, peripheral vascular disease, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X and impotence.

193. The method of embodiment 191, wherein treating or preventing a cholesterol disorder comprises decreasing blood cholesterol levels.

194. The method of embodiment 191, wherein treating or preventing a cholesterol disorder comprises increasing blood ApoA-I levels.

195. The method of embodiment 191, wherein the therapeutically effective amount of the compound of Formula IV is administered with a pharmaceutically acceptable carrier in a pharmaceutically acceptable composition.

196. The method of embodiment 191, wherein the therapeutically effective amount of the compound of Formula IV is sufficient to establish a concentration ranging from about 0.001 μM to about 100 μM in the mammal.

197. The method of embodiment 196, wherein the concentration ranges from about 1 μM to about 20 μM .

198. The method of embodiment 191, where in the therapeutically effective amount of compound of Formula IV is sufficient to establish a concentration range from about 1 mg/kg to 30 mg/kg in the mammal.

199. The method of embodiment 191, wherein the compound of Formula IV is 3-(4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one.

Pharmaceutical Formulations and Methods of Treatment

[0116] The present disclosure also provides pharmaceutical compositions comprising compounds as disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal and parenteral (e.g. subcutaneous, intramuscular, intradermal, or intravenous) administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used.

[0117] Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of the compound as powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such formulations may be prepared by any suitable method of pharmacy which includes the step of bringing into association the active

compound and the carrier or excipient (which may constitute one or more accessory ingredients). The carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the active compound. Other pharmacologically active substances may also be present including other compounds. The formulations of the invention may be prepared by any of the well known techniques of pharmacy consisting essentially of admixing the components.

[0118] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate, and the like. Liquid pharmacologically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active compound as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension. In general, suitable formulations may be prepared by uniformly and intimately admixing the active compound with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or molding a powder or granules of the compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s).

Molded tablets may be made by molding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

[0119] Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound in a flavored base, usually sucrose and acacia or tragacanth, and pastilles comprising the compound in an inert base such as gelatin and glycerin or sucrose and acacia.

[0120] Formulations of the present invention suitable for parenteral administration comprise sterile aqueous preparations of the compounds, which are approximately isotonic with the blood of the intended recipient. These preparations are administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the compound with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention may contain from 0.1 to 5% w/w of the active compound.

[0121] Formulations suitable for rectal administration are presented as unit-dose suppositories. These may be prepared by admixing the compound with one or more conventional solid carriers, for example, cocoa butter, and then shaping the resulting mixture.

[0122] Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers and excipients which may be used include Vaseline, lanoline, polyethylene glycols, alcohols, and combinations of two or more thereof. The active compound is generally present at a concentration of from about 0.1% to about 15% w/w of the composition, for example, from about 0.5 to about 2%.

[0123] The amount of active compound administered may be dependent on the subject being treated, the subject's weight, the manner of administration and the judgment of the prescribing physician. For example, a dosing schedule may involve the daily or semi-daily administration of the encapsulated compound at a perceived dosage of about 1 μg to about 1000 mg. In another embodiment, intermittent administration, such as on a monthly or yearly basis, of a dose of the encapsulated compound may be employed. Encapsulation facilitates access to the site of action and allows the administration of the active ingredients simultaneously, in theory producing a synergistic effect. In accordance with standard dosing regimens, physicians will readily determine optimum dosages and will be able to readily modify administration to achieve such dosages.

[0124] A therapeutically effective amount of a compound or composition disclosed herein can be measured by the therapeutic effectiveness of the compound. Compounds of the invention may be administered in a dose of about 1 $\mu\text{g}/\text{kg}$ to about 200 mg/kg daily; such as from about 1 $\mu\text{g}/\text{kg}$ to about 150 mg/kg, from about 1 mg/kg to about 200 mg/kg, from about 1 $\mu\text{g}/\text{kg}$ to about 100 mg/kg, from about 1 $\mu\text{g}/\text{kg}$ to about 1 mg/kg, from about 50 $\mu\text{g}/\text{kg}$ to about 200 mg/kg, from about 10 $\mu\text{g}/\text{kg}$ to about 1 mg/kg, from about 10 $\mu\text{g}/\text{kg}$ to about 100 $\mu\text{g}/\text{kg}$, from about 100 μg to about 10 mg/kg, and from about 500 $\mu\text{g}/\text{kg}$ to about 50 mg/kg. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being used. In one embodiment, the therapeutically effective amount of a disclosed compound is sufficient to establish a maximal plasma concentration ranging from about 0.001 μM to about 100 μM , e.g., from about 1 μM to about 20 μM . Preliminary doses as,

for example, determined according to animal tests, and the scaling of dosages for human administration is performed according to art-accepted practices.

[0125] Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are preferable.

[0126] The therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the therapeutic which achieves a half-maximal inhibition of symptoms) as determined in cell culture assays or animal models. Levels in plasma may be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay. Examples of dosages are: about 0.1 x IC₅₀, about 0.5 x IC₅₀, about 1 x IC₅₀, about 5 x IC₅₀, 10 x IC₅₀, about 50x IC₅₀, and about 100 x IC₅₀.

[0127] Data obtained from the cell culture assays or animal studies can be used in formulating a range of dosage for use in humans. Therapeutically effective dosages achieved in one animal model may be converted for use in another animal, including humans, using conversion factors known in the art (see, e.g., Freireich et al., *Cancer Chemother. Reports* 50(4):219-244 (1966) and Table 1 for Equivalent Surface Area Dosage Factors).

Table 1

To: From:	Mouse (20 g)	Rat (150 g)	Monkey (3.5 kg)	Dog (8 kg)	Human (60 kg)
Mouse	1	1/2	1/4	1/6	1/12
Rat	2	1	1/2	1/4	1/7
Monkey	4	2	1	3/5	1/3
Dog	6	4	3/5	1	1/2
Human	12	7	3	2	1

[0128] The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. Generally, a therapeutically effective amount may vary with the subject's age, condition, and sex, as well as the severity of the medical condition in the subject. The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment.

[0129] In one embodiment, a compound as disclosed herein, or a pharmaceutically acceptable salt or hydrate thereof, is administered in combination with another therapeutic agent. The other therapeutic agent can provide additive or synergistic value relative to the administration of a flavanoid or isoflavanoid compound alone. The therapeutic agent can be, for example, a statin; a PPAR agonist, e.g., a thiazolidinedione or fibrate; a bile-acid-binding-resin; a niacin; a RXR agonist; an anti-obesity drug; a hormone; a tyroprophostine; a sulfonylurea-based drug; a biguanide; an alpha-glucosidase inhibitor; apolipoprotein E; a cardiovascular drug; an HDL-raising drug; an HDL enhancer; or a regulator of the apolipoprotein A-IV and/or apolipoprotein genes.

[0130] In one embodiment, a method of treating or preventing cardiovascular, cholesterol or lipid related disorders comprises administering a therapeutically effective amount of a disclosed compound. The disclosed compound may be administered as a pharmaceutically acceptable composition, comprising a disclosed compound and a pharmaceutically acceptable carrier. Another embodiment provides methods for the prevention of a cardiovascular, cholesterol or lipid related disorder, comprising administering to a mammal a therapeutically effective amount of a presently disclosed compound or composition.

[0131] Exemplary cardiovascular, cholesterol or lipid related disorders include, but are not limited to acute coronary syndrome, angina pectoris, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, familial combined hyperlipidemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, multi-infarct dementia, myocardial infarction, peripheral vascular disease, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X and impotence.

[0132] As used herein, the term "cardiovascular disease" refers to diseases and disorders of the heart and circulatory system. These diseases are often associated with dyslipoproteinemias and/or dyslipidemias. "Endothelium

dysfunction(s)" include, but are not limited to, dysfunctions affecting blood vessel elasticity; peripheral vascular disease; coronary heart disease; myocardial infarction; cerebral infarction and restenosis. "Syndrome X" or "Metabolic Syndrome(s)" include, but are not limited to hypertension and dyslipidemia/dyslipoproteinemia.

[0133] In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient. In yet another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, e.g., stabilization of a discernible symptom, physiologically, e.g., stabilization of a physical parameter, or both. In yet another embodiment, "treatment" or "treating" refers to delaying the onset of a disease or disorder. For example, treating a cholesterol disorder may comprise decreasing blood cholesterol levels.

[0134] One embodiment provides a compound for administration to a patient, such as a human, as a preventative measure against cardiovascular, cholesterol or lipid related disorder. As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. In another embodiment, the present compositions are administered as a preventative measure to a patient, such as a human having a genetic predisposition to, for example, a cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, Alzheimer's Disease, hypertension, atherosclerosis, or inflammation.

[0135] In another embodiment, the compositions of the invention are administered as a preventative measure to a patient having a non-genetic predisposition to, for example, cardiovascular disease, a dyslipidemia, a dyslipoproteinemia, Alzheimer's Disease, hypertension, atherosclerosis, or inflammation. Examples of such non-genetic predispositions include, but are not limited to, cardiac bypass surgery and percutaneous transluminal coronary angioplasty, which often leads to restenosis, an accelerated form of atherosclerosis; diabetes in women, which often leads to polycystic ovarian disease; and cardiovascular disease, which often leads to impotence. Accordingly, the present compositions may be used for the prevention of one disease or disorder and concurrently treating another (e.g., prevention of polycystic ovarian disease while treating diabetes; prevention of impotence while treating a cardiovascular disease).

[0136] Angioplasty and open heart surgery, such as coronary bypass surgery, may be required to treat cardiovascular diseases, such as atherosclerosis. These surgical procedures entail using invasive surgical devices and/or implants, and are associated with a high risk of restenosis and thrombosis. Accordingly, the compounds of the invention may be used as coatings on surgical devices (e.g., catheters) and implants (e.g., stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.

[0137] The present invention provides methods for the treatment or prevention of a dyslipidemia comprising administering to a patient a therapeutically effective amount of a presently disclosed compound. In one embodiment, the compound is administered as a pharmaceutically acceptable

composition. As used herein, the term "dyslipidemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipids. To the extent that levels of lipids in the blood are too high, the disclosed compounds or compositions may be administered to a patient to restore normal levels. Normal levels of lipids are reported in medical treatises known to those of skill in the art.

[0138] Dyslipidemias which the disclosed compounds or compositions are useful for preventing or treating include but are not limited to hyperlipidemia and low blood levels of high density lipoprotein (HDL) cholesterol. Hyperlipidemia includes, but is not limited to, familial hypercholesterolemia; familial combined hyperlipidemia; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypertriglyceridemia; hypercholesterolemia; high blood levels of ketone bodies (e.g., beta-OH butyric acid); high blood levels of Lp(a) cholesterol; high blood levels of low density lipoprotein (LDL) cholesterol; high blood levels of very low density lipoprotein (VLDL) cholesterol and high blood levels of non-esterified fatty acids.

[0139] One embodiment provides methods for altering lipid metabolism in a patient, e.g., increasing the ratio of HDL to LDL in the blood of a patient, comprising administering to the patient a composition of the invention in an amount effective alter lipid metabolism.

[0140] Another embodiment provides methods for the treatment or prevention of a dyslipoproteinemia comprising administering to a patient a therapeutically effective amount of a disclosed compound or composition. As used herein, the term "dyslipoproteinemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipoproteins. To the extent that levels

of lipoproteins in the blood are too high, the disclosed compounds or compositions are administered to a patient to restore normal levels. Conversely, to the extent that levels of lipoproteins in the blood are too low, the disclosed compounds or compositions are administered to a patient to restore normal levels. Normal levels of lipoproteins are reported in medical treatises known to those of skill in the art.

[0141] Dyslipoproteinemias which the disclosed compounds or compositions are useful for preventing or treating include, but are not limited to, high blood levels of LDL; high blood levels of apolipoprotein B (apo B); high blood levels of Lp(a); high blood levels of apo(a); high blood levels of VLDL; low blood levels of HDL; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypoalphalipoproteinemia; lipoprotein abnormalities associated with diabetes mellitus; lipoprotein abnormalities associated with obesity; lipoprotein abnormalities associated with Alzheimer's Disease; and familial combined hyperlipidemia.

[0142] One embodiment provides methods for elevating the levels of HDL associated proteins, such as ApoA-I, in the blood of a mammal, comprising administering to the mammal a composition comprising a disclosed compound or composition in an amount effective to elevate levels of HDL associated proteins in the mammal.

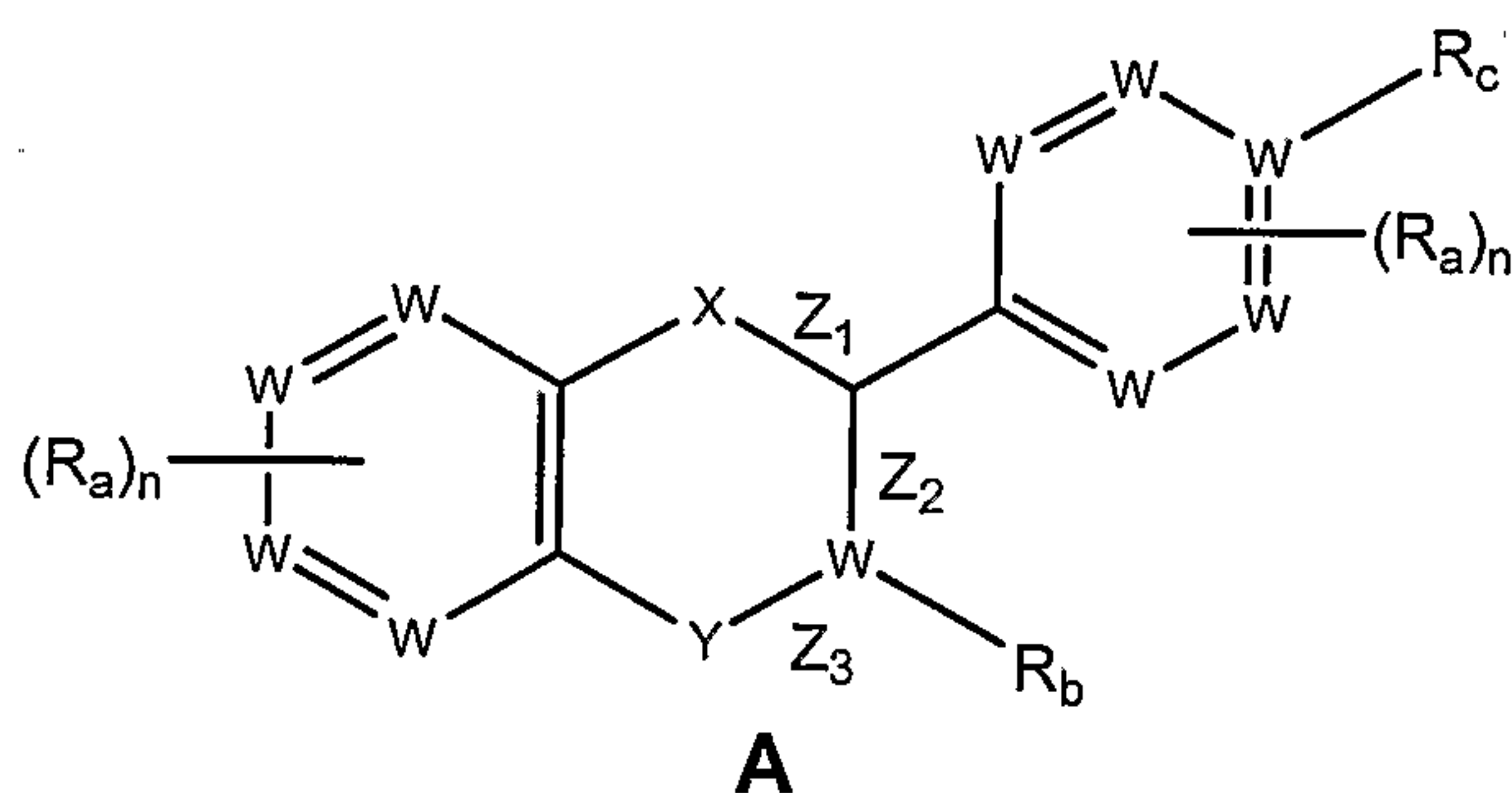
[0143] Another embodiment provides methods for the treatment or prevention of Alzheimer's Disease, hypertension, and/or atherosclerosis, comprising administering to a mammal a therapeutically effective amount of a disclosed compound or composition. As used herein, "treatment or prevention of

Alzheimer's Disease" encompasses treatment or prevention of lipoprotein abnormalities associated with Alzheimer's Disease.

[0144] "Diseases and conditions associated with diabetes mellitus" as defined herein comprise, but are not restricted to, hyperglycemia, hyperinsulinaemia, hyperlipidaemia, insulin resistance, impaired glucose metabolism, obesity, diabetic retinopathy, macular degeneration, cataracts, diabetic nephropathy, glomerulosclerosis, diabetic neuropathy, erectile dysfunction, premenstrual syndrome, vascular restenosis, ulcerative colitis, skin and connective tissue disorders, foot ulcerations, metabolic acidosis, arthritis, osteoporosis and impaired glucose tolerance.

PREPARATION OF COMPOUNDS

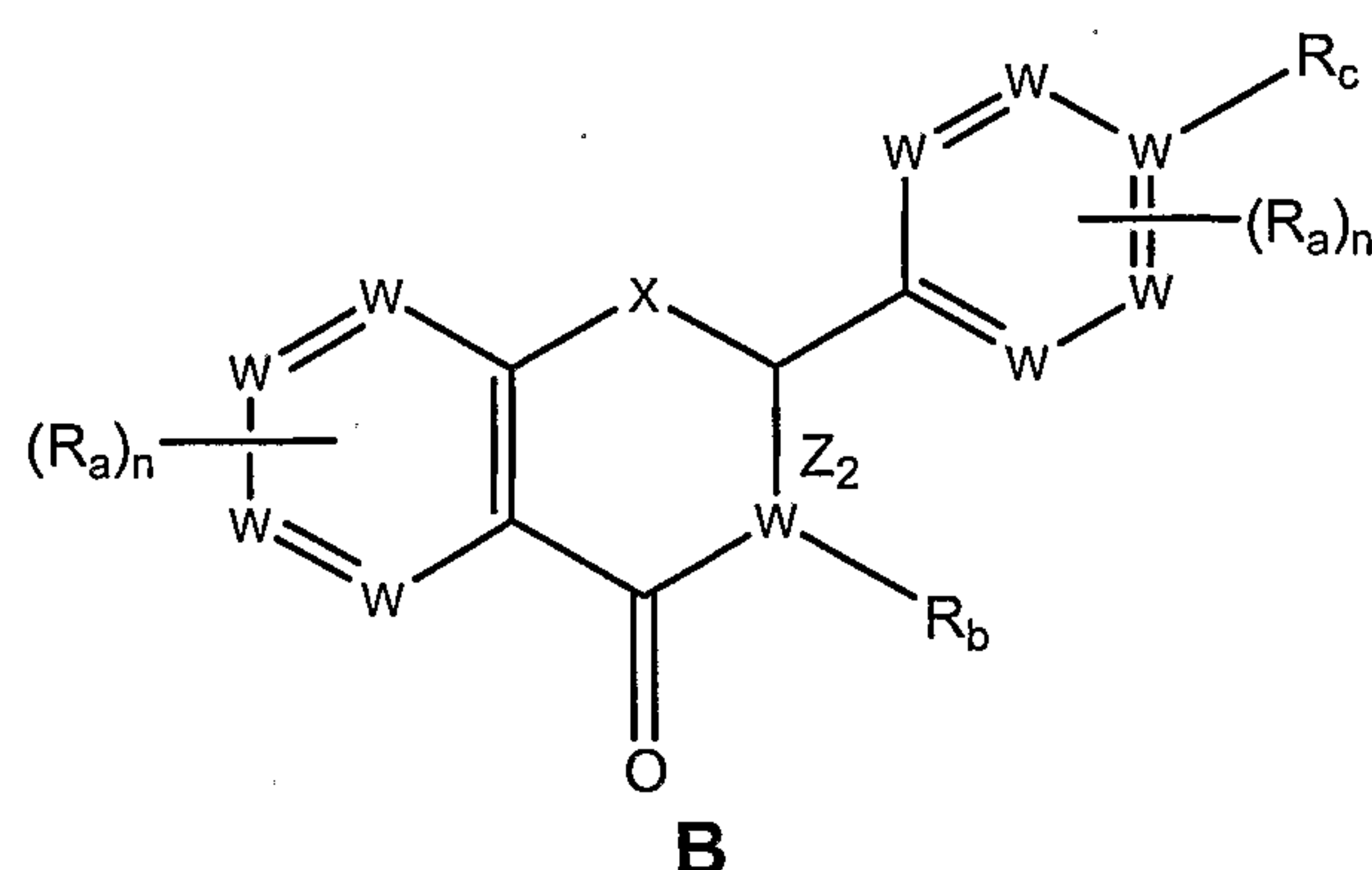
[0145] Flavanoid compounds may be represented by the general structure of Formula **A**.



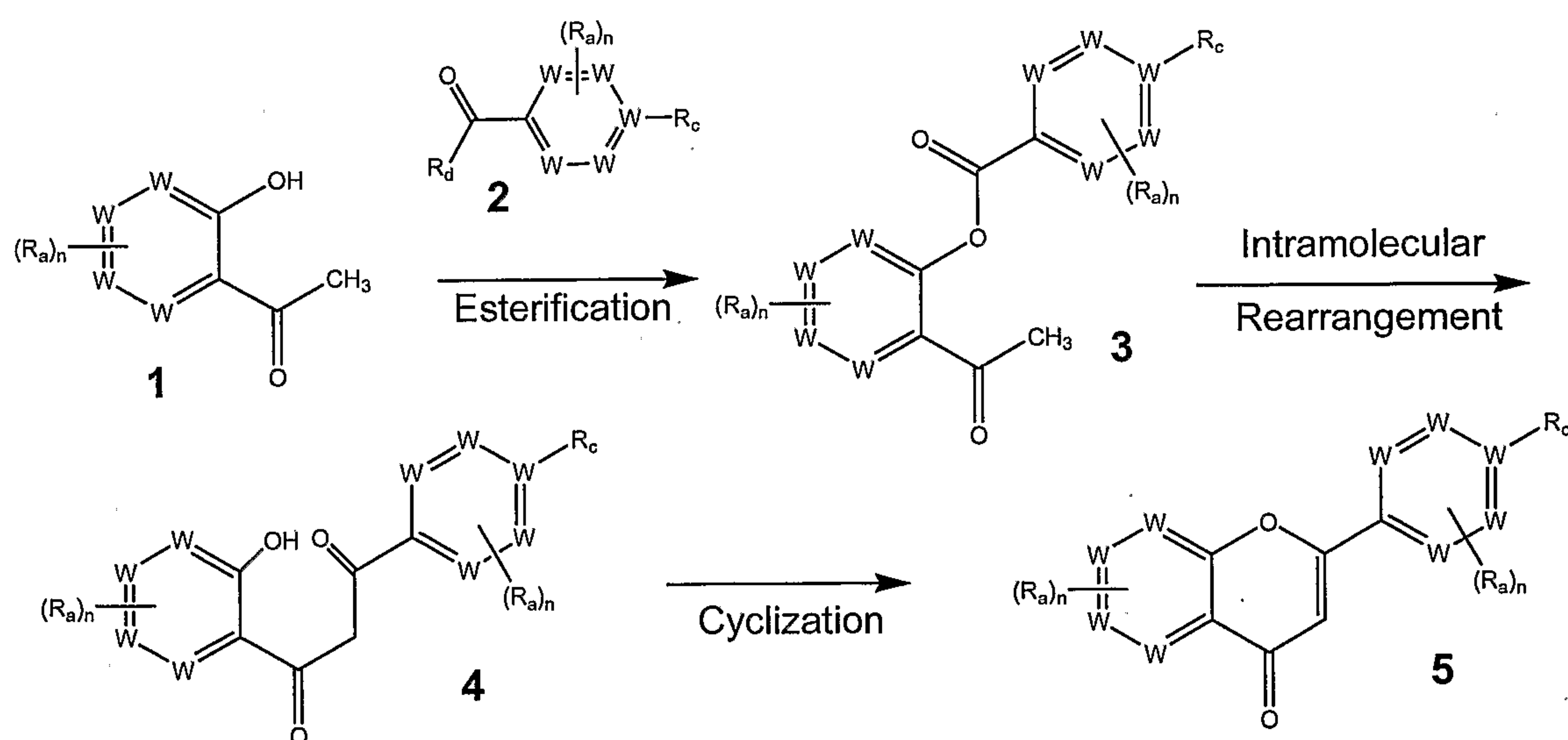
[0146] R_a may be selected from groups including, but not limited to, alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide and thioketone. R_b may be selected from groups including, but not limited to, alkyl, amino, cyano, halogen and hydrogen. R_c represents substituents such as alkyl, alkoxy, halogen, hydroxyl and hydrogen. It should be appreciated that these designations are non-limiting examples of the flavanoid compounds disclosed herein.

[0147] One of ordinary skill will appreciate that flavanoid compounds as disclosed herein may be synthesized from readily available starting materials as outlined below.

[0148] Formula **B** represents a general formula for flavanoid compounds comprising a phenyl-chromene:



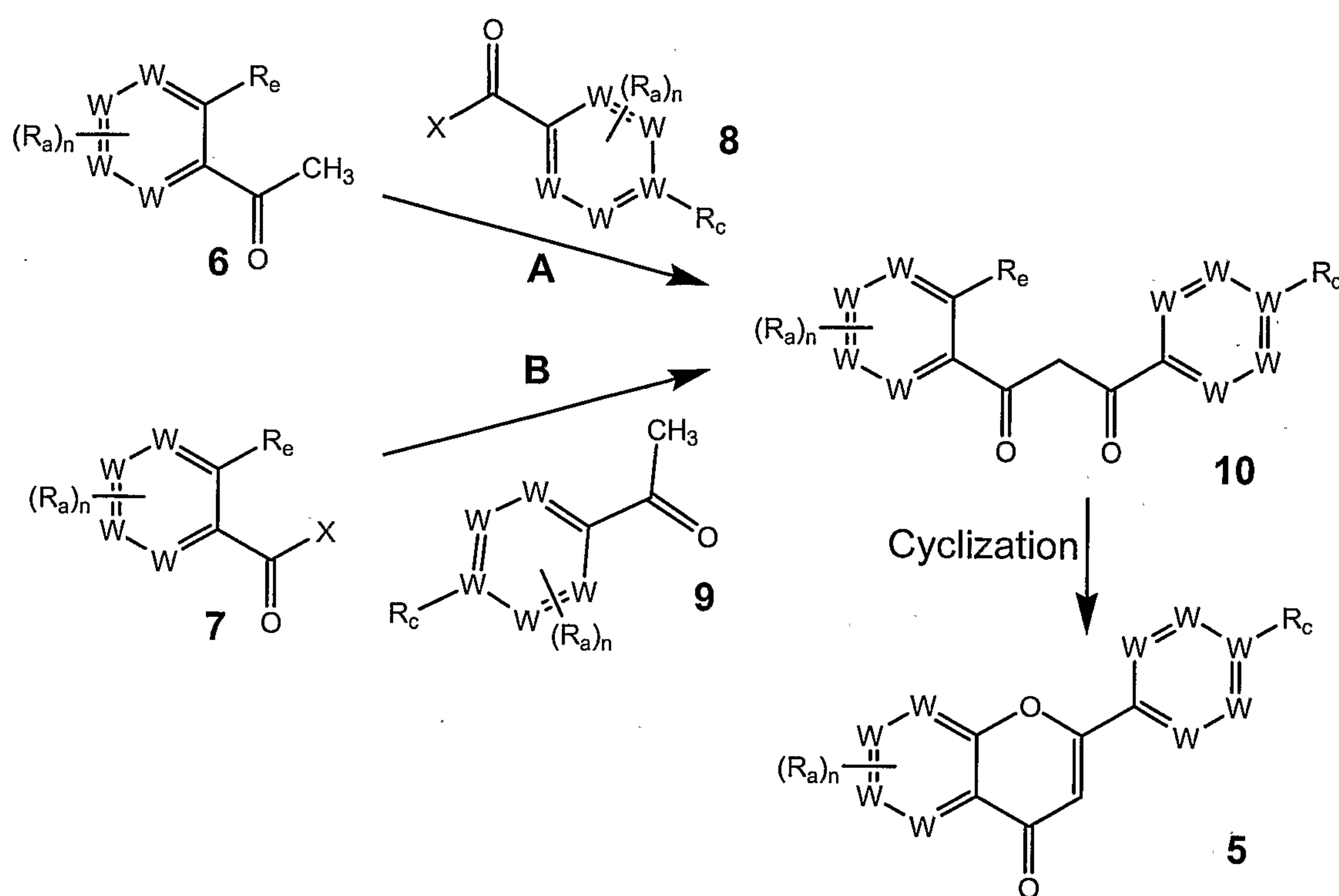
[0149] Flavanoids of Formula **B** can be synthesized by the procedure of Scheme 1:



[0150] Acid chloride **2** ($R_d = \text{Cl}$) may be used directly in a reaction with acetophenone **1** to provide ester **3**. The acid chloride may also be generated *in situ* by exposing the carboxylic acid **2** ($R_d = \text{OH}$) to a chlorinating agent such as POCl_3 . Ester **3** can be converted into diketone **4** via intramolecular

rearrangement. Rearrangement may be achieved using a catalytic amount of base, such as potassium t-butoxide, KOH, NaH and the like. Cyclization of phenol **4** to flavanoid **5** can be achieved by heating phenol **4** in the presence of a strong protic (HCl, AcOH, HI, AcOH, HBr, and mixtures thereof) or Lewis (BBr₃) acid.

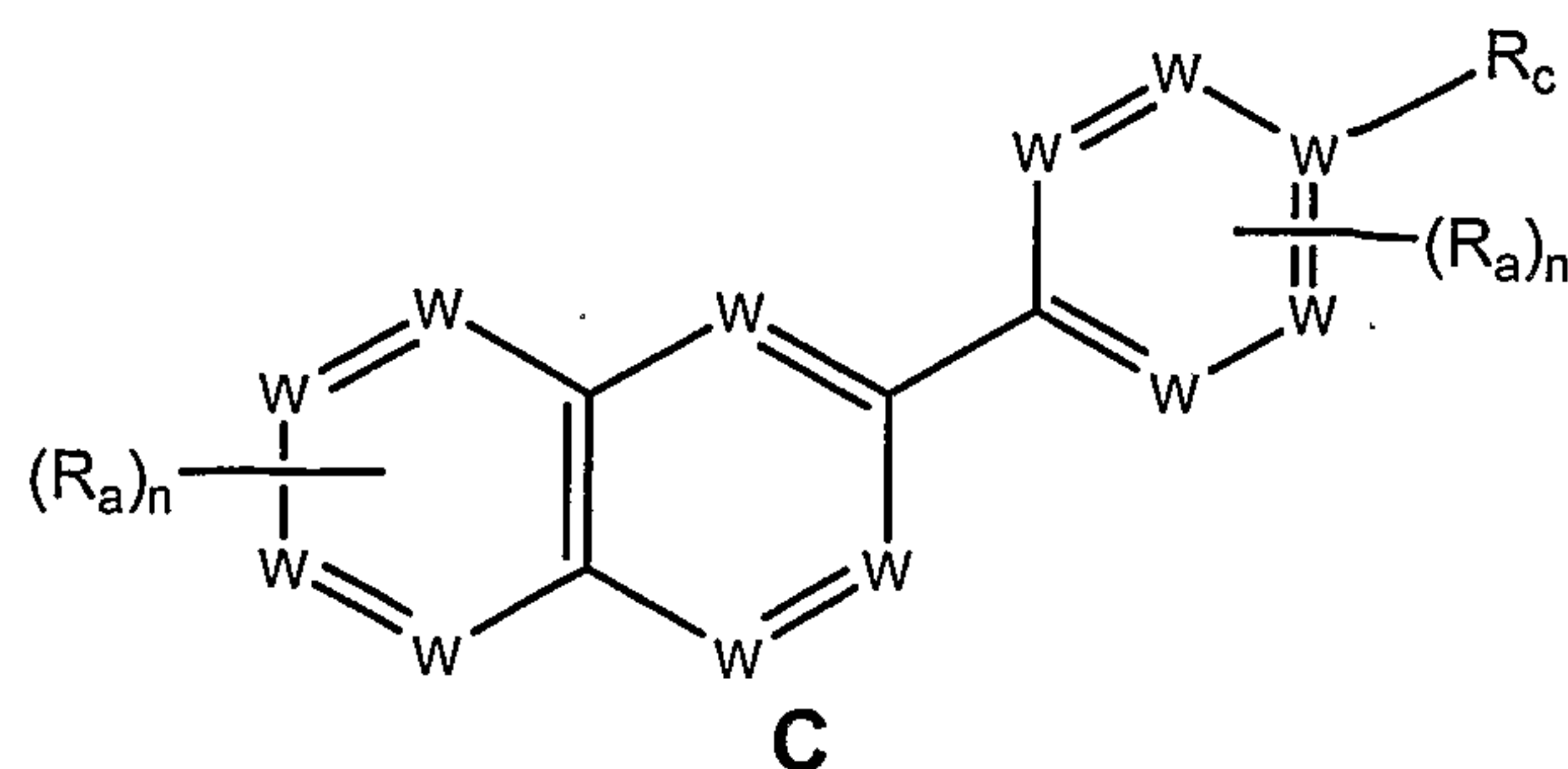
[0151] Flavanoid compounds can be synthesized following the procedure of Scheme 2:



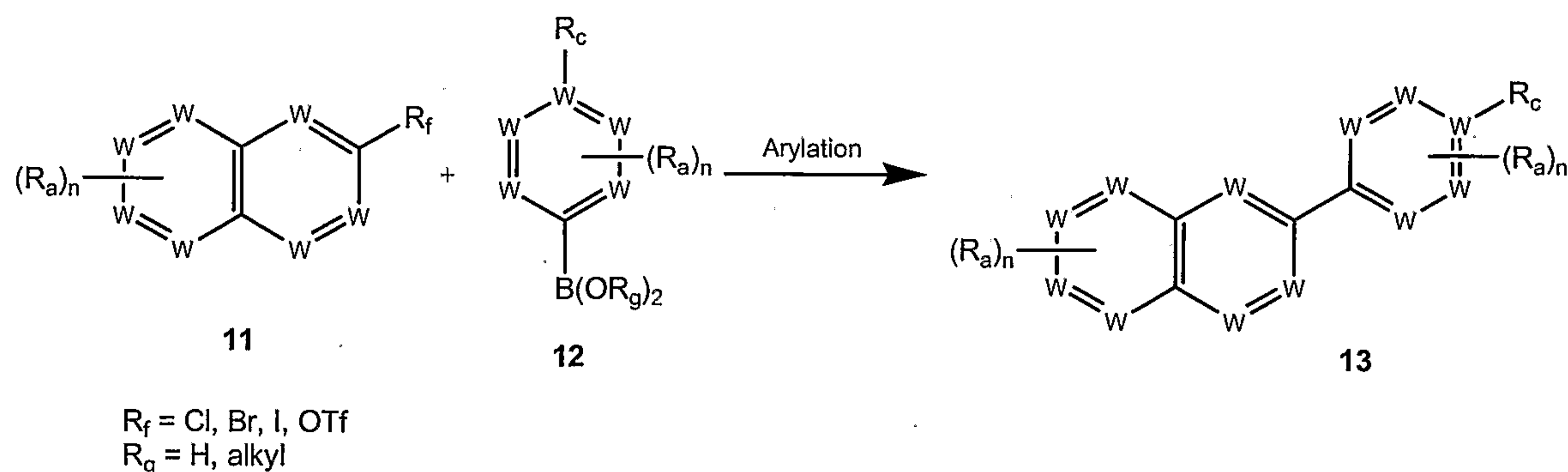
Scheme 2

[0152] Diketone **10** may be prepared by first exposing methyl ketones **6** or **9** to basic conditions, such as potassium t-butoxide, KOH, NaH and the like, to form the corresponding enolate. Then, reaction with acyl halide **8** or **7** (X = Hal), respectively, affords diketone **10**. Cyclization of diketone **10** to flavanoid **5** may likewise be accomplished by a number of methods. When R_e = F, exposure of **10** to heat and a polar solvent results in ring closure via nucleophilic aromatic substitution. Alternatively, strong protic or Lewis acids may be used when R_e = alkoxy, SH, or NH₂. Exemplary acids include HCl, AcOH, HI, AcOH, HBr, BBr₃, and mixtures thereof.

[0153] Formula **C** represents flavanoid compounds comprising a naphthyl:



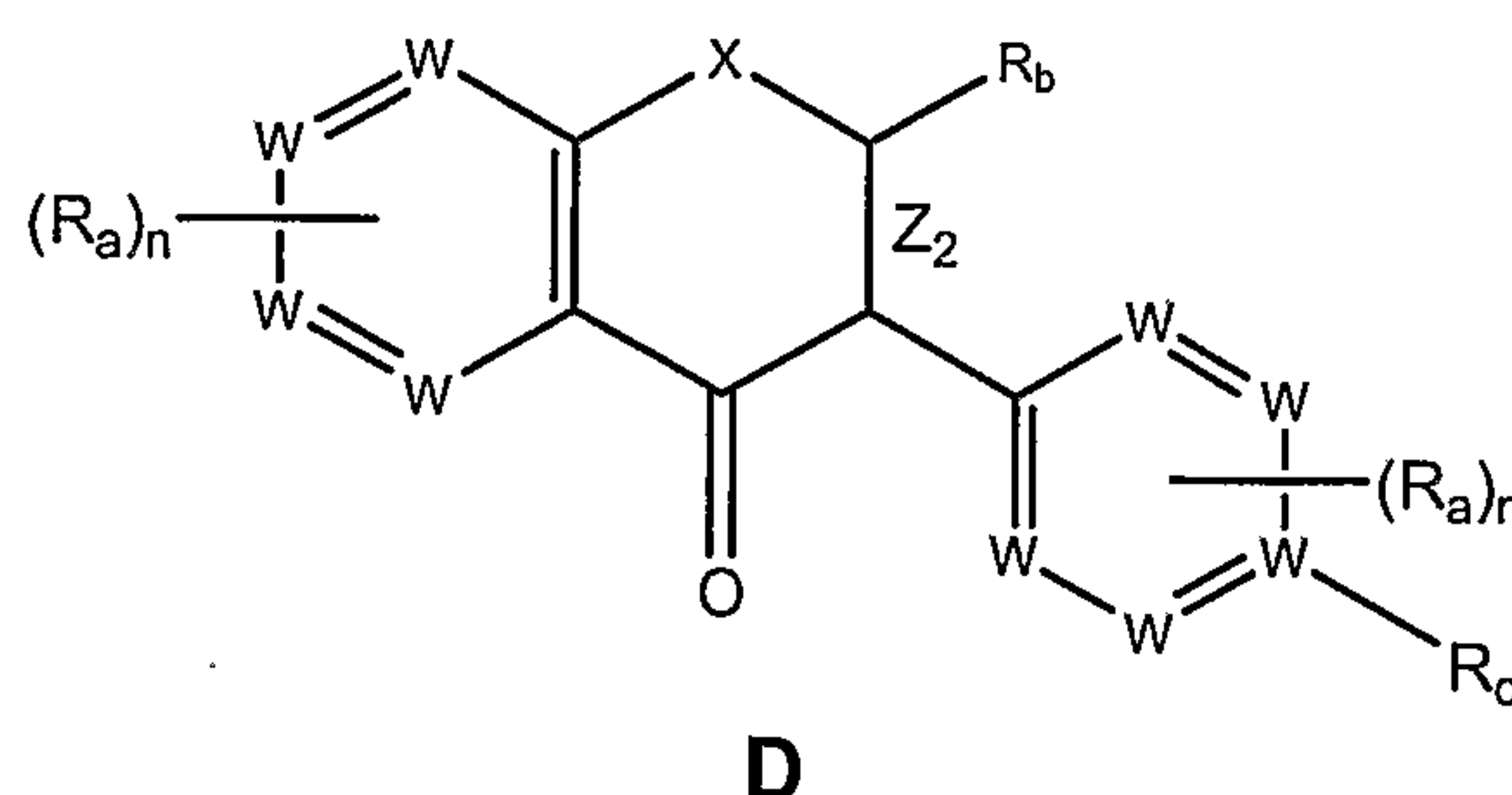
[0154] Flavanoids of Formula **C** can be prepared via the procedure of Scheme 3.



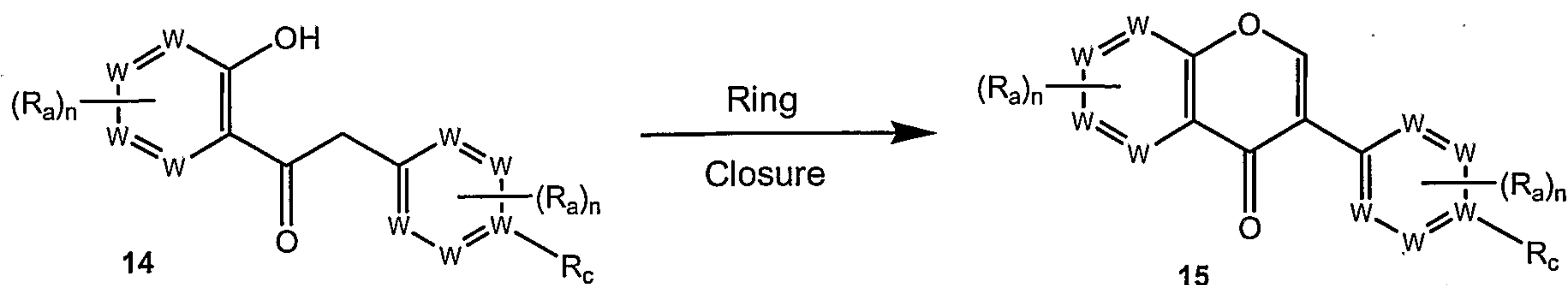
Scheme 3

[0155] Arylation of naphthalene analog **11** with boronic acid (or boronic ester) **12** occurs by a Pd-catalyzed Suzuki coupling. Suitable Pd catalysts include $\text{Pd}(\text{Ph}_3)_4$ along with non-phosphine Pd catalysts, such palladium acetate. Other coupling procedures that may be used in the synthesis of flavanoid **13** include Stille coupling.

[0156] Formula **D** represents a general formula for isoflavanoid compounds:

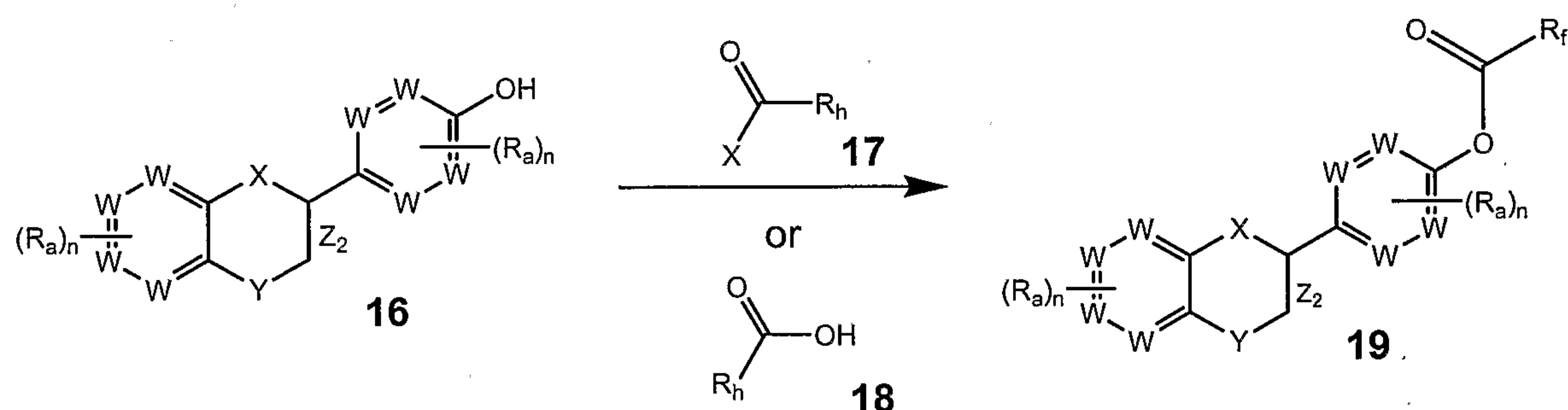


[0157] Scheme 4 illustrates a general synthesis of compounds of Formula **D**.

**Scheme 4**

[0158] Treatment of phenol **14** with boron trifluoride etherate and methane sulfonylchloride gives isoflavanoid **15**. Variations of the Scheme 4 procedure include the method described by Fokialakis et al., *Chemistry & Biology* 11: 397-406 (2004).

[0159] Prodrugs of flavanoid compounds can be prepared according to Scheme 5:

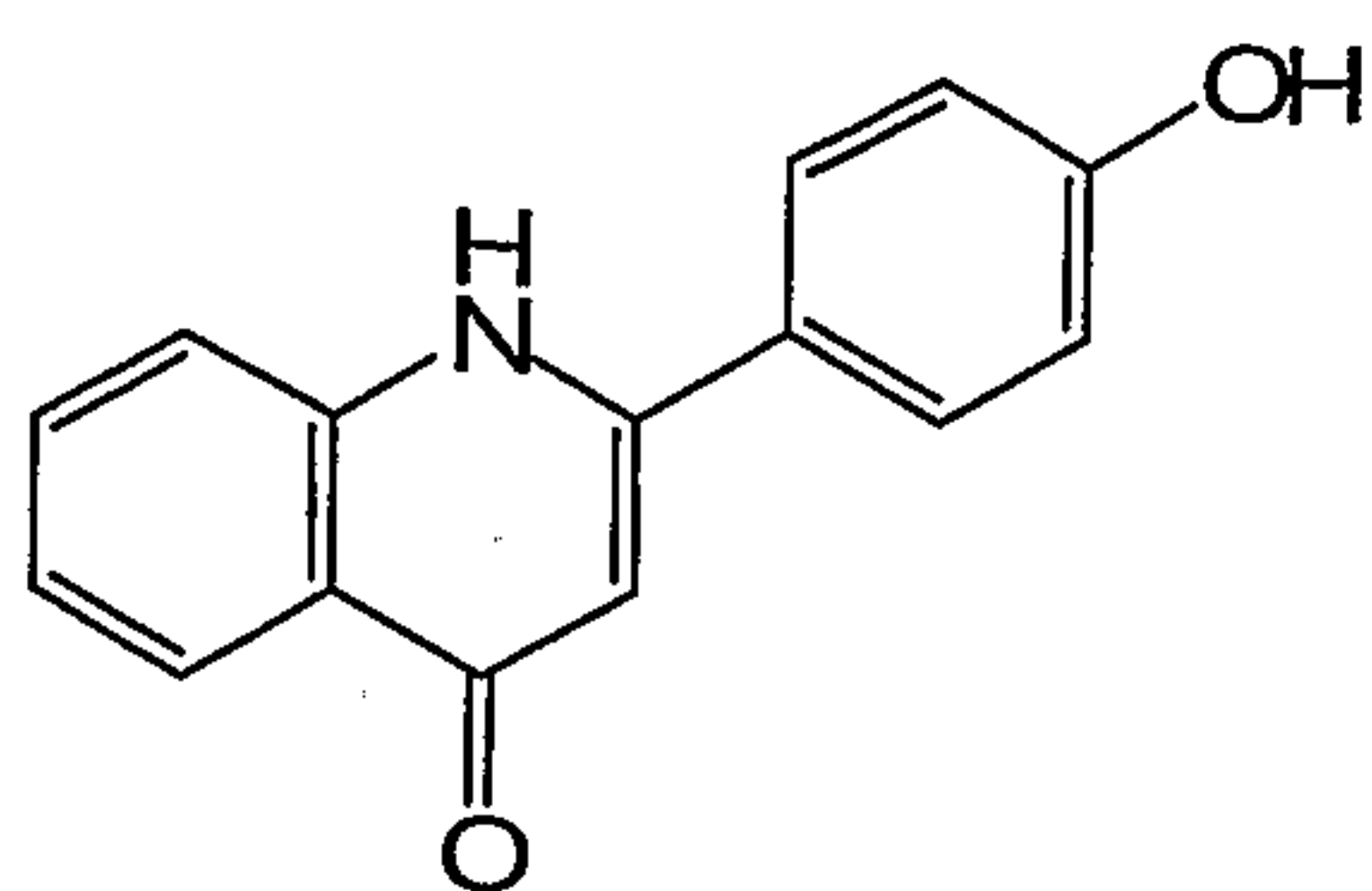
**Scheme 5**

Prodrug esters **19** can be synthesized by treating phenol **16** with acid halide **17**. Suitable acid halides include acid chlorides and bromides. Alternatively, esterification of phenol **16** with acid **18** in the presence of a carbodiimide, such as EDCI, affords ester **19**.

