OPHTHALMIC COMPOSITIONS AND METHODS FOR THE TREATMENT OF EYE DISORDERS

PRIORITY

[0001] The present application claims the benefit of following Indian Provisional Patent Application No. 201841024038 filed on 27 June 2018, Indian Provisional Patent Application No. 201841024496 filed on 1 July 2018 and Indian Provisional Patent Application No. 201841028857 filed on 31 July 2018 the entire disclosure of which is relied on for all purposes and is incorporated into this application by reference.

FIELD OF THE INVENTION

[0002] This disclosure generally relates to compounds and compositions for the treatment of eye disorders. More particularly, this invention relates to treating subjects with a pharmaceutically acceptable dose of compounds, crystals, solvates, enantiomer, stereoisomer, esters, hydrates, or mixtures thereof.

BACKGROUND OF THE INVENTION

[0003] Age-related eye diseases, in many cases are not sudden but tend to develop slowly as a person ages. Of the many age-related eye diseases, there are four major ones that are recognized and that can be detected and treated if a comprehensive eye examination is performed. These four age-related eye diseases are Macular Degeneration, Cataracts, Glaucoma and Diabetic Retinopathy are expected to dramatically increases if left untreated can cause serious vision loss and blindness. Populations are most at risk for developing eye disease is unaware of the factors that make them susceptible.

[0004] Diseases of the eye leading to blindness are almost exclusively a function of ageing. As the proportion of the elderly population increases around the world, the prevalence and effects of age-related eye diseases are also increasing. The leading causes of blindness and low vision are primarily age-related eye diseases such as age-related macular degeneration, cataract, diabetic retinopathy, and glaucoma. Age-related cataract will become an even larger percentage

of the causes of blindness worldwide, and glaucoma and age-related macular degeneration will emerge as public health issues.

[0005] Most common eye problems include Refractive errors, Cataracts - clouded lenses, Optic nerve disorders, including glaucoma, Retinal disorders - problems with the nerve layer at the back of the eye, Macular degeneration - a disease that destroys sharp, central vision, Diabetic eye problems and Conjunctivitis - an infection also known as pinkeye.

[0006] Presbyopia is the progressive loss of accommodation resulting in loss of the visual ability to focus on objects located at different distances. Accommodation in humans is performed by ciliary muscle and iris sphincter contractions, convergence and changes in the shape and position of the lens. The latter action is passive, meaning that the lens changes are dependent on the ciliary muscle and iris contractions. Also, when the centre of the accommodation is active, the ciliary muscle contraction is stimulated and miosis and convergence occurs in normal binocular patients.

[0007] Haematopoietic stem cell transplantation (SCT) is an established and potentially curative treatment modality for various malignant and non-malignant haematologic diseases. Unfortunately, patients treated with allo-SCT often develop graft-versus-host disease (GVHD), a potentially life-threatening multi-organ systemic disease associated with significant morbidity and mortality. Ocular GVHD (oGVHD) affects 40–60% of patients treated with allo-SCT. Although oGVHD may be the only manifestation of GVHD, it is more frequently seen together with other systemic manifestations and 50–90% of patients with systemic GVHD also have oGVHD.

[0008] Typically, oGVHD involves the anterior segment of the eye, including the lid, lacrimal gland, conjunctiva and cornea. Clinically, the condition manifests primarily as dry eye disease (DED), with keratoconjunctivitis sicca (KCS), and resembles the clinical findings seen in other immunologically mediated inflammatory diseases of the ocular surface. DED is defined as a ‘disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort’. Although DED can occur without keratitis, the terms DED and KCS are often used interchangeably. Patients with DED usually experience symptoms such as redness, photophobia, foreign body sensation, excessive tearing, discharge, blurring of vision and pain.

The ocular surface affliction is irreversible in many cases and patients often experience a significant reduction in quality of life.

[0009] Keratoconjunctivitis sicca, more commonly known as dry eye, is an extremely common and often unrecognized disease. It is the condition in ophthalmology that in its mild grade of severity will affect most of the population at one time or other. Due to a wide variety of presentations and symptoms, it often frustrates the ophthalmologists as well as patients. Due to multifactorial and elusive etiology, it is often challenging to treat dry eye. Ocular surface disorders are also clinically important to treat especially in terms of visual acuity. Xero-dacryology is therefore becoming a very important branch of ophthalmology. Recent studies have given insight into the inflammatory etiology of dry eye. The conventional and main approach to the treatment of dry eye is providing lubricating eye drops or tear substitutes. However, the newer treatment approach is to target the underlying cause of dry eye instead of conventional symptomatic relief.

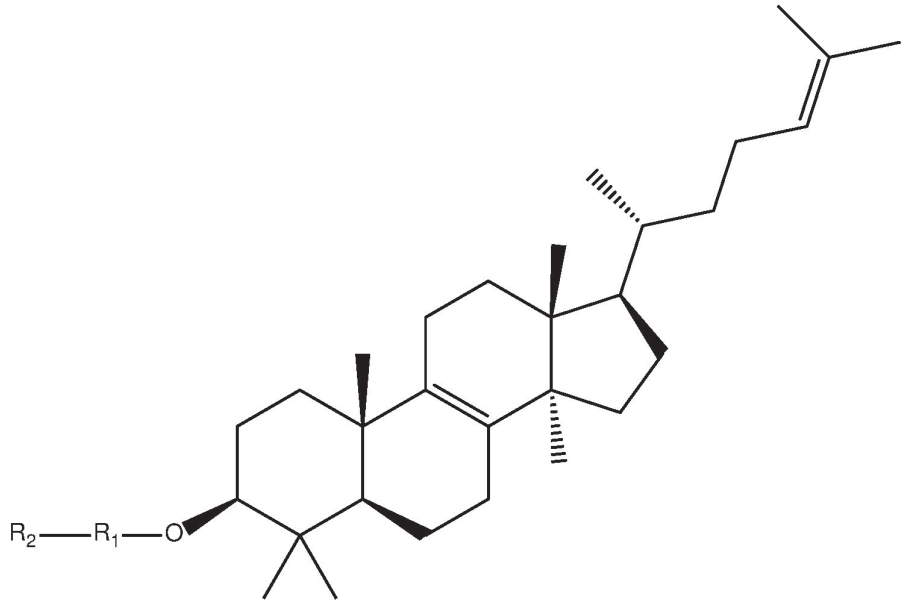
[0010] Cataract still is a leading cause of visual impairment worldwide. Despite the fact that 90% of cataracts in the world are reported in developing countries, its social, physical and economic impact is still substantial in the developed world. Cataract is a common cause of visual impairment in the elderly that is often noticed by patients at an early stage, and surgery is often effective in restoring vision. Nevertheless, cataract surgery still remains a major healthcare cost in Asia, Europe and other Western countries. Progressive ageing of the European population is linked to the increase of incidence and prevalence of cataract. Therefore, a review of modifiable risk factors of cataract and the evaluation of aspects that affect total costs of cataract surgeries is needed. Cataract is a multifactorial disease associated with age, female sex, genetic predisposition, smoking, diabetes mellitus, drug intake and environmental exposure to UVB radiation.

[0011] Managing acute pathology of often relies on the addressing underlying pathology and symptoms of the disease. There is currently a need in the art for new compositions to treatment or delay of the onset of eye disorders and its associated complications progression.

SUMMARY OF THE INVENTION

[0012] The present invention provides compounds, compositions containing these compounds and methods for using the same to treat, prevent and/or ameliorate the effects of the conditions such as eye disorders.

[0013] The invention herein provides compositions comprising of formula I or pharmaceutical acceptable hydrates or solvates thereof. The invention also provides pharmaceutical compositions comprising one or more compounds of formula I or intermediates thereof and one or more of pharmaceutically acceptable carriers, vehicles or diluents. These compositions may be used in the treatment of eye disorders and its associated complications.



Formula I

and pharmaceutically acceptable hydrates, solvates, enantiomers, and stereoisomers thereof;

[0014] wherein,

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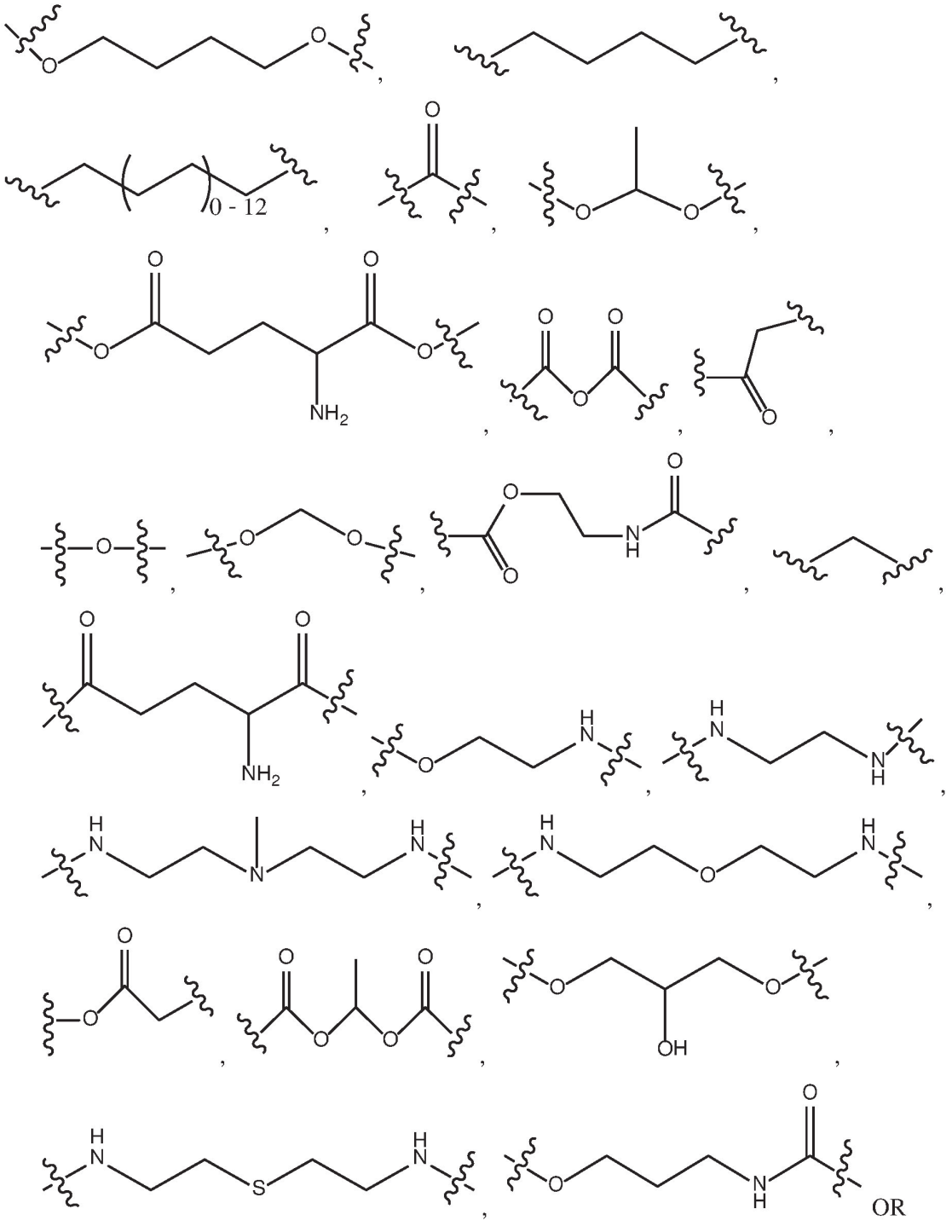
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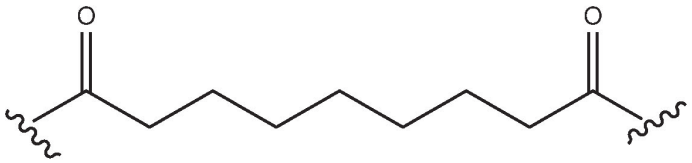

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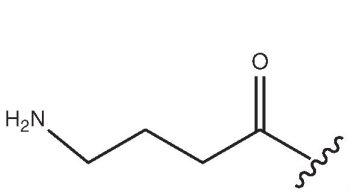

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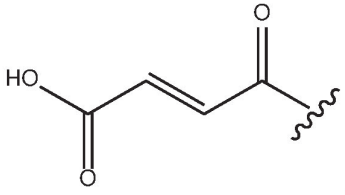

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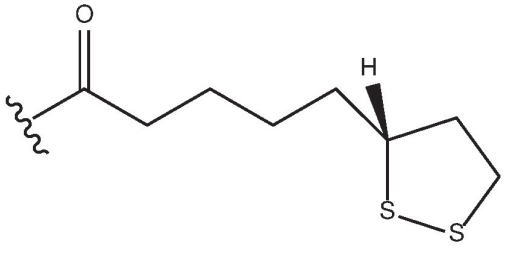

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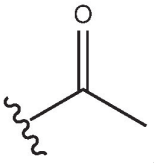

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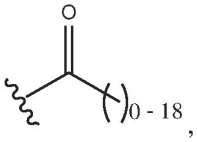

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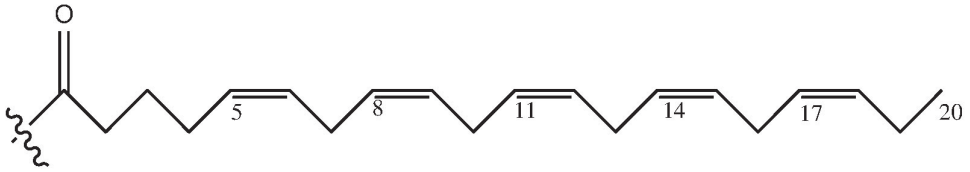

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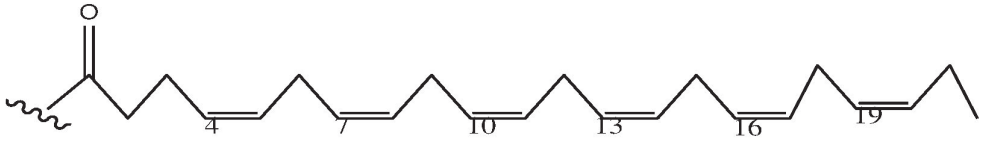

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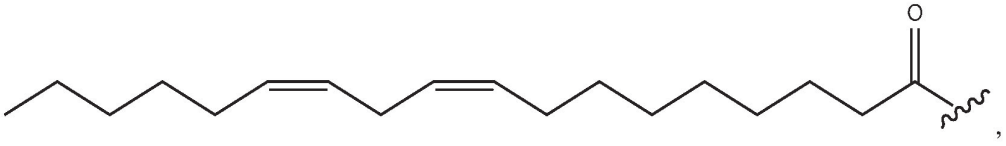

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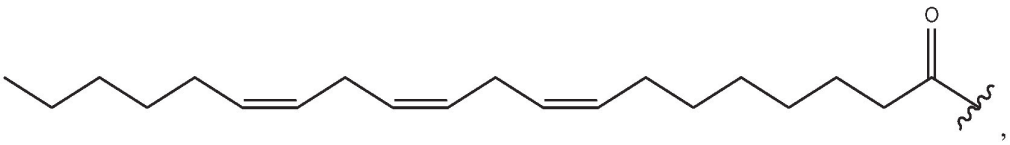

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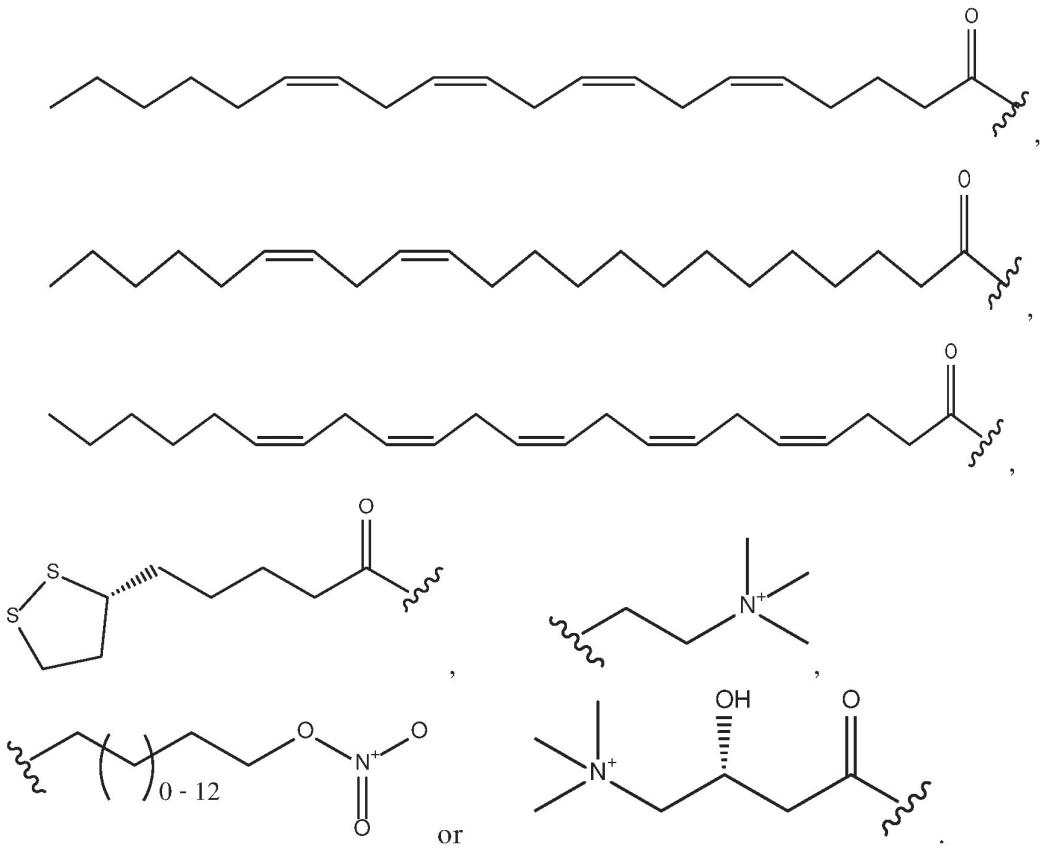
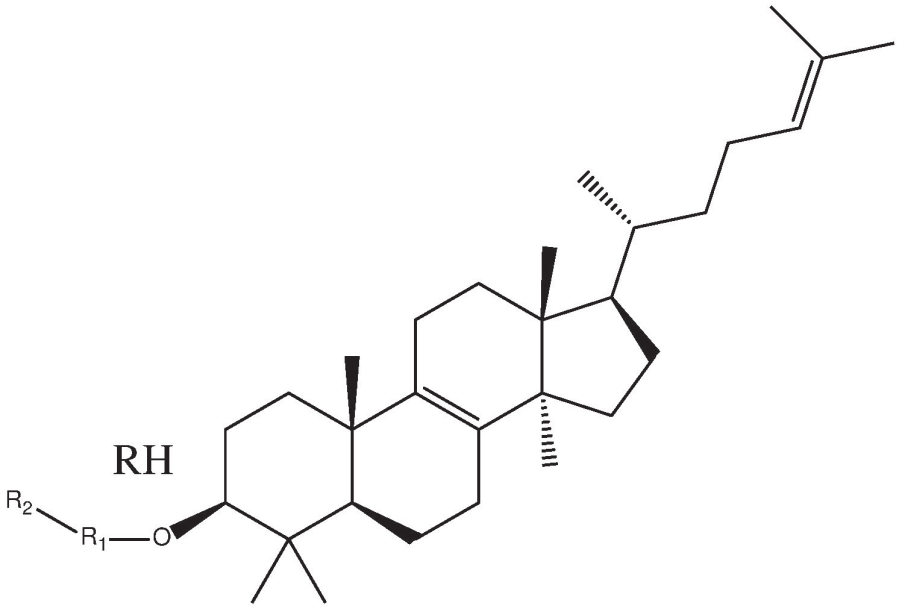


[0015] In another aspect, the compounds of formula II are described:

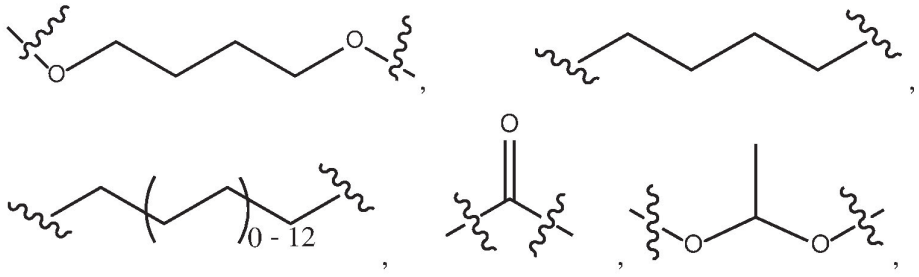


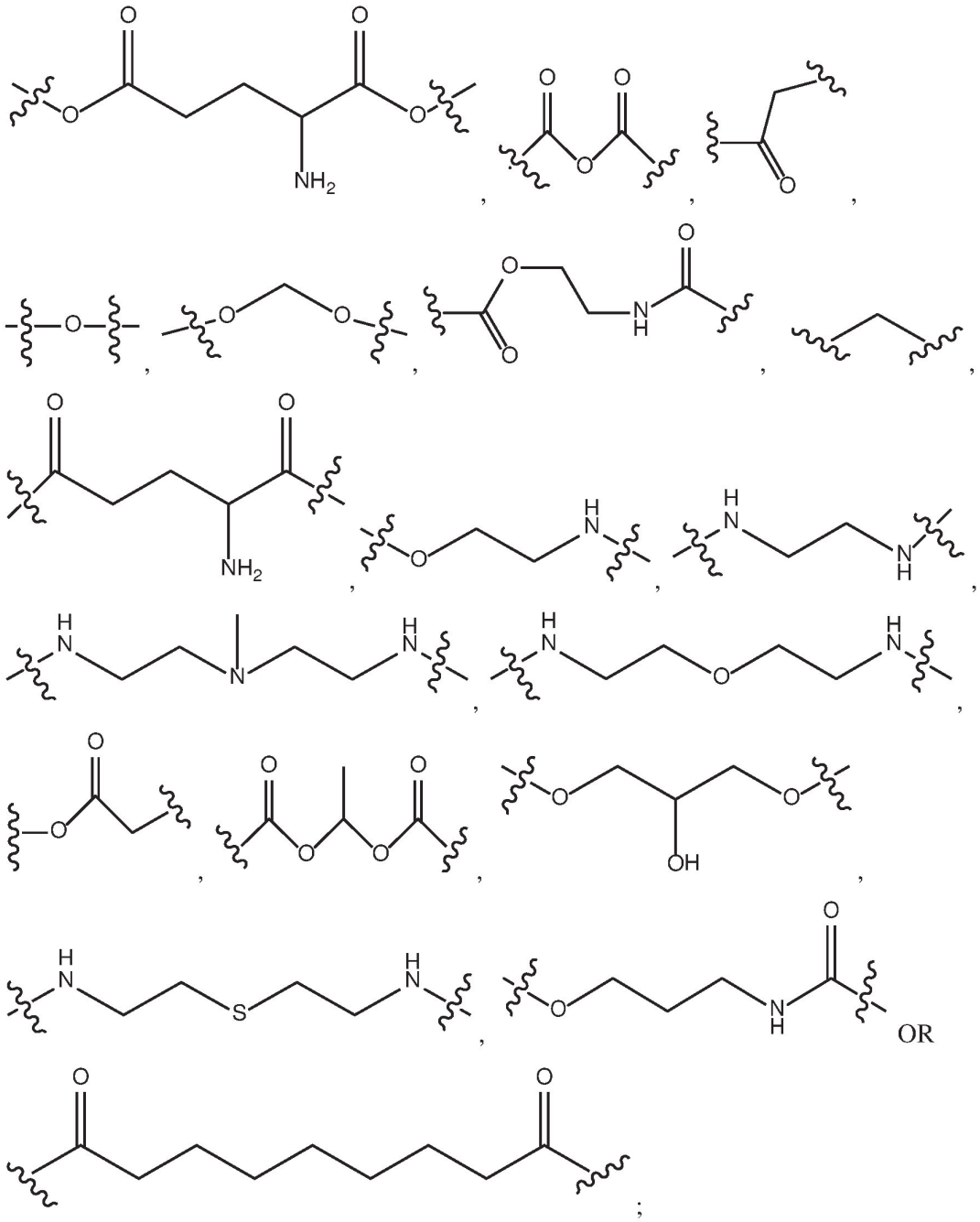
Formula II

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0016] wherein,

R1 represents Null,





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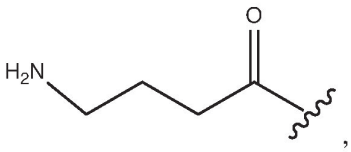
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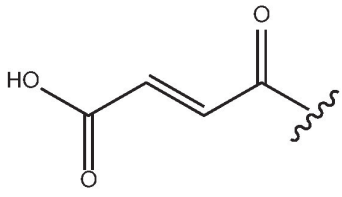
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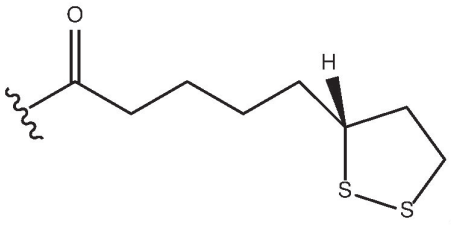
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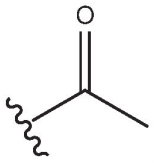
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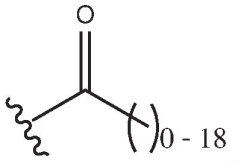
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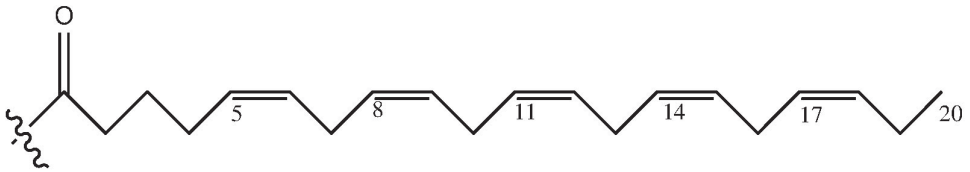
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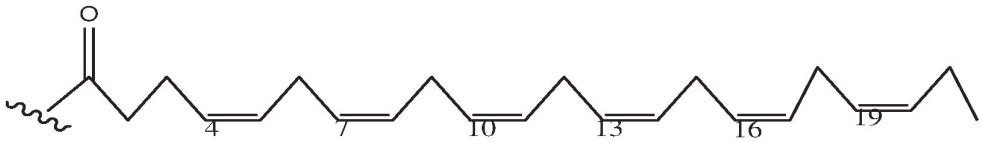
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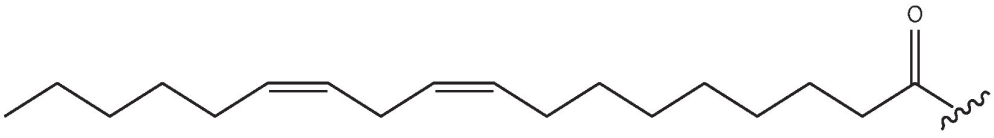
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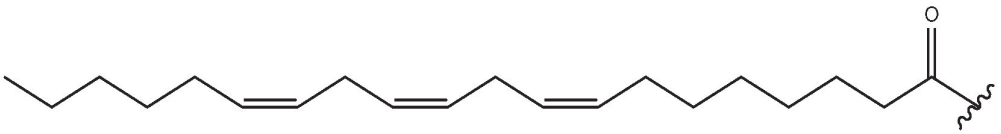
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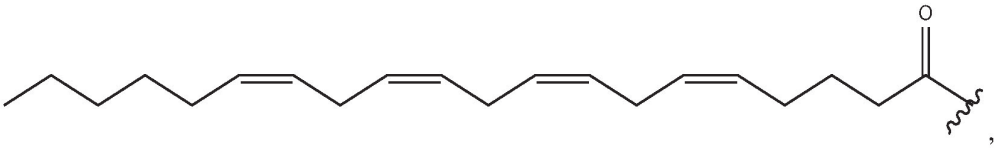
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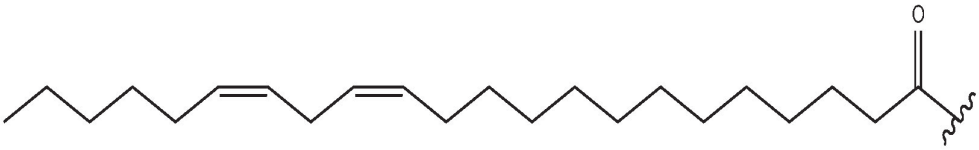
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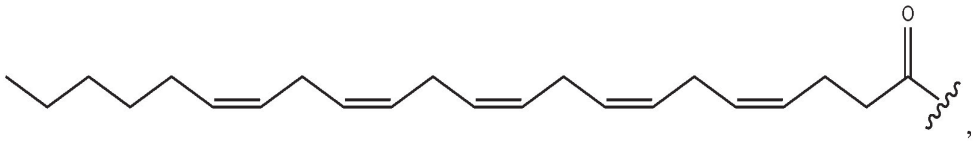

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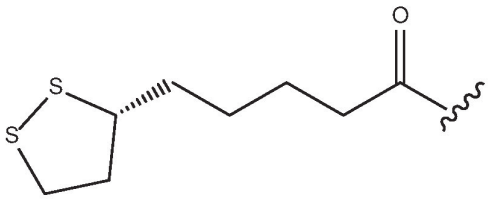

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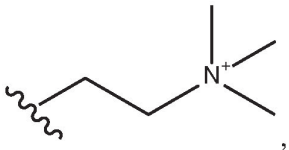

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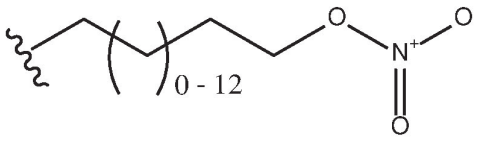

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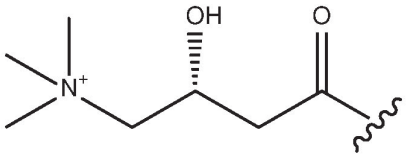

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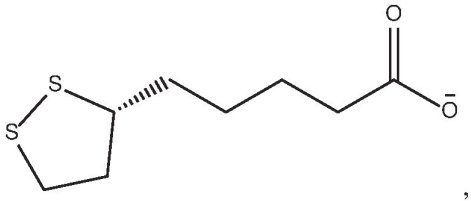

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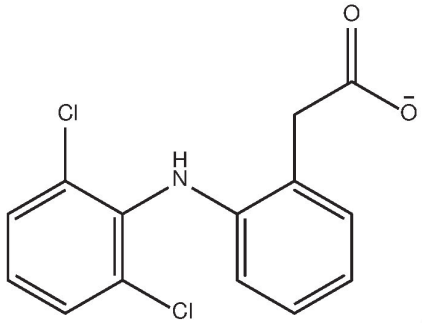

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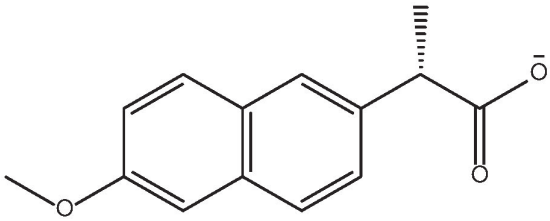

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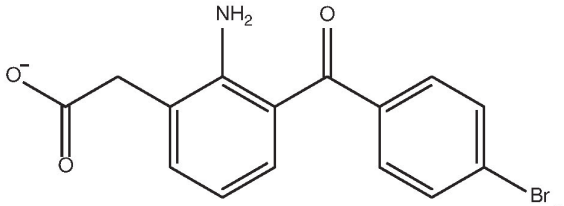

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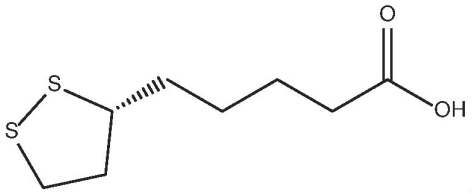

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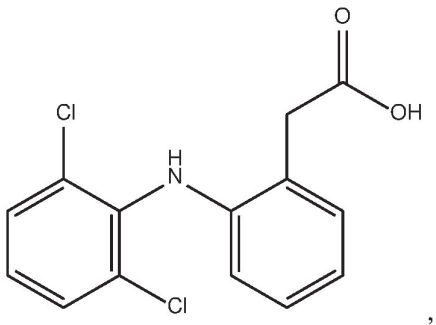

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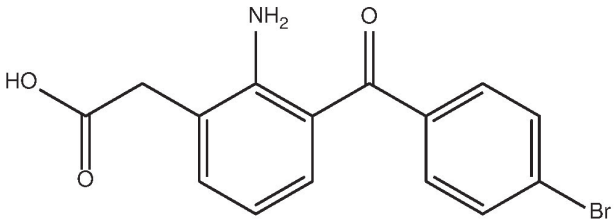

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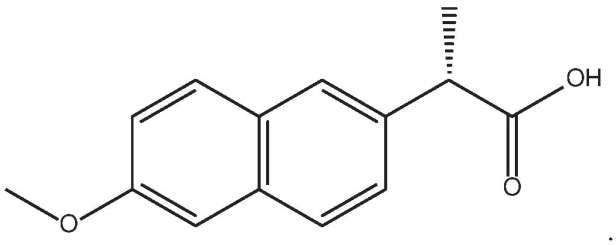

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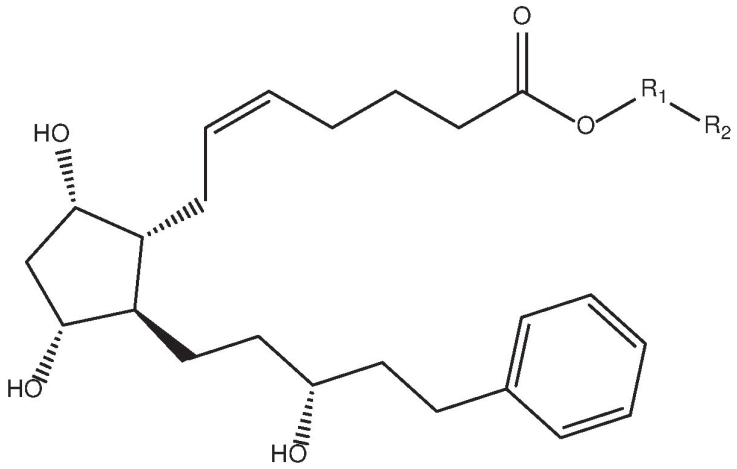
[0017] In another aspect, the compounds of formula III are described:

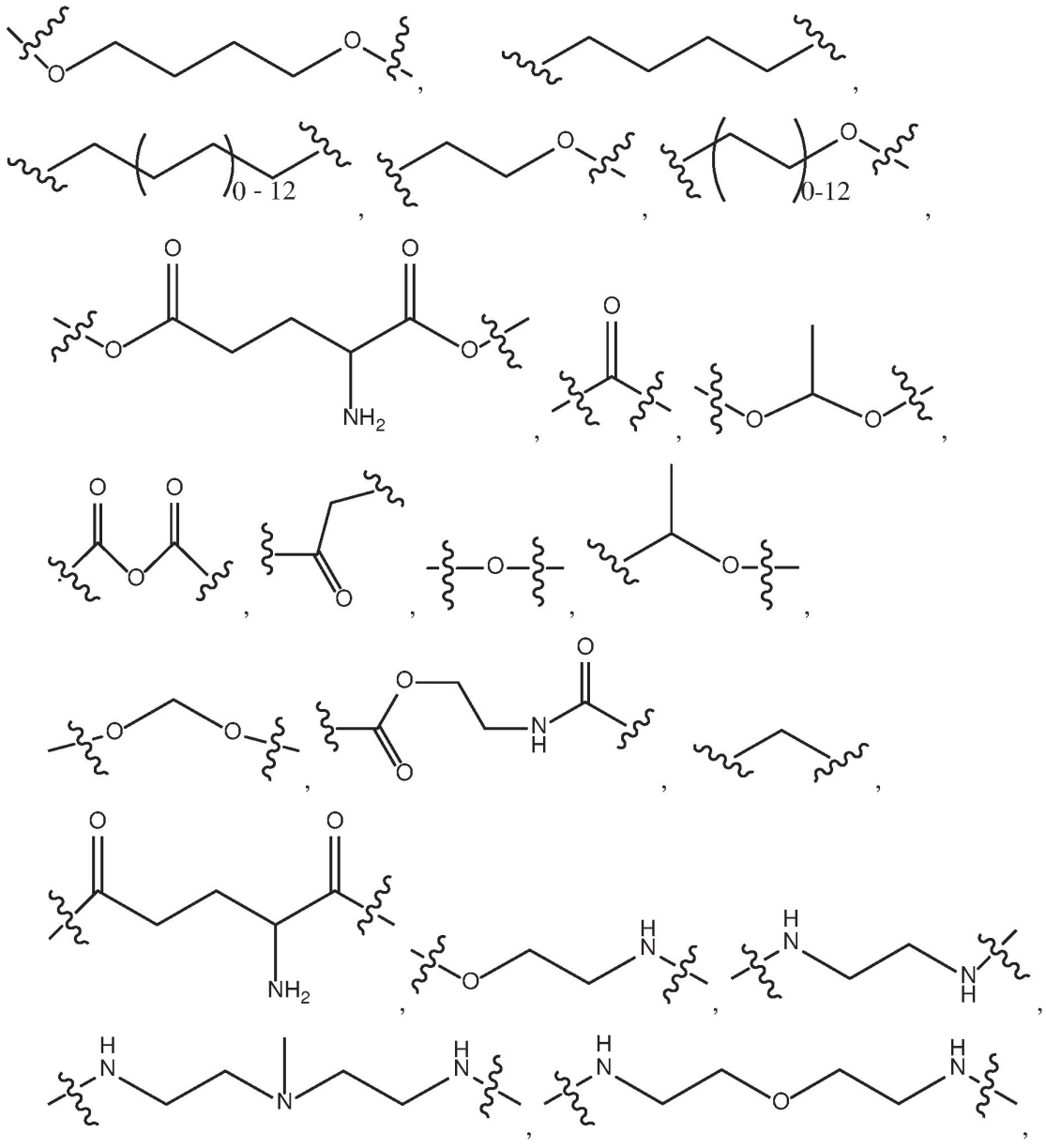


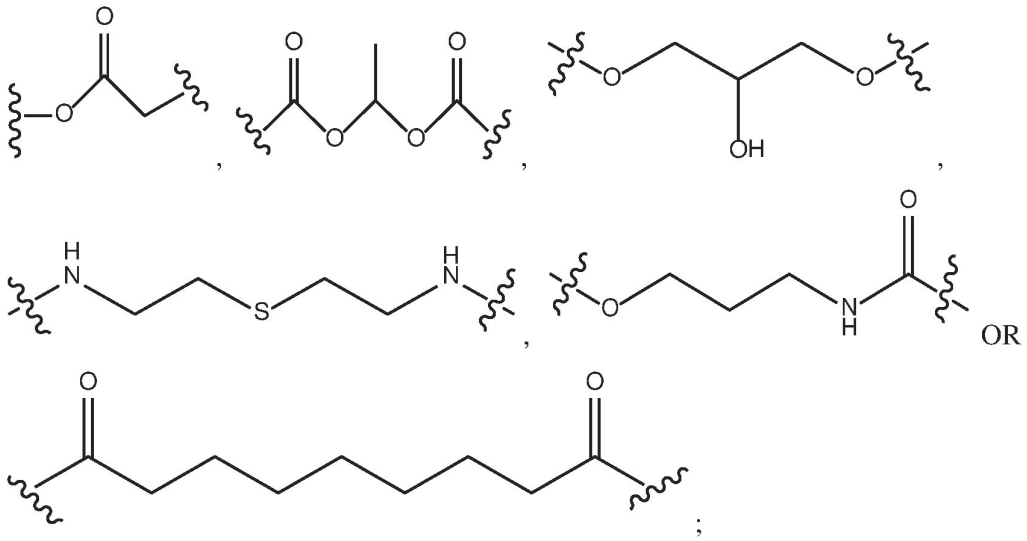
Formula III

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

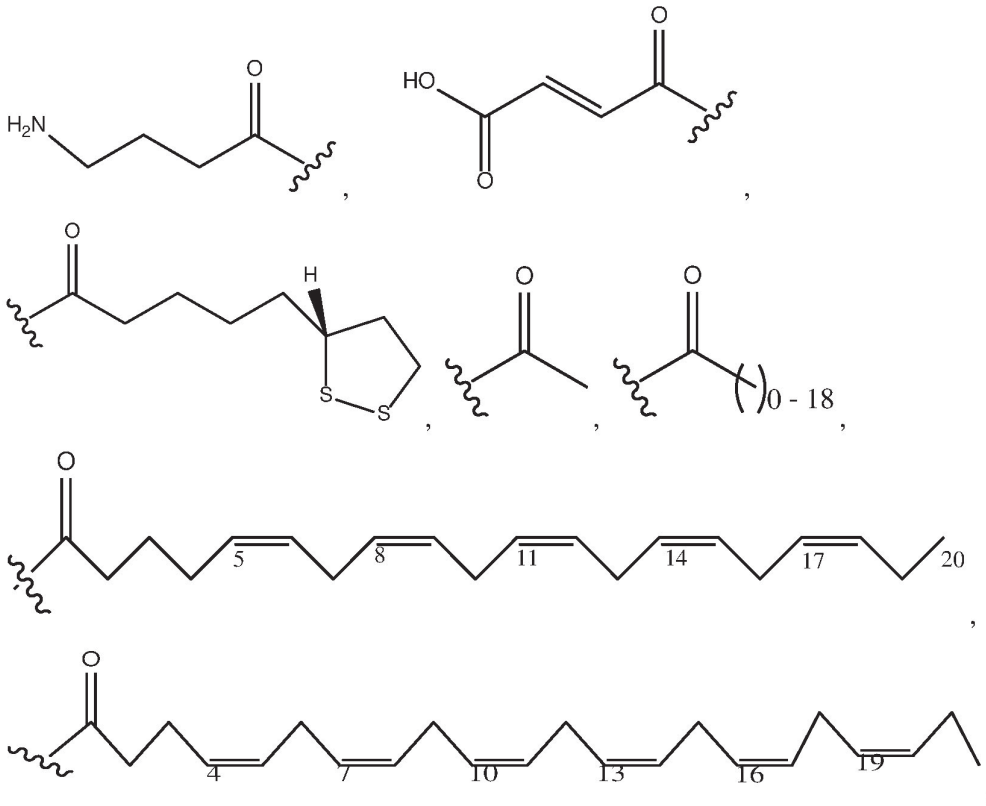
[0018] wherein,

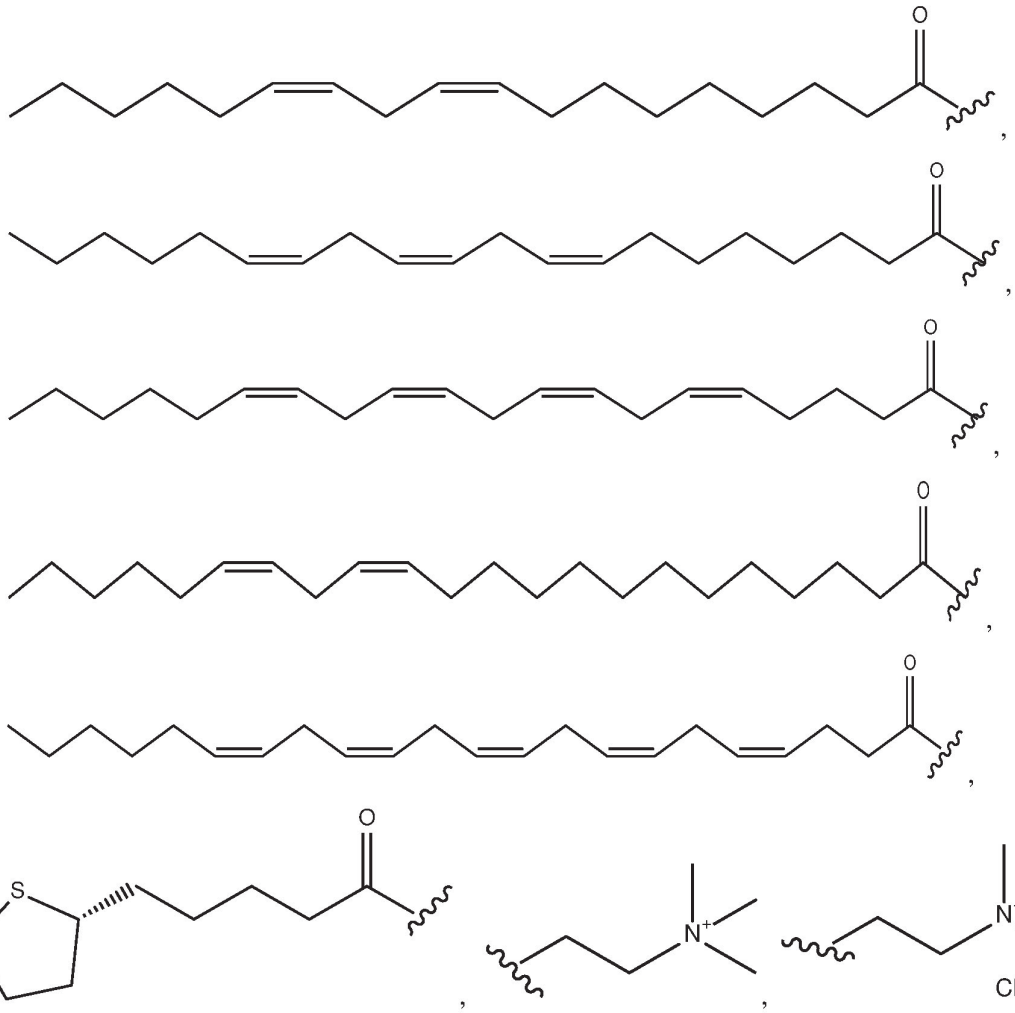
R1 represents Null,





R_2 represents

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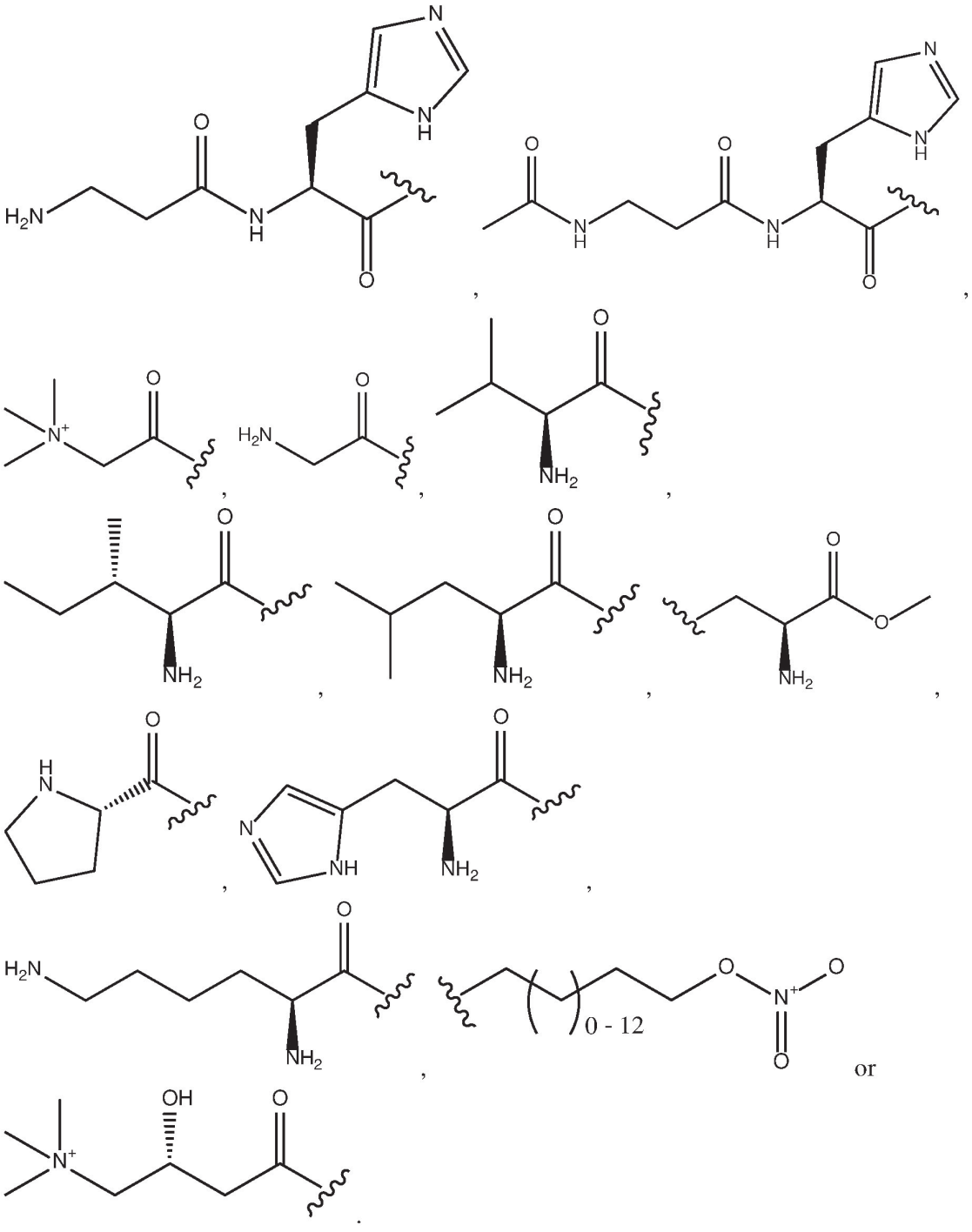
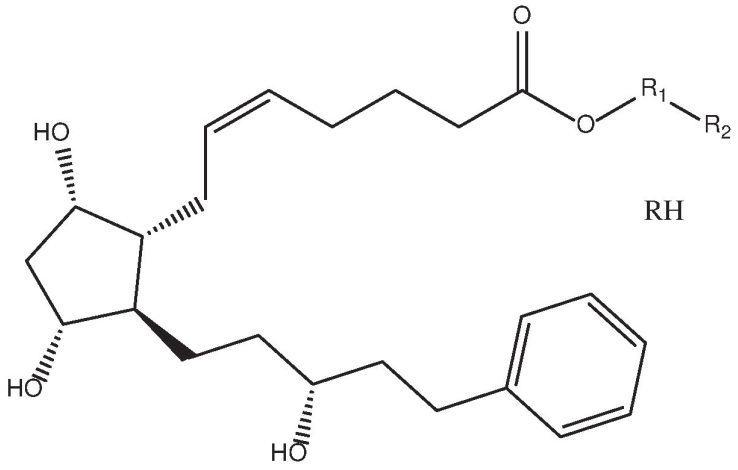


or

[0019] In another aspect, the compounds of formula IV are described:



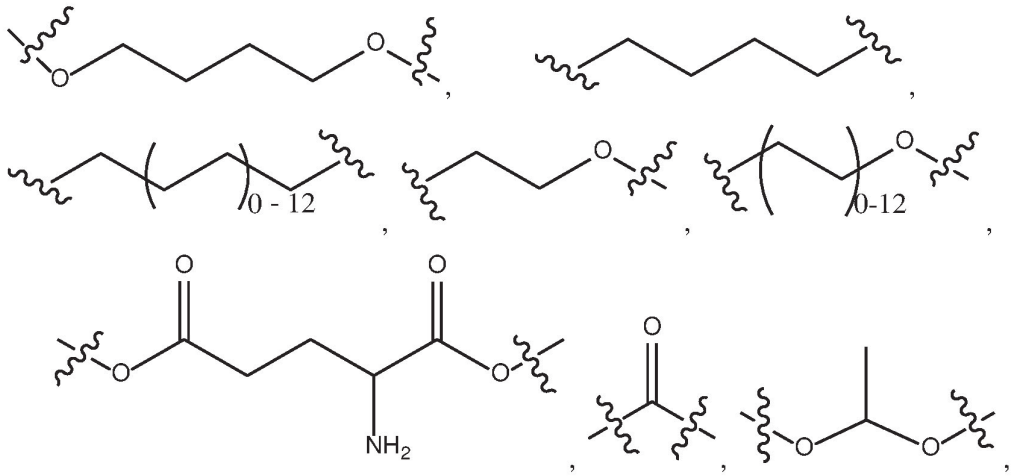
RH

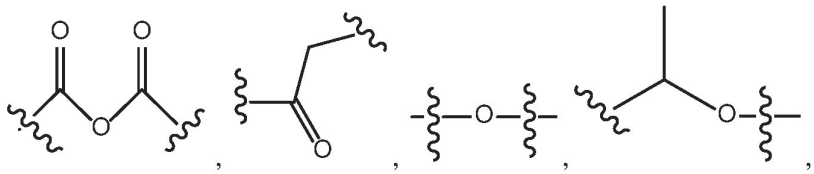
Formula IV

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0020] wherein,

R^1 represents Null,

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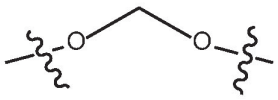
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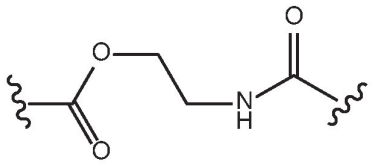
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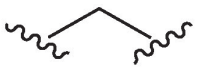
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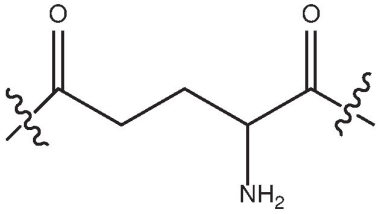
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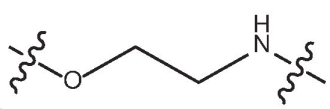
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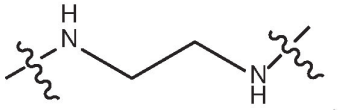
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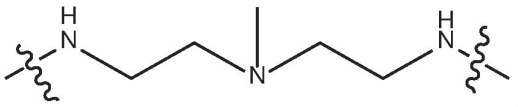
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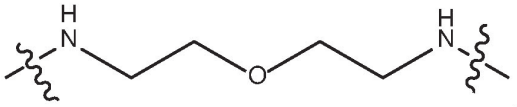
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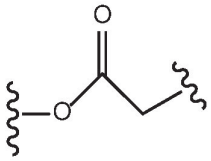
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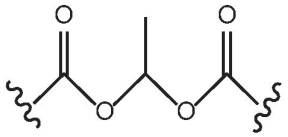
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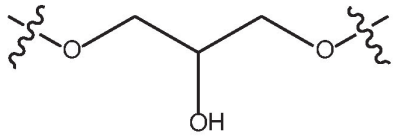
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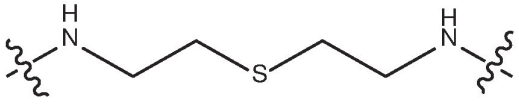
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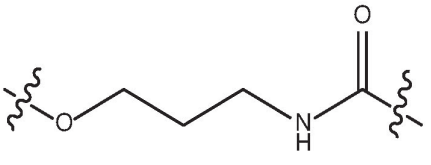
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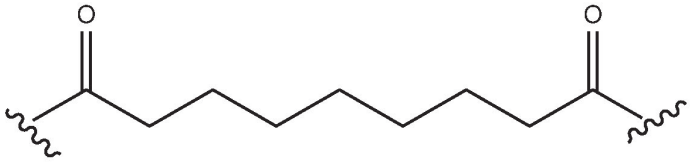
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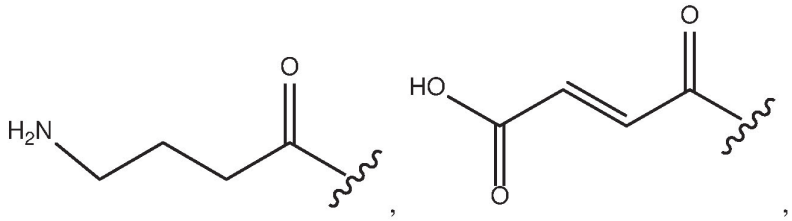
R_2 represents



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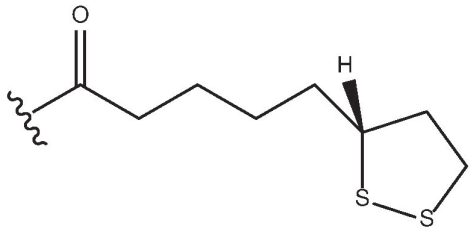

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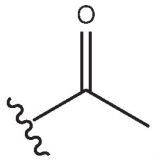

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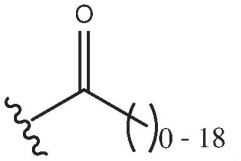

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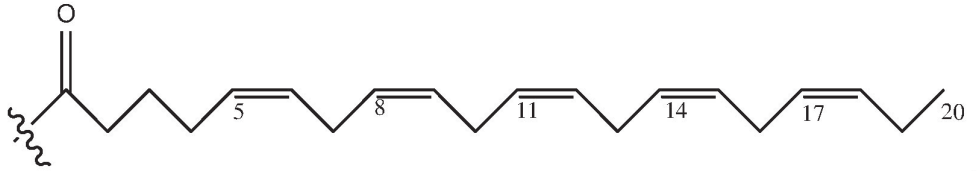

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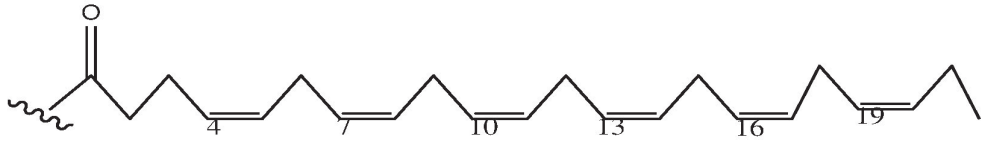

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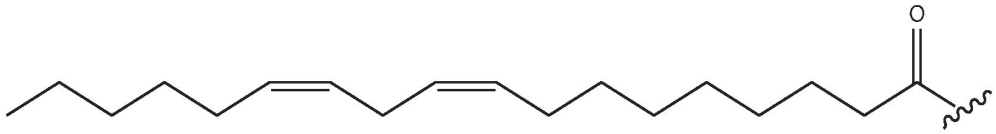

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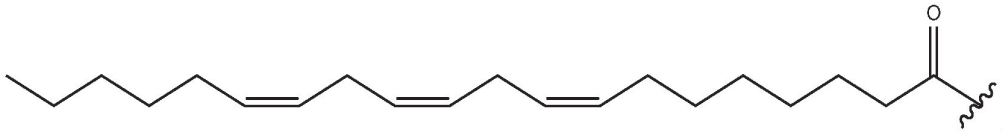

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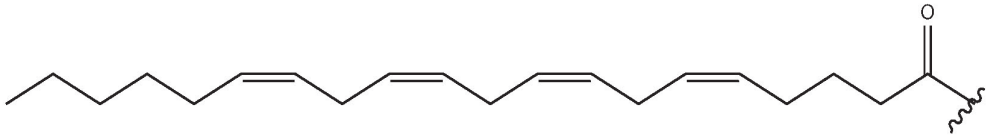

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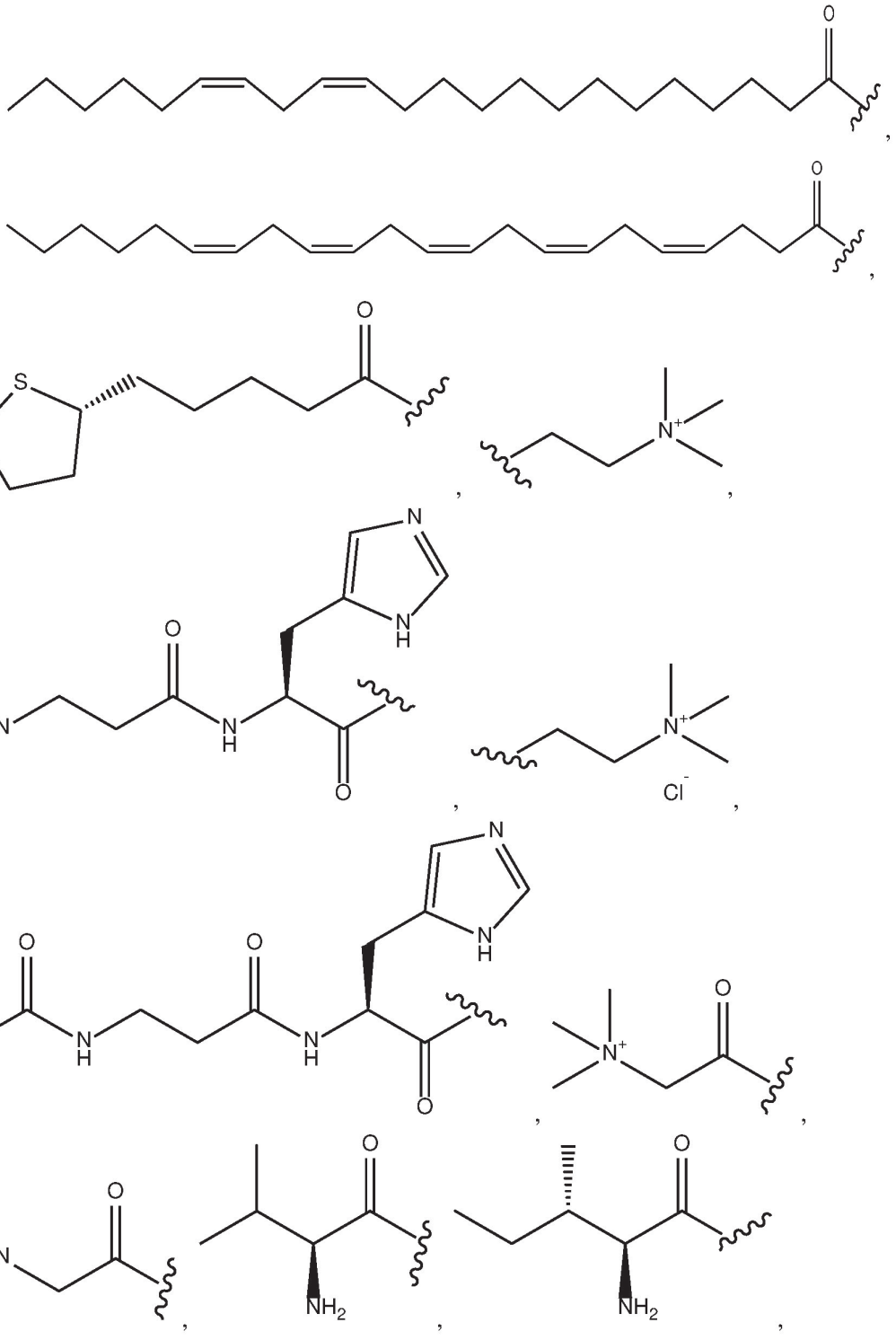
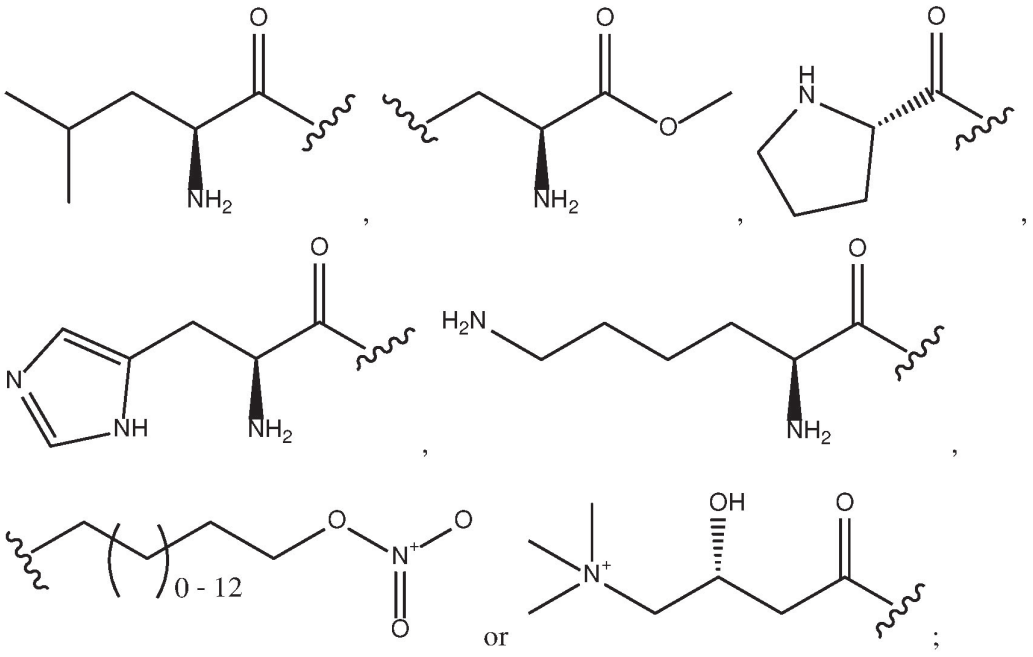
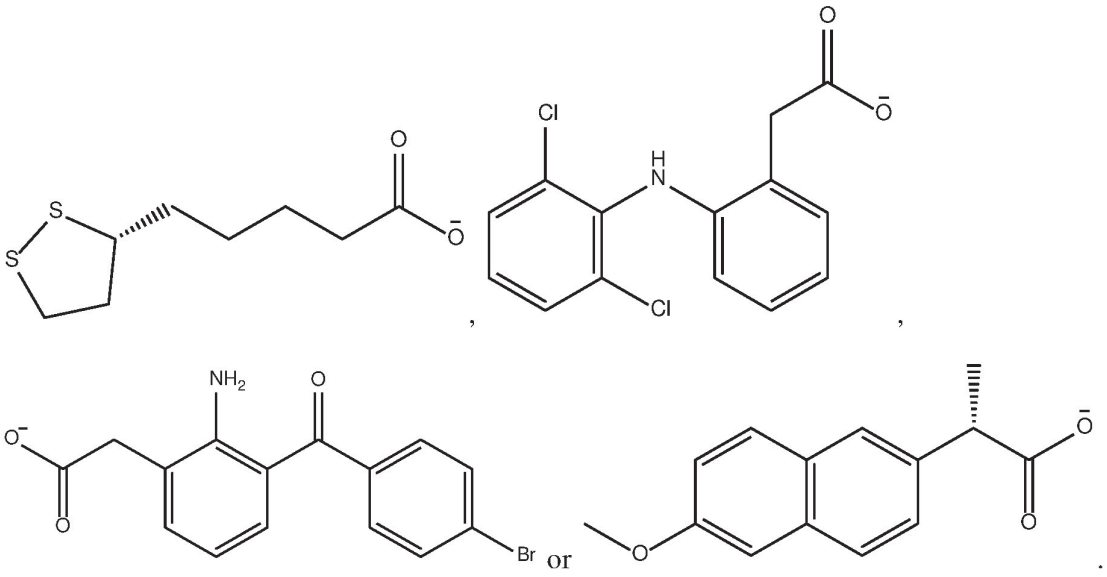
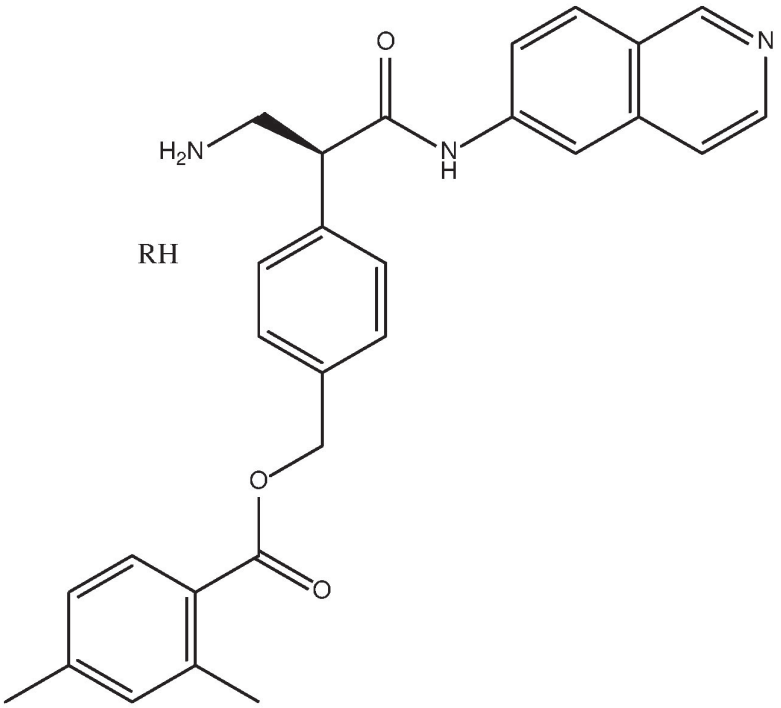




RH represents



[0021] In another aspect, the compounds of formula V are described:

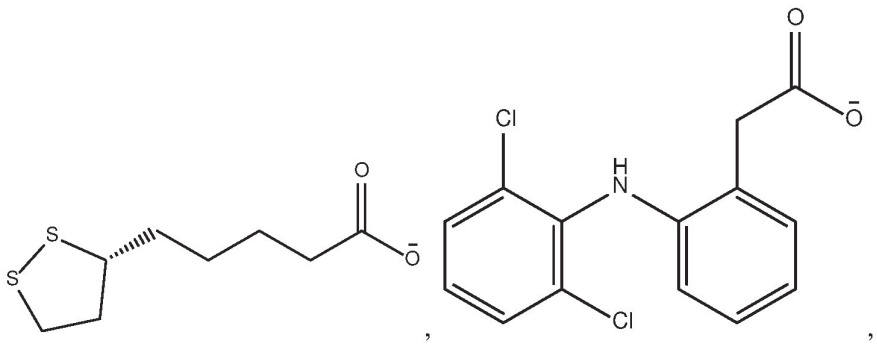


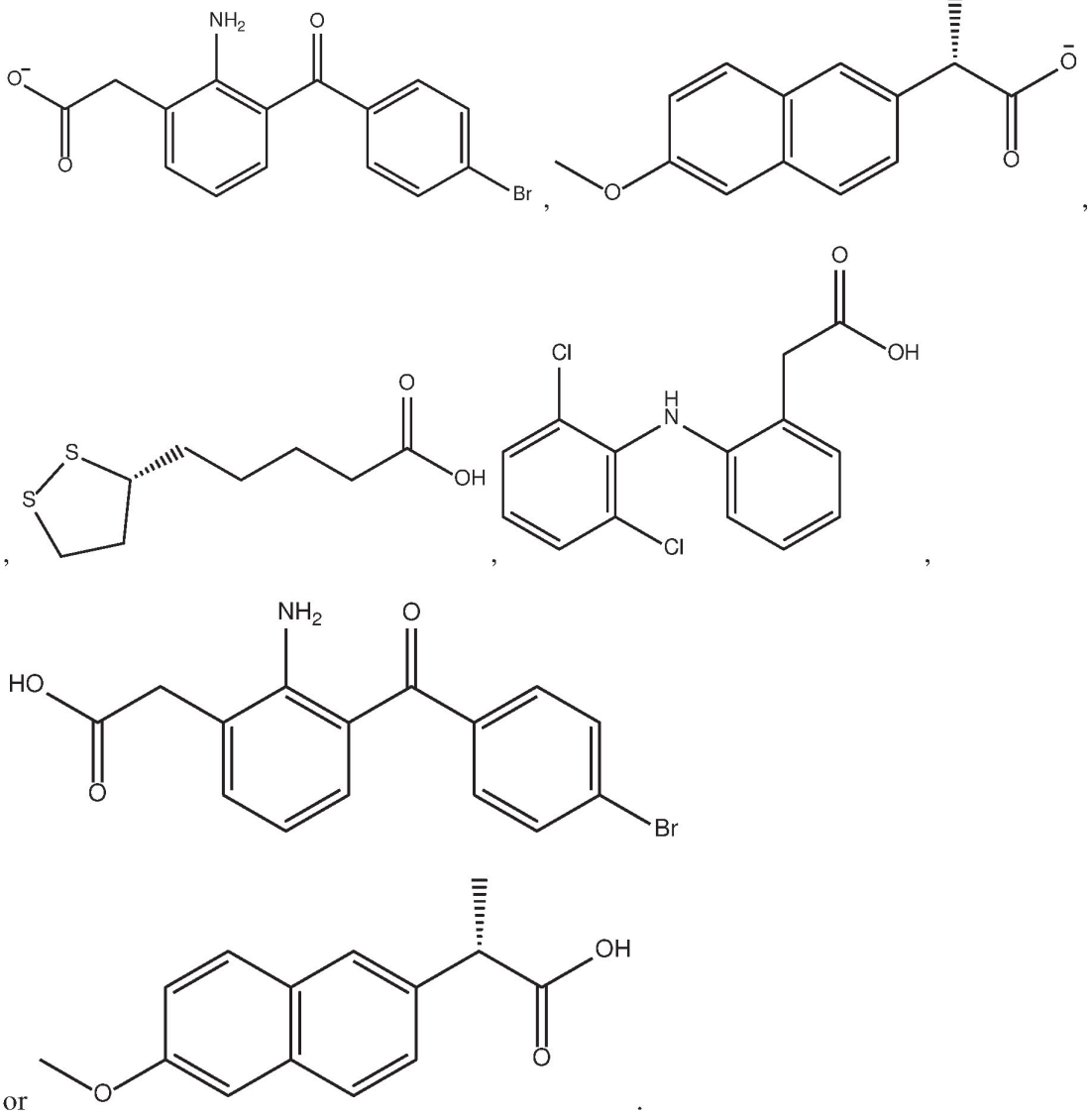
Formula V

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

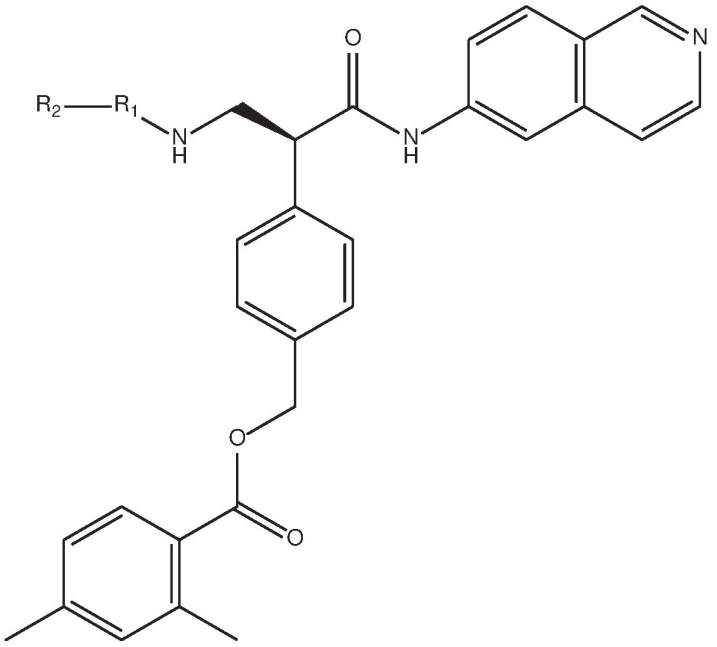
[0022] wherein,

RH represents





[0023] In another aspect, the compounds of formula VI are described:

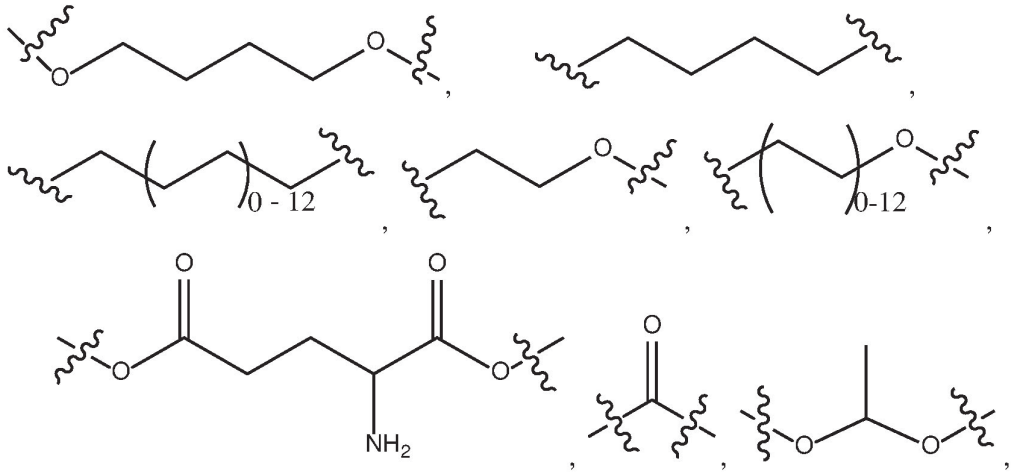


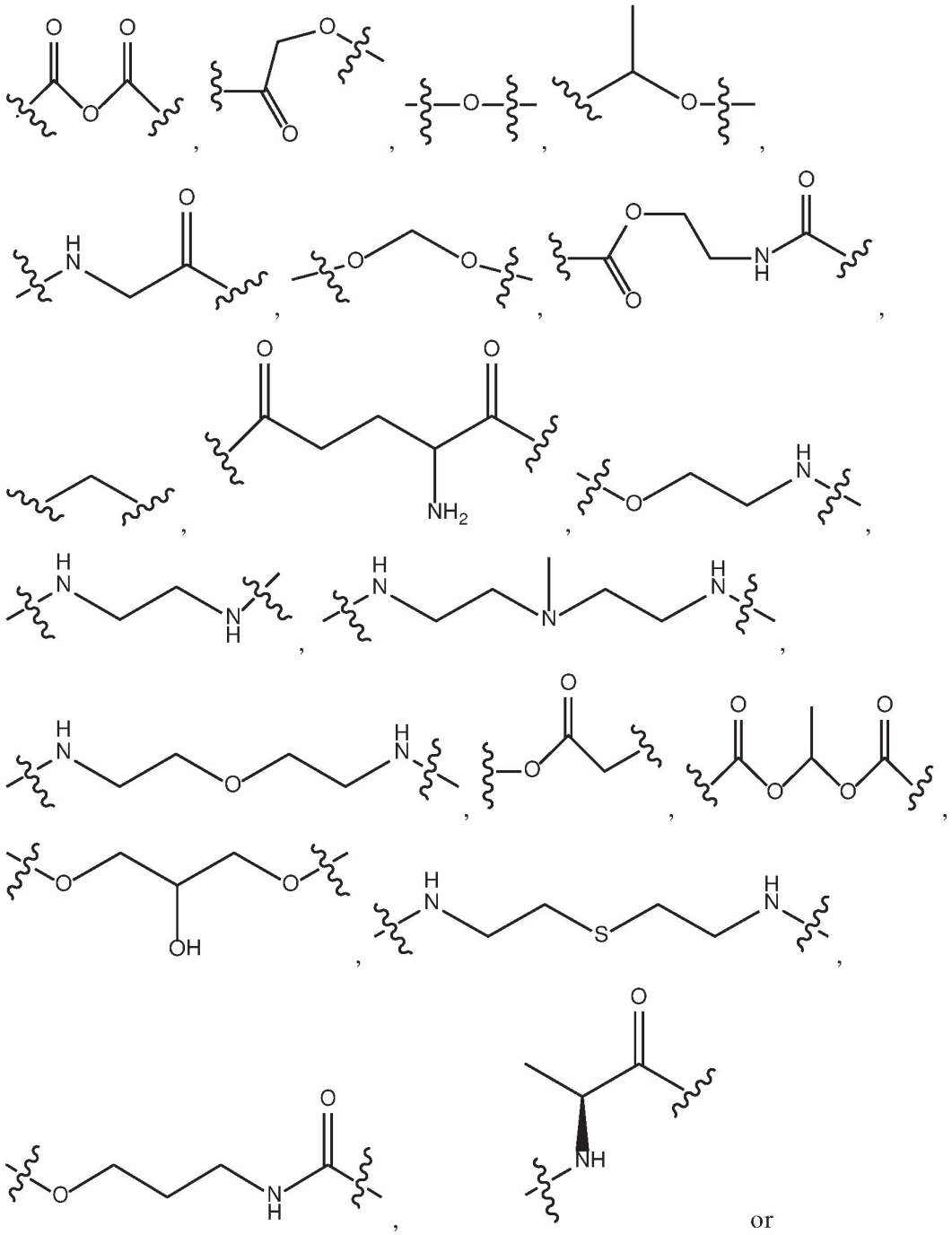
Formula VI

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0024] wherein,

R^1 represents Null,





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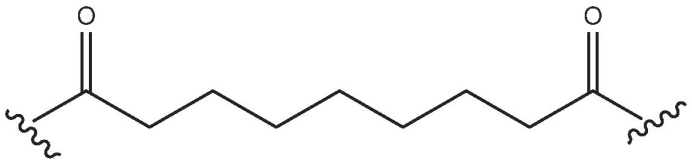

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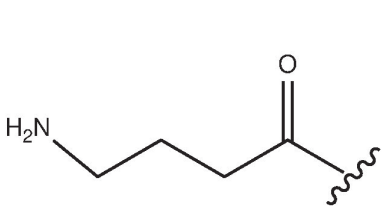
R_2 represents



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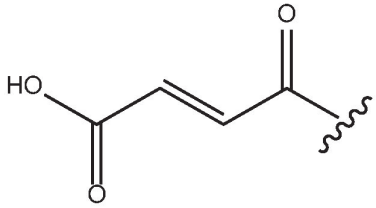

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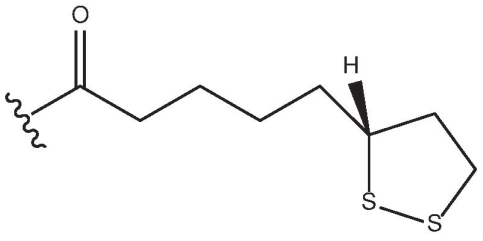

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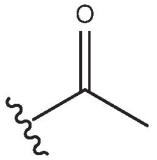

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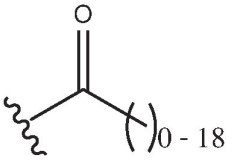

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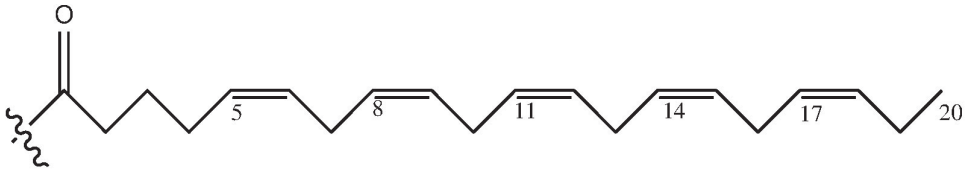

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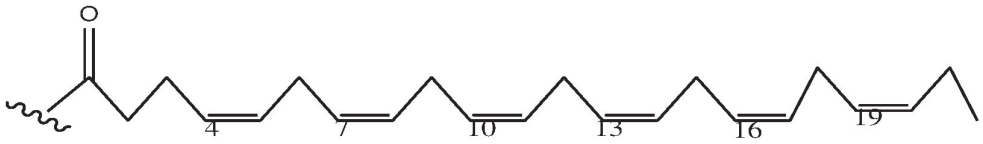

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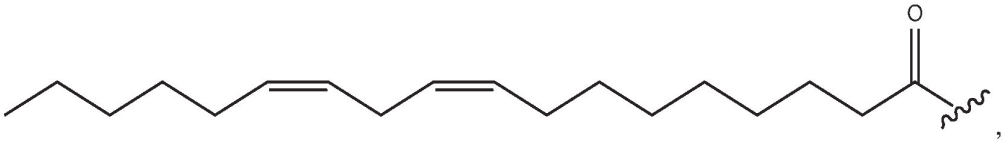

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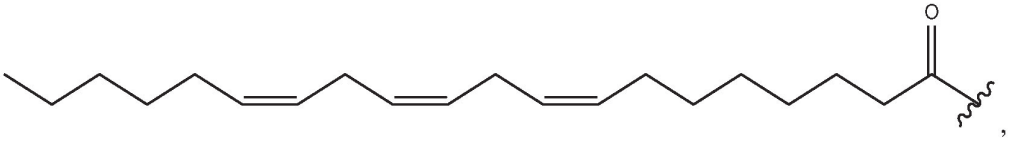

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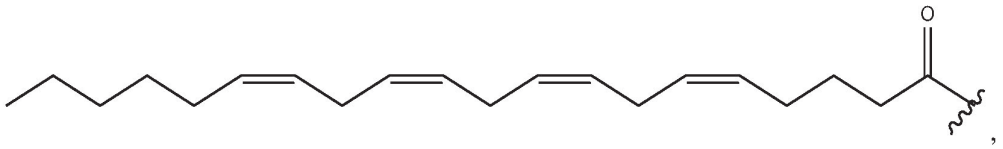
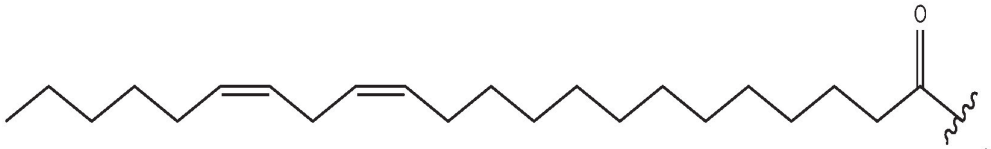
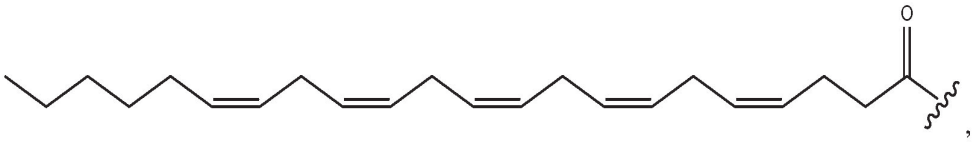
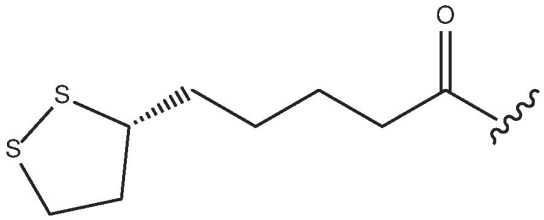
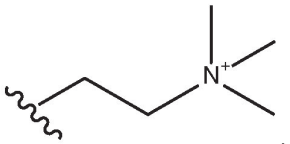
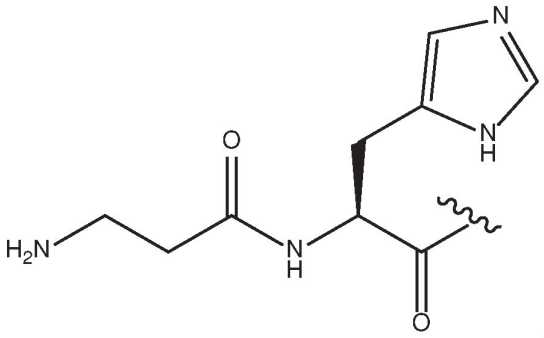
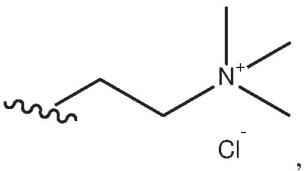
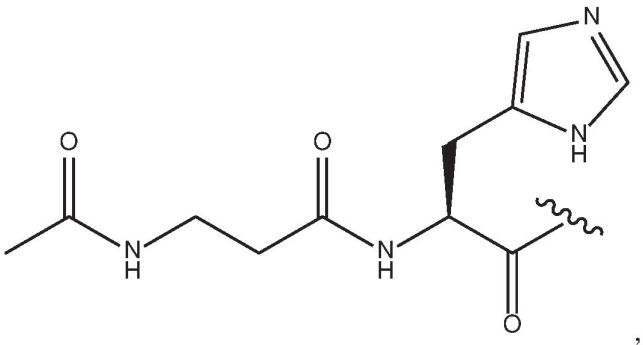
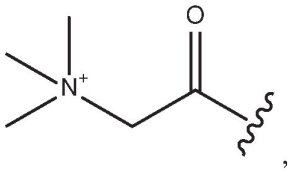
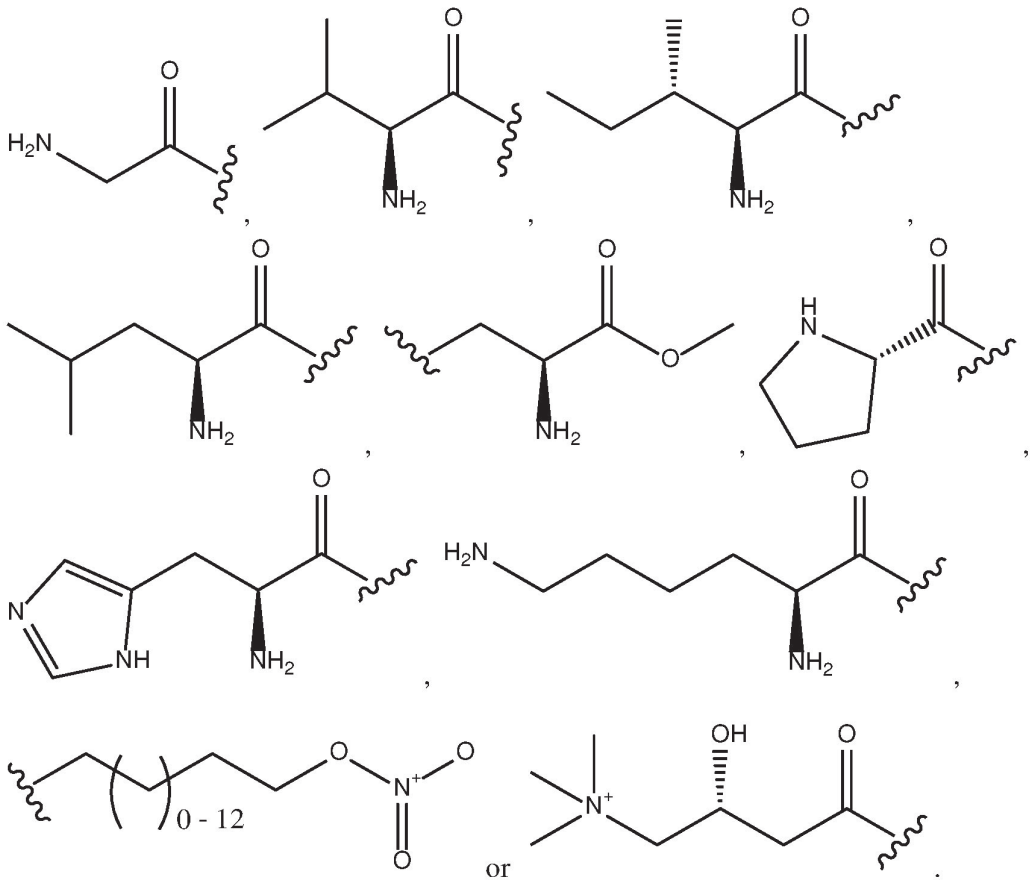
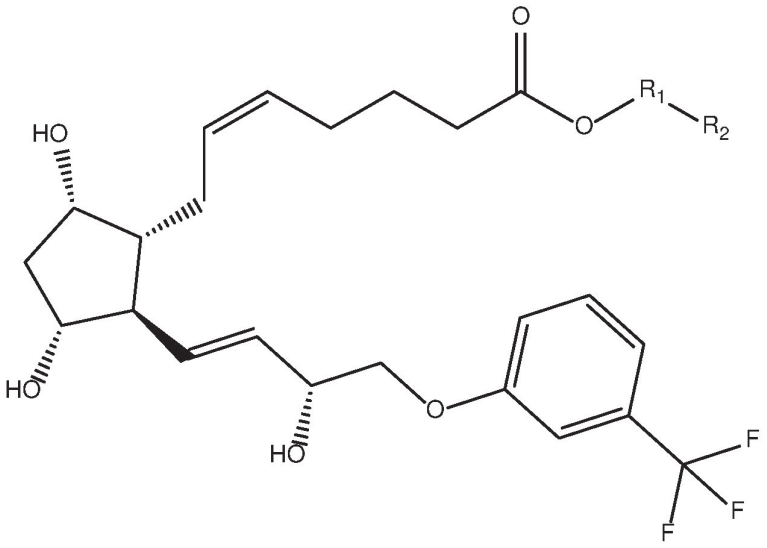












[0025] In another aspect, the compounds of formula VII are described:

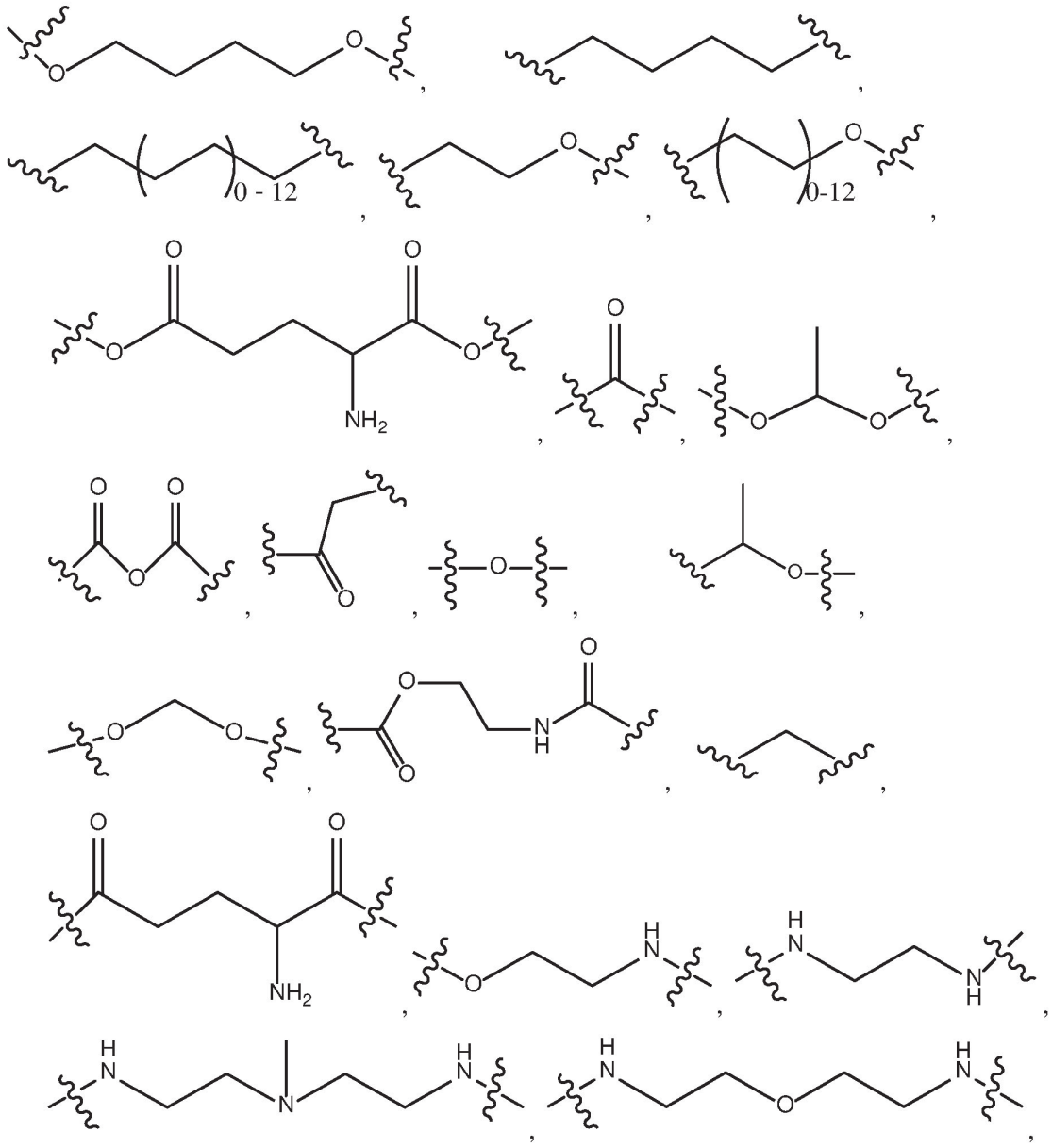


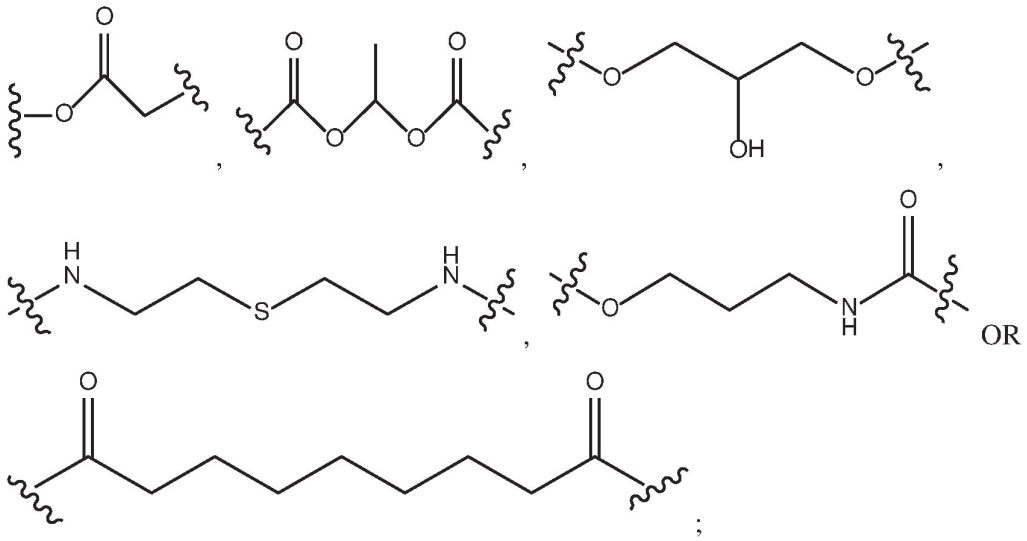
Formula VII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

