Title: HIGH AFFINITY SMALL MOLECULE C5A RECEPTOR MODULATORS

BACKGROUND

Field of the Invention

This invention relates to low molecular weight, non-peptidic, non-peptidomimetic, organic molecules that act as modulators of mammalian complement C5a receptors, preferably ones that act as high affinity C5a recptor ligands. The invention also relates to such ligands that act as antagonists (including inverse agonists) of complement C5a receptors, preferably human C5a receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It further relates to the use of such compounds in treating a variety of inflammatory and immune system disorders. Additionally, this invention relates to the use such compounds as probes for the localization of C5a receptors.

Background of the Invention

C5a, a 74 amino acid peptide, is generated in the complement cascade by the cleavage of the complement protein C5 by the complement C5 convertase enzyme. C5a has both anaphylatoxic (e.g., bronchoconstricting and vascular spasmogenic) and chemotactic effects. Therefore, it is active in engendering both the vascular and cellular phases of inflammatory responses. Because it is a plasma protein and, therefore, generally almost instantly available at a site of an inciting stimulus, it is a key mediator in terms of initiating the complex series of events that results in augmentation and amplification of an initial inflammatory stimulus. The anaphylatoxic and chemotactic effects of the C5a peptide are believed to be mediated through its interation with the C5a receptor (CD88 antigen), a 52 kD membrane bound G-protein coupled receptor (GPCR). C5a is a potent chemoattractant for polymorphonuclear leukocytes, bringing neutrophils, basophils, eosinophils and monocytes to sites of inflammation and/or cellular injury. C5a is one of the most

potent chemotactic agents known for a wide variety of inflammatory cell types. C5a also "primes" or prepares neutrophils for various antibacterial functions, e.g., phagocytosis. Additionally, C5a stimulates the release of inflammatory mediators (e.g., histamines, TNF-α, IL-1, IL-6, IL-8, prostaglandins, and leukotrienes) and the release of lysosomal enzymes and other cytotoxic components from granulocytes. Among its other actions, C5a also promotes the production of activated oxygen radicals and the contraction of smooth muscle.

Considerable experimental evidence implicates increased levels of C5a in a number of autoimmune diseases and inflammatory and related disorders.

Antagonists that block the binding of C5a to its receptor or other agents, including inverse agonists, which modulate signal transduction associated with C5a-receptor interactions, can inhibit the pathogenic events, including chemotaxis, associated with anaphylatoxin activity contributing to such inflammatory and autoimmune conditions. Despite many attempts, no one has previously been able to provide any small molecule (less than 700 Daltons MW, or amu) non-peptide, non-peptidomimetic, non-peptoid, C5a antagonist that is essentially free of agonist activity at the C5a receptor and that exhibits a binding affinity for the C5a receptor of less than 1 micromolar, and preferably less than 100 nanomolar.

Description of Related Art

Certain modified C5a peptides (i.e., modifications of C5a) have been identified as partial C5a antagonists and have been shown to block a number of C5a mediated actions including neutrophil chemotaxis, neutropenia and superoxide formation. Various C5a peptidomimetic compounds have also been reported as modulating C5a activity, including cyclic peptoids (a peptoid is a peptidomimetic compound comprising an oligomeric assemblage of naturally occurring amino acids that have been N-substituted). Typically these C5a modulatory compounds exhibit a molecular weight greater than 500 Daltons, and generally greater than 700 Daltons.

SUMMARY OF THE INVENTION

The present invention provides novel compounds that are small molecule C5a receptor antagonists that are non-peptide, non-peptidomimetic, and are preferably free of C5a receptor agonist activity, which compounds exhibit high affinity for the C5a receptor, i.e., an affinity constant for binding to the C5a receptor of less than 1 micromolar. Highly preferred compounds exhibit very high affinity for the C5a receptor, i.e., an affinity constant for binding to the C5a receptor of less than 100 nanomolar. Preferred compounds are C5a receptor antagonists (including inverse agonists). Preferred antagonists exhibit an antagonist EC_{50} (which as usd herein includes IC_{50}) of less than 1 micromolar, preferably less than 100 nanomolar, in an assay of C5a mediated chemotaxis. Preferred C5a receptors are mammalian, preferably primate receptors, including human C5a receptors, and may either be cloned, recombinantly expressed receptors or naturally expressed receptors. In certain preferred embodiments, compounds of the invention exhibit an affinity for human C5a receptors that is higher than for rodent C5a receptors, preferably at least five times higher, more preferably ten times higher.

The compounds of the present invention do not interact with dopamine receptors with even moderate affinity, i.e., they do not bind to dopamine receptors with K_i values of less than 100 micromolar. Preferred compounds of the invention do not bind to any naturally occurring receptors other than C5a receptors with high affinity, and preferably they do not bind to any naturally occurring receptors other than C5a receptors with even moderate affinity.

In certain embodiments these compounds also possess one or more, and preferably two or more, three or more, four or more, or all of the following properties in that they are: 1) multi-aryl in structure (having a plurality of un-fused or fused aryl groups), 2) heteroaryl in structure, 3) orally available in vivo (such that a sub-lethal or preferably a pharmaceutically acceptable oral dose can provide a detectable in vivo effect such as a reduction of C5a-induced neutropenia), 4) comprised of fewer than four, preferably fewer than three, or fewer than two, or no amide bonds, and 5)

capable of inhibiting leukocyte chemotaxis at nanomolar concentrations and preferably at sub-nanomolar concentrations.

In a highly preferred aspect, the invention provides non-peptidic, non-peptidomimetic, low molecular weight compounds that act as high affinity antagonists of the human C5a receptor. Specifically exemplified representative compounds include, but are not limited to optionally substituted arylimidazoles (i.e. imidazoles having one or more ring substituents of optionally substituted carbocyclic aryl or optionally substituted heteroaryl), optionally substituted arylpyridyls (i.e.pyridyls having one or more ring substituents of optionally substituted carbocyclic aryl or optionally substituted heteroaryl), optionally substituted aryl-substituted cycloalkylimidazoles (i.e.cycloalkylimidazoles having one or more ring substituents of optionally substituted carbocyclic aryl or optionally substituted heteroaryl), optionally substituted arylpyrazoles (i.e.pyrazoles having one or more ring substituents of optionally substituted carbocyclic aryl or optionally substituted heteroaryl), optionally substituted benzimidazoles, optionally substituted aryl-substituted tetrahydroisoquinolines (i.e.tetrahydroisoquinolines having one or more ring substituents of optionally substituted carbocyclic aryl or optionally substituted heteroaryl), and optionally substituted biaryl carboxamides (i.e. a carboxamide that has one or more optionally substituted bi-carboxylic aryl or heteroaryl substituents). Novel intermediates useful for synthesizing compounds of the invention are also provided.

Preferred compounds of the invention are compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to C5a receptors.

The invention also provides pharmaceutical compositions comprising compounds of the invention, including those of Formula I, including otppinally substituted arylimidazoles, optionally substituted arylpyridyls, optionally substituted aryl-substituted cycloalkylimidazoles, optionally substituted arylpyrazoles, optionally substituted benzimidazoles, optionally substituted aryl-substituted tetrahydroisoquinolines, and optionally substituted biaryl carboxamides. The C5a receptor antagonist compounds described herein are particularly useful in

the treatment of C5a-mediated inflammation, e.g., inflammation associated with various inflammatory and immune system disorders. The invention further comprises a method of treating a patient in need of such anti-inflammatory treatment or immune treatment an effective amount of a compound of the invention, e.g. an amount of a compound of the invention sufficient to yield a plasma concentration of the compound (or its active metabolite, if a pro-drug) high enough to inhibit white blood cell (e.g., neutrophil) chemotaxis in vitro. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention. For treating non-human animals of any particular species, a compound exhibiting high affinity for the C5a receptor of that particular species is preferred.

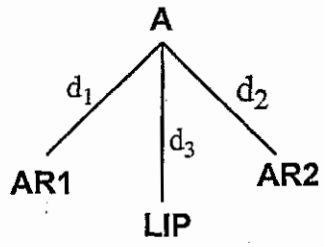
In a separate aspect, the invention provides methods of using compounds of the invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly C5a receptors, e.g., in tissue sections (e.g., via autoradiography) or in vivo (e.g., via positron emission tomography, PET, or single positron emission computed tomography, SPECT, scanning and imaging).

The invention provides compounds and compositions that are useful as inhibitors of C5a-mediated chemotaxis (e.g., they may be used as standards in assays of such chemotaxis). The invention additionally comprises methods of inhibiting C5a-mediated cellular chemotaxis, preferably leukocyte (e.g., neutrophil) chemotaxis. These methods comprise contacting white blood cells, particularly primate white blood cells, especially human white blood cells, with one or more compounds of the invention. Preferably the concentration is sufficient to inhibit chemotaxis of white blood cells in an *in vitro* chemotaxis assay, so that the levels of chemotaxis observed in a control assay (e.g., one to which a compound of the invention has not been added) are significantly higher (significantly here measured as $p \leq 0.05$ using a conventional parametric statistical analysis method such as a

student's T-test) than the levels observed in an assay to which a compound of the invention has been added.

Accordingly, a broad aspect of the invention is directed to non-peptidic organic (carbon-containing) molecules, having a molecular mass of less than 700 amu, that exhibit C5a antagonist activity or C5a inverse agonist activity with an EC_{50} of less than 500 nM in an assay of C5a mediated leukocyte chemotaxis.

More particularly the invention includes compounds of Formula I,



Formula I

wherein:

AR1 and AR2 are independently carbocyclic aryl or heteroaryl;

LIP represents an alkyl, carbocyclic aryl, heteroaryl, or arylalkyl;

A is oxygen or nitrogen;

d_1 represents the distance between A and the geometric center of AR1 and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound;

d_2 represents the distance between A and the geometric center of AR2 and is between 5 and 10 angstroms in at least one energetically accessible conformer of the compound; and

d_3 represents the distance between A and the nearest atom of LIP and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound. Preferred compounds of Formula I exhibit antagonist (including inverse agonist) activity at C5a Receptors, and essentially no or little agonist activity at this receptor. Preferably such compounds contain one or more heteroaryl rings.

Preferred compounds of the invention exhibit good activity in standard *in vitro* C5 receptor mediated chemotaxis assay, specifically the assay as specified in

Example 12, which follows and is defined below. Alternative preferred assays include the calcium mobilization assay. Preferred compounds of the invention exhibit an EC_{50} of about 500 nM or less in such a standard C5a mediated chemotaxis assay, more preferably an EC_{50} of about 200 nM or less in such a standard C5a mediated chemotaxis assay, still more preferably an EC_{50} of about 100, 50, 25 and 10 nM in such a standard C5a mediated chemotaxis assay, even more preferably an EC_{50} of about 5 nM in such a standard C5a mediated chemotaxis assay.

The invention includes additional methods such as methods for localizing C5a recerptors in tissue section samples, comprising cotacting a tissue sample with detectably labelled one or more compounds of the invention that are preferably detectably labeled, optionally washing the contacted tissue sample, and detecting the bound compound associated with the tissue sample. Suitable detectable labels include e.g. ^{125}I, tritium, ^{32}P, ^{99}Tc or the like. A variety of detection methods could be employed include single emission photono computed tomography ("SPECT").

Other aspects of the invention are discussed *infra*.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is the sequence of SEQ ID NO-1.

DETAILED DESCRIPTION OF THE INVENTION

Preferred compounds of the invention include carbon-containing molecules that comprise:

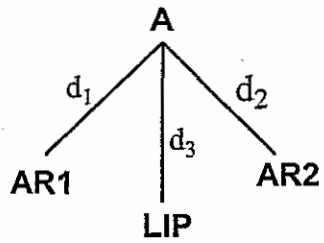
i) having a molecular mass of less than 700 amu;

ii) that is nonpeptidic;

iii) that exhibits C5a antagonist activity or C5a inverse agonist activity with an EC_{50} of less than 500 nM in an assay of C5a mediated leukocyte chemotaxis; and

iv) exhibits less than 10% intrinsic agonist activity in an assay of leukocyte chemotaxis.

Among such compounds, particularly preferred are those that contain one or more heteroaryl and/or carbocyclic rings. For example, preferred are compounds of the following formula:



AR1 and AR2 are independently optionally substituted carbocyclic aryl or optionally substituted heteroaryl;

LIP represents an optionally substituted alkyl, optionally substituted carbocyclic aryl, optionally substituted heteroaryl, or optionally substituted arylalkyl;

A is oxygen or nitrogen;

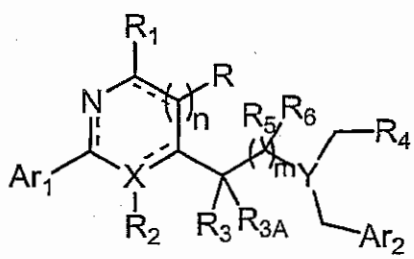
d_1 represents the distance between A and the geometric center of AR1 and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound;

d_2 represents the distance between A and the geometric center of AR2 and is between 5 and 10 angstroms in at least one energetically accessible conformer of the compound; and

d_3 represents the distance between A and the nearest atom of LIP and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound.

Preferred compounds of the invention also include heterocycles of the following formula II :

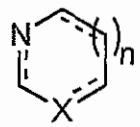
II



or a pharmaceutically acceptable salt thereof, wherein the compound exhibits an EC_{50} of 1uM or less in an assay of C5a mediated chemotaxis,

wherein:

the ring system represented by



is a 5 to 7 membered heterocycle that may be either aromatic or partially unsaturated;

X is N, C, or CR_7, wherein R_7 is hydrogen, hydroxy, halogen, amino, cyano, nitro, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl or optionally substituted (cycloalkyl)alkyl;

Y is N or CH;

n is 0, 1, or 2;

m is 0, 1, or 2;

R and R_1 are independently chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, optionally substituted haloalkyl, optionally substituted alkoxy, optionally substituted mono- or dialkylamino, optionally substituted

alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

When n is 0, R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

When n is 1, R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of the above Formula II include those compounds wherein:

R and R_1 are independendently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen,

nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

R_7 is hydrogen, hydroxy, halogen, amino, cyano, nitro, or haloalkyl, or

R_7 is alkoxy, mono- or dialkylamino, alkyl, alkenyl, alkynyl or (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

When n is 0, R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino;

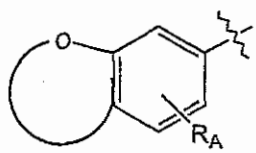
When n is 1, R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, each of which may be unsubstituted or substituted with

one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; or

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:



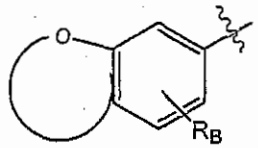
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; and

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl,

mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino.

Additional preferred compounds of the above formula II include those wherein

R and R_1 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

When n is 0, R_1 and R_3 may be joined to form a C_3-C_8 cycloalkyl or C_3-C_8 heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano,

trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

When n is 1, R and R_3 may be joined to form a C_3-C_8 cycloalkyl or C_3-C_8 heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

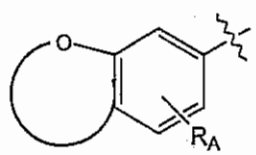
R_7 is hydrogen, hydroxy, halogen, amino, cyano, nitro, or haloalkyl,

R_7 is alkoxy, mono- or di(C_1-C_6)alkylamino, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl or (C_3-C_8cycloalkyl) C_1-C_3alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:

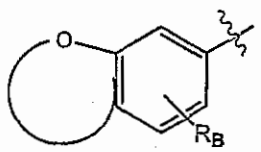


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 and Ar_2 are independently chosen from phenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl,

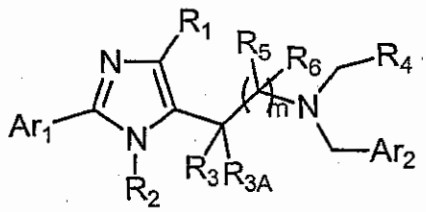
hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; and

ii) bicyclic oxygen-containing groups of the formula:

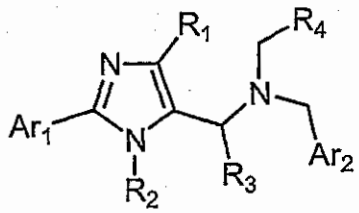


wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still additional preferred compounds of the aboveformula II include those compounds of the following fomula:



and additionally include those compounds of the following formula:



m is 0, 1, or 2;

R_1 is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

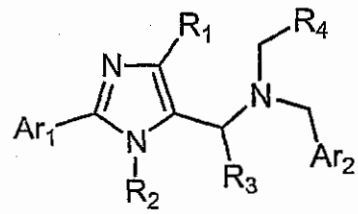
R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Additional preferred compounds of the above formula II include those compounds of the following formula:



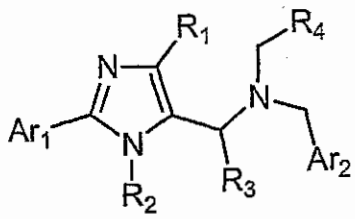
wherein:

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl.

Additional preferred compounds of the above formula II include those compounds of the following formula:



wherein:

Ar_1 is phenyl, phenylalkyl, thienyl, imidazolyl, pyridyl, pyrimidyl, benzodioxinyl, benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 2;

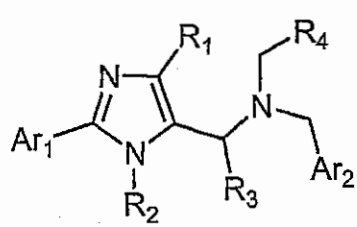
R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds of the above formula II include those compounds of the following formula:



wherein:

Ar_1 is phenyl, phenylalkyl, thienyl, imidazolyl, pyridyl, pyrimidyl, benzodioxinyl, benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 4;

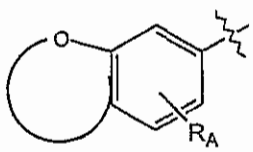
R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl; and

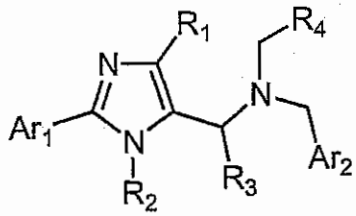
R_4 is phenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds of the above formula II include those compounds of the following formula:



wherein:

Ar_1 is phenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in formula II;

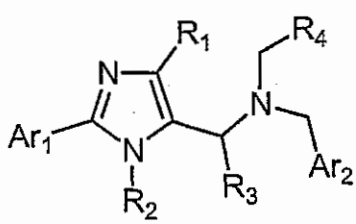
R_1 is hydrogen, methyl, ethyl, or optionally substituted phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds of the above formula II include those of the following formula:



wherein:

Ar_1 is phenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 4;

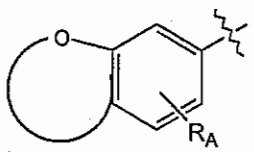
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

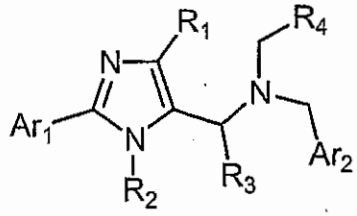
R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still additional preferred compounds of the above formula Ii include of the following formula:

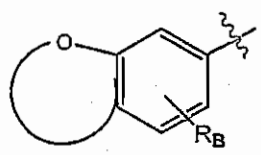


wherein:

Ar_1 is phenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

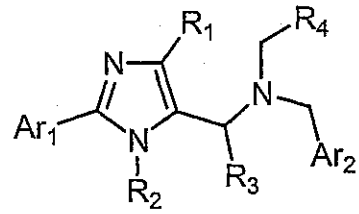
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still further preferred compounds of the above formula II include those of the following formula:

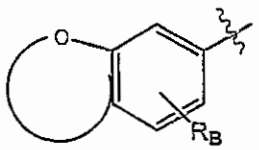


wherein:

Ar_1 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

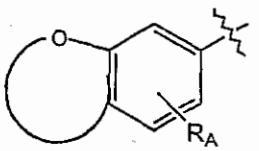
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

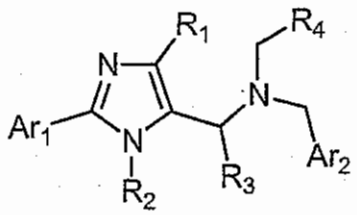
R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Preferred compounds of the invention also include those of the following formula III:

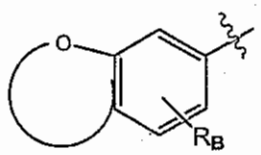


III

or a pharmaceutically acceptable salt thereof, wherein:

Ar_1 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_1 is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_1 is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl,

pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

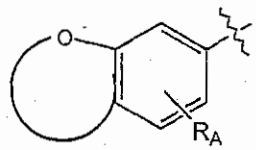
ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl,

N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Preferred compounds of the above formula III include those wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds of formula III include those wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still additional preferred compounds of formula III above include those wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

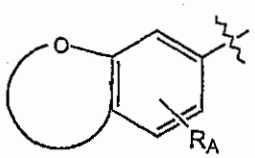
Preferred compounds of formula III above also include those wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

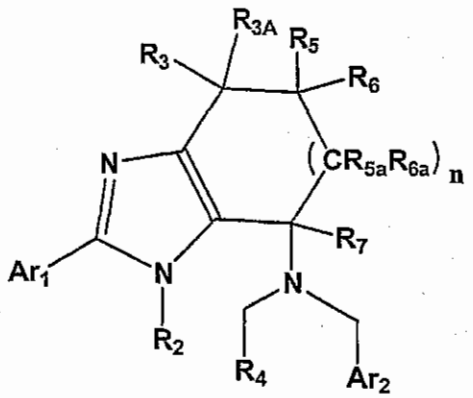
R_3 is hydrogen or methyl; and

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl; hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

The invention also includes compounds of the following formula IV:



IV

or a pharmaceutically acceptable salt thereof, wherein:

n is an integer from 0 to 3; and

R_2 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted;

R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

R_7 represents hydrogen or alkyl;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

Also preferred are compounds of that formula IV above (such preferred compounds referred to as compounds of formula IV-A) wherein n, R_3, R_{3A}, R_5, R_6, R_{5a}, R_{6a}, and R_7 are as defined in that formula IV, and

R_2 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluormethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

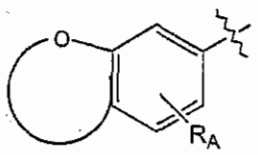
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-

alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

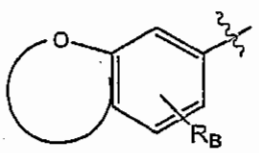


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –XR_B, wherein X and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_mNH$-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and -$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl),

-N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -$NHS(O)_x$(alkyl), -$S(O)_x$(alkyl), -$S(O)_xNH$(alkyl), -$S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

Also preferred are compounds of formula IV above wherein (such preferred compounds referred to as compounds of formula IV-B)

n is defined as in formula IV above, and

R_3 and R_{3A} are the same or different and represent hydrogen or

C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a C_{3-8} cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl ring;

R_{5a} and R_{6b} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R_2 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl) C_{1-3} alkyl, or C_1-C_6 haloalkyl, each or which unsubstituted or substituted by one or more of

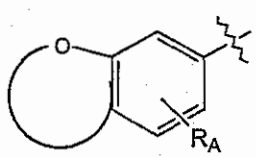
halogen, nitro, cyano, trifluormethyl, trifluoromethoxy, C_{1-3} haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

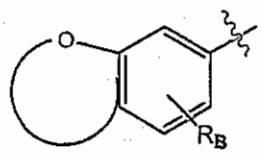


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or

substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$NH(C_1-C_6 alkyl), -S(O)$_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

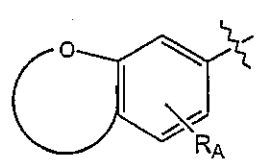
Also preferred are compounds of formula IV above (such preferred referred to as compounds of formula IV-C) wherein n, R_2, R_3, R_{3A}, R_5, R_6, R_{5a}, R_{6a}, and R_7 are as defined in formula IV above,

R_4 is hydrogen or

C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



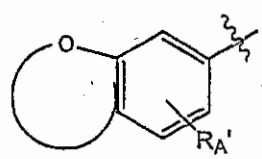
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is phenyl, thienyl, or pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which is unsubstituted or substituted with up to four substituents independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below;

Ar_2 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A' represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl,

C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_m$NH-, -$S(O)_mNR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

Further preferred are compounds of the above formula IV-C wherein:

R_3 and R_4 are the same or different and represent hydrogen or methyl;

R_5 and R_6 are the same or different and represent hydrogen or methyl; and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl.

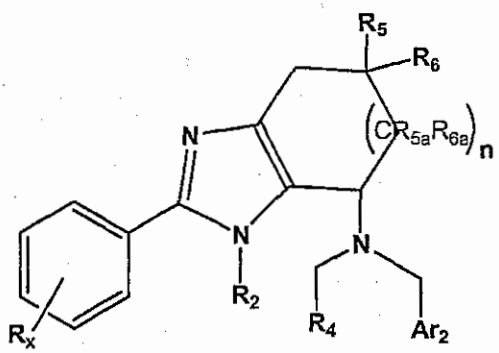
Further preferred are compounds of the above formula IV-C wherein:

R_3 and R_4 are hydrogen;

R_5 and R_6 are the same or different and represent hydrogen or methyl; and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl.

Further preferred are compounds of the above formula IV-C wherein:



or a pharmaceutically acceptable salt thereof, wherein:

n is an integer from 0 to 3; and

R_2 is hydrogen or

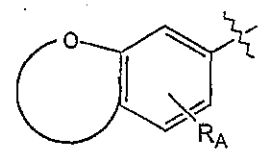
alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted;

R_4 is hydrogen or

C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

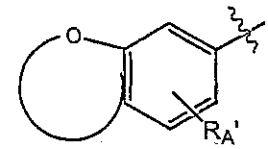
R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_2 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –XR_B, wherein X and R_B are as defined below; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A' represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_m$NH-, -$S(O)_m$$NR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

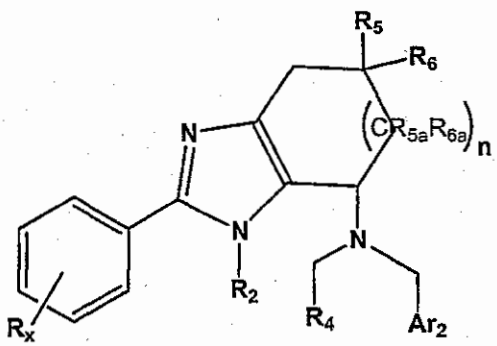
oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$NH(C_1-C_6 alkyl), -S(O)$_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

R_5 and R_6 are the same or different and represent hydrogen or methyl;

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

Further preferred are compounds of the above formula IV-C wherein:



or a pharmaceutically acceptable salt thereof, wherein:

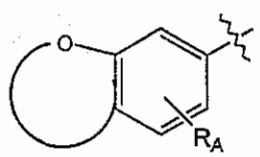
n is an integer from 0 to 3; and

R_4 is hydrogen or

C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

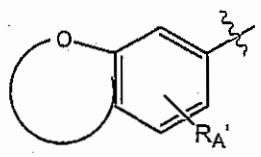


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_2 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-

C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –XR_B, wherein X and R_B are as defined below; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A' represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_mNH$-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_xNH$(C_1-C_6 alkyl), -$S(O)_xN$(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5 and R_6 are the same or different and represent hydrogen or methyl;

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

Further preferred are compounds of the above formula IV-C wherein:

Ar_2, R_X, and n are as defined in formula IV-C,

or a pharmaceutically acceptable salt thereof, wherein:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; and

R_4 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl.

Further preferred are compounds of the above formula IV-C,

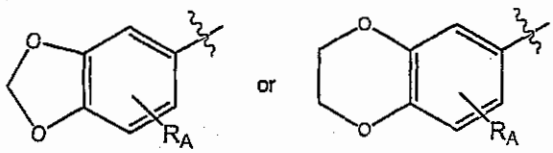
or a pharmaceutically acceptable salt thereof, wherein:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is phenyl, which may be unsubstituted or substituted with:

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen containing group of the formula:



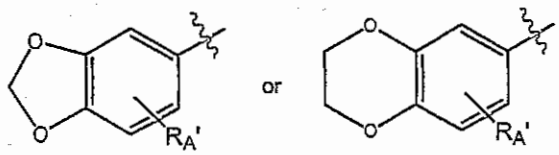
wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

Ar_2 is phenyl which is unsubstituted or optionally substituted or substituted with up to four groups independently selected from:

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-

alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, trifluoromethyl, and trifluoromethoxy or $-XR_B$, wherein X and R_B are as defined for formula IV-C; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A, R_A', and n are as defined in formula IV-C.

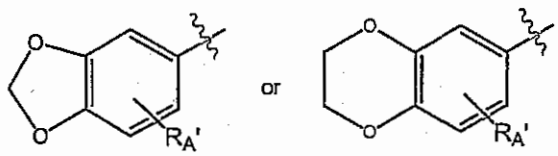
Also preferred are compounds of formula IV-C as specified above, wherein:

n is an integer from 0 to 3;

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

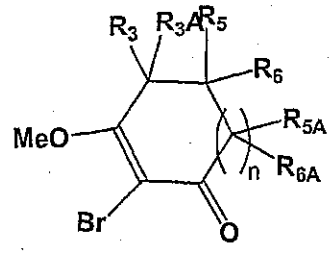
R_4 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

Ar_2 is a bicyclic oxygen containing group of the formula:



wherein R_A' represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds include those of the following formula V:



V

wherein:

n is an integer from 0 to 3;

R_3 and R_{3A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring; and

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy.

Preferred compounds of formula V include those compounds wherein:

R_3 and R_{3A} are the same or different and represent hydrogen or C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms; and

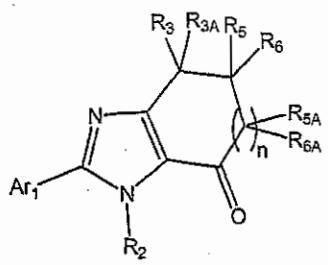
R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

Preferred compounds of formula V include thosae compounds wherein:

R_3 and R_4 are hydrogen; and

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl.

The invention also includes compounds of the following formula VI:



VI

wherein:

n is an integer from 0 to 3;

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted;

R_3 and R_4 are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; and

Ar_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted arylalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

Preferred compounds of formula VI include those compounds wherein:

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_2-C_8 (cycloalkyl)C_1-C_4 alkyl, or C_1-C_8 haloalkyl;

R_3 and R_{3a} are the same or different and represent hydrogen or C_1-C_6 alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms; and

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms;

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

Ar_1 is phenyl, thienyl, or pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which is unsubstituted or substituted with up to four substituents independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

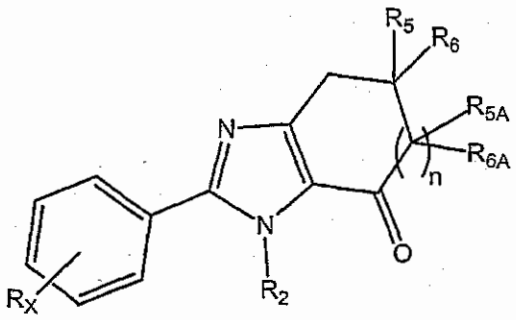
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl),

-N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$NH(C_1-C_6 alkyl), -S(O)$_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

Preferred compounds of the above formula VI include those of the following formula:



wherein:

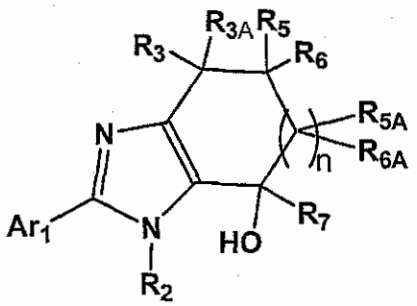
n is 0, 1, or 2:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

The invention also includes compounds of the following formula VII:



VII

wherein:

n is an integer from 0 to 3; and

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted;

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen or alkyl; or

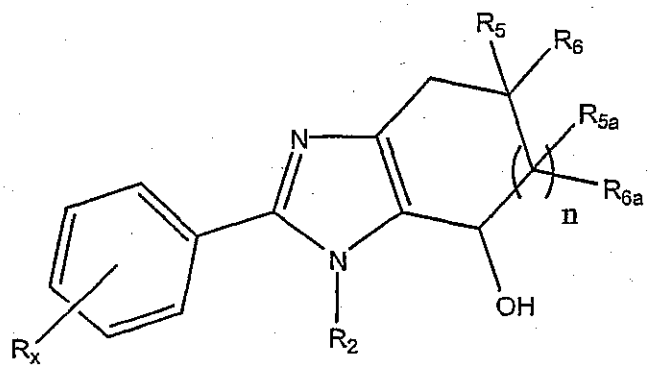
R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

R_7 represents hydrogen or alkyl; and

Ar_1 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

Preferred compounds of formula VII include those of the following formula:



wherein:

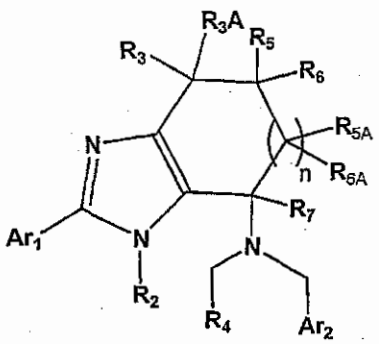
n is an integer from 0 to 3;

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

The invention also includes methods of syntesis of compounds of the invention. In particular, the invention includes methods to synthesis compounds of the following formula VIII:



VIII

wherein:

n is an integer from 0 to 3; and

R_2 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted;

R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring;

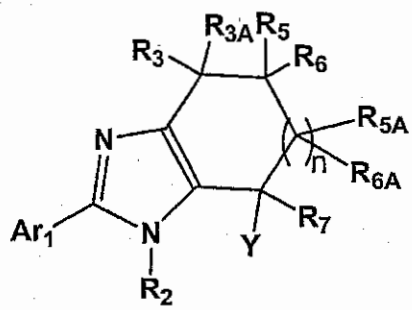
R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

R_7 represents hydrogen or alkyl;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

the process comprising:

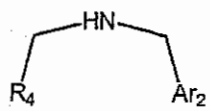
reacting a compound of the formula:



wherein Y is halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base,

with a secondary amine of the formula:



In that synthetic method, preferred are compounds (referred to as compounds of formula VIII-A) wherein

n and Y are as defined above for formula VIII;

R_3 and R_{3A} are the same or different and represent hydrogen or

C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a C_{3-8} cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R_2 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl) C_{1-3} alkyl, or C_1-C_6 haloalkyl, each or which unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluormethyl, trifluoromethoxy, C_{1-3} haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

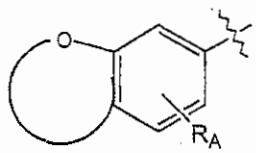
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of

C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

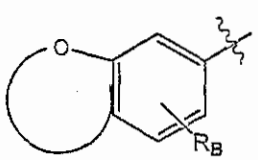


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –XR_B, wherein X and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -C(=O)NR_C-, -$S(O)_m$NH-, -$S(O)_m$$NR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -C(=O)$NHS(O)_m$-, and -$NR_CS(O)_m$- (where m is 0, 1, or 2); and

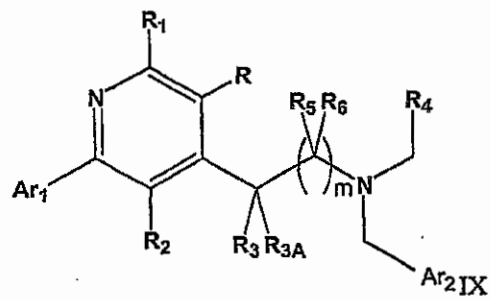
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

The invention also includes compounds of the above formula VIII and VIII-A, and pharmaceutically acceptable salts of such compounds.

The invention also provides compounds of the following formula IX:



or a pharmaceutically acceptable salt thereof, wherein:

m is 0, 1, or 2;

R is hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl,

optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl; or

R is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

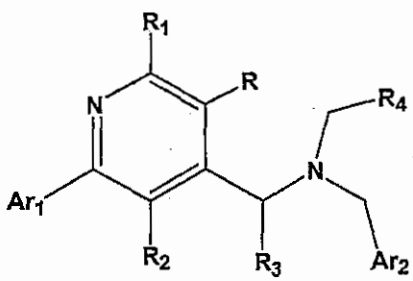
R_1, R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of formula IX include those of the following formula IX-A:



IX-A

wherein Ar_1, Ar_2, R, R_1, R_2, R_3, and R_4 are for formula IX above.

Preferred compounds of formula IX-A above include those wherein:

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino; or

R is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; and

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

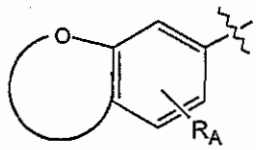
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl,

benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, $-XR_B$, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

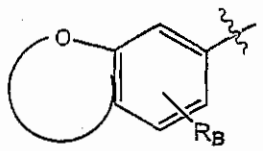


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, -O-, $-S(O)_m-$, -NH-, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl),

-N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x(C_1-C_6$ alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

Additional preferred compounds of formula IX-A include those wherein:

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy,

haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

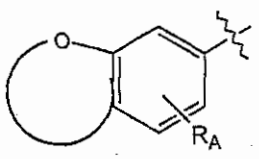
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl,

substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

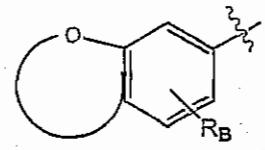
R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –XR_B, wherein X and R_B are as defined below; and



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_m$NH-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and -$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_xNH$(C_1-C_6 alkyl), -$S(O)_xN$(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

Additional preferred compounds of formula IX-A above include those wherein:

R is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-

C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy;

R_1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

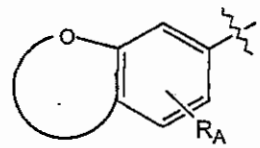
R_2 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

R_3 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:

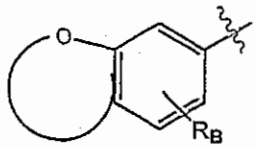


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 and Ar_2 are independently chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl,

isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still additional preferred compounds of formula IX-A include those compounds wherein:

R is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy;

R_1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

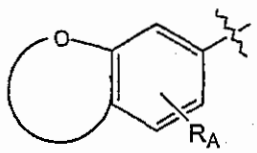
R_2 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

R_3 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



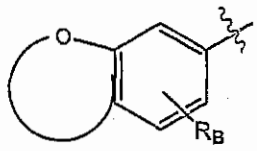
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Still further preferred compounds of formula IX above include those wherein

R is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, or phenyl;

R_1 is hydrogen, methyl or ethyl;

R_2 is C_3-C_6 alkyl;

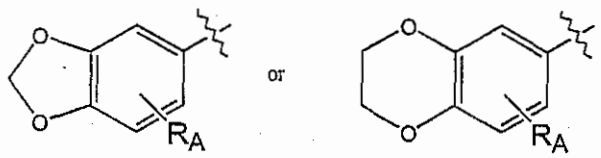
R_3 is hydrogen, methyl or ethyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:

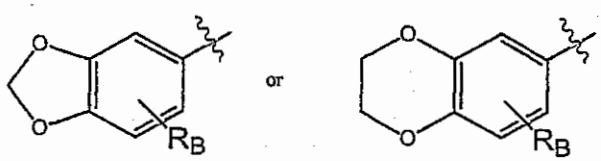


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

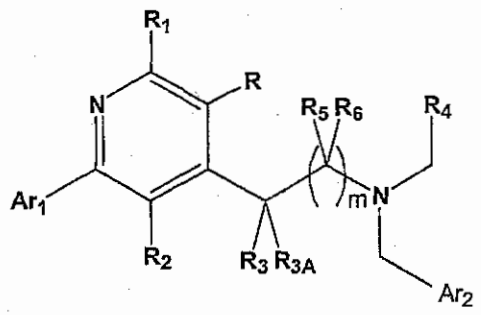
Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

The invention also include compounds of the following formula X:



X

wherein:

m is 0, 1, or 2;

R is hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl; or

R is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

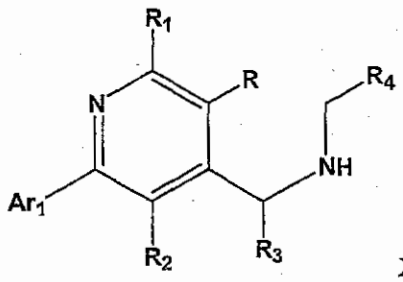
R_1, R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of formula X include those of the following formula X-A:



X-A

wherein Ar_1, R, R_1, R_2, R_3, R_4 are as defined for formula X above.

Additional preferred compounds of formula X include those wherein:

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy; mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with

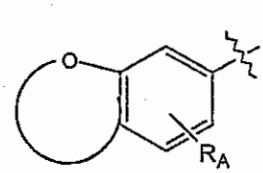
up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



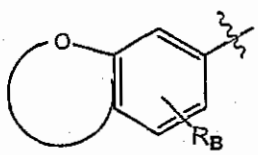
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$NH(C_1-C_6 alkyl), -S(O)$_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

Additional preferred compounds of formula X above include those wherein:

R is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, or phenyl;

R_1 is hydrogen, methyl or ethyl;

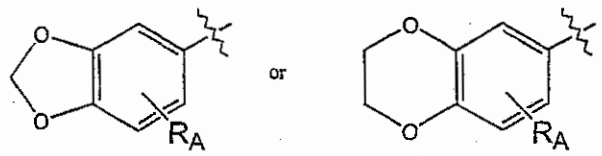
R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl or ethyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

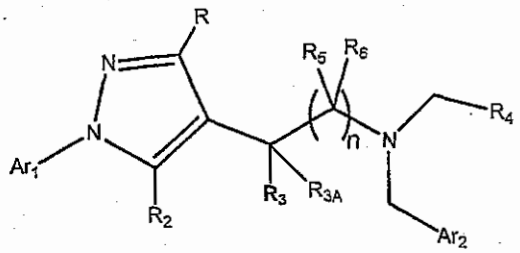
R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 is phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

The invention also includes compounds of the following formula XI:



XI

or pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally

substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

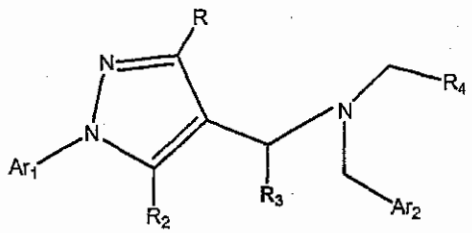
R and R_3 may be joined to form an optionally substituted saturated carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ring of from 5 to 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

The invention further includes compounds of the following formula XII:



XII

or a pharmaceutically acceptable salt thereof, wherein:

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2 and R_3 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form an optionally substituted carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ring of from 5 ro 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of formula XII above include wherein R and R_3 are not joined.

Also preferred are compounds of formula XII wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl,

pyrimidyl, pyrazinyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

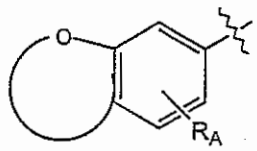
ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

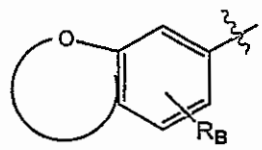


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –XR_B, wherein X and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, -O-, $-S(O)_m-$, -NH-, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x$(alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

Additional preferred compounds of formula XII include those wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

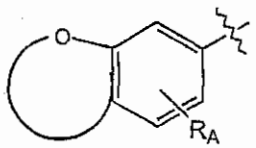
ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, *N*-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –XR_B, wherein X and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:

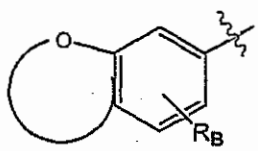


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-XR_B$, wherein X and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_mNH$-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_xNH$(C_1-C_6 alkyl), -$S(O)_xN$(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

Also preferred are compounds of formula XII wherein:

R is hydrogen, halogen, hydroxy, C_1-C_6 alkoxy, haloalkyl, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_2 is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl and haloalkyl;

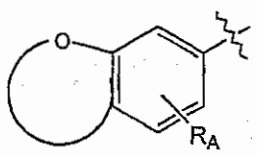
R_3 is hydrogen C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

R_4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl,

R_4 is a bicyclic oxygen-containing group of the formula:

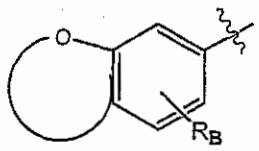


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, and benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Also preferred are compounds of formula XII wherein:

R, R_2, R_3, R_4, and Ar_2 are as defined in formula XII;

Ar_1 is phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

Also preferred are compounds of formula XII wherein:

R, R_2, and R_3 are as defined in formula XII;

Ar_1 is phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

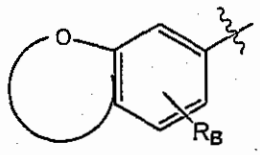
R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which

may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Also preferred are compounds of formula XII wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy,

C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

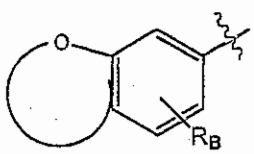
R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Also preferred are compounds of formula XII wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

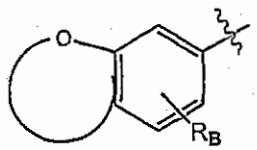
R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino;

Ar_1 is phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl,

benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Also preferred are compounds of formula XII wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

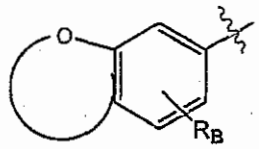
R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono

or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

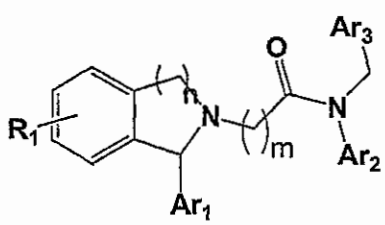
Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

The invention also includes compounds of the following formula XIII:



XIII

or a pharmaceutically acceptable salt thereof, wherein:

n is 1, 2, or 3

represents a carbon chain that may be substituted with hydrogen, halogen, cyano, nitro amino, mono or dialkyl amino, alkenyl, alkynyl, alkoxy, trifluoromethyl, trifluoromethoxy, straight or branched chain alkyl, or cycloalkyl, and n is 1, 2, or 3;

Ar_1, Ar_2, and Ar_3 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

R_1 represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or dialkylaminocarbonyl, sulfonamido, and mono or dialkylsulfonamido.

Also preferred are compounds of formula XIII wherein

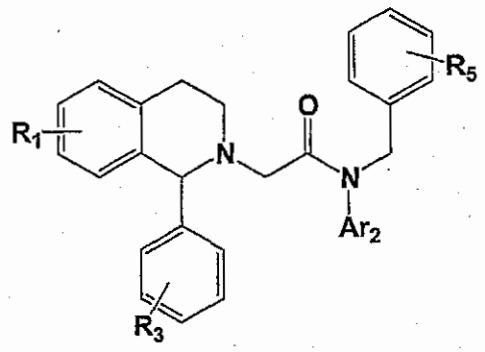
n, m, and R_1 are defined as for formula XIII above;

Ar_1 and Ar_3 are independently chosen from phenyl, pyridyl, and pyrimidinyl each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido; and

Ar_2 represents suberanyl, indanyl, tetrhydronaphtyl, or indolyl, each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl,

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido.

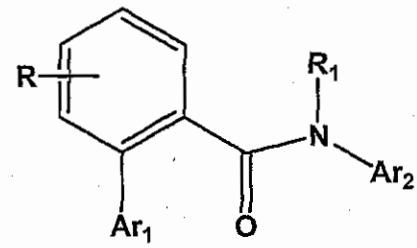
Also preferred are compounds of formula XIII above wherein:



R_1, R_3, and R_5 each represent up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, and mono or di(C_1-C_6)alkylsulfonamido; and

represents suberanyl, indanyl, tetrhydronaphtyl, or indolyl, each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido.

The invention also includes compounds of the followinf formula XIV:



or a pharmaceutically acceptable salt, thereof, wherein:

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or dialkylsulfonamido;

R_1 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_1 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of formula XIV include those (referred to herein as compounds of formula XIV-A) wherein

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$),

mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

R_1 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 is phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, benzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

Ar_1 is chosen from phenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, and pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, and N-(C_1-C_6)alkylsulfonylaminocarbonyl; and

Ar_2 is chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, pyrrolyl, pyrrolylalkyl, furanyl, furanylalkyl, thienyl, thienylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimidylalkyl, pyrazinyl, pyrazinylalkyl, benzimidazolyl, benzimidazolylalkyl, imidazopyrdinyl, imidazopyrdinylalkyl, naphthyl, napthylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, benzofuranyl,

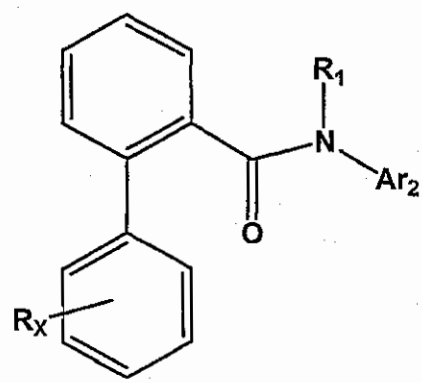
benzofuranylalkyl, benzodioxinyl, benzodioxinylalkyl, benzodioxolyl, benzodioxolylalkyl, quinolinyl, quinolinylalkyl, isoquinolinyl, isoquinolinylalkyl, each of which may be optionally substituted or substituted with up to four groups independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, mono- or di(C_1-C_6)alkylamino(C_1-C_6)alkyl, amino(C_1-C_6)alkoxy, C_1-C_6 alkoxyC_1-C_6 alkyl, C_1-C_6 alkoxyC_1-C_6 alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl,

benzyl (which may be unsubstituted or substituted with one or more substituents independently chosen from halogen, C_1-C_6alkyl, and C_1-C_6alkoxy),

-C_1-C_6 alkylNR_2R_3 or -C_1-C_6alkoxy NR_2R_3 wherein the point of attachment to Ar_2 is at the C_1-C_6 alkyl or C_1-C_6 alkoxy, and R_2 and R_3 are hydrogen, or straight or branched chain alkyl and are optionally substituted with halogen, hydroxy, or C_1-C_6 alkoxy and R_2 and R_3 may be taken together with the nitrogen to which they are attached to form a heterocycloalkyl group.

Preferred compopunds of formula XIV-A include those wherein:



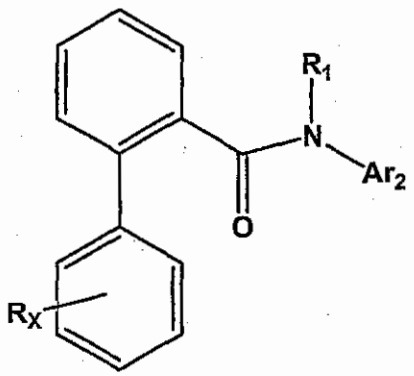
wherein:

Ar_2 is as defined in Claim in formula XIV-A;

R_X represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and

R_1 is C_1-C_6alkyl, C_3-C_8cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4alkyl, phenyl, phenylC_1-C_6alkyl, chromanyl, chromanylC_1-C_6alkyl, imidazolyl, imidazolylC_1-C_6alkyl ,pyridyl, pyridylC_1-C_6alkyl, pyrimidyl, pyrimidylC_1-C_6alkyl,pyrazinyl, pyrazinylC_1-C_6alkyl, indolyl, indolylC_1-C_6alkyl, indanyl, indanylC_1-C_6alkyl, benzodioxolyl, or benzodioxolylC_1-C_6alkyl each or which may be unsubstituted or substituted with up to 4 substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino.

Additional preferred compounds of formula XIV-A includes those of the following formula:



wherein:

R_X represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy substituted with 0-2 R_2, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R_1 is phenyl, phenylC_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalky(C_1-C_4 alkyl), naphthyl, napthylC_1-C_6alkyl, indanyl, indanylC_1-C_6 alkyl, benzodioxolanyl, or benzodioxolanylC_1-C_6 alkyl, each of which may be substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl; and

Ar_2 represents phenyl, benzyl, indanyl, indanyl-CH_2-, benzodioxolanyl, or benzodioxolanyl-CH_2-; each of which is substituted by up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl.

Additional preferred compounds of formula XIV includes those wherein:

Ar_2 is as defined for formula XIV;

R represents up to 4 groups independently chosen from hydrogen, halogen, amino, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, and trifluoromethoxy;

R_1 is phenyl, benzyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), naphthyl, naphthyl-CH_2-, indanyl, indandyl-CH_2-, benzodioxolanyl-CH_2-, or benzodioxolanyl, each of which may be substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl; and

Ar_1 is chosen from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and amino.

Also preferred are compounds of the formula XIV above wherein:

R represents up to 4 groups independently chosen from hydrogen, halogen, amino, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, and trifluoromethoxy;

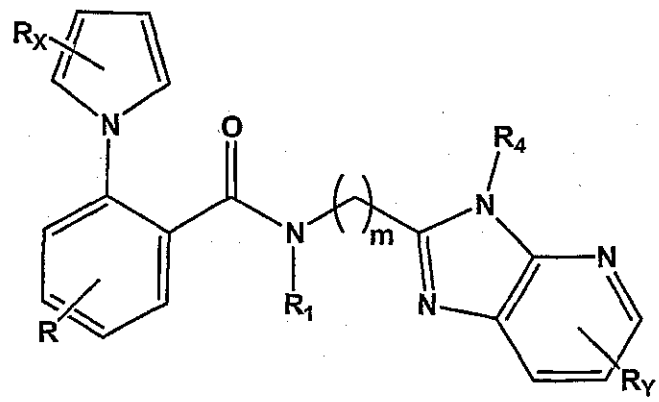
R_1 is benzyl which is unsubstituted or substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl;

Ar_1 is chosen from pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and amino; and

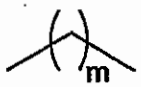
Ar_2 is chosen from phenyl, benzyl, indolyl, indolyl-CH_2-, indanyl, indanyl-CH_2-, chromanyl, chromanyl-CH_2-, benzofuranyl, benzofuranyl-CH_2-, benzodioxinyl, benzodioxinyl-CH_2-, benzodioxolyl-CH_2-, and benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

Preferred compounds of formula XIV also include thos eof the following formula IV-B:



wherein:

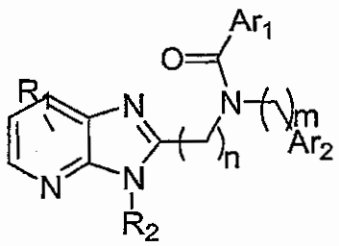
m is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydoxy, halogen, or amino;

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6alkyl, C_2-C_6 alkenyl, C_1-C_6alkynyl, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino;

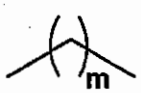
R_X and R_Y each represent up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and

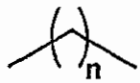
R_1 and R_4 are independently selected from C_1-C_6alkyl, C_3-C_8cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4alkyl, phenyl, phenylC_1-C_6alkyl, pyridyl, and pyridylC_1-C_6alkyl, each or which may be unsubstituted or substituted with up to 4 substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino.

The invention also provides compounds of the following formula XV:



or a pharmaceutically acceptable salt thereof, wherein;

m is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydoxy, halogen, or amino;

n is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydoxy, halogen, or amino;

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, and(cycloalkyl)alkyl;

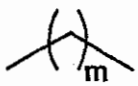
R_2 is

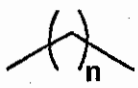
i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl) alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, mono- or dialkylamino; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

Preferred compounds of formula XV include those of the following formula:

m is 1 and  represents a carbon chain which is unsubstituted;

n is 1 and  represents a carbon chain which is unsubstituted;

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 cycloalkyl, and(C_3-C_8 cycloalkyl) C_1-C_4 alkyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

Ar_1 and Ar_2 are independently chosen from phenyl, phenyl(C_1-C_4)alkyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl, and pyrazinyl, each of which may be unsubstituted or optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

Compounds of the invention may have one or more asymmetric centers or planes. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms (racemates), by asymmetric synthesis, or by synthesis from optically active starting materials. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. *Cis* and *trans* geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral (enantiomeric and diastereomeric), and racemic forms, as well as all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

Some compounds of the invention may exist as tautomers. Unless otherwise specified any description or claim of one tautomeric form is intended to encompass the other tautomer.

Specifically preferred compounds include those shown in the FIGS. 1 through 6. In those figures, the substituent X depicts the moiety linkage to the base compound whose strucutre is shown at the top of each Figure.

Addiional preferred compounds of the invention include the following (compounds structures are shown directly above the compound chemical name in many instances):

1-(1-butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenyl methyl])aminomethylimidazole;

1-(1-butyl)-2-phenyl-5-(1-[N-{3,4-methylenedioxyphenylmethyl}-N-phenylmethyl]amino)ethylimidazole;

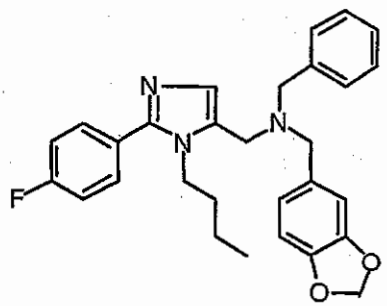
1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])amino-methylimidazole;

1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl-methyl]-N-phenylmethyl)aminomethylimidazole;

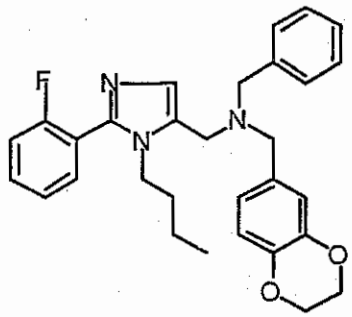
1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl) aminomethylimidazole;

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;

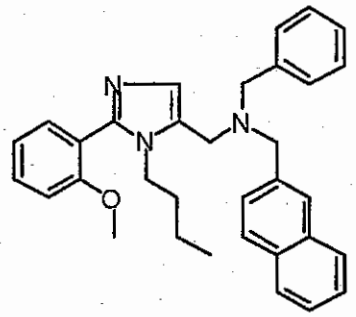
1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl) aminomethylimidazole;



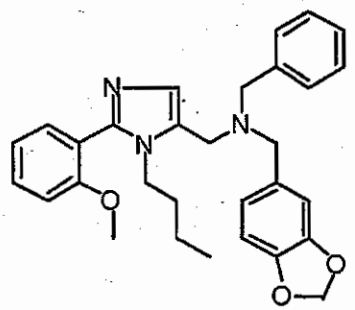
1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;



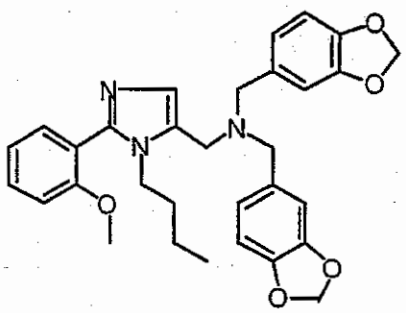
1-(1-Butyl)-2-(2-fluorophenyl)-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)amino- methylimidazole;



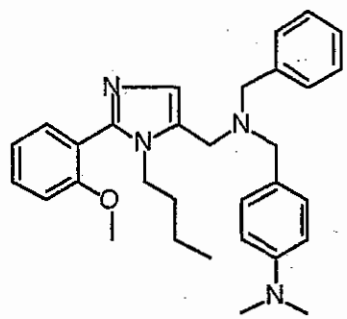
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[naphtha-2-ylmethyl]-N-phenylmethyl)amino-methylimidazole;



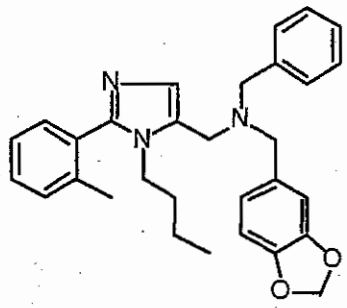
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;



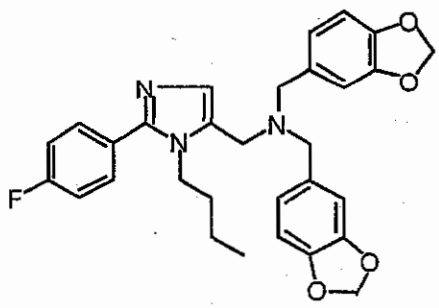
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole;



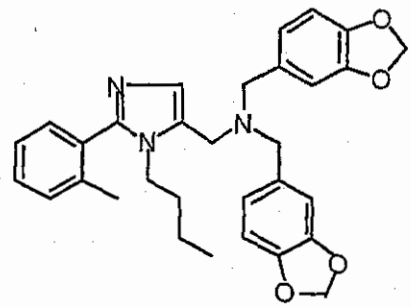
1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole;



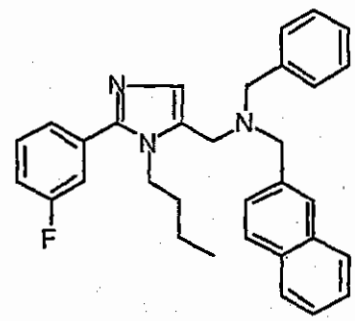
1-(1-Butyl)-2-(2-methylphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;



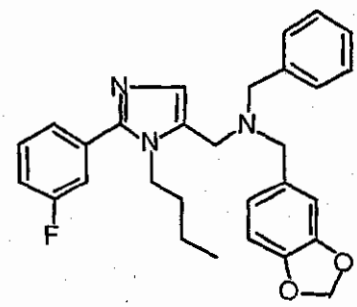
1-(1-Butyl)-2-(4-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole;



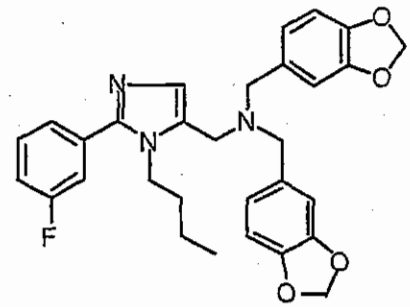
1-(1-Butyl)-2-(2-methylphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole;



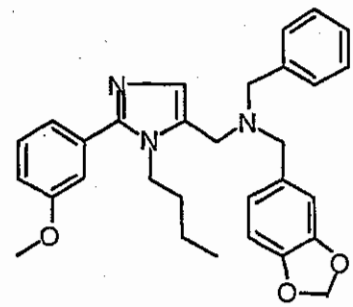
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[naphth-2-ylmethyl]-N-phenylmethyl)amino methylimidazole;



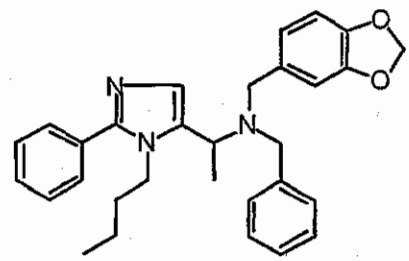
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole;



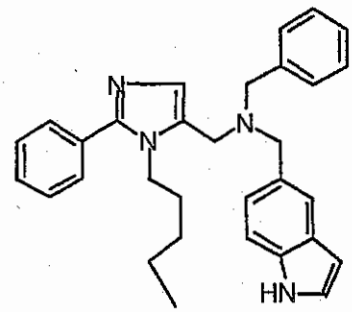
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole;



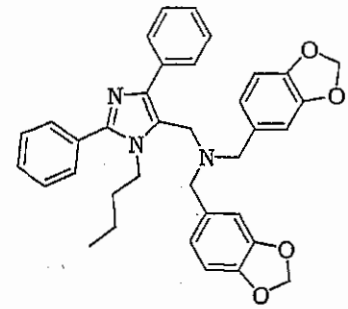
1-(1-Butyl)-2-(3-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)- aminomethylimidazole;



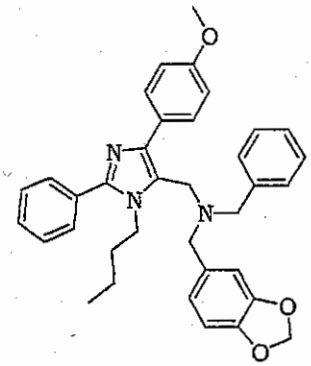
1-(1-Butyl)-2-phenyl-5-{1-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)amino} ethylimidazole;



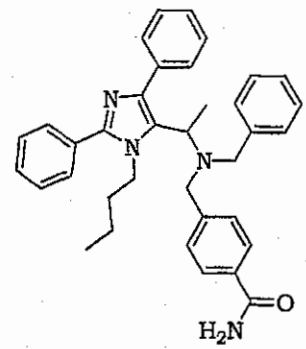
1-(1-Pentyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole;



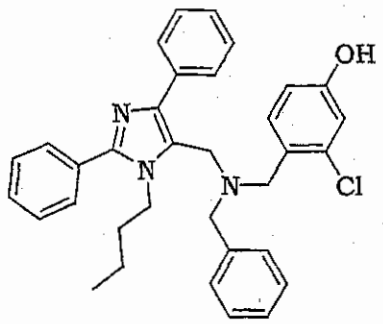
Bis-benzo[1,3]dioxol-5-ylmethyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amine



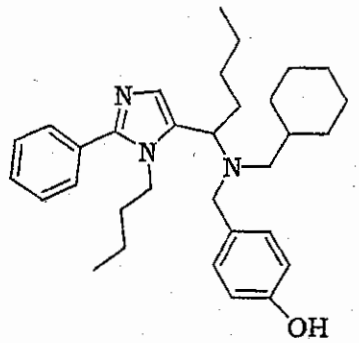
Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-5-(4-methoxy-phenyl)-2-phenyl-3*H*-imidazol-4-ylmethyl]-amine



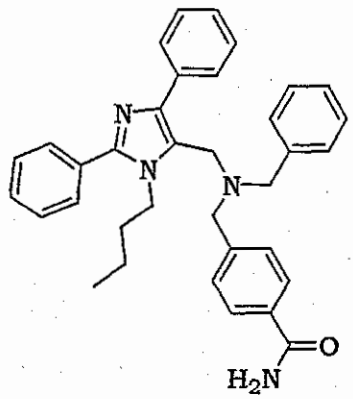
4-({Benzyl-[1-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-yl)-ethyl]-amino}-methyl)-benzamide



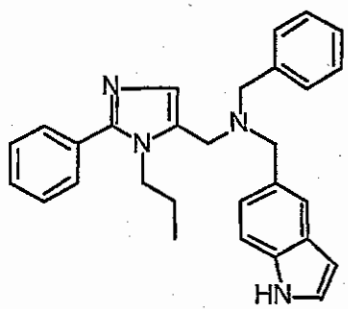
4-{[Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-3-chloro-phenol



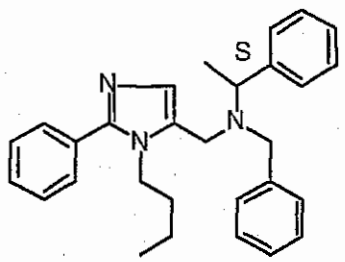
4-({[1-(3-Butyl-2-phenyl-3*H*-imidazol-4-yl)-pentyl]-cyclohexylmethyl-amino}-methyl)-phenol



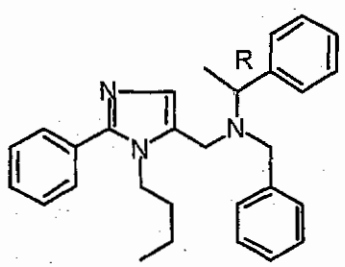
4-{[Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-benzamide



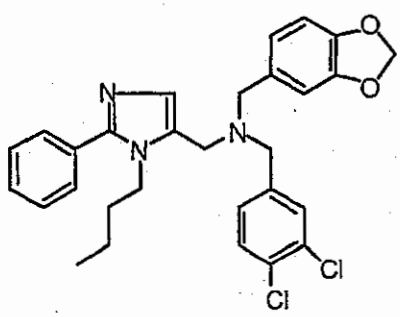
1-(1-Propyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole;



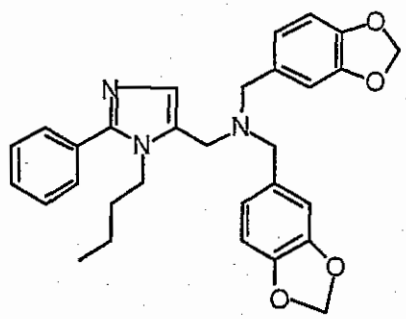
1-(1-Butyl)-2-phenyl-5-(N-[1-(*S*)-phenylethyl]-N-phenylmethyl)aminomethylimidazole;



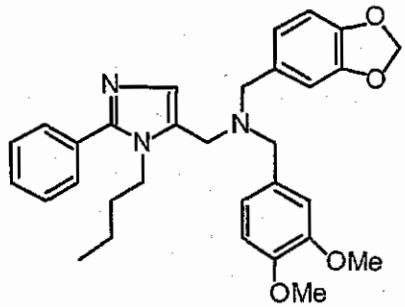
1-(1-Butyl)-2-phenyl-5-(N-[1-(*R*)-phenylethyl]-N-phenylmethyl)aminomethylimidazole;



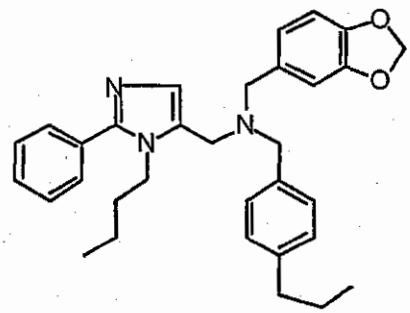
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenyl]methyl)aminomethylimidazole;



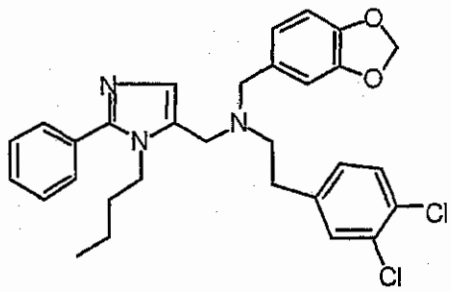
1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole;



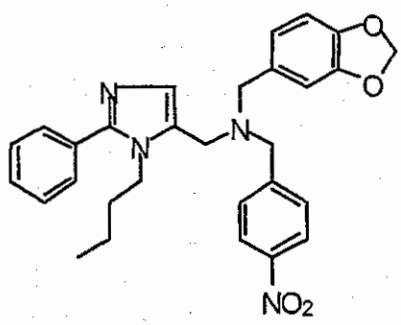
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-methoxyphenylmethyl])-aminomethylimidazole;



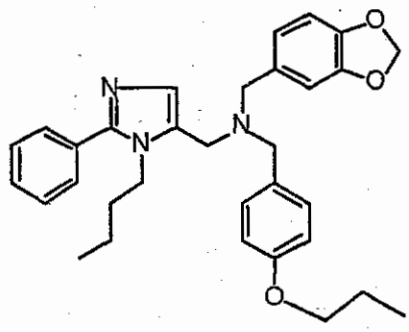
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyl}phenylmethyl]) aminomethylimidazole;



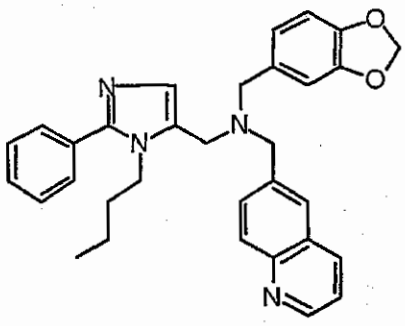
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenylethyl])
aminomethylimidazole;



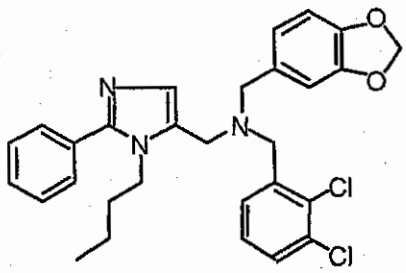
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-nitrophenylmethyl])
aminomethylimidazole;



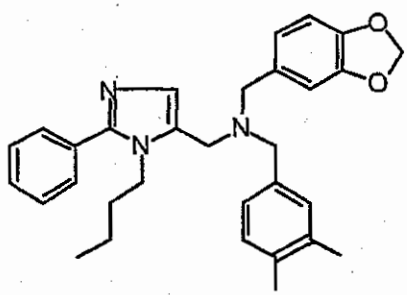
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyloxy} phenylmethyl])aminomethylimidazole;



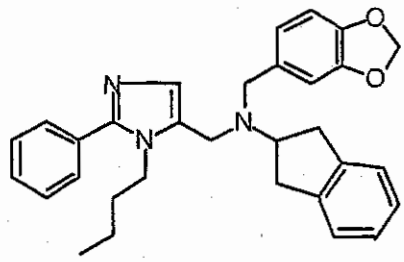
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[quinol-6-ylmethyl])- aminomethylimidazole;



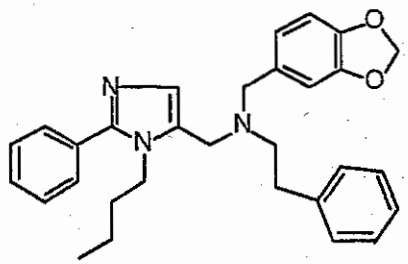
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2,3-dichlorophenylmethyl])-aminomethylimidazole;



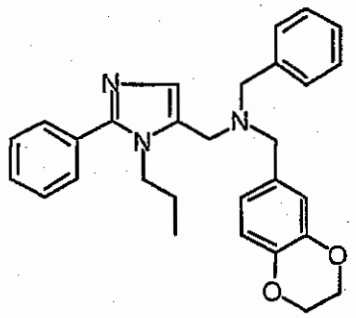
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dimethylphenylmethyl])-aminomethylimidazole;



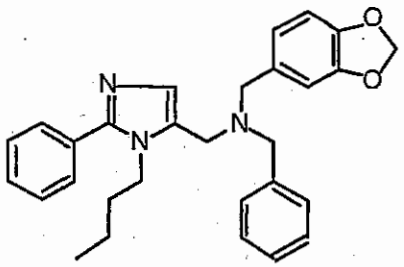
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[indan-2-yl])-aminomethylimidazole;



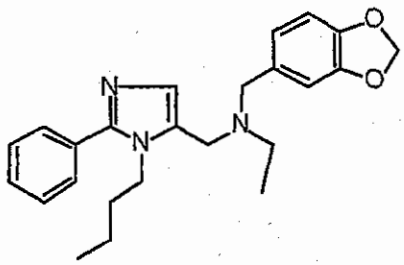
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-phenylethyl])amino-methylimidazole;



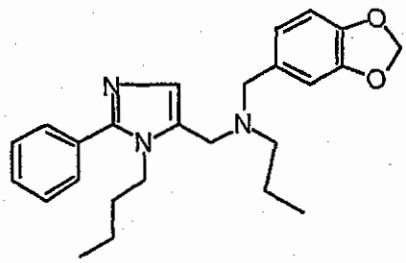
1-(1-Propyl)-2-phenyl-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



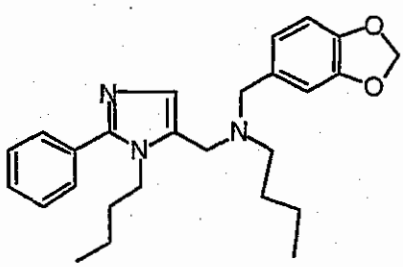
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



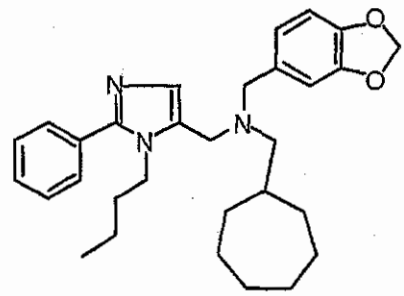
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-ethyl)aminomethylimidazole;



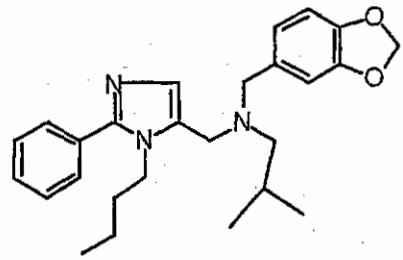
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-propyl])aminomethyl-imidazole;



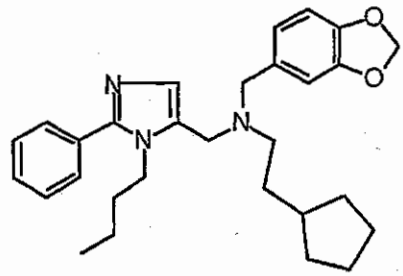
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-butyl])aminomethyl-imidazole;



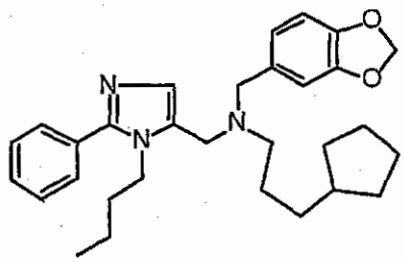
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cycloheptylmethyl)amino-methylimidazole;



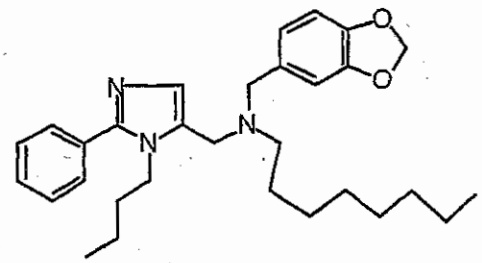
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-isobutyl)aminomethyl-imidazole;



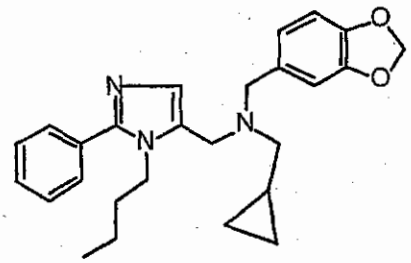
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-cyclopentylethyl])amino-methylimidazole;



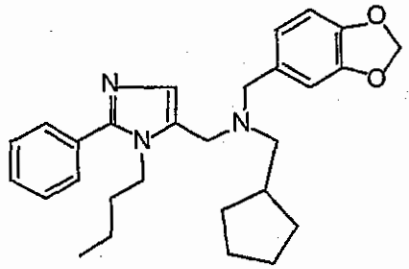
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3-cyclopentylpropyl])amino-methylimidazole;



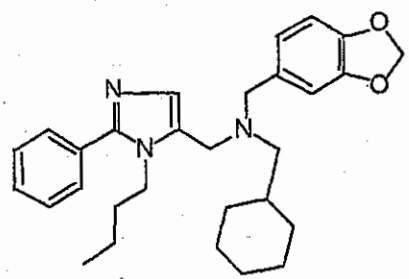
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-n-octyl])aminomethyl-imidazole;



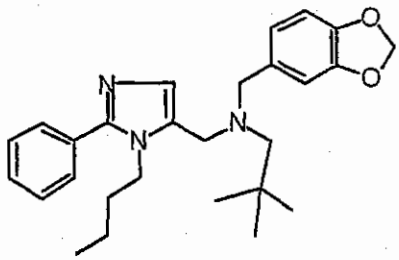
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopropylmethyl)amino-methylimidazole;



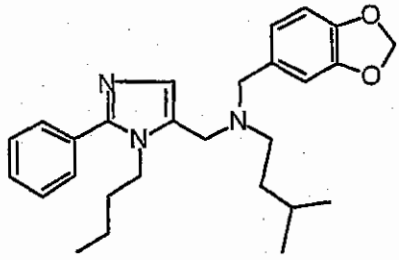
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopentylmethyl)amino-methylimidazole;



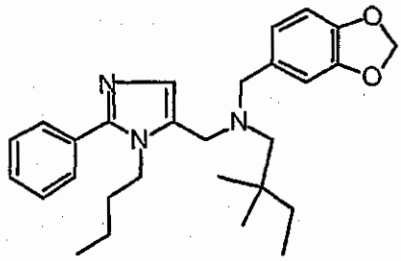
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclohexylmethyl)amino-methylimidazole;



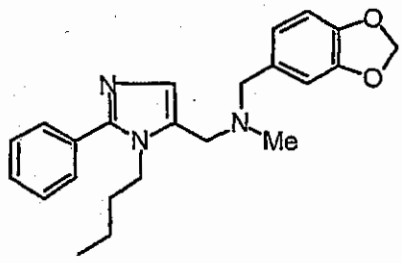
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[t-amyl])aminomethylimidazole;



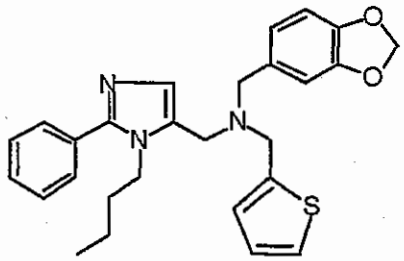
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{3-methyl}butyl)]amino-methylimidazole;



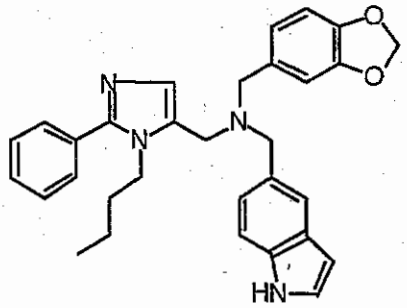
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{2,2-dimethyl}butyl]) aminomethylimidazole;



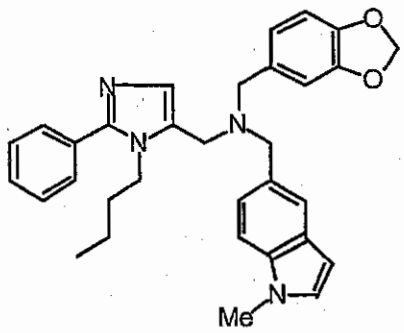
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-methyl)aminomethylimidazole;



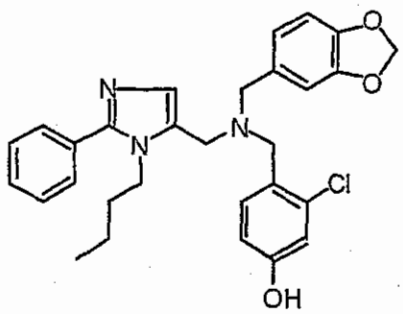
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-thiophenylmethyl])amino-methylimidazole;



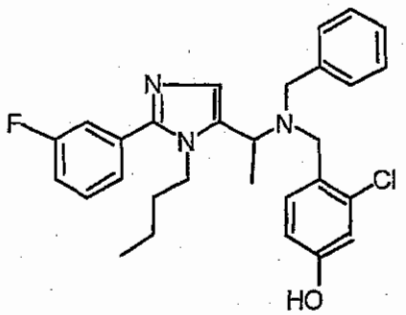
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[indol-5-ylmethyl])amino-methylimidazole;



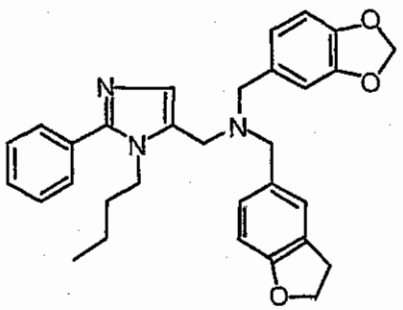
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[{1-methylindol-5-yl}methyl])aminomethylimidazole;



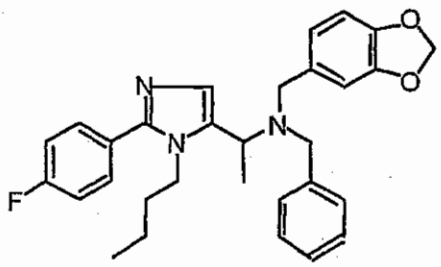
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-hydroxy-2-chlorophenyl]-methyl)aminomethylimidazole;



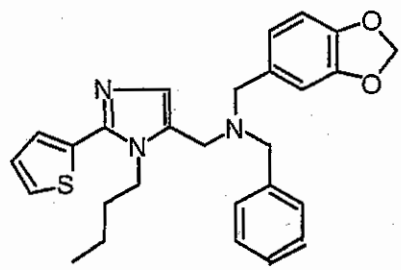
1-(1-Butyl)-2-(3-fluorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenyl}methyl-N-phenylmethyl]) aminoethylimidazole;



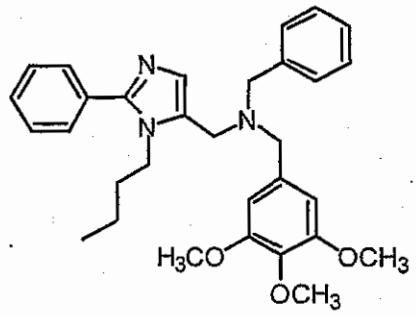
1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[2,3-dihydrobenzo[b]furan-5-yl]methyl)aminomethylimidazole;



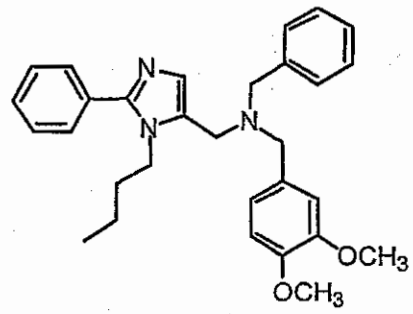
1-Butyl-2-(4-fluorophenyl)-5-(1-[N-{3,4-methylenedioxyphenyl}methyl-N-phenylmethyl]-amino)ethylimidazole;



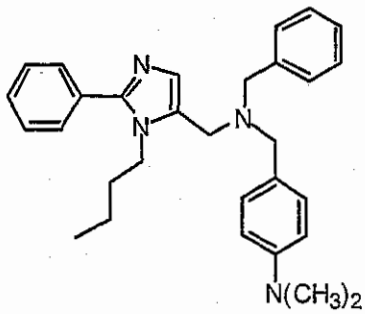
1-(1-Butyl)-2-(2-thienyl)-5-(N-[3,4-methylenedioxyphenyl]methyl-N-phenylmethyl] aminomethylimidazole;



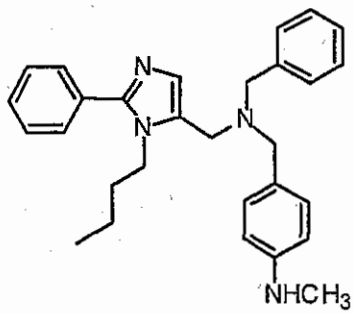
1-(1-Butyl)-2-phenyl-5-(N-[3,4,5-trimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole;



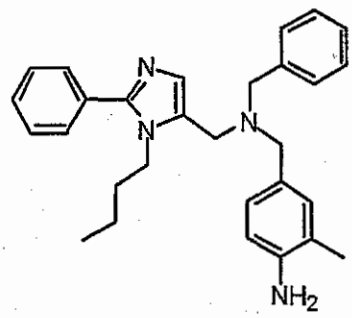
1-(1-Butyl)-2-phenyl-5-(N-phenylmethyl-N-[3,4-dimethoxyphenylmethyl])aminomethyl-imidazole;



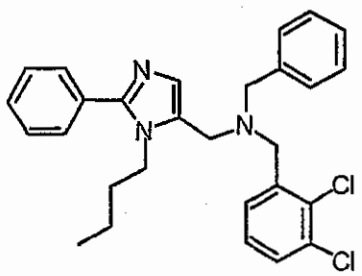
1-(1-Butyl)-2-phenyl-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



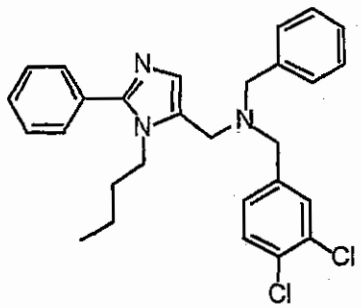
1-(1-Butyl)-2-phenyl-5-(N-[4-methylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



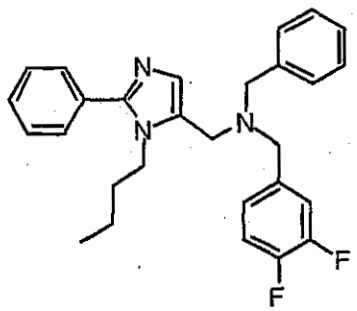
1-(1-Butyl)-2-phenyl-5-(N-[3-methyl-4-aminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole);



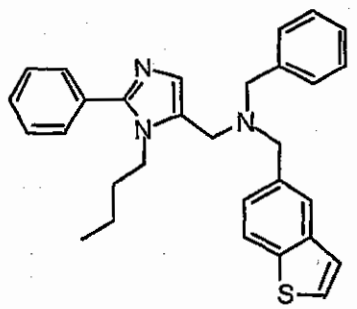
1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



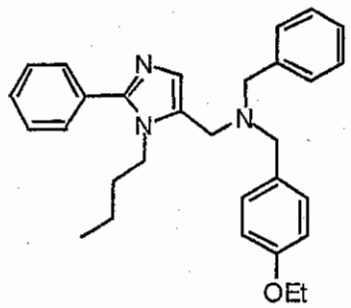
1-(1-Butyl)-2-phenyl-5-(N-[3,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



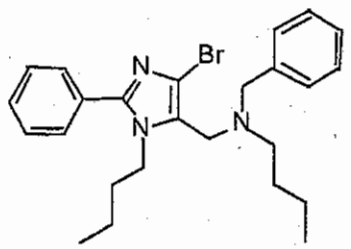
1-(1-Butyl)-2-phenyl-5-(N-[3,4-difluorophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



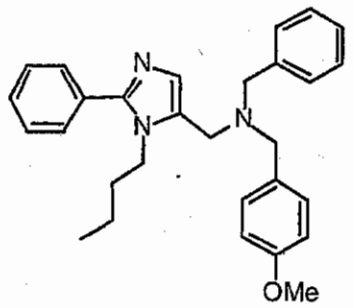
1-(1-Butyl)-2-phenyl-5-(N-(benzo[b]thiophen-5-ylmethyl)-N-phenylmethyl)aminomethyl-imidazole;



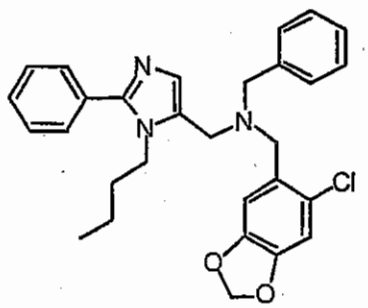
1-(1-Butyl)-2-phenyl-5-(N-[4-ethoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole;



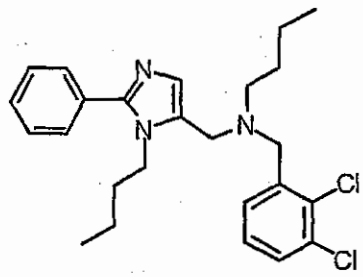
1-(1-Butyl)-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;



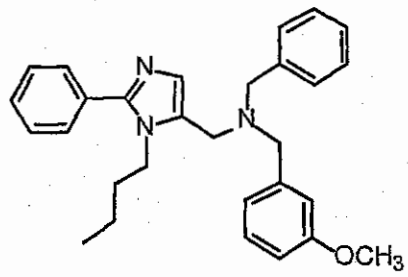
1-(1-Butyl)-2-phenyl-5-(N-[4-methoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole;



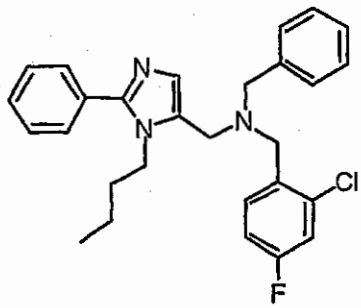
1-(1-Butyl)-2-phenyl-5-(N-[6-chloro-3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole;



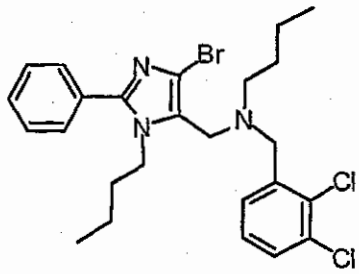
1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethylimidazole;



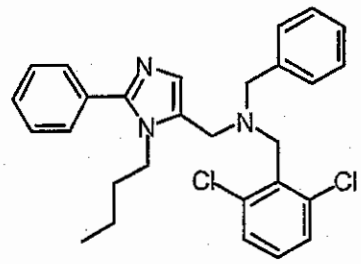
1-(1-Butyl)-2-phenyl-5-(N-[3-methoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole;



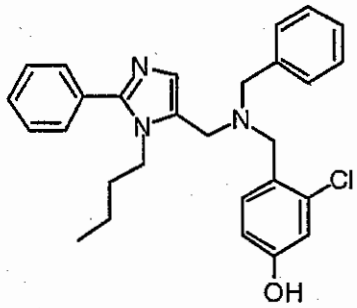
1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-fluorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



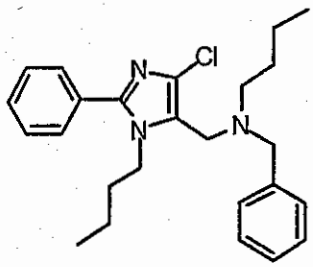
1-(1-Butyl)-2-phenyl-4-bromo-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethyl-imidazole;



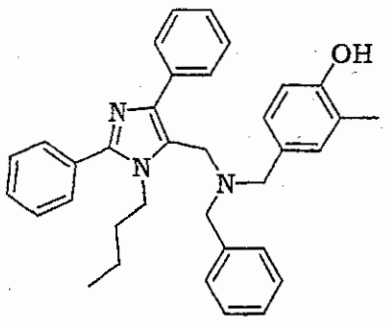
1-(1-Butyl)-2-phenyl-5-(N-[2,6-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



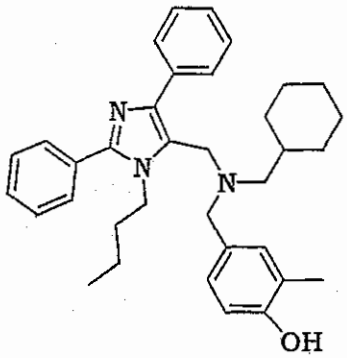
1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



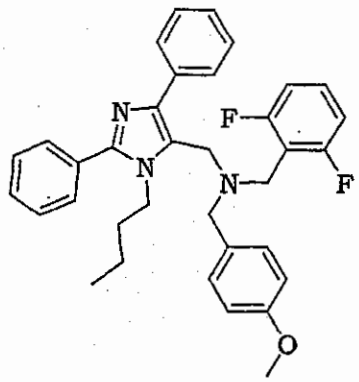
1-(1-Butyl)-2-phenyl-4-chloro-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;



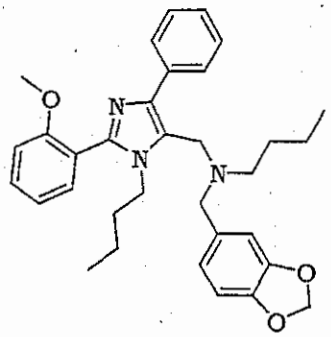
4-{[Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-2-methyl-phenol



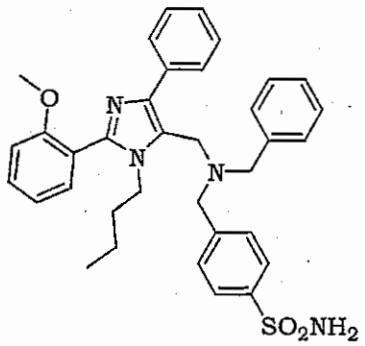
4-{[(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-cyclohexylmethyl-amino]-methyl}-2-methyl-phenol



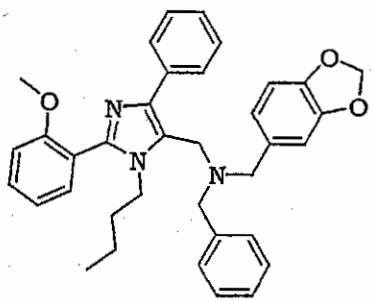
(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(2,6-difluoro-benzyl)-(4-methoxy-benzyl)-amine



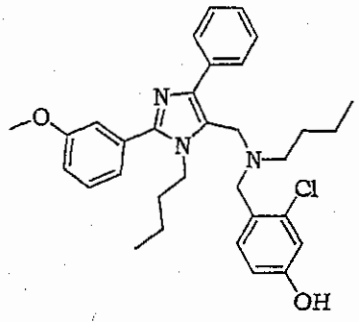
Benzo[1,3]dioxol-5-ylmethyl-butyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3*H*-imidazol-4-yl methyl]-amine



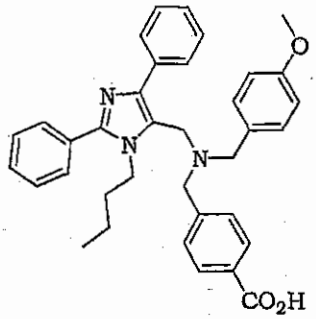
4-({Benzyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3*H*-imidazol-4-ylmethyl]-amino}-methyl)-benzenesulfonamide



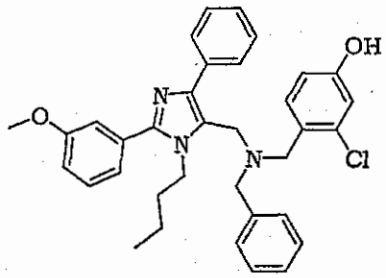
Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3*H*-imidazol-4-yl methyl]-amine



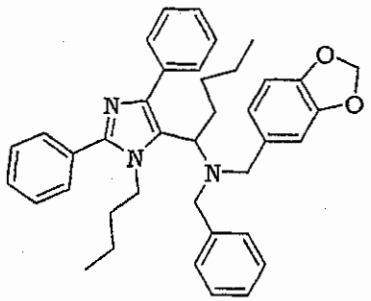
4-({Butyl-[3-butyl-2-(3-methoxy-phenyl)-5-phenyl-3*H*-imidazol-4-ylmethyl]-amino}-methyl)-3-chloro-phenol



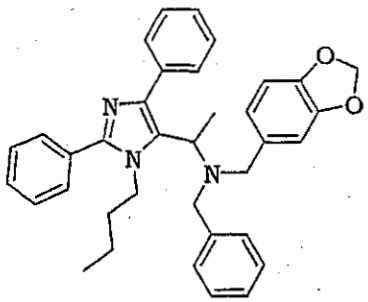
4-{[(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(4-methoxy-benzyl)-amino]-methyl}-benzoic acid



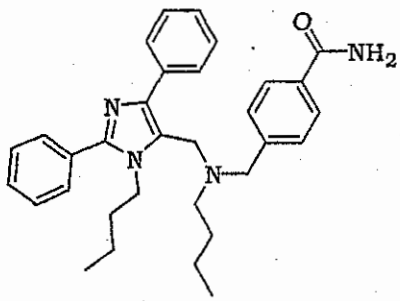
4-({Benzyl-[3-butyl-2-(3-methoxy-phenyl)-5-phenyl-3*H*-imidazol-4-ylmethyl]-amino}-methyl)-3-chloro-phenol



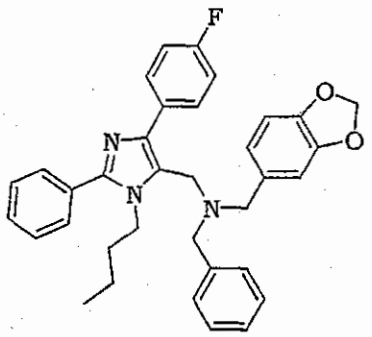
Benzo[1,3]dioxol-5-ylmethyl-benzyl-[1-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-yl)-pentyl]-amine



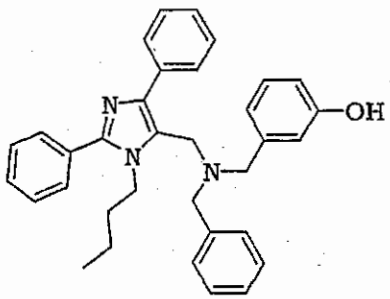
Benzo[1,3]dioxol-5-ylmethyl-benzyl-[1-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-yl)-ethyl]-amine



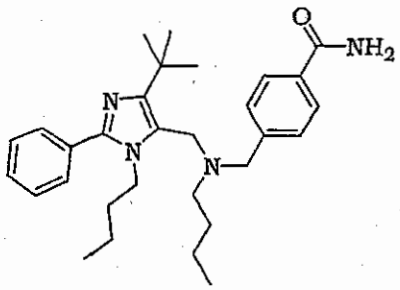
4-{[Butyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-benzamide



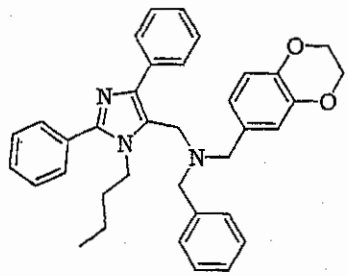
Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-5-(4-fluoro-phenyl)-2-phenyl-3*H*-imidazol-4-ylmethyl]-
amine



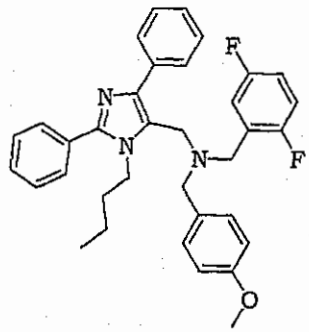
3-{[Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-phenol



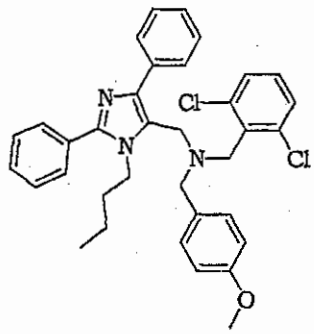
4-{[Butyl-(3-butyl-5-*tert*-butyl-2-phenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-benzamide



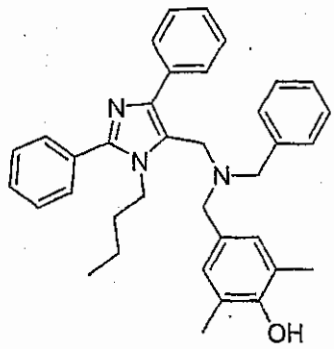
Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-amine



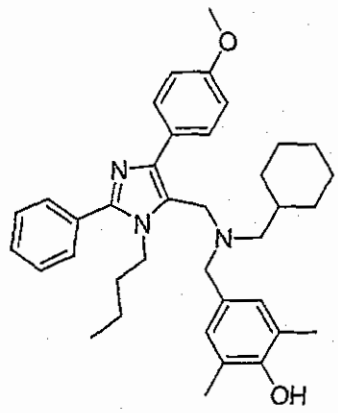
(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(2,5-difluoro-benzyl)-(4-methoxy-benzyl)-amine



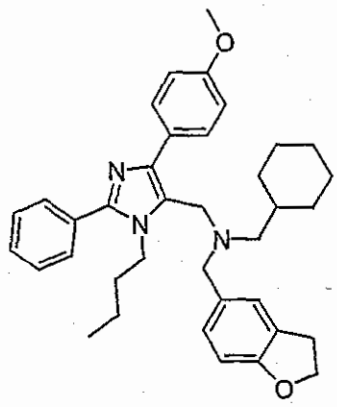
(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(2,6-dichloro-benzyl)-(4-methoxy-benzyl)-amine



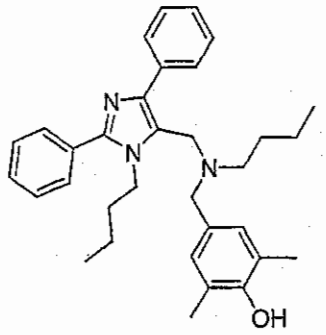
4-{[Benzyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-2,6-dimethyl-phenol



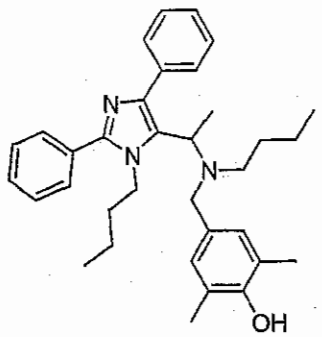
4-({[3-Butyl-5-(4-methoxy-phenyl)-2-phenyl-3*H*-imidazol-4-ylmethyl]-cyclohexylmethyl-amino}-methyl)-2,6-dimethyl-phenol



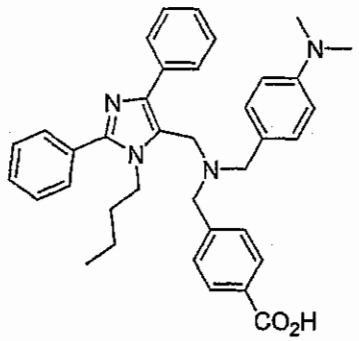
[3-Butyl-5-(4-methoxy-phenyl)-2-phenyl-3*H*-imidazol-4-ylmethyl]-cyclohexylmethyl-(2,3-dihydro-benzofuran-5-ylmethyl)-amine



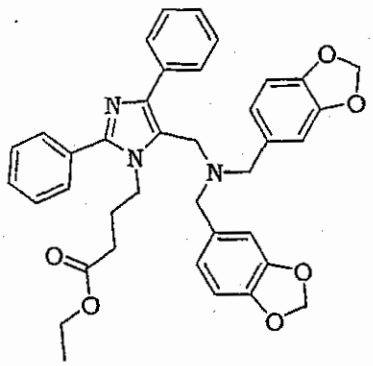
4-{[Butyl-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-amino]-methyl}-2,6-dimethyl-phenol



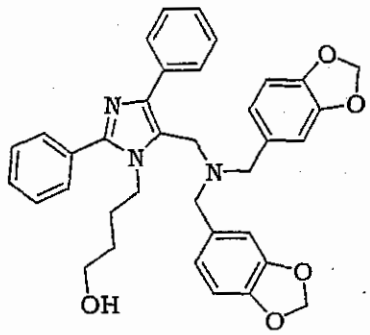
4-({Butyl-[1-(3-butyl-2,5-diphenyl-3*H*-imidazol-4-yl)-ethyl]-amino}-methyl)-2,6-dimethyl-phenol



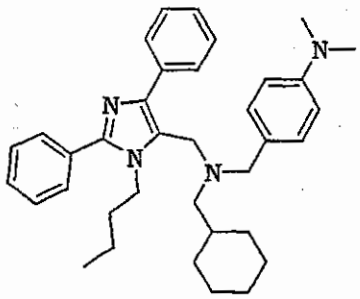
4-{[(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-(4-dimethylamino-benzyl)-amino]-methyl}-benzoic acid



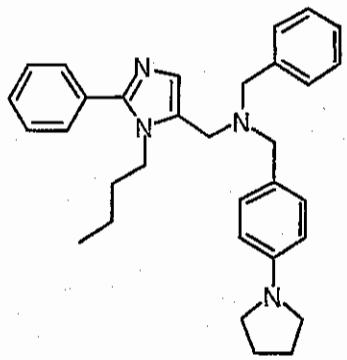
4-{5-[(Bis-benzo[1,3]dioxol-5-ylmethyl-amino)-methyl]-2,4-diphenyl-imidazol-1-yl}-butyric acid ethyl ester



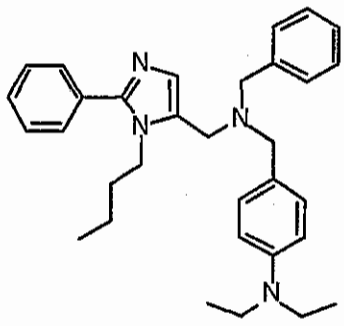
4-{5-[(Bis-benzo[1,3]dioxol-5-ylmethyl-amino)-methyl]-2,4-diphenyl-imidazol-1-yl}-butan-1-ol



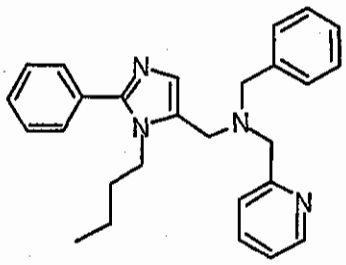
{4-{[(3-Butyl-2,5-diphenyl-3*H*-imidazol-4-ylmethyl)-cyclohexylmethyl-amino]-methyl}-phenyl}-dimethyl-amine



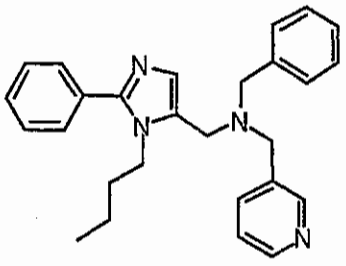
1-(1-Butyl)-2-phenyl-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



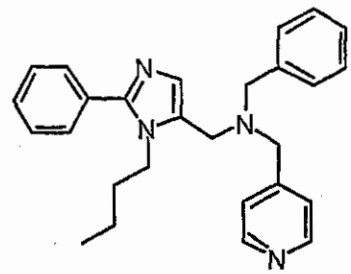
1-(1-Butyl)-2-phenyl-5-(N-[4-diethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole;



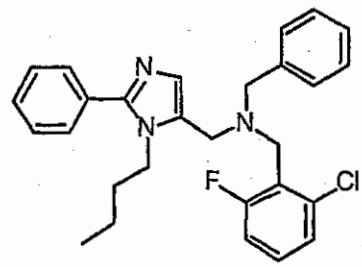
1-(1-Butyl)-2-phenyl-5-(N-[pyridin-2-ylmethyl]-N-phenylmethyl)aminomethylimidazole;



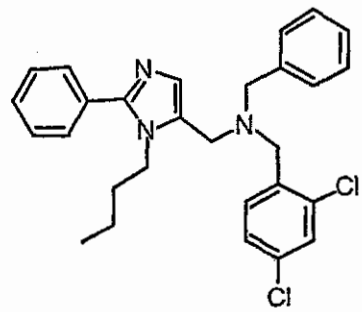
1-(1-Butyl)-2-phenyl-5-(N-[pyridin-3-ylmethyl]-N-phenylmethyl)aminomethylimidazole;



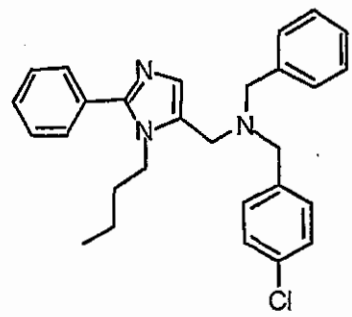
1-(1-Butyl)-2-phenyl-5-(N-[pyridin-4-ylmethyl]-N-phenylmethyl)aminomethylimidazole;



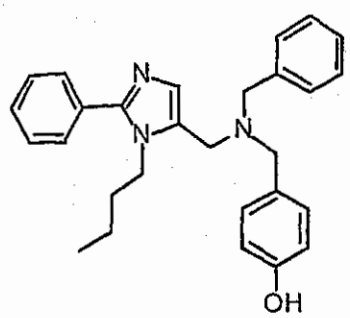
1-(1-Butyl)-2-phenyl-5-(N-[2-fluoro-6-chlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole);



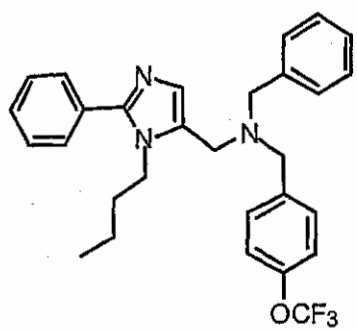
1-(1-Butyl)-2-phenyl-5-(N-[2,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole);



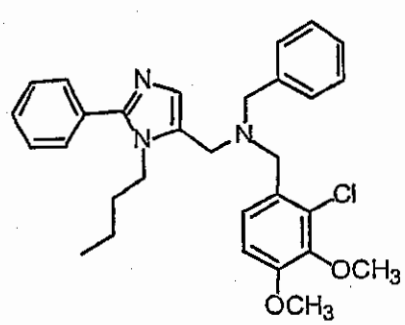
1-(1-Butyl)-2-phenyl-5-(N-[4-chlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



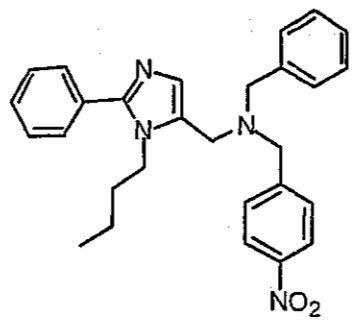
1-(1-Butyl)-2-phenyl-5-(N-[4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole;



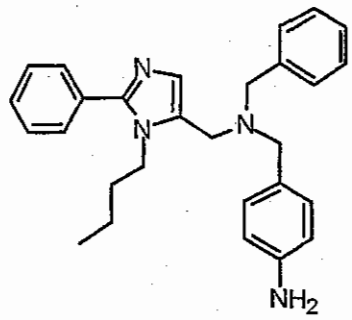
1-(1-Butyl)-2-phenyl-5-(N-[4-trifluoromethoxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole);



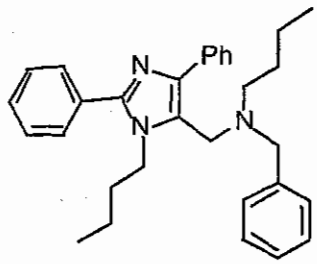
1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-3,4-dimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole);



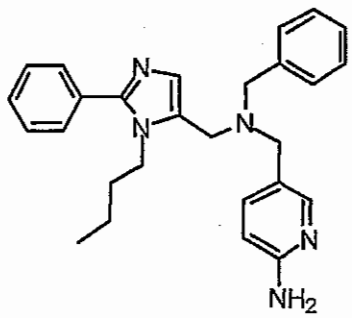
1-(1-Butyl)-2-phenyl-5-(N-[4-nitrophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



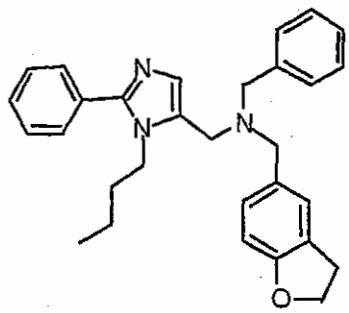
1-(1-Butyl)-2-phenyl-5-(N-[4-aminophenylmethyl]-N-phenylmethyl)aminomethylimidazole;



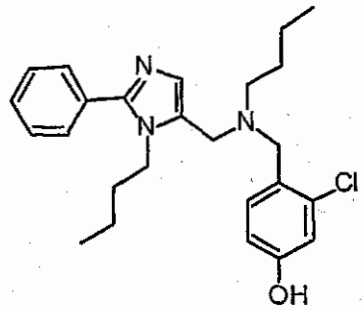
1-(1-Butyl)-2,4-diphenyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;



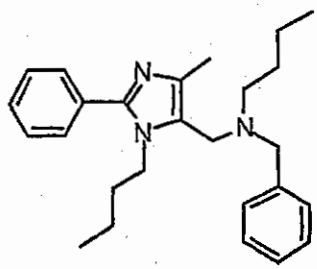
1-(1-Butyl)-2-phenyl-5-(N-[2-aminopyridin-5-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole



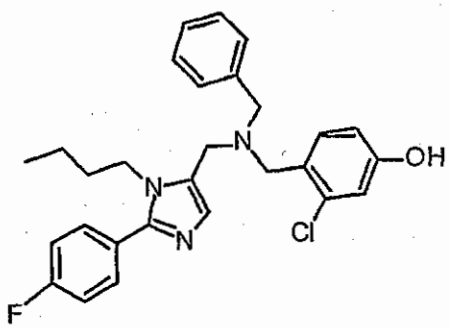
1-(1-Butyl)-2-phenyl-5-(N-[2,3-dihydrobenzo[b]furan-5-ylmethyl]-N-phenylmethyl)amino-methylimidazole;



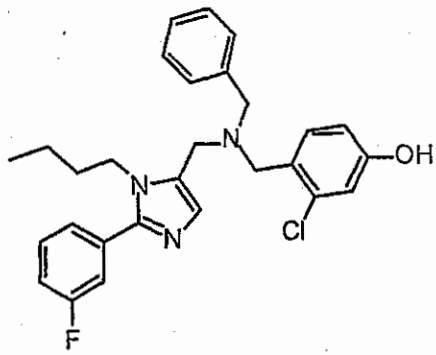
1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-[1-butyl])aminomethyl-imidazole)



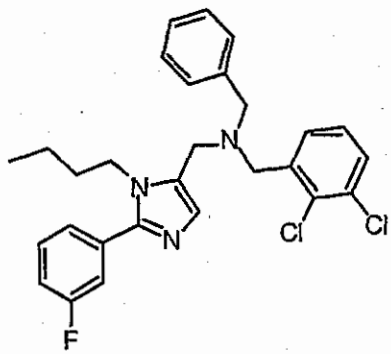
1-(1-Butyl)-2-phenyl-4-methyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole;



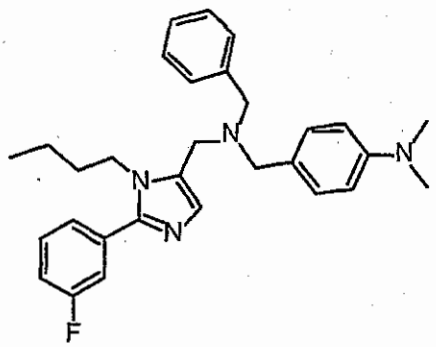
1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole;



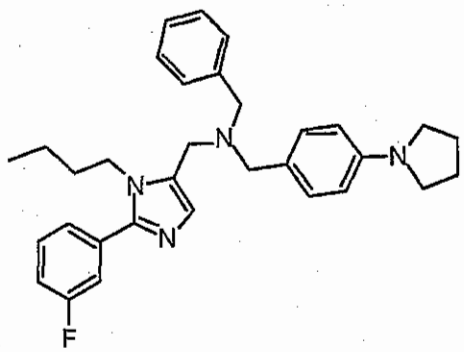
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole;



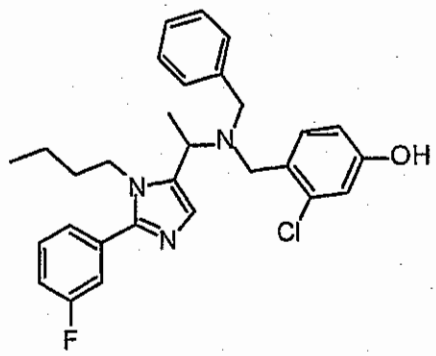
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)amino-methylimidazole;



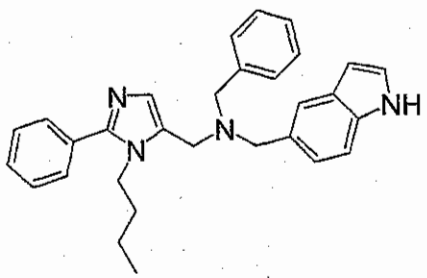
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl)amino-methylimidazole;



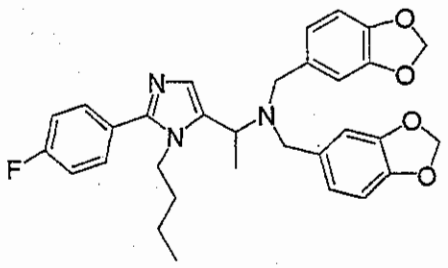
1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)amino-methylimidazole;



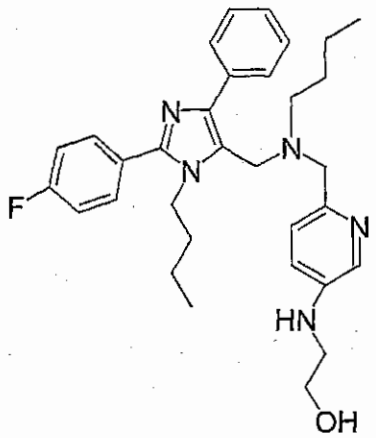
1-(1-Butyl)-2-(3-chlorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenylmethyl}-N-phenylmethyl] amino)ethylimidazole;



1-(1-Butyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)aminomethylimidazole;



1-(1-Butyl)-2-(4-fluorophenyl)-5-(1-N,N-di[3,4-methylenedioxyphenylmethyl]amino)ethylimidazole;



2-{[5-({Butyl[(1-butyl-2,4-diphenylimidazol-5-yl)methyl]amino}methyl)-2-pyridyl]amino}ethan-1-ol;

As discussed above, preferred compounds of the invention exhibit good activity in standard *in vitro* C5 receptor mediated chemotaxis assay, specifically the assay as specified in Example 12, which follows. References herein to "standard *in vitro* C5 receptor mediated chemotaxis assay" are inteided to refer to that protocol as defined in Example 12 which follows. Preferred compounds of the invention exhibit an EC_{50} of about 100 μM or less in such a standard C5a mediated chemotaxis assay, more preferably an EC_{50} of about 10 μM or less in such a standard C5a mediated chemotaxis assay, still more preferably an EC_{50} of about 1 μM in such a standard C5a mediated chemotaxis assay, even more preferably an EC_{50} of about 0.1 μM in such a standard C5a mediated chemotaxis assay.

Additional assays suitable for determining the effects of small molecule compounds on C5a receptor binding and receptor modulatory activity, as well as assays suitable for measuring their effects on C5a-induced neutropenia in vivo, can be found in the published literature, for example in US patent 5,807,824, which is incorporated herein by reference for its disclosure in this regard in Examples 6-9, columns 19-23, as well as for its discussion of complement and inflammation at columns 1-2. Those of skill in the art will recognize that such assays can be readily adapted to the use of cells or animals of different species as deemed appropriate.

In one aspect of the invention, one or more compounds of the invention, preferably in solution in a pharmaceutically acceptable carrier as a pharmaceutical preparation, is used to perfuse a donor organ prior to transplantation of the organ into a recipient patient. Such perfusion is preferably carried out using a solution comprising an concentration of the compound of the invention that is an effective amount sufficient to inhibit C5a mediated effects in vitro or in vivo. Such perfusion preferably reduces the severity or frequency of one or more of the inflammatory sequelae following organ transplantation when compared to that occurring in control (including, without restriction, historical control) transplant recipients who have received transplants of donor organs that have not been so perfused.

Definitions

In certain situations, the compounds of of the invention may contain one or more asymmetric elements such as stereogenic centers, stereogenic axes and the like, e.g. asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. For compounds with two or more asymmetric elements, these

compounds can additionally be mixtures of diastereomers. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis, synthesis from optically pure precursors or by resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

The term "substituted", as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =0), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C, and ^{14}C.

When any variable occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R*, then said group may optionally be substituted with up to two R* groups and R* at each occurrence is selected independently from the definition of R*. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As indicated herein, various substituents of the compounds of the present invention and various formulae set forth herein are "optionally substituted", including, e.g., Ar_1, Ar_2, R, R_1, R_2, R_3, R_{3A}, R_4, R_5, R_6, R_7, R_A, R_A', R_B, and R_C. When substituted, those substituents may be substituted at one or more of any of the available positions, typically 1, 2, 3, or 4 positions, by one or more suitable groups such as those disclosed herein.

Suitable groups or "substituted" moities of compounds of the invention include e.g., halogen such as fluoro, chloro, bromo or iodo; cyano; hydroxyl; nitro; azido; alkanoyl such as a C_{1-6} alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon, or 2, 3, 4, 5 or 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5, or 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms, or 1, 2, 3, 4, 5 or 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e.g. an Ar group being a substituted or unsubstituted biphenyl moiety); arylalkyl having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with benzyl being a preferred group; aralkoxy having 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms, with O-benzyl being a preferred group; or a heteroaromatic or heteroalicyclic group having 1 to 3 separate or fused rings with 3 to about 8 members per ring and one or more N, O or S atoms, e.g. coumarinyl, quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl, benzothiazolyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolidinyl.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups, having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. Preferred alkyl

groups are C_1-C_8 and C_{1-6} alkyl groups. Especially preferred alkyl groups are methyl, ethyl, propyl, butyl, 3-pentyl. The term C_{1-6} alkyl as used herein includes alkyl groups consisting of 1 to 6 carbon atoms, which may contain a cyclopropyl moiety. Suitable examples are methyl or ethyl.

"Cycloalkyl" is intended to include saturated ring groups, having the specified number of carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl and brigded or caged saturated ring groups such as norbornane or adamantane and the like.

In the term "(C_{3-6} cycloalkyl)C_{1-4} alkyl", as defined above, the point of attachment is on the alkyl group. This term encompasses, but is not limited to, cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

"Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more unsaturated carbon-carbon bonds, which may occur in any stable point along the chain, such as ethenyl and propenyl.

"Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration comprising one or more triple carbon-carbon bonds that may occur in any stable point along the chain, such as ethynyl and propynyl.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_v(X^i)_{wi}(H_{2v+1-\Sigma(wi)})$ where v = 1 to 3; X^i = F(i=1), Cl(i=2), Br(i=3), I(i=4) and $\Sigma w_i \leq 2v+1$). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl.

"Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

As used herein, the term "carbocyclic aryl" indicates aromatic groups containing only carbon in the aromatic ring. Such aromatic groups may be further

substituted with carbon or non-carbon atoms or groups. Typical carbocyclic aryl groups contain 1 to 3 separate of fused rings and from 6 to about 18 ring atoms, without heteroatoms as ring members. Specifically preferred carbocyclic aryl groups include phenyl, napthyl, including 1-naphthyl and 2-naphthyl, and acenaphthyl.

By the term "energetically accessible conformer" is meant any conformer of a compound that falls within about a 15 Kcal/mol window above the lowest energy conformation (as for example that found in a monte carlo or systematic confirmational search) by using MM2, MM3, or MMFF force fields as implemented in molecular modeling software such as MacroModel® v 7.0, Schrödinger, Inc., Portland, Oregon United Stats and Jersey City, New Jersey, United States, http://www.schrodinger.com or the like.

Peptidomimetic compounds are generally compounds with "chemical structures derived from bioactive peptides which imitate natural molecules" (Murray Goodman and Seonggu Ro, "Peptidomimetics for Drug Design" chapter twenty in Burger's Medicinal Chemistry and Drug Discovery, Volume 1: Principles and Practice, Manfred E. Wolff, ed. John Wiley & Sons, Inc., NY, 1995, pp. 801-861.) As used herein and in the claims, the term peptidomimetic additionally comprises peptoid compounds, which are compounds that comprise oligomers of N-substituted natural amino acids, and the term further comprises any compound having more than two amide bonds.

As used herein, the terms "heteroaryl" and "heteroalicyclic" group are intended to indicate a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated, partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, 0 and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The term heteroaryl indicates that the group contains at least 1 aromatic ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings

described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized.

It is preferred that when the total number of S and 0 atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and 0 atoms in the heterocycle is not more than 1, 2, or 3, more typically 1 or 2. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heteroaryl groups and other heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl.