EXAMPLES

[0160] Examples of flavanoid compounds of Formula I include, but are not limited to, the following compounds:

- a) 2-(4-Hydroxy-phenyl)-1H-quinolin-4-one

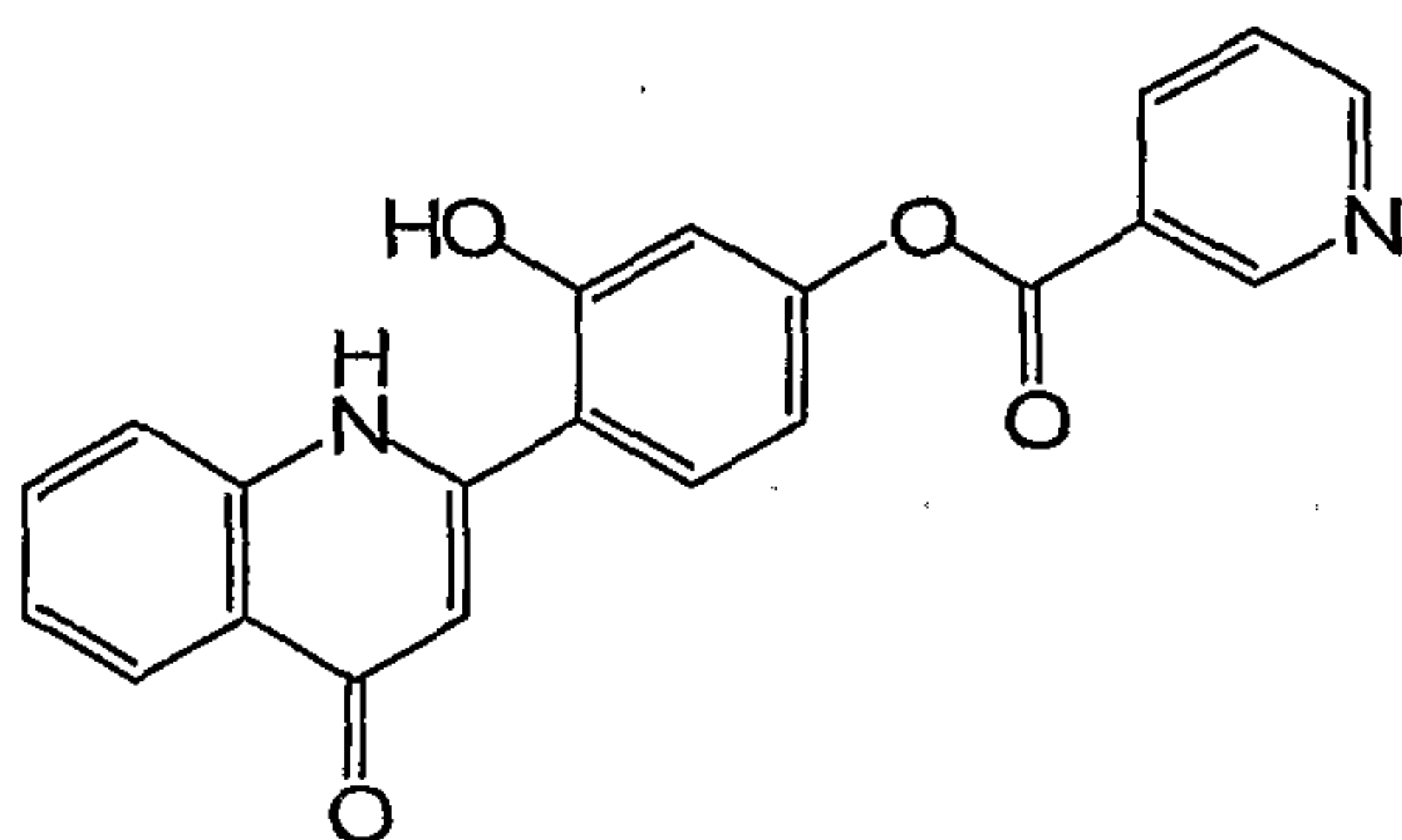


and its derivatives, including, but not limited to:

- 2-(2,4-Dihydroxy-phenyl)-1H-quinolin-4-one
- 2-(3,4-Dihydroxy-phenyl)-1H-quinolin-4-one
- 5-Hydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 6-Hydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 7-Hydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 8-Hydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 5,7-Dihydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 6,7- Dihydroxy -2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 7,8- Dihydroxy -2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 2-(2,4-Dihydroxy-phenyl)-7-hydroxy-1H-quinolin-4-one
- 2-(3,4-Dihydroxy-phenyl)-7-hydroxy-1H-quinolin-4-one
- 5,6-Dihydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 5,8-Dhydroxy-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 2-(2,4-Dihydroxy-phenyl)-5-hydroxy-1H-quinolin-4-one
- 2-(3,4-Dihydroxy-phenyl)-5-hydroxy-1H-quinolin-4-one
- 2-(2-Fluoro-4-hydroxy-phenyl)-1H-quinolin-4-one
- 2-(3-Fluoro-4-hydroxy-phenyl)-1H-quinolin-4-one
- 5-Fluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 6-Fluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
- 7-Fluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one

8-Fluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 5,7-Difluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 6,7-Difluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 7,8-Difluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 7-Fluoro-2-(2-fluoro-4-hydroxy-phenyl)-1H-quinolin-one
 7-Fluoro-2-(3-fluoro-4-hydroxy-phenyl)-1H-quinolin-4-one
 5,6-Difluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 5,8-Difluoro-2-(4-hydroxy-phenyl)-1H-quinolin-4-one
 5-Fluoro-2-(2-fluoro-4-hydroxy-phenyl)-1H-quinolin-4-one
 5-Fluoro-2-(3-fluoro-4-hydroxy-phenyl)-1H-quinolin-4-one
 Nicotinic acid 5-hydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester
 Nicotinic acid 2-hydroxy-5-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester
 Nicotinic acid 4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester
 Nicotinic acid 2-(4-hydroxy-phenyl)-4-oxo-1,4-dihydro-quinolin-5-yl ester
 Nicotinic acid 2-(4-hydroxy-phenyl)-4-oxo-1,4-dihydro-quinolin-6-yl ester
 Nicotinic acid 2-(4-hydroxy-phenyl)-4-oxo-1,4-dihydro-quinolin-7-yl ester
 Nicotinic acid 2-(4-hydroxy-phenyl)-4-oxo-1,4-dihydro-quinolin-8-yl ester

b) Nicotinic acid 4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester



and its derivatives, including, but not limited to:

Nicotinic acid 3-hydroxy-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(6-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-
phenyl ester

Nicotinic acid 2-hydroxy-4-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-
phenyl ester

Nicotinic acid 4-(5,7-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(6,7-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(7,8-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-
phenyl ester

Nicotinic acid 3-hydroxy-4-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-
phenyl ester

Nicotinic acid 4-(5,6-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,8-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-fluoro-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 2-fluoro-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(8-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-fluoro-4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl
ester

Nicotinic acid 2-fluoro-4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl
ester

Nicotinic acid 4-(5,7-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(6,7-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(7,8-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-fluoro-4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl
ester

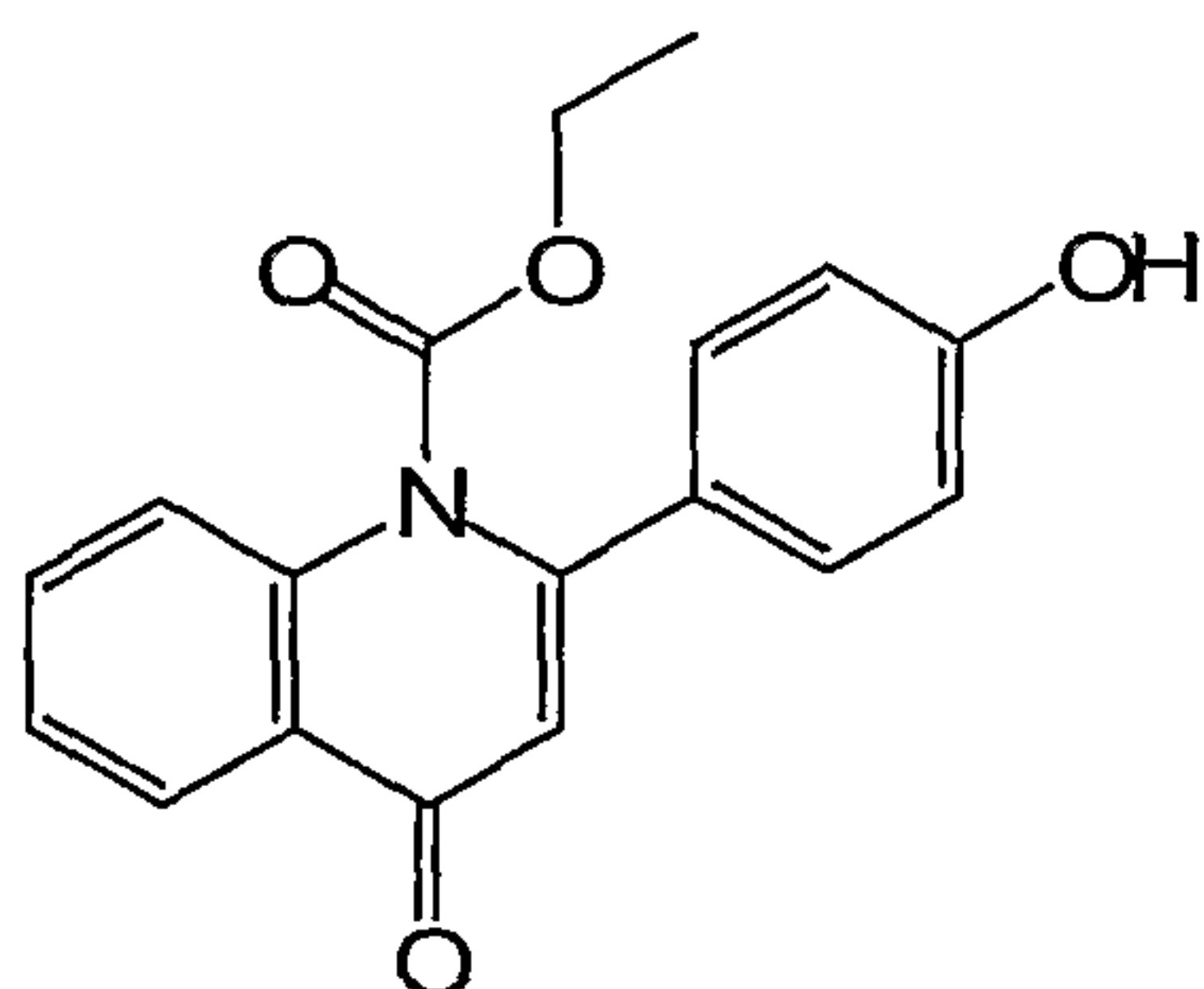
Nicotinic acid 2-fluoro-4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl
ester

Nicotinic acid 4-(5,6-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,7-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,8-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

c) 2-(4-Hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl
ester



and its derivatives, including, but not limited to:

2-(3,4-Dihydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

6-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

7-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

8-Hydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,7-Dihydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

6,7-Dihydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

7,8-Dihydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(3,4-Dihydroxy-phenyl)-7-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,6-Dihydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,8-Dihydroxy-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(3,4-Dihydroxy-phenyl)-5-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(3-Fluoro-4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5-Fluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

6-Fluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

7-Fluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

8-Fluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,7-Difluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

6,7-Difluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

7,8-Difluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

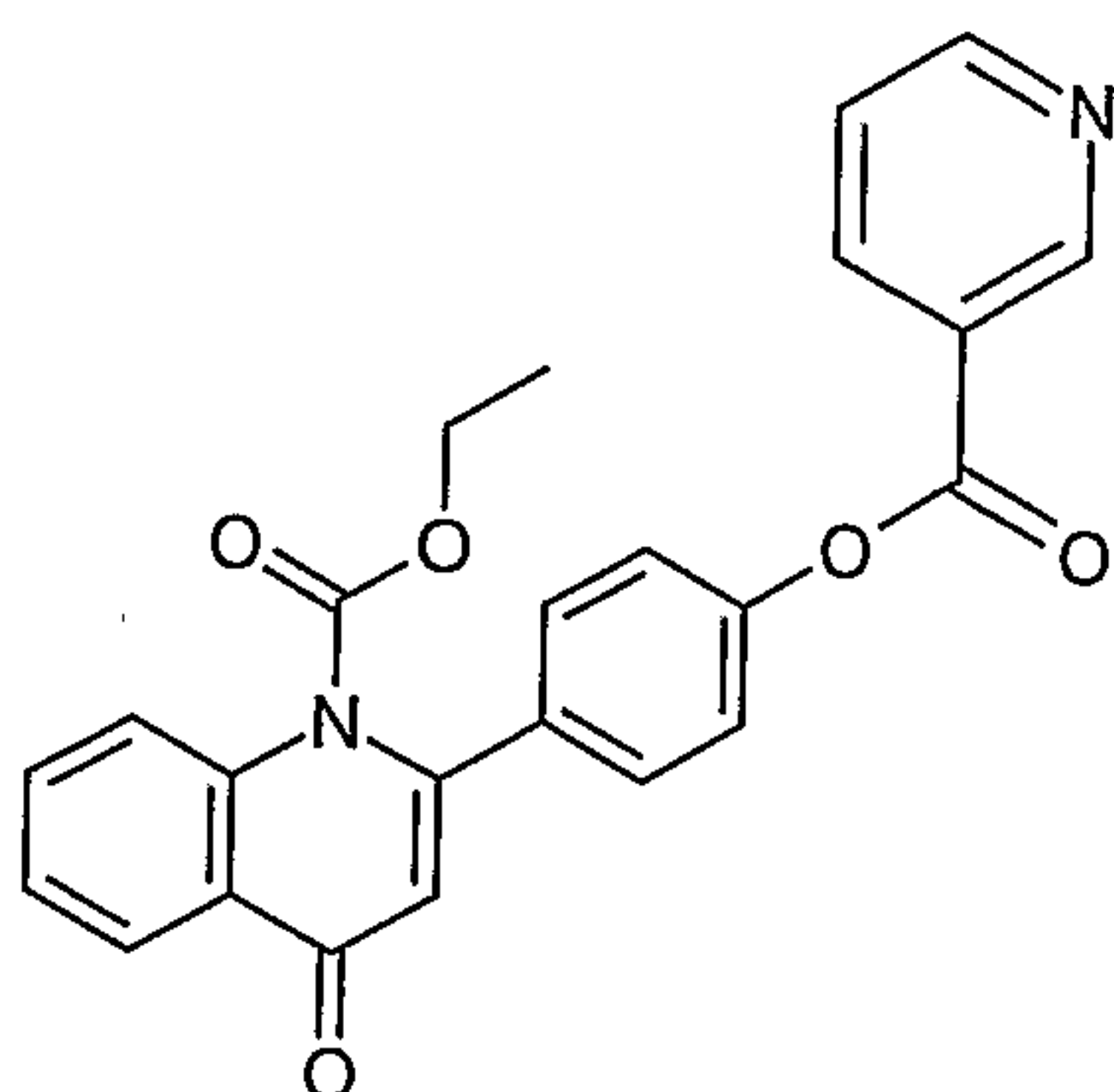
7-Fluoro-2-(3-fluoro-4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,6-Difluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,8-Difluoro-2-(4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5-Fluoro-2-(3-fluoro-4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

d) 4-Oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester



and its derivatives, including but not limited to:

2-[3-Hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5-Hydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

6-Hydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

7-Hydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

8-Hydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

7-Hydroxy-2-[3-hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,7-Dihydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

6,7-Dihydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

7,8-Dihydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

5-Hydroxy-2-[3-hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,6-Dihydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

5,8-Dihydroxy-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

2-[3-Fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5-Fluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

6-Fluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

7-Fluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

8-Fluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

7-Fluoro-2-[3-fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,7-Difluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

6,7-Difluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

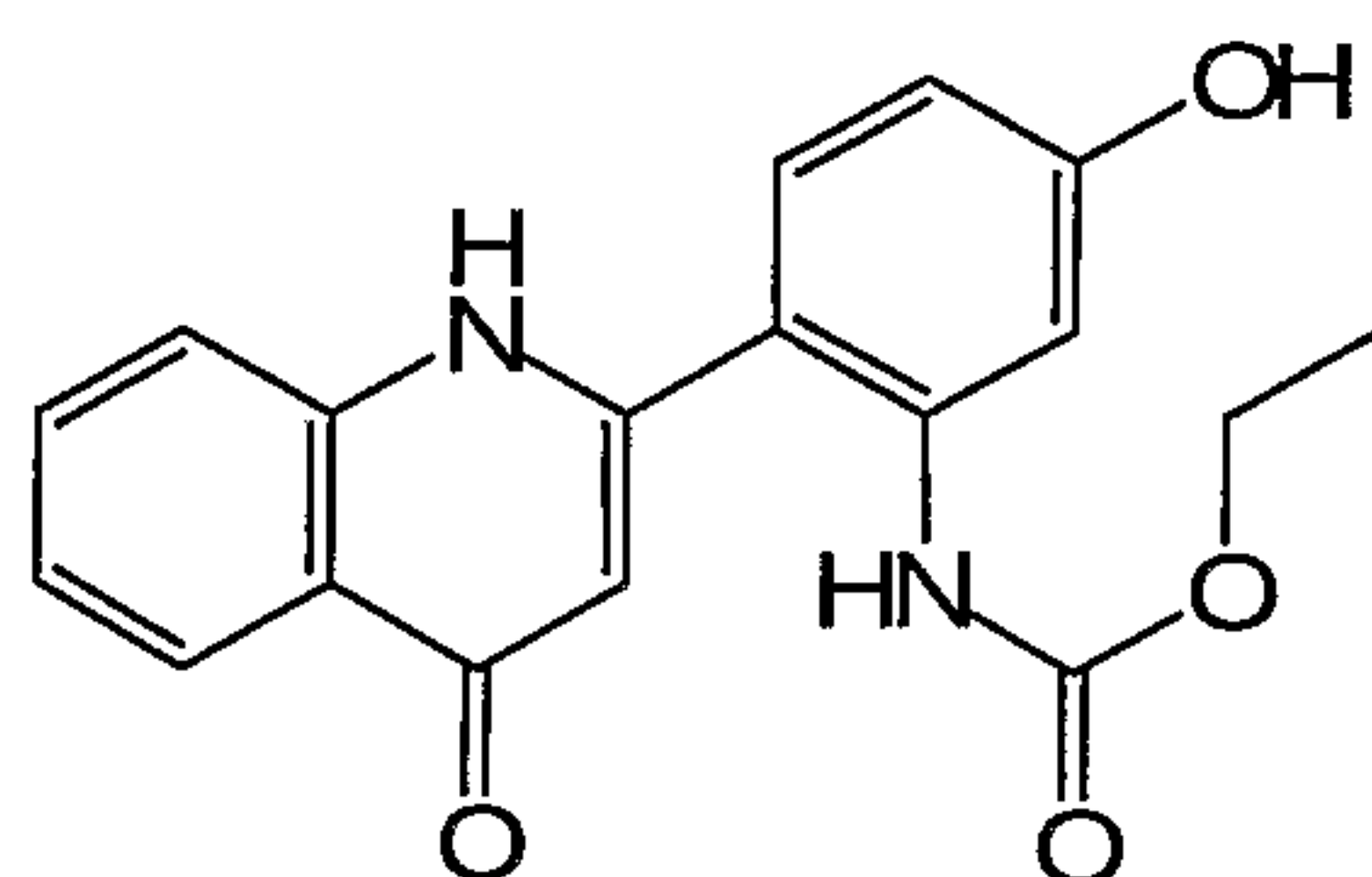
7,8-Difluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

5-Fluoro-2-[3-fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

5,6-Difluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

5,8-Difluoro-4-oxo-2-[4-(pyridine-3-carbonyloxy)-phenyl]-4H-quinoline-1-carboxylic acid ethyl ester

e) [5-Hydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester



and its derivatives, including but not limited to:

[3,5-Dihydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[2-(5,7-Dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(6,7-Dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(7,8-Dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[3,5-Dihydroxy-2-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[2-(5,6-Dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(5,8-Dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[3,5-Dihydroxy-2-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[3-Fluoro-5-hydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[4-Fluoro-5-hydroxy-2-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl]-carbamic acid ethyl ester

[2-(5-Fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(6-Fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(7-Fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(8-Fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(5,7-Difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(6,7-Difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(7,8-Difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[3-Fluoro-2-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[4-Fluoro-2-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

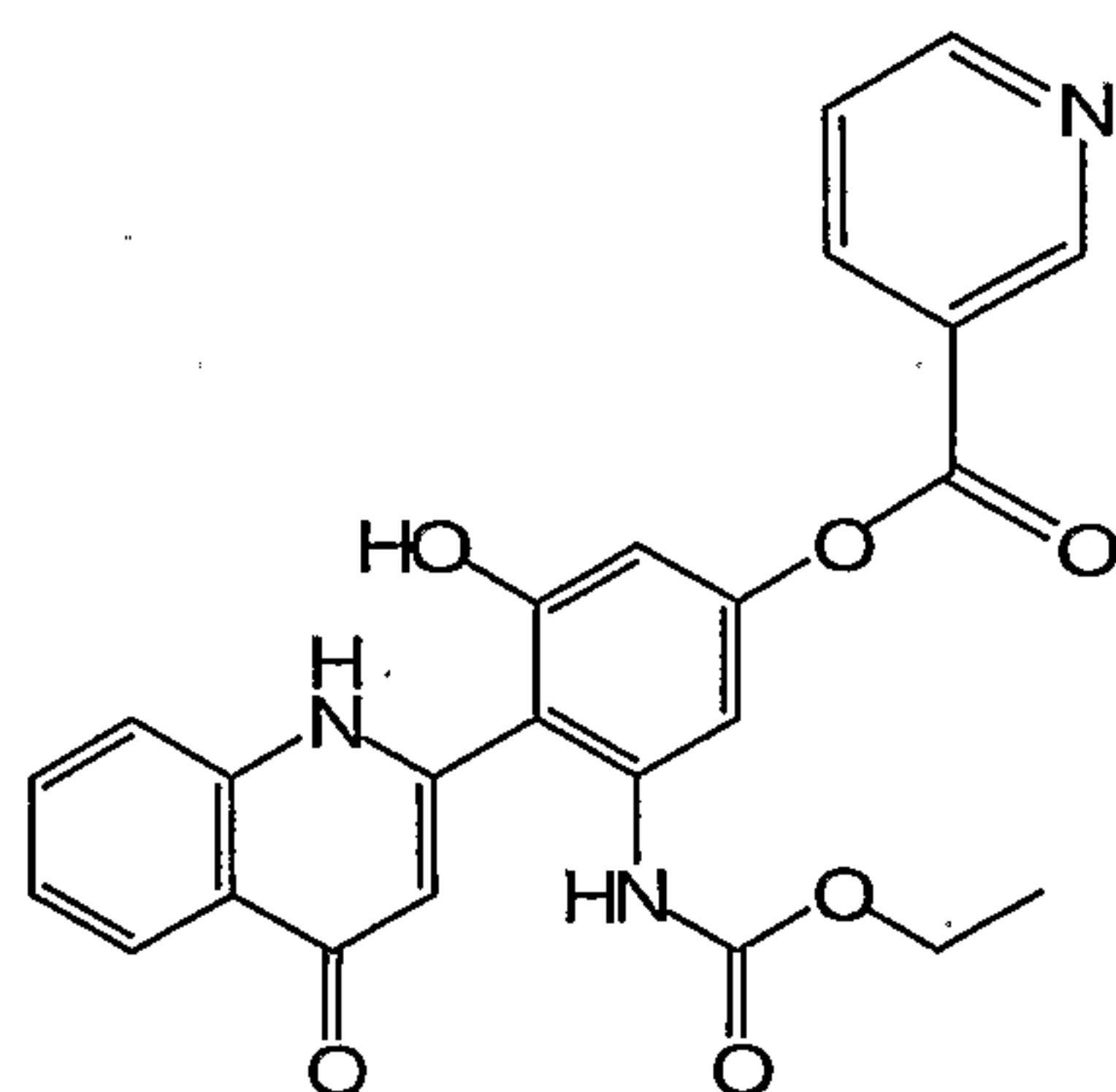
[2-(5,6-Difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[2-(5,8-Difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[4-Fluoro-2-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-carbamic acid ethyl ester

[4-Fluoro-2-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-5-hydroxy-phenyl]-
carbamic acid ethyl ester

f) Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-1,4-dihydro-quinolin-
2-yl)-phenyl ester



and its derivatives, including but not limited to:

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-1,4-dihydro-
quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(7-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,7-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(6,7-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(7,8-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(5-hydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,6-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(5,8-dihydroxy-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-fluoro-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-fluoro-4-(4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-fluoro-4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-fluoro-4-(7-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,7-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(6,7-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(7,8-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

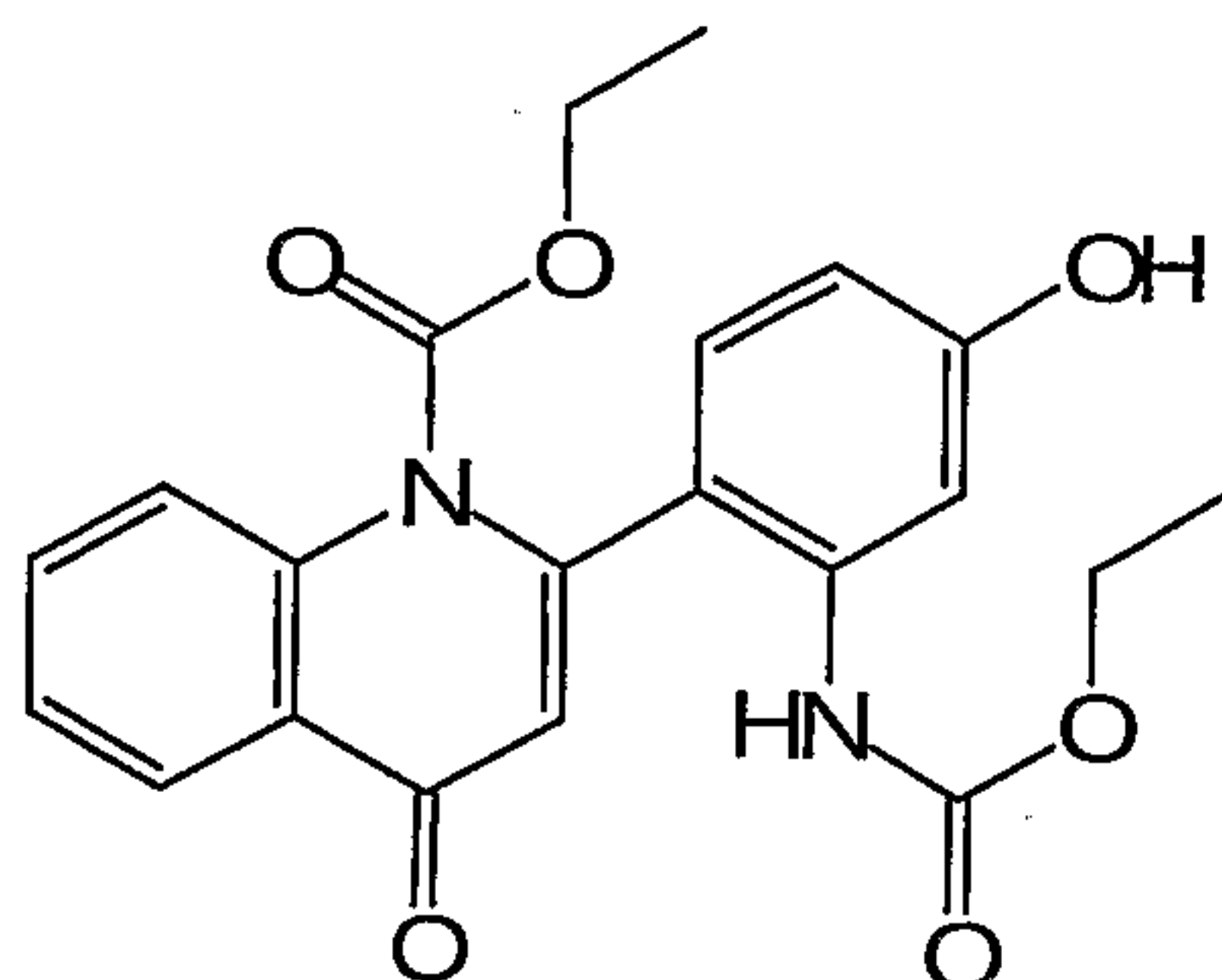
Nicotinic acid 3-ethoxycarbonylamino-5-fluoro-4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-fluoro-4-(5-fluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-phenyl ester

Nicotinic acid 4-(5,6-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

Nicotinic acid 4-(5,8-difluoro-4-oxo-1,4-dihydro-quinolin-2-yl)-3-ethoxycarbonylamino-phenyl ester

g) 2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester



and its derivatives, including but not limited to:

2-(2-Ethoxycarbonylamino-4,5-dihydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-5-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-6-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-7-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-5-fluoro-4-hydroxy-phenyl)-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

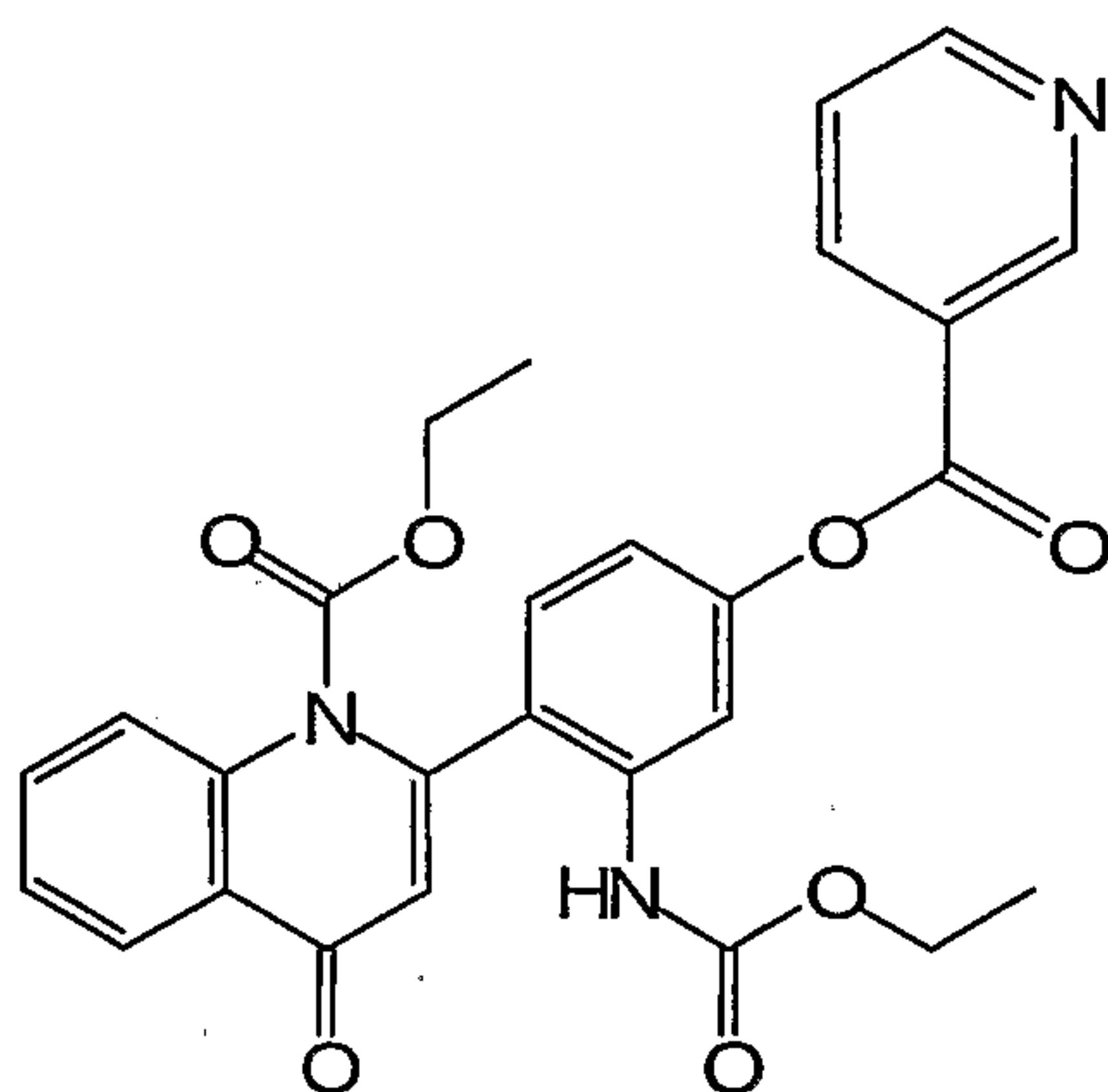
2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-5-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-6-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-7-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-(2-Ethoxycarbonylamino-4-hydroxy-phenyl)-7-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

h) 2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester



and its derivatives:

2-[2-Ethoxycarbonylamino-5-hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-6-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-7-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-8-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-5-hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-7-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,7-dihydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-6,7-dihydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-7,8-dihydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-5-hydroxy-4-(pyridine-3-carbonyloxy)-phenyl]-5-hydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,6-dihydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,8-dihydroxy-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-5-fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-6-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-7-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-8-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-5-fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-7-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,7-difluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-6,7-difluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

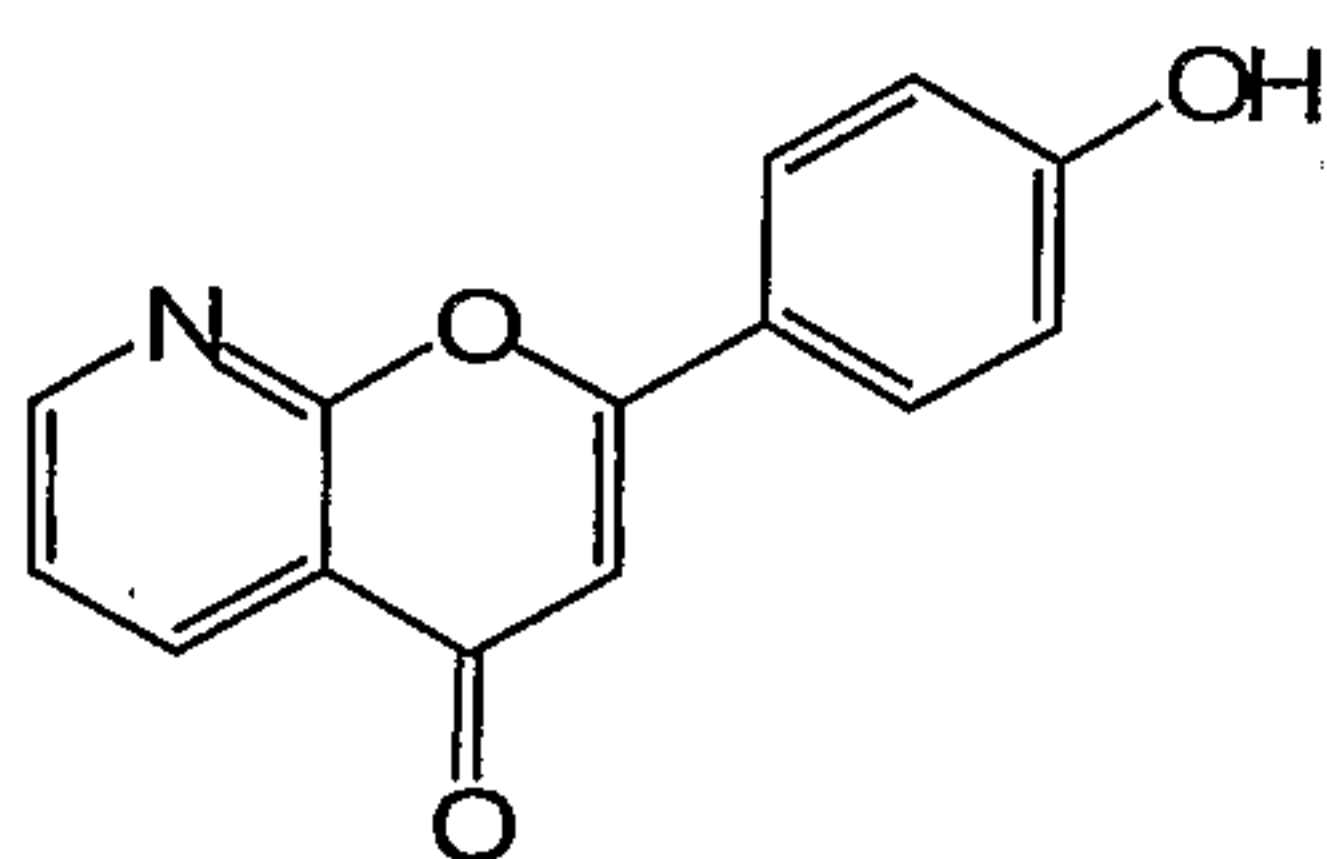
2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-7,8-difluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-5-fluoro-4-(pyridine-3-carbonyloxy)-phenyl]-5-fluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,6-difluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

2-[2-Ethoxycarbonylamino-4-(pyridine-3-carbonyloxy)-phenyl]-5,8-difluoro-4-oxo-4H-quinoline-1-carboxylic acid ethyl ester

i) 2-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one



and its derivatives, including but not limited to:

2-(2,4-Dihydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

2-(3,4-Dihydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

5-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

6-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

7-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

Nicotinic acid 4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(5-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(6-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(7-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl
ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-carbamic acid
ethyl ester

[3,5-Dihydroxy-2-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-carbamic
acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-carbamic
acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-
carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-
carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl]-
carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-
yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

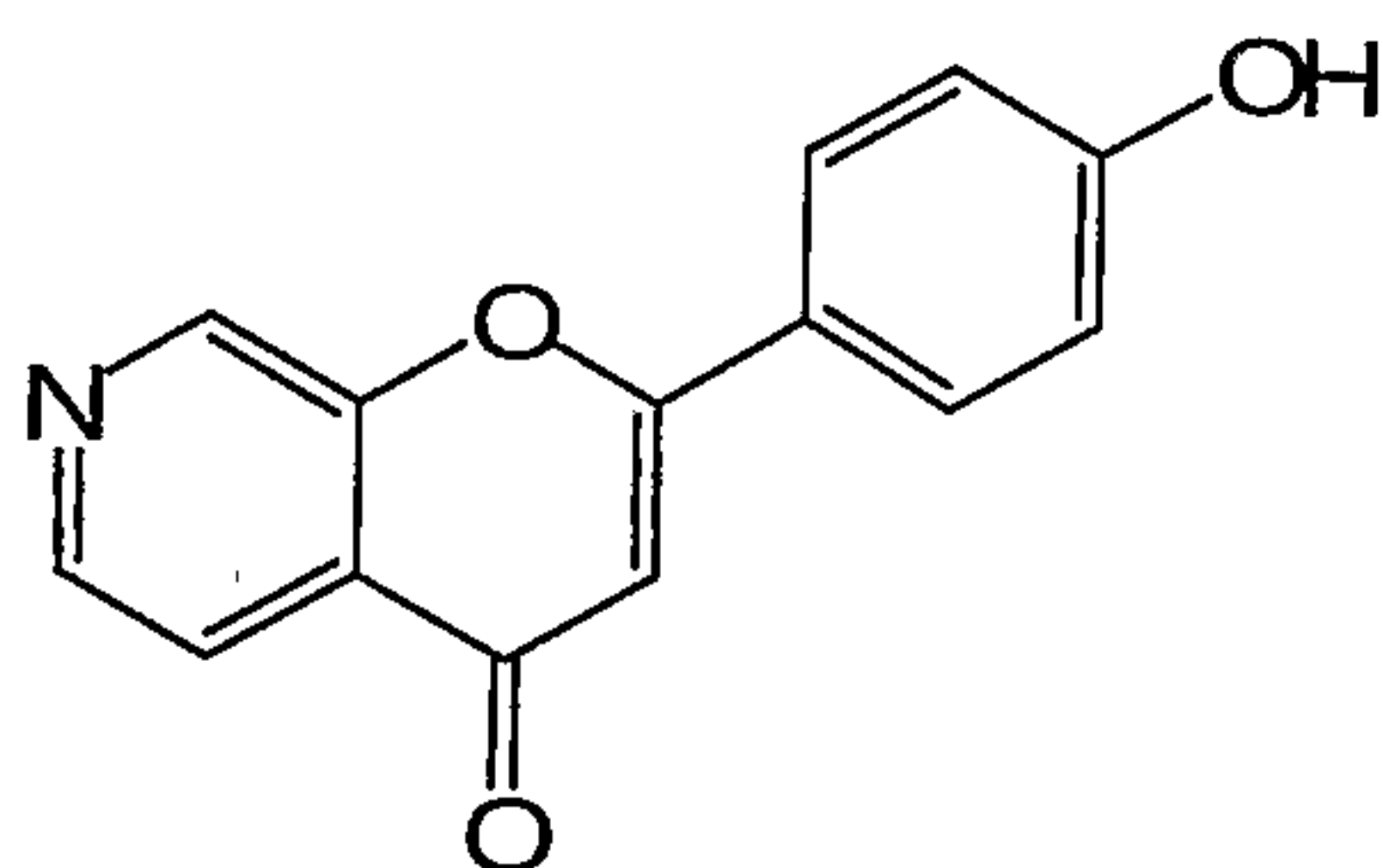
Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-4H-pyrano[2,3-b]pyridin-2-yl)-phenyl ester

j) 2-(4-Hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one



and its derivatives, including but not limited to:

2-(2,4-Dihydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

2-(3,4-Dihydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

5-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

6-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

8-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

Nicotinic acid 4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(5-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(6-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[3,5-Dihydroxy-2-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

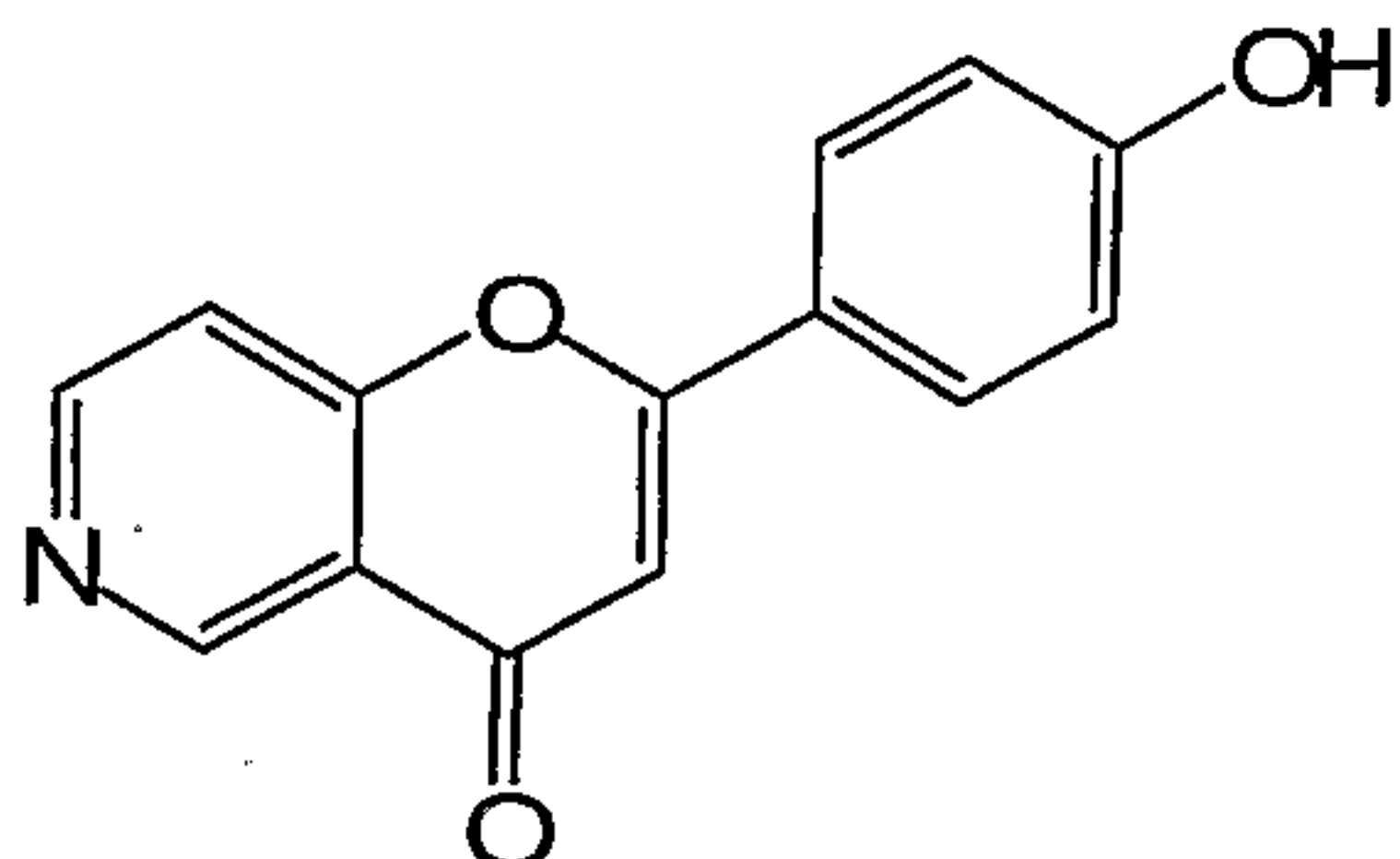
Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-4H-pyrano[2,3-c]pyridin-2-yl)-phenyl ester

k) 2-(4-Hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one



and its derivatives, including but not limited to:

2-(2,4-Dihydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

2-(3,4-Dihydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

5-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

7-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

8-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

Nicotinic acid 4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(5-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(7-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[3,5-Dihydroxy-2-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

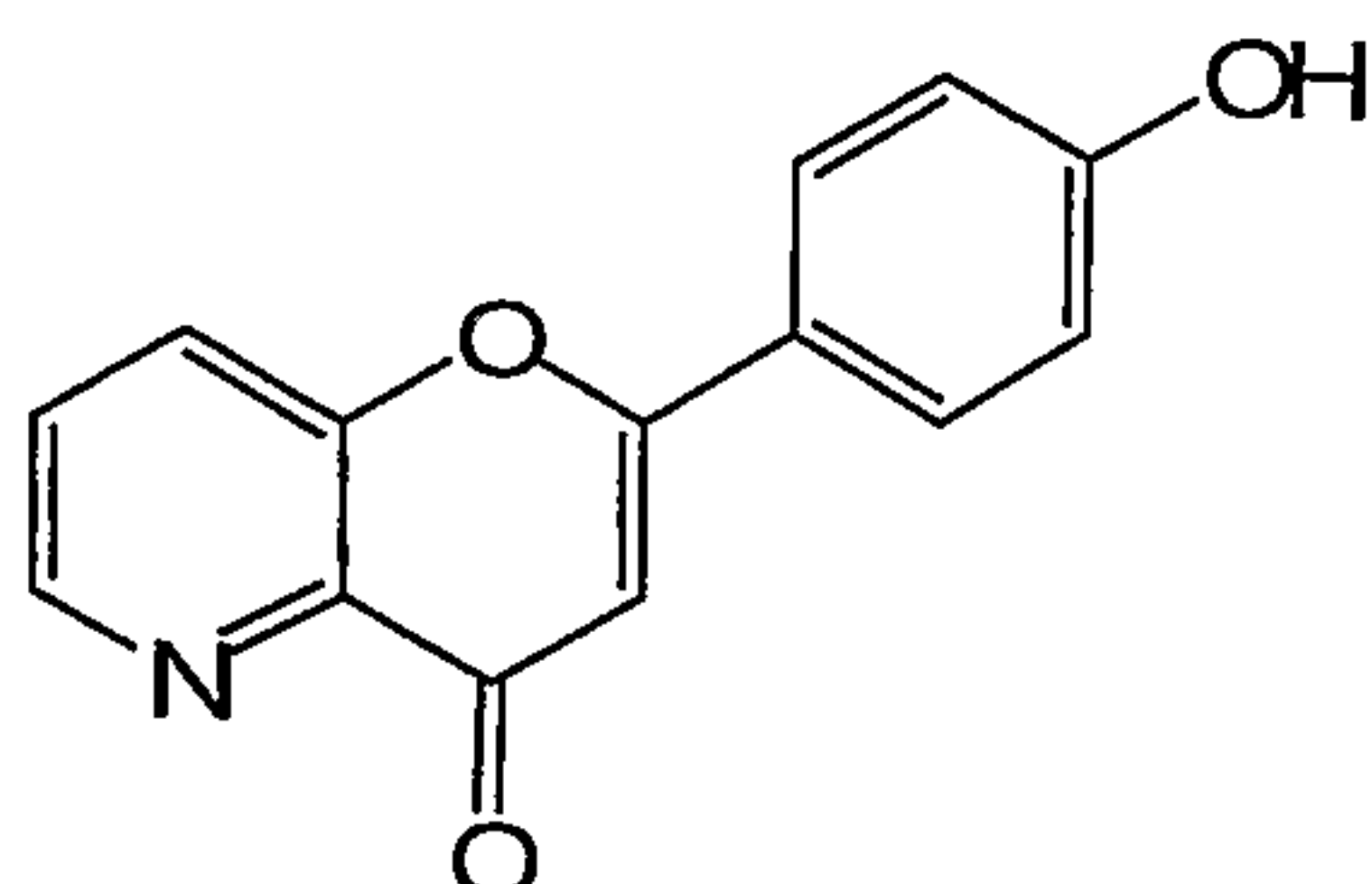
Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-4H-pyrano[3,2-c]pyridin-2-yl)-phenyl ester

l) 2-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one



and its derivatives, including but not limited to:

2-(2,4-Dihydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

2-(3,4-Dihydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

6-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

7-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

8-Hydroxy-2-(4-hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

Nicotinic acid 4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(6-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(7-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl
ester

Nicotinic acid 4-(8-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl
ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic acid
ethyl ester

[3,5-Dihydroxy-2-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic
acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl]-carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