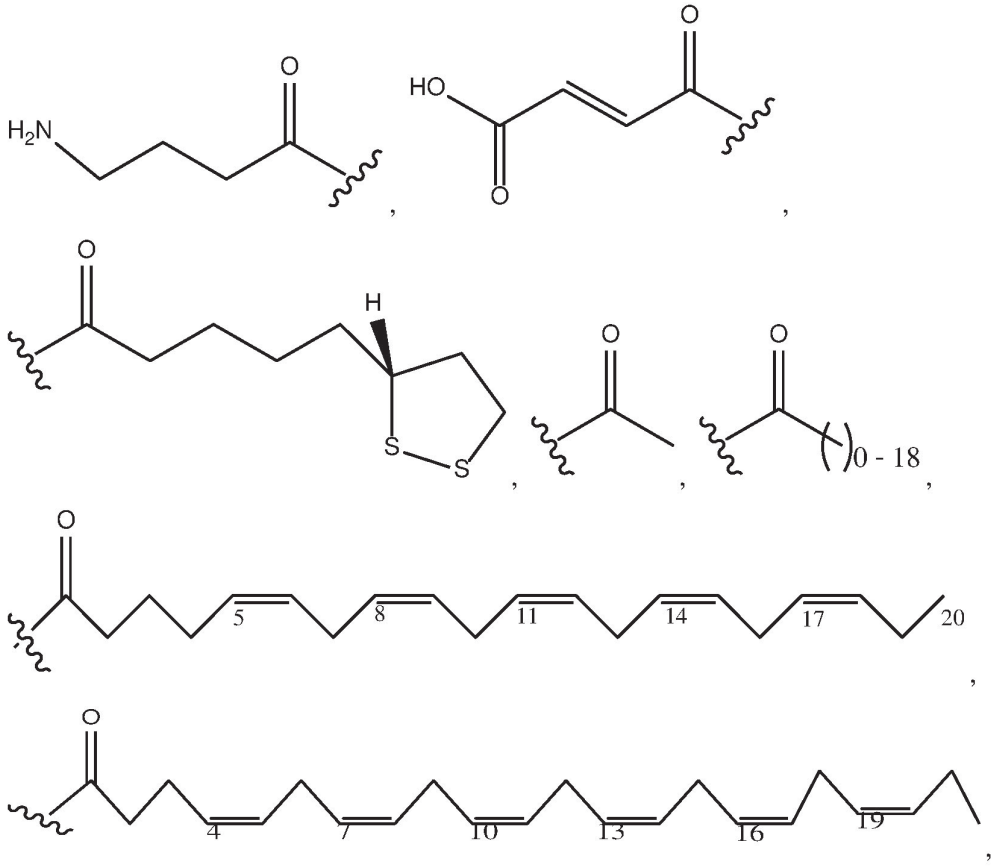
[0026] wherein,

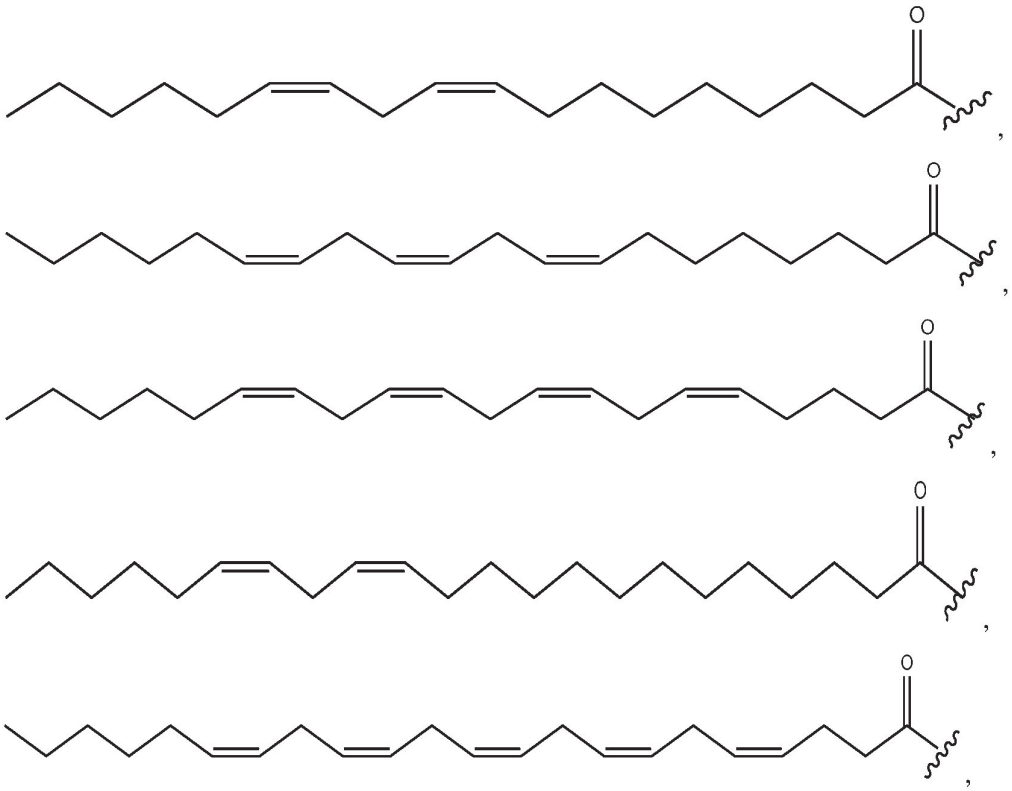
R^1 represents Null,

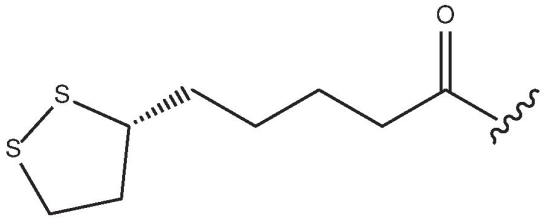


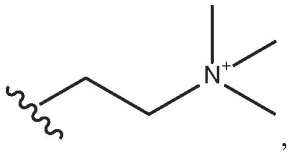


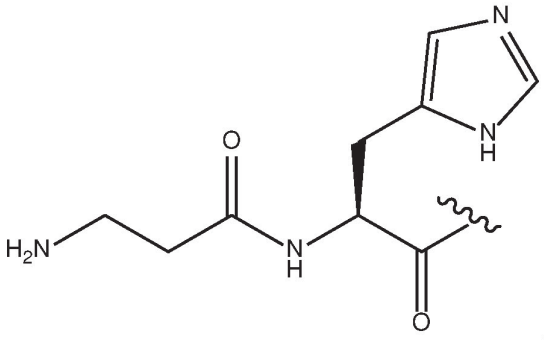
R_2 represents

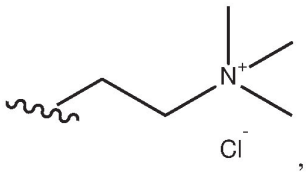


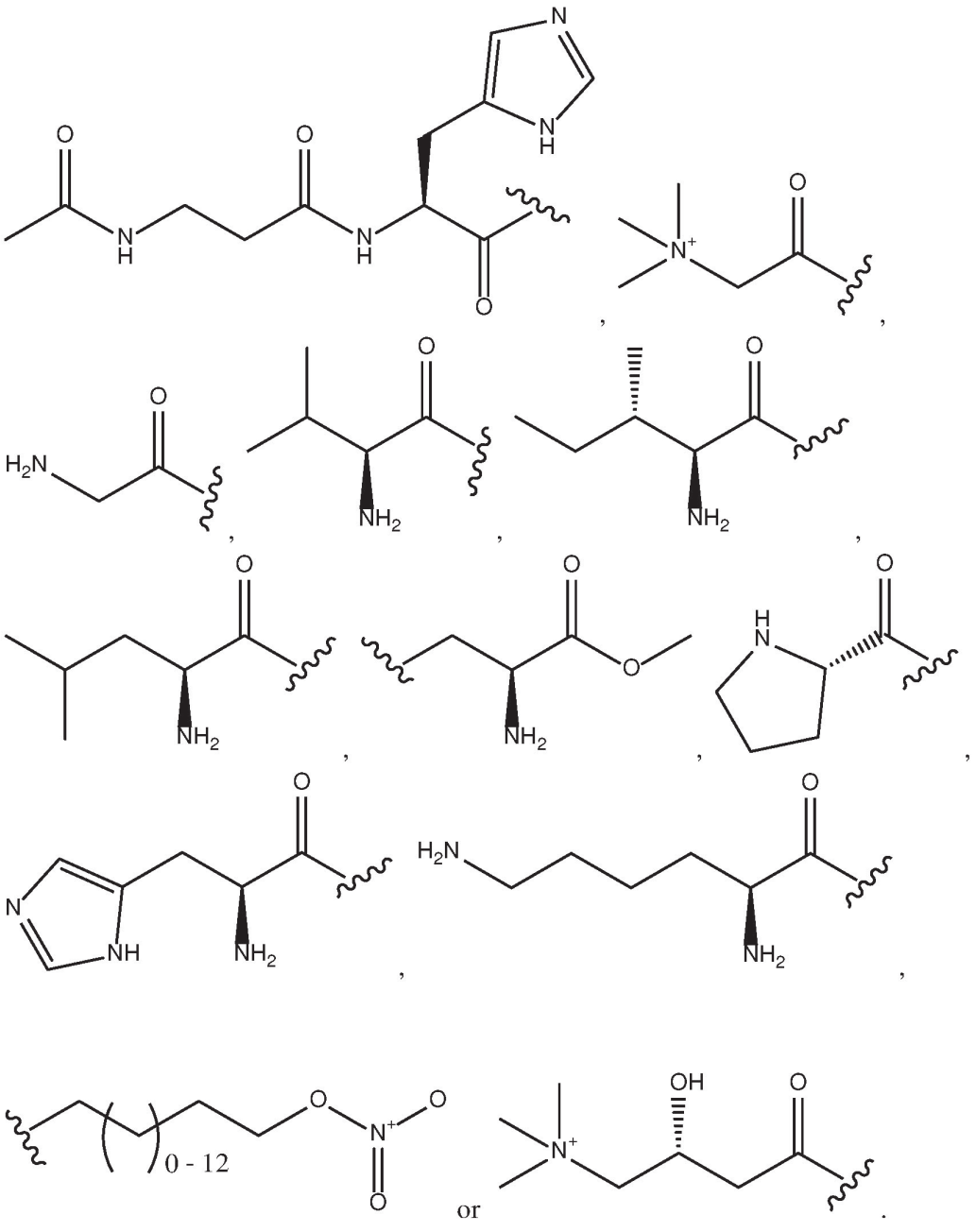




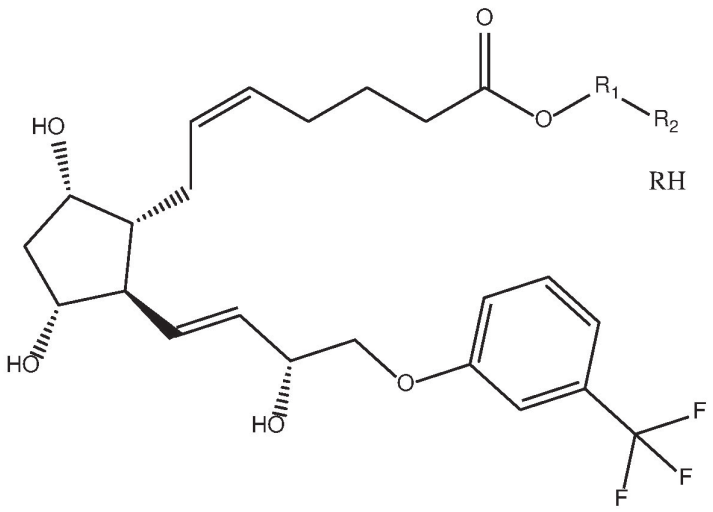








[0027] In another aspect, the compounds of formula VIII are described:

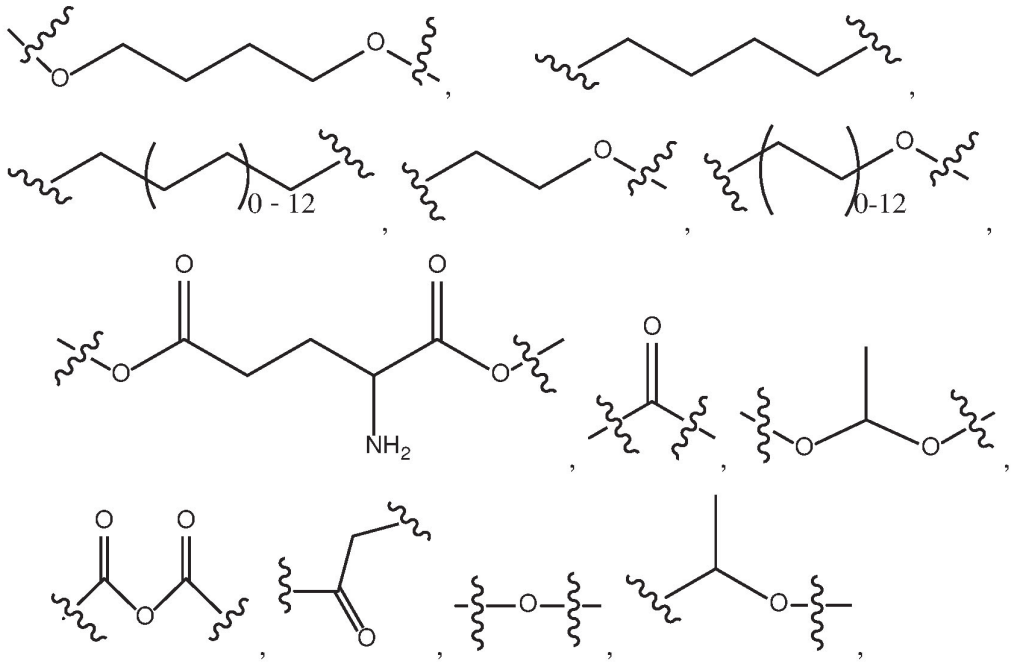


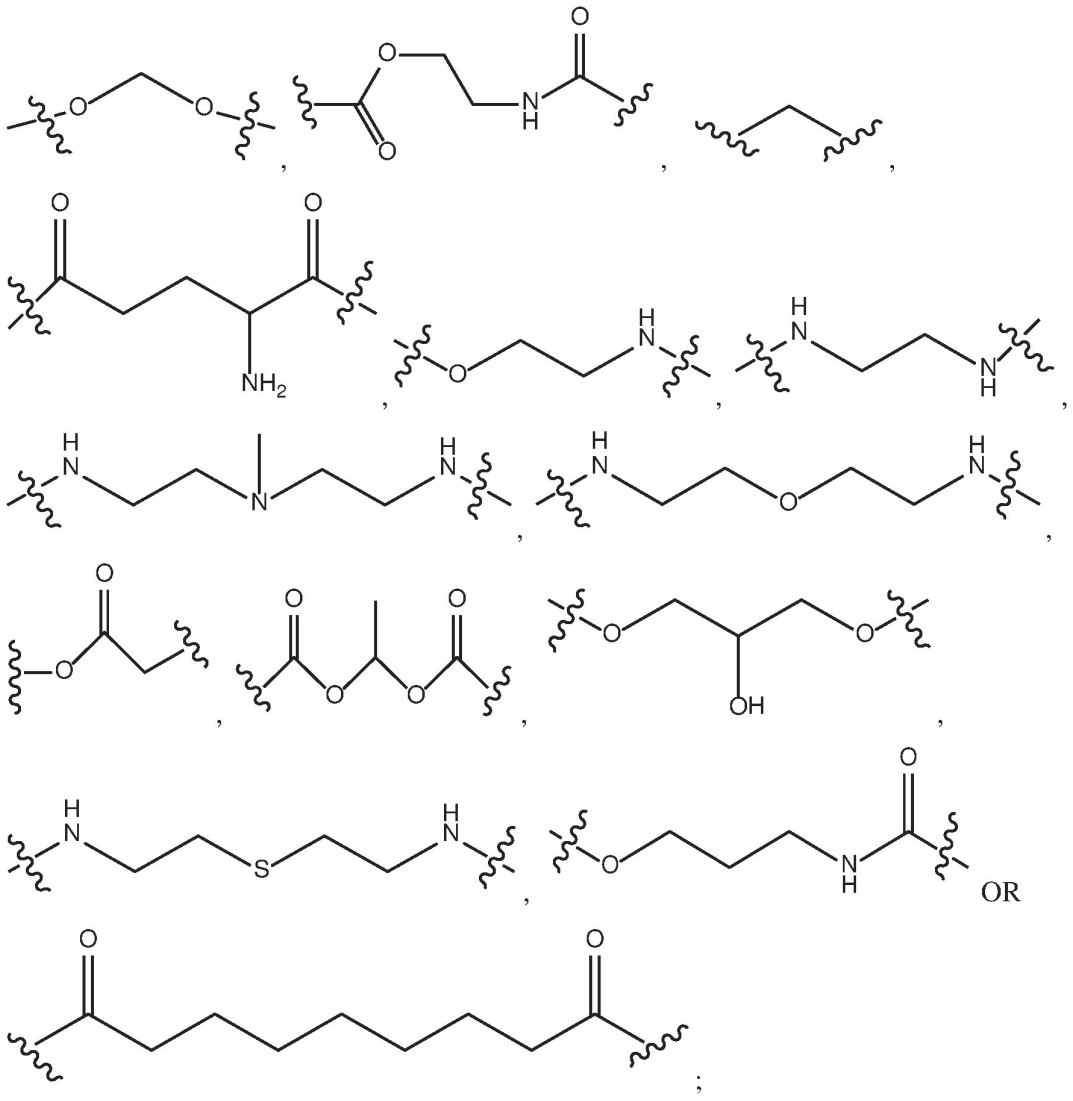
Formula VIII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

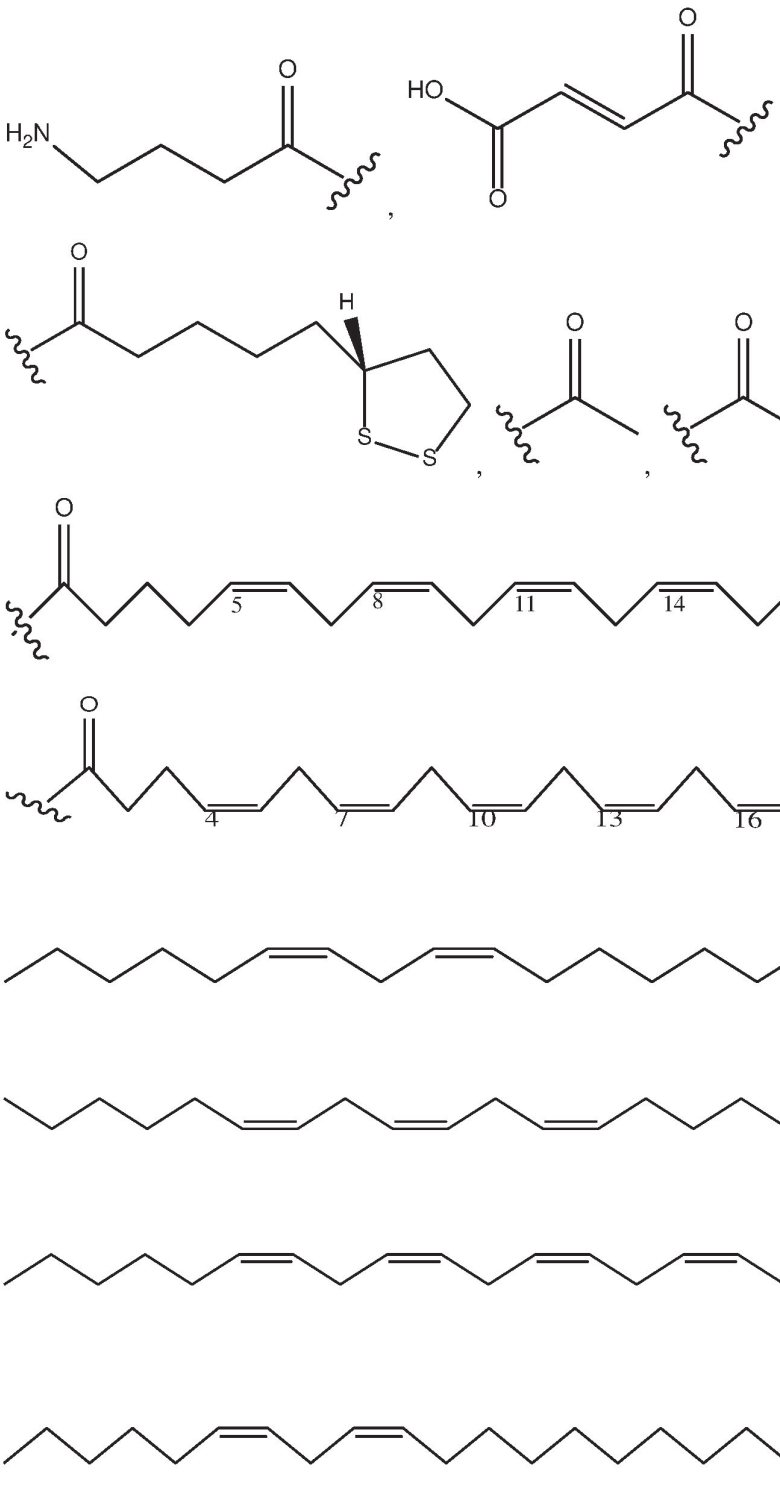
[0028] wherein,

R^1 represents Null,





R_2 represents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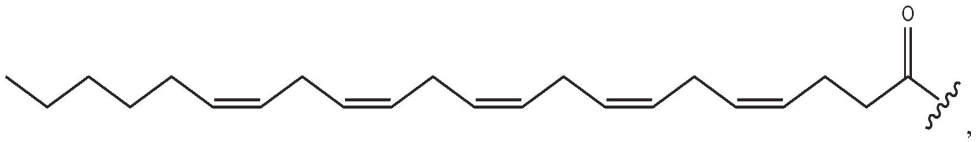
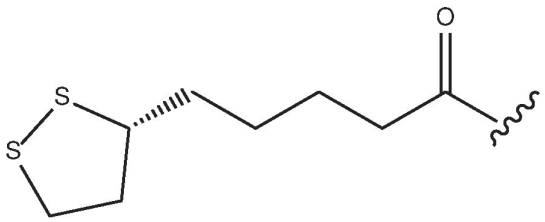
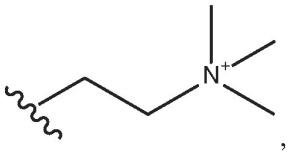
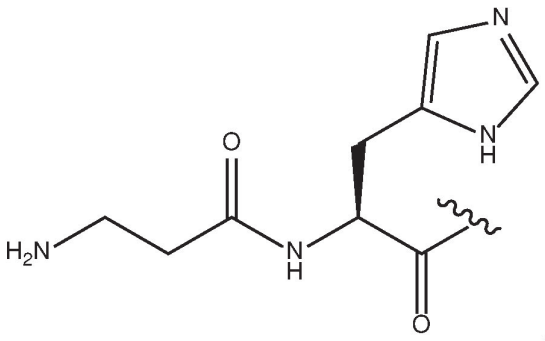
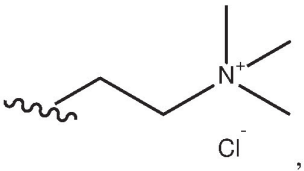
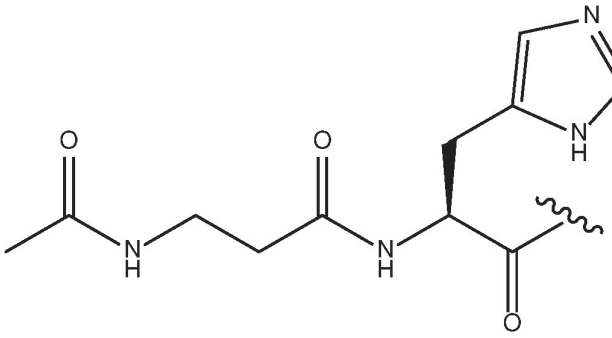
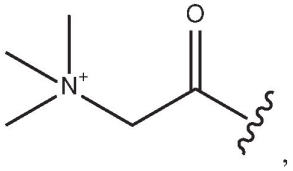
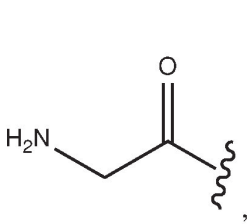
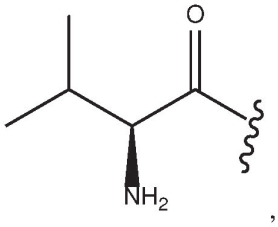
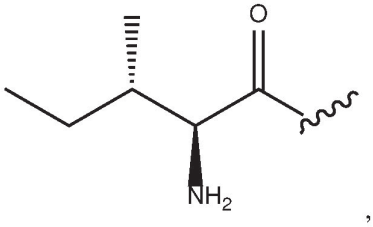
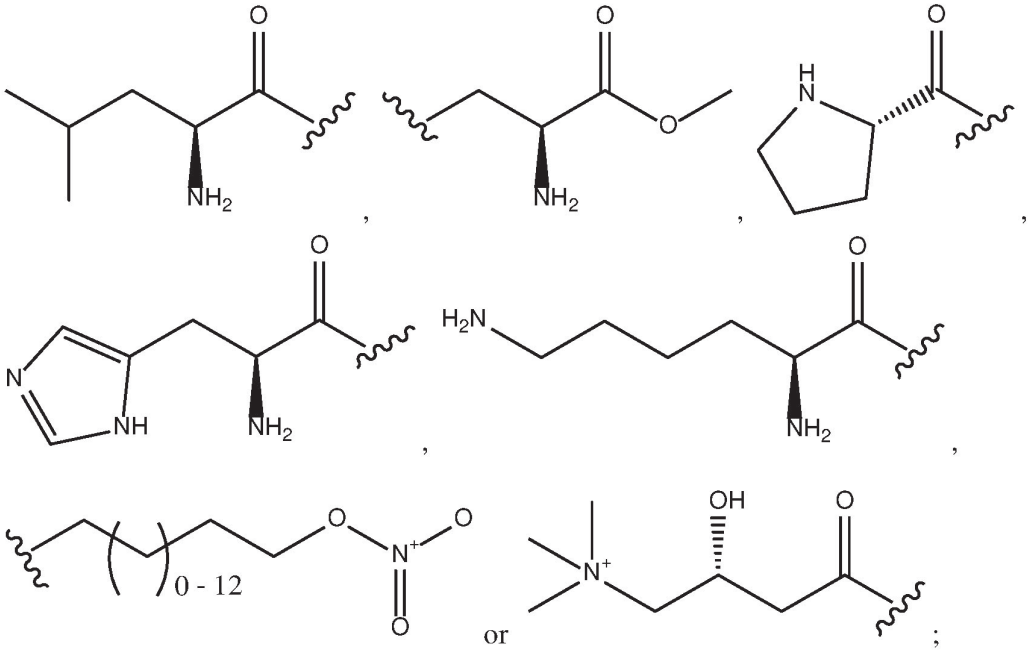
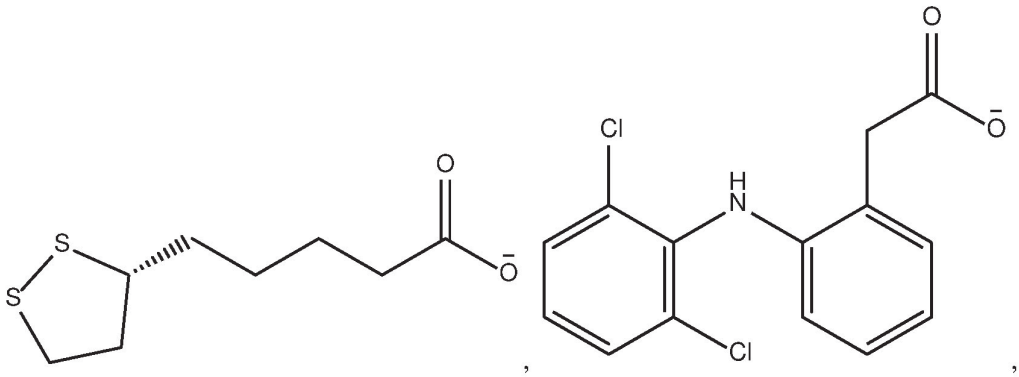
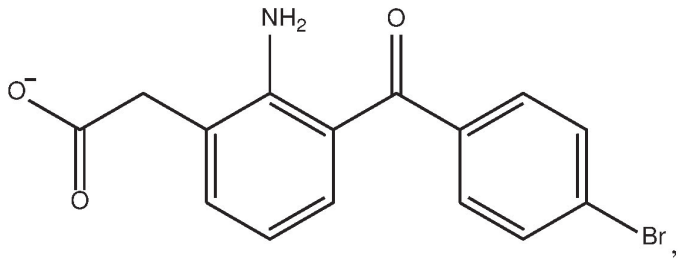













RH represents





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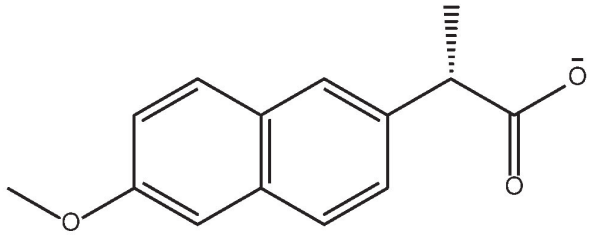

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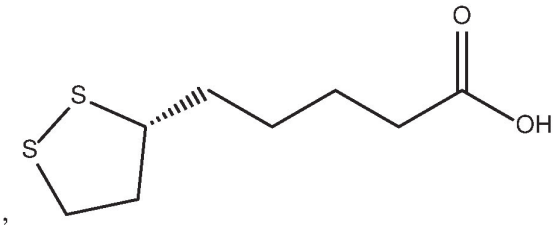

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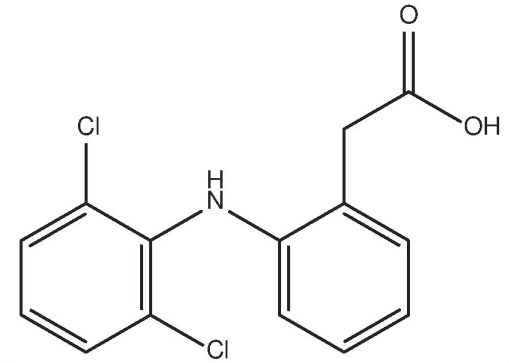

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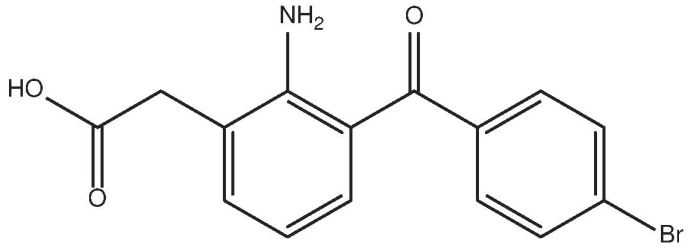
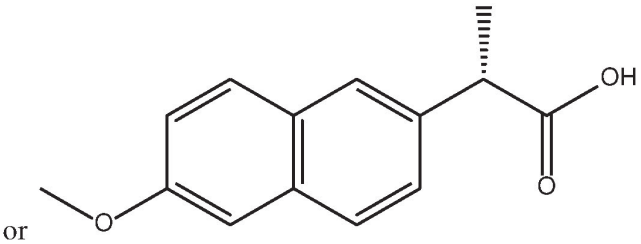
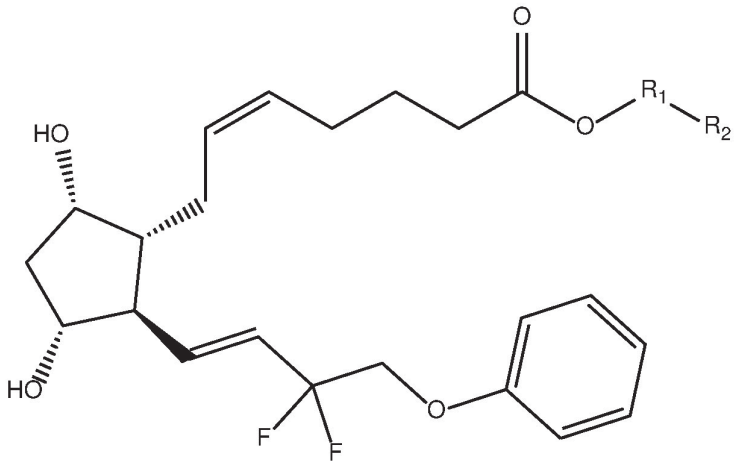




or .

[0029] In another aspect, the compounds of formula IX are described:

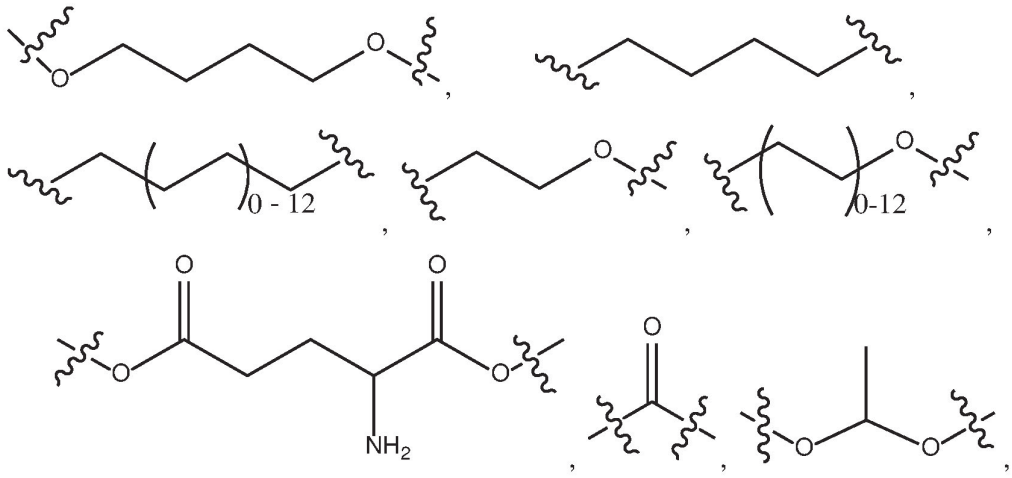


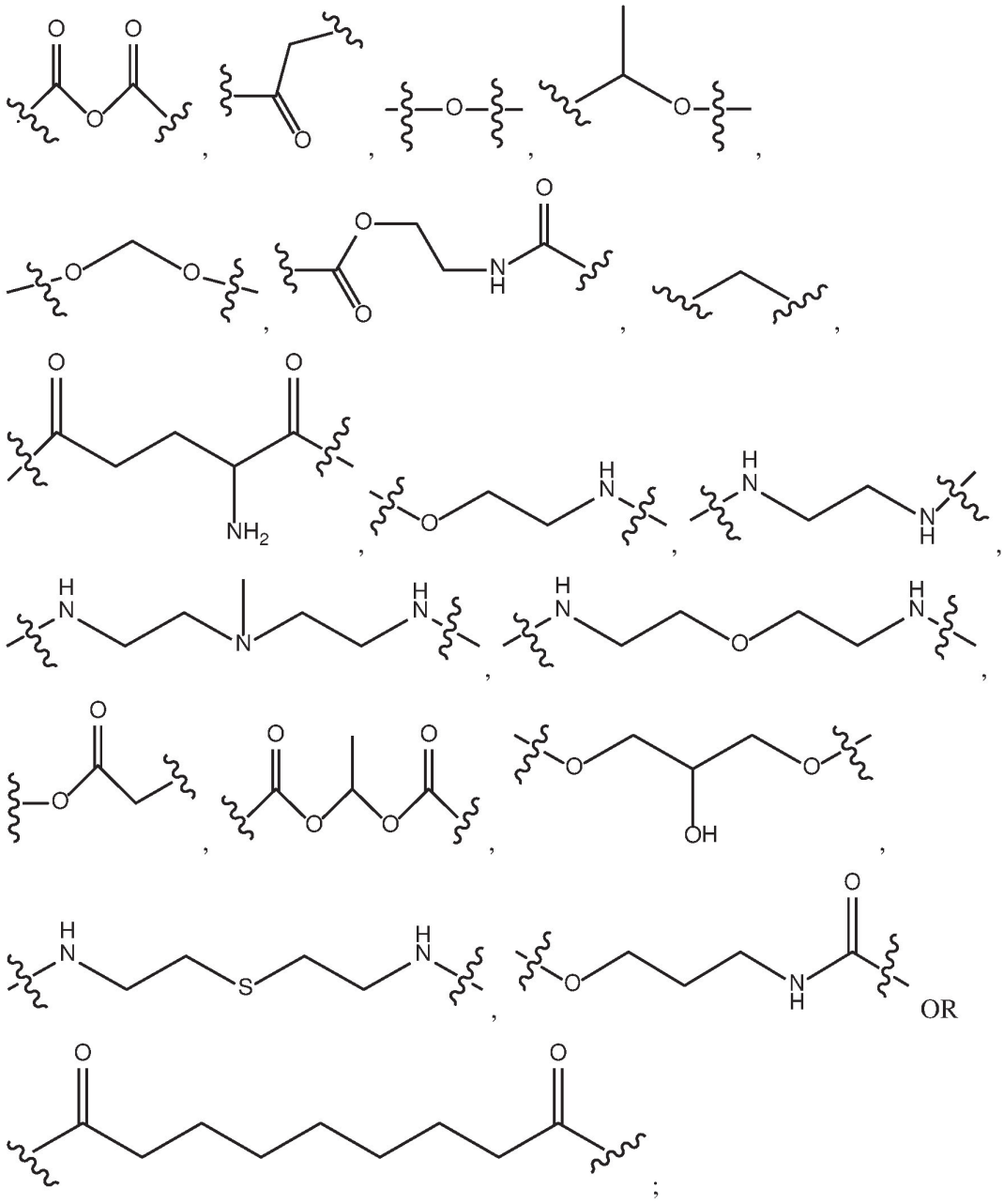
Formula IX

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0030] wherein,

R^1 represents Null,

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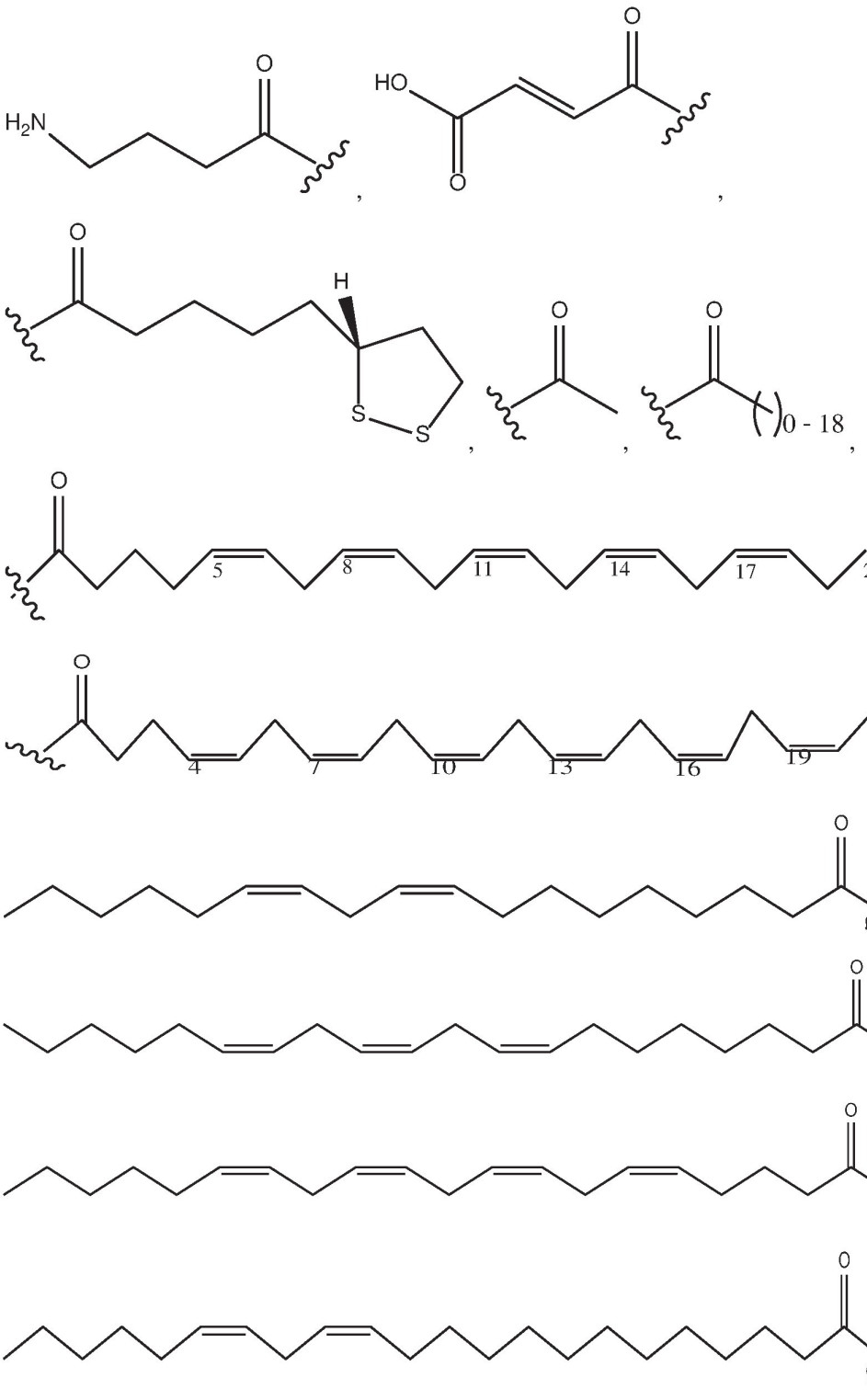
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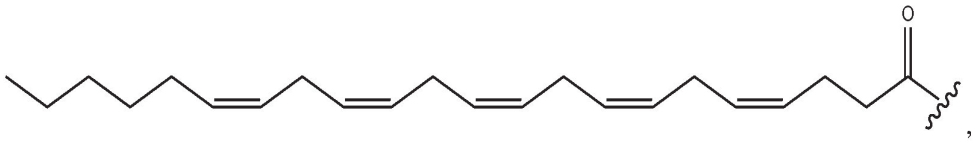
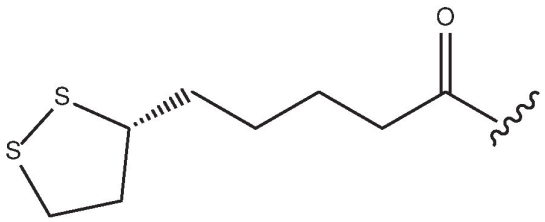
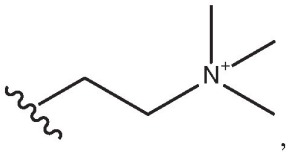
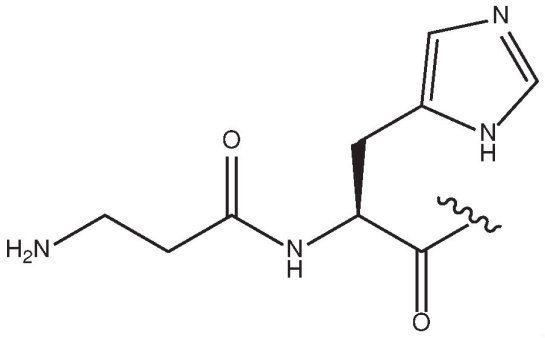
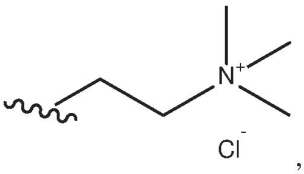
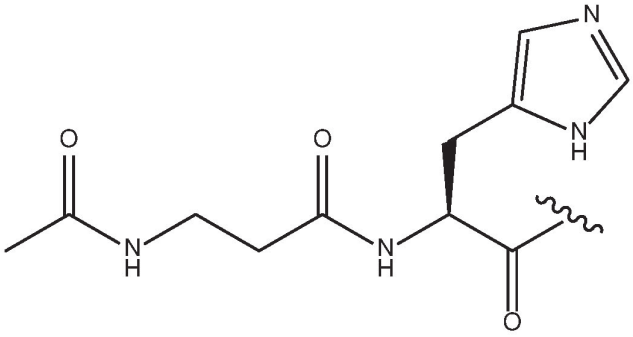
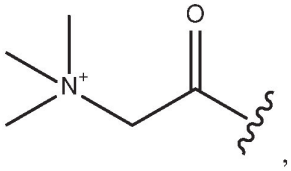
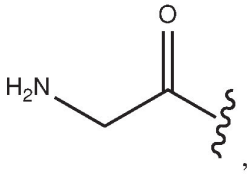
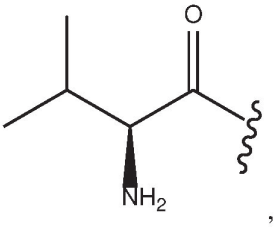
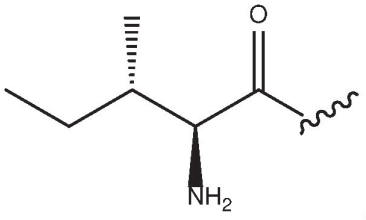
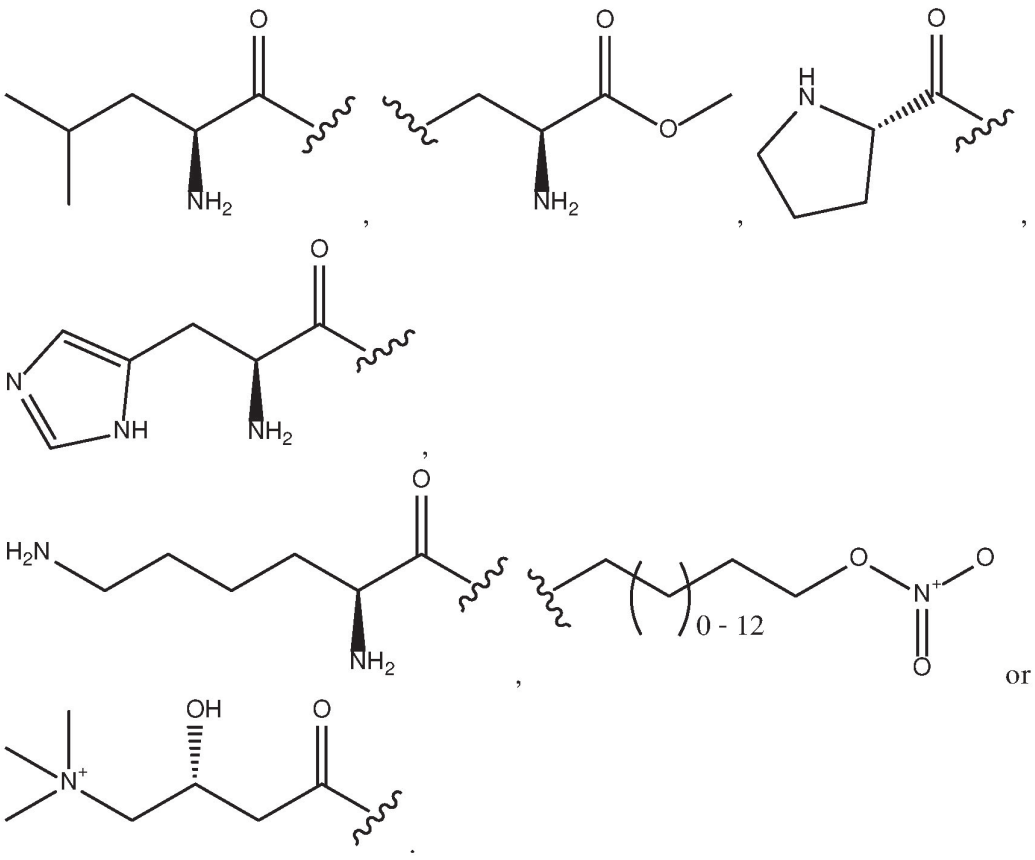
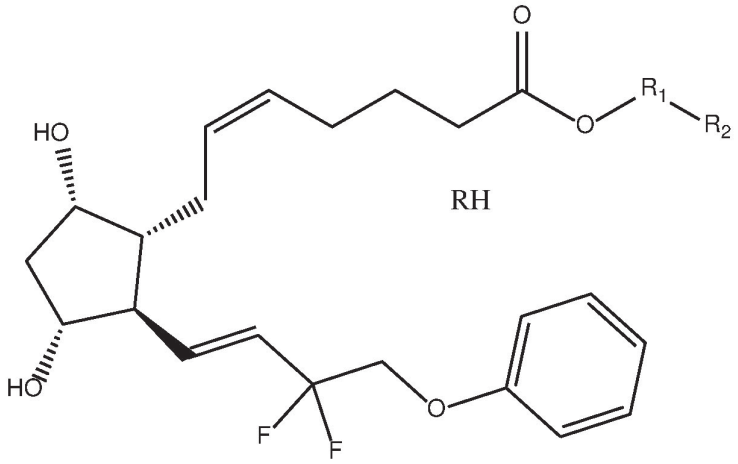













[0031] In another aspect, the compounds of formula X are described:

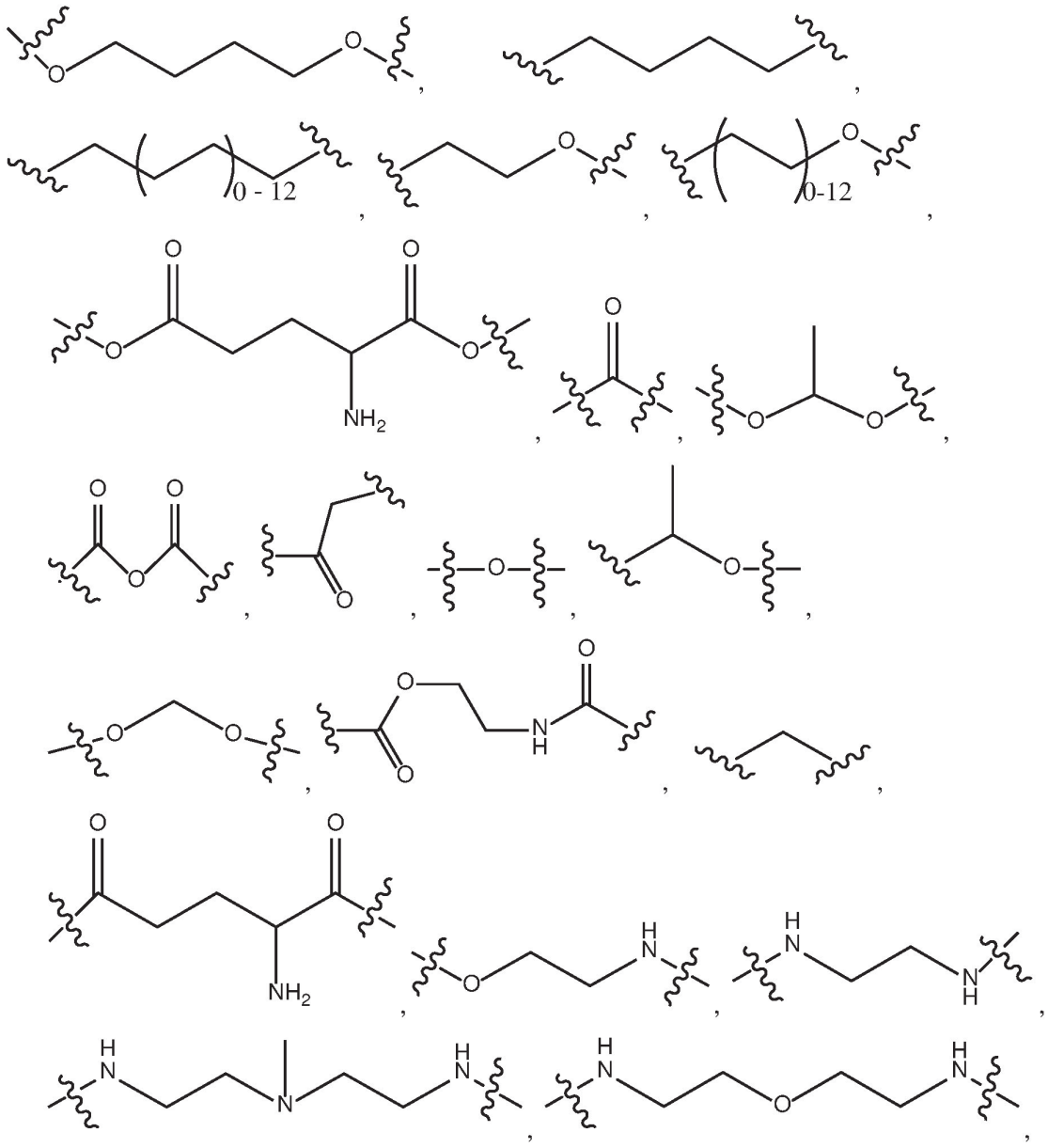


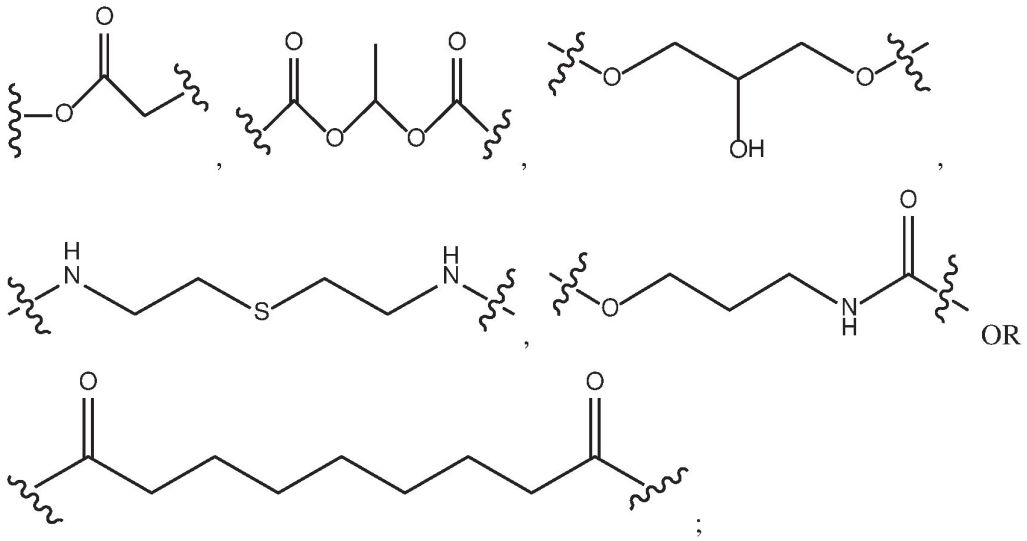
Formula X

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

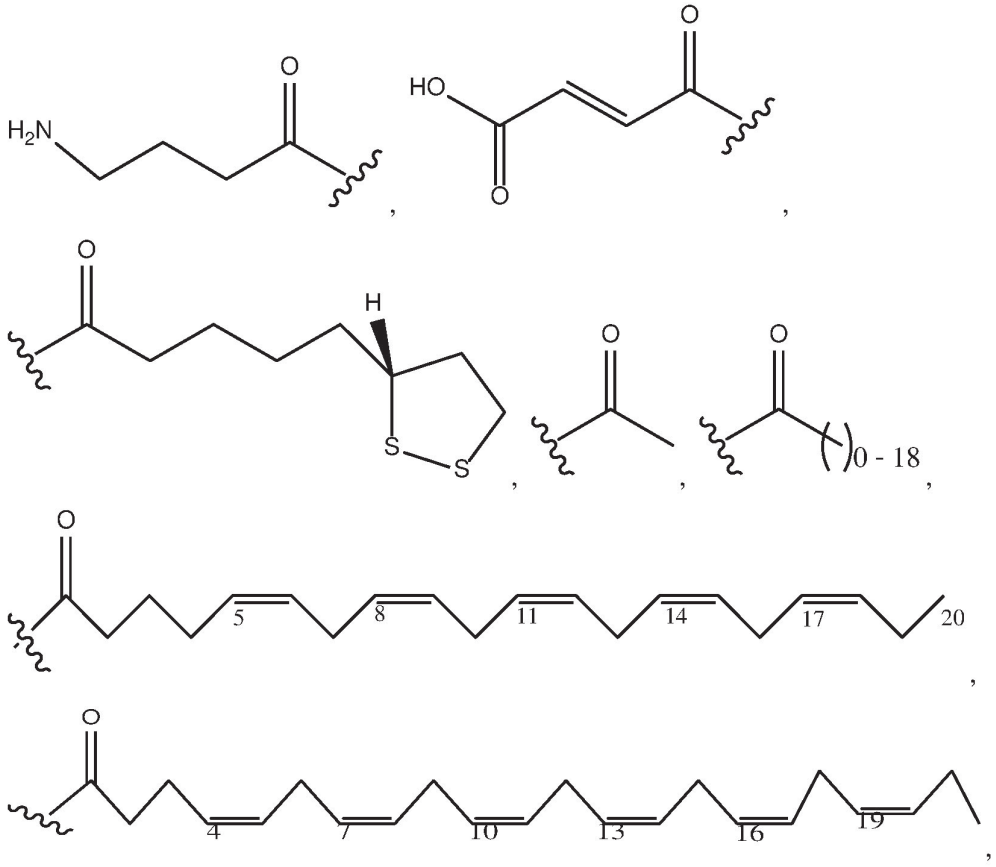
[0032] wherein,

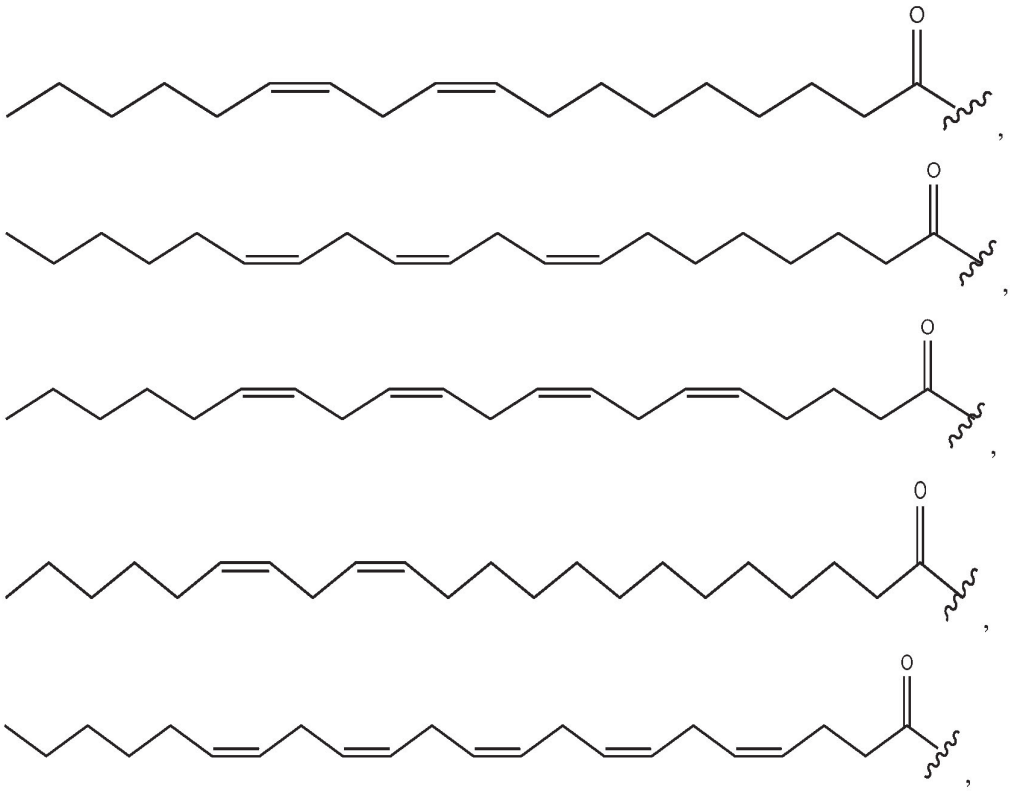
R^1 represents Null,

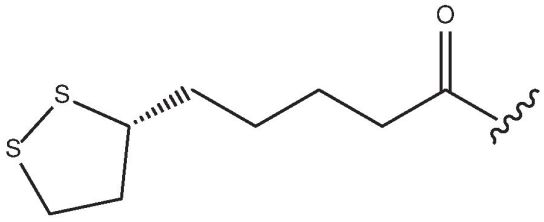


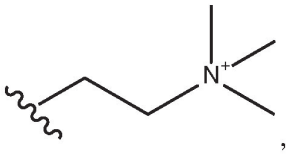


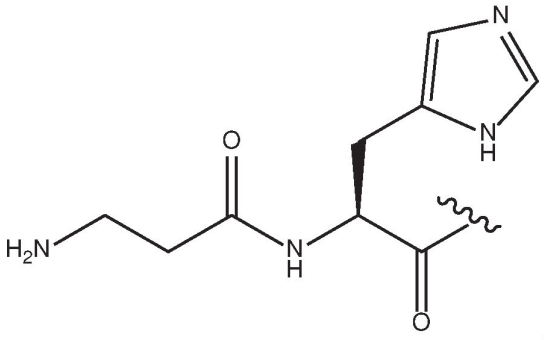
R_2 represents

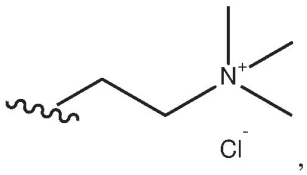


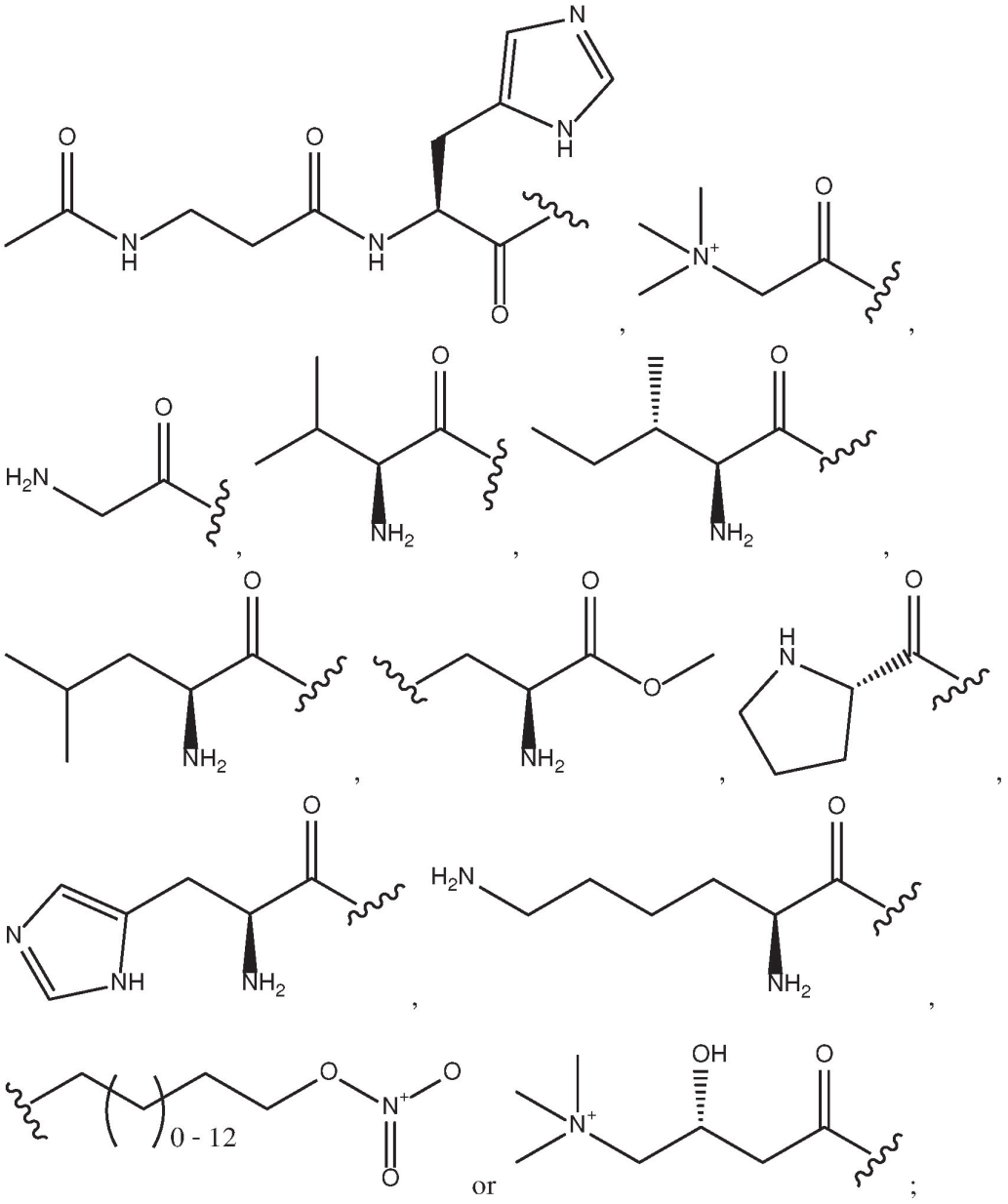




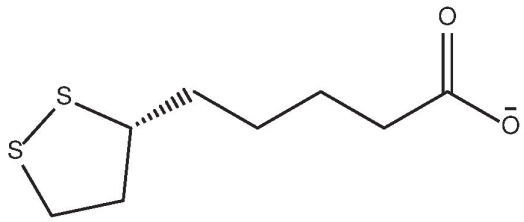








RH represents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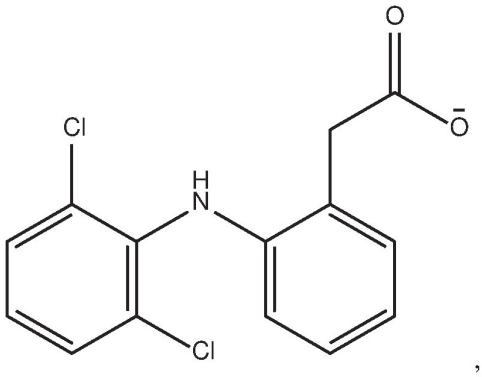
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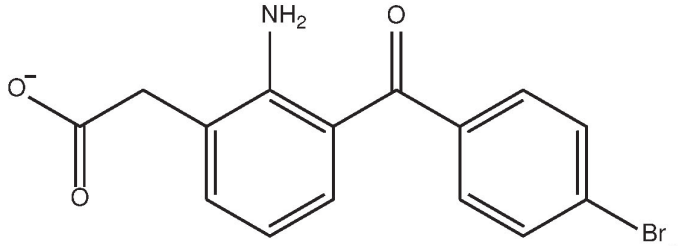
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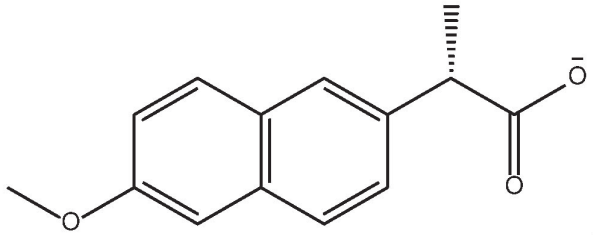
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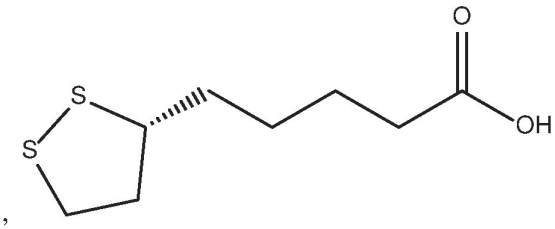
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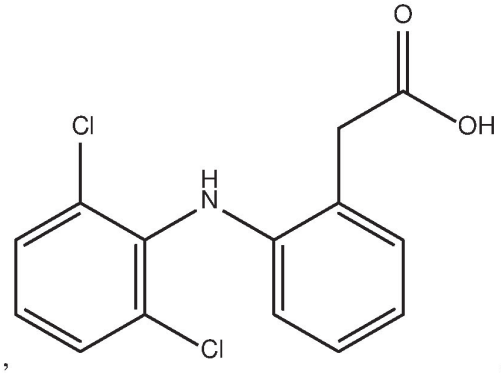
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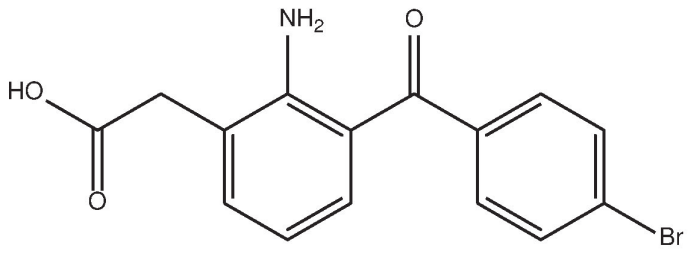
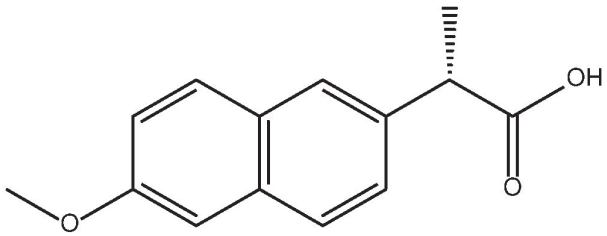
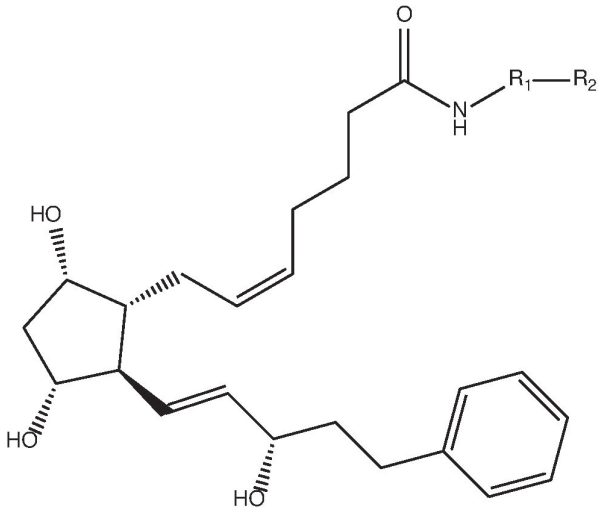




or .