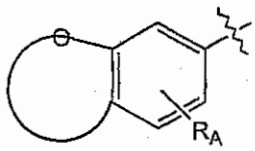
Preferred heteroaryl groups include, but are not limited to, pyridinyl,

pyrimidinyl, furanyl, and thienyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

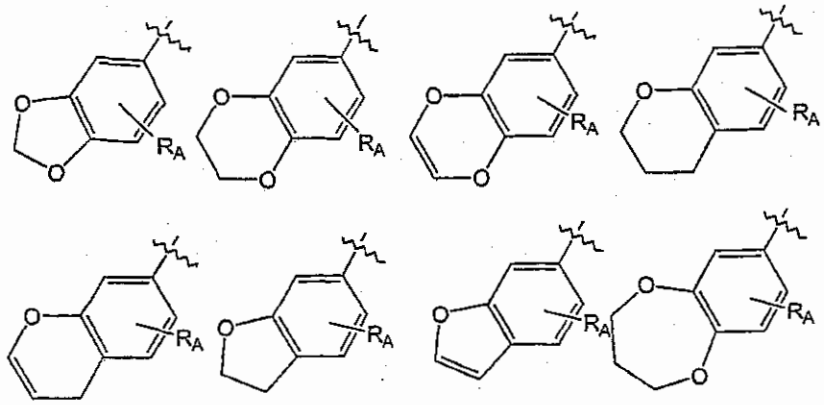
The term "halogen" indicates fluorine, chlorine, bromine, or iodine.

The term "pharmaceutically acceptable salts" includes, but is not limited to non-toxic salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrite or salts with an organic acids such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, salicylate and stearate. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. The present invention also encompasses the prodrugs of the compounds disclosed.

Examples of bicyclic oxygen containing groups of the formula:



(R_A may also be indicated R_B) include the following:



Methods of Treating Patients

The present invention provides methods of treating patients suffering from diseases or disorders involving pathologic activation of C5a receptors. Such diseases and disorders may include the following.

Such disorders that may be autoimmune in nature and are suitable for

treatment in accordance with the present invention include e.g. rheumatoid arthritis, systemic lupus erythematosus (and associated glomerulonephritis), psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome (and associated glomerulonephritis and pulmonary hemorrhage), and immunovasculitis. Such inflammatory and related conditions include neutropenia, sepsis, septic shock, Alzheimer's disease, stroke, inflammation associated with severe burns, lung injury, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis, traumatic central nervous system injury and ischemic heart disease, and ischemia-reperfusion injury, as well as acute (adult) respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), tissue graft rejection, and hyperacute rejection of transplanted organs. Also included are pathologic sequellae associated with insulin-dependent diabetes mellitus (including diabetic retinopathy), lupus nephropathy, Heyman nephritis, membranous nephritis and other forms of glomerulonephritis, contact sensitivity responses, and inflammation resulting from contact of blood with artificial surfaces that can cause complement activation, as occurs, for example, during extracorporeal circulation of blood (e.g., during hemodialysis or via a heart-lung machine, for example, in association with vascular surgery such as coronary artery bypass grafting or heart valve replacement) such as extracorporeal post-dialysis syndrome, or in association with contact with other artificial vessel or container surfaces (e.g., ventricular assist devices, artificial heart machines, transfusion tubing, blood storage bags, plasmapheresis, plateletpheresis, and the like).

Treatment methods of the invention include in general administration to a patient a therapeutically effective amount of one or more compounds of the invention. Suitable patients include those subjects suffering from or susceptible to (i.e. propylactic treatment) a disorder or disease identified herein. Typical patients

for treatment in accordance with the invention include mammals, particularly primates, especially humans. Other suitable subjects include domesticated companion animals such as a dog, cat, horse, and the like, or a livestock animal such as cattle, pig, sheep and the like.

Pharmaceutical Preparations

The compounds of the invention may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes injections and the like, such as subcutaneous, intradermal, intravascular (e.g., intravenous), intramuscular, intrasternal, spinal, intrathecal, and like injection or infusion techniques, with subcutaneous, intramuscular and intravascular injections or infusions being preferred. In addition, there is provided a pharmaceutical formulation comprising a compound of the invention and a pharmaceutically acceptable carrier. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of the invention may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These

excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monosterate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

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

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for

example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of the invention may be administered parenterally, preferably in a sterile non-toxic, pyrogen-free medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment or preventions of conditions involving pathogenic C5a activity, particularly those disorders list in the "background of the invention" section (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily, three times daily, or less is preferred, with a dosage regimen of once daily or 2 times daily being particularly preferred.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination (i.e., other drugs being administered to the patient), the severity of the particular disease undergoing therapy, and other factors, including the judgment of the prescribing medical practitioner.

Preferred compounds of the invention will have favorable pharmacological properties. Such properties include, but are not limited to bioavailability (e.g., oral bioavailibilty, preferably high enough to permit oral administration of doses of less than 2 grams, preferably of less than or equal to one gram), low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lifes. Distribution in the body to sites of complement activity is also desirable, e.g., compounds used to treat CNS disorders will preferably penetrate the blood brain barrier, while low brain levels of compounds used to treat periphereal disorders are typically preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocyctes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

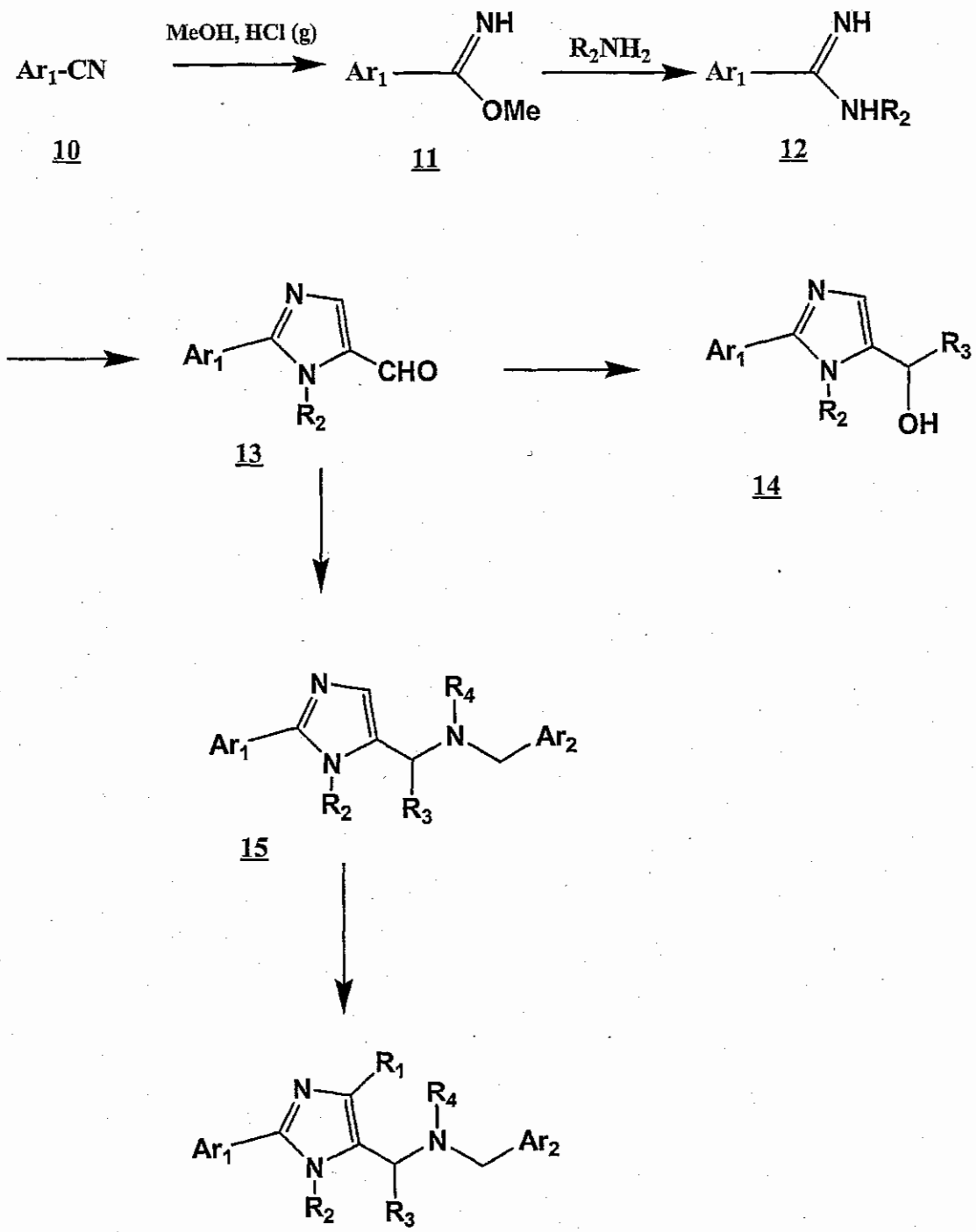
Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

Compound half-life is inversely proportional to the frequency of dosage required for the effective administration of a compound. *In vivo* half-lifes of compounds may be predicted, e.g., from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Preparation of compounds

Representative methods for preparing the compounds of the invention are shown in the following Schemes. Schemes 1 and 2 show the preparation of arylimidazole compounds. Scheme 1 illustrates the preparation of arylimidazole compounds where R_1 is hydrogen or halogen. Scheme 2 represents of the preparation of aryl imidazole compounds where R_1 is alkyl. Within Schemes 1 and 2 the variables Ar_1, Ar_2, R_1, R_2, R_3 and R_4 ~ are defined as above for Formula I.

Scheme1. Synthesis of 1-Alkyl-2-aryl-5-aminomethylimidazoles



As shown in Scheme **1**, an appropriately substituted arylnitrile **10** is converted to the imidate **11** via treatment with hydrogen chloride gas in methanol followed by subsequent treatment with base to release the free base. Amidine **12** is prepared from **11** by treatment with a primary amine. 2-Arylimidazole-4-carboxaldehyde **13** is prepared from **12** by one of several methods described in the chemical literature,

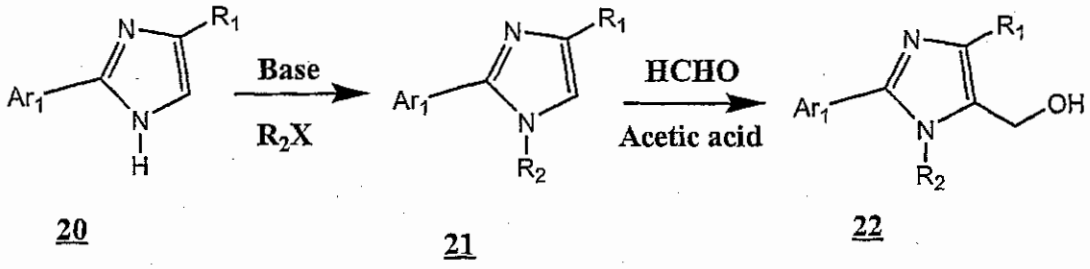
for instance, by treatment with 2-bromo-3-isopropoxyacrolein in the presence of base. See, for example, J. Org, Chem., 62: 8449 (Shilcrat et al., 1997).

Aldehyde **13** can then be transformed into hydroxymethylimidazole **14** either by reduction (for cases where R_4 is hydrogen) or by treatment with the appropriate organometallic (for cases where R_4 is C1-C6 alkyl). The hydroxy group of **14** is converted to either a halogen or sulfonate ester leaving group. Treatment of this intermediate with an appropriate secondary amine in the presence of base provides 2-aryl-4-aminomethylimidazole **15**. Alternatively , the aminoalkyl functionality of **15** may be elaborated by sequential amination-acylation-reduction steps. In situations where R_1 is a halogen, it may be prepared from **15** (R_1=H) by treatment with the molecular halogen, a halosuccinimide or the like.

As shown in Scheme 2, an appropriately substituted 2-aryl-4-substitutedimidazole **20** can be N-alkylated by treatment with base such as sodium hydride and an alkyl halide or alkylsulfonate ester to provide the trisubstituted imidazole **21**. Hydroxymethylation of **21** under the conditions of the Mannich reaction provides hydroxymethylimidazole **22**. In examples where R_3 is alkyl, hydroxymethyl derivative **24** is prepared from **22** by oxidation to aldehyde **23** and subsequent treatment with an appropriate organometallic reagent such as an alkyl lithium or Grignard reagent. Conversion of **22** or **24** to the desired 2-aryl-5-aminomethylimidazoles is carried out by conversion of the hydroxymethyl to a halogen or sulfonate ester leaving group followed by treatment with a secondary amine. Alternatively, the aminoalkyl functionality of the 2-aryl-5-aminomethylimidazole product may be elaborated by sequential amination-acylation-reduction steps.

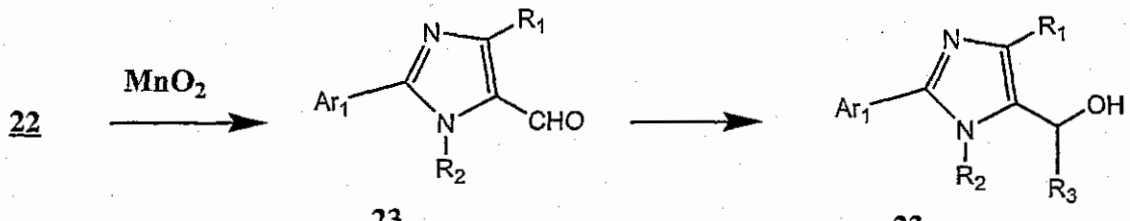
Scheme 2. Synthesis of 2-Arylimidazoles

Where R_2 is alkyl:



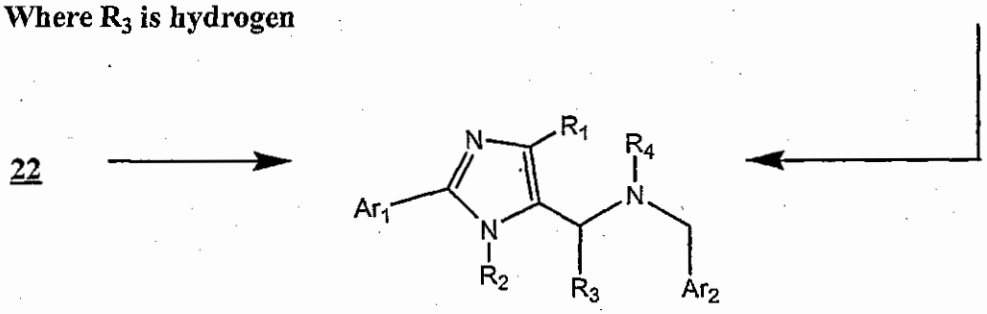
20 21 22

Where R_3 is alkyl:



23 23

Where R_3 is hydrogen

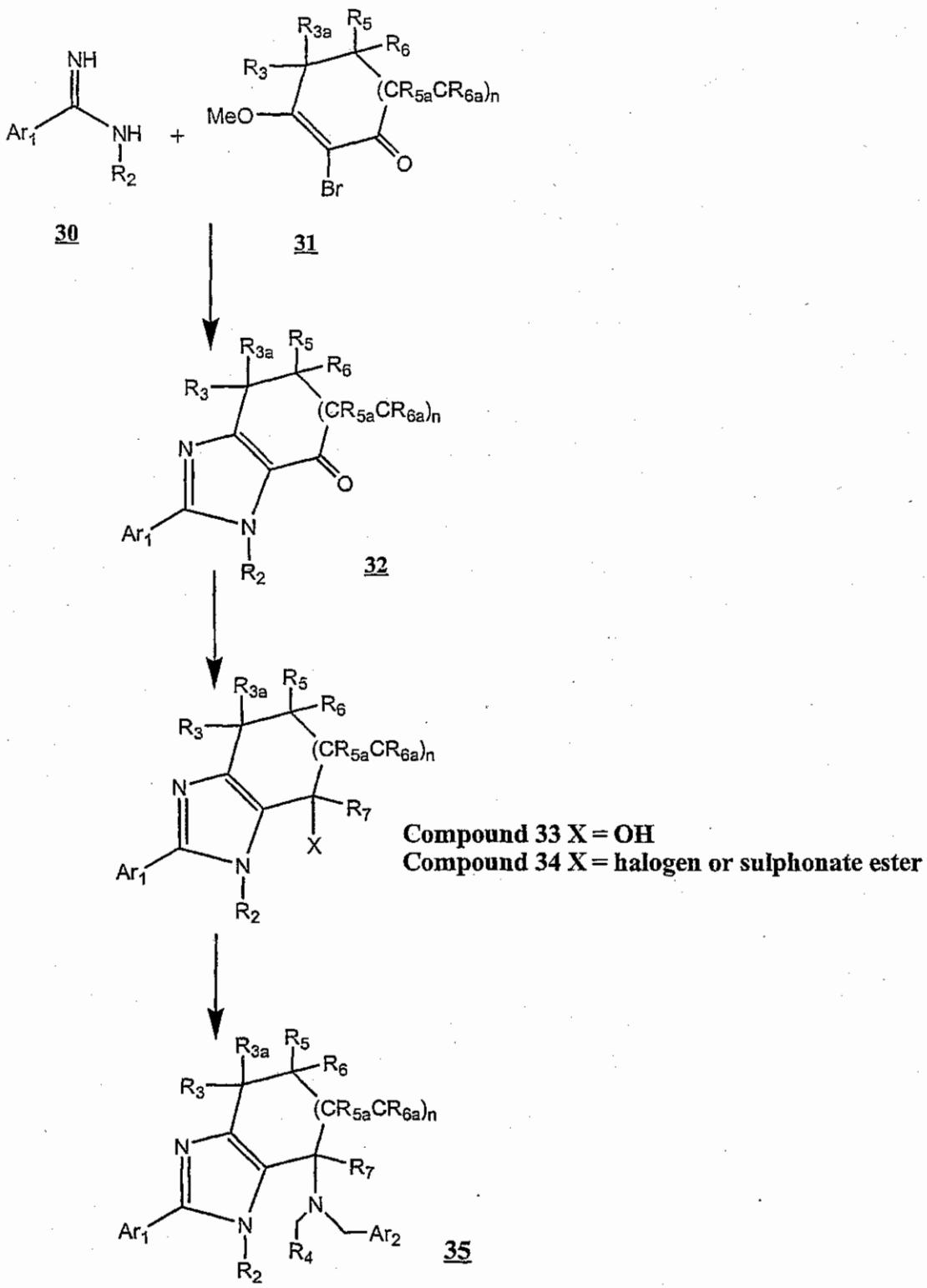


The 2-aryl-4-substitutedimidazole **20** may be prepared by methods described in the chemical literature, for instance, via condensation of an arylamidine with a halomethyl or hydroxymethyl ketone.

Cycloalkylimidazoles

An illustration of the preparation of compounds of the Cycloalkylimidazole compounds of the present invention is given in Scheme 3. Within Scheme 3 the variables n, Ar_1, Ar_2, R_2, R_3, R_{3a}, R_4, R_5, R_6, R_{5a}, R_{6a}, R_7 and X are defined previously.

Scheme 3. Preparation of Cycloalkylimidazoles



As shown in Scheme **3**, an appropriately substituted arylamidine **30** is condensed with an appropriately substituted 2-halo-3-alkoxyenone **31** to provide a 2-aryl-4,5-

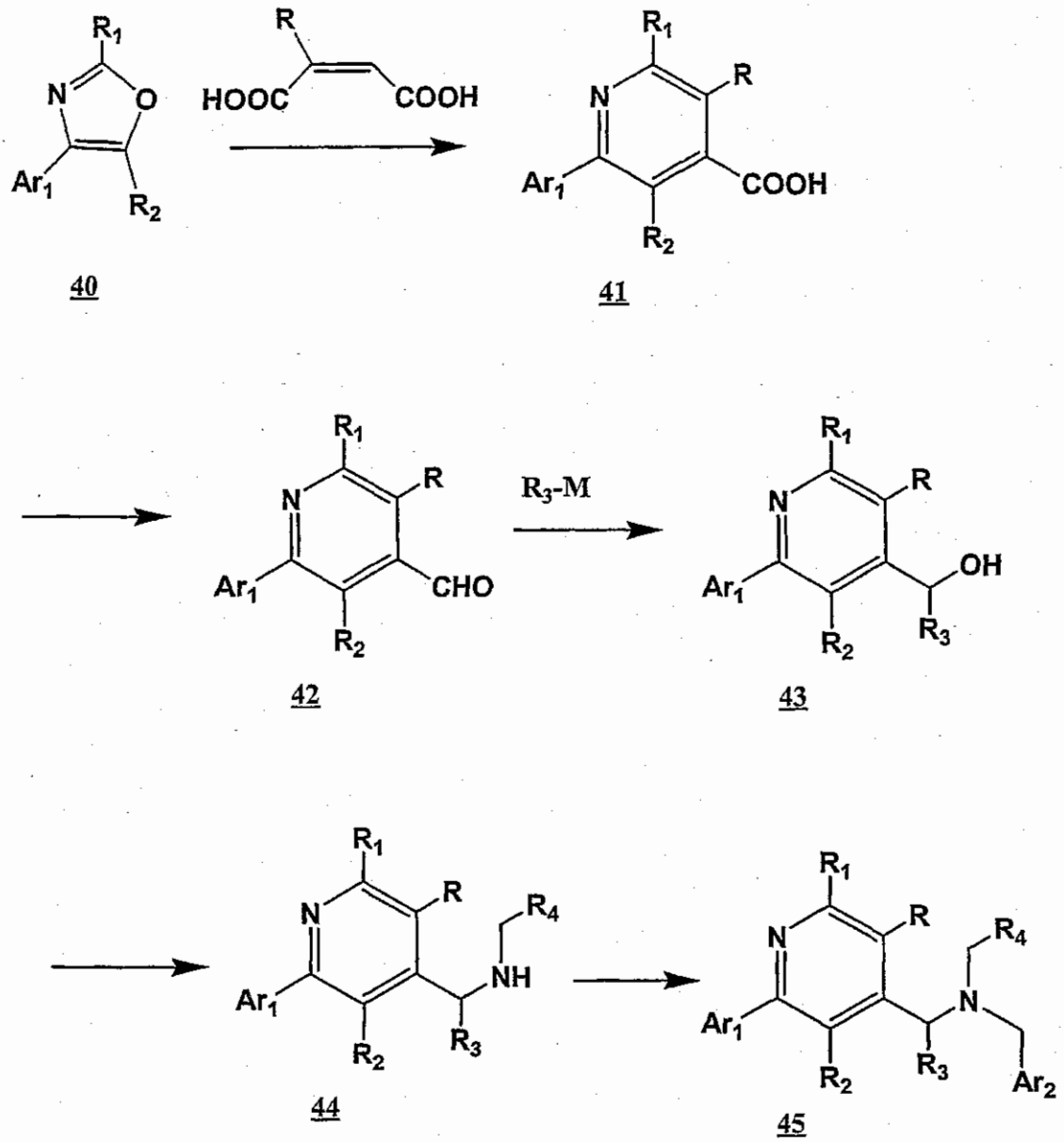
cycloalkylimidazole **32**. The ketone functionality of **32** can be either reduced (R_7 = H) or treated with an appropriate organometallic (for cases where R_7 is alkyl) to give the cyclic alcohol **33**. Compounds of general formula **34** can be prepared from **33** by one of several methods described in the chemical literature, for instance, by treatment with thionyl chloride or by treatment with an alkyl or arylsulphonyl chloride in the presence of base.

Compounds of formula **34** can then be transformed into compounds of general Formula **35** by direct treatment with the appropriate secondary amine. Alternatively, the X functionality of **34** may be transformed into a tertiary amine in a stepwise manner. In this case, **34** would be treated with a primary amine to provide an intermediate secondary amine. This, in turn, could be alkylated to give cycloalkylimidazole compounds of the invention.

Pyridines

An illustration of the preparation of pyridine compounds of the present invention is given in Scheme 4. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. Within Scheme 4 the variables Ar_1, Ar_2, R, R_1, R_2, R_3, and R_4 are defined as previously described.

Scheme 4. Preparation of Aryl pyridines



40 41 42 43 44 45

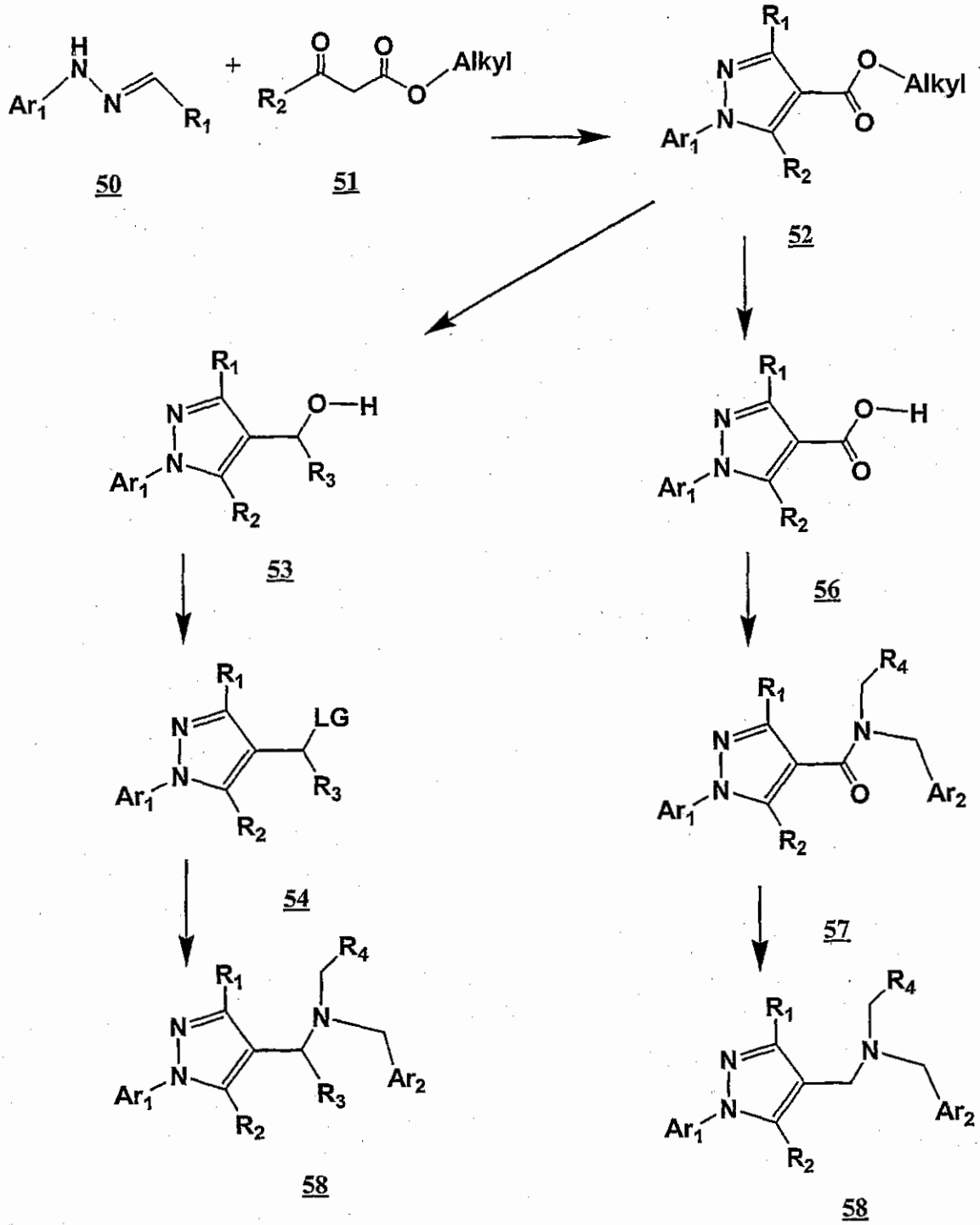
As shown in Scheme **4**, an appropriately substituted 4-phenyloxazole **40** is condensed with an appropriately substituted maleic acid to provide a 2-phenylisonicotinic acid **41**. The carboxylic acid functionality of **41** can be reduced directly to the primary alcohol (**43**, R_3 = H) or converted by methods known to the art to an intermediate aldehyde **42** and subsequently treated with the appropriate organometallic (for cases where R_3 is alkyl) to give a secondary alcohol **43**. Compounds of general formula **44** can be prepared from **43** by one of several

methods described in the chemical literature, for instance, by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a primary amine. Compounds of formula **44** can then be transformed into compounds of formula **45** by direct treatment with the appropriate alkylating agent or, alternatively, by reductive alkylation. Alternatively, the tertiary amine functionality of formula **45** may be realized directly from compounds of formula **43** by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a secondary amine.

Pyrazoles

An illustration of the preparation of arylpyrazole compounds of the present invention is given in Scheme 5. Within Scheme 5 the variables Ar_1, Ar_2, R_1, R_2, R_3, and R_4 are defined as previously described.

Scheme 5. Preparation of Arylpyrazoles

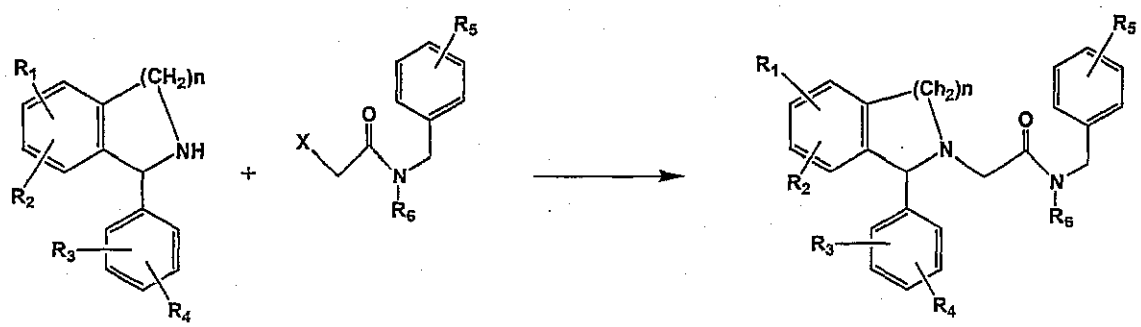


As shown in Scheme **5**, an appropriately substituted phenylhydrazine adduct **50** is condensed with an appropriately substituted α-ketoester **51**, in the presence of a Lewis acid, preferably $ZnCl_2$, with heating at 50 – 200 °C, preferably at 125 °C to provide a 1-phenylpyrazole ester **52**. The carboxylic acid functionality of **52** can be reduced directly to the primary alcohol (**53**, R_3 = H) or converted by methods known

to the art to an intermediate aldehyde and subsequently treated with the appropriate the appropriate organometallic (for cases where R_3 is alkyl) to give a secondary alcohol **53**. Compounds of general formula **54**, where LG represents a leaving group, can be prepared from **53** by one of several methods described in the chemical literature, for instance, by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a primary amine. Compounds of formula **54** can then be transformed into compounds of formula **58** by sequential treatment with the appropriate primary amine followed by direct alkylation or reductive alkylation of the intermediate secondary amine. Alternatively, the tertiary amine functionality of formula **58** may be realized directly from compounds of formula **53** by initial treatment with thionyl chloride or with an alkyl or arylsulphonyl chloride in the presence of base, followed by subsequent condensation with a secondary amine.

An alternative route to the preparation of compounds of Formula **58** from the 1-phenylpyrazole ester **52** may be realized by hydrolysis of **52** to a carboxylic acid of general structure **56**, followed by amide formation to provide **57** and, finally, reduction of the amide functionality to the tertiary amine of **58** (R_3=H).

Scheme 6. Preparation of 2-(1-aryl-1,2,3,4-tetrahydroiso quinolin-2-yl) acetamides and bicyclics of other ring sizes (n=0, 1, 2, 3, etc)



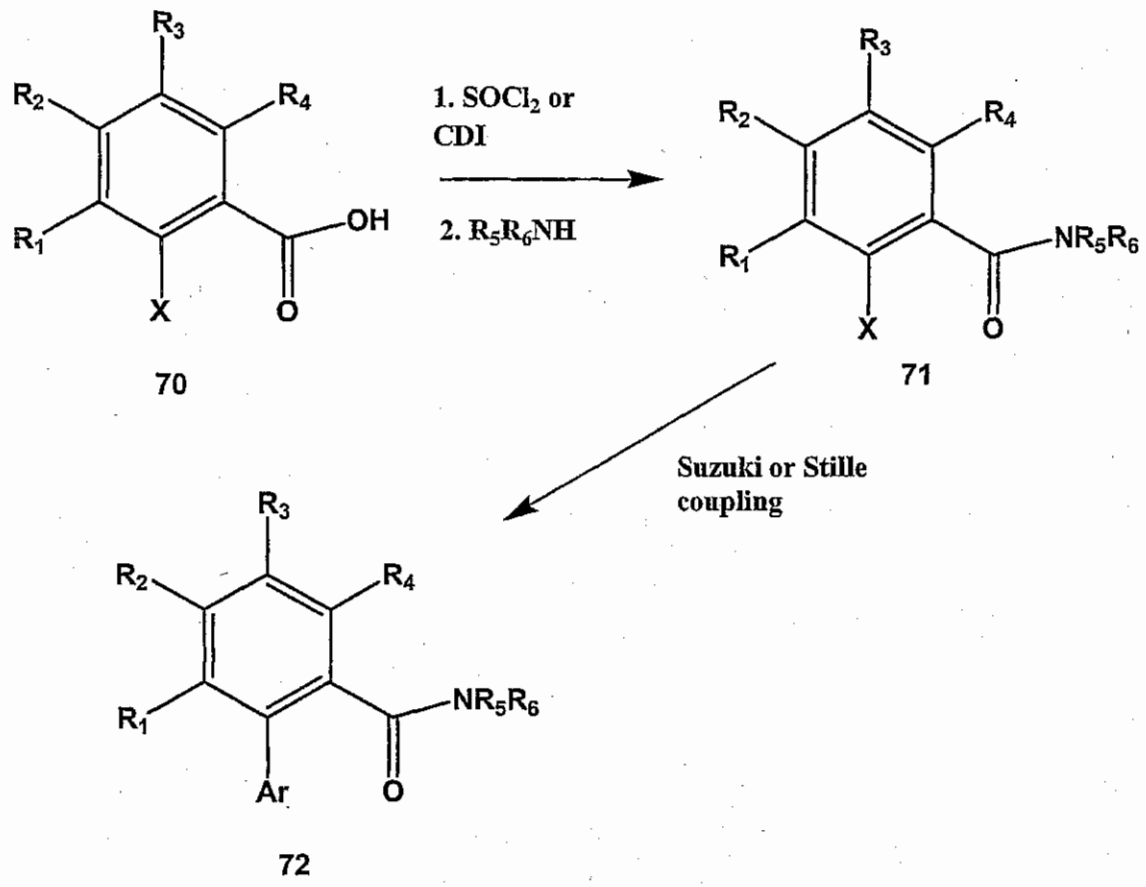
60 61 62

The 2-(1,2,3,4-tetrahydroisoquinolin-2-yl) acetamides of general formula **62** of the present invention may be prepared according to the procedure described

graphically in Scheme 6, wherein a compound of general Formula **60**, prepared according to literature procedures, (for example: Scully, Frank E., Jr.; Schlager, John J. Synthesis of dihydroisoquinolines and 1-substituted tetrahydroisoquinolines. Heterocycles (1982), 19(4), 653-6 or Shinohara, Tatsumi; Takeda, Akira; Toda, Jun; Terasawa, Noriyo; Sano, Takehiro. A highly efficient synthesis of 1-methyl-, 1-benzyl-, and 1-phenyl-1,2,3,4-tetrahydroisoquinolines by a modified Pummerer reaction. Heterocycles (1997), 46: 555-566.) is combined (in an appropiate solvent in the presence of an organic or inorganic base) with an appropriately substituted acetamide derivative possessing a leaving group X at its 2 position. For example, X may be halogen, alkyl or aryl sulfonate, or polyfluoroalkylsulfonate. Acetamides of general Formula **61** may be prepared via condensation of the appropriate secondary amine with a 2-haloacetylhalide (such as 2-chloroacaetyl chloride) in the presence of base. Alternatively acetamides of general formula **61** can be prepared by condensation of the appropriate secondary amine with either a 2-(alkylsulfonylester)acetic acid or 2-(arylsulfonylester)acetic acid in the pressence of an coupling agent such as CDI or the like.

Within Scheme 6, R_1, R_2, R_3, R_4 and R_5 may be the same or different and are chosen from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, trifluoromethyl, trifluoromethoxyl, cyano, nitro, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or dialkylaminocarbonyl, sulfonamido, mono or dialkylsulfonamido, amino, mono- or di-alkylamino, aceto, acetoxy or 3,4-methylenedioxy or ethylenedioxy. The term n refers to an integer from 1 to 3. R_6 may be C_1-C_9 straight or branched chain alkyl, benzyl (substituted or unsubstituted), phenylethyl (substituted or unsubstituted), phenylpropyl (substituted or unsubstituted), or may be cycloalkyl fused with an aromatic group such as 1,2,3,4-tetrahydronaphthyl, 1- or 2- indanyl or suberanyl.

Scheme 7. Preparation of Ortho Biarylamides



70 71 72

The preparation of the ortho biarylamides of the present invention may be carried out via a series of chemical transformations similar to those displayed graphically in Scheme 7. An individual skilled in the art may find modifications of one or several of the synthetic steps described herein without diverting significantly from the overall synthetic scheme.

Thus, as shown, the synthetic route begins with a benzoic acid of general structure 70 possessing a group X at the ortho position. This X group may be iodine, bromine, chlorine, sulfonate ester or polyfluoroalkylsulfonate ester. The benzoic acid may also be substituted by up to four independently chosen substitutents represented by the variables R_1-R_4. Examples of suitable substituents include hydrogen, chlorine, fluorine, cyano, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, trifluoromethyl, trifluoromethoxy, nitro, amino, mono or dialkyl amino, sulfonamido, mono or dialkylsulfonamido, alkylthio e.g. methylthio, alkylsulfoxide, alkylsulfone, acetyl, acetoxy, alkoxycarbonyl

(COOAlkyl) or dialkylaminocarbonyl (CON[alkyl]$_2$). Additionally, two adjacent groups (i.e R_1 and R_2, or R_2 and R_3 or R_3 and R_4) may be taken together with a chain of from 3 to 5 methylene carbons to form a alkyl ring of from five to seven carbons fused to the benzoic acid moiety. Additionally, two adjacent groups (i.e R_1 and R_2, or R_2 and R_3 or R_3 and R_4) may be taken together with an alkyloxy chain, for example OCH_2O or OCH_2CH_2O to form an oxygen-containing moiety (in this example methylenedioxy or ethylenedioxy, respectively) fused to the benzoic acid.

This benzoic acid is then activated by conversion to an acid chloride with thionyl chloride, oxalyl chloride or the like. Alternatively, it may be activated by treatment with carbonyldiimidazole or a similar agent. The activated benzoic acid is then treated with an appropriate secondary amine in the presence of base to provide a tertiary amide of general structure 71.

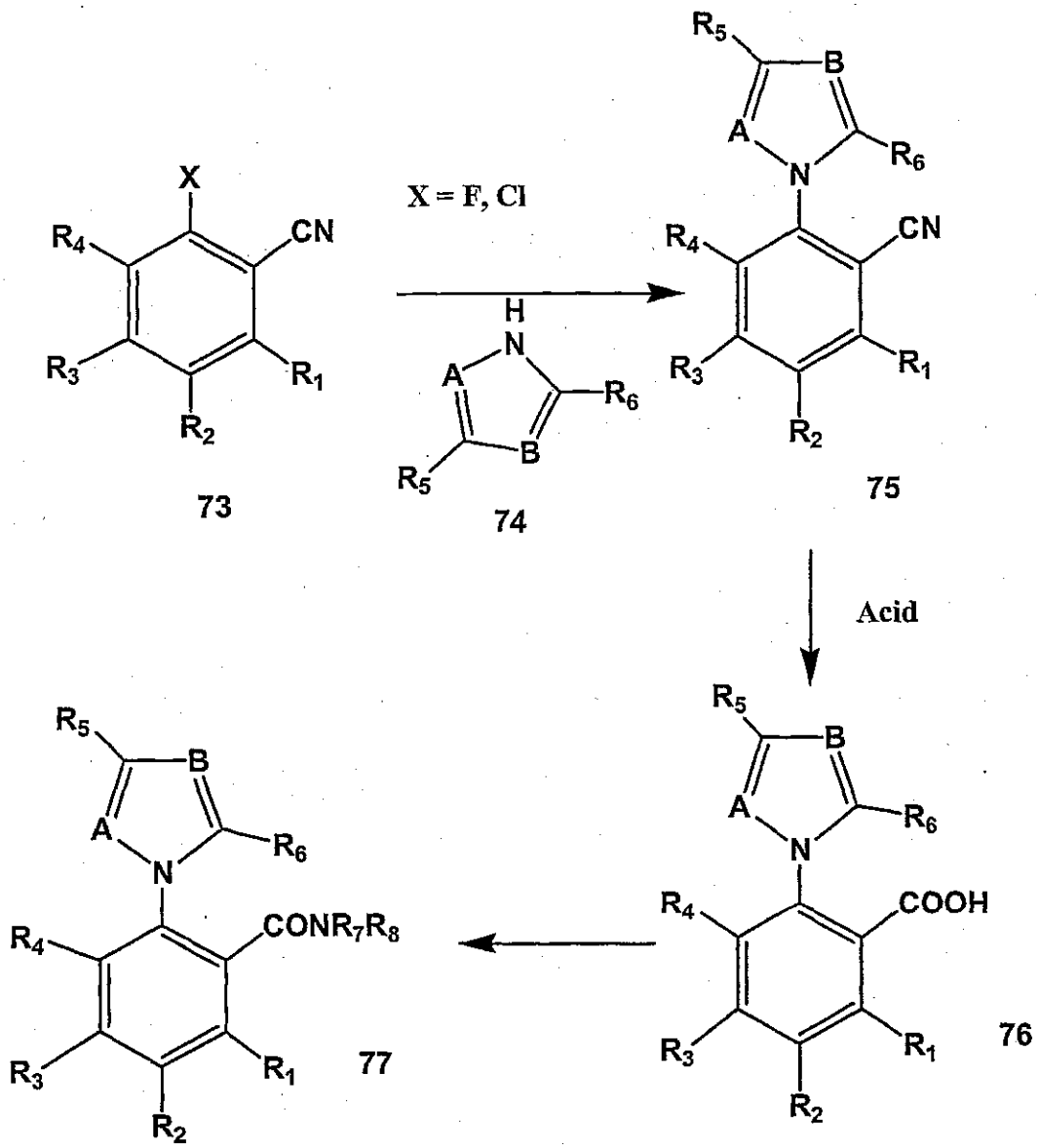
Amide 71 is then converted to the biaryl structure 72 through the use of aryl coupling reactions know in the chemical literature. Examples of such reactions are the Stille reaction where an aryl trialkyltin reagent is coupled to an appropriate aryl in the presence of a catalyst such as palladium or nickel; or a Suzuki reaction where a arylboronic acid is coupled to an appropriate aryl in the presence of a nickel or palladium catalyst in the presence of base.

The group "Ar" of General structure 72 may be a phenyl which may be substituted with up to five additional independently chosen substitutents, e.g. hydrogen, halogen, cyano, C_1-C_6 straight or branched chain alkyl, C1-C6 straight or branched chain alkoxy, trifluoromethyl, trifluoromethoxy, nitro, amino, mono or dialkyl amino, sulfonamido, mono or dialkylsulfonamido, alkylthio e.g. methylthio, alkylsulfoxide, alkylsulfone, acetyl, acetoxy, hydroxycarbonyl (COOH), alkoxycarbonyl (COOAlkyl), aminocarbonyl ($CONH_2$), monoalkylaminocarbonyl, dialkylaminocarbonyl (CON[alkyl]$_2$, methylenedioxy or ethylenedioxy.

The Ar of General Structure 72 may also represent a heteroaryl group such as 1- or 2- thienyl or 1- or 2- furanyl. Such a heteroaryl group which may be additionally substituted by up to three independently chosen substituents, such as hydrogen, halogen, cyano, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or

branched chain alkoxy, trifluoromethyl, trifluoromethoxy, dialkyl amino, sulfonamido, mono or dialkylsulfonamido, alkylthio e.g. methylthio, alkylsulfoxide, alkylsulfone, acetyl, acetoxy, hydroxycarbonyl (COOH), alkoxycarbonyl (COOAlkyl), aminocarbonyl ($CONH_2$), monoalkylcarbonyl, dialkylaminocarbonyl ($CON[alkyl]_2$.

Scheme 8. General Preparation of Azaaryl benzamides



The preparation of 2-imidazolyl, 2-pyrrazolyl and 2-(1,2,4)-triazolyl benzamides begins with an appropriately substituted benzonitrile derivative having a leaving group X at the position ortho to the carboxylic acid functionality. Most

commonly this group would be a fluorine or chlorine group. This benzonitrile may be optionally substituted or additionally substituted by up to four substituents (R_1-R_4) which may be the same or different (examples of such substituents are: hydrogen, halogen, cyano, C_1-C_6 straight or branched chain alkyl, C_1-C_6 straight or branched chain alkoxy, trifluoromethyl, trifluoromethoxy, nitro, amino, mono or dialkyl amino, sulfonamido, mono or dialkylsulfonamido, methylthio, alkylsulfoxide, alkylsulfone, acetyl, acetoxy, alkoxycarbonyl (COOAlkyl) or dialkylaminocarbonyl (CON[alkyl]$_2$).

The benzonitrile **73** is mixed with the azaheterocycle **74** (wherein A and B may be either nitrogen or carbon with the caveat that both A and B not be carbon. R_5 and R_6 may be the same as those groups described for R_1-R_4.) This condensation may be carried out either in a single phase system in an appropriate solvent and base, or in a two-phase manner using a phase transfer catalyst.

2-Azaheterocyclicbenzonitrile **75** is the hydrolyzed to the corresponding benzoic acid **76** via means common to the chemical literature, for instance mineral acid.

The benzoic acid **76** is then activated via thionyl chloride, CDI or other means known to the chemical literature and condensed with an appropriately substituted secondary amine toprovide the desired final products **77**.

EXAMPLES

The general methods given in Schemes 1 to 8 above for the preparation of compounds of the present invention are further illustrated by the following examples. Specifically, the methods given in Schemes 1 and 2 for the preparation of aryl imidazoles are illustrated by Examples 1-4, shown below. An example of the method shown in Scheme 3 for the preparation of cycloalkylimidazoles is given in example 5, and example of the method shown in Scheme 4 for the preparation of arylpyridines is given in example 6, and an example of the method shown in Scheme 5 for the preparation of arylpyrazoles is given in example 7. The method shown by Scheme 6 for the preparations of 2-(1-Aryl-1,2,3,4-tetrahydroisoquinolin-2-yl)acetamides is further illustrated in example 8. The methods shown in Schemes 7

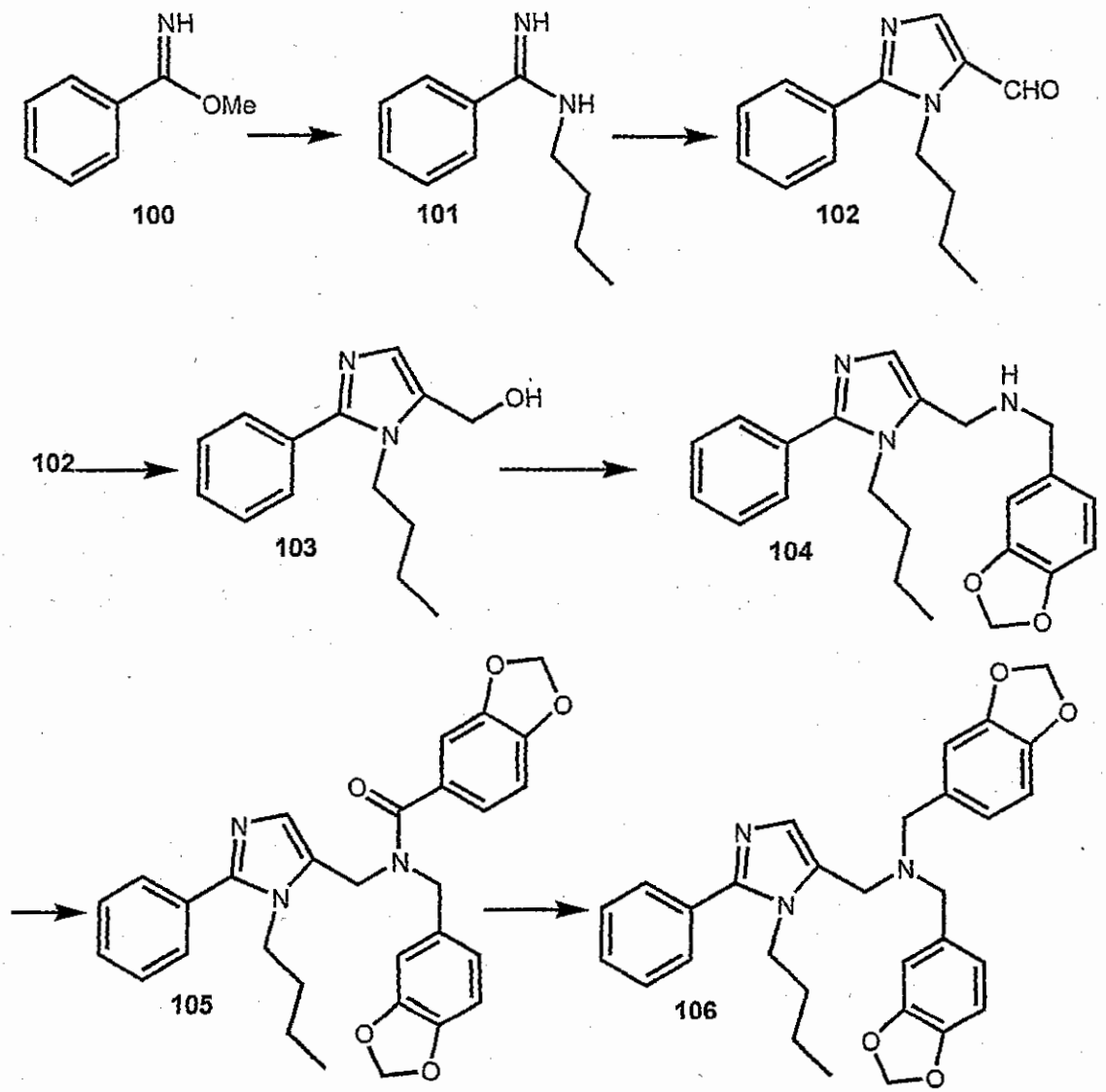
and 8 for the preparation of ortho biarylamides and azaarylamides, respectively, are exemplified in Examples 9 and 10. Unless otherwise specified all starting materials and reagents are of standard commercial grade, and are used without further purification, or are readily prepared from such materials by routine methods. Those skilled in the art of organic synthesis will recognize that starting materials and reaction conditions may be varied to achieve the desired end product.

Example 1. Preparation of an arylimidazole compound: 1-(1-butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenyl methyl])aminomethylimidazole (Compound 106).

N-(n-butyl)-benzamidine (**101**). To a solution of methyl benzimidate hydrochloride (12 g, 0.07 mole) in dimethylformamide (DMF, 20 mL) is added 7 ml of triethylamine at 0 °C. After 2 h the reaction is filtered to remove triethylamine hydrochloride. To the filtrate is added 3.68 g of 1-butylamine and the mixture is heated to 60 °C for 6 h. After cooling the mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate and concentrated to provide 13.28 g of the amidine as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.4 (m, 3H), 3.37 (bm, 2H), 1.62 (m, 2H), 1.42 (m, 2H), 0.95 (t, J = 7 Hz, 3H).

1-(1-Butyl)-2-phenylimidazole-5-carboxaldehyde (**102**). To a solution of **101** (13.28 g) and 2-bromo-3-isopropoxyacrolein (22 g) in chloroform (150 ml) is added potassium carbonate (15.5 g) and water (19 ml). The mixture is stirred at room temperature overnight. The aqueous layer is discarded and the organic layer is washed with water (3X 100 mL), dried (Na_2SO_4) and concentrated. The residue is purified via flash chromatography (5% MeOH/$CHCl_3$) to provide the desired imidazole carboxaldehyde as a pale yellow oil (21.55 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.90 (s, 1H), 7.55 (m, 2H), 7.45 (m, 3H), 4.38 (t, J = 8Hz, 2H), 1.75 (m, 2H), 1.22 (m, 2H), 0.91 (t, J = 7 Hz, 3H).

Representative preparation of a 1-Alkyl-2-aryl-4-aminomethylimidazole: 1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylendioxyphenylmethyl]) aminomethylimidazole)



1-(1-Butyl)-2-phenyl-5-hydroxymethylimidazole (103). Aldehyde **102** is dissolved in methanol (150 mL). Sodium borohydride (3 g) is added in portions. After the addition was complete, the reaction is diluted with water and concentrated. The residue is dissolved in ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated. The product is purified by flash chromatography on silica gel (5% MeOH/$CHCl_3$) to give 4.17 g of **103** as a cream colored solid. ^{1}H-NMR (400 MHz,

$CDCl_3$): δ 0.79 (3H, t, d=7.4), 1.18 (2H, m, d=7.4), 1.60 (2H, m, d=7.6), 4.03 (2H, dd, d=7.6), 4.56 (2H, s), 6.84 (1H, s), 7.39-7.50 (3H, m),7.50-7.53 (2H, m).

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl])aminomethylimidazole (**104**). Hydroxymethylimidazole **103** (0.82 g) is dissolved in chloroform (10 ml) and treated with thionyl chloride (1 ml). The solution is heated to 50 °C for 30 min, cooled and evaporated. The residue is washed with benzene and evaporated to give the intermediate chloromethyl hydrochloride as a white powder which is taken up in acetonitrile (30 mL). This is added dropwise to a solution of piperonylamine (5 ml) in acetonitrile (10 mL). The reaction is allowed to stand overnight and then evaporated. The residue is taken up in ethyl acetate and washed with water. The organic layer is dried (Na_2SO_4) and concentrated. Purification on silica gel (10% MeOH/$CHCl_3$) provides the product as a pale yellow oil (0.91 g). ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (3H, t, d=7.4), 1.18 (2H, m, d=7.4), 1.56 (2H, m, d=7.4), 3.75 (4H, s), 4.04 (2H, dd, d=8), 5.92 (2H, s), 6.76 (2H, m), 6.84 (1H,s), 6.97 (1H, s), 7.38-7.44 (3H, m), 7.53-7.56 (2H, m).

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl methyl]-N-(3,4-methylenedioxyphenylcarboxyl) aminomethylimidazole (**105**). Compound **104** (160 mg, 0.44 mmol) is dissolved in chloroform (5 ml, pentene stabilized) and treated sequentially with piperonyloyl chloride (100 mg) and triethylamine (1 ml). The mixture is stirred at room temperature overnight. The solution is concentrated and the residue taken up in ethyl acetate. The organic is washed with water, dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (5% MeOH/$CHCl_3$) provides compound **105** as a pale yellow oil (240 mg). ^1H-NMR (400 MHz, $CDCl_3$): δ 0.75 (3H, br), 1.16 (2H, br), 1.49 (2H, br), 4.01 (2H, br), 4.54 (2H, br), 4.68 (2H, br), 5.97 (2H, s), 5.99 (2H, s), 6.66 (2H, d, d=7.2), 6.80 (2H, t, d=8), 6.98-7.02 (2H, m), 7.40-7.47 (3H, m), 7.56 (2H, d, d=6.8).

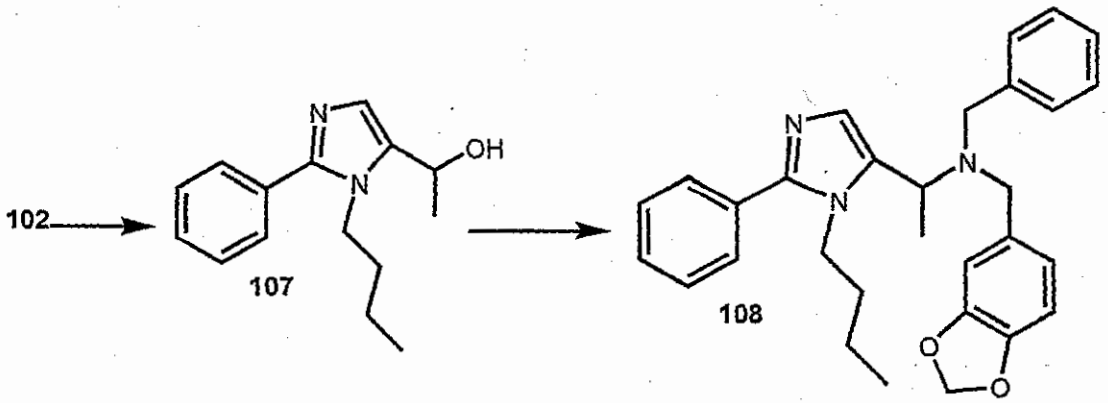
1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxy phenylmethyl])-aminomethylimidazole (**106**). Amide **105** (215 mg) in tetrahydrofuran (THF, 3 ml) is added dropwise to a solution of alane (1 M in THF, 2 ml) and the resulting solution

is stirred for 2.5 h at room temperature. A solution of sodium hydroxide (15% NaOH, 1 ml) is added and the mixture is extracted with chloroform. The organic extracts are dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provided compound **106** as a colorless oil (115 mg). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.70 (3H, t, d=7.6), 0.98 (2H, m, d=7.6), 1.30 (2H, m), 3.44 (4H, s), 3.52 (2H, s), 3.98 (2H, dd, d=8), 5.92 (4H, s), 6.74 (4H, s), 6.69 (2H, s), 7.02 (1H, s), 7.36-7.42 (3H, m), 7.54 (2H, dd, d=1.4, 6.6). The hydrochloride salt (m.p. 187-190 °C) was prepared in isopropanol.

Example 2. Preparation of 1-(1-butyl)-2-phenyl-5-(1-[N-(3,4-methylenedioxyphenylmethyl)-N-phenylmethyl]amino)ethylimidazole (Compound **108**).

1-Butyl-2-phenyl-5-(1-hydroxyethyl)imidazole (107). A solution of aldehyde **102** (230 mg) in diethyl ether (30 mL) is placed in a separatory funnel and treated with a solution of

Preparation of 1-(1-Butyl)-2-phenyl-5-(1-[N-[{3,4-methylendioxyphenylmethyl]}-N-[phenylmethyl]aminoethylimidazole)



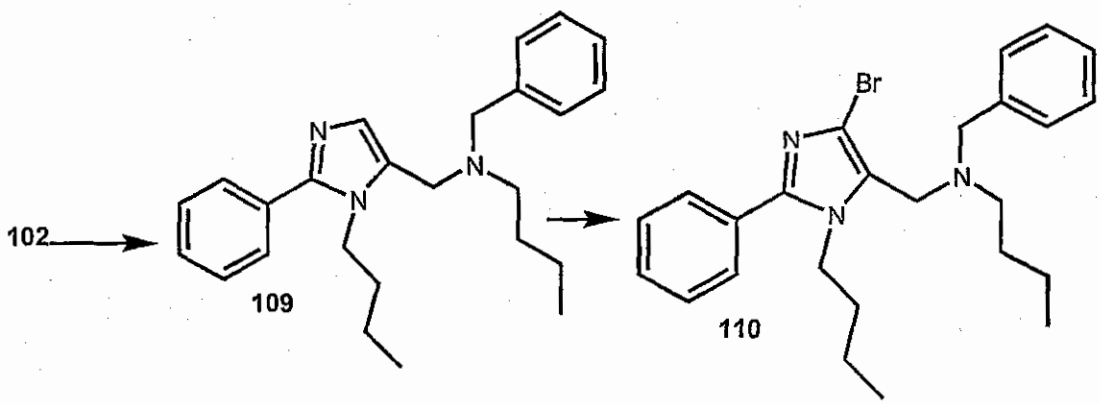
methyl lithium (1.4 M in THF, 1.5 ml). After 10 min, the solution is washed with ammonium chloride solution (1 M, 20 ml), dried (Na_2SO_4) and concentrated. The resulting dark oil is purified by preparative TLC (10% MeOH/$CHCl_3$) to provide compound **107** as a colorless oil (180 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 2

Hz, 2H), 7.4 (m, 3H), 7.01 (s, 1H), 4.86 (q, J = 7 Hz, 1H), 4.18 (m, 1H), 4.0 (m, 1H), 1.63 (d, J = 6.6 Hz, 3H), 1.63 (m, 2H), 1.23 (m, 2H), 0.81 (t, J = 7 Hz, 3H).

1-Butyl-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]-N-phenylmethyl)aminoethylimidazole (**108**). A solution of compound 107 (80 mg) in chloroform (10 ml) is treated with thionyl chloride (1 ml) and heated to 50 °C for 30 min. The solution is then concentrated, diluted with chloroform and reconcentrated to provide the intermediate chloromethyl hydrochloride as an oil. This material is taken up in chloroform (5 ml) and treated sequentially with N-benzylpiperonylamine (80 mg) and triethylamine. After stirring overnight, the reaction is washed with saturated potassium carbonate solution, dried (Na_2SO_4) and concentrated. Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provides compound **108** as a colorless oil (62 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.43 (m, 1H), 7.2-7.3 (m, 9H), 6.74-6.86 (m, 4H), 5.94 (s, 2H), 4.82 (q, J = 6.8 Hz, 1H), 4.33 (m, 2H), 3.78 (s, 2H), 3.53 (s, 2H), 1.83 (d, J = 6.8 Hz, 3H), 1.62-1.68 (m, 2H), 1.21 (q, J = 7.8 Hz, 2H), 0.82 (t, J = 7.8 Hz, 3H).

Example 3. Preparation of 1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])amino-methylimidazole (Compound **110**).

Preparation of 1-(1-Butyl)-2-phenyl-4-bromo-5-[N-phenylmethyl-N-[1-butyl]) aminomethylimidazole)



1-Butyl-2-phenyl-5-(N-benzyl-N-butyl)aminomethylimidazole (**109**). A solution of compound **102** (115 mg) and N-butylbenzylamine (85 mg) in toluene (10 ml) is allowed to stand overnight. Treatment of the reaction with sodium borohydride (100 mg) and ethanol (2 mL) followed by aqueous workup and purification on silica gel (10% MeOH/$CHCl_3$) provides compound **109** as a colorless oil (35 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.2-7.5 (m, 10H), 6.98 (s, 1H), 4.0 (t, J = 8 Hz, 2H), 3.55 (s, 2H), 3.52 (s, 2H), 2.42 (t, J = 8 Hz, 2H), 1.2-1.55 (m, 6 H), 1.05 (m, 2H), 0.84 (t, J = 7 Hz, 3H), 0.72 (t, J = 7 Hz, 3H).

1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole (**110**). To a solution of **109** (30 mg) in acetonitrile (4 mL) was added N-bromosuccinimide (16 mg). The resulting mixture was heated to 60 °C and the progress of the reaction followed by TLC. The cooled reaction mixture was diluted with ethyl acetate and washed twice with water. Purification by preparative thin layer chromatography (10% MeOH/$CHCl_3$) provided compound **110** as a colorless oil (22 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.2-7.5 (m, 10 H), 3.98 (t, J = 8 Hz, 2H), 3.55 (s, 2H), 3.53 (s, 2H), 2.46 (t, J = 7 Hz, 2H), 1.52 (m, 2H), 1.3 (m, 4H), 0.98 (q, J = 7 Hz, 2H), 0.84 (t, J = 7 Hz, 3H), 0.70 (t, J = 7 Hz, 3H).

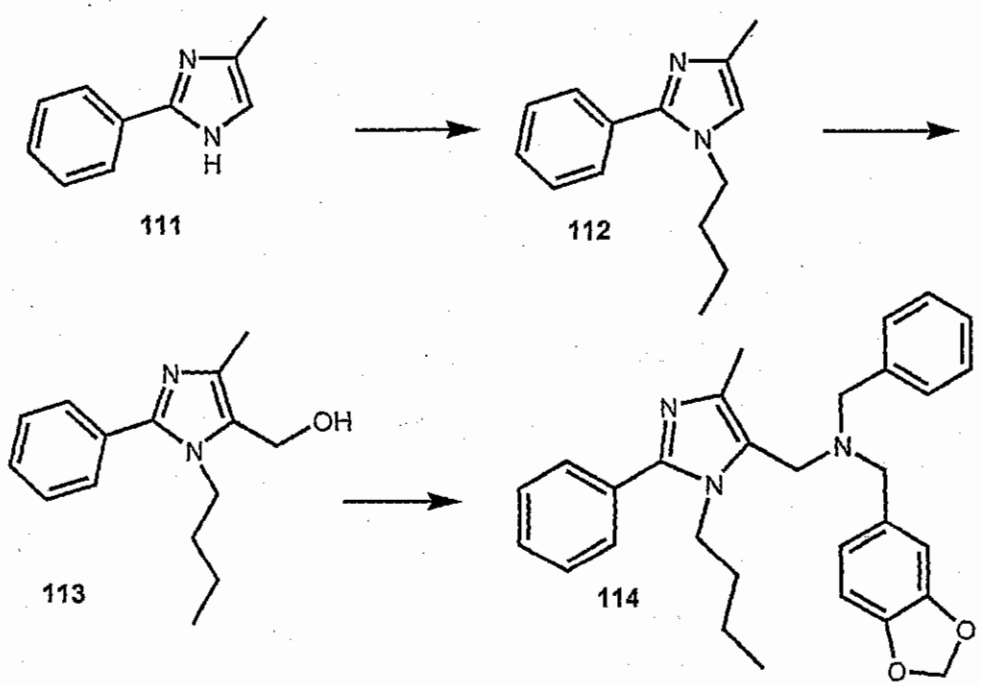
Example 4. Preparation of 1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl-methyl]-N-phenylmethyl)aminomethylimidazole. (Compound 114).

1-Butyl-2-phenyl-4-methylimidazole (**112**). To a solution of 4-methyl-2-phenylimidazole (**111**, 15.8 g) in dimethylformamide (100 ml) is added sodium hydride (4.4 g, 60% in mineral oil) in small portions. After the addition is complete, the mixture was stirred for an additional 20 min and treated with 1-iodobutane (18.8 g). The reaction is fitted with a reflux condensor and heated at 100 °C for 12 h. The cooled reaction mixture is partitioned between water (300 ml) and diethyl ether (300 ml). The organic layer is washed with water (3X 200 ml), dried (Na_2SO_4) and concentrated to provide 20.5 g of N-butylimidazoles. Analysis by ^1H-NMR and GC-MS revealed mixture of 1-butyl-2-phenyl-4-methylimidazole (**112**) and 1-butyl-2-

phenyl-5-methylimidazole in a ratio of 11.5/1. The mixture was carried on to the next step without purification.

1-Butyl-2-phenyl-4-methyl-5-hydroxymethylimidazole (**113**). A solution of **112** (1 g) in acetic acid (10 mL) and 40% aqueous formaldehyde (2 mL) is refluxed for 14 h. The reaction is then concentrated and dried by repeated reconcentration with toluene. The residue is purified by column chromatography (10% MeOH/$CHCl_3$). The fractions are assayed by GC and those fractions uncontaminated by the isomeric hydroxymethylimidazole combined. Concentration of the combined fractions provides compound **113** (320 mg) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.4-7.6 (m, 6H), 4.61 (s, 2H, CH_2OH), 4.02 (t, J = 7 Hz, 2H, NCH_2), 2.22 (s, 3H, Me), 1.63 (m, 2H, 1.25 (m, 2H), 0.81 (t, J = 7 Hz, 3H).

Preparation of 1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl]-N-phenylmethyl) aminomethylimidazole



1-Butyl-2-phenyl-4-methyl-5-(N-benzyl-N-butyl)aminomethylimidazole (114). Compound 114 (23 mg) is prepared from **113** (50 mg) in a method similar to that used to obtain compound **108**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.5-7.55 (m,2H), 7.38-7.42 (m, 3H), 7.23-7.30 (m, 5H), 3.95 (t, J = 7.5 Hz, 2H), 3.55 (s, 2H), 3.53 (s, 2H),

2.40 (t, J = 7 Hz, 2H), 2.22 (s, 3H), 1.25-1.40 (m, 6H), 1.05 (m, 2H), 0.82 (t, J = 7 Hz, 3H). 0.70 (t, J = 7 Hz, 3H); MS (LCMS) *m/e* 390 (M^++1)

Example 5. Preparation of a cycloalkylimidazole compound: 4-{[butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol

N-(n-butyl)-benzamidine (**120**). To a solution of methyl benzimidate hydrochloride (12 g, 0.07 mole) in dimethylformamide (DMF, 20 mL) is added 7 ml of triethylamine at 0 °C. After 2 h the reaction is filtered to remove triethylamine hydrochloride. To the filtrate is added 3.68 g of 1-butylamine and the mixture is heated to 60 °C for 6 h. After cooling the mixture is partitioned between ethyl acetate and water. The organic layer is washed with brine, dried over sodium sulfate and concentrated to provide 13.28 g of the amidine as a yellow oil. ^{1}H NMR ($CDCl_3$) 7.55 (m, 2H), 7.4 (m, 3H), 3.37 (bm, 2H), 1.62 (m, 2H), 1.42 (m, 2H), 0.95 (t, J = 7 Hz, 3H).

2-Bromo-3-methoxycyclopentenone (**131**) is prepared via the method of Curran et al JACS, vol 112, page 5601. To a suspension of 1,3-cyclopentanedione (10 g) in chloroform (700 ml) is added a N-bromosuccinimide (18.2 g). The mixture is refluxed for 2 h, cooled and concentrated. Methanol (700 mL) and p-toluenesulfonic acid (1 g) are added and the solution is refluxed overnight. The mixture is concentrated to 100 ml, diluted with methylene chloride (500 mL) and poured into water. The aqueous layer is discarded and the organic layer is washed with water (3 X 100 mL), dried (Na_2SO_4) and concentrated. The residue is crystallized from ethyl acetate to give **131** as tan crystals (1.67 g).

1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-one (Compound **132**). To a mixture of amidine **130** (3.52 g, 20 mmol) and enone 13 (4.58 g, 24 mmol) in chloroform (40 mL) and water (5 mL) was added solid potassium carbonate (3.32 g, 24 mmol). The resulting mixture is refluxed overnight. After cooling, the mixture is washed with water, dried (Na_2SO_4) and concentrated. Purification on silica gel eluting with 25% ethyl acetate/hexane gives the desired product **132** (3.0 g) LC-MS

(M^++1): 255. ^{1}H-NMR (δ, $CDCl_3$): 0.84 (t, J = 7.6 Hz, 3H), 1.23 (dt, J = 7.0, 7.6 Hz, 2H), 1.81 (m, 2H), 2.95 (m, 4H), 4.13 (t, J = 7.6 Hz, 2H) 7.5-7.45 (m, 3H), 7.76-7.6 (m, 2H) ppm.

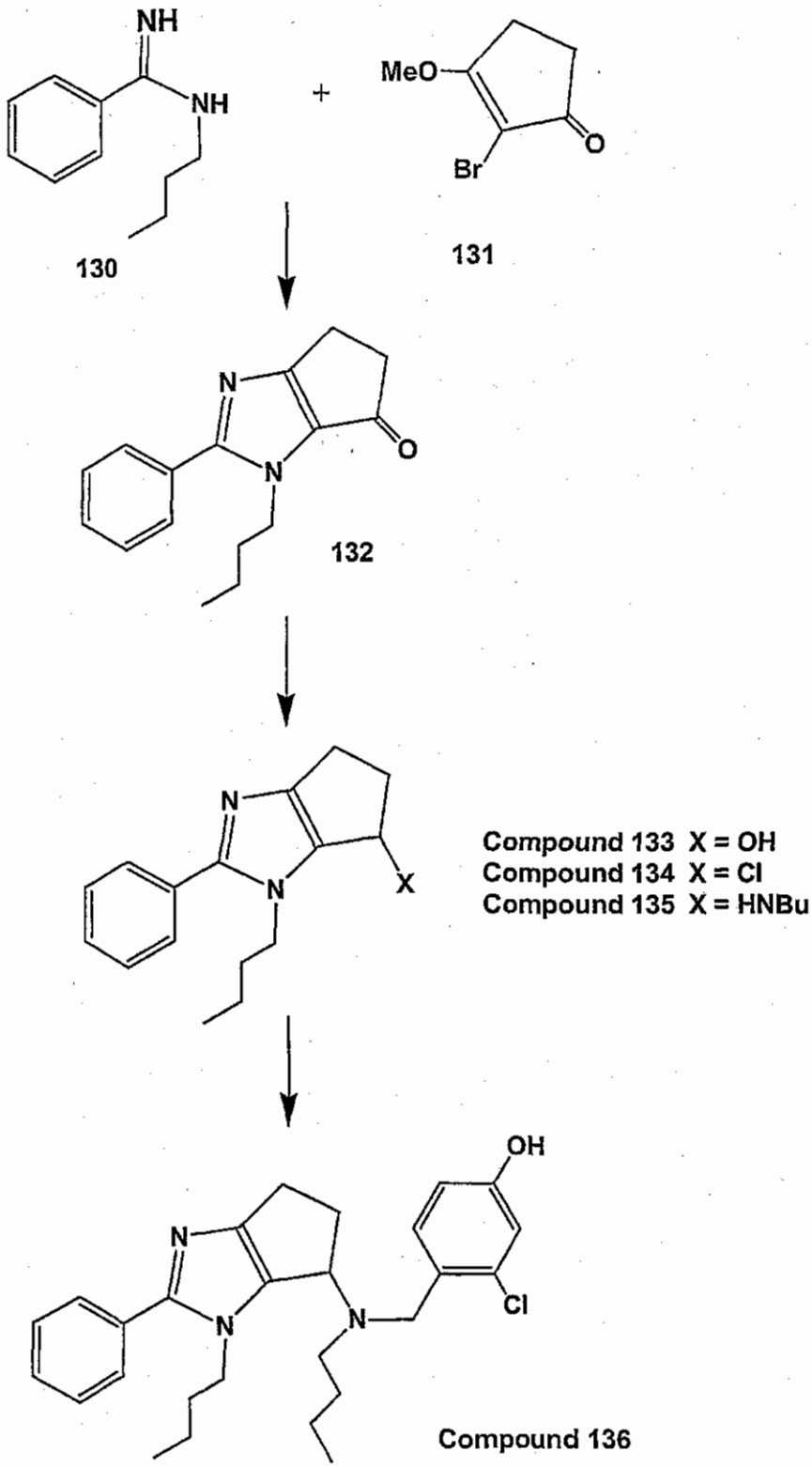
1-Butyl-2-phenyl-4,5-dihydrocyclopenty[1,2-d]imidazol-6-ol (Compound 133). To a solution of **132** (2.68 g) in methanol (20 mL) is added sodium borohydride (1.5 equiv) and the mixture stirred overnight. The mixture is concentrated, diluted with chloroform and washed with 0.5 N NH_4Cl solution. The organic layer is dried (Na_2SO_4) and concentrated to provide the desired product **133**. LC-MS (M + 1) 257.

Butyl(1-butyl-2-phenyl-4,5,6-trihydrocyclopentyl[3,2-d]imidazol-6-yl))amine (Compound **135**). Compound **133** (2 g) is dissolved in chloroform (20 mL) and thionyl chloride (5 mL) and the resulting solution is stirred at room temperature overnight. The solvent and excess thionyl chloride are evaporated and the crude chloride **134** was dissolved in n-butylamine (10 mL). After 2 h, the excess butylamine was evaporated, the residue dissolved in ethyl acetate and the organic solution washed with 5% NaOH solution and water. The organic layer was dried and concentrated. The organic residue is purified by column chromatography on silaica gel eluting with 10% CH_3OH in $CHCl_3$ to provide the desired secondary amine **135** in 82% yield. LC-MS (M+1) 312 ^{1}H-NMR (chemical shift, $CDCl_3$): 0.83 (t, J = 7.2 Hz, 3H), 0.9 (t, J = 7.2 Hz, 3H), 1.23 (q, J = 7.2 Hz, 2H), 1.35 (q, J = 7.2 Hz, 2H), 1.46 (m, 2H), 1.70 (m, 2H), 2.24 (m, 1H), 2.55-2.66 (m, 4H), 2.73-2.80 (m, 2H), 3.97-4.04 (m, 2H), 4.30 (d, J = 5.6 Hz, 1H), 7.37-7.44 (m, 3H), 7.55-7.57 (m, 2H).

4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta[3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol (Compound 5, Table 1). To a solution of compound **135** (50 mg) in 1,2-dichloroethane (2 mL) and 2-chloro-4-hydroxybenzaldehyde (30 mg) is added sodium triacetoxyborohydride (100 mg). The resulting mixture is allowed to stir overnight. After washing with 0.5 ammonium chloride solution, the organic layer is dried (Na_2SO_4) and concentrated. Purification

using preparative thin layer chromatography eluting with 5% $CH_3OH/CHCl_3$ provides the desired product **136** as an oil (21 mg). LC-MS (M+1) 452, (M-1) 450. ^{1}H-NMR (chemical shift, $CDCl_3$): 0.74 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 7.2 Hz, 3H), 1.11 (q, J = 7.2 Hz, 2H), 1.21-1.33 (m, 2H), 1.41-1.51 (m, 4H), 2.34-2.44 (m, 3H), 2.51-2.57 (m, 1H), 2.60-2.67 (m, 1H), 2.69-2.75 (m, 1H), 3.38 (d, J = 7.6 Hz, 1H), 3.47 (d, J = 13.6 Hz, 1H), 3.65 (d, J = 13.6 Hz, 1H), 3.78-3.96 (m, 1H), 6.62 (dd, J = 8,2 Hz, 1H), 6.78 (d, J = 2 Hz, 1H), 7.07 (d, J = 8 Hz, 1H), 7.35-7.41 (m, 3H), 7.45-7.48 (m, 2H).

Preparation of 4-{[Butyl(1-butyl-2-phenyl(4,5,6-trihydrocyclopenta [3,2-d]imidazol-6-yl))amino]methyl}-3-chlorophenol



Example 6. Preparation of 2-phenyl-4-(N,N-di{2H-Benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}amino)methyl-3-butylpyridine

4-Phenyl-5-butyloxazole (140). A mixture of α-bromohexanophenone (25.5 g, 0.1 mole), ammonium formate (22 g, 0.35 mole) and formic acid (110 mL) was refluxed with stirring for 3 h. The reaction mixture was poured onto ice and made basic with 10 N NaOH and extracted with ether. The organic layer was washed with water, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane. To provide the desired compound as an oil (8.3 g, 41 %); ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 7.55 (m, 2H), 7.40 (s, 1H), 7.34 (dd, J = 7,7 Hz, 2H), 7.22 (dd, J = 7, 7 Hz, 1H), 2.74 (m, 2H), 1.6 (m, 2H), 1.30 (m, 2H), 0.84 (t, J = 7 Hz, 3H) ppm.

2-Phenyl-3-butylisonicotinic acid (141). A mixture of 4-phenyl-5-butyloxazole (12, 5 g, 25 mmol) and maleic acid (3.5 g, 30 mmol) is heated at 100 °C for 30 min. After cooling, the semisolid mass is triturated with ether and the solid collected by filtration . ^{1}H NMR (δ, $CDCl_3$, 400 MHz) 11.68 (brs, 1H), 8.72 (d, J = 6.0 Hz, 1H), 7.73 (d, J = 5.6 Hz, 1H), 7.48-7.51 (m, 2H), 7.42-7.44 (m, 2H), 6.25 (s, 1H), 2.86 (d, J = 7.6 Hz, 2H), 1.36 (m, 2H), 1.11 (dt, J = 7.6, 7.2 Hz, 2H), 0.68 (t, J = 7.6 Hz, 3H). MS (M+1): 256, (M - 1) 254.

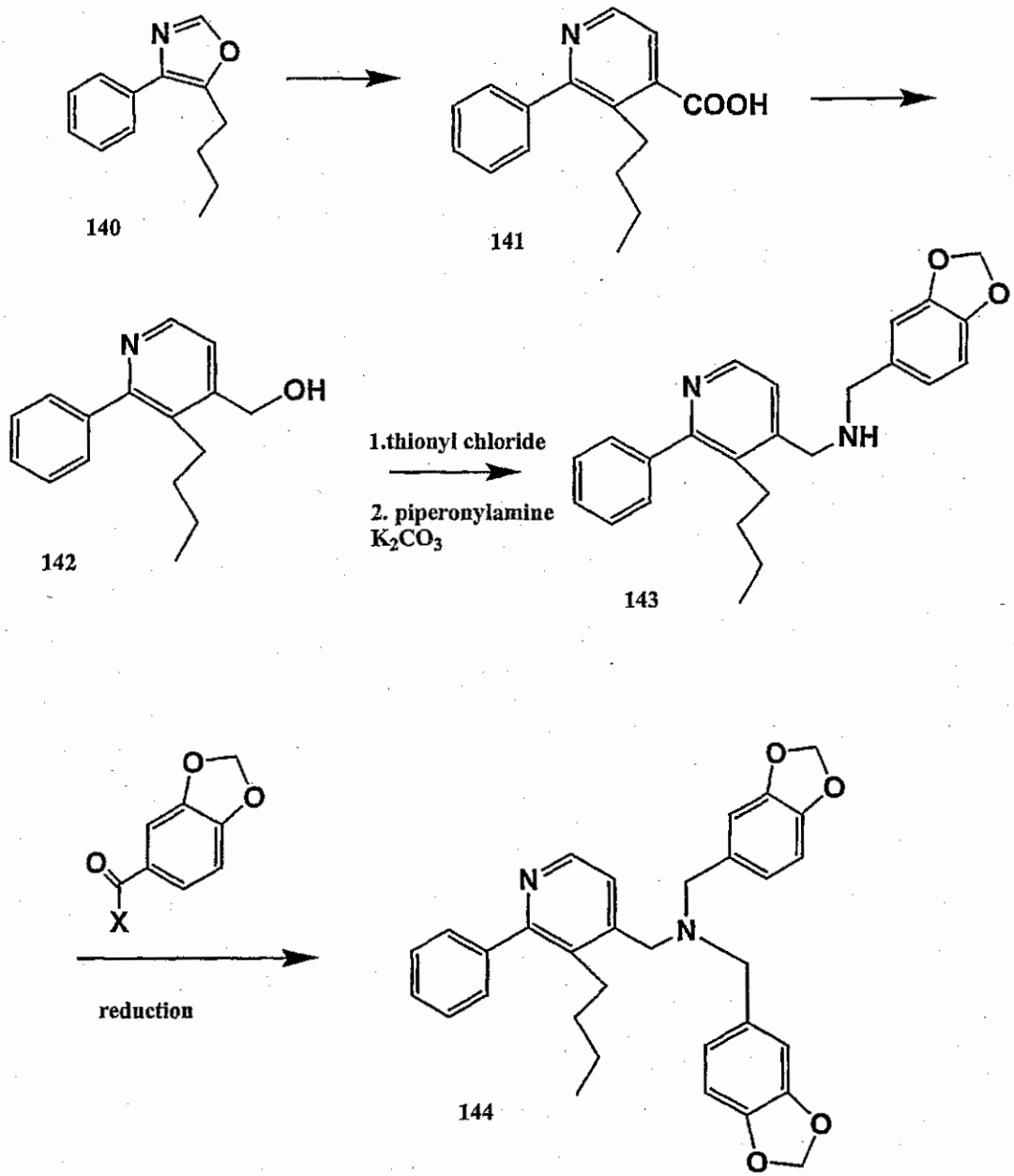
2-Phenyl-4-hydroxymethyl-3-butylpyridine (142). 4 mL of a 1M solution of lithium aluminum hydride in tetrahydrofuran is added to a solution of 2-phenyl-3-butylisonicotinic acid (13, 510 mg, 2 mmol) in tetrahydrofuran (20 mL). The reaction is stirred overnight and then quenched with 5 mL of 15% aqueous NaOH. The resulting mixture is extracted with ether, dried (Na_2SO_4) and concentrated to provide the desired hydroxymethylpyridine as an oil (470 mg). LC-MS (M+1): 242; ^{1}H NMR (, $CDCL_3$) 8.35 (1H, d, J = 5.2 Hz), 7.30-7.39 (6H, m), 4.59 (2H, s), 2.43 (2H, t, J = 8.0 Hz), 1.23 (2H, m), 1.13 (2H, m), 0.70 (3H, t, J = 7.2 Hz).

2-Phenyl-4-(*N*-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3-butylpyridine (143). Thionyl chloride (200 mg, 1.67 mmol) is added to a solution of 2-phenyl-4-hydroxymethyl-3-butylpyridine (400 mg, 1.66 mmol) in pentene stabilized chloroform (8 mL) and the mixture is heated to 50 °C for 2 h. The resulting

mixture is cooled, washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and concentrated. The resulting crude chloride is taken up in dimethylformamide (10 mL) and added dropwise to a refluxing solution of piperonylamine (1.0 g, 4 equiv) in dimethylformamide (30 mL) containing 3 g of powdered potassium carbonate. After the addition is complete, the resulting mixture is refluxed for an additional 3 h, cooled and partitioned between water (200 mL) and ether (100 mL). The ethereal layer is washed 2 times with water, dried (Na_2SO_4) and concentrated. The resulting material is purified by chromatography on silica eluting with 10% $CH_3OH/CHCl_3$ to give the desired secondary amine 15. LC-MS (M+1): 375.3; ^{1}H-NMR (δ, $CDCl_3$): 0.73 (3H, t, J = 7.2 Hz), 1.15 (2H, m J = 7.2 Hz), 1.30 (2H, m), 2.58 (2H, t, J = 8.0 Hz), 3.79 (2H, s), 3.83 (2H, s), 5.93 (2H, s), 6.75-6.82 (2H, m), 6.89 (1H, d, J = 1.2 Hz), 7.36-7.42 (6H, m), 8.45 (1H, d, J = 4.8 Hz) ppm.

2-Phenyl-4-(*N*,*N*-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl})aminomethyl-3-butylpyridine (144). To a solution of 14 (38 mg) in dichloroethane (5 mL) was added piperonal (30 mg). The resulting mixture was stirred for 3 h after which time sodium triacetoxyborohydride (150 mg) is added in one portion and the resulting mixture is stirred overnight. The reaction mixture was quenched with 10% ammonium hydroxide solution (5 ml). The organic layer is washed with water and extracted with 1N HCl solution. The acidic extract is made basic with 1N NaOH solution and extracted with chloroform. The organic extract is dried (Na_2SO_4) and concentrated. The resulting oil is purified on preparative thin layer chromatography eluting with 10% $CH_3OH/CHCl_3$ to give the desired tertiary amine **144** as an oil (18 mg). LC-MS (M+1): 509.4; ^{1}H-NMR (δ, $CDCl_3$): 0.71 (3H, t, J = 7.2 Hz), 1.10 (2H, m, J = 7.2 Hz), 2.60 (2H, t, J = 8.0 Hz), 3.48 (4H, s), 3.58 (2H, s), 5.94 (4H, s), 6.75 (1H, d, J = 8.0 Hz),6.80 (1H, dd, J = 0.8, 8.0 Hz), 6.91 (1H, d, J = 0.8 Hz), 7.36-7.43 (5H, m), 7.56 (1H, d, J = 5.2 Hz), 8.47 (1H, d, J = 5.2 Hz) ppm.

Preparation of 2-Phenyl-4-(N,N-di{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}) aminomethyl-3-butylpyridine



Example 7. Preparation of an Arylpyrazole:

1,3-diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-butylamino)methyl-5-propylpyrazole

N'-Phenyl-N-phenylhydrazone (150). Benzaldehyde (9.81 g, 9.25 mmol) is added at 0-5 °C to a solution of phenyl hydrazine (10 g, 9.25 mmol) in ethanol (100 mL). A cream colored solid forms and the reaction mixture is allowed to stand for 2h. The solid is collected by filtration, washed with ice-cold ethanol and dried under vacuum to provide the desired compound, compound 150 (14.92 g);LC-MS m/z 197.2, ^{1}H NMR (δ, $CDCl_3$, 400 MHz) ppm.

Ethyl 1,3-diphenyl-5-propylpyrazole-4-carboxylate (152). A mixture of 150 (5 g, 25.5 mmol) and ethyl butyrylacetate (20.2 g, 128 mmol) and a catalytic amount of zinc chloride is heated at 125 °C under an air atmosphere for 3h. The reaction vessel is fitted with a short path distillation head and excess ethyl butyrylacetate iss distilled away under vacuum. The resulting material is purified by column chromatography on silica eluting with 10% ethyl acetate in hexanes to provide the desired ester **152** as a yellow oil (6.39 g) which crystallizes upon standing. Recrystallization from diisopropyl ether provides a white solid. ^{1}H NMR (δ, $CDCl_3$, 400 MHz) MS (M+1): 335.2

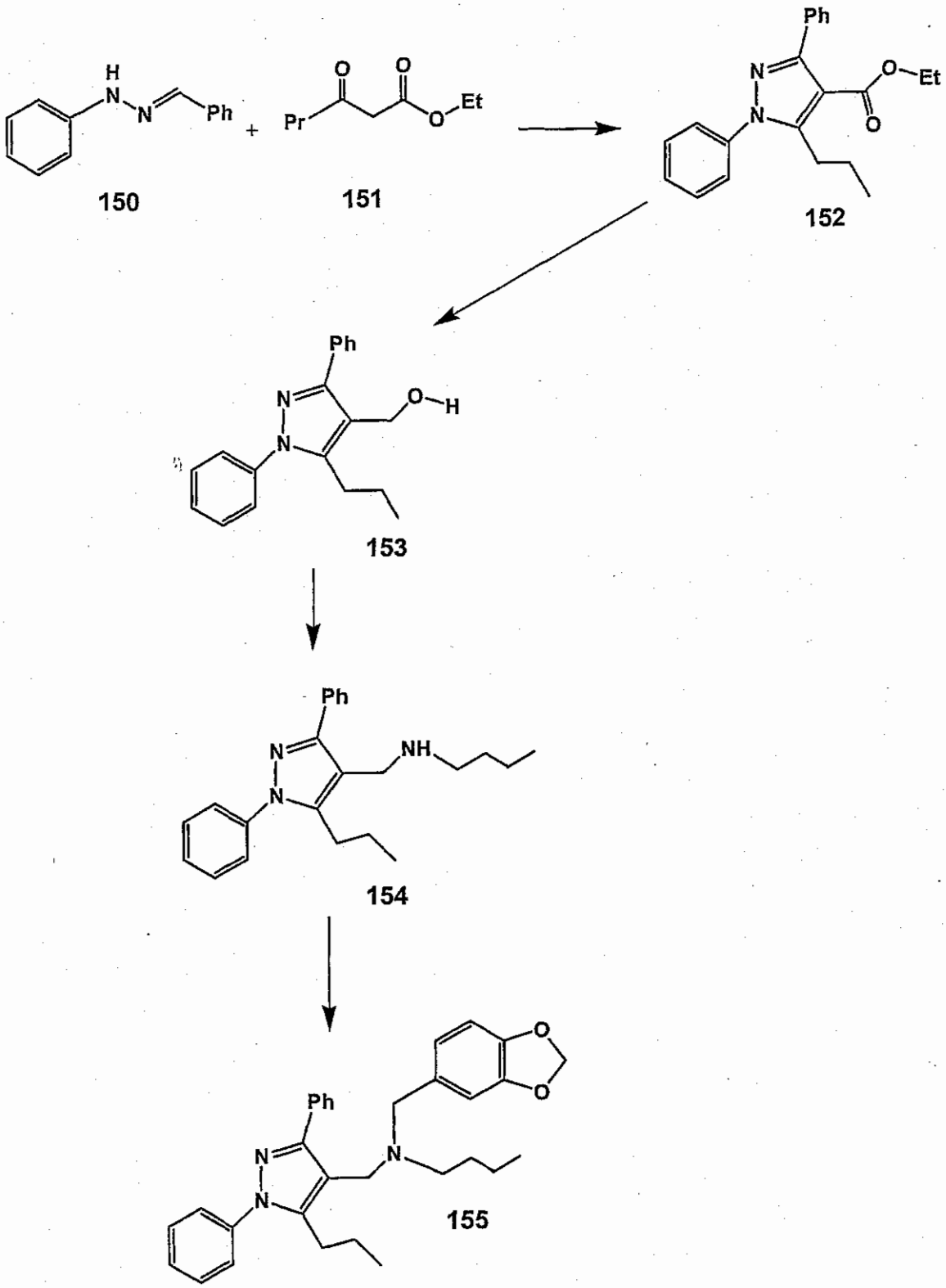
1,3-Diphenyl-4-hydroxymethyl-5-propylpyrazole (153). To a solution of ester 153 (670 mg, 2 mmol) in tetrahydrofuran (20 mL) is added 4 mL of a 1M solution of lithium aluminum hydride in tetrahydrofuran. The reaction is stirred overnight and then quenched with 5 mL of 15% aqueous NaOH. The resulting mixture is extracted with ether, dried (Na_2SO_4) and concentrated to provide the desired hydroxymethylpyrazole as an oil (505 mg). LC-MS (M+1): 293.3; ^{1}H NMR (δ, $CDCL_3$) 7.86 (dd, J = 8.4 Hz, 2H), 7.34-7.52 (m, 8H), 4.65 (s, 2H), 2.72 (t, J = 8.0 Hz, 2H), 1.52 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H).

[(1,3-Diphenyl-5-propylpyrazol-4-yl)methyl]butylamine (154). To a solution of 18 (289 mg) in pentene stabilized chloroform (8 mL) is added thionyl chloride (1 mL) and the mixture heated to 60 °C for 2 h. The resulting mixture is cooled, washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and concentrated. The resulting crude chloride is taken up in dimethylformamide (3 mL)

and added dropwise to a solution of butylamine (1.0 g) in dimethylformamide (10 mL) containing 2 g of powdered potassium carbonate. After the addition is complete, the resulting mixture is stirred for an additional 3 h and partitioned between water (20 mL) and ether (10 mL). The ethereal layer is washed 2 times with water, dried (Na_2SO_4) and concentrated. The resulting material is purified by chromatography on silica eluting with 10% $CH_3OH/CHCl_3$ to give the desired secondary amine **155** (190 mg). LC-MS (M+1): 348.3; ^{1}H-NMR (δ, $CDCl_3$): 7.87 (dd, J = 8.0, 1.6 Hz, 2H), 7.32-7.48 (m, 8H), 3.77 (s, 2H), 2.70 (m, 4H), 1.48 (m, 4H), 1.34 (m, 2H), 0.91 (t, J = 7.6 Hz, 3H), 0.87 (t, J = 7.6 Hz, 3H) ppm.

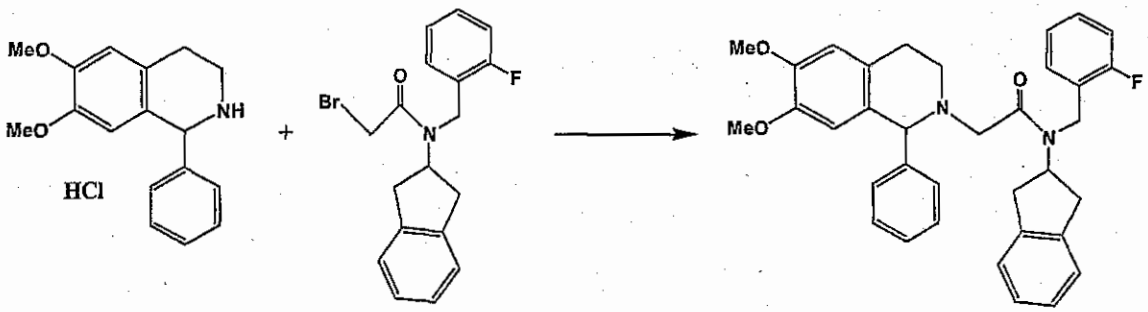
1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl}-N-butylamino)methyl-5-propylpyrazole (Compound 155). To a solution of **154** (35 mg) in dichloroethane (5 mL) is added piperonal (30 mg). The resulting mixture is stirred for 3 h after which time sodium triacetoxyborohydride (150 mg) is added in one portion and the resulting mixture is stirred overnight. The reaction mixture is quenched with 10% ammonium hydroxide solution (5 ml). The organic layer is washed with water and extracted with 1N HCl solution. The acidic extract is made basic with 1N NaOH solution and extracted with chloroform. The organic extract is dried (Na_2SO_4) and concentrated. The resulting oil is purified on preparative thin layer chromatography eluting with 10% $CH_3OH/CHCl_3$ to give the desired tertiary amine (**Compound 155**) as an oil (24 mg). LC-MS (M+1): 482.5; ^{1}H-NMR (δ, $CDCl_3$): 7.87 (d, J = 7.2 Hz, 2H), 7.47 (d, J = 4.4 Hz, 4H), 7.33-7.43 (m, 4H), 6.77 (s, 1H), 6.70 (s, 2H), 5.92 (s, 2H), 3.56 (s, 2H), 3.42 (s, 2H), 2.74 (t, J = 8.0 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H), 1.42 (m, 4H), 1.21 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H) ppm.

Preparation of 1,3-Diphenyl-4-(N-{2H-benzo[3,4-d]-1,3-dioxolan-5-ylmethyl} -N-butylamino)methyl-5-propylpyrazole



150 151 152 153 154 155

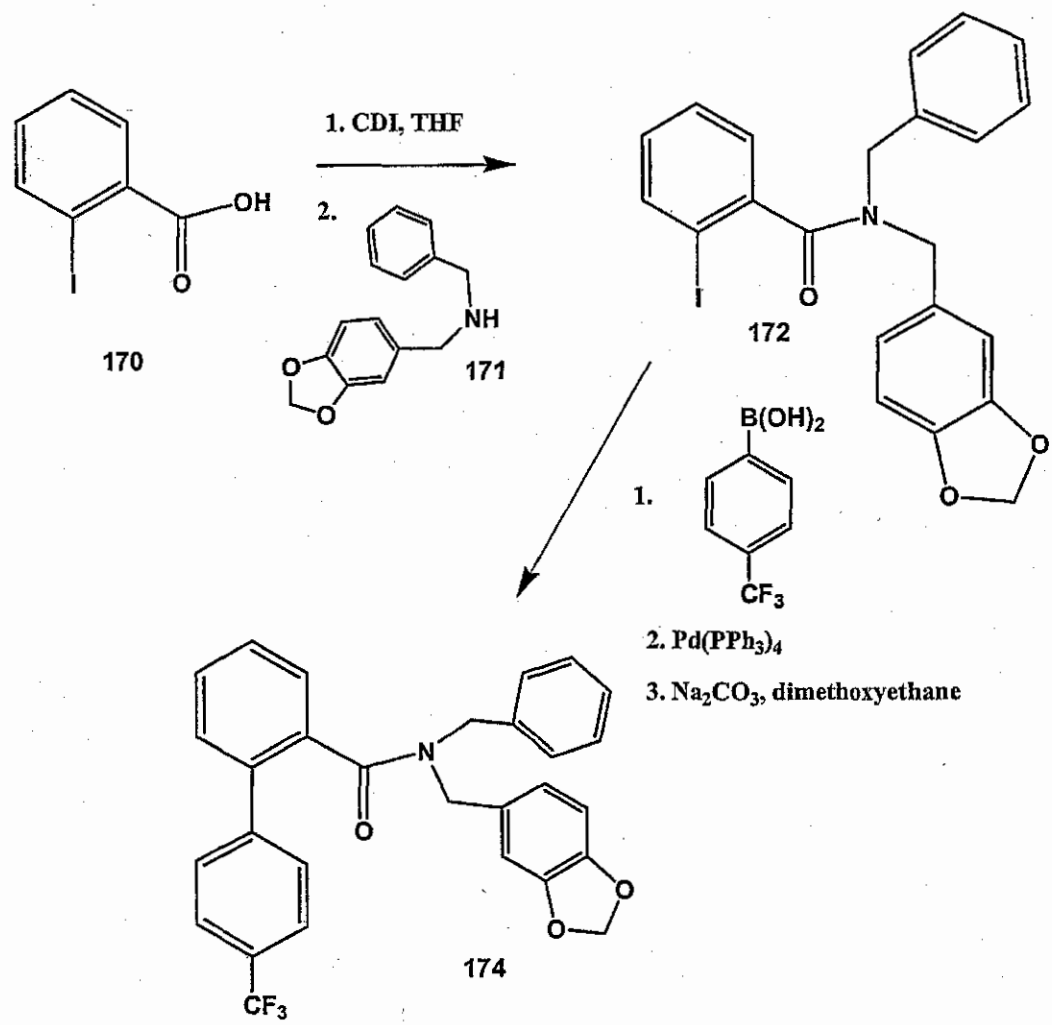
Example 8. Synthesis of *N*-(1-fluorobenzyl)-*N*-indan-2-yl-2-(6, 7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl) acetamide (162). A mixture of 6, 7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**160**, 153 mg, 0.5 mmol), *N*-(1-fluorobenzyl)-*N*-indan-2-yl-2-bromoacetamide (**161**, 180 mg, 0.5 mmol) and potassium carbonate (500 mg) in acetonitrile is heated at 80 °C overnight. After cooling, the mixture is filtered and concentrated. The resulting residue is purified by column chromatography eluting with 5% methanol in chloroform to provide the title product (**162**) as a thick oil (215 mg, 78%). ^{1}H NMR ($CDCl_3$) 6.8-7.3 (m, 14H), 6.60(s, 1H), 6.05 (s, 1H),



160 161 162

Example 9. Preparation of 4'Trifluoromethyl-biphenyl-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-benzyl-amide (**174**). 1,1'-carbonyldiimidazole (175 mg) is added to a solution of 2-iodobenzoic acid (248 mg, 1 mmol)(**170**) in tetrahydrofuran (THF, 5 ml). The resulting mixture is stirred overnight at room temperature. A solution of N-3,4-methylenedioxybenzyl-N-benzylamine (241 mg, 1 equiv)(**171**) in THF (2 mL) is added and the resulting solution is stirred for 1 h, quenched with water and extracted with diethyl ether. The organic extracts are dried (Na_2SO_4) and concentrated. The residual material is taken up in dimethoxyethane (10 mL) and a catalytic amount (20 mg) of tetrakis(triphenylphosphine)palladium(0) is added. The resulting mixture is stirred under an argon atmosphere for 10 min and solid 4-trifluoromethyllphenylboronic acid (150 mg) is added in one portion. A second phase of 1N aqueous Na_2SO_4 is added and the mixture is warmed to 80 °C for 6 h under a argon atmosphere. The solution is cooled, diluted with water and ethyl acetate and filtered through a pad of

celite. The organic phase is dried over sodium sulfate and concentrated. Purification on silica eluting with 20% ethyl acetate in hexane provided the desired biphenylamide product (**174**)(410 mg). The proton NMR displays a doubled pattern commonly observed for amides which possess some rotational restriction about the amide nitrogen at room temperature. The ratio of the rotomers is approximately equal. ^{1}H NMR (CDCl3) 3.50 and 3.62 (two doublets, J = X Hz, 1H), 3.72 and 3.83 (two doublets, J = X Hz, 1H), 4.10 and 4.18 (two doublets, J = X Hz, 1H), 5.09 and 5.16 (two doublets, J = x Hz, 1H), 5.95 (d, J = X Hz, 2H, OCH_2O), 6.30 (m, 1.5 H), 6.46 (d, J = 1 Hz, 0.5 Hz), 6.60 and 6.66 (two doublets, J = X Hz, 1H), 6.80 (bd, J = X Hz, 1H), 6.86 (m, 1H), 7.16-7.62 (m, 11 H).



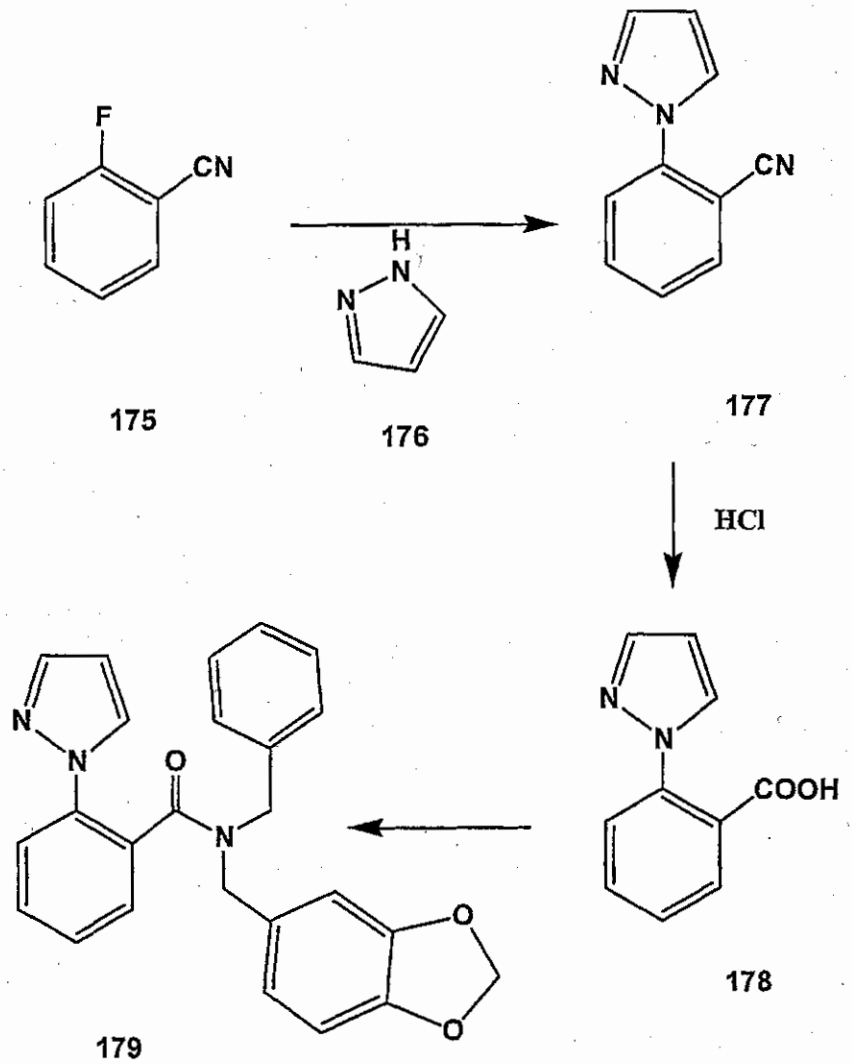
4'-Trifluoromethyl-biphenyl-2-carboxylic acid benzo[1,3]dioxol-5-ylmethyl-benzyl-amide

Example 10. Preparation of N-Benzo[1,3]dioxol-5-ylmethyl-N-benzyl-2-pyrazol-1-yl-benzamide

2-Pyrazol-1-yl-benzonitrile, Compound 177. A solution of 20 mmol of 2-fluorobezonitrile and 40 mmol of pyrrazole is mixed together in dimethylformaide with 1 equivalent of potassium hydroxide and a catalytic amount of 18-crown-6. The mixture is stirred at room temperature overnight, quenched with water and ethyl acetate and extracted with ethyl acetate. The organic extract is washed repeatedly with 1 N NaOH solution. The organic layer is then diluted with ether and washed with 1N HCl solution, dried and concentrated. 1H NMR ($CDCl_3$) 6.55 (t, J = 2 Hz, 1H), 7.42 (M, 1H), 7.65-7.82 m, 4H), 8.15 (d, J = 1 Hz, 1H).

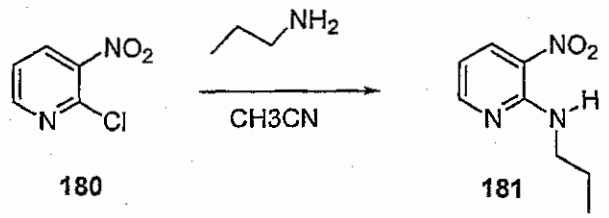
2-Pyrazol-1-yl-benzoic acid, Compound 178. A solution of compound 177 in conc HCl is refluxed overnight, cooled and concentrated. The product is precipitated by addition of 1 N NaOH until pH of 5-6, filtered and dried. 1H ($CDCl_3$) 6.52 (t, J = 3 Hz, 1H), 7.40 (d, J = 8 Hz, 1H), 7.50 (t, J = 8 Hz, 1H) 7.62 (t, J = 8 hz, 1H), 7.81 (m, 2H), 8.12 (d, J = 8 Hz, 1H).

N-Benzo[1,3]dioxol-5-ylmethyl-N-benzyl-2-pyrazol-1-yl-benzamide, Compound 179. 1.1 equiv of carbonyl diimidazole is added to a solution of benzoic acid 178 (200 mg) in tetrahydrofuran (5 mL); the reaction is stirred at room temperaturte for 3 h. After this time *N*-piperonyl-*N*-benzylamine (0.25 g) is added in one portion. After 30 min, the reaction is filtered, diluted with ether and washed with water. The organic layer is dried (Na_2SO_4) and purified over column chromatography to provide the desired product (390 mg). The proton NMR displays a typically doubled pattern. ^1H ($CDCl_3$) 3.83 and 4.32 (two doublets, J = 16 Hz, 1H), 3.91 (two doublets, J = 8 Hz, 1H), 4.18 two doublets (J = 6 Hz, 1H), 5.0 and 5.1 (two doublets, J = 14 Hz, 1H), 5.93 and 5.98 (s and doublet, J = 2 Hz, 2H, OCH_2O), 6.35-6.40 (m, 2H), 6.51 (d, J = 4 Hz, 0.5 H), 6.4 (m, 1.5 H), 7.0-7.88 m, 15H). LC-MS 412.3



Example 11. Preparation of N-benzoyl-N-(4-methoxybenzyl)-N-(1-propyl-2-methyleno-7-azabenzimidazole

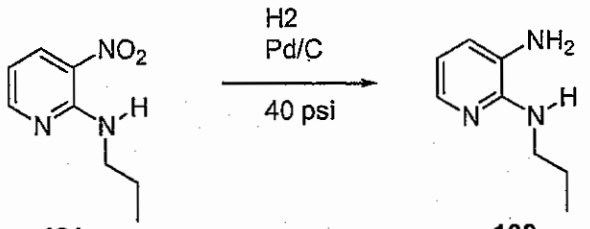
2-aminopropyl-3-nitropyridine



2-chloro-3-nitroaminopyridine (**180**) (5.5 g, 35 mmol) is dissolved in 150 mL acetonitrile at room temperature. Propylamine (21 g, 350 mmol) is added dropwise and the reaction mixture is stirred for 5 hours at room temperature. The solvent and excess propylamine are removed *in vacuo*. The residue is dissolved in 150 mL ethyl acetate and washed once with 100 mL saturated $NaHCO_3$ solution and once

with 100 mL brine. The organic layer is dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 6.3 g of 2-aminopropyl-3-nitropyridine (**181**).

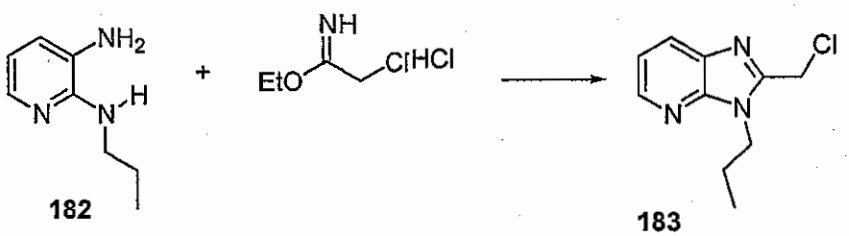
2-aminopropyl-3-aminopyridine.



181 182

2-aminopropyl-3-nitropyridine (171)(6.3 g, 35 mmol) is dissolved in 100 mL 1/1 ethyl acetate / ethanol in a Parr shaker bottle. Nitrogen is bubbled through the solution for 2 minutes followed by the addition of 10% Pd/C (500 mg). The suspension is hydrogenated on a Parr apparatus under 40 psi of H_2 until hydrogen uptake ceased. The suspension is filtered through Celite and the solvent evaporated *in vacuo* to afford 5.3 g of the 2-aminopropyl-3-aminopyridine (**182**).

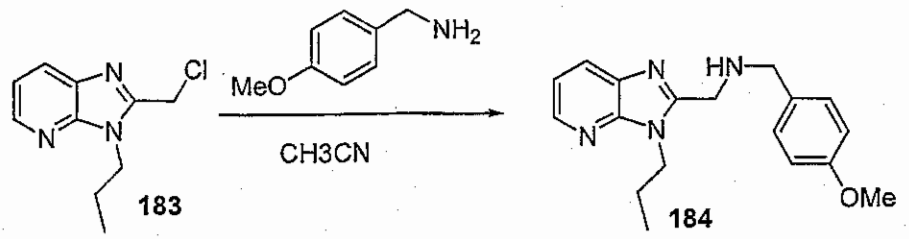
1-propyl-2-chloromethyl-7-azabenzimidazole



182 183

2-aminopropyl-3-aminopyridine (172) (5.3 g, 35 mmol) is dissolved in 100 mL $CHCl_3$ at room temperature. Ethyl chloromethylimidate hydrochloride (14 g, 89 mmol) is added followed by K_2CO_3 (25 g, 180 mmol). The suspension was stirred vigorously at room temperature for 3 hours. The reaction mixture is filtered through Celite and the solvent removed *in vacuo*. The residue is passed through a short plug of silica gel eluting with ethyl acetate to afford 3.7 g of 1-propyl-2-chloromethyl-7-azabenzimidazole (**183**).

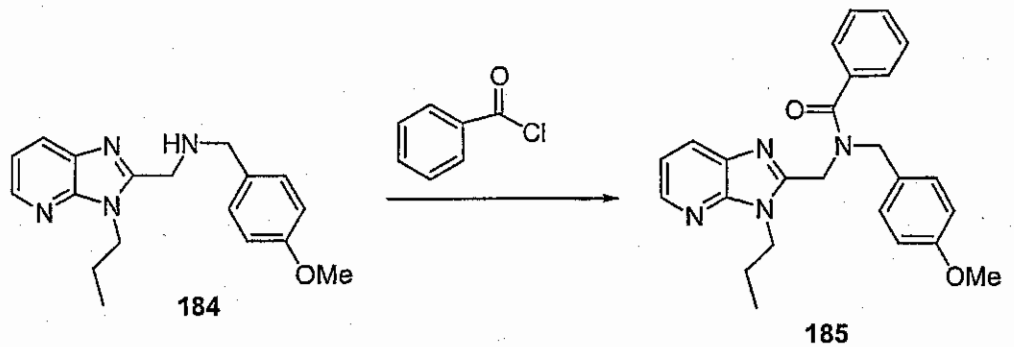
1-propyl-2-(4-methoxybenzylamino)methyl-7-azabenzimidazole.



183 184

4-Methoxybenzylamine (3.8 g, 27 mmol) is dissolved in 20 mL dry acetonitrile. 1-propyl-2-chloromethyl-7-azabenzimidazole (**173**)(940 mg, 4.5 mmol) dissolved in 4.5 mL acetonitrile is added dropwise. The mixture is stirred 10 hours at room temperature. The solvent is removed *in vacuo* and the residue dissolved in 20 mL ethyl acetate. This solution is washed once with 20 mL 1 N NaOH, once with 20 mL water, once with 20 mL 5% HOAc in water, then once with 5 N NaOH. The organic phase was dried over $MgSO_4$, filtered, then concentrated *in vacuo*. The product mixture is purified by flash chromatography eluting with ethyl acetate followed by 95/5/1 ethyl acetate / methanol / triethylamine to afford 850 mg of the 1-propyl-2-(4-methoxybenzylamino)methyl-7-azabenzimidazole (**184**).

N-benzoyl-N-(4-methoxybenzyl)-N-(1-propyl-2-methyleno-7-azabenzimidazole



184 185

1-propyl-2-(4-methoxybenzylamino)methyl-7-azabenzimidazole (174)(19 mg, 0.06 mmol) is dissolved in 0.6 mL toluene. Saturated sodium bicarbonate solution in water (0.3 mL) is added followed by benzoyl chloride (11 mg, 0.08 mmol). The reaction mixture is stirred at room temperature for 10 hours. It is then diluted with 5 mL ethyl acetate and transferred to a separatory funnel. The aqueous layer is removed and the organic phase washed once with 1N NaOH, once with 5 mL water, then and once with mL brine. The organic phase is dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The product is purified by preparatory tlc eluting with

1/1 ethyl acetate / hexanes to afford 20 mg of the desired compound (**185**). NMR 400 MHz ($CDCl_3$) 8.39 ppm (br d, 1 H), 8.15 ppm (br d, 1 H), 7.52 ppm (m, 1.5 H), 7.40 ppm (s, 1.5 H), 7.22 (m, 1 H), 7.18 ppm (br d, 1 H), 6.83 ppm, (d, J = 4 Hz, 2 H), 4.93 ppm (br s, 2 H), 4.71 ppm (br s, 1 H), 4.39 ppm (br s, 1 H), 3.79 ppm (s, 3 H), 1.89 ppm (br m, 2 H), 0.98 pp, (br t, 3 H).

Example 12

Assay for C5a Receptor Mediated Chemotaxis

This assay is a standard assay of C5a receptor mediated chemotaxis.

Human promonocytic U937 cells or purified human or non-human neutrophilis are treated with dibutyryl cAMP for 48 hours prior to performing the assay. Human neutrophils or those from another mammalian species are used directly after isolation. The cells are pelleted and resuspended in culture media containing 0.1% fetal bovine serum (FBS) and 10 ug/ml calcein AM (a fluorescent dye). This suspension is then incubated at 37 °C for 30 minutes such that the cells take up the fluorescent dye. The suspension is then centrifuged briefly to pellet the cells, which are then resuspended in culture media containing 0.1% FBS at a concentration of approximately 3 x 10^6 cells/mL. Aliquots of this cell suspension are transferred to clean test tubes, which contain vehicle (1% DMSO) or varying concentrations of a compound of interest, and incubated at room temperature for at least 30 minutes. The chemotaxis assay is performed in ChemoTx™ 101-8, 96 well plates (Neuro Probe, Inc. Gaitherburg, MD). The bottom wells of the plate are filled with medium containing 0-10 nM of C5a, preferably derived from the same species of mammal as are the neutrophils or other cells (e.g., human C5a for the human U937 cells). The top wells of the plate are filled with cell suspensions (compound or vehicle-treated). The plate is then placed in a tissue culture incubator for 60 minutes. The top surface of the plate is washed with PBS to remove excess cell suspension. The number of cells that have migrated into the bottom well is then determined using a fluorescence reader. Chemotaxis index (the ratio of migrated cells to total number of cells loaded) is then calculated for each compound concentration to determine an IC_{50} value.

As a control to ensure that cells retain chemotactic ability in the presence of the compound of interest, the bottom wells of the plate may be filled with varying concentrations chemo-attractants that do not mediate chemotaxis via the C5a receptor, e.g. zymosan-activated serum (ZAS), N-formylmethionyl-leucyl-phenylalanine (FMLP) or leukotriene B4 (LTB4), rather than C5a, under which conditions the compounds of the invention preferably do not inhibit chemotaxis.

Preferred compounds of the invention exhibit IC_{50} values of less than 1 μM in the above assay for C5a mediated chemotaxis.

Example 13

Determination of dopamine D_4 receptor binding activity

The following assay is a standard assay for determining the binding affinity of compounds to dopamine D_4 receptors.

Pellets of Chinese hamster ovary (CHO) cells containing recombinantly expressing primate dopamine D4 receptors are used for the assays. The dopamine D_4 receptor expression vector may be the pCD-PS vector described by Van Tol et al. (Nature (1991) 358: 149-152). The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer containing 120 mM NaCl, 5 mM $MgCl_2$ and 1 mM EDTA at 4°C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 120 mM NaCl.

Incubations for dopaminergic binding are carried out at 25°C and contain 0.4 ml of tissue sample, 0.1 nM ^{3}H-YM 09151-2 (Nemonapride, cis-5-Chloro-2-methoxy-4-(methylamino)-N-(2-methyl-2-(phenylmethyl)-3-pyrrolidinyl)benzamide) and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding found in the presence of 1 uM spiperone; without further additions, nonspecific binding is less than 20% of total binding.

Example 14. Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by

carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^{3}H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

Example 15: Baculoviral Preparations (For C5a Expression)

The human C5a (hC5a) receptor baculoviral expression vector was co-transfected along with BACULOGOLD DNA (BD PharMingen, San Diego, CA) into *Sf*9 cells. The *Sf*9 cell culture supernatant was harvested three days post-transfection. The recombinant virus-containing supernatant was serially diluted in Hink' s TNM-FH insect medium (JRH Biosciences, Kansas City) supplemented Grace's salts and with 4.1mM L-Gln, 3.3 g/L LAH, 3.3 g/L ultrafiltered yeastolate and 10% heat-inactivated fetal bovine serum (hereinafter "insect medium") and plaque assayed for recombinant plaques. After four days, recombinant plaques were selected and harvested into 1 ml of insect medium for amplification. Each 1 ml volume of recombinant baculovirus (at passage 0) was used to infect a separate T25 flask

containing 2 x 10^6 S*f*9 cells in 5 mls of insect medium. After five days of incubation at 27°C, supernatant medium was harvested from each of the T25 infections for use as passage 1 inoculum.

Two of seven recombinant baculoviral clones were then chosen for a second round of amplification, using 1 ml of passage 1 stock to infect 1 x 10^8 cells in 100 ml of insect medium divided into 2 T175 flasks. Forty-eight hours post infection, passage 2 medium from each 100ml prep was harvested and plaque assayed for titer. The cell pellets from the second round of amplification were assayed by affinity binding as described below to verify recombinant receptor expression. A third round of amplification was then initiated using a multiplicity of infection of 0.1 to infect a liter of S*f*9 cells. Forty hours post-infection the supernatant medium was harvested to yield passage 3 baculoviral stock.

The remaining cell pellet is assayed for affinity binding using the "Binding Assays" described by DeMartino et al., 1994, J. Biol. Chem. 269 #20, pp.14446-14450 at page 14447, adapted as follows. Radioligand is 0.005-0.500nM [^{125}I]C5a (human recombinant), New England Nuclear Corp., Boston, MA; the hC5a receptor-expressing baculoviral cells are used instead of 293 cells; the assay buffer contains 50 mM Hepes pH. 7.6, 1 mM $CaCl_2$, 5 mM $MgCl_2$, 0.1% BSA, pH 7.4, 0.1 mM bacitracin, and 100 KIU/ml aprotinin; filtration is carried out using GF/C WHATMAN filters (presoaked in 1.0% polyethyeneimine for 2 hours prior to use); and the filters are washed twice with 5 mLs cold binding buffer without BSA, bacitracin, or aprotinin.

Titer of the passage 3 baculoviral stock is determined by plaque assay and a multiplicity of infection, incubation time course, binding assay experiment is carried out to determine conditions for optimal receptor expression.

A multiplicity of infection of 0.1 and a 72-hour incubation were the best infection parameters found for hC5a receptor expression in up to 1-liter S*f*9 cell infection cultures.

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Example 16: Baculoviral Infections

Log-phase Sf9 cells (INVITROGEN Corp., Carlsbad CA), are infected with one or more stocks of recombinant baculovirus followed by culturing in insect medium at 27°C. Infections are carried out either only with virus directing the expression of the hC5a receptor or with this virus in combination with three G-protein subunit-expression virus stocks: 1) rat Ga_{i2} G-protein-encoding virus stock (BIOSIGNAL #V5J008), 2) bovine b1 G-protein-encoding virus stock (BIOSIGNAL #V5H012), and 3) human g2 G-protein-encoding virus stock (BIOSIGNAL #V6B003), which may be obtained from BIOSIGNAL Inc., Montreal.

The infections are conveniently carried out at a multiplicity of infection of 0.1:1.0:0.5:0.5. At 72 hours post-infection, a sample of cell suspension is analyzed for viability by trypan blue dye exclusion, and the remaining Sf9 cells are harvested via centrifugation (3000 rpm/ 10 minutes/ 4°C).

Example 17: Purified Recombinant Insect Cell Membranes

Sf9 cell pellets are resuspended in homogenization buffer (10 mM HEPES, 250 mM sucrose, 0.5 ÿg/ml leupeptin, 2 ÿg/ml Aprotinin, 200 ÿM PMSF, and 2.5 mM EDTA, pH 7.4) and homogenized using a POLYTRON homogenizer (setting 5 for 30 seconds). The homogenate is centrifuged (536 x g/ 10 minutes/ 4°C) to pellet the nuclei. The supernatant containing isolated membranes is decanted to a clean centrifuge tube, centrifuged (48,000 X g/ 30 minutes, 4°C) and the resulting pellet resuspended in 30 ml homogenization buffer. This centrifugation and resuspension step is repeated twice. The final pellet is resuspended in ice cold Dulbecco's PBS containing 5 mM EDTA and stored in frozen aliquots at -80°C until needed. The protein concentration of the resulting membrane preparation (hereinafter "P2 membranes") is conveniently measured using a Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 100-150 mg of total membrane protein.

Example 18: Agonist-Induced GTP Binding

Agonist-stimulated GTP-gamma^{35}S binding ("GTP binding") activity can be used to identify agonist and antagonist compounds and to differentiate neutral antagonist compounds from those that possess inverse agonist activity. This activity can also be used to detect partial agonism mediated by antagonist compounds. A compound being analyzed in this assay is referred to herein as a "test compound." Agonist-stimulated GTP binding activity is measured as follows: Four independent baculoviral stocks (one directing the expression of the hC5a receptor and three directing the expression of each of the three subunits of a heterotrimeric G-protein) are used to infect a culture of *Sf*9 cells as described in Example 16.

Agonist-stimulated GTP binding on purified membranes (prepared as described in Example 17) is assessed using hC5a (Sigma Chemical Co., St. Louis, Missouri, USA) as agonist in order to ascertain that the receptor/G-protein-alpha-beta-gamma combination(s) yield a functional response as measured by GTP binding.

P2 membranes are resuspended by Dounce homogenization (tight pestle) in GTP binding assay buffer (50 mM Tris pH 7.0, 120 mM NaCl, 2 mM MgCl2, 2 mM EGTA, 0.1% BSA, 0.1 mM bacitracin, 100KIU/mL aprotinin, 5 μM GDP) and added to reaction tubes at a concentration of 30 ug protein/reaction tube. After adding increasing doses of the agonist hC5a at concentrations ranging from 10^{-12} M to 10^{-6} M, reactions are initiated by the addition of 100 pM GTP gamma^{35}S. In competition experiments, non-radiolabeled test compounds (e.g., compounds of the invention) are added to separate assays at concentrations ranging from 10^{-10} M to 10^{-5} M along with 10 nM hC5a to yield a final volume of 0.25 mL.

Neutral antagonists are those test compounds that reduce the C5a-stimulated GTP binding activity towards, but not below, baseline (the level of GTP bound by membranes in this assay in the absence of added C5a or other agonist and in the further absence of any test compound).

In contrast, in the absence of added C5a certain preferred compounds of the invention will reduce the GTP binding activity of the receptor-containing membranes below baseline, and are thus characterized as inverse agonists. If a test compound that displays antagonist activity does not reduce the GTP binding activity below baseline in the absence of the C5a agonist, it is characterized as a neutral antagonist.

An antagonist test compound elevates GTP binding activity above baseline in the absence of added hC5a in this GTP binding assay is characterized as having partial agonist activity. Preferred antagonist compounds of the invention do not elevate GTP binding activity under such conditions more than 10% above baseline, preferably not more than 5% above baseline, and most preferably not more than 2% above baseline.