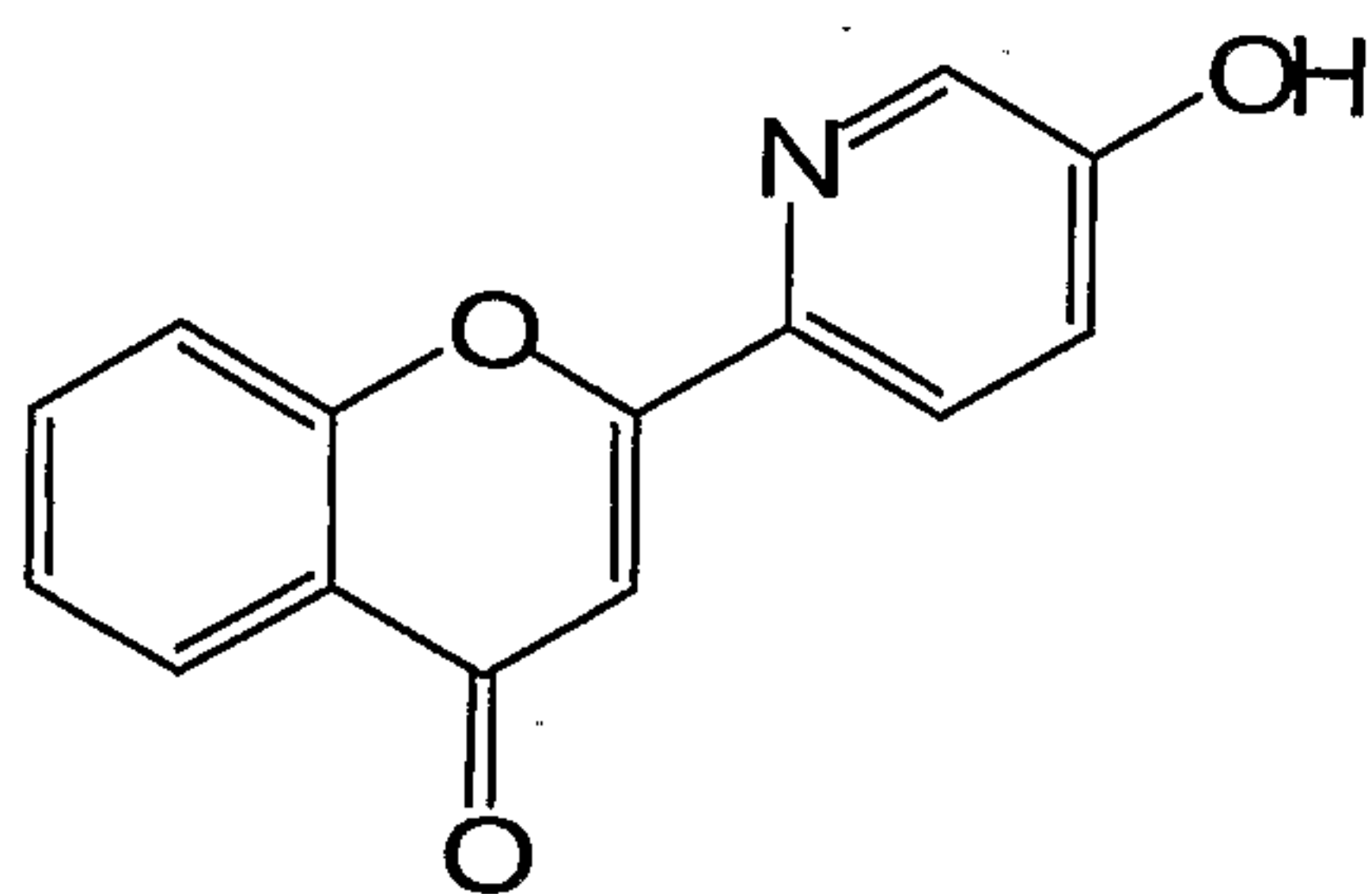
Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-4H-pyrano[3,2-b]pyridin-2-yl)-phenyl ester

m) 2-(5-Hydroxy-pyridin-2-yl)-chromen-4-one



and its derivatives, including but not limited to:

2-(5,6-Dihydroxy-pyridin-2-yl)-chromen-4-one

2-(3,5-Dihydroxy-pyridin-2-yl)-chromen-4-one

2-(4,5-Dihydroxy-pyridin-2-yl)-5-hydroxy-chromen-4-one

5-Hydroxy-2-(5-hydroxy-pyridin-2-yl)-chromen-4-one

6-Hydroxy-2-(5-hydroxy-pyridin-2-yl)-chromen-4-one

7-Hydroxy-2-(5-hydroxy-pyridin-2-yl)-chromen-4-one

8-Hydroxy-2-(5-hydroxy-pyridin-2-yl)-chromen-4-one

Nicotinic acid 6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 2-hydroxy-6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 5-hydroxy-6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 4-hydroxy-6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 6-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 6-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 6-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 6-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

[5-Hydroxy-2-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic acid ethyl
ester

[5,6-Dihydroxy-2-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic acid ethyl
ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic
acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic
acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl]-carbamic acid ethyl ester

Nicotinic acid 5-ethoxycarbonylamino-6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-6-(4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

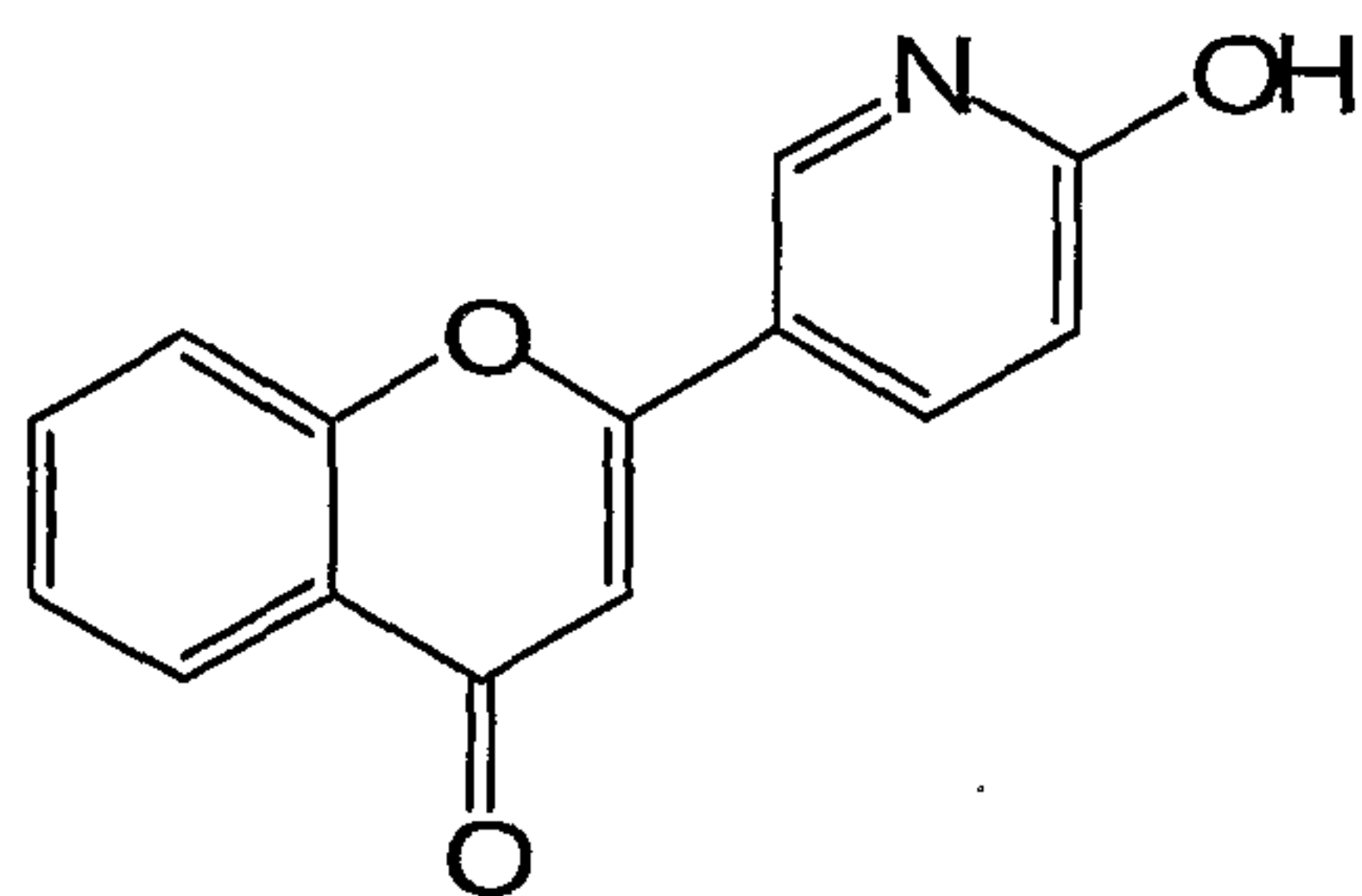
Nicotinic acid 5-ethoxycarbonylamino-6-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 5-ethoxycarbonylamino-6-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 5-ethoxycarbonylamino-6-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

Nicotinic acid 5-ethoxycarbonylamino-6-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-3-yl ester

n) 2-(6-Hydroxy-pyridin-3-yl)-chromen-4-one



and its derivatives, including but not limited to:

2-(2,6-Dihydroxy-pyridin-3-yl)-chromen-4-one

5-Hydroxy-2-(6-hydroxy-pyridin-3-yl)-chromen-4-one

6-Hydroxy-2-(6-hydroxy-pyridin-3-yl)-chromen-4-one

7-Hydroxy-2-(6-hydroxy-pyridin-3-yl)-chromen-4-one

8-Hydroxy-2-(6-hydroxy-pyridin-3-yl)-chromen-4-one

Nicotinic acid 5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-hydroxy-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-hydroxy-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 5-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 5-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 5-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 5-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

[6-Hydroxy-3-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[4,6-Dihydroxy-3-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[6-Hydroxy-3-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[6-Hydroxy-3-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[6-Hydroxy-3-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[6-Hydroxy-3-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl]-carbamic acid ethyl ester

[2-Hydroxy-5-(4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

[2,6-Dihydroxy-3-(4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

[2-Hydroxy-5-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

[2-Hydroxy-5-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

[2-Hydroxy-5-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

[2-Hydroxy-5-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-4-yl]-carbamic acid ethyl ester

Nicotinic acid 4-ethoxycarbonylamino-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-ethoxycarbonylamino-6-hydroxy-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-ethoxycarbonylamino-5-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-ethoxycarbonylamino-5-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-ethoxycarbonylamino-5-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 4-ethoxycarbonylamino-5-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-ethoxycarbonylamino-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-ethoxycarbonylamino-4-hydroxy-5-(4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

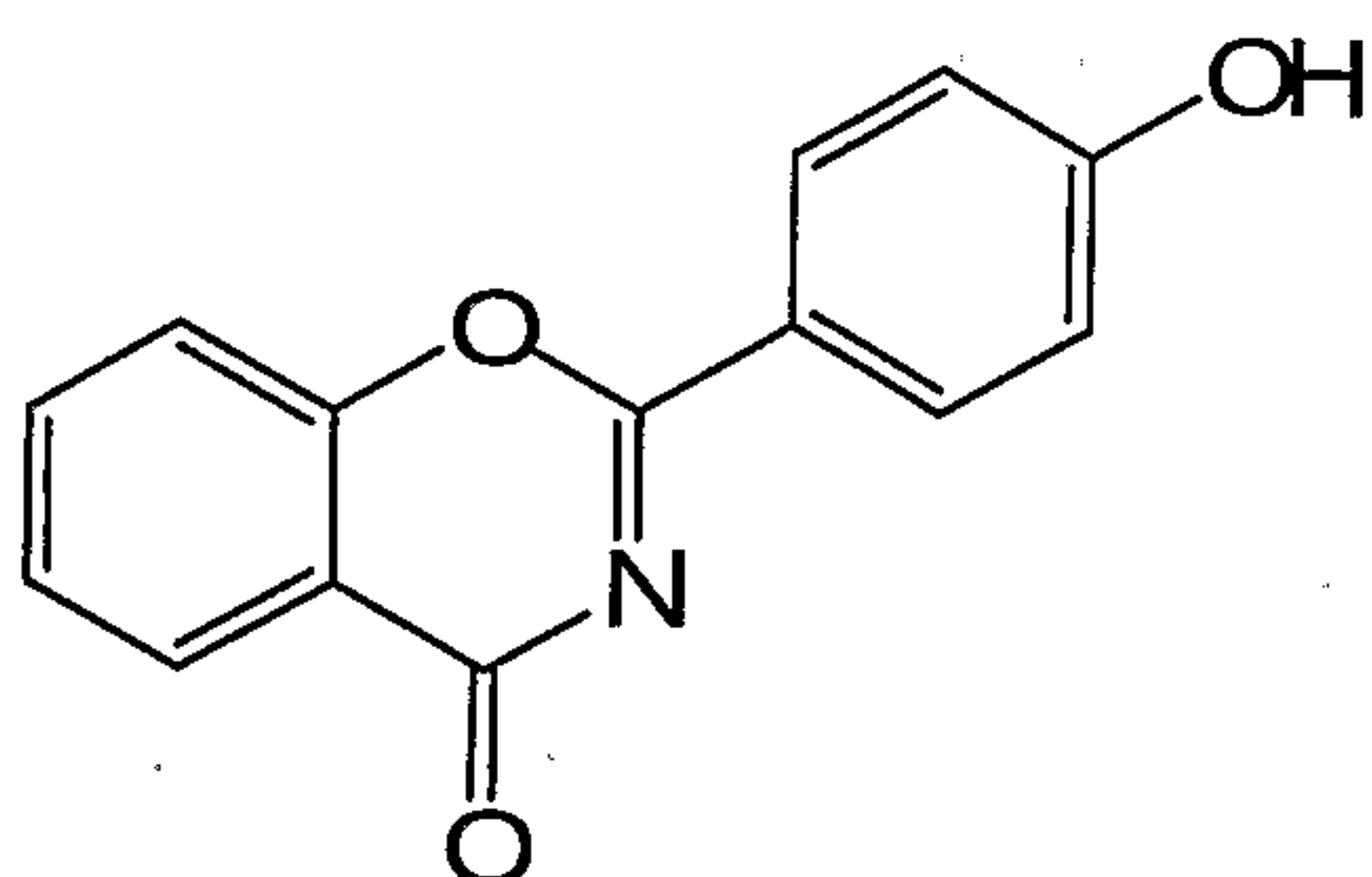
Nicotinic acid 6-ethoxycarbonylamino-5-(5-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-ethoxycarbonylamino-5-(6-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-ethoxycarbonylamino-5-(7-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

Nicotinic acid 6-ethoxycarbonylamino-5-(8-hydroxy-4-oxo-4H-chromen-2-yl)-pyridin-2-yl ester

o) 2-(4-Hydroxy-phenyl)-benzo[e][1,3]oxazin-4-one



and its derivatives, including but limited to:

2-(2,4-Dihydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

2-(3,4-Dihydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

5-Hydroxy-2-(4-hydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

6-Hydroxy-2-(4-hydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

7-Hydroxy-2-(4-hydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

8-Hydroxy-2-(4-hydroxy-phenyl)-benzo[e][1,3]oxazin-4-one

Nicotinic acid 4-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 4-(5-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 4-(6-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 4-(7-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

[5-Hydroxy-2-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-carbamic acid

ethyl ester

[3,5-Dihydroxy-2-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-carbamic

acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-carbamic

acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-

carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-

carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-

carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl]-

carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-benzo[e][1,3]oxazin-2-

yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-benzo[e][1,3]oxazin-2-

yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-

benzo[e][1,3]oxazin-2-yl)-phenyl ester

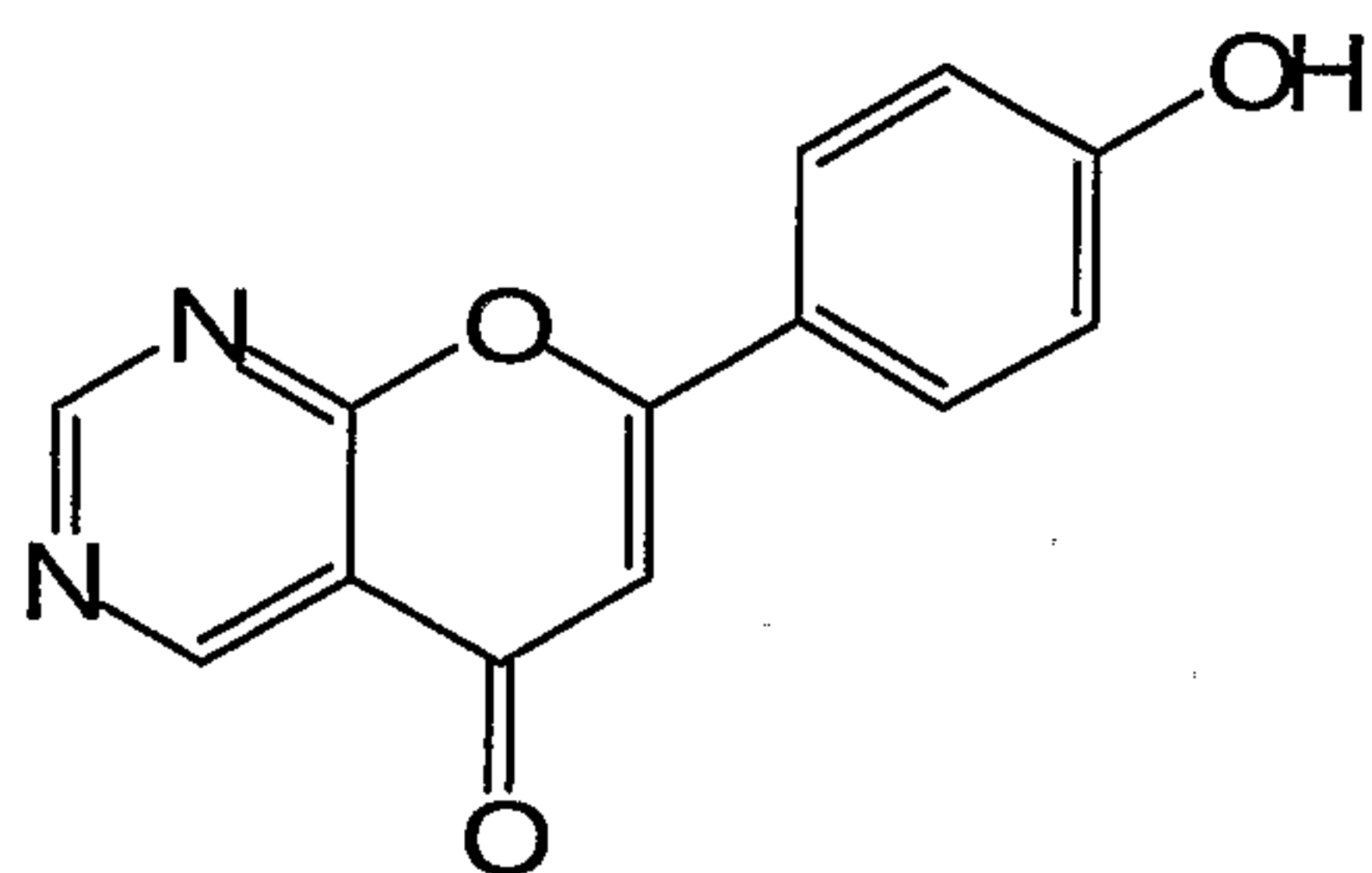
Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-4H-benzo[e][1,3]oxazin-2-yl)-phenyl ester

p) 7-(4-Hydroxy-phenyl)-pyrano[2,3-d]pyrimidin-5-one



and its derivatives, including but not limited to:

7-(2,4-Dihydroxy-phenyl)-pyrano[2,3-d]pyrimidin-5-one

7-(3,4-Dihydroxy-phenyl)-pyrano[2,3-d]pyrimidin-5-one

4-Hydroxy-7-(4-hydroxy-phenyl)-pyrano[2,3-d]pyrimidin-5-one

2-Hydroxy-7-(4-hydroxy-phenyl)-pyrano[2,3-d]pyrimidin-5-one

Nicotinic acid 4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 4-(4-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 4-(2-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

[5-Hydroxy-2-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl]-carbamic acid ethyl ester

[3,5-Dihydroxy-2-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(4-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(2-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl]-carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

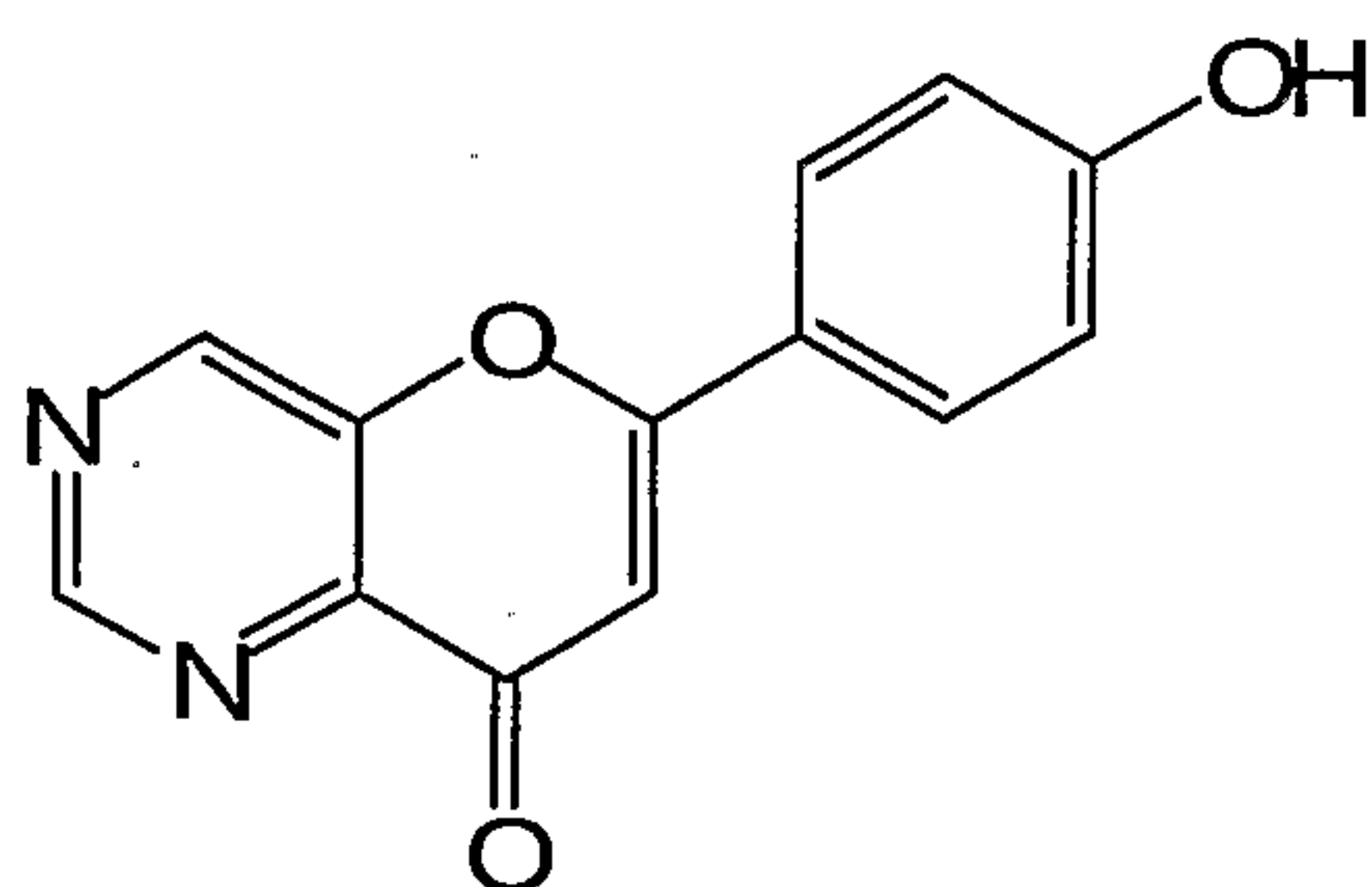
Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(2-hydroxy-5-oxo-5H-pyrano[2,3-d]pyrimidin-7-yl)-phenyl ester

q) 6-(4-Hydroxy-phenyl)-pyrano[3,2-d]pyrimidin-8-one



and its derivatives, including but not limited to:

6-(2,4-Dihydroxy-phenyl)-pyrano[3,2-d]pyrimidin-8-one

6-(3,4-Dihydroxy-phenyl)-pyrano[3,2-d]pyrimidin-8-one

2-Hydroxy-6-(4-hydroxy-phenyl)-pyrano[3,2-d]pyrimidin-8-one

4-Hydroxy-6-(4-hydroxy-phenyl)-pyrano[3,2-d]pyrimidin-8-one

Nicotinic acid 4-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl
ester

Nicotinic acid 2-hydroxy-4-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl
ester

Nicotinic acid 4-(2-hydroxy-8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl
ester

Nicotinic acid 4-(2-hydroxy-8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl
ester

[5-Hydroxy-2-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl]-carbamic acid
ethyl ester

[3,5-Dihydroxy-2-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl]-carbamic
acid ethyl ester

[4,5-Dihydroxy-2-(8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl]-carbamic
acid ethyl ester

[5-Hydroxy-2-(2-hydroxy-8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl]-
carbamic acid ethyl ester

[5-Hydroxy-2-(4-hydroxy-8-oxo-8H-pyrano[3,2-d]pyrimidin-6-yl)-phenyl]-
carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-oxo-8H-pyrano[3,2-d]pyrimidin-
6-yl)-phenyl ester

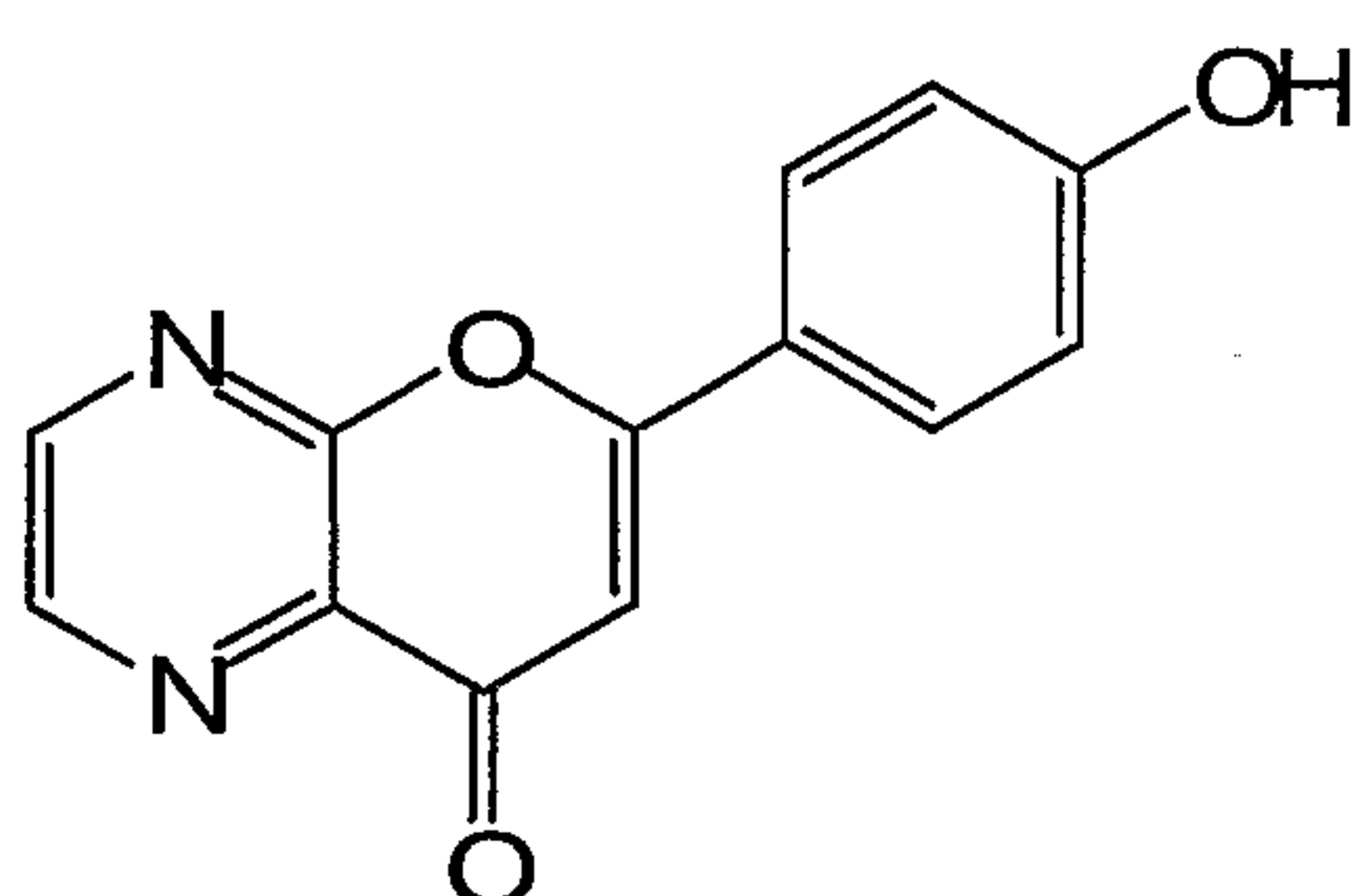
Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(8-oxo-8H-pyrano[3,2-
d]pyrimidin-6-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(8-oxo-8H-pyrano[3,2-
d]pyrimidin-6-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(2-hydroxy-8-oxo-8H-pyrano[3,2-
d]pyrimidin-6-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-hydroxy-8-oxo-8H-pyrano[3,2-
d]pyrimidin-6-yl)-phenyl ester

r) 6-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyrazin-8-one



and its derivatives, including, but not limited to:

6-(2,4-Dihydroxy-phenyl)-pyrano[2,3-b]pyrazin-8-one

6-(3,4-Dihydroxy-phenyl)-pyrano[2,3-b]pyrazin-8-one

2-Hydroxy-6-(4-hydroxy-phenyl)-pyrano[2,3-b]pyrazin-8-one

3-Hydroxy-6-(4-hydroxy-phenyl)-pyrano[2,3-b]pyrazin-8-one

Nicotinic acid 4-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl ester

Nicotinic acid 3-hydroxy-4-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl
ester

Nicotinic acid 2-hydroxy-4-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl
ester

Nicotinic acid 4-(2-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl
ester

Nicotinic acid 4-(3-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl
ester

[5-Hydroxy-2-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl]-carbamic acid
ethyl ester

[3,5-Dihydroxy-2-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl]-carbamic
acid ethyl ester

[4,5-Dihydroxy-2-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl]-carbamic
acid ethyl ester

[5-Hydroxy-2-(2-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl]-
carbamic acid ethyl ester

[5-Hydroxy-2-(3-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl]-
carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-oxo-8H-pyrano[2,3-b]pyrazin-6-
yl)-phenyl ester

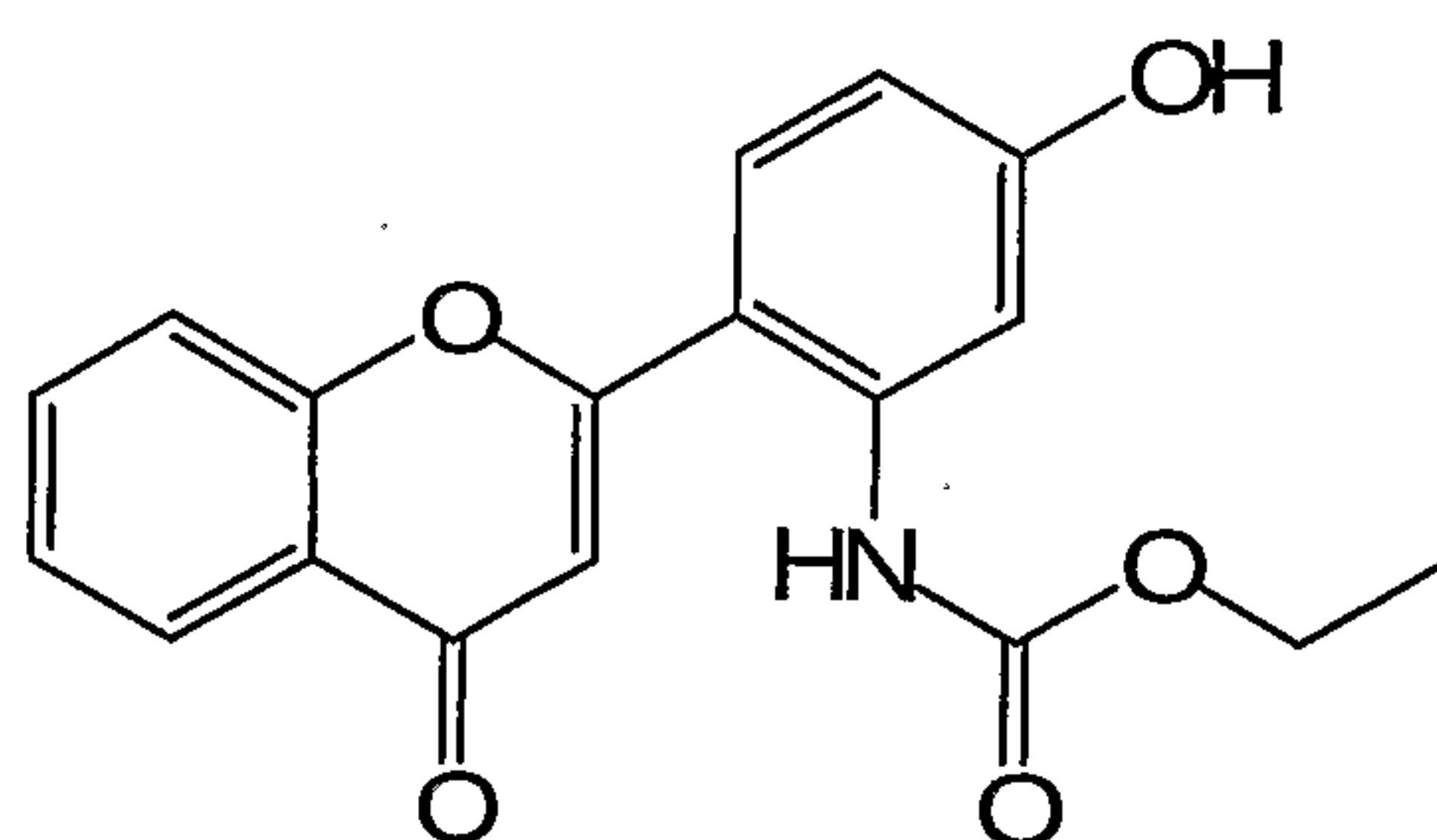
Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(8-oxo-8H-pyrano[2,3-
b]pyrazin-6-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(8-oxo-8H-pyrano[2,3-
b]pyrazin-6-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(2-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(3-hydroxy-8-oxo-8H-pyrano[2,3-b]pyrazin-6-yl)-phenyl ester

s) [5-Hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester



and its derivatives, including but not limited to:

[3,5-Dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5,6-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

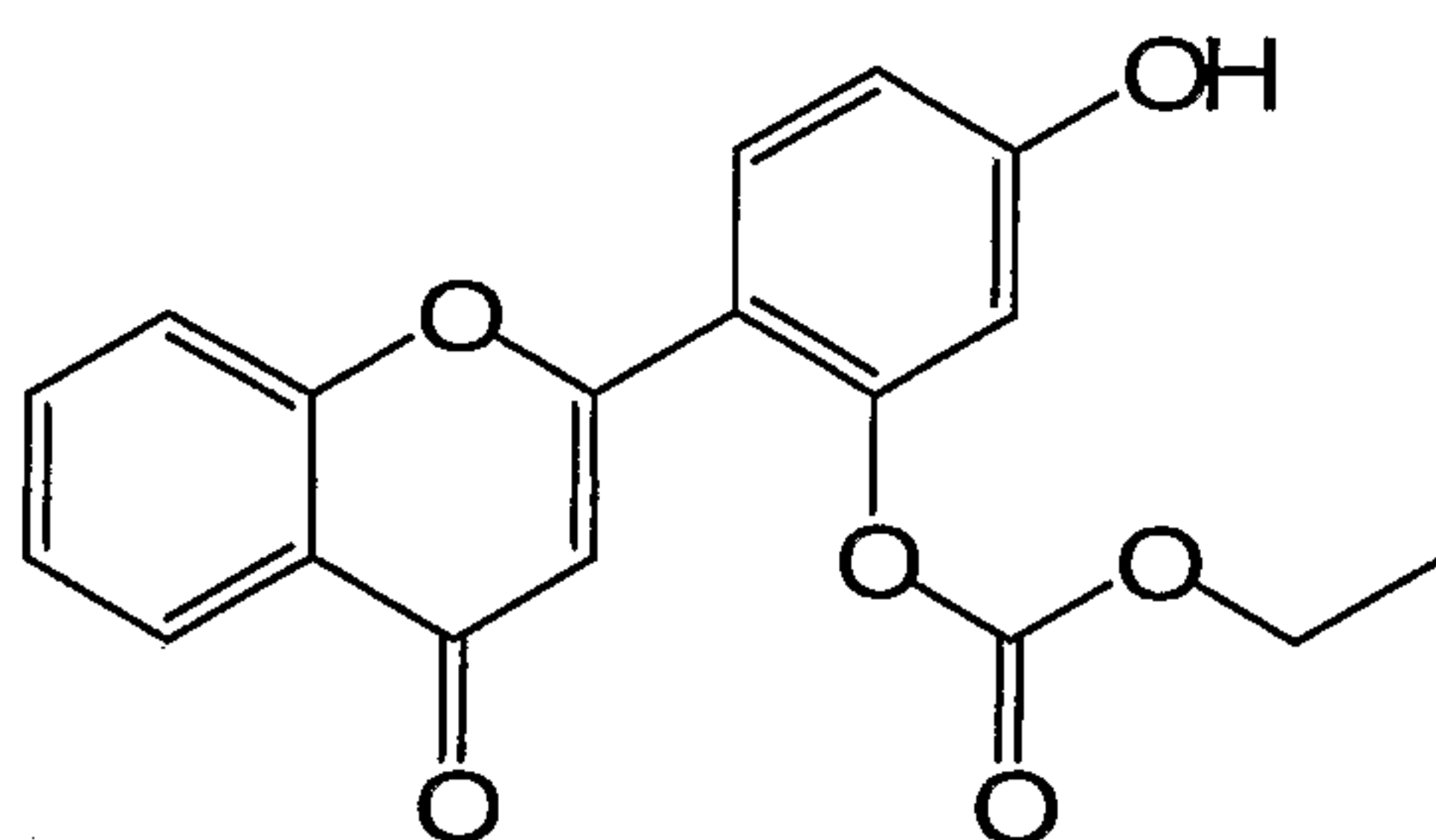
[5-Hydroxy-2-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(6,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-carbamic acid ethyl ester

t) Carbonic acid ethyl ester 5-hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl ester



and its derivatives, including but not limited to:

Carbonic acid 3,5-dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl ester ethyl ester

Carbonic acid 4,5-dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl ester ethyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(5-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(6-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(7-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(8-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(5,6-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

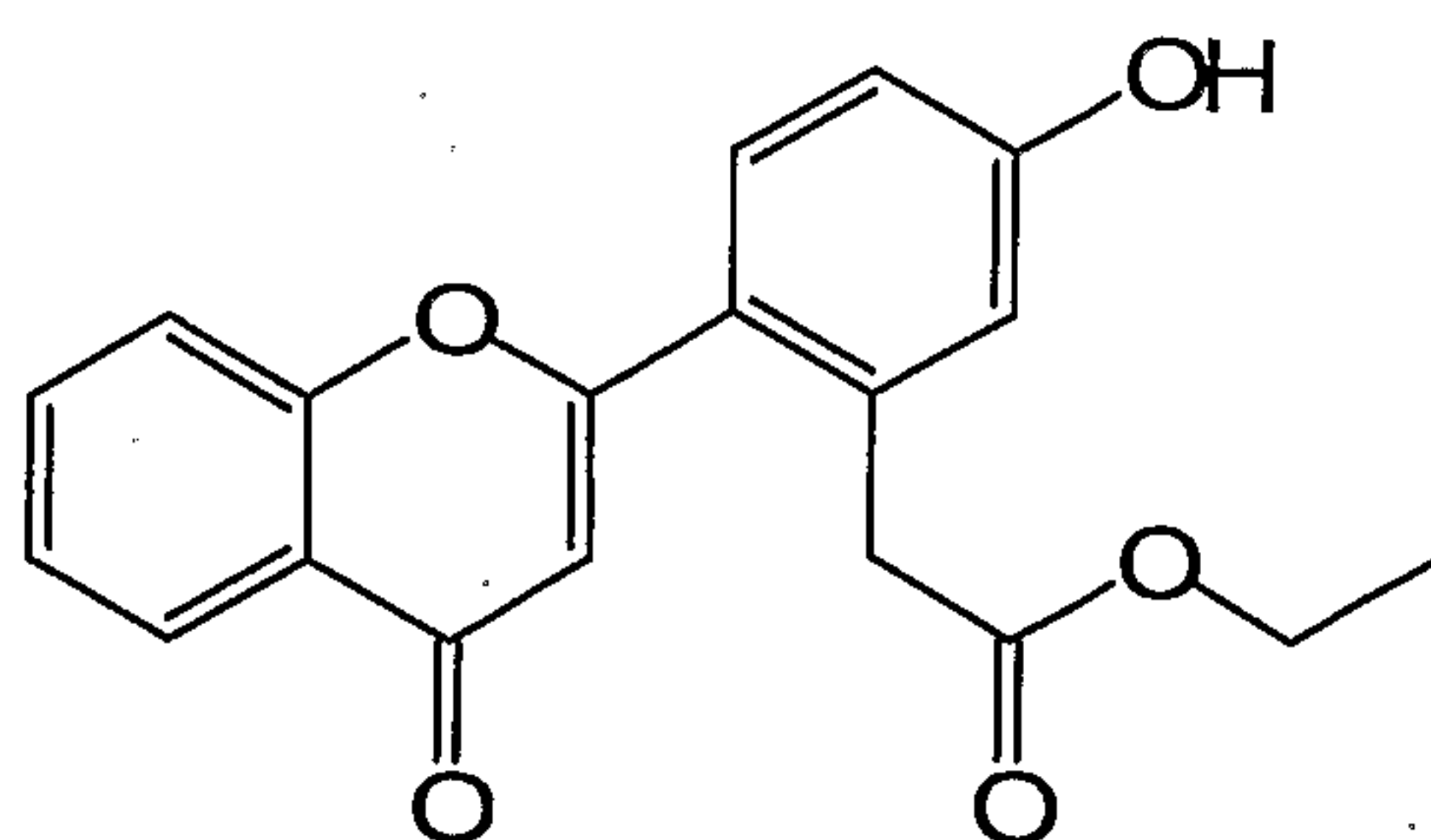
Carbonic acid ethyl ester 5-hydroxy-2-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(6,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(6,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Carbonic acid ethyl ester 5-hydroxy-2-(7,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

u) [5-Hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester



and its derivatives, including but not limited to:

[3,5-Dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[4,5-Dihydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(5-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(6-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(7-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(8-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

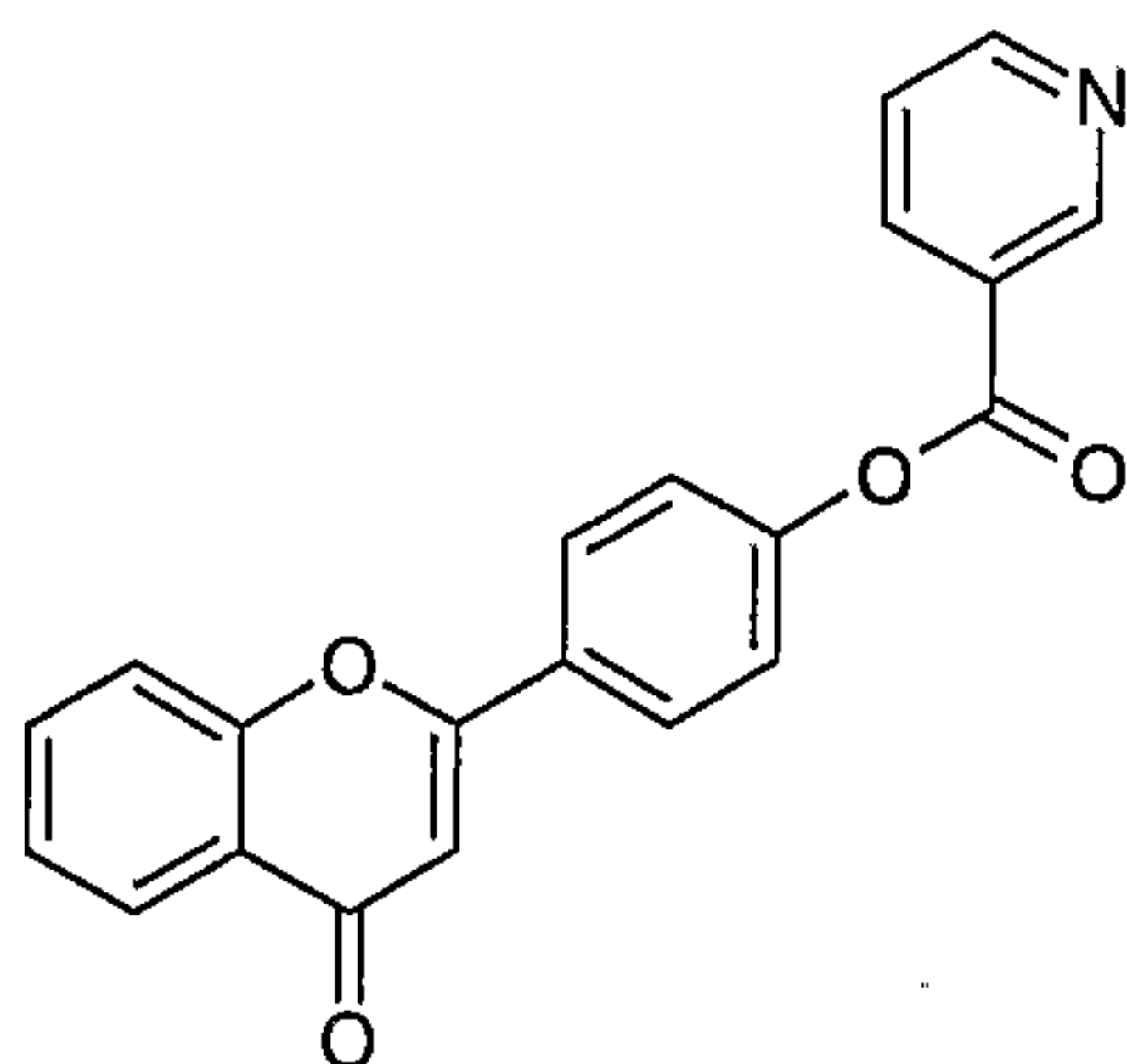
[5-Hydroxy-2-(5,6-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

[5-Hydroxy-2-(6,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl]-acetic acid ethyl ester

v) Nicotinic acid 4-(4-oxo-4H-chromen-2-yl)-phenyl ester



and its derivatives, including but not limited to:

Nicotinic acid 3-hydroxy-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 2-hydroxy-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(7-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(8-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5,6-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(7,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-fluoro-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 2-fluoro-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(7-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(8-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5,6-difluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(5,7-difluoro -4-oxo-4H-chromen-2-yl)-phenyl ester

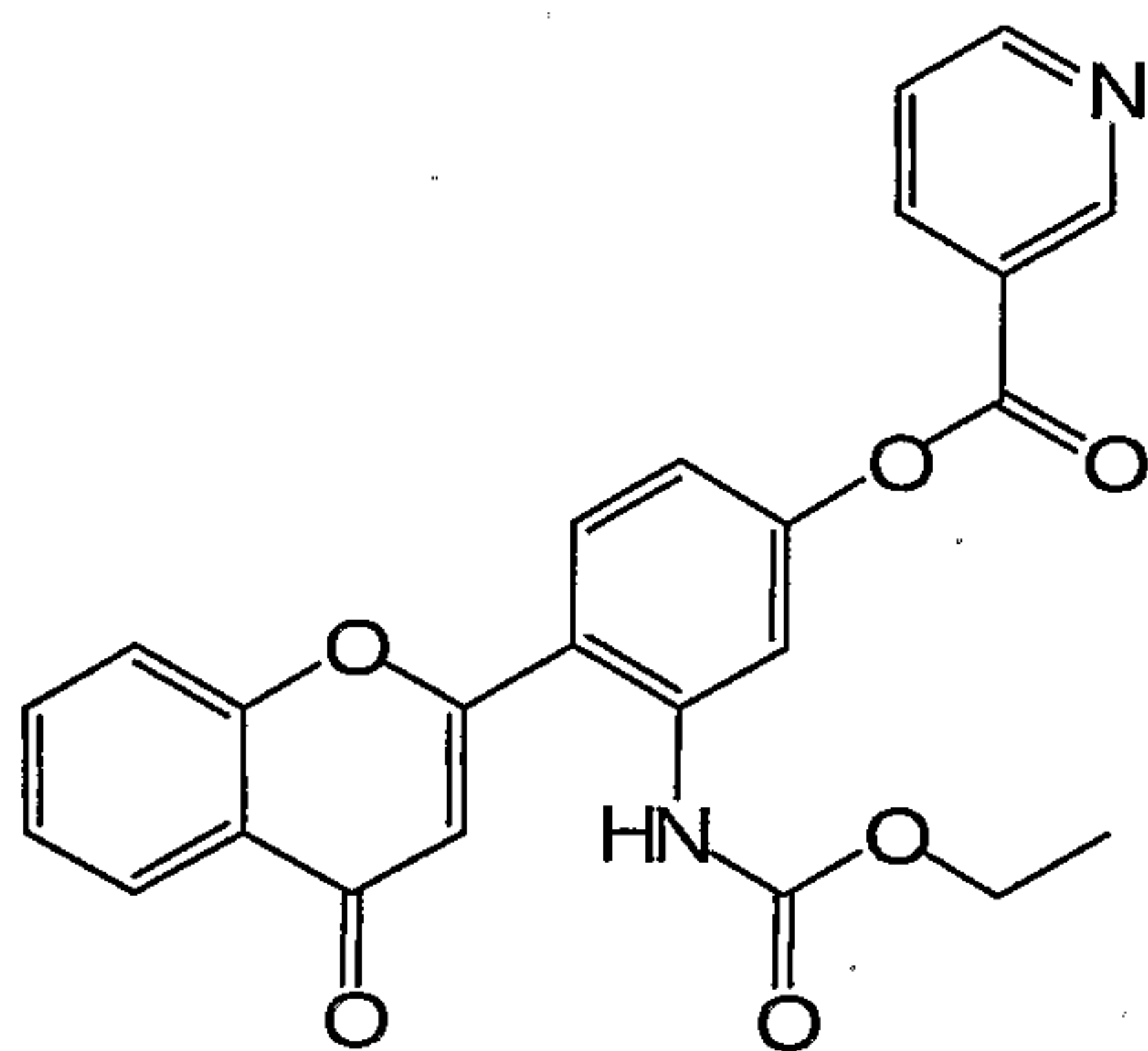
Nicotinic acid 4-(5,8-difluoro -4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6,7-difluoro -4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(6,8-difluoro -4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 4-(7,8-difluoro -4-oxo-4H-chromen-2-yl)-phenyl ester

w) Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-chromen-2-yl)-phenyl ester



and its derivatives, including but not limited to:

Nicotinic acid 3-ethoxycarbonylamino-5-hydroxy-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-hydroxy-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-hydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5,6-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6,7-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(6,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7,8-dihydroxy-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-5-fluoro-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 5-ethoxycarbonylamino-2-fluoro-4-(4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(5-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

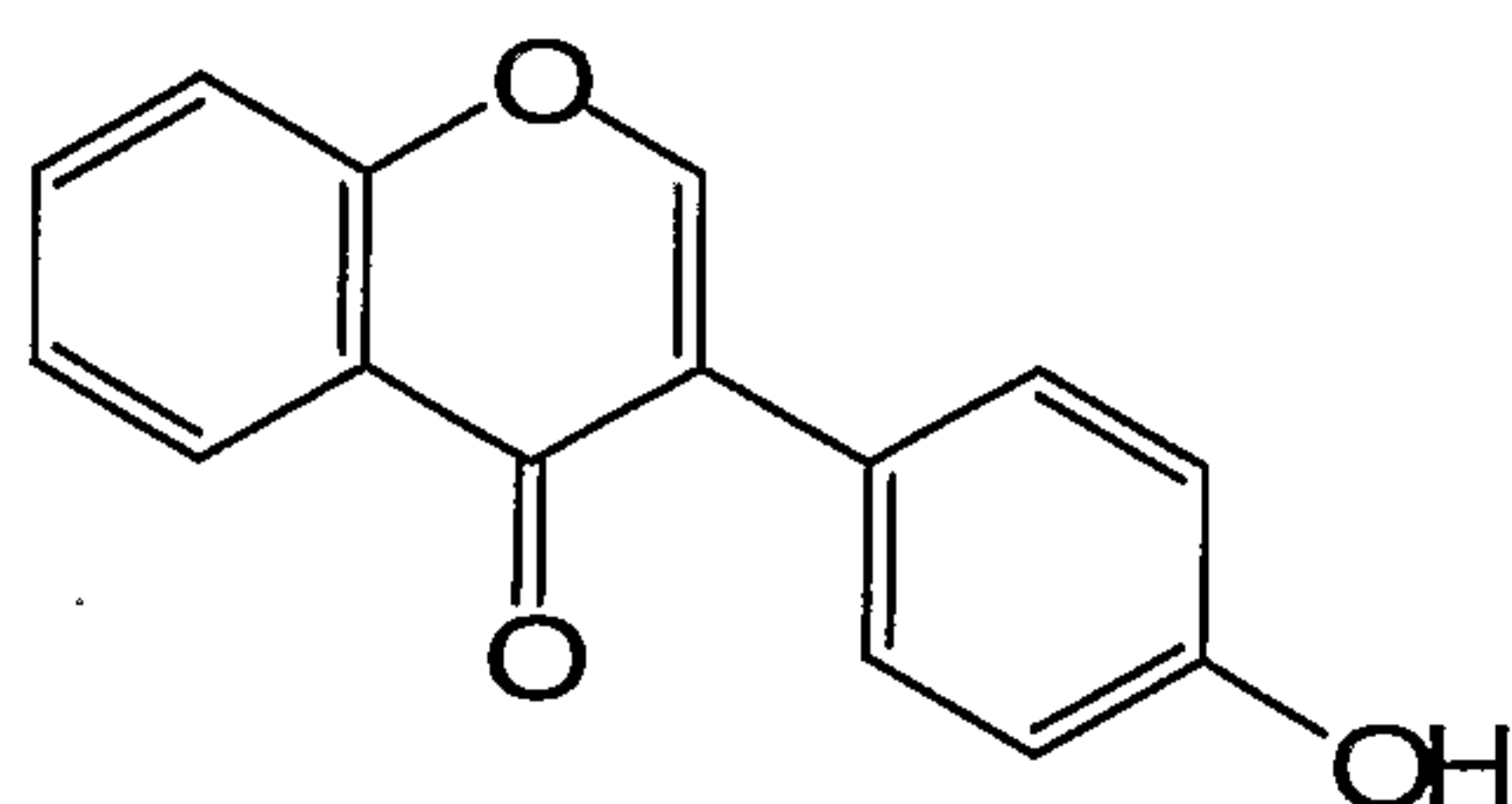
Nicotinic acid 3-ethoxycarbonylamino-4-(6-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(7-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(8-fluoro-4-oxo-4H-chromen-2-yl)-phenyl ester

[0161] Examples of isoflavanoid compounds of Formula 4 include, but are not limited to, the following compounds.

a) 3-(4-Hydroxy-phenyl)-chromen-4-one



and its derivatives, including but not limited to:

3-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

3-(4-Hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one

3-(4-Hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one

3-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

3-(5-Hydroxy-pyridin-2-yl)-chromen-4-one

3-(6-Hydroxy-pyridin-3-yl)-chromen-4-one

3-(4-Hydroxy-phenyl)-benzo[e][1,2]oxazin-4-one

Nicotinic acid 4-(4-oxo-4H-chromen-3-yl)-phenyl ester

Nicotinic acid 4-(4-oxo-4H-pyrano[2,3-b]pyridin-3-yl)-phenyl ester

Nicotinic acid 4-(4-oxo-4H-pyrano[2,3-c]pyridin-3-yl)-phenyl ester

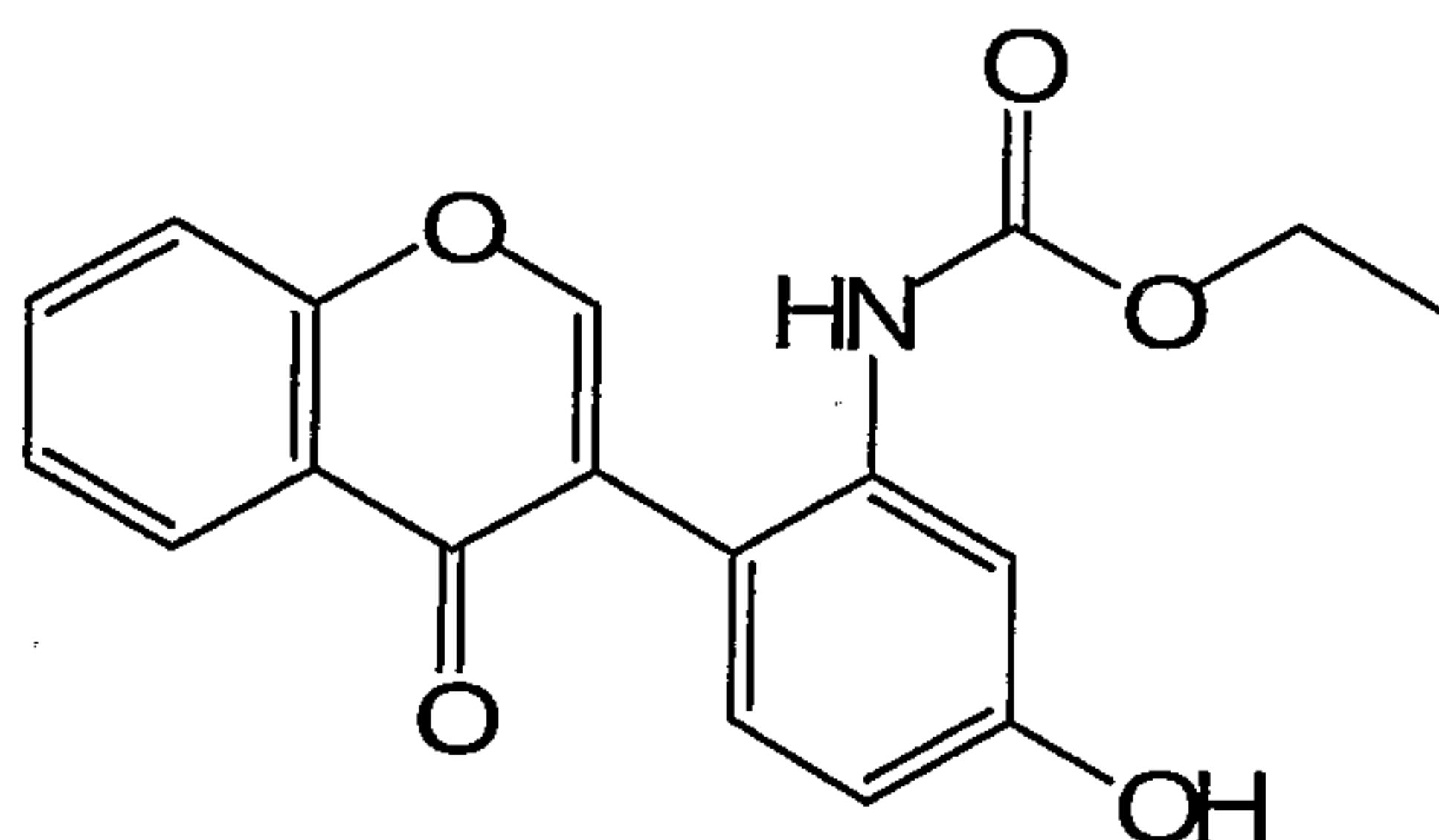
Nicotinic acid 4-(4-oxo-4H-pyrano[3,2-c]pyridin-3-yl)-phenyl ester

Nicotinic acid 4-(4-oxo-4H-pyrano[3,2-b]pyridin-3-yl)-phenyl ester

Nicotinic acid 6-(4-oxo-4H-chromen-3-yl)-pyridin-3-yl ester

Nicotinic acid 5-(4-oxo-4H-chromen-3-yl)-pyridin-2-yl ester

b) [5-Hydroxy-2-(4-oxo-4H-chromen-3-yl)-phenyl]-carbamic acid ethyl ester



and its derivatives:

[5-Hydroxy-2-(4-oxo-4H-pyrano[2,3-b]pyridin-3-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[2,3-c]pyridin-3-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[3,2-c]pyridin-3-yl)-phenyl]-carbamic acid ethyl ester

[5-Hydroxy-2-(4-oxo-4H-pyrano[3,2-b]pyridin-3-yl)-phenyl]-carbamic acid ethyl ester

[6-Hydroxy-3-(4-oxo-4H-chromen-3-yl)-pyridin-2-yl]-carbamic acid ethyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-chromen-3-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[2,3-b]pyridin-3-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[2,3-c]pyridin-3-yl)-phenyl ester

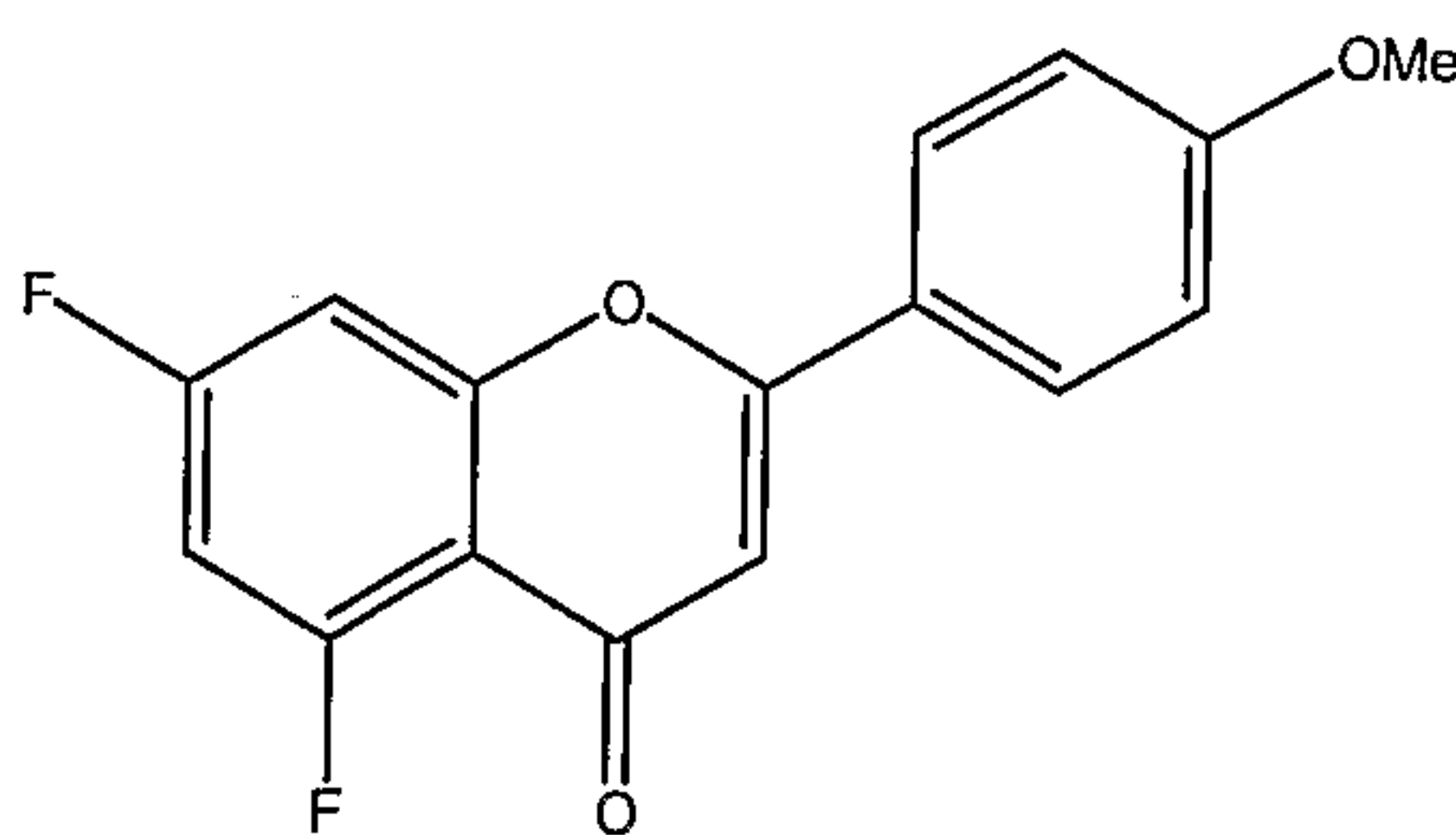
Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[3,2-c]pyridin-3-yl)-phenyl ester

Nicotinic acid 3-ethoxycarbonylamino-4-(4-oxo-4H-pyrano[3,2-b]pyridin-3-yl)-phenyl ester

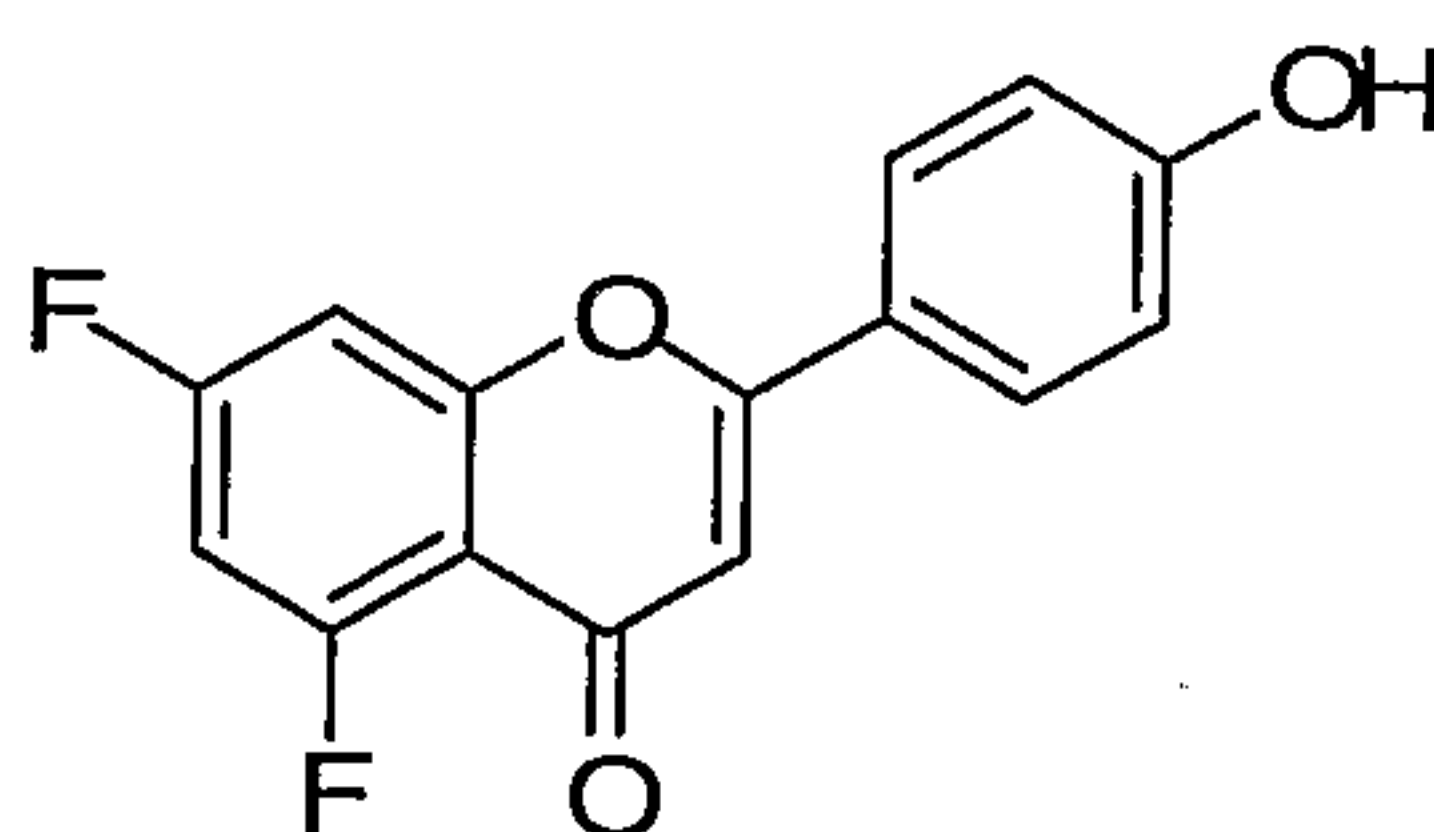
Nicotinic acid 6-ethoxycarbonylamino-5-(4-oxo-4H-chromen-3-yl)-pyridin-2-yl ester.

[0162] The following compounds were obtained from commercially available sources (such as Indofine Chemical Company, Inc.): 2-(4-hydroxyphenyl)-chromen-4-one; 6-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one; 5,7-dihydroxy-2-phenyl-4H-chromen-4-one; 5-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one; 7-hydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one; 7-hydroxy-2-phenyl-4H-chromen-4-one; 5-hydroxy-2-phenyl-4H-chromen-4-one; 2-phenyl-4H-chromen-4-one; 2-(3-hydroxyphenyl)-4H-chromen-4-one; 7-methoxy-2-(4-hydroxyphenyl)-4H-chromen-4-one; 2-(4-hydroxy-3-methoxyphenyl)-4H-chromen-4-one; 5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-chroman-4-one; 5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-chromen-4-one; and 3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)-4H-chromen-4-one.

[0163] Abbreviations used herein denote the following compounds, reagents and substituents: acetic acid (AcOH); 2,2'-azobisisobutyronitrile (AIBN); *N*-bromosuccinimide (NBS); *N*-tert-butoxycarbonyl (Boc); *t*-butyldimethylsilyl (TBDMS); *m*-chloroperoxybenzoic acid (*m*CPBA); dimethylaminopyridine (DMAP); dichloromethane (DCM); dimethylformamide (DMF); dimethylsulfoxide (DMSO); ethanol (EtOH); ethyl acetate (EtOAc); 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI); 1-hydroxybenzotriazole (HOBT); iodomethane (MeI); lithium hexamethyldisilazide (LHMDS); methanol (MeOH); methoxymethyl (MOM); tetrahydrofuran (THF).

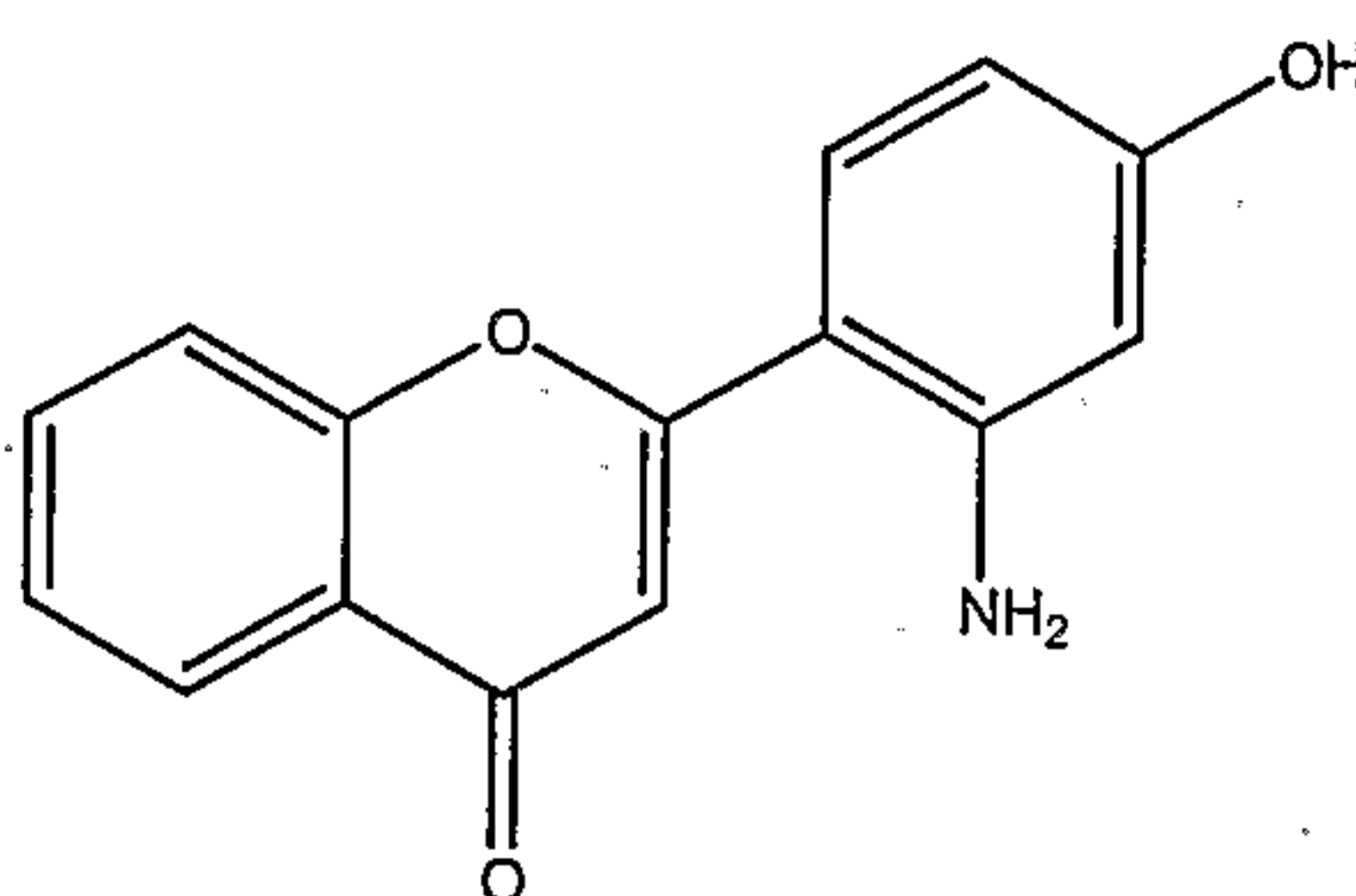
Example 1**5,7-Difluoro-2-(4-methoxy-phenyl)-chromen-4-one**

[0164] In a 100 mL 3-neck round-bottomed flask fitted with condenser and magnetic stirrer were placed dry THF (20 mL) and p-methoxy acetophenone (0.386 g, 2.57 mmol) under nitrogen. To this solution, LHMDs (2.69 mL as a 1M solution in THF, 2.57 mmol) was added drop wise at 25 °C. After completion of addition, the mixture was stirred for 30 min at rt, then 2,4,6-trifluoro-benzoyl chloride (0.5 g, 2.57 mmol) in THF (5 mL) was added slowly at rt via syringe. The reaction mixture was stirred overnight at rt. The reaction was quenched with saturated NH₄Cl solution (10 mL). The organic layer was separated and aqueous layer was extracted with EtOAc. The combined organic layer was dried over Na₂SO₄, concentrated to give crude product, which was purified by column chromatography using 20% EtOAc in hexane, to give 215 mg of 1-(2,4,6-trifluoro-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (27%). 1-(2,4,6-trifluoro-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (100 mg) in DMSO (2 mL) was heated at 100-110 °C for 1 h. Then the reaction mixture was cooled to rt and diluted with water. The product was filtered and dried to give 62 mg of 5,7-difluoro-2-(4-methoxy-phenyl)-chromen-4-one (68%). MS (ES) *m/z*: 289.07 (M+1); ¹⁹F-NMR (DMSO-d₆): δ -101.9, -109.2.

Example 2

5,7-Difluoro-2-(4-hydroxyphenyl)-4H-chromen-4-one

[0165] In a 50 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 5,7-Difluoro-2-(4-methoxyphenyl)-4H-chromen-4-one (0.425 g, 1.47 mmol), hydroiodic acid (10 mL) and acetic acid (5 mL). The reaction mixture was heated 110 °C for 4 h. The reaction mixture was cooled to room temperature and diluted with water. The precipitate was filtered off, washed with water and dried to give the title compound (220 mg, 54%). Selected data for the title compound: MS (ES) m/z : 275.10 ($M+1$); ^{19}F -NMR ($\text{DMSO}-d_6$): δ -106.2, -113.4.

Example 32-(2-Amino-4-hydroxy-phenyl)-4H-chromen-4-one

[0166] In a 100 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2'-hydroxyacetophenone (2.76 g, 20.28 mmol), 2-nitro-4-methoxybenzoic acid (4.0 g, 20.28 mmol) and pyridine (60 mL). POCl_3 (3.11 g, 20.28 mmol) was added slowly on cooling. The reaction mixture was stirred for 24 h at rt under nitrogen. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to give 2-acetylphenyl-4-methoxy-2-nitrobenzoate (6.24 g, 97%).

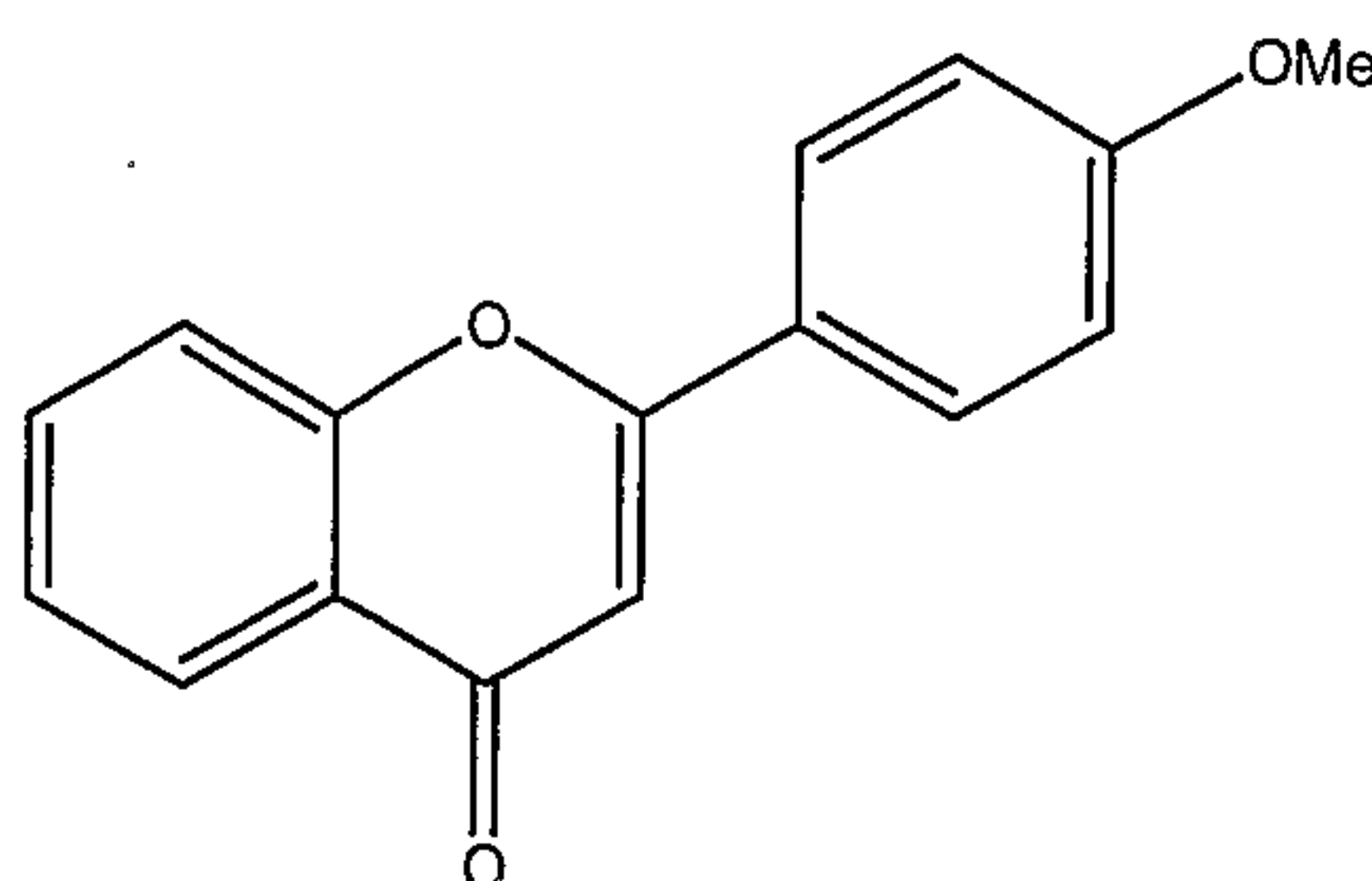
[0167] To a solution of 2-acetylphenyl-4-methoxy-2-nitrobenzoate (6.22 g, 19.71 mmol) in THF (100 mL), was added potassium t-butoxide (2.89 g, 23.65 mmol) and the reaction mixture was stirred for 24 h at rt under N_2 . The reaction mixture was poured into a saturated aqueous solution of NH_4Cl . The organic layer

was separated, washed with water, dried and concentrated to give the crude compound, which was purified by column chromatography using 50 % ethyl acetate in hexane to give 1-(2-hydroxyphenyl)-3-(4-methoxy-2-nitrophenyl)propane-1,3-dione (5.92 g, 95%).

[0168] 1-(2-Hydroxyphenyl)-3-(4-methoxy-2-nitrophenyl)propane-1,3-dione (5.92 g, 18.77 mmol) was dissolved in a mixture of 48% HCl (2 mL) and acetic acid (35 mL) and heated at 100 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried and concentrated to give the crude compound, which was purified by column chromatography using 5% ethyl acetate in CH₂Cl₂ to give 2-(4-methoxy-2-nitrophenyl)-4H-chromen-4-one (3.92 g, 70%).

[0169] 2-(4-Methoxy-2-nitrophenyl)-4H-chromen-4-one (1.5 g, 5.04 mmol) was dissolved in ethanol (30 mL) and heated at reflux. SnCl₂ (4.97 g, 26.23 mmol) was added. The mixture was heated under reflux for 20 min. The reaction mixture was cooled to rt diluted with water, neutralized and extracted with ethyl acetate to give the crude compound. This was purified by column chromatography using 3% MeOH in CH₂Cl₂ to give 2-(2-amino-4-methoxyphenyl)-4H-chromen-4-one (790 mg, 58%).

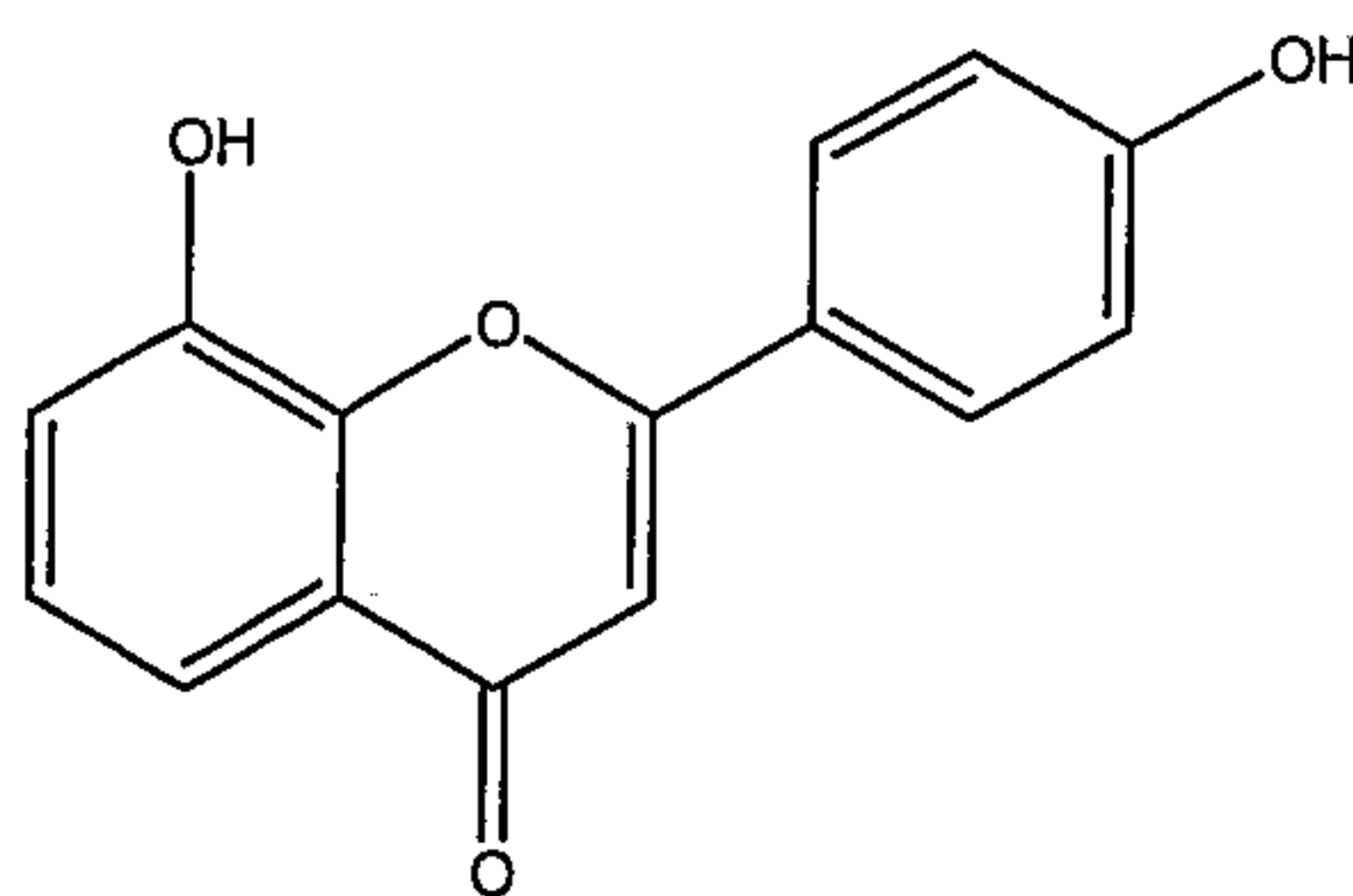
[0170] To a 50 mL round-bottomed flask fitted with condenser and magnetic stirrer was added 2-(2-amino-4-methoxyphenyl)-4H-chromen-4-one (770 mg, 2.88 mmol), hydroiodic acid (10 mL) and acetic acid (4 mL). The reaction mixture was heated to 110 °C for 8 h. The reaction mixture was cooled to rt and diluted with water. The precipitate was filtered off, washed with water and dried to give the crude compound, which was purified by column chromatography using 2% MeOH in CH₂Cl₂, to give 2-(2-amino-4-hydroxy-phenyl)-chromen-4-one (357 mg, 49%). MS (ES) *m/z*: 254.05 (M+1), 149.00, 134.01, and 121.00.

Example 4**2-(4-Methoxy-phenyl)-4H-chromen-4-one**

[0171] In a 50 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2'-hydroxy acetophenone (1.0 g, 7.34 mmol) and pyridine (10 mL). To this mixture was added 4-methoxybenzoyl chloride (1.5 g, 8.81 mmol) and DMAP as a catalyst. The reaction was stirred for overnight at rt. The reaction mixture was poured into cold water and extracted with EtOAc. The combined organic layer was washed with water, brine, dried and solvent was removed afford 2-acetylphenyl 4-methoxybenzoate (1.9 g, 95%).

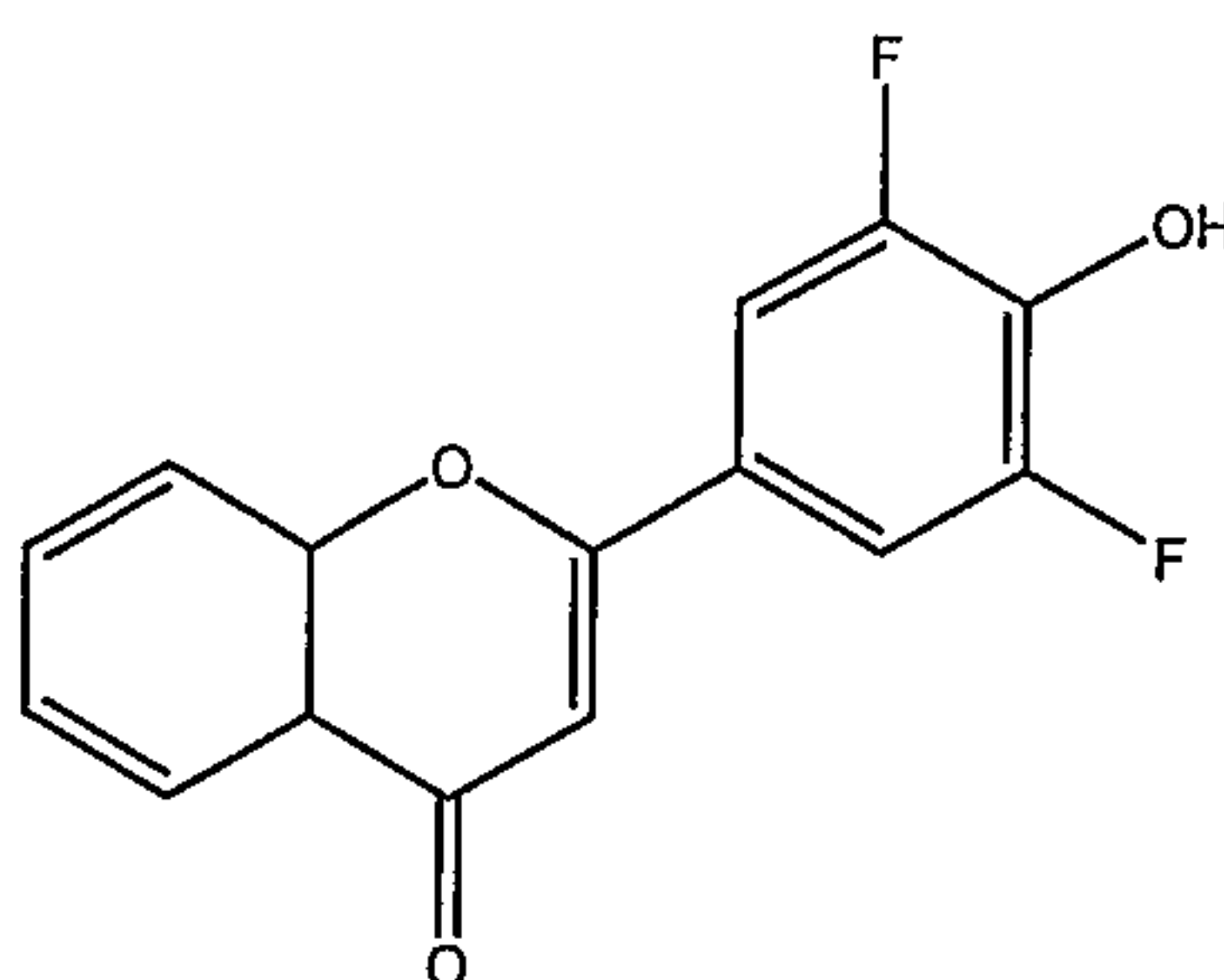
[0172] To solution of 2-acetylphenyl 4-methoxybenzoate (1.907 g, 7.05 mmol) in pyridine (10 mL) was added powdered KOH (1.49 g, 21.16 mmol). The reaction was stirred for 30 min at rt. The yellow viscous material was dissolved in water, neutralized and extracted to give crude product which was purified by column chromatography using 30% EtOAc in hexane to afford 450 mg (23%) of 1-(2-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione.

[0173] To a solution of 1-(2-hydroxy-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (200 mg, 0.74 mmol) in dichloromethane (15 mL) was added BBr₃ (185 mg, 0.74 mmol, 1M solution in dichloromethane) slowly at 0 °C, and then stirred for overnight at rt. Then MeOH was added at 0 °C to quench the unreacted BBr₃. The organic layer was washed with water, dried and concentrated to give a crude product, which was purified by column chromatography using 30% EtOAc in hexane to afford 50 mg (26 %) of 2-(4-methoxy-phenyl)-4H-chromen-4-one. MS (ES) *m/z*: 253.08 (M+1), and 149.00.

Example 58-Hydroxy-2-(4-hydroxy-phenyl)-4H-chromen-4-one

[0174] To a solution of 4-methoxyacetophenone (2.0 g, 13.3 mmol) and methyl 2,3-dimethoxybenzoate (3.135 g, 15.98 mmol) in DMF (100 mL), was added a NaH (1.065 g, 26.63 mmol) and the reaction mixture was stirred for 24 h at rt under N₂. The reaction mixture was poured into ice water and products were extracted with EtOAc. The organic layer was separated, washed with water, dried and concentrated to afford 1-(2,3-dimethoxy-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (3.1 g, 74%).

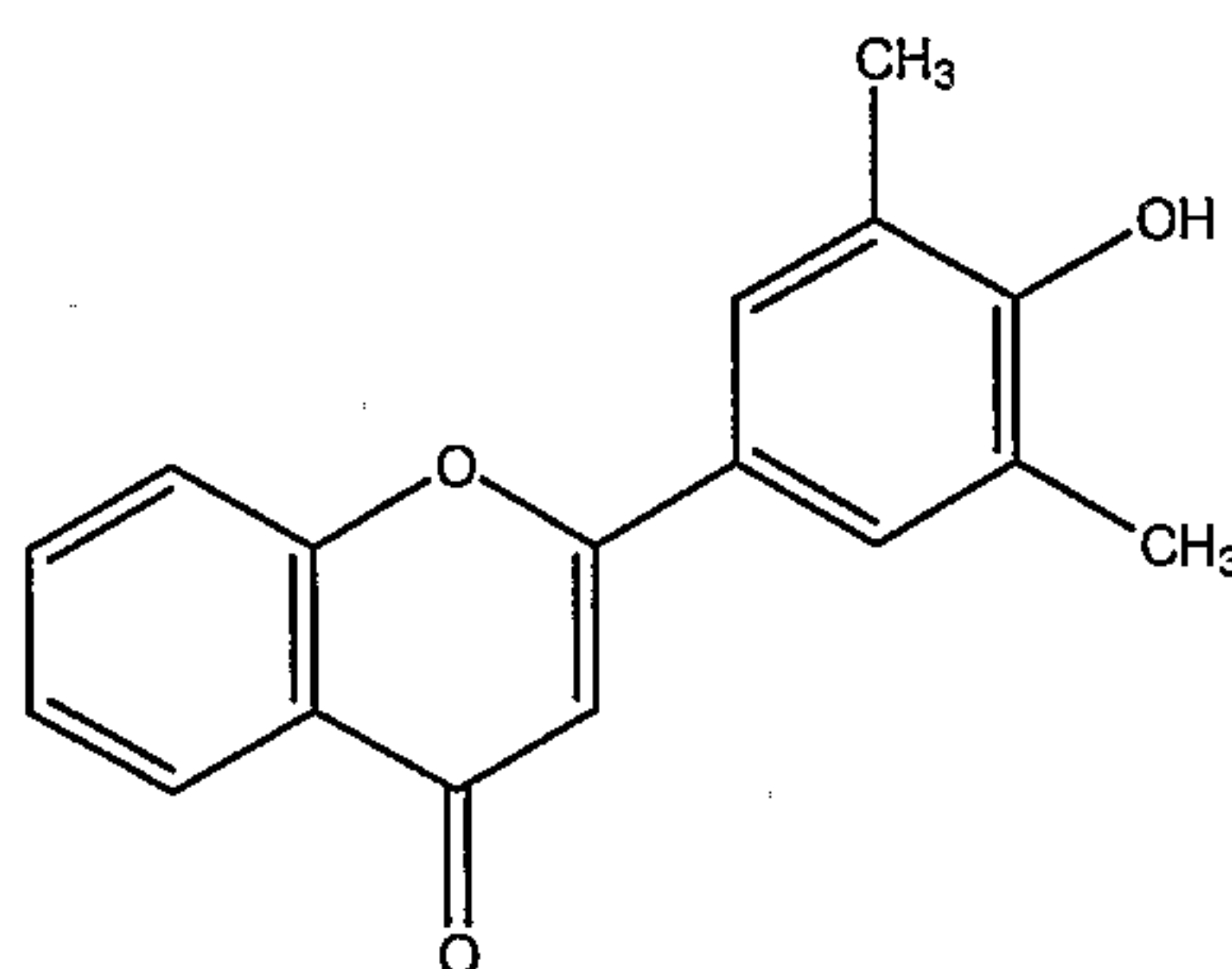
[0175] 1-(2,3-Dimethoxy-phenyl)-3-(4-methoxy-phenyl)-propane-1,3-dione (3.1 g, 9.86 mmol) was dissolved in mixture of HI (10 mL) and AcOH (10 mL) and heated at 110 °C for 4 days. The reaction mixture was cooled to rt, diluted with water and solids were filtered. The solid product was washed with water, dried and purified by column chromatography, using 30% EtOAc in dichloromethane to give 1.3 g (52%) of 8-hydroxy-2-(4-hydroxy-phenyl)-4H-chromen-4-one. MS (ES) *m/z* : 255.08 (M+1), and 154.15.

Example 62-(3,5-Difluoro-4-hydroxyphenyl)chromen-4-one

[0176] To a solution of 2'-hydroxyacetophenone (0.68 g, 5 mmol) in 10 mL anhydrous pyridine was added 3,5-difluoro-4-methoxybenzoyl chloride (1.03 g, 5 mmol) and the reaction mixture was stirred at rt for 15 h under nitrogen

atmosphere. The reaction mixture was poured into 100 mL 2N HCl. The solid was filtered off, washed with water and dried under vacuum to give a white solid (1.44 g, 94%). The compound (1.42 g, 4.63 mmol) was dissolved in 10 mL anhydrous pyridine. Powdered KOH (0.78 g, 13.9 mmol) was added and the reaction mixture was stirred at rt overnight under nitrogen. Water (50 mL) was added and the solid was isolated by filtration, and washed with water to give yellow solid (1.05 g, 74%). To a suspension of the yellow solid (0.82 g, 2.67 mmol) in 6 mL glacial AcOH was added 3 drops of conc. HCl and the reaction mixture was stirred at 110 °C for 2 h. The mixture was cooled to rt and 50 mL water was added. The solid was isolated by filtration, washed with water and dried under vacuum to give 2-(3,5-difluoro-4-methoxyphenyl)chromen-4-one as a white solid (0.61 g, 79%). 2-(3,5-Difluoro-4-methoxyphenyl)chromen-4-one was suspended in 15 mL hydroiodic acid. Glacial AcOH (6 mL) was added and the reaction mixture was stirred at 110 °C for 4 h. The mixture was cooled to rt. Water (100 mL) was added and the solid was isolated by filtration, washed with water and dried under vacuum. The crude compound was washed with 1:1 dichloromethane and MeOH (15 mL) to give 2-(3,5-difluoro-4-hydroxyphenyl)-4H-chromen-4-one (0.416 g, 73%) as a pale yellow solid. MS (ES) m/z : 275.04 (M+1); Mp. 275-276 °C.