[0033] In another aspect, the compounds of formula XI are described:

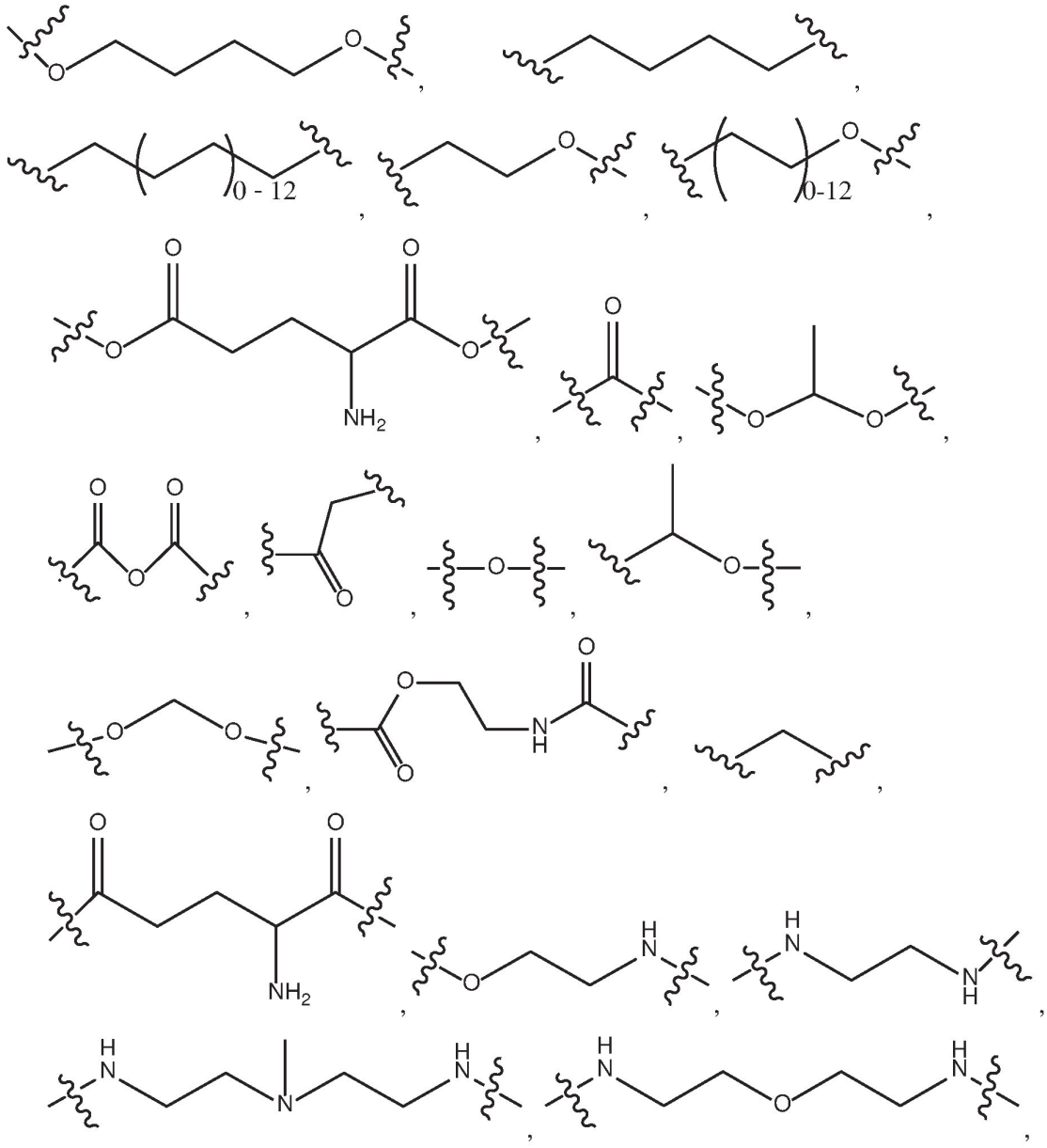


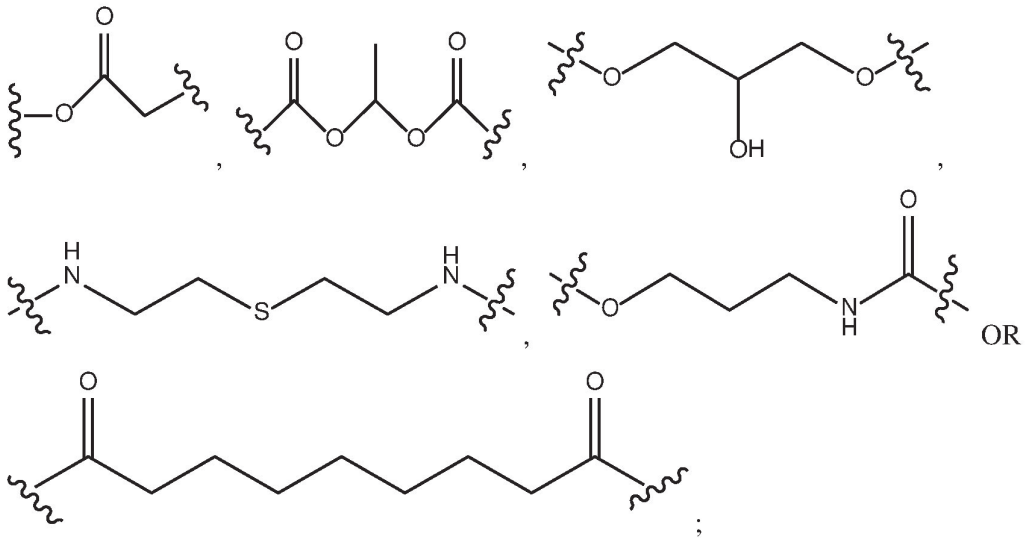
Formula XI

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

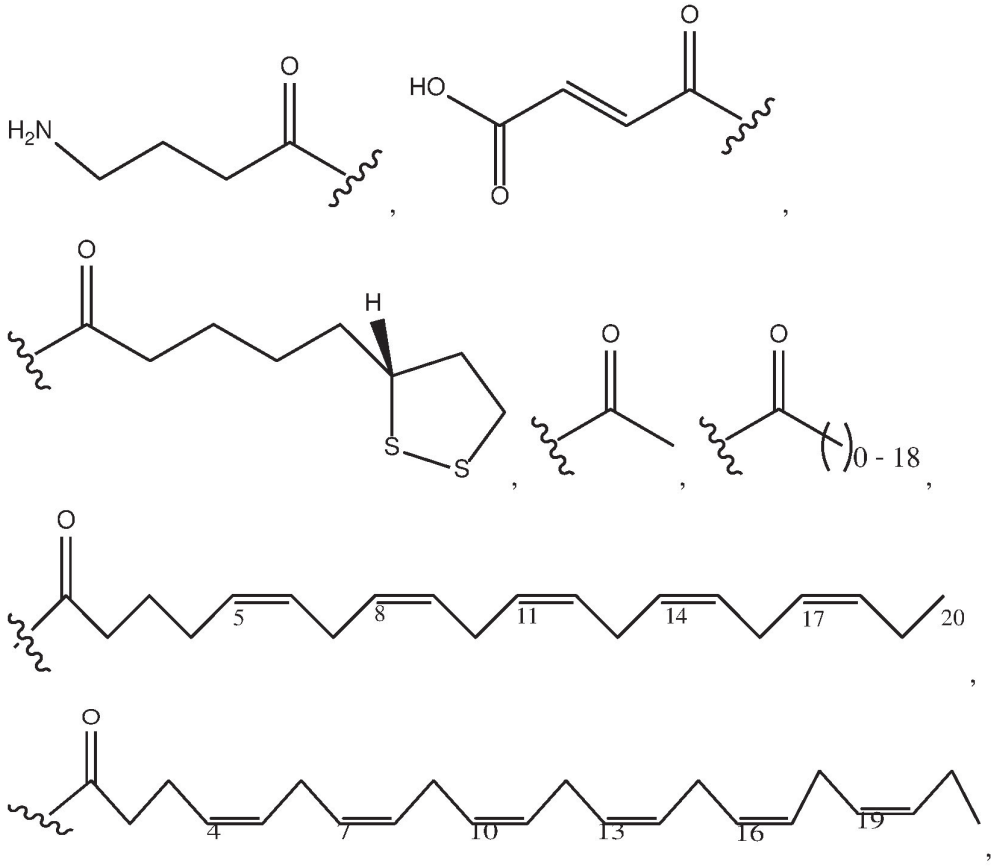
[0034] wherein,

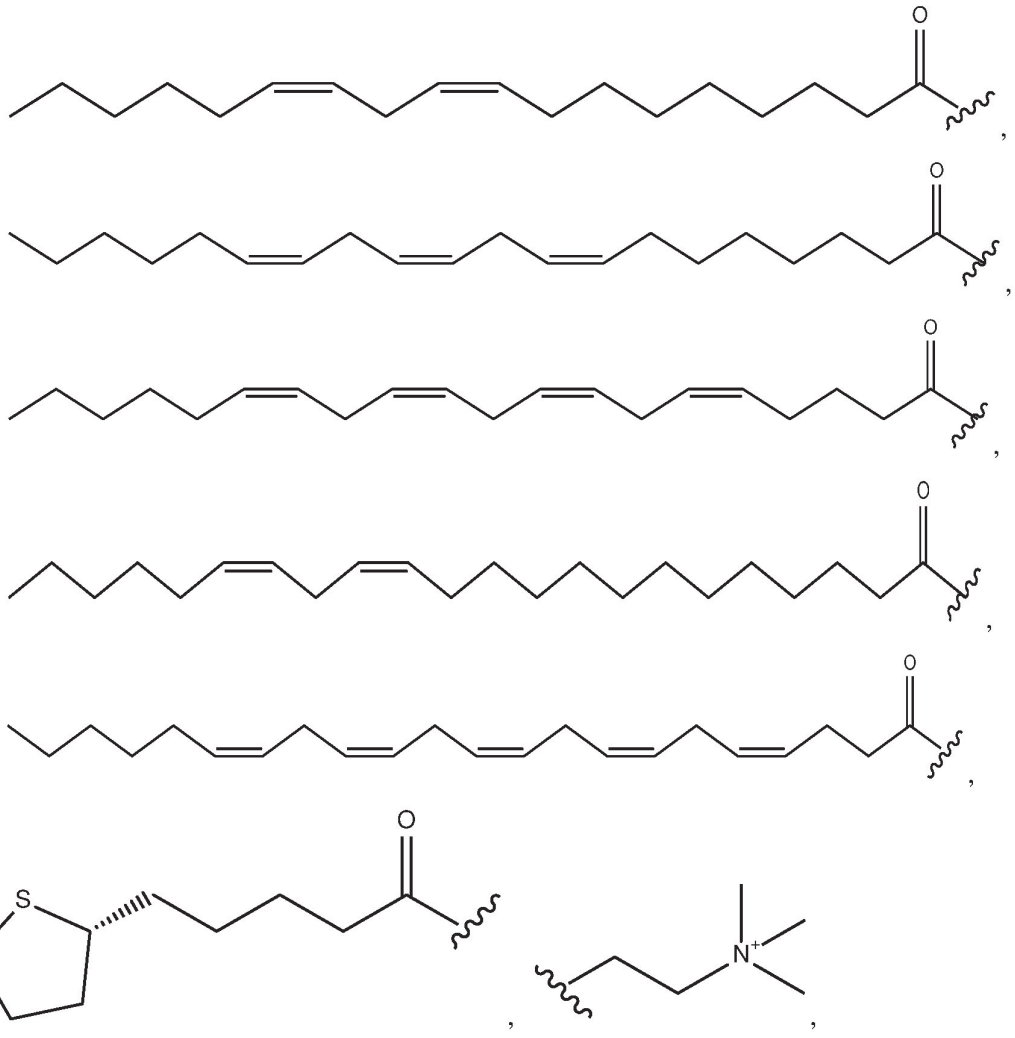
R^1 represents Null,

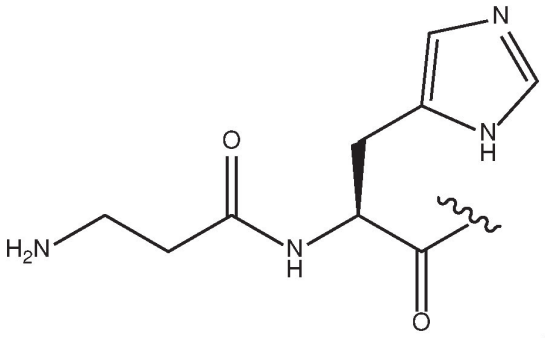
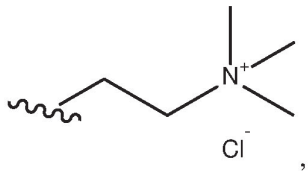
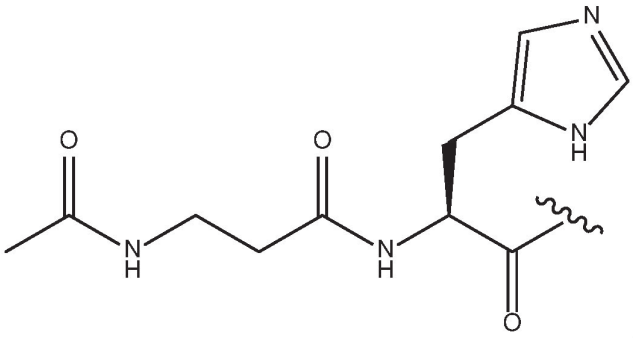
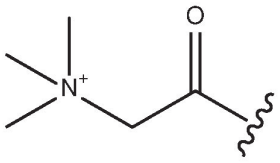
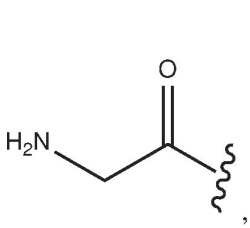

0 - 12
0-12



R_2 represents




O
O
O
O
O
S
S
O
N+


N
H
O
H_2N
N
H
O
,

N^+
Cl^-
,

N
H
O
N
H
O
N
H
O
,

N^+
O
,

H_2N
O
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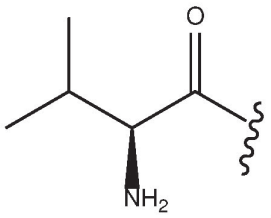
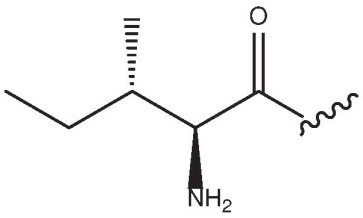

O
NH_2
,

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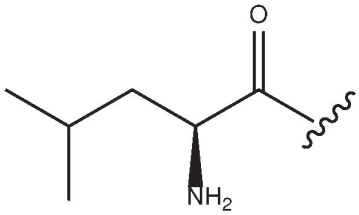
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NH_2
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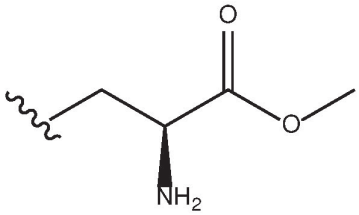
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O
NH_2
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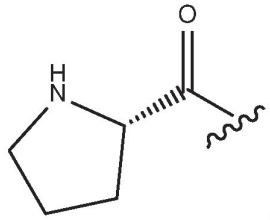
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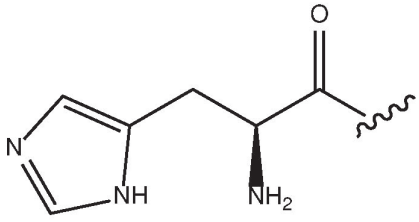
,

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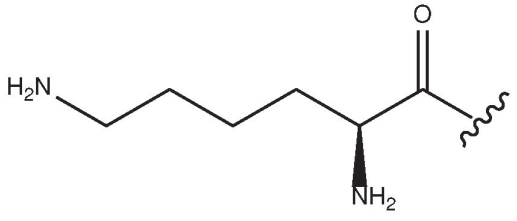
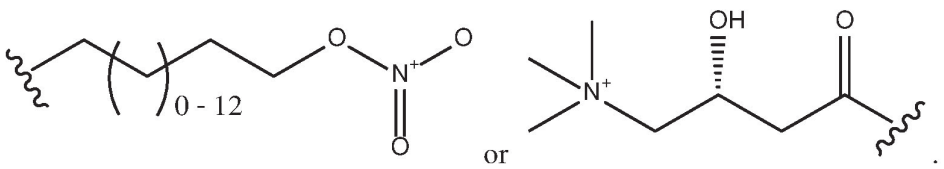
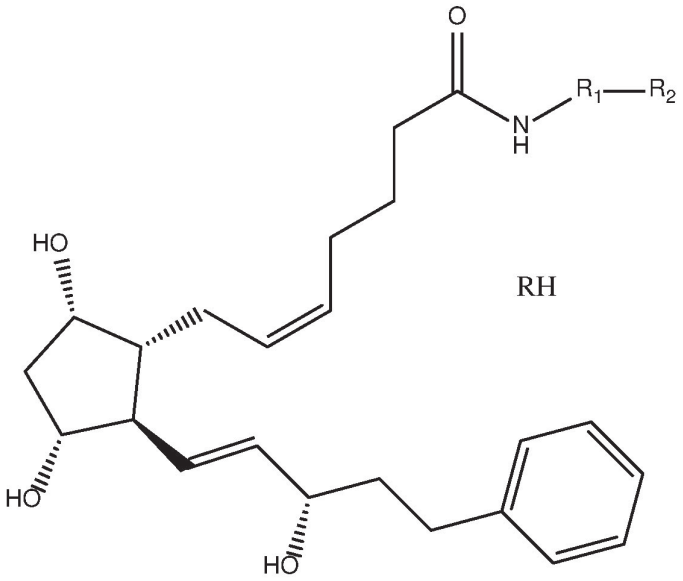
N
NH
NH_2
,

H_2N
O
NH_2
,



[0035] In another aspect, the compounds of formula XII are described:

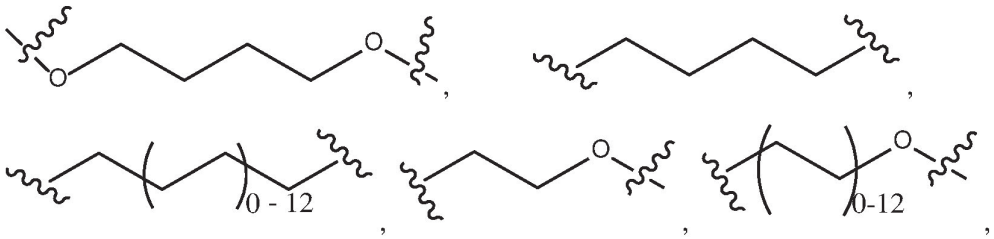


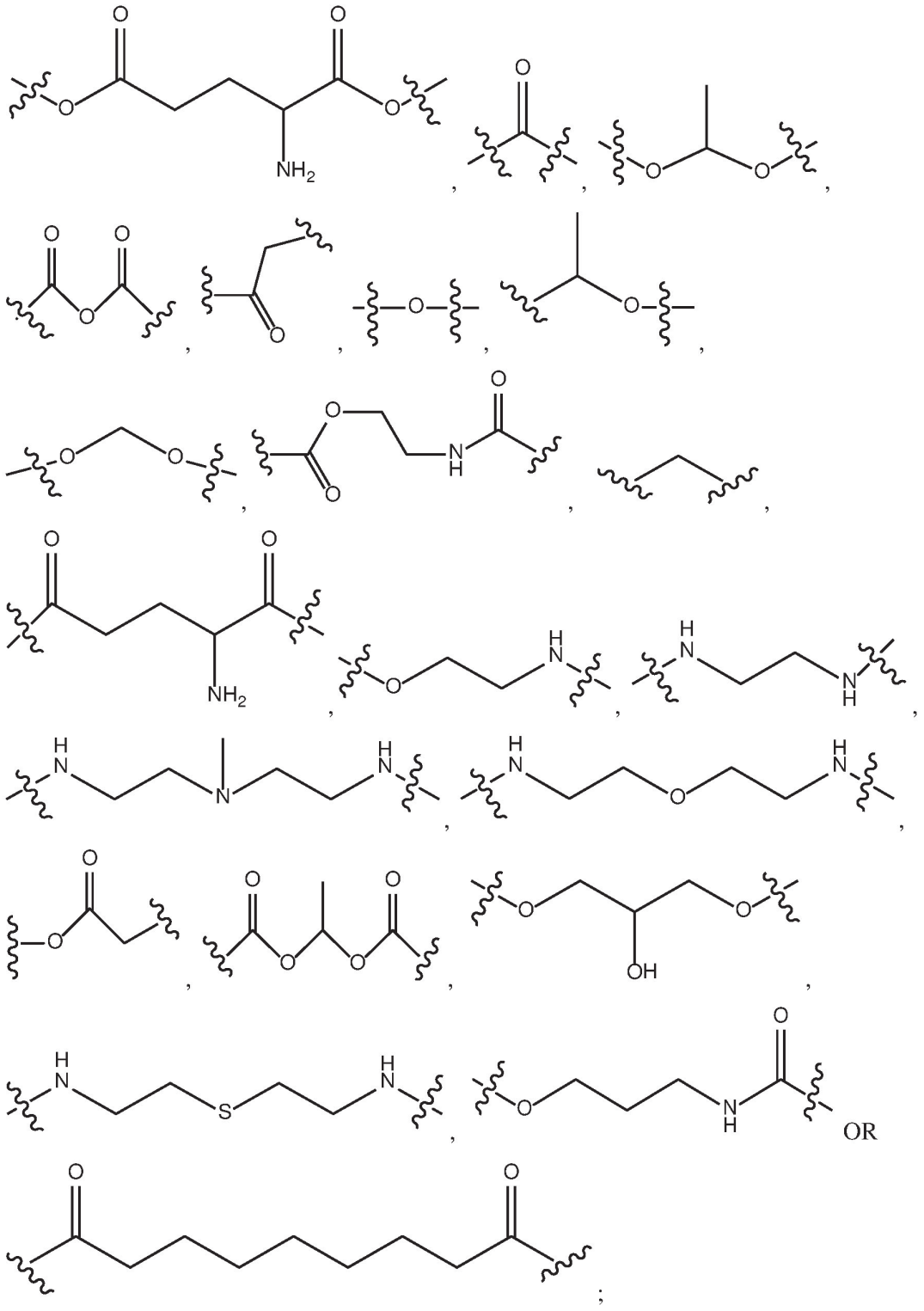
Formula XII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

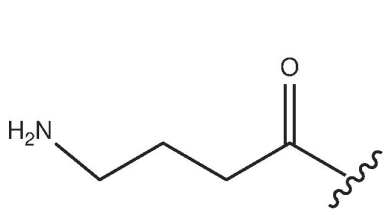
[0036] wherein,

R^1 represents Null,





R_2 represents



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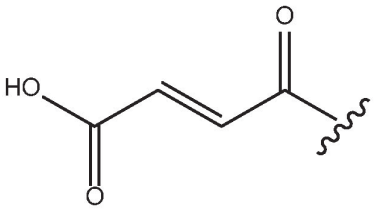

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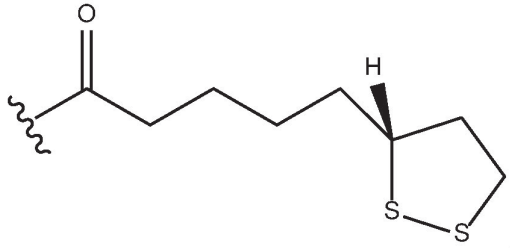

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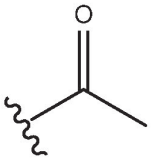

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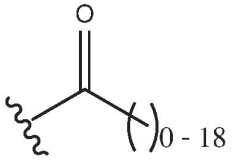

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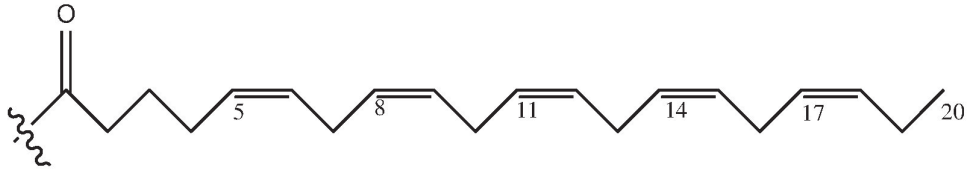

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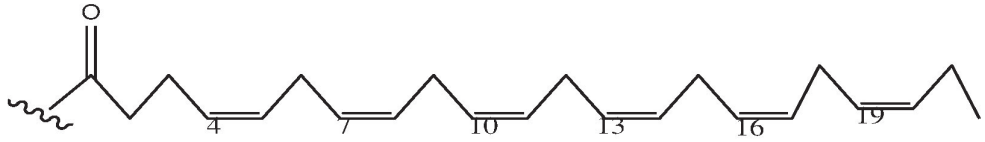

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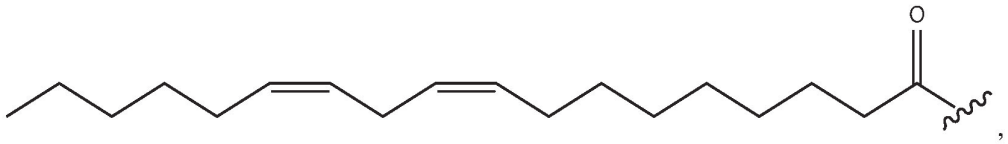

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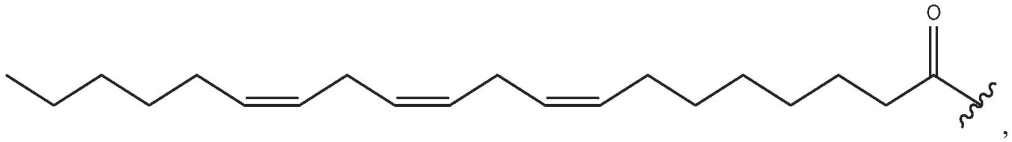

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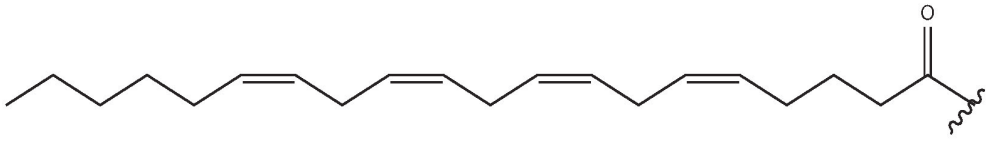

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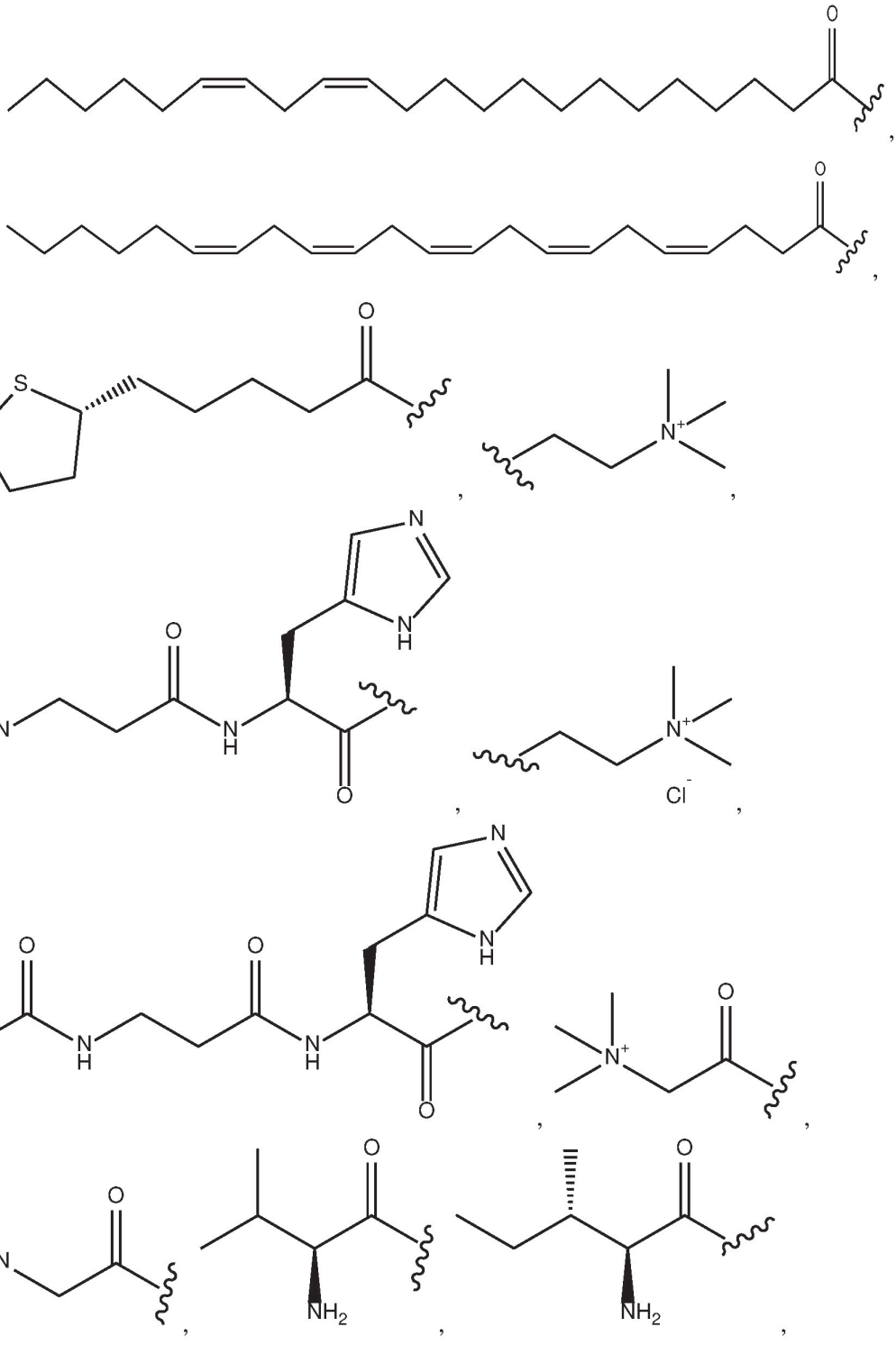
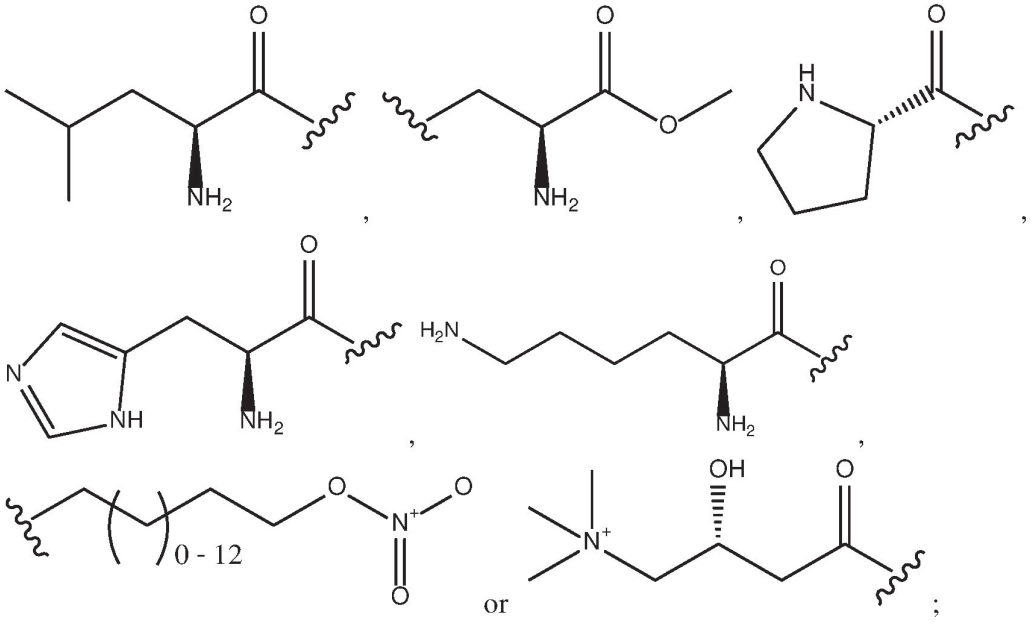
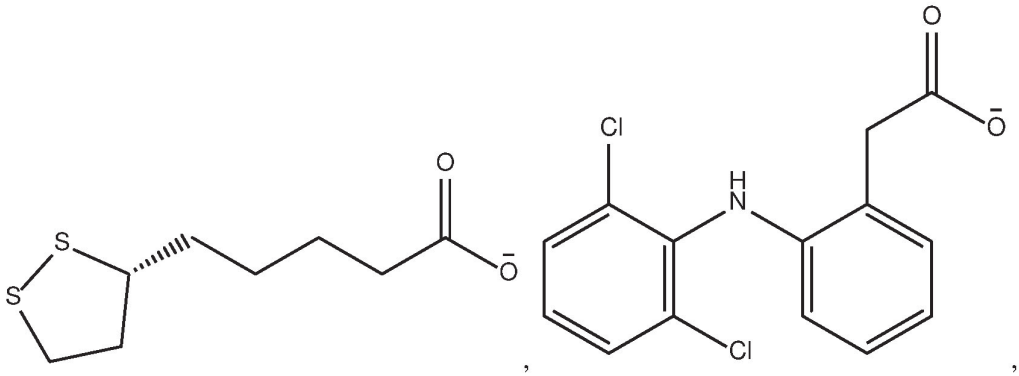
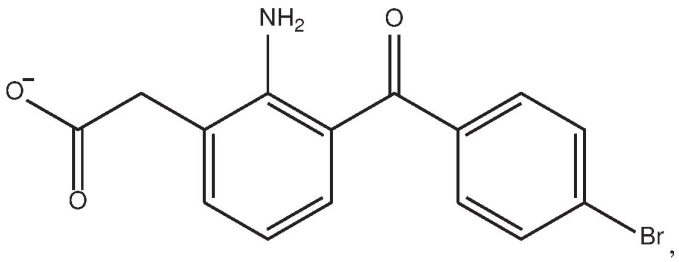




RH represents





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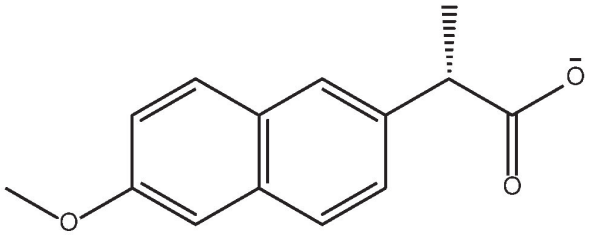

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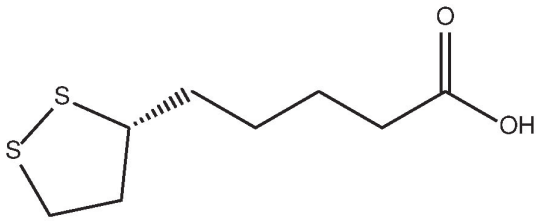

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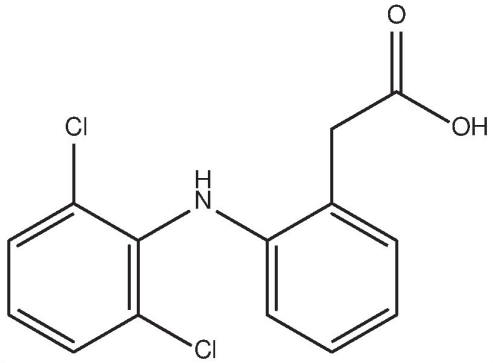

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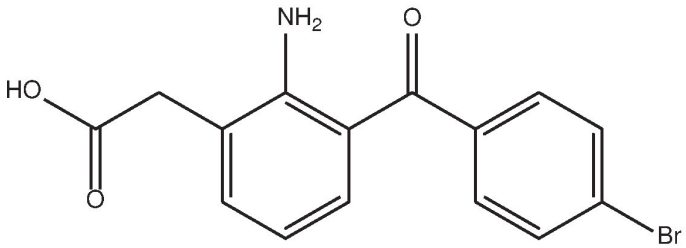
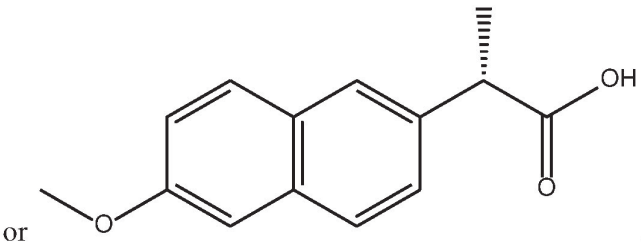
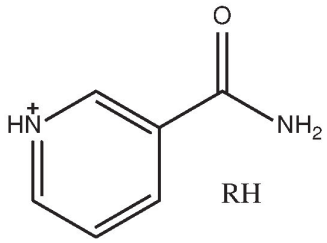




or .