Following a 60-minute incubation at room temperature, the reactions are terminated by vacuum filtration over GF/C filters (pre-soaked in wash buffer, 0.1% BSA) followed by washing with ice-cold wash buffer (50 mM Tris pH 7.0, 120mM NaCl). The amount of receptor-bound (and thereby membrane-bound) GTP gamma^{35}S is determined by measuring the bound radioactivity, preferably by liquid scintillation spectrometry of the washed filters. Non-specific binding is determined using 10 mM GTP gamma ^{35}S and typically represents less than 5 percent of total binding. Data is expressed as percent above basal (baseline). The results of these GTP binding experiments may be conveniently analyzed using SIGMAPLOT software (SPSS Inc., Chicago, Illinois, USA).

EXAMPLE 19 Calcium Mobilization Assays

A. Response to C5a

U937 cells are grown in differentiation media (1 mM dibutyrl cAMP in RPMI 1640 medium containing 10% fetal bovine serum) for 48 hrs at 37 C then reseeded onto 96-well plates suitable for use in a FLIPR™ Plate Reader (Molecular Devices Corp., Sunnyvale CA). Cells are grown an additional 24 hours (to 70-90%

confluence) before the assay. The cells are then washed once with Krebs Ringer solution. Fluo-3 calcium sensitive dye (Molecular Probes, Inc. Eugene, OR) is added to 10 ug/mL and incubated with the cells at room temperature for 1 to 2 hours. The 96 well plates are then washed to remove excess dye. Fluorescence responses, measured by excitation at 480 nM and emission at 530 nM, are monitored upon the addition of human C5a to the cells to a final concentration of 0.01-30.0 nM, using the FLIPR™ device (Molecular Devices). Differentiated U937 cells typically exhibit signals of 5,000-50,000 Arbitrary Fluorescent Light Units in response to agonist stimulation.

B. Assays for Determination of ATP Responses

Differentiated U937 cells (prepared and tested as described above under "A. Response to C5a") are stimulated by the addition of ATP (rather than C5a) to a final concentration of 0.01 to 30 uM. This stimulation typically triggers a signal of 1,000 to 12,000 arbitrary fluorescence light units. Certain preferred compounds of the invention produce less than a 10%, preferably less than a 5%, and most preferably less than a 2% alteration of this calcium mobilization signal when this control assay is carried out in the presence or absence of the compounds.

C. Assays for the Identification of Receptor Modulatory Agents: Antagonists and Agonists

Those of skill in the art will recognize that the calcium mobilization assay described above may be readily adapted for identifying test compounds as having agonist or antagonist activity, at the human C5a receptor.

For example, in order to identify antagonist compounds, differentiated U937 cells are washed and incubated with Fluo-3 dye as described above. One hour prior to measuring the fluorescence signal, a subset of the cells is incubated with a 1 M concentration of at least one compound to be tested. The fluorescence response upon the subsequent addition of 0.3 nM (final concentration) human recombinant

C5a is monitored using the FLIPR™ plate reader. Antagonist compounds elicit at least a 2-fold decrease in the fluorescence response relative to that measured in the presence of human C5a alone. Preferred antagonist compounds elicit at least a 5-fold, preferably at least a 10-fold, and more preferably at least a 20-fold decrease in the fluorescence response relative to that measured in the presence of human C5a alone. Agonist compounds elicit an increase in fluorescence without the addition of C5a, which increase will be at least partially blocked by a known C5a receptor antagonist.

Example 20. Assays to evaluate agonist activity of small molecule C5a receptor antagonists

Preferred compounds of the invention are C5a receptor antagonists that do not possess significant (e.g., greater than 5%) agonist activity in any of the C5a mediated functional assays discussed herein. Specifically, this undesired agonist activity can be evaluated, for example, in the GTP binding assay of Example 18, by measuring small molecule mediated GTP binding in the absence of the natural agonist, C5a. Similarly, in a calcium mobilization assay e.g., that of Example 19, a small molecule compound can be directly assayed for the ability of the compound to stimulate calcium levels in the absence of the natural agonist, C5a. The preferred extent of C5a agonist activity exhibited by compounds of the invention is less than 10%, more preferably less than 5% and most preferably less than 2% of the response elicited by the natural agonist, C5a.

EXAMPLE 21. Expression of a C5a receptor

A human C5a receptor cDNA was obtained by PCR using 1) a forward primer adding a Kozak ribosome binding site and 2) a reverse primer that added no additional sequence, and 3) an aliquot of a Stratagene Human Fetal Brain cDNA library as template. The sequence of the resulting PCR product is set forth as SEQ ID NO:1. The PCR product was subcloned into the cloning vector pCR-Script AMP (STRATAGENE, La Jolla,CA) at the Srf I site. It was then excised using the restriction enzymes EcoRI and NotI and subcloned in the appropriate orientation for

expression into the baculoviral expression vector pBacPAK 9 (CLONTECH, Palo Alto, CA) that had been digested with EcoRI and NotI.

As set forth in the tables appended hereto, R groups do not necessarily correlate with those R groups shown in the text of the specification or in the claims.

The following table 1 (204-313) is a list of preferred 1,2,5 substituted imidazoles of the present invention;

The following table 2 (314-419) is a list of preferred 1,2,4,5 substituted imidazoles of the present invention;

The following table 3 (420-421) is a list of preferred pyrazoles of the present invention;

The following table 4 (422-423) is another list of preferred 1,2,4,5 substituted imidazoles of the present invention;

The following table 5 (424-456) is a list of preferred amides of the present invention; and

The following table 6 (457-458) is a list of preferred amides of the present invention.

Additional Aspects of Preferred Compounds of the Invention

The most preferred compounds of the invention are suitable for pharmaceutical use in treating human patients. Accordingly, such preferred compounds do not exhibit single or multiple dose acute or long-term toxicity, mutagenicity (e.g., as determined in a bacterial reverse mutation assay such as an Ames test), teratogenicity, tumorogenicity, or the like, and rarely trigger adverse effects (side effects) when administered at therapeutically effective dosages. For example, preferred compounds of the invention will not prolong heart QT intervals (e.g., as determined by electrocardiography, e.g., in guinea pigs, minipigs or dogs). Therapeutically effective doses or concentrations of such compounds do not cause liver enlargement when fed to or injected into laboratory animals (e.g., mice or rats) and do not promote the release of liver enzymes (e.g., ALT, LDH, or AST) from hepatocytes in vitro or in vivo.

Because side effects are often due to undesirable receptor activation or antagonism, preferred compounds of the invention exert their receptor-modulatory effects with high specificity. This means that they only bind to, activate, or inhibit the activity of certain receptors other than C5a receptors with affinity constants of greater than 100 nanomolar, preferably greater than 1 micromolar, more preferably greater than 10 micromolar and most preferably greater than 100 micromolar. Such receptors preferably are selected from neurotransmitter receptors such as alpha- or beta-adrenergic receptors, muscarinic receptors (particularly m1, m2, or m3 receptors), dopamine receptors, and metabotropic glutamate receptors; and also include histamine receptors and cytokine receptors, e.g., interleukin receptors, particularly IL-8 receptors. Such receptors may also include GABAA receptors, bioactive peptide receptors (other than C5a receptors, including NPY or VIP receptors), neurokinin receptors, bradykinin receptors, hormone receptors (e.g., CRF receptors, thyrotropin releasing hormone receptors, or melanocyte-concentrating hormone receptors).

Additionally, preferred compounds of the invention do not inhibit or induce microsomal cytochrome P450 enzyme activities, such as CYP1A2 activity, CYP2A6 activity, CYP2C9 activity, CYP2C19 activity, CYP2D6 activity, CYP2E1 activity, or CYP3A4 activity. Preferred compounds of the invention also do not exhibit cytotoxicity in vitro or in vivo, are not clastogenic, e.g., as determined using a mouse erythrocyte precursor cell micronucleus assay, an Ames micronucleus assay, a spiral micronucleus assay, or the like and do not induce sister chromatid exchange, e.g., in Chinese hamster ovary cells.

Highly preferred C5a receptor antagonist compounds of the invention also inhibit the occurrence of C5a-induced oxidative burst (OB) in inflammatory cells, e.g., neutrophil, as can be conveniently determined using an in vitro neutrophil OB assay.

Initial characterization of preferred compounds of the invention can be conveniently carried out using a C5a receptor binding assay or functional assay, such as set forth in the Examples, and may be expedited by applying such assays in

a high throughput screening setting.

The following Tables depict further preferred compounds of the invention. In those Tables, the vriable X indicates the pouint of attachment of the specified moiety to the structure shown at the top of the Table.

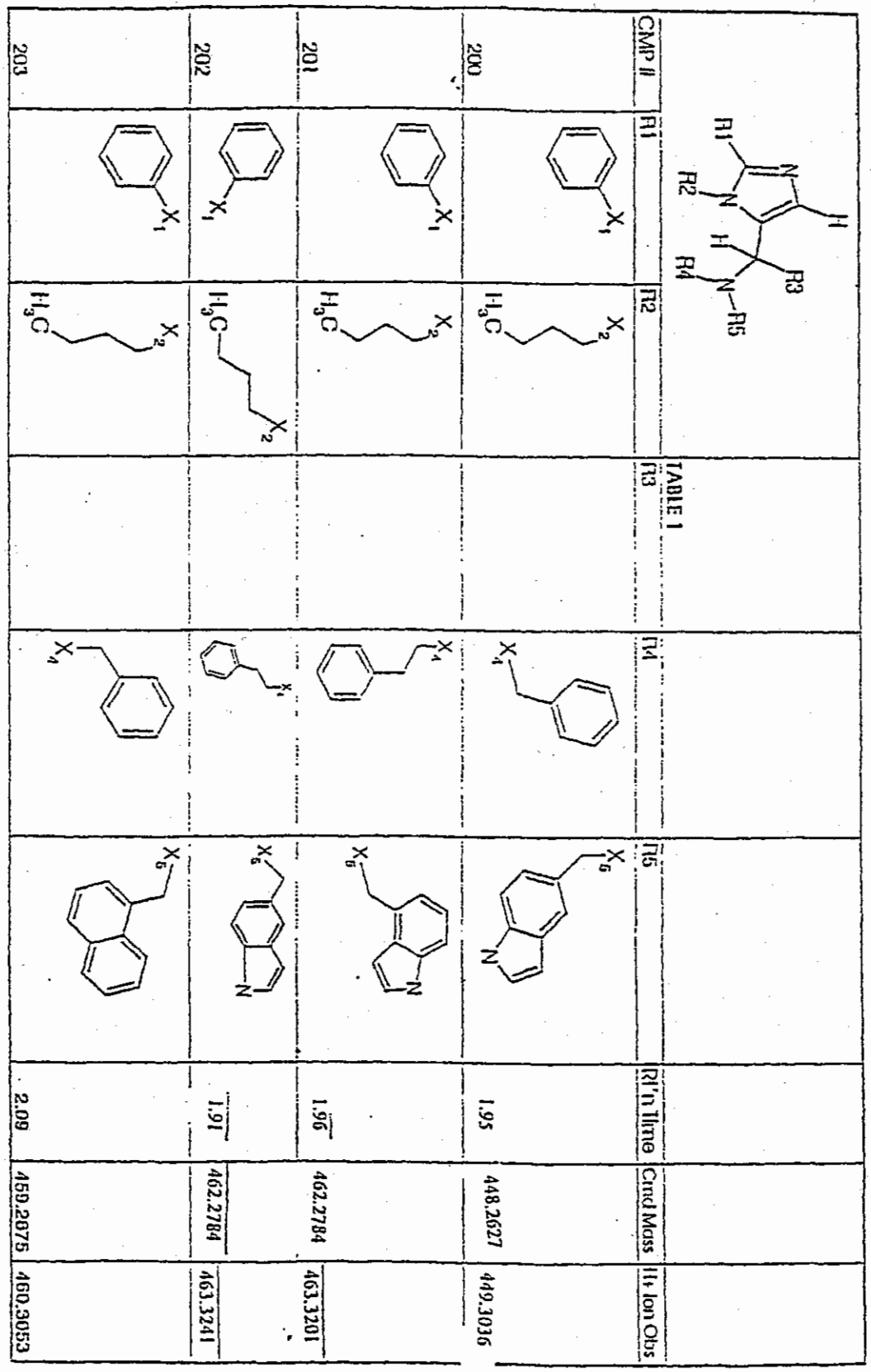
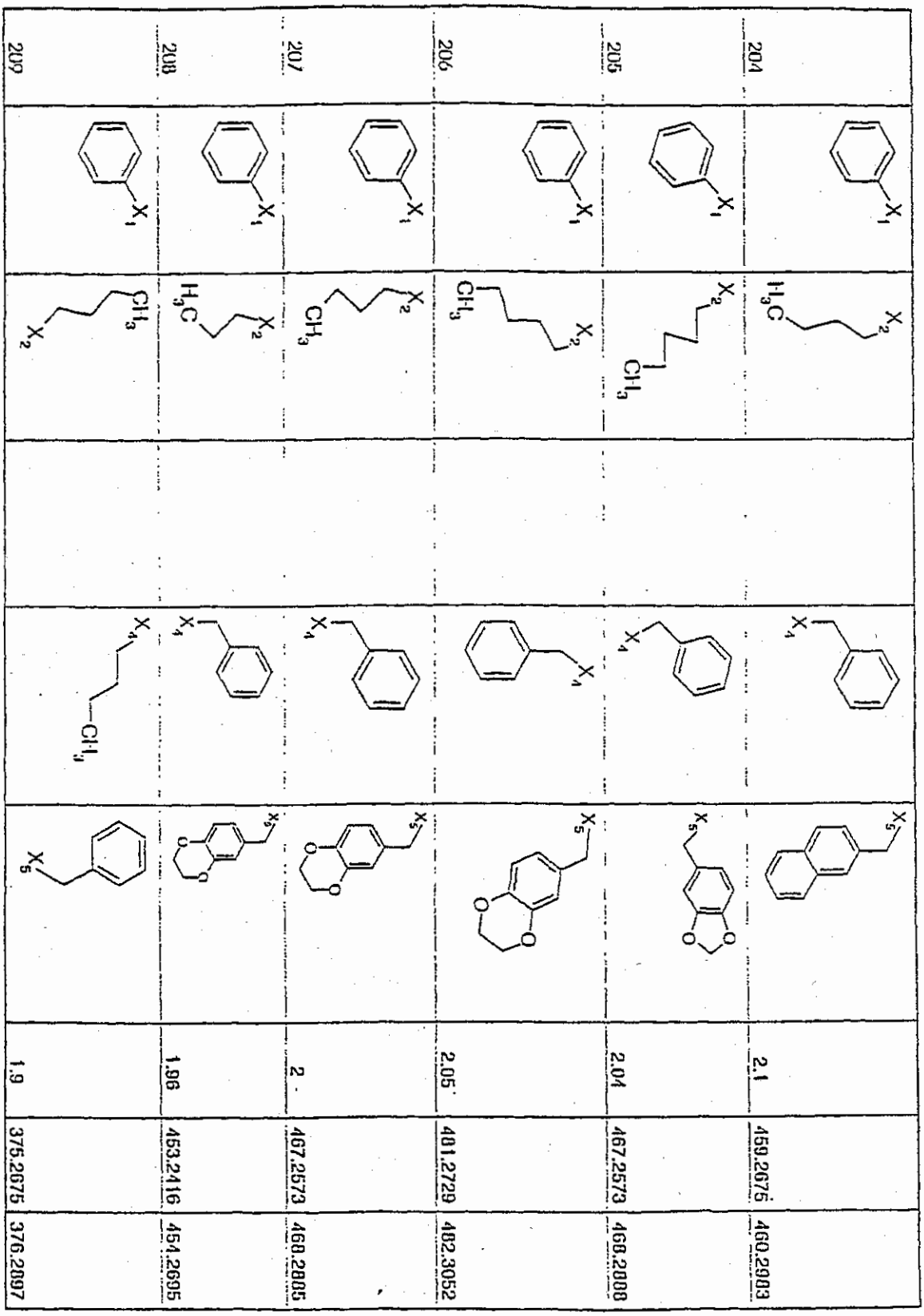
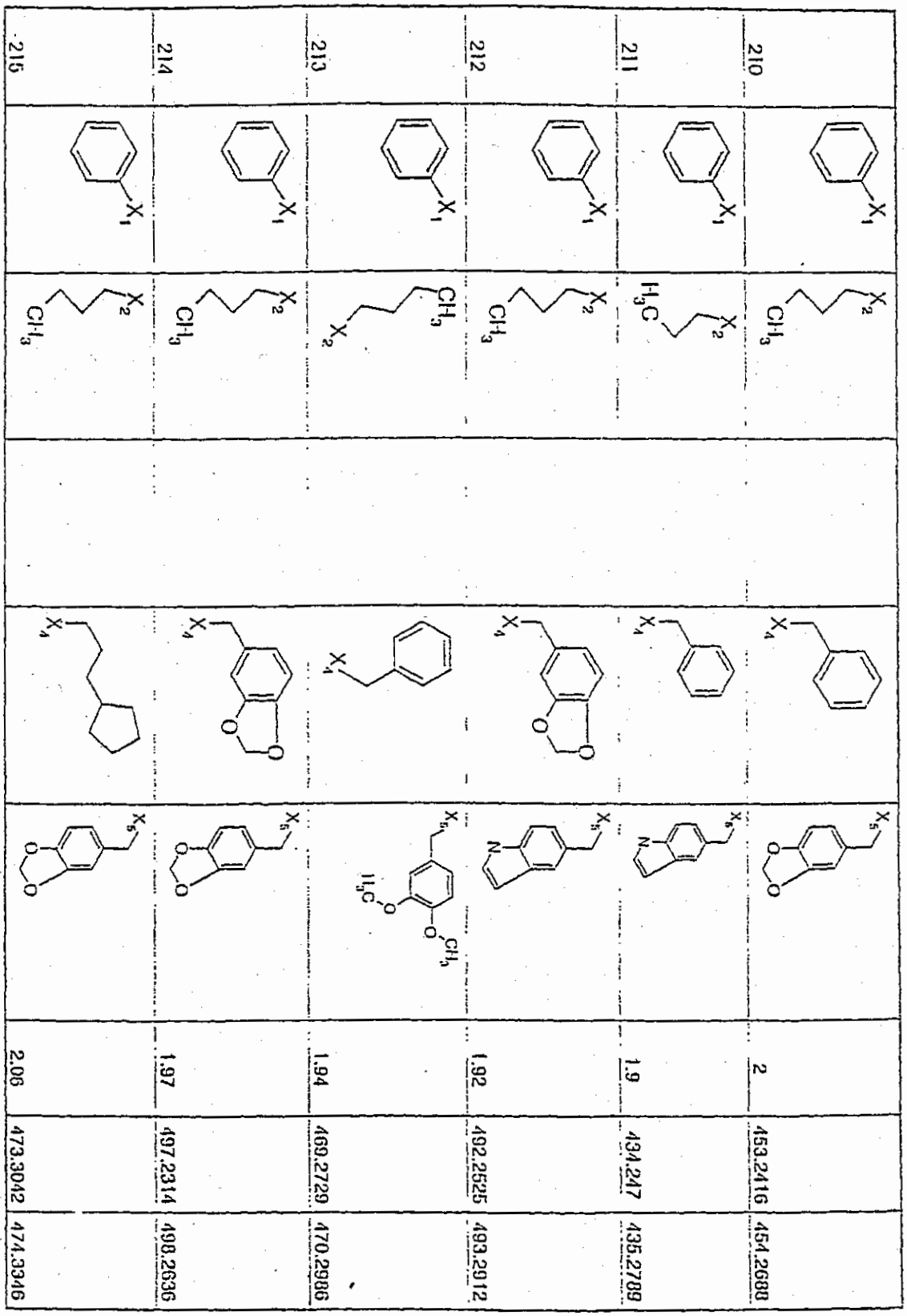


TABLE 1

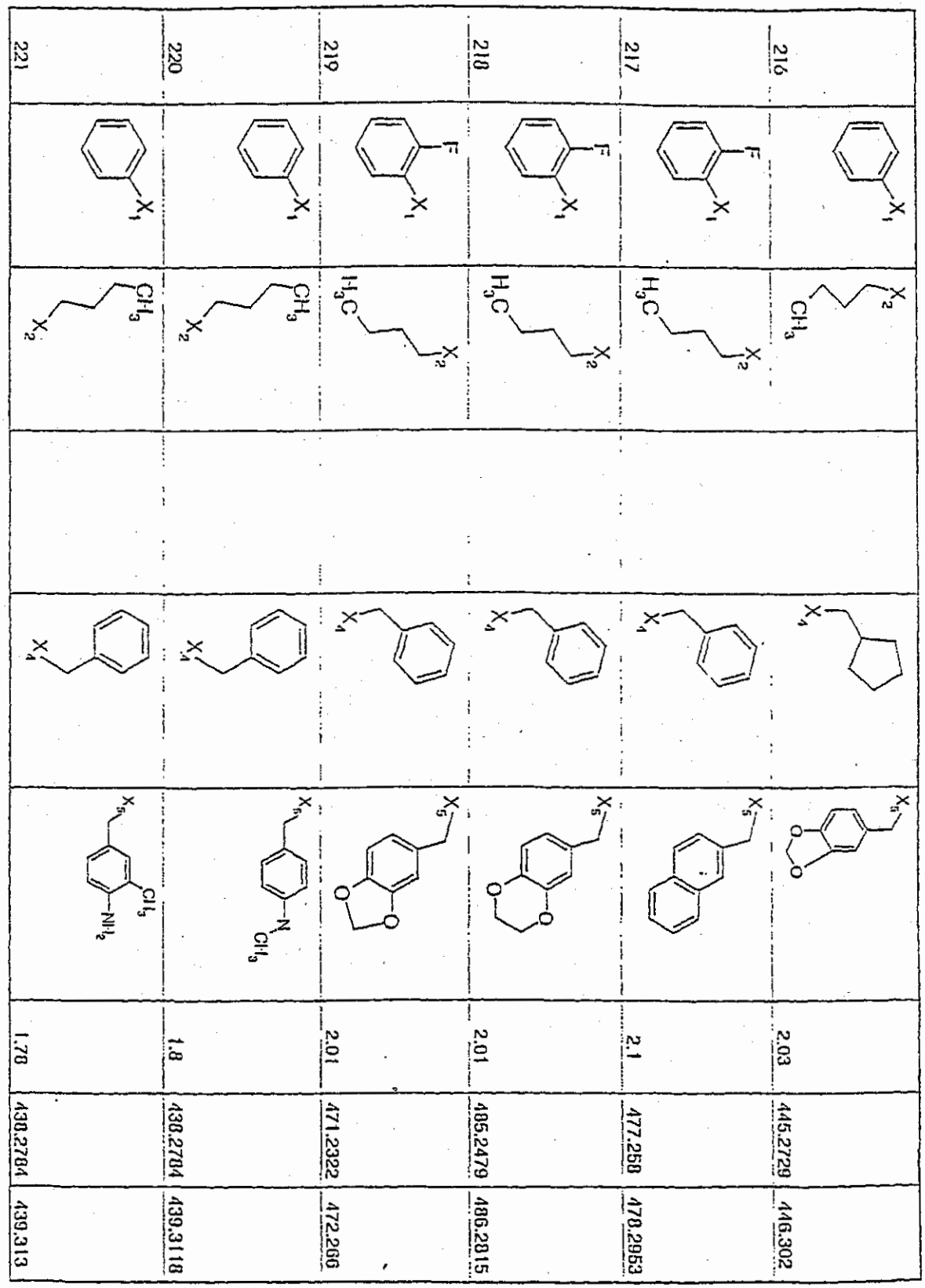
CMP #	R1	R2	R3	R4	R5	RT in Time	Cmd Mass	H+ Ion Obs
200						1.95	448.2627	449.3036
201						1.96	462.2784	463.3201
202						1.91	462.2784	463.3241
203						2.09	459.2075	460.3053



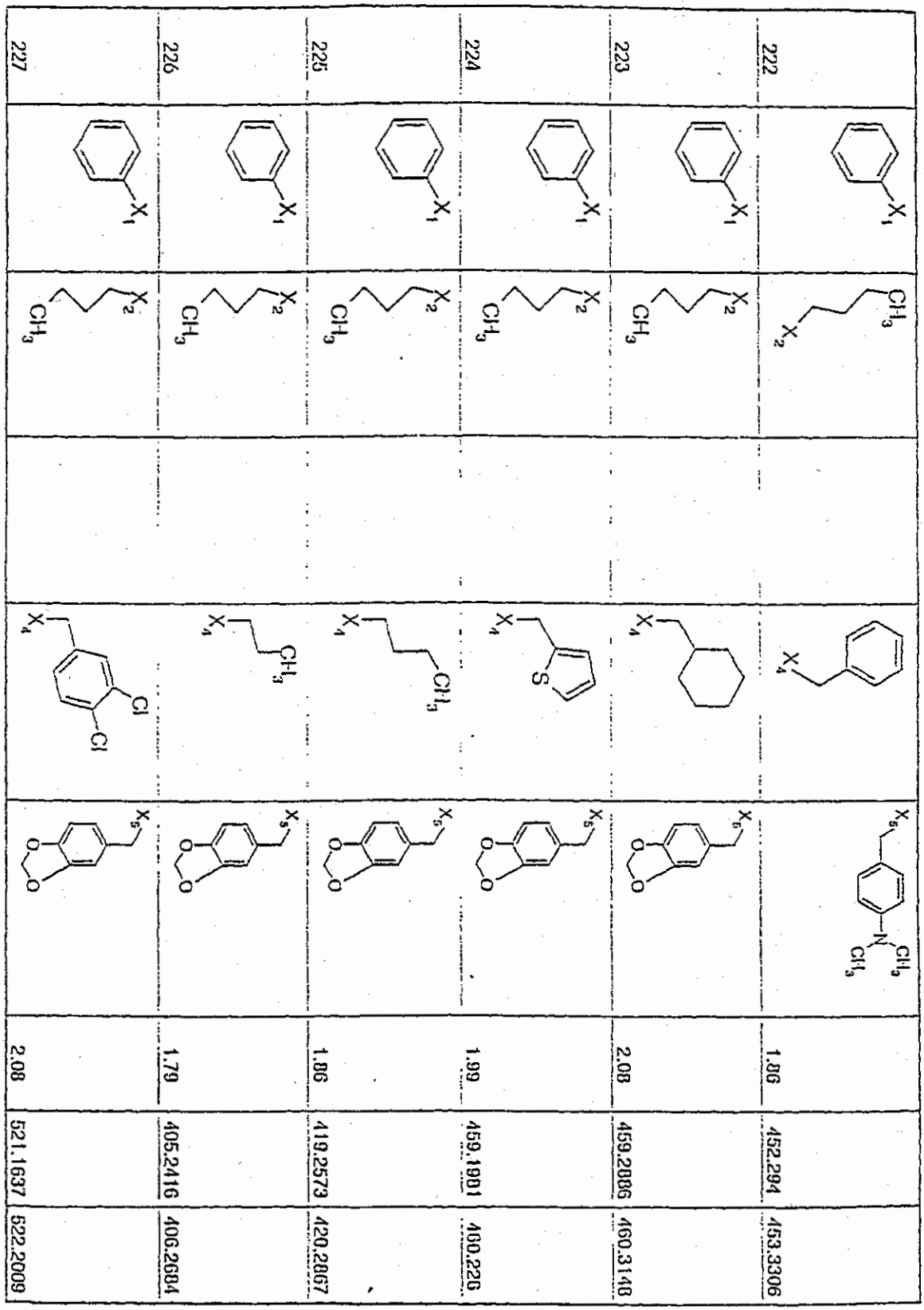
204				2.1	459.2675	460.2903	
205				2.04	467.2573	468.2008	
206				2.05	481.2729	482.3052	
207				2	467.2573	468.2805	
208				1.96	453.2416	454.2695	
209				1.9	375.2675	376.2097	



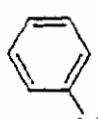
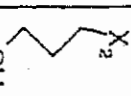
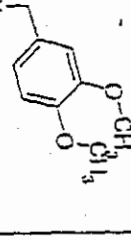
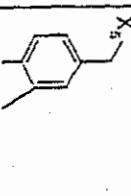
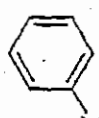
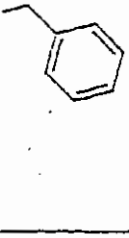
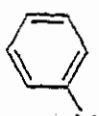
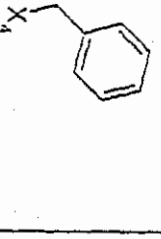
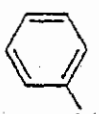
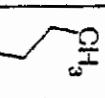
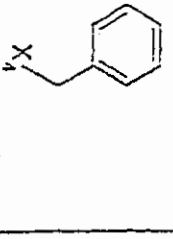
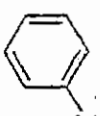
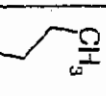
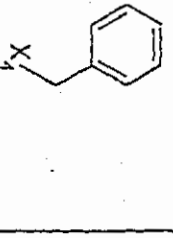
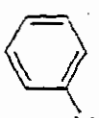
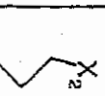
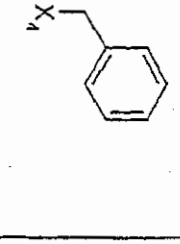
210						2	453.2416	454.2688
211						1.9	434.247	435.2789
212						1.92	492.2525	493.2912
213						1.94	469.2729	470.2986
214						1.97	497.2314	498.2636
215						2.06	473.3042	474.3346

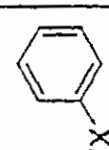
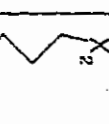
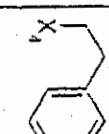
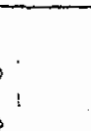
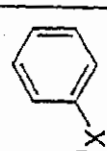
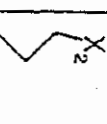
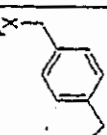
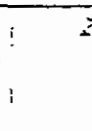
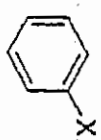
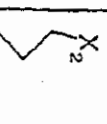
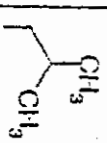
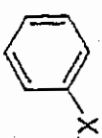
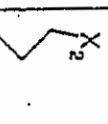
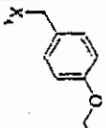
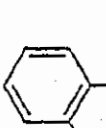
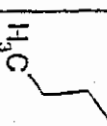
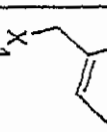
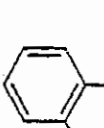
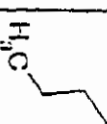
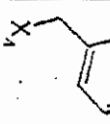


216				2.03	445.2729	446.302		
217				2.1	477.258	478.2953		
218				2.01	485.2479	486.2815		
219				2.01	471.2322	472.266		
220				1.8	438.2784	439.3118		
221				1.78	438.2784	439.313		



222					1.86	452.294	453.3306	
223					2.08	459.2806	460.3148	
224					1.99	459.1901	460.226	
225					1.86	419.2573	420.2867	
226					1.79	405.2416	406.2684	
227					2.08	521.1637	522.2009	

228					1.91	513.2628	514.2951
229					2.02	461.2467	462.2794
230					2	461.2467	462.2892
231					2.05	465.2239	466.267
232					2.1	477.1739	478.2021
233					1.98	462.2784	463.3135

234								
235						2.07	535.1793	536.2415
236						2.11	495.2886	496.3355
237								
238						2	483.2522	484.3027
239						1.87	482.3046	483.3743

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242						2.01	483.2532	484.3157
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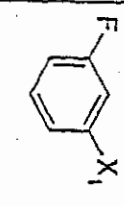
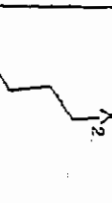
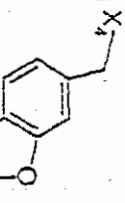
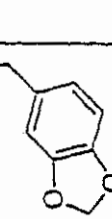
246						2	511.2471	512.3024
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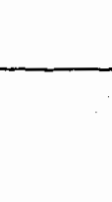
248						1.98	515.222	516.2795
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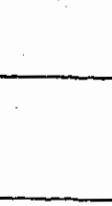
250						2.06	503.2573	504.3187
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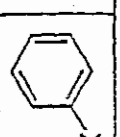
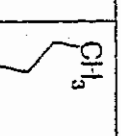
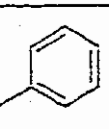
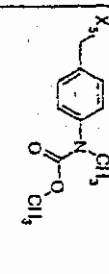
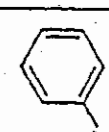
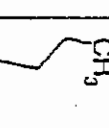
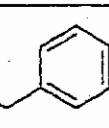
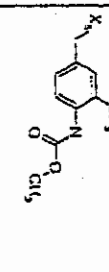
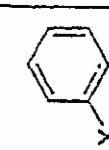
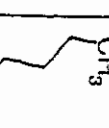
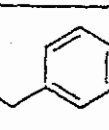
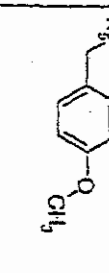
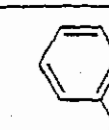
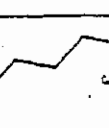
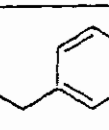
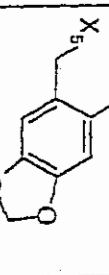
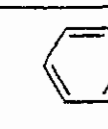
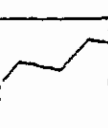
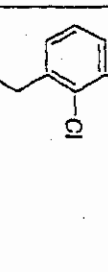
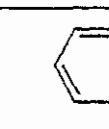
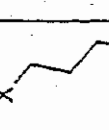
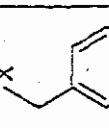
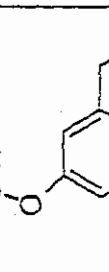
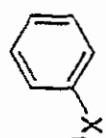
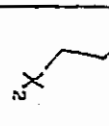
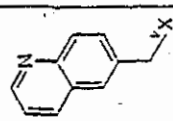
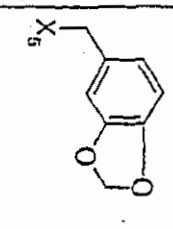
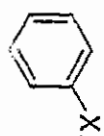
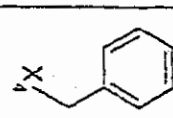
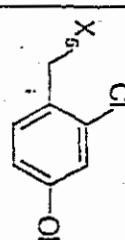
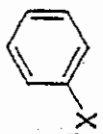
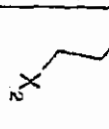
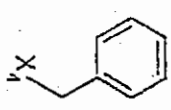
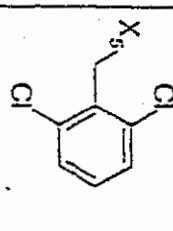
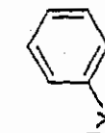
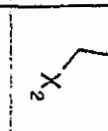
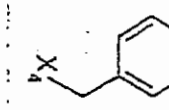
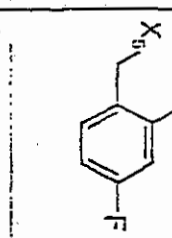
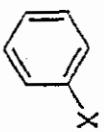
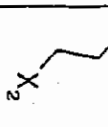
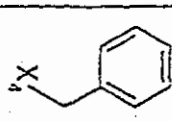
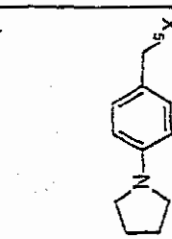
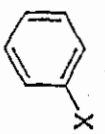
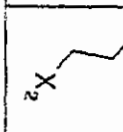
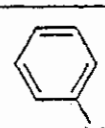
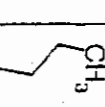
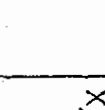
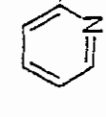
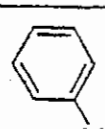
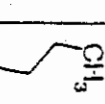
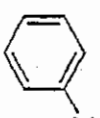
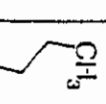
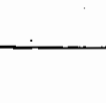
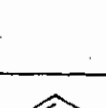
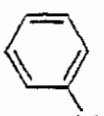
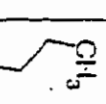
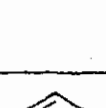
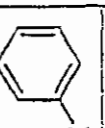
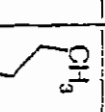
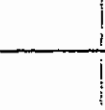
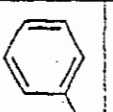
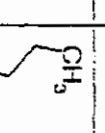
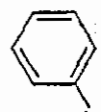
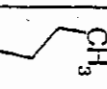
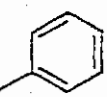
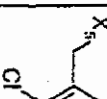
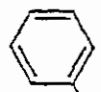
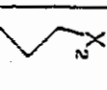
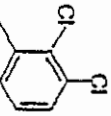
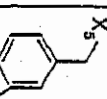
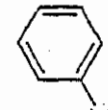
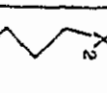
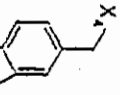
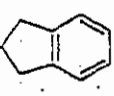
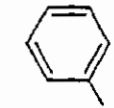
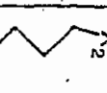
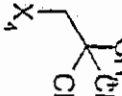
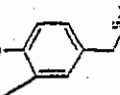
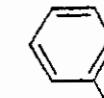
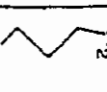
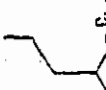
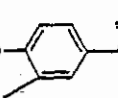
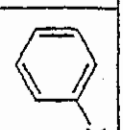
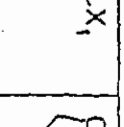
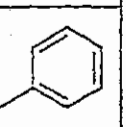
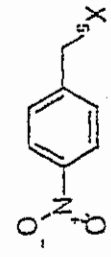
252						1.95	496.2838	497.3316
253						1.93	496.2838	497.3374
254						1.99	439.2624	440.3063
255						2.05	487.2027	488.258
256						2.1	443.1895	444.2521
257						2	439.2624	440.3058

258						1.78	504.2525	505.3216
259						1.97	459.2077	460.287
260						2.06	477.1739	478.2339
261						2.06	461.2034	462.2581
262								
263						1.76	480.3253	481.4043

264						1.75	410.247	411.2961
265						2.01	503.2339	504.2863
266						2.07	493.2341	494.2973
267						1.88	425.2467	426.2948
268						2.05	443.2128	444.2672
269						2.04	461.2034	462.255

270						2.1	477.1739	478.2429
271						2.06	521.1637	522.2083
272						2.02	479.2573	480.2964
273						2.03	433.2729	434.3264
274						1.9	433.2729	434.3161
275						1.74	424.2627	425.298

276							1.98	454.2369	455.2756
277							2.09	496.1644	496.227
278							1.86	470.2846	471.3502
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280							2.02	487.2027	488.2712
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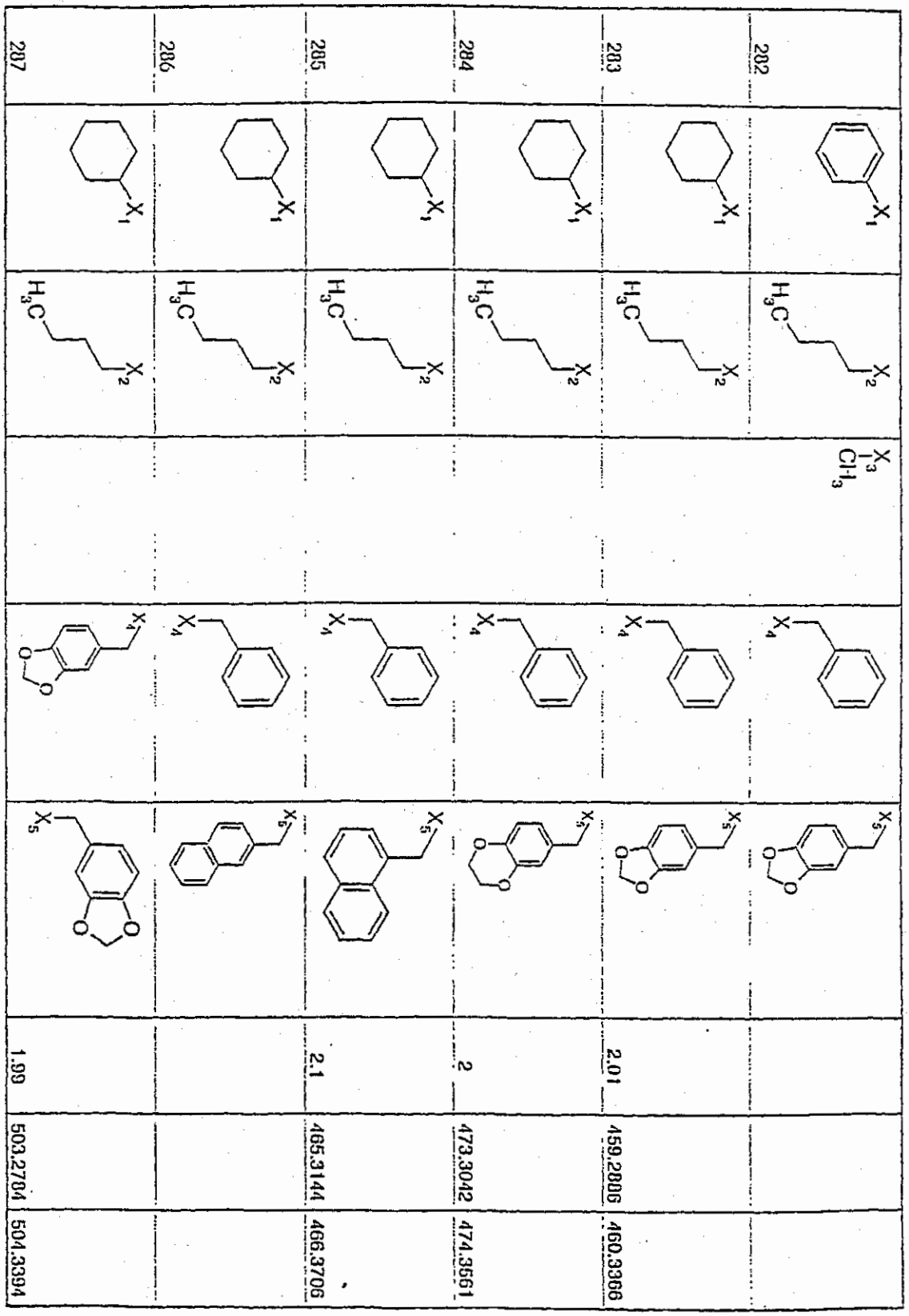

282								
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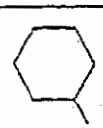
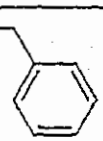
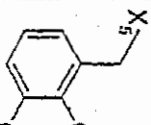
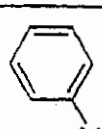
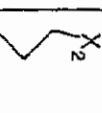
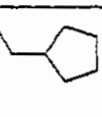
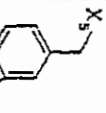
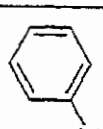
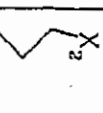
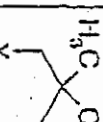
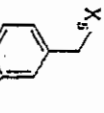
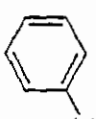
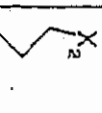
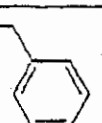
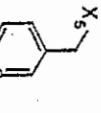
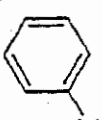
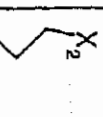
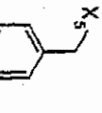
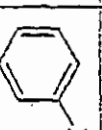
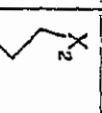
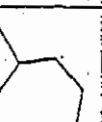
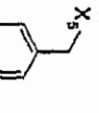
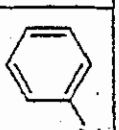
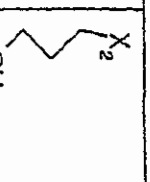
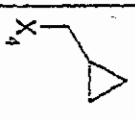
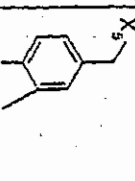
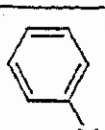
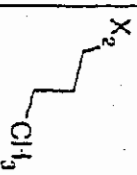
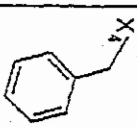
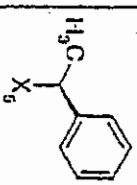
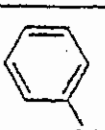
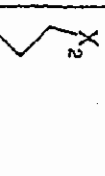
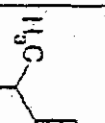
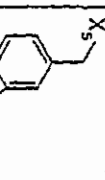
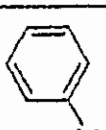
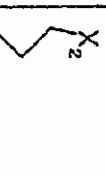
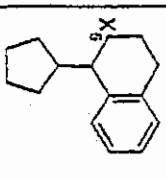
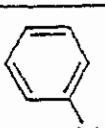
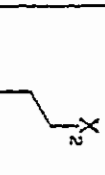
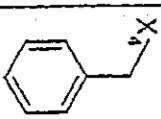
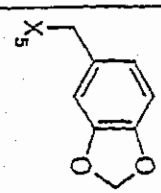
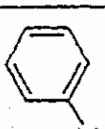
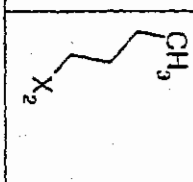
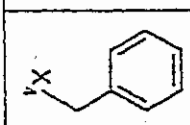
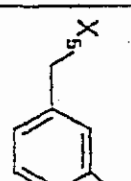
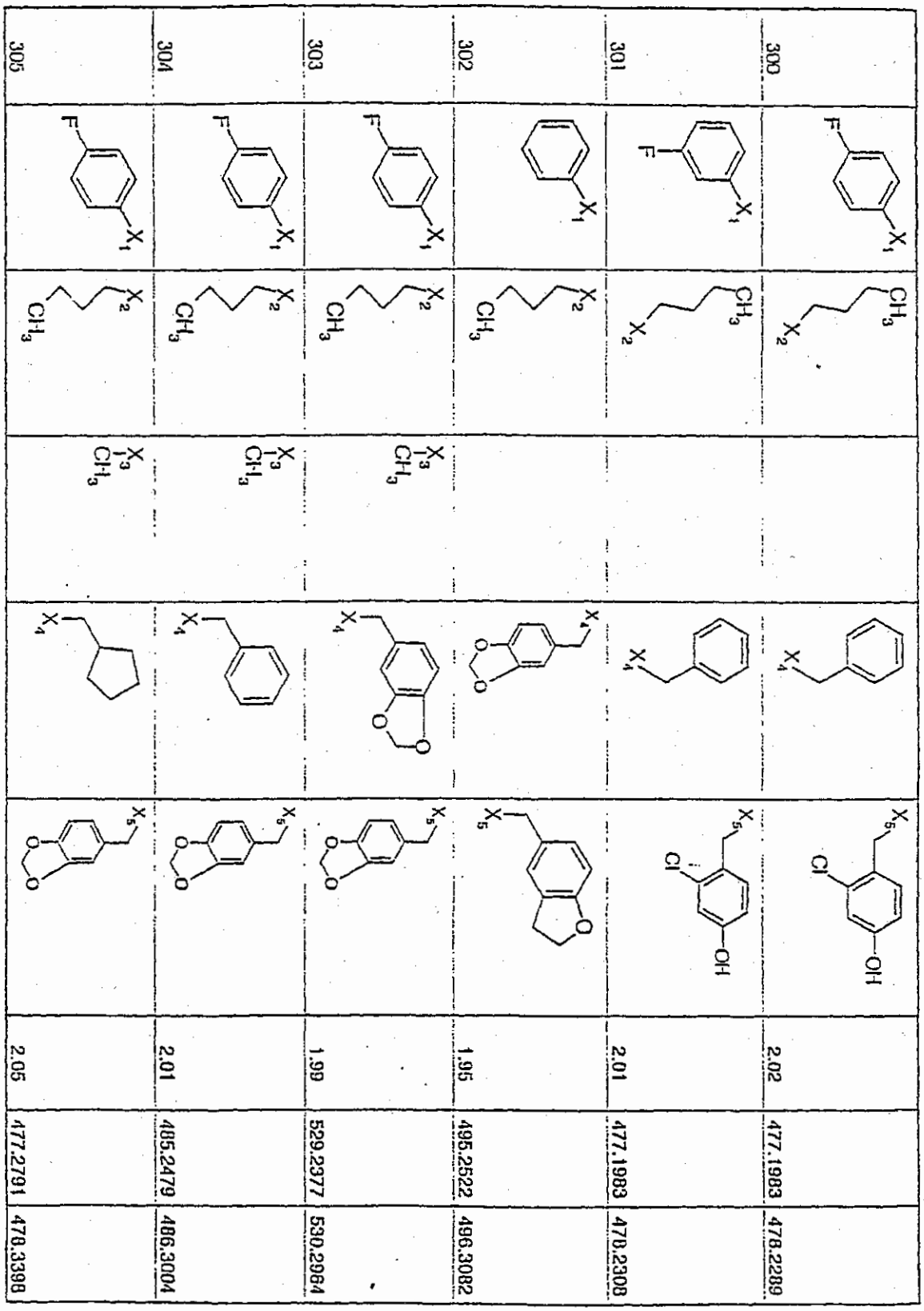
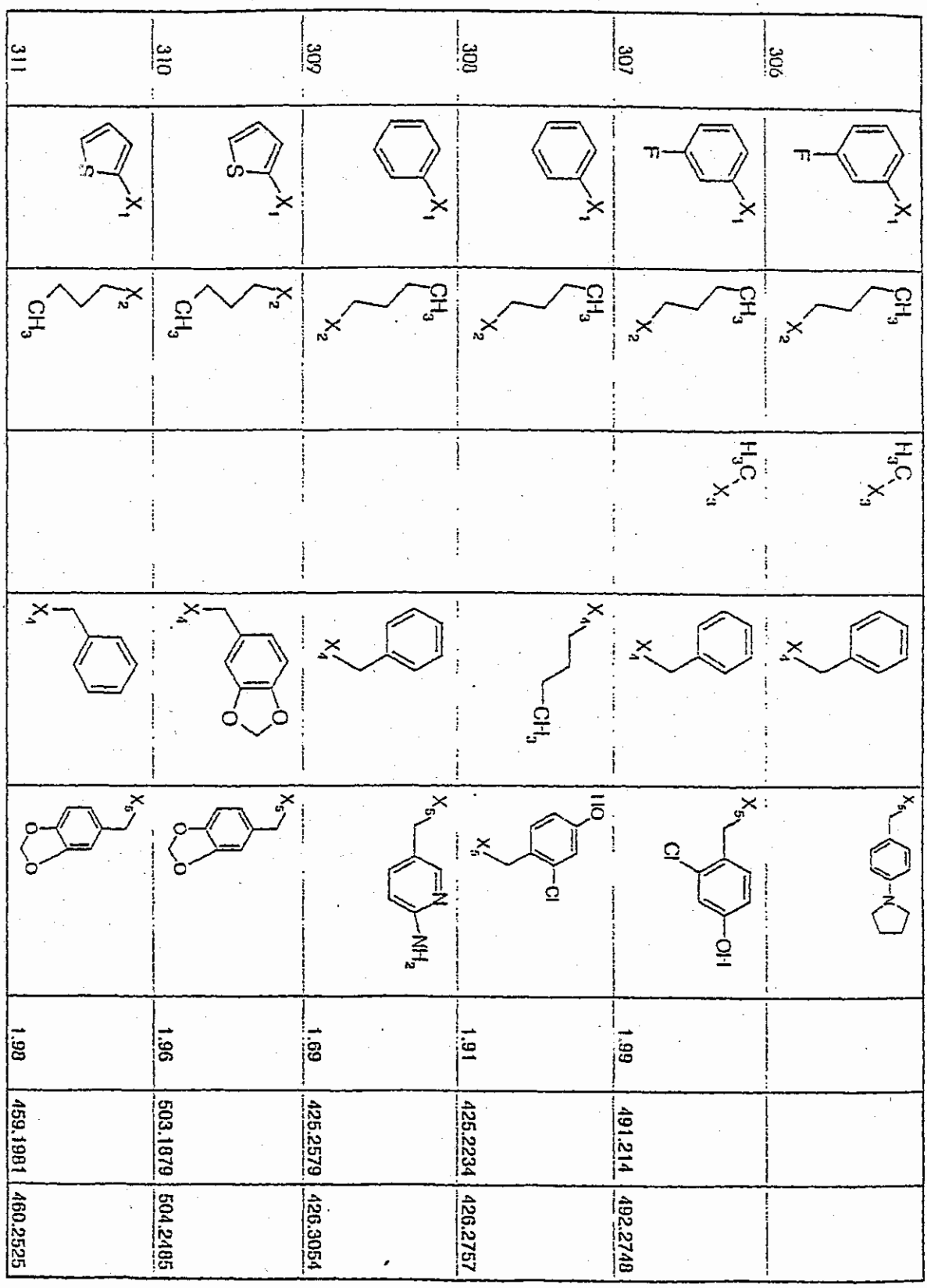
288							
289						1.99	459.2886	460.3446
290						2.07	447.2886	448.3307
291						2.06	481.2729	482.3294
292						2.08	475.3199	476.3839
293						2.11	473.3042	474.361

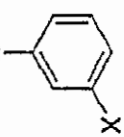
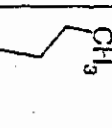
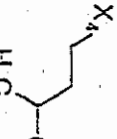
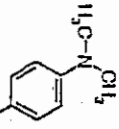
294						1.76	417.2416	418.2879
295						2.05	423.2675	424.2875
296						2.05	467.2573	468.2819
297						2.01	413.2031	414.3154
298						2.05	467.2573	468.2849
299						2.02	451.2624	452.2898

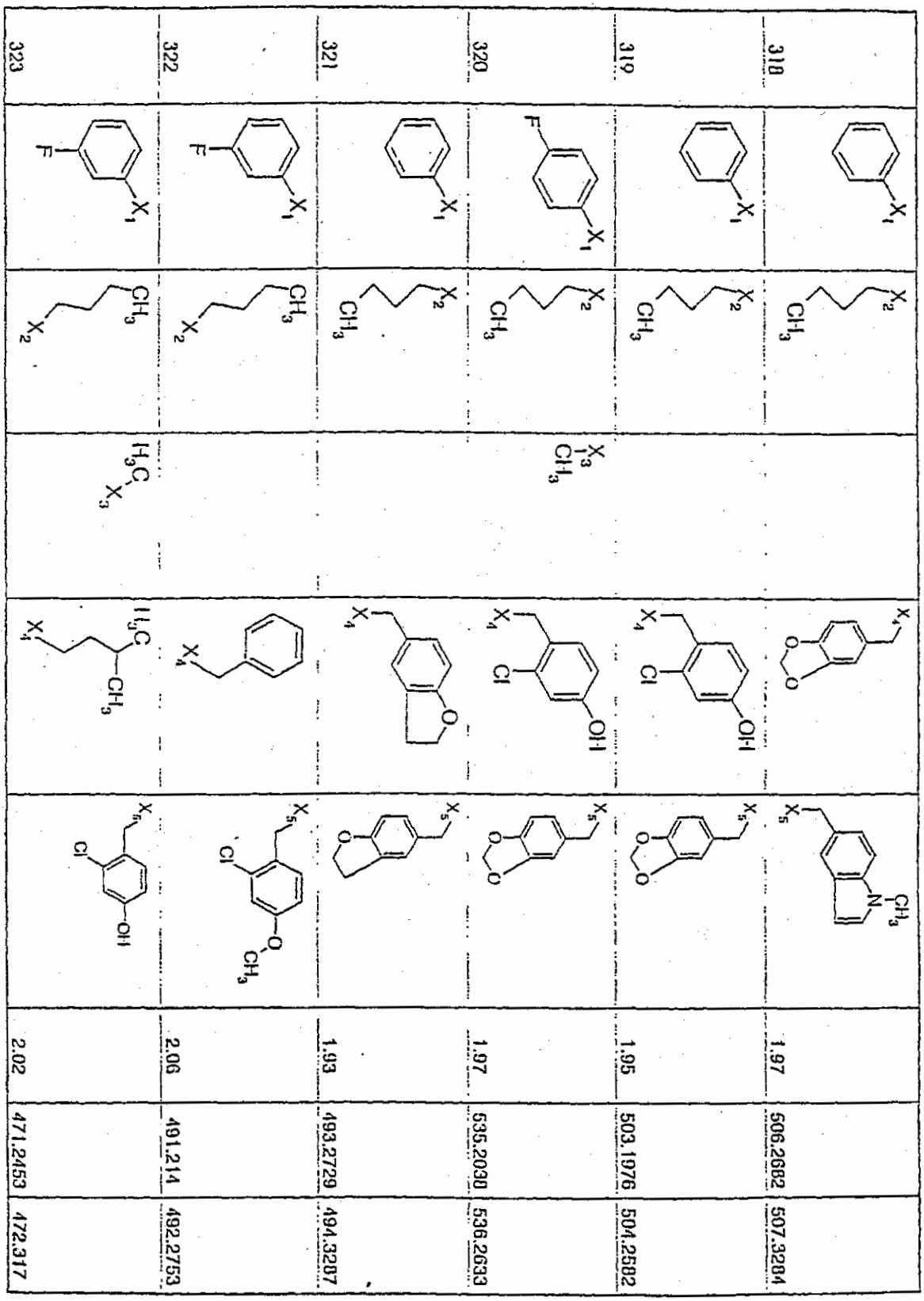


300					2.02	477.1983	478.2289
301					2.01	477.1983	478.2308
302					1.95	495.2522	496.3082
303					1.99	529.2377	530.2964
304					2.01	485.2479	486.3004
305					2.05	477.2791	478.3398

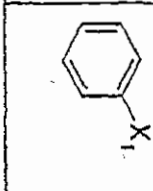
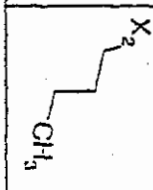
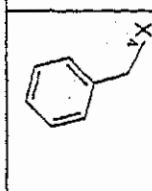
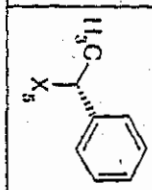
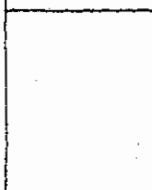


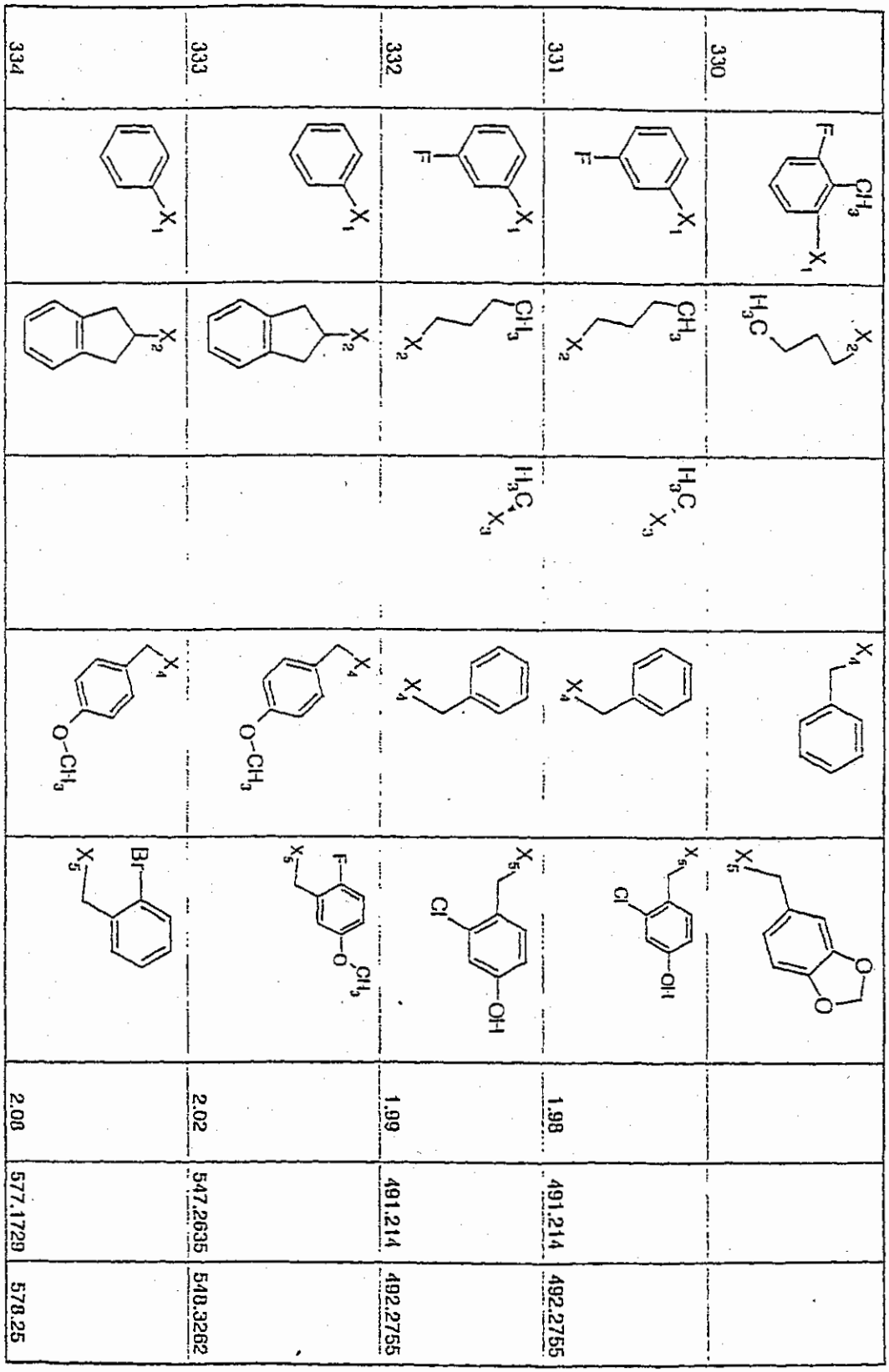
306							
307					1.99	491.214	492.2748
308					1.91	425.2234	426.2757
309					1.69	425.2579	426.3054
310					1.96	503.1879	504.2485
311					1.98	459.1981	460.2525

312						1.99	451.2293	452.2899
313						1.99	469.2529	470.3111
314						2.01	483.2606	484.3253
315						1.78	512.3315	513.4124
316						1.81	432.3253	433.3902
317						1.83	450.3159	451.3883

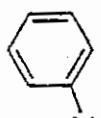
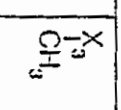
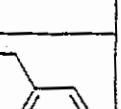
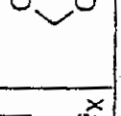
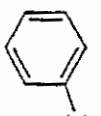
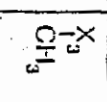
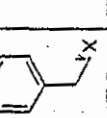
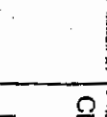
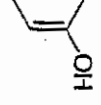
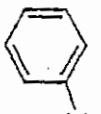
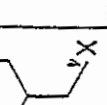
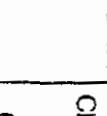
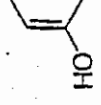
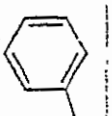
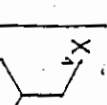
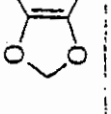
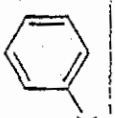
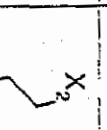
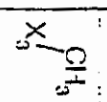
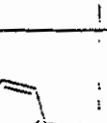
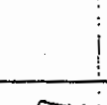
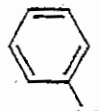
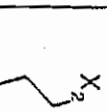
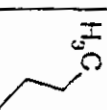
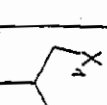


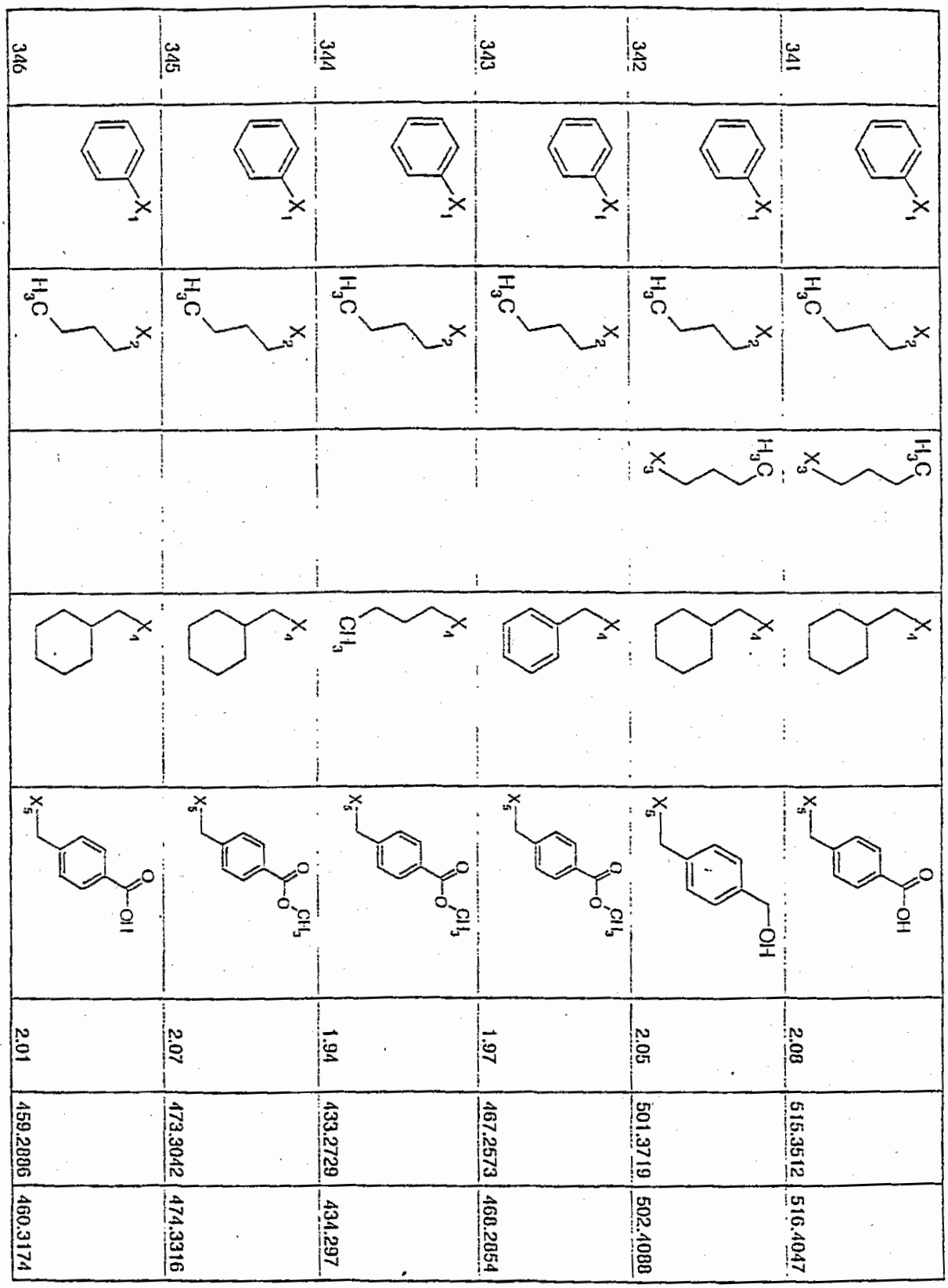
318						1.97	506.2682	507.3284
319						1.95	503.1976	504.2582
320						1.97	535.2030	536.2633
321						1.93	493.2729	494.3287
322						2.06	491.214	492.2753
323						2.02	471.2453	472.317

324						1.92	443.214	444.2721
325						1.99	457.2296	458.2892
326						1.97	457.2296	458.2943
327						1.87	449.2042	450.3473
328						2.1	475.1957	476.2632
329						2.02	423.2675	424.3092



330								
331							1.98	491.214	492.2755
332							1.99	491.214	492.2755
333							2.02	547.2635	548.3262
334							2.00	577.1729	578.25

335							1.96	511.2471	512.298
336							1.95	517.2132	518.2731
337							2.15	521.3173	522.3696
338							2.15	515.3512	516.4249
339							1.88	493.2522	494.3056
340							2.05	487.3563	488.4303



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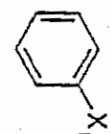
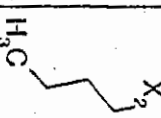
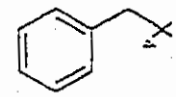
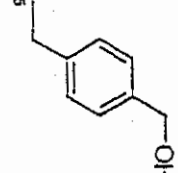
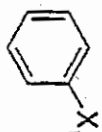
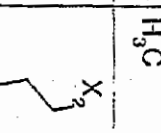
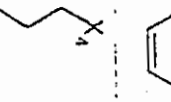
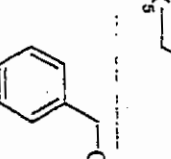
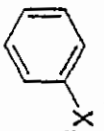
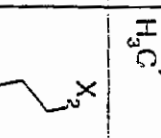
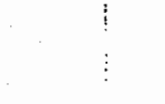
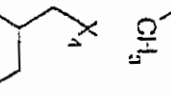
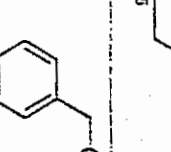
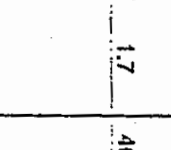
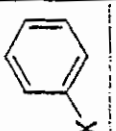
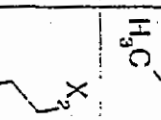
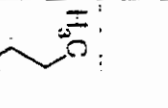
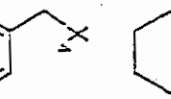
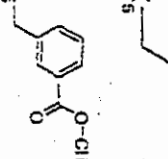
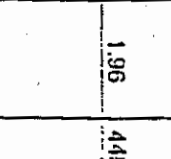
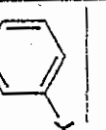
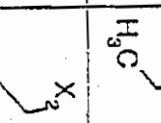
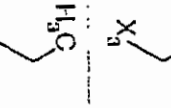
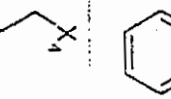
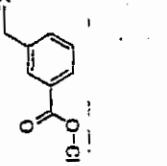
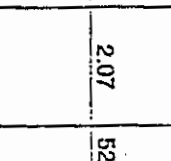
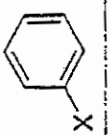
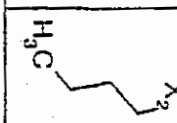
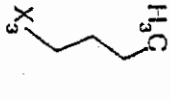
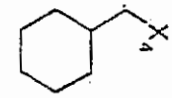
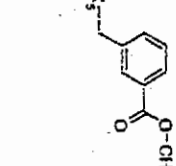
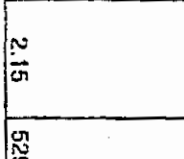
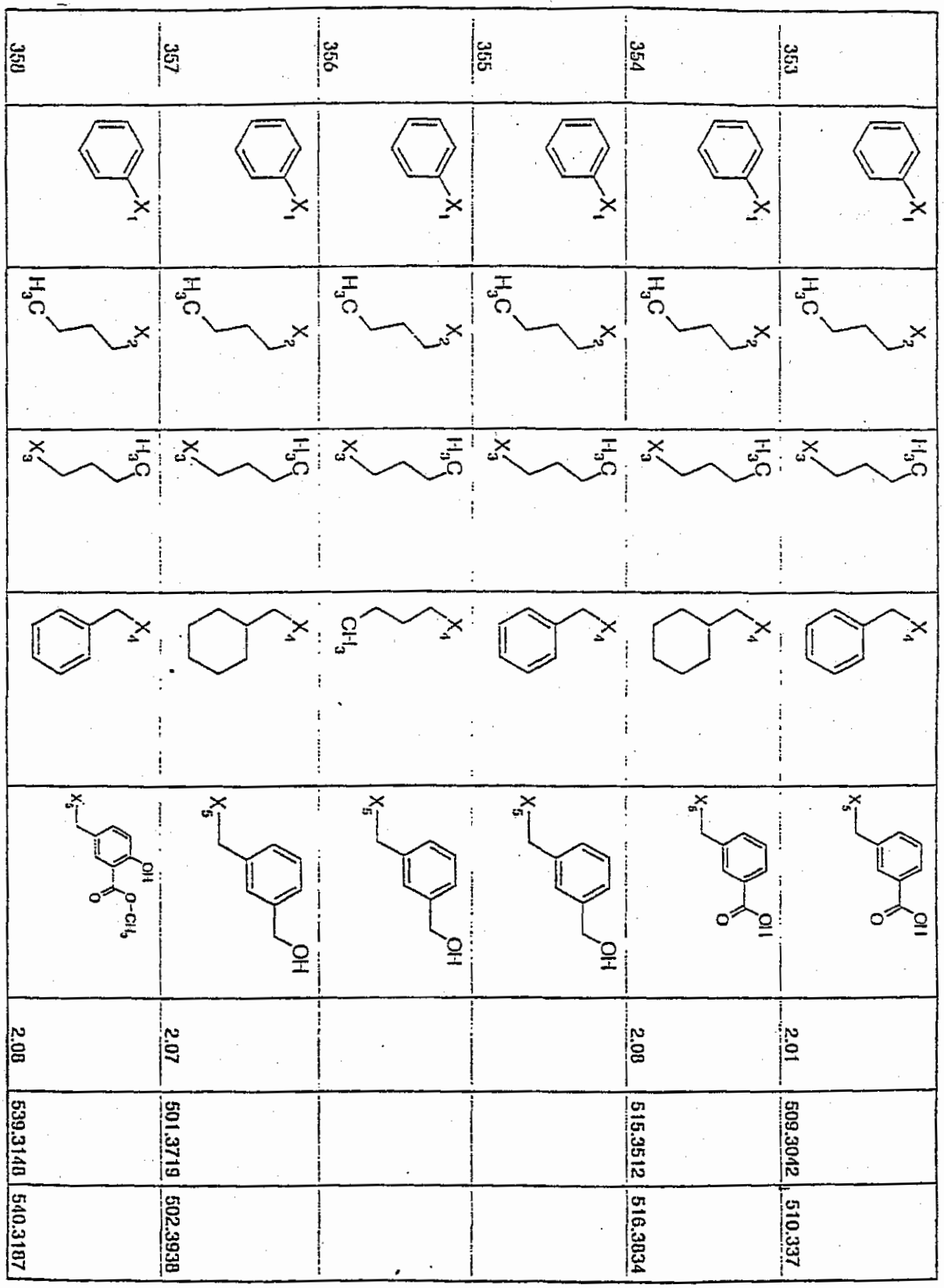
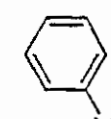
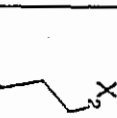
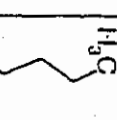
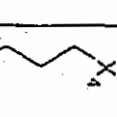
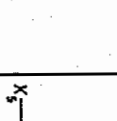
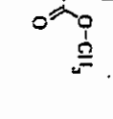
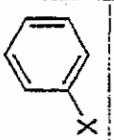
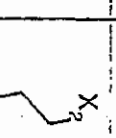
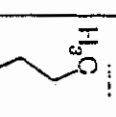
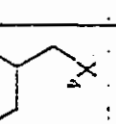
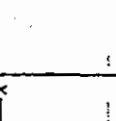
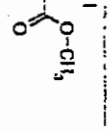
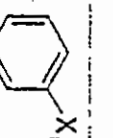
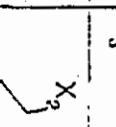
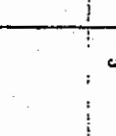
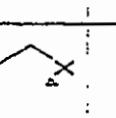
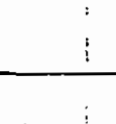
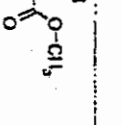
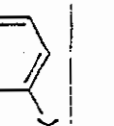
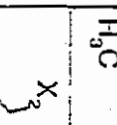
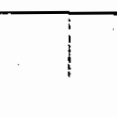
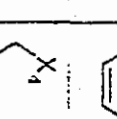
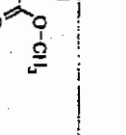
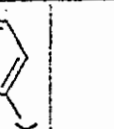
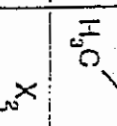
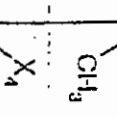
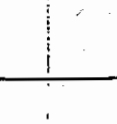
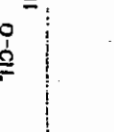
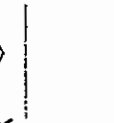
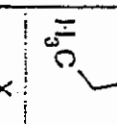
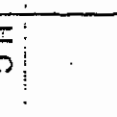
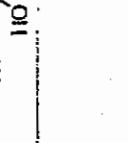
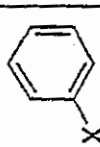
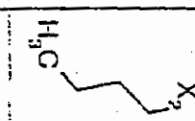
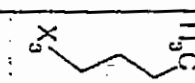
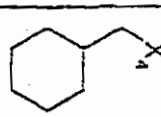
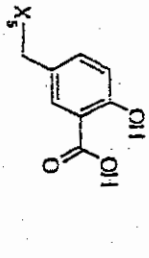
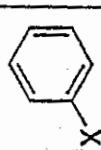
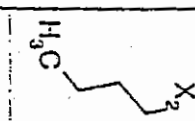
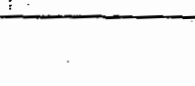
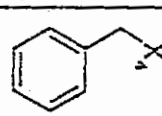
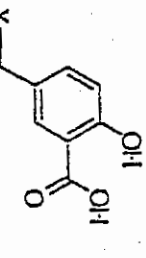
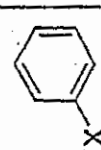
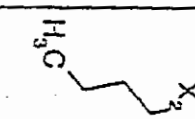
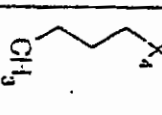
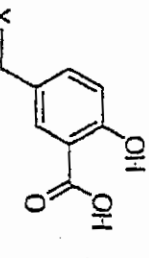
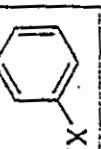
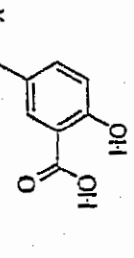
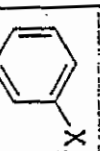
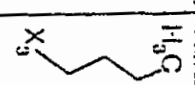
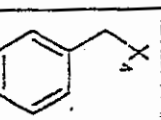
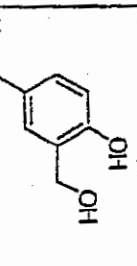
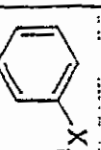
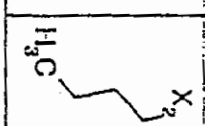
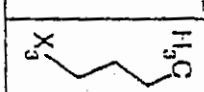
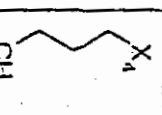
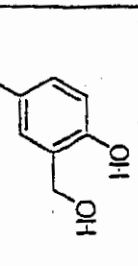
342						2.05	501.3719	502.4088
343						1.97	467.2573	468.2054
344						1.94	433.2729	434.297
345						2.07	473.3042	474.3316
346						2.01	459.2886	460.3174

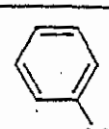
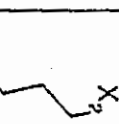
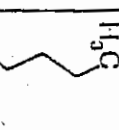
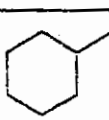
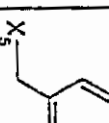
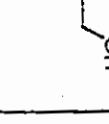
347							1.88	439.2624	440.2939
348							1.7	405.278	406.3116
349							1.96	445.3093	446.3387
350							2.07	523.3199	524.3464
351							2.04	489.3355	490.3575
352							2.15	529.3668	530.3951

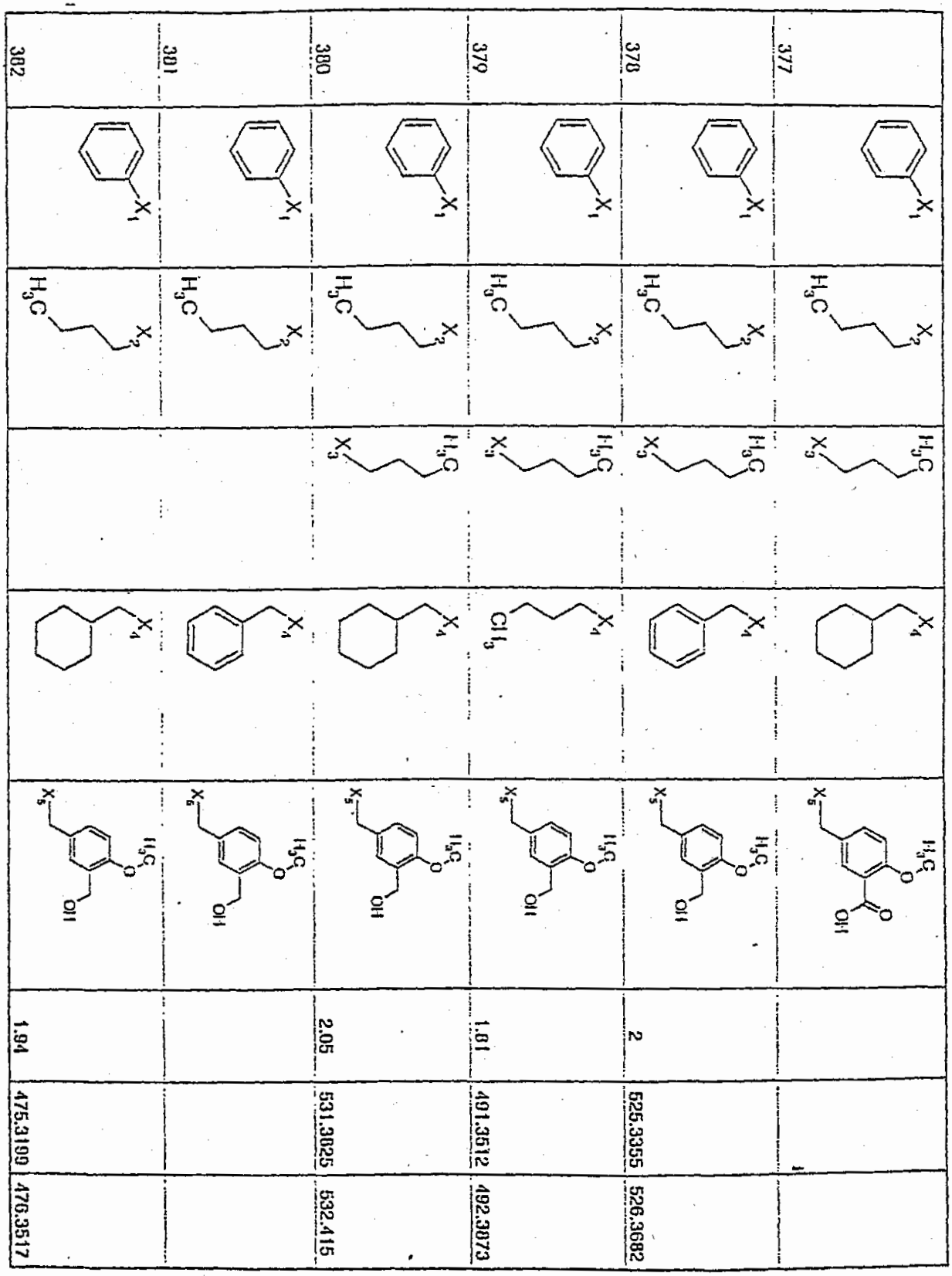


353						2.01	509.3042	510.337
354						2.08	515.3512	516.3034
355								
356								
357						2.07	501.3719	502.3938
358						2.08	539.3148	540.3187

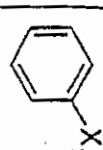
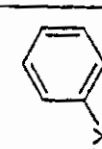
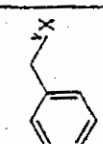
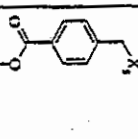
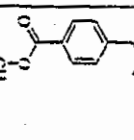
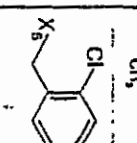
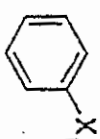
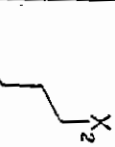
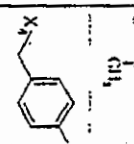
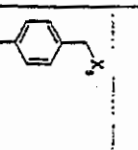
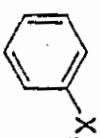
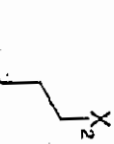
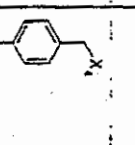
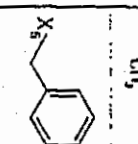
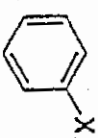
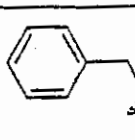
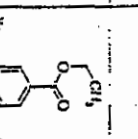
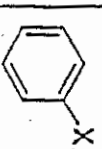
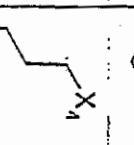
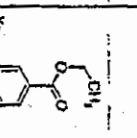
359							2.04	505.3304	506.3531
360							2.16	545.3618	546.3911
361							2	483.2522	484.2723
362							1.93	449.2679	450.2899
363							2.00	489.2991	490.3192
364							2.06	525.2991	526.36

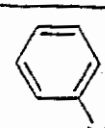
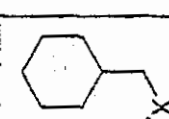
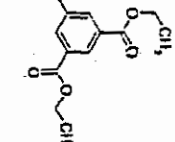
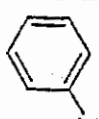
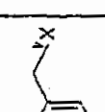
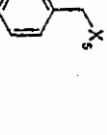
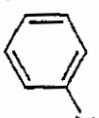
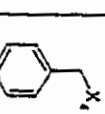
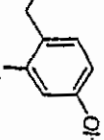
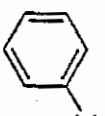
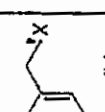
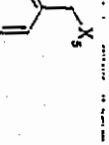
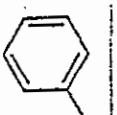
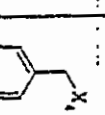
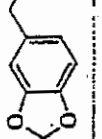
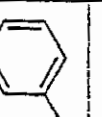
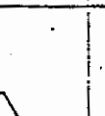
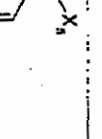
365						2.12	531.3461	532.3955
366						1.95	469.2365	470.2861
367						1.8	435.2522	436.2069
368						2.03	475.2035	476.3151
369						1.94	511.3199	512.3583
370						1.72	477.3355	478.3816

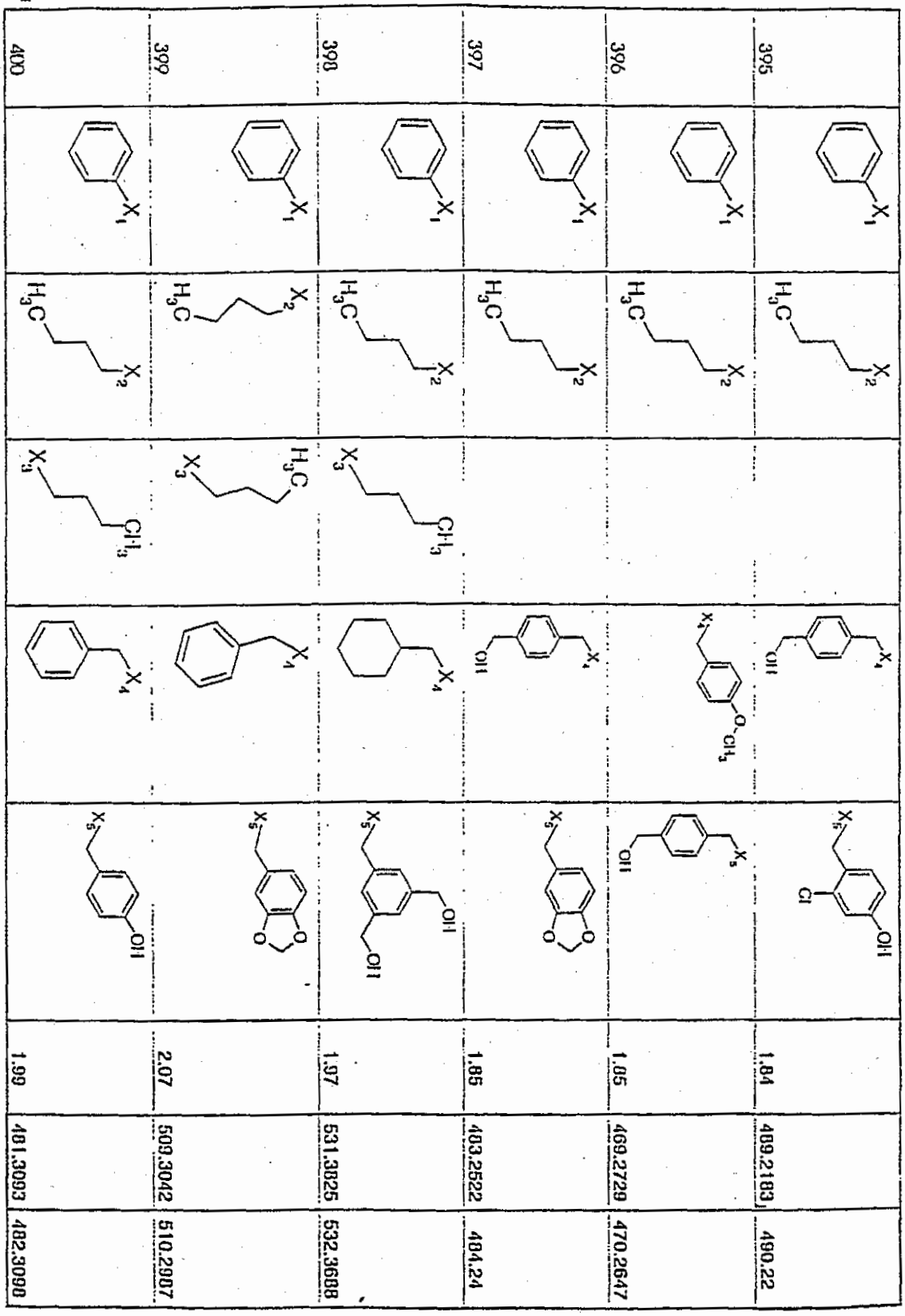
371							1.90	517.3668	510.4061
372							2.02	553.3304	554.3617
373							1.96	519.3461	520.382
374							2.09	559.3774	560.4091
375							1.92	497.2679	490.3003
376							2	503.3148	504.343



377								
378						2	525.3355	526.3682
379						1.81	491.3512	492.3873
380						2.05	531.3025	532.415
381							475.3199	476.3517
382						1.94		

383						1.86	483.2522	484.2405
384						1.94	517.2132	518.2035
385						1.97	497.2679	498.2453
386						1.95	511.2471	512.2275
387						2.06	553.2941	554.2720
388						2.05	519.3097	520.2906

389							2.13	559.341	560.3246
390							1.78	469.2365	470.2301
391							1.00	503.1976	504.1985
392							1.89	483.2522	484.2435
393							1.89	497.2314	498.227
394							1.71	455.2573	456.2579



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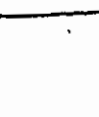
397							1.85	483.2522	484.24
398							1.97	531.3825	532.3688
399							2.07	509.3042	510.2907
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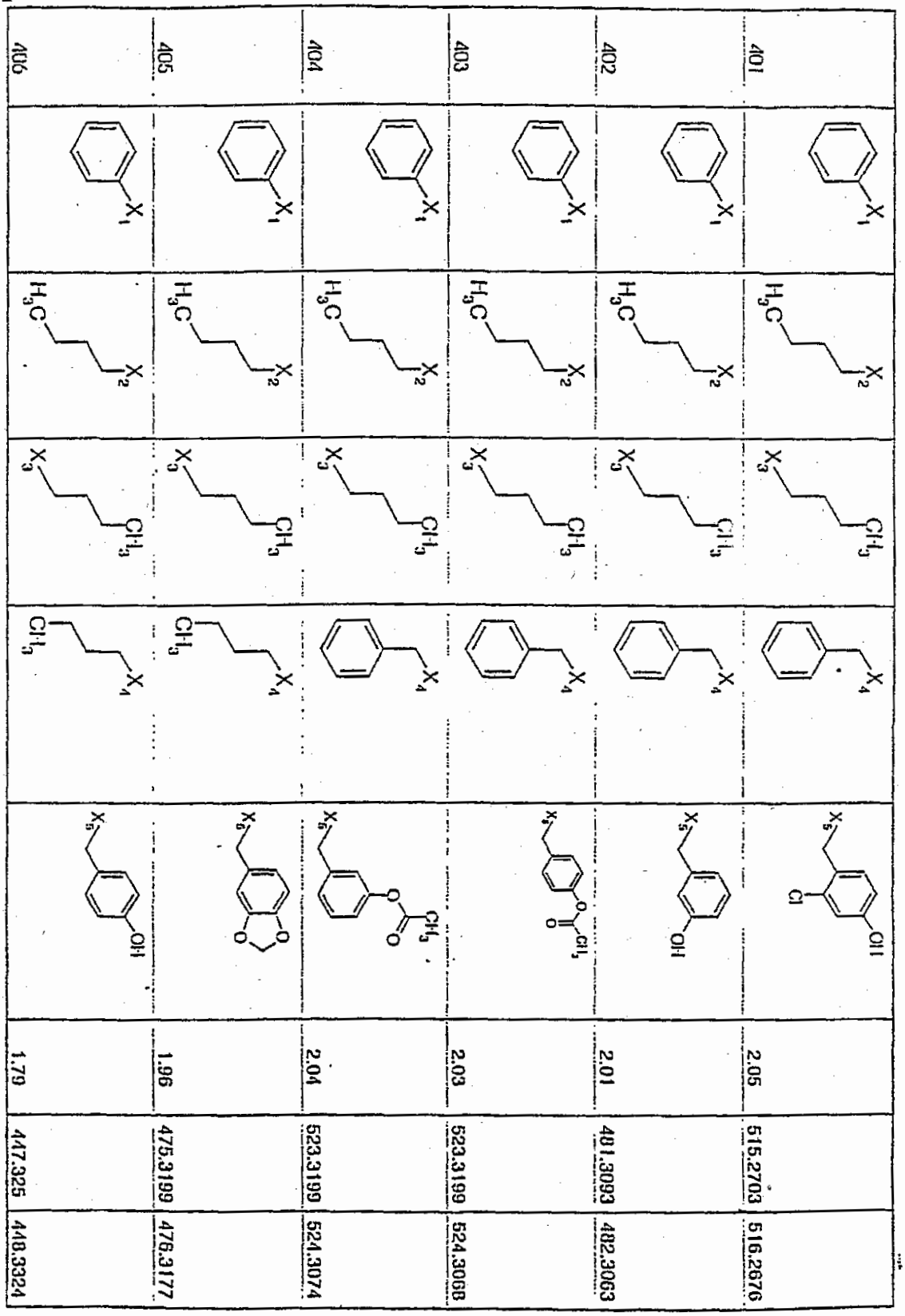
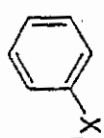
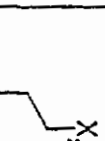
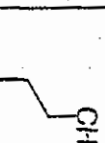
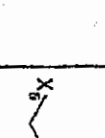
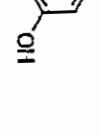


407							2.02	401.286	482.2977
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409							1.97	489.3355	490.3298
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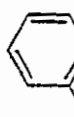
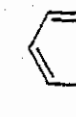
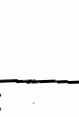
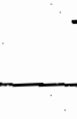
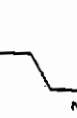
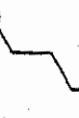
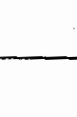
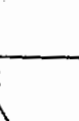
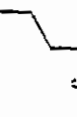
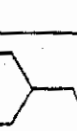
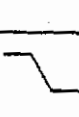
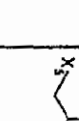
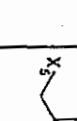
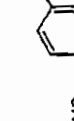
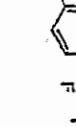
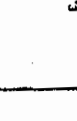
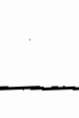
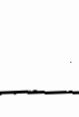
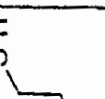
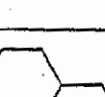
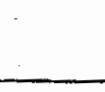
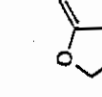
411							2.08	495.325	496.3224
412							1.92	461.3496	462.3352

413							2.15	501.3719	502.3614
414							2.1	515.3124	516.3123
415							2.08	495.325	496.3101
416							2.01	461.3406	462.3389
417							2.16	501.3719	502.3629
418									

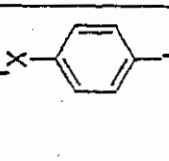
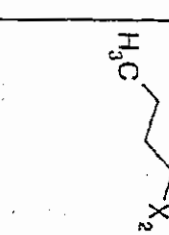
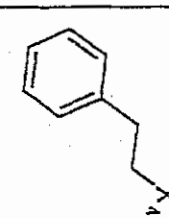
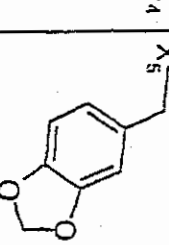
419								
420							2.08	514.4036
421							2.14	515.3512
422							2.14	521.3173
423								

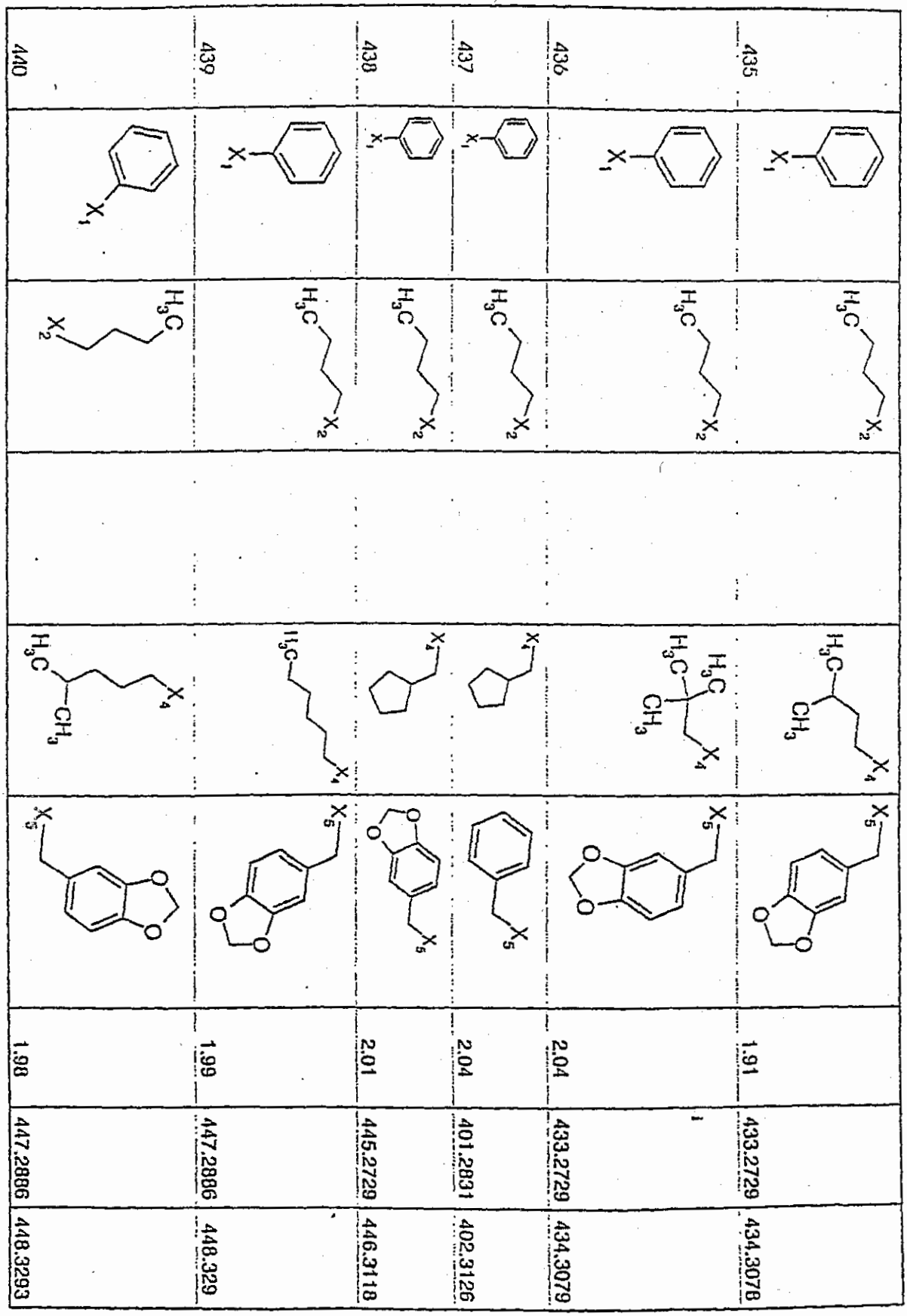
1	515.423
	516.3379
	522.3266

TABLE 1A

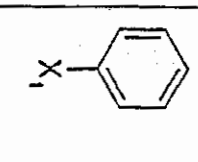
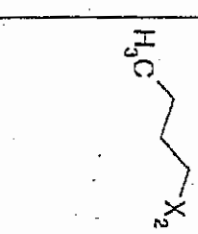
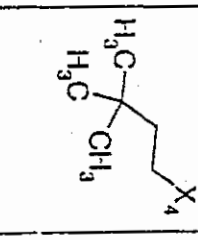
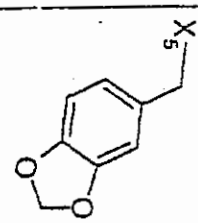
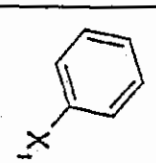
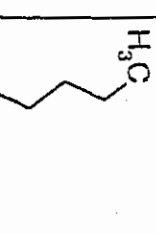
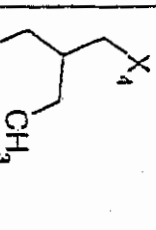
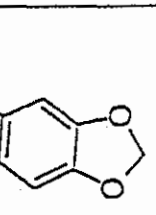
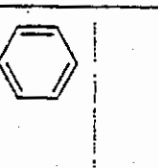
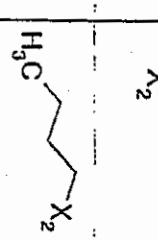
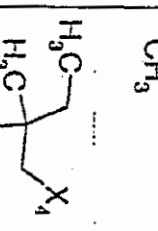
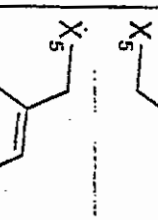
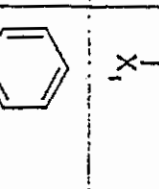
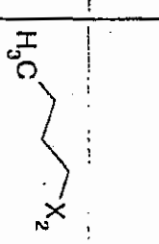
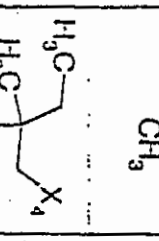
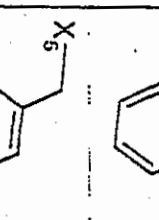
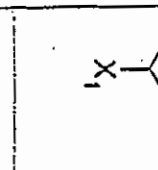
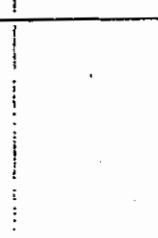
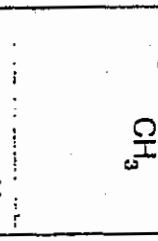
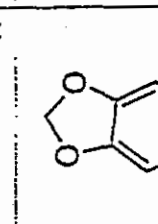
R3 is H unless otherwis specified

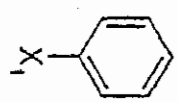
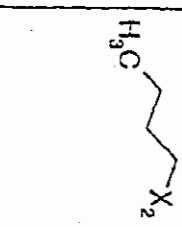
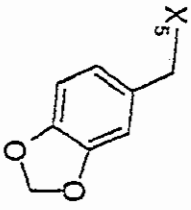
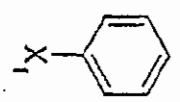
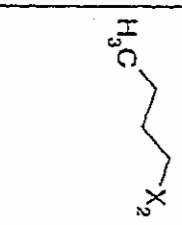
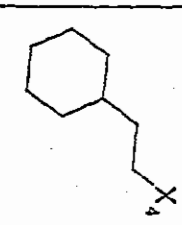
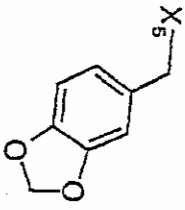
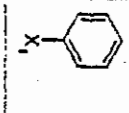
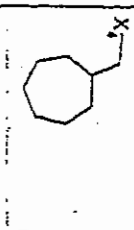
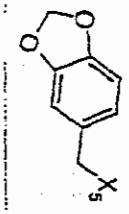
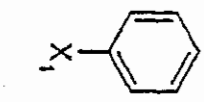
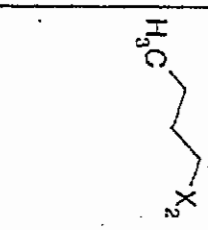
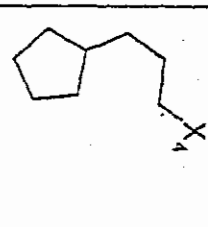
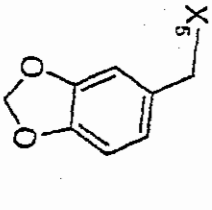
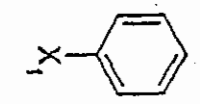
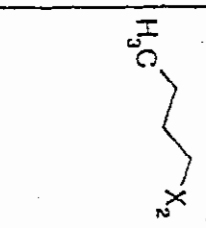
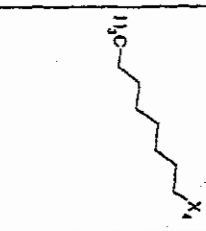
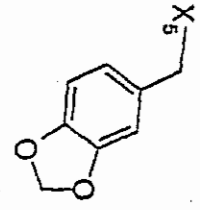
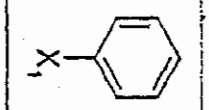
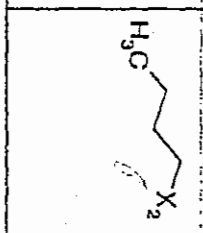
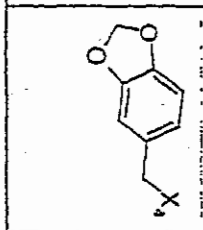
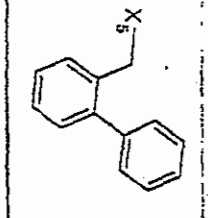
CMP #	R1	R2	R3	R4	R5	Rtn. Time	Cmd Mass	H+ Ion Obs
424						2.02	427.2424	428.2541
425						2.06	441.258	442.2744
426						2.1	455.2737	456.2899
427						2.08	455.2737	456.2953
428						2.13	469.2893	470.3137

429						2.02	485.2479	486.2833
430						2.15	481.3093	482.332
431						1.98	419.2573	420.2856
432						1.91	431.2573	432.2898
433						1.92	433.2729	434.3079
434								



435						1.91	433.2729		434.3078
436						2.04	433.2729		434.3079
437						2.04	401.2831		402.3126
438						2.01	445.2729		446.3118
439						1.99	447.2886		448.329
440						1.98	447.2886		448.3293

441					1.95	447.2886	448.3331
442					2.06	447.2886	448.3315
443					2.09	403.2907	404.3406
444					2.07	447.2886	448.3365
445					1.99	459.2886	460.3416
446					2.07	459.2886	460.3427

447						2.04	461.3042	462.362
448						2.04	473.3042	474.3634
449						2.12	473.3042	474.3605
450						2.05	473.3042	474.3627
451						2.09	475.3199	476.3831
452						2.09	529.2729	530.334

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454						2.02	423.2675	424.3183
455						2.01	409.2518	410.3021
456						2.07	459.2675	460.326
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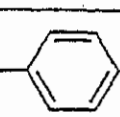
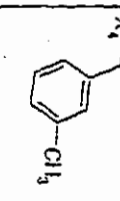
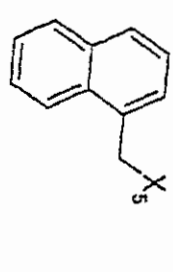
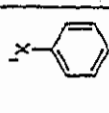
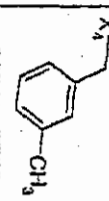
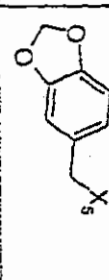
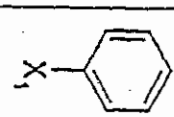
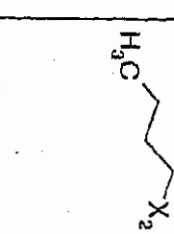
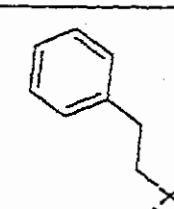
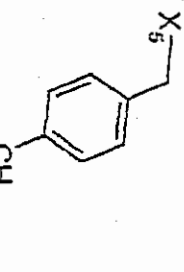
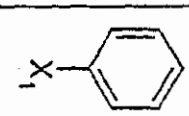
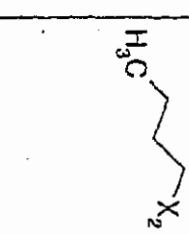
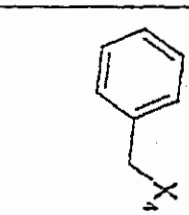
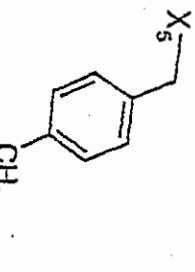
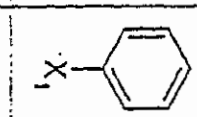
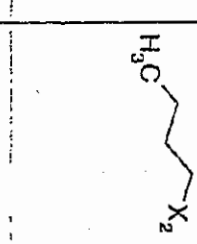
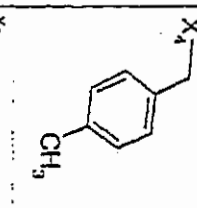
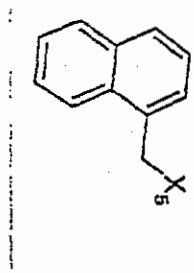
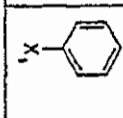
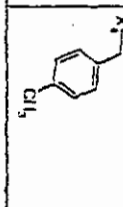
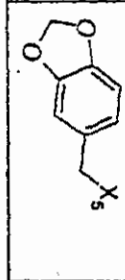
460						2.11	473.2831	474.3436
461						2.04	467.2573	468.3188
462						2.06	437.2831	438.3386
463								
464						2.11	473.2831	474.3465
465						2.03	467.2573	468.3192

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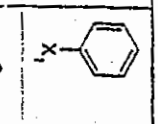
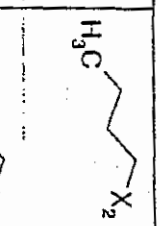
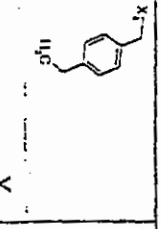
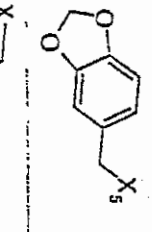
467						2.1	473.2831	474.3467
468						2.02	467.2573	468.3227
469						1.99	471.2322	472.3021
470						2.02	441.258	442.3175
471						1.98	471.2322	472.3026
472						2.03	441.258	442.3185

473						2.01	427.2424	428.3031
474						2.07	477.258	478.3228
475						1.99	471.2322	472.3008
476						2.1	451.2987	452.3606
477						2.08	437.2831	438.351
478						2.14	487.2987	488.3652

479							2.07	481.2729	482.3446
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481							2.08	437.2831	438.346
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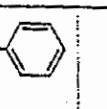
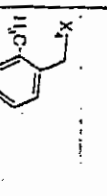
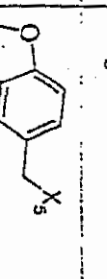
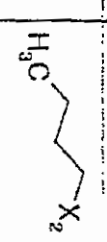
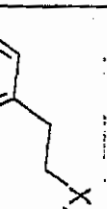
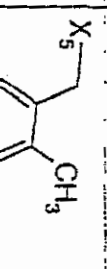
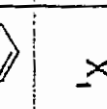
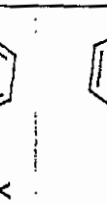
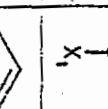
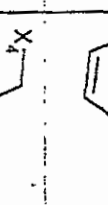
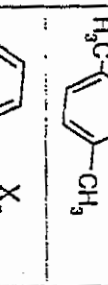
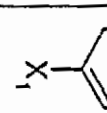
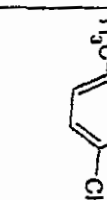
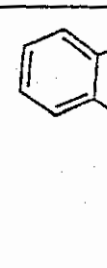
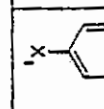
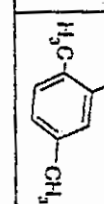
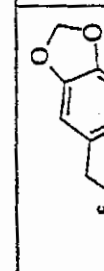
486						2.09	451.2987	452.3614
487						2.08	437.2831	438.3399
488						2.06	481.2729	482.3407
489						2.11	451.2987	452.3647
490						2.09	437.2831	438.3419
491						2.14	487.2987	488.3654
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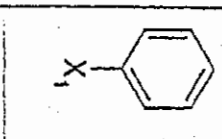
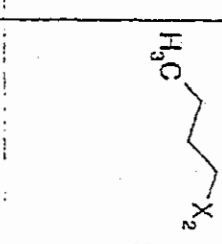
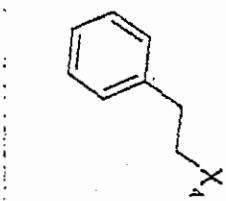
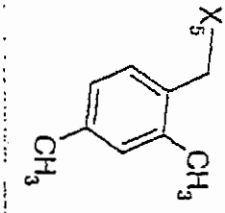
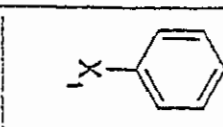
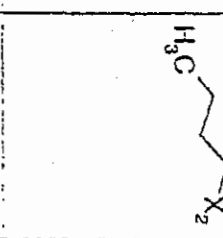
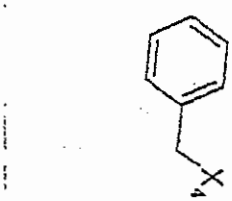
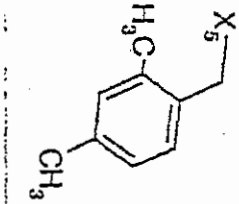
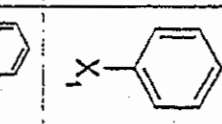
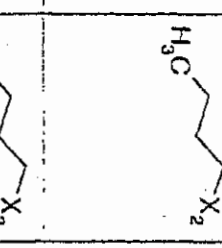
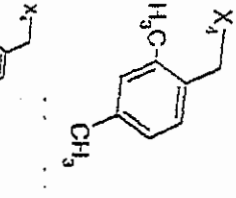
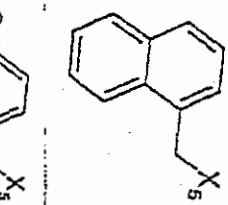
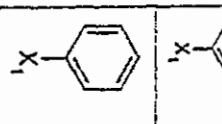
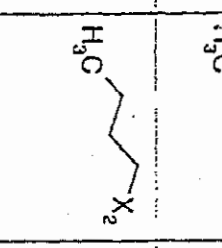
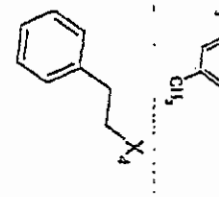
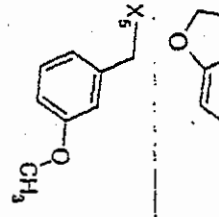
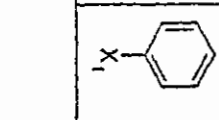
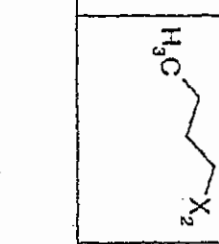
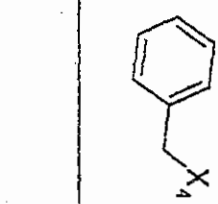
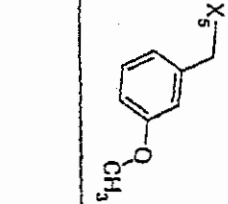
493						2.1	451.2987	452.3654
494						2.09	437.2831	438.3447
495						2.14	487.2987	488.3656
496						2.07	481.2729	482.3421
497						2.02	453.278	454.3456
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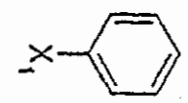
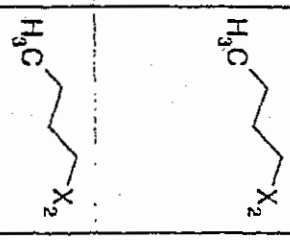
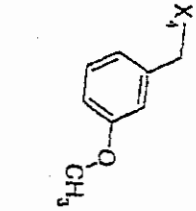
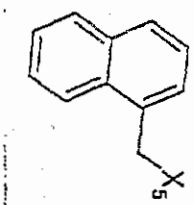
499							2.06	489.278	490.3461
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501							2	453.278	454.3479
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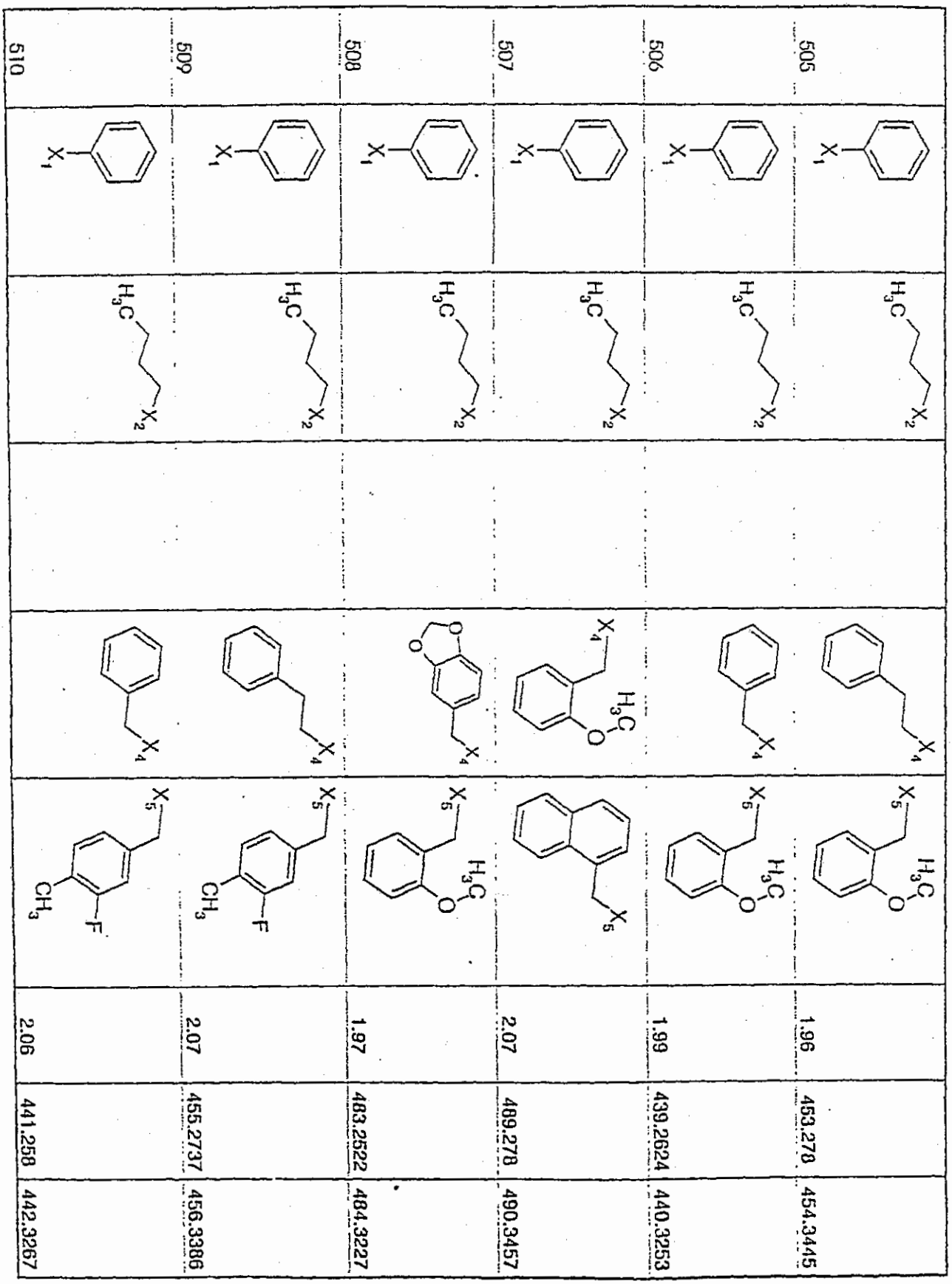
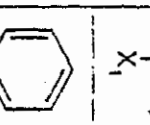
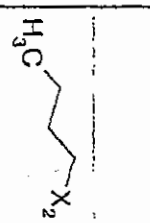
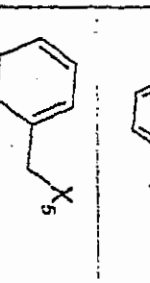
503							2.06	489.278	490.3477
504							1.97	483.2522	484.3253



505					1.96	453.278	454.3445
506					1.99	439.2624	440.3253
507					2.07	489.278	490.3457
508					1.97	483.2522	484.3227
509					2.07	455.2737	456.3386
510					2.06	441.258	442.3267

511						2.11	491.2737	492.3441
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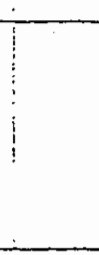
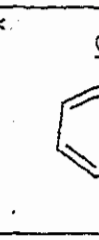
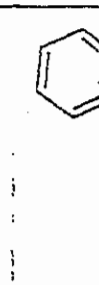
513						2.04	441.258	442.3253
514						2.03	485.2479	486.3174
515						2.05	455.2737	456.3376
516						2.04	441.258	442.325
517						2.1	491.2737	492.3412

518						2.02	485.2479	486.3193
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520						2.12	493.2285	494.3027
521						2.04	487.2027	488.2797
522						2.06	457.2285	458.2941
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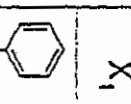
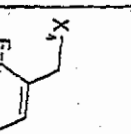
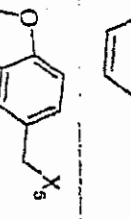
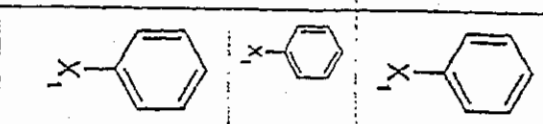
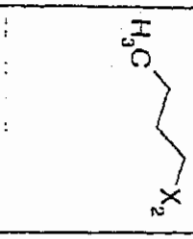
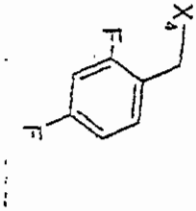
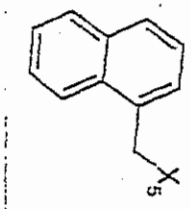
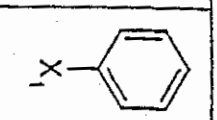
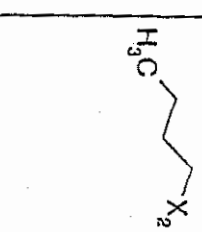
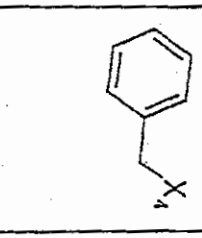
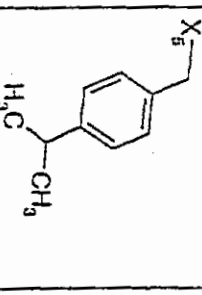
525						2.03	487.2027	488.278

526						2	489.2228	490.2792
527						2.02	445.2329	446.2807
528						2.06	495.2486	496.2982
529						2	489.2228	490.2744
530						2.01	445.2329	446.282
531						2.07	495.2486	496.2984
532						1.99	489.2228	490.2794

533					2.08	495.2486	496.3038
534					2	489.2228	490.2825
535					2.14	465.3144	466.3682
536					2.13	451.2987	452.3522
537					2.19	501.3144	502.3722
538					2.11	495.2886	496.3486

539						2.12	451.2987	452.3553
540						2.16	501.3144	502.3736
541						2.1	495.2886	496.3533
542						2.05	467.2937	468.352
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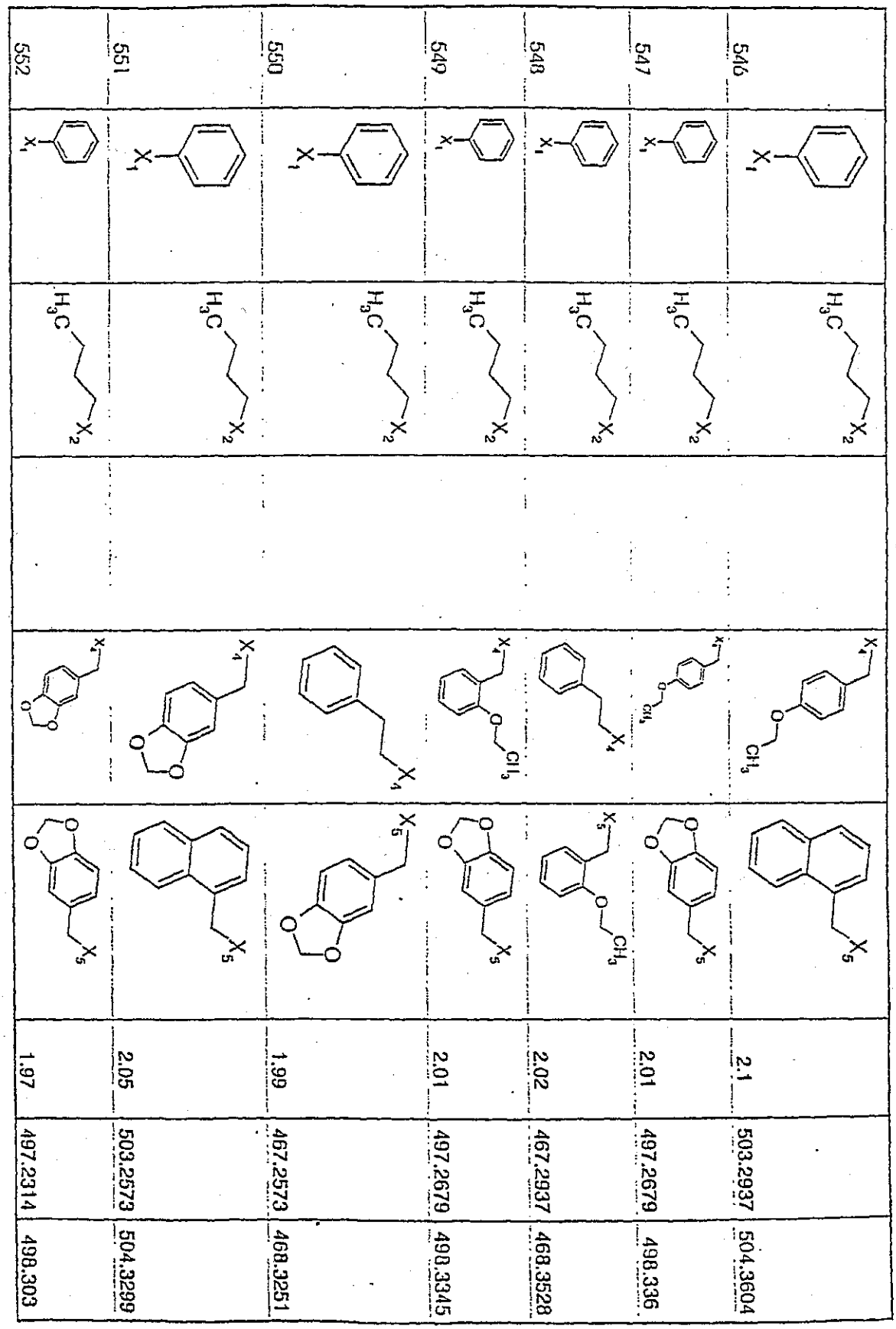
545						2.02	497.2679	498.3338