Example 7

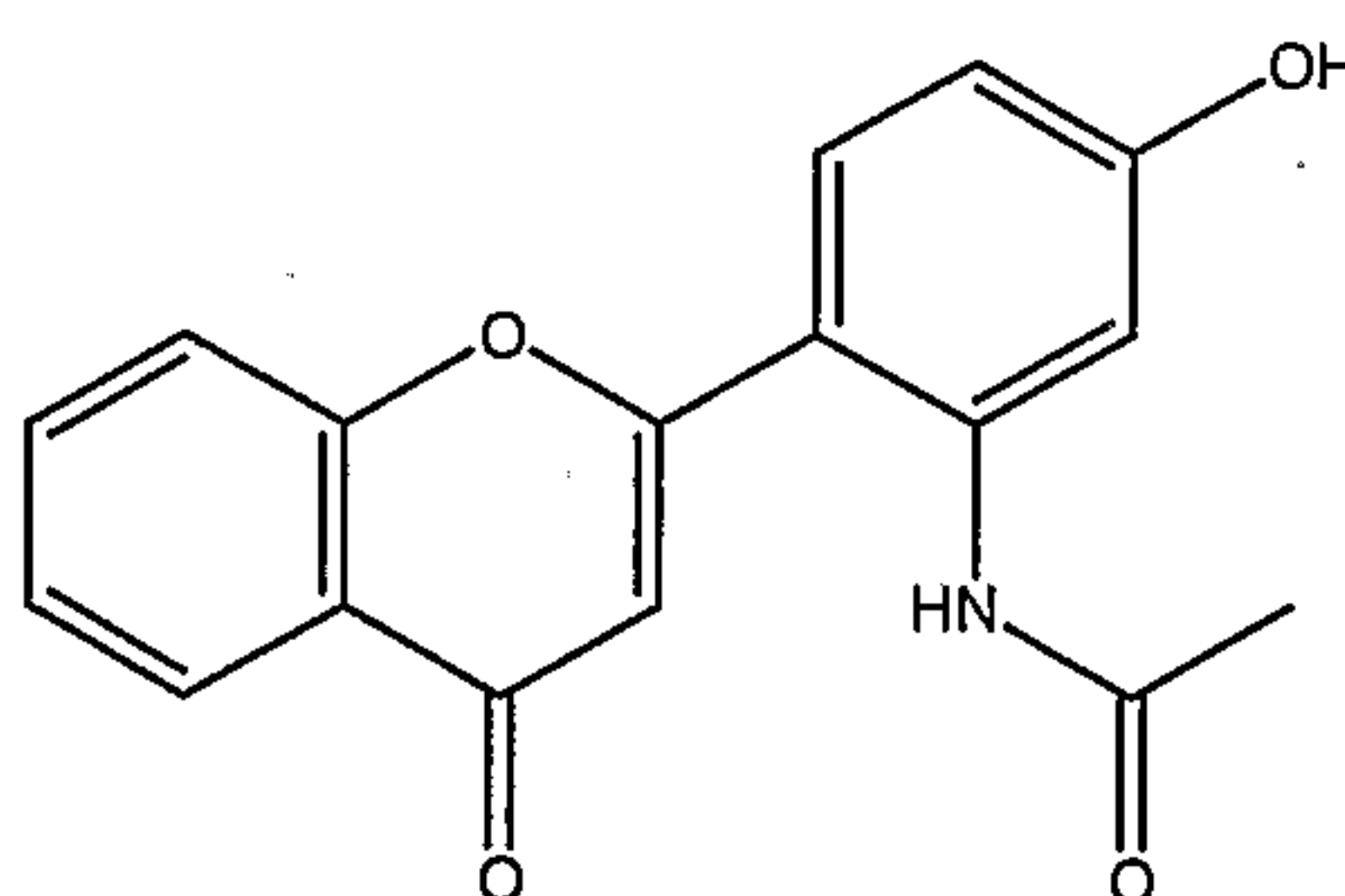


2-(4-Hydroxy-3,5-dimethylphenyl)-4H-chromen-4-one

[0177] To a solution of 2-hydroxyacetophenone (1.361 g, 10 mmol) in 20 mL anhydrous pyridine was added 3,5-dimethyl-4-methoxybenzoic acid (2.162 g, 12 mmol). The mixture was cooled to 0 °C and phosphorous oxychloride (1 mL) was added. A white precipitate was formed. The reaction mixture was stirred at rt for 2 h under nitrogen atmosphere. Then the reaction mixture was poured into 100 mL cold 2N HCl and extracted with EtOAc (2x200 mL). The combined organic

layers were washed with water and brine and dried over anhydrous Na_2SO_4 . The solvent was removed under vacuum to give a colorless liquid (2.89 g, 97%), which was used in the next step without further purification. The compound (2.88 g, 9.65 mmol) was dissolved in 10 mL anhydrous pyridine. Powdered potassium hydroxide (1.62 g, 28.95 mmol) was added and the reaction mixture was stirred at rt overnight under nitrogen. Water (100 mL) was added and the mixture was neutralized to pH 7 with conc. HCl. The yellow solid was filtered off, washed with water and dried under vacuum. Yield: 1.16 g, 40%. To a suspension of the yellow solid (1.14 g, 3.83 mmol) in 8 mL glacial AcOH was added 4 drops of conc. HCl and the reaction mixture was stirred at 110 °C for 2 h. The mixture was cooled to rt and water (50 mL) was added. The solid was isolated by filtration and washed with water and dried under vacuum to give 2-(4-methoxy-3,5-dimethyl phenyl) chromen-4-one (1.05 g, 98%) as a pale green solid. 2-(4-methoxy-3,5-dimethyl phenyl) chromen-4-one was suspended in 20 mL hydroiodic acid and 8 mL glacial AcOH was added. The reaction mixture was stirred at 110 °C for 2 h. The mixture was cooled to rt. Water (100 mL) was added and the solid was isolated by filtration, washed with water and dried under vacuum. The crude compound was washed with 1:1 dichloromethane and methanol (20 mL) to give 0.763 g of 2-(4-hydroxy-3,5-dimethylphenyl)-4H-chromen-4-one (85%) as a pale yellow solid. MS (ES) m/z : 267.06 ($M+1$); Mp. 255-256 °C.

Example 8

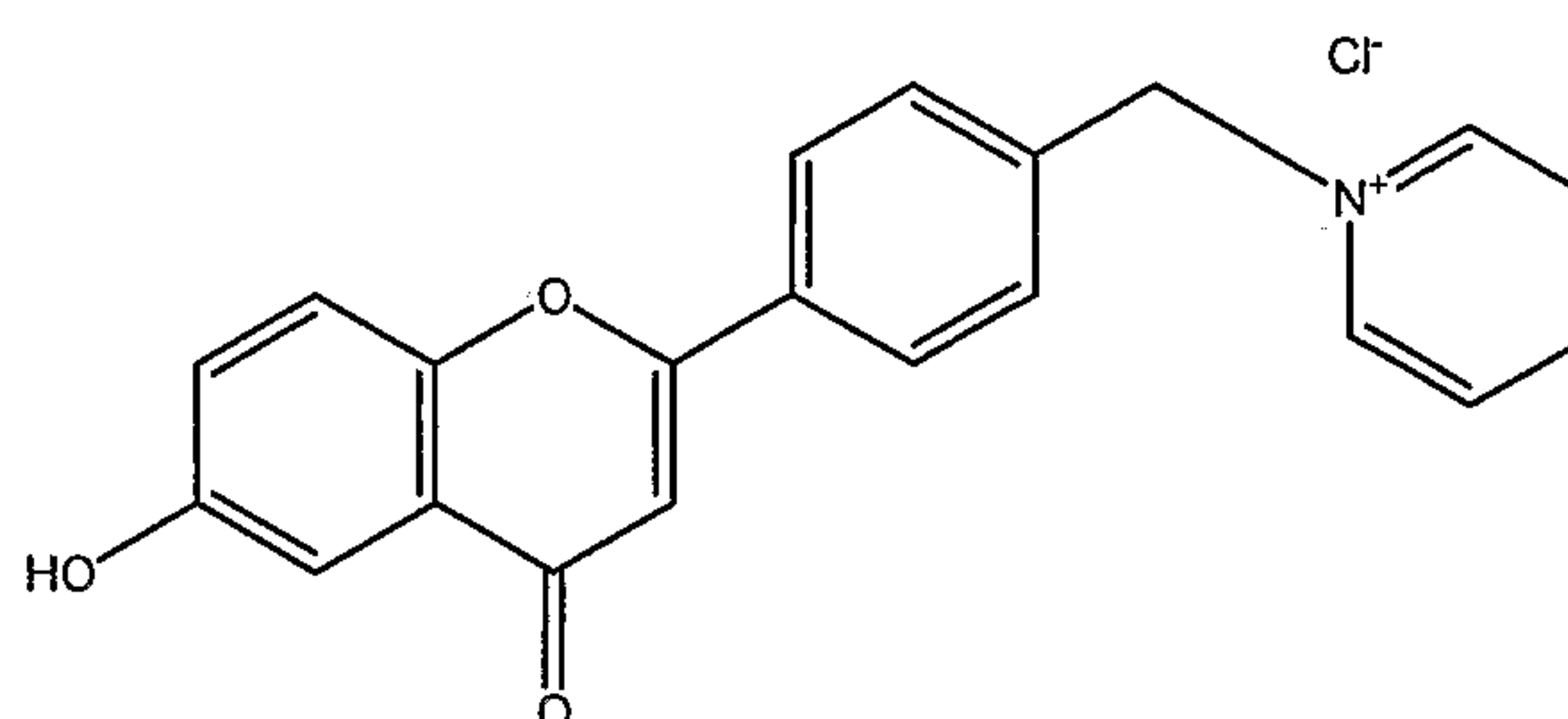


N-[5-Hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]acetamide

[0178] In a 50 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2-(2-amino-4-hydroxy-phenyl)-chromen-4-one (150 mg, 0.592 mmol), Ac_2O (181 mg, 1.776 mmol), and pyridine (5 mL) and then the reaction mixture was stirred for 24 h at rt. The reaction mixture was poured into water and extracted with EtOAc. The organic layer washed with water, dried and

concentrated to give the intermediate (228 mg, 99%). To a solution of the intermediate (228 mg, 0.676 mmol) in MeOH: THF (5 mL: 5 mL), K₂CO₃ (112 mg, 0.811 mmol) was added and stirred for 2 h at rt. Then the reaction mixture was neutralized by dilute HCl and extracted by EtOAc, the combined organic layers were washed with water, brine, dried and concentrated to give a crude product, which was purified by column chromatography using 2% MeOH in dichloromethane to afford *N*-[5-hydroxy-2-(4-oxo-4H-chromen-2-yl)-phenyl]acetamide (100 mg, 50%). MS (ES) *m/z*: 296.15 (M+1); Mp. 253-255 °C.

Example 9

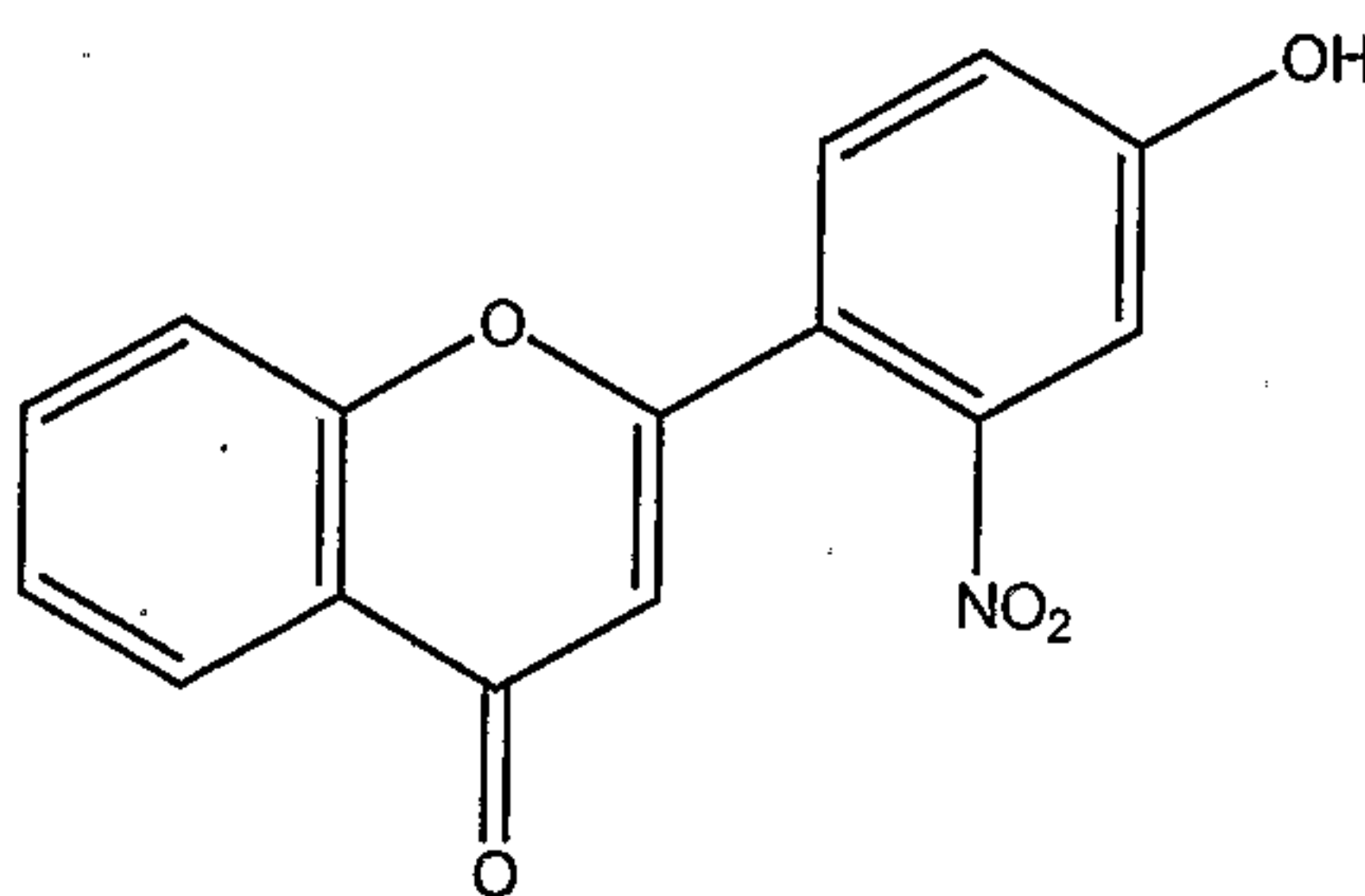


1-[4-(6-Hydroxy-4-oxo-4H-chromen-2-yl)benzyl]pyridinium chloride

[0179] In a 100 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2'-hydroxy-5'-methoxyacetophenone (2.0 g, 12.03 mmol), 4-acetoxymethylbenzoic acid (2.4 g, 12.03 mmol) and pyridine (20 mL). POCl₃ (1.8 g, 12.03 mmol) was added slowly on cooling. The reaction mixture was stirred for 24 h at rt under nitrogen. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed with water, dried and concentrated to give the product (3.08 g, 72%). To a solution of this product (3.08 g, 8.99 mmol) in THF (50 mL), was added potassium t-butoxide (1.32 g, 10.07 mmol) and the reaction mixture was stirred for 24 h at rt under N₂. The reaction mixture was poured into saturated aqueous NH₄Cl. The organic layer was separated, washed with water, dried and concentrated to give the crude diketone (3.07 g, 99%). The diketone compound (3.07 g, 8.96 mmol) was dissolved in a mixture of 48% HCl (2 mL) and AcOH (20 mL) and heated at 100 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried and concentrated to give cyclized product (1.38 g, 47%). To a solution of the cyclized product (1.2 g, 3.69

mmol) in THF (30 mL), K_2CO_3 (613 mg, 4.44 mmol) was added and the mixture was stirred overnight at rt. Then the reaction mixture was neutralized by dilute HCl and extracted by EtOAc, the combined organic layers were washed with water, brine, dried and concentrated to give a crude product (548 mg, 52%). A mixture of the 6-methoxyflavone analogue (400 mg, 1.41 mmol) and pyridinium hydrochloride (8 g) was heated at 190 °C for 4 h. The reaction mixture was cooled to rt, diluted with water, neutralized with $NaHCO_3$ and filtered to give the crude product. This was purified by crystallization using MeOH/ dichloromethane/ EtOAc to give 200 mg of 1-[4-(6-hydroxy-4-oxo-4H-chromen-2-yl)benzyl]pyridinium chloride (51%). MS (ES) m/z : 330.89 (M), 329.86 (M-1); Mp. 243-247 °C.

Example 10



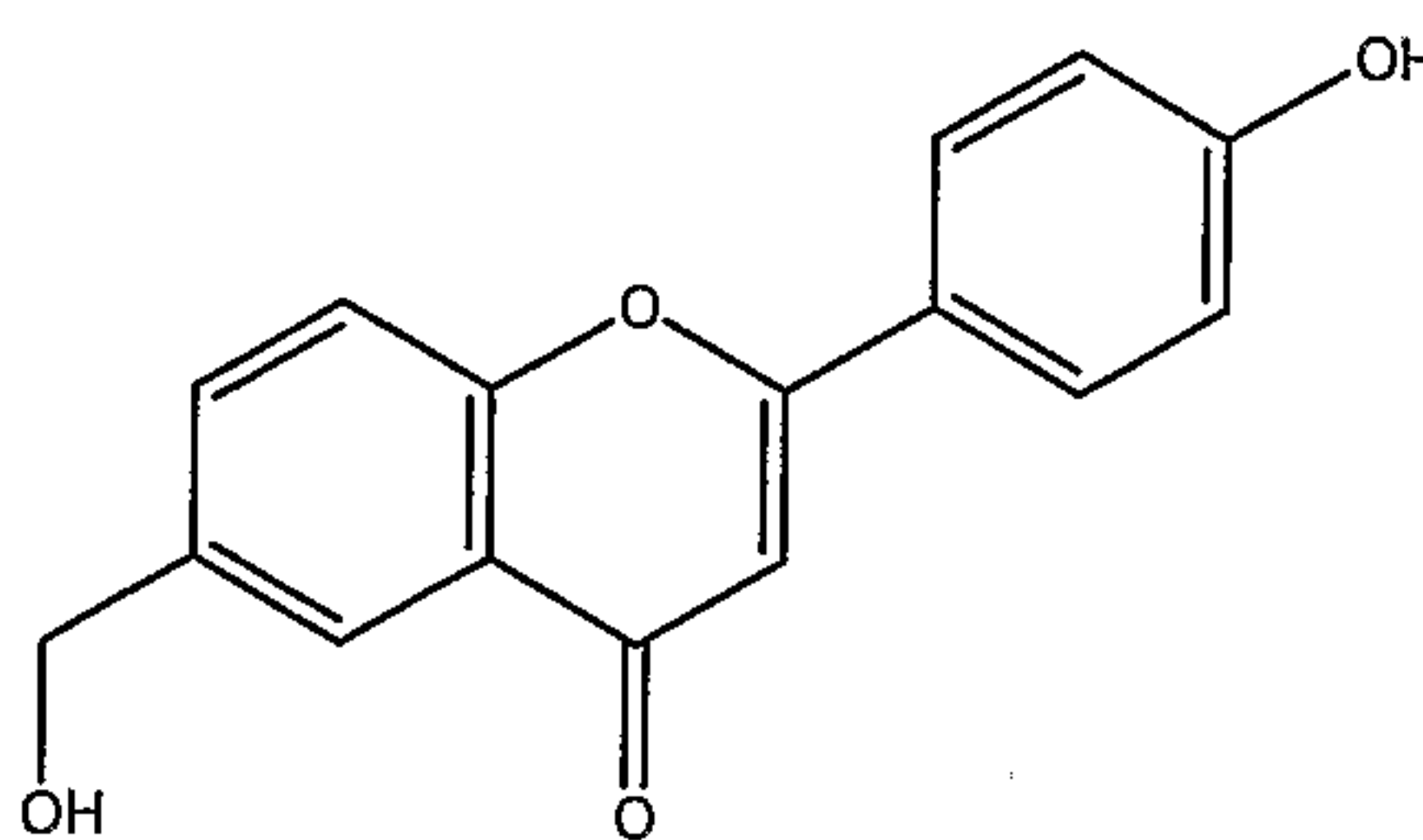
2-(4-Hydroxy-2-nitrophenyl)chromen-4-one

[0180] In a 100 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2'-hydroxyacetophenone (2.76 g, 20.28 mmol), 2-nitro-4-methoxybenzoic acid (4.0 g, 20.28 mmol) and pyridine (60 mL). $POCl_3$ (3.11 g, 20.28 mmol) was added slowly on cooling. The reaction mixture was stirred for 24 h at rt under nitrogen. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated to give product (6.24 g, 97%). To a solution of the product (817 mg, 2.59 mmol) in THF (10 mL), was added potassium t-butoxide (380 mg, 3.11 mmol), and the reaction mixture was stirred for 24 h at rt under N_2 . The reaction mixture was poured into a saturated aqueous solution of NH_4Cl . The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated to give the diketone (800 mg, 97%).

[0181] The diketone compound (800 mg, 2.53 mmol) was dissolved in a mixture of 48% HCl (1 mL) and acetic acid (7 mL) and heated at 100 °C for 1 h.

The reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to the crude product, which was purified by crystallization to give (500 mg, 67 %) of cyclized product. The product (500 mg, 1.68 mmol) and pyridinium hydrochloride (8 g) were mixed and heated at 190 °C for 4 h. The reaction mixture was cooled to rt, diluted with water, neutralized by NaHCO_3 and filtered to give 2-(4-hydroxy-2-nitrophenyl)chromen-4-one (430 mg, 92 %). MS (ES) m/z : 284.88 ($M+1$), 283.86 (M); Mp. 277-279 °C.

Example 11



6-Hydroxymethyl-2-(4-hydroxyphenyl)chromen-4-one

[0182] A suspension of 2'-hydroxyacetophenone (5 g) and paraformaldehyde (1.9 g) in 20 mL of conc. HCl was stirred at 35 °C for 4 h, until the formation of a yellow precipitate. 2'-Hydroxy-5'-chloromethylacetophenone was filtered off, air dried and used for the next step without further purification. 2'-Hydroxy-5'-chloromethylacetophenone (6.8 g) was dissolved in 100 mL of dry MeOH and NaOMe (25 w% in MeOH, 15.9 g) was slowly added. The resulting solution was stirred at rt overnight. After the reaction, 1M HCl was slowly added to neutralize the reaction mixture. The reaction mixture was dried by direct addition of anhydrous MgSO_4 and concentrated by evaporation of the MeOH. The residue was loaded on a column with 20% EtOAc/Hexane as an eluent to isolate 2'-hydroxy-5'-methoxymethylacetophenone (4.9 g, 74%).

[0183] A mixture of 2'-hydroxy-5'-methoxymethylacetophenone (1.2 g) and 20 mL of pyridine was stirred for 15 min, before the addition of 4-methoxybenzoyl chloride (1.14 g). The formed solution was stirred at rt overnight. HCl (1 M) was slowly added to neutralize the reaction solution. Then 50 mL of water was added, and the resulting solution was extracted by EtOAc (3 x 50 mL). The combined organic layers were dried over MgSO_4 and evaporated under

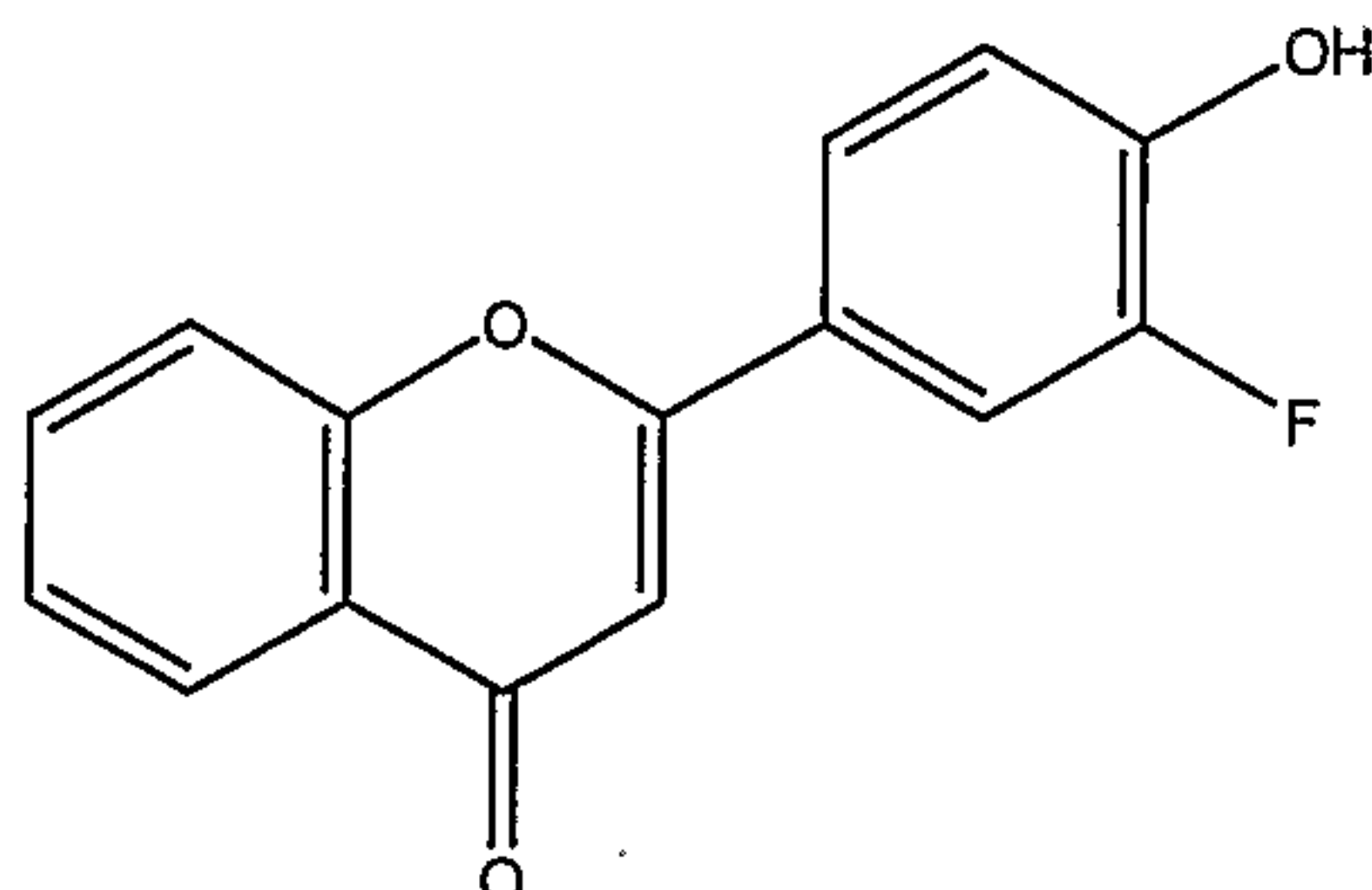
vacuum. The residue was passed through a silica gel column quickly with 40% EtOAc/hexane as an eluent to afford benzoate (1.46 g, 70%). To the solution of benzoate (2.3 g) in dry THF (30 mL) was slowly added NaH (0.92 g, 60% in mineral oil). The solution was heated to reflux overnight. The solution was cooled to rt and neutralized by adding 1M HCl. Water (50 mL) was added and the resulting solution was extracted with EtOAc (3 x 50 mL). After drying the combined organic layers over MgSO₄ and evaporation of solvent, the product was assayed by ¹H-NMR and the crude diketone was used directly in the next step reaction without further purification.

[0184] A mixture of the diketone (1.1 g), 30 mL of AcOH and 3 mL of conc. HCl was stirred at 105 °C for 15 min. Then water (30 mL) was added and the resulting solution was extracted by EtOAc (3 x 30 mL). The combined organic layers were dried over MgSO₄, evaporated under vacuum and purified by column chromatography on silica gel (40% EtOAc/Hexane) to afford the cyclized compound (0.68 g, 66%). To the solution of the cyclized compound (0.6 g) in dichloromethane (20 mL), 10 mL of 1 M BBr₃ were added slowly. The resulting black solution was stirred at rt for 24 h. After the reaction, 50 mL of water was slowly added to the stirring solution. Then 30 mL of EtOAc and Na₂CO₂ powder was added. After the neutralization, conc. HCl was used to acidify the solution to pH 2. The mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were concentrated and purified by column chromatography on silica gel (5% MeOH/dichloromethane) to afford 6-bromomethyl-2-(4-hydroxyphenyl)chromen-4-one (0.4 g, 60%).

[0185] To a solution of 6-bromomethyl-2-(4-hydroxyphenyl)chromen-4-one (250 mg, 0.754 mmol) in dioxane:DMF (10:2, 12 mL), was added potassium acetate (500 mg, 3.77 mmol). The mixture was heated at 100 °C for 3 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated to give crude product (225 mg, 96%). To a solution of the crude product (220 mg, 0.711 mmol) in MeOH:THF (5 mL: 5 mL) was added K₂CO₃ (216 mg, 1.56 mmol) and the mixture was stirred for 24 h at rt. Then the reaction mixture was neutralized by dilute HCl and extracted by EtOAc, the combined organic layers were washed with water, brine, dried and concentrated to give a

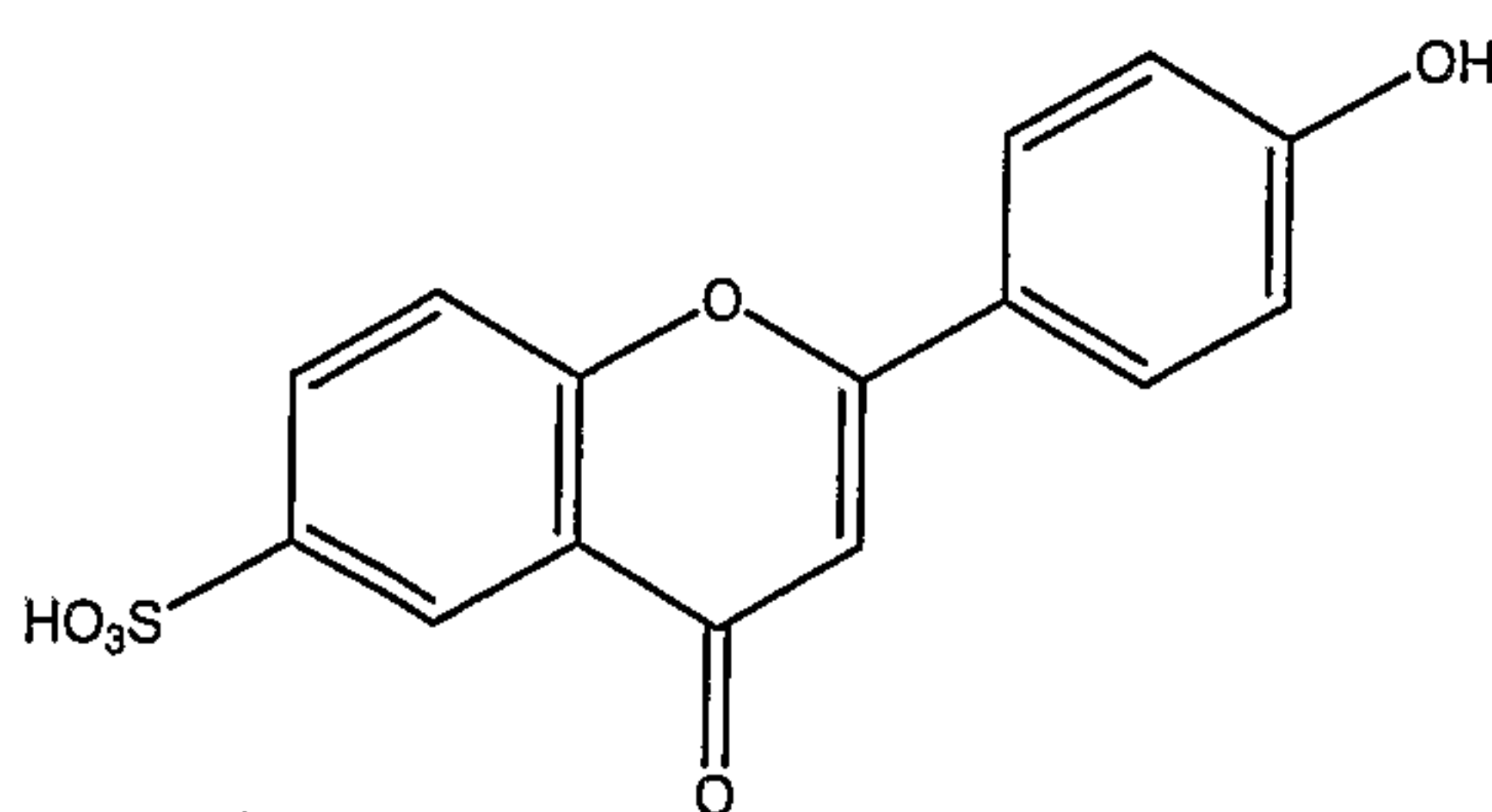
crude product, which was purified by column chromatography using 5% MeOH in dichloromethane, to afford 6-hydroxymethyl-2-(4-hydroxyphenyl)chromen-4-one (80 mg, 42%). MS (ES) m/z : 269.88 (M+1), 268.85 (M); Mp. 246-247 °C.

Example 12



2-(3-Fluoro-4-hydroxyphenyl)chromen-4-one

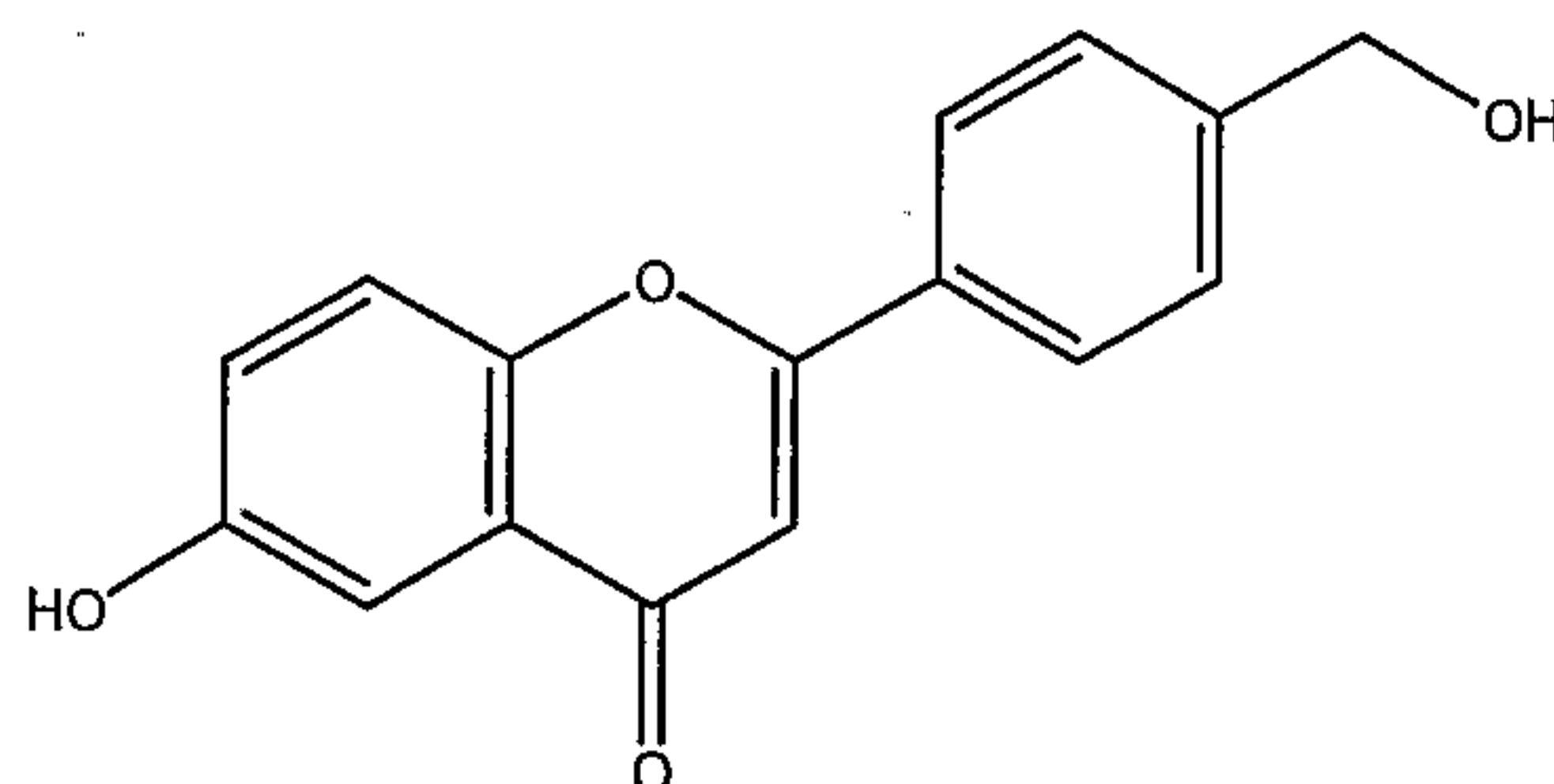
[0186] To a solution of 2'-hydroxyacetophenone (1.36 g, 10 mmol) in 20 mL anhydrous pyridine was added 3-fluoro-4-methoxybenzoyl chloride (1.89 g, 10 mmol) and the reaction mixture was stirred at rt for 15 h under a nitrogen atmosphere. The reaction mixture was poured into 200 mL of 2 N HCl. The formed solid was isolated by filtration, washed with water and dried under vacuum to give a white solid (2.76 g, 95.7%). The compound (2.68 g, 9.3 mmol) was dissolved in 10 mL anhydrous pyridine. Powdered potassium hydroxide (1.57 g, 27.9 mmol) was added and the reaction mixture was stirred at rt overnight under nitrogen. Water (100 mL) was added, the solid was isolated by filtration and washed with water to give a yellow solid (1.83 g, 68%). The compound (1.78 g, 6.17 mmol) was suspended in 15 mL glacial AcOH. Five drops of conc. HCl was added and the reaction mixture was stirred at 110 °C for 2 h, then cooled to rt. Water (100 mL) was added. The formed solid was separated by filtration, washed with water and dried under vacuum to give 2-(3-fluoro-4-methoxyphenyl)chromen-4-one as a white solid (1.62 g, 97%). 2-(3-Fluoro-4-methoxyphenyl)chromen-4-one (1.6 g, 5.92 mmol) was suspended in 40 mL of HI. Glacial AcOH (15 mL) was added and the reaction mixture was stirred at 110 °C for 4 h, then cooled to rt. Water (200 mL) was added, and the solid was isolated by filtration, washed with water and dried under vacuum. The crude compound was washed with 1:1 dichloromethane and methanol (15 mL) to give 1.1 g of 2-(3-fluoro-4-hydroxyphenyl)chromen-4-one (72%) as a pale yellow solid. MS (ES) m/z : 257.91 (M+1), 256.88 (M); Mp. 275-276 °C.

Example 13**2-(4-Hydroxyphenyl)-4-oxo-4H-chromene-6-sulfonic acid**

[0187] To a solution of 2'-hydroxyacetophenone (5.43 g, 40 mmol) in cyclohexane (28 mL) was added dimethylcarbonate (28 mL). The mixture was stirred under nitrogen and heated to 60 °C. Chlorosulfonic acid was added over a period of 15 min. Liberated HCl was removed by trapping with solid NaOH. On completion of the addition, the reaction mixture was heated to 70 °C for 1 h and then cooled to rt. The solid was filtered off, washed with a mixture of dimethyl carbonate and cyclohexane (1:1, 20 mL) and dried under vacuum to give 3-acetyl-4-hydroxybenzene sulfonic acid as yellow solid (4.5 g, 52%). 3-Acetyl-4-hydroxybenzene sulfonic acid (2.16 g, 10 mmol) was suspended in 20 mL anhydrous pyridine. 4-Methoxybenzoyl chloride (3.4 g, 20 mmol) was added slowly at rt. Stirring continued under nitrogen for 15 h. Excess pyridine was removed under reduced pressure. The solid obtained was dried under vacuum. This material was used without further purification. This crude compound (~10 mmol) was dissolved in 10 mL anhydrous pyridine. Powdered KOH (2.8 g, 50 mmol) was added and the reaction mixture was stirred at rt for 14 h under nitrogen. Water (10 mL) was added and the mixture was concentrated to dryness. The crude product was taken in 10 mL of glacial AcOH. Five drops of concentrated HCl was added and the reaction mixture was stirred at 110 °C for 4 h, then cooled to rt. The yellow solid was isolated by filtration, washed with AcOH and dried under vacuum to give 2-(4-methoxy phenyl)-4-oxo-4H-chromene-6-sulfonic acid (0.475 g, 14%) as yellow solid. The product (0.375 g, 1.13 mmol) was suspended in HI (7 mL). Glacial AcOH (3 mL) was added and the reaction mixture was stirred at 110 °C for 2 h, then cooled to rt. The solid was isolated by filtration, washed with AcOH and dried under vacuum. The crude compound was triturated with ether to afford 2-(4-hydroxyphenyl)-4-oxo-4H-chromene-6-sulfonic

acid (0.2 g, 55%) as yellow solid. MS (ES) m/z : 319.88 (M+1), 318.85 (M); ^{13}C -NMR (DMSO- d_6): δ 177.5, 163.7, 161.7, 156.1, 146.1, 132.1, 129.1, 123.1, 122.3, 122.2, 118.7, 116.6, 105.5.

Example 14

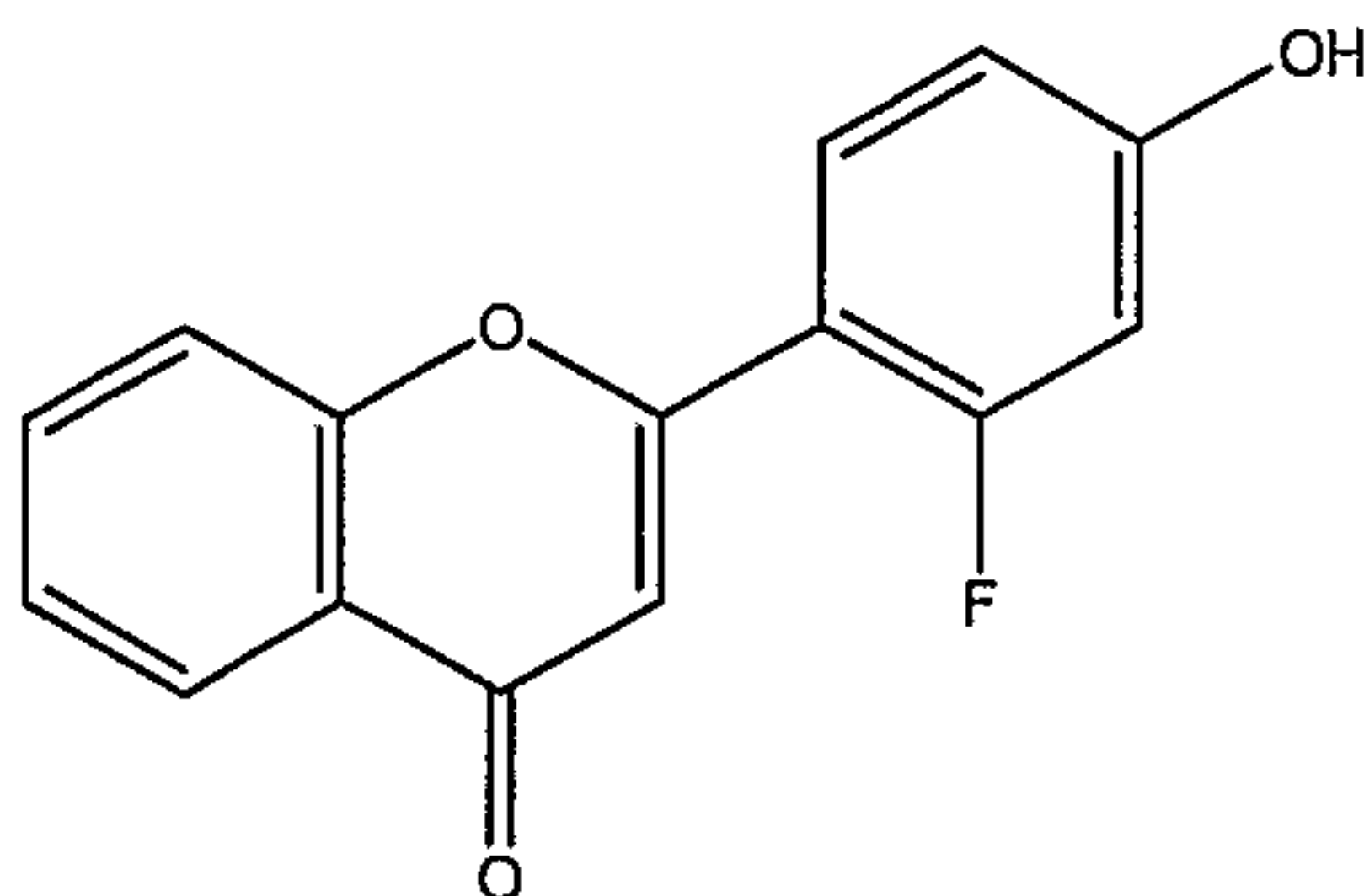


6-Hydroxy-2-(4-hydroxymethylphenyl)chromen-4-one

[0188] In a 100 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2'-hydroxy-5'-acetoxyacetophenone (2.63 g, 13.54 mmol), 4-acetoxymethyl benzoic acid (2.63 g, 13.54 mmol) and pyridine (20 mL). POCl_3 (2.07 g, 13.54 mmol) was added slowly on cooling. Then the reaction mixture was stirred for 24 h at rt under nitrogen. The reaction mixture was poured into ice water and extracted with EtOAc. The organic layer was washed with water, dried and concentrated to give product (3.0 g, 60%). A solution of this product (3.0 g, 8.10 mmol) in THF (50 mL), was added potassium t-butoxide (1.187 g, 9.72 mmol) and the reaction mixture was stirred for 24 h at rt under N_2 . The reaction mixture was poured into saturated aqueous solution of NH_4Cl . The organic layer was separated, washed with water, dried and concentrated to give crude diketone (3.0 g, 99%). The mentioned diketone (3.0 g, 8.10 mmol) was taken into a mixture of 48% HCl (2 mL) and AcOH (25 mL) and heated at 100 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried and concentrated to give the di-acetyl flavone (1.2 g, 74%). To a solution of the di-acetyl flavone (228 mg, 0.676 mmol) in methanol: THF (5 ml: 5 mL), K_2CO_3 (112 mg, 0.811 mmol) was added and stirred for 2 h at rt, then the reaction mixture was neutralized by dilute HCl and extracted with EtOAc. The combined organic layers were washed with water, brine, dried and concentrated to give a crude product, which was purified by column chromatography using 2% MeOH in dichloromethane, to give 100 mg of 6-hydroxy-2-(4-

hydroxymethylphenyl)chromen-4-one (50%). MS (ES) m/z: 269.90 (M+1), 268.91 (M); Mp. 262-265 °C.

Example 15

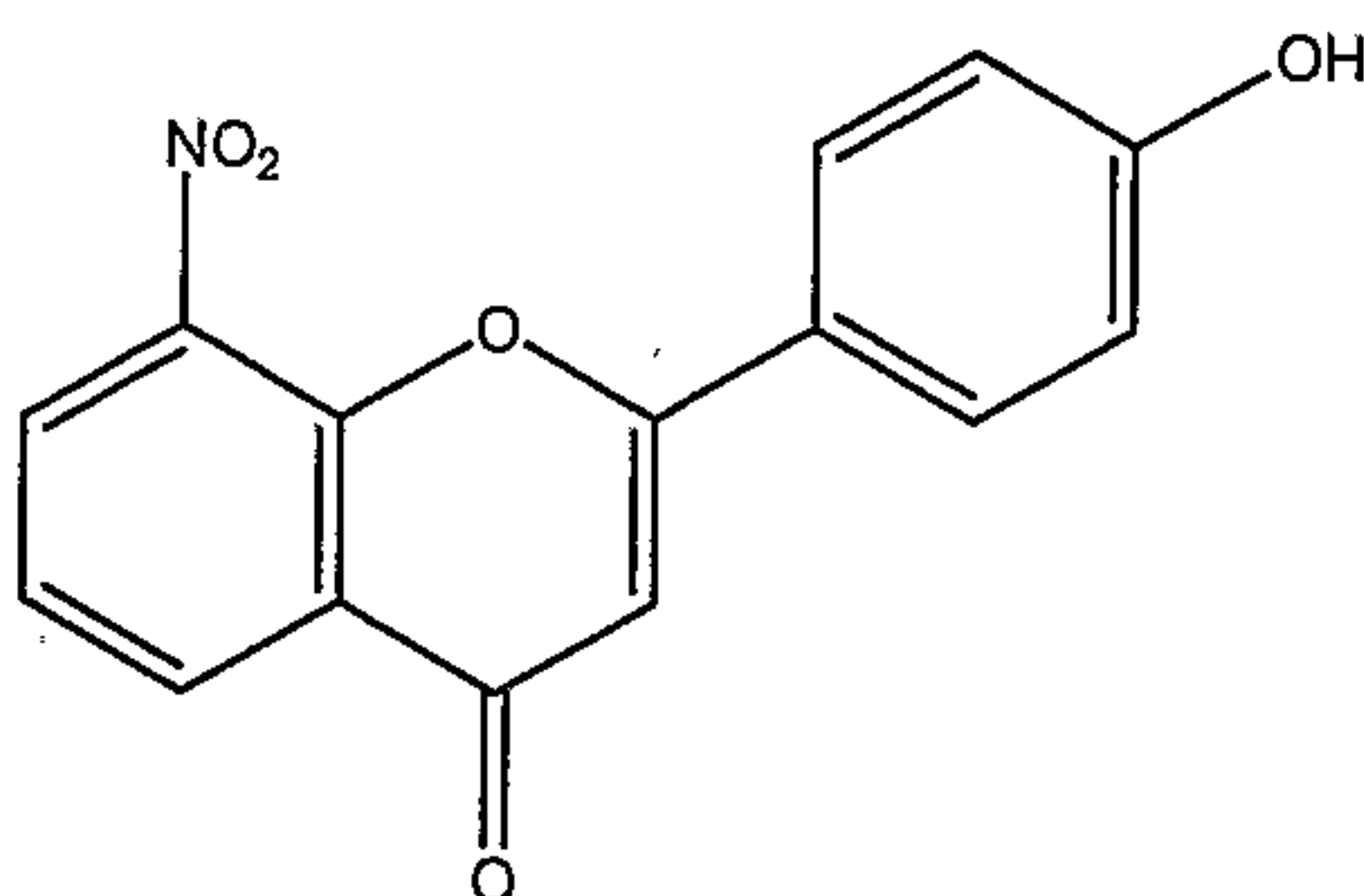


2-(2-Fluoro-4-hydroxyphenyl)chromen-4-one

[0189] To a solution of 2-fluoro-4-hydroxybenzoic acid (1.87 g, 12 mmol) in 30 mL pyridine was added acetic anhydride (1.84 g, 18 mmol) and catalytic amount of DMAP and the reaction mixture was stirred at rt for 15 h. The pyridine was removed under reduced pressure; the residue was dissolved in EtOAc (100 mL), washed with 1N HCl (20 mL), water (20 mL) and dried over anhydrous Na₂SO₄. Removal of solvent gave 2-fluoro-4-acetoxybenzoic acid in 57% yield (1.35 g). To a suspension of 2-fluoro-4-acetoxybenzoic acid (1.33 g, 6.71 mmol) in 10 mL anhydrous dichloromethane was added oxalyl chloride (2.56 g, 20.13 mmol). Two drops of DMF was added and the reaction mixture was stirred at rt for 3 h. The solvent and excess oxalyl chloride were removed under reduced pressure to give 1.48 g of 2-fluoro-4-acetoxybenzoyl chloride which was used in next step without purification. To a solution of 2'-hydroxyacetophenone (0.93 g, 6.83 mmol) in 15 mL anhydrous pyridine was added 2-fluoro-4-acetoxybenzoyl chloride (1.48 g, 6.83 mmol) and the reaction mixture was stirred at rt for 15 h under nitrogen atmosphere. Then the reaction mixture was poured into 100 mL 2N HCl, extracted with EtOAc (200 mL). The crude compound was purified by column chromatography (Silica Gel 230-400 mesh; 20% EtOAc in hexanes as eluent) to give 4-acetoxy-2-fluorobenzoic acid 2-acetyl phenyl ester (1.14 g, 53%). The ester compound (0.74 g, 2.34 mmol) was dissolved in 10 mL anhydrous THF. Potassium tert-butoxide (0.53 g, 4.68 mmol) was added in portions and stirred at rt under nitrogen for 1 h. A yellow solid was formed. The reaction mixture was quenched with 15 mL saturated aqueous ammonium chloride. EtOAc (100 mL) was added and the organic phase was separated and dried over anhydrous

Na₂SO₄. Removal of solvent gave crude product (0.725 g) which was used in next step without further purification. This crude compound (0.72 g, 2.62 mmol) was dissolved in 10 mL glacial AcOH, conc. HCl (1 mL) was added and the reaction mixture was stirred at 110 °C for 4 h. The reaction mixture was cooled to rt. The solid was isolated by filtration, washed with AcOH and dried under vacuum to give 126 mg (21%) over 2 steps. MS (ES) m/z: 256.89 (M), 255.86 (M-1); Mp. 287-289 °C.