[0037] In another aspect, the compounds of formula XIII are described:

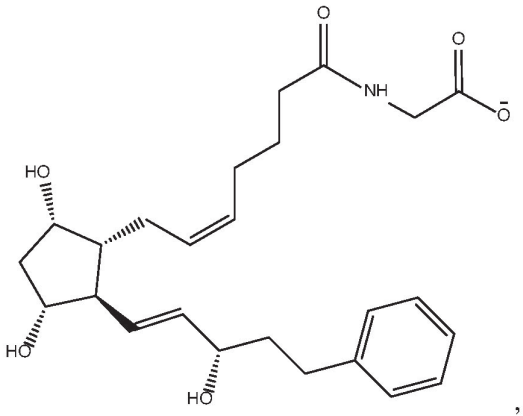


Formula XIII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0038] wherein,

RH independently represents



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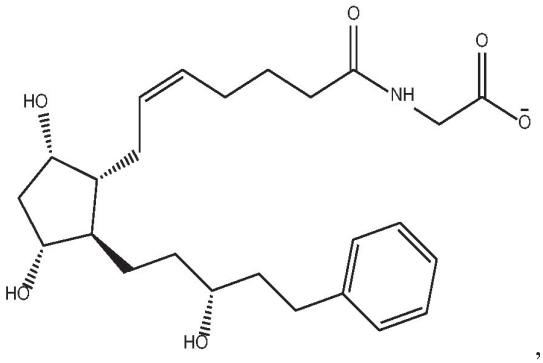

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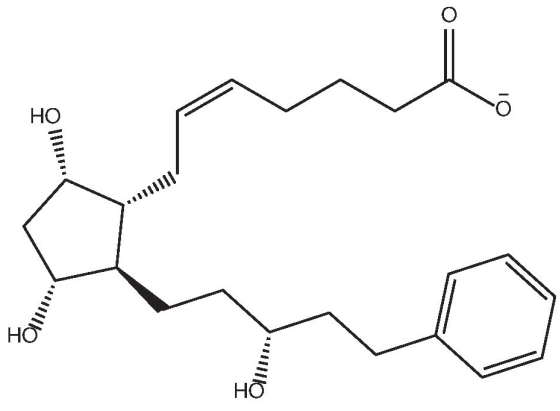

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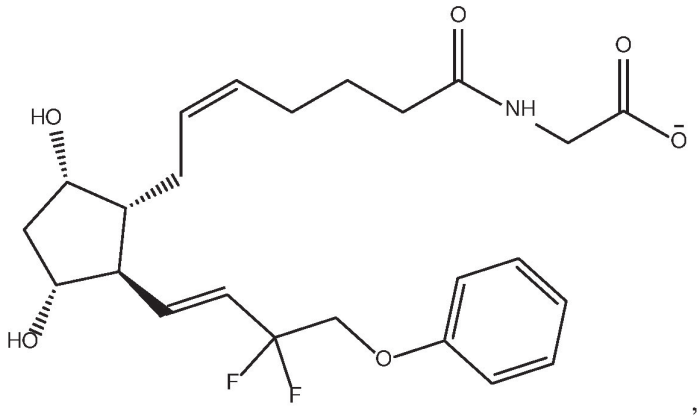

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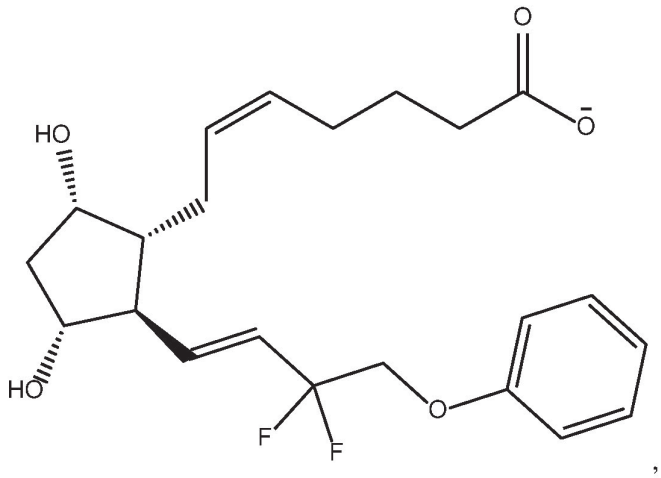

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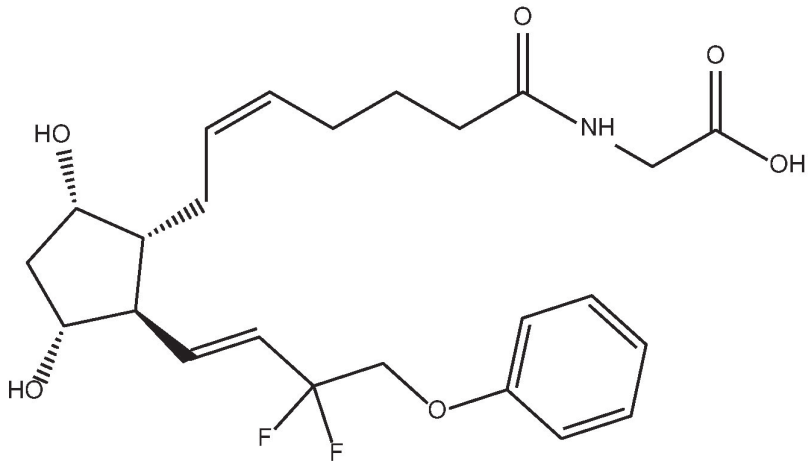
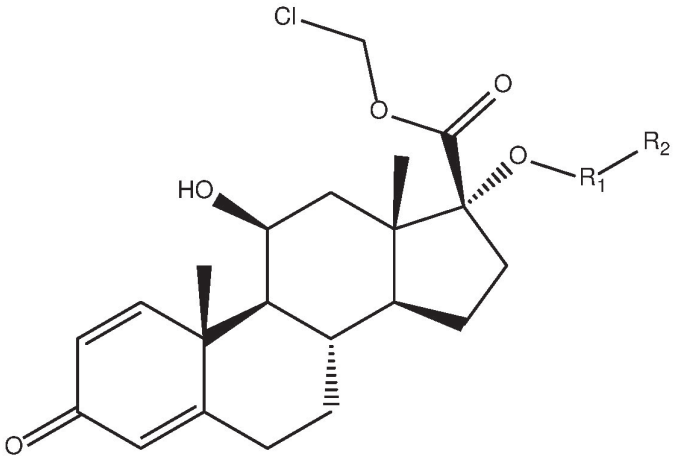
OR



.

[0039] In another aspect, the compounds of formula XIV are described:



RH

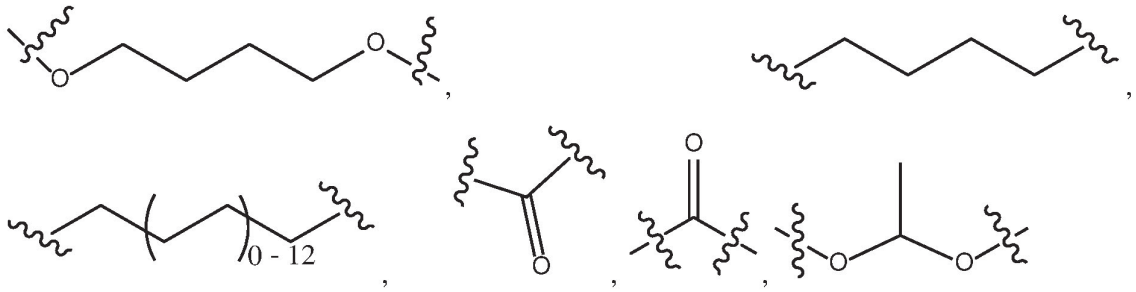
Formula XIV

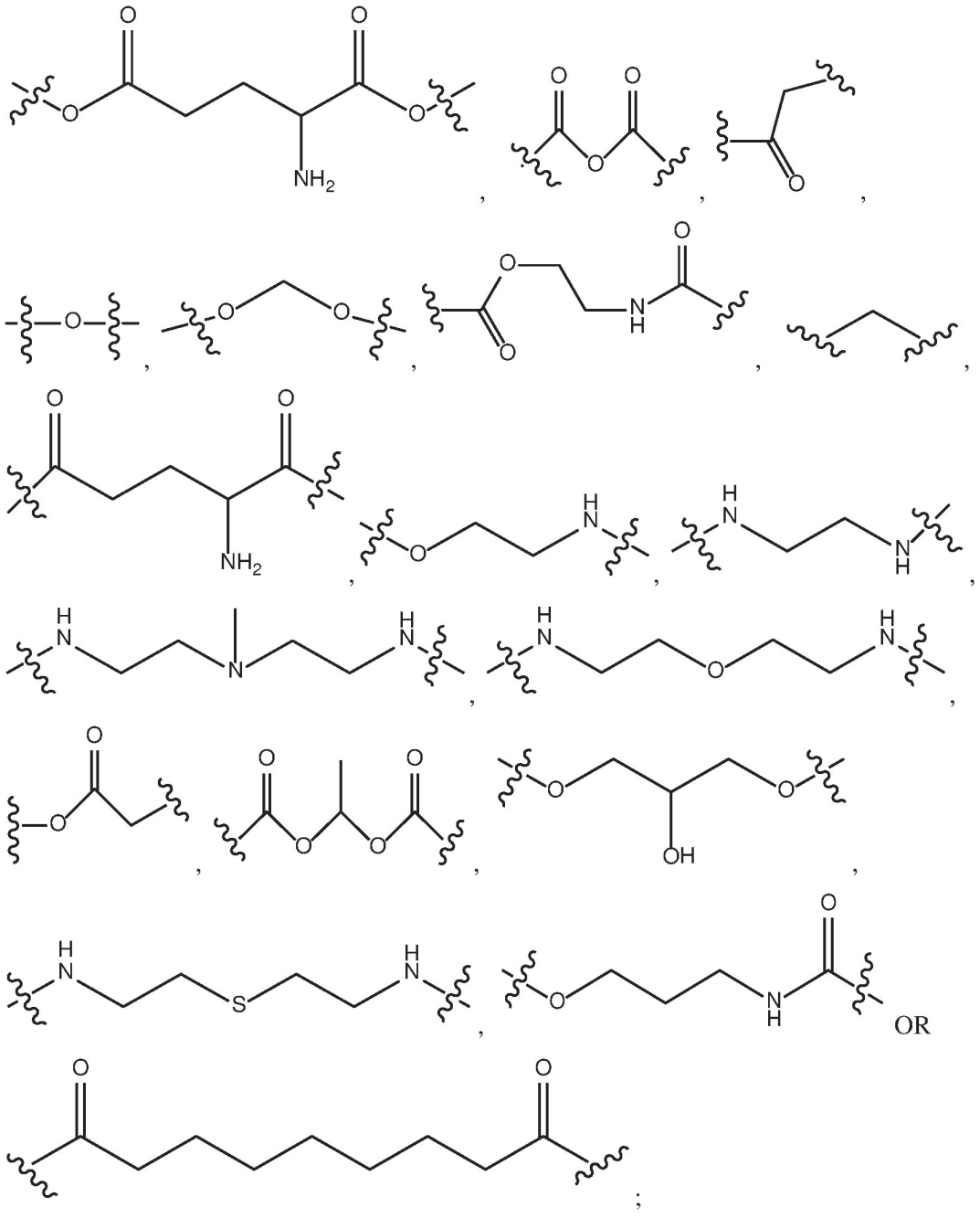
and pharmaceutically acceptable hydrates, solvates, enantiomers, and stereoisomers thereof;

[0040] wherein,

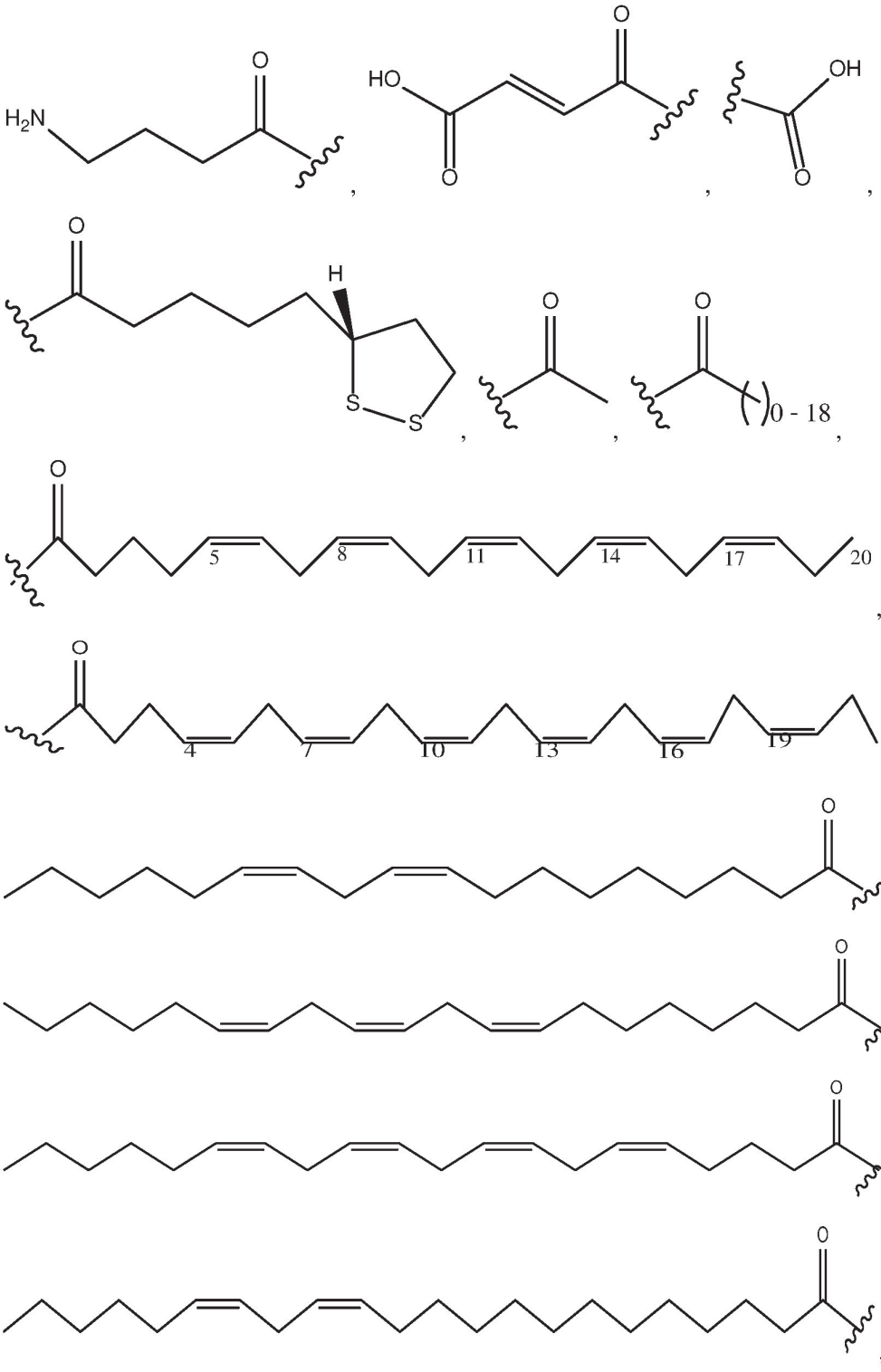
R^1 independently represents

NULL,





R^2 independently represents


H2N
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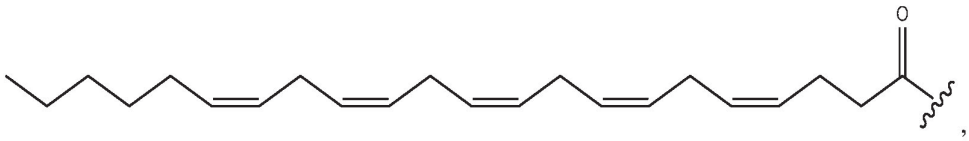
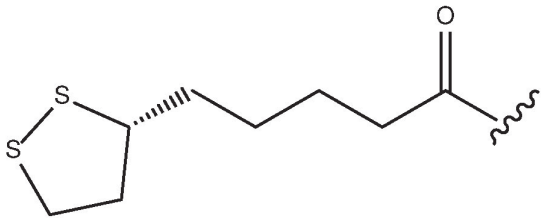
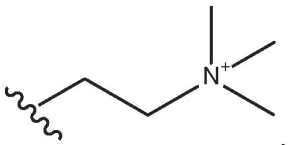
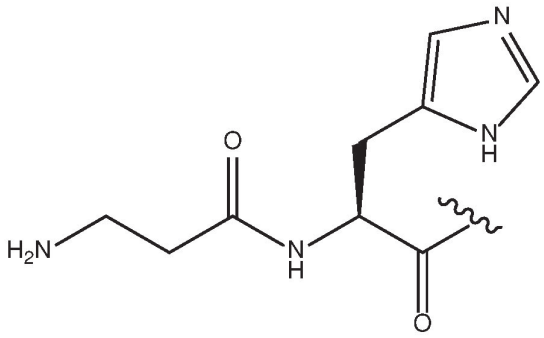
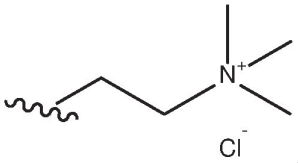
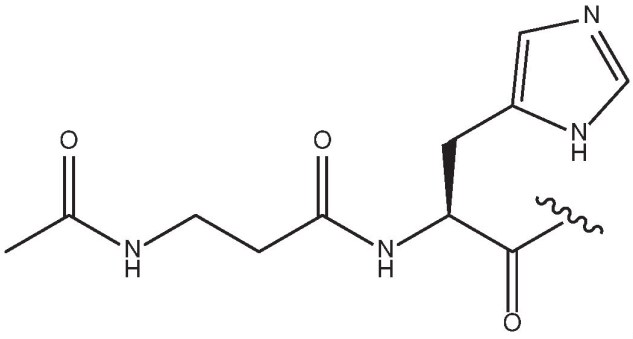
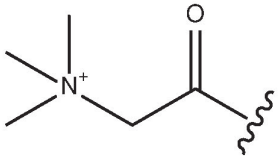
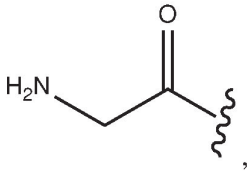
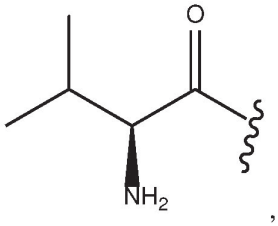
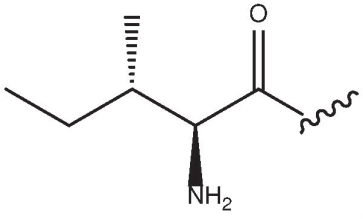
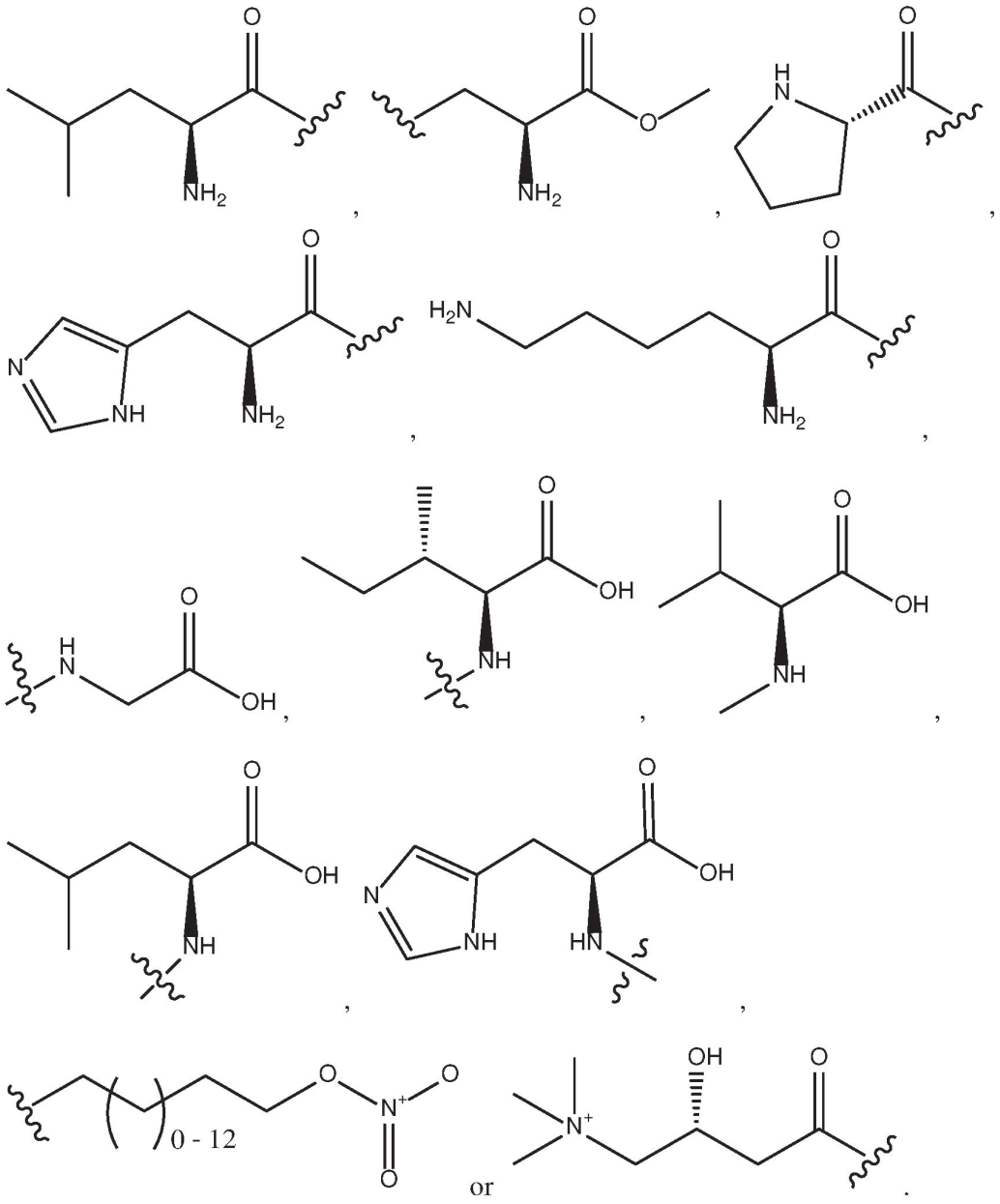
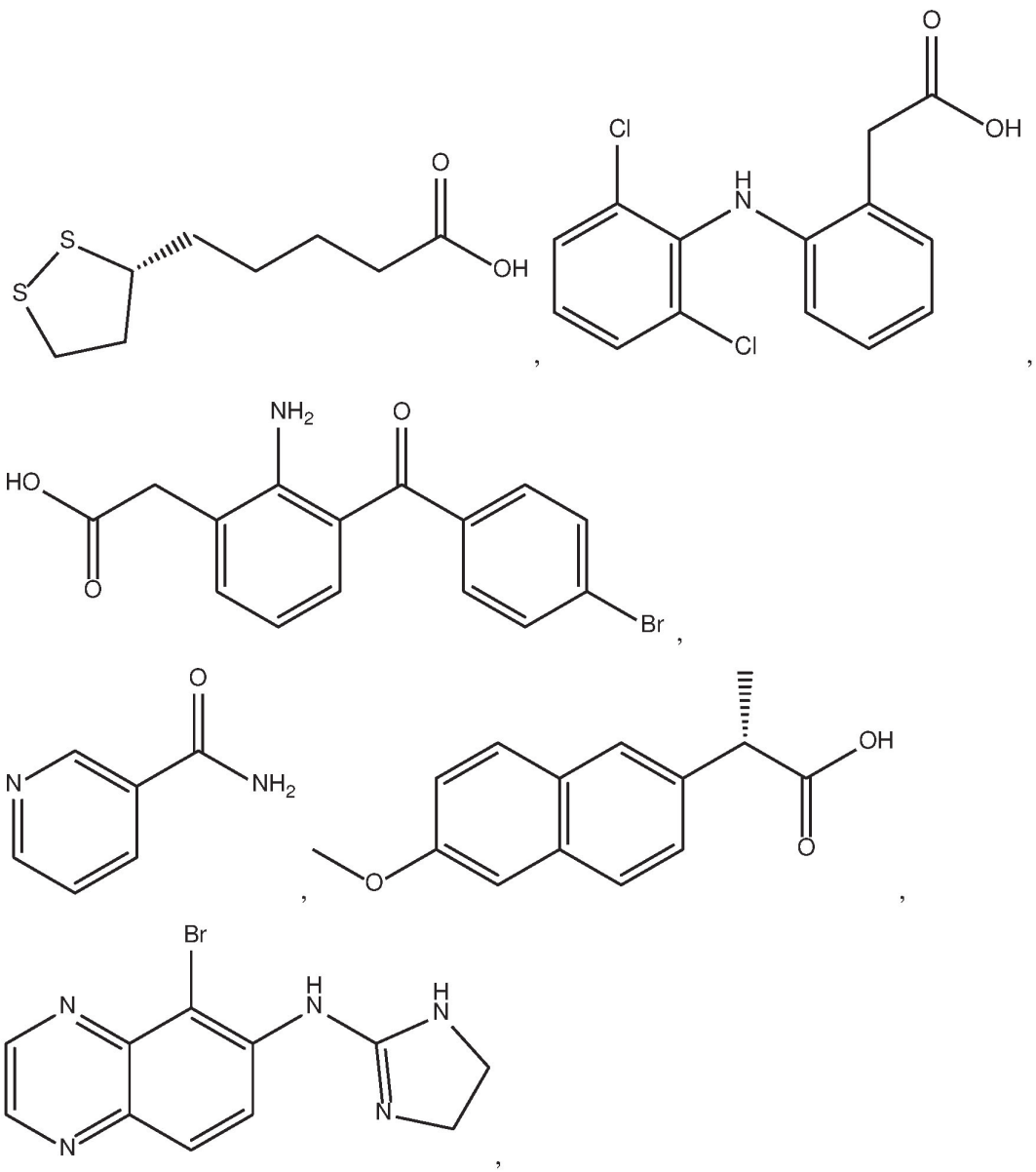













RH independently represents

NULL,

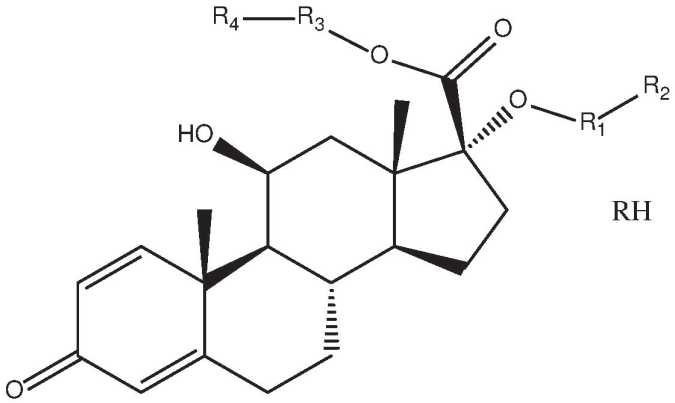


caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid,

gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, acid, alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

[0041] The compositions are typically compounds in the forms of hydrates or solvates of loteprednol derivative and a moiety [RH] containing compound selected [RH] in which the loteprednol derivative is protonated / unprotonated based on the derivative functionality and the moiety [RH] of the pharmaceutically acceptable salt is at least in partially ionic form. In some instances, however, for example depending on the pH of the environment, the composition may be in the form of a mixture of loteprednol derivative and a component represented by [RH]. The invention also provides pharmaceutical compositions comprising compositions of formula XIV and pharmaceutically acceptable excipients.

[0042] In another aspect, the compounds of formula XV are described:



RH

Formula XV

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0043] wherein,

R^1, R^3 independently represents

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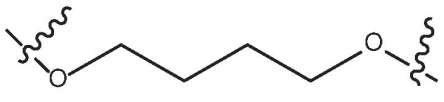

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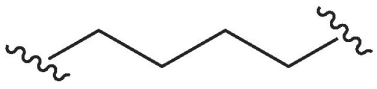

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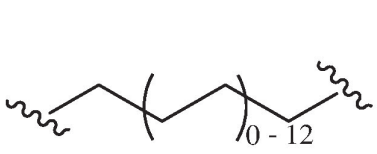

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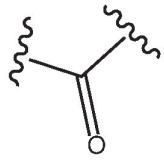

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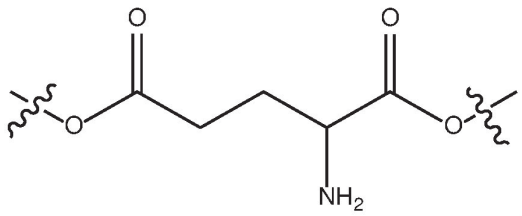

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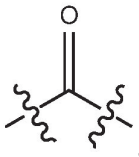

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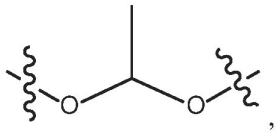

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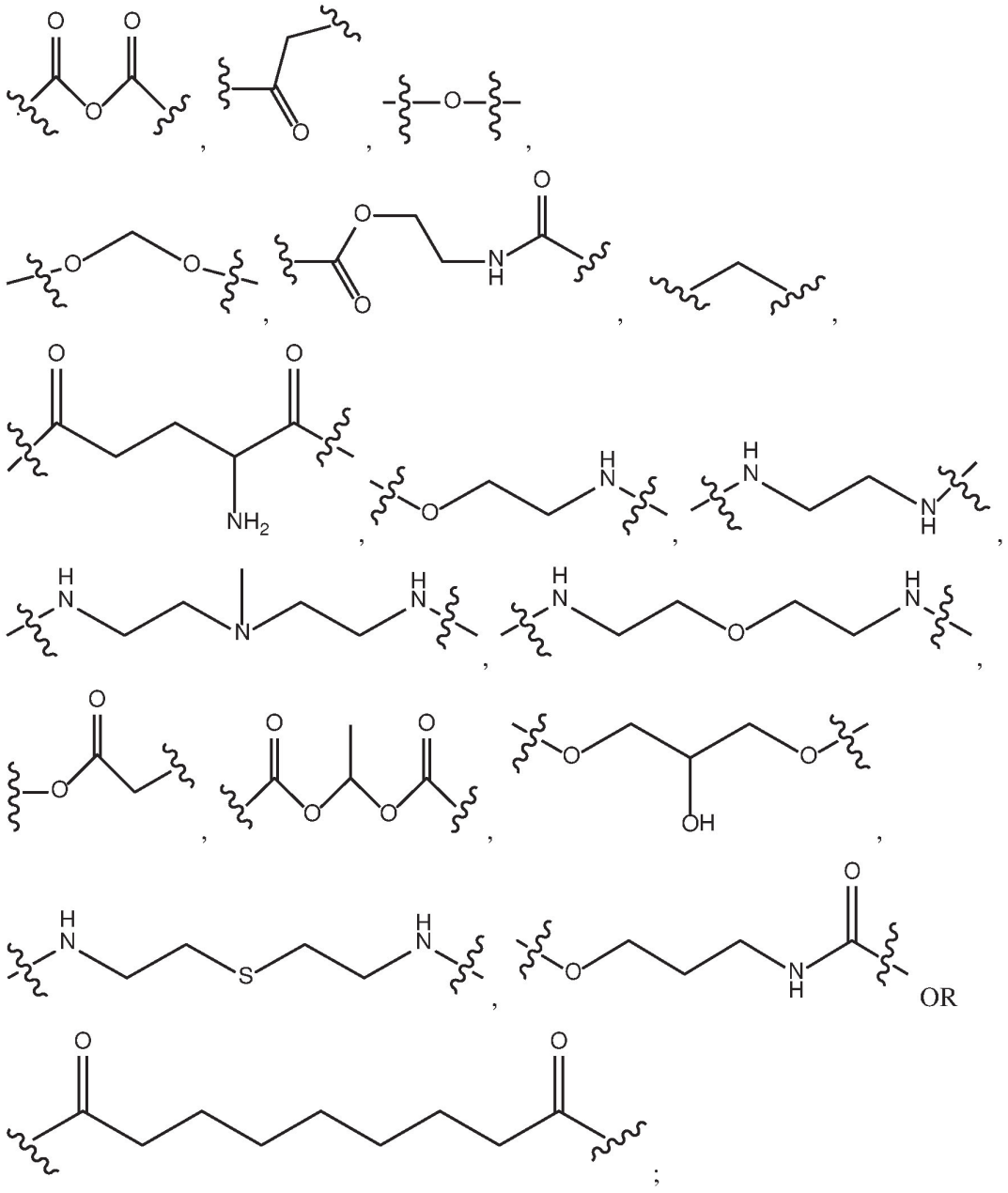
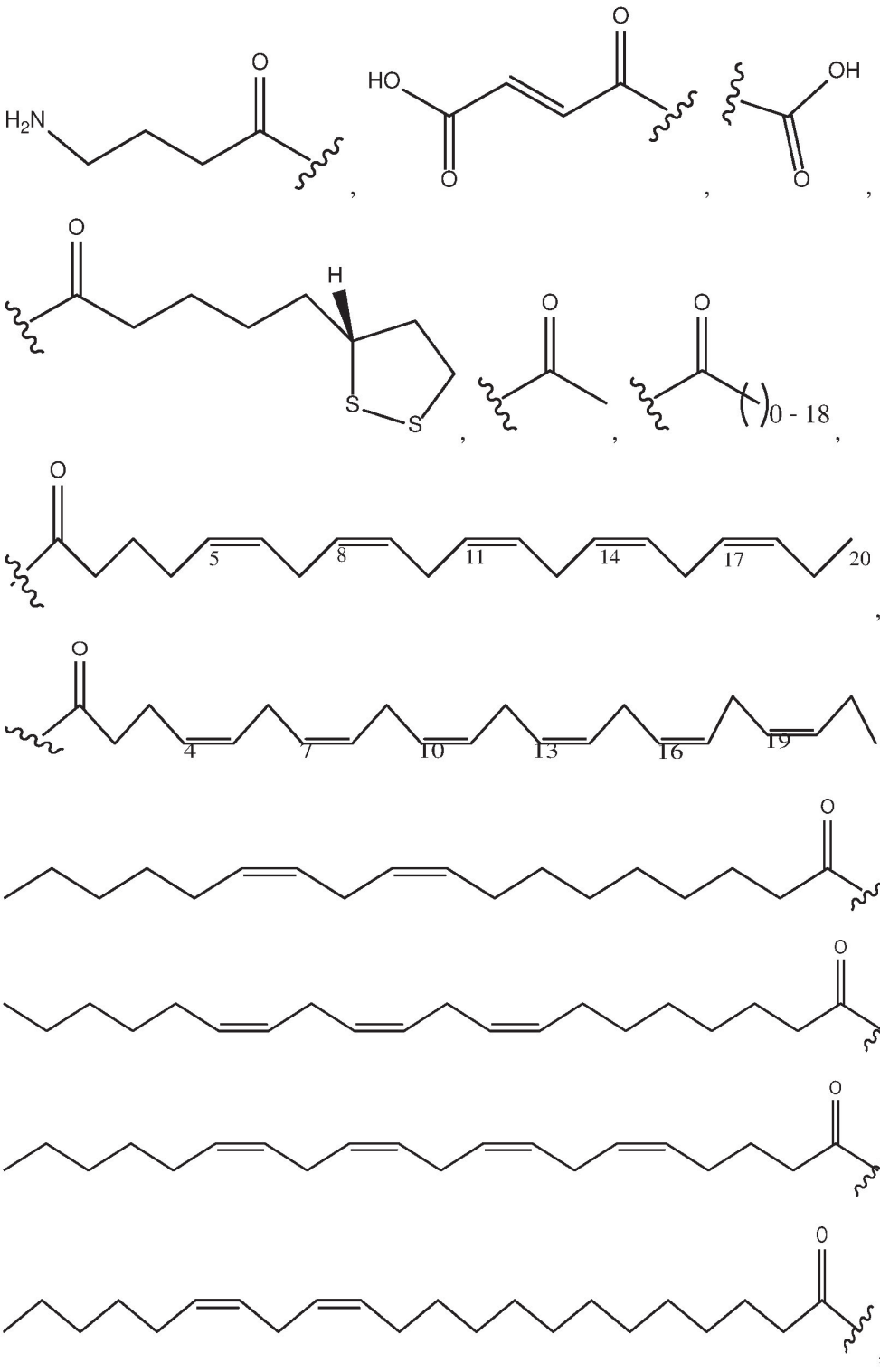