546						2.1	503.2937	504.3604
547						2.01	497.2679	498.336
548						2.02	467.2937	468.3528
549						2.01	497.2679	498.3345
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551						2.05	503.2573	504.3299
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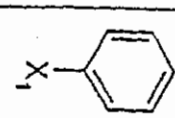
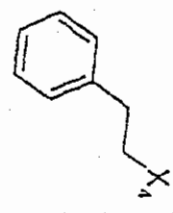
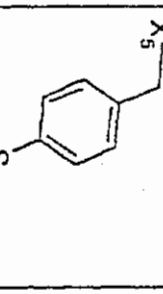
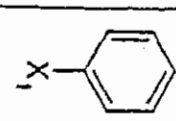
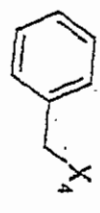
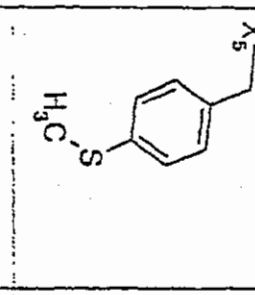
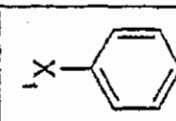
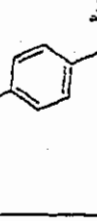
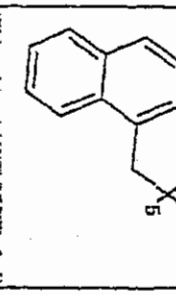
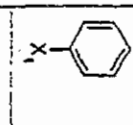
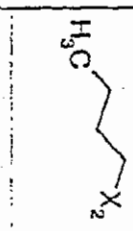
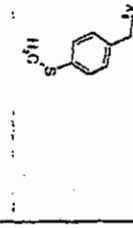
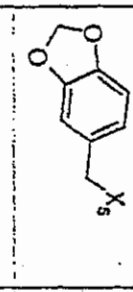
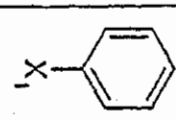
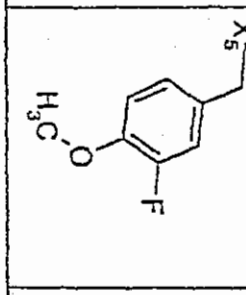
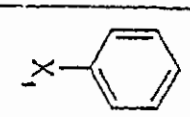
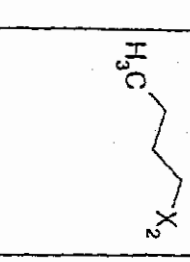
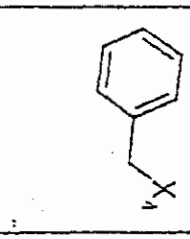
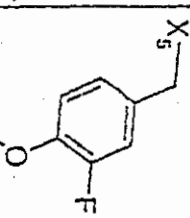
553						2.05	469.2552	470.3185
554						2.05	455.2395	456.3164
555						2.1	505.2552	506.3273
556						2.03	499.2293	500.3005
557						1.99	471.2686	472.3348

558						1.98	457.2529	458.3177
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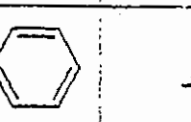
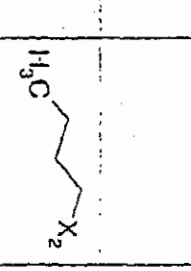
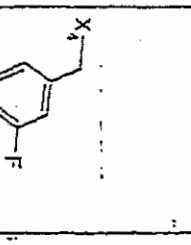
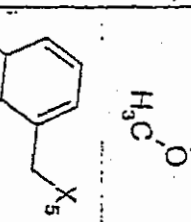
560						1.96	501.2428	502.3192
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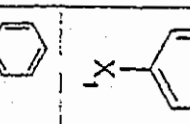
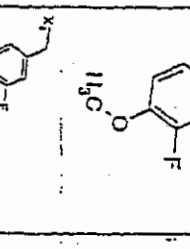
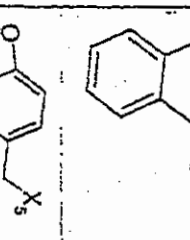
562						2.14	507.2441	508.3201
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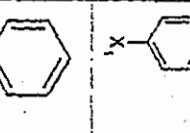
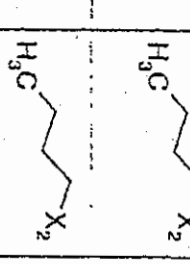
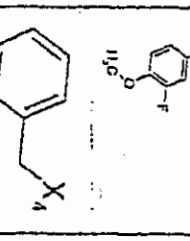
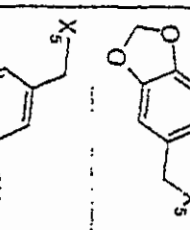
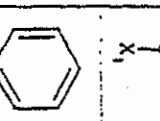
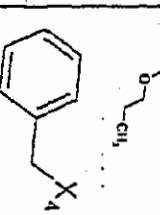
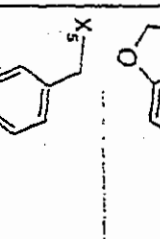
564						2.04	505.1932	506.2737

565						2.17	465.3144	466.3809
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567						2.15	479.33	480.3981
568						2.14	465.3144	466.3795
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570						2.06	511.2835	512.3632
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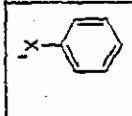
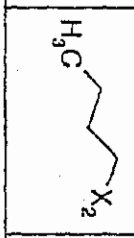
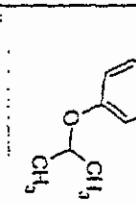
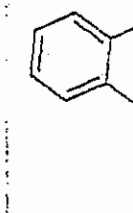
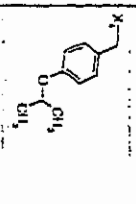
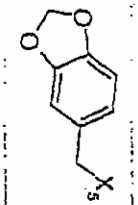
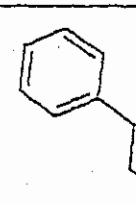
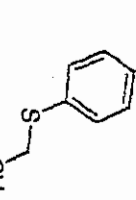
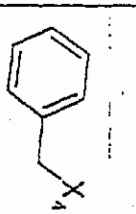
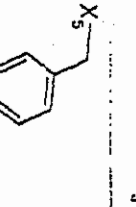
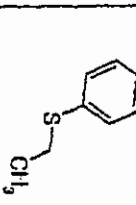
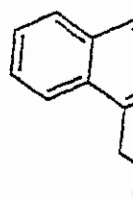
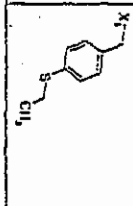
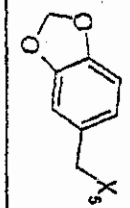
572						2.12	517.3093	518.3871
573						2.04	511.2835	512.3613
574						2.1	483.2708	484.3423
575						2.08	469.2552	470.3222
576						2.13	519.2708	520.3477
577						2.06	513.245	514.3214

578						2.02	481.2141	482.2768
579						2	525.2039	526.2794
580						2.08	513.2392	514.3017
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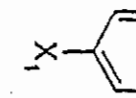
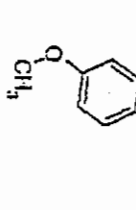
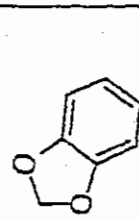
584						2.03	461.2034	462.2718
585						2.08	511.2191	512.2936
586						2.01	505.1932	506.2769
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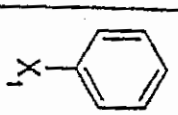
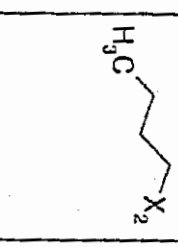
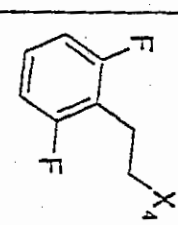
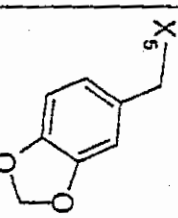
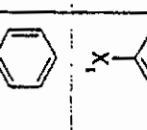
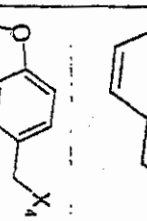
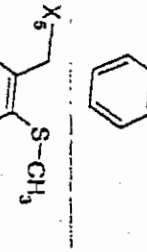
588						1.99	527.2784	528.3599
589						2.02	459.2486	460.326

590						2.01	503.2384	504.3166
591						2.06	469.2552	470.3206
592						2.03	513.245	514.321
593						2	467.2573	468.3217
594						1.97	511.2471	512.3246
595						2.07	533.1904	534.271

596						2.09	501.1779	502.2556
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600						2.05	555.1901	556.1432
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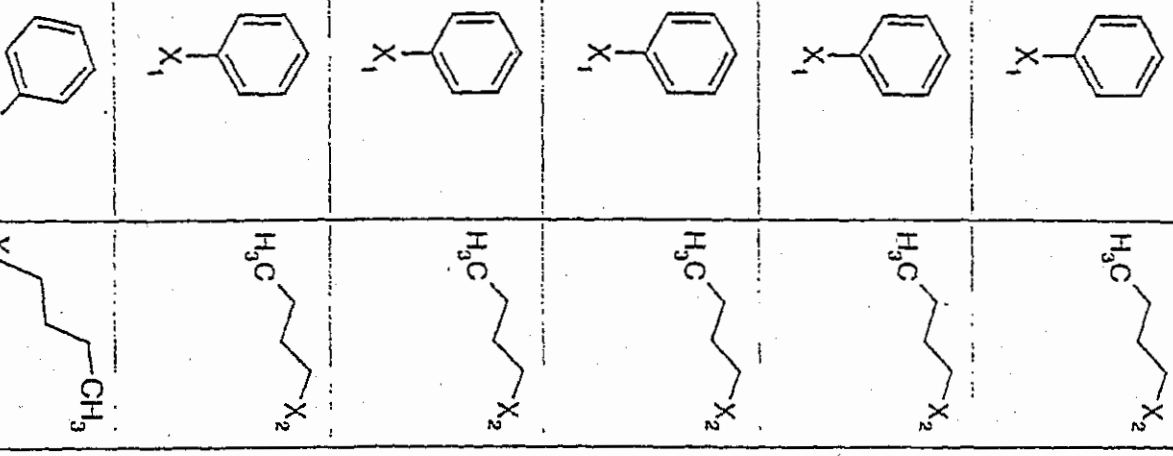
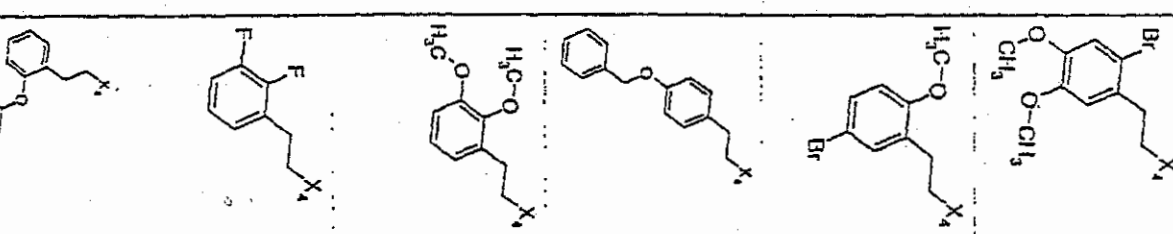
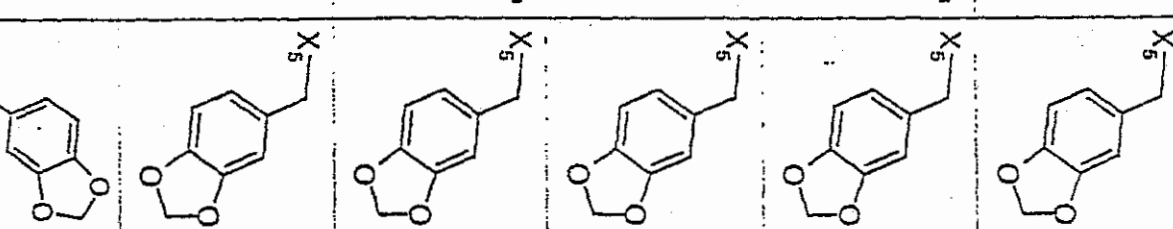
604					1.99	605.1889	606.17
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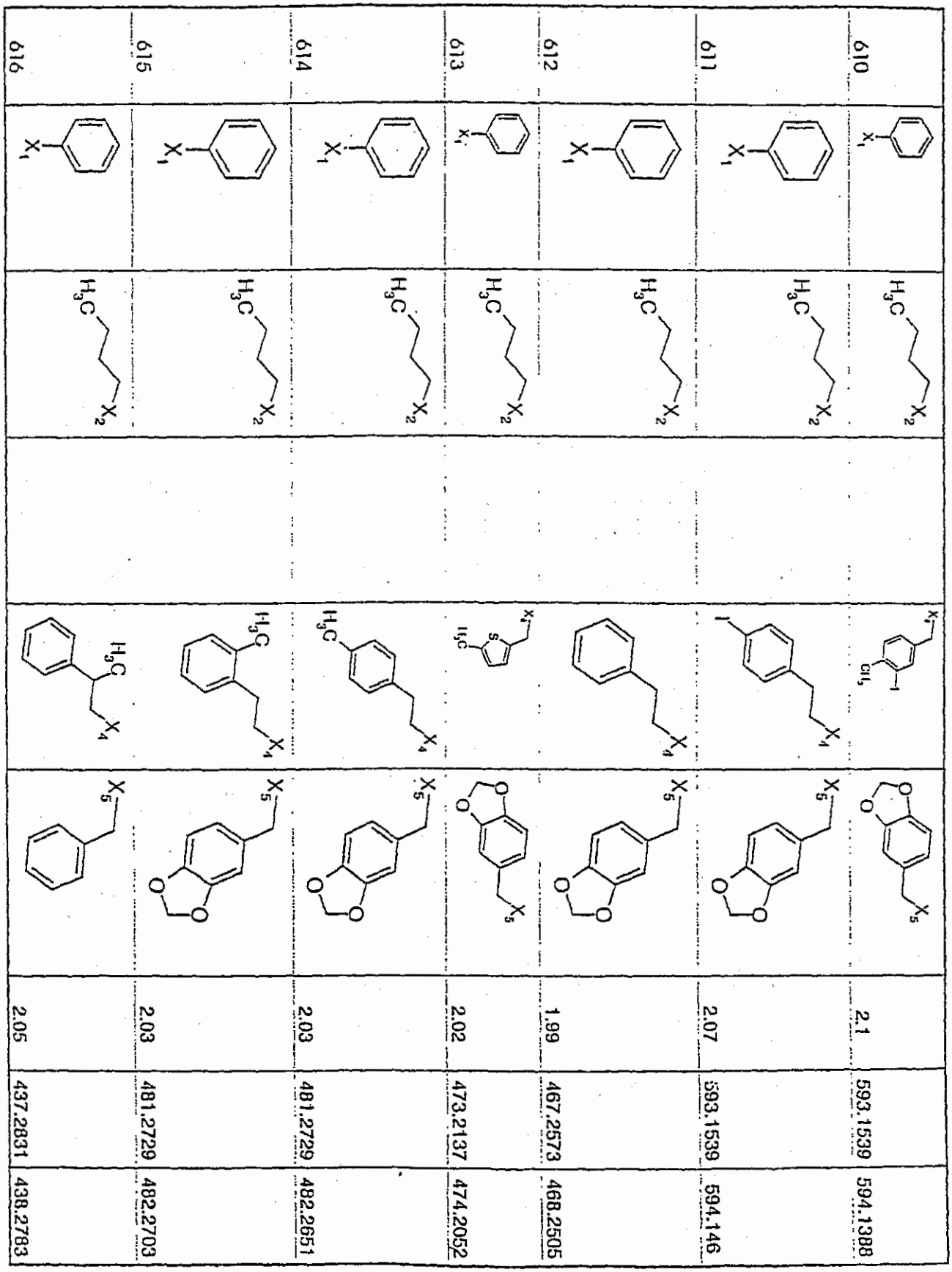

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612							1.99	467.2573	468.2505
613							2.02	473.2137	474.2052
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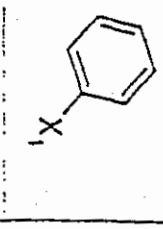
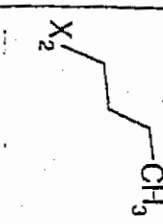
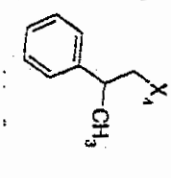
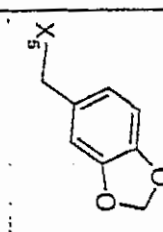
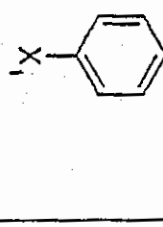
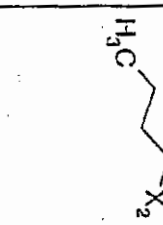
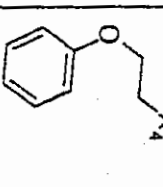
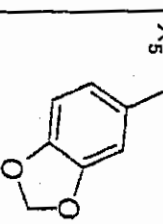
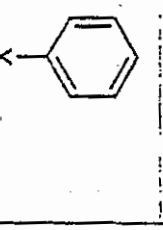
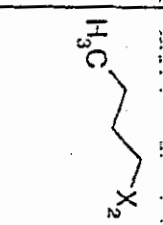
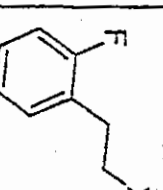
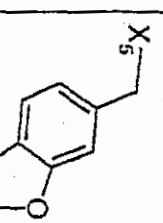
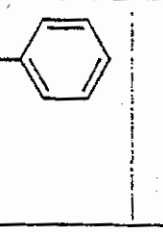
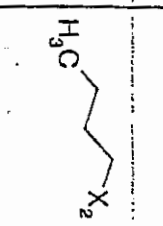
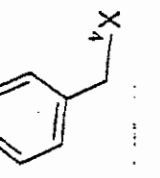
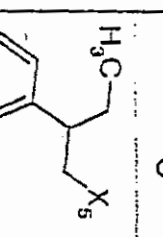
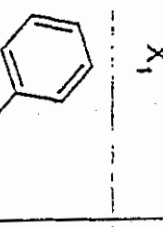
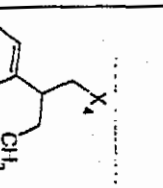
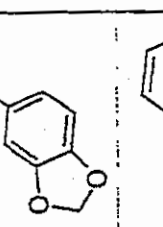
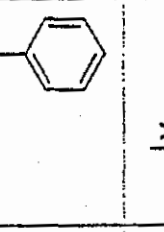
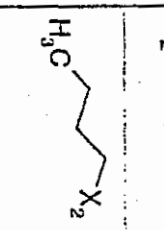
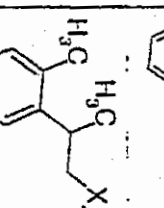
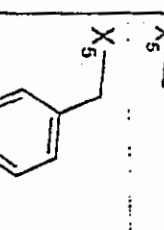
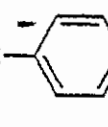
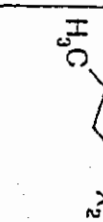
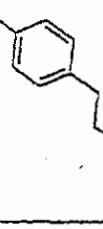
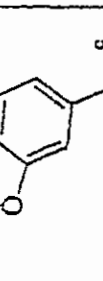
615							2.03	481.2729	482.2703
616							2.05	437.2831	438.2783

617						2.03	481.2729	482.2692
618						1.98	483.2522	484.2532
619						2	485.2479	486.2474
620						2.08	451.2987	452.2939
621						2.07	495.2886	496.2867
622						2.08	451.2987	452.2961

623								
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629						2.03	497.2679	498.2339
630						1.98	513.2628	514.2338
631						2.11	545.3042	546.2813
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633						2.01	509.3042	510.2987
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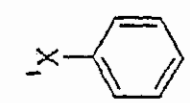
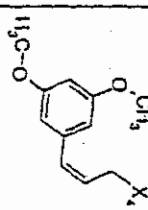
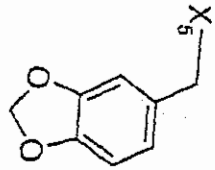
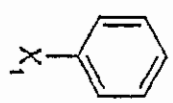
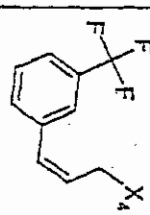
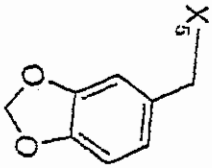
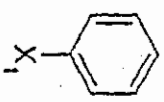
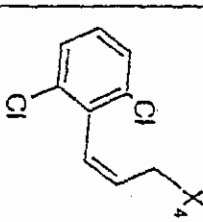
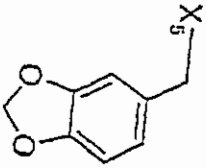
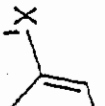
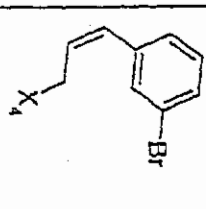
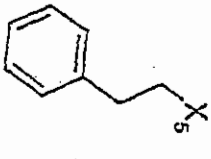
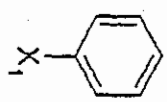
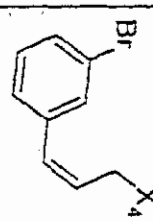
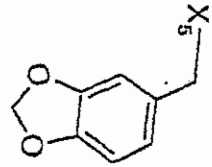
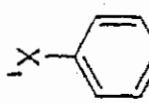
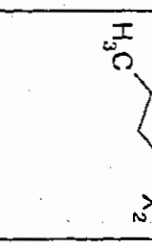
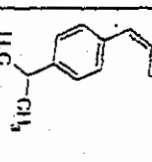
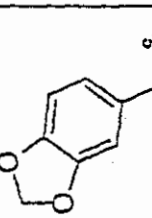
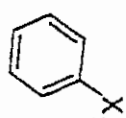
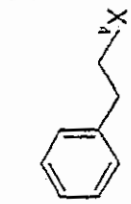
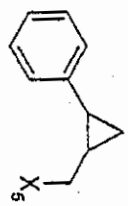
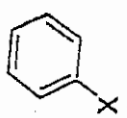
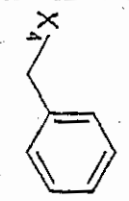
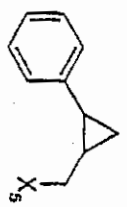
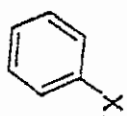
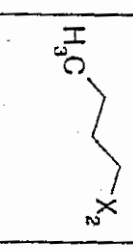
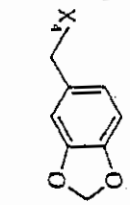
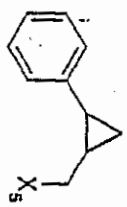
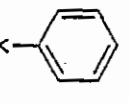
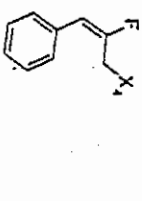
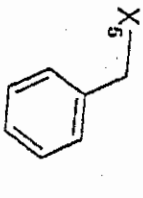
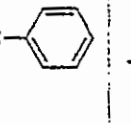
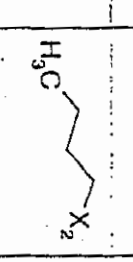
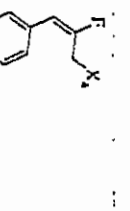
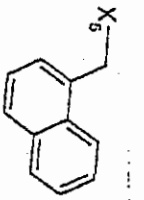
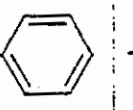
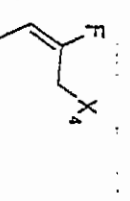
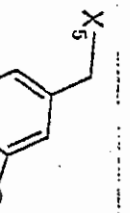
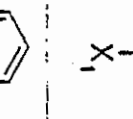
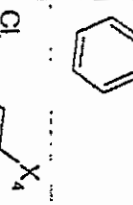
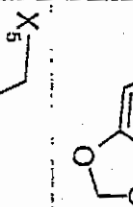
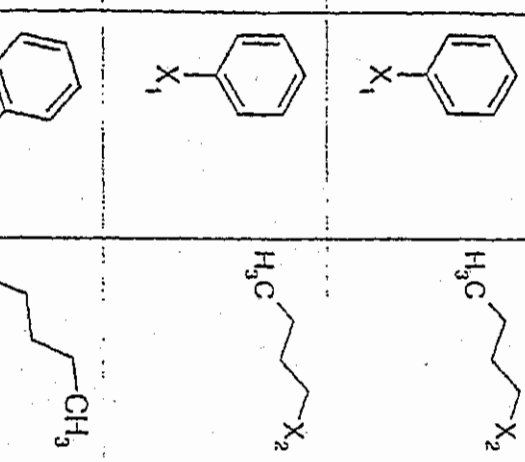
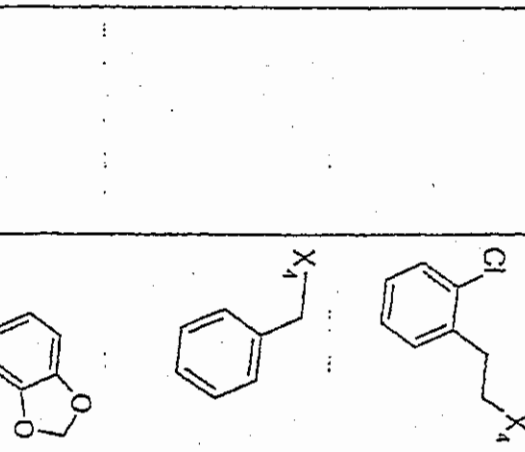
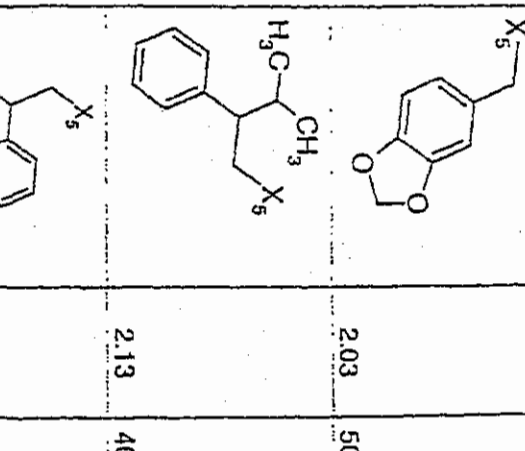
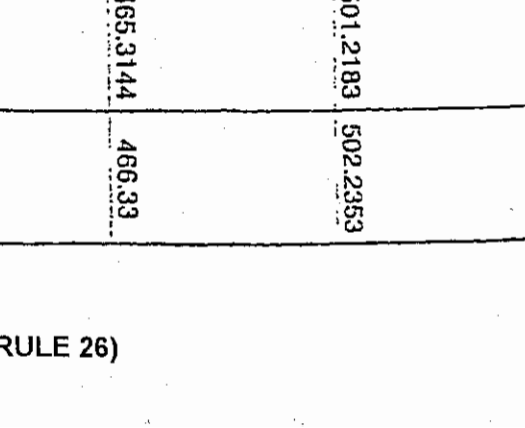
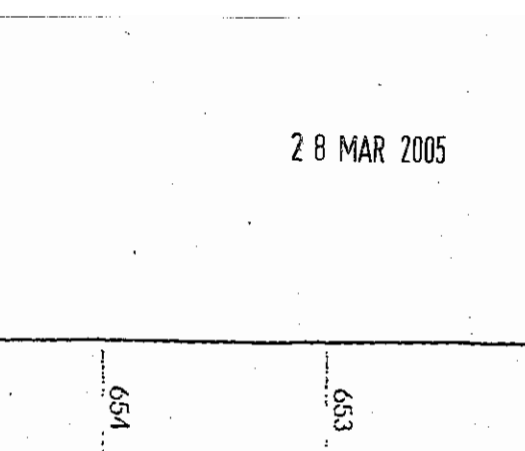
635						2.01	539.2784	540.2756
636						2.06	547.2447	548.2516
637								
638						2.09	527.1936	528.22
639								

640						1.99	441.2239	442.2316
641						2.09	491.2395	492.2484
642						1.97	485.2137	486.2251
643						2.07	475.2624	476.2701
644						1.95	469.2365	470.2487
645						2.11	521.3042	522.3236

646						2.01	463.2987	464.304
647						2.02	449.2831	450.2887
648						1.99	493.2729	494.2809
649						2.06	453.258	454.2635
650						2.11	503.2737	504.279
651						2.05	497.2479	498.2578
652						2.05	457.2285	458.2423

653					2.03	501.2183	502.2353
654					2.13	465.3144	466.33
655					2.1	509.3042	510.315
656					2.04	467.2937	468.3029
657					2.02	511.2835	512.2963
658					2.06	467.2937	468.3049

659						2.04	511.2835	512.2961
660						2.07	481.3093	482.3199
661						2.05	525.2991	526.3086
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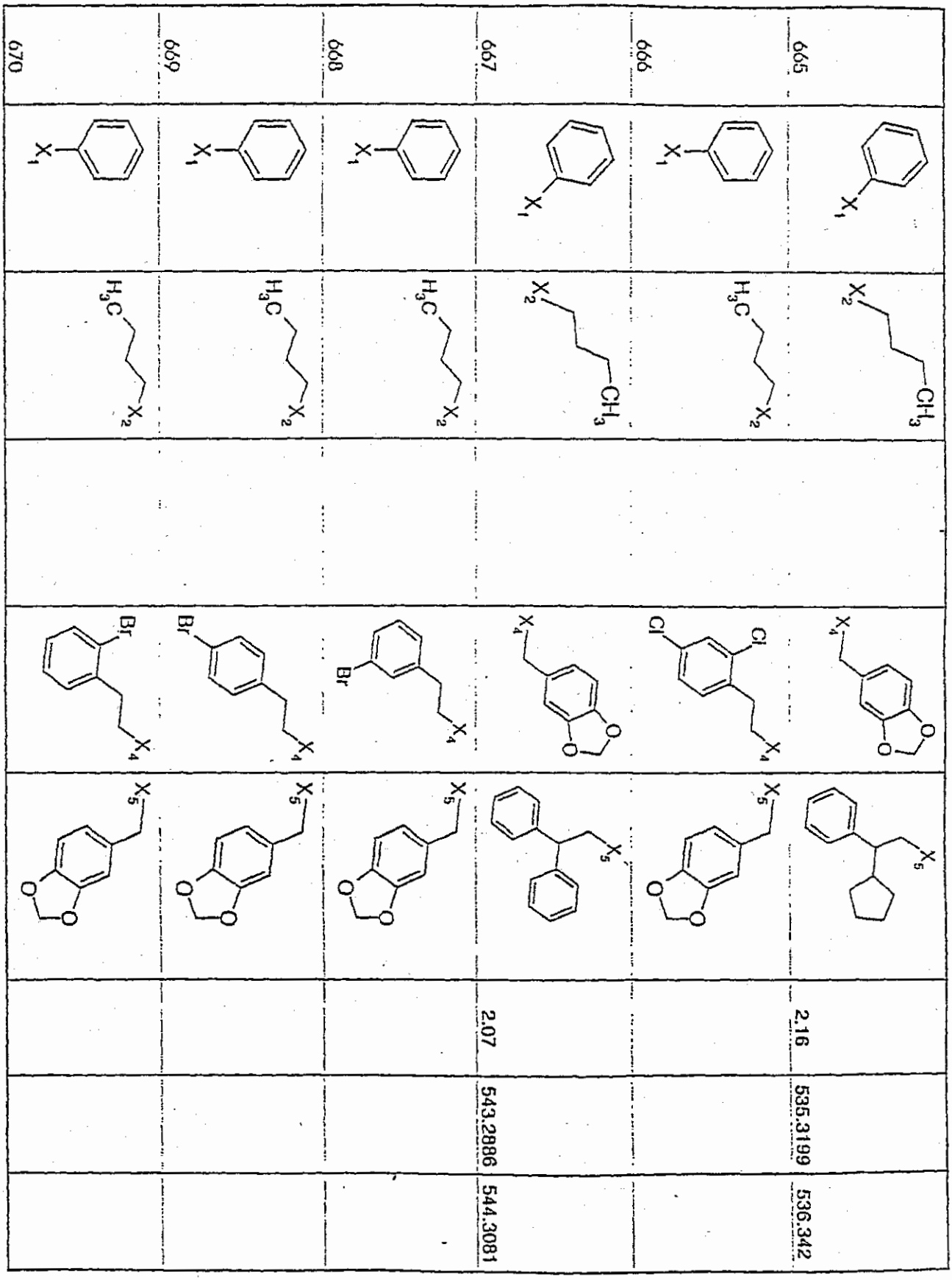

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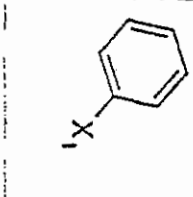
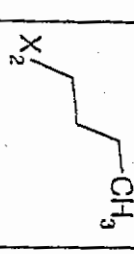
669								
670								

671						2.19	549.3355	550.3612
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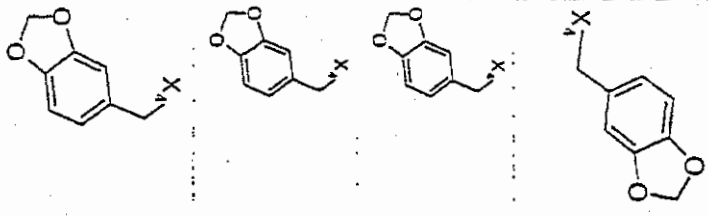
674						1.96	513.2628	514.2808
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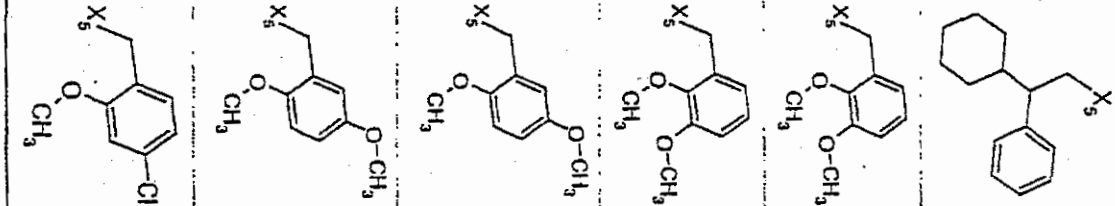
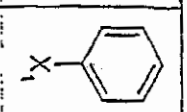
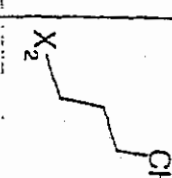
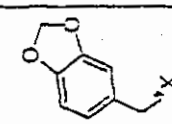
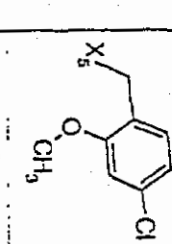
676						2.03	517.2132	518.2341

677							502.2102
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680						2.11	515.1936
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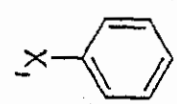
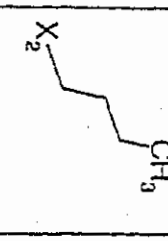
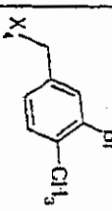
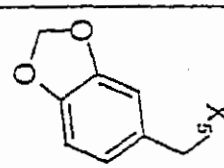
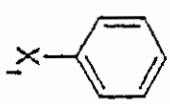
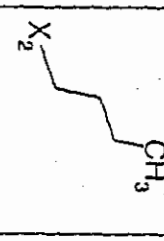
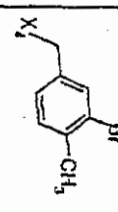
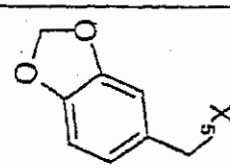
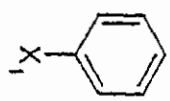
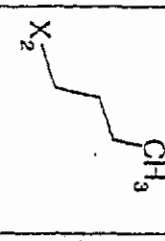
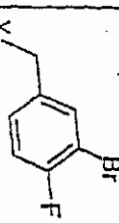
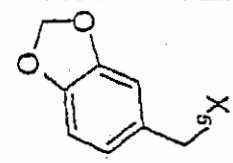
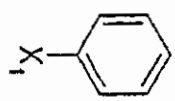
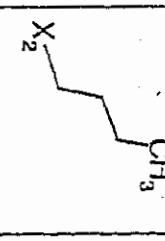
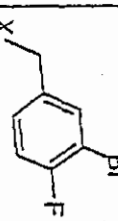
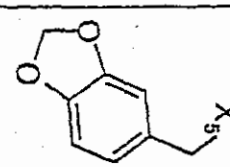
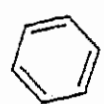
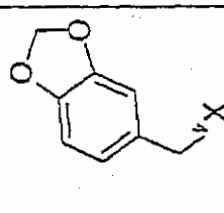
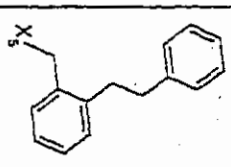
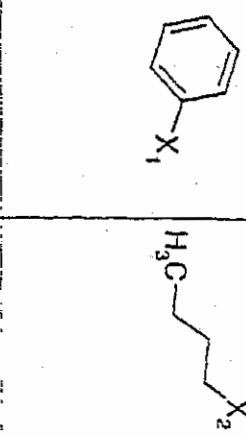
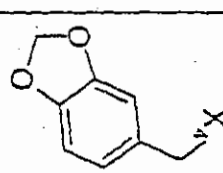
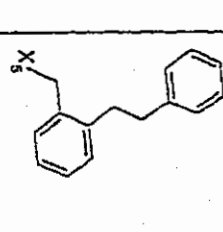
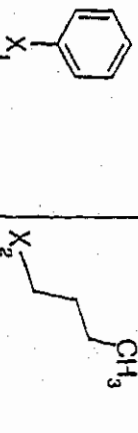
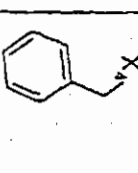
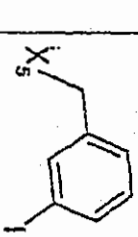
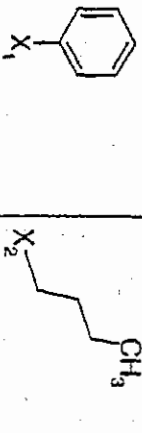
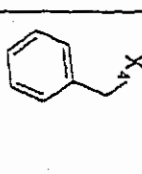
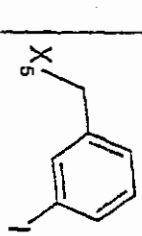
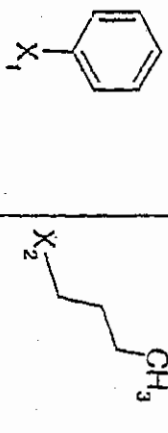
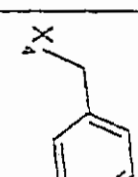
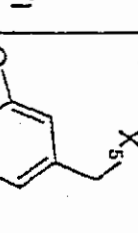
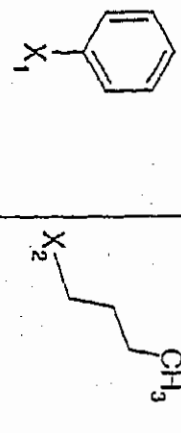
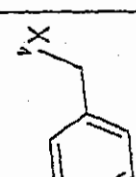
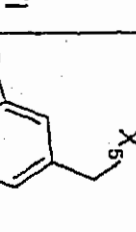
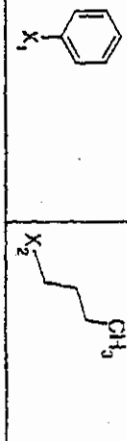
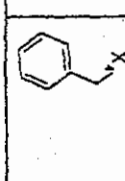
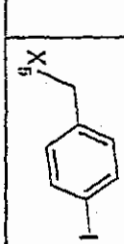
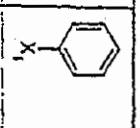
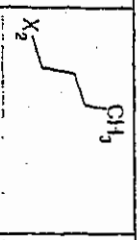
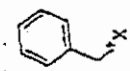
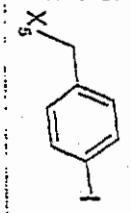
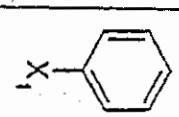
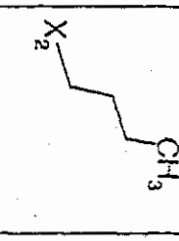
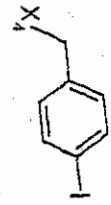
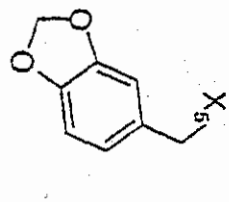
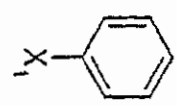
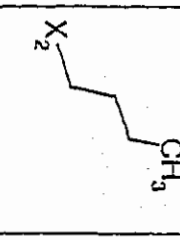
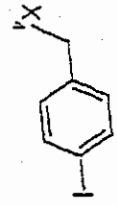
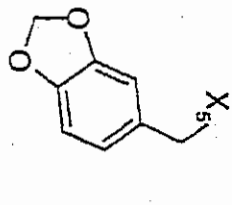
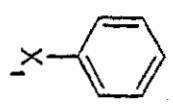
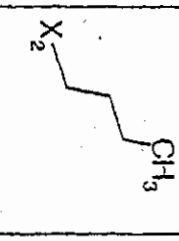
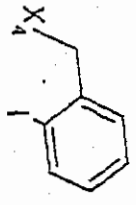
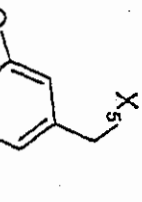
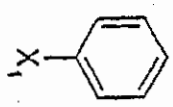
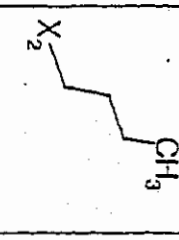
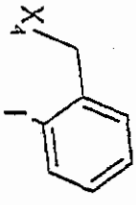
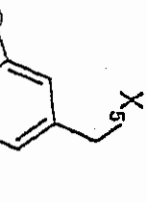
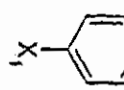
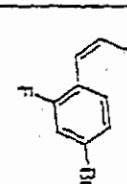
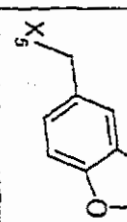
683							552.23

684						546.202	545.1678	2.08
685								
686								
687								
688						558.3334	557.3042	2.13

689							
690						2.07	535.1484	536.1722
691								
692						2.06	579.1383	580.1661
693								
694						2.07	535.1484	536.1789

695								
696						2.05	579.1383	580.1685
697								
698						2.04	579.1383	580.1639
699								

700							532.2447
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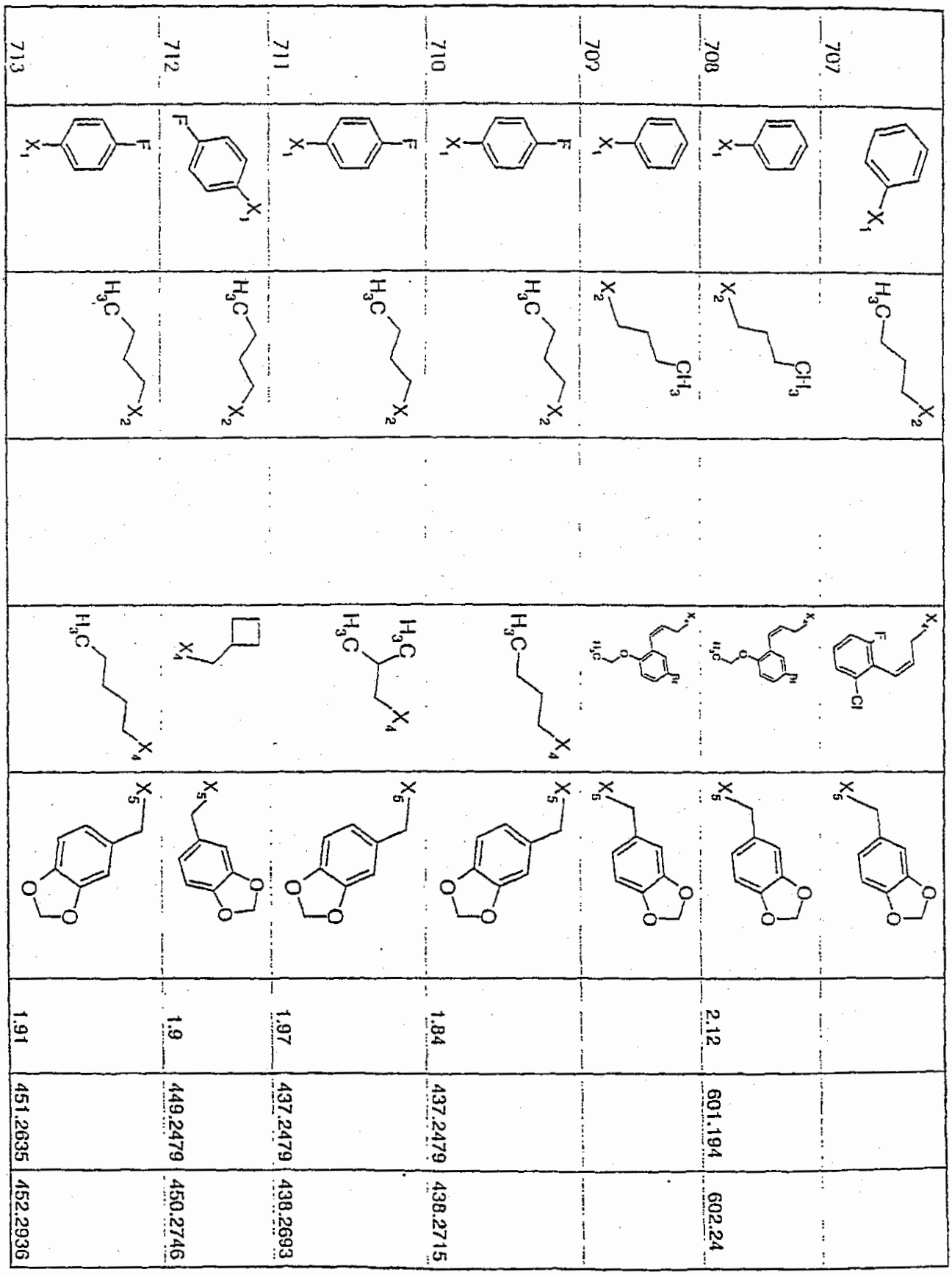

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709										
710								1.84	437.2479	438.2715
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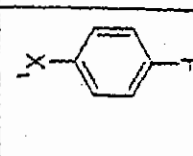
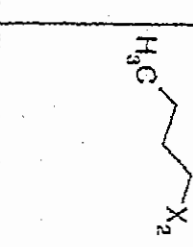
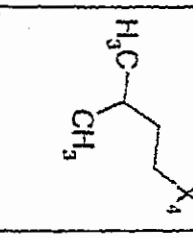
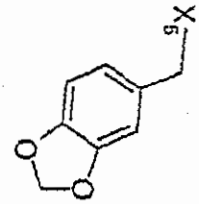
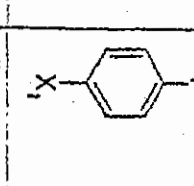
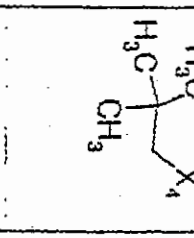
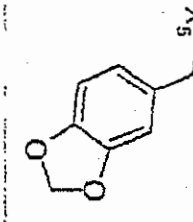
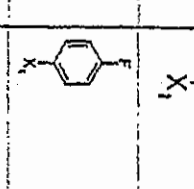
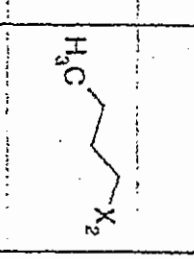
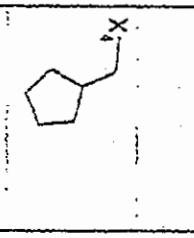
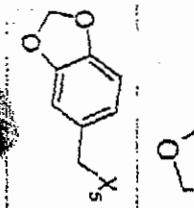
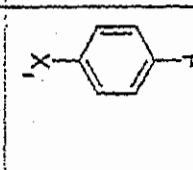
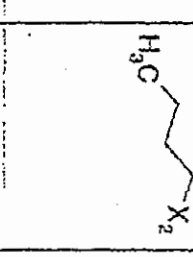
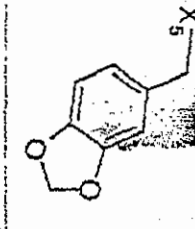
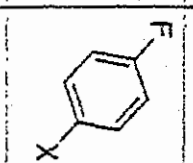
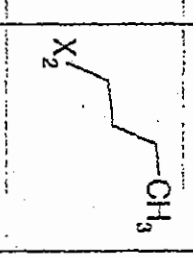
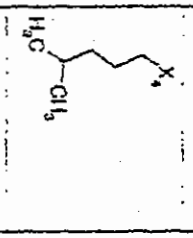
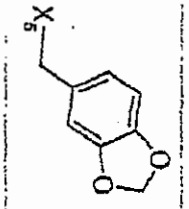
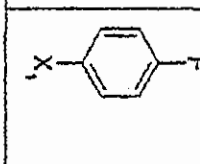
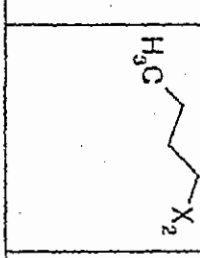
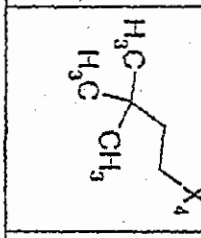
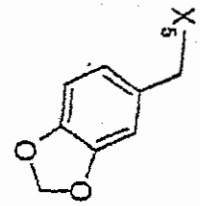
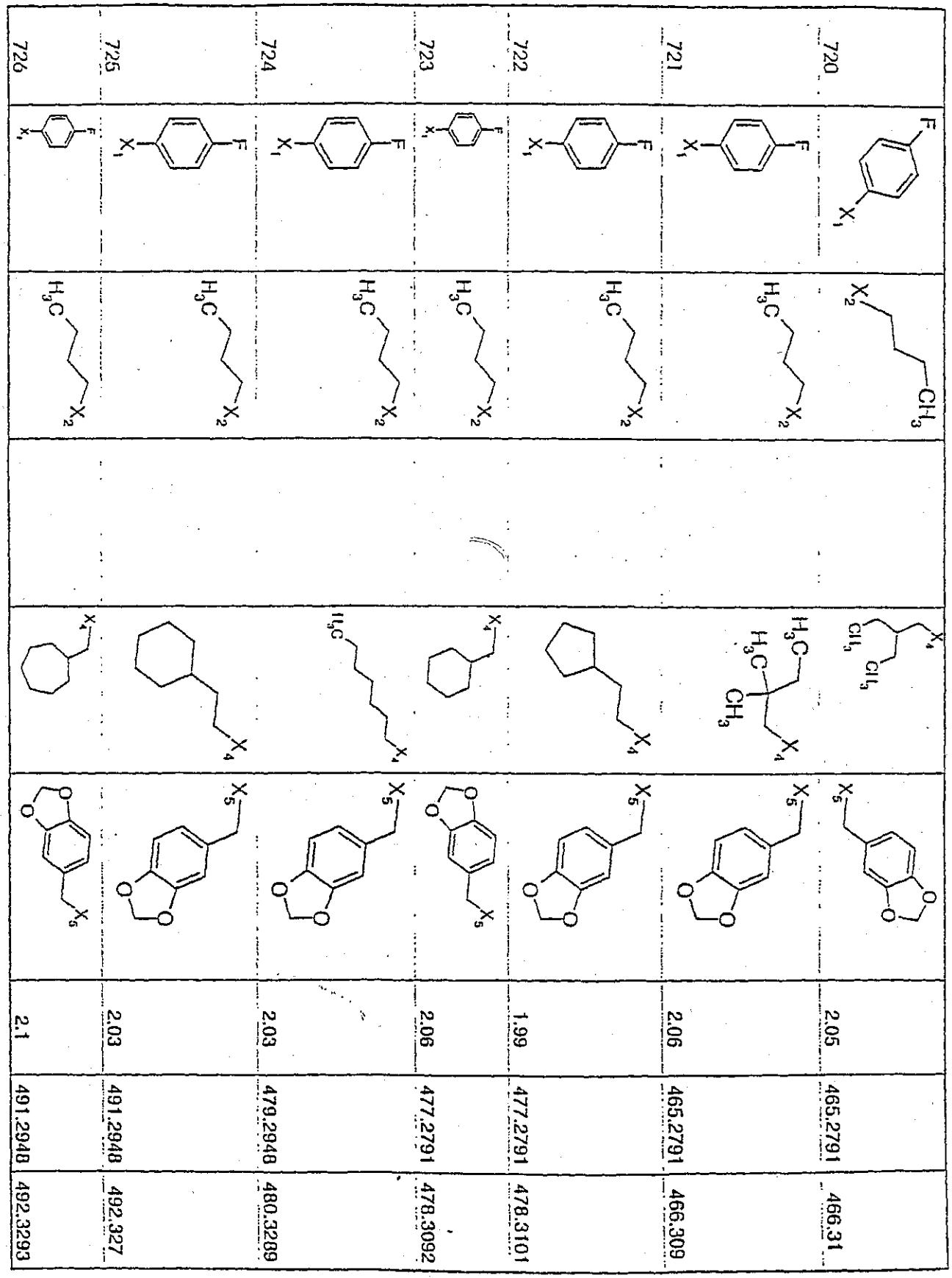
714						1.91	451.2635	452.2922
715						2.02	451.2635	452.2937
716						2	463.2635	464.2918
717						1.98	465.2791	466.3056
718						1.97	465.2791	466.3057
719						1.94	465.2791	466.3067



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721				2.06	465.2791	466.309	
722				1.99	477.2791	478.3101	
723				2.06	477.2791	478.3092	
724				2.03	479.2948	480.3289	
725				2.03	491.2948	492.327	
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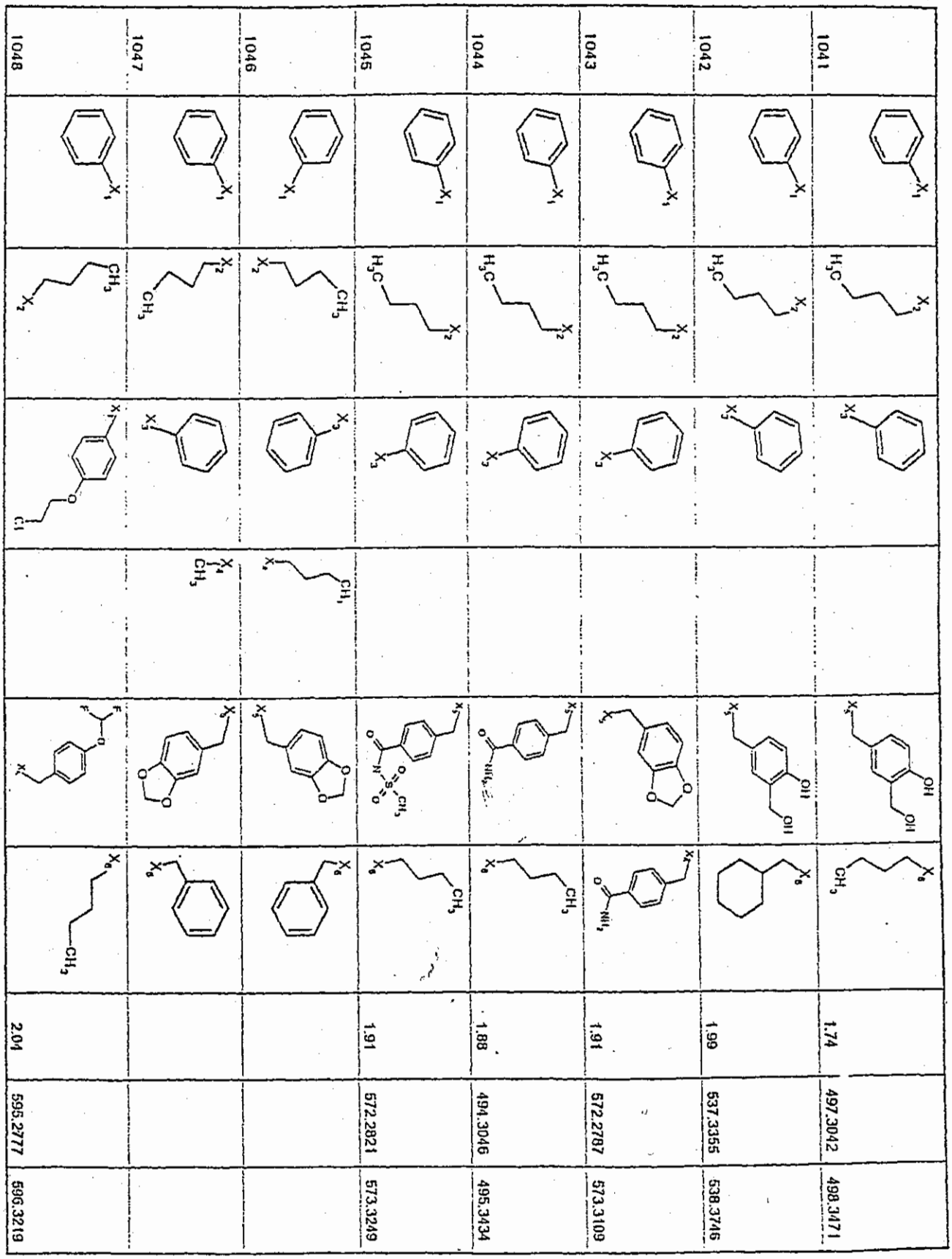

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1044						1.88	494.3046		495.3434
1045						1.91	572.2821		573.3249
1046									
1047									
1048						2.04	595.2777		596.3219

1049							1.85	588.3231	589.3849
1050							1.72	554.3621	555.4208
1051							2	547.301	548.3278
1052							1.78	582.357	583.4136
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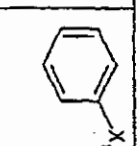
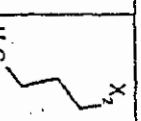
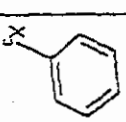
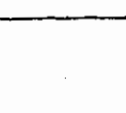
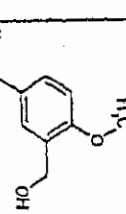
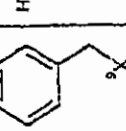
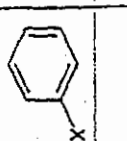
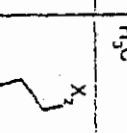
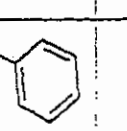
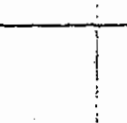
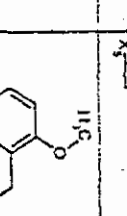
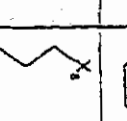
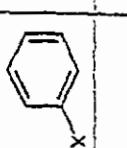
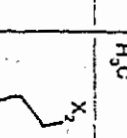
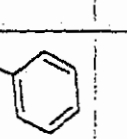
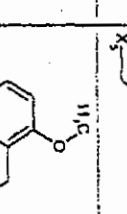
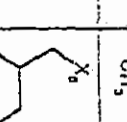
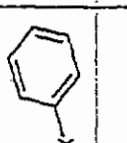
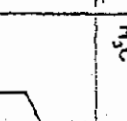
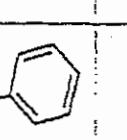
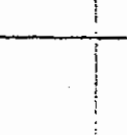
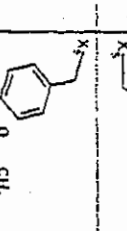
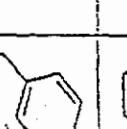
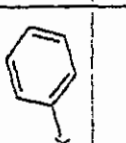
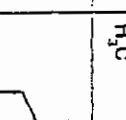
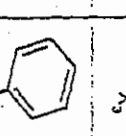
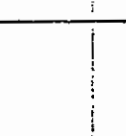
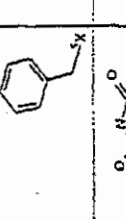
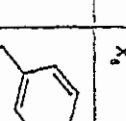
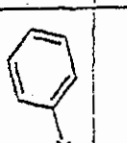
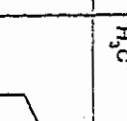
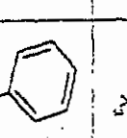
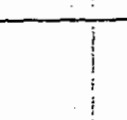
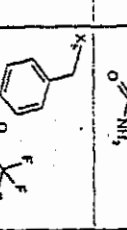
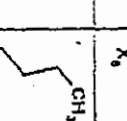
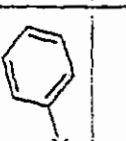
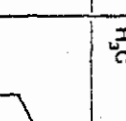
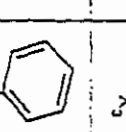
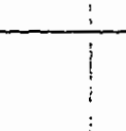
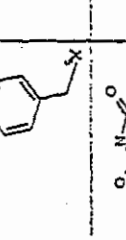
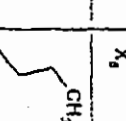
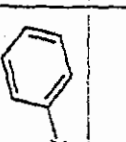
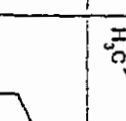
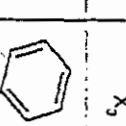
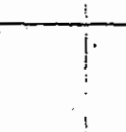
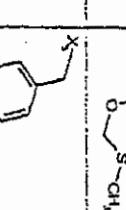
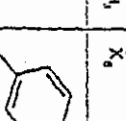
1056									1.97	545.3042	546.3319
1057									1.81	511.3199	512.3505
1058									2.04	561.3512	562.3625
1059									1.93	606.2665	607.3164
1060									1.91	528.2989	529.3276
1061											
1062									1.98	527.2971	528.3281
1063									2.09	561.2814	562.3166

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1067							1.79	580.2508	581.3011
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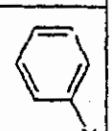
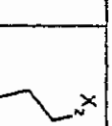
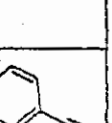
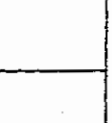
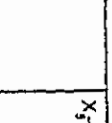
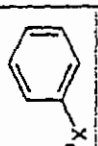
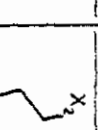
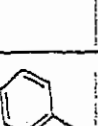
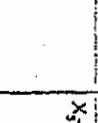
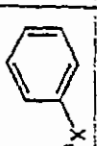
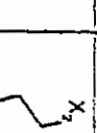
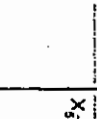
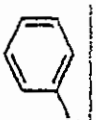
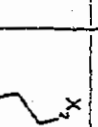
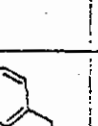
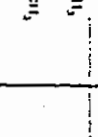
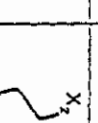
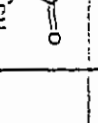
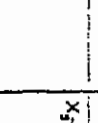
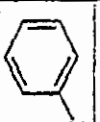
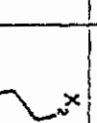
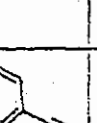
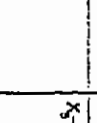
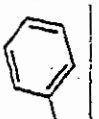
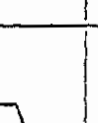
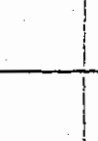
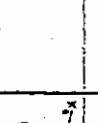
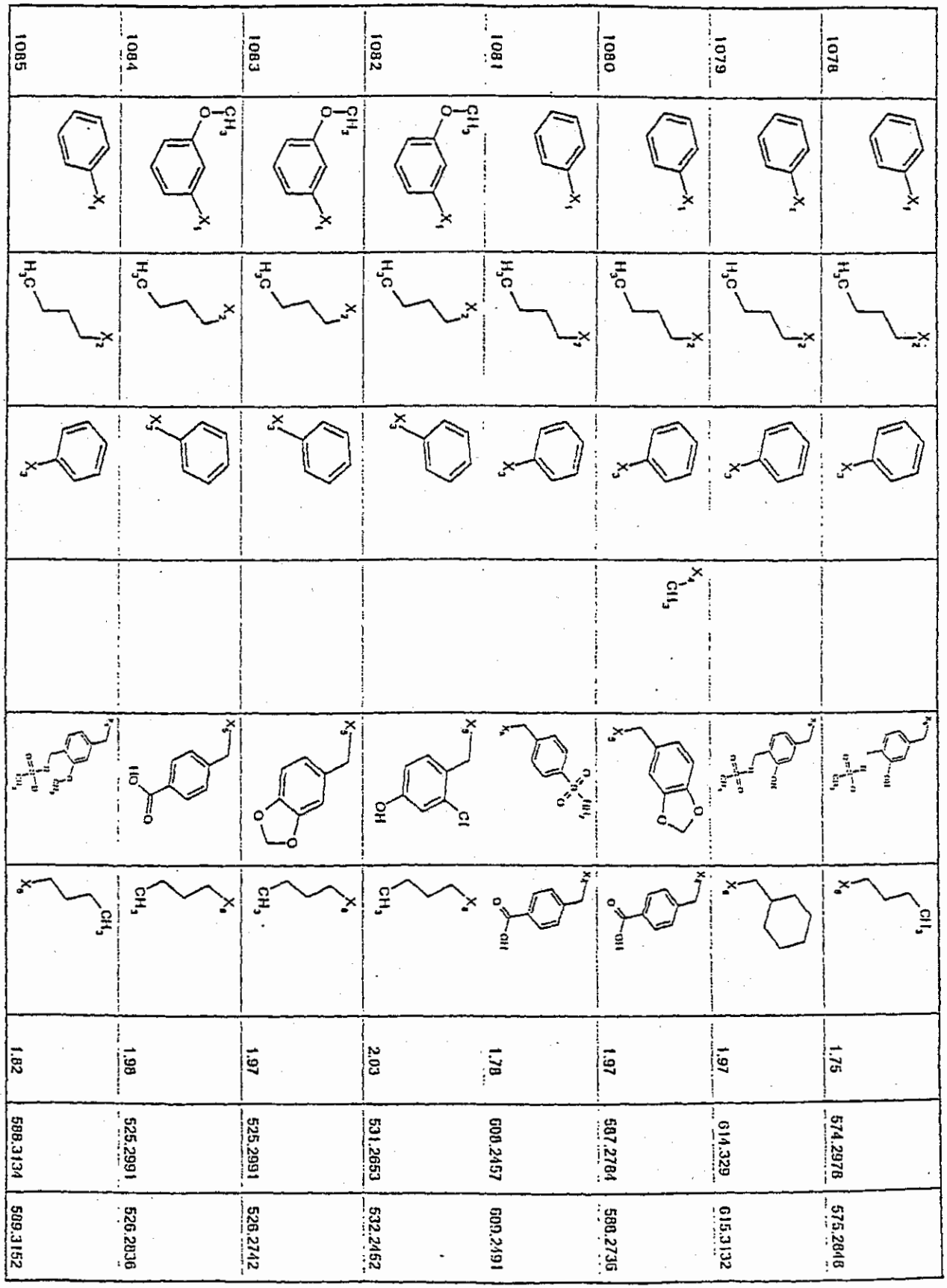
1071							1.96	520.2838	521.3221
1072							1.88	602.2927	603.3342
1073							1.93	631.3192	632.3643
1074							1.78	552.3464	553.3979
1075							1.9	582.3206	583.3616
1076							1.95	534.2995	535.3354
1077							1.99	571.3311	572.3079



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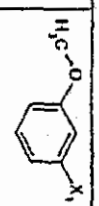
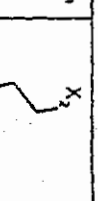
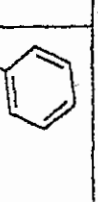
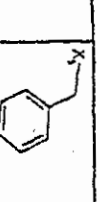
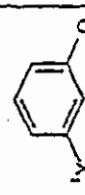
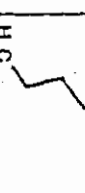
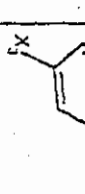
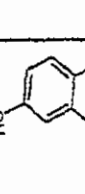
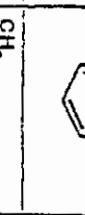
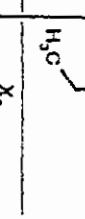
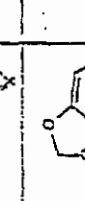
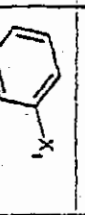
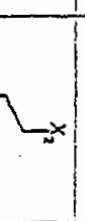
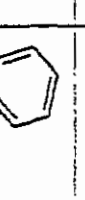
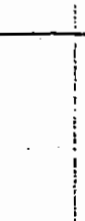
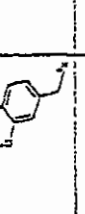
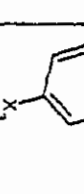
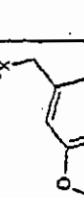
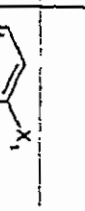
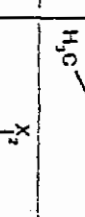
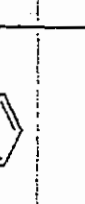
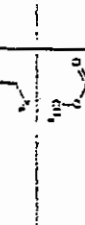
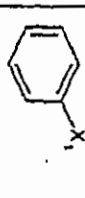
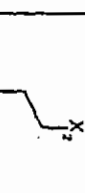
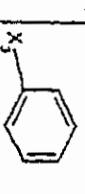
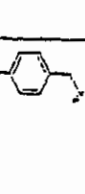
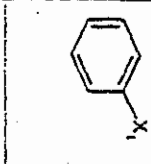
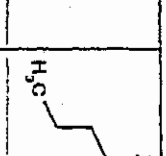
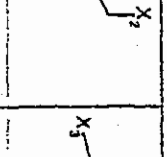
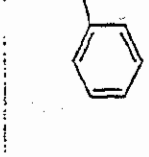
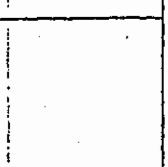
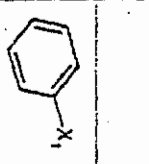
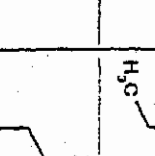
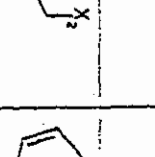
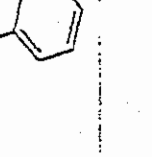
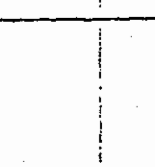
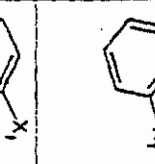
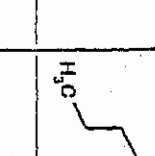
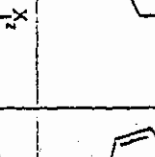
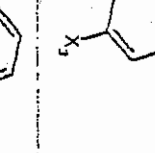
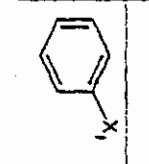
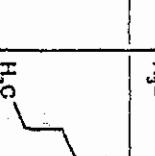
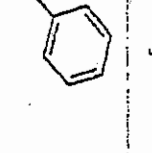
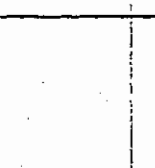
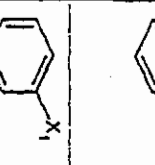
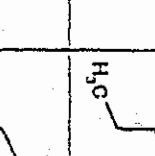
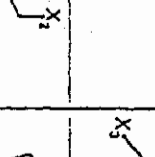
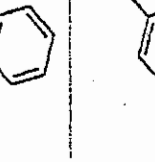
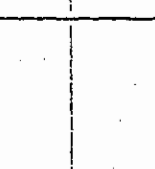
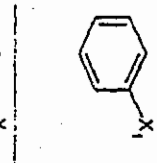
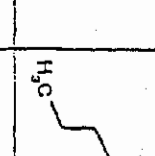
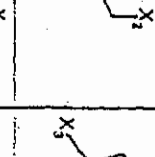
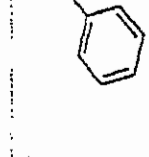
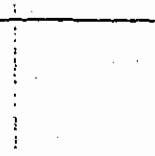
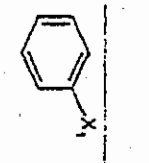
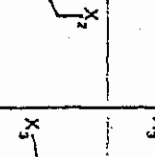
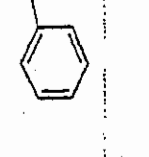
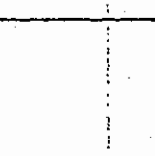
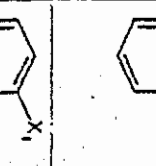
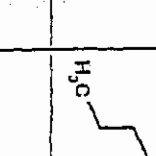
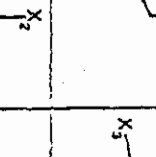
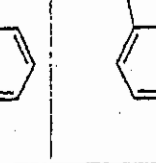
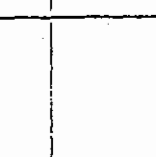
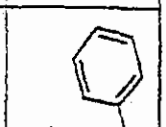
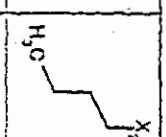
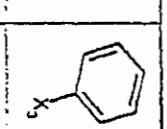
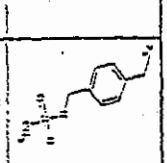
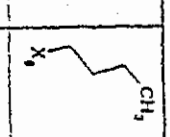
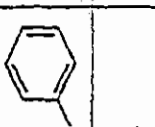
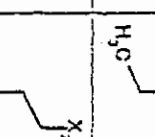
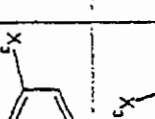
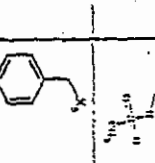
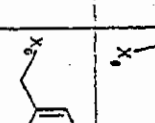
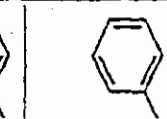
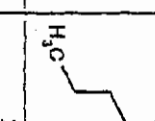
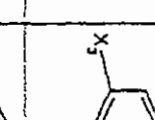
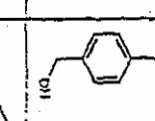
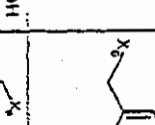
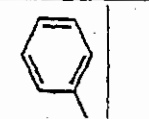
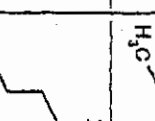
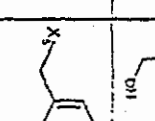
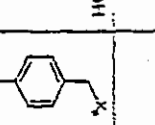
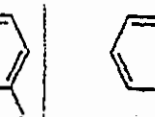
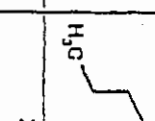
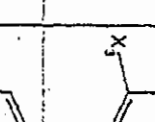
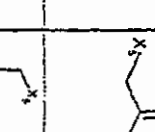
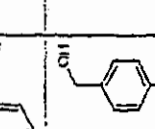
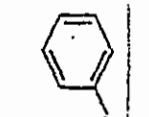
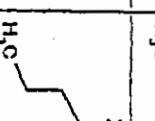
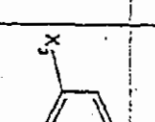
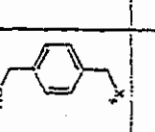
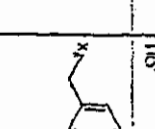
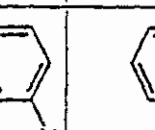
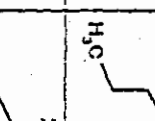
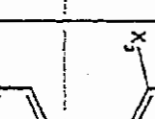
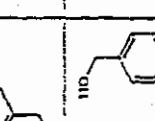
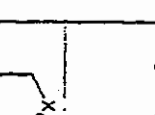
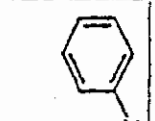
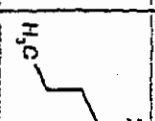
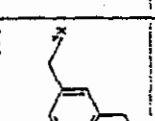
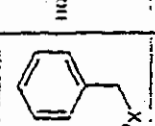
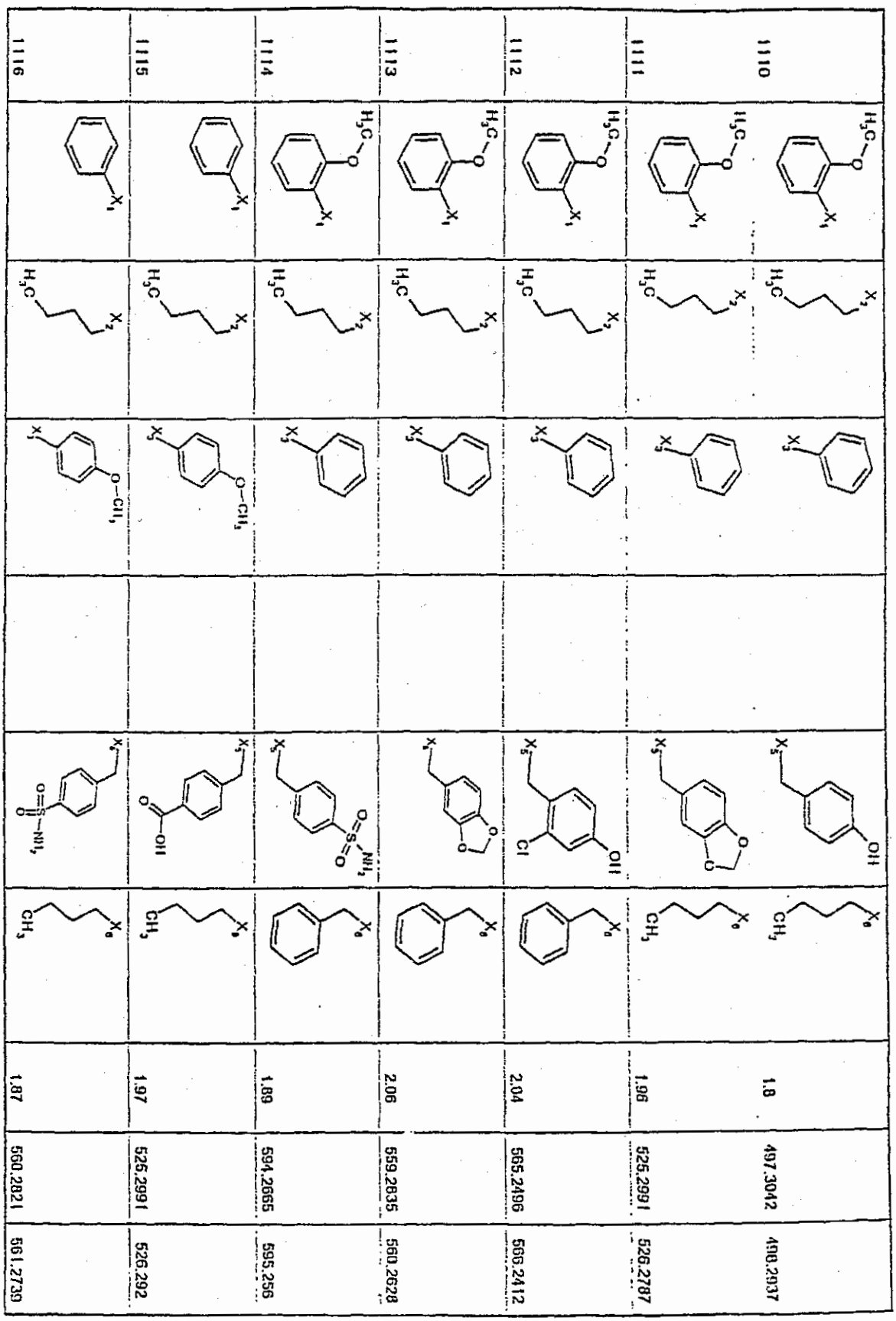
1079							1.97	614.329	615.3132
1080							1.97	587.2784	588.2736
1081							1.78	600.2457	600.2491
1082							2.03	531.2653	532.2452
1083							1.97	525.2991	526.2742
1084							1.98	525.2991	526.2036
1085							1.82	588.3134	589.3152

1086							1.93	511.3199	512.2905
1087							2.06	565.2496	566.2386
1088							2.07	559.2835	560.2629
1089							1.99	559.2835	560.2698
1090							2.02	628.3447	629.3398
1091							2	593.2348	594.2117
1092							1.95	559.2835	560.2643
1093							2.02	593.2445	594.2274

1094							2.03	573.2991	574.271
1095							1.71	607.2617	608.2644
1096							2.11	629.3254	630.3112
1097							2.11	595.341	596.3187
1098							1.89	545.2678	546.2605
1099							1.96	579.2289	580.2228
1100							1.97	559.2835	560.2682
1101							1.94	573.2628	574.2623

1102							1.83	558.3029	559.2951
1103							1.87	531.2886	532.2817
1104							1.93	565.2496	566.240
1105							1.95	545.3042	546.2853
1106							1.89	545.3042	546.2955
1107							1.98	551.3612	552.3348
1108							1.83	594.2301	595.2273
1109							2.01	531.2653	532.2531



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1111						1.96	525.2991	526.2787	
1112						2.04	565.2496	566.2412	
1113						2.06	559.2835	560.2628	
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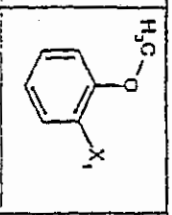
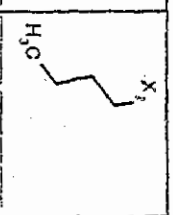
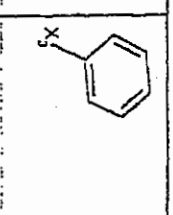
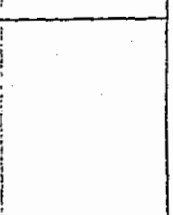
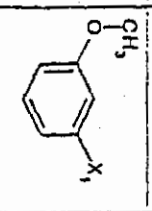
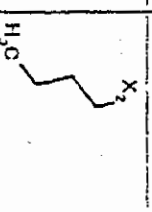
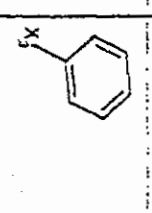
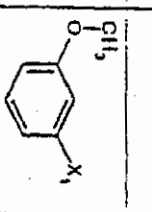
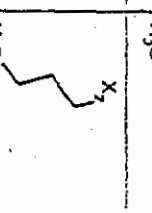
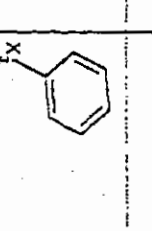
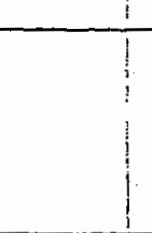
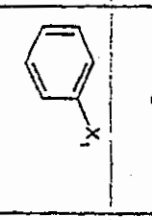
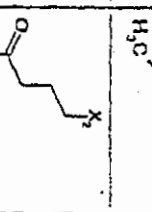
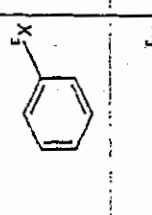
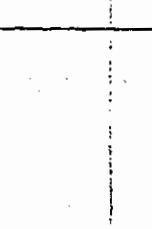
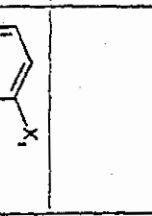
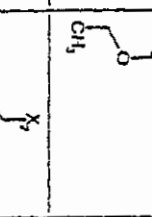
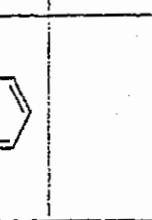
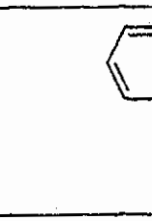
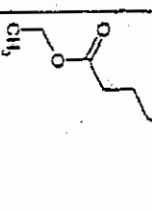
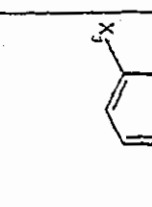
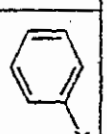
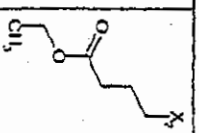
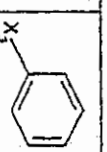
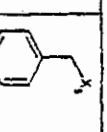
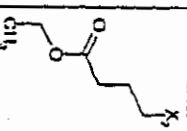
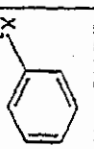
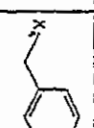
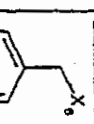
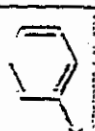
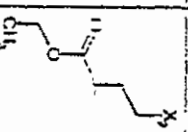
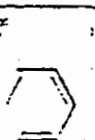
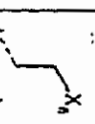
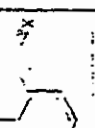
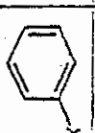
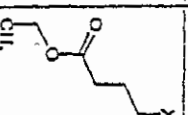
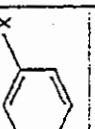
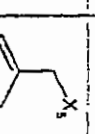
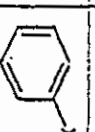
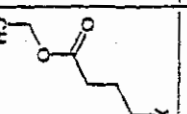
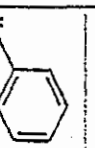
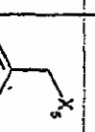
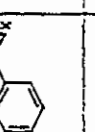
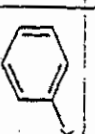
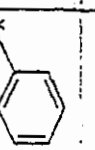
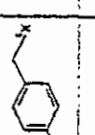
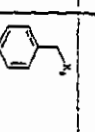
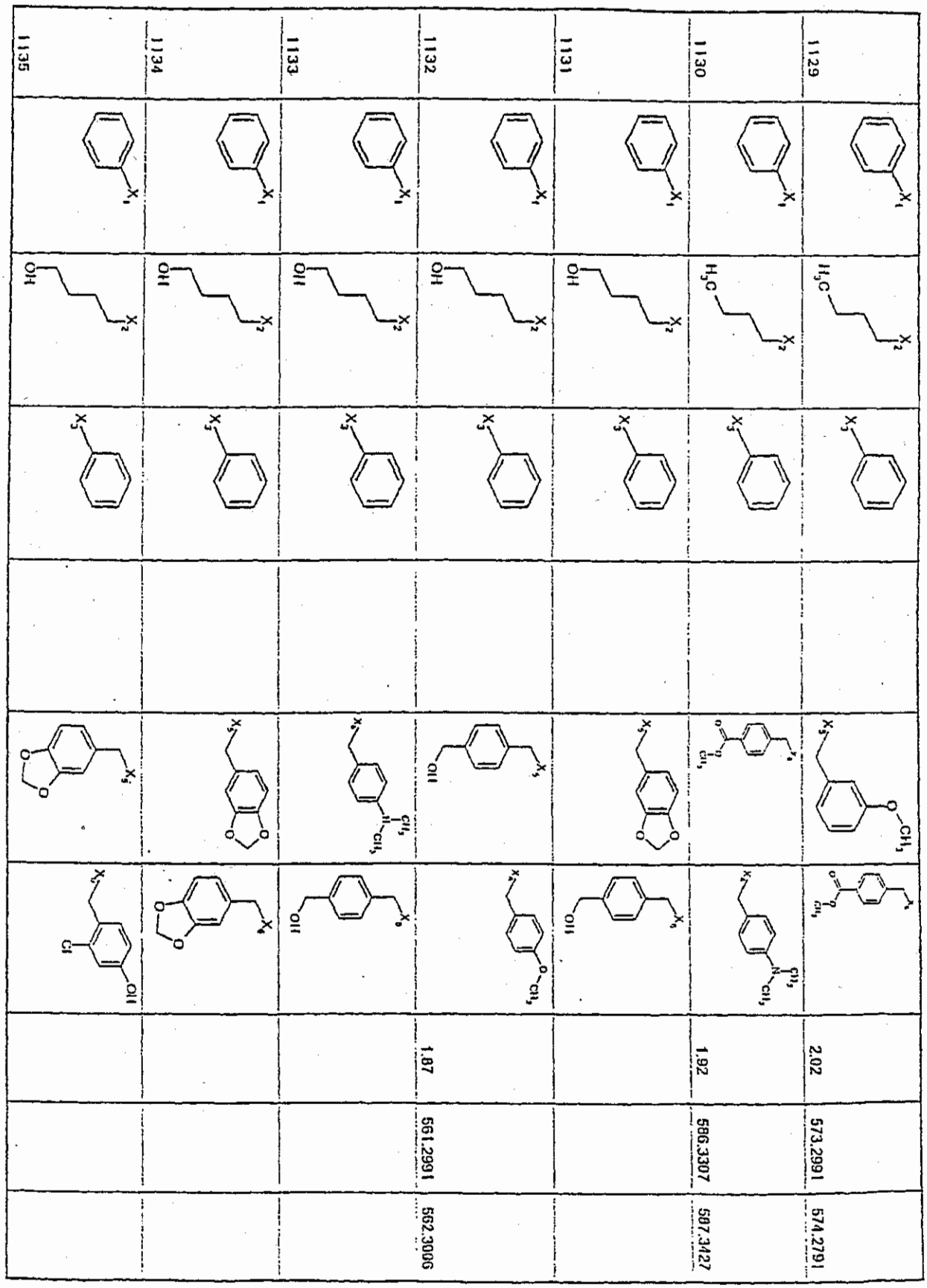
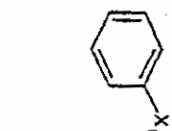
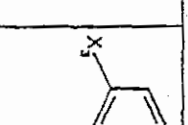
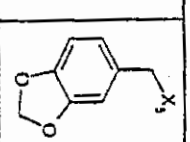
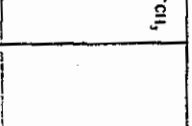
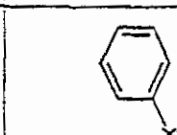
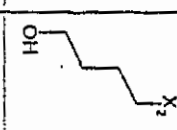
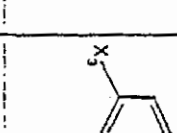
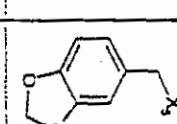
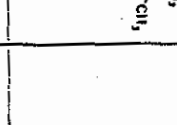
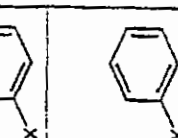
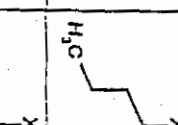
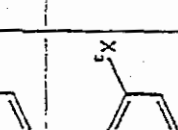
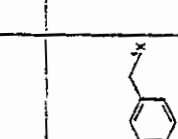
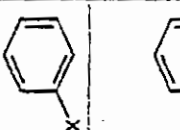
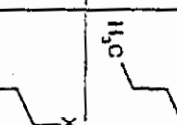
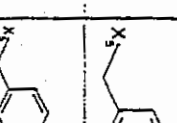
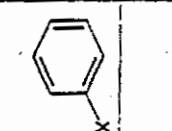
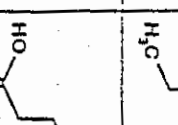
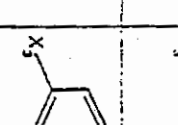
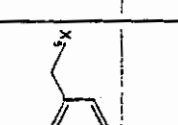
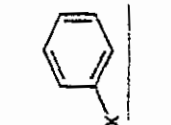
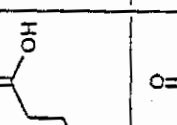
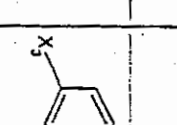
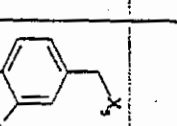
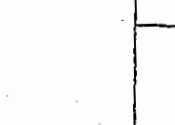
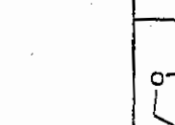
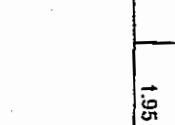
1117						1.86	560.2821	561.2766
1118						1.88	560.2821	561.2753
1119						1.89	524.3151	525.3075
1120						2	645.2839	646.274
1121						1.99	651.25	652.2567
1122						2.01	631.3046	632.2967

1123							1.89	644.3362	615.35
1124							2.01	631.2602	632.2625
1125							2	637.2344	638.2382
1126							2.01	617.289	618.2725
1127							1.9	630.3206	631.3359
1128							2.07	627.2709	628.2573



1129							2.02	573.2991	574.2791
1130							1.92	586.3307	587.3427
1131									
1132							1.87	561.2991	562.3006
1133									
1134									
1135									

1136								1.81	558.3359	559.3449
1137										
1138										
1139										
1140								1.81	558.3359	559.3449
1141								1.96	603.2369	604.2373
1142								1.95	609.2031	610.2124

1143							2.02	613.2552	614.2456
1144							1.96	559.2835	560.2794
1145							1.86	572.3161	573.3293
1146							1.98	603.2733	604.278
1147							2.05	575.3148	576.3073
1148							2.04	539.3148	540.3035
1149							2.01	631.3046	632.2966
1150							1.91	508.3202	509.323

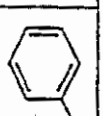
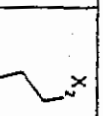
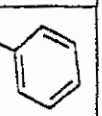
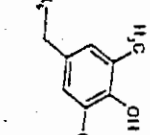
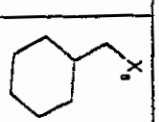
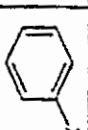
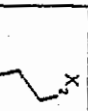
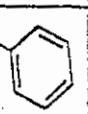
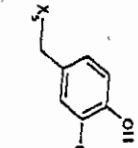
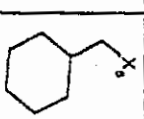
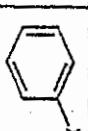
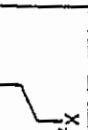
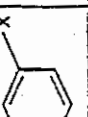
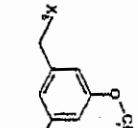
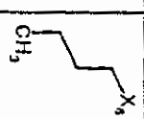
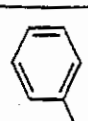
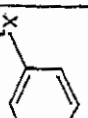
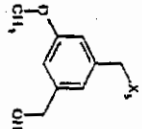
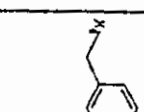
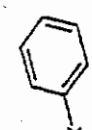
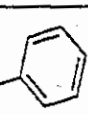
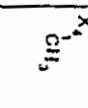
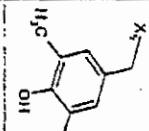
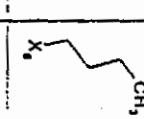
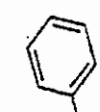
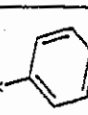
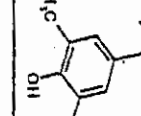
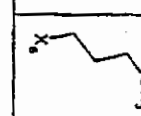
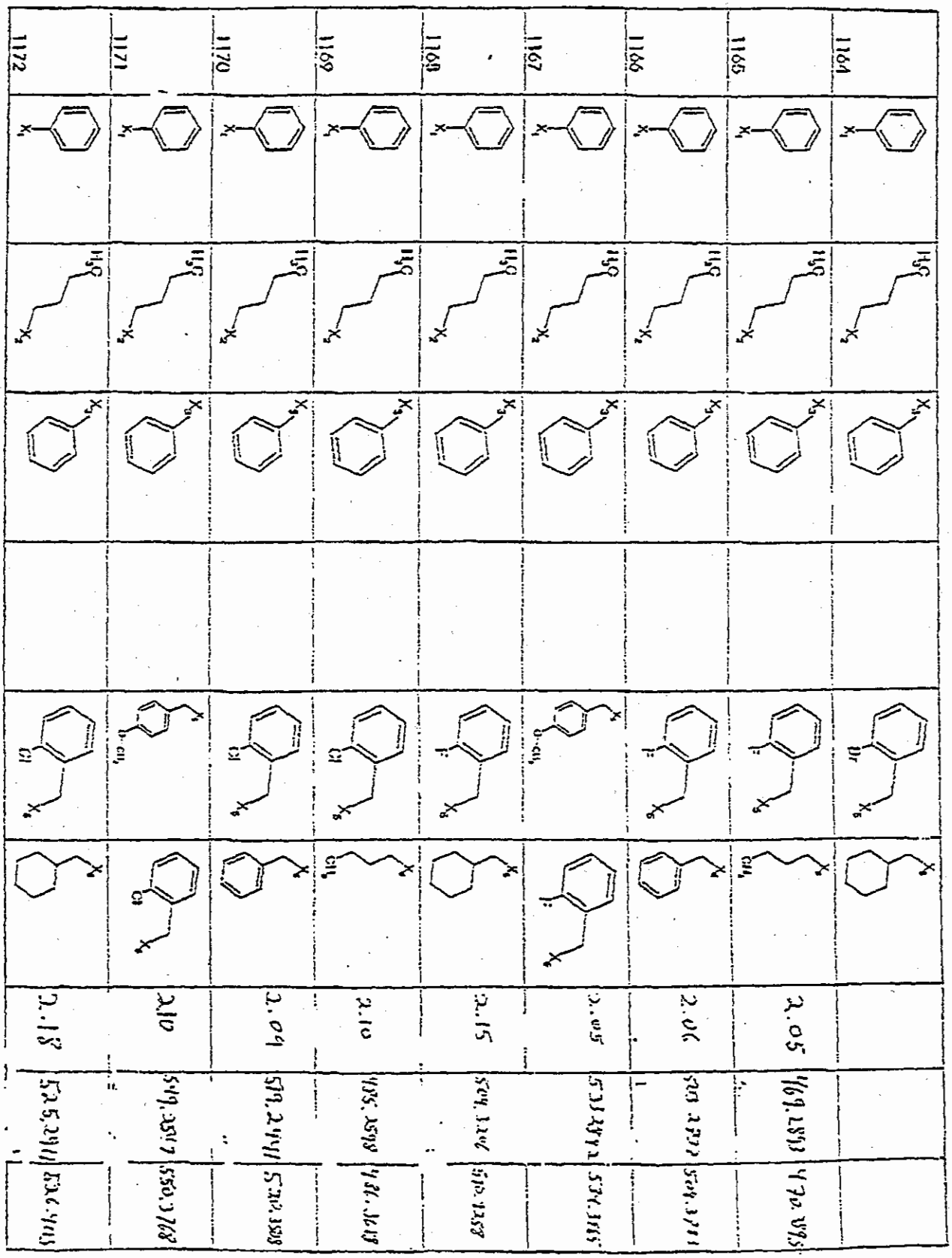
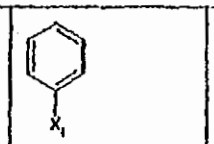
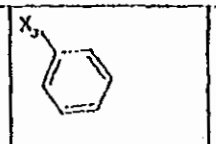
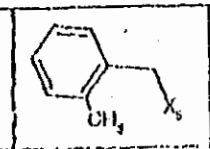
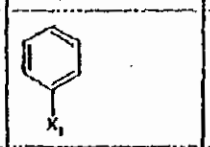
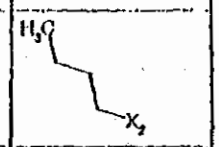
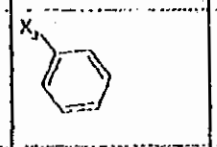
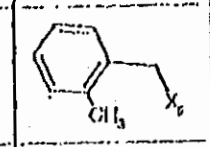
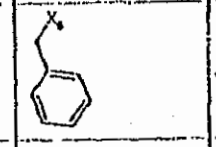
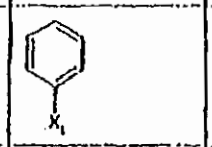
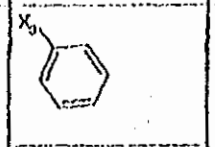
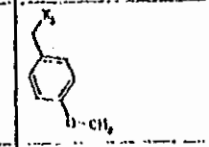
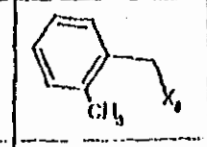
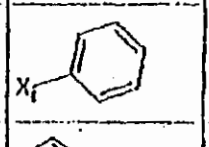
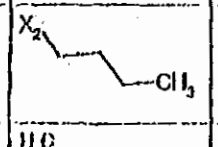
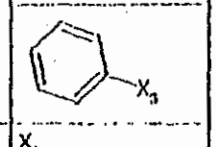
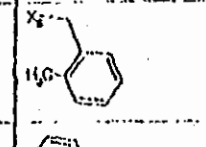
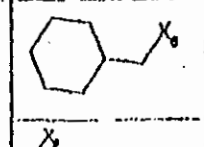
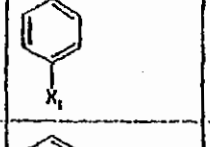
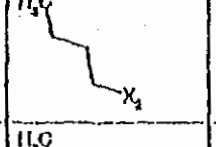
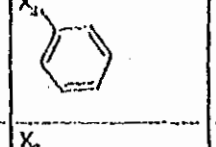
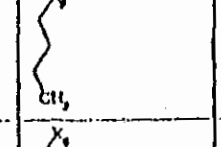
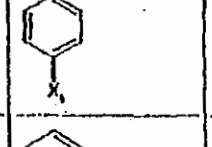
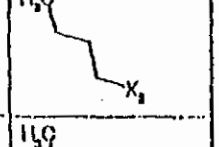
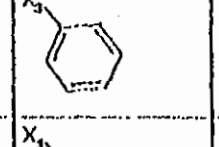
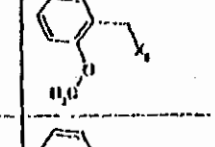
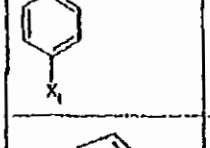
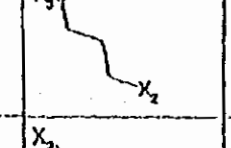
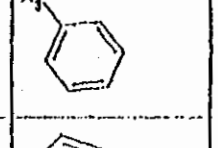
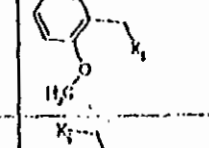
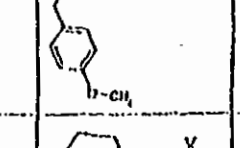
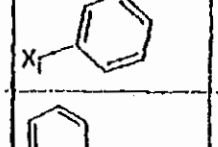
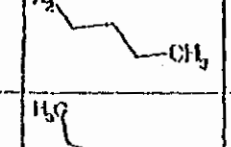
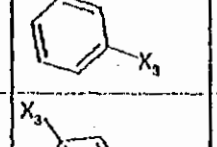
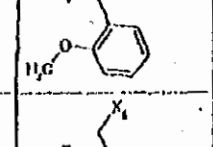
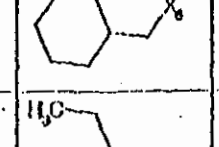
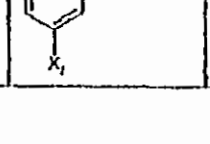
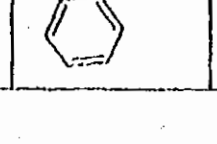
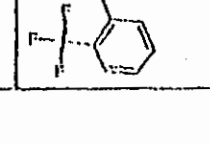
1151							2.1	535.3563	536.3535
1152							2.07	521.3406	522.3412
1153							1.88	511.3199	512.3171
1154							1.85	575.3148	576.3098
1155							1.91	509.3406	510.3491
1156							1.86	495.325	496.3272

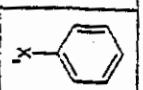
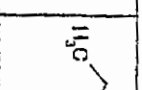
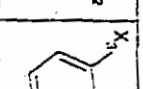
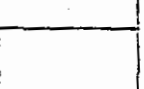
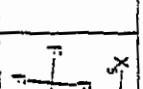
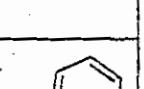
TABLE 2A

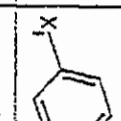
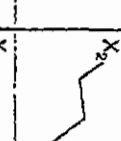
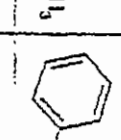
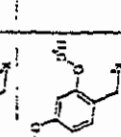
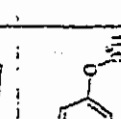
R4 is H unless otherwise specified

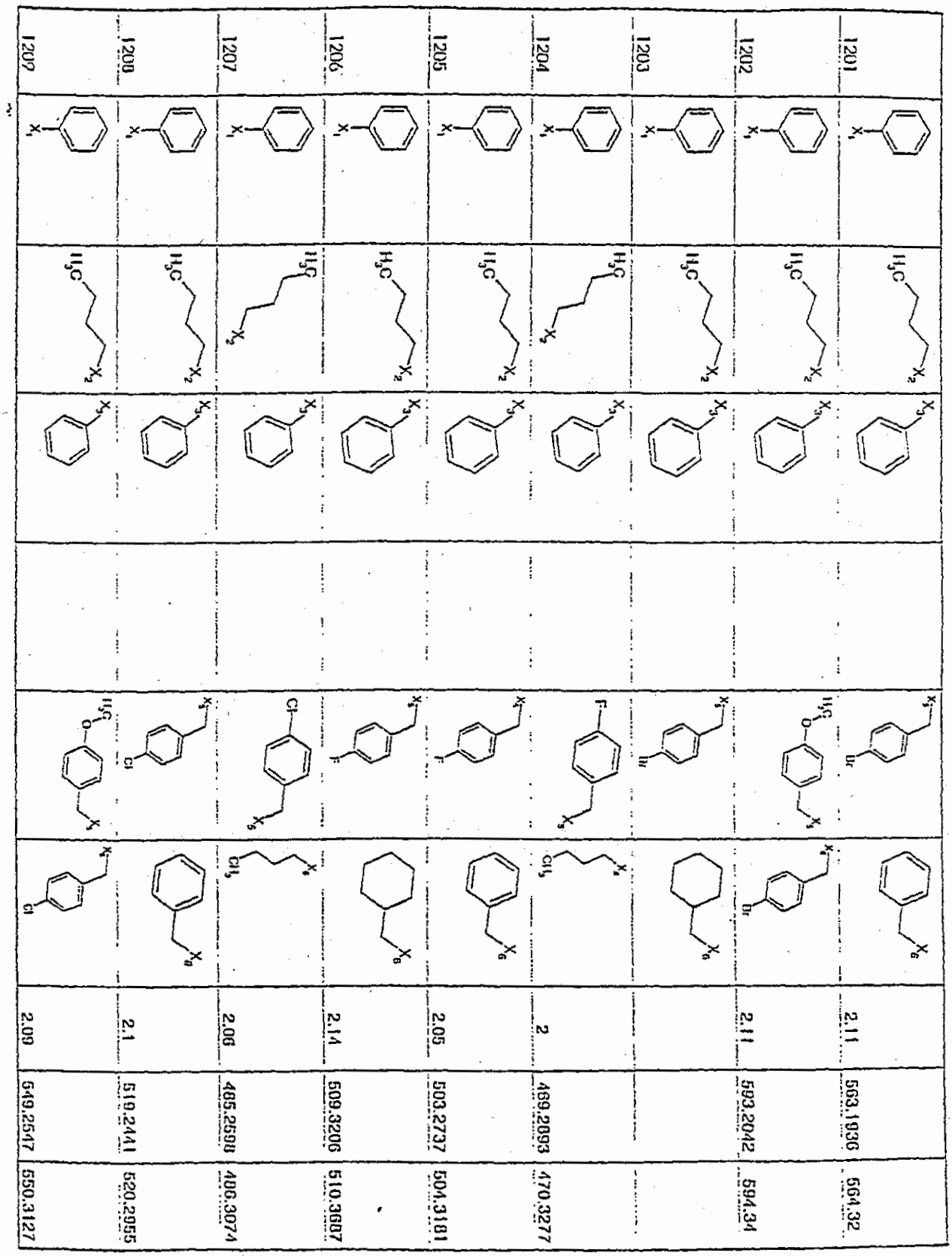
CMP #	R1	R2	R3	R4	R5	R6	Rt, time	Cmp Mass	Ion Obs
1157							1.90	451.2907	452.3944
1158							2.07	485.2831	486.3753
1159							2.05	515.2936	516.3962
1160							2.15	491.33	492.4342
1161							2.11	529.2093	530.32
1162							2.11	563.1936	564.31
1163							2.11	593.2042	594.33



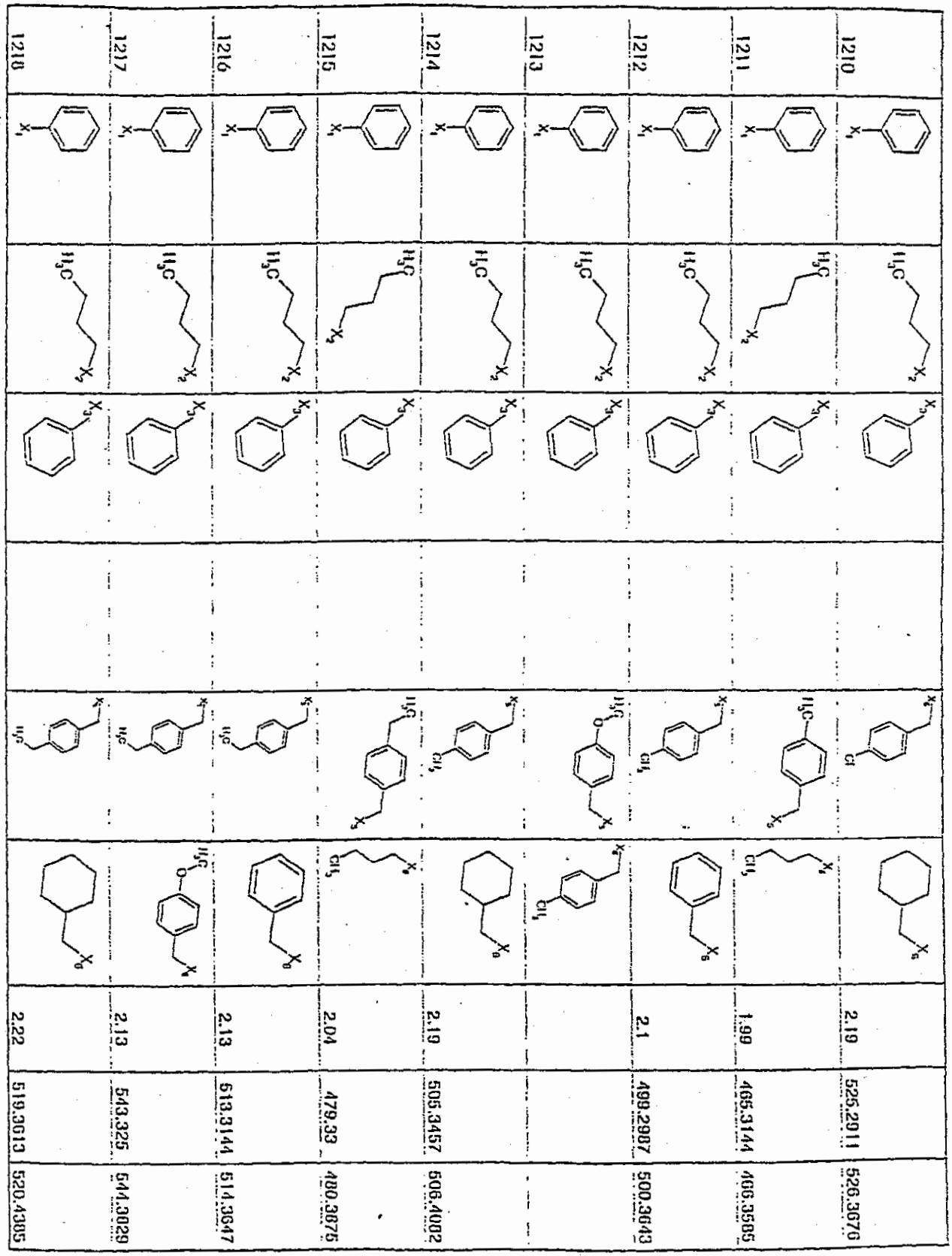
1173							2.06	465.3144	466.4148
1174							2.10	499.2987	500.4012
1175							2.10	529.3093	530.4219
1176									
1177							1.88	481.3093	482.4177
1178							2.07	515.2936	516.4023
1179							2.05	545.3042	546.4252
1180							2.12	521.3406	522.4584
1181							2.11	519.2861	520.4012

1102									2.09	553.2705	554.3081
1103									2.1	583.2011	584.4049
1104									2.17	559.3174	560.4424
1105									1.95	495.325	496.4399
1106									2.11	529.3093	530.4105
1107									2.09	559.3199	560.4452
1108											
1109									2.15	519.2208	520.3397
1110									2.15	553.2051	554.3284

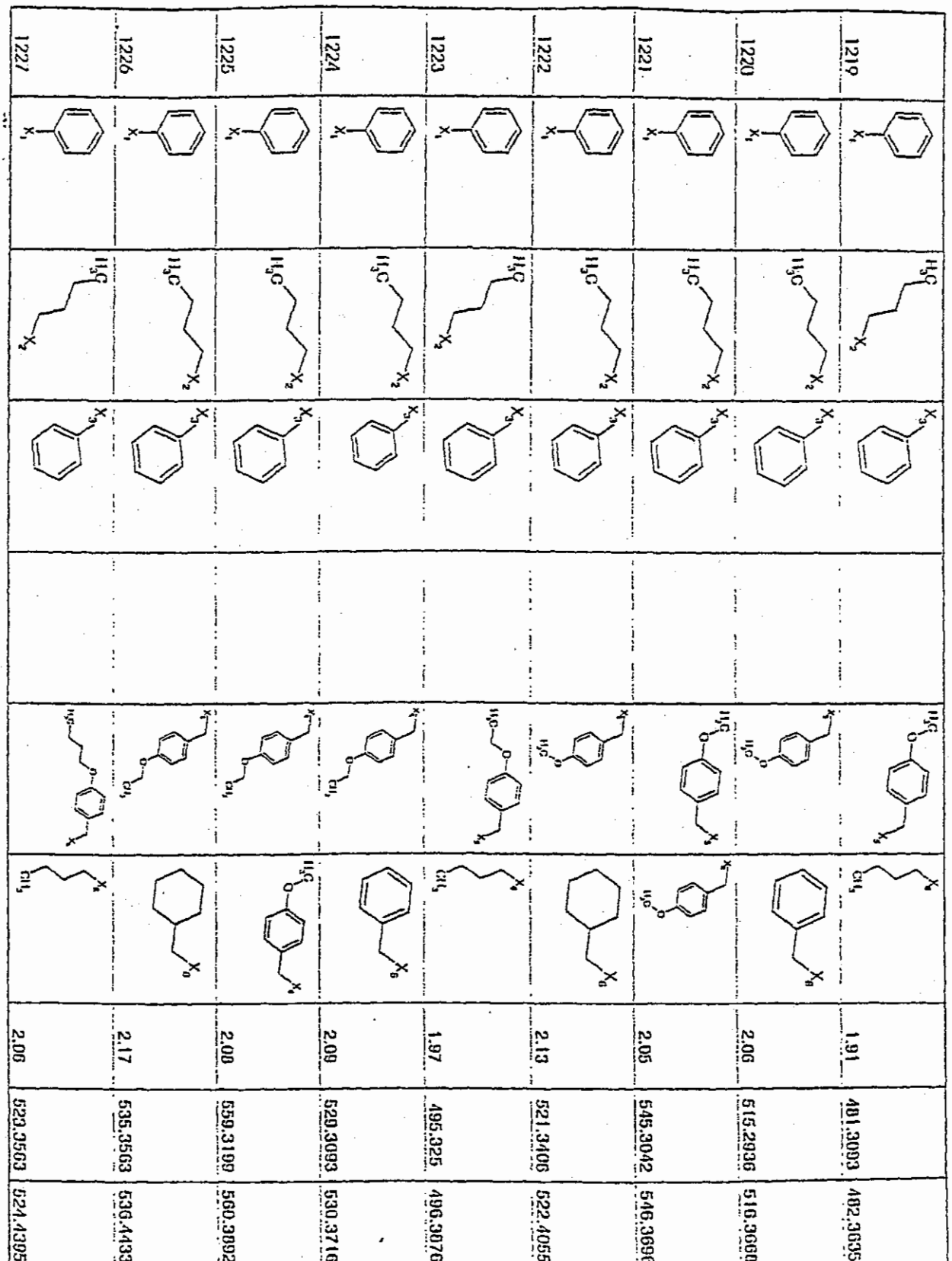
1191								2.26	559.2521	560.3608
1192								1.85	511.3199	512.4327
1193								2.05	545.3042	546.4219
1194								2.04	575.3148	576.4352
1195								2.09	551.3512	552.4758
1196								1.91	511.3199	512.4201
1197								2.05	545.3042	546.4178
1198								2.05	575.3148	576.4329
1199								2.12	551.3512	552.4684
1200								2.09	529.2093	530.33



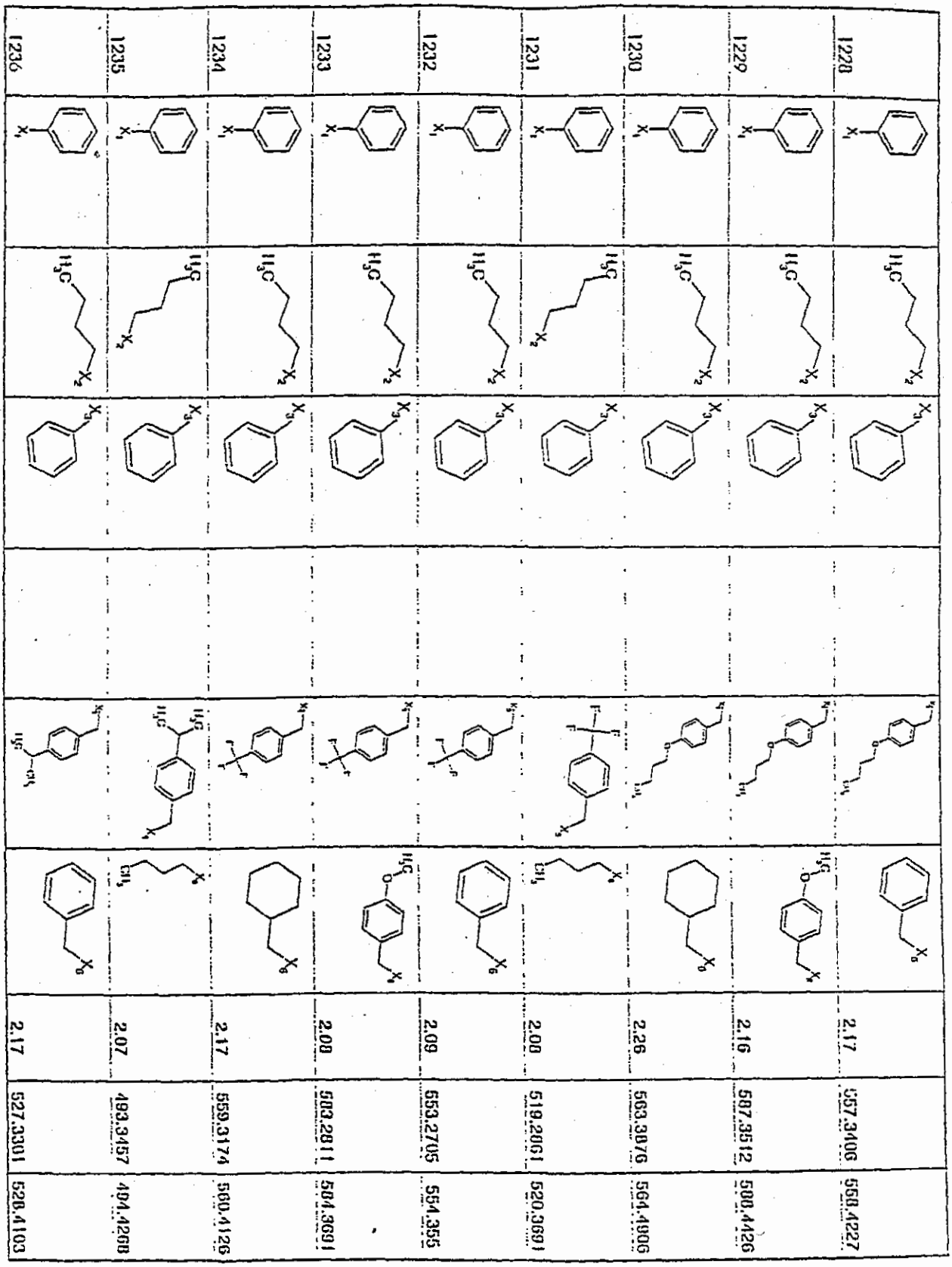
1201								2.11	563.1936	564.32
1202								2.11	593.2042	594.34
1203										
1204								2	469.2093	470.3277
1205								2.05	503.2737	504.3181
1206								2.14	509.3206	510.3687
1207								2.06	465.2598	466.3074
1208								2.1	519.2441	520.2955
1209								2.09	549.2547	550.3127



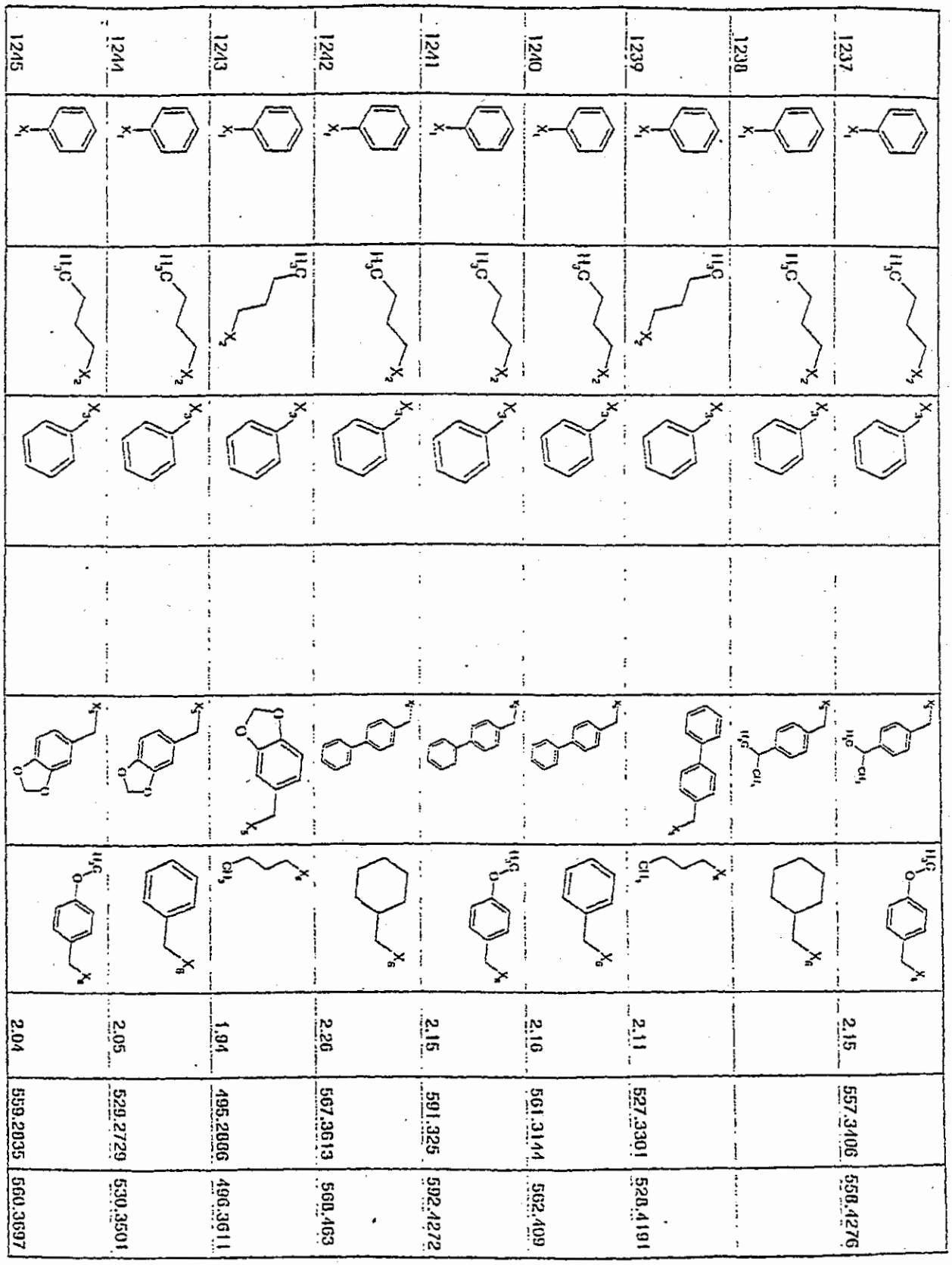
1210							2.19	526.2911	526.3670	
1211							1.99	465.3144	466.3505	
1212							2.1	499.2987	500.3643	
1213										
1214							2.19	505.3457	506.4002	
1215							2.04	479.33	480.3875	
1216							2.13	513.3144	514.3647	
1217							2.13	543.325	544.3029	
1218							2.22	519.3613	520.4305	



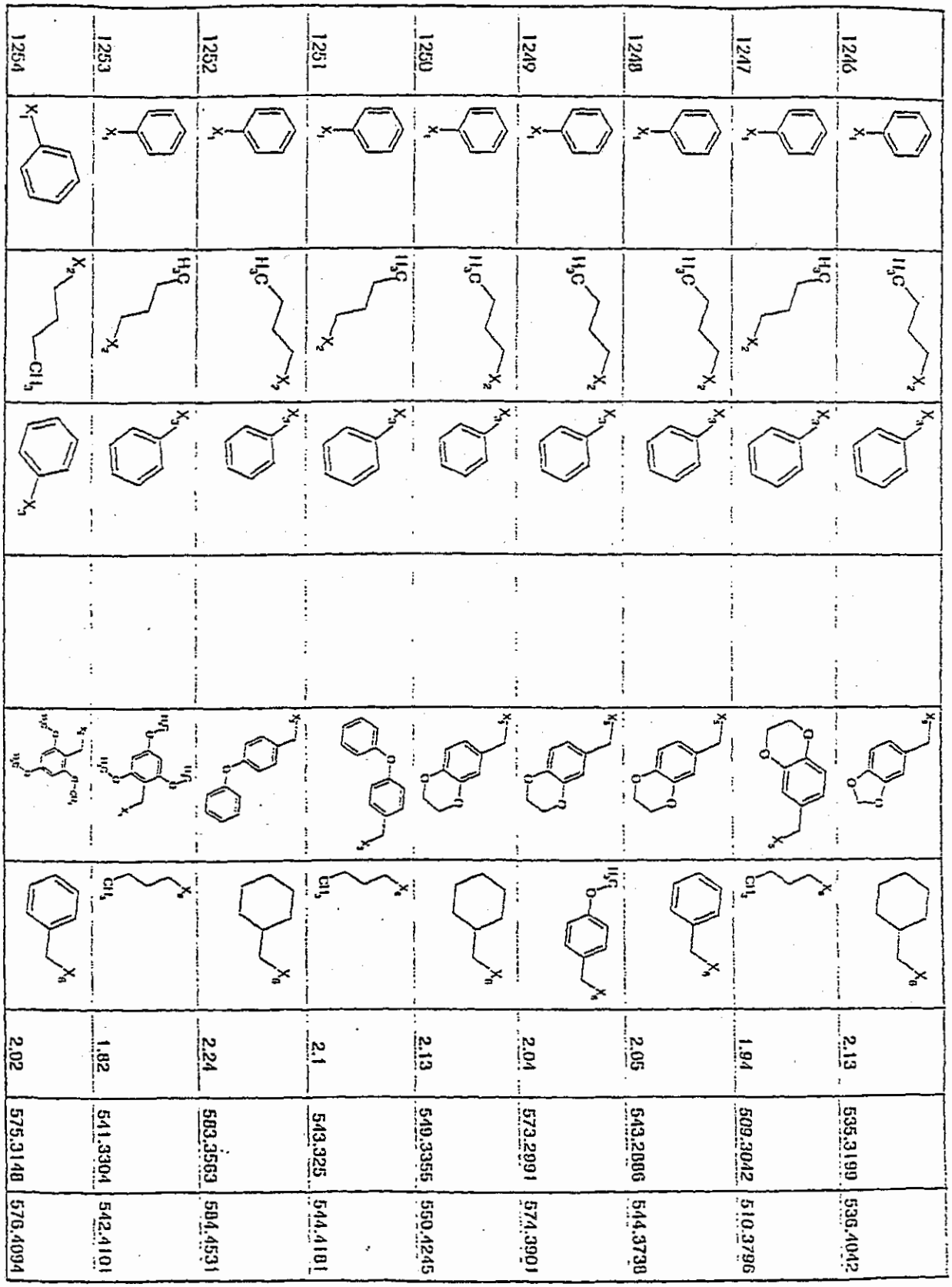
1219										1.91	481.3093	482.3695
1220										2.06	515.2936	516.3660
1221										2.05	545.3042	546.3696
1222										2.13	521.3406	522.4055
1223										1.97	495.325	496.3876
1224										2.09	529.3093	530.3716
1225										2.08	559.3199	560.3092
1226										2.17	535.3563	536.4433
1227										2.06	523.3563	524.4395