Example 16

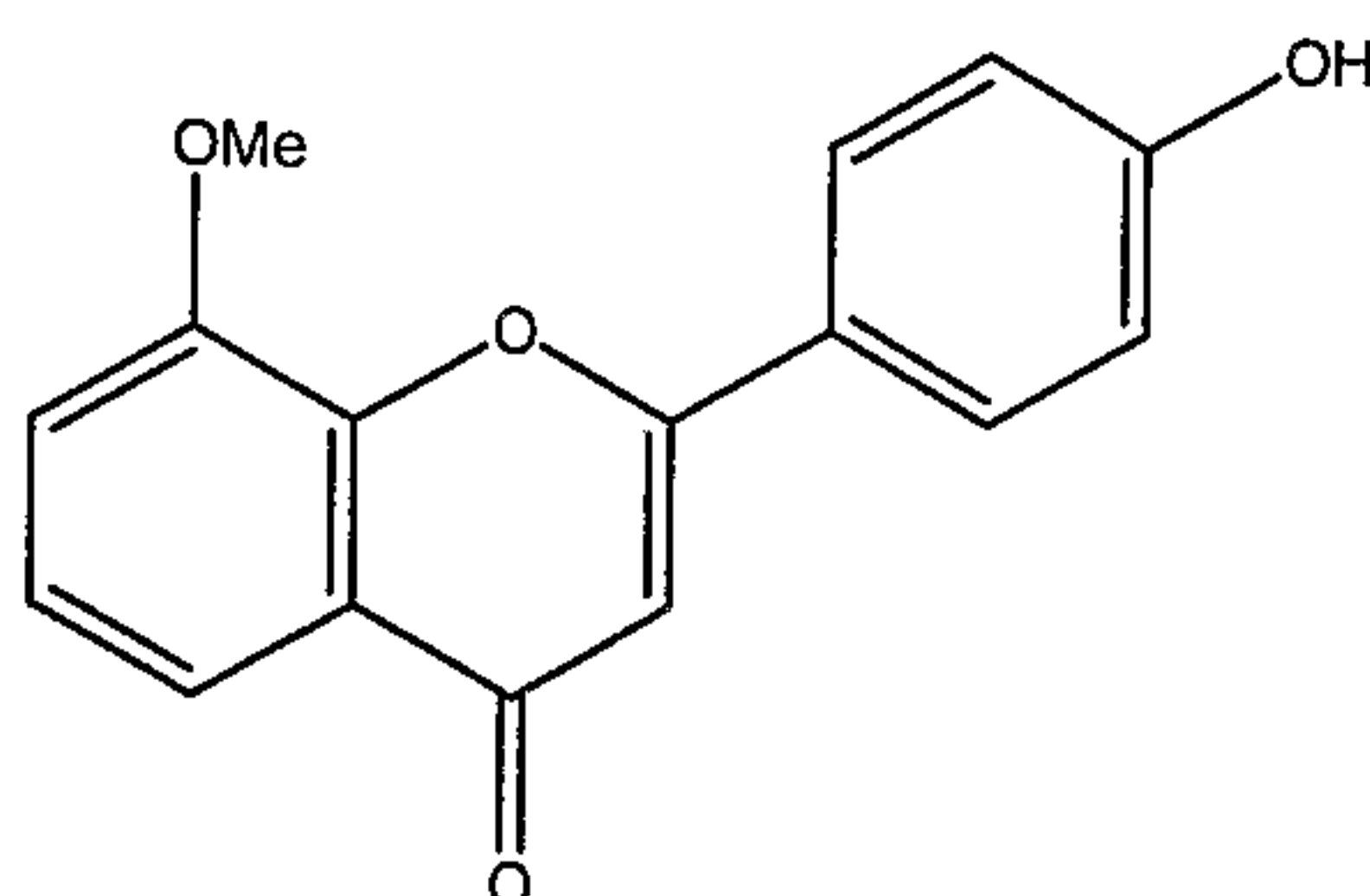


2-(4-Hydroxyphenyl)-8-nitro-4H-chromen-4-one

[0190] In a 250 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2-hydroxy-3-nitro-acetophenone (1.0 g, 5.52 mmol), 4-methoxybenzoyl chloride (0.94 g, 5.52 mmol) and pyridine (20 mL). The reaction mixture was stirred for 24 h at rt under nitrogen. The reaction mixture was poured into ice-water and extracted with EtOAc. The organic layer was washed with water, dried and concentrated to give crude product (1.7 g, 99%). To a solution of the crude product (1.56 g, 4.95 mmol) in THF (50 mL), was added potassium t-butoxide (666 mg, 5.94 mmol) and the reaction mixture was stirred for 16 h at rt under N₂. The reaction mixture was poured into a saturated solution of NH₄Cl. The organic layer was separated, washed with water, dried and concentrated to give the crude diketone (1.5 g, 99%). The diketone (1.5 g, 4.76 mmol) was dissolved in a mixture of 48% HCl (1 mL) and AcOH (15 mL) and heated at 100 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried and concentrated to give cyclized product, which was purified by crystallization to give 760 mg of compound in 54% yield. A mixture of the cyclized compound (360 mg, 1.21 mmol) and pyridinium hydrochloride (5 g) was heated at 190 °C for 3 h. The reaction mixture was cooled to rt, diluted with water, neutralized with NaHCO₃ and

filtered to give crude product, which purified by chromatography using 5% MeOH in dichloromethane to give 196 mg of 2-(4-hydroxyphenyl)-8-nitro-4H-chromen-4-one (57%). MS (ES) m/z: 284.88 (M+1), 283.88 (M); Mp. 299-301 °C.

Example 17

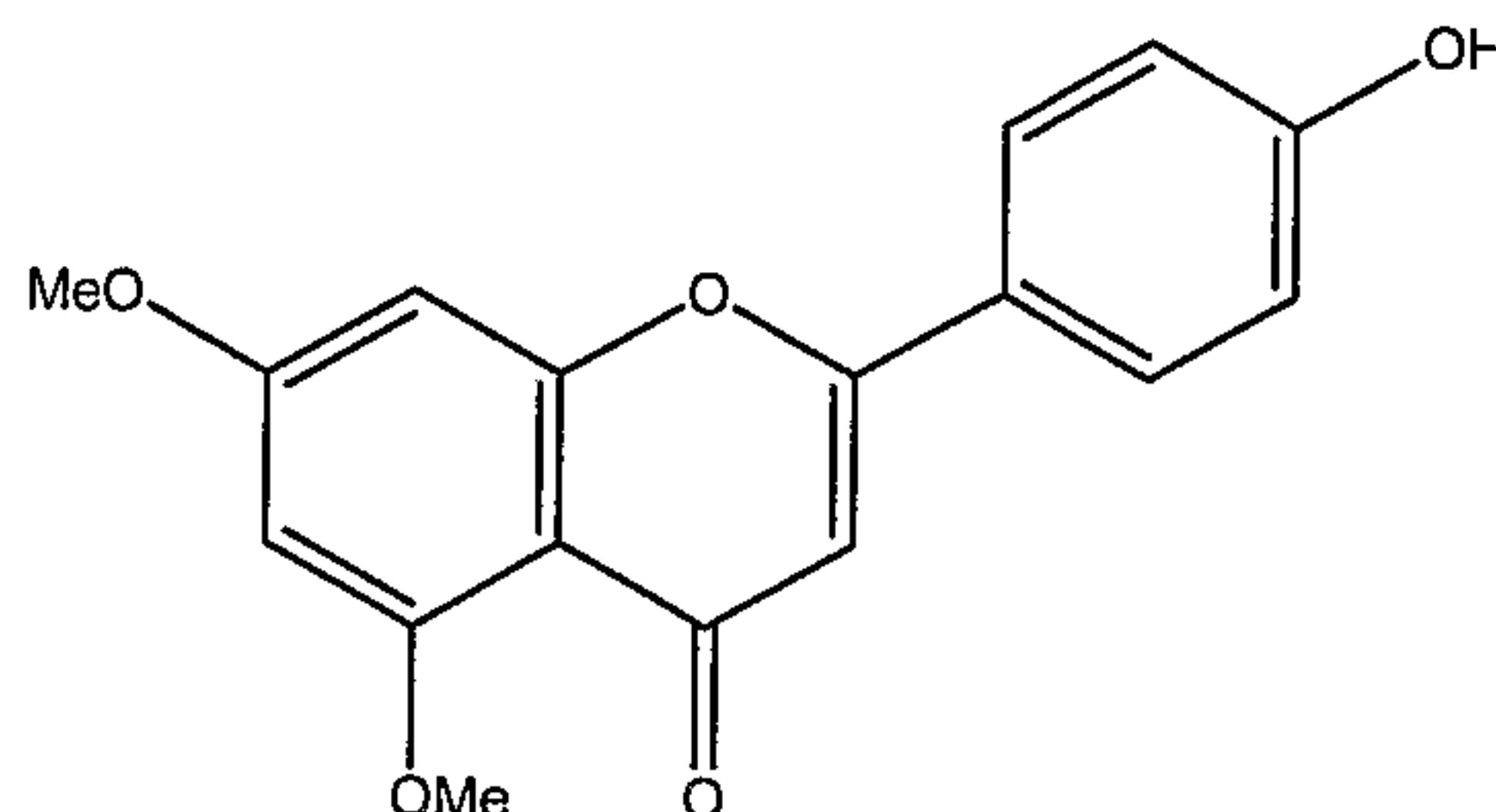


2-(4-Hydroxyphenyl)-8-methoxy-4H-chromen-4-one

[0191] In a 250 mL dry flask was charged with 2-hydroxy-3-methoxybenzoic acid (6.0 g, 36.0 mmol) and anhydrous THF (20 mL) under N₂. Methyl lithium in an ether solution (1.6 M, 73.5 mL, 117.6 mmol) was added dropwise over 20 min. The reaction mixture was heated to reflux for 20 h. After cooling the mixture was poured into 25 mL of brine with 6 N HCl and extracted with 100 mL of EtOAc. The organic layer was further washed with brine three times and dried over sodium sulfate. The solvent was evaporated and the residue was purified by column (hexane: EtOAc 2.5:1) to give 1-(2-hydroxy-3-methoxyphenyl)-ethanone (4.3, 71.8%). 1-(2-Hydroxy-3-methoxyphenyl)-ethanone (1.0 g, 6.0 mmol), 4-acetoxybenzoic acid (1.08 g, 6.0 mmol) and phosphorus oxychloride (0.923 g, 6.0 mmol) in 10 mL pyridine were stirred at rt overnight. The reaction mixture was poured into water (100 mL) and the isolated solid was washed with water. The solid was dissolved in dichloromethane and purified by column chromatography (hexane:EtOAc 2:1) to give the intermediate (1.05 g, 53.13%). Potassium tert-butoxide (0.4 g, 3.5 mmol) was added to this intermediate (1.05 g, 3.2 mmol) in 20 mL anhydrous THF. The reaction mixture was stirred for 4 h at rt. The mixture was poured into water (100 mL) with 1 mL AcOH (adjusted pH to 6-7.0). The solid was further rinsed with water and dissolved in dichloromethane. The organic layer was wash with brine and dried over sodium sulfate. The crude compound was treated with AcOH and two drops of concentrated HCl solution and heated to 110 °C for 1 h. The AcOH was evaporated and the solid residue was dissolved in MeOH and potassium carbonate (3.8 mmol) was added. The

reaction mixture was stirred for 1 hour at rt. The reaction mixture was neutralized with AcOH and the solvent was evaporated. The residue was poured into water and the solid was collected by filtration and purified by column to give 150 mg of 2-(4-hydroxyphenyl)-8-methoxy-4H-chromen-4-one (17.4%). MS (ES) m/z: 269.93 (M+1), 268.91 (M); Mp. 281-283 °C.

Example 18

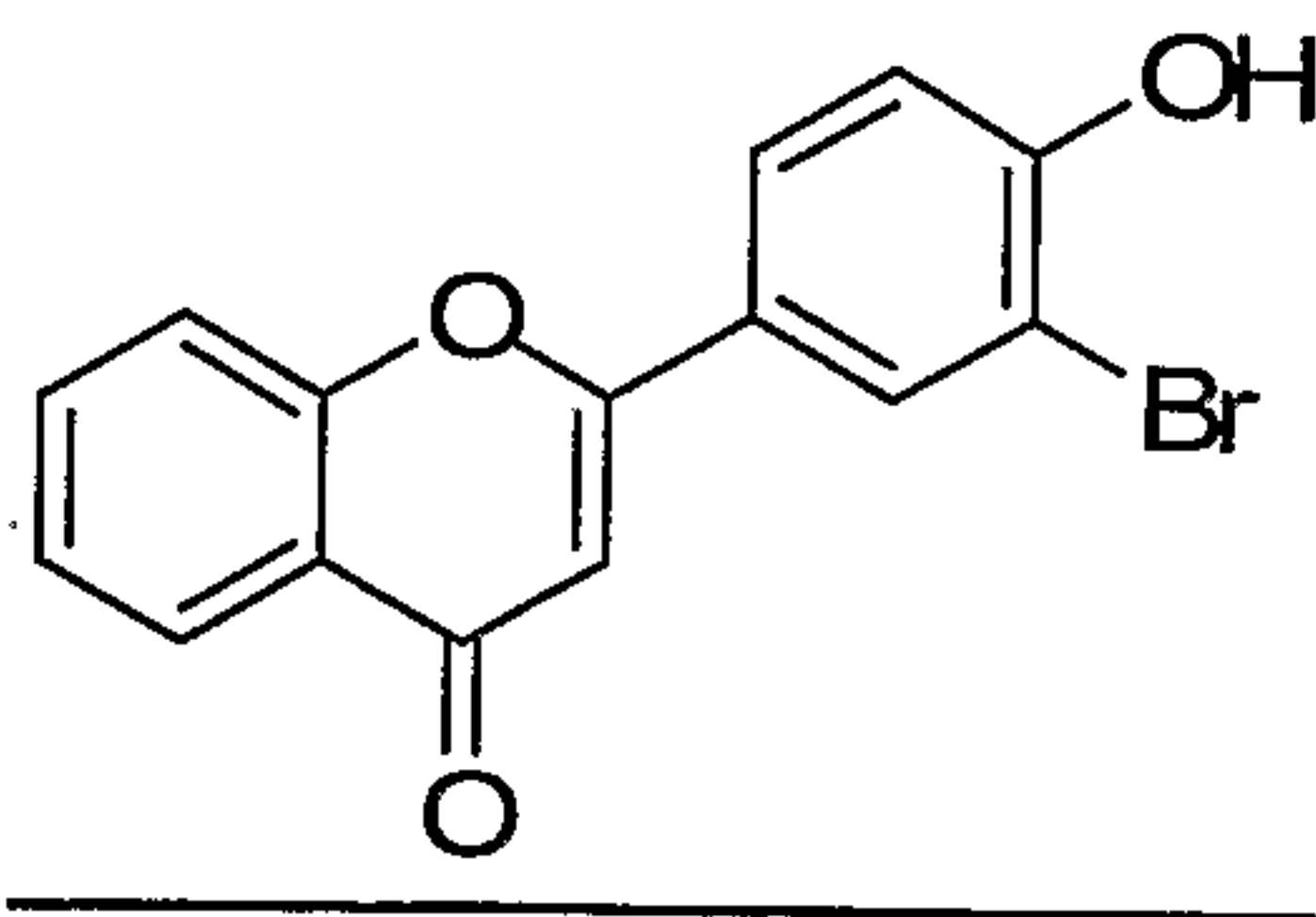


2-(4-Hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one

[0192] To a solution of 4',6'-dimethoxy-2'-hydroxy acetophenone (1.96 g, 10 mmol) in 20 mL anhydrous pyridine was added 4-acetoxy benzoic acid (2.16 g, 12 mmol). The mixture was cooled to 0 °C and phosphorous oxychloride (1 mL) was added. A white precipitate was formed. The reaction mixture was stirred at rt for 2 h under nitrogen atmosphere. The reaction mixture was poured into 100 mL cold 2 N HCl. The mixture was extracted with EtOAc (2x200 mL). The combined organic layers were washed with water and brine and dried over anhydrous Na₂SO₄. The solvent was removed under vacuum to give a gummy solid product (3.36 g, 94%), which was used in next step without further purification. The gummy product (3.35 g, 9.35 mmol) was dissolved in 30 mL anhydrous THF. Potassium tert-butoxide (2.1 g, 18.7 mmol) was added in portions and the mixture was stirred at rt under nitrogen for 15 h. A yellow solid was formed. The reaction was quenched with saturated aqueous ammonium chloride solution (30 mL). EtOAc (100 mL) was added and the organic layer was separated and dried over anhydrous Na₂SO₄. Removal of solvent gave fluffy solid (2.52 g) which was used in next step without further purification. The fluffy solid (1.0 g, 2.79 mmol) was dissolved in glacial AcOH (8 mL). Concentrated HCl (5 drops) was added and the reaction mixture was stirred at 110 °C for 2.5 h. The mixture was cooled to rt and water (50 mL) was added. The solid was filtered off, washed with water and dried under vacuum. The crude compound was purified by column chromatography

(Silica Gel 230-400 mesh; 30% EtOAc in hexanes as eluent) to give 204 mg of 2-(4-hydroxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (25%) as an off-white solid. MS (ES) m/z: 299.94 (M+1), 298.93 (M); Mp. 301-303 °C.

Example 19

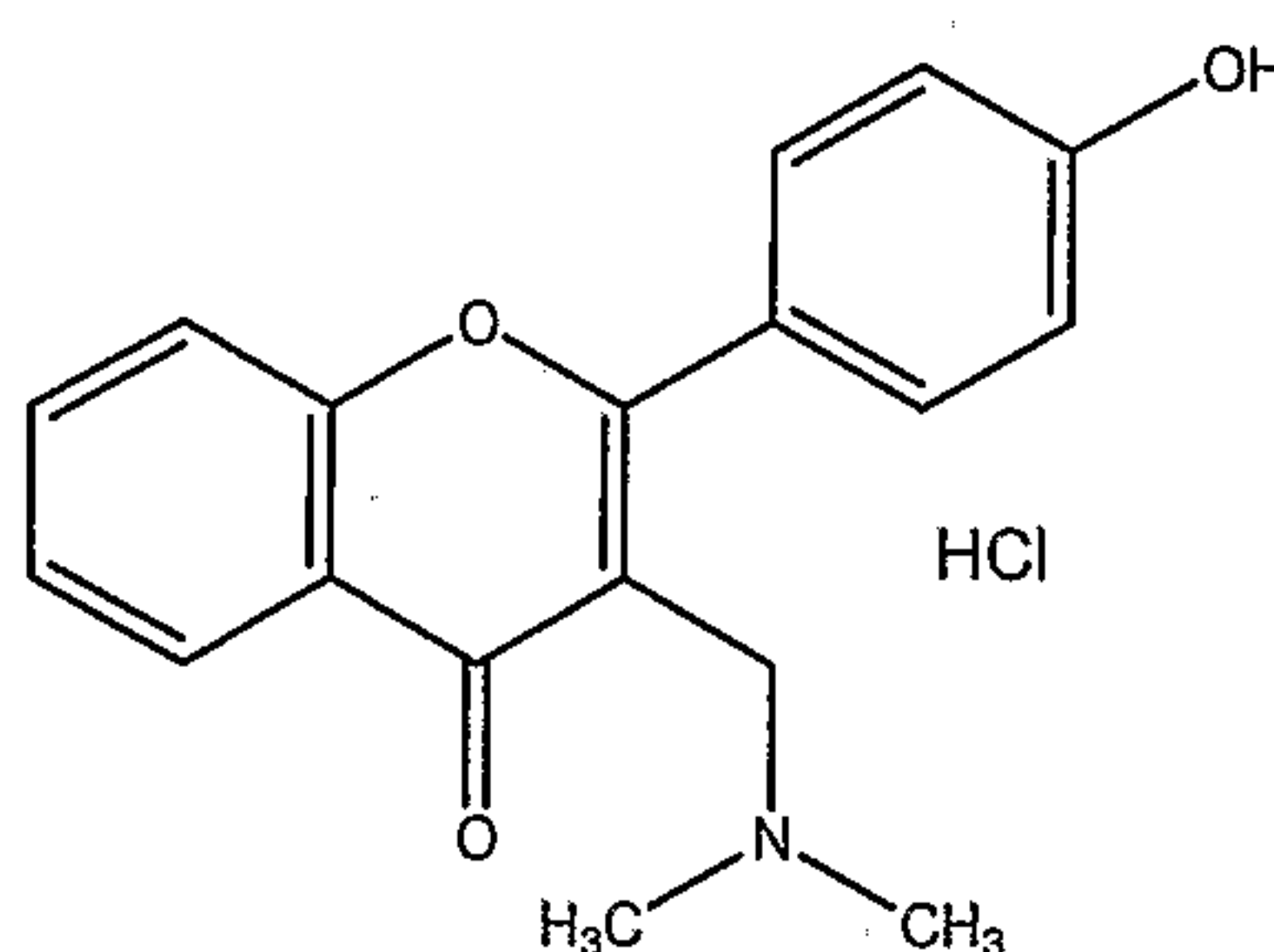


2-(3-Bromo-4-hydroxyphenyl)-4H-chromen-4-one

[0193] To a solution of 3-bromo-4-hydroxy-benzoic acid (3.0 g, 13.83 mmol) in dichloromethane (100 mL) and pyridine (20 mL) was added acetyl chloride (1.1 mL, 15.20 mmol) and the resulting mixture was stirred at rt for 1 h. The reaction was quenched with water (50 mL) and acidified with HCl (1 N) to adjust pH = 1~2. The mixture was extracted with dichloromethane (3 x 100 mL) and concentrated to afford 4-acetoxy-3-bromo-benzoic acid (3.6 g, 100%). To a solution of 4-acetoxy-3-bromo-benzoic acid (3.60 g, 13.83 mmol) in dichloromethane (100 mL) at rt was added oxalyl chloride (1.8 mL, 20.75 mmol) and DMF (0.5 mL), sequentially. The resulting mixture was stirred at rt for 1 h. The mixture was concentrated to afford the acid chloride. To a solution of the freshly prepared acid chloride in dichloromethane (100 mL) were added 2'-hydroxyacetophenone (2.5 mL, 20.75 mmol) and triethylamine (3.9 mL, 27.66 mmol). This mixture was stirred at rt for 2 h. The reaction was quenched with water (100 mL) and extract with dichloromethane (3 x 150 mL). The combined organic layers were concentration to afford an oily residue, which was purified by column chromatography using 30% EtOAc in hexane to give the phenol ester (4.5 g, 86%). A solution of the phenol ester (4.0 g, 10.61 mmol) in THF (100 mL) was mixed with potassium t-butoxide (1.6 g, 14.32 mmol) and stirred at 60 °C for 1.5 h. This mixture was cooled to rt, diluted with water (100 mL) and acidified with HCl (1 N) to adjust pH = 5~6. The mixture was extract with dichloromethane (3 x 100 mL) and the combined organic layers were concentration to give a yellow solid residue. The residue was purified by column chromatography using 30% EtOAc in

hexane to give the diketone (2.3 g, 58%). A solution of the diketone (1.50 g, 3.98 mmol) in AcOH (100 mL) and HCl (conc., 2 mL) was stirred at reflux for 16 h. This mixture was cooled to rt, diluted with water (100 mL), extracted with dichloromethane (3 x 100 mL) and concentrated. The residue was purified by column chromatography using 50 % EtOAc in hexane to give the flavone acetate (0.4 g, 28%). A solution of the flavone acetate (0.53 g, 1.48 mmol) in MeOH (80 mL) and water (20 mL) was mixed with potassium carbonate (1.10 g, 8.00 mmol) and was stirred at rt for 1 h. The solid was filtered off, washed with water, hexanes, and dichloromethane sequentially to give 390 mg of product (83%) as a light yellow solid. MS (ES) m/z: 318.84 + 316.84 (two isotopes of M); Mp. 273.5-274.9 °C.

Example 20

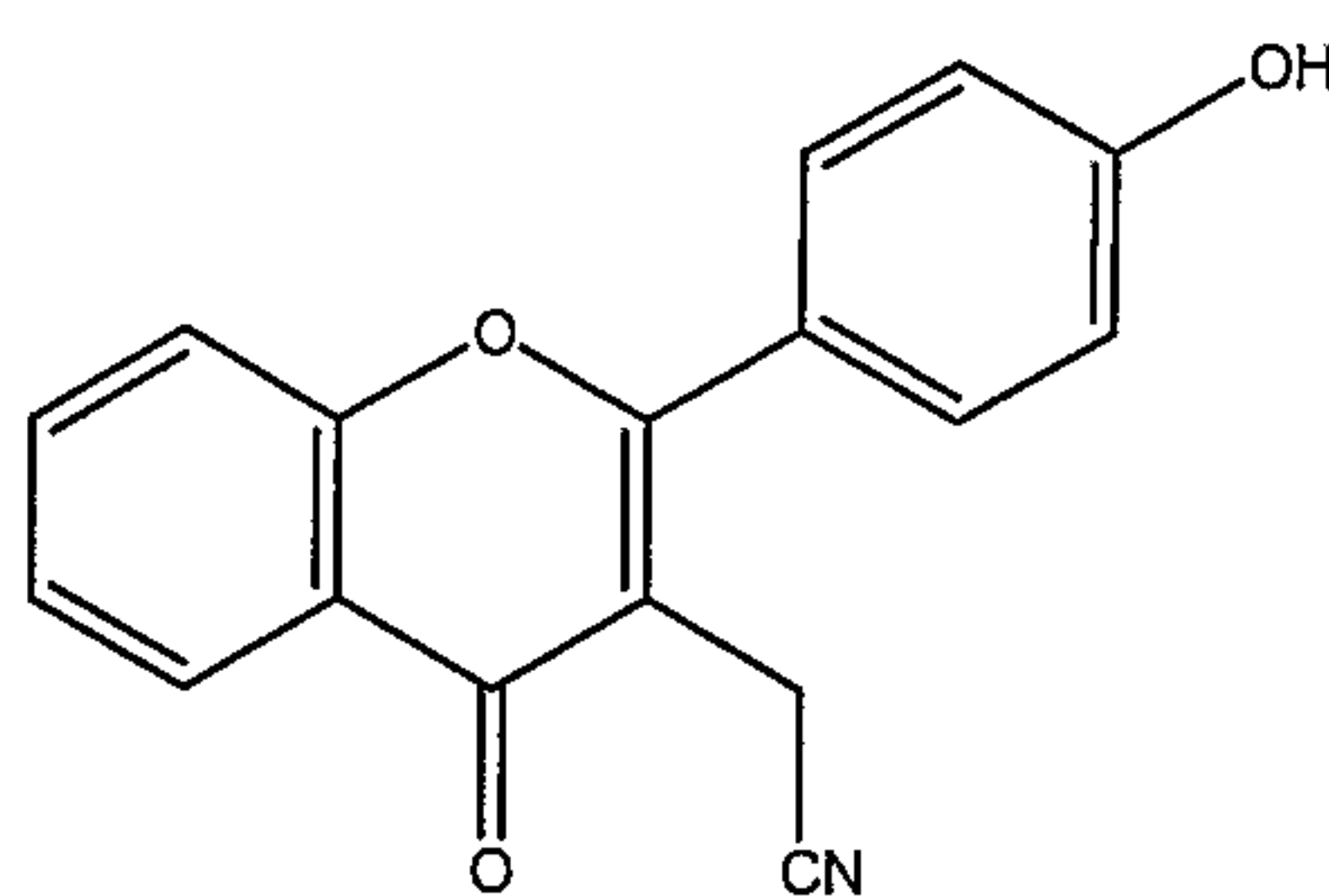


3-((Dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one hydrochloride

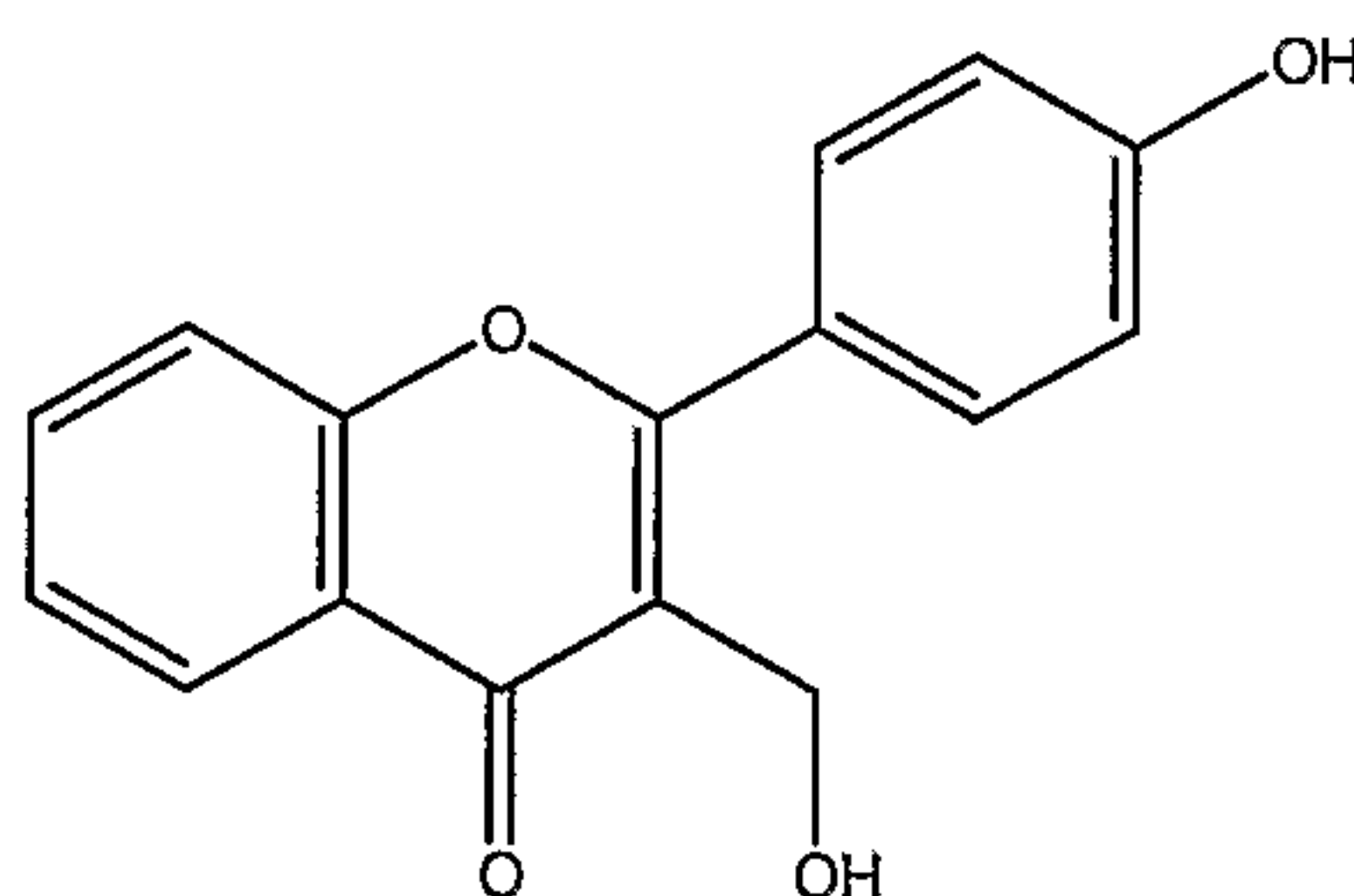
[0194] A 100 mL dry flask was charged with 2'-hydroxy propiophenone (10.0 g, 67 mmol), 4-acetoxybenzoic acid (12.0 g, 67 mmol), phosphorus oxychloride (6.7 mL, 73 mmol), pyridine (25 mL) and anhydrous dichloromethane (10 mL) sequentially. The reaction mixture was stirred at rt for 3 h then poured into 150 mL of cold water. EtOAc (3 x 100 mL) was used to extract the compound out of the aqueous layer. The combined organic layers were washed with sodium bicarbonate, brine and dried over sodium sulfate. The residue was purified by column chromatography (hexane: EtOAc 2:1) to afford 14.6 g of the corresponding phenol ester (77%). To a solution of the phenol ester (14.0 g, 51.5 mmol) in THF (200 mL) was added potassium tert-butoxide (8.64 g, 77.2 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction was quenched by adding water (100 mL), then extracted with dichloromethane (3 x 100 mL). The combined organic layers were concentrated to afford a solid residue. This residue

was dissolved in AcOH (160 mL) and concentrated HCl (5 mL) and the mixture was stirred at reflux for 8 h. The reaction was quenched by adding water (100 mL). The reaction mixture was extracted with dichloromethane (3 x 100 mL) and concentrated to afford a solid residue. This solid was re-dissolved in MeOH (200 mL) and water (200 mL) and the solution was mixed with potassium carbonate (16 g) and stirred at rt for 2 h. The MeOH was removed and the aqueous layer was acidified with HCl (1 N) to pH= 5. The solid was filtered off and further washed with water, EtOAc and dichloromethane to afford the flavone analog (7.5 g, 58% over two step). A solution of the flavone (6.9 g, 27.4 mmol) in acetic anhydride (50 mL) was stirred at reflux for 16 h. The mixture was cooled to rt and poured into ice water (300 mL). The mixture was extracted with dichloromethane (3 x 100 mL) and concentrated to afford a light yellow solid as the corresponding flavone acetate (6.8 g, 84%). To a solution of the flavone acetate (6.8 g, 23.1 mmol) in carbon tetrachloride (200 mL) at reflux was added NBS (4.12 g, 23.1 mmol) and benzoyl peroxide (0.56 g, 2.31 mmol). The reaction was stirred at reflux for 4 h and then quenched with HCl (0.5 N, 100 mL). The reaction mixture was extracted with dichloromethane (3 x 100 mL) and the combined organic layers were concentrated to afford 3-bromomethyl-2-(4-hydroxyphenyl)-4H-chromen-4-one as a light yellow compound (8.6 g, 100%).

[0195] A solution of 3-((dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one hydrochloride (0.3 g, 0.8 mmol) in DMF (20 mL) was mixed with dimethylamine solution in THF (2 mL, 4 mmol) and was stirred at 45 °C for 24 h. The reaction mixture was extract with EtOAc (3 x 100 mL) and concentrated to an oily residue. This residue was re-dissolved in MeOH (50 mL) and water (50 mL), mixed with potassium carbonate (1 g), and stirred at rt for 0.5 h. The mixture was extracted with dichloromethane (3 x 50 mL) and concentrated to afford an oil. This oil was re-dissolved in dichloromethane (10 mL) and mixed with HCl in ether (10 mL, 20 mmol) and stirred at rt for 1 h. The resulting solid was filtered and washed with dichloromethane and hexanes to give 3-((dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one hydrochloride a light yellow solid product (0.24 g, 90%). MS (ES) *m/z*: 295.98 (M); Mp. 271.5-272.3 °C.

Example 212-(2-(4-Hydroxyphenyl)-4-oxo-4H-chromen-3-yl)acetonitrile

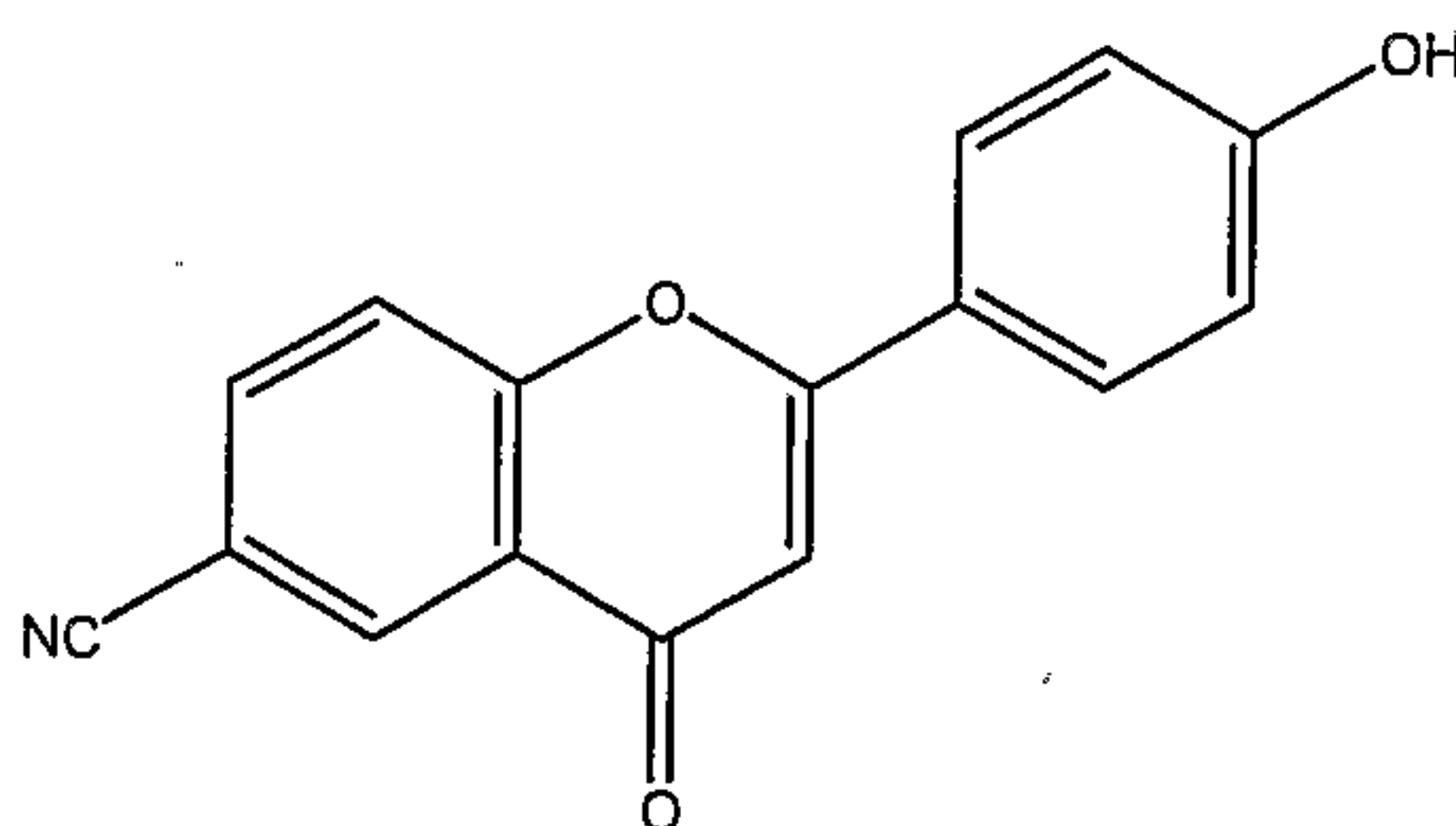
[0196] A solution of 3-bromomethyl-2-(4-hydroxyphenyl)-4H-chromen-4-one (0.3 g, 0.8 mmol) in DMF (15 mL), water (15 mL), and NaCN (0.12 g, 2.4 mmol) was stirred at 45 °C for 24 h. The reaction mixture was extracted with EtOAc (3 x 100 mL) and concentrated to afford a solid residue. This residue was re-dissolved in MeOH (50 mL) and water (50 mL) and was mixed with potassium carbonate (1 g) and stirred at rt for 0.5 h. MeOH was removed, the aqueous layer was acidified with HCl (1 N) to pH= 5. The solid was filtered off and then purified by column chromatography (hexane: EtOAc 1:2). The resulting solid was re-crystallized from dichloromethane and hexanes to give 2-(2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl)acetonitrile as a light yellow solid product (0.14 g, 63%). MS (ES) *m/z*: 278.94 (M+1), 277.93 (M); Mp. 258.2-259.5 °C.

Example 223-(Hydroxymethyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one

[0197] A solution of 3-bromomethyl-2-(4-hydroxyphenyl)-4H-chromen-4-one (0.50 g, 1.5 mmol) and sodium acetate (1.24 g, 15.0 mmol) in AcOH (20 mL) was heated to reflux for 15 h. AcOH was removed and the residue was poured into water and extracted with EtOAc (100 mL). The organic phase was further washed with brine and dried over sodium sulfate. The residue was mixed with potassium carbonate (0.52 g) and MeOH (10 mL) and stirred for 2 h. AcOH (1.0

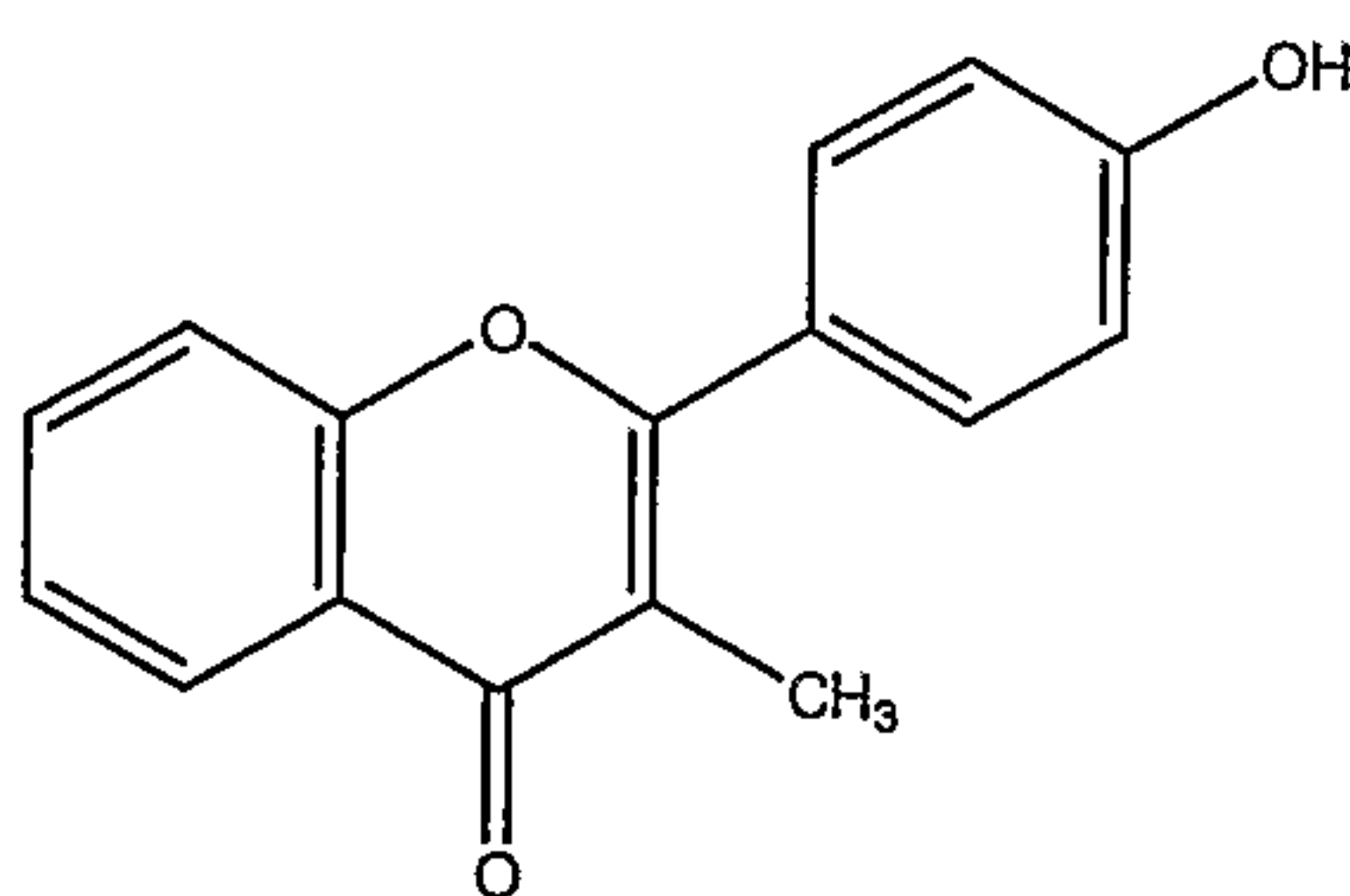
mL) was added and MeOH was removed. The residue was poured into water and the solid was washed additionally with water and hexane to give 3-(hydroxymethyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one (0.265 g, 62.6%). MS (ES) m/z : 269.94 ($M+1$), 268.94 (M); Mp. 234-235 °C.

Example 23

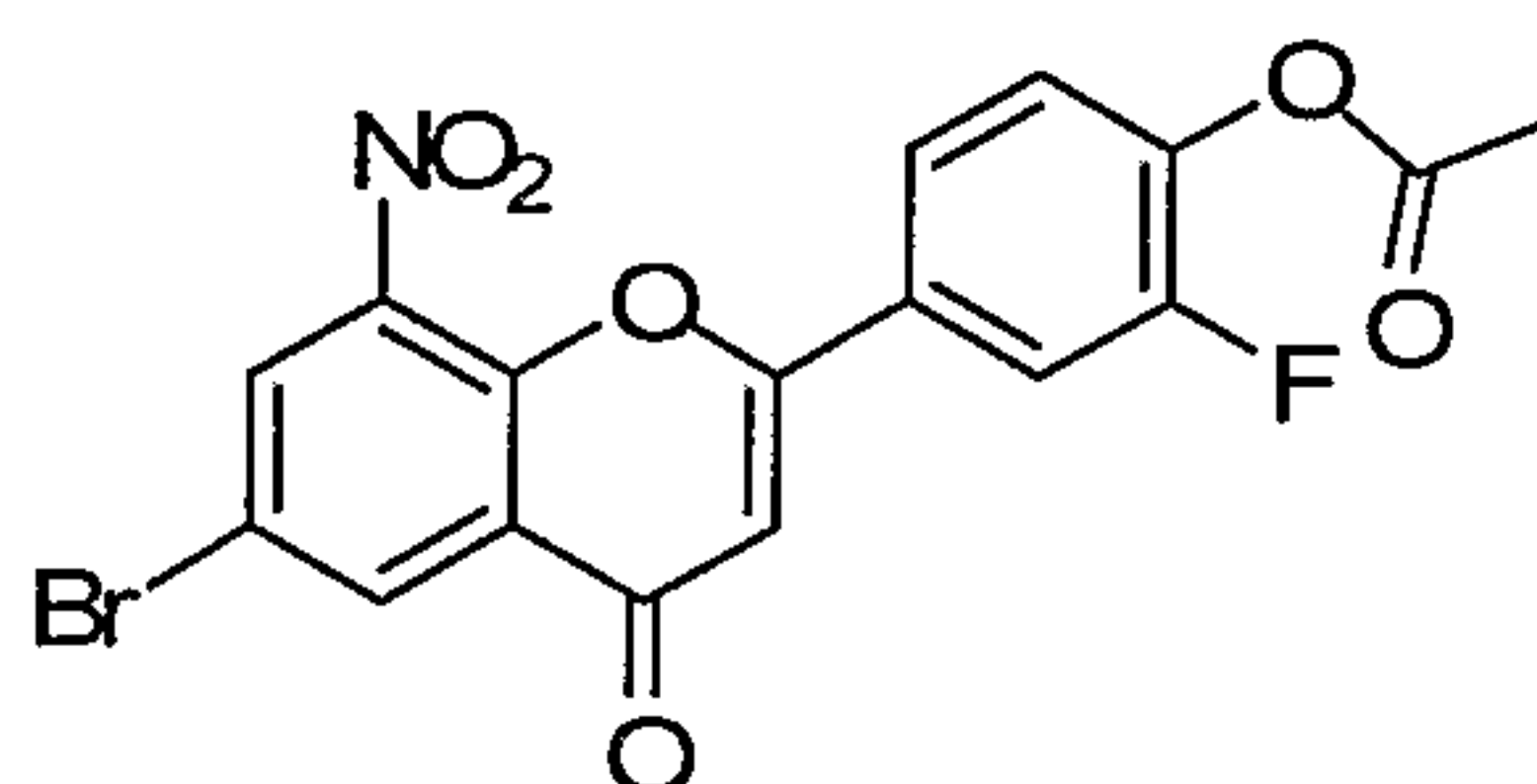


2-(4-Hydroxyphenyl)-4-oxo-4H-chromene-6-carbonitrile

[0198] 2-Acetyl-4-cyanophenol (0.78 g, 4.84 mmol), 4-acetoxybenzoic acid (0.872 g, 4.84 mmol) and phosphorus oxychloride (0.5 mL) and pyridine (2.0 mL) were mixed in anhydrous dichloromethane (10 mL). The reaction mixture was stirred overnight at rt and then poured into cold water and extracted with dichloromethane (150 mL). The organic layer was washed with sodium bicarbonate, brine and dried over sodium sulfate followed by concentration. The crude compound (1.40 g, 89.5%) was obtained after evaporation of the solvent. The crude compound (1.4 g, 4.33 mmol) was dissolved into dry THF (20 mL) and potassium tert-butoxide (0.51 g, 4.55 mmol) was added and the reaction mixture was stirred at rt for 2 h. The solvent was removed, followed by addition of water (50 mL) and EtOAc (150 mL) was used to extract out the compound. The organic layer was washed with brine and dried over sodium sulfate. The crude product (1.20 g) and 4 drops of sulfuric acid were added to AcOH (15 mL). The reaction mixture was heated to 110 °C for 1 h. AcOH was removed and sodium bicarbonate solution was added followed by extraction with EtOAc. The organic layer was washed with brine and dried over sodium sulfate and concentrated. The crude and potassium carbonate (1.1 g) was added to MeOH (20 mL). The reaction mixture was stirred for 2 h. AcOH (1.0 mL) was added and MeOH was removed. The residue was purified by preparative HPLC to give 70 mg of 2-(4-hydroxyphenyl)-4-oxo-4H-chromene-6-carbonitrile. MS (ES) m/z : 264.91 ($M+1$), 263.90 (M); Mp. 296-298 °C.

Example 242-(4-Hydroxyphenyl)-3-methyl-4H-chromen-4-one

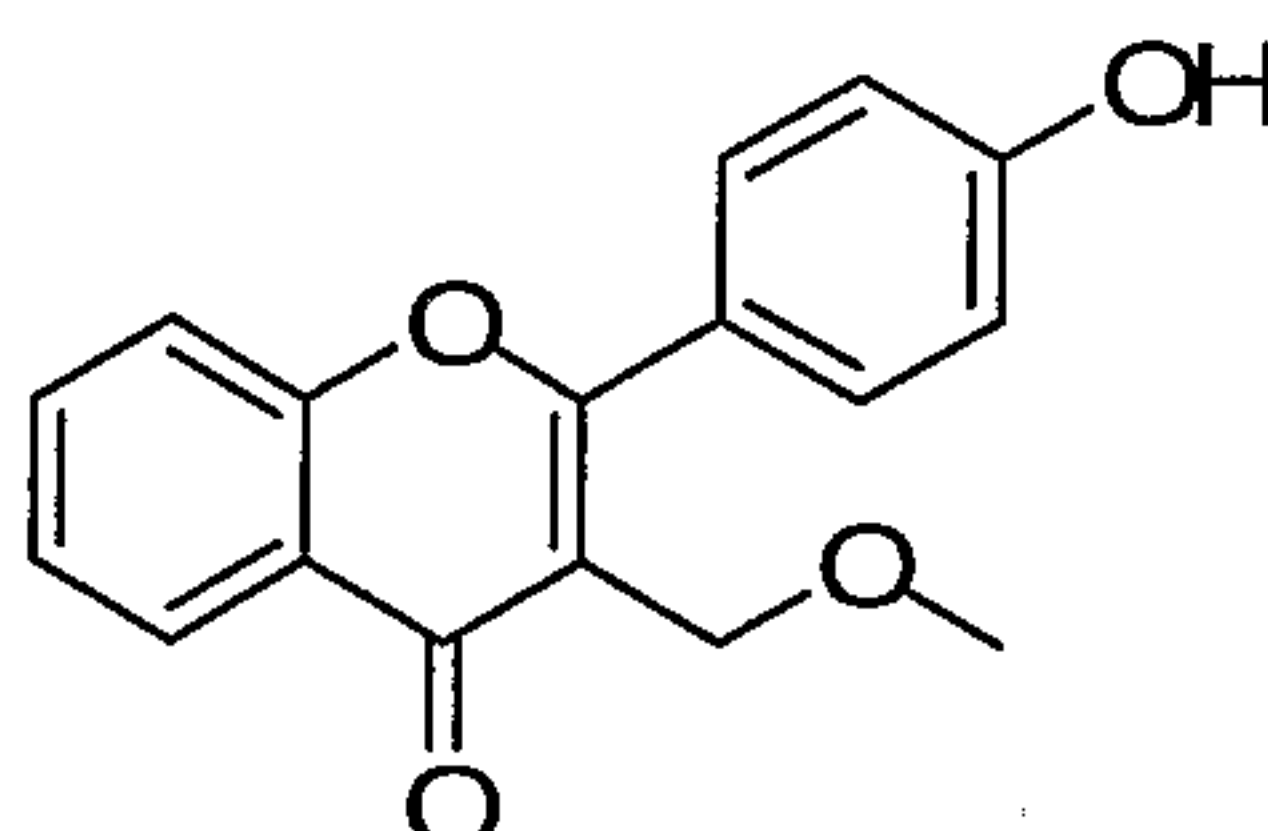
[0199] A 100 mL dry flask was charged with 2'-hydroxy propiophenone (10.0 g, 0.067 mol), 4-acetoxybenzoic acid (12.0 g, 0.067 mol), POCl₃ (6.7 mL, 0.073 mol), pyridine (25 mL) and anhydrous dichloromethane (10 mL). The reaction mixture was kept at rt with stirring for 3 hours then poured into 150 mL of cold water. The mixture was extracted with EtOAc (150 mL) and the organic layer was washed with sodium bicarbonate, brine and dried over sodium sulfate. The crude compound was purified by column chromatography (hexane : EtOAc 2:1) to give the intermediate (14.6 g, 70.2%). The intermediate (14.0 g, 44.8 mmol) was dissolved in dry THF (150 mL) and potassium tert-butoxide (5.28 g, 47.0 mmol) was added. The reaction mixture was stirred at rt for 2 h. The mixture was concentrated and water (50 mL) was added, followed by extraction with EtOAc (150 mL). The organic layer was washed with brine and dried over sodium sulfate. The crude compound (11.0 g, 35.2 mmol) was dissolved into AcOH (30 mL) and 37% HCl (2.0 mL) was added. The reaction was carried out at 110 °C for 2 h. AcOH was removed and 7.0 g potassium carbonate and 40 mL methanol were added followed by stirring overnight. AcOH (5.0 mL) was added to the mixture and methanol was removed. Water (50 mL) was added to the residue. The mixture was stirred for a while to obtain the solid, which was filtered off and further washed with water and EtOAc to give 3.70 g of 2-(4-hydroxyphenyl)-3-methyl-4H-chromen-4-one (41.7%). MS (ES) *m/z*: 253.89 (M+1), 252.90 (M); Mp. 241-242 °C.

Example 254-(6-Bromo-8-nitro-4-oxo-4H-chromen-2-yl)-2-fluorophenyl acetate

[0200] To a solution of 2'-hydroxy-5'-bromoacetophenone (10 g, 46.5 mmol) in carbon tetrachloride (60 mL) at reflux was added 70% nitric acid (5.2 mL, 79.6 mmol). The reaction mixture was stirred at reflux for 40 min. and then cooled to rt. The resulting solid was filtered off and washed with water and hexanes to provide 2'-hydroxy-3'-nitro-5'-bromoacetophenone (10.19 g, 84%). To a solution of 3-fluoro-4-hydroxybenzoic acid (3.0 g, 19.2 mmol) in pyridine (20 mL) and dichloromethane (50 mL) was added acetyl chloride (1.8 mL, 25 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was washed with HCl (1 N, 2x100 mL), and concentrated to afford 3-fluoro-4-acetoxybenzoic acid (3.18 g, 83%). To a solution of 3-fluoro-4-acetoxybenzoic acid (3.18 g, 16.1 mmol) in dichloromethane (100 mL) was added oxalyl chloride (2.1 mL, 24.0 mmol) and DMF (0.2 mL) sequentially. The resulting mixture was stirred at rt for 1 h and then concentrated to afford the corresponding acid chloride. A mixture of the acid chloride, 2'-hydroxy-3'-nitro-5'-bromoacetophenone (4.17 g, 16.1 mmol) and triethylamine (8.9 mL, 64.2 mmol) in dichloromethane (100 mL) was stirred at rt for 1 h and then concentrated. The residue was re-dissolved in THF (100 mL) and mixed with potassium tert-butoxide (4.0 g, 35.3 mmol). The reaction was stirred at rt for 16 h and then quenched by adding water (100 mL). The mixture was extracted with dichloromethane (3x100 mL) and concentration to afford the crude diketone as a yellow solid. This solid was re-dissolved in AcOH (100 mL) and HCl (conc., 5 mL) and the mixture was stirred at reflux for 20 h. The reaction was quenched with water (100 mL), extracted with dichloromethane (3x100 mL) and concentrated. A solution of the resulting residue in MeOH (50 mL) and water (50 mL) was mixed with potassium carbonate (2 g) and stirred at rt for 2 h. MeOH was removed and the aqueous layer was acidified with HCl (1 N) to pH= 5. The solid was filtered off and washed with water, acetone, and dichloromethane

sequentially to provide a solid of the flavone analog (1.85 g, 30% five steps combined). To a solution of the flavone analog (1.85 g, 4.87 mmol) in pyridine (50 mL) and dichloromethane (100 mL) at rt was added acetyl chloride (1.1 mL, 14.6 mmol) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was washed with HCl (1 N, 2x100 mL), and concentrated to afford a solid residue, which was purified by column chromatography (hexane: EtOAc 2:1). The resulting solid was re-crystallized from EtOAc and hexanes to afford 4-(6-bromo-8-nitro-4-oxo-4H-chromen-2-yl)-2-fluorophenyl acetate (1.1 g, 54%) as a light yellow solid. MS (ES) *m/z*: 423.78, 421.77; Mp. 236.2-238.5 °C.

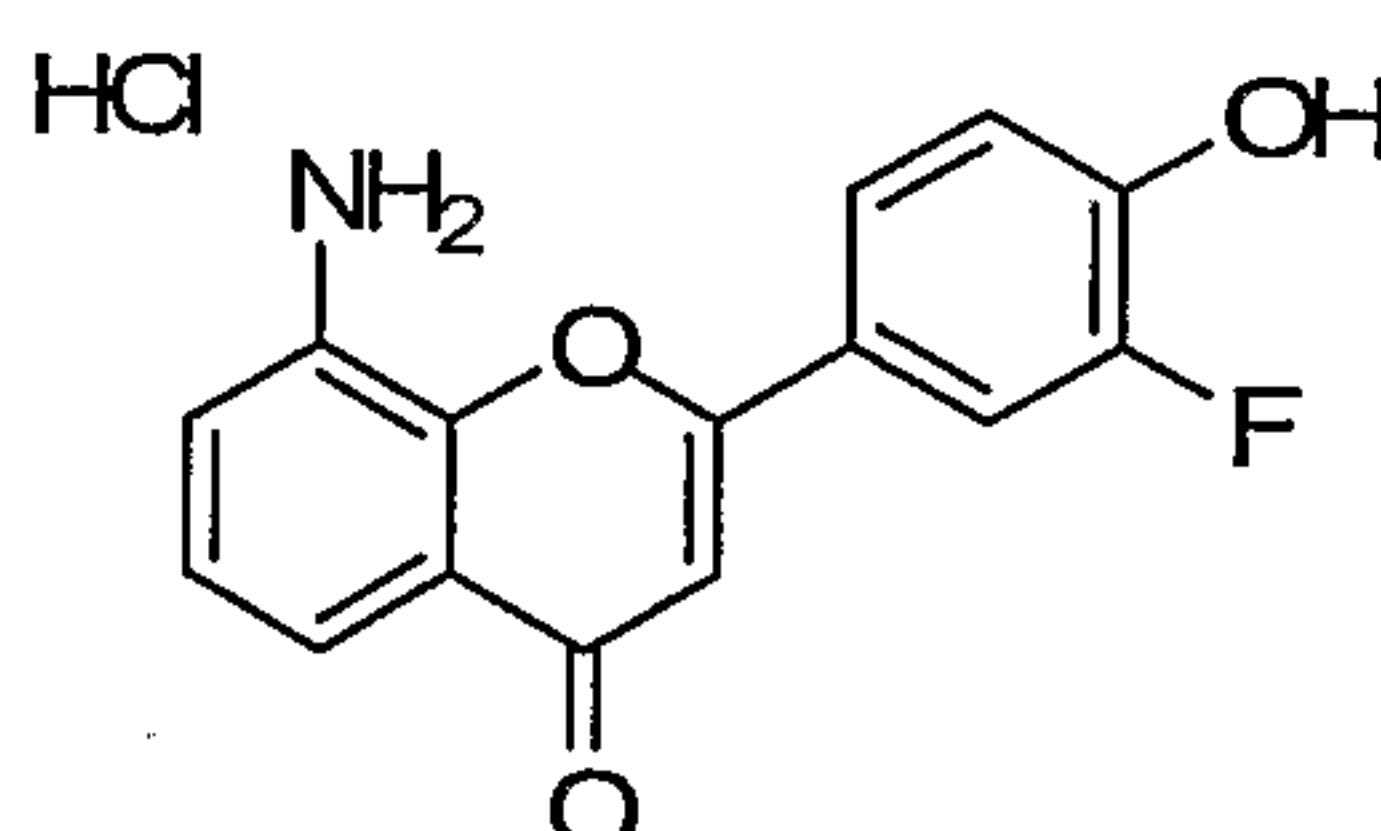
Example 26



2-(4-Hydroxyphenyl)-3-(methoxymethyl)-4H-chromen-4-one

[0201] A mixture of 3-bromomethyl-2-(4-hydroxyphenyl)-4H-chromen-4-one (0.52 g, 1.57 mmol), sodium methoxide (1.36 mL, 6.28 mmol, 25% in MeOH) and anhydrous MeOH (10 mL) was stirred overnight at rt. The reaction mixture was neutralized by addition of AcOH and the solvent was removed. The residue was poured into water and the solid was collected and purified by column chromatography (hexane : EtOAc 2:1) to give 155 mg of 2-(4-hydroxyphenyl)-3-(methoxymethyl)-4H-chromen-4-one (35.0%). MS (ES) *m/z*: 283.95 (M+1), 282.93 (M); Mp. 237-239 °C.

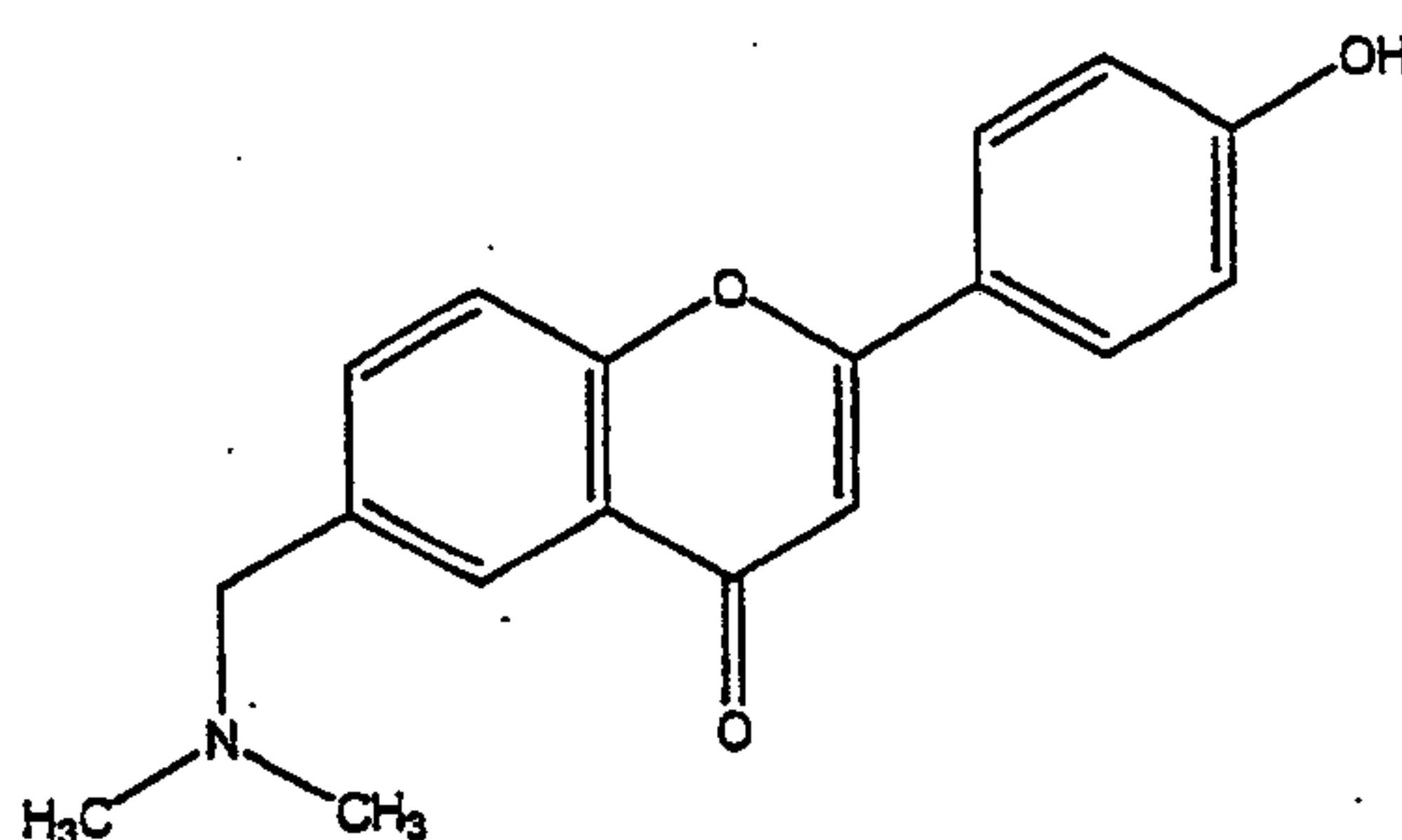
Example 27



8-Amino-2-(3-fluoro-4-hydroxyphenyl)-4H-chromen-4-one hydrochloride

[0202] A Parr Bottle charged with a solution of 4-(6-bromo-8-nitro-4-oxo-4H-chromen-2-yl)-2-fluorophenyl acetate (0.8 g, 1.90 mmol) in THF (350 mL) and palladium carbon (10% on carbon, 0.2 g) was subjected for hydrogenation at 50 psi at rt for 16 h. The reaction mixture was passed through a Celite™ pad and the filtrate was concentrated. The resulting solid was filtered off and washed with dichloromethane to afford the aminoflavone analog as a brown solid (0.5 g, 85%). A solution of the aminoflavone analog (0.5 g, 1.60 mmol) in MeOH (50 mL) and water (20 mL) was mixed with potassium carbonate (1 g) and stirred at rt for 1 h. The MeOH was removed and the aqueous layer was neutralized with HCl (1 N). The resulting solid was filtered off, washed with MeOH, dichloromethane, and hexanes sequentially to provide the hydrolyzed product (0.204 g, 48%). To a solution of the hydrolyzed analog (0.106 g, 0.391 mmol) in MeOH (20 mL) was added HCl ether solution (5 mL, 10 mmol) and the reaction mixture was stirred at rt for 1 h. The MeOH was removed, and the resulting solid was filtered off and washed with a mixture of MeOH-dichloromethane (10:1) to afford 82 mg of 8-amino-2-(3-fluoro-4-hydroxyphenyl)-4H-chromen-4-one hydrochloride (68%). MS (ES) m/z : 271.97; Mp. 256.4-258.5 °C.

Example 28

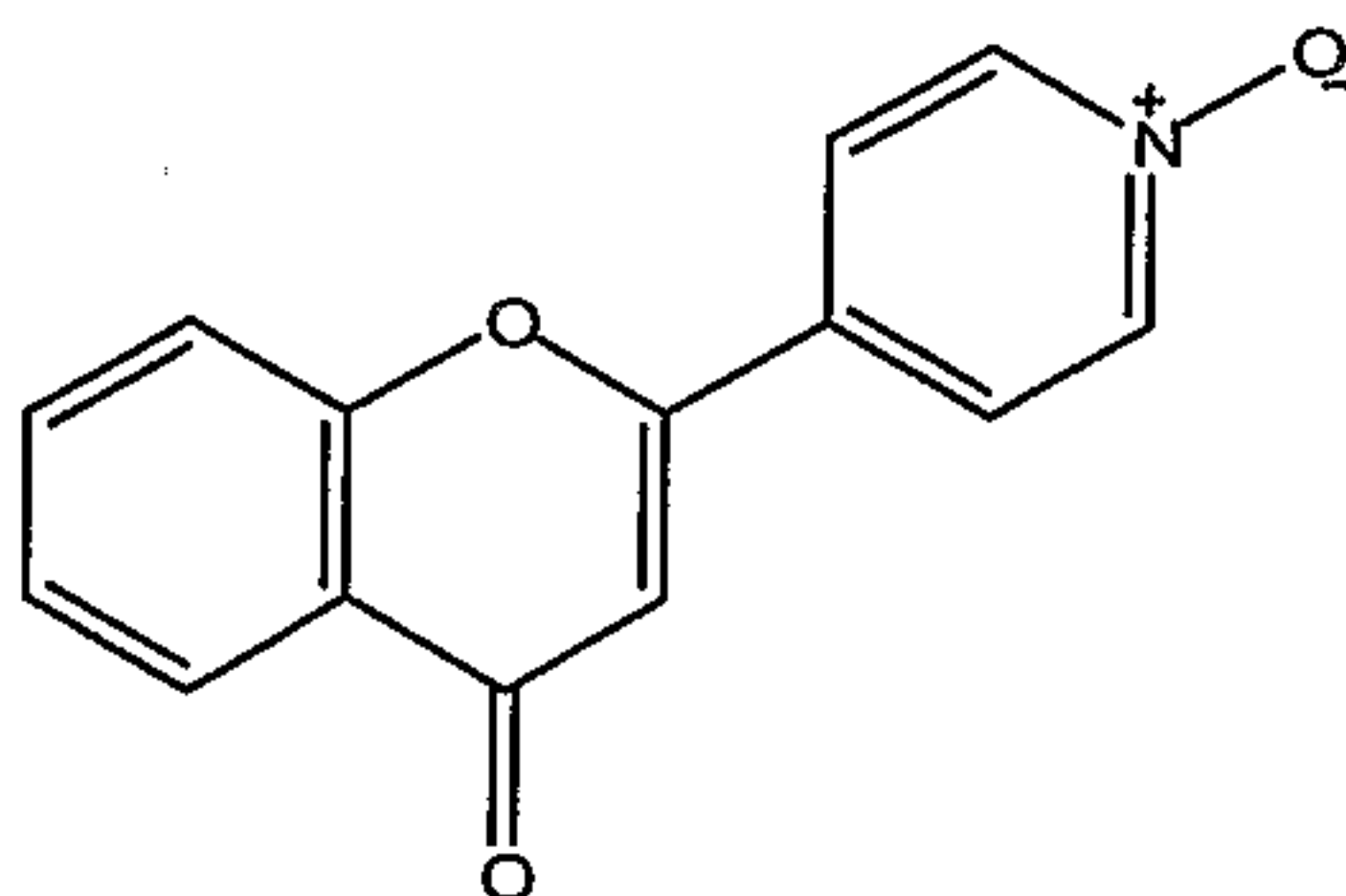


6-((Dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one

[0203] Dimethylamine (1M solution in THF, 1.2 mL) was added to 6-bromomethyl-2-(4-hydroxyphenyl)chromen-4-one (206 mg, 0.62 mmol) dissolved in dry THF (10 mL). The reaction mixture was stirred at rt for 17 hr. Most of the solvent was then removed *in vacuo* and the yellowish residue was suspended in 20 mL of water. The resulting suspension was stirred at rt for 30 min and the solid was removed by filtration, washed with water, ether, and air-dried to afford 6-

((dimethylamino)methyl)-2-(4-hydroxyphenyl)-4H-chromen-4-one (125 mg, 68%).
MS (ES) m/z : 296.98 (M+1), 295.97 (M); Mp. 99-102 °C.

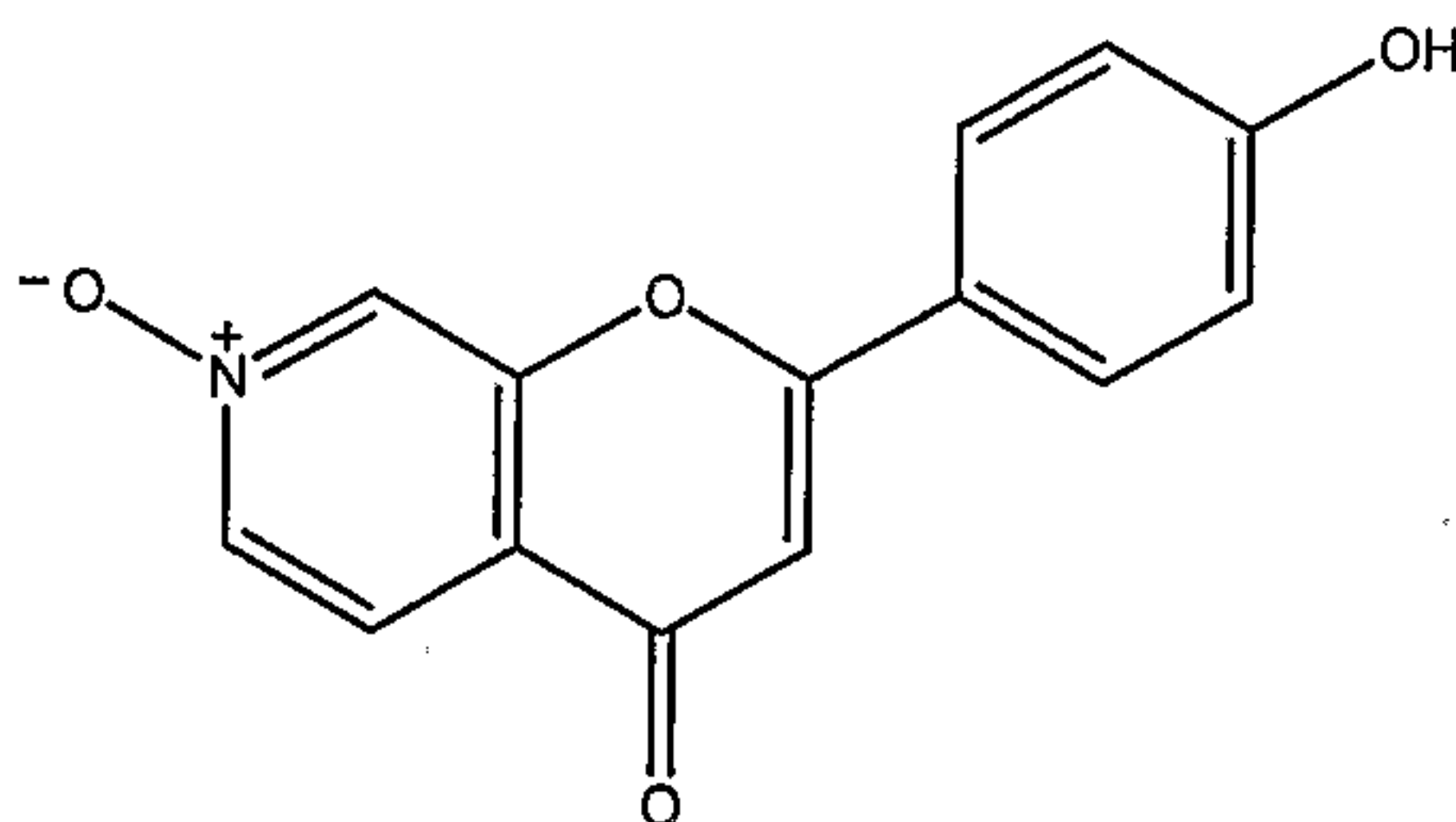
Example 29



2-(1-Oxy-pyridin-4-yl)-chromen-4-one

[0204] To a solution of 2-pyridin-4-yl-chromen-4-one (0.3 g, 1.35 mmol) in 15 mL anhydrous dichloromethane was added *m*-chloroperoxybenzoic acid (57 – 86%) (0.33 g, 1.35 mmol) at 0 °C and the mixture was stirred for 10 min. under nitrogen. The ice-bath was removed and the stirring was continued at rt for 4 h. A white precipitate was formed. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 0.5 N aq. NaOH solution (12 mL). The organic layer was dried over anhydrous Na₂SO₄. The solvent was removed and triturated with ether to afford 2-(1-oxy-pyridin-4-yl)-chromen-4-one (0.27 g, 84%). MS (ES) m/z : 239.89 (M); Mp. 258-259 °C.

Example 30

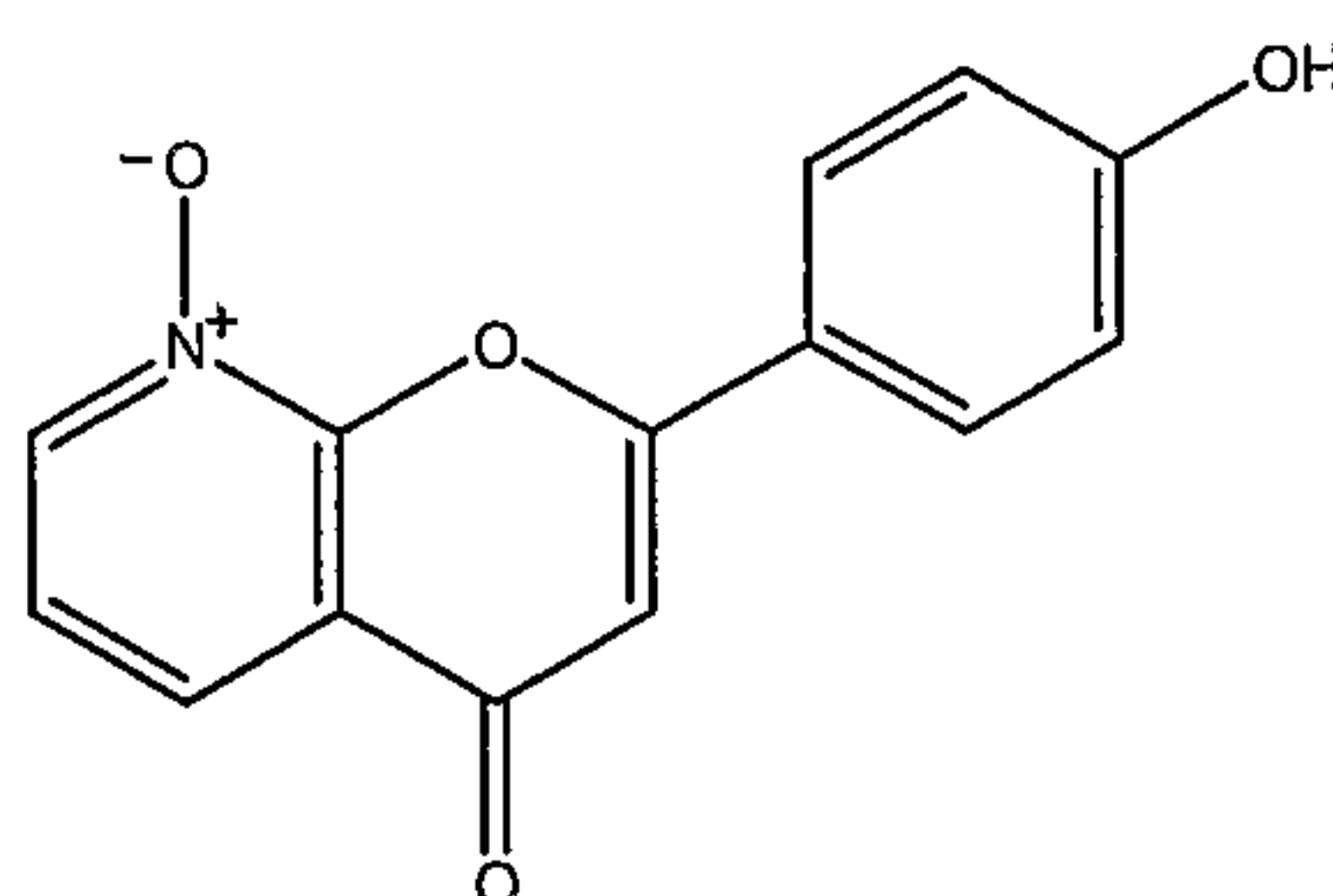


2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-c]pyridine 7-oxide

[0205] A mixture of 2-(4-hydroxyphenyl)-pyrano[2,3-c]pyridin-4-one (0.50 g, 2.09 mmol), acetyl chloride (0.164 g, 2.09 mmol) and anhydrous pyridine (2.5 mL) was stirred at rt overnight. The mixture was then poured into water (100 mL) and stirred for 30 min. The solid was filtered and further washed with water and dry to give the ester (0.586 g, 99%). The ester (0.230 g, 0.82 mmol) and 3-chloroperoxybenzoic acid (0.242 g, 0.98 mmol) were added to dichloromethane

(10 mL) and the reaction mixture was stirred at rt for 2 weeks. The mixture was concentrated and potassium carbonate (0.60 g) and MeOH (10 mL) was added and the reaction mixture was stirred for 1 h. AcOH was added to adjust pH to 6.0-7.0, and the solvent was removed. The residue was poured into water. The solid was collected by filtration and washed with EtOAc to give 120 mg (57.4%) of 2-(4-hydroxyphenyl)-4-oxo-4H-pyrano[2,3-c]pyridine 7-oxide. MS (ES) m/z : 255.90 (M); Mp. 307-308 °C.

Example 31

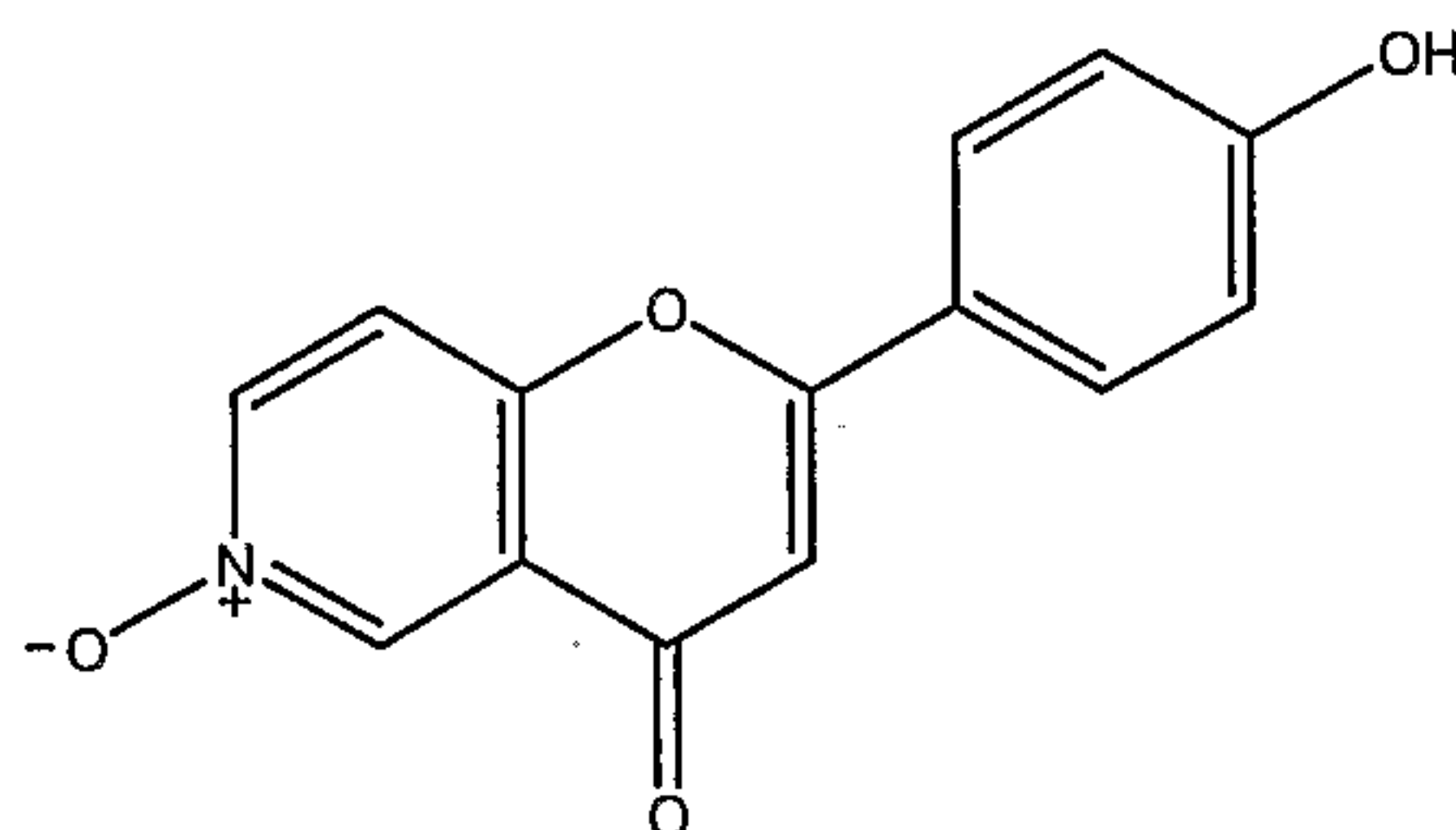


2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-b]pyridine 8-oxide

[0206] In a 50 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one (1.5 g, 6.27 mmol), Ac₂O (700 mg, 6.89 mmol) and a catalytic amount of DMAP (50 mg) in pyridine (10 mL) and the reaction mixture was stirred for 16 h at rt. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer washed with water, dried and concentrated to give a 2-(4-acetoxyphenyl)-pyrano[2,3-b]pyridin-4-one (930 mg, 53%). To a stirred solution of the 4-acetoxy compound (930 mg, 3.30 mmol) in CH₂Cl₂ (50 mL), mCPBA (1.9 g, 11.3 mmol) was added and the reaction mixture was stirred at rt for 5 days. The reaction mixture was diluted with CH₂Cl₂ and washed with NaHCO₃ solution. The organic layer was separated, washed with water, brine, dried and concentrated to give crude product, which was purified by column chromatography, using 5% methanol in CH₂Cl₂ to give 168 mg of *N*-oxide product in 17% yield. To a solution of the acetoxy *N*-oxide (168 mg, 0.565 mmol) in methanol: THF (10 mL : 10 mL), K₂CO₃ (156 mg, 1.13 mmol) was added and the mixture was stirred for 2 h at rt. The reaction mixture was neutralized by dilute HCl. The solid was isolated by filtration, washed with water and dried to give 2-(4-hydroxyphenyl)-4-oxo-4H-

pyrano[2,3-b]pyridine 8-oxide (150 mg, 100%). MS (ES) m/z : 255.90 (M); Mp. 314-315 °C.

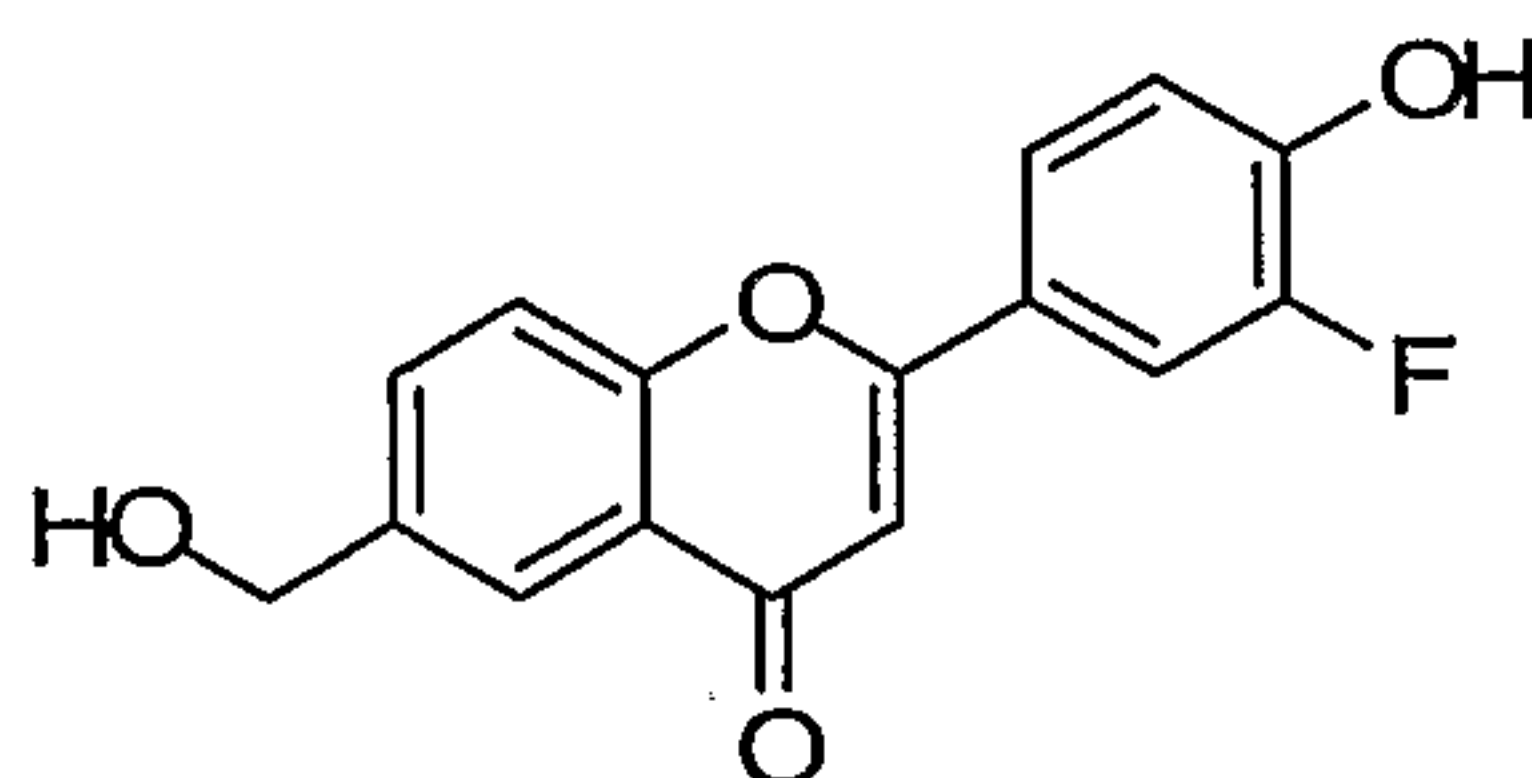
Example 32



2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[3,2-c]pyridine 6-oxide

[0207] A solution of 2-(4-hydroxyphenyl)-pyrano[3,2-c]pyridin-4-one (1.75 g, 7.32 mmol) in acetic anhydride (50 mL) was stirred at reflux for 16 h. The reaction mixture was cooled to rt, quenched with water (100 mL), extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were concentrated. The resulting residue was purified by column chromatography (hexane: ethyl acetate 1:1 to 1:3) to provide 1.3 g of the corresponding acetate (63%). A solution of the acetate (0.4 g, 1.42 mmol) and mCPBA (1.0 g, 4.70 mmol) in CH₂Cl₂ (50 mL) was stirred at rt for 11 days. The CH₂Cl₂ was removed by concentration. The residue was re-dissolved in MeOH (150 mL) and water (120 mL) and was mixed with potassium carbonate (1.0 g). The mixture was stirred at rt for 1 hour and neutralized with HCl (1 N). The resulting solid was filtered off, washed with water, MeOH, and CH₂Cl₂ sequentially to afford a light yellow solid of 2-(4-hydroxyphenyl)-4-oxo-4H-pyrano[3,2-c]pyridine 6-oxide (0.21 g, 58%). MS (ES) m/z : 255.96 (M); 322.8-323.4 °C

Example 33

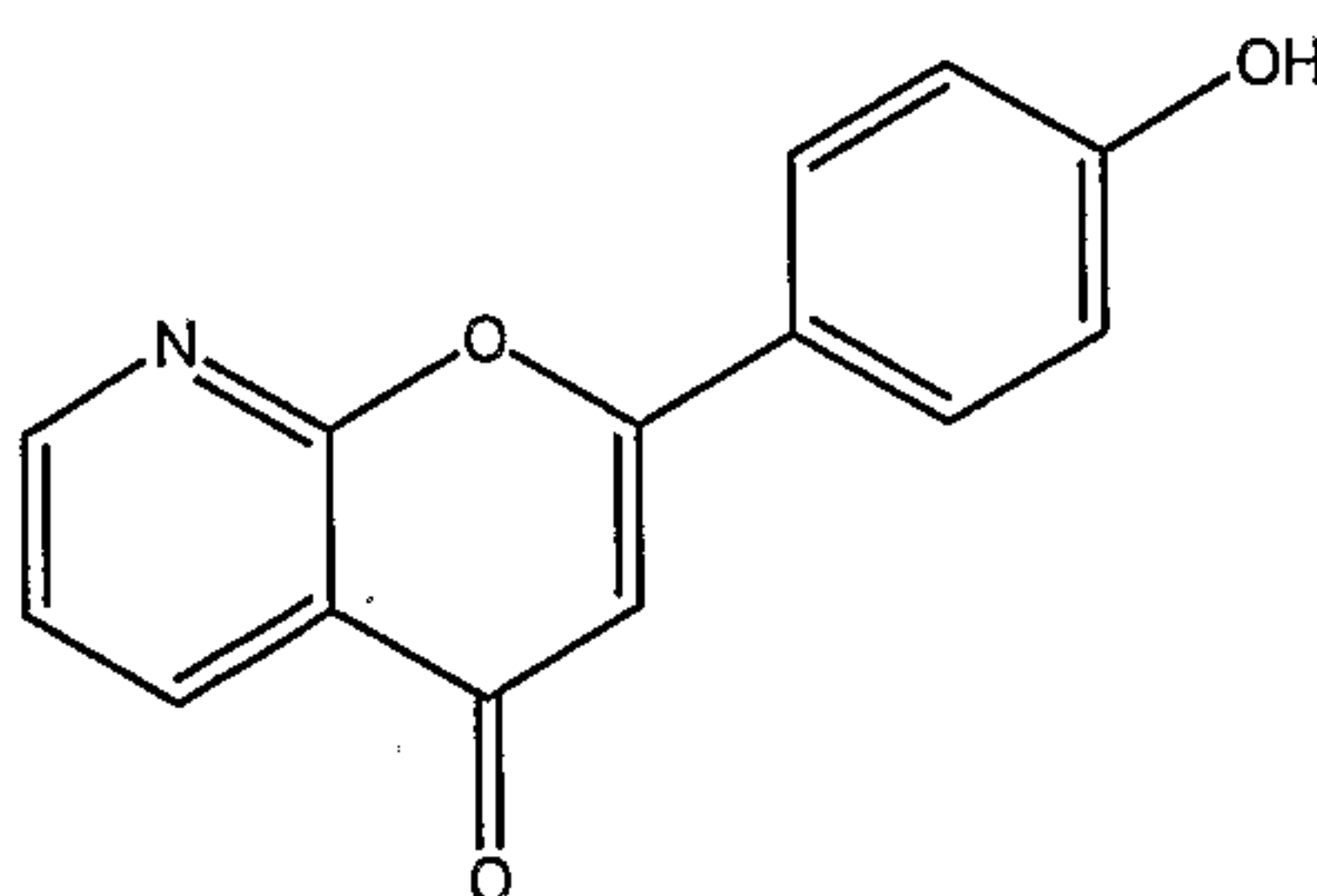


2-(3-Fluoro-4-hydroxyphenyl)-6-(hydroxymethyl)-4H-chromen-4-one

[0208] In a 100 mL round-bottomed flask fitted with condenser and magnetic stirrer were placed 2-hydroxy-5-methoxymethyl acetophenone (1.62 g,

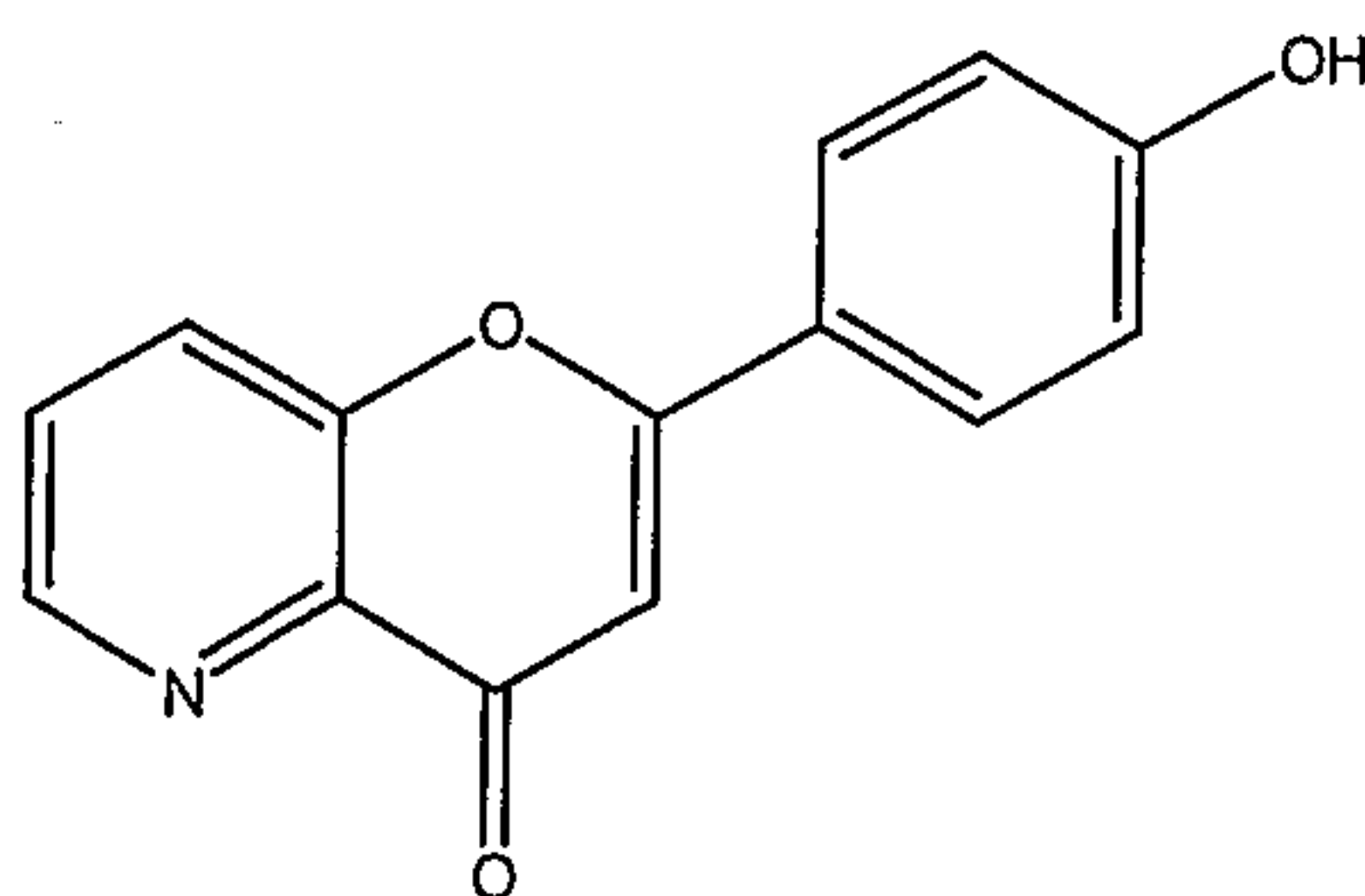
9.014 mmol), 4-methoxy-3-fluoro benzoyl chloride (1.7 g, 9.014 mmol) and pyridine (20 mL). The reaction mixture was stirred for 16 h at rt under nitrogen. The reaction mixture was poured into ice-water. The solids were filtered off, washed with water and dried to give the intermediate (2.33 g, 78%). To a solution of this intermediate (2.33 g, 7.01 mmol) in THF (50 mL), was added potassium *t*-butoxide (945 mg, 8.42 mmol) and the reaction mixture was stirred for 16 h at rt under N₂. The reaction mixture was poured into saturated solution of NH₄Cl. The organic layer was separated, washed with water, dried and concentrated to give crude intermediate diketone (2.3 g, 98.7%).