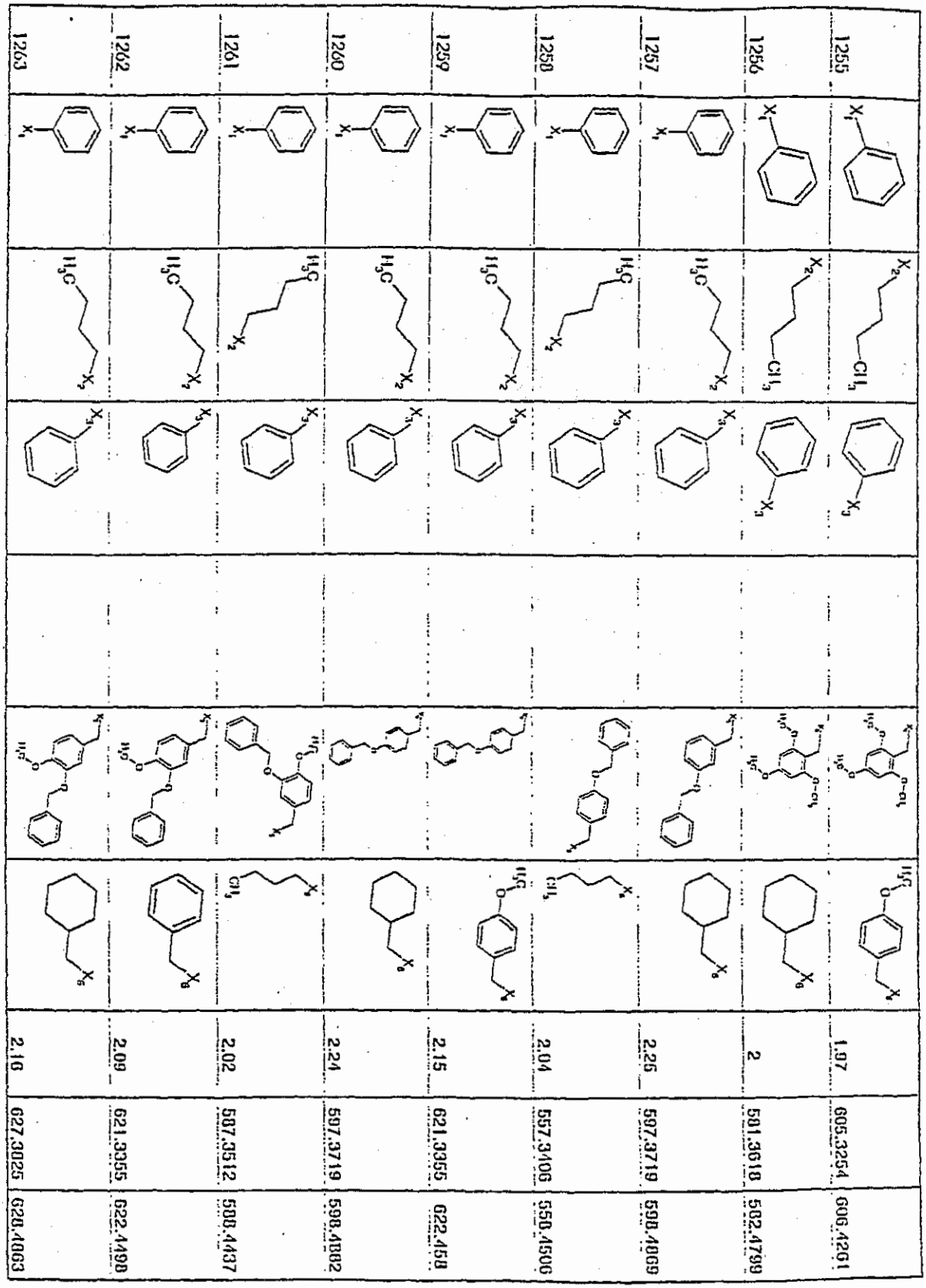
1228							2.17	557.3406	558.4227
1229							2.16	587.3512	588.4426
1230							2.26	563.3876	564.4906
1231							2.08	519.2961	520.3691
1232							2.09	553.2705	554.355
1233							2.08	583.2811	584.3691
1234							2.17	559.3174	560.4126
1235							2.07	493.3457	494.4268
1236							2.17	527.3301	528.4103



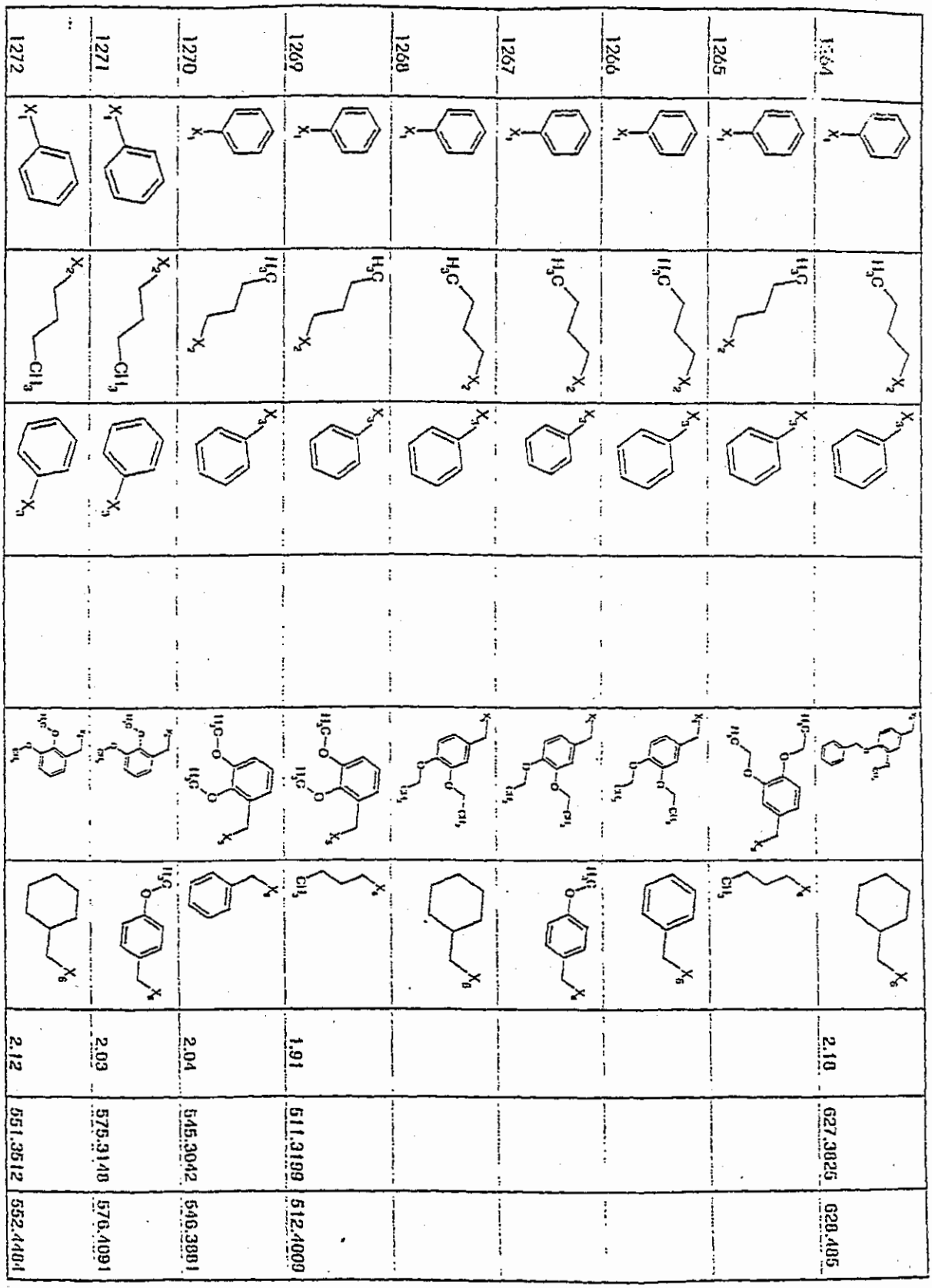
1237							2.15	557.3406	558.4276
1238									
1239							2.11	527.3301	528.4191
1240							2.16	561.3144	562.409
1241							2.15	591.325	592.4272
1242							2.26	567.3613	568.463
1243							1.91	495.2886	496.3611
1244							2.05	529.2729	530.3501
1245							2.04	559.2035	560.3097



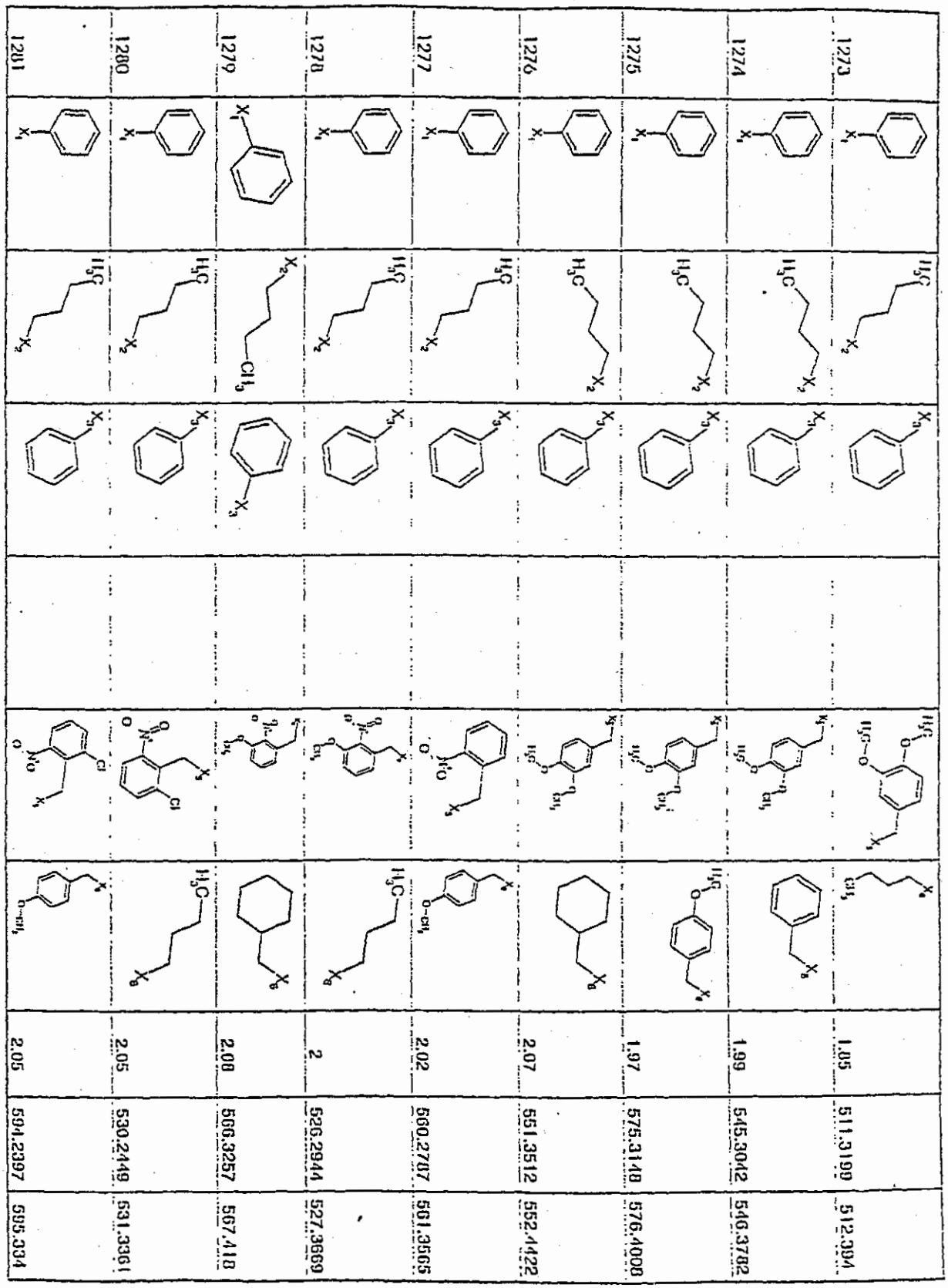
1246							2.13	535.3199	536.4042
1247							1.94	509.3042	510.3796
1248							2.05	543.2986	544.3738
1249							2.04	573.2991	574.3901
1250							2.13	549.3355	550.4245
1251							2.1	543.325	544.4101
1252							2.24	583.3563	584.4531
1253							1.82	541.3304	542.4101
1254							2.02	575.3148	576.4094



1255							1.97	605.3254	606.4261
1256							2	581.3618	582.4799
1257							2.25	597.3719	598.4069
1258							2.04	557.3406	558.4506
1259							2.15	621.3355	622.458
1260							2.24	597.3719	598.4882
1261							2.02	587.3512	588.4437
1262							2.09	621.3355	622.4498
1263							2.16	627.3025	628.4063



1264								2.10	627.3825	628.405
1265										
1266										
1267										
1268										
1269								1.91	511.3199	512.4009
1270								2.04	545.3042	546.3991
1271								2.03	575.3148	576.4091
1272								2.12	551.3512	552.4404



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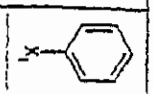
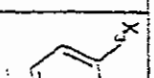
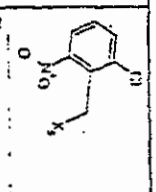
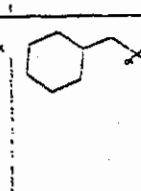
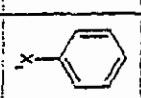
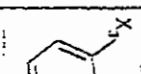
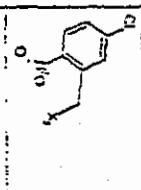
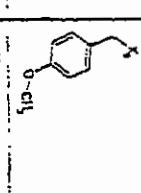
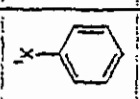
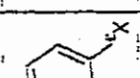
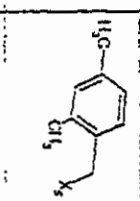
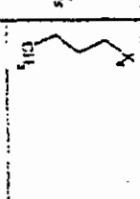
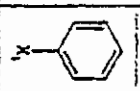
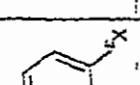
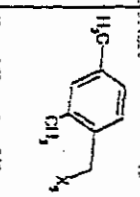
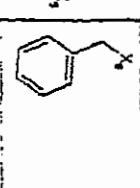
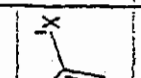
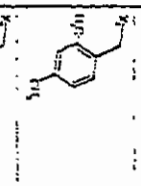
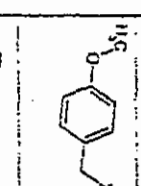
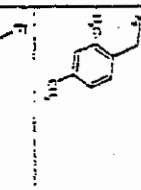
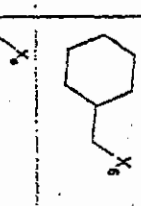
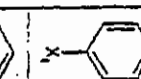
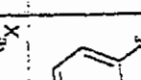
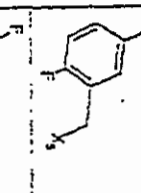
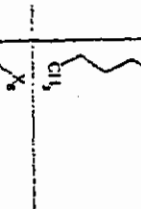
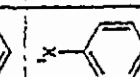
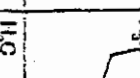
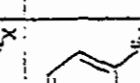
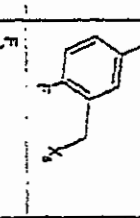
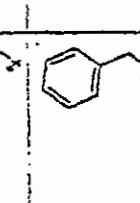
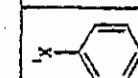
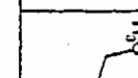
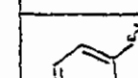
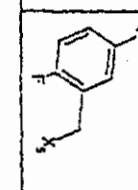
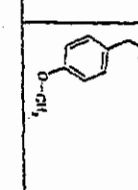
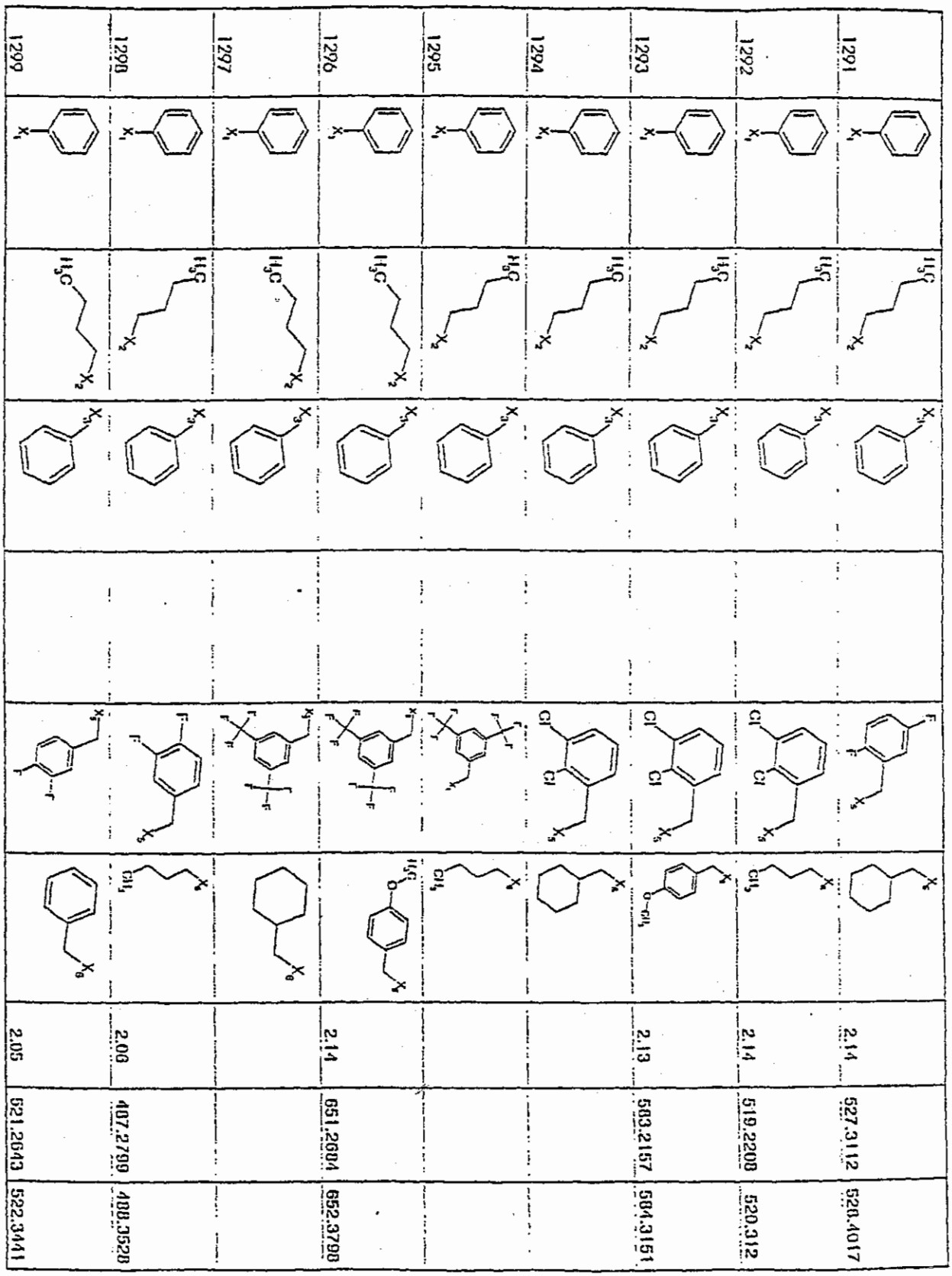
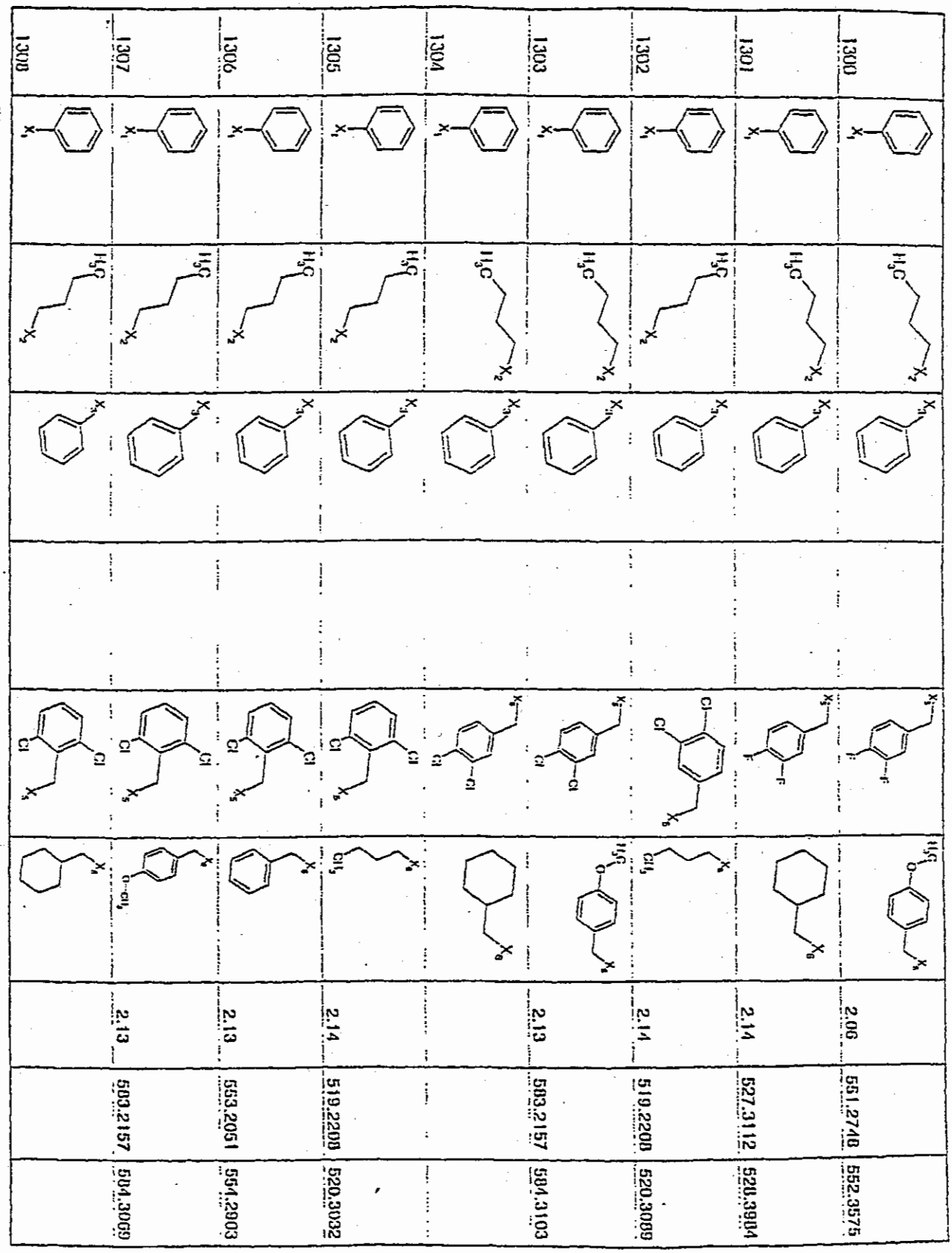
1274							1.99	545.3042	546.3782	
1275							1.97	575.3148	576.4008	
1276							2.07	551.3512	552.4422	
1277							2.02	560.2787	561.3565	
1278							2	526.2944	527.3669	
1279							2.08	566.3257	567.418	
1280							2.05	530.2449	531.3361	
1281							2.05	594.2397	595.334	

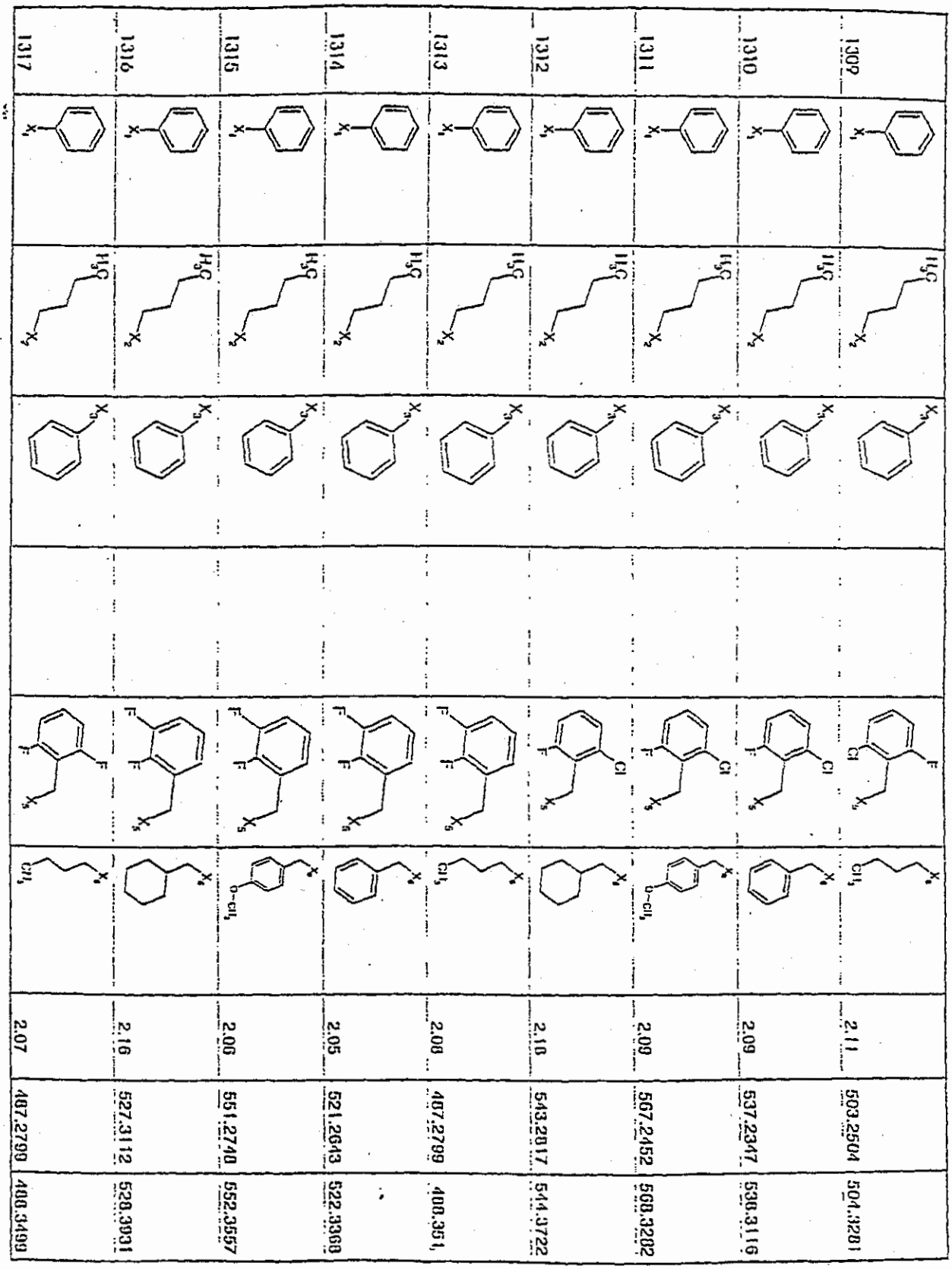
1282								2.12	570.2762	571.3751
1283								2.07	594.2397	595.3354
1284								2.08	479.33	480.4123
1285								2.14	513.3144	514.3954
1286								2.13	543.325	544.4046
1287										
1288								2.05	407.2799	408.3539
1289								2.06	521.2649	522.3414
1290								2.05	551.2748	552.3583

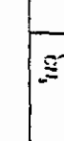
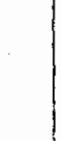


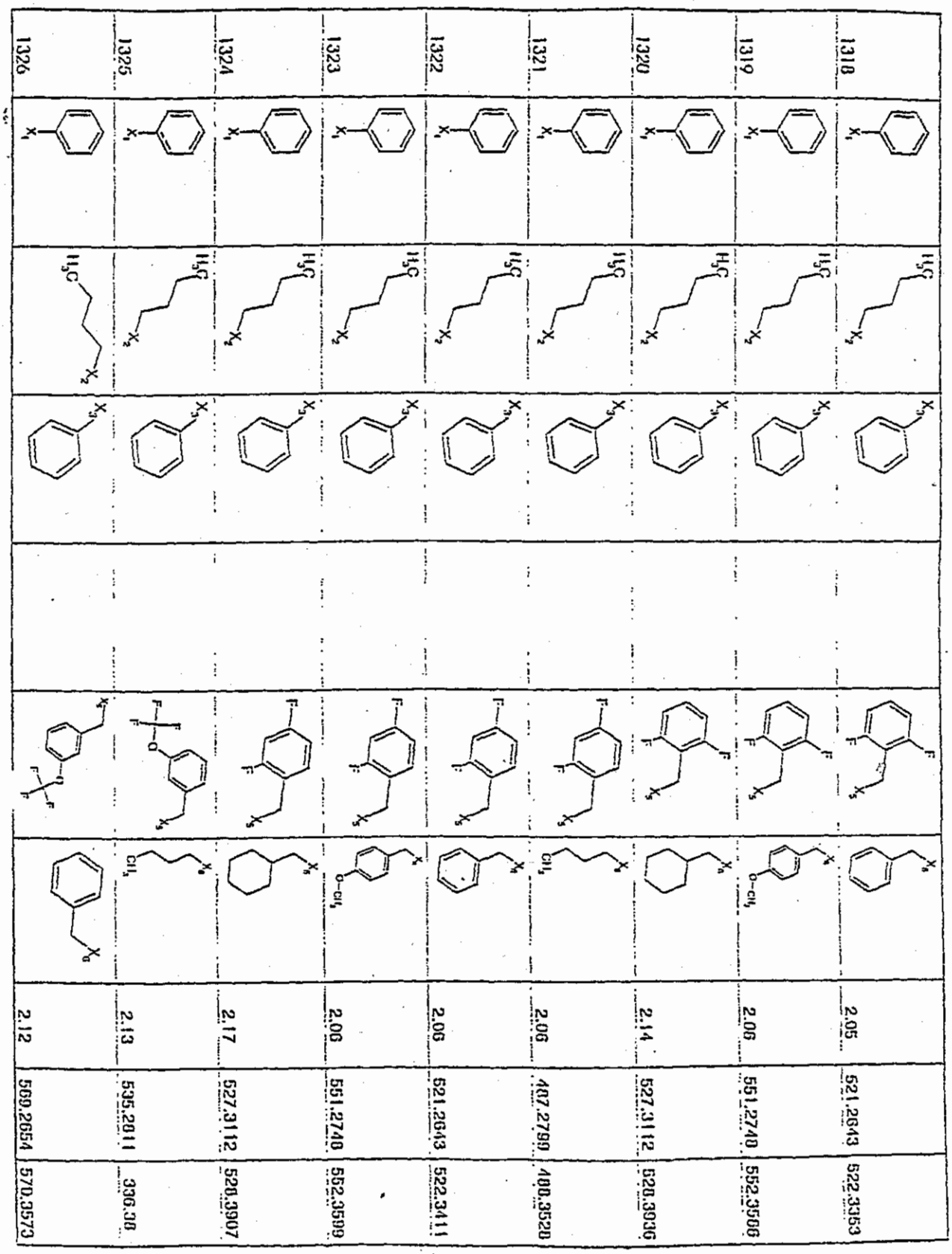
1291								2.14	527.3112	528.4017
1292								2.14	519.2208	520.312
1293								2.13	583.2157	584.3151
1294										
1295										
1296								2.14	651.2604	652.3798
1297										
1298								2.08	407.2799	408.3528
1299								2.05	521.2643	522.3441



1300							2.06	551.2748	552.3575	
1301							2.14	527.3112	528.3904	
1302							2.14	519.2209	520.3089	
1303							2.13	583.2157	584.3103	
1304										
1305							2.14	519.2208	520.3032	
1306							2.13	553.2051	554.2903	
1307							2.13	583.2157	584.3069	
1308										



1309								2.11	503.2504	504.3281
1310								2.09	537.2347	538.3116
1311								2.09	567.2452	568.3202
1312								2.16	543.2817	544.3722
1313								2.08	487.2799	488.3499
1314								2.05	521.2643	522.3369
1315								2.06	551.2740	552.3557
1316								2.16	527.3112	528.3931
1317								2.07	487.2799	488.3499



1318							2.05	521.2643	522.3353	
1319							2.06	551.2748	552.3566	
1320							2.14	527.3112	528.3936	
1321							2.06	487.2799	488.3528	
1322							2.06	521.2643	522.3411	
1323							2.06	551.2748	552.3599	
1324							2.17	527.3112	528.3907	
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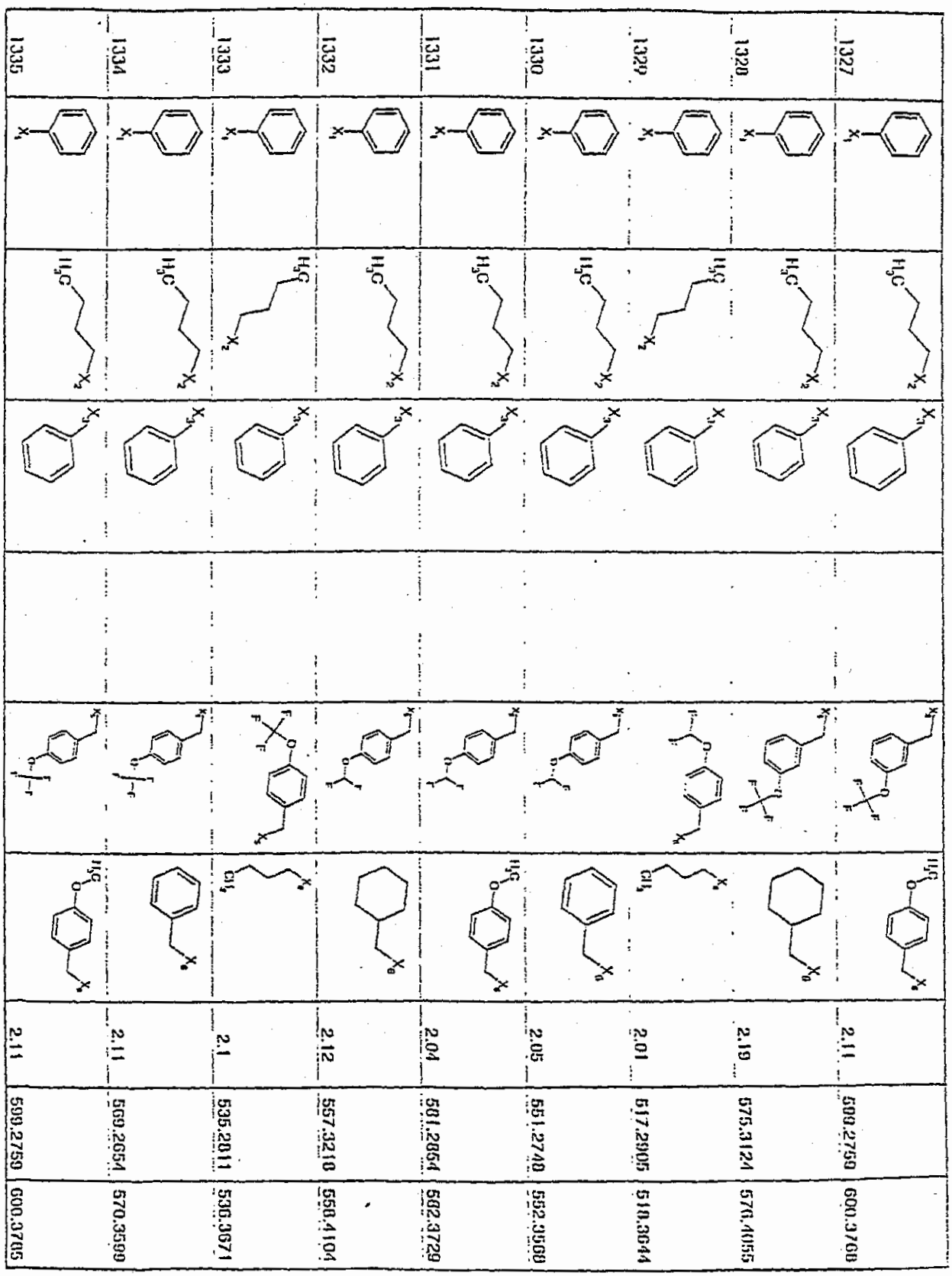
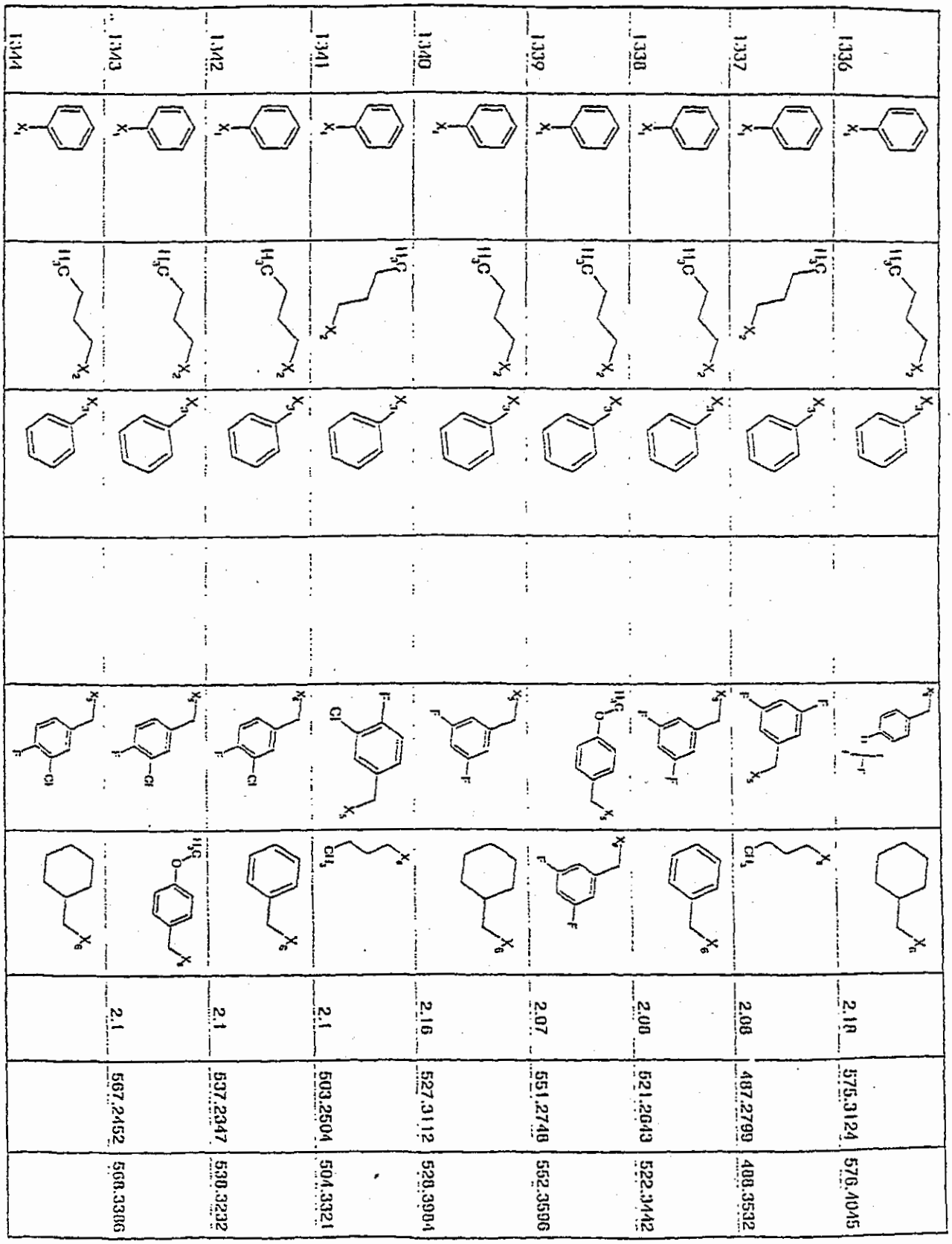
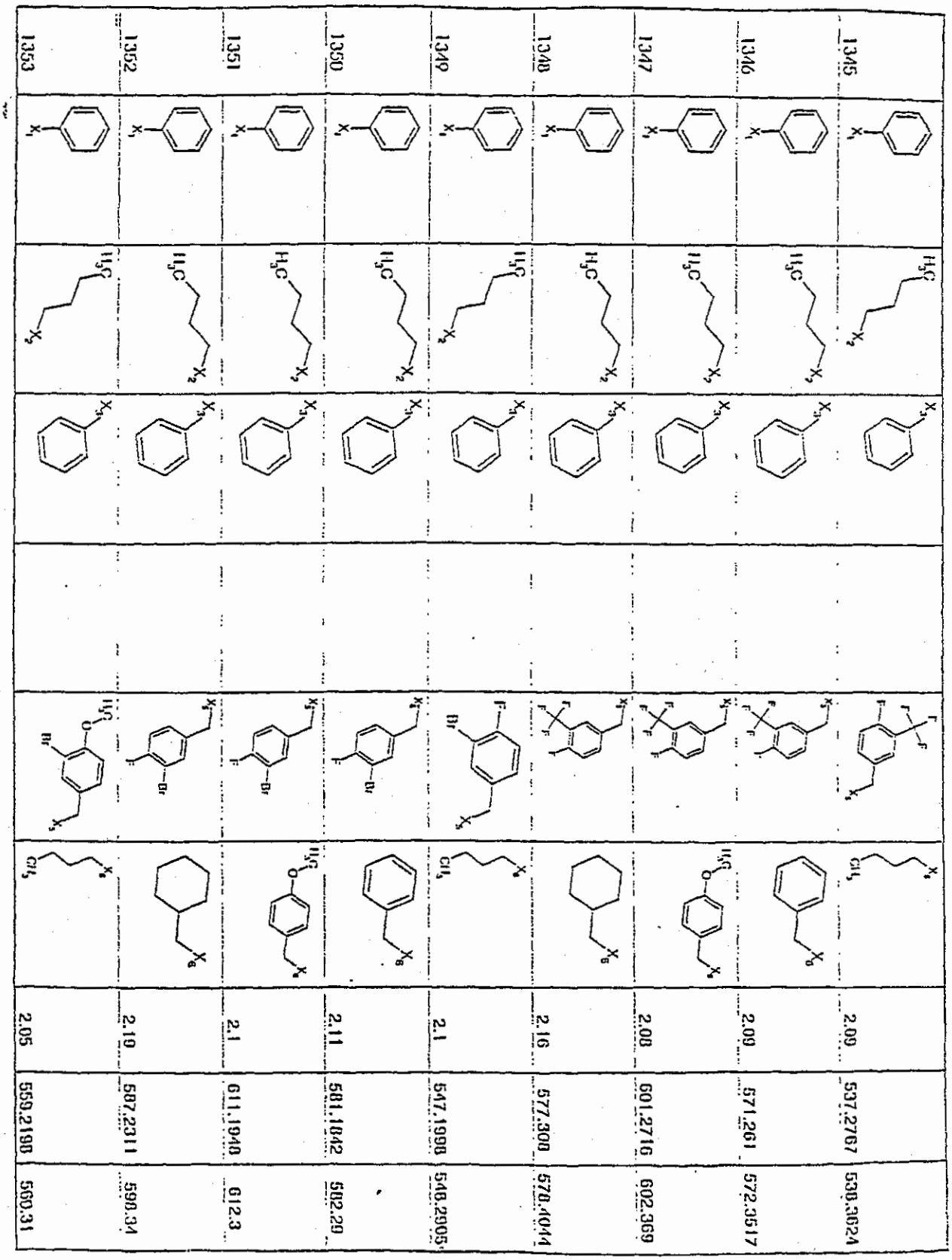
1326							2.12	569.2654	570.3573	



1327							2.11	599.2759	600.3768	
1328							2.19	575.3124	576.4055	
1329							2.01	517.2905	518.3644	
1330							2.05	551.2749	552.3569	
1331							2.04	581.2854	582.3729	
1332							2.12	557.3218	558.4104	
1333							2.1	535.2811	536.3671	
1334							2.11	569.2654	570.3599	
1335							2.11	599.2759	600.3785	

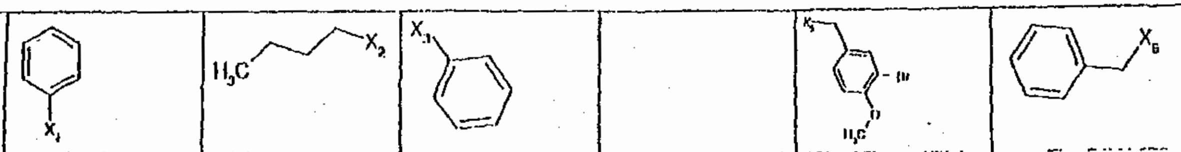
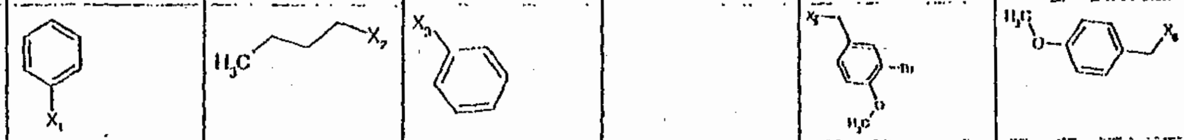
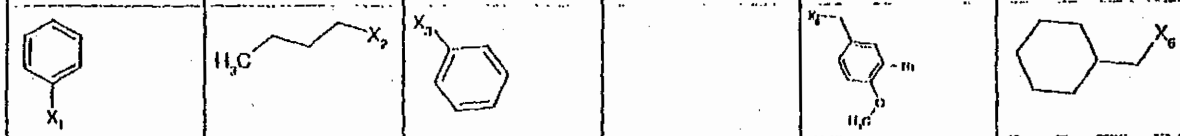
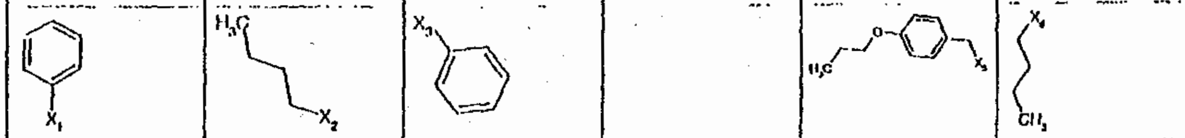
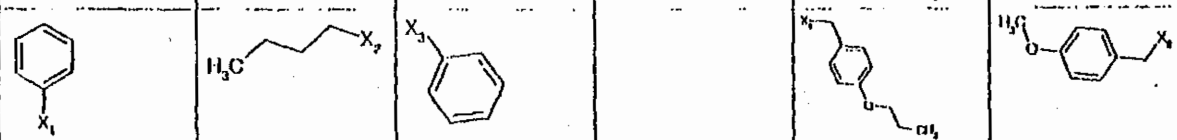
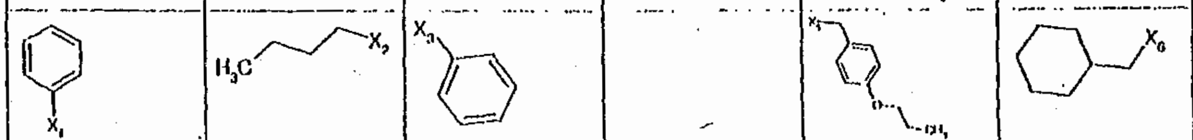


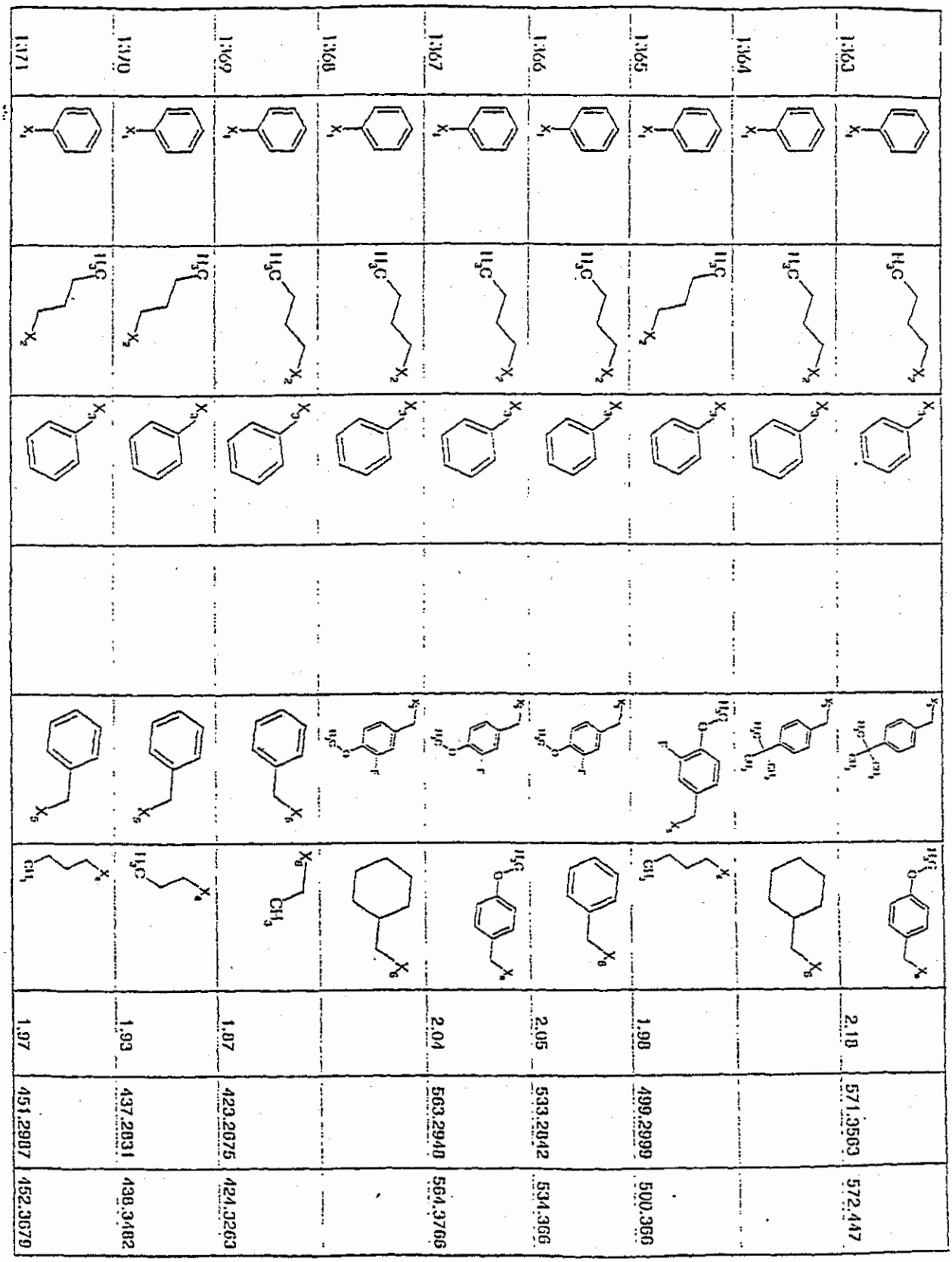
1336							2.18		575.3124	576.4045
1337							2.08		487.2799	488.3532
1338							2.09		521.2643	522.3442
1339							2.07		551.2748	552.3596
1340							2.16		527.3112	528.3904
1341							2.1		503.2504	504.3321
1342							2.1		537.2347	538.3232
1343							2.1		567.2452	568.3386
1344										



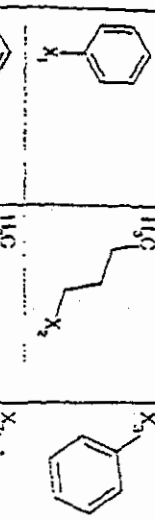
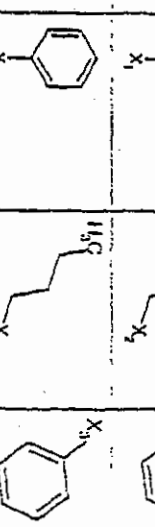
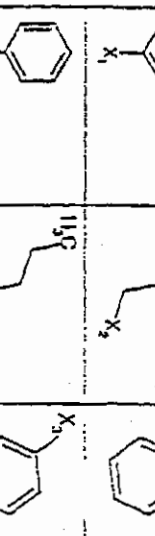
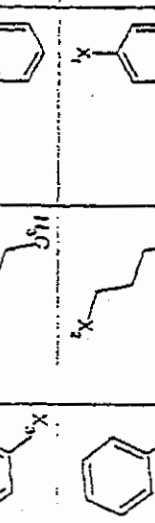
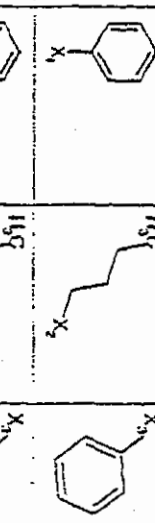
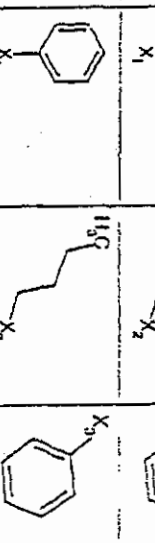
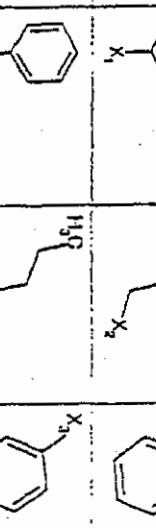
1345								2.09	537.2767	538.3624
1346								2.09	571.261	572.3517
1347								2.08	601.2716	602.369
1348								2.16	577.308	578.4044
1349								2.1	547.1998	548.2905
1350								2.11	581.1842	582.29
1351								2.1	611.1940	612.3
1352								2.19	587.2311	588.34
1353								2.05	559.2198	560.31

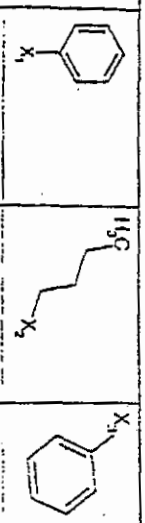
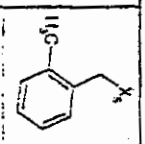
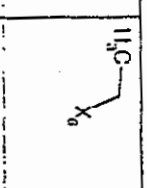
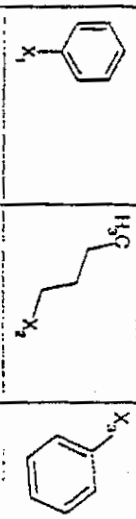
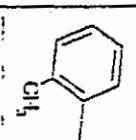
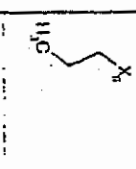
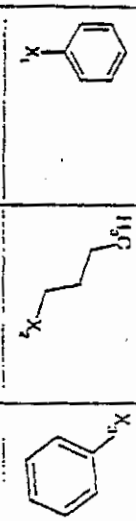
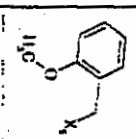
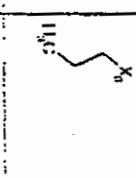
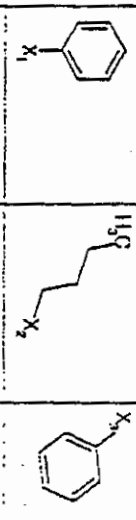
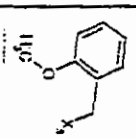
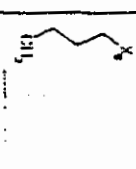
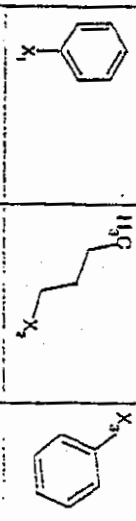
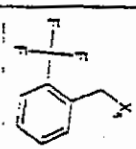
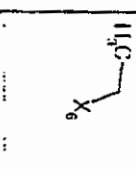
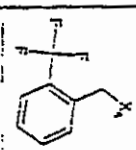
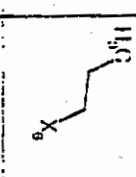
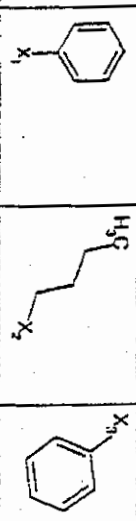
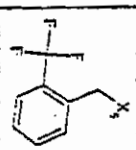
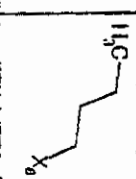
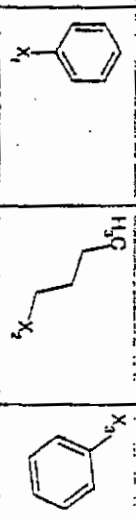
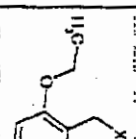
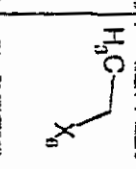
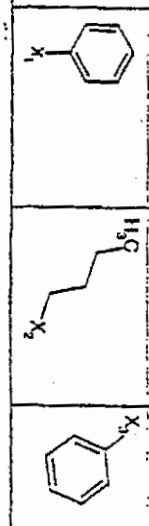
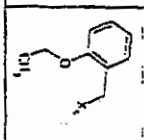
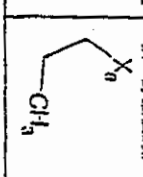
2 8 MAR 2005

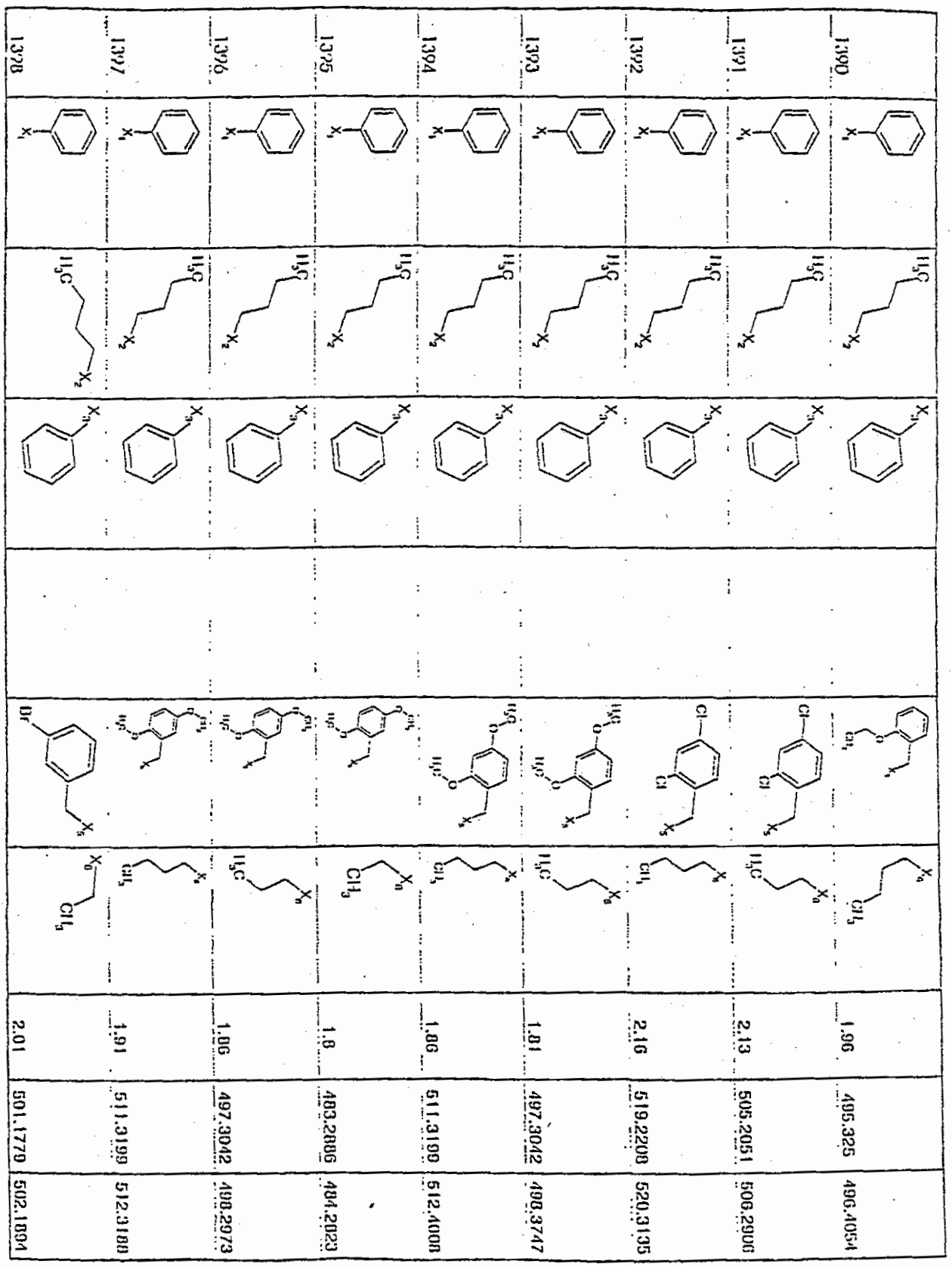
1354				
1355		2.08	623.2147	624.31
1356				
1357		2.02	509.3406	510.4212
1358		2.14	543.325	544.3902
1359		2.13	573.3355	574.4336
1360				
1361		2.11	507.3614	508.4463
1362		2.19	541.3457	542.4313



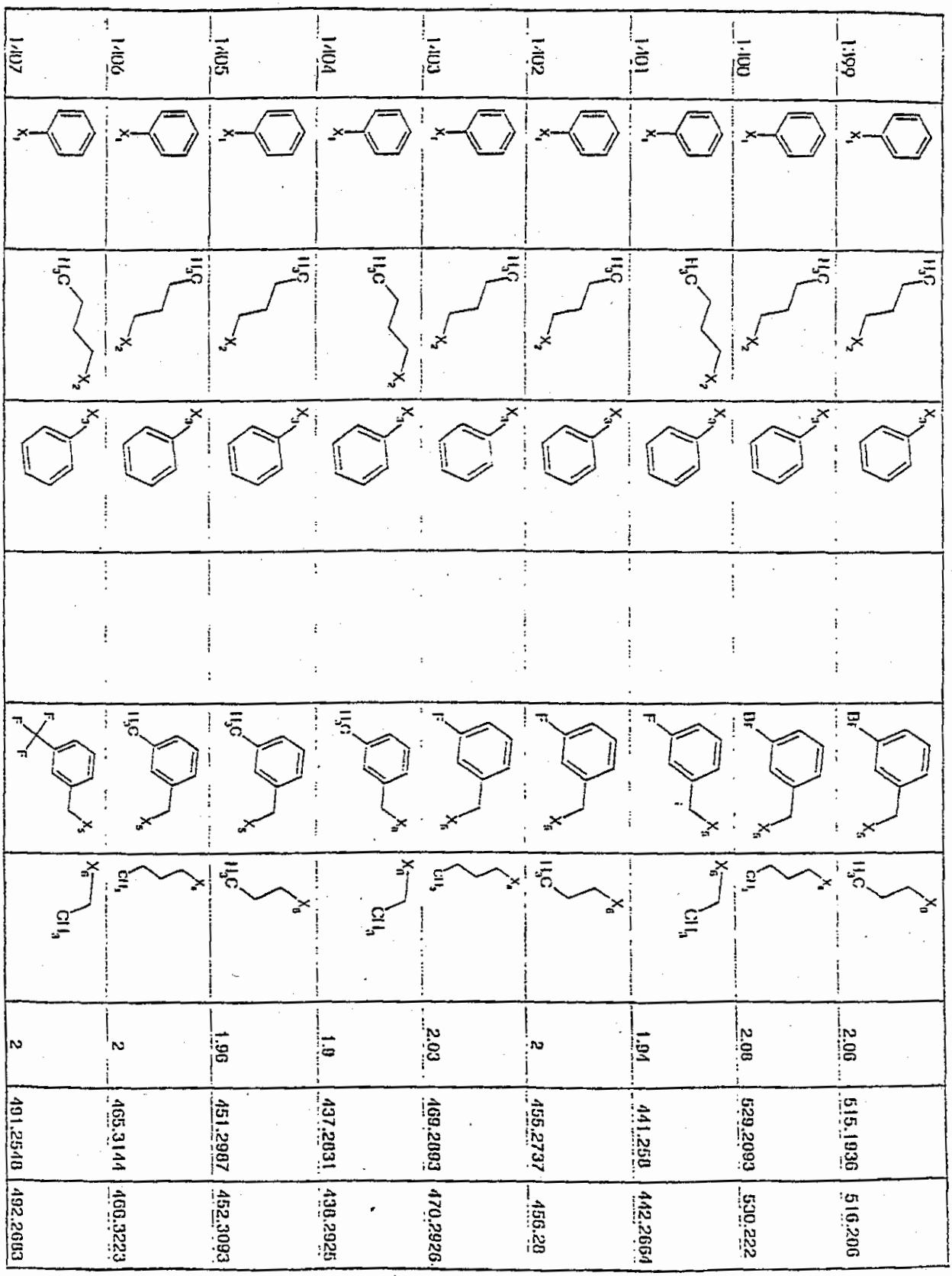
1363								2.10	571.3563	572.447
1364										
1365								1.98	499.2999	500.366
1366								2.05	533.2042	534.366
1367								2.04	563.2948	564.3766
1368										
1369								1.87	423.2075	424.3263
1370								1.93	437.2831	438.3482
1371								1.97	451.2987	452.3679

1372							2.03	501.1779	502.2567	
1373							2.08	515.1936	516.27	
1374							2.12	529.2093	530.29	
1375							1.96	441.258	442.3167	
1376							2.01	455.2737	456.3356	
1377							2.05	469.2893	470.3576	
1378							2.02	457.2285	458.3003	
1379							2.07	471.2441	472.3165	
1380							2.11	485.2598	486.3203	

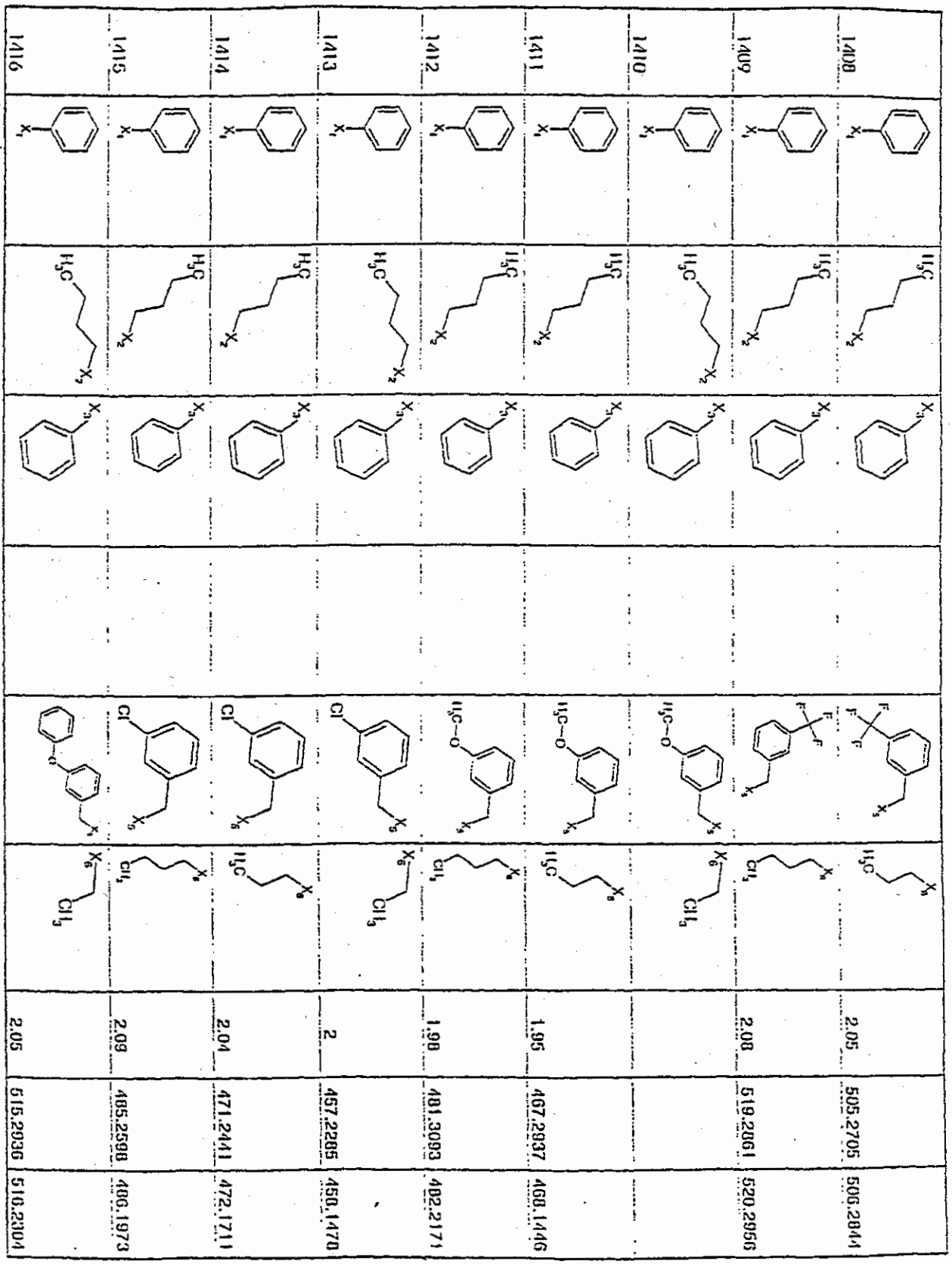
1301							1.97	437.2931	438.3451
1302							2.02	451.2987	452.3978
1303							1.85	467.2937	468.3646
1304							1.80	481.3093	482.3853
1305							2.04	491.2540	492.3256
1306							2.07	505.2705	506.3494
1307							2.11	519.2861	520.37
1308							1.94	467.2937	468.3647
1309							1.91	481.3093	482.3842



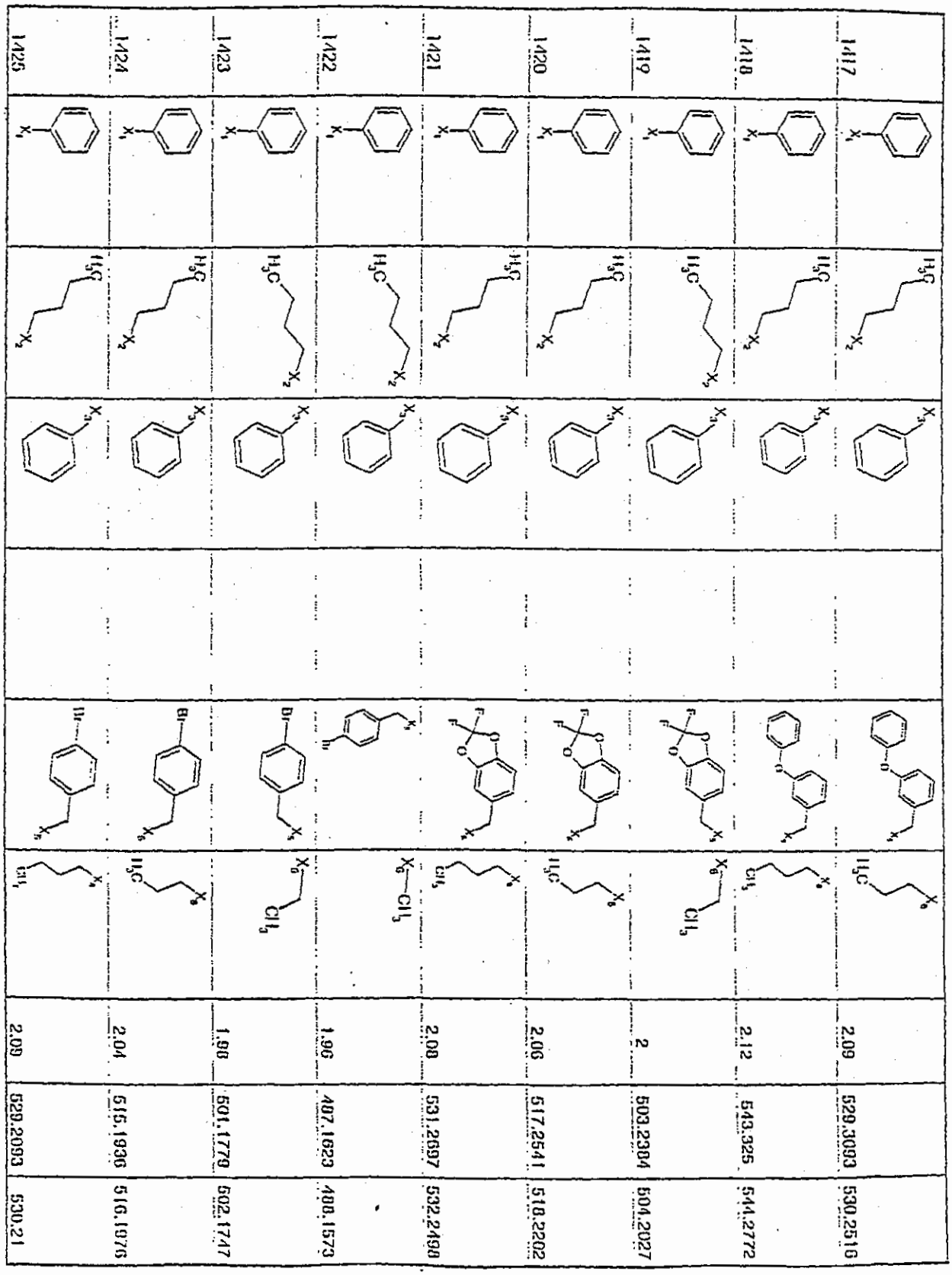
1390							1.96		495.325	496.4054
1391							2.13		505.2051	506.2906
1392							2.16		519.2208	520.3135
1393							1.81		497.3042	498.3747
1394							1.86		511.3199	512.4008
1395							1.8		483.2806	484.2023
1396							1.96		497.3042	498.2973
1397							1.91		511.3199	512.3188
1398							2.01		501.1779	502.1894



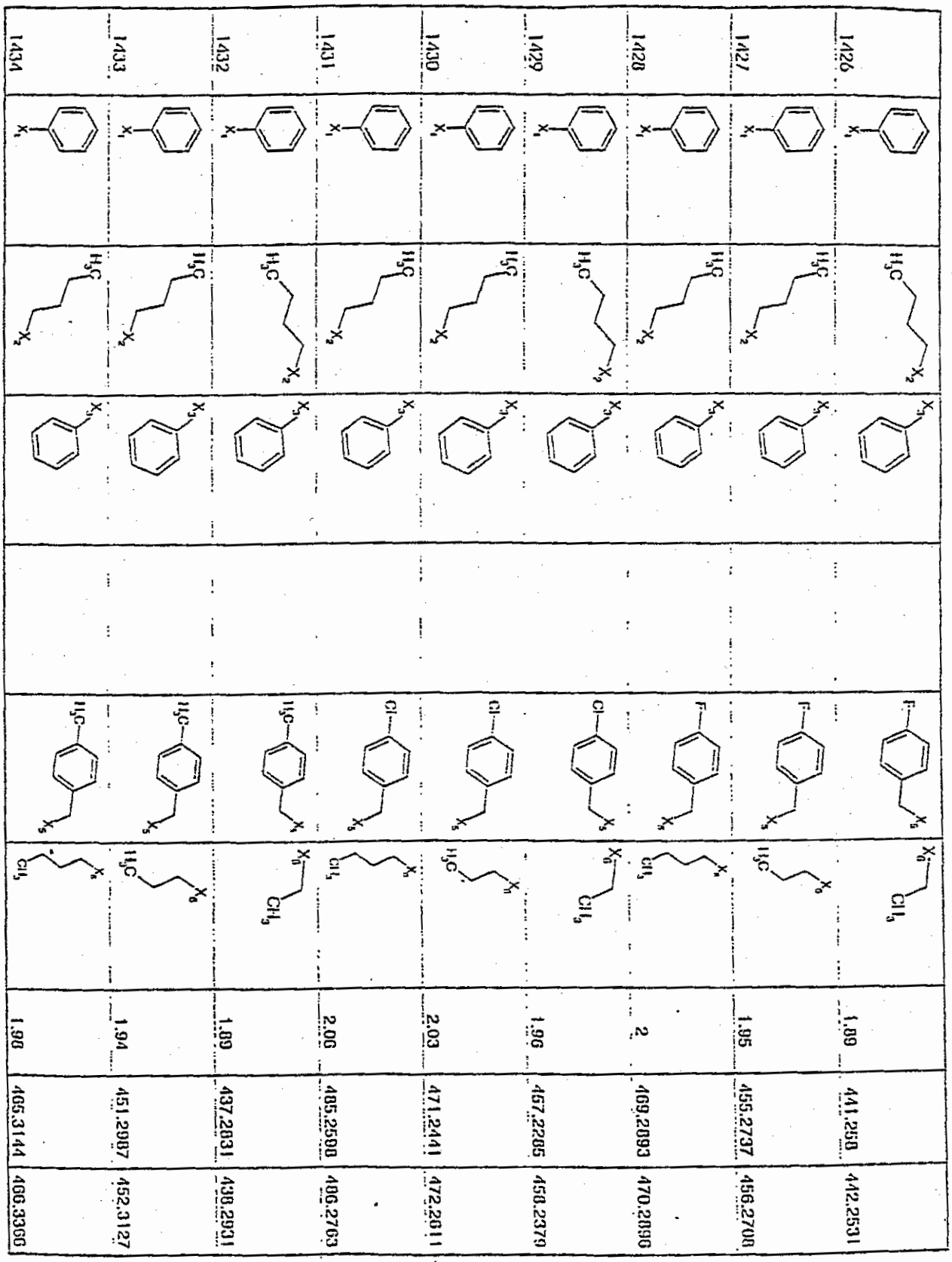
1999								2.06	515.1936	516.206
1000								2.08	529.2093	530.222
1001								1.94	441.258	442.2664
1002								2	455.2737	456.28
1003								2.03	469.2893	470.2926
1004								1.9	437.2631	438.2925
1005								1.96	451.2987	452.3093
1006								2	465.3144	466.3223
1007								2	491.2548	492.2693



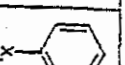
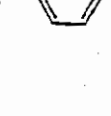
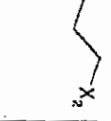
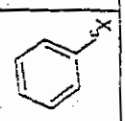
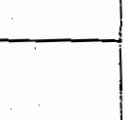
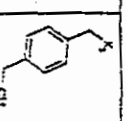
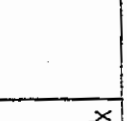
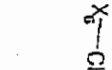
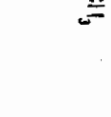
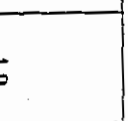
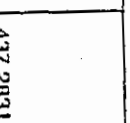
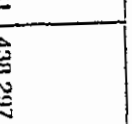
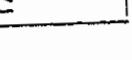
1408							2.05		505.2705	506.2041
1409							2.08		519.2861	520.2956
1410										
1411							1.95		467.2937	468.1446
1412							1.98		481.3093	482.2171
1413							2		457.2285	458.1478
1414							2.04		471.2441	472.1711
1415							2.09		485.2598	486.1973
1416							2.05		515.2936	516.2304

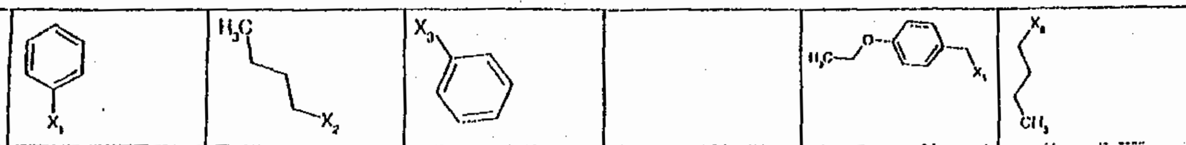
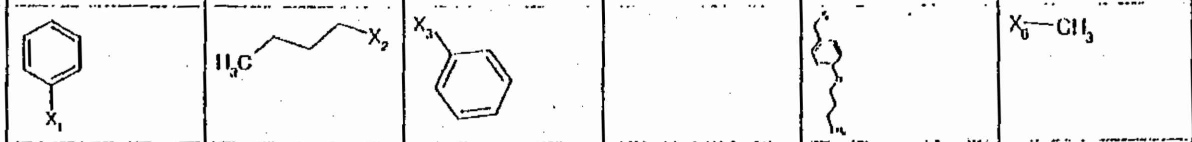
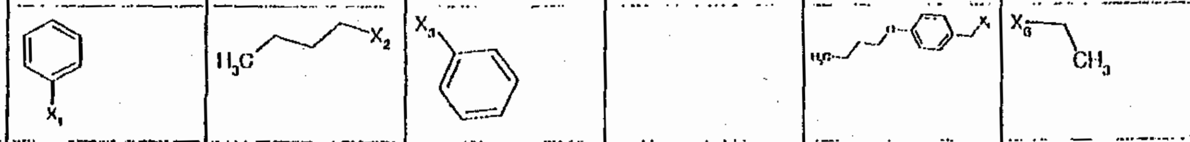
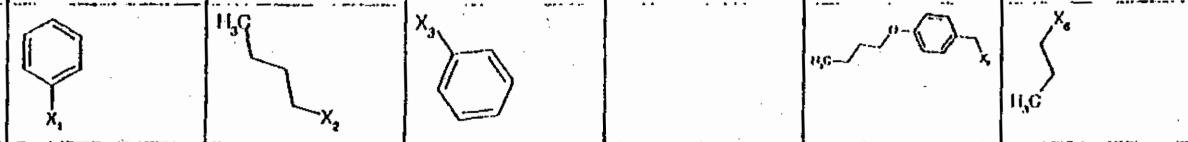
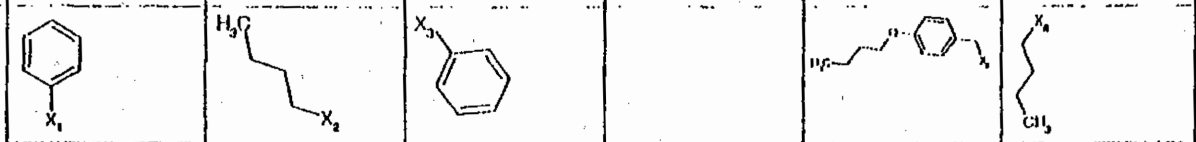
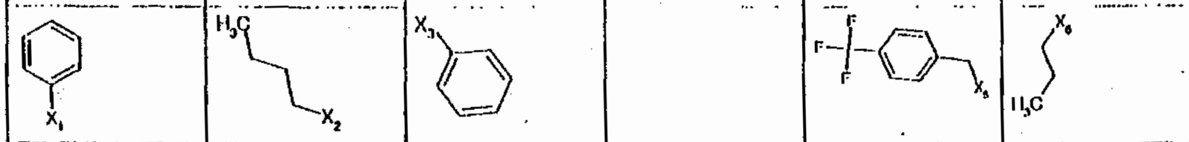


1417							2.09	529.3093	530.2516		
1418							2.12	543.325	544.2772		
1419							2	503.2304	504.2027		
1420							2.06	517.2541	518.2202		
1421							2.08	531.2697	532.2498		
1422							1.96	487.1623	488.1573		
1423							1.98	501.1779	502.1747		
1424							2.04	515.1936	516.1976		
1425							2.09	529.2093	530.21		

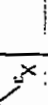


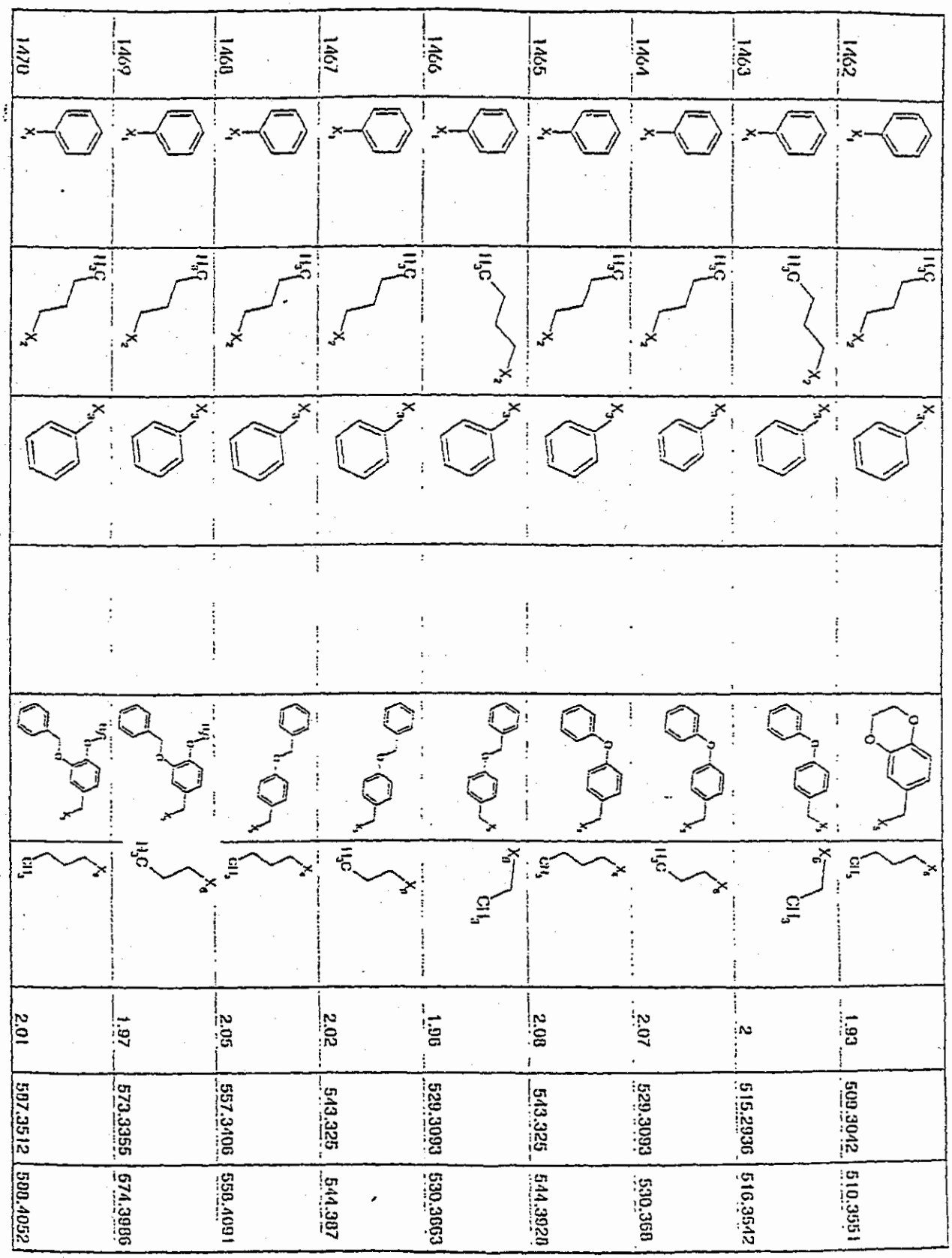
1426									1.89	441.258	442.2531
1427									1.95	455.2737	456.2708
1428									2	469.2893	470.2896
1429									1.96	467.2285	468.2379
1430									2.03	471.2441	472.2611
1431									2.06	485.2598	486.2763
1432									1.89	437.2831	438.2931
1433									1.94	451.2987	452.3127
1434									1.98	465.3144	466.3366

1435									1.9	437.2831	438.2971
1436									1.93	451.2907	452.3194
1437									1.99	465.3144	466.3413
1438									2.03	479.33	480.3660
1439									1.81	453.278	454.3067
1440									1.98	467.2937	468.3209
1441									1.91	481.3093	482.3407
1442									1.87	467.2937	468.3278
1443									1.93	481.3093	482.3461

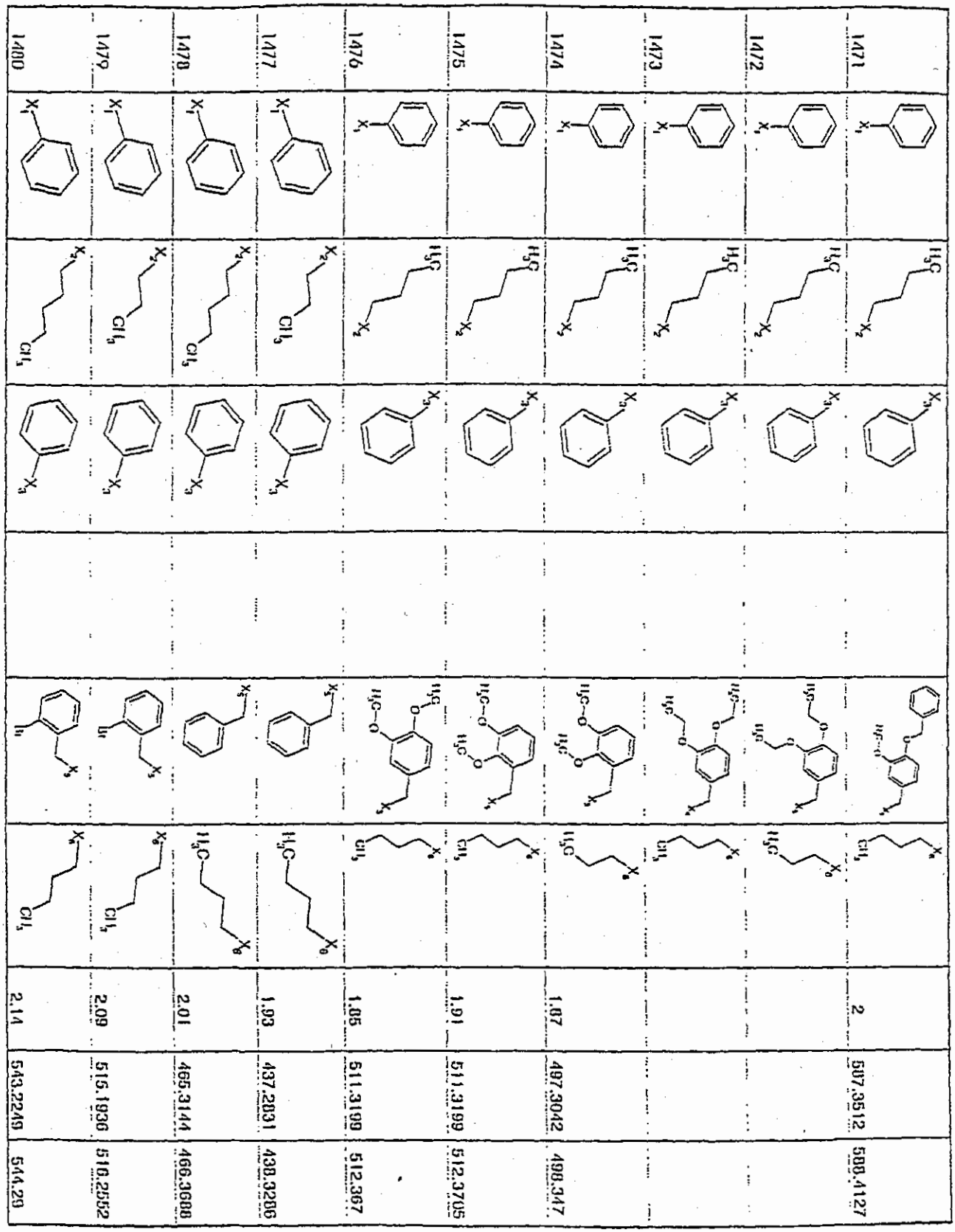
1444		1.95	495.325	496.3688
1445		1.95	481.3093	482.356
1446		1.97	495.325	496.3746
1447		2.03	509.3406	510.4019
1448		2.05	523.3563	524.4143
1449		2.05	505.2705	506.3199
1450		2.08	519.2861	520.3441
1451		1.95	451.2987	452.3453
1452		1.97	465.3144	466.3662

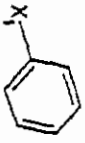
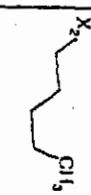
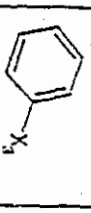
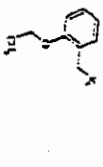
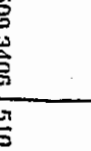
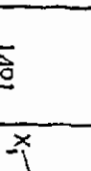
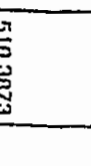
SUBSTITUTE SHEET (RULE 26)

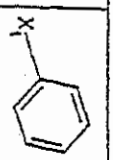
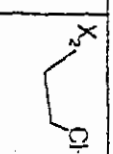
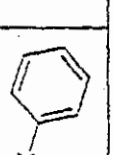
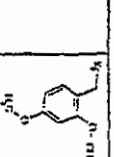
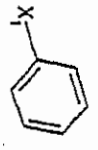
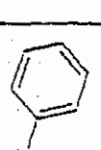
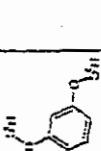
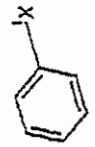
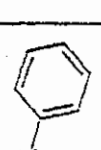
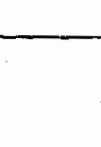
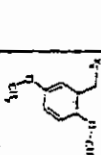
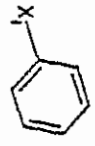
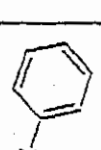
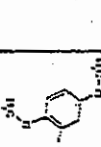
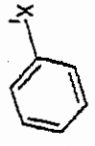
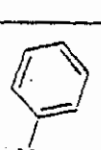
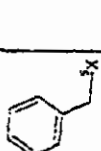
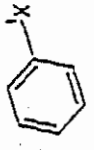
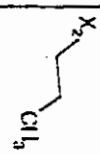
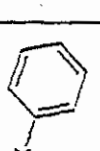
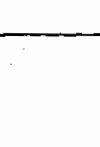
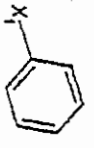
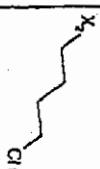
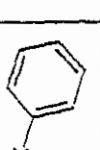
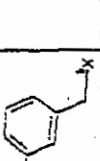
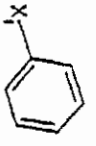
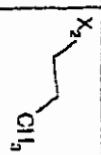
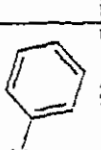
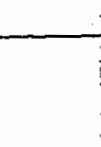
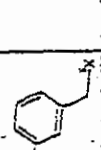
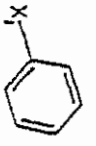
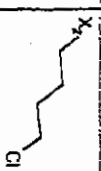
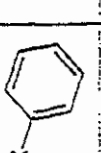
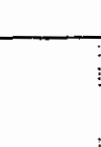
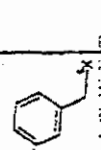
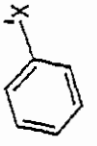
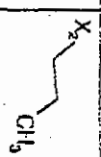
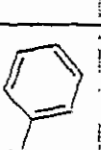
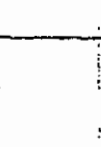
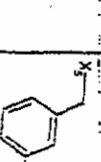
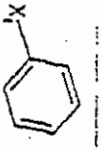
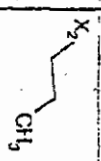
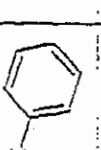
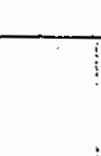
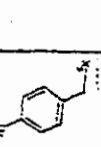
1453								2.03	479.33	490.3838
1454								2.07	493.3457	494.4073
1455								2.07	513.3144	514.367
1456								1.8	453.2416	454.2623
1457								1.83	467.2573	468.2991
1458								1.9	481.2729	482.3166
1459								1.94	495.2886	496.3361
1460								1.82	481.2729	482.3166
1461								1.89	495.2886	496.3342

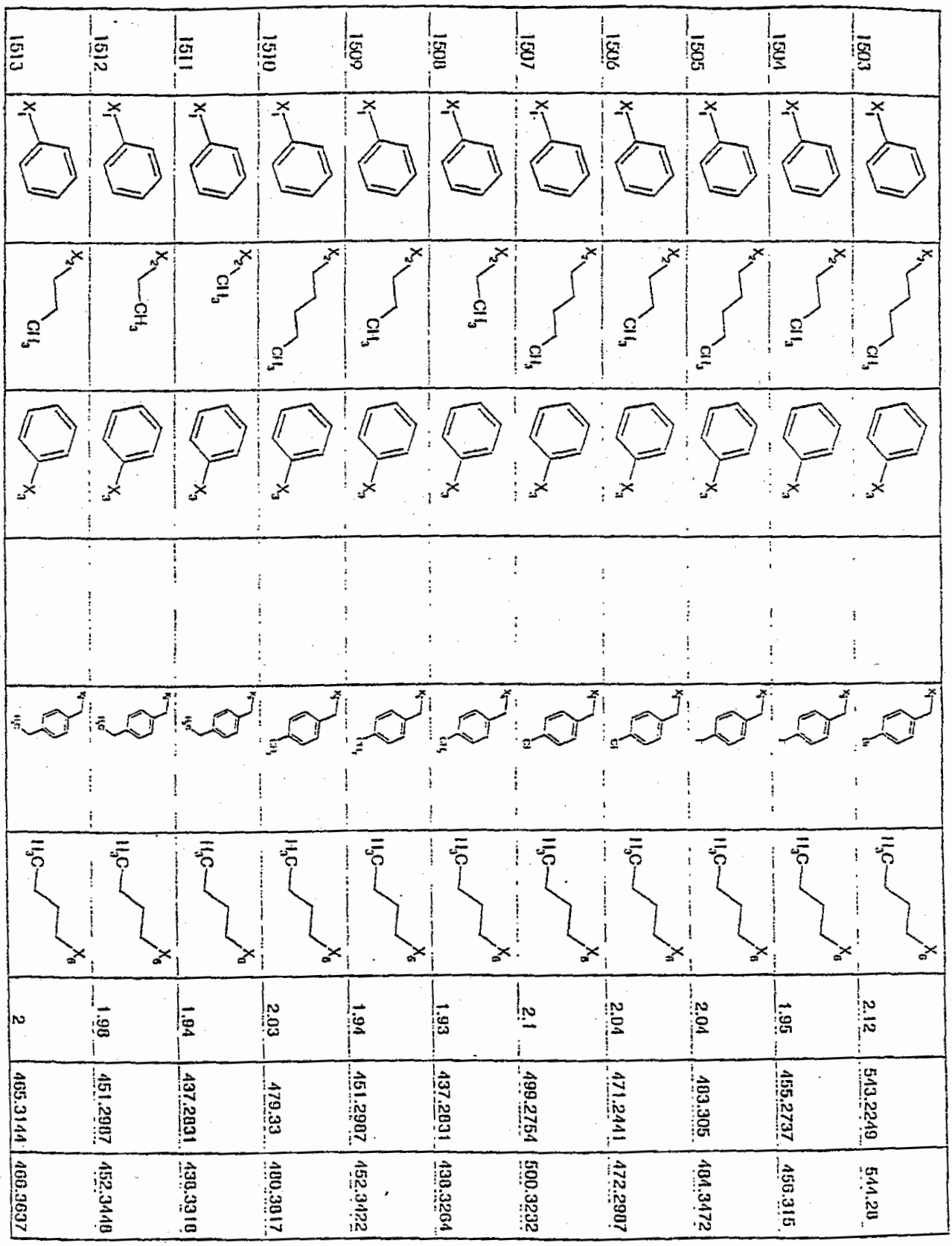


1462								1.93	509.3042	510.3551
1463								2	515.2936	516.3542
1464								2.07	529.3093	530.368
1465								2.08	543.325	544.3920
1466								1.96	529.3093	530.3663
1467								2.02	543.325	544.387
1468								2.05	557.3406	558.4091
1469								1.97	573.3355	574.3986
1470								2.01	507.3512	508.4052



1481								2	455.2737	456.3135
1482								2.08	493.305	494.3603
1483								2.04	457.2205	458.2748
1484								2.06	471.2441	472.2985
1485								2.13	499.2754	500.3322
1486								2.1	479.33	480.3871
1487								1.84	467.2937	468.3388
1488								1.93	495.325	496.3778
1489								2.07	505.2705	506.204
1490								1.91	481.3093	482.3268
1491								2	509.3406	510.3873

1492								1.81	497.3042	499.338
1493								1.89	525.3355	526.3015
1494								1.86	497.3042	498.313
1495								1.94	525.3355	526.3023
1496								2	455.2737	456.3067
1497								1.95	451.2987	452.3412
1498								2.05	479.33	480.3812
1499								1.95	467.2937	468.3324
1500								2.02	495.325	496.3729
1501								2.06	471.2441	472.2934
1502								2.05	515.1936	516.24



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1507								2.1	499.2754	500.3232
1508								1.93	437.2831	438.3264
1509								1.94	451.2987	452.3422
1510								2.03	479.33	480.3817
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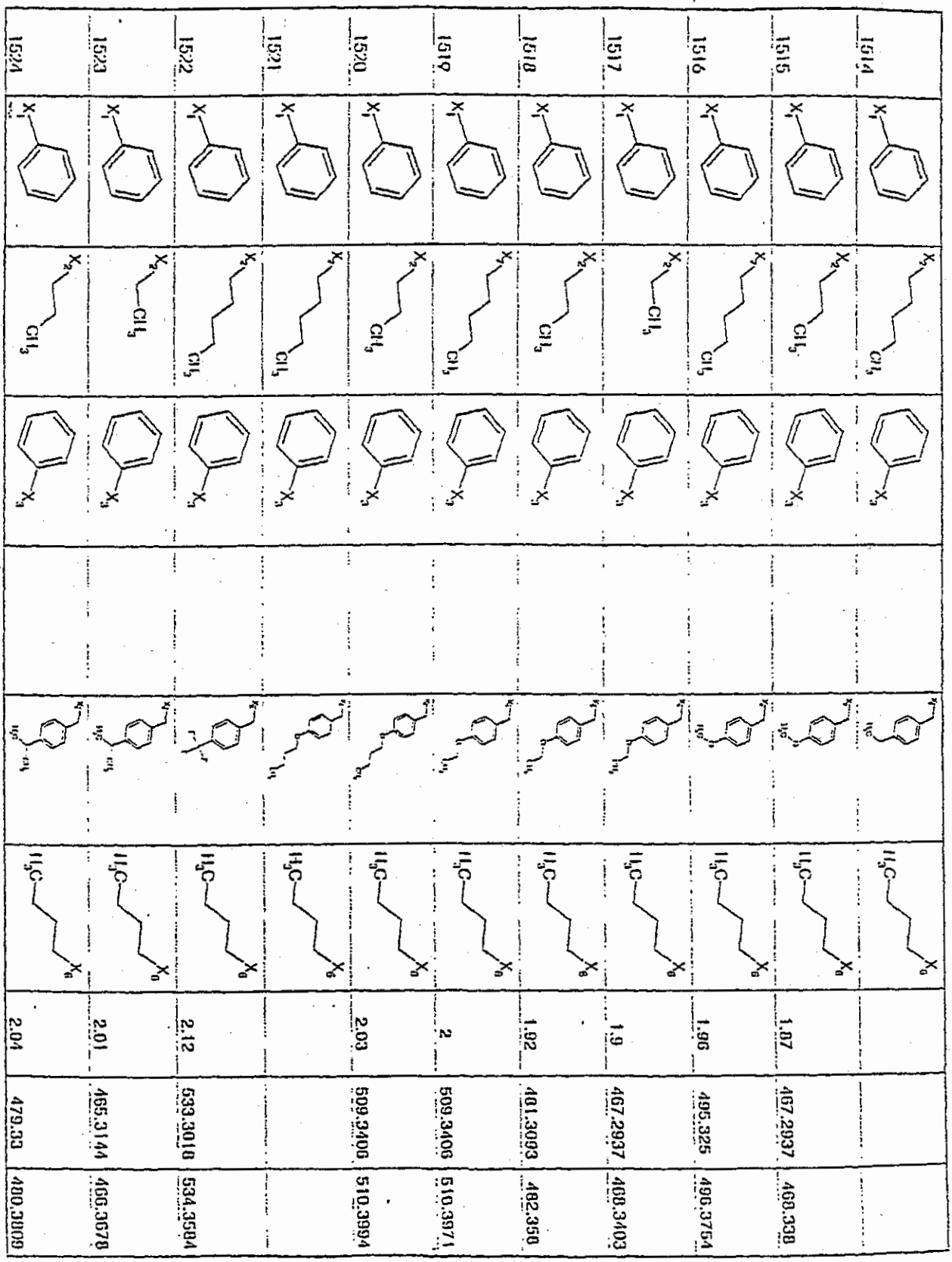

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1518							1.92	481.3093	482.356
1519							2	509.3406	510.3971
1520							2.03	509.3406	510.3994
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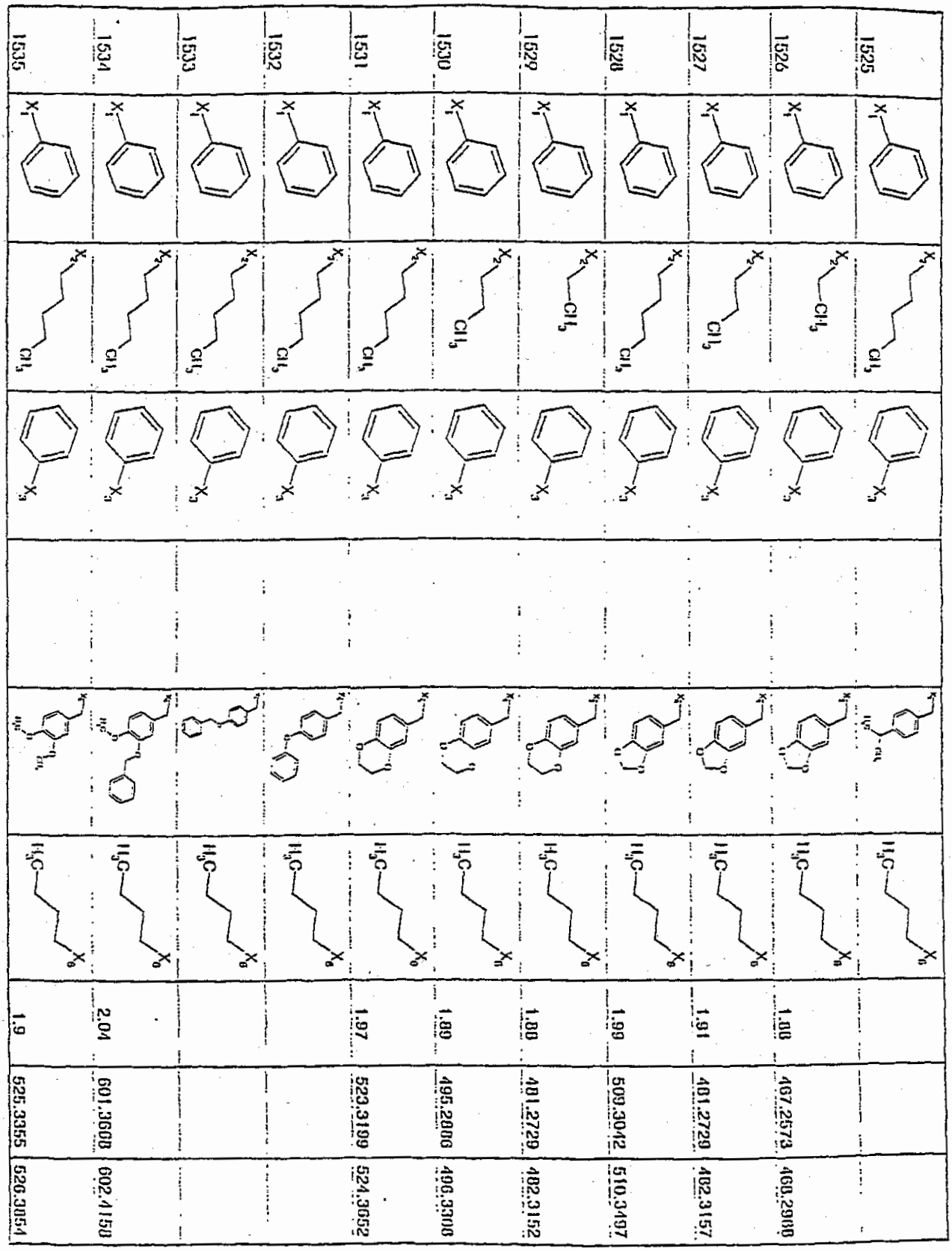

1525											
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1527									1.91	481.2729	482.3157
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1529									1.88	481.2729	482.3152
1530									1.89	495.2886	496.3308
1531									1.97	523.3199	524.3652
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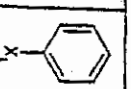
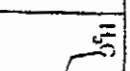
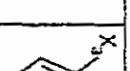
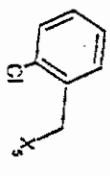
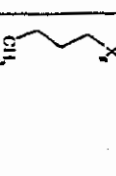
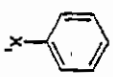
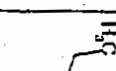
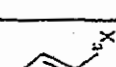
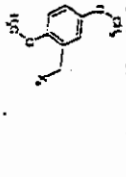
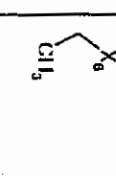
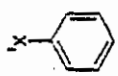
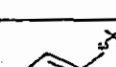
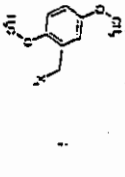
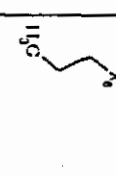
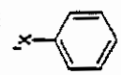
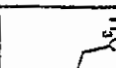
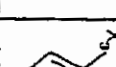
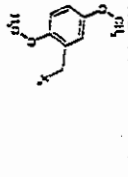
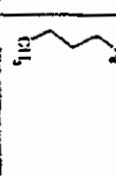
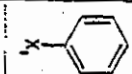
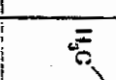
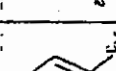
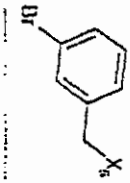
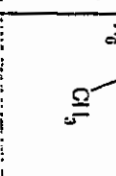
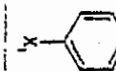
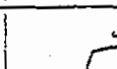
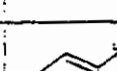
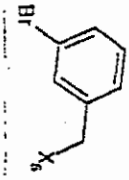
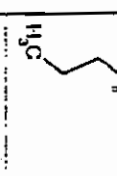
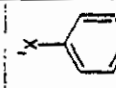
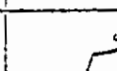
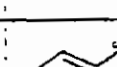
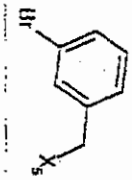
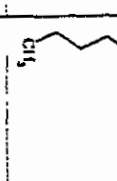
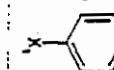
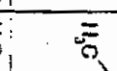
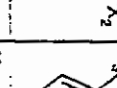
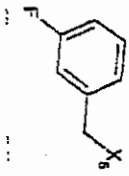
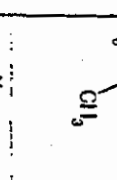
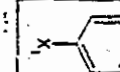
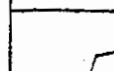
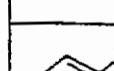
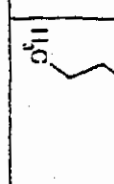
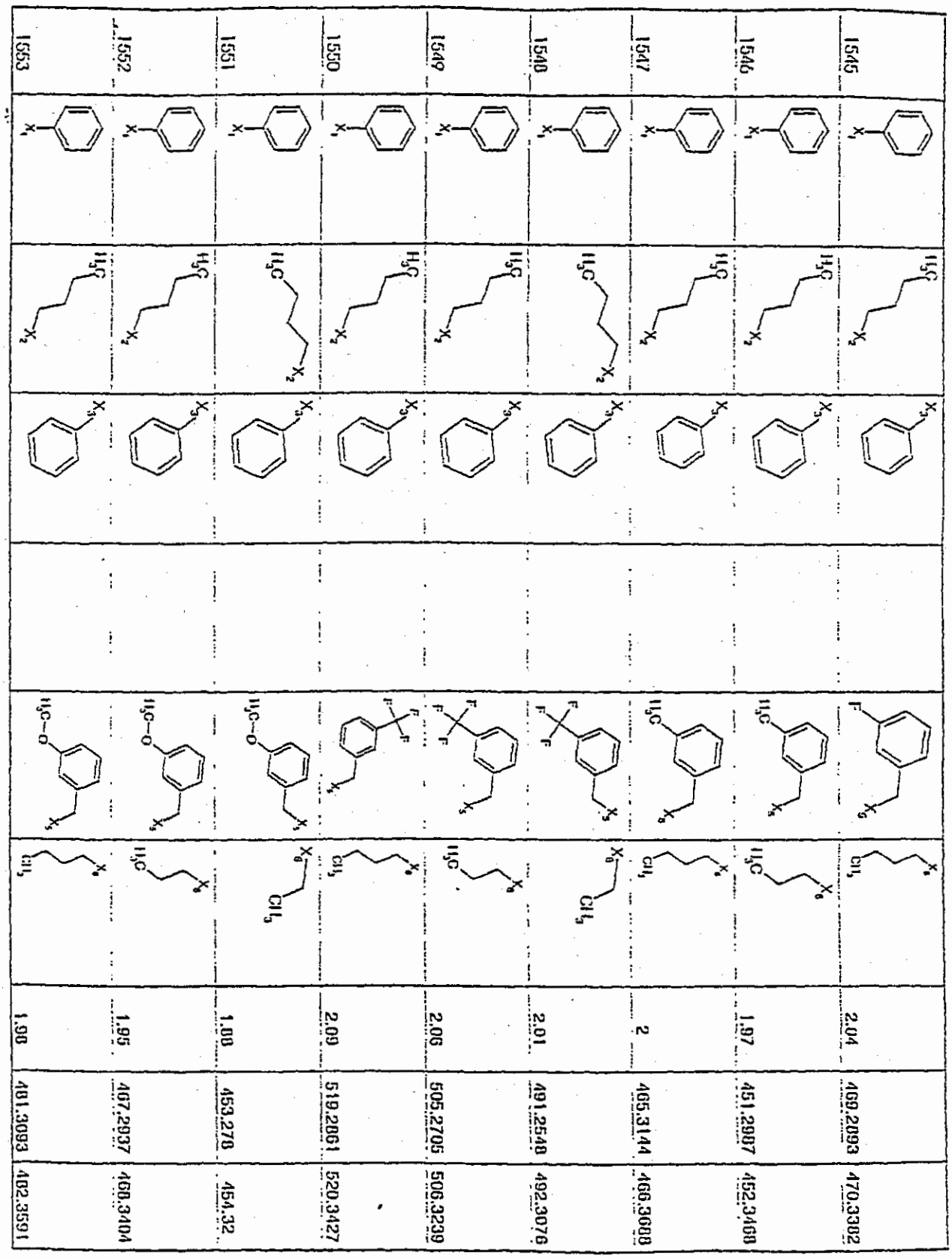
1536							2.1	485.2598	486.306
1537							1.8	493.2096	494.3271
1538							1.06	497.3042	498.3447
1539							1.91	511.3199	512.3699
1540							2.02	501.1779	502.23
1541							2.07	515.1936	516.24
1542							2.11	529.2093	530.27
1543							1.94	441.258	442.2997
1544							1.99	455.2737	456.321



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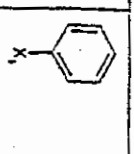
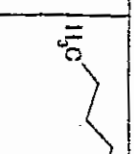
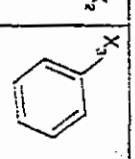
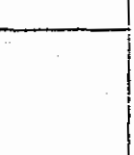
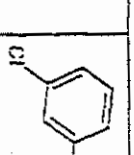
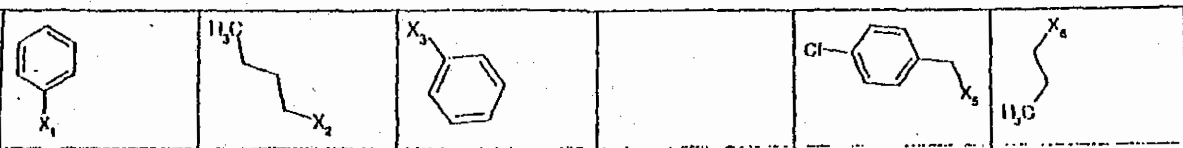
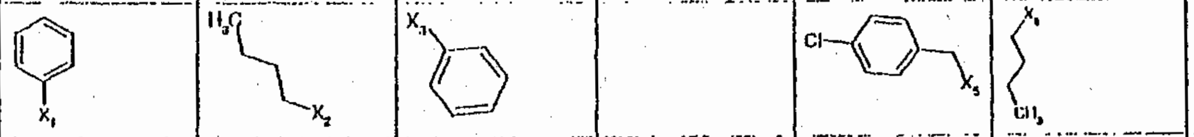
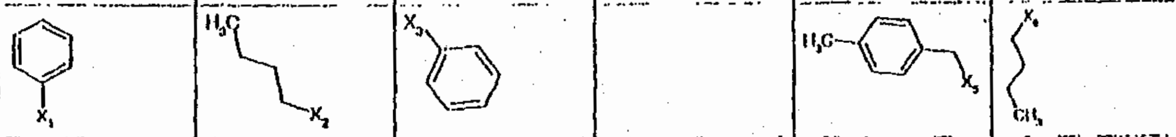
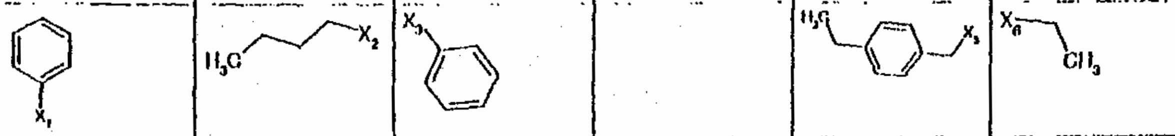
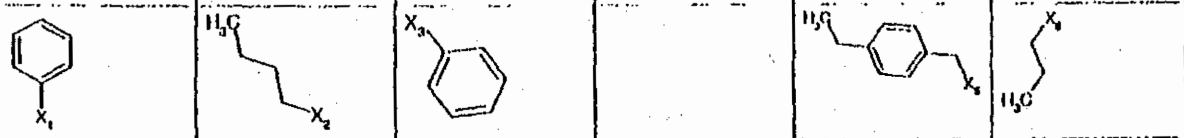
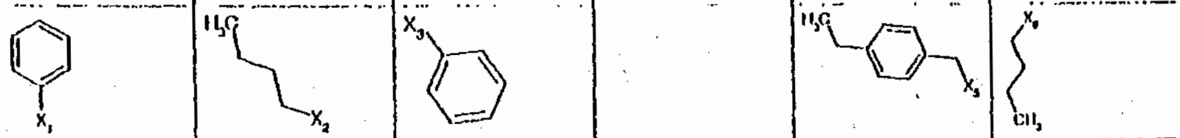
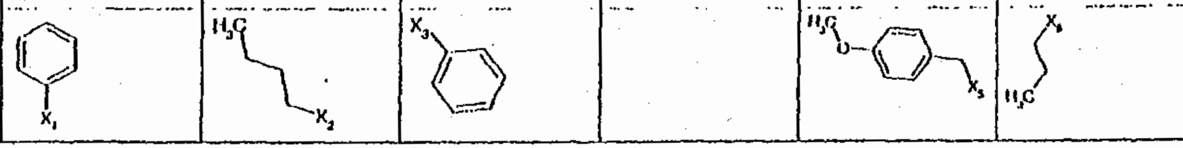
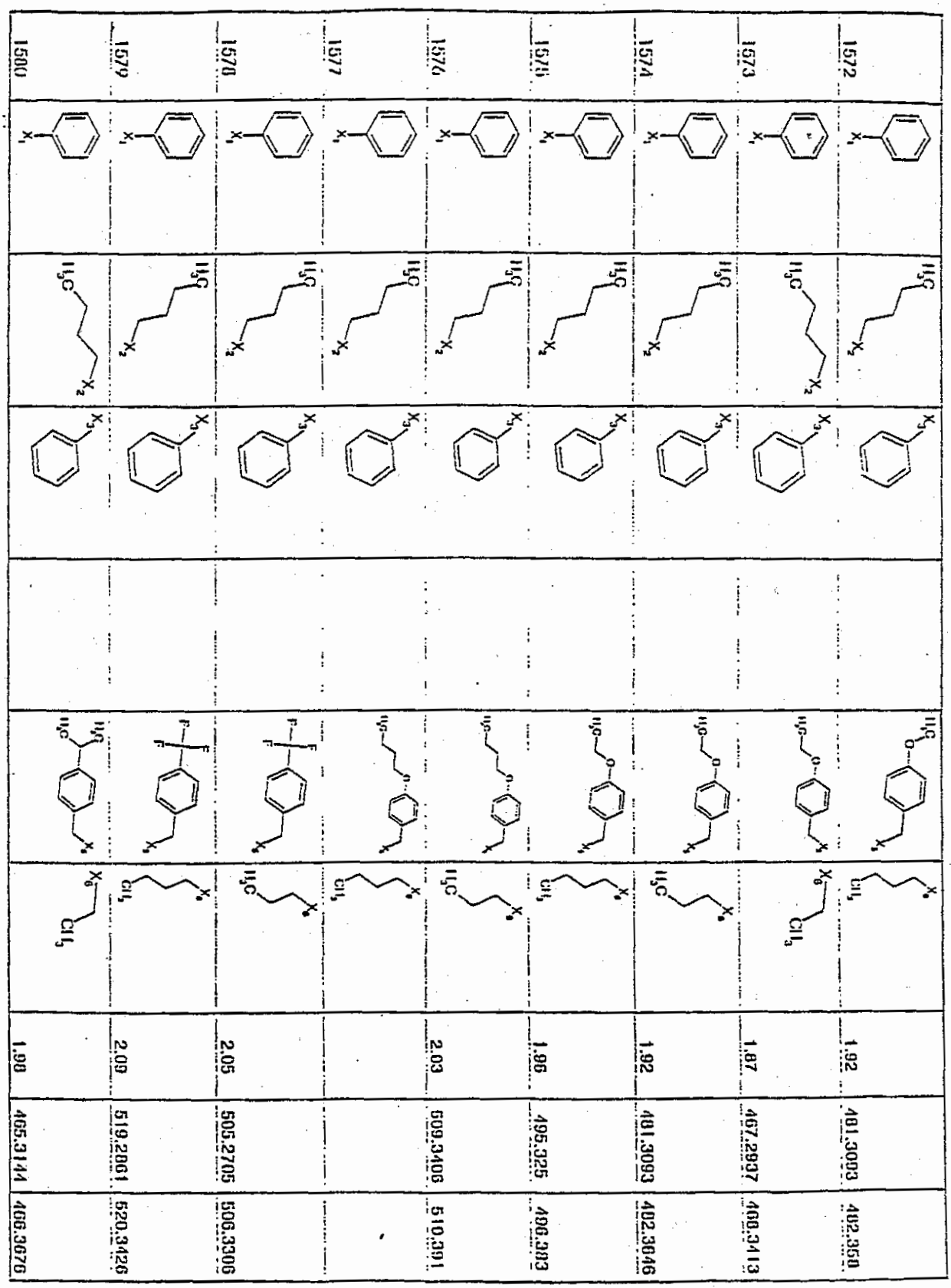
1546							1.97	451.2987	452.3469	
1547							2	465.3144	466.3608	
1548							2.01	491.2548	492.3076	
1549							2.06	505.2705	506.3239	
1550							2.09	519.2861	520.3427	
1551							1.99	453.278	454.32	
1552							1.95	467.2937	468.3404	
1553							1.98	481.3093	482.3591	

1554									1.99	457.2205	458.2709
1555									2.05	471.2441	472.2944
1556									2.09	485.2598	486.3078
1557									2.11	529.3093	530.3656
1558									2.05	515.1936	516.25
1559									2.09	529.2093	530.2775
1560									1.97	455.2737	456.3232
1561									2	469.2893	470.3403
1562									1.98	457.2285	458.2003

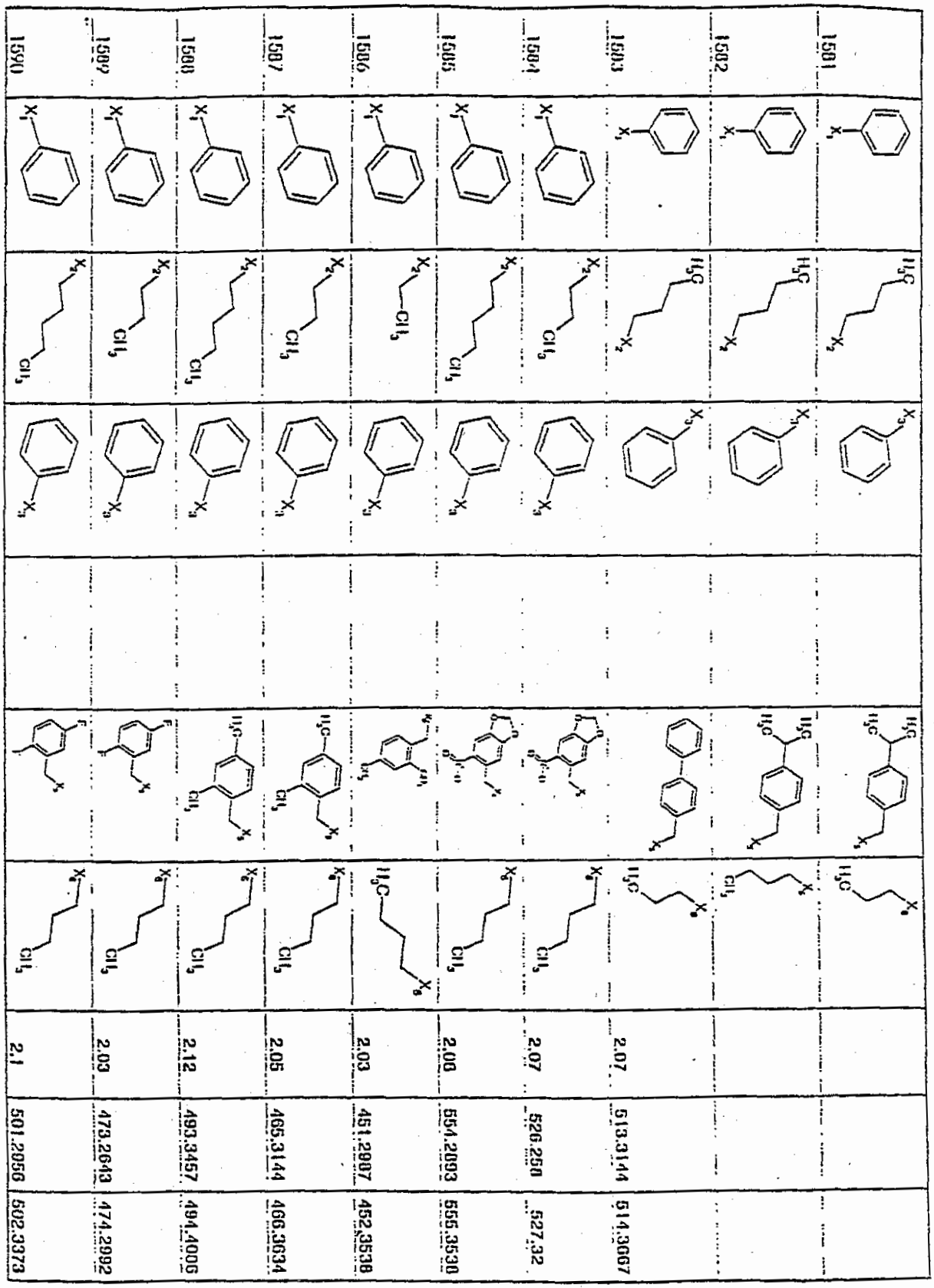
2 8 MAR 2005

1563		2.03	471.2441	472.2929
1564		2.07	485.2598	486.3048
1565		1.95	451.2987	452.3467
1566		1.99	465.3144	466.3694
1567		1.94	451.2907	452.3482
1568		2	465.3144	466.3705
1569		2.04	479.33	480.3848
1570		1.81	453.278	454.3195
1571		1.88	467.2937	468.3429

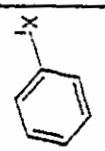
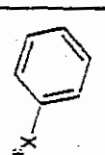
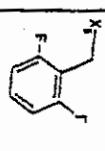
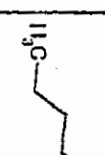
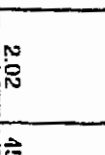
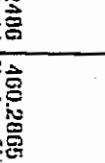
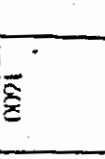
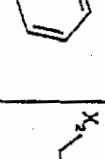
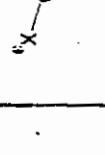
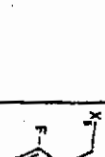
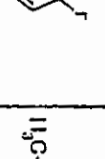
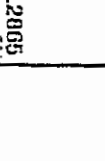
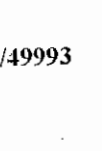
SUBSTITUTE SHEET (RULE 26)

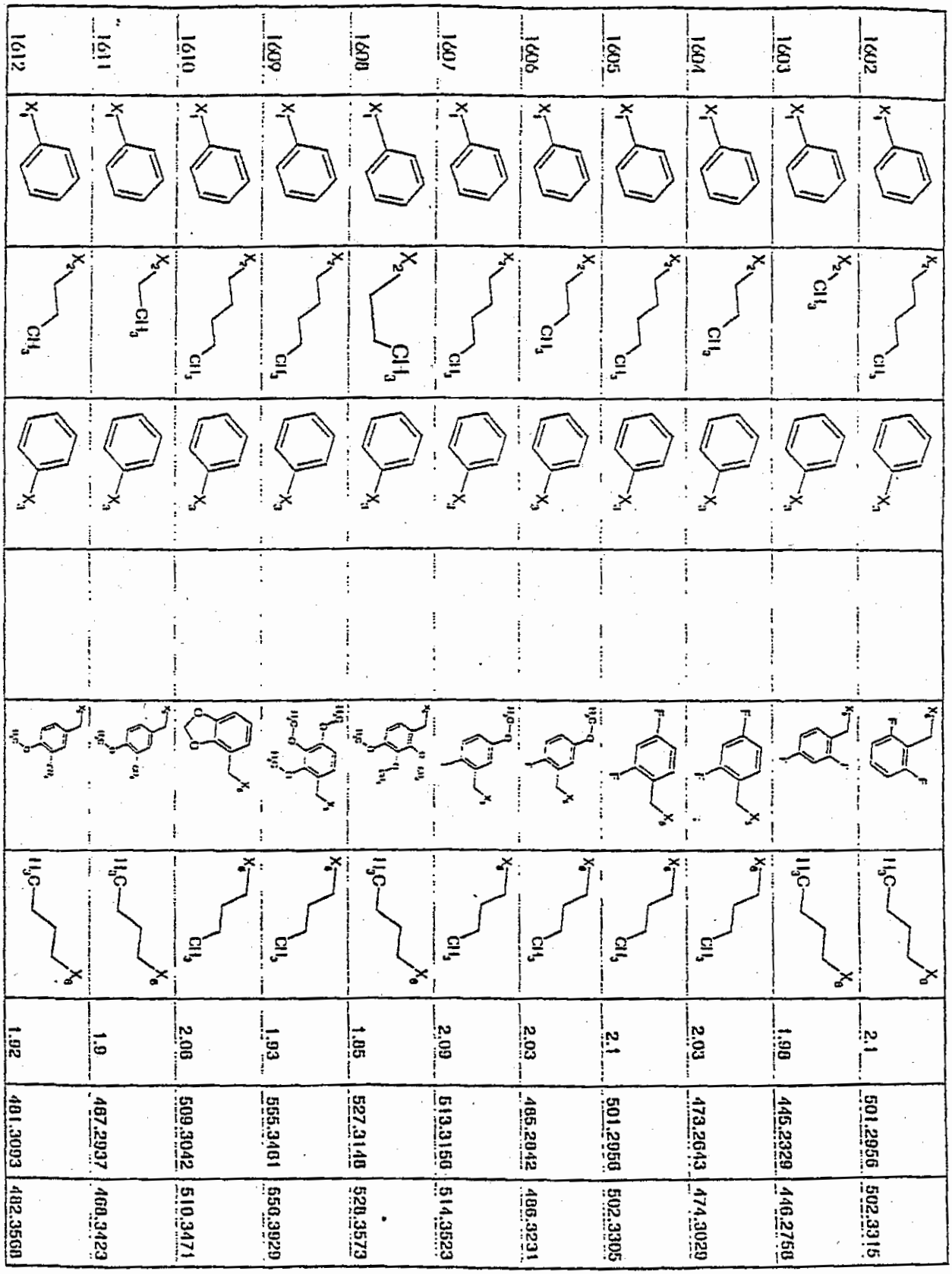


1572							1.92	481.3093	482.359	
1573							1.87	467.2937	468.3413	
1574							1.92	481.3093	482.3646	
1575							1.96	495.325	496.383	
1576							2.03	509.3406	510.391	
1577										
1578							2.05	505.2705	506.3306	
1579							2.09	519.2861	520.3426	
1580							1.98	465.3144	466.3676	

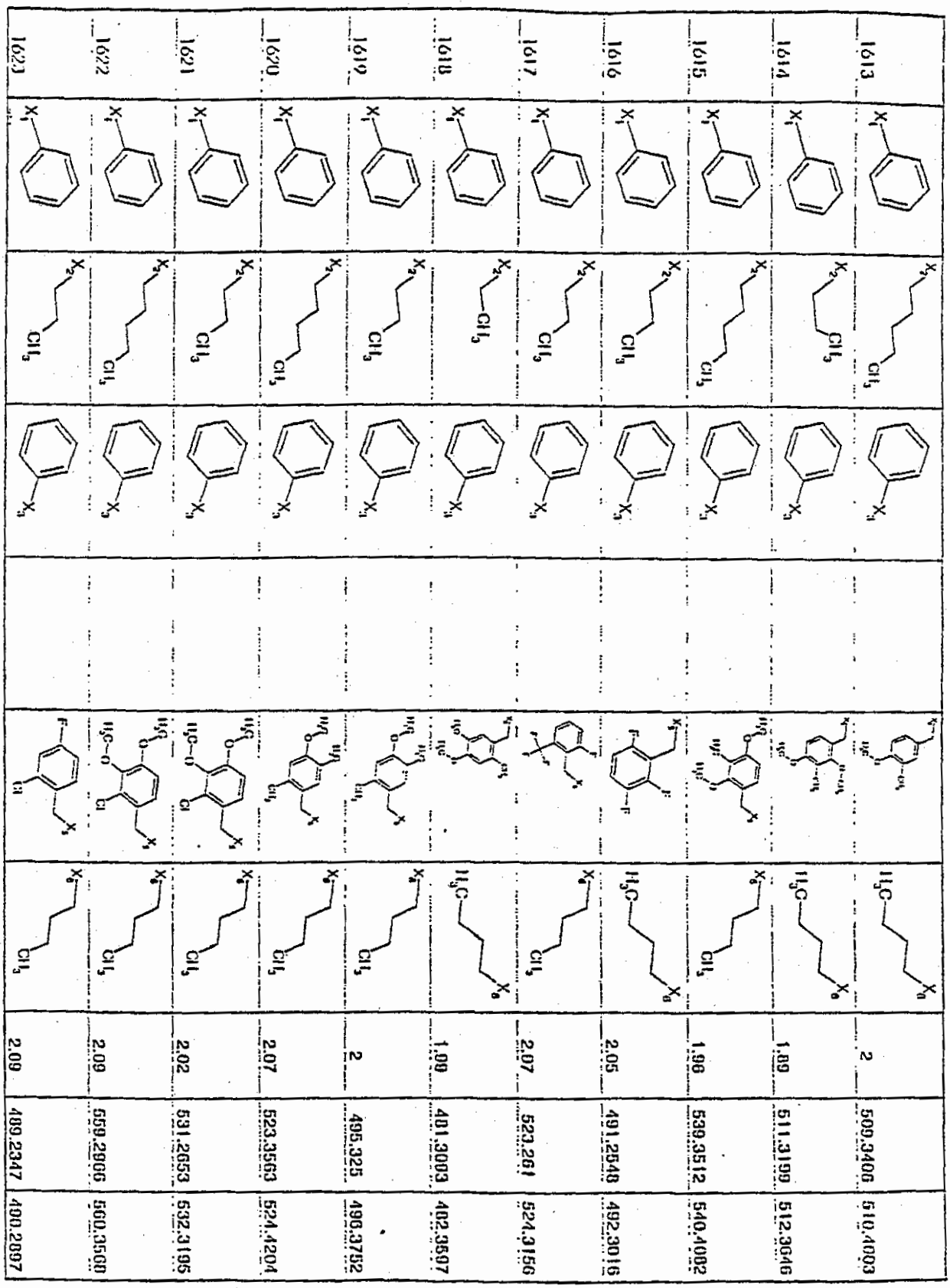


1581									
1582									
1583						2.07	513.3144	514.3067	
1584						2.07	526.258	527.32	
1585						2.00	554.2093	555.3530	
1586						2.03	451.2987	452.3530	
1587						2.05	465.3144	466.3634	
1588						2.12	493.3457	494.4006	
1589						2.03	473.2643	474.2992	
1590						2.1	501.2956	502.3373	

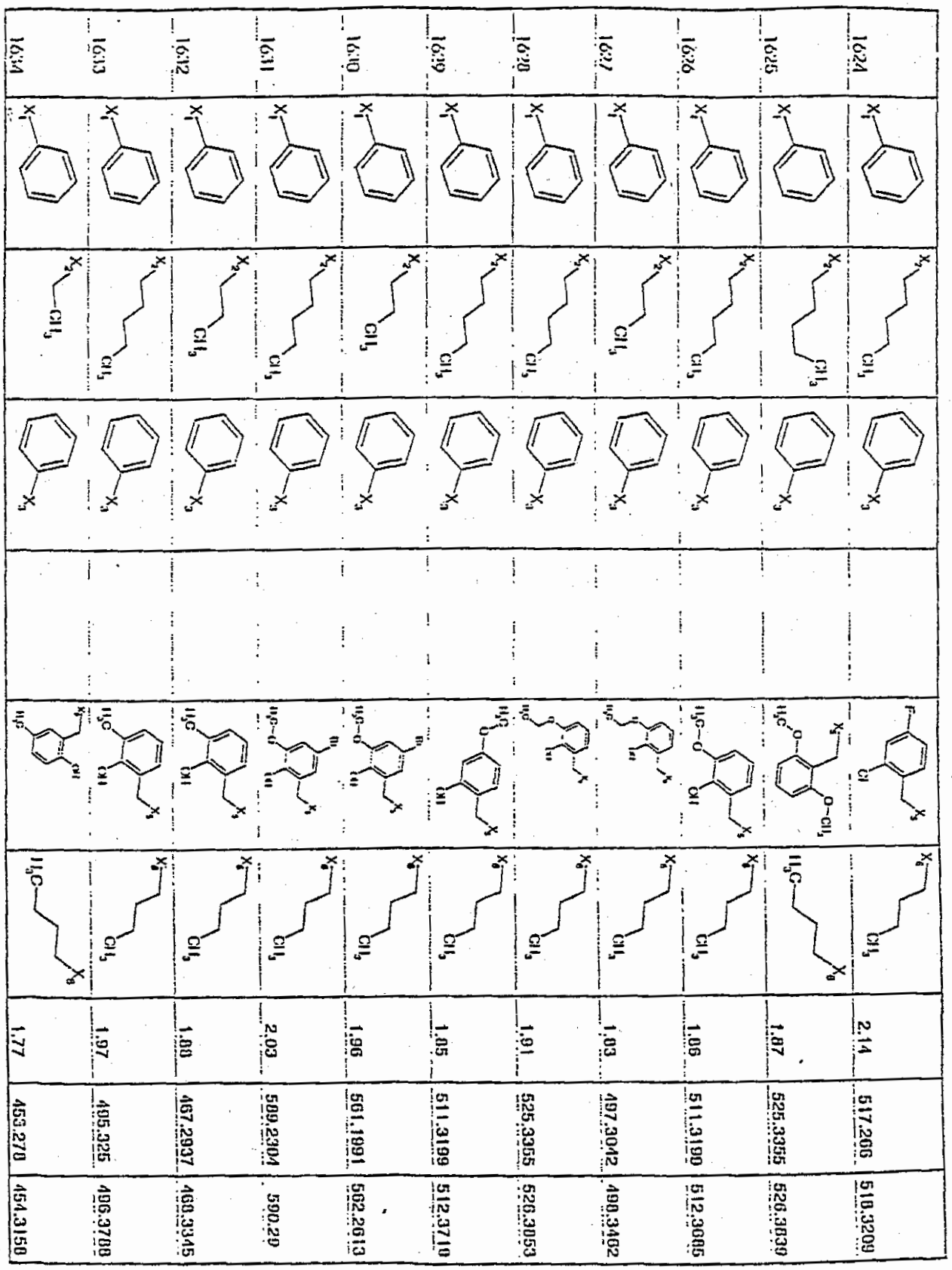
1591									2.1	491.1095	492.2394
1592									2.11	505.2051	506.2584
1593									2.18	533.2365	534.3019
1594									2.06	475.2191	476.2581
1595									2.08	489.2347	490.2656
1596									2.14	517.266	518.3196
1597									2.04	473.2643	474.3057
1598									2.1	501.2956	502.3344
1599									2	445.2929	446.2716
1600									2.02	459.2406	460.2805
1601									2.05	473.2643	474.3071



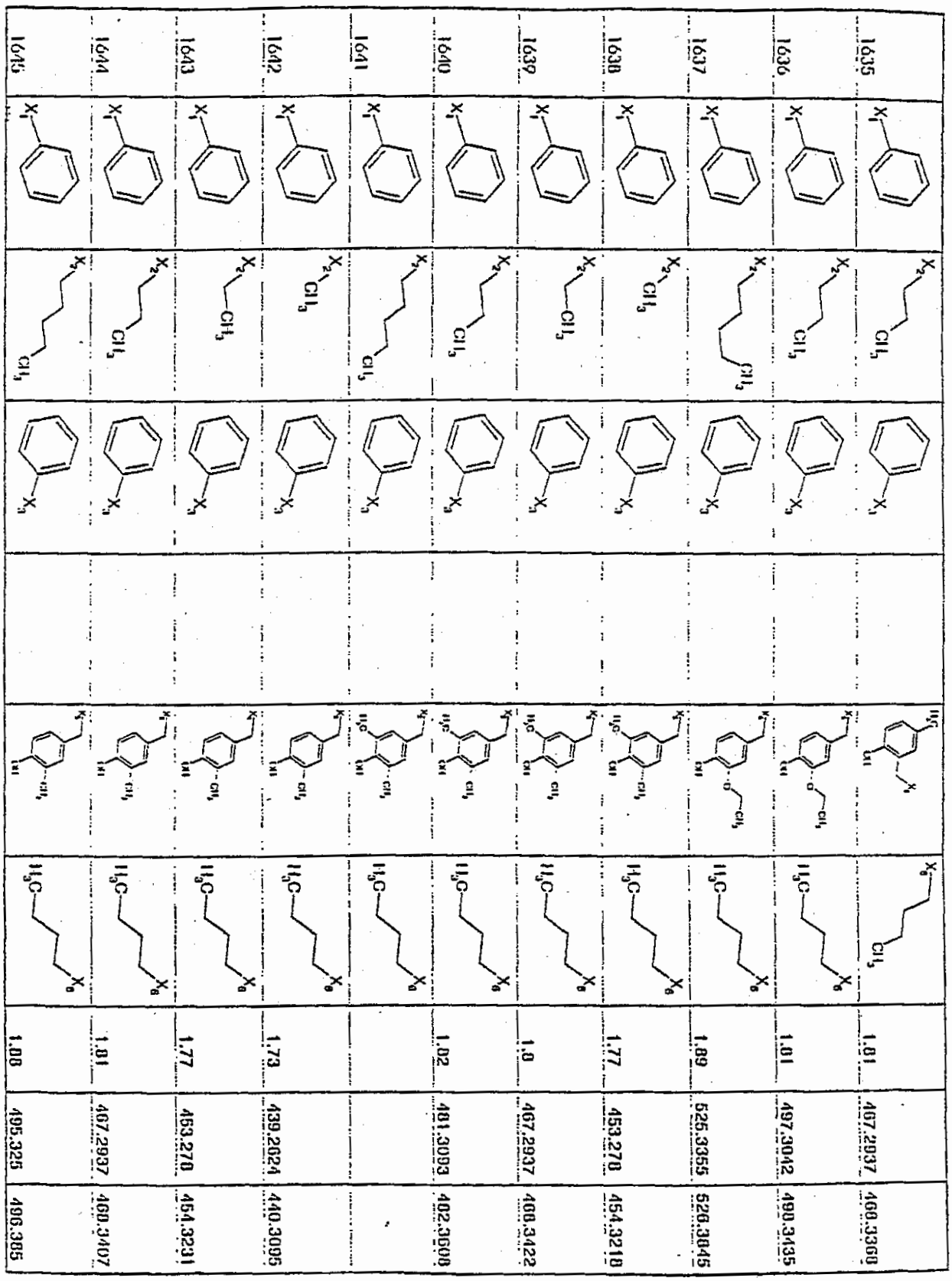
1602							2.1	501.2956	502.3315	
1603							1.99	445.2329	446.2758	
1604							2.03	473.2643	474.3029	
1605							2.1	501.2958	502.3305	
1606							2.03	485.2642	486.3231	
1607							2.09	513.3150	514.3523	
1608							1.85	527.3148	528.3573	
1609							1.93	555.3461	556.3929	
1610							2.08	509.3042	510.3471	
1611							1.9	467.2937	468.3423	
1612							1.92	481.3093	482.3568	



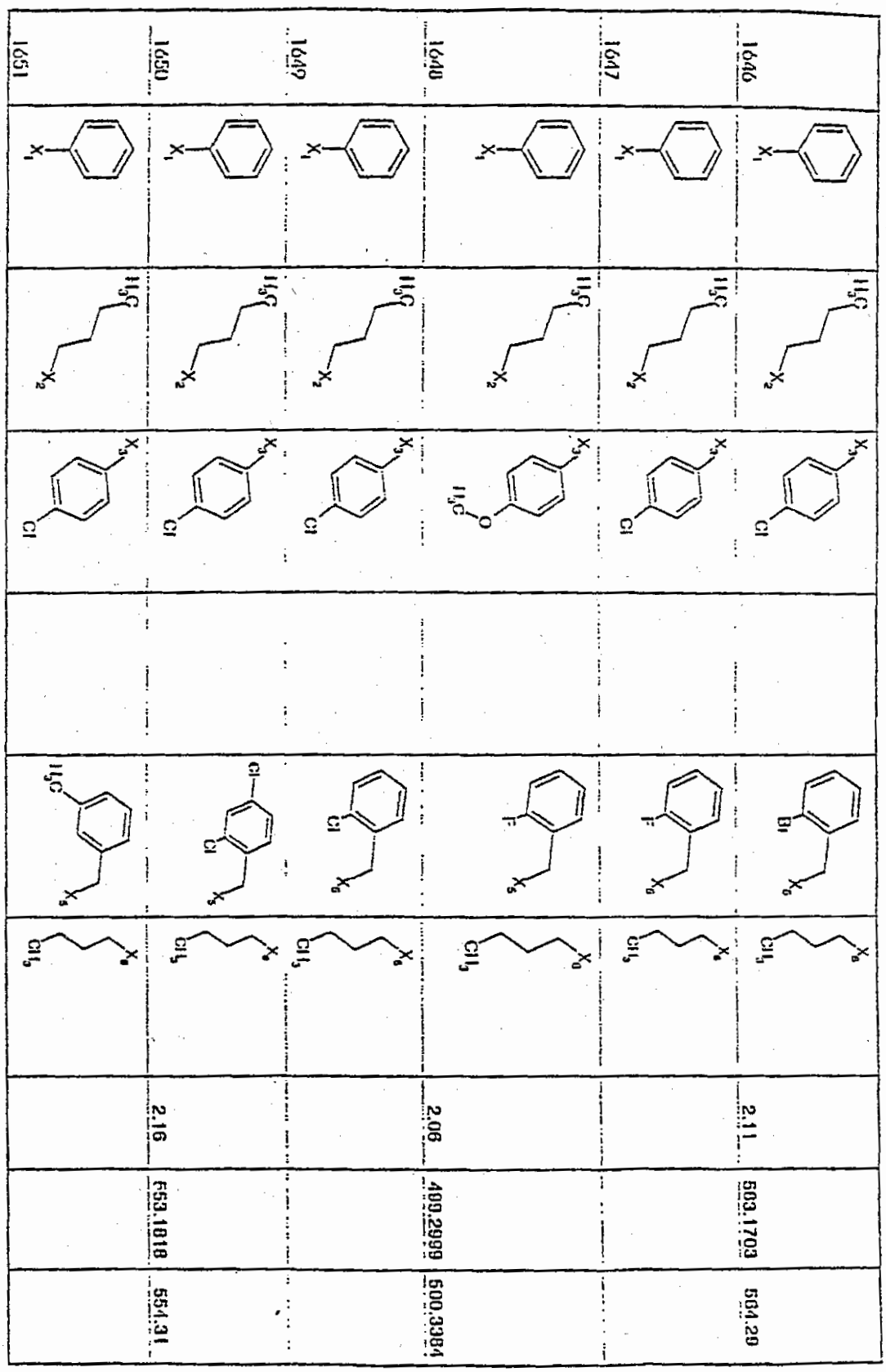
1613								2	509.3406	510.4003
1614								1.89	511.3199	512.3046
1615								1.96	539.3512	540.4092
1616								2.05	491.2548	492.3016
1617								2.07	523.261	524.3156
1618								1.99	401.3003	402.3597
1619								2	495.325	496.3792
1620								2.07	523.3563	524.4204
1621								2.02	531.2653	532.3195
1622								2.09	559.2966	560.3508
1623								2.09	489.2347	490.2897



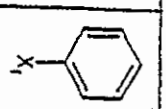
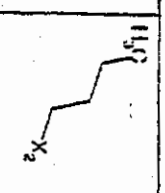
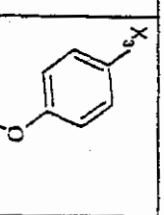
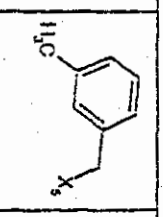
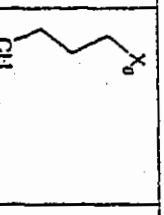
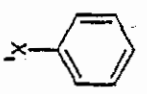
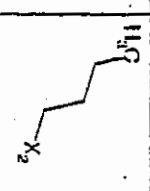
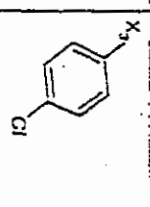
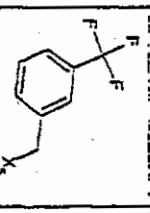
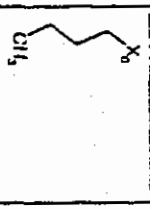
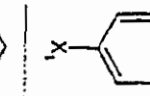
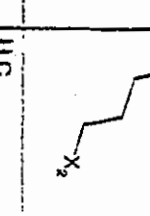
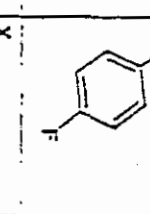
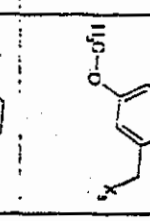
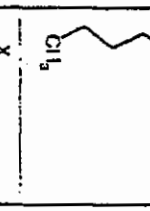
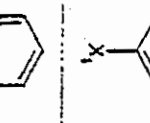
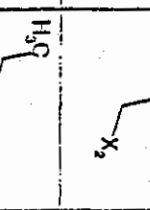
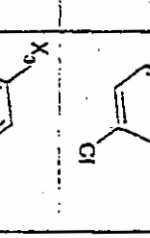
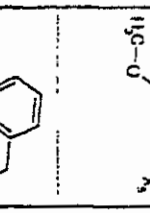
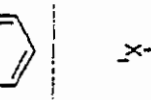
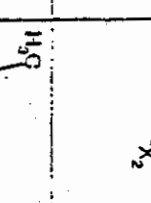
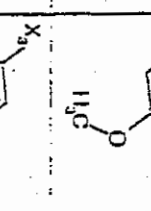
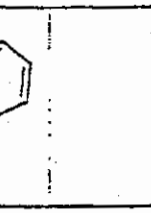
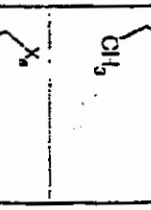
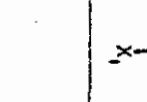
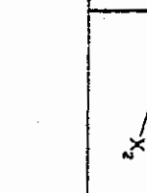
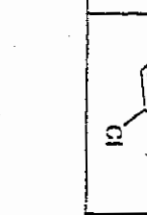
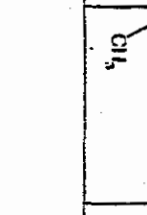
1624						2.14	517.266	518.3209
1625						1.87	525.3355	526.3639
1626						1.06	511.3199	512.3085
1627						1.03	497.3042	498.3462
1628						1.91	525.3355	526.3053
1629						1.05	511.3199	512.3719
1630						1.96	561.1991	562.2613
1631						2.03	589.2304	590.29
1632						1.89	467.2937	468.3345
1633						1.97	495.325	496.3708
1634						1.77	453.270	454.3150

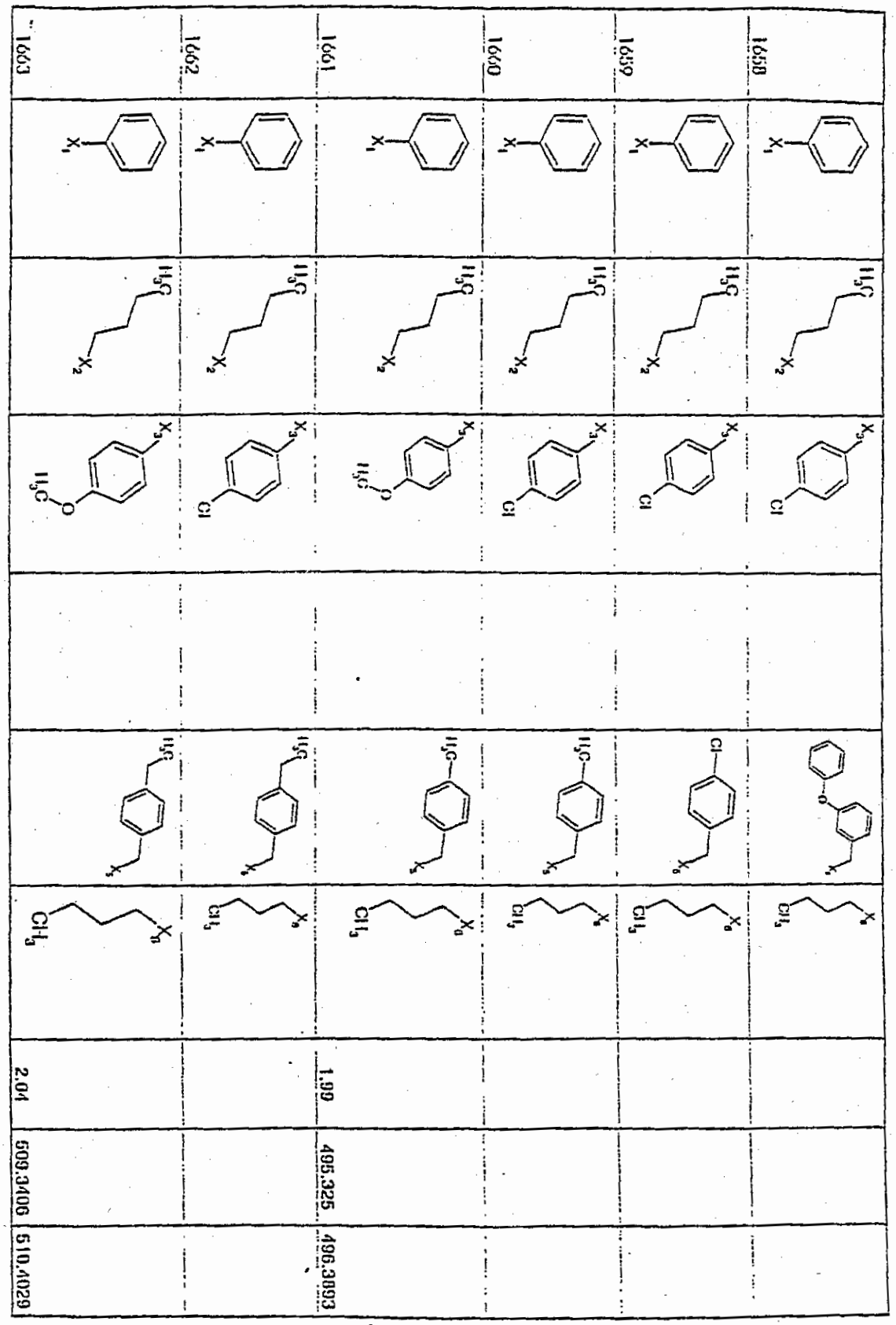


1635								1.01	467.2937	490.3369	
1636								1.01	497.3042	490.3435	
1637								1.89	525.3355	526.3045	
1638								1.77	453.270	454.3218	
1639								1.9	467.2937	466.3422	
1640								1.02	481.3093	482.3609	
1641											
1642								1.73	439.2624	440.3095	
1643								1.77	453.270	454.3231	
1644								1.81	467.2937	468.3407	
1645								1.08	495.325	496.385	

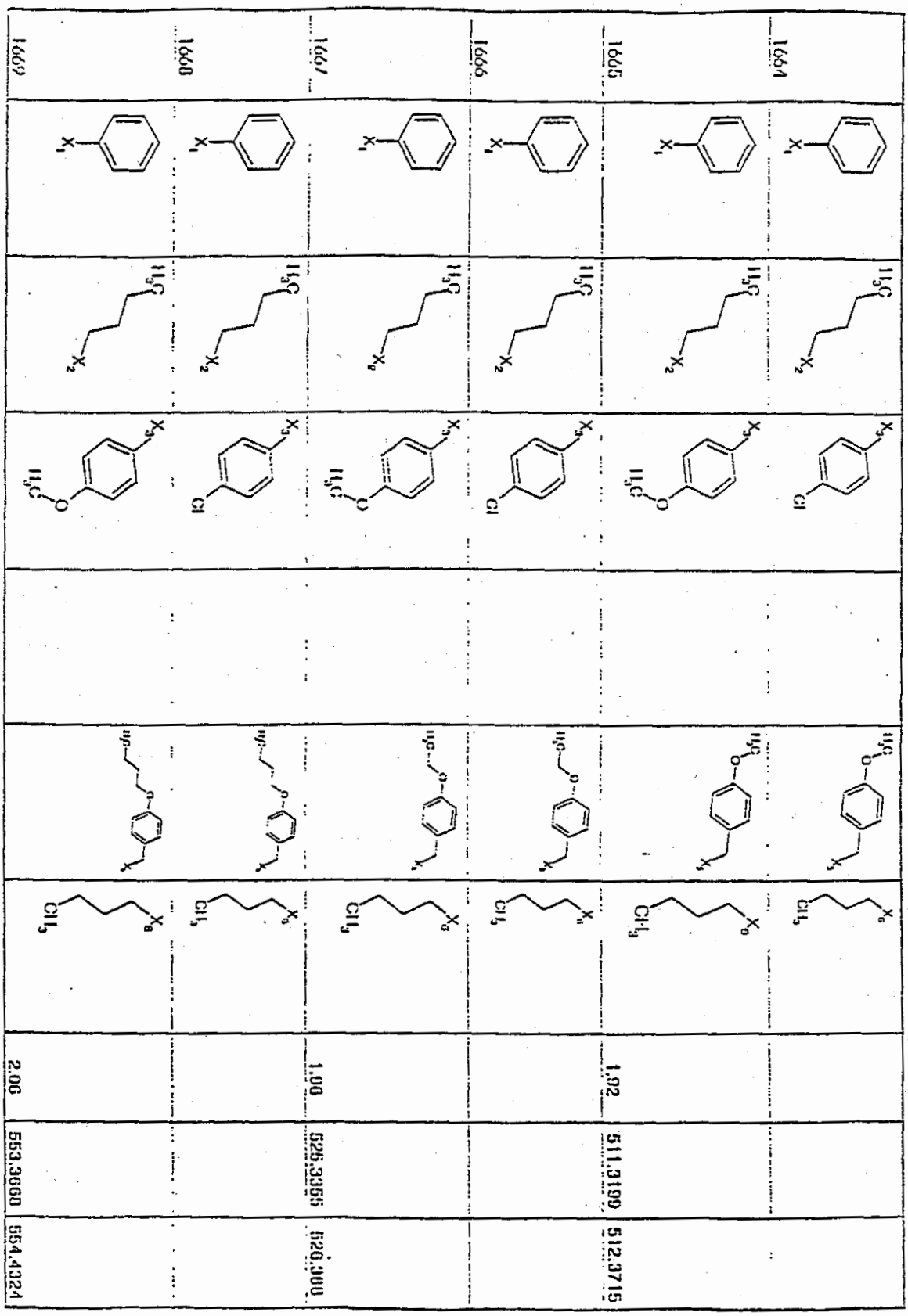


1646								2.11	503.1703	504.29
1647										
1648								2.08	499.2999	500.3384
1649										
1650								2.16	553.1818	554.31
1651										

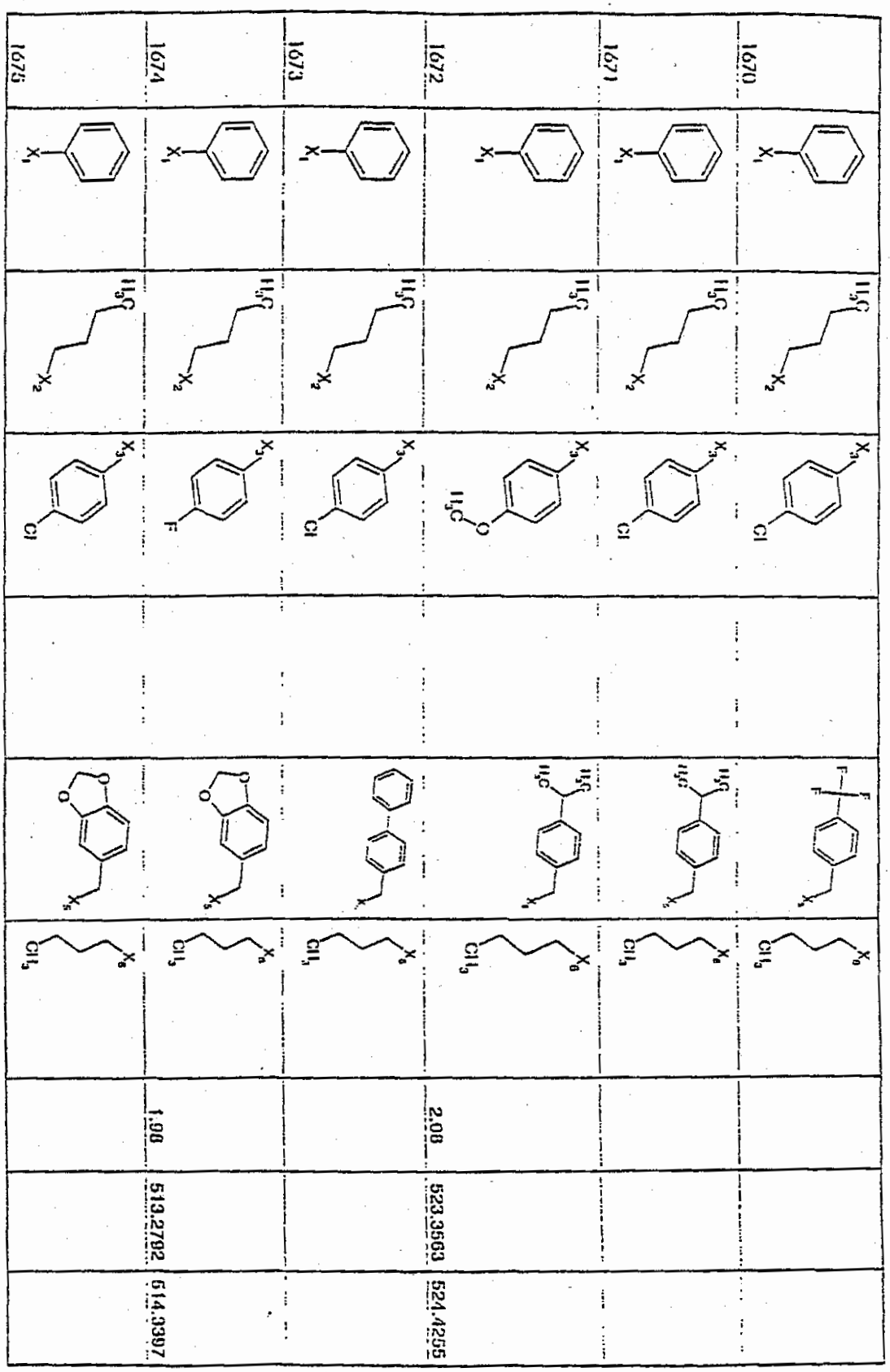
1652								2.01	495.325	496.3744
1653										
1654								2	499.2999	500.344
1655										
1656								2	511.3199	512.3674
1657										

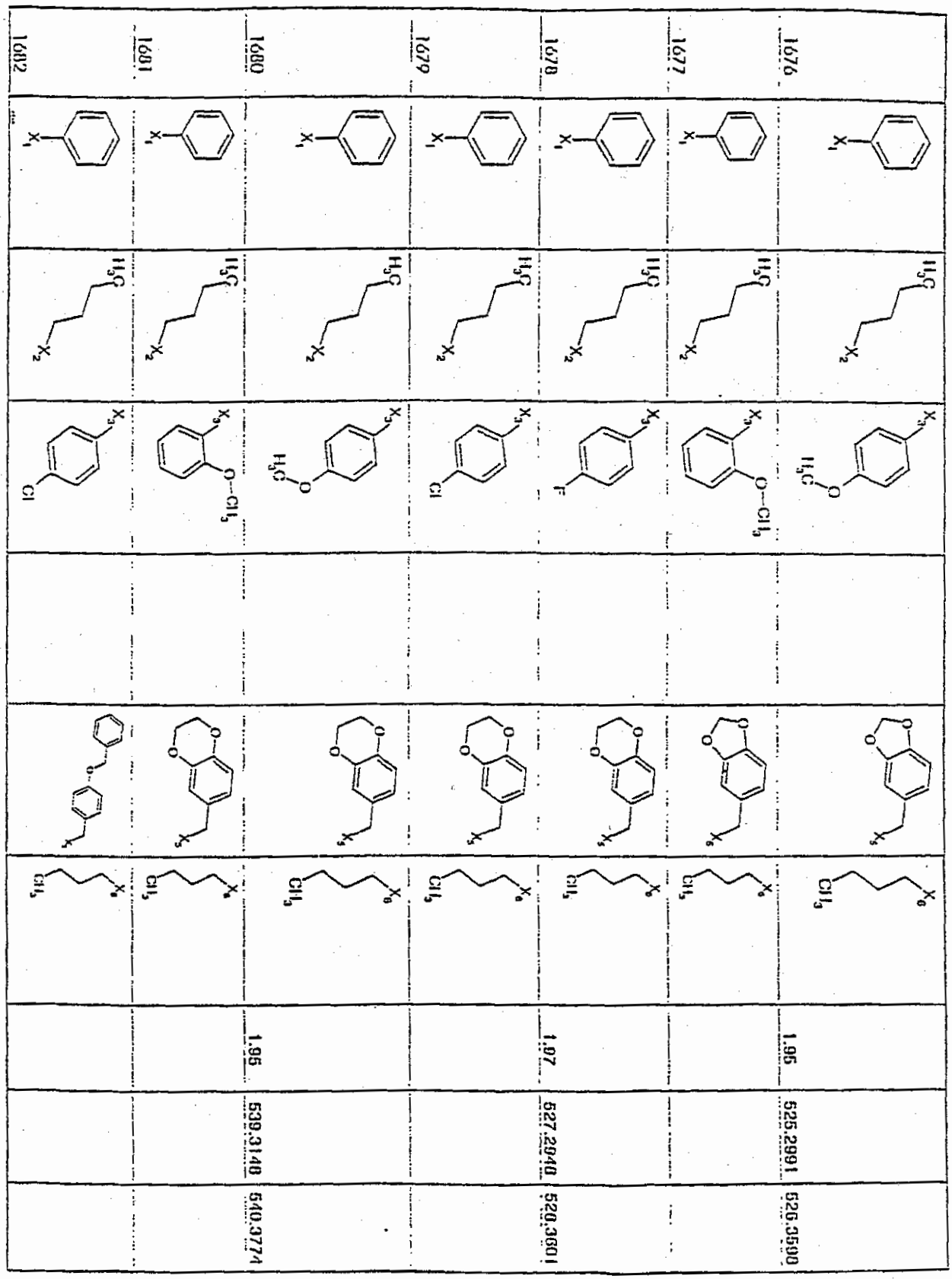


1658									
1659									
1660									
1661						1.99	495.325	496.3093	
1662									
1663									



1664										
1665								1.92	511.3199	512.3715
1666										
1667								1.90	525.3355	526.3909
1668										
1669								2.06	553.3668	554.4324





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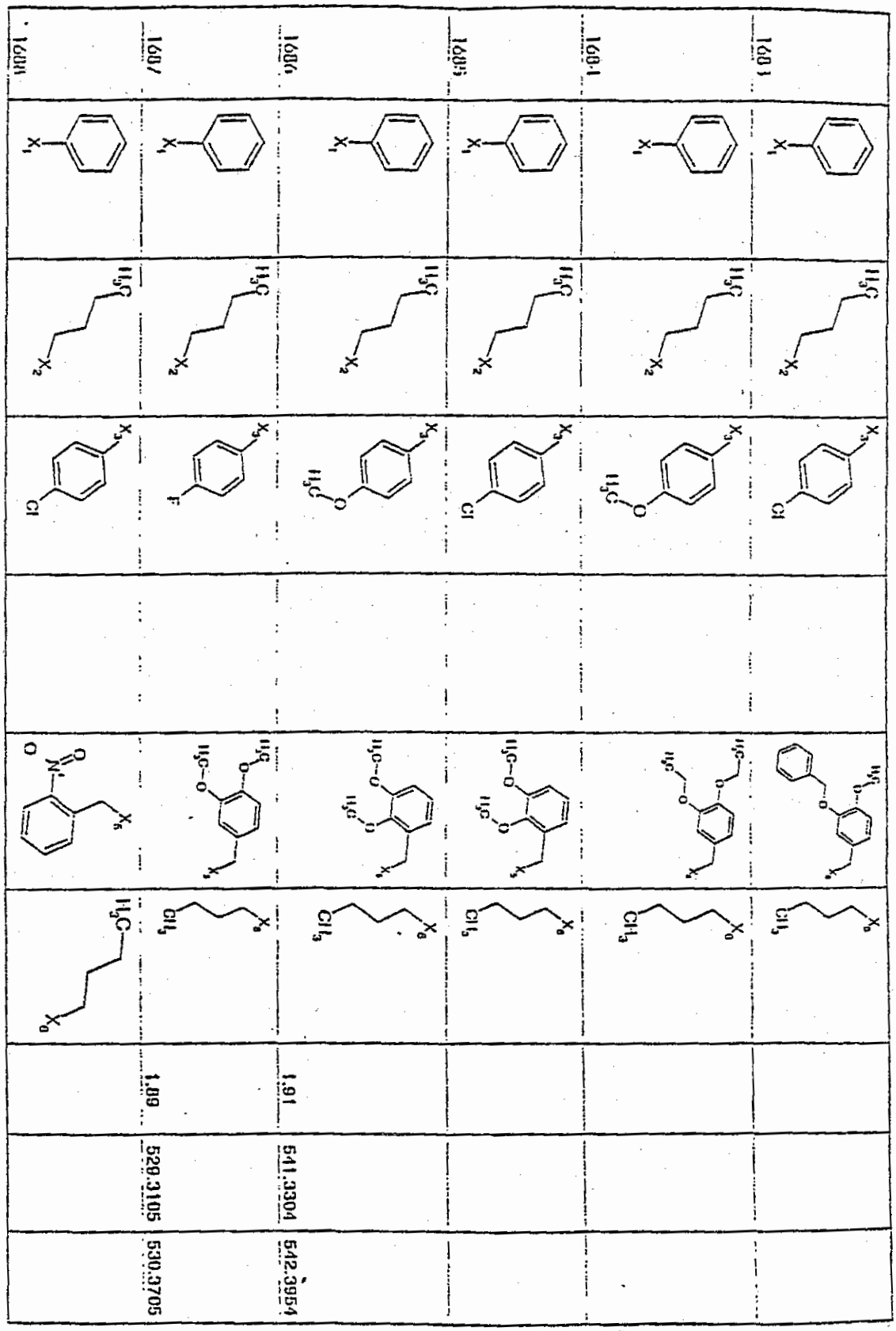
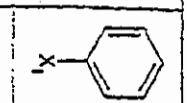
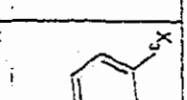
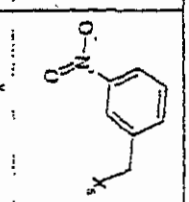
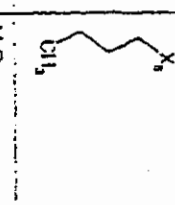
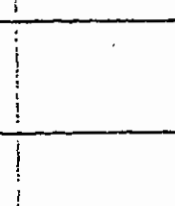
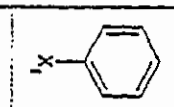
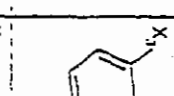
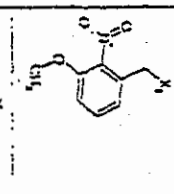
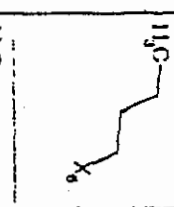
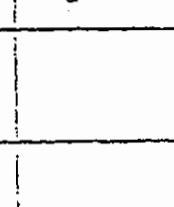
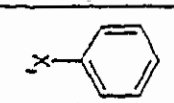
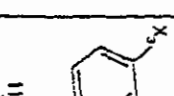
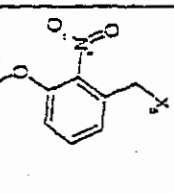
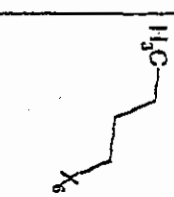
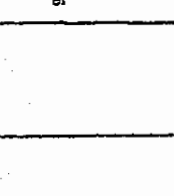
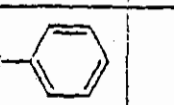
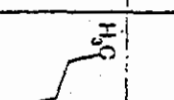
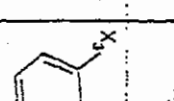
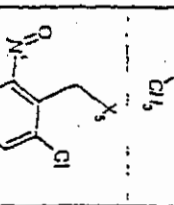
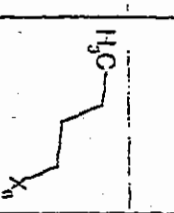
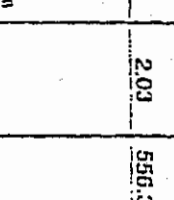
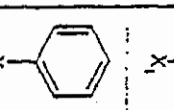
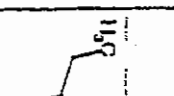
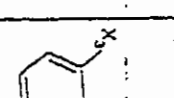
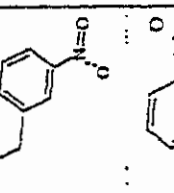
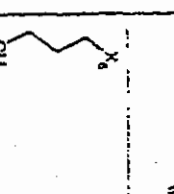
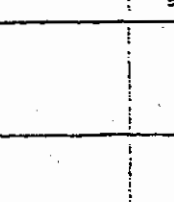
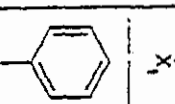
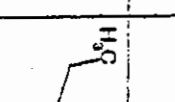
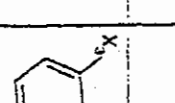
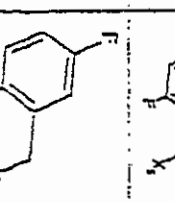
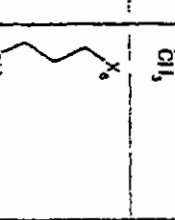
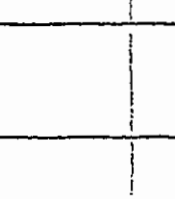
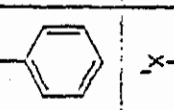
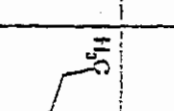
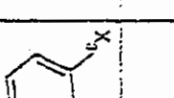
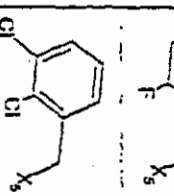
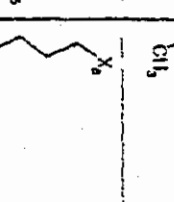
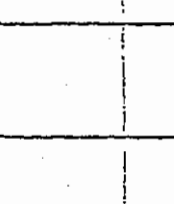
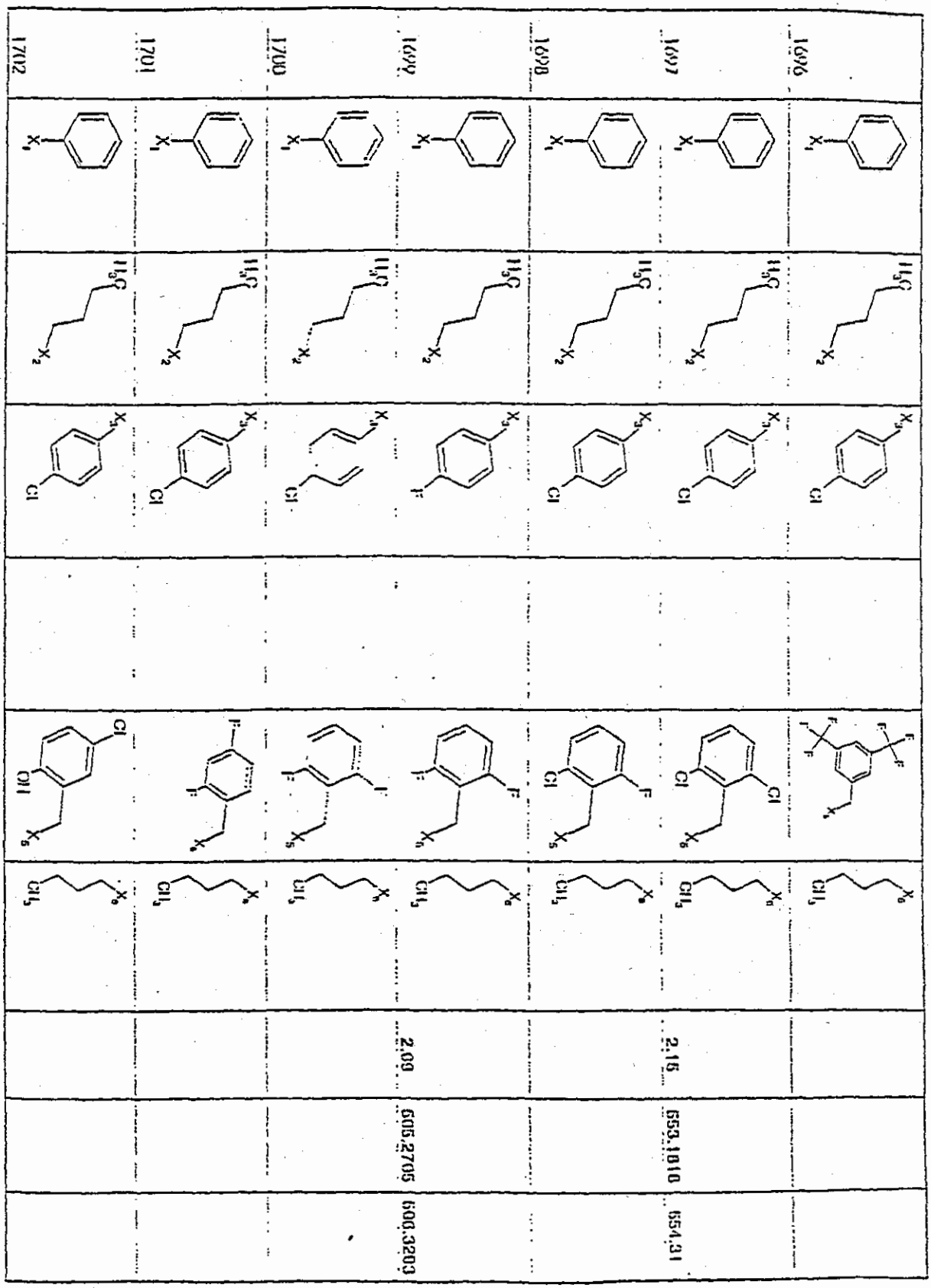
1677										
1678								1.97	527.2940	529.3601
1679										
1680								1.95	539.3148	540.3774
1681										
1682										



1601									
1601-1									
1601-2									
1601-3									
1601-4									
1601-5									
1601-6								1.91	541.3304	542.3954
1601-7								1.89	529.3105	530.3705
1601-8										

1689									
1690									
1691								2.03	556.3049	557.3685
1692										
1693										
1694										
1695										



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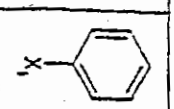
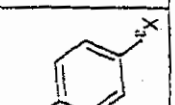
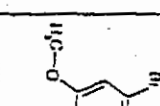
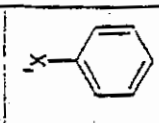
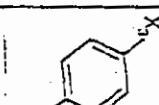
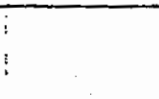
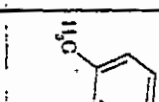
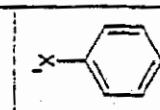
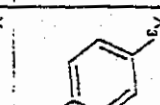
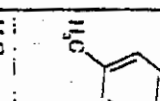
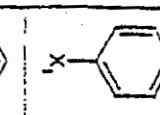
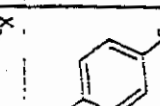
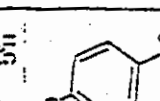
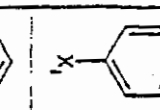
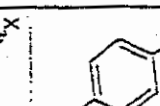
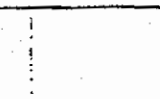
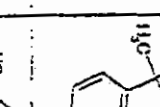
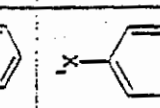
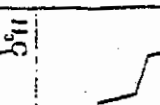
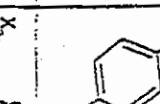
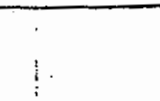
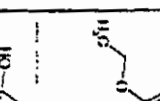
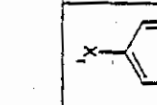
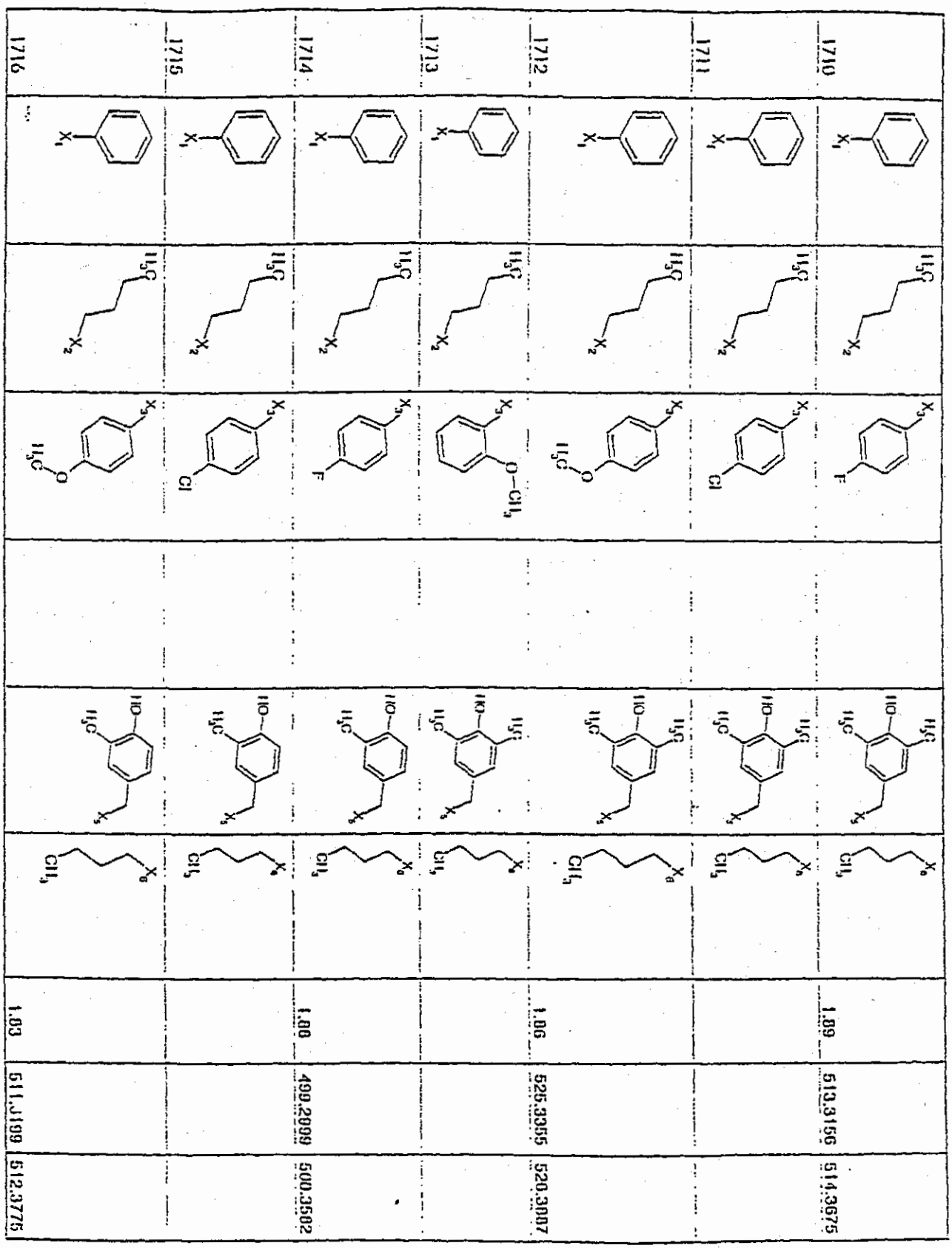
1703								608.2943	500.3529	
1704								609.1758	509.2999	1.95
1705										
1706										
1707										
1708								529.3105	530.3679	1.07
1709										



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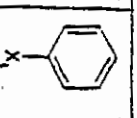
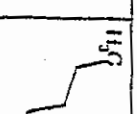
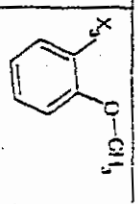
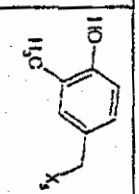
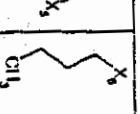
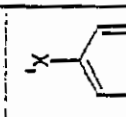
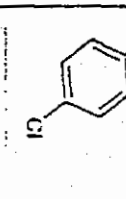
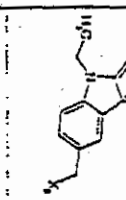
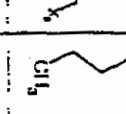
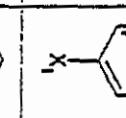
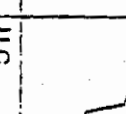
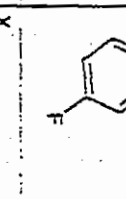
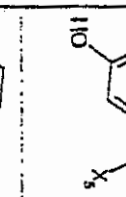
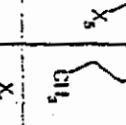
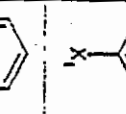
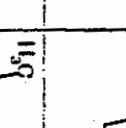
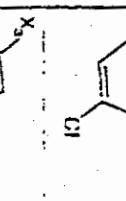
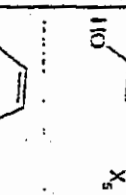
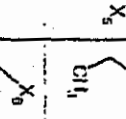
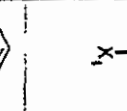
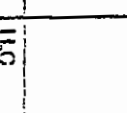
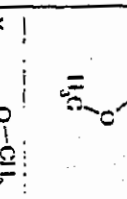
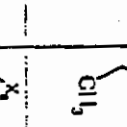
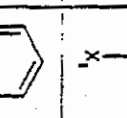
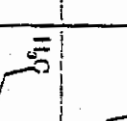
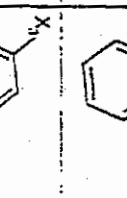
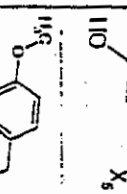
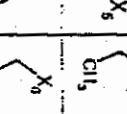
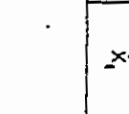
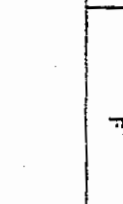
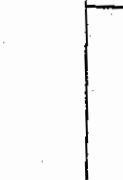
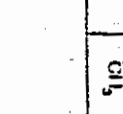
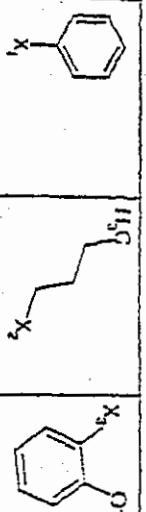
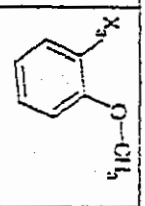
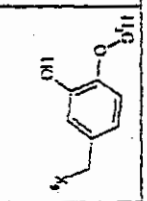
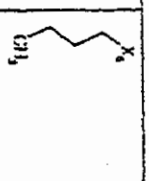
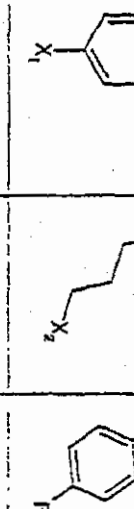
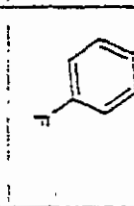
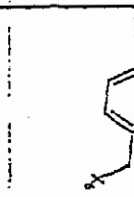
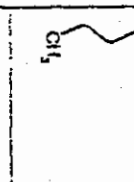
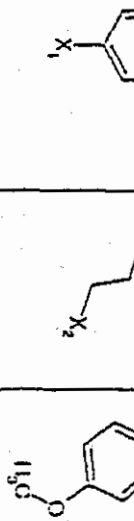
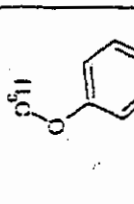
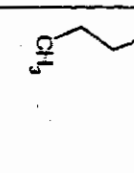
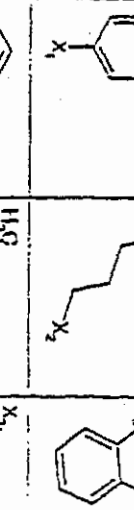
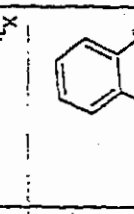
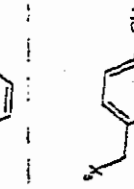
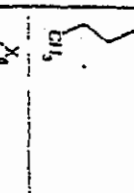
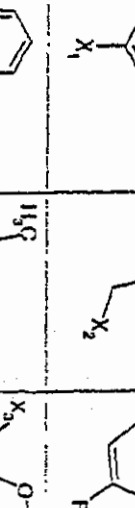
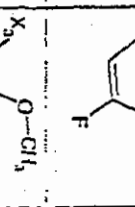
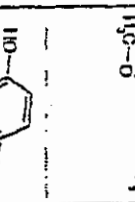
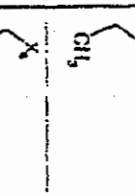
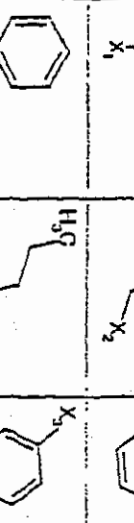
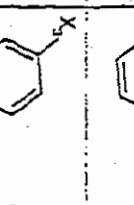
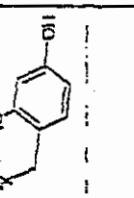
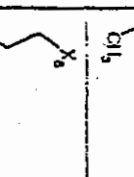
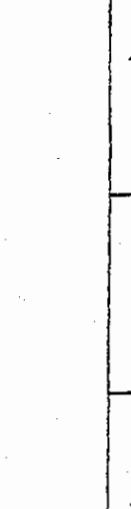
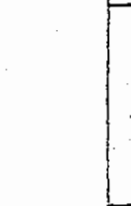
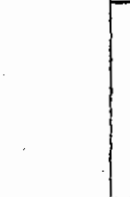
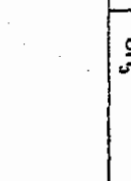
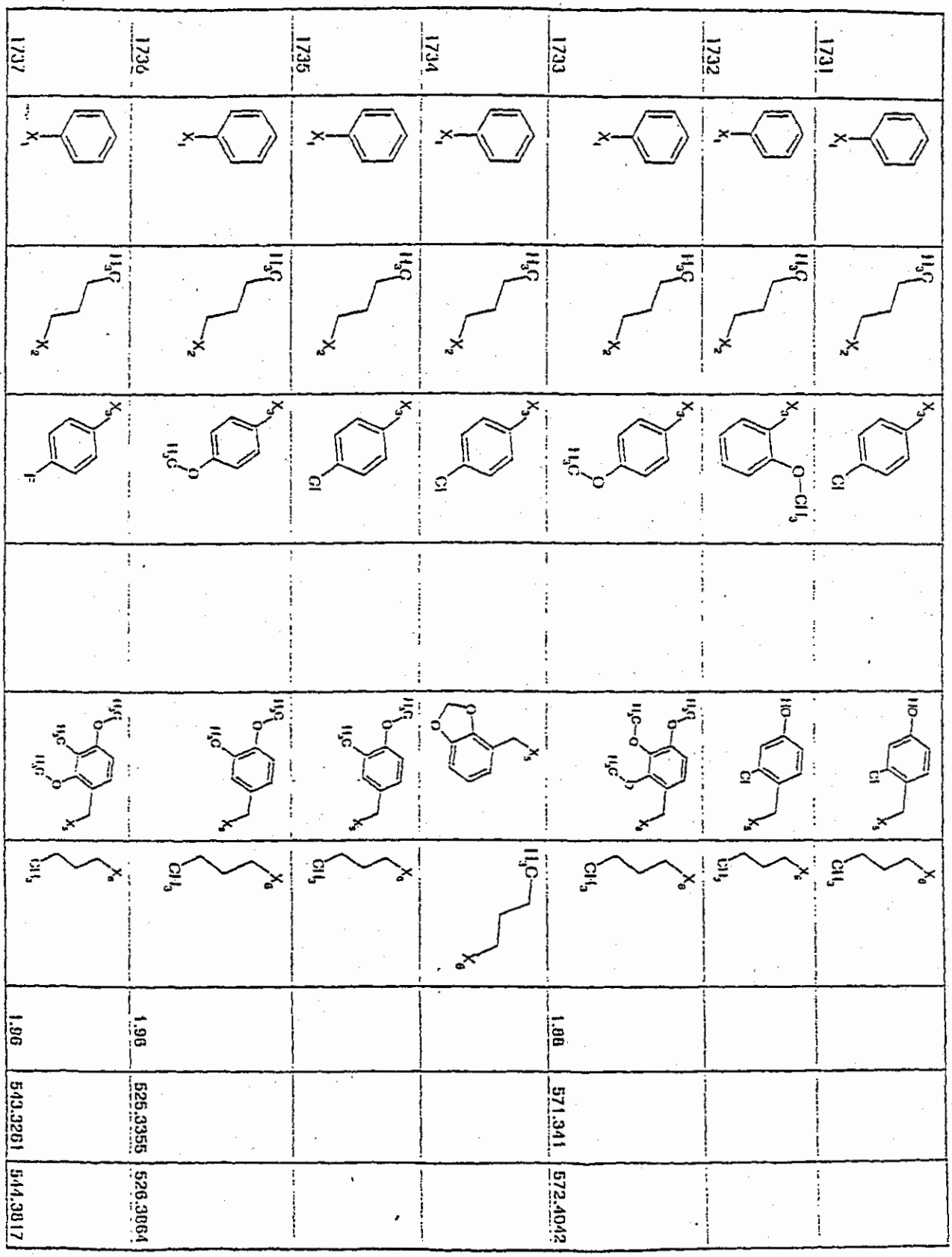
1717										
1718										
1719								1.91	405.2842	406.3395
1720										
1721								1.99	497.3042	498.3593
1722										
1723								1.88	515.2948	516.3523

1724										
1725								1.03	495.2842	496.3419
1726								1.8	497.3042	498.3629
1727										
1720								1.03	515.2940	516.3555
1729										
1730								2.04	519.2452	520.3127



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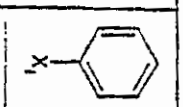
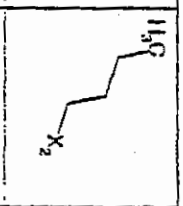
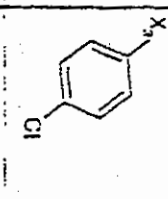
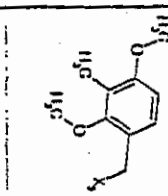
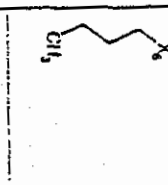
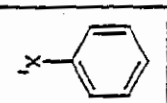
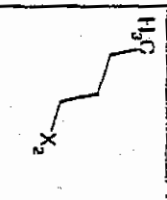
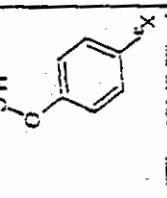
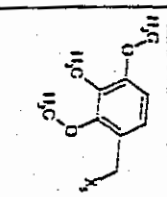
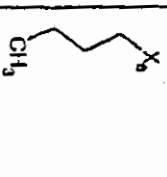
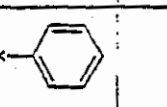
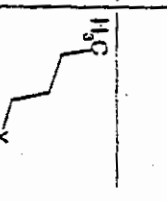
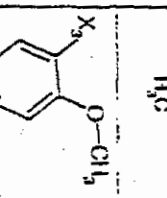
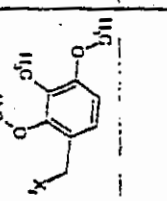
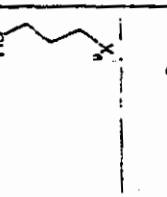
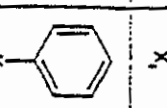
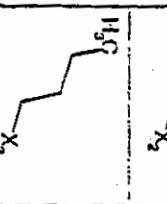
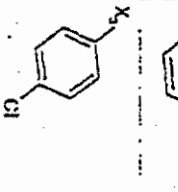
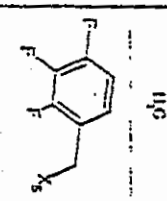
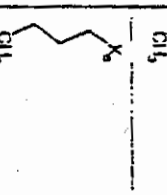
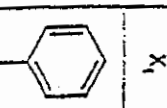
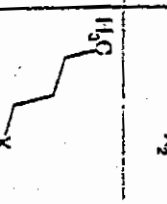
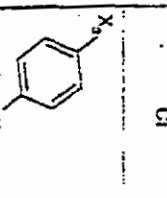
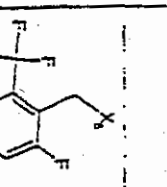
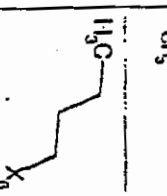
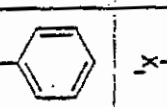
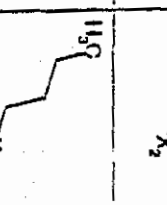
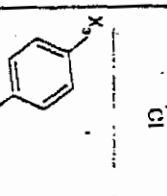
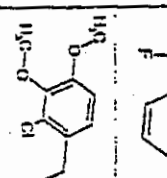
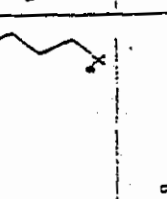
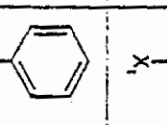
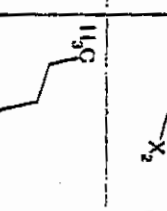
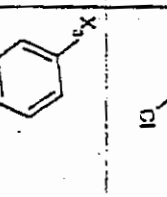
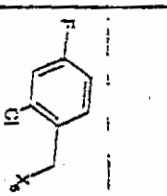
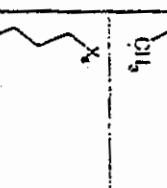
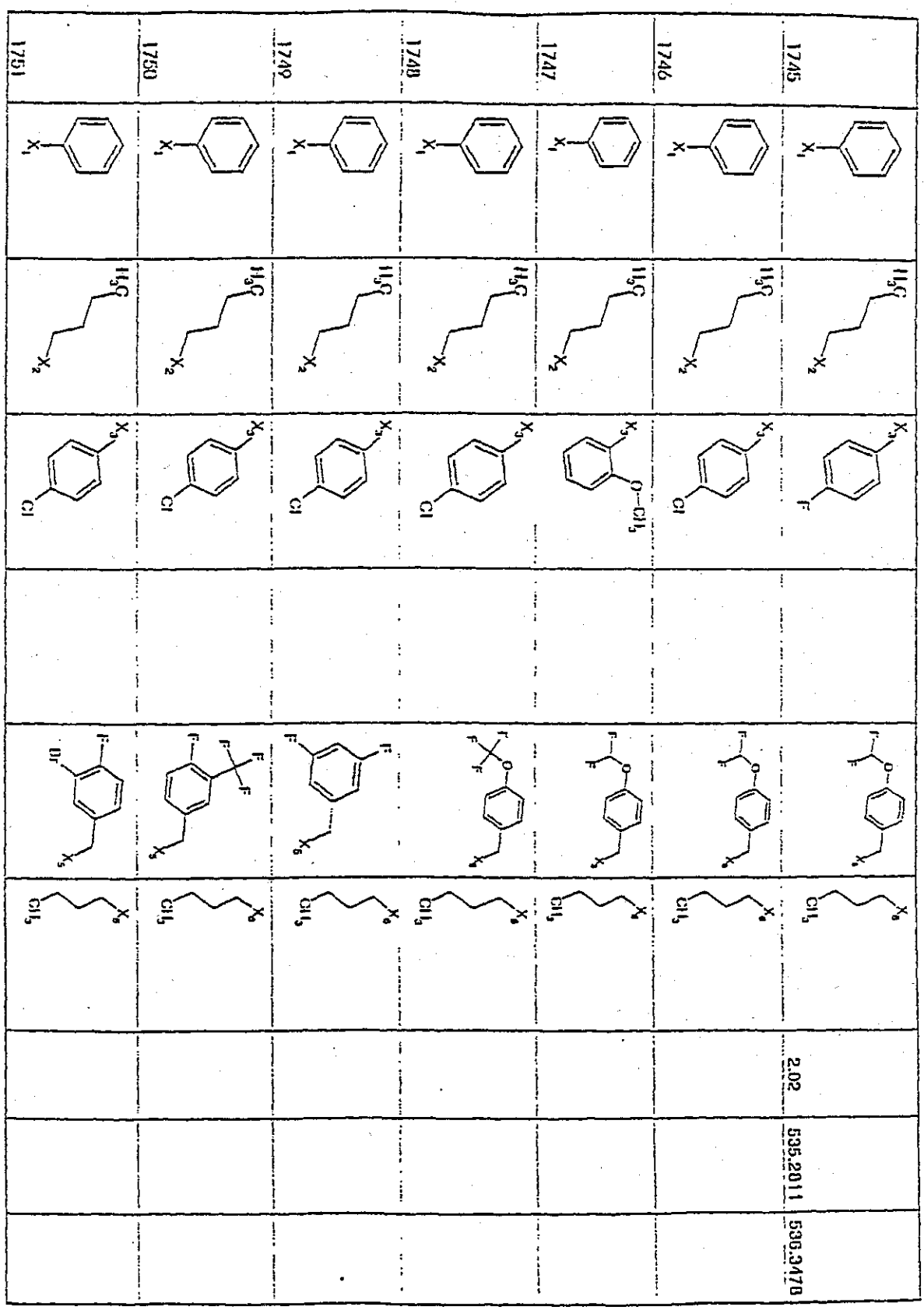
1738									
1739							1.92	555.3401	550.3902
1740									
1741									
1742									
1743									
1744									



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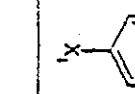
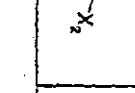
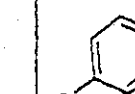
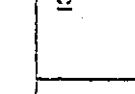
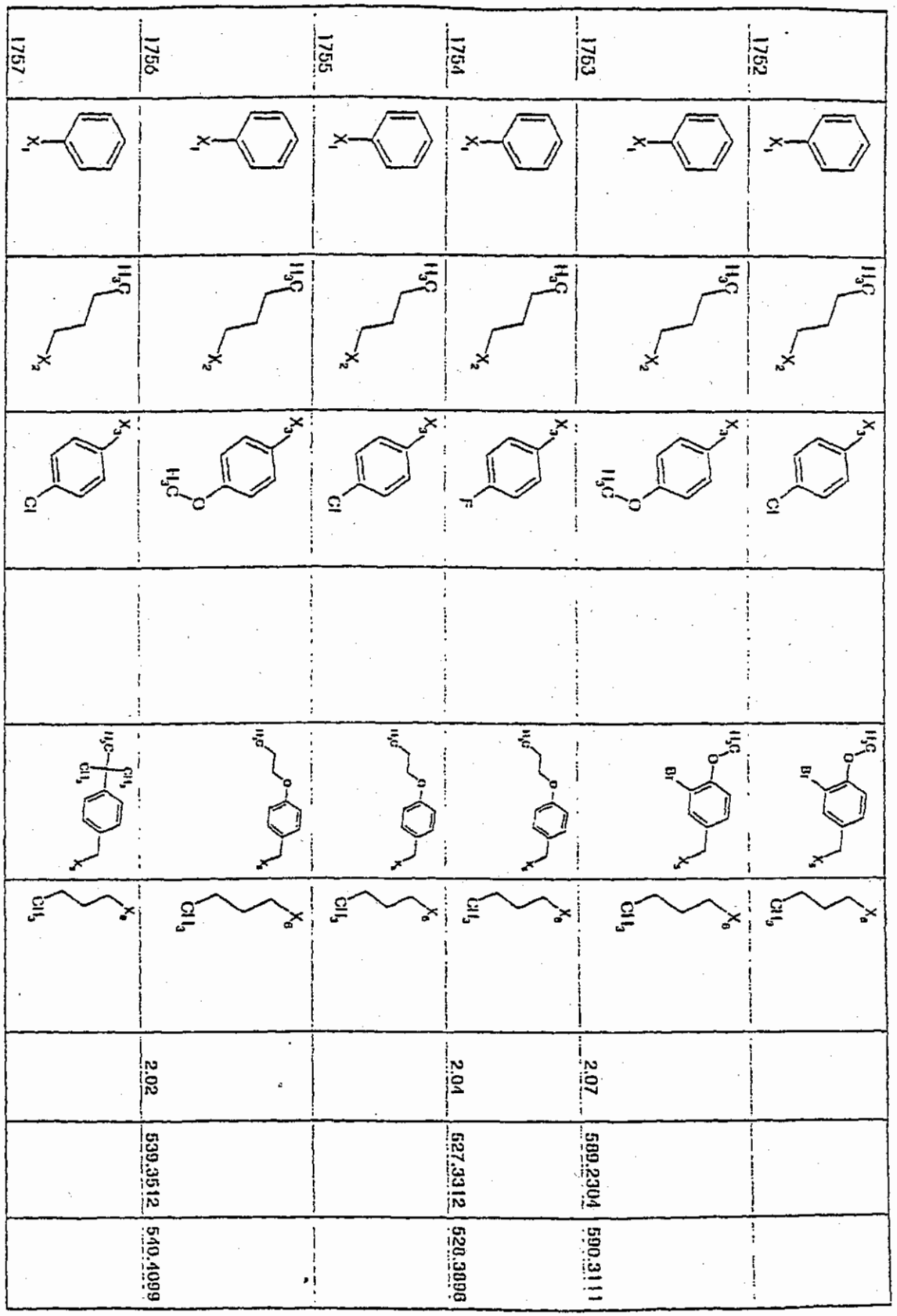
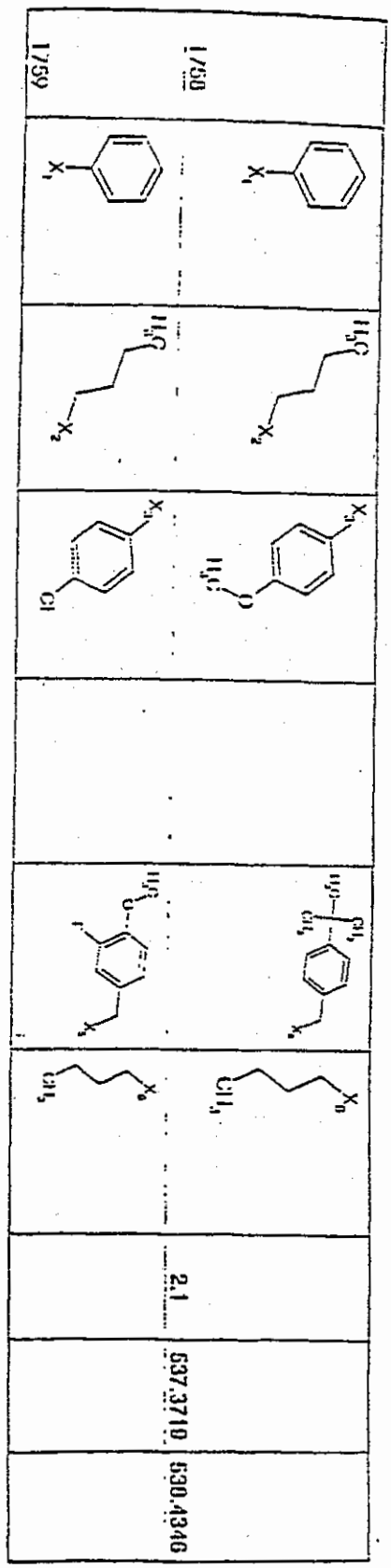
1749											
1750											
1751											



1752								
1753						2.07	589.2304	590.3111
1754						2.04	627.3312	628.3998
1755								
1756						2.02	539.3512	540.4099
1757								



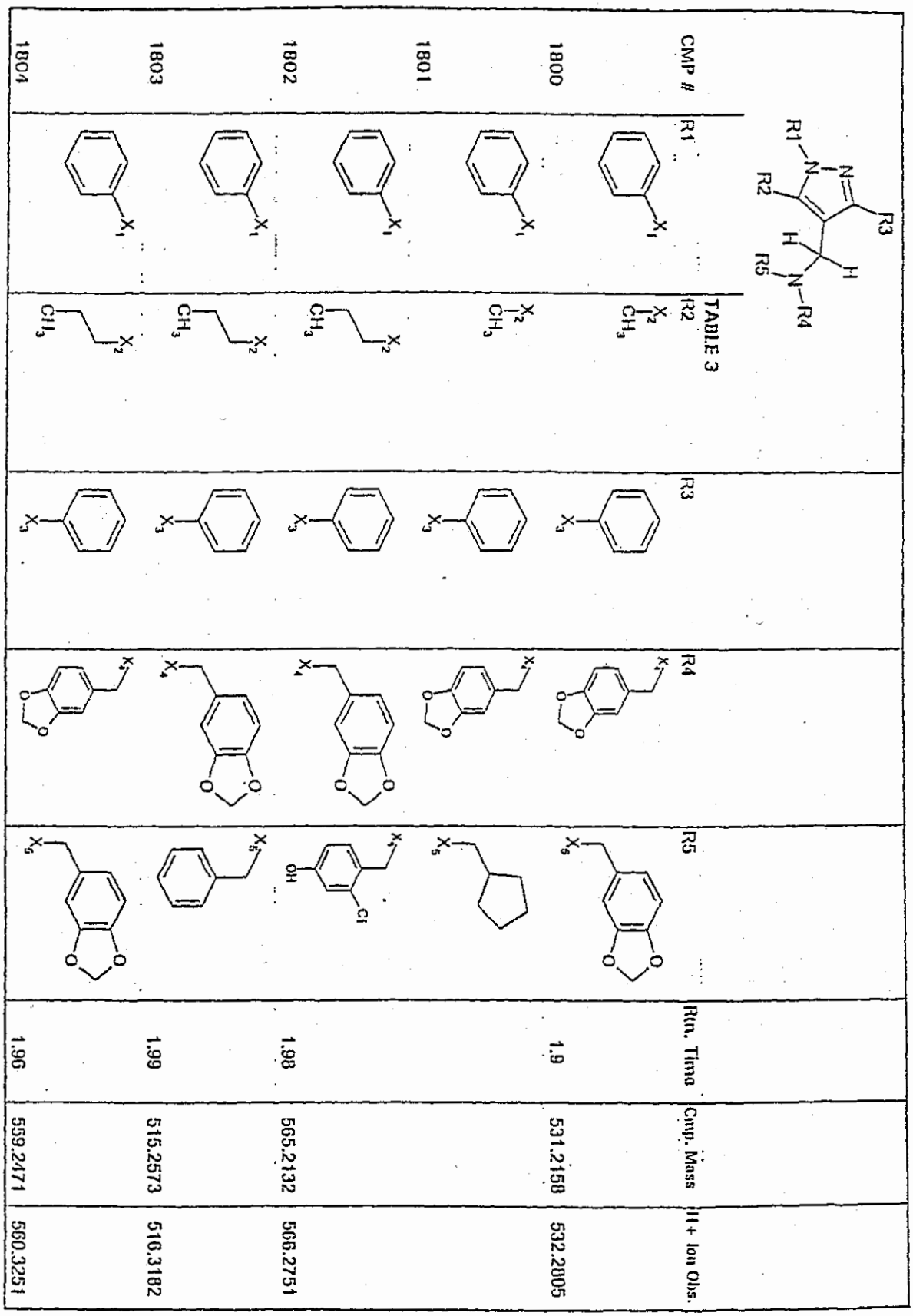
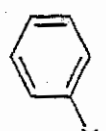
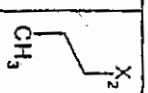
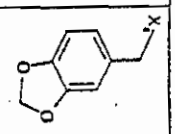
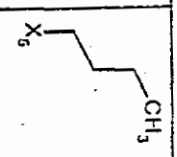
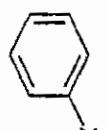
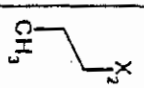
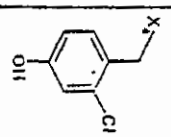
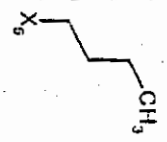
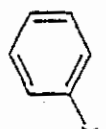
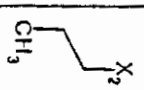
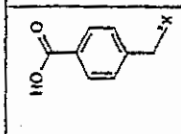
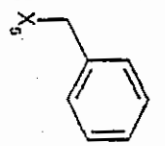
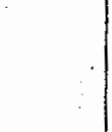


TABLE 3

CMP #	R1	R2	R3	R4	R5	Rtn. Time	Cmp. Mass	H+ Ion Obs.
1800						1.9	531.2158	532.2805
1801								
1802						1.98	565.2132	566.2751
1803						1.99	515.2573	516.3182
1804						1.96	559.2471	560.3251

1805						1.87	481.2729	482.34
1806						2.01	521.2234	522.2083
1807						1.91	487.239	488.3032
1808						2.07	515.2573	516.2089

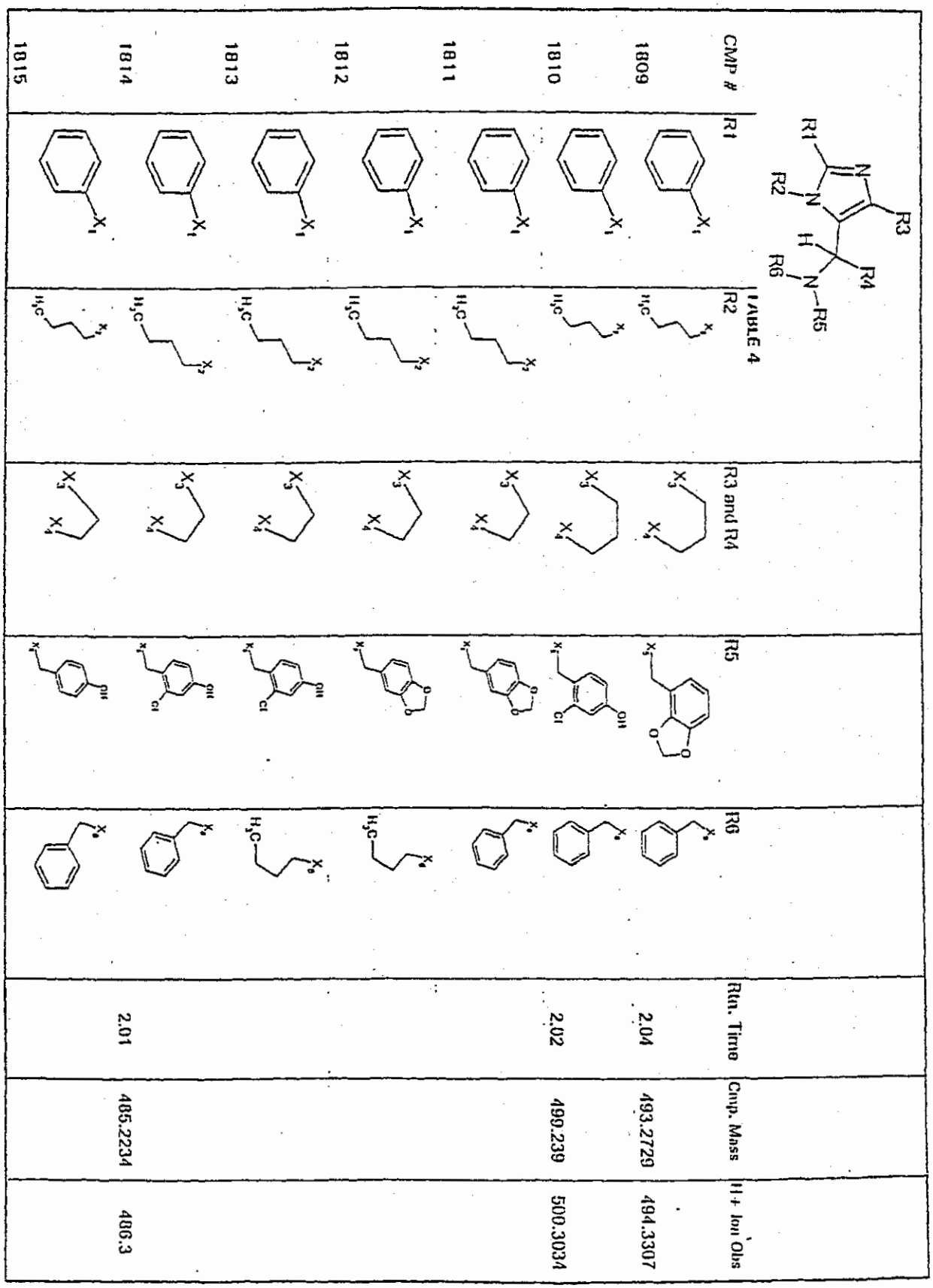
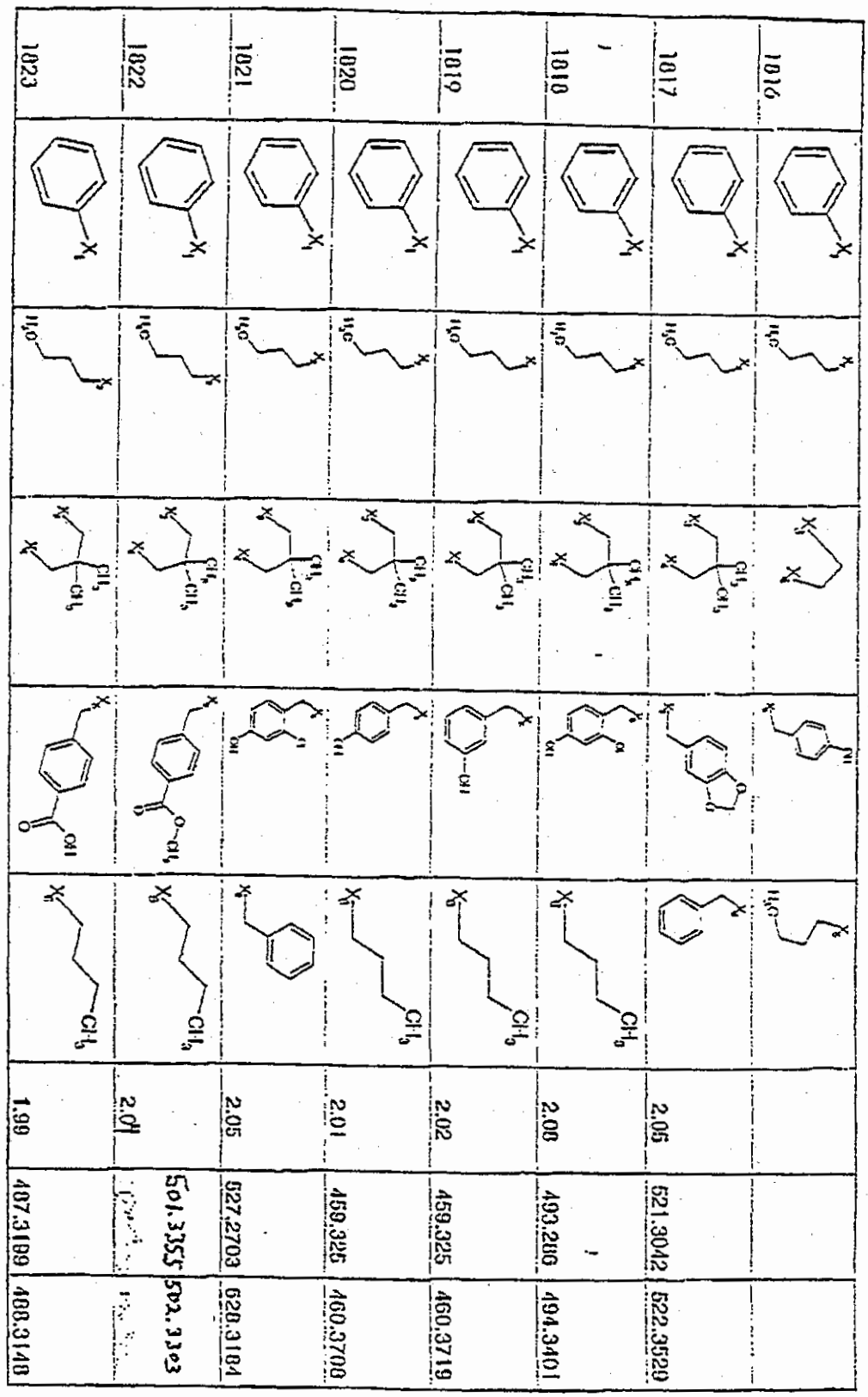


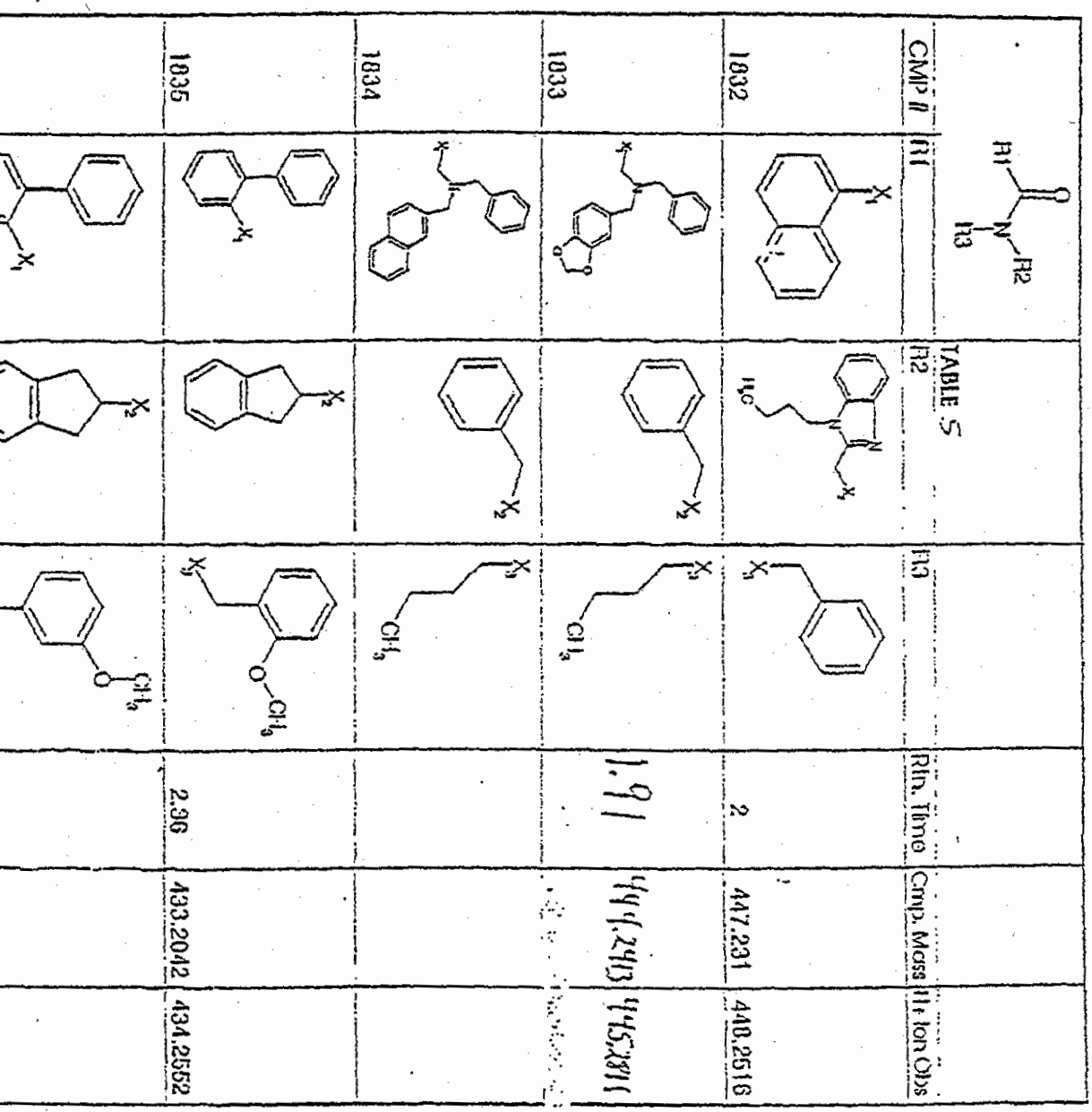
TABLE 4

CMP #	R1	R2	R3 and R4	R5	R6	Rtn. Time	Cmp. Mass	H+ Ion Obs
1809						2.04	493.2729	494.3307
1810						2.02	499.239	500.3034
1811								
1812								
1813								
1814						2.01	485.2234	486.3
1815								

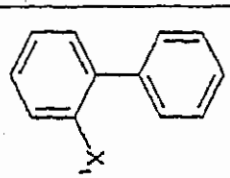
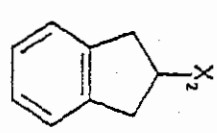
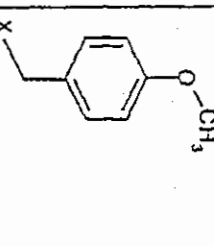
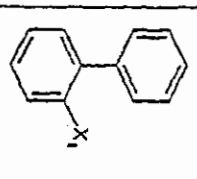
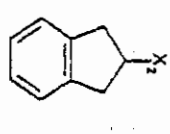
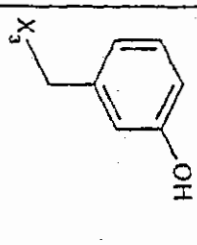
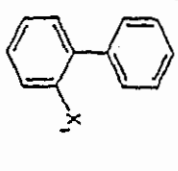
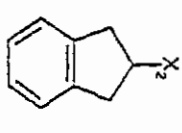
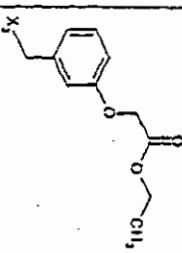
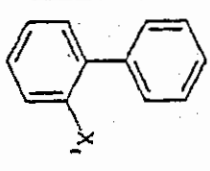
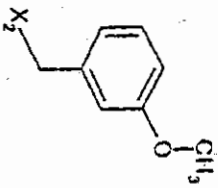
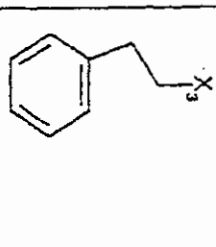
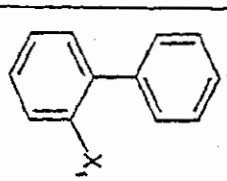
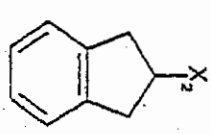
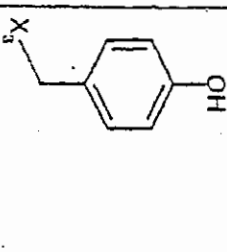


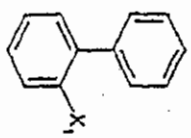
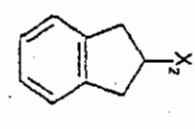
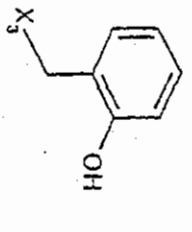
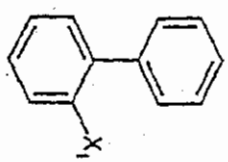
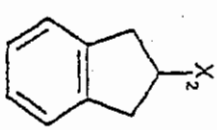
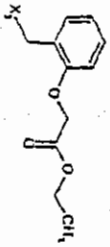
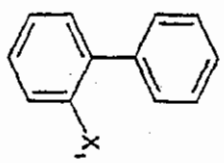
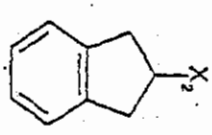
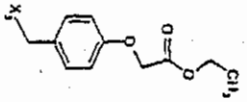
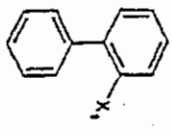
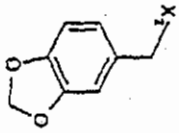
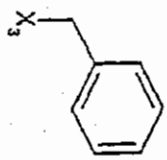
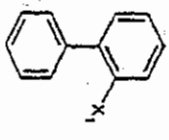
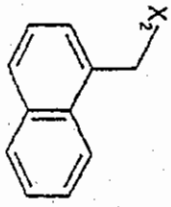
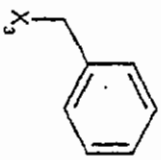
1016									
1017							2.05	521.3042	522.3529
1018							2.08	493.2810	494.3401
1019							2.02	459.325	460.3719
1020							2.01	459.325	460.3709
1021							2.05	527.2703	528.3184
1022							2.01	501.3355	502.3303
1023							1.99	487.3189	488.3140

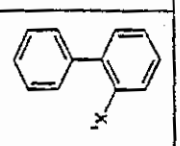
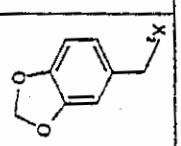
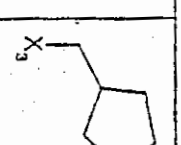
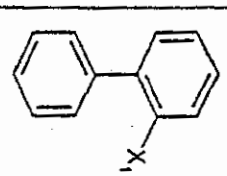
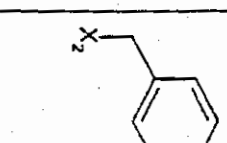
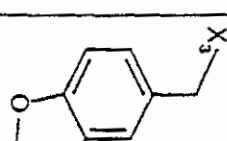
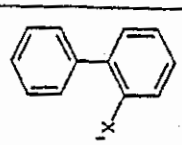
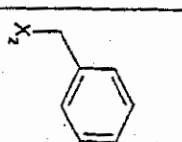
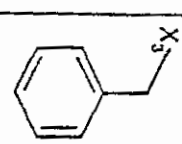
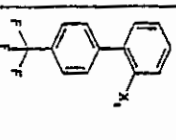
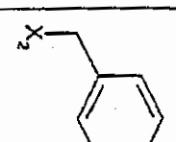
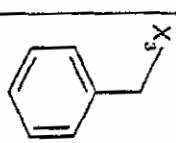
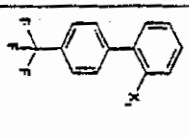
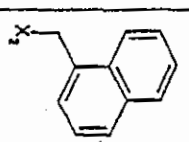
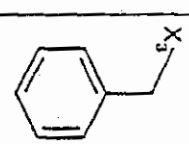
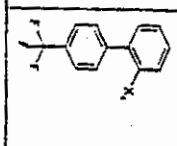
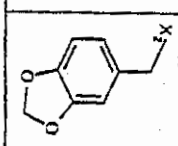
TABLE 5

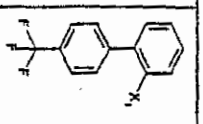
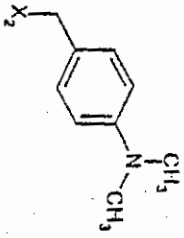
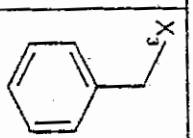
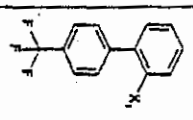
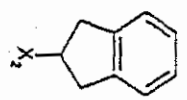
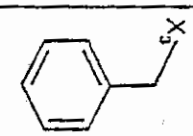
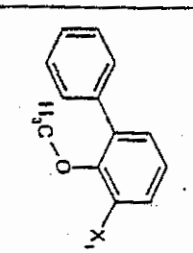
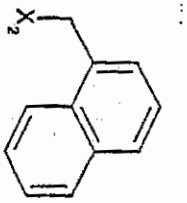
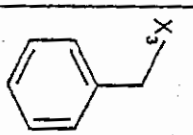
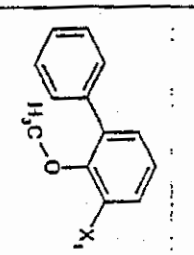
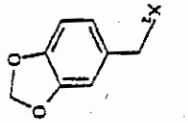
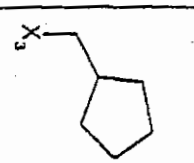
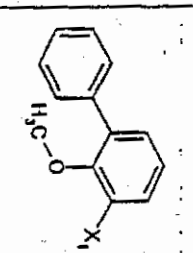
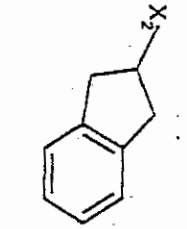
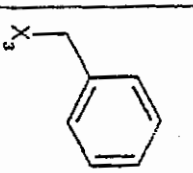
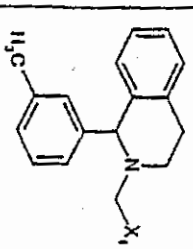
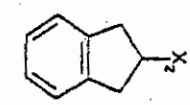
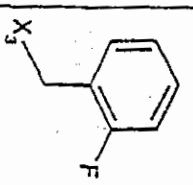


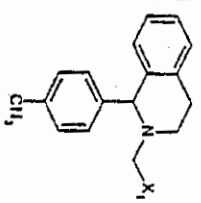
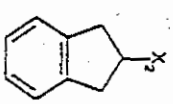
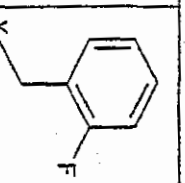
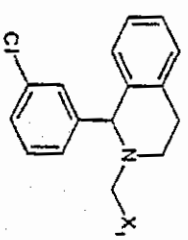
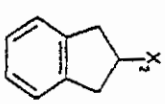
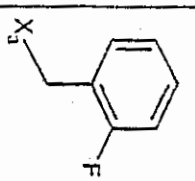
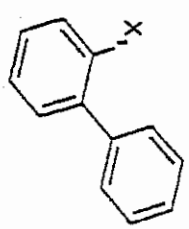
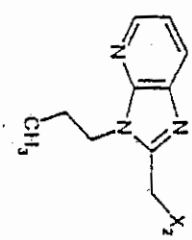
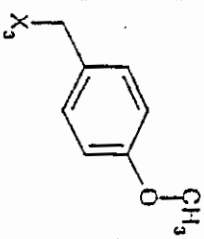
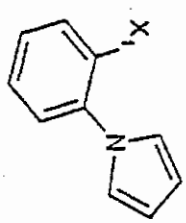
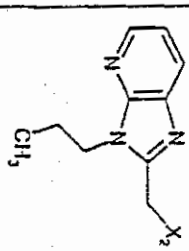
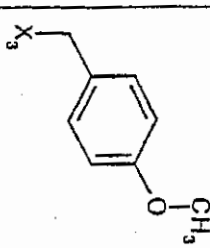
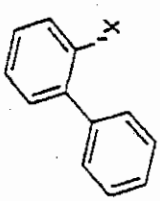
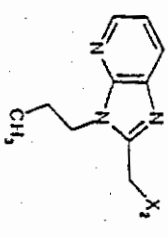
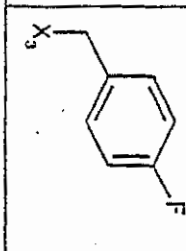
CMP #	R1	R2	R3	Rtn. Time	Cmp. Mass	H+ Ion Obs
1832				2	447.231	448.2516
1833				1.91	444.2413	445.2491
1834						
1835				2.36	433.2042	434.2552
1836				2.33	433.2042	434.2509

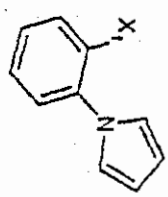
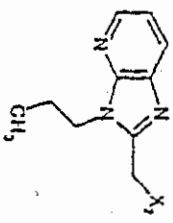
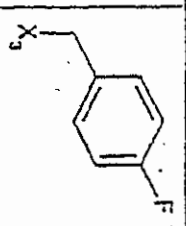
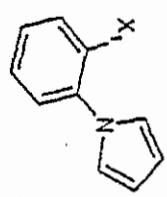
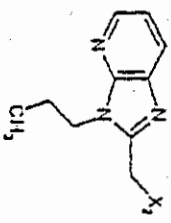
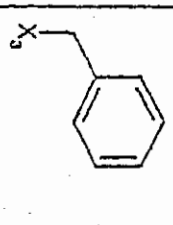
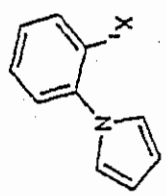
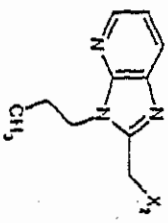
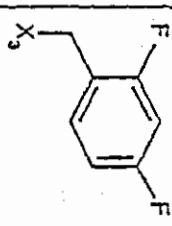
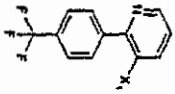
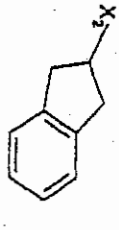
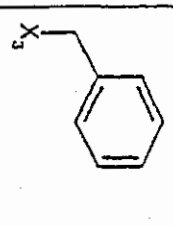
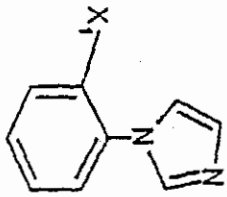
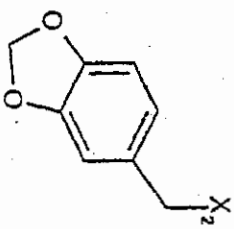
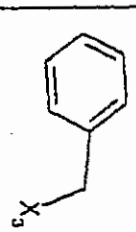
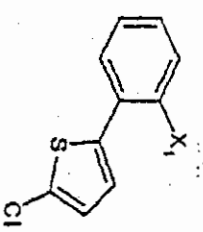
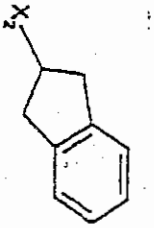
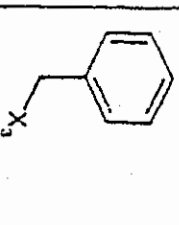
1837				2.33	433.2042	434.2613
1838				2.22	419.1885	420.2401
1839				2.3	505.2253	506.2785
1840				2.31	421.2042	422.2463
1841				2.2	419.1885	420.2424

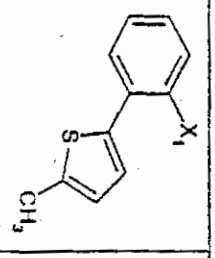
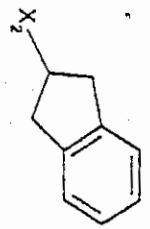
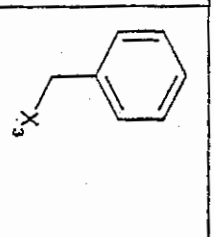
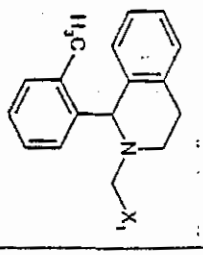
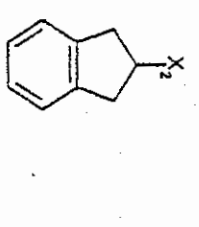
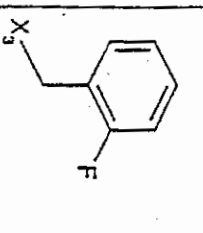
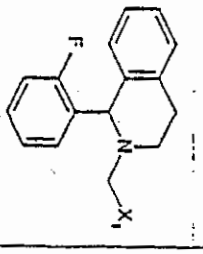
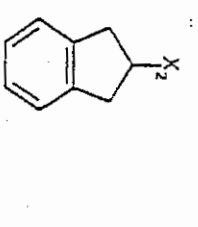
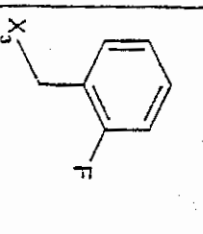
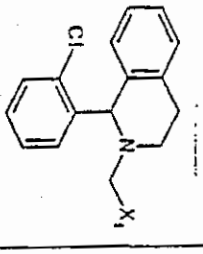
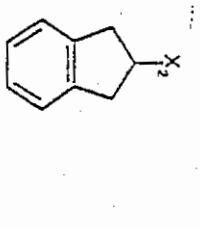
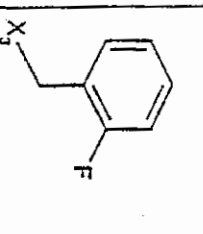
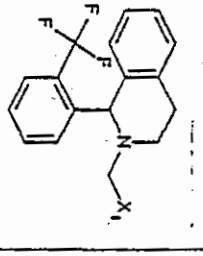
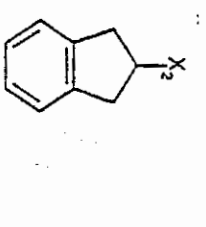
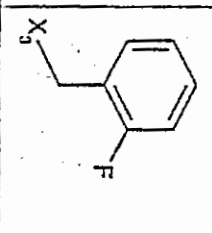
1842				2.27	419.1885	420.2401
1843				2.32	505.2253	506.2746
1844				2.3	505.2253	506.2814
1845				2.27	421.1678	422.2155
1846				2.4	427.1936	428.2449

1847				2.33	413.1991	414.2406
1848				2.25	465.1576	466.216
1849				2.12	420.2202	421.262
1850				2.33	489.1552	490.2146
1851				2.46	495.181	496.2438
1852				2.37	481.1865	482.2455

1853				2.17	488.2076	489.2776
1854				2.4	471.181	472.2344
1855				2.49	457.2042	458.2641
1856				2.4	443.2097	444.2538
1857				2.42	433.2042	434.2522
1858						

1859						
1860						
1861				2.17	490.2369	491.2785
1862				2.1	479.2321	480.2817
1863						

1864					486.248	444.1614
1865					485.2027	443.1111
1866				2.15	485.2027	443.1111
1867				2.29	472.1762	473.2223
1868				1.78	411.1583	412.1952
1869				2.44	443.1111	444.1614

1870				2.4	423.1657	424.1971
1871				2.11	504.2577	505.2372
1872				2.08	508.2326	509.2144
1873				2.21	524.2031	525.1942
1874				2.4	558.2294	559.21

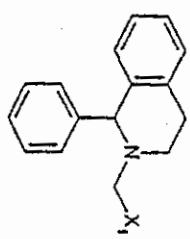
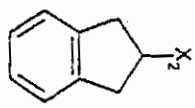
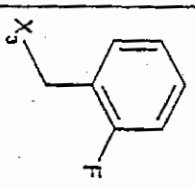
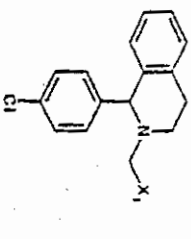
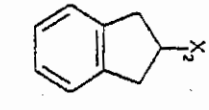
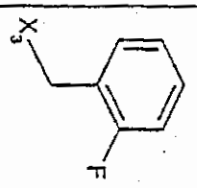
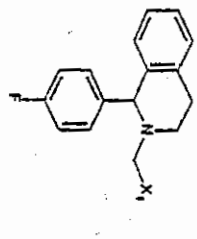
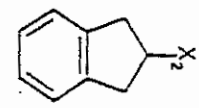
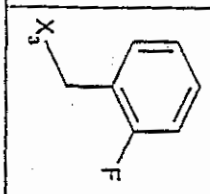
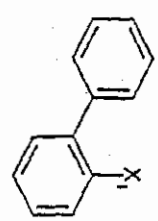
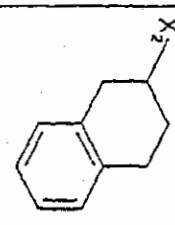
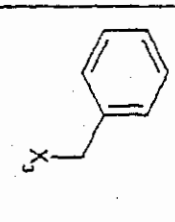
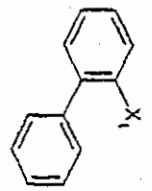
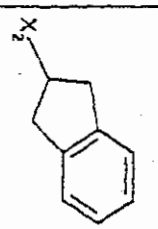
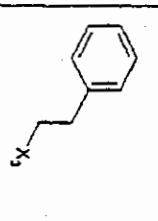
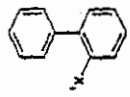
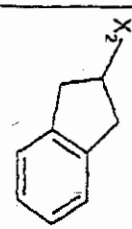
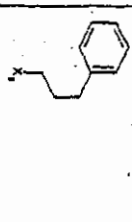
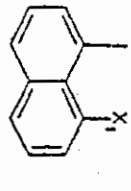
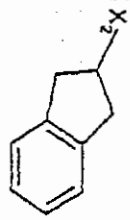
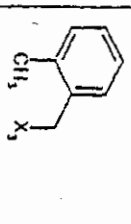
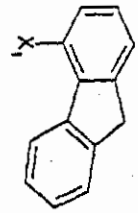
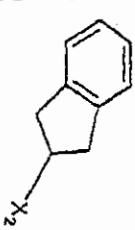
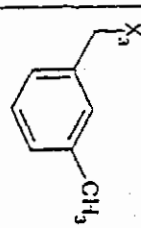
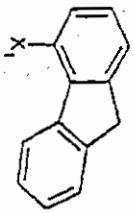
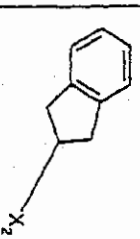
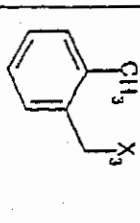
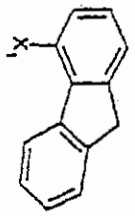
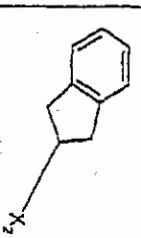
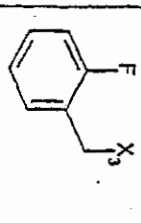
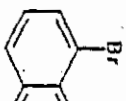
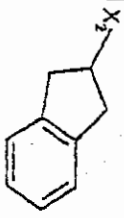
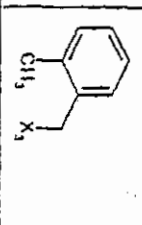
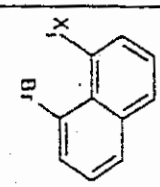
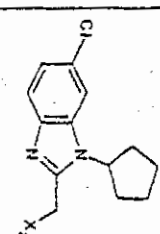
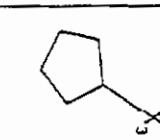
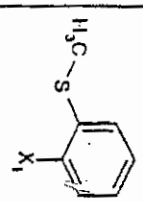
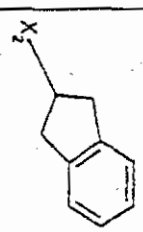
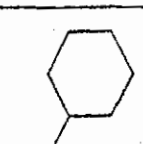
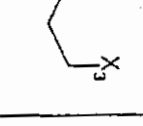
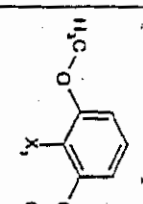
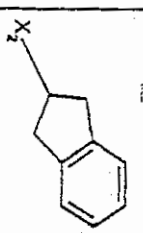
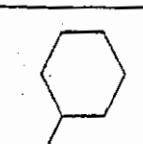
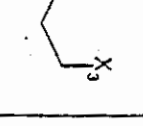
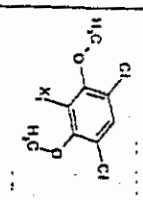
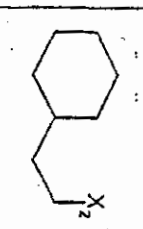
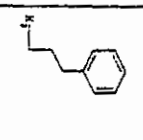
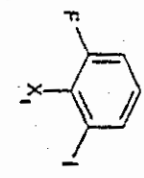
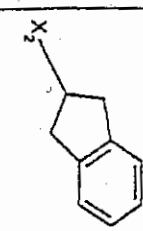
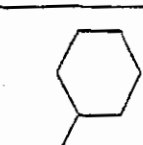
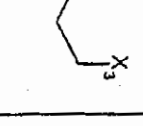
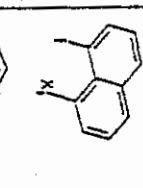
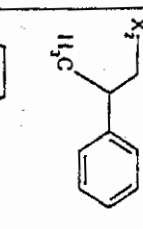
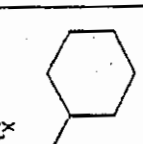
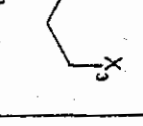
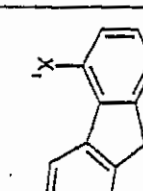
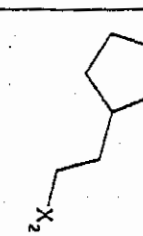
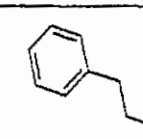
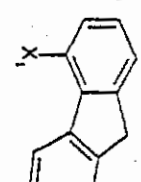
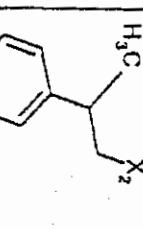
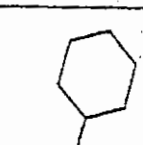
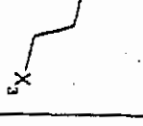
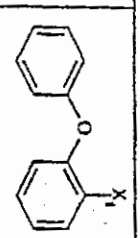
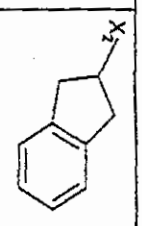
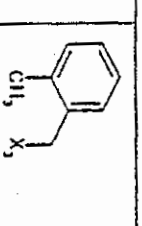
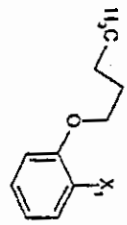
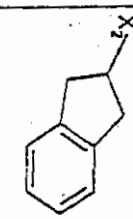
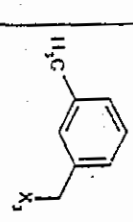
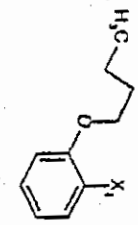
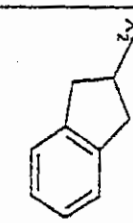
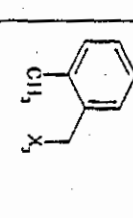
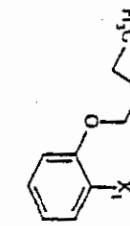
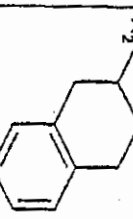
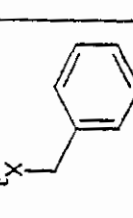
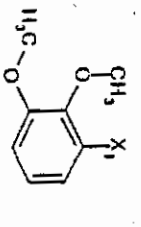
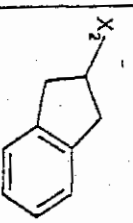
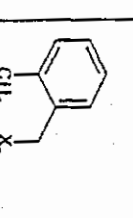
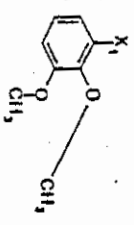
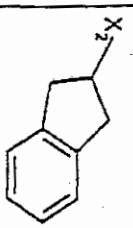
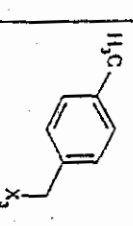
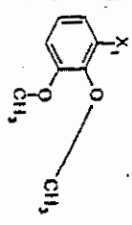
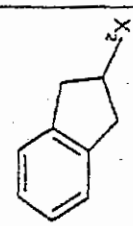
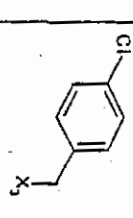
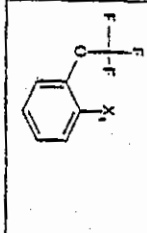
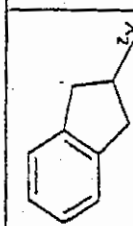
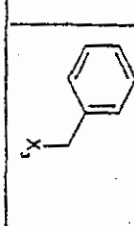
1875				2.01	490.242	491.2217
1876				2.11	524.2031	525.1987
1877				2.04	508.2326	509.2227