[0209] The diketone compound (2.3 g, 6.92 mmol) was taken into a mixture of HCl (1 mL) and acetic acid (15 mL) and heated at 100 °C for 1 h. The reaction mixture was cooled to rt, diluted with water and extracted with ethyl acetate. The organic layer was washed with water, brine, dried and concentrated to give 1.75 g of the intermediate in 80.6% yield. In a 100 mL dry round-bottomed flask fitted with condenser and magnetic stirrer were placed this intermediate (925 mg, 2.94 mmol) in CH₂Cl₂ (30 mL). BBr₃ (2.21 g, 8.83 mmol, 1M solution in CH₂Cl₂) was added slowly at 0 °C. The reaction mixture was stirred for 16 h at rt under nitrogen. The reaction mixture was quenched by carefully adding methanol. The solvent was removed under reduced pressure and the resulting solid was washed with water and dried to give 1.0 g of crude 3'-fluoro-4'-methoxy-5-bromo methyl flavone in 97% yield. To a solution of 5-bromomethyl flavone (1.0 g, 2.86 mmol) in DMF (20 mL), potassium acetate (845 mg, 8.60 mmol) was added. The mixture was heated at 100 °C for 1 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na₂SO₄ and concentrated to give crude acetyl flavone (810 mg, 86%). To a solution of the acetyl flavone (810 mg, 2.47 mmol) in methanol (15 mL), K₂CO₃ (1.02 g, 7.41 mmol) was added and the reaction mixture was stirred for 2 h at rt. The solvent was removed and the product was taken in to water and neutralized by dilute HCl. The solid was separated by filtration, washed with water and dried to give 2-(3-fluoro-4-hydroxyphenyl)-6-(hydroxymethyl)-4H-chromen-4-one in 38% yield. MS (ES) *m/z*: 286.96 (M); Mp. 256-258 °C.

Example 342-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one

[0210] In a 500 mL dry round bottom flask with reflux condenser and magnetic stirrer was placed with 2-chloro-3-ethyl nicotinate (40.0 g, 215.5 mmol) in methanol (200 mL). CH_3ONa in methanol (25%, 65 mL, 301.7 mmol) was added slowly and the reaction mixture was refluxed for 16 h. The reaction was cooled to rt, quenched by addition of a saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed well with water, brine, dried over Na_2SO_4 and concentrated to give 35 g of 2-methoxy-3-methyl nicotinate with 97% yield. Sodium hydride (60% in oil, 9.21 g, 230.3 mmol) was added to a dry 500 mL round bottom flask followed by 100 mL DMF. 4-Methoxyacetophenone (31.45 g, 209.44 mmol) in 50 mL dry DMF was added dropwise at 0 °C over 30 min. The reaction mixture was stirred for 1 h at rt. 2-Methoxynicotinic acid methyl ester (35 g, 209.44 mmol) was dissolved in 50 mL dry DMF and added slowly, keeping the temperature at 0 °C. The mixture was stirred for 16 h at rt, then quenched by addition of a saturated aqueous NH_4Cl solution and diluted with water. The solid was filtered off, washed with water and dried to give 56.7 g diketo product in 95% yield.

[0211] The diketo compound (56.7 g, 198.9 mmol) was added to a 1 L round bottom flask together with pyridinium hydrochloride (345 g). The mixture was heated at 190 °C for 5 h. The reaction mixture was cooled to rt and diluted with water. The solid was isolated by filtration and purified by column chromatography using 5% methanol in CH_2Cl_2 to give 2-(4-hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one (23.25 g, 48.8%). MS (ES) m/z : 240.07 ($\text{M}+1$); ^{13}C -NMR (DMSO-d_6): δ 178.2, 164.2, 161.8, 160.8, 153.9, 136.3, 129.2, 123.2, 121.8, 116.8, 116.75, 116.74, 105.7.

Example 352-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one

[0212] In a 500 mL round-bottom flask fitted with condenser and magnetic stirrer were placed MeOH (250 mL), 3-hydroxypyridine-2-carboxylic acid (10.0 g, 71.9 mmol) and concentrated H₂SO₄ (3 mL). The reaction mixture was heated at 64 °C for 24 hs. The reaction mixture was cooled to rt. The solvent was removed under reduced pressure; the residue was partitioned between EtOAc (150 mL) and water (20 mL). Solid sodium carbonate was added to adjust pH to 6. The organic layer was separated, dried over Na₂SO₄, concentrated to give 3.5 g of crude 3-hydroxypyridine-2-carboxylic acid methyl ester (32%).

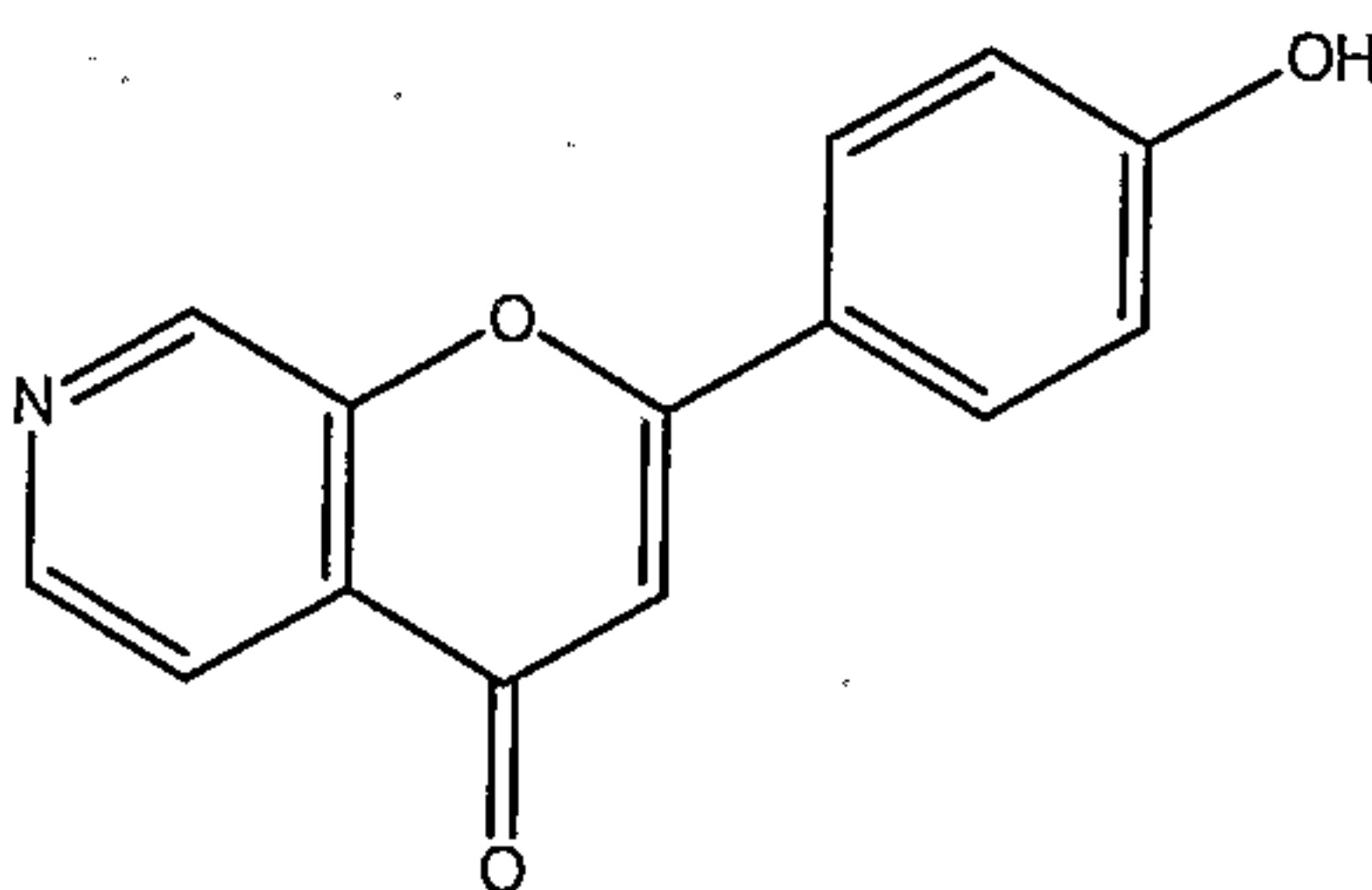
[0213] In a 50 mL round-bottom flask fitted with magnetic stirrer were placed 3-hydroxypyridine-2-carboxylic acid methyl ester (3.5 g, 22.80 mmol), K₂CO₃ (3.46 g, 25.0 mmol), MeI (4.87 g, 34.3 mmol) and DMF (20 mL). The reaction mixture was stirred for 18 h at rt under nitrogen. The reaction mixture was diluted with EtOAc (30 mL) and water (10 mL). The organic layer was separated and aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated to give the crude product. The crude product was purified by column chromatography using 30% EtOAc in hexane to give 2.1 g of 3-methoxypyridine-2-carboxylic acid methyl ester (54%).

[0214] In 100 mL round-bottom flask fitted with magnetic stirrer were placed the NaH (1.62 g of 60% suspension in mineral oil, 40 mmol) and the solution of 3-methoxypyridine-2-carboxylic acid methyl ester (3.5 g, 20 mmol) in anhydrous DMF (20 mL). The mixture was stirred for 15 min at rt under N₂, then the solution of 4-methoxyacetophenone (3.3 g, 22 mmol) was added via syringe. The reaction mixture was stirred overnight at rt, then 10% aqueous solution of NaHSO₄ was used to adjust pH to 7. The organic layer was separated and aqueous layer was extracted with EtOAc. The combined organic extracts were

dried over Na_2SO_4 and concentrated to give the crude product. The crude product was purified by column chromatography using 30% EtOAc in hexane to give 4.68 g of 1-(4-methoxyphenyl)-3-(3-methoxypyridin-2-yl) propane-1,3-dione (80%).

[0215] In 50 mL round-bottom flask fitted with magnetic stirrer were placed 1-(4-methoxyphenyl)-3-(3-methoxypyridin-2-yl) propane-1,3-dione (4.68 g, 16 mmol) and 45% aqueous solution of HBr (25 mL). The reaction mixture was refluxed for 3 h, then cooled down to rt. Solid NaHCO_3 was used to adjust pH to 7, followed by EtOAc (30 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic extracts were dried over Na_2SO_4 , concentrated to give the crude product, which was purified by column chromatography using 30% MeOH in EtOAc to give 125 mg of 2-(4-hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one (3.2 %). MS (ES) m/z : 240.09 ($M+1$), and 149.06.

Example 36

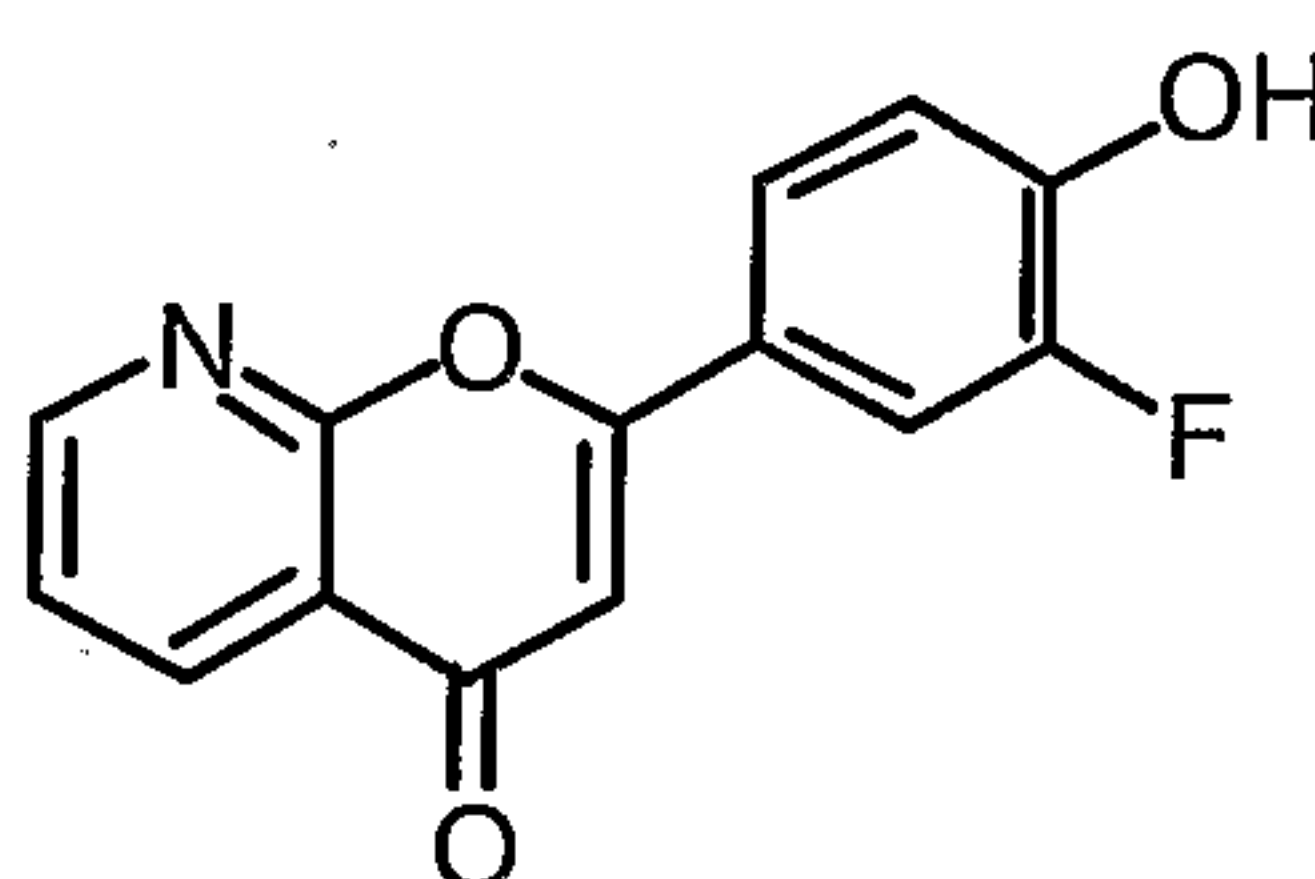


2-(4-Hydroxyphenyl)-pyrano[2,3-c]pyridin-4-one

[0216] A 50 mL flask was charged with 5.0 g (0.0354 mol) 3-fluoroisonicotinic acid and thionyl chloride (3.88 mL, 0.053 mol). The mixture was heated to reflux for 1 h, then the excess thionyl chloride was evaporated under vacuum. Anhydrous methanol was added to the residue and the mixture was heated to reflux for one hour. The reaction mixture was poured into sodium bicarbonate solution and pH was adjusted to 7.0. The mixture was extracted with EtOAc and the organic layer was dry over sodium sulfate. The organic solvent was evaporated yielding the product (4.80 g, 88%). A 50 mL dry flask was charged with methyl 3-fluoroisonicotinate (3.50 g, 0.0227 mol), 4-methoxyacetophenone (3.60 g, 0.024 mol) and 10 mL dry DMF under nitrogen. Sodium hydride (1.82 g, 60% in oil) was added and the reaction was stirred for 30 min, then poured into ammonium chloride solution and extracted with EtOAc and

dried over sodium sulfate. The solution was concentrated and the residue was pass through a column (EtOAc : hexane 1:3) to give the product (3.50 g, 54.0%). A 50 mL flask was charged with this product (0.5 g, 1.75 mmol) and pyridine hydrogen chloride (2.02 g, 17.5 mmol) and heat to 190 °C for 4 h. The mixture was poured into a sodium bicarbonate solution and the solid was collected by filtration, washed with EtOAc and methanol to give 2-(4-hydroxyphenyl)-pyrano[2,3-c]pyridin-4-one as a yellow product (0.36 g, 86%). MS (ES) m/z: 240.90 (M+1), 239.89 (M); Mp.294-296 °C.

Example 37



2-(3-Fluoro-4-hydroxyphenyl)pyrano[2,3-b]pyridine-4-one

[0217] Methyl 2-methoxynicotinate was synthesized from ethyl 2-chloronicotinate with sodium methoxide as in Example 34. A 50 mL flask was charged with methyl 2-methoxynicotinate (2.50 g, 0.015 mol), 10 mL dry DMF and 60% NaH (0.745 g, 0.0186 mol) with magnetic stirring. 3'-Fluoro-4'-methoxyacetophenone (2.60 g, 0.0155 mol) in 6 mL anhydrous DMF was added over 5-10 min. After addition, the reaction mixture was stirred for 30 min. The mixture was poured into 50 mL NH₄Cl solution, the yellow solid was filtered and further washed with water and purified by column chromatography (hexane:EtOAc 4:1) to get (3.0 g, 66.4%) of product. A 50 mL flask was charged with this product (0.8 g, 2.64 mmol) and pyridine hydrogen chloride (3.04 g, 26.4 mmol) and heated to 190 °C for 4 h. The mixture was poured into sodium bicarbonate solution and the solid was collected by filtration, washed with EtOAc and MeOH and passed through a column (methanol:dichloromethane 1:4) to afford 400 mg of 2-(3-fluoro-4-hydroxyphenyl)pyrano[2,3-b]pyridine-4-one (59%). MS (ES) m/z: 257.85 (M); Mp. 267-268 °C.

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

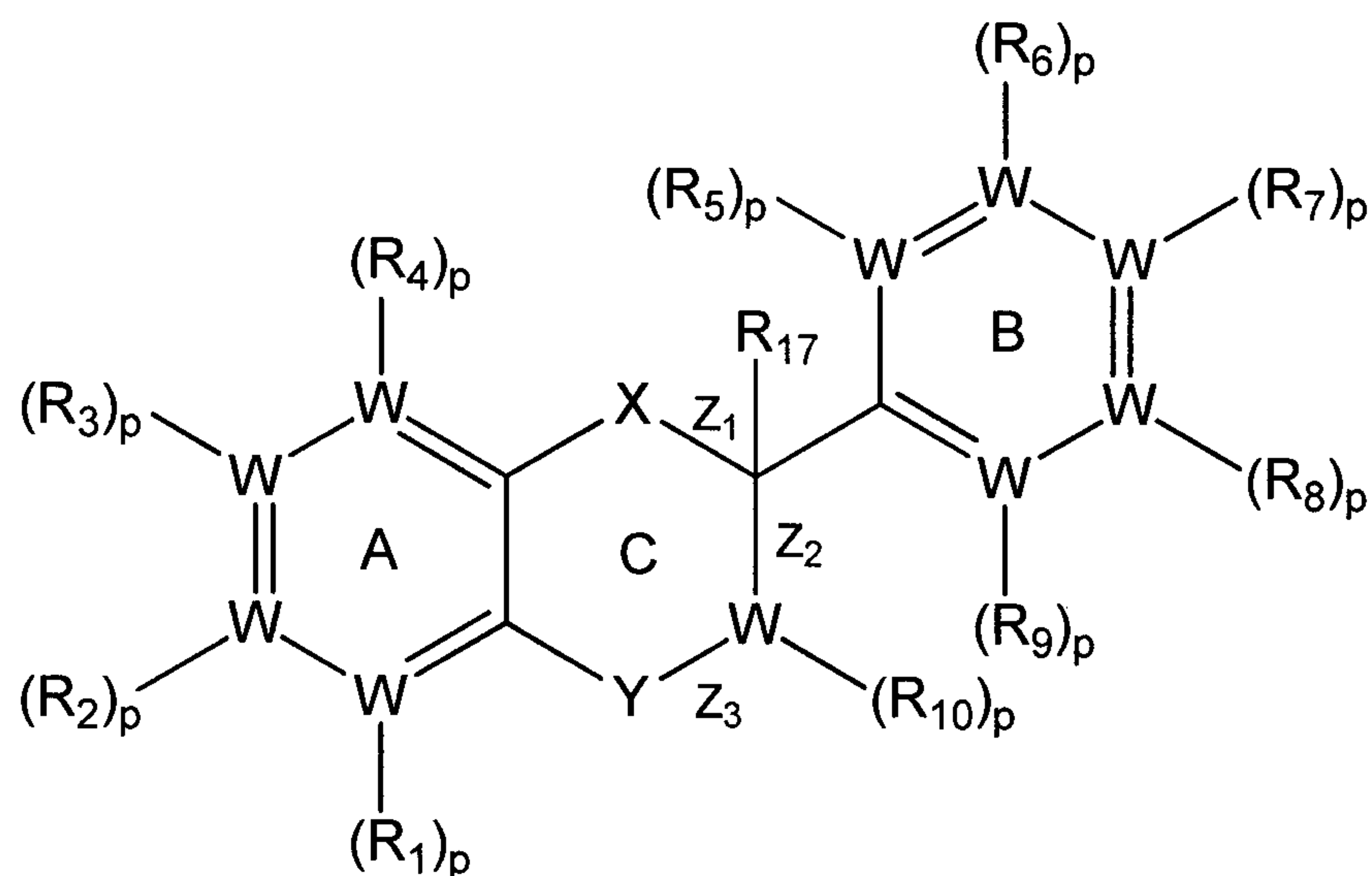
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

WHAT IS CLAIMED IS:

1. Use of a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, for increasing ApoA-I expression wherein

X is O;

Y is CO;

R₁, R₂, R₃, R₄, R₅, R₉, R₁₀, and R₁₇ are each independently alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, nitro, phosphate, sulfide, sulfinyl, sulfonyl, sulfonic acid, sulfonamide or thioketone, or

two adjacent substituents selected from R₁, R₂, R₃, R₄, R₅, R₆, R₈, R₉, and R₁₀ are connected in a 5 or 6-membered ring to form a bicyclic aryl or bicyclic heteroaryl;

R₇ is hydroxyl;

R₆ and R₈ are independently arylalkyl, carboxy, cyano, cycloalkyl, ester, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, hydroxyalkyl, hydroxyaryl, ketone, perfluoroalkyl, perfluorocycloalkyl, perfluoroalkoxy, O-sulfate, or O-glucoronidate,

subject to the proviso that R₆ and R₈ are not both simultaneously hydrogen;

each W is independently C or N, wherein if W is N, then p is 0 and if W is C, then p is 1;

at least one W is N;

Z₁ and Z₃ are each a single bond; and

Z₂ is a double bond.

2. The use according to claim 1, wherein

R₁, R₂, R₃, R₄, R₅, R₉, R₁₀, and R₁₇ are independently

vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl,

methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl,

ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, 4-butyl-2-hexynyl,

phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl,

cyclohexanes, cyclohexenes, cyclopentanes, cyclopentenes;

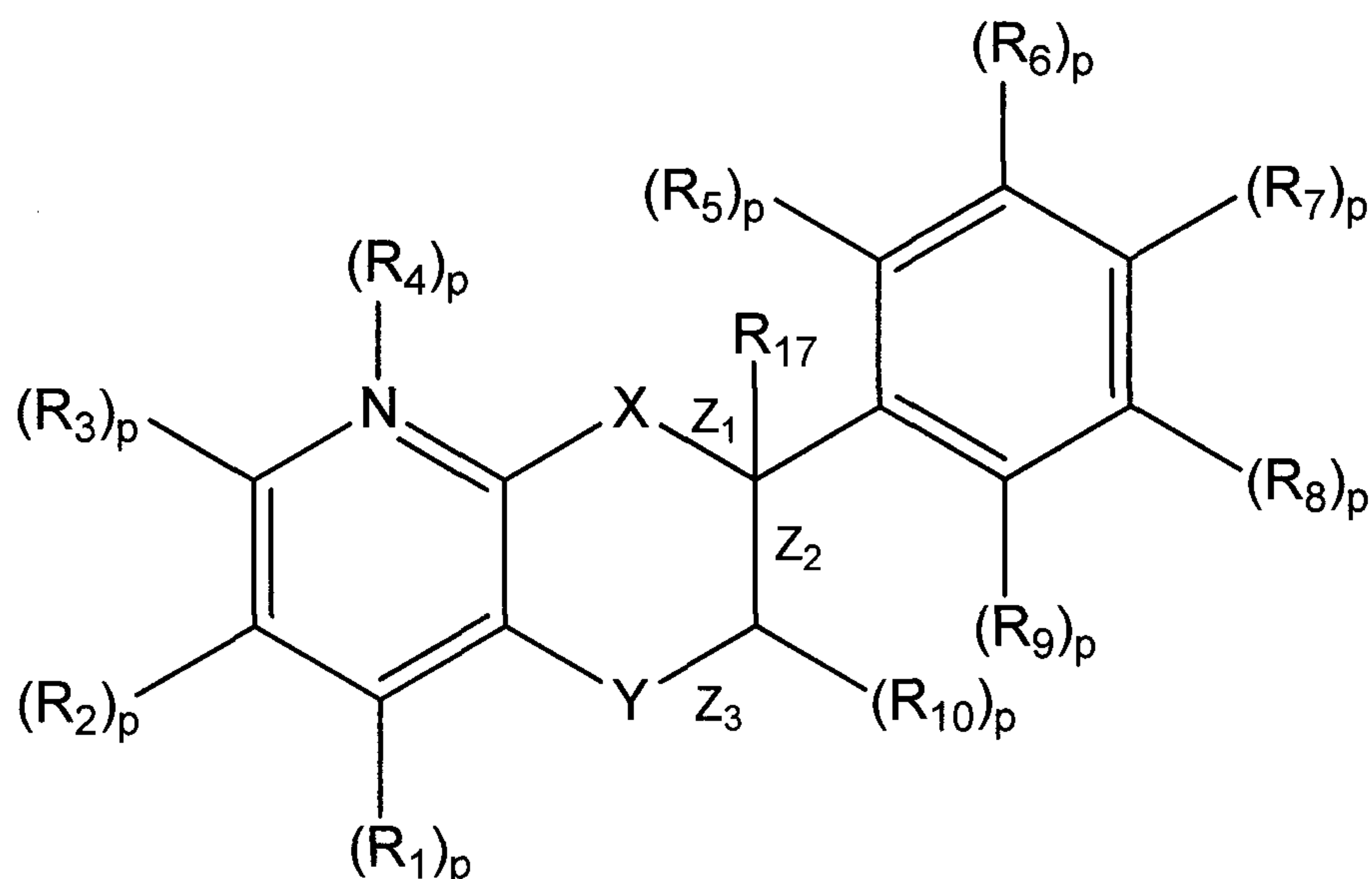
F, Cl, Br, I,

pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3)-triazolyl, (1,2,4)-triazolyl, pyrazinyl, pyrimidyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phenyl, isoxazolyl, oxazolyl,

acridinyl, benzimidazolyl, benzofuryl, benzothiazolyl, benzothieryl, benzoxazolyl, biotinyl, cinnolinyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, furyl, homopiperidinyl, imidazolidinyl, imidazolinyl, imidazolyl, indolyl, isoquinolyl, isothiazolidinyl, isothiazolyl, isoxazolidinyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazinyl, pyrazolyl, pyrazolinyl, pyridazinyl, pyridyl, pyrimidinyl, pyrimidyl, pyrrolidinyl,

pyrrolidin-2-onyl, pyrrolinyl, pyrrolyl, quinolinyl, quinoxaloyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thiomorpholinyl, thiopyranyl, or triazolyl.

3. The use according to claim 1 or 2, wherein Formula I has the structure:



or a pharmaceutically acceptable salt thereof.

4. A compound selected from:
- 2-(3-Fluoro-4-hydroxyphenyl)pyrano[2,3-b]pyridine-4-one;
 - 2-(4-Hydroxy-3-methylphenyl)-4H-pyrano[2,3-b]pyridine-4-one;
 - 2-(3-Chloro-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one;
 - 2-(3-Bromo-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one;
 - 2-(4-Hydroxy-3-methoxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one;
 - 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-c]pyridine 7-oxide;
 - 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-b]pyridine 8-oxide;
 - 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[3,2-c]pyridine-6-oxide;

2-(5-Hydroxy-pyridin-2-yl)-chromen-4-one;
 2-(6-Hydroxy-pyridin-3-yl)-chromen-4-one;
 2-(4-Hydroxy-3-(hydroxymethyl)phenyl)-4H-pyrano[2,3-b]pyridine-4-one;
 2-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one;
 2-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one;
 2-(4-Hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one;
 2-(4-Hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one;
 2-(1-Oxy-pyridin-4-yl)-chromen-4-one;

or a pharmaceutically acceptable salt thereof.

5. 2-(3-Fluoro-4-hydroxyphenyl)pyrano[2,3-b]pyridine-4-one or a pharmaceutically acceptable salt thereof.
6. 2-(4-Hydroxy-3-methylphenyl)-4H-pyrano[2,3-b]pyridine-4-one or a pharmaceutically acceptable salt thereof.
7. 2-(3-Chloro-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one or a pharmaceutically acceptable salt thereof.
8. 2-(3-Bromo-4-hydroxyphenyl)-4H-pyrano[2,3-b]pyridin-4-one or a pharmaceutically acceptable salt thereof.
9. 2-(4-Hydroxy-3-methoxyphenyl)-4H-pyrano[2,3-b]pyridine-4-one or a pharmaceutically acceptable salt thereof.
10. 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-c]pyridine 7-oxide or a pharmaceutically acceptable salt thereof.
11. 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[2,3-b]pyridine 8-oxide or a pharmaceutically acceptable salt thereof.
12. 2-(4-Hydroxyphenyl)-4-oxo-4H-pyrano[3,2-c]pyridine-6-oxide or a

pharmaceutically acceptable salt thereof.

13. 2-(5-Hydroxy-pyridin-2-yl)-chromen-4-one or a pharmaceutically acceptable salt thereof.

14. 2-(6-Hydroxy-pyridin-3-yl)-chromen-4-one or a pharmaceutically acceptable salt thereof.

15. 2-(4-Hydroxy-3-(hydroxymethyl)phenyl)-4H-pyrano[2,3-b]pyridine-4-one or a pharmaceutically acceptable salt thereof.

16. 2-(4-Hydroxy-phenyl)-pyrano[2,3-b]pyridin-4-one or a pharmaceutically acceptable salt thereof.

17. 2-(4-Hydroxy-phenyl)-pyrano[3,2-b]pyridin-4-one or a pharmaceutically acceptable salt thereof.

18. 2-(4-Hydroxy-phenyl)-pyrano[2,3-c]pyridin-4-one or a pharmaceutically acceptable salt thereof.

19. 2-(4-Hydroxy-phenyl)-pyrano[3,2-c]pyridin-4-one or a pharmaceutically acceptable salt thereof.

20. 2-(1-Oxy-pyridin-4-yl)-chromen-4-one or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition, comprising a compound according to any one of claims 1 to 20, and a pharmaceutically acceptable carrier.

22. The compound according to any one of claims 4 to 20, or the pharmaceutical composition of claim 21, for use in treating or preventing cardiovascular, cholesterol, or lipid related disorders.

23. The compound or pharmaceutical composition according to claim 22, wherein the cardiovascular, cholesterol, or lipid related disorder is acute coronary syndrome, angina pectoris, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, familial combined hyperlipidemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, multi-infarct dementia, myocardial infarction, peripheral vascular disease, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X or impotence.

24. The use according to any one of claims 1 to 3 for treating or preventing cardiovascular, cholesterol, or lipid related disorders.

25. The use according to claim 24, wherein the cardiovascular, cholesterol, or lipid related disorder is acute coronary syndrome, angina pectoris, arteriosclerosis, atherosclerosis, carotid atherosclerosis, cerebrovascular disease, cerebral infarction, congestive heart failure, congenital heart disease, coronary heart disease, coronary artery disease, coronary plaque stabilization, dyslipidemias, dyslipoproteinemias, endothelium dysfunctions, familial hypercholesterolemia, familial combined hyperlipidemia, hypertension, hyperlipidemia, intermittent claudication, ischemia, ischemia reperfusion injury, ischemic heart diseases, multi-infarct dementia, myocardial infarction, peripheral vascular disease, restenosis, renal artery atherosclerosis, rheumatic heart disease, stroke, thrombotic disorder, transitory ischemic attacks, and lipoprotein abnormalities associated with Alzheimer's disease, obesity, diabetes mellitus, syndrome X or impotence.

FIGURE 1

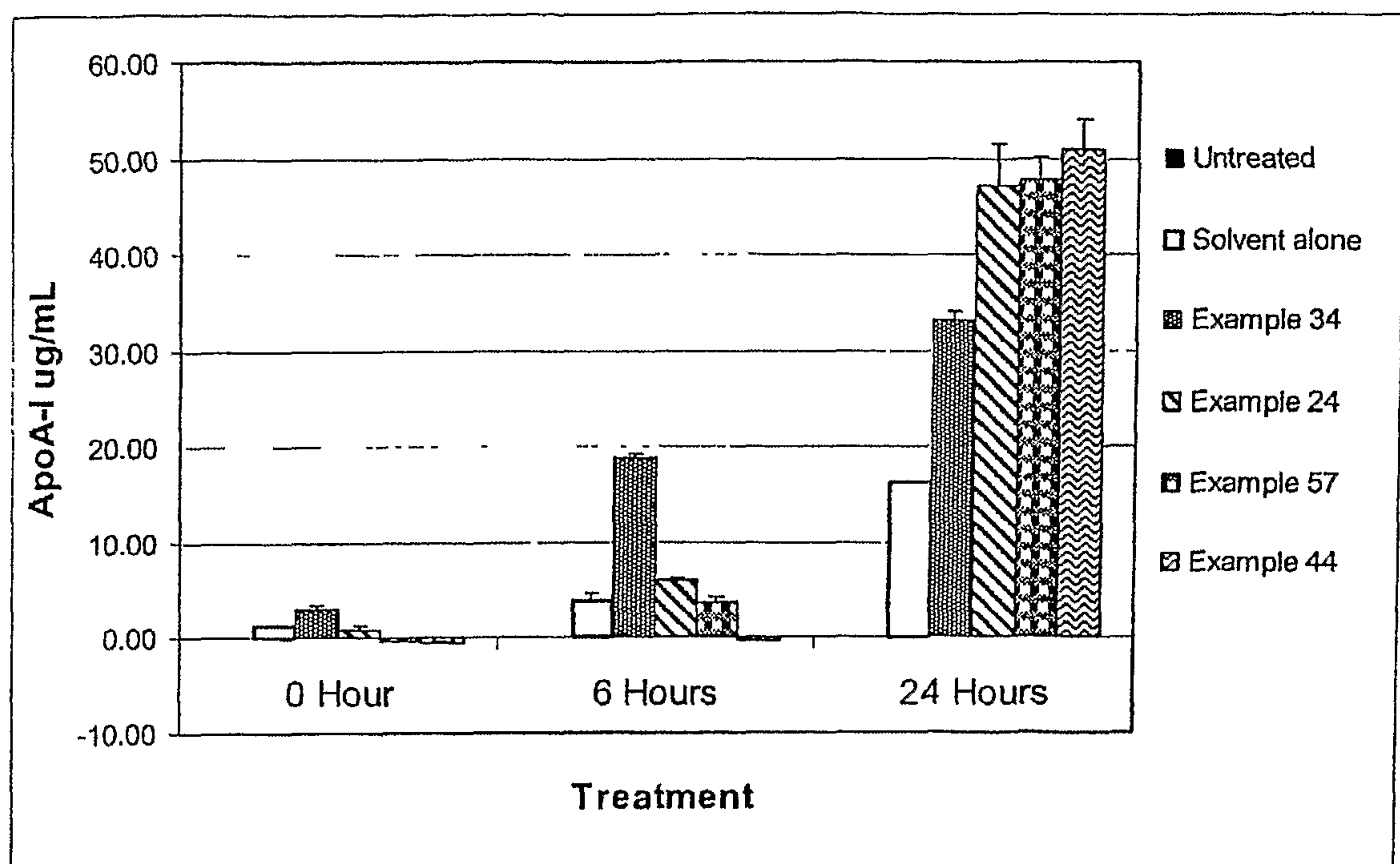


FIGURE 2

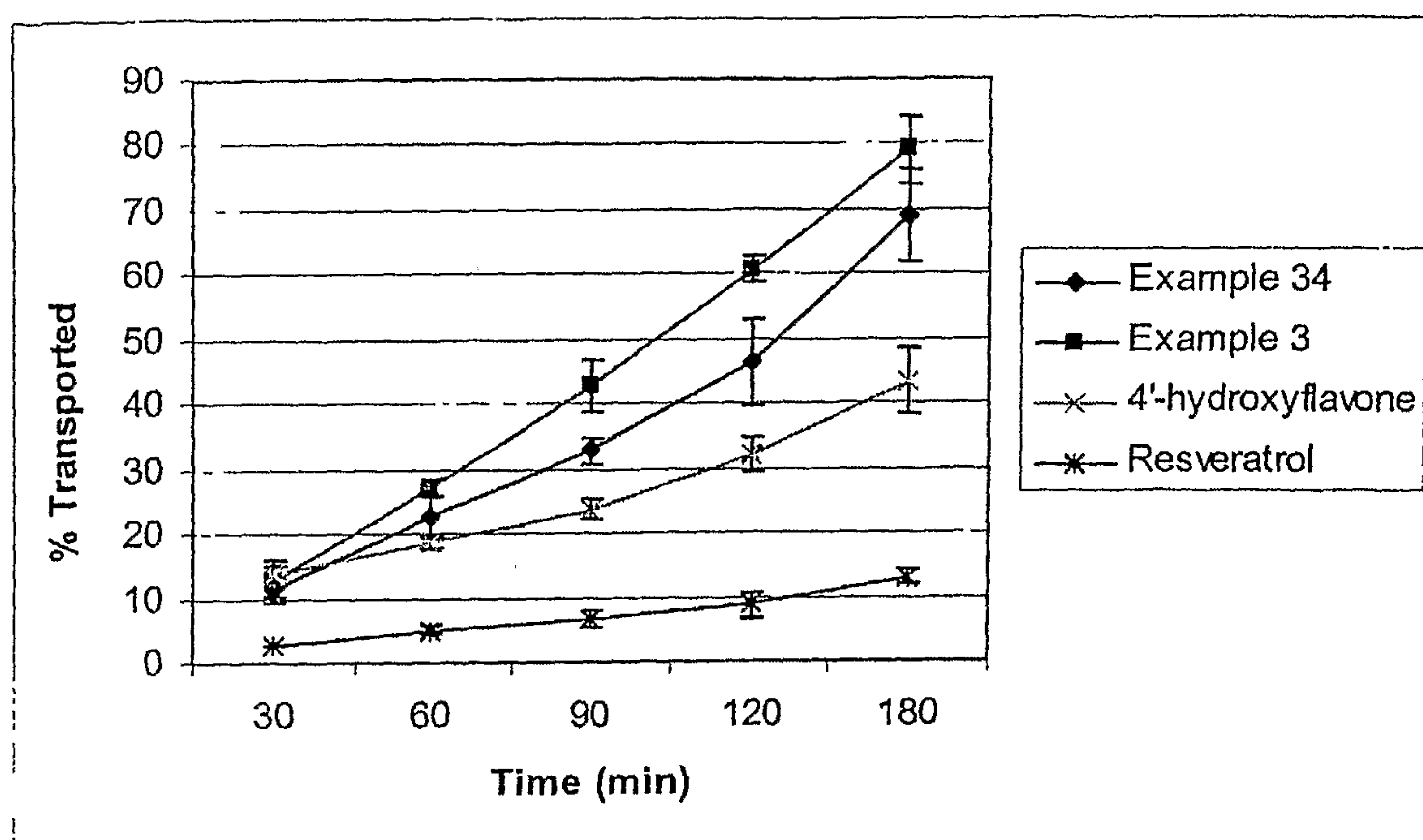


FIGURE 3A

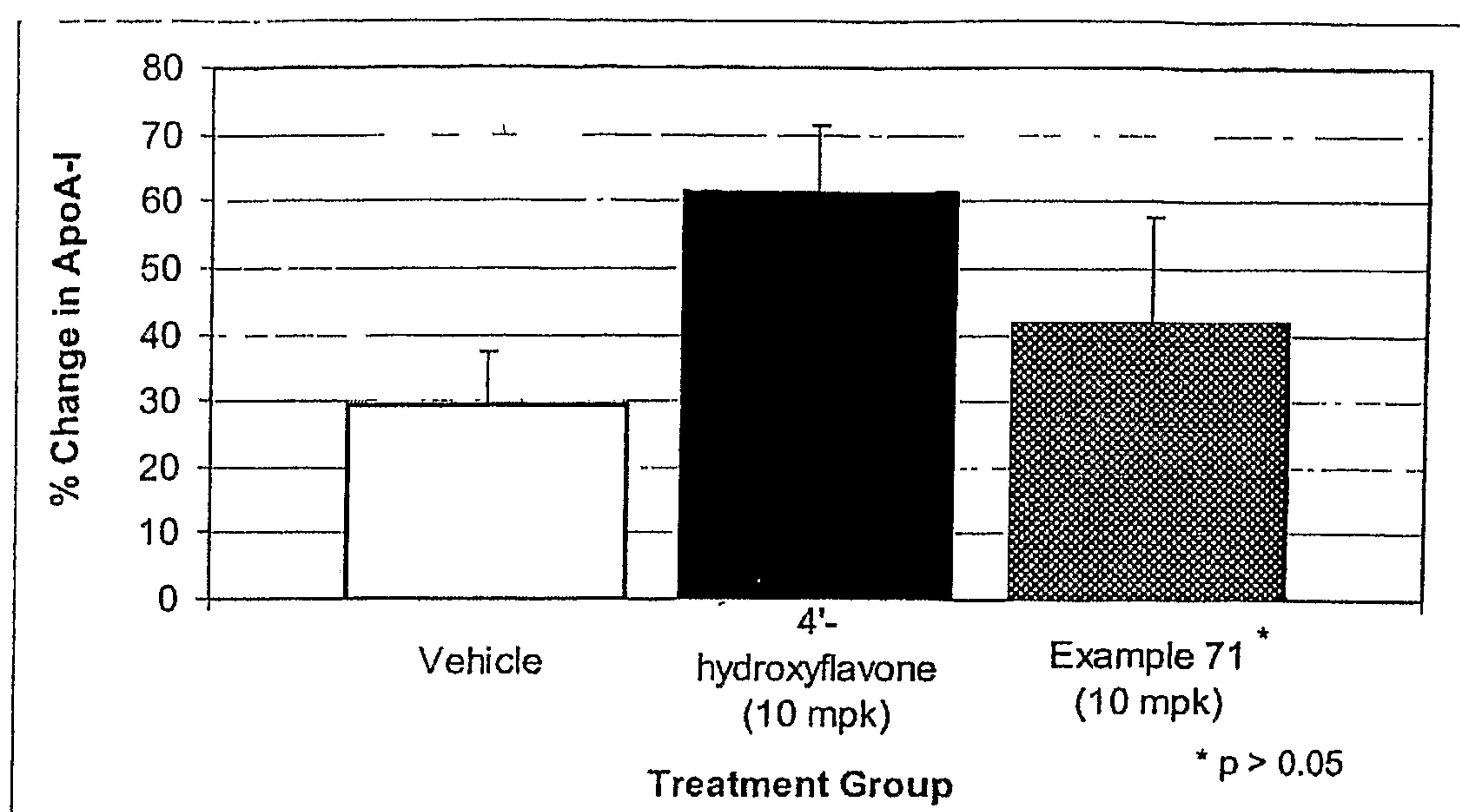


FIGURE 3B

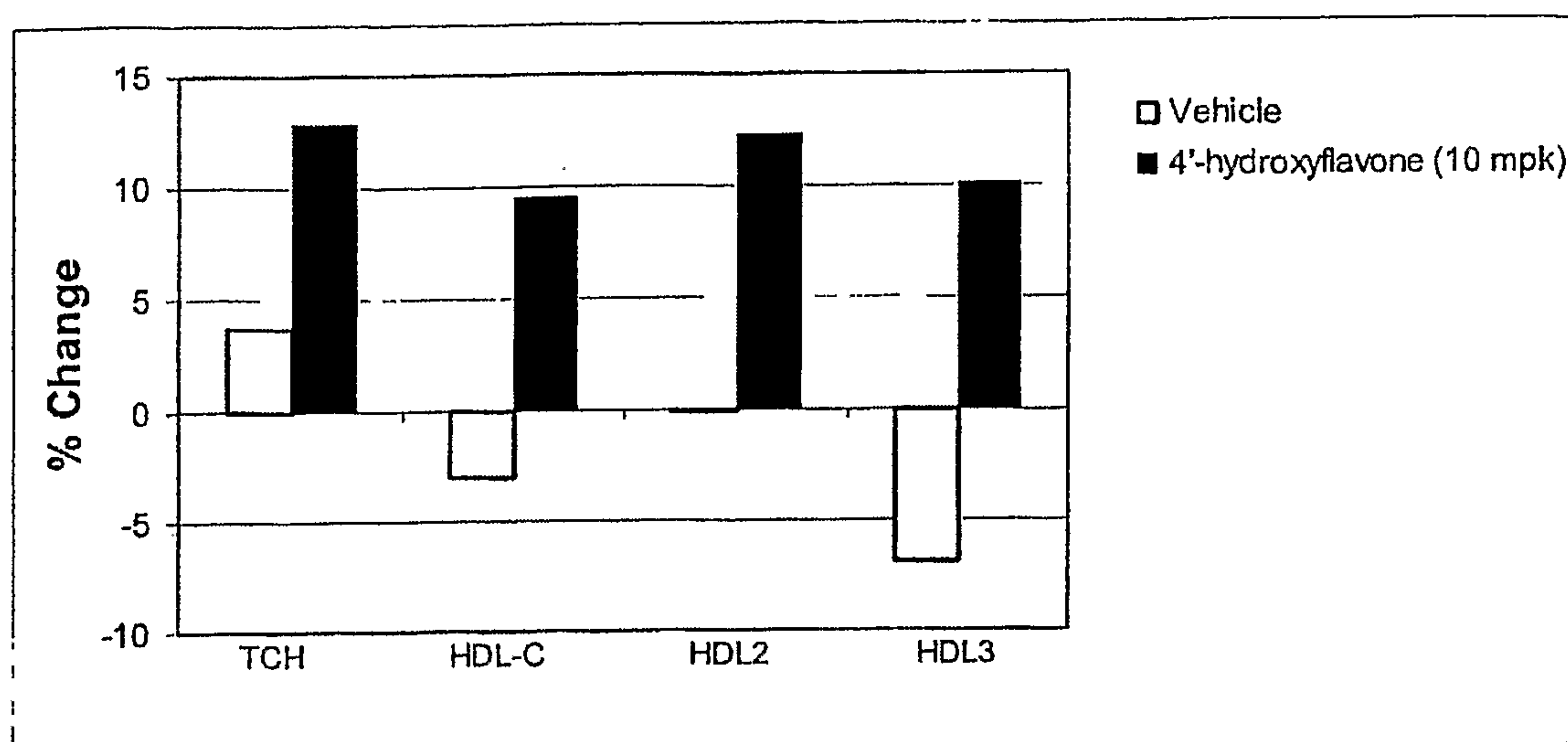


FIGURE 3C