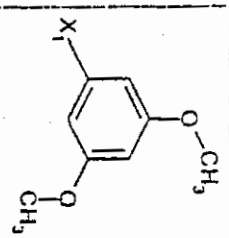
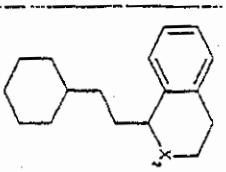
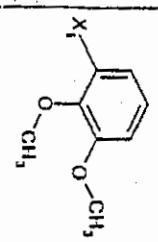
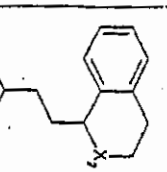
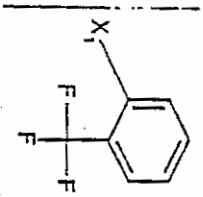
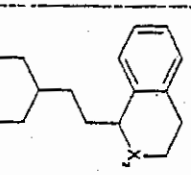
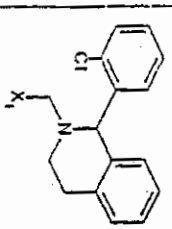
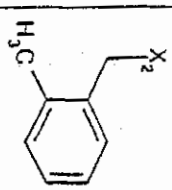
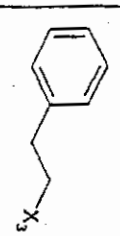
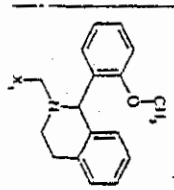
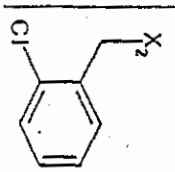
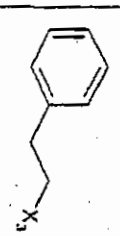
TABLE 5

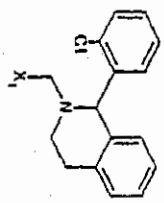
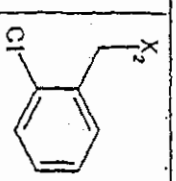
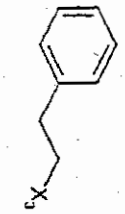
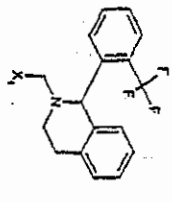
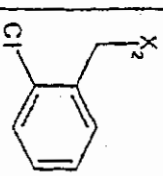
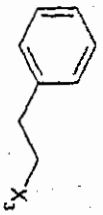
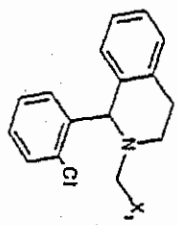
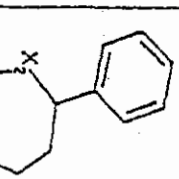
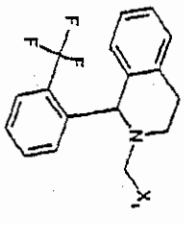
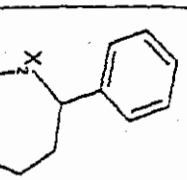
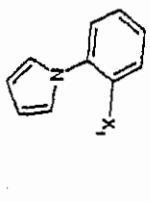
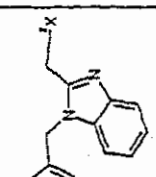
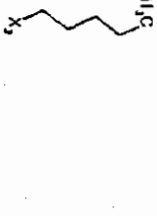
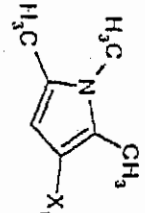
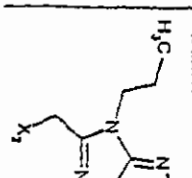
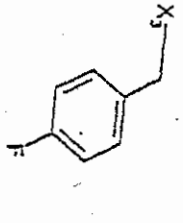
CMP #	R1	R2	R3	Rtn. Time	Cmp. Mass	H+ Ion Obs
1878				2.43	417.2093	418.29
1879				2.42	417.2093	418.2941
1880				2.4	417.2093	418.2959
1881				2.35	421.1842	422.275
1882				2.53	411.2562	412.3455
1883				2.57	423.2562	424.3539
1884				2.42	437.1546	438.1642

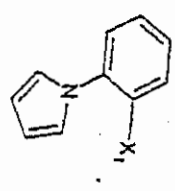
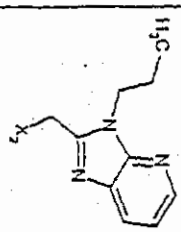
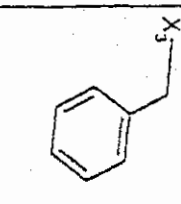
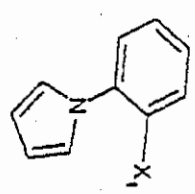
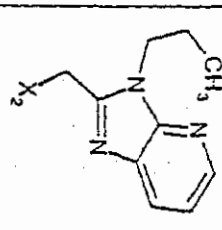
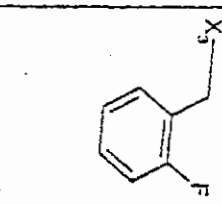
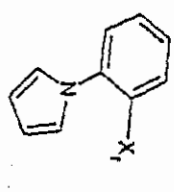
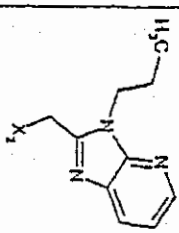
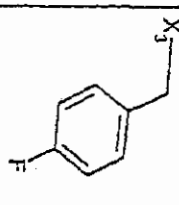
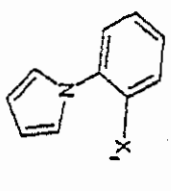
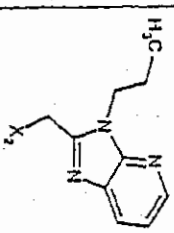
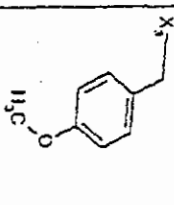
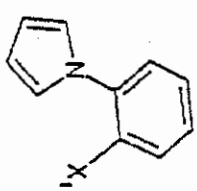
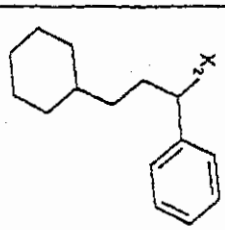
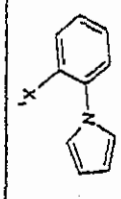
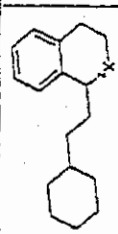
1885					2.37	417.2093	418.2095
1886					2.41	417.2093	418.2095
1887					2.42	431.2249	432.2221
1888					2.48	517.0903	518.1107
1889					2.46	429.2093	430.2187
1890					2.48	429.2093	430.2192
1891					2.41	433.1842	434.2012
1892					2.46	469.1041	470.13

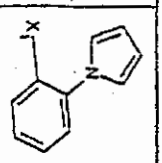
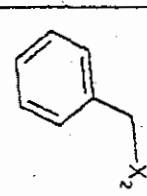
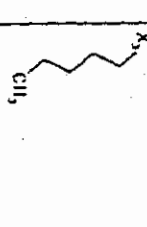
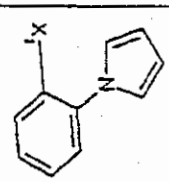
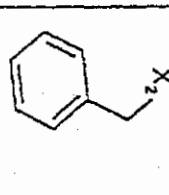
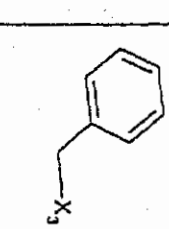
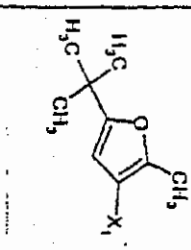
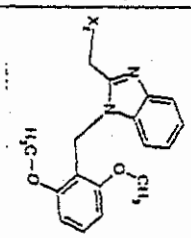
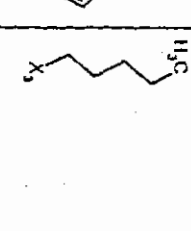
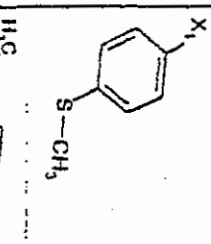
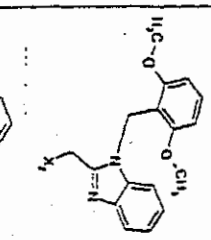
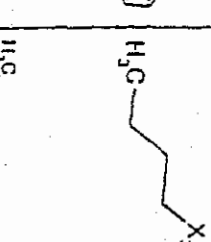
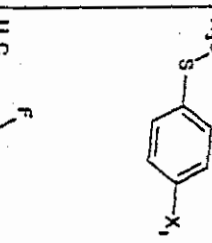
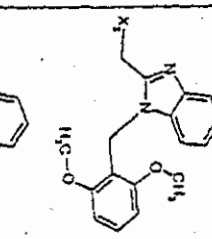
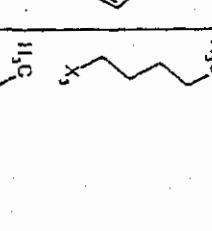
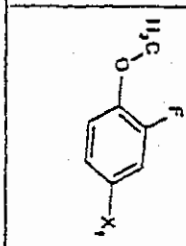
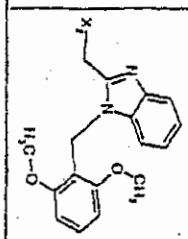
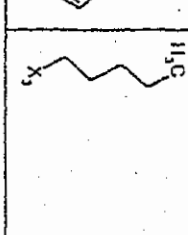
1893					2.21	549.1182	550.13
1894					2.49	393.2126	394.2145
1895					2.39	407.246	408.2388
1896					2.75	477.1837	478.2005
1897							
1898					2.6	525.1529	526.1517
1899					2.47	409.2406	410.246
1900					2.58	437.2719	438.2745

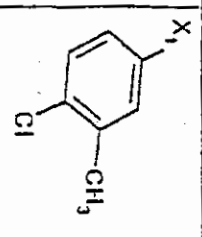
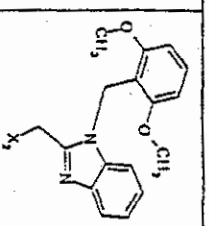
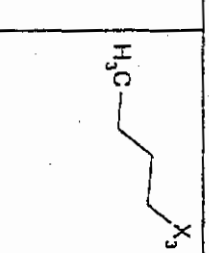
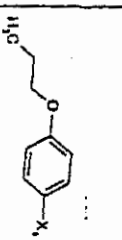
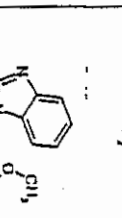
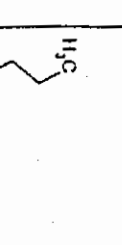
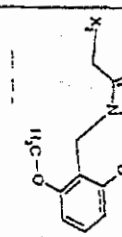
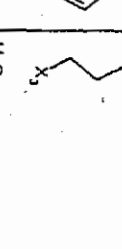
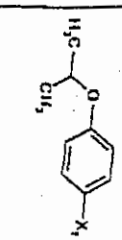
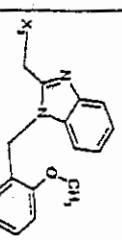
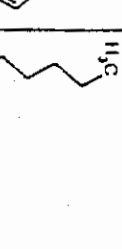
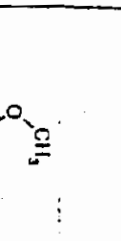
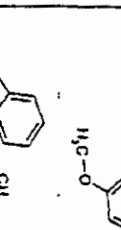
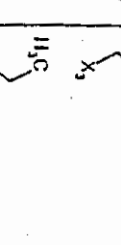
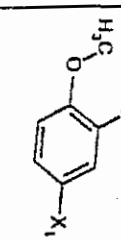
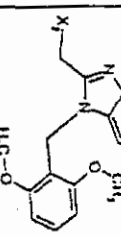
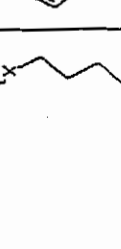
1901				2.38	433.2042	434.2162
1902				2.44	413.2355	414.2371
1903				2.42	413.2355	414.239
1904				2.39	413.2355	414.2406
1905				2.27	401.1991	402.2075
1906				2.28	401.1991	402.2055
1907				2.3	421.1445	422.163
1908				2.28	411.1446	412.1578

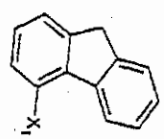
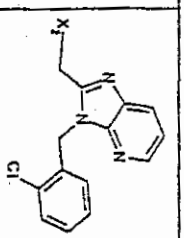
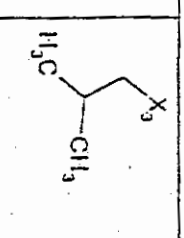
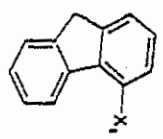
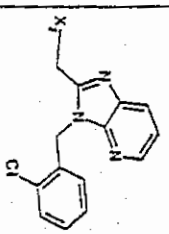
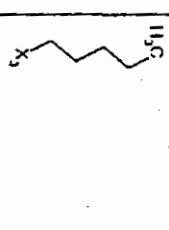
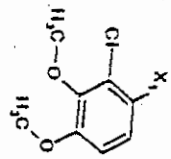
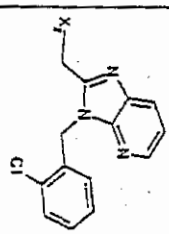
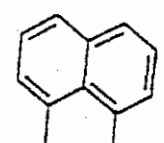
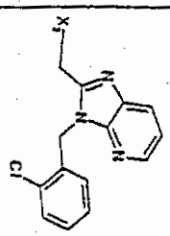
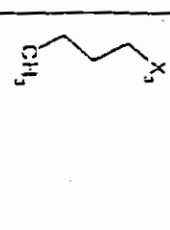
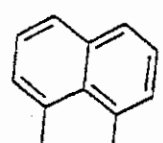
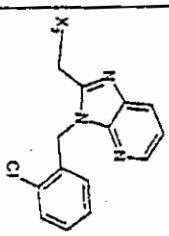
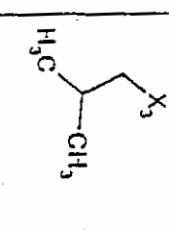
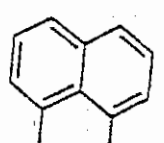
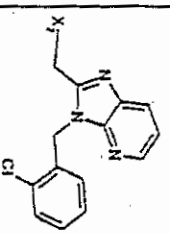
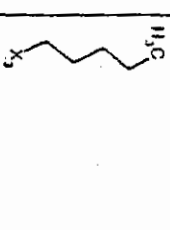
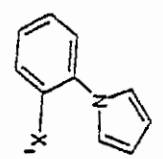
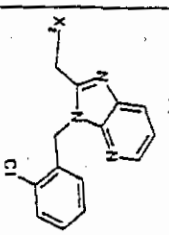
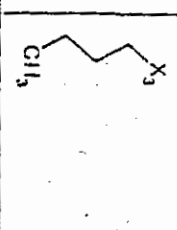
1909				2.47		407.246	408.2634
1910				2.45		407.246	408.2503
1911				2.46		415.2123	416.2284
1912				2.16		508.2281	509.2342
1913				1.99		524.2231	525.2272

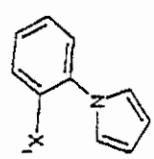
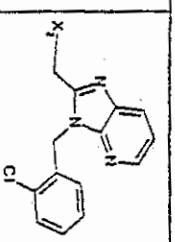
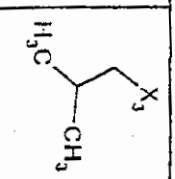
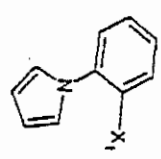
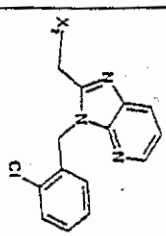
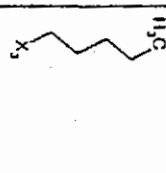
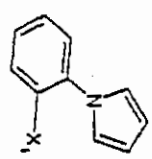
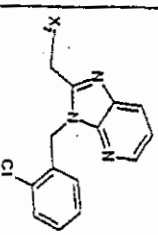
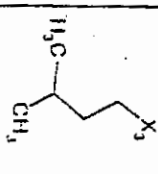
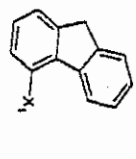
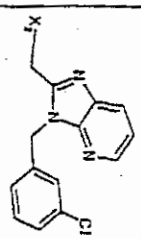
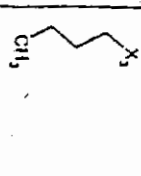
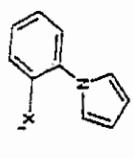
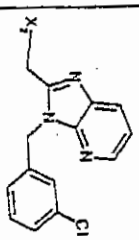
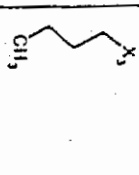
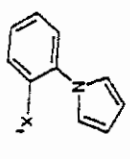
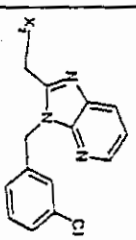
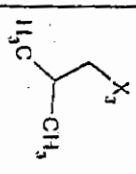
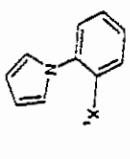
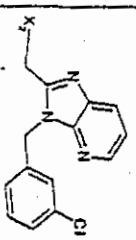
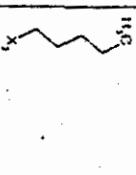
1914					2.19	528.1735	529.1874
1915					2.38	562.1999	563.214
1916							
1917							
1918					2.13	494.2482	495.2661
1919							

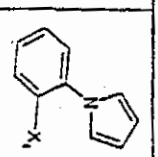
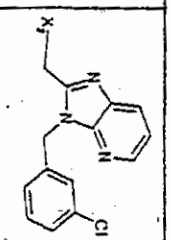
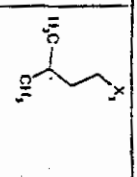
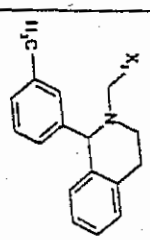
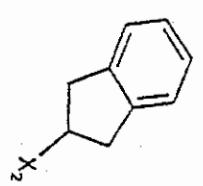
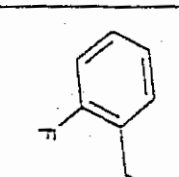
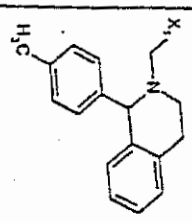
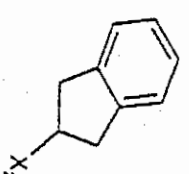
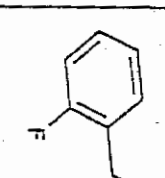
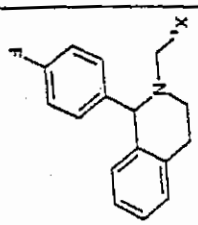
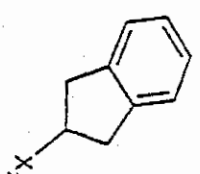
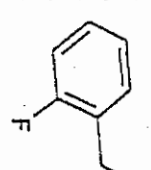
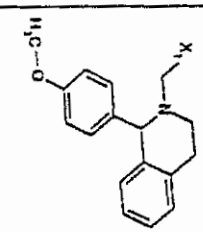
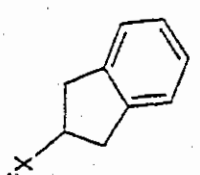
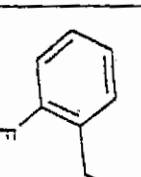
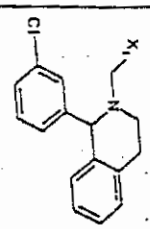
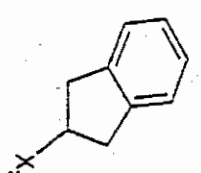
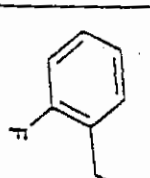
1920					2.13	449.2216	450.2522
1921					2.11	467.2121	468.2447
1922					2.14	467.2121	468.2424
1923					2.11	479.2321	480.2583
1924					2.52	400.2515	401.2748
1925					2.52	412.2515	413.2805

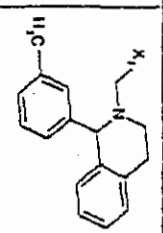
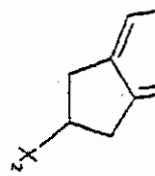
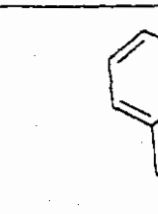
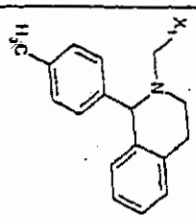
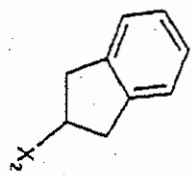
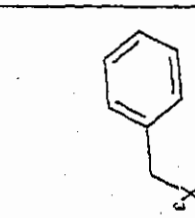
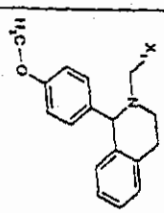
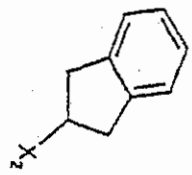
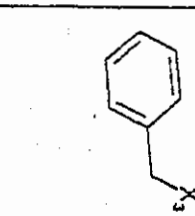
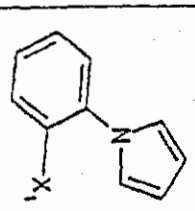
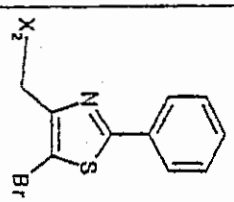
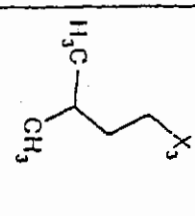
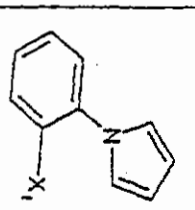
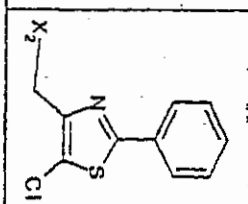
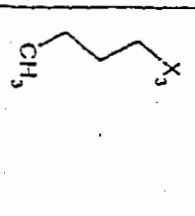
1926				2.28	346.2045	347.2321
1927				2.25	366.1732	367.2062
1928				2.11	531.3097	532.3127
1929				1.96	503.2243	504.2599
1930				2	517.2399	518.2693
1931				1.96	519.2534	520.2534

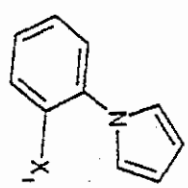
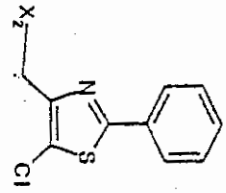
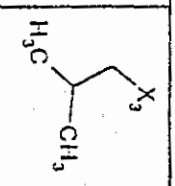
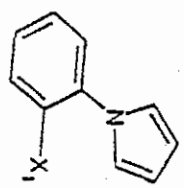
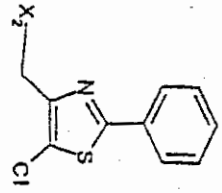
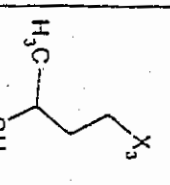
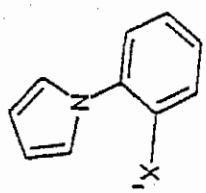
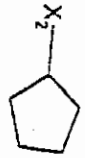
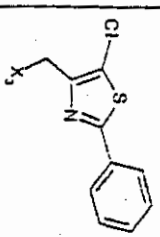
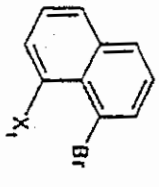
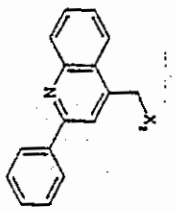
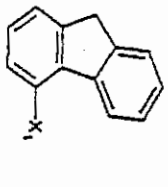
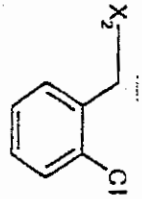
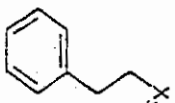
1932				2.02	505.2132	506.2226
1933				2.05	529.2941	530.2949
1934				2.03	529.2941	530.2936
1935				1.92	531.2733	532.2859
1936				1.91	531.2733	532.2828
1937				2.27	520.203	521.2229

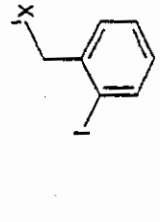
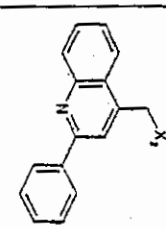
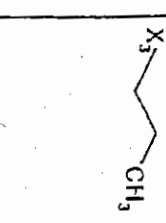
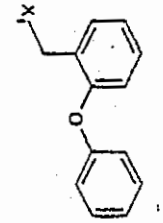
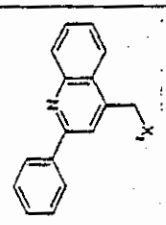
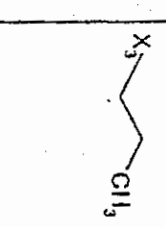
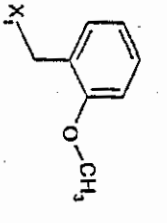
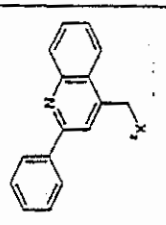
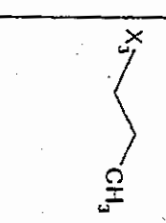
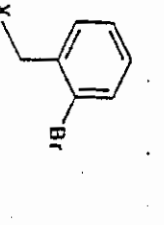
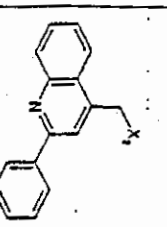
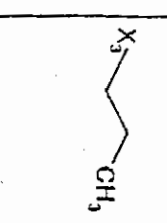
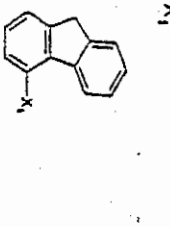
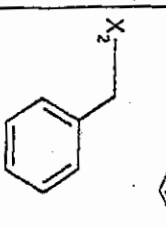
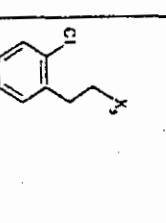
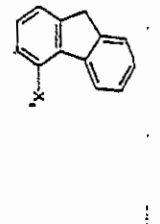
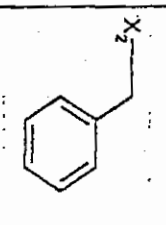
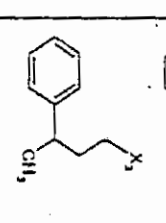
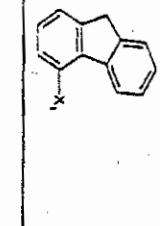
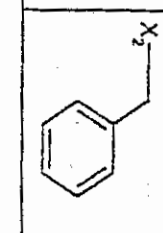
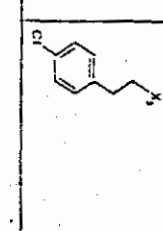
1938				2.25	520.203	521.2301
1939				2.32	534.2186	535.2426
1940				2.19	540.1695	541.1906
1941				2.23	560.0978	561.14
1942				2.23	560.0978	561.14
1943				2.28	574.1135	575.16
1944						

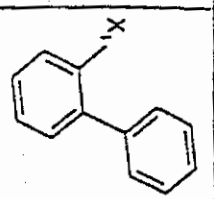
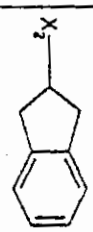
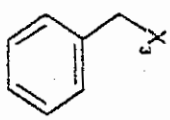
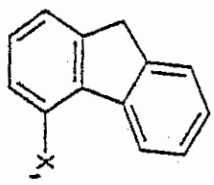
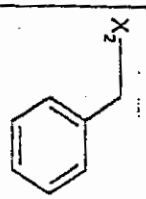
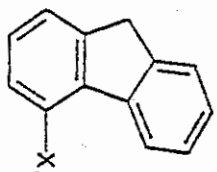
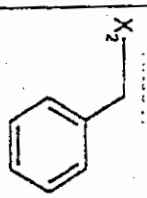
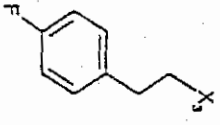
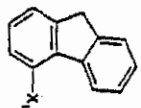
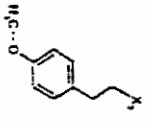
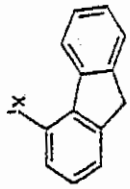
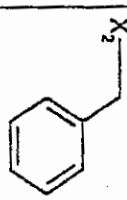
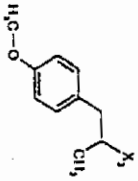
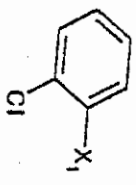
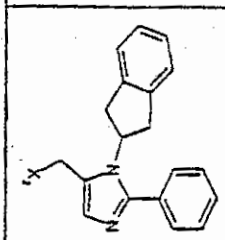
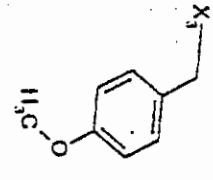
1945				2.19	497.1982	498.2381
1946				2.26	511.2139	512.2437
1947				2.25	511.2139	512.2531
1948				2.3	520.203	521.2333
1949				2.25	497.1982	498.2341
1950				2.25	497.1982	498.2305
1951				2.3	511.2139	512.2459

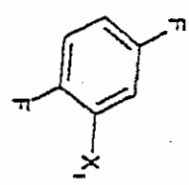
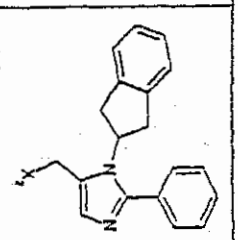
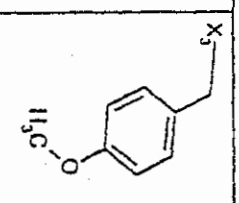
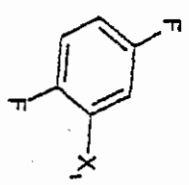
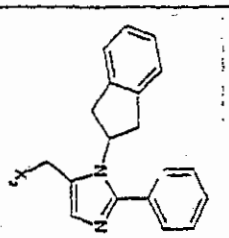
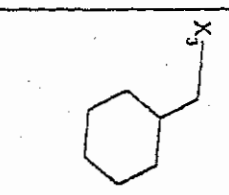
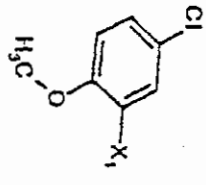
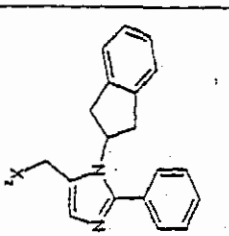
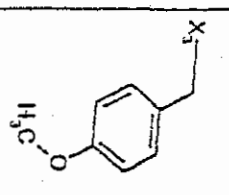
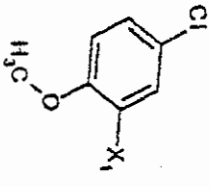
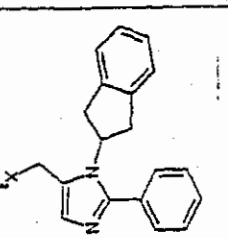
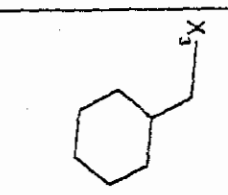
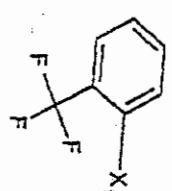
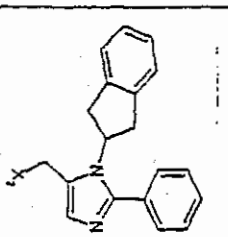
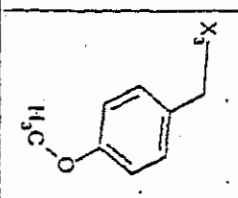
1952				2.3	511.2139	512.2452
1953				2.07	504.2577	505.2828
1954				2.07	504.2577	505.2755
1955				2.05	508.2326	509.2624
1956				2.03	520.2526	521.2831
1957						

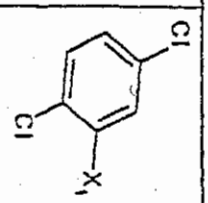
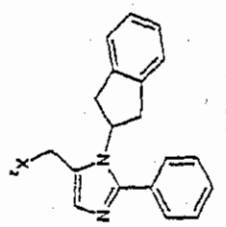
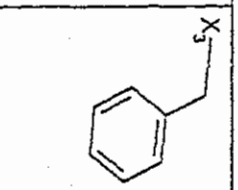
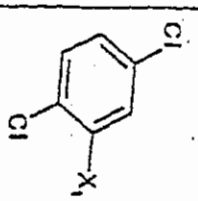
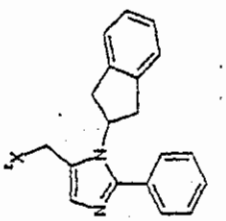
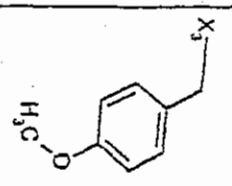
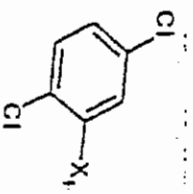
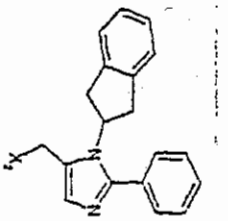
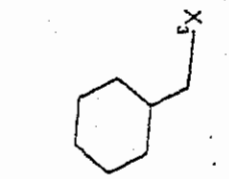
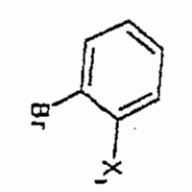
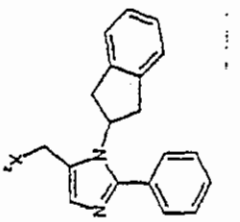
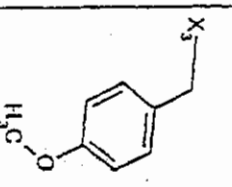
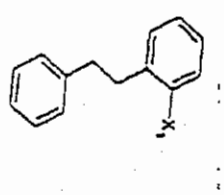
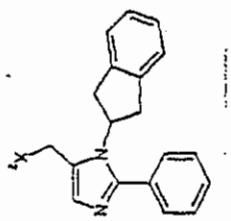
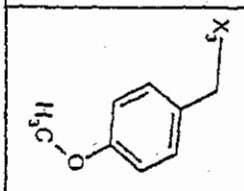
1958				2.05	486.2671	487.2196
1959				2.06	486.2671	487.2379
1960				2.02	502.262	503.2366
1961				2.55	507.098	508.09
1962				2.49	449.1329	450.125

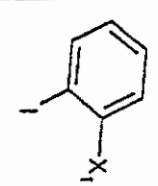
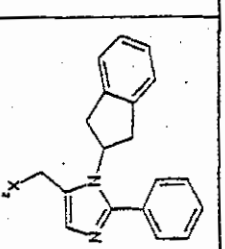
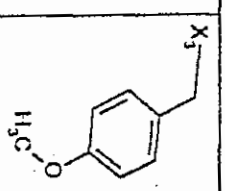
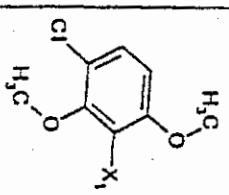
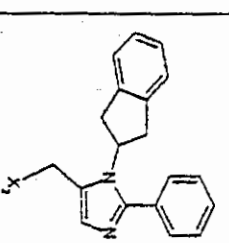
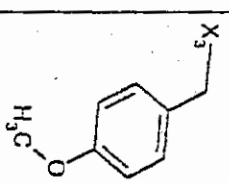
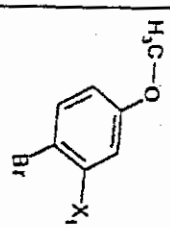
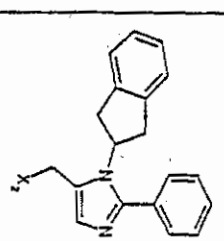
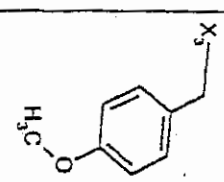
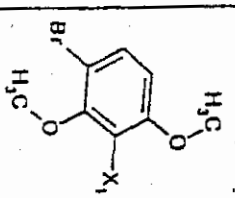
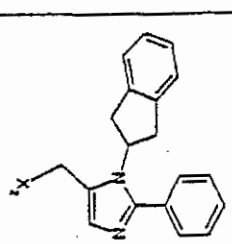
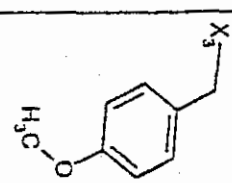
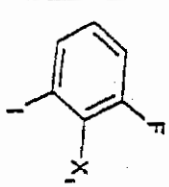
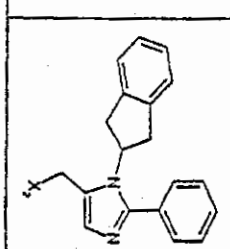
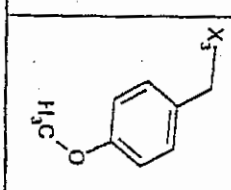
1963				2.49	449.1329	450.1363
1964				2.55	463.1485	464.155
1965				2.5	461.1329	462.152
1966				2.13	508.115	509.1421
1967				2.39	437.1546	438.191

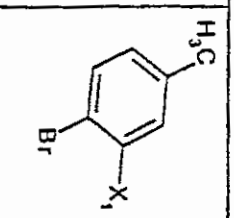
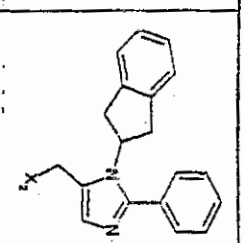
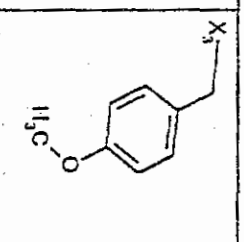
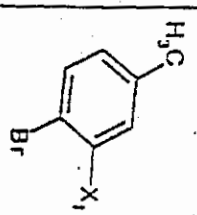
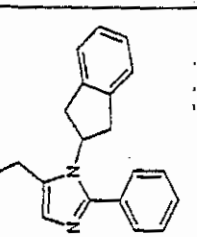
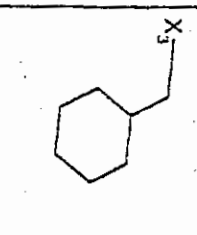
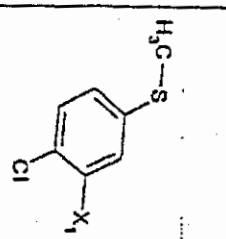
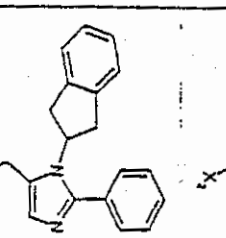
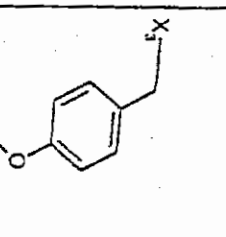
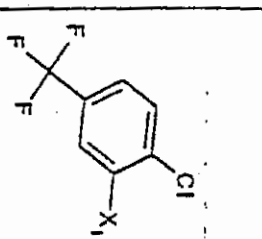
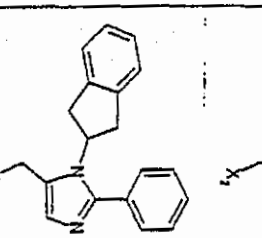
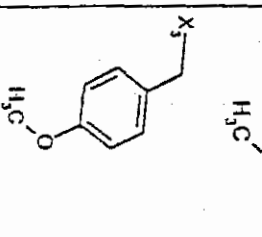
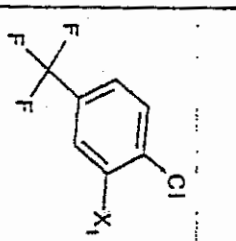
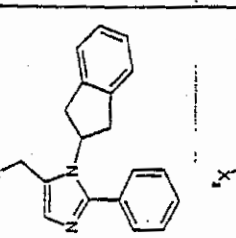
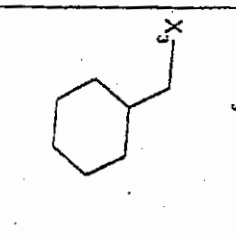
1968				2.1	520.1011	521.1198
1969				2.16	486.2307	487.2447
1970				2.01	424.2151	425.2368
1971				2.08	472.115	473.1456
1972				2.38	437.1546	438.1952
1973				2.37	431.2249	432.2486
1974				2.38	437.1546	438.1897

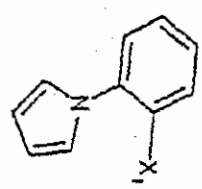
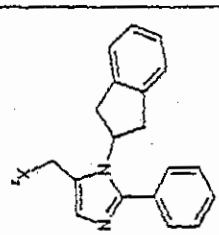
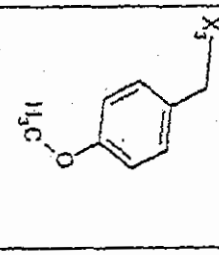
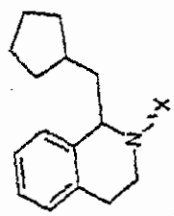
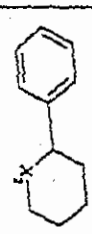
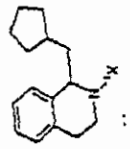
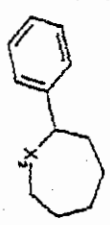
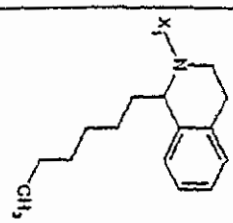
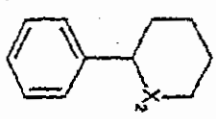
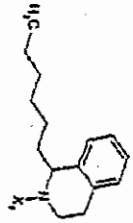
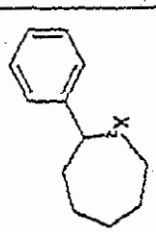
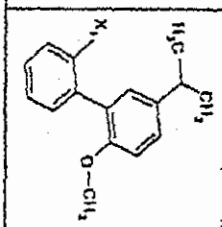
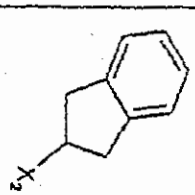
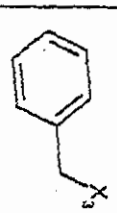
1975				2.33	403.1936	404.224
1976				2.36	415.1936	416.2279
1977				2.3	421.1842	422.218
1978				2.29	433.2042	434.2361
1979				2.32	447.2198	448.251
1980				1.88	547.2026	548.3105

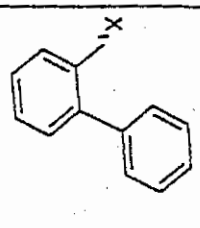
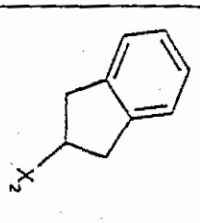
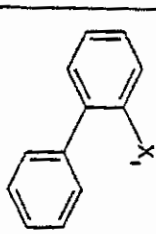
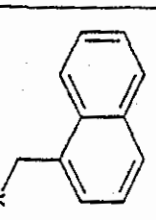
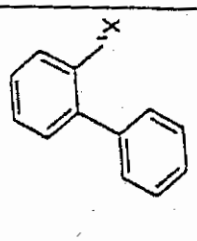
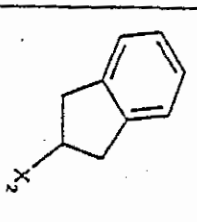
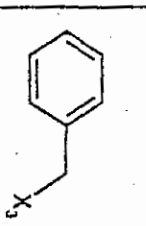
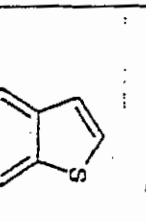
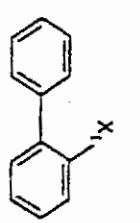
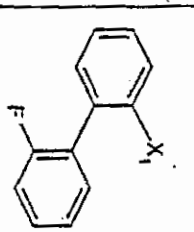
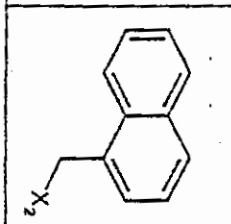
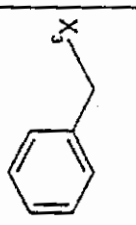
1981				1.9	549.2228	550.3254
1982				1.97	525.2592	526.3528
1983				1.94	577.2132	578.3243
1984				2.01	553.2496	554.3531
1985				1.92	581.229	582.3329

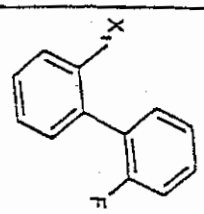
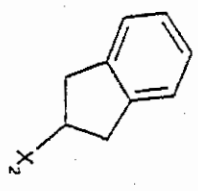
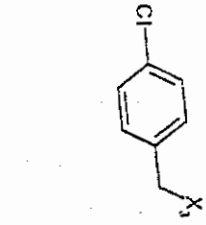
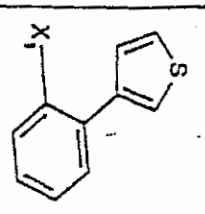
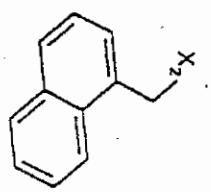
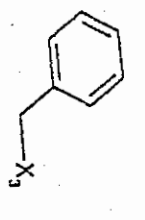
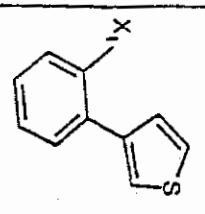
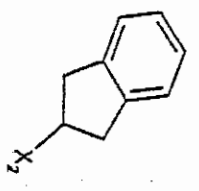
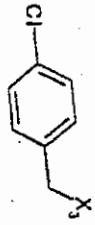
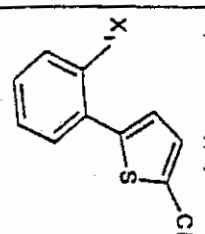
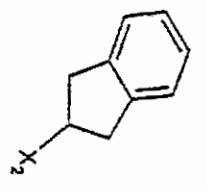
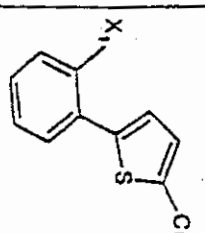
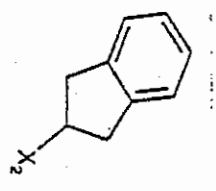
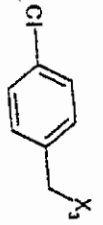
1986				1.95	551.1531	552.2697
1987				1.95	581.1637	582.2848
1988				2.03	557.2001	558.311
1989				1.9	591.1522	592.27
1990				2.02	617.3042	618.4236

1991				1.92	639.1383	640.2621
1992				1.95	607.2238	608.3556
1993				1.92	621.1627	622.29
1994				1.96	651.1733	652.31
1995				1.93	657.1288	658.2678

1996				1.95	605.1678	606.29
1997				2.02	581.2042	582.32
1998				1.96	593.1904	594.3127
1999				1.97	615.1901	616.3185
2000				2.04	591.2264	592.3466

2001				578.2682	579.3848	1.93
2002						
2003						
2004						
2005						
2006				475.2511	476.2856	2.47

2007					2.36	403.1936	404.2317
2008					2.42	427.1936	428.2387
2009					2.43	437.1546	438.2044
2010					2.39	433.15	434.1996
2011					2.39	445.1842	446.226

2012				/	2.41	455.1452	456.196
2013					2.41	433.15	434.1984
2014					2.42	443.1111	444.1632
2015					2.47	443.1111	444.1649
2016					2.53	477.0721	478.137

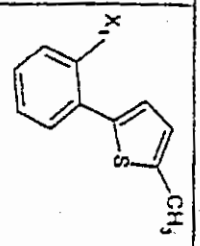
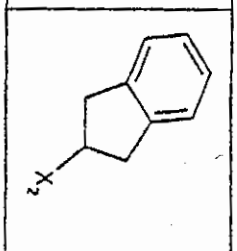
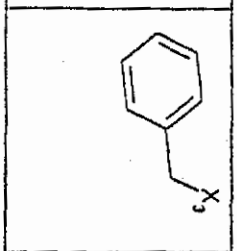
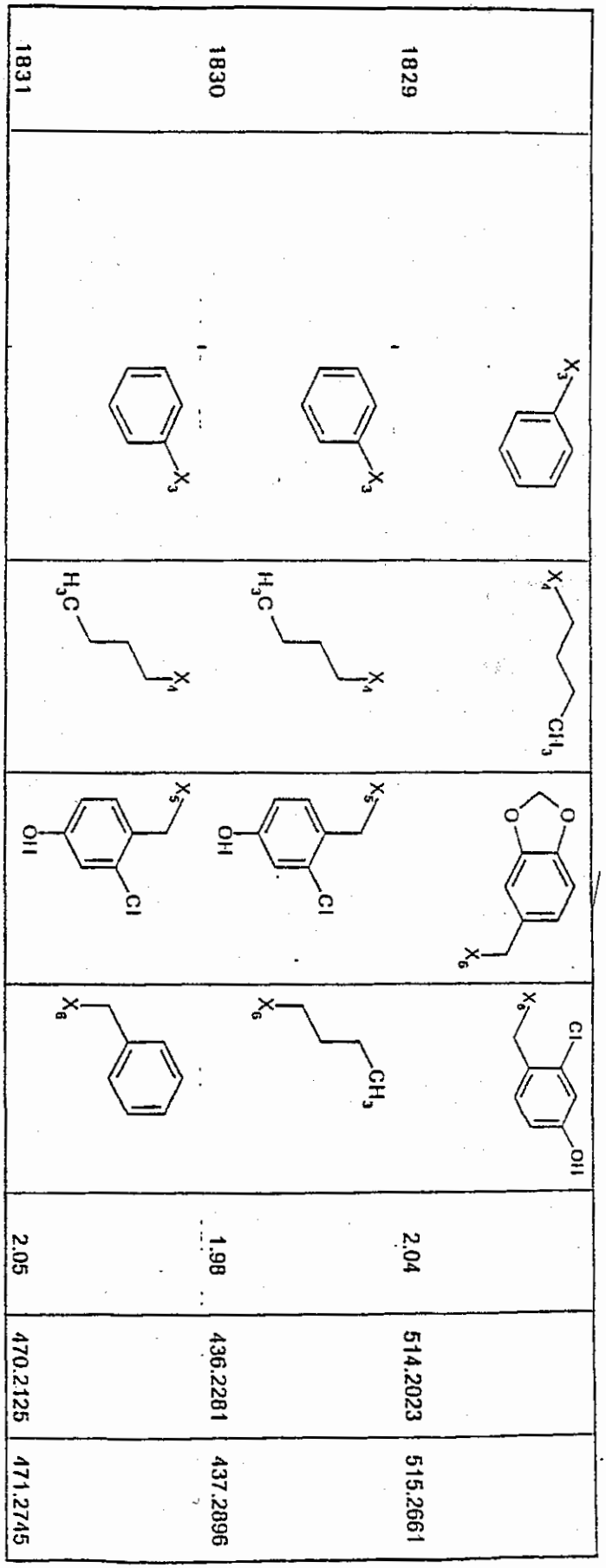
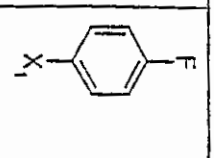
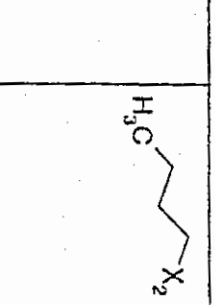
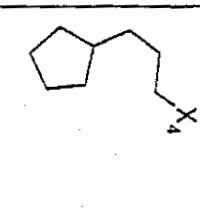
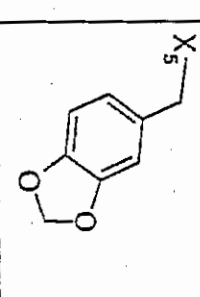
2017				2.41	423.1657	424.2055

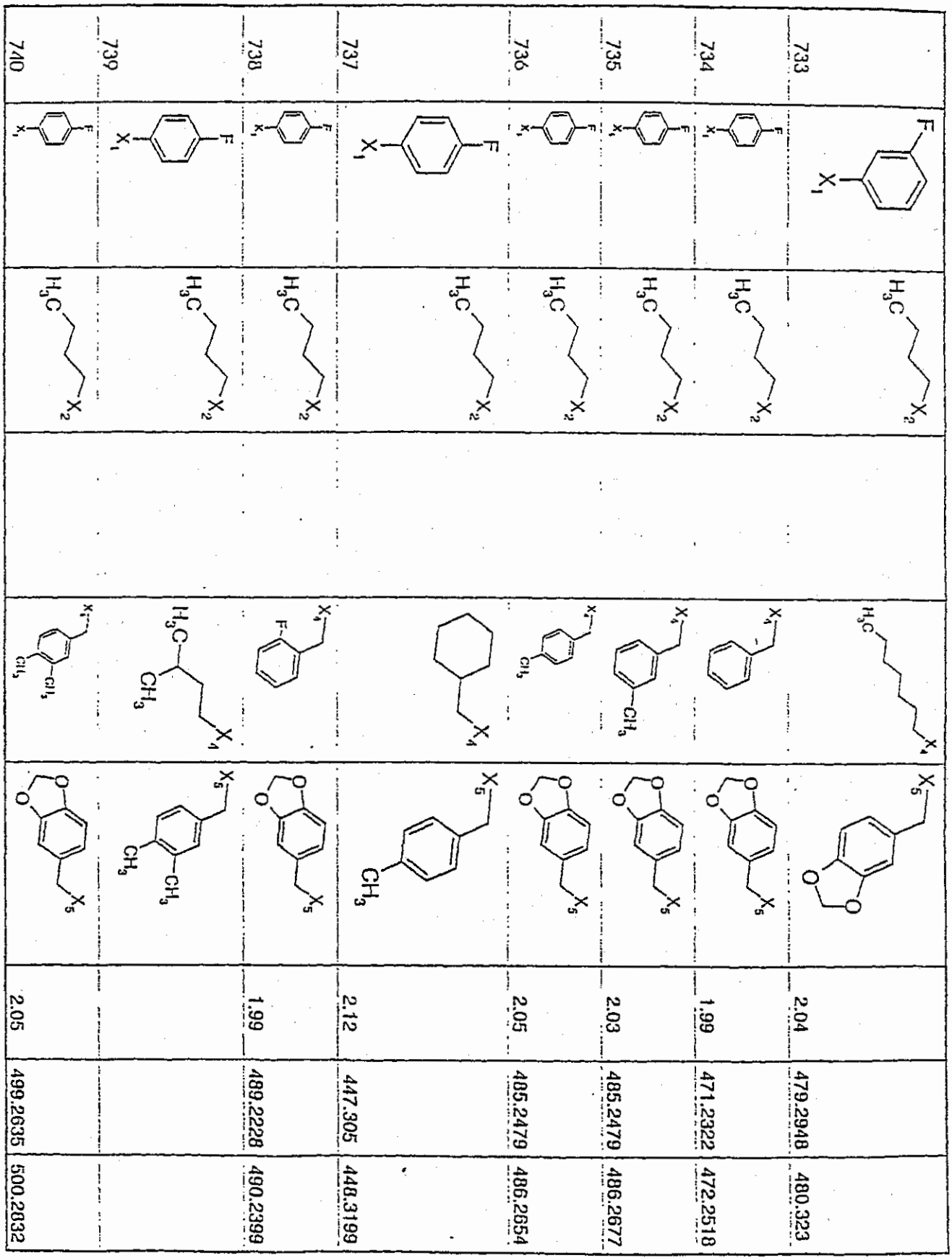
TABLE 6

CMP #	R1 or R1 and R2	R3	R4	R5	R6	Rtn. time	Cmp. Mass	H+ Ion Obs.
1824						1.91	424.2151	425.2364
1825						2.17	558.2518	559.2742
1826						2.2	514.262	515.286
1827						2.09	508.2362	509.2629
1828						2.1	464.2464	465.2729

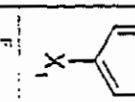
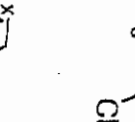
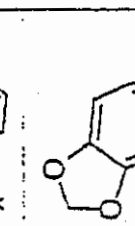
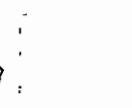
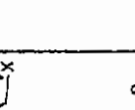


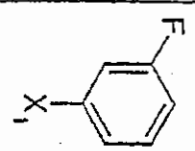
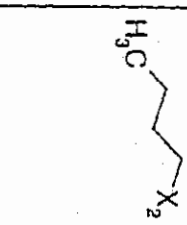
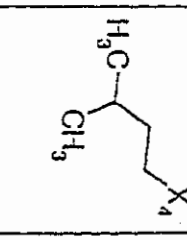
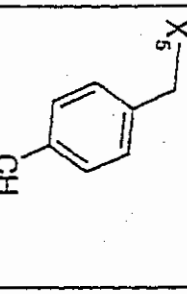
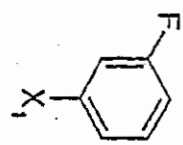
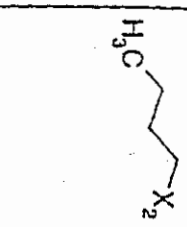
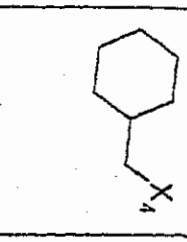
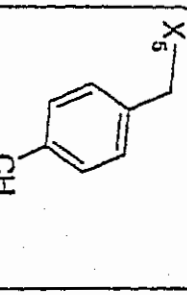
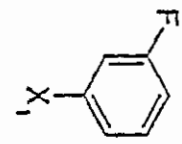
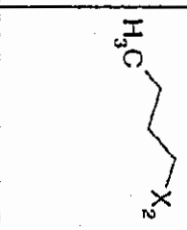
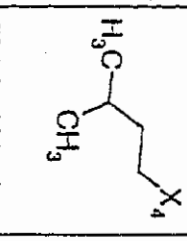
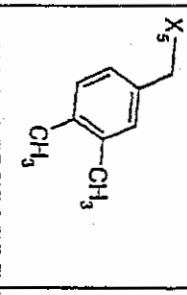
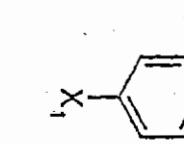
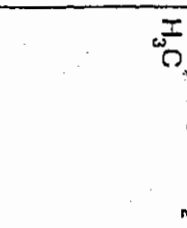
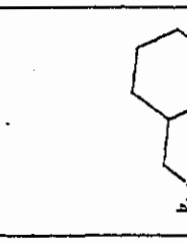
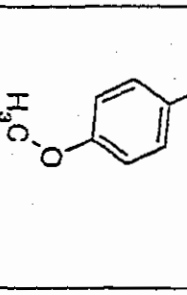
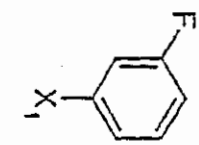
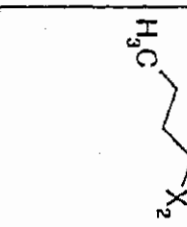
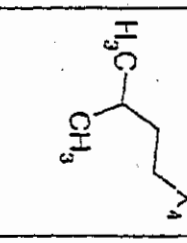
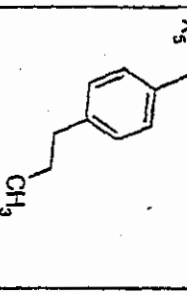
1829					2.04	514.2023	515.2661
1830					1.98	436.2281	437.2896
1831					2.05	470.2125	471.2745

727						2.04	491.2948	492.3288
728						2.08	493.3105	494.3472
729						2.06	465.2791	466.3023
730						2.08	465.2791	466.3028
731						1.99	477.2791	478.3062
732						2.07	477.2791	478.3031

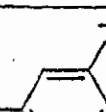
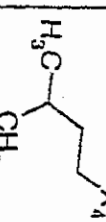
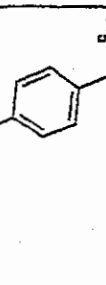


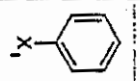
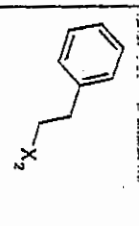
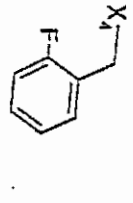
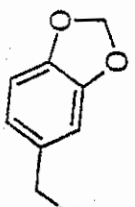
733						2.04	479.2948	480.323	
734						1.99	471.2322	472.2518	
735						2.03	485.2479	486.2677	
736						2.05	485.2479	486.2654	
737						2.12	447.305	448.3199	
738						1.99	489.2228	490.2399	
739						2.05	499.2635	500.2832	
740									

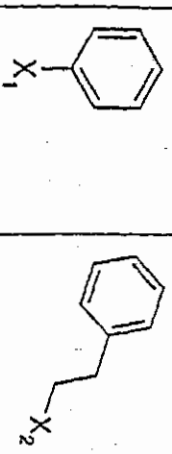
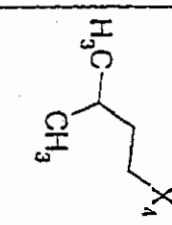
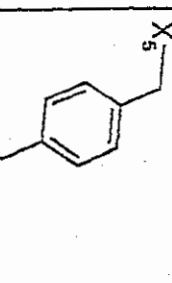
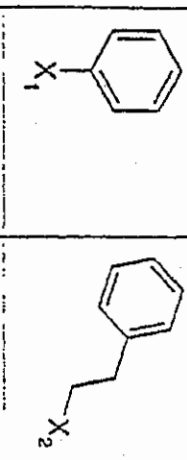
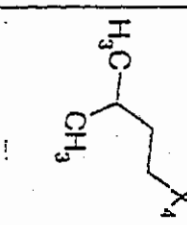
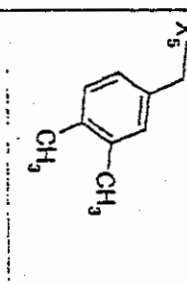
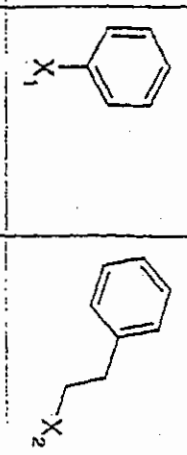
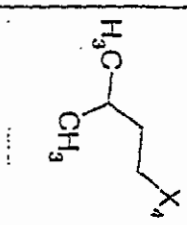
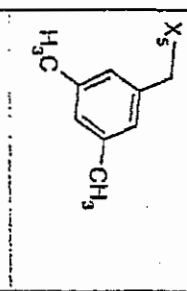
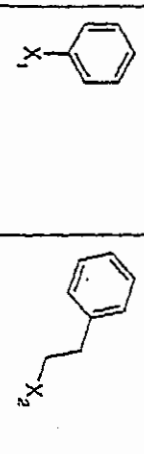
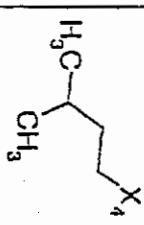
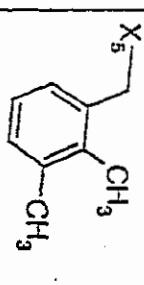
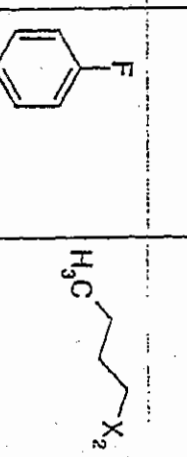
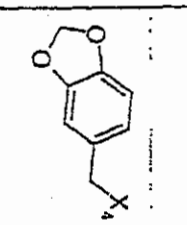
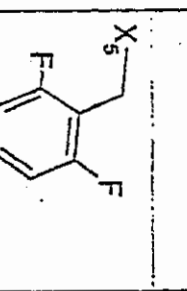
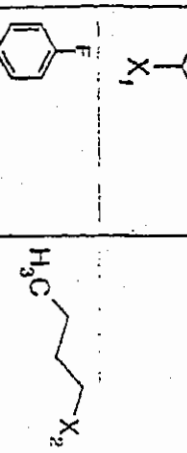
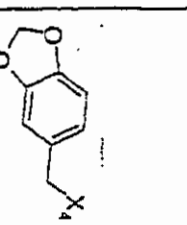
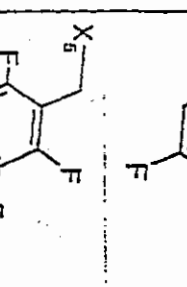
741						2.14	461.3206	462.3372
742						2.04	499.2635	500.2898
743						1.9	451.2635	452.2902
744						1.96	515.222	516.245
745						2.06	477.2791	478.3002
746						2.03	517.2199	518.246
747						2.08	433.2893	434.3055

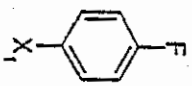
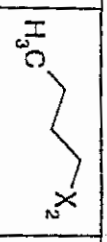
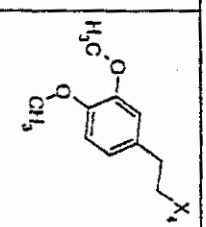
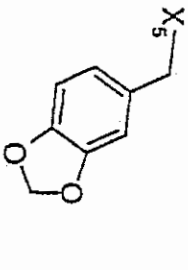
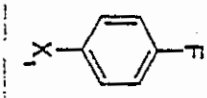
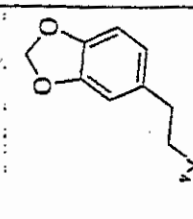
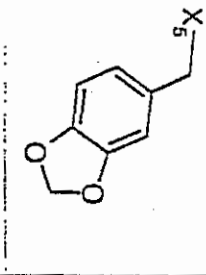
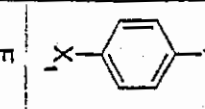
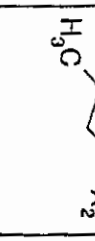
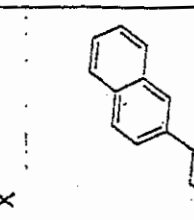
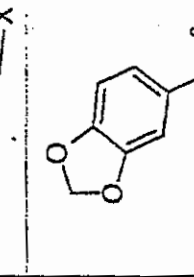
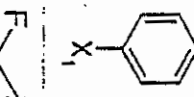
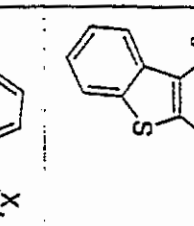
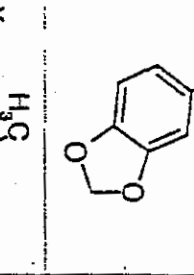
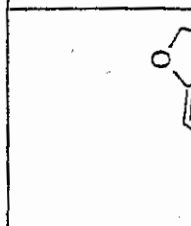
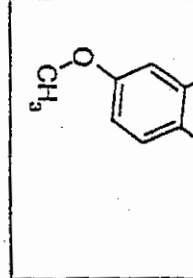
748						1.96	421.2893	422.306
749						2.11	447.305	448.3214
750						1.99	435.305	436.3263
751						2.05	463.2999	464.3266
752						2.05	449.3206	450.3442

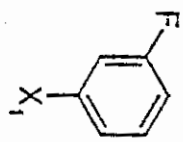
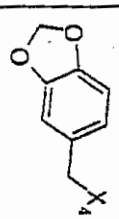
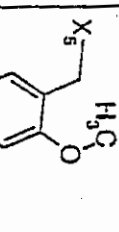
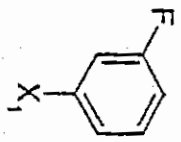
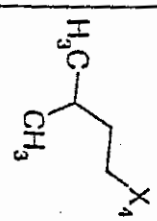
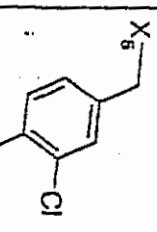
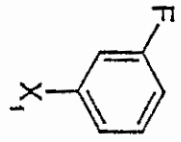
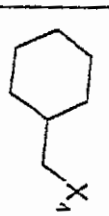
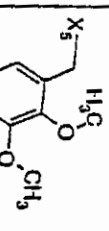
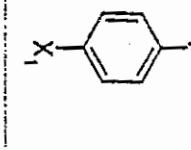
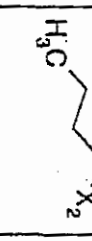
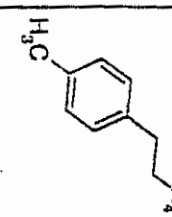
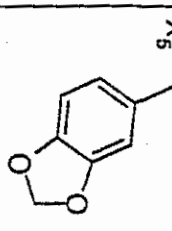
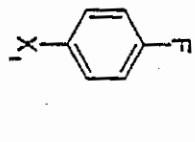
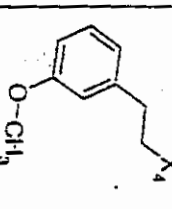
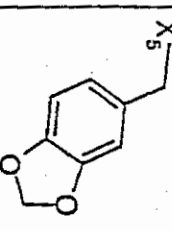
753						2.04	449.3206	450.3435
754						2.18	475.3363	476.3594
755						1.91	451.2635	452.2869
756						1.97	515.222	516.2496
757						2.06	477.2791	478.3031
758						1.99	453.2614	454.2874

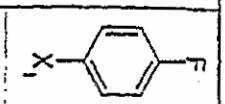
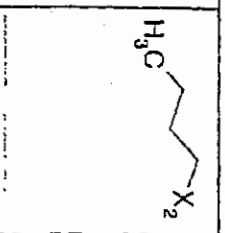
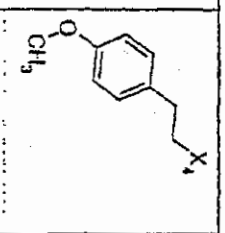
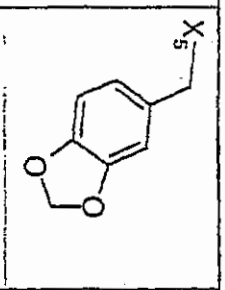
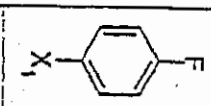
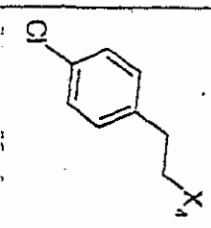
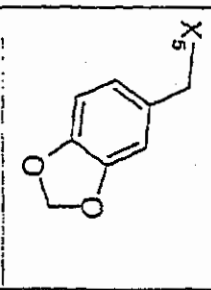
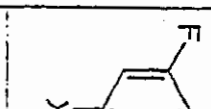
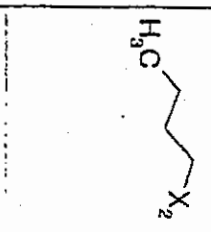
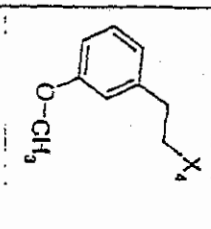
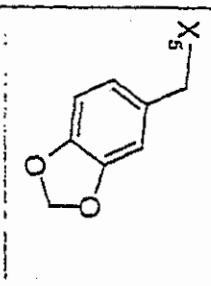
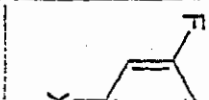
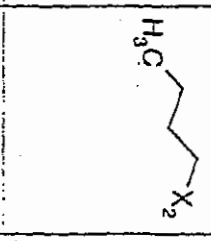
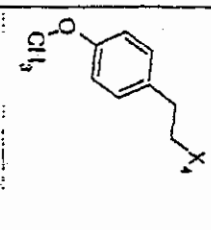
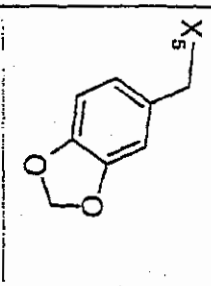
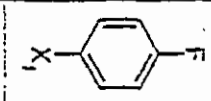
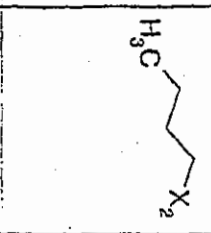
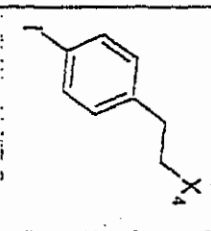
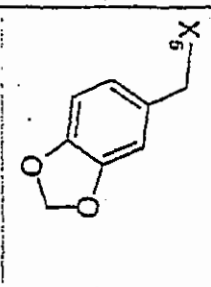
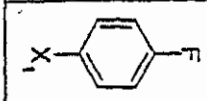
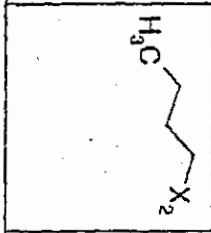
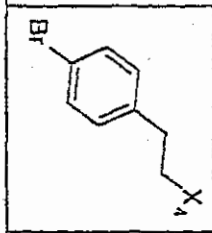
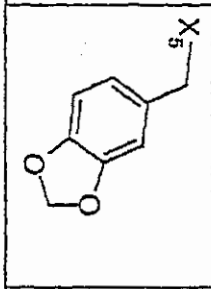
759						2.02	517.2199	518.2543
760						2.1	463.3363	464.3699
761						2.03	467.277	468.306
762						1.98	531.2534	532.2854
763						1.97	531.2534	532.2903
764						1.93	531.2534	532.285

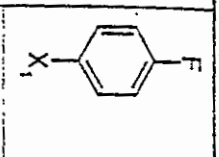
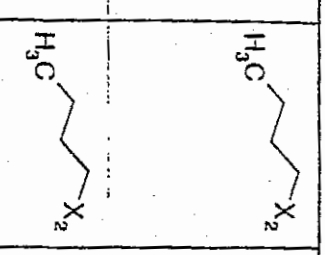
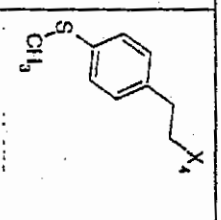
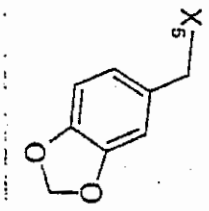
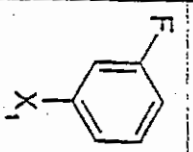
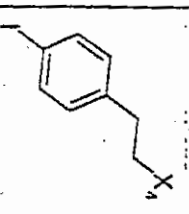
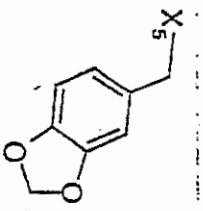
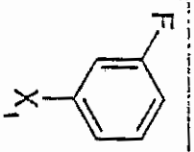
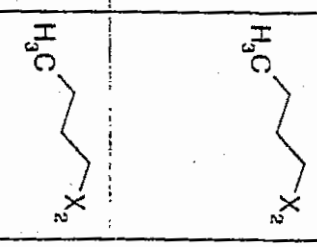
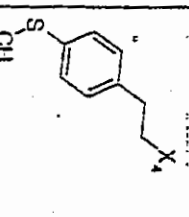
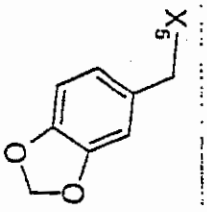
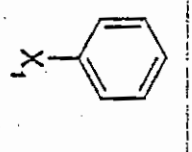
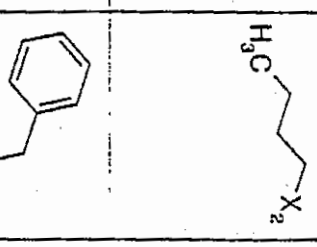
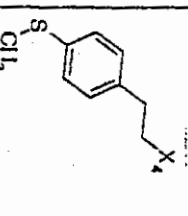
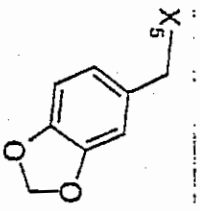
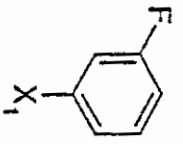
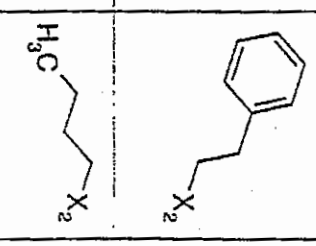
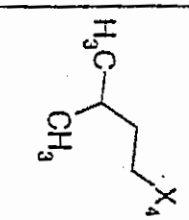
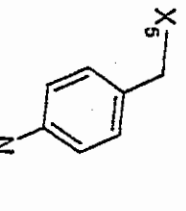
765						2.06	539.1542	540.1926
766						2.04	549.1427	550.1876
767						2.04	549.1427	550.1861
768						2.03	549.1427	550.1867
769						2.13	575.2948	576.329
770								
771								

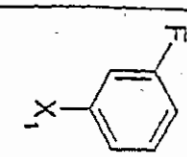
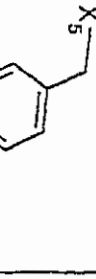
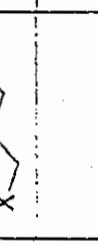
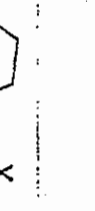
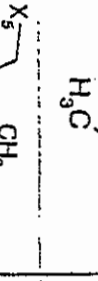
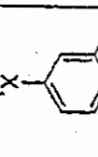
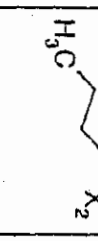
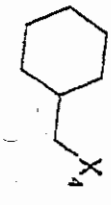
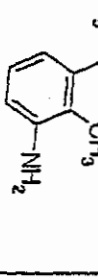
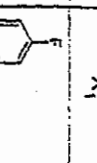
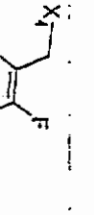
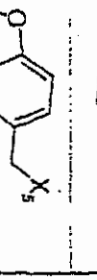
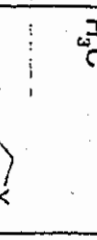
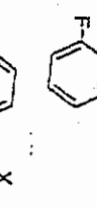
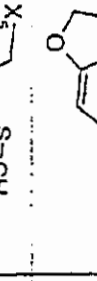
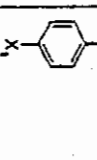
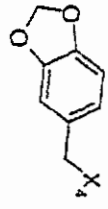
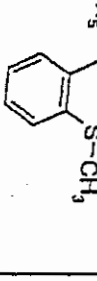
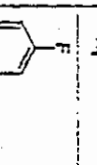
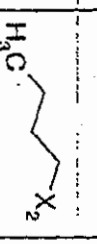
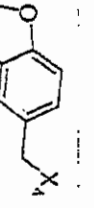
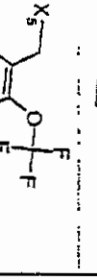
772								
773						2.02	465.3144	466.3379
774						2.01	465.3144	466.3359
775						2.06	465.3144	466.3358
776						1.99	525.2039	526.2423
777						1.99	525.2039	526.2429

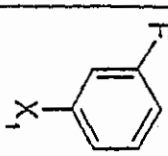
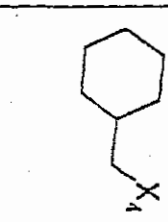
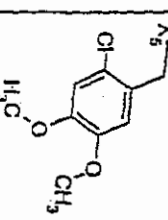
778						1.93	545.269	546.3107
779								536.3018
780						2.07	535.2635	536.3018
781						2.09	555.2356	556.2706
782						1.97	531.2534	532.2892

783						1.94	531.2534	532.2867
784						2	471.2453	472.2802
785						2	523.321	524.354
786						2.03	499.2635	500.2993
787						1.98	515.2584	516.2964

788						1.98	515.2584	516.2967
789						2.03	519.2089	520.2536
790						1.99	515.2584	516.2904
791						1.98	515.2584	516.3315
792						2.06	611.1445	612.2336
793						2.05	563.1584	564.26

794						2.03	531.2356	532.3217
795						2.06	611.1445	612.2438
796						2.02	531.2356	532.3212
797						2.03	561.245	562.3386
798						1.74	436.3002	437.386

799							1.88	462.3159	463.4108
800							1.87	462.3159	463.4136
801							1.97	507.2133	508.3045
802							2.01	517.2199	518.3113
803							2.02	555.2145	556.3143
804							2.02	667.2281	668.3466
805							2.06	563.1584	564.27

806						2.06	551.181	552.2875
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808						2.09	559.2635	560.3663
809						2.03	473.2301	474.313
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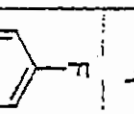
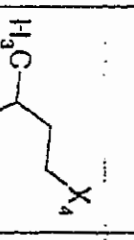
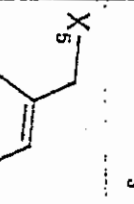
812						2.09	527.2715	528.3815

813						2.05	521.2479	522.3471
814								
815						2.09	455.2504	456.3523
816						2.07	519.2089	520.3145
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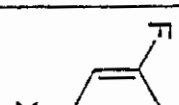
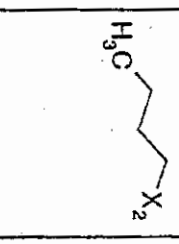
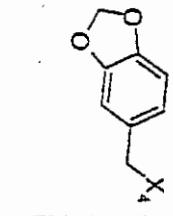
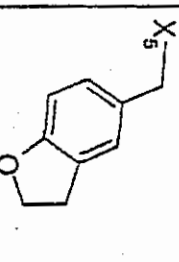
819						2.04	475.2999	476.4023
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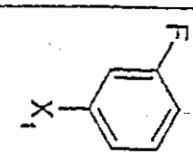
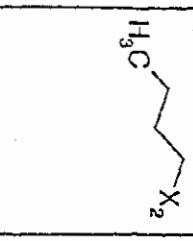
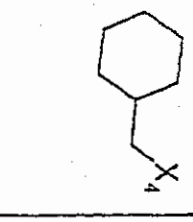
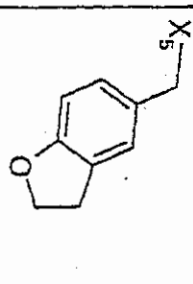
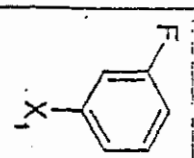
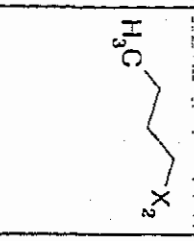
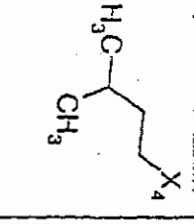
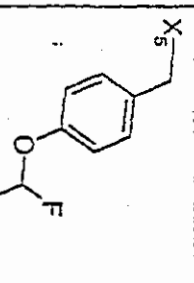
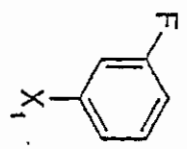
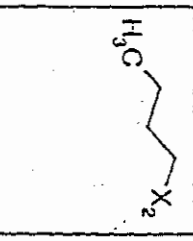
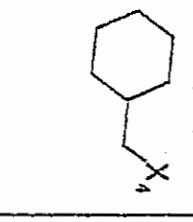
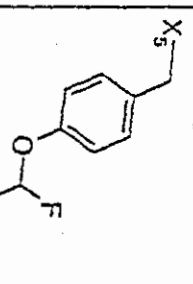
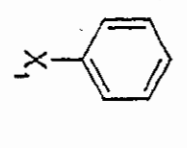
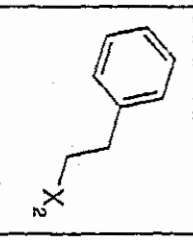
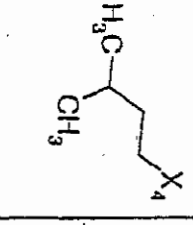
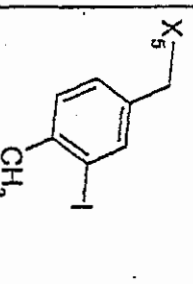
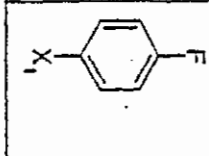
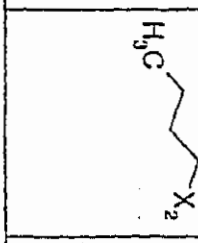
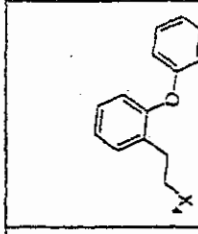
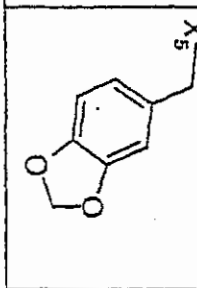
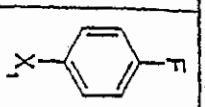
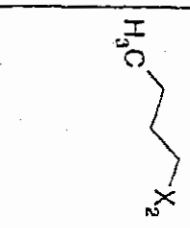
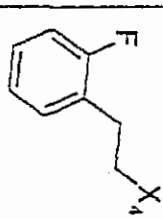
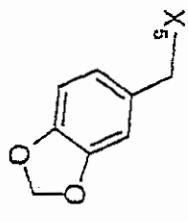
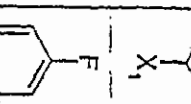
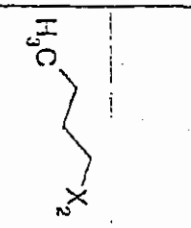
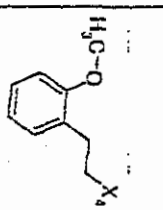
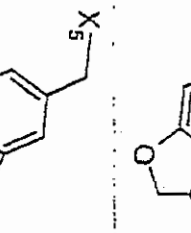
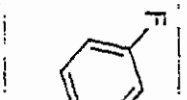
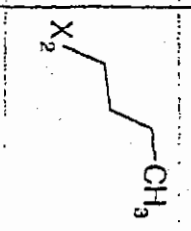
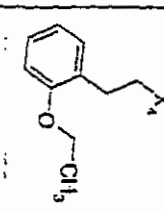
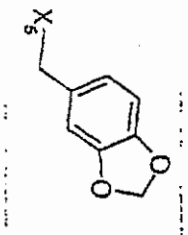
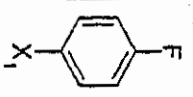
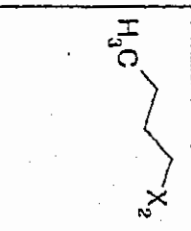
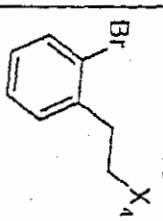
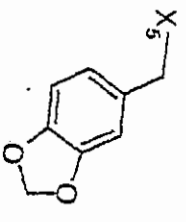
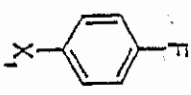
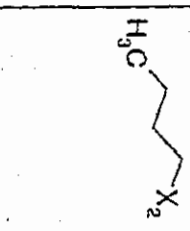
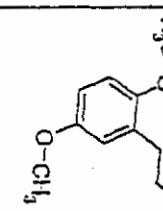
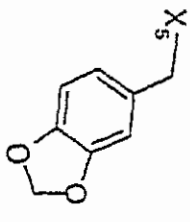
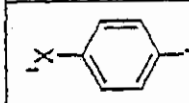
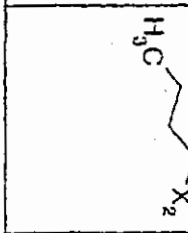
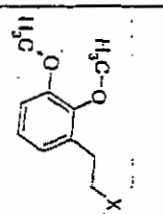
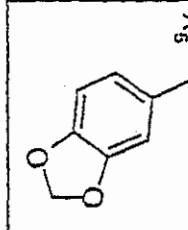
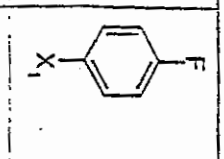
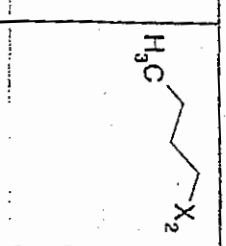
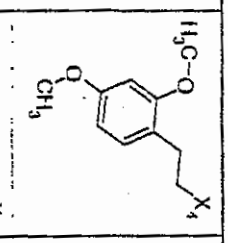
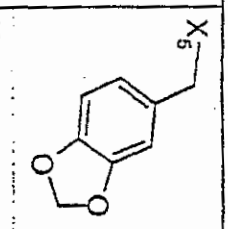
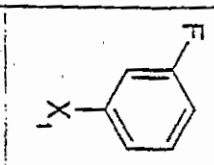
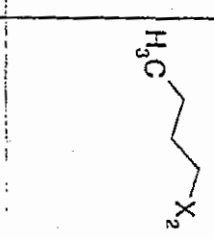
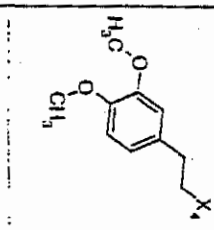
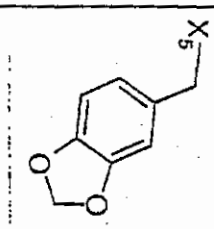
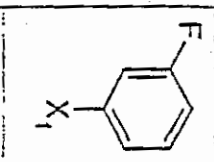
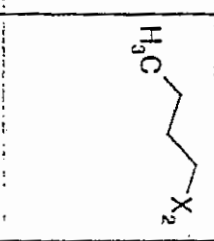
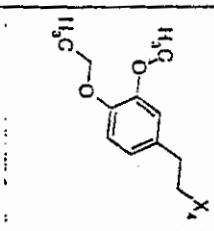
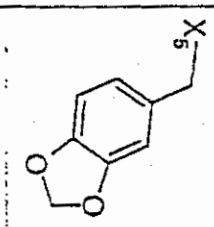
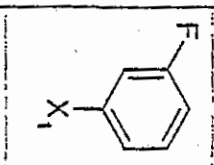
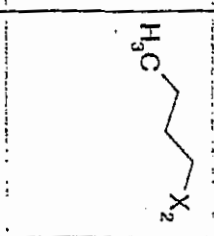
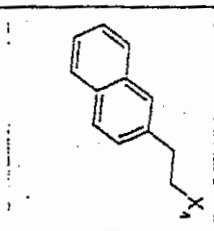
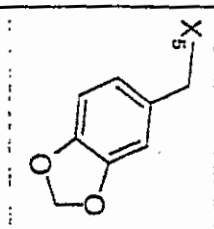
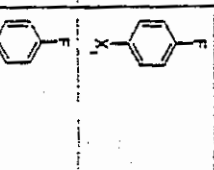
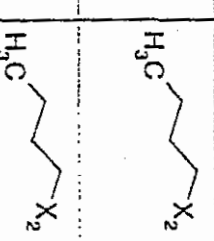
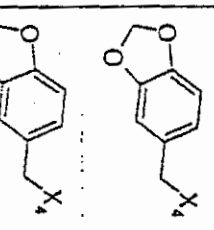
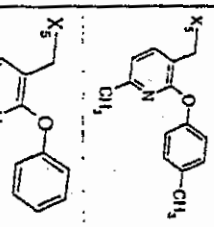
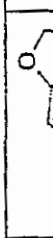
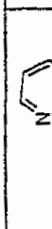
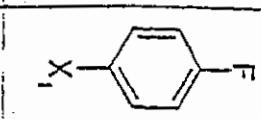
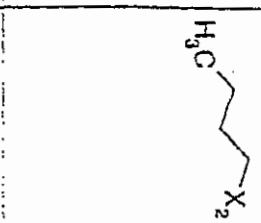
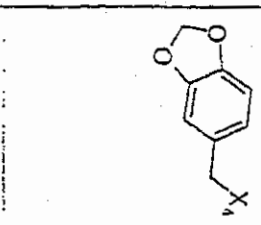
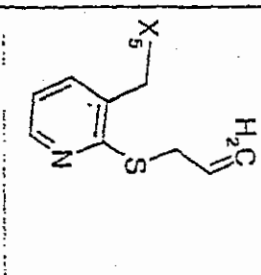
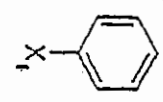
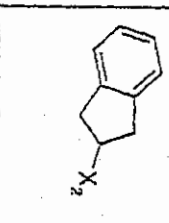
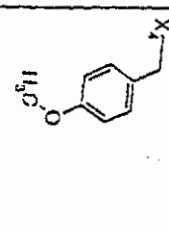
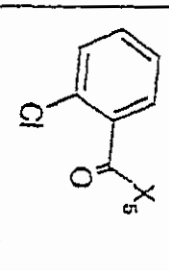
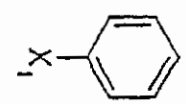
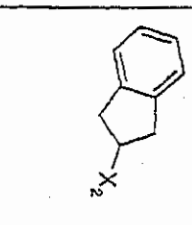
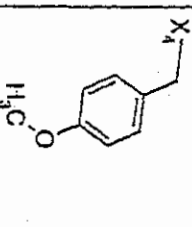
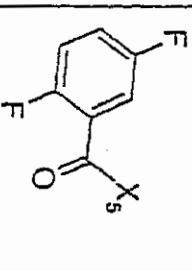
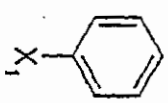
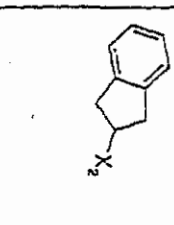
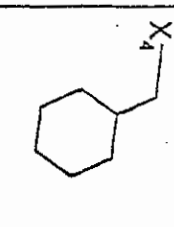
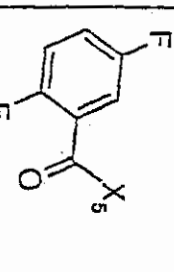
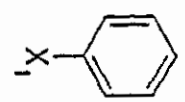
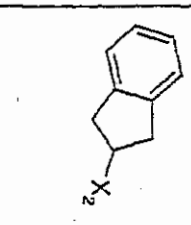
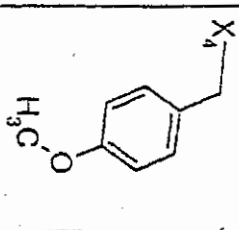
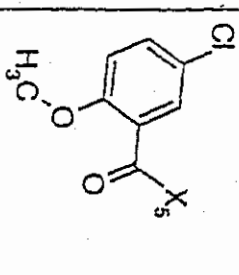
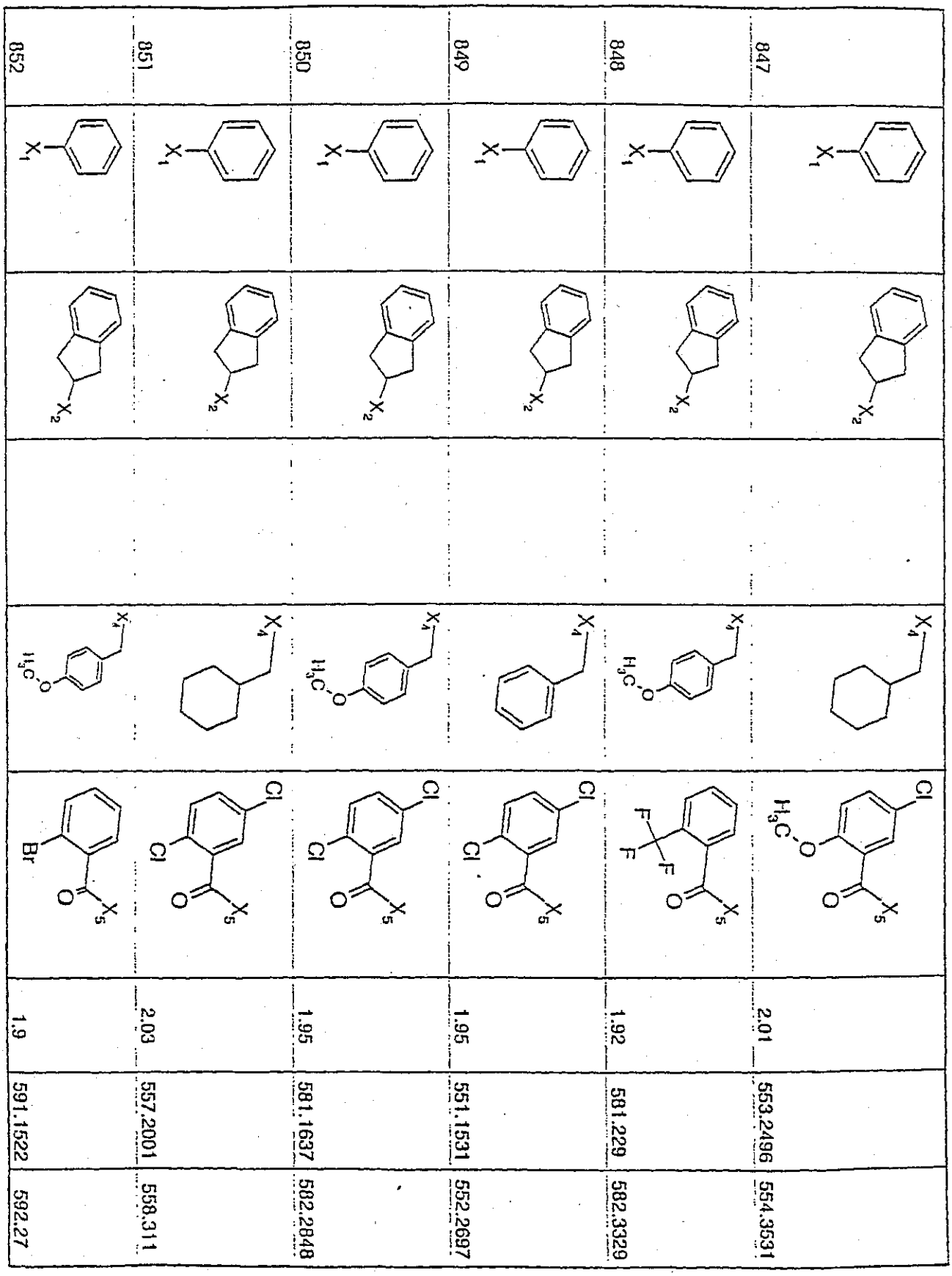
824								

825						2.04	475.2999	476.3996
826						1.97	473.2654	474.3578
827						2.08	499.281	500.3929
828								
829						2.08	577.274	578.3961

830						2	503.2384	504.3399
831						1.99	515.2584	516.3593
832						2.03	529.274	530.3805
833						2.03	563.1584	564.2842
834						1.98	545.269	546.3808
835						1.97	545.269	546.374

836						1.98	545.269	546.3859
837						1.92	545.269	546.3798
838						1.96	559.2846	560.3983
839						2.05	535.2635	536.3757
840						2.04	592.285	593.4103
841								

842						2.01	544.2308	545.3511
843						1.88	547.2026	548.3105
844						1.9	549.2228	550.3254
845						1.97	525.2592	526.3528
846						1.94	577.2132	578.3243



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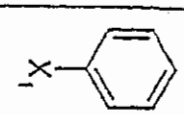
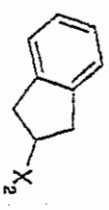
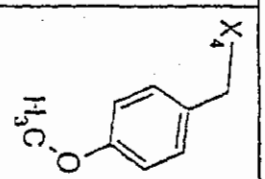
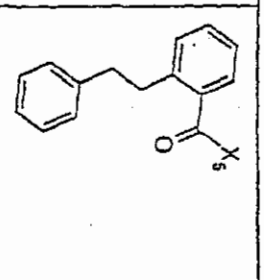
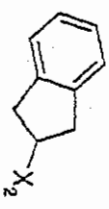
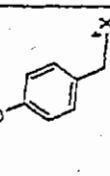
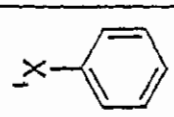
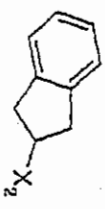
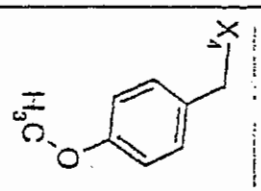
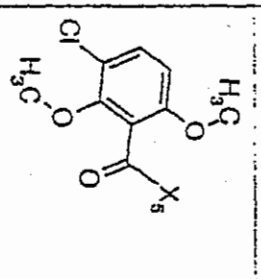
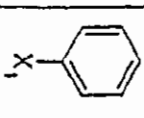
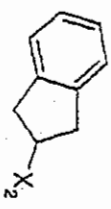
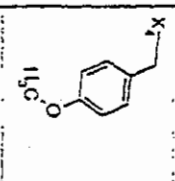
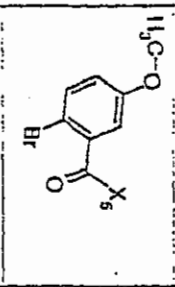
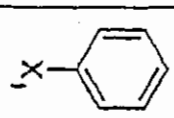
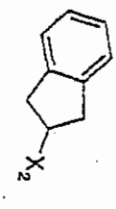
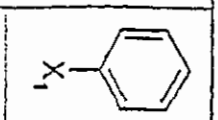
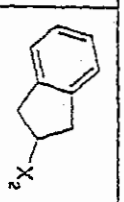
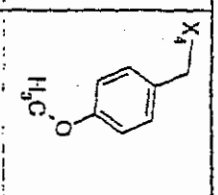
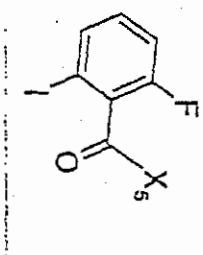
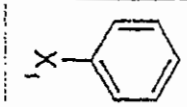
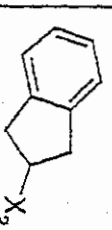
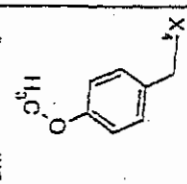
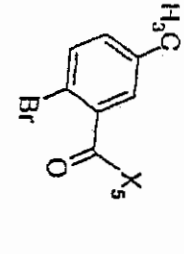
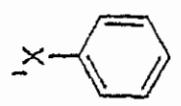
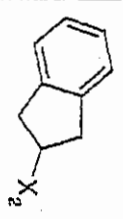
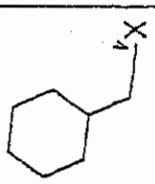
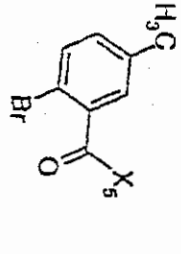
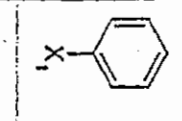
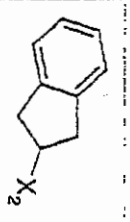
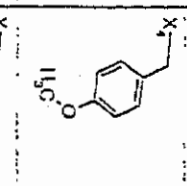
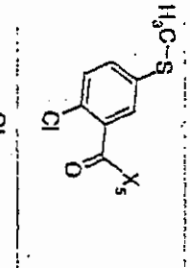
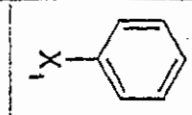
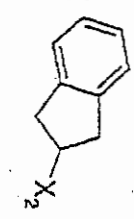
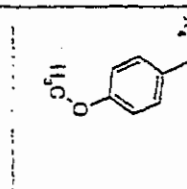
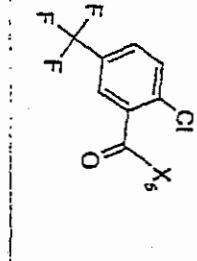
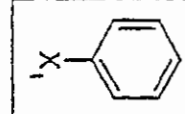
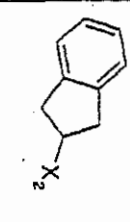
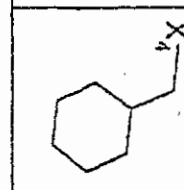
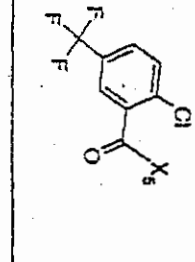
848					1.92	581.229	582.3329	
849					1.95	551.1531	552.2697	
850					1.95	581.1637	582.2848	
851					2.03	557.2001	558.311	
852					1.9	591.1522	592.27	

853						2.02	617.3042	618.4236
854						1.92	639.1383	640.2621
855						1.95	607.2238	608.3556
856						1.92	621.1627	622.29
857						1.96	651.1733	652.31

858						1.93	657.1288	658.2678
859						1.95	605.1678	606.29
860						2.02	581.2042	582.32
861						1.96	593.1904	594.3127
862						1.97	615.1901	616.3185
863						2.04	591.2264	592.3466

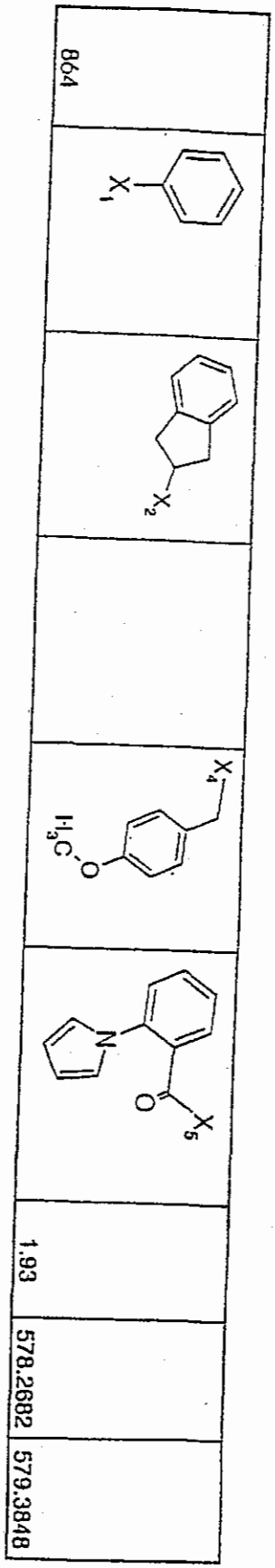
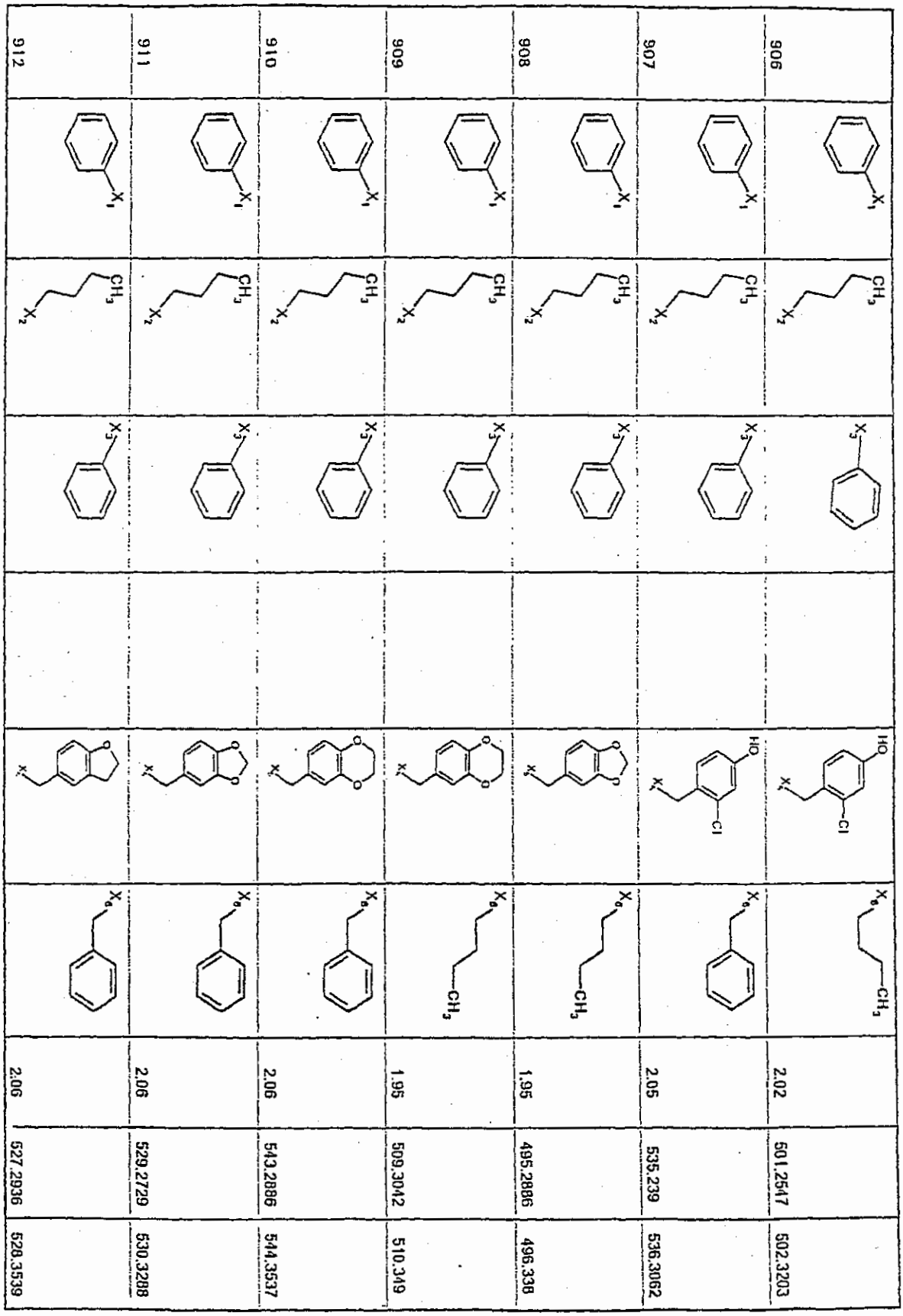
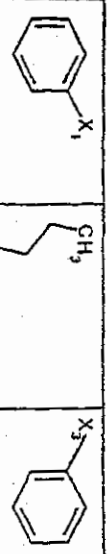
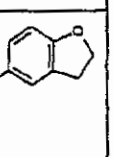
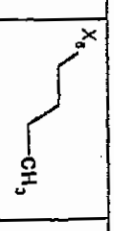
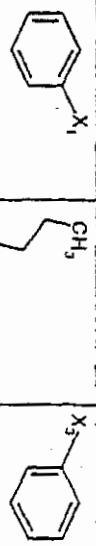
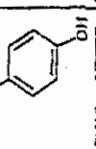
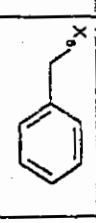
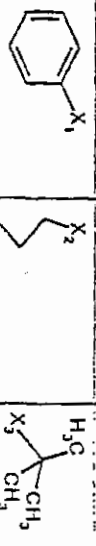
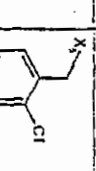
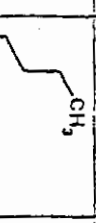
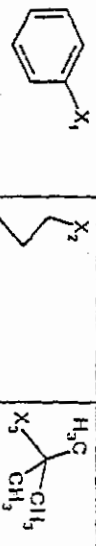
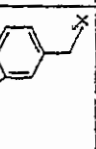
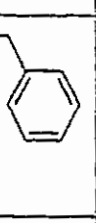
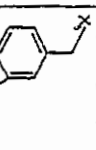
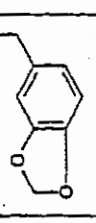
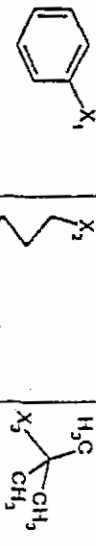
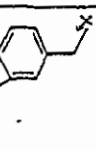
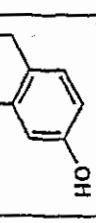
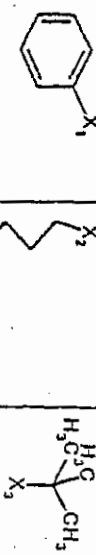
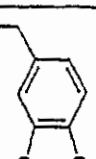
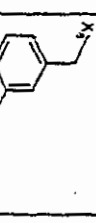
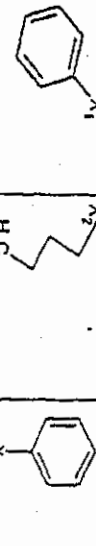
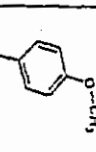
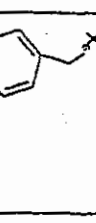

864
1.93
578.2682
579.3848

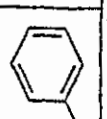
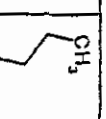
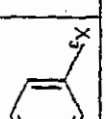
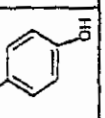
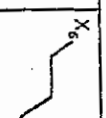
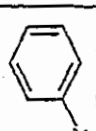
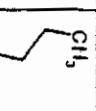
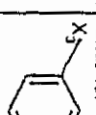
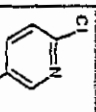
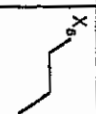
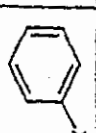
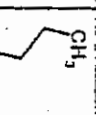
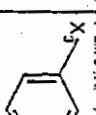
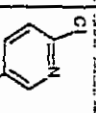
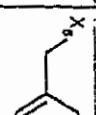
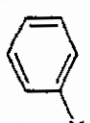
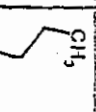
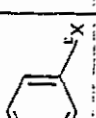
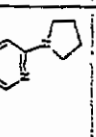
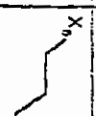
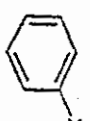
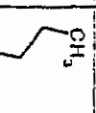
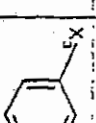
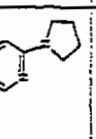
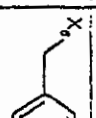
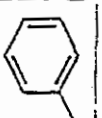
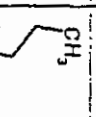
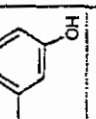
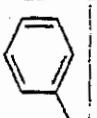
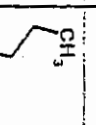
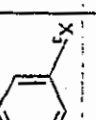
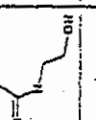
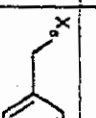
TABLE 2

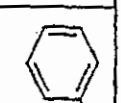
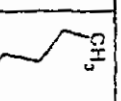
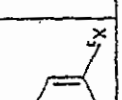
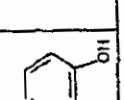
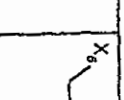
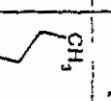
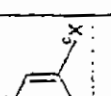
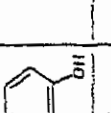
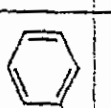
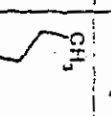
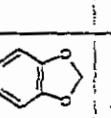
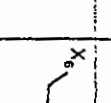
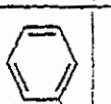
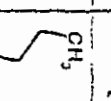
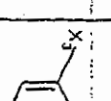
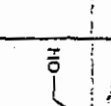
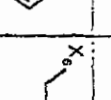
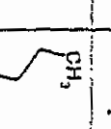
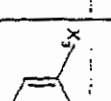
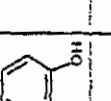
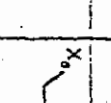
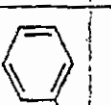
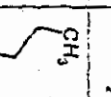
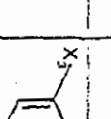
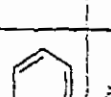
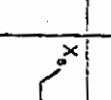
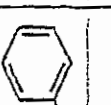
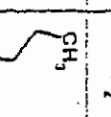
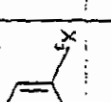
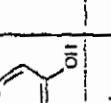
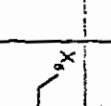
CMP #	R1	R2	R3	R1	R5	R6	Ret. Time	Cmd. Mass	H+ Ion Obs
900							1.99	453.1779	456.2343
901									
902							1.96	409.2285	410.2904
903							1.98	451.2987	452.3564
904							1.91	389.2831	390.327
905							2.06	515.2703	516.3389

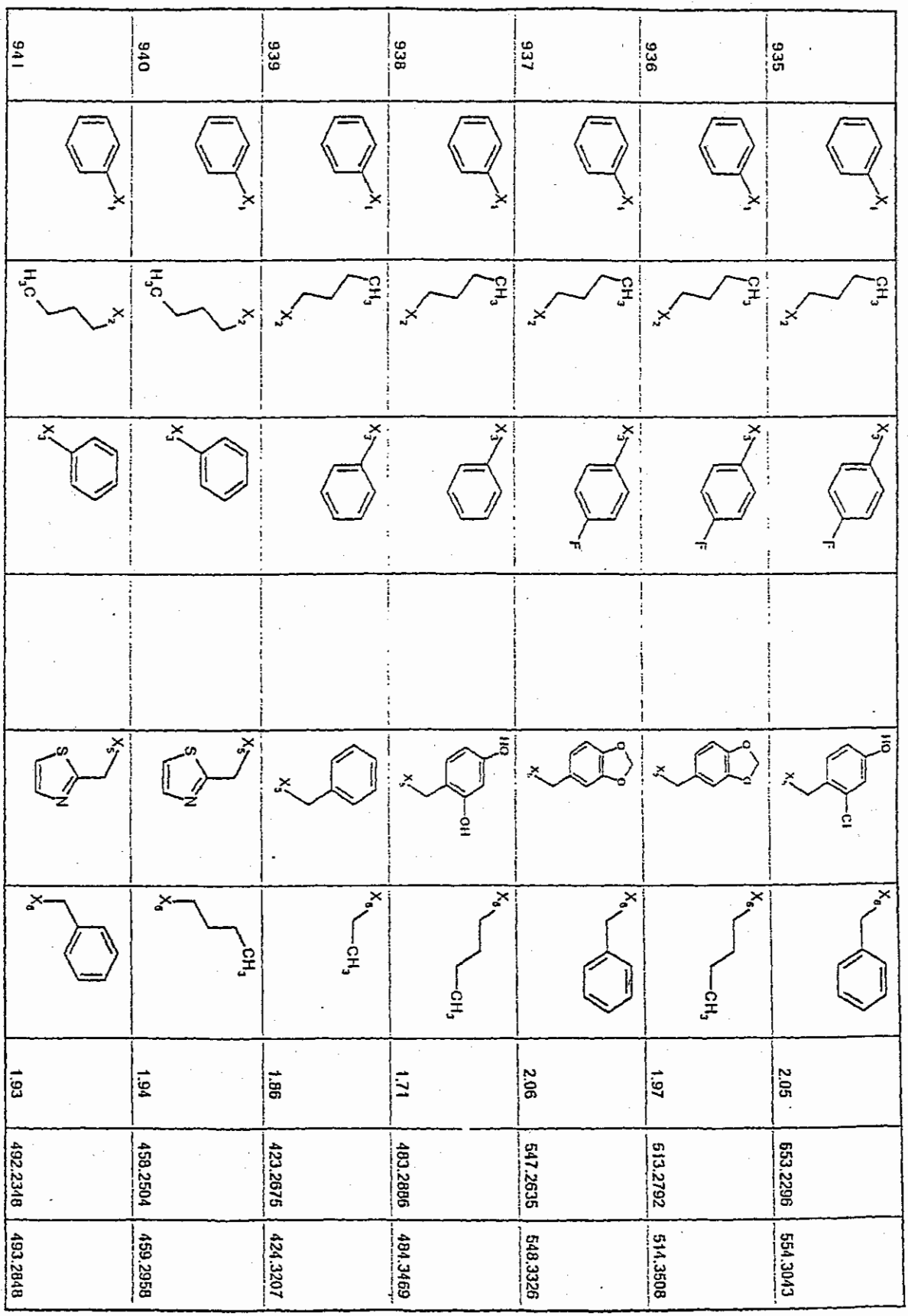


906						2.02	501.2547	502.3203	
907						2.05	535.239	536.3062	
908						1.95	495.2886	496.338	
909						1.95	509.3042	510.349	
910						2.06	543.2886	544.3537	
911						2.06	529.2729	530.3288	
912						2.06	527.2936	528.3539	

913							1.91	493.3093	494.3662
914							1.98	501.278	502.3292
915							2.04	481.286	482.3375
916							2.06	509.3042	510.3504
917							2.04	553.2941	554.3566
918							2.01	559.2602	560.3214
919							1.98	559.2602	560.3226
920							2.07	515.2936	516.3561

921								1.8	467.2937	468.3449
922								1.97	486.255	487.3133
923								1.96	520.2394	521.3087
924								1.77	521.3519	522.4169
925								1.79	555.3362	556.421
926								2.06	565.2496	566.3239
927								1.76	515.3155	516.3049

928							2.02	531.2653	532.3318
929							1.79	497.3042	498.3625
930							1.95	525.2991	526.3686
931							1.74	511.3311	512.3882
932							2	531.2886	532.3475
933							2	469.2893	470.3573
934							2.03	519.2452	520.3179



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936							1.97	513.2792	514.3508
937							2.06	547.2635	548.3326
938							1.71	483.2886	484.3469
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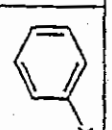
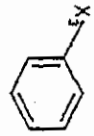
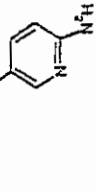
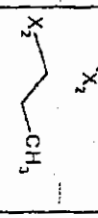
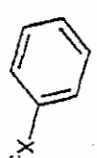
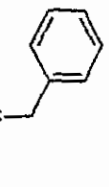
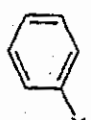
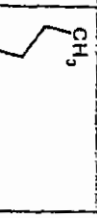
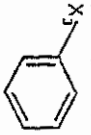
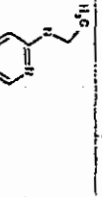
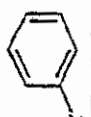
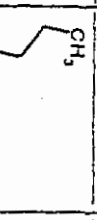
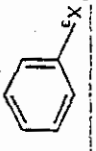
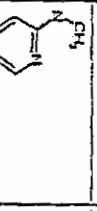
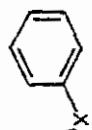
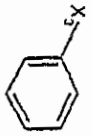
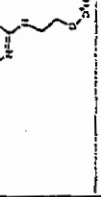
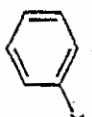
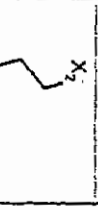
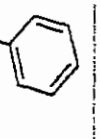
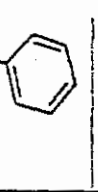
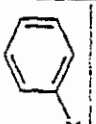
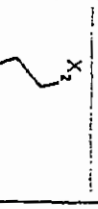
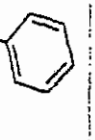
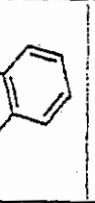
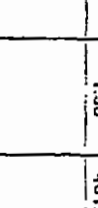
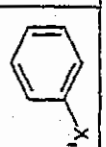
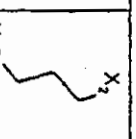
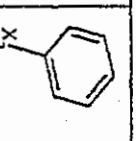
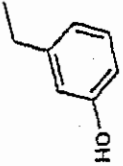
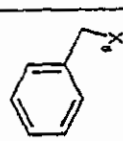
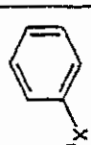
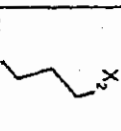
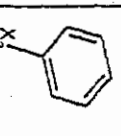
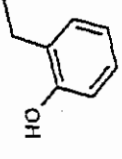
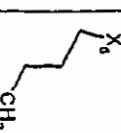
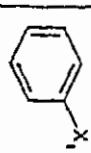
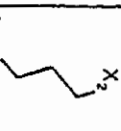
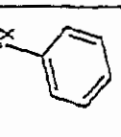
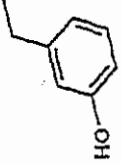
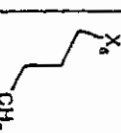
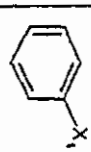
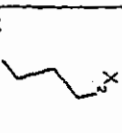
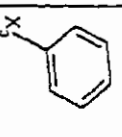
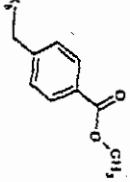
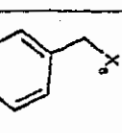
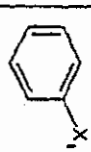
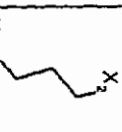
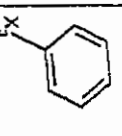
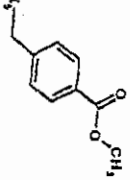
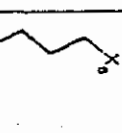
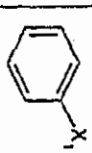
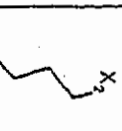
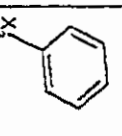
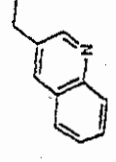
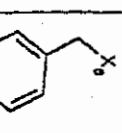
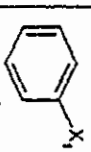
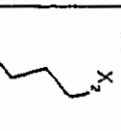
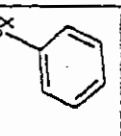
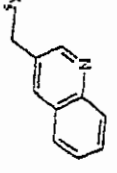
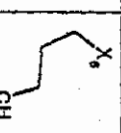
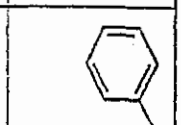
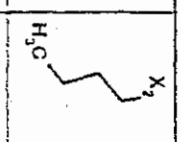
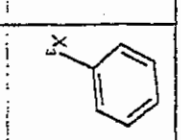
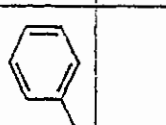
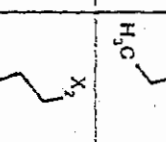
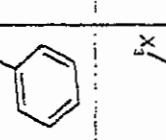
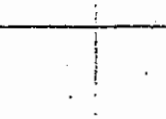
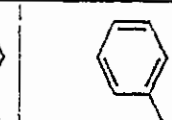
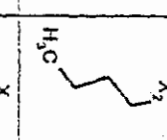
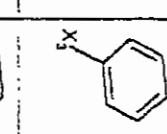
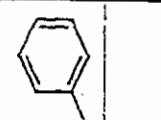
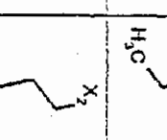
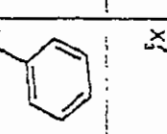
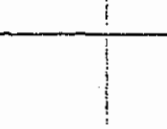
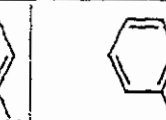
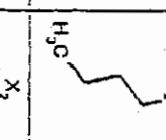
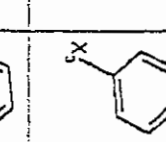
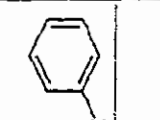
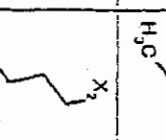
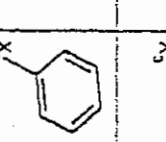
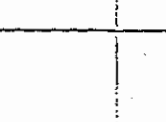
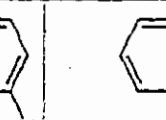
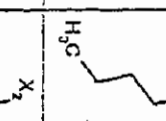
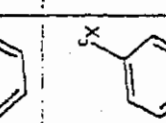
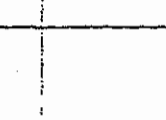
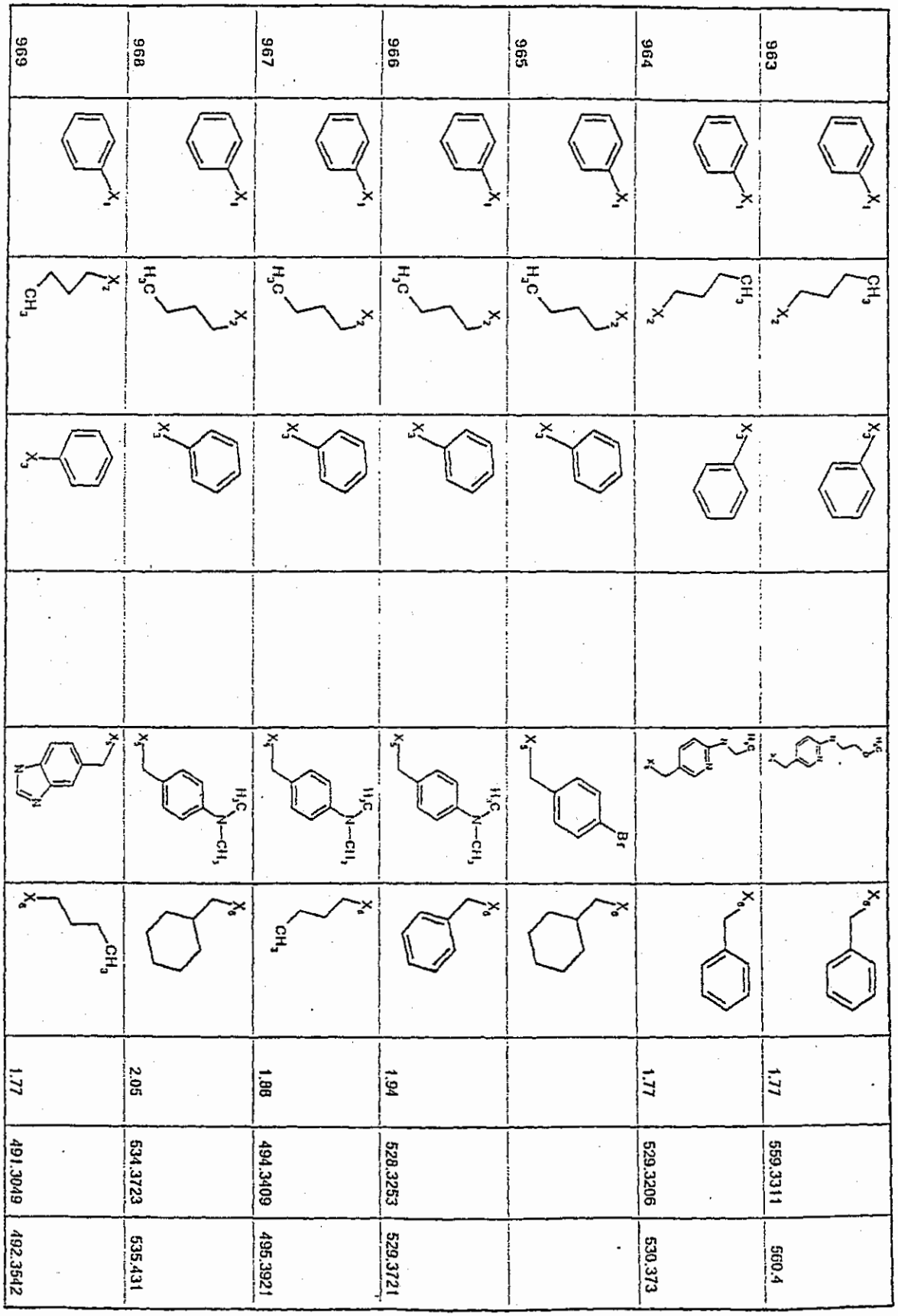
940							1.94	458.2504	459.2958
941							1.93	492.2348	493.2848

942							1.74	467.3049	468.3629
943							1.92	437.2831	438.2847
944							1.77	495.3362	496.4057
945							1.74	481.3206	482.3654
946							1.76	525.3467	526.4145
947							1.98	481.2729	482.3188
948							2.01	501.278	502.3374

949							1.99	501.278	502.3323
950							1.88	467.2937	468.3544
951							1.88	467.2937	468.352
952							2.04	543.2886	544.3618
953							2.03	509.3042	510.364
954							1.93	536.294	537.3635
955							1.94	502.3097	503.3694

956						2.05	542.3409	543.4108
957						1.92	481.3093	482.3674
958						1.99	529.2729	530.3309
959						1.97	495.2886	496.3324
960						2.08	535.3199	536.3663
961						1.93	502.3097	503.3532
962						2.06	542.3409	543.387



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964							1.77	529.3206	530.373
965									
966							1.94	528.3253	529.3721
967							1.88	494.3409	495.3921
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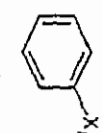
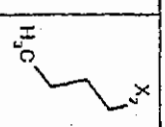
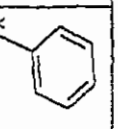
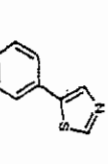
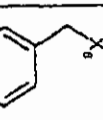
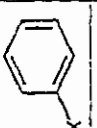
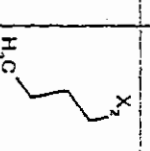
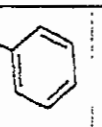
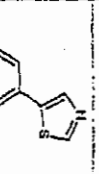
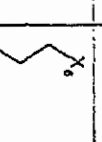
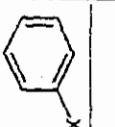
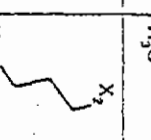
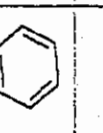
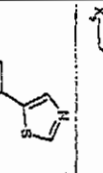
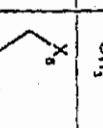
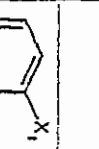
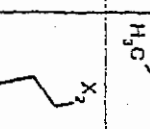
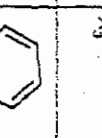
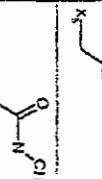
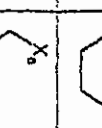
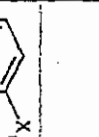
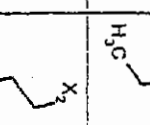
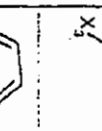
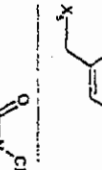
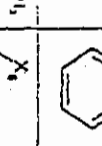
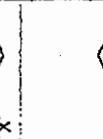
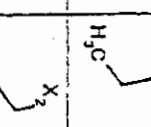
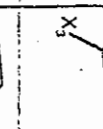
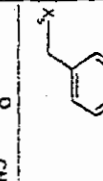
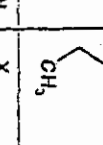
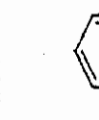
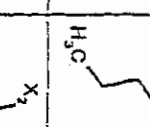
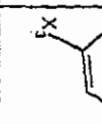
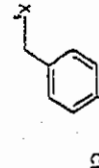
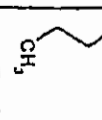
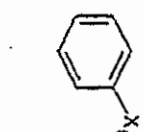
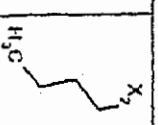
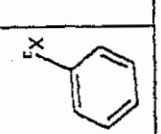
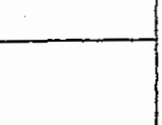
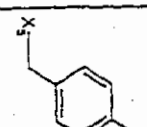
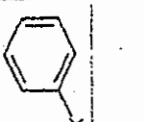
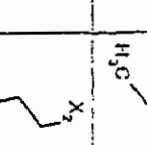
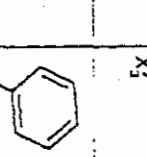
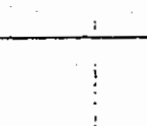
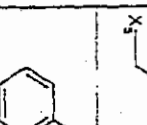
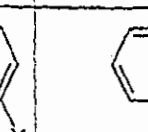
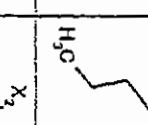
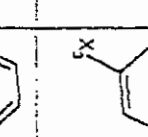
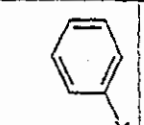
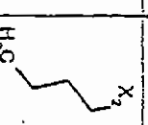
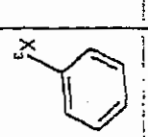
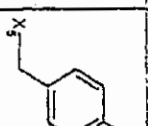
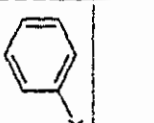
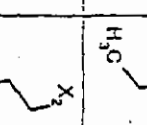
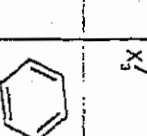
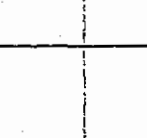
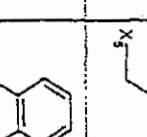
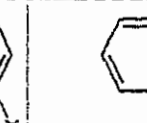
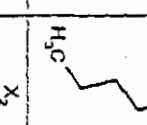
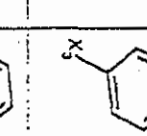
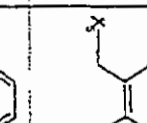
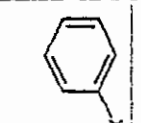
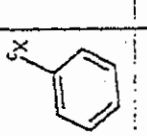
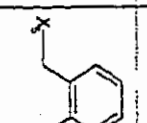
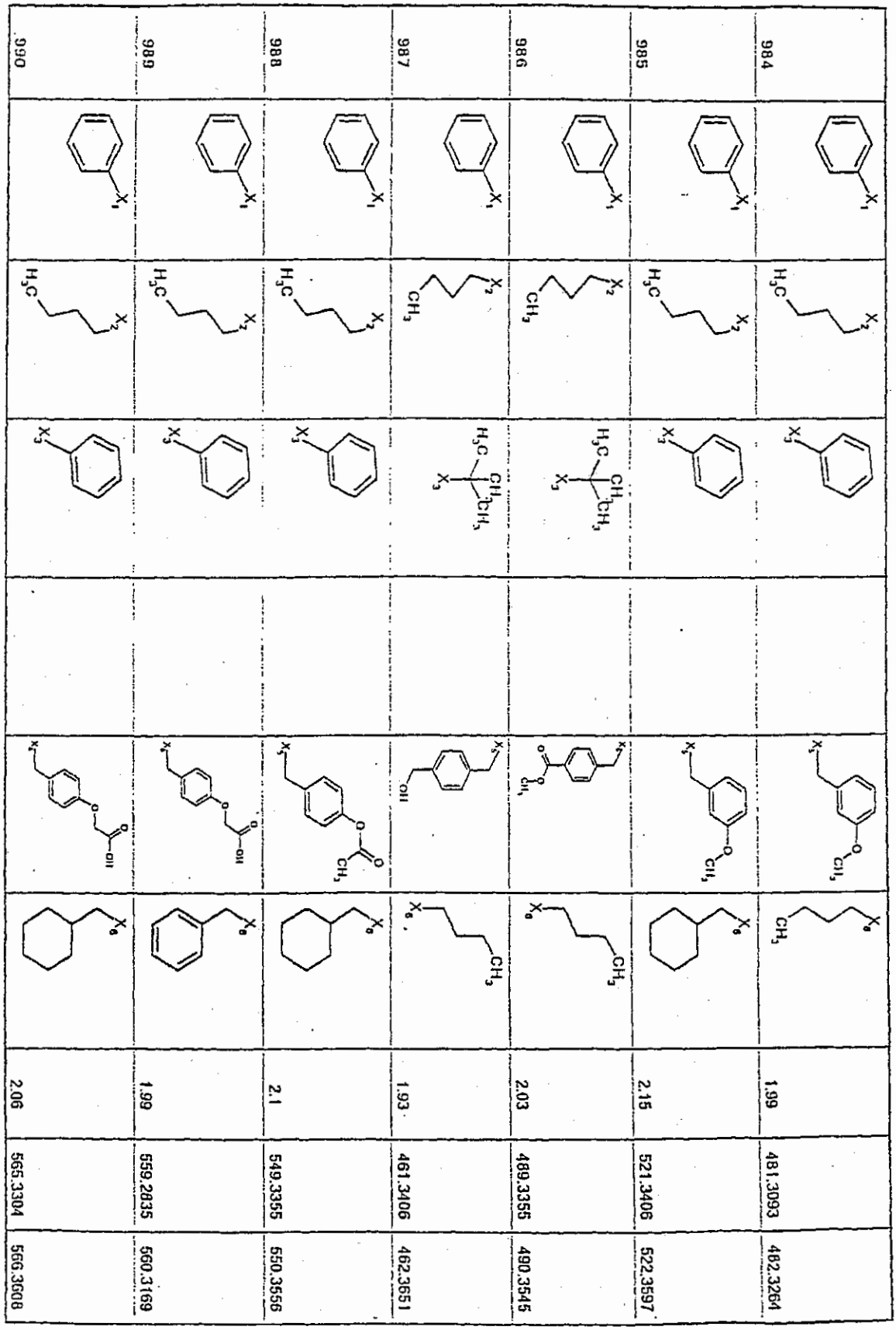
970								2.03	568.2661	569.3215
971								1.98	534.2817	535.3365
972								2.14	574.313	575.38
973								1.94	542.3046	543.3302
974								1.89	508.3202	509.3457
975								1.91	522.3359	523.3574
976								2.03	562.3672	563.3868

977							1.96	515.2936	516.3203
978							1.86	481.3093	482.3423
979							2.05	521.3406	522.3715
980							2.06	516.2936	516.3033
981							1.89	481.3093	482.3204
982							2.12	521.3406	522.3559
983							2.06	516.2936	516.3141



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985					2.15	521.3406	522.3597	
986					2.03	489.3355	490.3545	
987					1.93	461.3406	462.3651	
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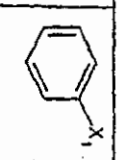
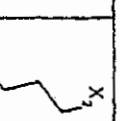
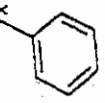
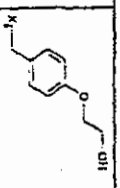
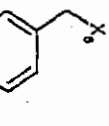
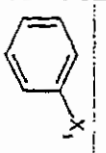
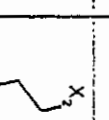
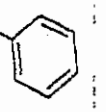
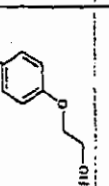
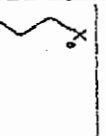
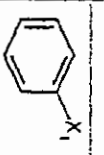
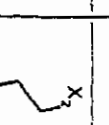
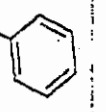
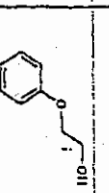
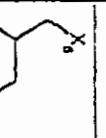
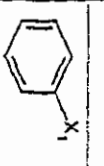
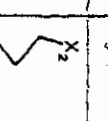
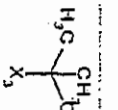
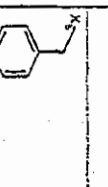
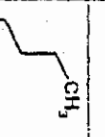
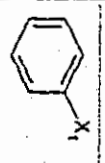
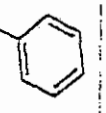
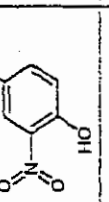
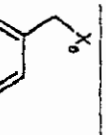
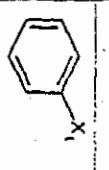
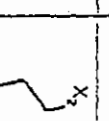
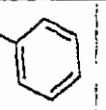
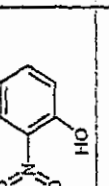
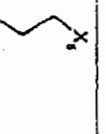
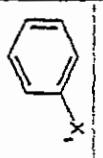
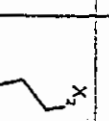
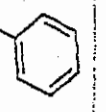
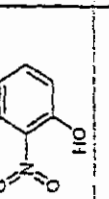
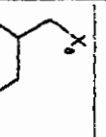
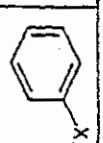
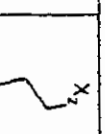
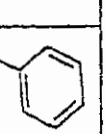
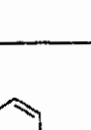
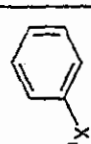
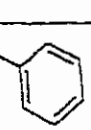
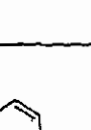
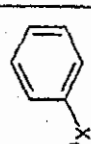
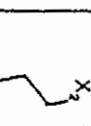
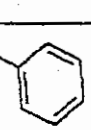
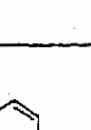
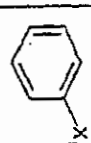
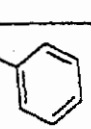
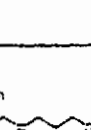
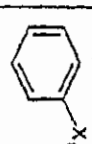
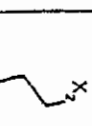
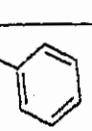
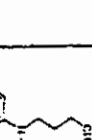
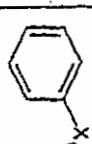
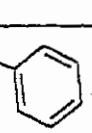
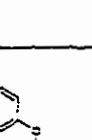
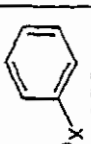
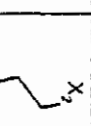
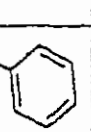
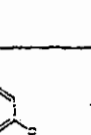
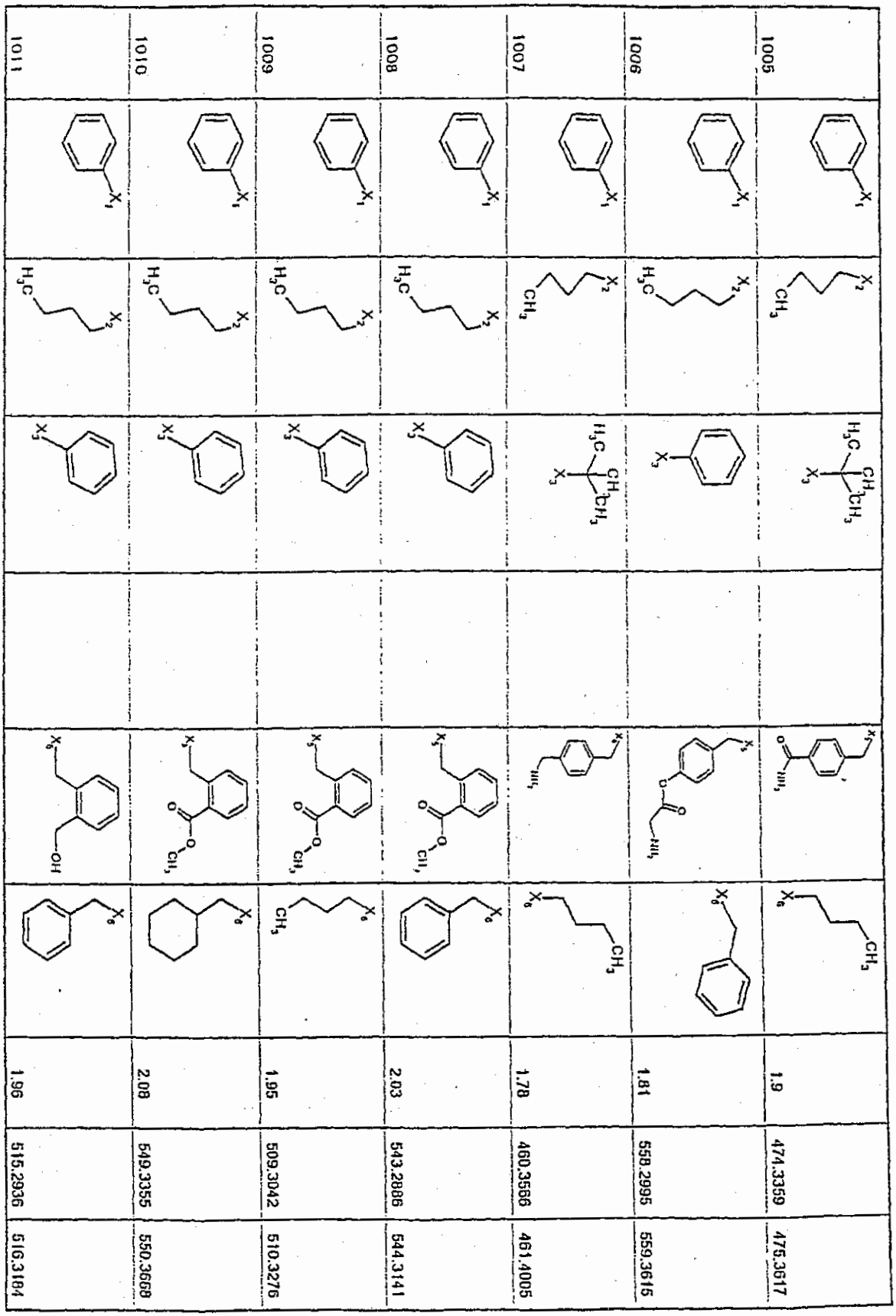
989					1.99	559.2835	560.3169	
990					2.06	565.3304	566.3608	

991							1.98	546.3042	546.332
992							1.82	511.3199	512.3492
993							2.05	551.3512	552.3806
994							1.91	488.3515	489.3748
995							2.02	546.2631	547.2886
996							2	512.2787	513.3031
997							2.11	552.3101	553.335

998								2.02	546.2631	547.2888
999								2.03	512.2787	513.3018
1000								2.11	552.3101	553.3454
1001								2.06	578.4349	579.501
1002								2.14	618.4661	619.54
1003								1.71	552.3828	553.43
1004.								1.92	592.4141	593.47



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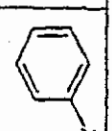
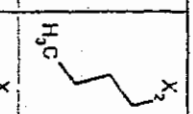
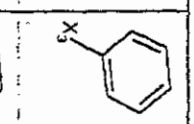
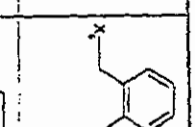
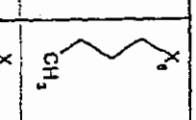
1006							1.81	558.2995	559.3615	
1007							1.78	460.3566	461.4005	
1008							2.03	543.2886	544.3141	
1009							1.95	509.3042	510.3276	
1010							2.08	549.3355	550.3668	
1011							1.96	515.2936	516.3184	

1012							1.84	481.3093	482.3309
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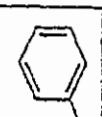
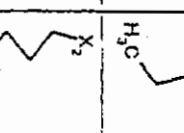
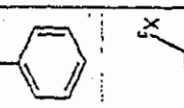
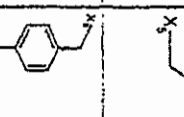
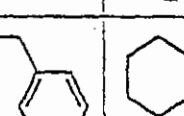
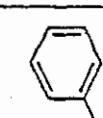
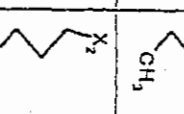
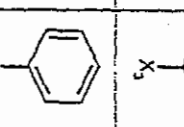
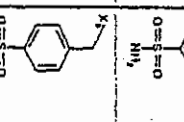
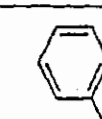
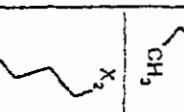
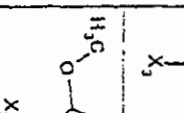
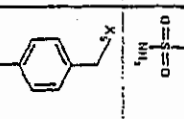
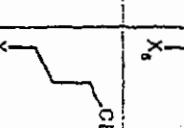
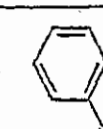
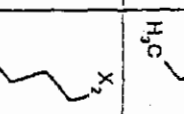
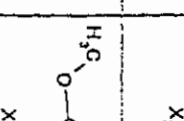
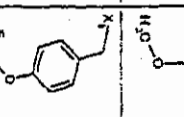
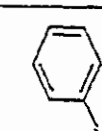
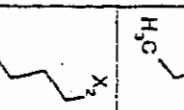
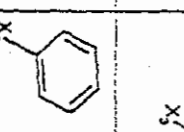
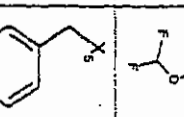
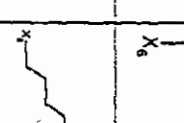
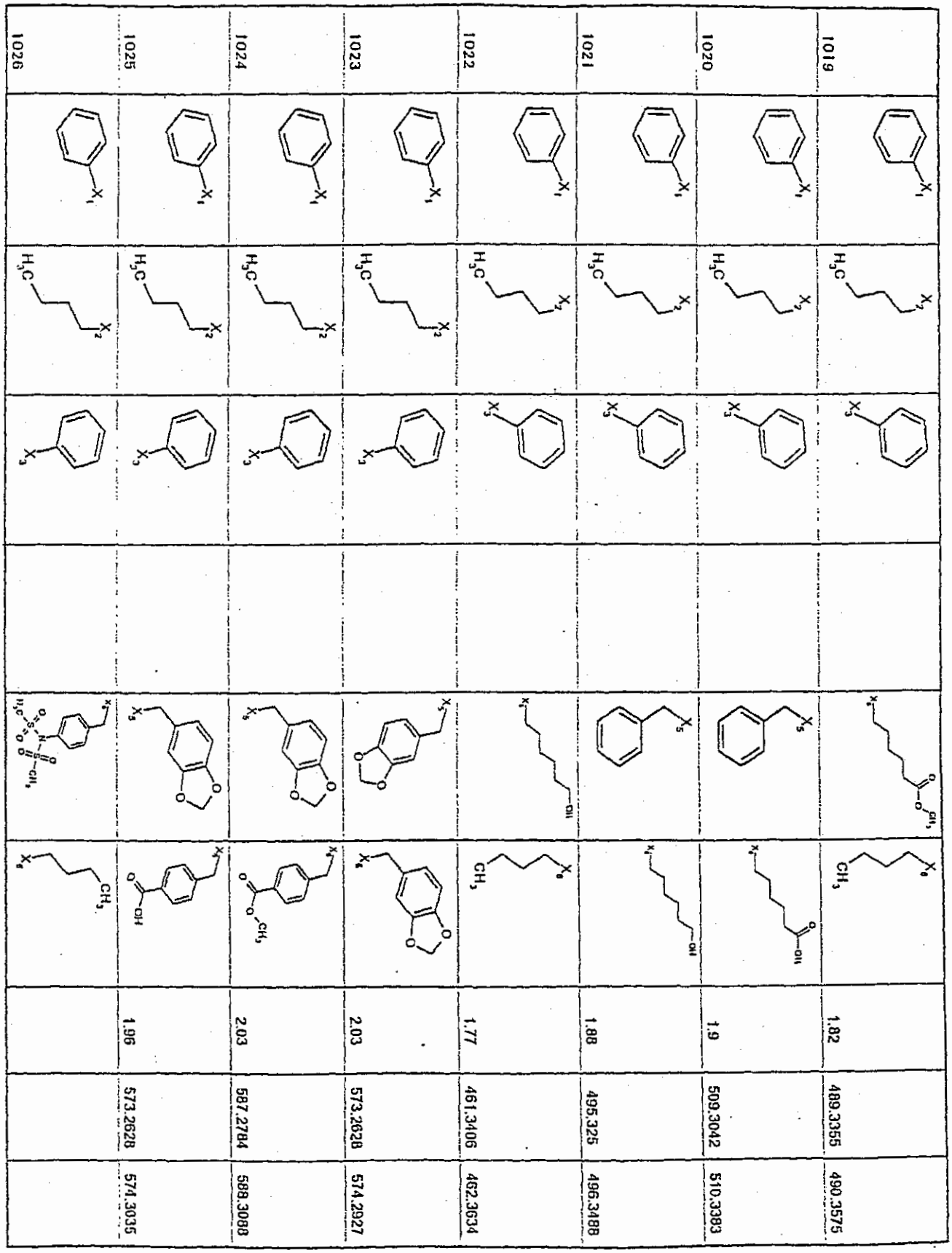
1014							1.88	564.2559	565.3013
1015							1.87	530.2715	531.3078
1016							1.88	511.3199	512.3484
1017							1.98	547.301	548.3231
1018							1.96	523.3199	524.3481



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1020								1.9	509.3042	510.3383
1021								1.88	495.325	496.3488
1022								1.77	461.3406	462.3634
1023								2.03	573.2628	574.2927
1024								2.03	587.2784	588.3088
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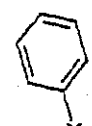
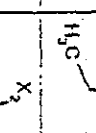
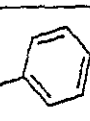
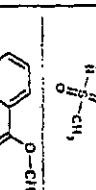
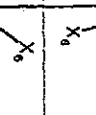
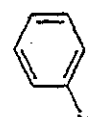
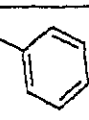
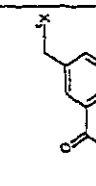
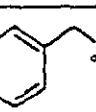
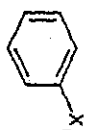
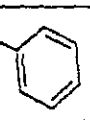
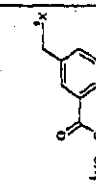
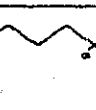
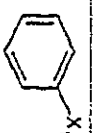
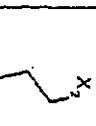
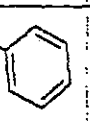
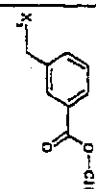
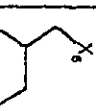
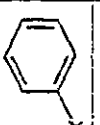
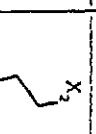
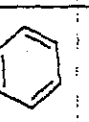
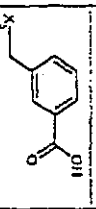
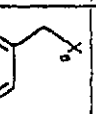
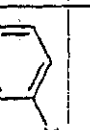
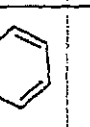
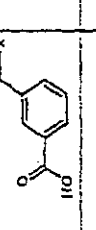
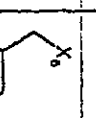
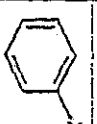
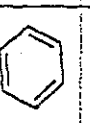
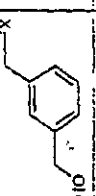
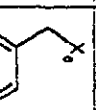
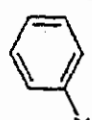
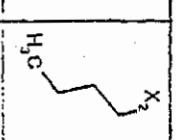
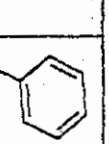
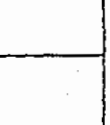
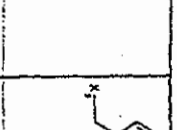
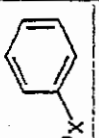
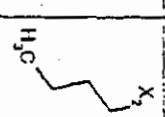
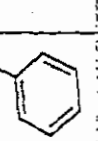
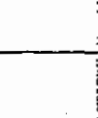
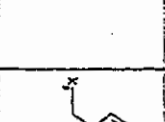
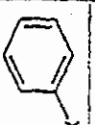
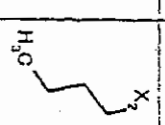
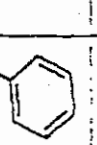
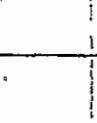
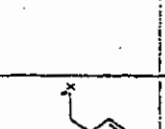
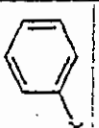
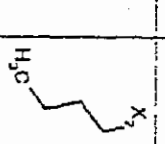
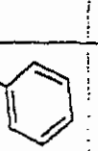
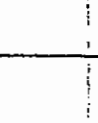
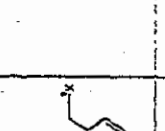
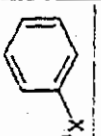
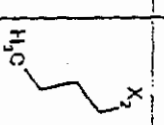
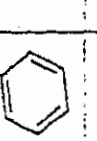
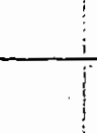
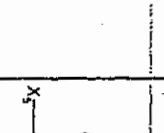
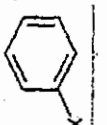
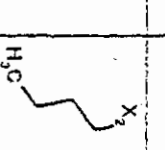
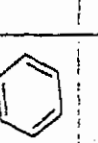
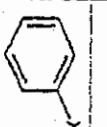
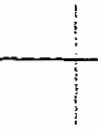
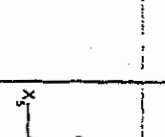
1026										

1027							1.85	544.2872	545.3313
1028							2.03	543.2886	544.3122
1029							2.03	509.3042	510.3173
1030							2.12	549.3355	550.3542
1031							1.98	529.2729	530.2999
1032							2.08	535.3199	536.3453
1033							1.97	516.2936	516.3203

1034							1.87	481.3093	482.3294
1035							2.06	559.2835	560.311
1036							2.03	525.2991	526.3195
1037							2.17	565.3304	566.35
1038									
1039							2.12	551.3148	552.3455
1040							1.93	531.2886	532.3281

CLAIMS

What is claimed is:

1. A carbon-containing compound

i) having a molecular mass of less than 700 amu;

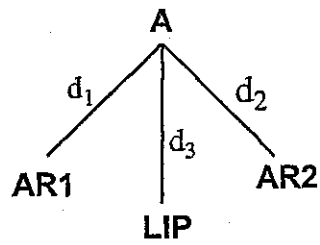
ii) that is nonpeptidic and non-peptidomimetic;

iii) that exhibits C5a antagonist activity with an IC_{50} of less than 200 nM in an assay of C5a mediated chemotaxis or calcium mobilization; and

iv) that exhibits less than 10% agonist activity in a GTP binding assay.

2. A compound according to claim 1, which contains one or more heteroaryl rings.

3. A compound according to Claim 1 of the formula:



AR1 and AR2 are independently carbocyclic aryl or heteroaryl;

LIP represents an alkyl, cycloalkyl, carbocyclic aryl, heteroaryl, or arylalkyl;

A is oxygen or nitrogen;

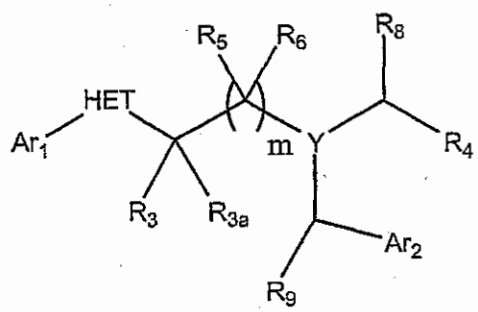
d_1 represents the distance between A and the geometric center of AR1 and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound;

d_2 represents the distance between A and the geometric center of AR2 and is between 5 and 10 angstroms in at least one energetically accessible conformer of the compound; and

d_3 represents the distance between A and the nearest atom of LIP and is between 3 and 6 angstroms in at least one energetically accessible conformer of the compound.

4. A compound of claim 1, 2 or 3 that is an optionally substituted arylimidazole, an optionally substituted arylpyridyl, an optionally substituted aryl-substituted cycloalkylimidazole, an optionally substituted arylpyrazole, an optionally substituted benzimidazole, an optionally substituted aryl-substituted tetrahydroisoquinoline,or an optionally substituted biaryl carboxamide.

5. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

wherein:

the ring system represented by HET is any optionally substituted heterocycle comprising a nitrogen or oxygen that can act as a hydorgen bond acceptor;

Y is N or CH;

m is 0, 1, or 2;

R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

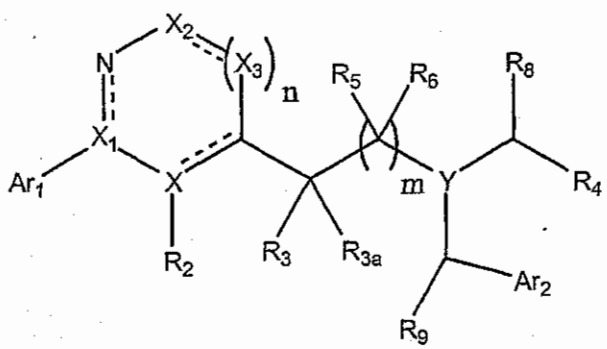
R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

6. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

wherein:

m is 0, 1, or 2;

n is 0 or 1,

X and X_1 are independently chosen from C and N,

X_2 is C-R_1 or N,

X_3 is C-R or N,

R and R_1 are independently chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

when n is 0, R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

when n is 1, R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

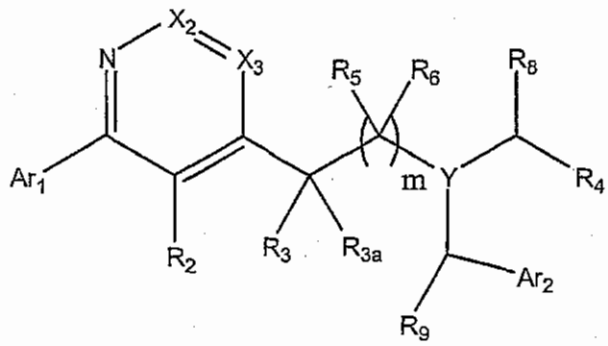
R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

7. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

wherein:

m is 0, 1, or 2;

X_2 is C-R_1 or N,

X_3 is C-R or N,

R and R_1 are independently chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

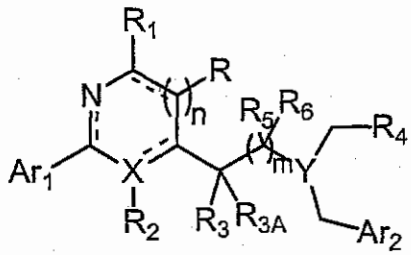
R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

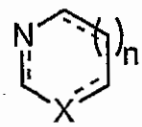
8. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof,

wherein:

the ring system represented by



is a 5 to 7 membered heterocycle that may be either aromatic or partially unsaturated;

X is N or C;

Y is N or CH;

n is 0, 1, or 2;

m is 0, 1, or 2;

R and R_1 are independently chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

when n is 0, R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

when n is 1, R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

9. A compound according to Claim 8, wherein

R and R_1 are independendently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2 is hydrogen, hydroxy, halogen, amino, cyano, nitro, or haloalkyl, or

R_2 is alkoxy, mono- or dialkylamino, alkyl, alkenyl, alkynyl or (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

R_3, R_{3A}, R_5, and R_6 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

when n is 0, R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino;

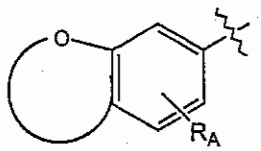
when n is 1, R and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, each of which may be unsubstituted or substituted with

one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; or

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:



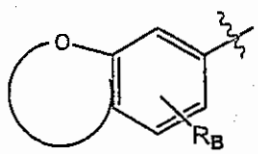
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; and

Ar_1 and Ar_2 are independently chosen from

i) phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl,

cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino.

10. A compound according to Claim 8, wherein

R and R_1 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy,

C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

when n is 0, R_1 and R_3 may be joined to form a C_3-C_8 cycloalkyl or C_3-C_8 heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

when n is 1, R and R_3 may be joined to form a C_3-C_8 cycloalkyl or C_3-C_8 heterocycloalkyl ring, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 is hydrogen, hydroxy, halogen, amino, cyano, nitro, or haloalkyl,

R_2 is alkoxy, mono- or di(C_1-C_6)alkylamino, C_1-C_6 alkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl or (C_3-C_8cycloalkyl) C_1-C_3alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_3, R_{3A}, R_5, and R_6 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

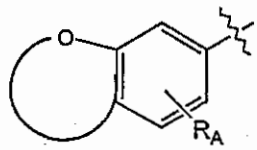
ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with

one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:

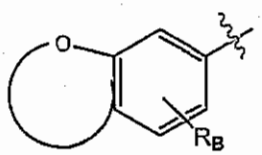


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 and Ar_2 are independently chosen from phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl,

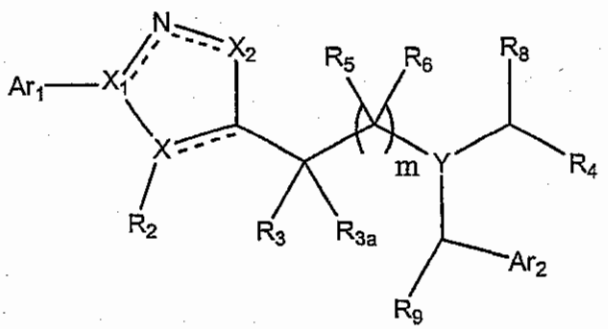
naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

11. A compound according to Claim 8 of the formula:



wherein:

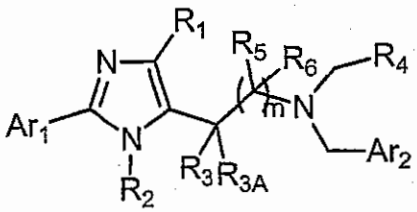
X and X_1 are independently chosen from C and N;

X_2 is C-R_1 or N;

m, Ar_1, Ar_2, R_1, R_2, R_3, R_{3A}, R_4, R_5, and R_6 are as defined in Claim 8;

R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

12. A compound of the formula:



wherein:

m is 0, 1, or 2;

R_1 is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl, optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2 is chosen from optionally substituted C_1-C_8 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkyl(C_1-C_8)alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, haloalkyl, aminoalkyl, each of which may be unsubstituted or preferrably substituted with one or more substituents selected from oxo (e.g. carbonyl), hydroxy, alkoxy, amide, ester, cyano, acetoxy or nitro.

R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_1 and R_3 may be joined to form a cycloalkyl or heterocycloalkyl ring, each of which may be optionally substituted;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

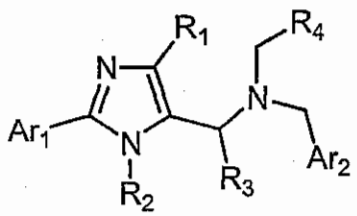
R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

13. A compound according to Claim 12 of the formula:

wherein m, Ar_1, Ar_2, R_1, R_2, R_3, and R_4 are as defined in Claim 12.

14. A compound according to Claim 12 of the formula:



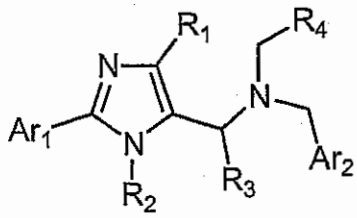
wherein:

R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl.

15. A compound according to Claim 12 of the formula:



wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, thienyl, imidazolyl, pyridyl, pyrimidyl, benzodioxinyl, benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 12;

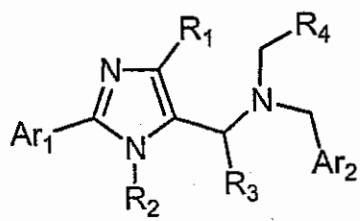
R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

16. A compound according to Claim 12 of the formula:



wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, thienyl, imidazolyl, pyridyl, pyrimidyl, benzodioxinyl, benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 12;

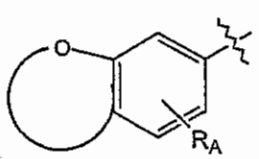
R_1 is hydrogen, C_1-C_7 alkyl, halogen or phenyl optionally substituted with C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

R_2 is C_1-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or C_1-C_7 alkyl; and

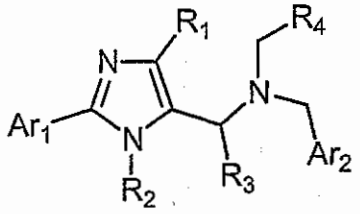
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

17. A compound according to Claim 12 of the formula:



wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 12;

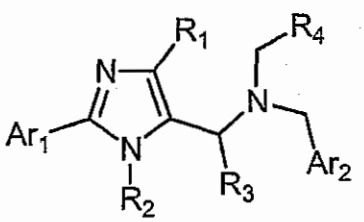
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

18. A compound according to Claim 12 of the formula:



wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is defined as in Claim 12;

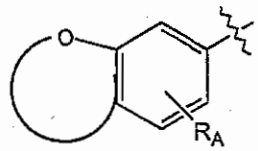
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

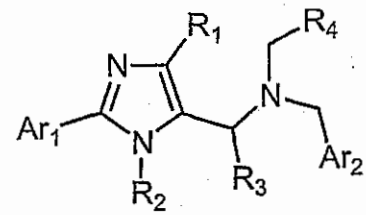
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

19. A compound according to Claim 12 of the formula:

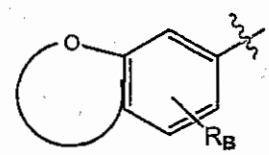


wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

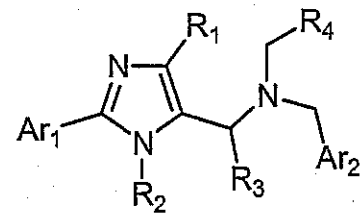
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

20. A compound according to Claim 12 of the formula:

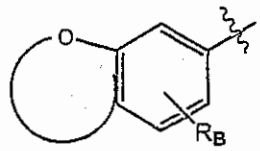


wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

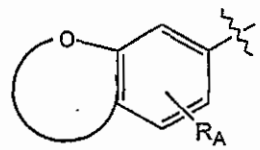
R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl; and

R_3 is hydrogen or methyl; and

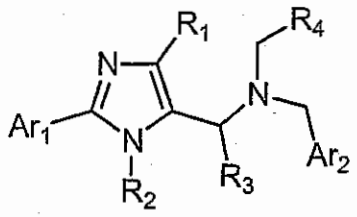
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

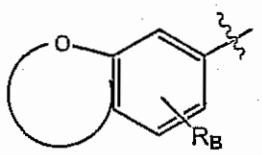
21. A compound according to Claim 12 of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is a bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_1 is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_1 is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl,

pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

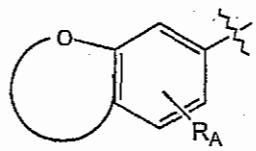
ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy,

amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

22. A compound according to Claim 21, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

23. A compound according to Claim 21, wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

24. A compound according to Claim 21, wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

R_4 is C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

25. A compound according to Claim 21, wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

R_3 is hydrogen or methyl; and

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

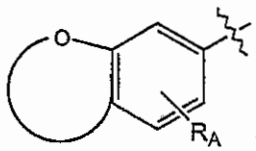
26. A compound according to Claim 21, wherein:

R_1 is hydrogen, methyl, ethyl, or phenyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

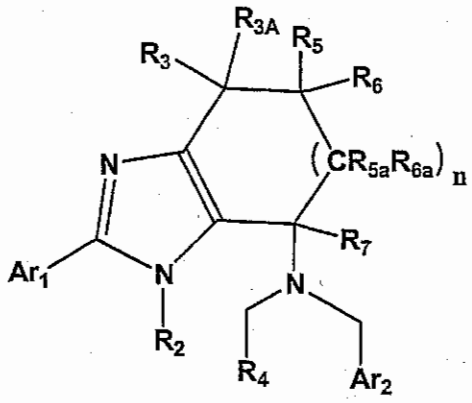
R_3 is hydrogen or methyl; and

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

27. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

n is an integer from 0 to 3; and

R_2 is chosen from optionally substituted C_1-C_8 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_8 cycloalkyl(C_1-C_8)alkyl, optionally substituted C_2-C_8 alkenyl, optionally substituted C_2-C_8 alkynyl, haloalkyl, aminoalkyl, each of which may be unsubstituted or preferrably substituted with one or more substituents selected from oxo (e.g. carbonyl), hydroxy, alkoxy, amide, ester, cyano, acetoxy or nitro.

R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

R_7 represents hydrogen or alkyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

28. A compound according to Claim 27, wherein:

n, R_2, R_3, R_{3A}, R_5, R_6, R_{5a}, R_{6a}, and R_7 are defined as in Claim 27, and

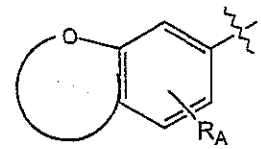
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids,

aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



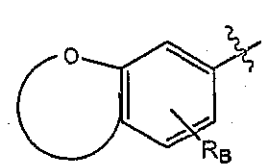
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, -O-, $-S(O)_m-$, -NH-, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, -NHC(=O)-,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x$(alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

29. A compound according to Claim 27, wherein:

n and R_2 are defined as in Claim 27, and

R_3 and R_{3A} are the same or different and represent hydrogen or

C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a C_{3-8} cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl ring;

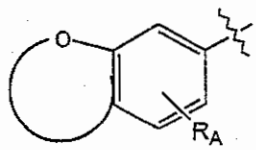
R_{5a} and R_{6b} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



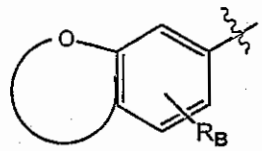
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or

substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$NH(C_1-C_6 alkyl), -S(O)$_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

30. A compound according to Claim 27, wherein

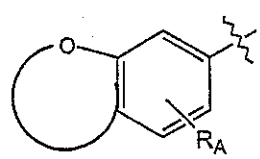
n, R_2, R_3, R_{3A}, R_5, R_6, R_{5a}, R_{6a}, and R_7 are as defined in Claim 27,

R_4 is hydrogen or

C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



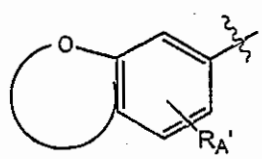
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, thienyl, or pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which is unsubstituted or substituted with up to four substituents independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below;

Ar_2 is phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A' represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -C(=O)NR_C-, -$S(O)_m$NH-, -$S(O)_m$$NR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -C(=O)$NHS(O)_m$-, and –$NR_C$$S(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

31. A compound according to Claim 30 wherein:

R_3 and R_4 are the same or different and represent hydrogen or methyl;

R_5 and R_6 are the same or different and represent hydrogen or methyl; and

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen and methyl.

32. A compound according to Claim 30 wherein:

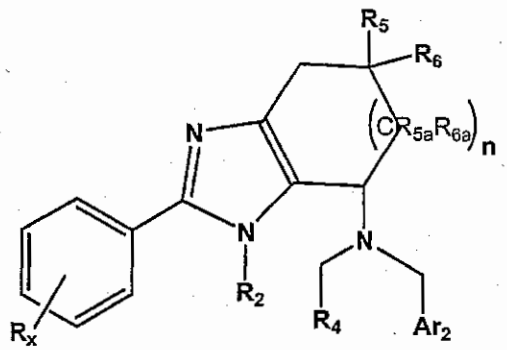
R_3 and R_4 are hydrogen;

R_5 and R_6 are the same or different and represent hydrogen or methyl; and

R_{5a} and R_{6a} are the same or different, and are independently selected at each

occurrence from hydrogen and methyl.

33. A compound according to Claim 30 of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

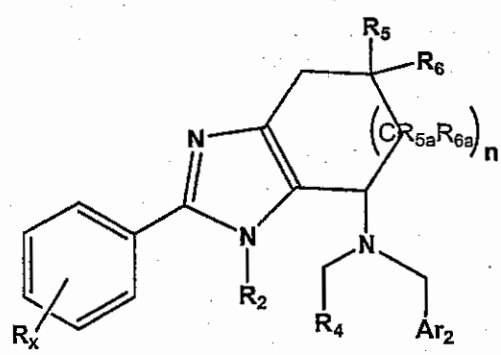
R_2, R_4, Ar_2, and n are as defined for Claim 30;

R_5 and R_6 are the same or different and represent hydrogen or methyl;

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

34. A compound according to Claim 32, of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R_4, Ar_2, and n are as defined for Claim 30;

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5 and R_6 are the same or different and represent hydrogen or methy

R_{5a} and R_{6a} are the same or different, and are independently chosen at each occurrence from hydrogen and methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

35. A compound according to Claim 33,

or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

Ar_2, R_X, and n are as defined for Claim 30

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl; and

R_4 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl.

36. A compound according to Claim 33,

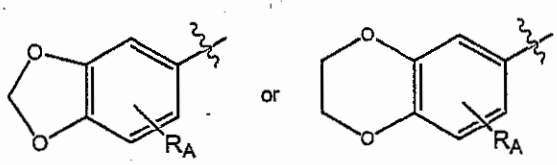
or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is phenyl, which may be unsubstituted or substituted with:

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4 alkyl, haloalkyl, C_1-C_6 alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen containing group of the formula:

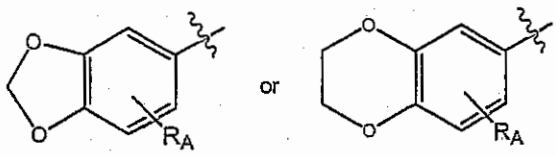


wherein R_A is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_4 alkyl, haloalkyl, alkoxy, halogen, hydroxy, amino, or mono- or di(C_1-C_6)alkylamino;

Ar_2 is phenyl which is unsubstituted or optionally substituted or substituted with up to four groups independently selected from:

halogen, C_1-C_7 alkyl, C_1-C_7 alkoxy, cyano, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, 1-morpholino, nitro, hydroxy, acetoxy, trifluoromethyl, and trifluoromethoxy or $-X_4R_B$, wherein X_4 and R_B are as defined for Claim 33; or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_A, R_A', and n are as defined in Claim 33.

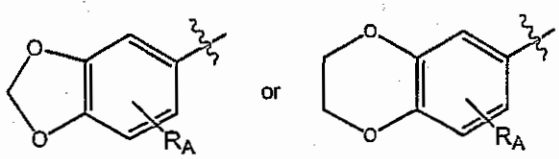
37. A compound according to Claim 33,

or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

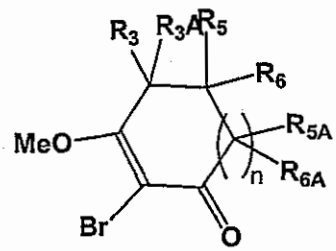
R_4 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

Ar_2 is a bicyclic oxygen containing group of the formula:



wherein R_A' and n are as defined for Claim 33.

38. A compound of the formula:



wherein:

n is an integer from 0 to 3;

R_3 and R_{3A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring; and

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy.

39. A compound according to Claim 38, wherein:

R_3 and R_{3A} are the same or different and represent hydrogen or C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms; and

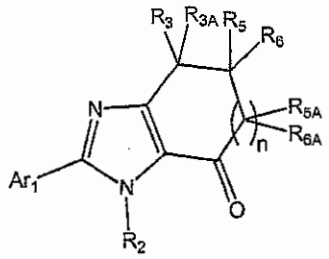
R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy.

40. A compound according to Claim 38, wherein:

R_3 and R_4 are hydrogen; and

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl.

41. A compound of the formula:



wherein:

n is an integer from 0 to 3;

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each of which may be substituted or unsubstituted;

R_3 and R_4 are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 is unsubstituted or substituted carbocyclic aryl, unsubstituted or substituted arylalkyl, or a unsubstituted or substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

42. A compound according to Claim 41 in which:

R_2 is C_1-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl, C_2-C_8 (cycloalkyl)C_1-C_4 alkyl, or C_1-C_8 haloalkyl;

R_3 and R_{3a} are the same or different and represent hydrogen or C_1-C_6 alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring of from three to six carbon atoms; and

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring of from three to six carbon atoms;

R_{5A} and R_{6A} are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, phenyl, thienyl, or pyridyl, pyrimidyl, dihydrobenzofuranyl, furanyl, benzodioxanyl, indolyl, each of which is unsubstituted or substituted with up to four substituents independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

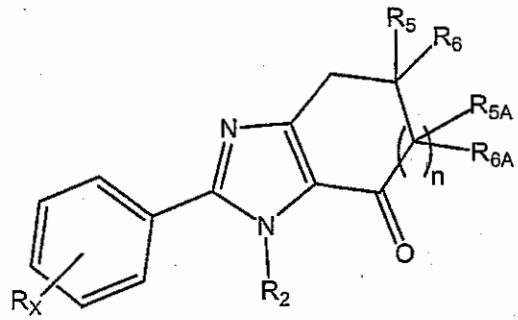
R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_1-C_6 alkyl), -NHS(O)$_x$(C_1-C_6 alkyl), -S(O)$_x$(C_1-C_6 alkyl), -

$S(O)_xNH(C_1\text{-}C_6$ alkyl), $-S(O)_xN(C_1\text{-}C_6$ alkyl)$(C_1\text{-}C_6$ alkyl), (where x is 0, 1, or 2).

43. A compound according to Claim 41 of the formula:



wherein:

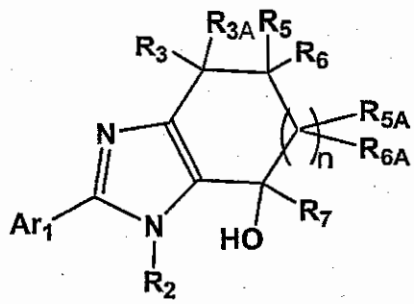
n is 0, 1, or 2:

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di$(C_1$-$C_6)$alkylamino, and amino$(C_1$-$C_6)$alkoxy.

44. A compound of the formula:



wherein:

n is an integer from 0 to 3; and

R_2 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted;

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3a}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen or alkyl; or

R_5 and R_6, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

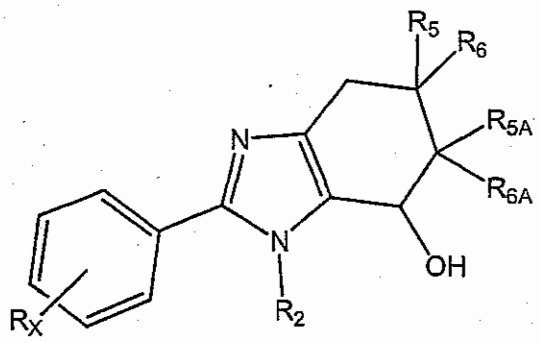
R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

R_7 represents hydrogen or alkyl; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

45. A compound according to Claim 44, of the formula:



wherein:

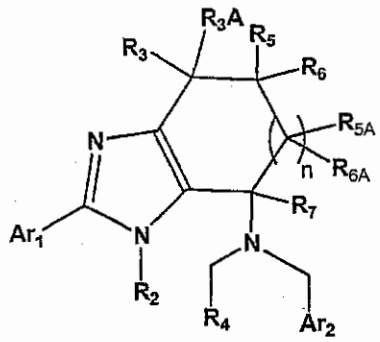
n is an integer from 0 to 3;

R_2 is C_3-C_8 straight or branched chain alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_5, R_6, R_{5A}, and R_{6A} are the same or different and represent hydrogen or methyl; and

R_X represents up to four substituents independently chosen from hydrogen, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

46. A process for preparing a compound of the formula:



wherein:

n is an integer from 0 to 3; and

R_2 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, or haloalkyl, each or which may be substituted or unsubstituted;

R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be substituted or unsubstituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaromatic or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms,

R_3 and R_{3A} are the same or different and represent hydrogen or alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, alkyl, or alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, alkyl, and alkoxy;

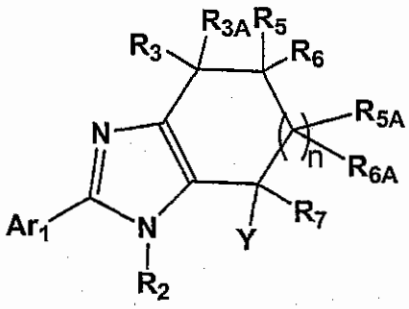
R_7 represents hydrogen or alkyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, or an optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 hetero atoms.

the process comprising:

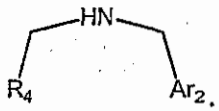
reacting a compound of the formula:



wherein Y is halogen or sulfonate ester,

in a suitable solvent in the presence of a suitable base,

with a secondary amine of the formula:



47. A process according to Claim 46, wherein

n and Y are as defined in Claim 46;

R_3 and R_{3A} are the same or different and represent hydrogen or

C_1-C_6 alkyl; or

R_3 and R_{3A}, taken together with the carbon atom to which they are attached, form a C_{3-8} cycloalkyl ring;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, C_1-C_6 alkyl, or C_1-C_6 alkoxy; or

R_5 and R_6, taken together with the carbon atom to which they are attached form a C_{3-8} cycloalkyl ring;

R_{5a} and R_{6a} are the same or different, and are independently selected at each occurrence from hydrogen, halogen, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

R_2 is hydrogen or

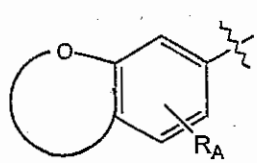
C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8} cycloalkyl, (C_{3-8} cycloalkyl) C_{1-3} alkyl, or C_1-C_6 haloalkyl, each or which unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluormethyl, trifluoromethoxy, C_{1-3} haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



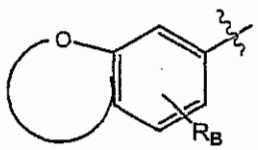
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, $-O-$, $-S(O)_m-$, $-NH-$, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

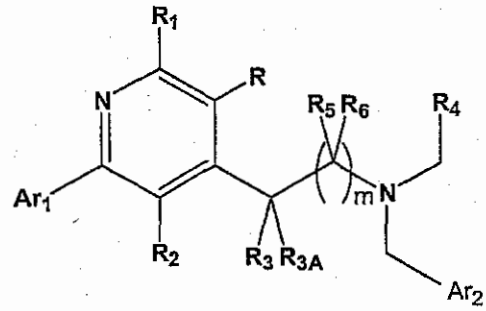
$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, $-O(C_1-C_6$ alkyl), $-NH(C_1-C_6$ alkyl), $-N(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), $-NHC(O)(C_1-C_6$ alkyl), $-N(C_1-C_6$ alkyl)$C(O)(C_{1-6}$ alkyl), $-NHS(O)_x(C_1-C_6$ alkyl), $-S(O)_x(C_1-C_6$ alkyl), $-S(O)_xNH(C_1-C_6$ alkyl), $-S(O)_xN(C_1-C_6$ alkyl)$(C_1-C_6$ alkyl), (where x is 0, 1, or 2).

48. A compound of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

m is 0, 1, or 2;

R is hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl; or

R is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_1, R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

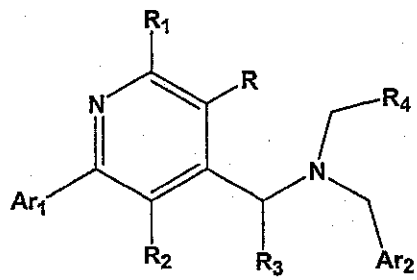
R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

49. A compound according to Claim 48, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

50. A compound according to Claim 48 of the formula



wherein Ar_1, Ar_2, R, R_1, R_2, R_3, and R_4 are as defined in Claim 48.

51. A compound according to Claim 50, wherein

R is selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino; or

R is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino; and

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

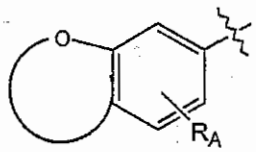
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl,

cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, $-X_4R_B$, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



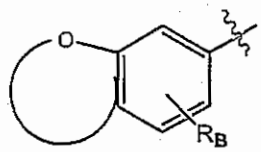
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, -O-, $-S(O)_m-$, -NH-, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$,

$-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl),

-N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), $-NHS(O)_x(C_1-C_6$ alkyl), $-S(O)_x$(alkyl), $-S(O)_xNH$(alkyl), $-S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

52. A compound according to Claim 50, wherein

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy,

haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R is selected from

phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

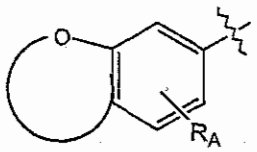
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl,

cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

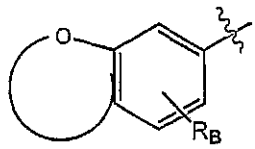
Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(

C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of $-CH_2-$, $-CHR_C-$, -O-, $-S(O)_m-$, -NH-, $-NR_C-$, $-C(=O)NH-$, $-C(=O)NR_C-$, $-S(O)_mNH-$, $-S(O)_mNR_C-$, $-NHC(=O)-$, $-NR_CC(=O)-$, $-NHS(O)_m-$, $-C(=O)NHS(O)_m-$, and $-NR_CS(O)_m-$ (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), $-NHS(O)_x$(C_1-C_6 alkyl), $-S(O)_x$(C_1-C_6 alkyl), $-S(O)_xNH$(C_1-C_6 alkyl), $-S(O)_xN$(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

53. A compound according to Claim 50, wherein:

R is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy;

R_1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

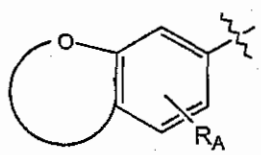
R_2 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

R_3 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:

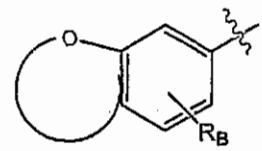


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, and

bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

54. A compound according to Claim 50, wherein:

R is hydrogen, halogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl, (C_3-C_8cycloalkyl)C_1-C_3alkyl, C_1-C_8 alkoxy, or C_1-C_8 haloalkyl, or

R is a phenyl which may be substituted by up to five substituents independently chosen from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, halogen, cyano, carboxylic acid, hydroxy, acetoxy, nitro, amino, mono or di(C_1-C_6)alkylamino, aminocarbonyl, sulfonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, 3,4-(1,2-ethylene)dioxy, trifluoromethyl or trifluoromethoxy;

R_1 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8 cycloalkyl (C_3-C_8cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

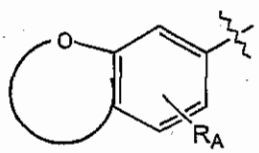
R_2 is C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 cycloalkyl or (C_3-C_8 cycloalkyl)C_1-C_3alkyl or C_1-C_8 haloalkyl;

R_3 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, or C_2-C_8 alkynyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:

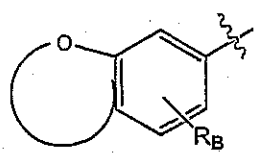


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl, or

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

55. A compound according to Claim 50, wherein

R is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, or phenyl;

R_1 is hydrogen, methyl or ethyl;

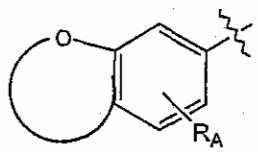
R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl or ethyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

R_4 is a bicyclic oxygen-containing group of the formula:

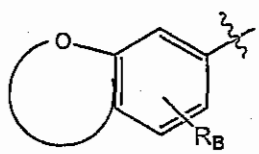


wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; and

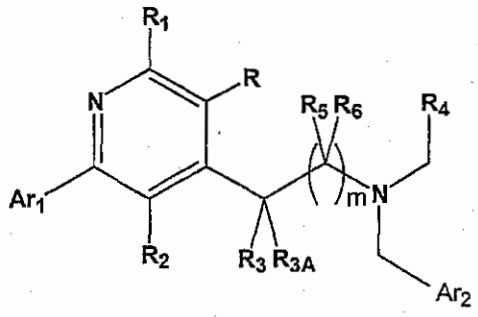
Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, and quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

Ar_2 is a bicyclic oxygen-containing group of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

56. A compound of the formula:



wherein:

m is 0, 1, or 2;

R is hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl; or

R is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_1, R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

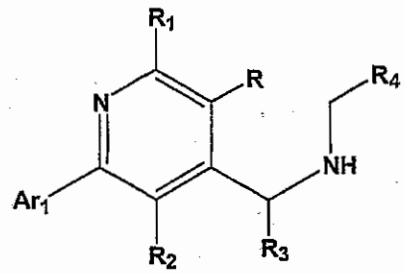
R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

57. A compound of the formula:



wherein Ar_1, R, R_1, R_2, R_3, R_4 are as defined in Claim 56.

58. A compound according to Claim 56, wherein:

R_1, R_2, and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R is selected from

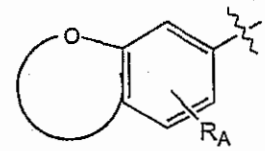
phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



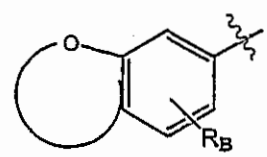
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -C(=O)NR_C-, -$S(O)_m$NH-, -$S(O)_mNR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -C(=O)$NHS(O)_m$-, and -$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl),

-N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

59. A compound according to Claim 56, wherein:

R is hydrogen, halogen, methyl, ethyl, methoxy, ethoxy, trifluoromethyl, or phenyl;

R_1 is hydrogen, methyl or ethyl;

R_2 is C_3-C_6 alkyl;

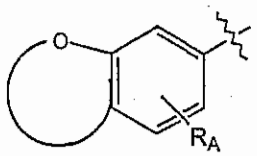
R_3 is hydrogen, methyl or ethyl;

R_4 is C_1-C_8 alkyl, C_3-C_8 cycloalkyl, or (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; or

R_4 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino; or

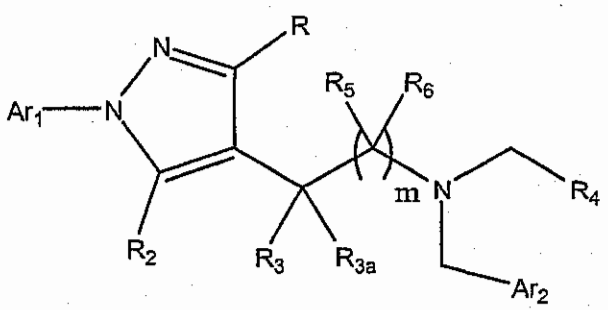
R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, phenyl, thienyl, or pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

60. A compound of the formula:



or pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

m is 0, 1, or 2;

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form an optionally substituted saturated carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ringof from 5 to 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

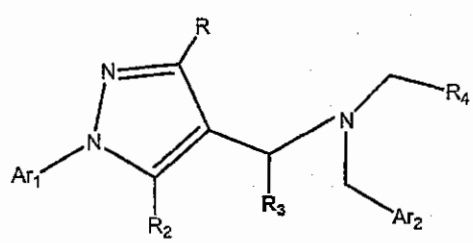
R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

61. A compound according to Claim 60, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

62. A compound according of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,
optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2 and R_3 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form an optionally substituted carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ring of from 5 ro 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

63. A compound according to Claim 62, wherein R and R_3 are not joined.

64. A compound according to Claim 62, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

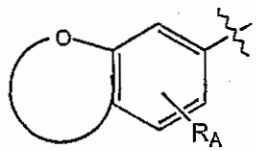
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl,

benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and $-X_4R_B$, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

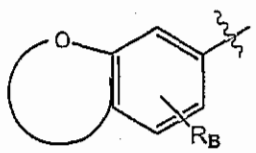
Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-

alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_m$NH-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl),

-N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -$NHS(O)_x$(alkyl), -$S(O)_x$(alkyl), -$S(O)_x$NH(alkyl), -$S(O)_x$N(alkyl)(alkyl), (where x is 0, 1, or 2).

65. A compound according to Claim 62, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy,

haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

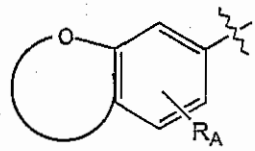
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally

substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



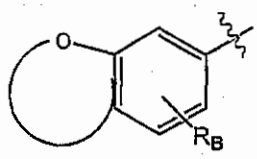
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –X_4R_B, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -C(=O)NR_C-, -$S(O)_m$NH-, -$S(O)_m NR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -C(=O)$NHS(O)_m$-, and –$NR_C S(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

66. A compound according to Claim 62, wherein:

R is hydrogen, halogen, hydroxy, C_1-C_6 alkoxy, haloalkyl, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or

di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

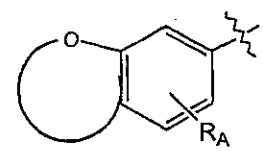
R_2 is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl and haloalkyl;

R_3 is hydrogen C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

R_4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl,

R_4 is a bicyclic oxygen-containing group of the formula:



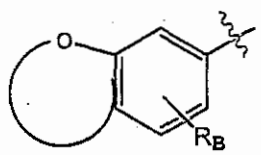
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, and benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

67. A compound according to Claim 66, wherein

R, R_2, R_3, R_4, and Ar_2 are as defined in Claim 66;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

68. A compound according to Claim 66, wherein:

R, R_2, and R_3 are as defined in Claim 66;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:

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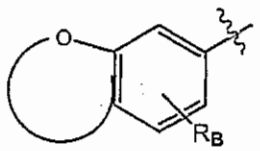


wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

69. A compound according to Claim 66, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

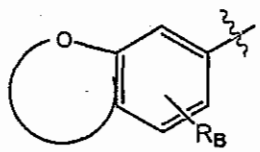
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-

C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

70. A compound according to Claim 66, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

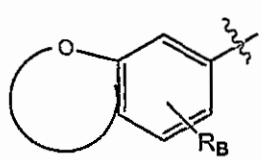
R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

71. A compound according to Claim 66, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

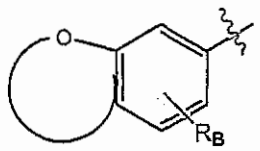
R_3 is hydrogen, methyl, or ethyl;

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

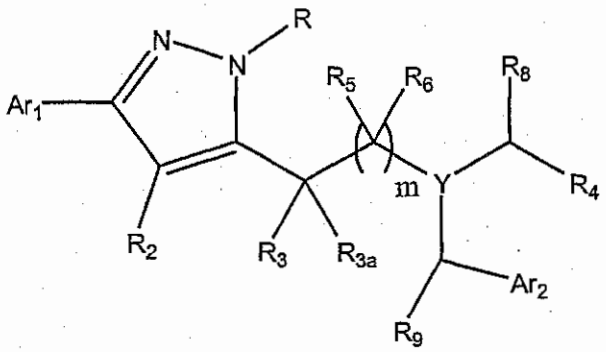
Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

72. A compound of the formula:



or pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

m is 0, 1, or 2;

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form an optionally substituted saturated carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ringof from 5 to 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

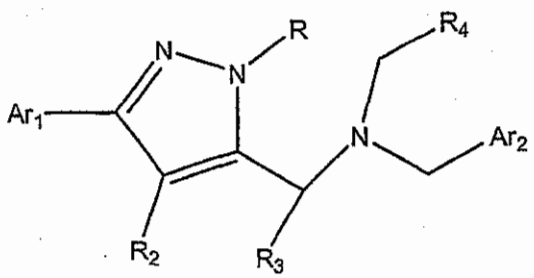
R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

73. A compound according to Claim 72, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

74. A compound according of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R is chosen from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted

alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted (cycloalkyl)alkyl,

optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms;

R_2 and R_3 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R and R_3 may be joined to form an optionally substituted carbocylic ring of from 5 to 8 members or an optionally substituted heterocyclic ring of from 5 ro 8 members;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

75. A compound according to Claim 74, wherein R and R_3 are not joined.

76. A compound according to Claim 74, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

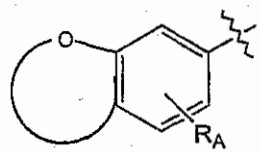
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally

substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



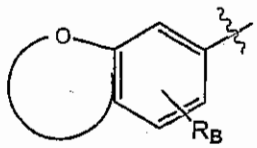
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_mNH$-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and -$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl),

-N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -$NHS(O)_x$(alkyl), -$S(O)_x$(alkyl), -$S(O)_xNH$(alkyl), -$S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

77. A compound according to Claim 74, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

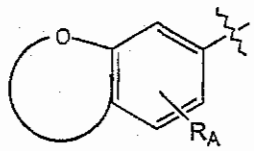
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl,

hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, –X_4R_B, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



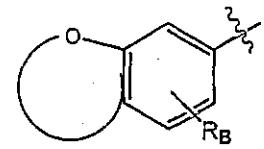
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and –X_4R_B, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_m$NH-, -$S(O)_mNR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

78. A compound according to Claim 74, wherein:

R is hydrogen, halogen, hydroxy, C_1-C_6 alkoxy, haloalkyl, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or

di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

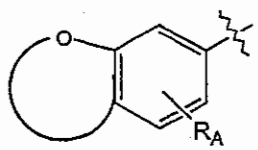
R_2 is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl and haloalkyl;

R_3 is hydrogen C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

R_4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl,

R_4 is a bicyclic oxygen-containing group of the formula:



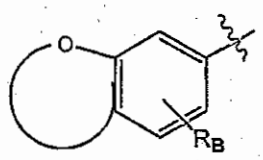
wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, and benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

79. A compound according to Claim 78, wherein

R, R_2, R_3, R_4, and Ar_2 are as defined in Claim 78;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

80. A compound according to Claim 78, wherein:

R, R_2, and R_3 are as defined in Claim 78;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl,

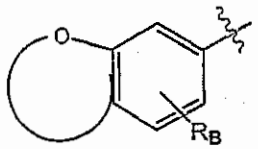
trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

81. A compound according to Claim 78, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

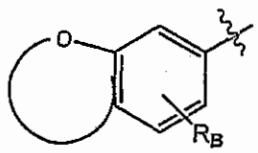
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-

C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

82. A compound according to Claim 78, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

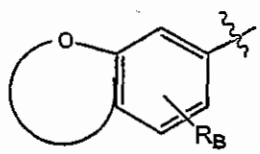
R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

83. A compound according to Claim 78, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

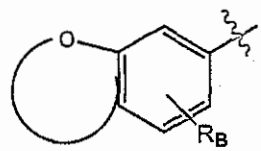
R_3 is hydrogen, methyl, or ethyl;

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

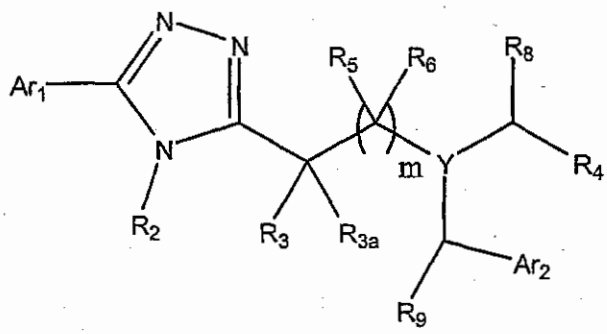
Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

84. A compound of the formula:



or pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

m is 0, 1, or 2;

R_2, R_3, R_{3A}, R_5, and R_6 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

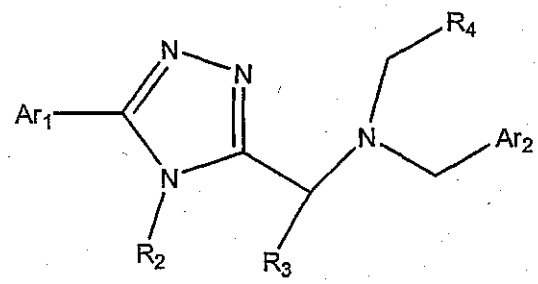
R_8 and R_9 are independently chosen from H or optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, (cycloalkyl)alkyl, haloalkyl, or the like.

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

85. A compound according to Claim 84, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

86. A compound according of the formula:



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

R_2 and R_3 are independently selected from hydrogen, hydroxy, halogen, amino, cyano, nitro, haloalkyl, alkoxy, mono- or dialkylamino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, and optionally substituted (cycloalkyl)alkyl;

R_4 is alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl each of which may be optionally substituted; or

R_4 is optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

87. A compound according to Claim 86, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, alkoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, and

ii) alkyl, alkenyl, alkynyl, cycloalkyl, and (cycloalkyl)alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or dialkylamino;

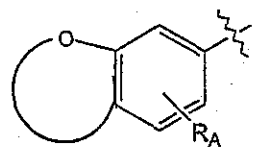
R_4 is hydrogen or

alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino and mono- or dialkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl,

oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and $-X_4R_B$, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

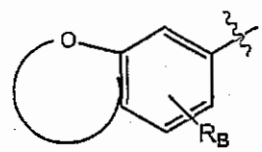
Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, mono- or

dialkylamino, aminoalkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or dialkylaminocarbonyl, N-alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl and –X_4R_B, wherein X_4 and R_B are as defined below;, and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkyl, alkenyl, alkynyl, alkoxy, amino, and mono- or dialkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -$C(=O)NR_C$-, -$S(O)_mNH$-, -$S(O)_mNR_C$-, -NHC(=O)-,

-$NR_CC(=O)$-, -$NHS(O)_m$-, -$C(=O)NHS(O)_m$-, and –$NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(alkyl), -NH(alkyl), -N(alkyl)(alkyl), -NHC(O)(alkyl), -N(alkyl)C(O)(alkyl), -$NHS(O)_x$(alkyl), -$S(O)_x$(alkyl), -$S(O)_xNH$(alkyl), -$S(O)_xN$(alkyl)(alkyl), (where x is 0, 1, or 2).

88. A compound according to Claim 86, wherein:

R is selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, and mono- or di(C_1-C_6)alkylamino,

iii) phenyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

R_2 and R_3 are independently selected from

i) hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, haloalkyl, and

ii) C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, each of which may be unsubstituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino;

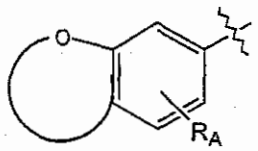
R_4 is hydrogen or

C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl,

benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, $-X_4R_B$, wherein X_4 and R_B are as defined below; or

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

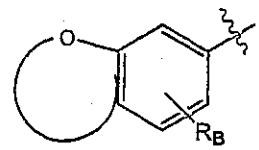
Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenylalkyl, chromanyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzimidazolyl, naphthyl, indolyl, indanyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, or quinoxalinyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of

carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl, and $-X_4R_B$, wherein X_4 and R_B are as defined below; and

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

X_4 is independently selected at each occurrence from the group consisting of -CH_2-, -CHR_C-, -O-, -$S(O)_m$-, -NH-, -NR_C-, -C(=O)NH-, -C(=O)NR_C-, -$S(O)_m$NH-, -$S(O)_m$$NR_C$-, -NHC(=O)-,

-NR_CC(=O)-, -$NHS(O)_m$-, -C(=O)$NHS(O)_m$-, and $-NR_CS(O)_m$- (where m is 0, 1, or 2); and

R_B and R_C, which may be the same or different, are independently selected at each occurrence from the group consisting of:

hydrogen, straight, branched, or cyclic alkyl groups, which may contain one or more double or triple bonds, each of which may unsubstituted or substituted with one or more substituent(s) selected from:

oxo, hydroxy, -O(C_1-C_6 alkyl), -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)(C_1-C_6 alkyl), -NHC(O)(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)C(O)(C_{1-6} alkyl), -$NHS(O)_x$(C_1-C_6 alkyl), -$S(O)_x$(C_1-C_6 alkyl), -$S(O)_x$NH(C_1-C_6 alkyl), -$S(O)_x$N(C_1-C_6 alkyl)(C_1-C_6 alkyl), (where x is 0, 1, or 2).

89. A compound according to Claim 86, wherein:

R is hydrogen, halogen, hydroxy, C_1-C_6 alkoxy, haloalkyl, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, and (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

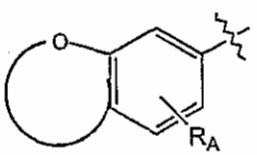
R_2 is selected from C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl and haloalkyl;

R_3 is hydrogen C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl;

R_4 is C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl,

R_4 is a bicyclic oxygen-containing group of the formula:



wherein R_A represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl,

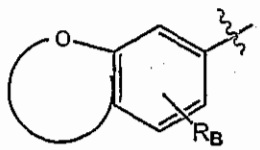
C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from

i) phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, and benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

ii) bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

90. A compound according to Claim 89, wherein

R, R_2, R_3, R_4, and Ar_2 are as defined in Claim 89;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy.

91. A compound according to Claim 89, wherein:

R, R_2, and R_3 are as defined in Claim 89;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

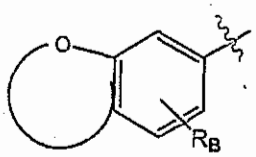
R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-

C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

92. A compound according to Claim 89, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or

R is phenyl substituted with up to five groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino, aminocarbonyl, sufonamido, mono or di(C_1-C_6)alkylsulfonamido, 3,4-methylenedioxy, and 3,4-(1,2-ethylene)dioxy;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino,

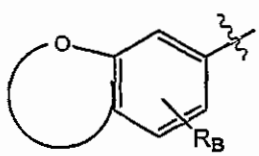
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl,

benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

93. A compound according to Claim 89, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

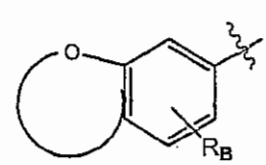
R_3 is hydrogen, methyl, or ethyl;

R_4 is C_3-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_8cycloalkyl, (C_{3-8} cycloalkyl)C_1-C_4alkyl, C_1-C_8 haloalkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy; and

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

94. A compound according to Claim 89, wherein:

R is hydrogen, C_1-C_8 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, or (C_3-C_8)cycloalkyl) C_1-C_3 alkyl, or phenyl;

R_2 is C_3-C_6 alkyl;

R_3 is hydrogen, methyl, or ethyl;

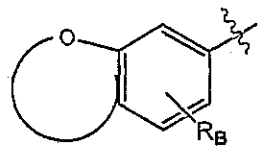
R_4 is phenyl, ethylenedioxyphenyl, methylenedioxyphenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or phenyl with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, and amino(C_1-C_6)alkoxy;

Ar_2 is phenyl, phenyl(C_1-C_4)alkyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, chromanyl, dihydrobenzofuranyl, naphthyl, indolyl, indanyl, benzo[b]thiophenyl, benzodioxanyl, benzodioxinyl, benzodioxolyl, or benz[d]isoxazolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6}

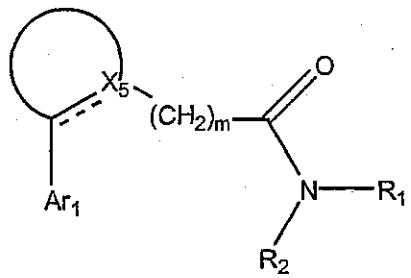
alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, 1-piperidyl; or

Ar_2 is bicyclic oxygen-containing groups of the formula:



wherein R_B represents 0 to 3 groups selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

95. A compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein:

X_5 is C, N or CH;

m is 0, 1, 2, or 3;

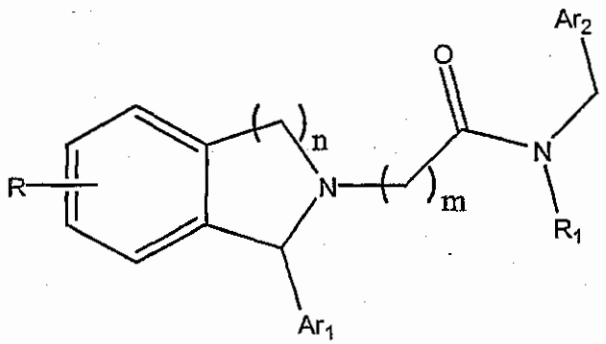
Ar_1 is chosen from optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

R_1 and R_2 are independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6

alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 and R_2 are independently chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

96. A compound according to Claim 95 of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is as defined in Claim 95;

m is 1, 2, or 3;

n is 1, 2, or 3;

$(\quad)_m$ represents a carbon chain that may be substituted with hydrogen, halogen, cyano, nitro amino, mono or dialkyl amino, alkenyl, alkynyl, alkoxy,

trifluoromethyl, trifluoromethoxy, straight or branched chain alkyl, or cycloalkyl;

Ar_1 and Ar_2 independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl or heteroalicyclic group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms; and

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or dialkylaminocarbonyl, sulfonamido, and mono or dialkylsulfonamido.

97. A compound according to Claim 96, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

98. A compound according to Claim 96, wherein

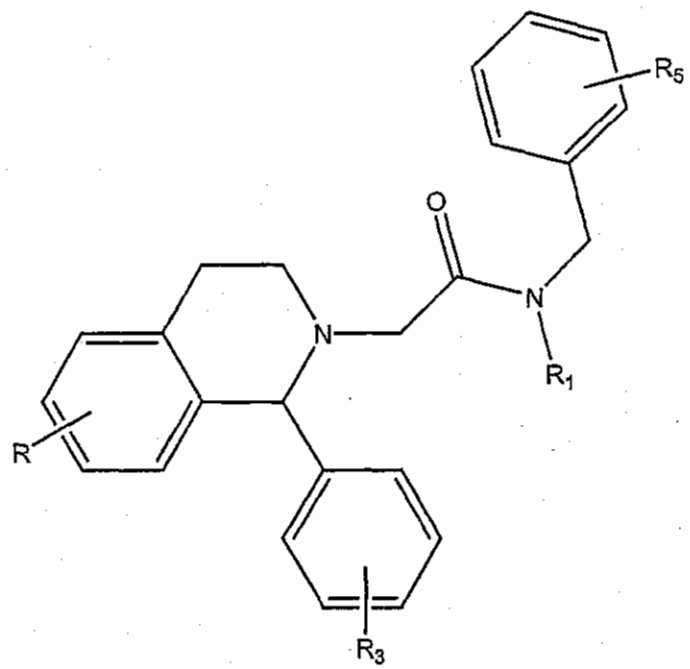
n, m, and R_1 are defined as in Claim 96;

Ar_1 is independently chosen from phenyl, pyridyl, and pyrimidinyl each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido; and

Ar_2 represents suberanyl, indanyl, tetrhydronaphtyl, or indolyl, each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl,

C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido.

99. A compound according to Claim 95 of the formula



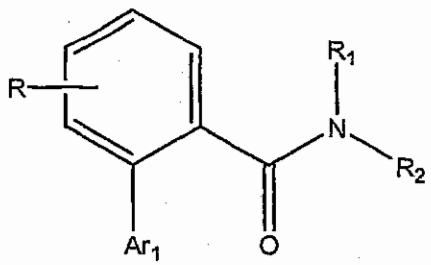
R, R_3, and R_5 each represent up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, and mono or di(C_1-C_6)alkylsulfonamido; and represents suberanyl, indanyl, tetrhydronaphtyl, or indolyl, each of which is optionally optionally substituted or substituted with up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8cycloalkyl) C_1-C_3alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-

C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido.

R_1 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 is chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

100. A compound according to Claim 95 of the formula:



or a pharmaceutically acceptable salt or prodrug, thereof, wherein:

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy carbonyl (COOH),

aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or dialkylsulfonamido;

R_1 and R_2 are independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 and R_2 are independently chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

Ar_1 is chosen from optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic, heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms, ethylenedioxyphenyl or methylenedioxyphenyl.

101. A compound according to Claim 100, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

102. A compound according to Claim 100, wherein

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

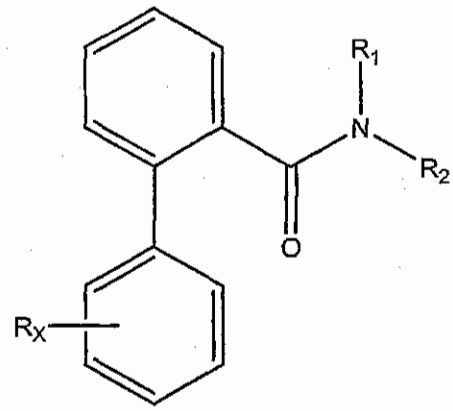
R_1 and R_2 are independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 and R_2 are independently chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

Ar_1 is chosen from ethylenedioxyphenyl, methylenedioxyphenl, phenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, and pyridyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy,

haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, and N-(C_1-C_6)alkylsulfonylaminocarbonyl; and

103. A compound according to Claim 102, of the formula



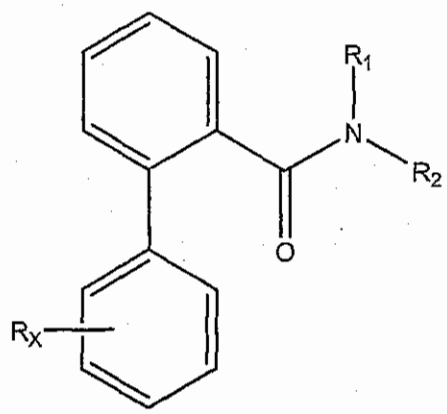
wherein:

R_2 is as defined in Claim 102;

R_X represents up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and

R_1 is C_1-C_6alkyl, C_3-C_8cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4alkyl, phenyl, phenylC_1-C_6alkyl, chromanyl, chromanylC_1-C_6alkyl, imidazolyl, imidazolylC_1-C_6alkyl ,pyridyl, pyridylC_1-C_6alkyl, pyrimidyl, pyrimidylC_1-C_6alkyl,pyrazinyl, pyrazinylC_1-C_6alkyl, indolyl, indolylC_1-C_6alkyl, indanyl, indanylC_1-C_6alkyl, benzodioxolyl, or benzodioxolylC_1-C_6alkyl each or which may be unsubstituted or substituted with up to 4 substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino.

104. A compound according to Claim 102, of the formula:



wherein:

R_X represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy substituted with 0-2 R_2, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl;

R_1 is phenyl, phenylC_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalky(C_1-C_4 alkyl), naphthyl, napthylC_1-C_6alkyl, indanyl, indanylC_1-C_6 alkyl, benzodioxolanyl, or benzodioxolanylC_1-C_6 alkyl, each of which may be substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl; and

R_2 is chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_2 is chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl,

C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

105. A compound according to Claim 102 wherein:

R_2 is as defined in Claim 102;

R represents up to 4 groups independently chosen from hydrogen, halogen, amino, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, and trifluoromethoxy;

R_1 is phenyl, benzyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl(C_1-C_4 alkyl), naphthyl, naphthyl-CH_2-, indanyl, indandyl-CH_2-, benzodioxolanyl-CH_2-, or benzodioxolanyl, each of which may be substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl; and

Ar_1 is chosen from ethylenedioxyphenyl, methylenedioxyphenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and amino.

106. A compound according to Claim 102 wherein:

R represents up to 4 groups independently chosen from hydrogen, halogen, amino, C_1-C_6 alkoxy, C_1-C_6 alkyl, trifluoromethyl, and trifluoromethoxy;

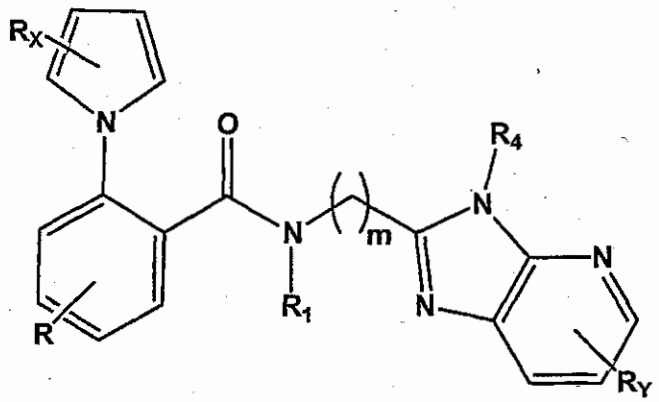
R_1 is benzyl which is unsubstituted or substituted by up to 4 groups chosen from halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl;

Ar_1 is chosen from ethylenedioxyphenyl, methylenedioxyphenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, trifluoromethyl, trifluoromethoxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, and amino; and

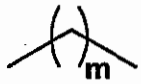
R_2 is chosen from phenyl, benzyl, indolyl, indolyl-CH_2-, indanyl, indanyl-CH_2-, chromanyl, chromanyl-CH_2-, benzofuranyl, benzofuranyl-CH_2-, benzodioxinyl, benzodioxinyl-CH_2-, benzodioxolyl-CH_2-, and benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from:

halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, and mono- or di(C_1-C_6)alkylamino.

107. A compound according to Claim 102, of the Formula



wherein:

m is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydroxy, halogen, or amino;

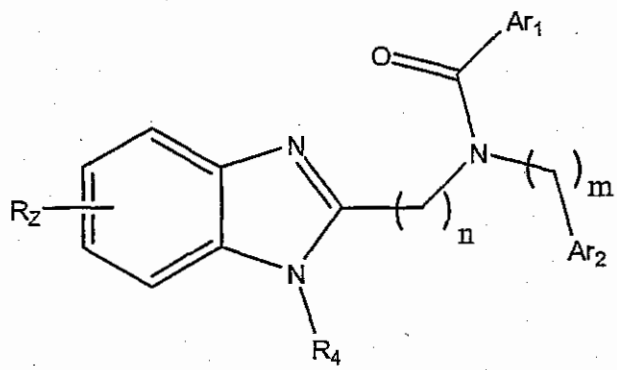
R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6alkyl, C_2-C_6 alkenyl, C_1-C_6alkynyl, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino;

R_X and R_Y each represent up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl; and

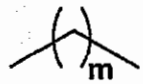
R_1 and R_4 are independently selected from C_1-C_6alkyl, C_3-C_8cycloalkyl, (C_3-C_8 cycloalkyl)C_1-C_4alkyl, phenyl, phenylC_1-C_6alkyl, pyridyl, and pyridylC_1-

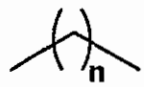
C_6alkyl, each or which may be unsubstituted or substituted with up to 4 substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino.

108. A compound according to Claim 1 of the formula



or a pharmaceutically acceptable salt, prodrug or hydrate thereof, wherein;

m is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydoxy, halogen, or amino;

n is 0, 1, 2, or 3, and  represents a carbon chain which is optionally substituted with methyl, ethyl, methoxy, ethoxy, hydoxy, halogen, or amino;

R_Z represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, and(cycloalkyl)alkyl;

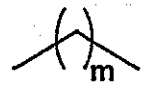
R_4 is chosen from alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl) alkyl, aryl and arylalkyl, each of which may be unsubstituted, optionally substituted or substituted by one or more of halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, alkoxy, amino, mono- or dialkylamino; and

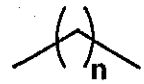
Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic or heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms.

109. A compound according to Claim 108, wherein the compound exhibits an IC_{50} of 1uM or less in an assay of C5a mediated chemotaxis or calcium mobilization.

110. A compound according to Claim 108, wherein

m is 1 and  represents a carbon chain which is unsubstituted;

n is 1 and  represents a carbon chain which is unsubstituted;

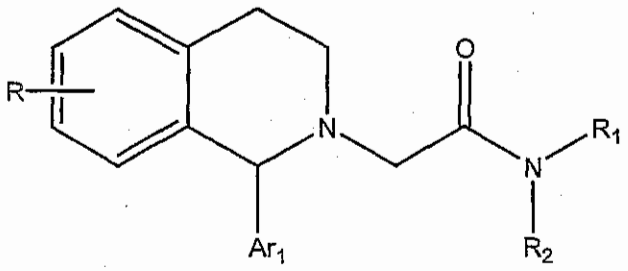
R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_2-C_6 cycloalkyl, and(C_3-C_8 cycloalkyl) C_1-C_4 alkyl;

R_2 is C_3-C_8 alkyl or C_3-C_8 cycloalkyl;

Ar_1 is ethylenedioxyphenyl, methylenedioxyphenyl, or;

Ar_1 and Ar_2 are independently chosen from phenyl, phenyl(C_1-C_4)alkyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, pyridyl, pyrimidyl, and pyrazinyl, each of which may be unsubstituted or optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino.

111. A compound according to Claim 95 of the formula

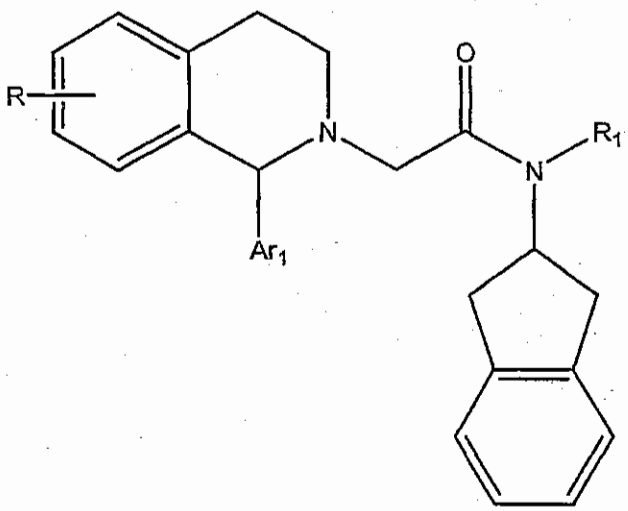


wherein:

Ar_1, R_1 and R_2 are as defined in Claim 95; and

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

112. A compound according to Claim 95 of the formula



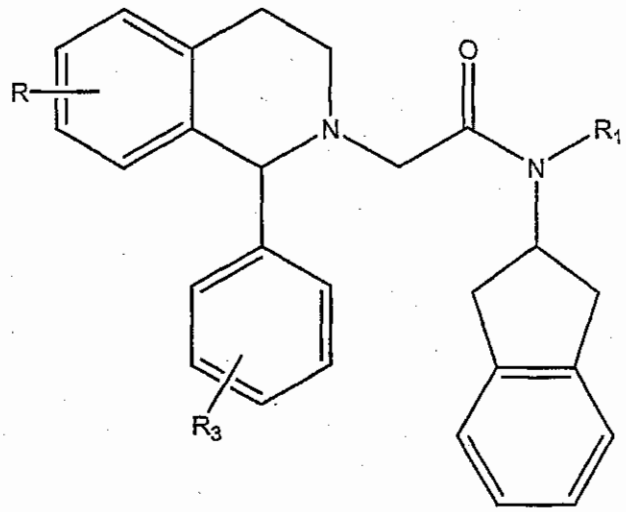
wherein:

Ar_1 and R_1 are as defined in Claim 95; and

R represents up to 4 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$),

mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

113. A compound according to Claim 95 of the formula

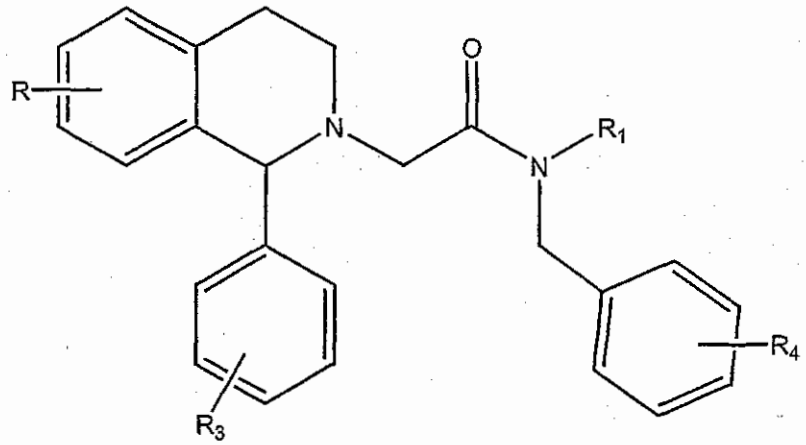


wherein:

R_1 is as defined in Claim 95; and

R and R_3 represent up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

114. A compound according to Claim 95 of the formula

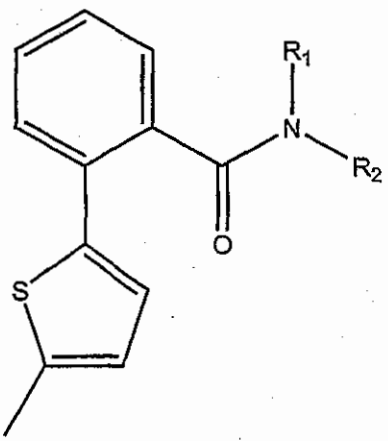


wherein:

R_1 is as defined in Claim 95; and

R, R_3 and R_4 represent up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, (C_3-C_8 cycloalkyl) C_1-C_3 alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, 3,4-methylenedioxy, ethylenedioxy, and mono or di(C_1-C_6)alkylsulfonamido;

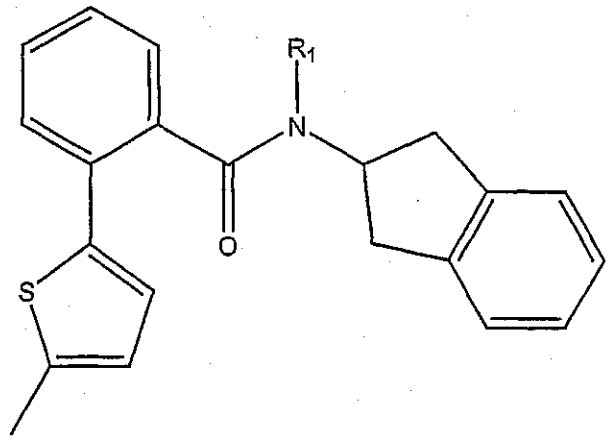
115. A compound according to Claim 95 of the formula



wherein:

R_1 and R_2 are as defined in Claim 95.

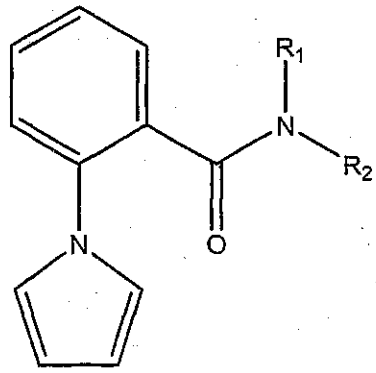
116. A compound according to Claim 95 of the formula



wherein:

R_1 is as defined in Claim 95.

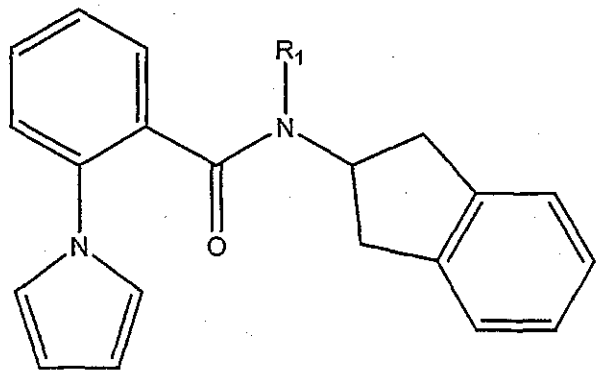
117. A compound according to Claim 95 of the formula



wherein:

R_1 and R_2 are as defined in Claim 95.

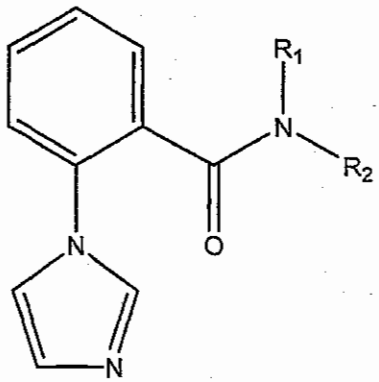
118. A compound according to Claim 95 of the formula



wherein:

R_1 is as defined in Claim 95.

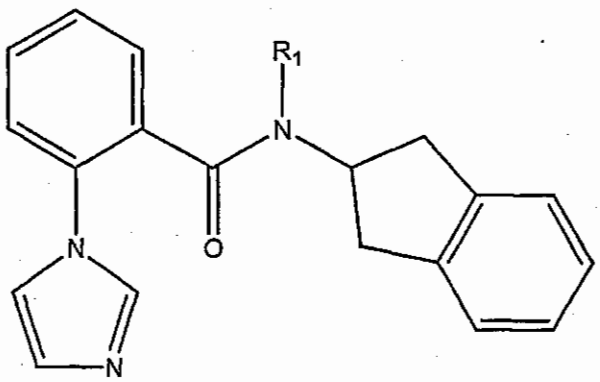
119. A compound according to Claim 95 of the formula



wherein:

R_1 and R_2 are as defined in Claim 95.

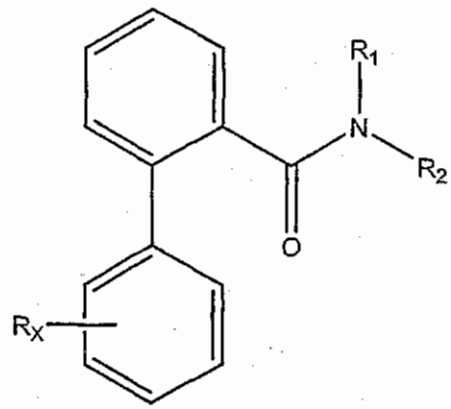
120. A compound according to Claim 95 of the formula



wherein:

R_1 is as defined in Claim 95.

121. A compound according to Claim 95 of the formula

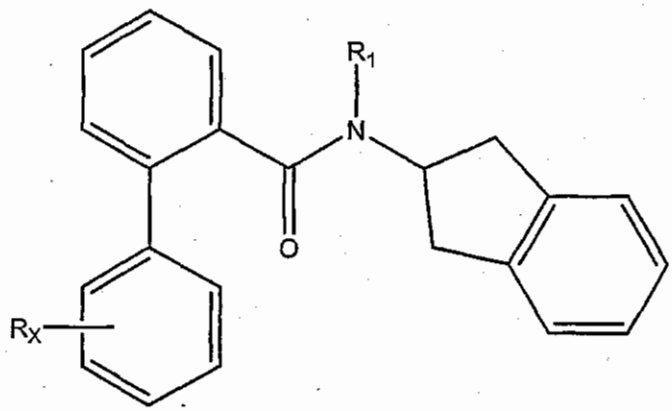


wherein:

R_1 and R_2 are as defined in Claim 95; and

R_X represents up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl.

122. A compound according to Claim 95 of the formula

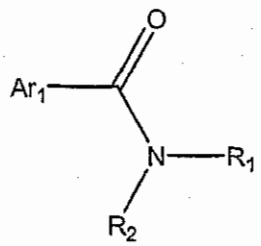


wherein:

R_1 is as defined in Claim 95; and

R_X represents up to 5 groups independently chosen from hydrogen, halogen, hydroxy, amino, C_1-C_6 alkoxy, acetoxy, mono- or di(C_1-C_6)alkylamino, cyano, nitro, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl.

123. A compound according to Claim 1 of the formula



wherein

R_1 and R_2 are independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

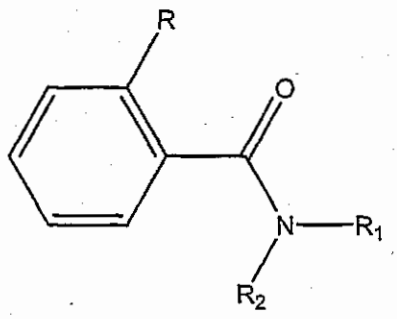
R_1 and R_2 are independently chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

Ar_1 is chosen from optionally substituted carbocyclic aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or an optionally substituted heteroalicyclic, heteroalicyclicalkyl group having from 1 to 3 rings, 3 to 8 members in each ring and from 1 to 3 heteroatoms, ethylenedioxyphenyl or methylenedioxyphenyl; and

124. A compound according to Claim 123 wherein

R_1 and R_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

125. A compound according to Claim 123 of the formula



wherein

R_1 and R_2 are independently chosen from C_{1-8} alkyl, C_{2-8} alkenyl, C_{2-8} alkynyl, C_{3-8}cycloalkyl, (C_{3-8} cycloalkyl)C_{1-4}alkyl, each or which may be unsubstituted or substituted with one or more substituents selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino and mono- or di(C_1-C_6)alkylamino, or

R_1 and R_2 are independently chosen from phenyl, phenylalkyl, chromanyl, chromanylalkyl, imidazolyl, imidazolylalkyl, pyridyl, pyridylalkyl, pyrimidyl, pyrimdylalkyl, pyrazinyl, pyrazinylalkyl, indolyl, indolylalkyl, indanyl, indanylalkyl, imidazopyridyl, azaimidazopyridyl, benzimidazoyl, benzimidazoylalkylbenzodioxolylalkyl, or benzodioxolyl, each of which may be optionally substituted or substituted with up to four groups independently selected from halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, haloalkyl, hydroxy, acetoxy, C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, amino(C_1-C_6)alkoxy, carboxylic acid, esters of carboxylic acids, aminocarbonyl, mono or di(C_1-

C_6)alkylaminocarbonyl, N-(C_1-C_6)alkylsulfonylaminocarbonyl, 1-azetidinyl, 1-pyrrolidinyl, and 1-piperidyl;

R is chosen from hydrogen, halogen, hydroxy, amino, alkoxy, acetoxy, mono- or dialkylamino, cyano, nitro, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, hydroxy carbonyl (COOH), aminocarbonyl ($CONH_2$), mono or di(C_1-C_6)alkylaminocarbonyl, sulfonamido, and mono or dialkylsulfonamido;

126. A compound according to Claim 125 wherein

R_1 and R_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

127. A compound according to Claim 95 wherein:

Ar_1 is bound to the ring bearing X_5 to form an optionally substituted heterocyclic 5-8 member ring.

128. A compound according to Claim 95 wherein:

R_1 and R_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

129. A compound according to Claim 95 wherein:

Ar_1 is bound to the ring bearing X_5 to form an optionally substituted heterocyclic 5-8 member ring; and

R_1 and R_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

130. A compound according to Claim 5 wherein:

R_4 and Ar_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

131. A compound according to Claim 8 wherein:

R_4 and Ar_2 are connected to form a 5-8 member optionally substituted carbocyclic or heterocyclic ring.

132. A compound according to Claim 3 wherein:

A has hydrogen bond acceptor ability.

133. A compound as set forth in any of Tables 1 through 6, or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

134. A compound that is:

1-(1-butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenyl methyl])aminomethylimidazole

1-(1-butyl)-2-phenyl-5-(1-[N-{3,4-methylenedioxyphenylmethyl}-N-phenylmethyl]amino)ethylimidazole

1-Butyl-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])amino-methylimidazole

1-(1-Butyl)-2-phenyl-4-methyl-5-(N-[3,4-methylenedioxyphenyl-methyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[1,4-benzodioxan-6-yl]methyl-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(2-fluorophenyl)-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)amino- methylimidazole

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[naphtha-2-ylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole

1-(1-Butyl)-2-(2-methoxyphenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(2-methylphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole

1-(1-Butyl)-2-(2-methylphenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[naphth-2-ylmethyl]-N-phenylmethyl)amino methylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N,N-di[3,4-methylenedioxyphenylmethyl])amino- methylimidazole

1-(1-Butyl)-2-(3-methoxyphenyl)-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)- aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-{1-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)amino} ethylimidazole

1-(1-Pentyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Propyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl) aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[1-(*S*)-phenylethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[1-(*R*)-phenylethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenyl]methyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N,N-di[3,4-methylenedioxyphenylmethyl]) aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-methoxyphenylmethyl])-aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyl}phenylmethyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dichlorophenylethyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-nitrophenylmethyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[4-{1-propyloxy} phenylmethyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[quinol-6-ylmethyl])- aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2,3-dichlorophenylmethyl])-aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3,4-dimethylphenylmethyl])-aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[indan-2-yl])-aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-phenylethyl])amino-methylimidazole

1-(1-Propyl)-2-phenyl-5-(N-[1,4-benzodioxan-6-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-ethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-propyl])aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-butyl])aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cycloheptylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-isobutyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-cyclopentylethyl])amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[3-cyclopentylpropyl])amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-n-octyl])aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopropylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclopentylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-cyclohexylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[t-amyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{3-methyl}butyl)]amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[1-{2,2-dimethyl}butyl]) aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-methyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[2-thiophenylmethyl])amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[indol-5-ylmethyl])amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenylmethyl]-N-[{1-methylindol-5-yl}methyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[4-hydroxy-2-chlorophenyl]-methyl)aminomethylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenyl}methyl-N-phenylmethyl]) aminoethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-methylenedioxyphenyl]methyl-N-[2,3-dihydrobenzo[b]furan-5-yl]methyl)aminomethylimidazole

1-Butyl-2-(4-fluorophenyl)-5-(1-[N-{3,4-methylenedioxyphenyl}methyl-N-phenylmethyl]-amino)ethylimidazole

1-(1-Butyl)-2-(2-thienyl)-5-(N-[3,4-methylenedioxyphenyl]methyl-N-phenylmethyl] aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4,5-trimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-phenylmethyl-N-[3,4-dimethoxyphenylmethyl])aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-methylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[3-methyl-4-aminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole)

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3,4-difluorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-(benzo[b]thiophen-5-ylmethyl)-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-ethoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-4-bromo-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-methoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[6-chloro-3,4-methylenedioxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[3-methoxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-fluorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-4-bromo-5-(N-[2,3-dichlorophenylmethyl]-N-[1-butyl])aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[2,6-dichlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-4-chloro-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-diethylaminophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-2-ylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-3-ylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[pyridin-4-ylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2-fluoro-6-chlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole)

1-(1-Butyl)-2-phenyl-5-(N-[2,4-dichlorophenylmethyl]-N-phenylmethyl)aminomethyl-imidazole)

1-(1-Butyl)-2-phenyl-5-(N-[4-chlorophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-hydroxyphenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-trifluoromethoxyphenylmethyl]-N-phenylmethyl)aminomethyl-imidazole)

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-3,4-dimethoxyphenylmethyl]-N-phenylmethyl)amino-methylimidazole)

1-(1-Butyl)-2-phenyl-5-(N-[4-nitrophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[4-aminophenylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2,4-diphenyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2-aminopyridin-5-ylmethyl]-N-phenylmethyl)aminomethyl-imidazole

1-(1-Butyl)-2-phenyl-5-(N-[2,3-dihydrobenzo[b]furan-5-ylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-[1-butyl])aminomethyl-imidazole) ;

Bis-benzo[1,3]dioxol-5-ylmethyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amine;

Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-5-(4-methoxy-phenyl)-2-phenyl-3H-imidazol-4-ylmethyl]-amine;

4-({Benzyl-[1-(3-butyl-2,5-diphenyl-3H-imidazol-4-yl)-ethyl]-amino}-methyl)-benzamide;

4-{[Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-3-chloro-phenol;

4-({[1-(3-Butyl-2-phenyl-3H-imidazol-4-yl)-pentyl]-cyclohexylmethyl-amino}-methyl)-phenol;

4-{[Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-benzamide;

4-{[Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-2-methyl-phenol;

4-{[(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-cyclohexylmethyl-amino]-methyl}-2-methyl-phenol;

(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(2,6-difluoro-benzyl)-(4-methoxy-benzyl)-amine;

Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(2,3-dihydro-benzo[1,4]dioxin-6-ylmethyl)-amine;

(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(2,5-difluoro-benzyl)-(4-methoxy-benzyl)-amine;

(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(2,6-dichloro-benzyl)-(4-methoxy-benzyl)-amine;

Benzo[1,3]dioxol-5-ylmethyl-butyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3H-imidazol-4-ylmethyl]-amine;

4-({Benzyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3H-imidazol-4-ylmethyl]-amino}-methyl)-benzenesulfonamide;

Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-2-(2-methoxy-phenyl)-5-phenyl-3H-imidazol-4-ylmethyl]-amine;

4-({Butyl-[3-butyl-2-(3-methoxy-phenyl)-5-phenyl-3H-imidazol-4-ylmethyl]-amino}-methyl)-3-chloro-phenol;

4-{[(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(4-methoxy-benzyl)-amino]-methyl}-benzoic acid;

4-({Benzyl-[3-butyl-2-(3-methoxy-phenyl)-5-phenyl-3H-imidazol-4-ylmethyl]-amino}-methyl)-3-chloro-phenol;

Benzo[1,3]dioxol-5-ylmethyl-benzyl-[1-(3-butyl-2,5-diphenyl-3H-imidazol-4-yl)-pentyl]-amine;

Benzo[1,3]dioxol-5-ylmethyl-benzyl-[1-(3-butyl-2,5-diphenyl-3H-imidazol-4-yl)-ethyl]-amine;

4-{[Butyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-benzamide;

Benzo[1,3]dioxol-5-ylmethyl-benzyl-[3-butyl-5-(4-fluoro-phenyl)-2-phenyl-3H-imidazol-4-ylmethyl]-amine;

3-{[Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-phenol;

4-{[Butyl-(3-butyl-5-tert-butyl-2-phenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-benzamide;

4-{[Benzyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-2,6-dimethyl-phenol;

4-({[3-Butyl-5-(4-methoxy-phenyl)-2-phenyl-3H-imidazol-4-ylmethyl]-cyclohexylmethyl-amino}-methyl)-2,6-dimethyl-phenol;

[3-Butyl-5-(4-methoxy-phenyl)-2-phenyl-3H-imidazol-4-ylmethyl]-cyclohexylmethyl-(2,3-dihydro-benzofuran-5-ylmethyl)-amine ;

(4-{[(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-cyclohexylmethyl-amino]-methyl}-phenyl)-dimethyl-amine;

4-{5-[(Bis-benzo[1,3]dioxol-5-ylmethyl-amino)-methyl]-2,4-diphenyl-imidazol-1-yl}-butan-1-ol;

(4-{[(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-cyclohexylmethyl-amino]-methyl}-phenyl)-dimethyl-amine;

4-{[Butyl-(3-butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-amino]-methyl}-2,6-dimethyl-phenol;

4-({Butyl-[1-(3-butyl-2,5-diphenyl-3H-imidazol-4-yl)-ethyl]-amino}-methyl)-2,6-dimethyl-phenol;

4-{[(3-Butyl-2,5-diphenyl-3H-imidazol-4-ylmethyl)-(4-dimethylamino-benzyl)-amino]-methyl}-benzoic acid

1-(1-Butyl)-2-phenyl-4-methyl-5-(N-phenylmethyl-N-[1-butyl])aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2-chloro-4-hydroxyphenylmethyl]-N-phenylmethyl)-aminomethylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[2,3-dichlorophenylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-dimethylaminophenylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-(3-fluorophenyl)-5-(N-[4-{1-pyrrolidinyl}phenylmethyl]-N-phenylmethyl)amino-methylimidazole

1-(1-Butyl)-2-(3-chlorophenyl)-5-(1-[N-{2-chloro-4-hydroxyphenylmethyl}-N-phenylmethyl] amino)ethylimidazole

1-(1-Butyl)-2-phenyl-5-(N-[indol-5-ylmethyl]-N-phenylmethyl)aminomethylimidazole

1-(1-Butyl)-2-(4-fluorophenyl)-5-(1-N,N-di[3,4-methylenedioxyphenylmethyl]amino)ethylimidazole

2-{[5-({Butyl[(1-butyl-2,4-diphenylimidazol-5-yl)methyl]amino}methyl)-2-pyridyl]amino}ethan-1-ol,

or a pharmaceutically acceptable salt, prodrug or hydrate thereof.

135. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 500 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

136. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 200 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

137. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 100 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

138. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 50 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

139. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 25 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

140. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 10 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

141. A compound of any one of claims 1 through 134 wherein the compound exhibits an IC_{50} of about 5 nM or less in a standard in vitro C5a mediated chemotaxis or calcium mobilization assay.

142. A compound of any one of claims 1 through 134 wherein the compound exhibits less than 5% agonist activity in a GTP binding assay.

143. A compound of any one of claims 1 through 134 wherein the compound exhibits a 10-fold selectivity for the antagonist activity over the compound's effects on ATP stimulated responses in a GTP binding assay.

144. A pharmaceutical composition comprising a compound of any one of claims 1 through 143 or a prodrug or hydrate thereof and a pharmaceutically acceptable carrier therefor.

145. A method for treating a patient suffering from or susceptible to a disease or disorder involving pathologic activation of C5a receptors, comprising administering to the patient an effective amount of a compound or composition of any one of claims 1 through 143.

146. A method for treating a patient suffering from or susceptible to an autoimmune disease or disorder, comprising administering to the patient an effective amount of a compound or composition of any one of claims 1 through 143.

147. A method for treating a patient suffering from or susceptible to rheumatoid arthritis, systemic lupus erythematosus, associated glomerulonephritis, psoriasis, Crohn's disease, vasculitis, irritable bowel syndrome, dermatomyositis, multiple sclerosis, bronchial asthma, pemphigus, pemphigoid, scleroderma, myasthenia gravis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, glomerulonephritis, pulmonary hemorrhage), or immunovasculitis, comprising administering to the patient an effective amount of a compound or composition of any one of claims 1 through 143.

148. A method for treating a patient suffering from or susceptible to an inflammatory condition, comprising adminstering to the patient an effective amount of a compound or composition of any one of claims 1 through 143.

149. A method for treating a patient suffering from or susceptble to neutropenia, sepsis, septic shock, Alzheimer's disease, stroke, inflammation associated with burns, lung injury, myocardial infarction, coronary thrombosis, vascular occlusion, post-surgical vascular reocclusion, artherosclerosis, traumatic central nervous system injury, ischemic heart disease, and ischemia-reperfusion injury, acute respiratory distress syndrome, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, tissue graft rejection, or hyperacute rejection of transplanted organs, comprising administering to the patient an effective amount of a compound or composition of any one of claims 1 through 143.

150. A method for treating a patient suffering from or susceptible to pathologic sequellae associated with insulin-dependent diabetes mellitus, lupus nephropathy, Heyman nephritis, membranous nephritis, glomerulonephritis, contact sensitivity responses, or inflammation resulting from contact of blood with artificial surfaces, comprising administering to the patient an effective amount of a compound or composition of any one claims 1 through 143.

151. A method of any one of claims 145 through 150 wherein the patient is a mammal.

152. A method of any one of claims 145 through 150 wherein the patient is a human.

153. A method for inhibiting C5a-promoted cellular chemotaixs, comprising administering to mammalian white blood cells a chemotaxis or calcium mobilization-inhibitor effecitve amount of a compound or composition of any one of claims 1 through 143.

154. The method of claim 153 wherein the white blood cells are human.

155. A method of localizing C5a recerptors in a tissue, comprising:

contacting a tissue with a detectably labelled compound or composition of any one of claims 1 through 143 under conditions that permit binding of the compound to the tissue; and

detecting the bound compound.

156. A method of reducing the severity or frequency of one or more inflammatory sequelae of organ transplantation comprising:

perfusing a donor organ, prior to transplantation of the organ into a recipient patient, with a liquid solution comprising a compound of Claim 1 in a pharmaceutically acceptable carrier, wherein the solution comprises a concentration of the compound that is sufficient,

to inhibit C5a-mediated chemotaxis of cells expressing a C5a receptor in vitro, or

to inhibit C5a-induced calcium mobilization in cells expressing the C5a receptor in vitro, or

to inhibit C5a- induced GTP binding to the membranes of cells expressing the C5a receptor in vitro, or

when present in vivo in an animal's bloodstream when a neutropenia-induction-sufficient amount of C5a is introduced into the bloodstream of the animal, to reduce the resulting C5a-induced neutropenia in vivo;

and

transplanting the donor organ so perfused into the recipient patient to produce a perfused transplant recipient patient;

wherein, following the production of a first plurality of such perfused transplant recipient patients, the severity or frequency of one or more inflammatory sequelae following organ transplantation in the first plurality of patients is reduced when compared to the severity or frequency of said one or more inflammatory sequelae following organ transplantation in a second plurality of control (including historical control) transplant recipient patients who have received transplants of donor organs that have not been so perfused.

157. A compound of any of claims 1 to 143 wherein the compound produces less than a 10%, 5% or 2% reduction of ATP-induced calcium mobilization in a calcium mobilization assay.