R^2, R^4 independently represents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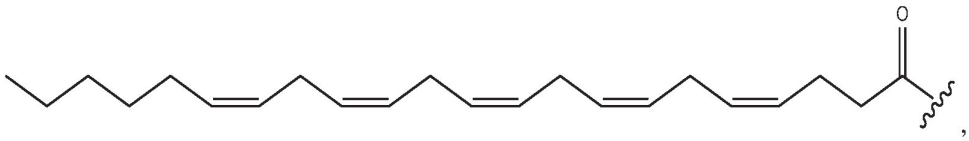
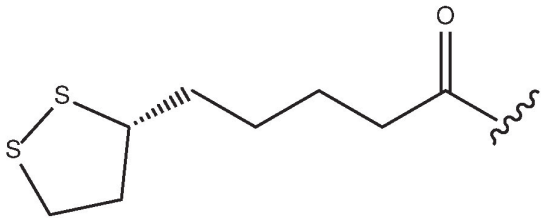
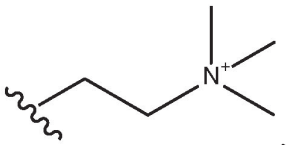
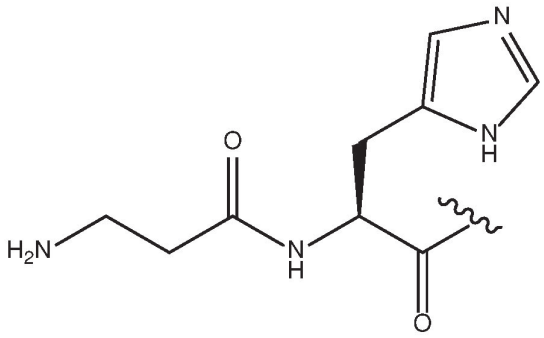
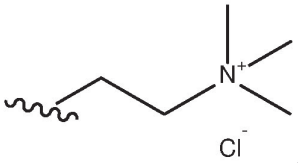
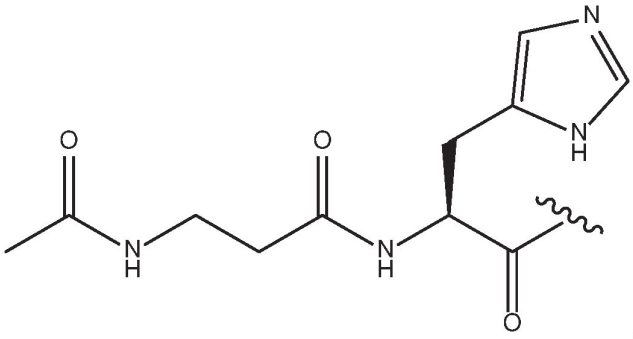
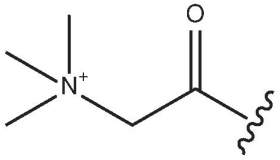
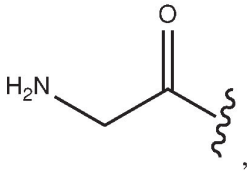
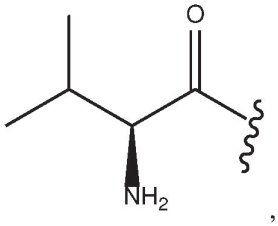
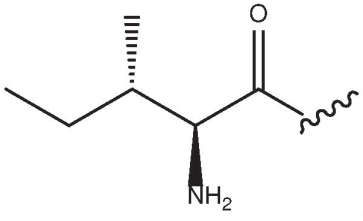
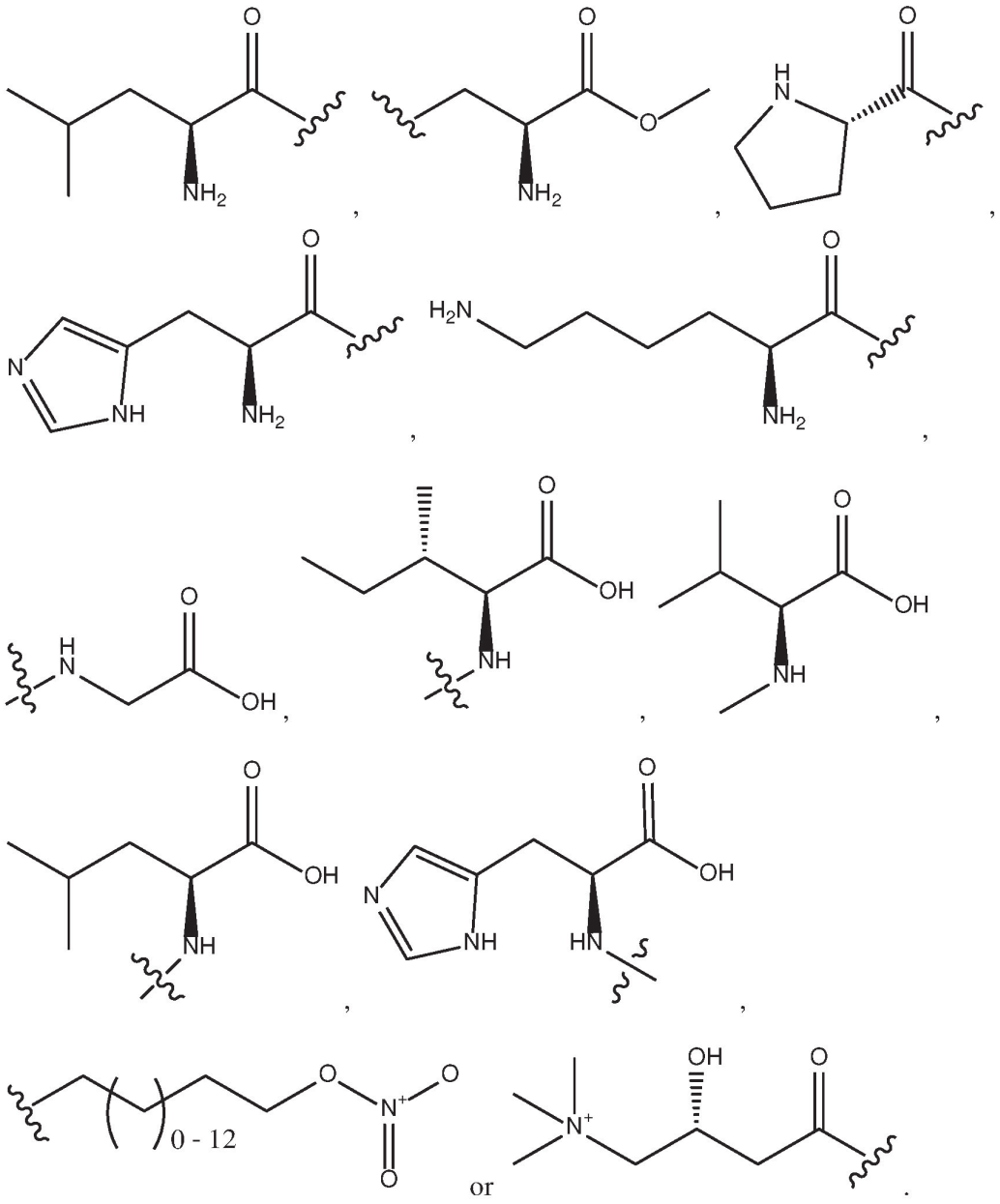
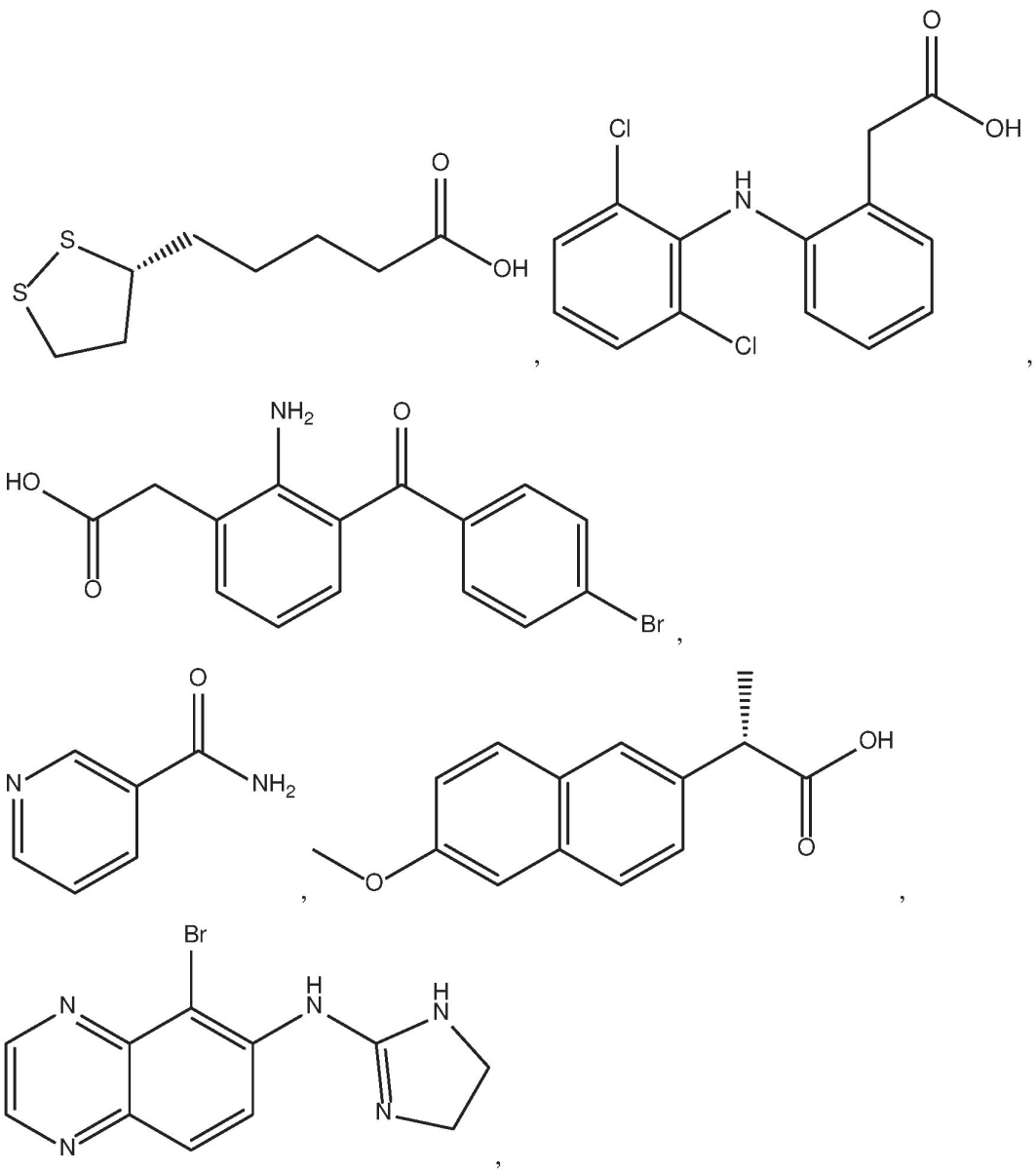













or .

RH independently represents

NULL,

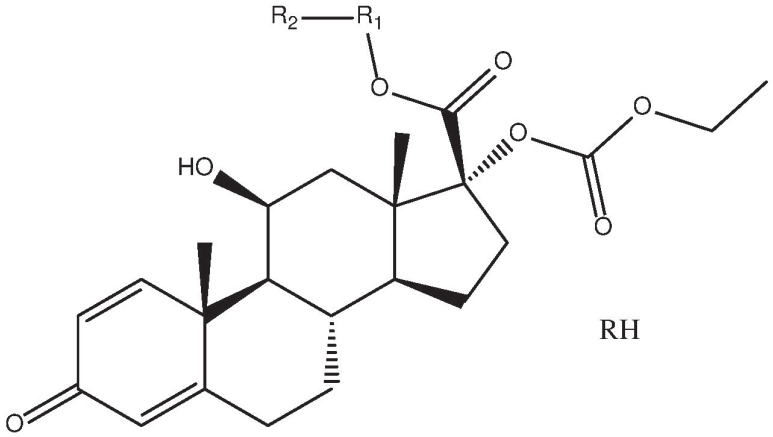


caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid,

gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, lauric acid, alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

[0044] The compositions are typically compounds in the forms of hydrates or solvates of loteprednol derivative and a moiety [RH] containing compound selected [RH] in which the loteprednol derivative is protonated / unprotonated based on the derivative functionality and the moiety [RH] of the pharmaceutically acceptable salt is at least in partially ionic form. In some instances, however, for example depending on the pH of the environment, the composition may be in the form of a mixture of loteprednol derivative and a component represented by [RH]. The invention also provides pharmaceutical compositions comprising compositions of formula XV and pharmaceutically acceptable excipients.

[0045] In another aspect, the compounds of formula XVI are described:



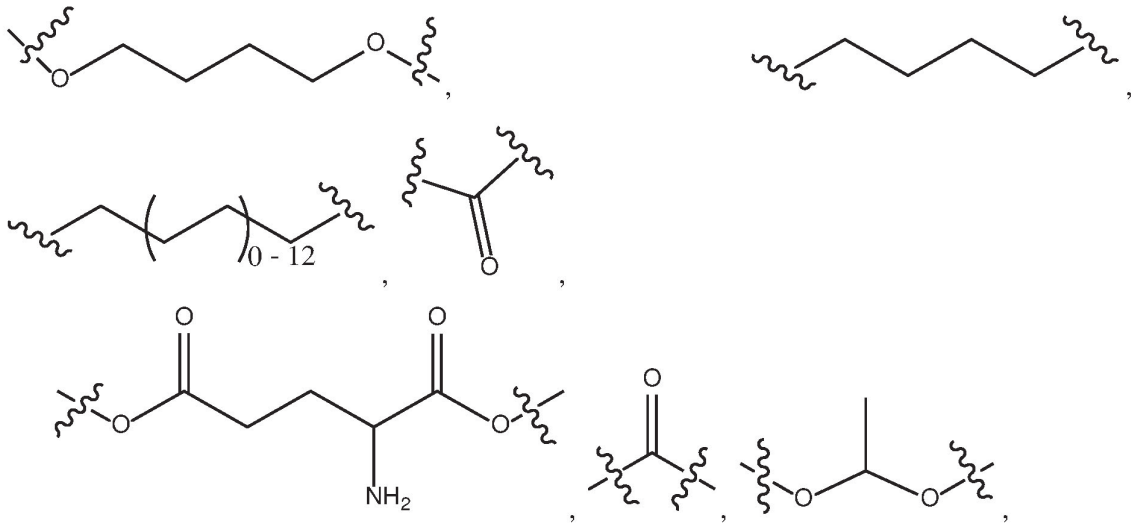
Formula XVI

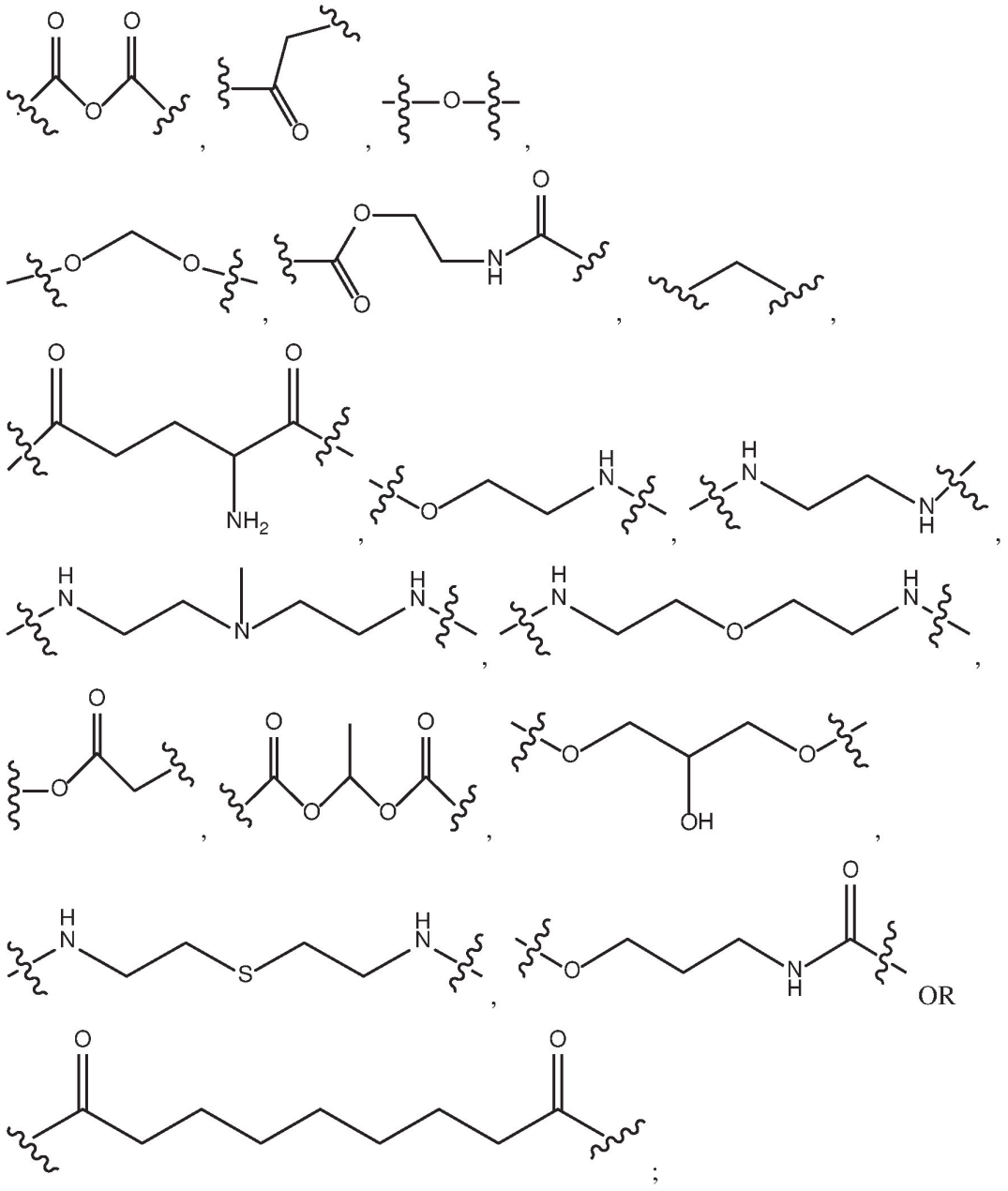
and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0046] wherein,

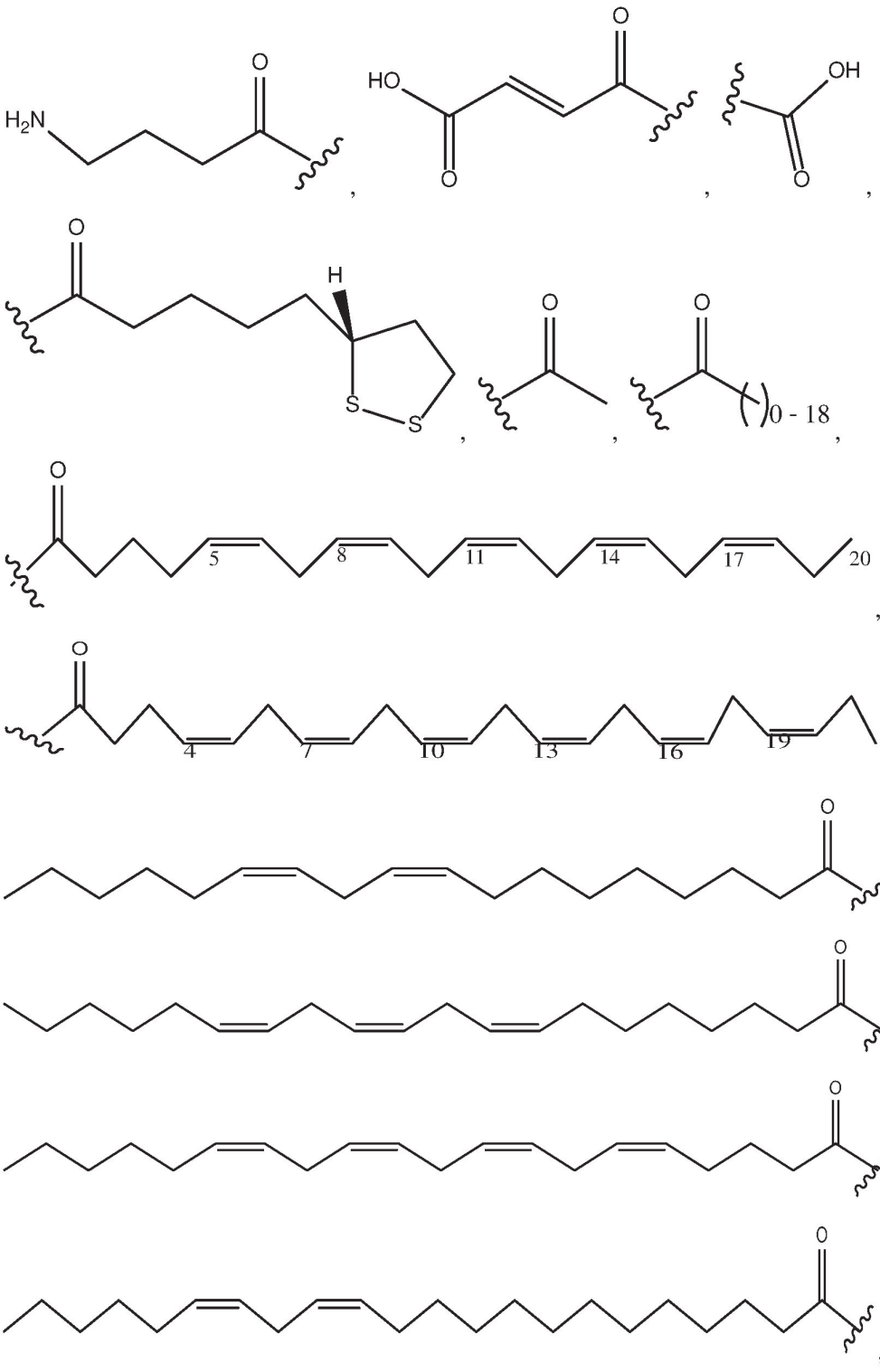
R^1 independently represents

NULL,





R^2 independently represents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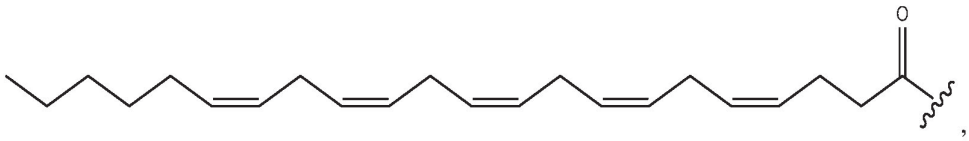
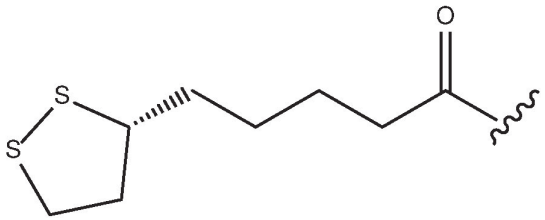
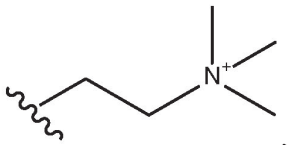
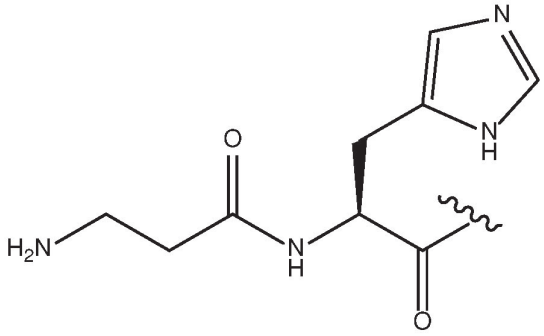
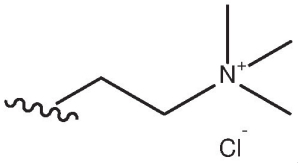
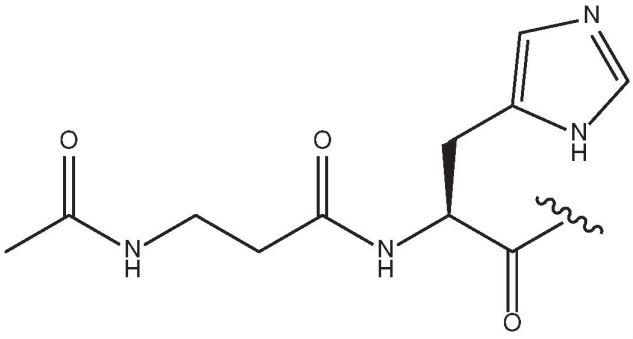
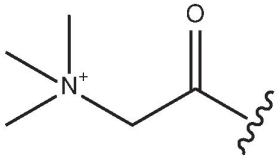
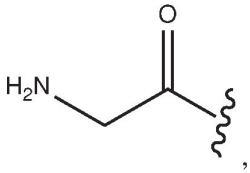
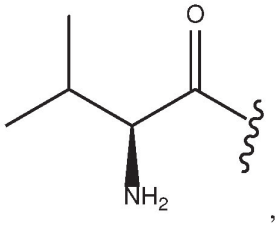
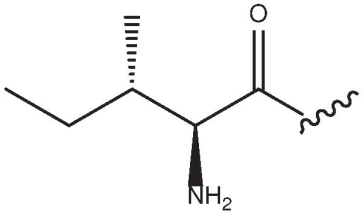
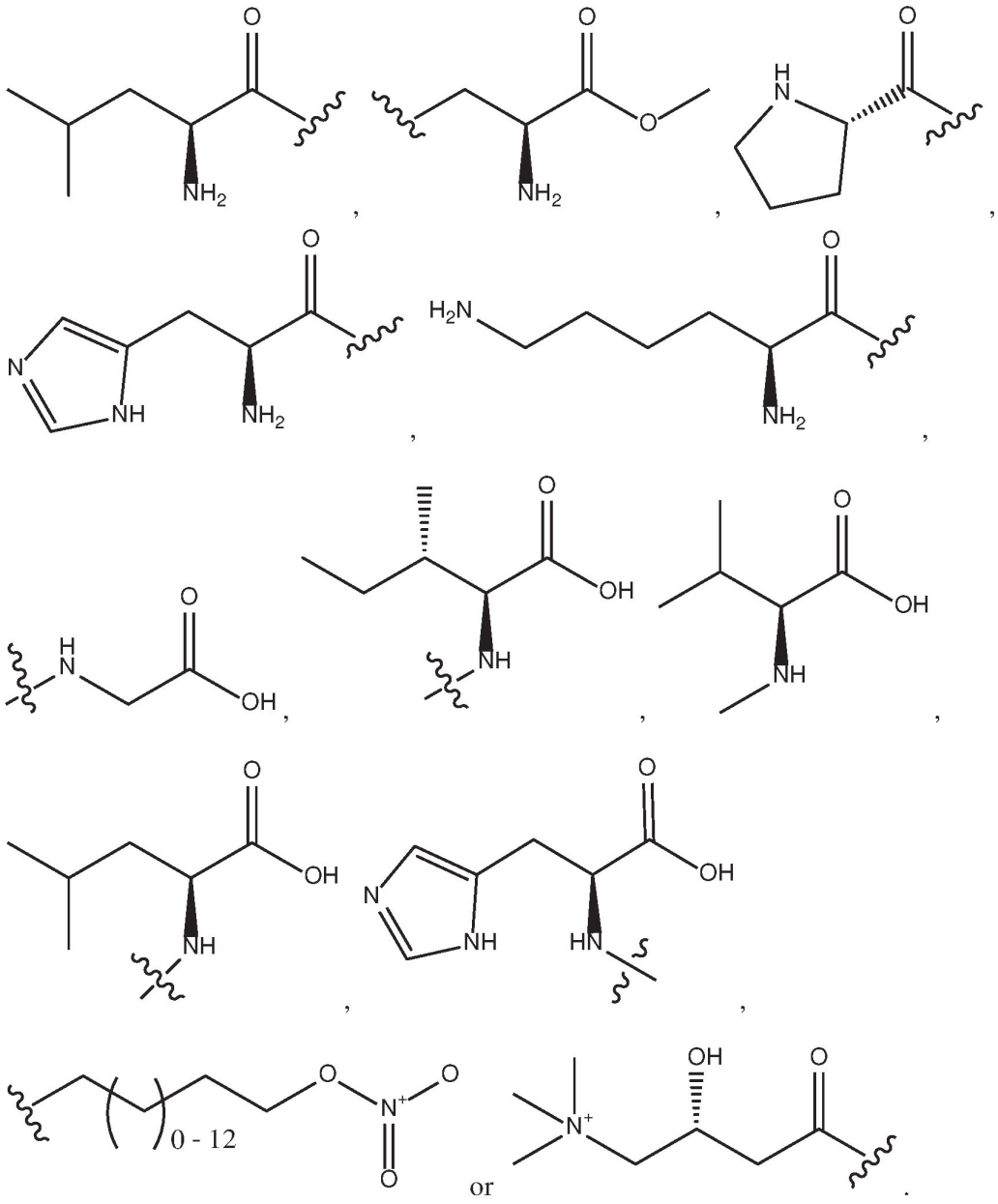
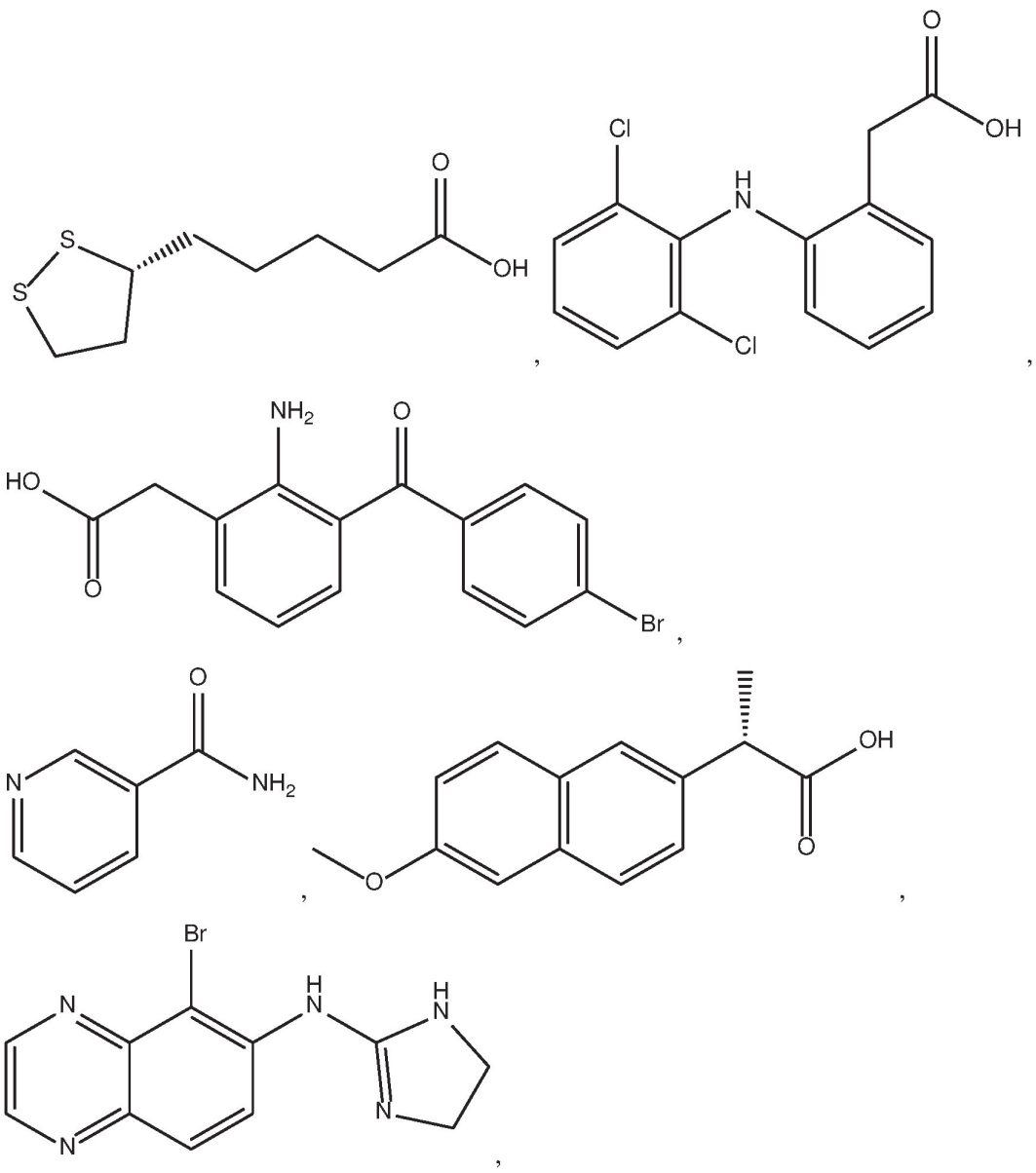













or

RH independently represents

NULL,

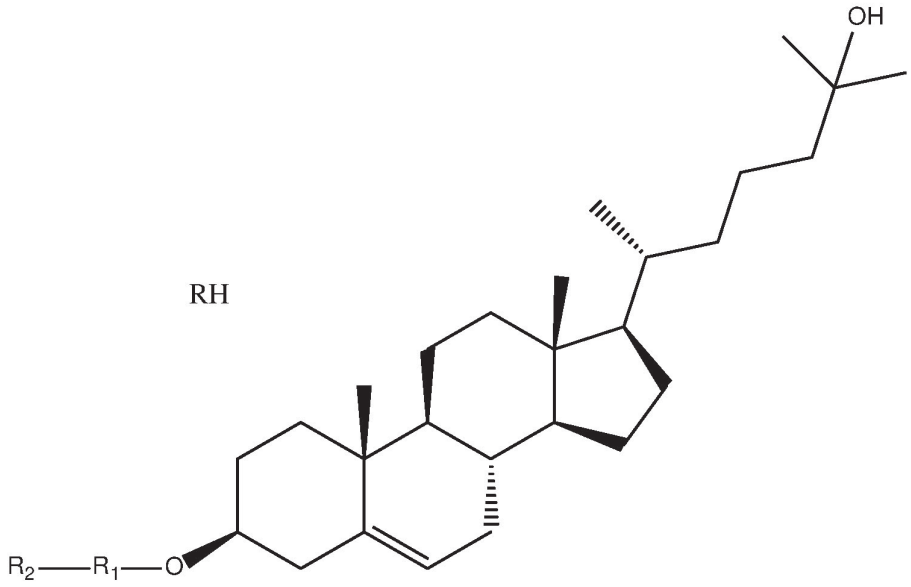


caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid,

gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

[0047] The compositions are typically compounds in the forms of hydrates or solvates of loteprednol derivative and a moiety [RH] containing compound selected [RH] in which the loteprednol derivative is protonated / unprotonated based on the derivative functionality and the moiety [RH] of the pharmaceutically acceptable salt is at least in partially ionic form. In some instances, however, for example depending on the pH of the environment, the composition may be in the form of a mixture of loteprednol derivative and a component represented by [RH]. The invention also provides pharmaceutical compositions comprising compositions of formula XVI and pharmaceutically acceptable excipients.

[0048] In another aspect, the compounds of formula XVII are described:



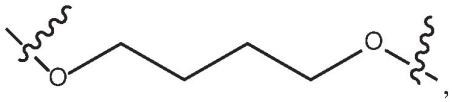
Formula XVII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

[0049] wherein,

R^1 independently represents

NULL,



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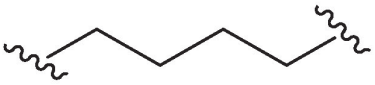

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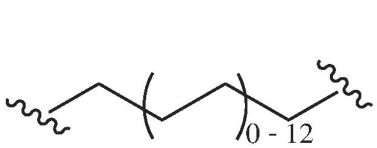

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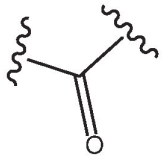

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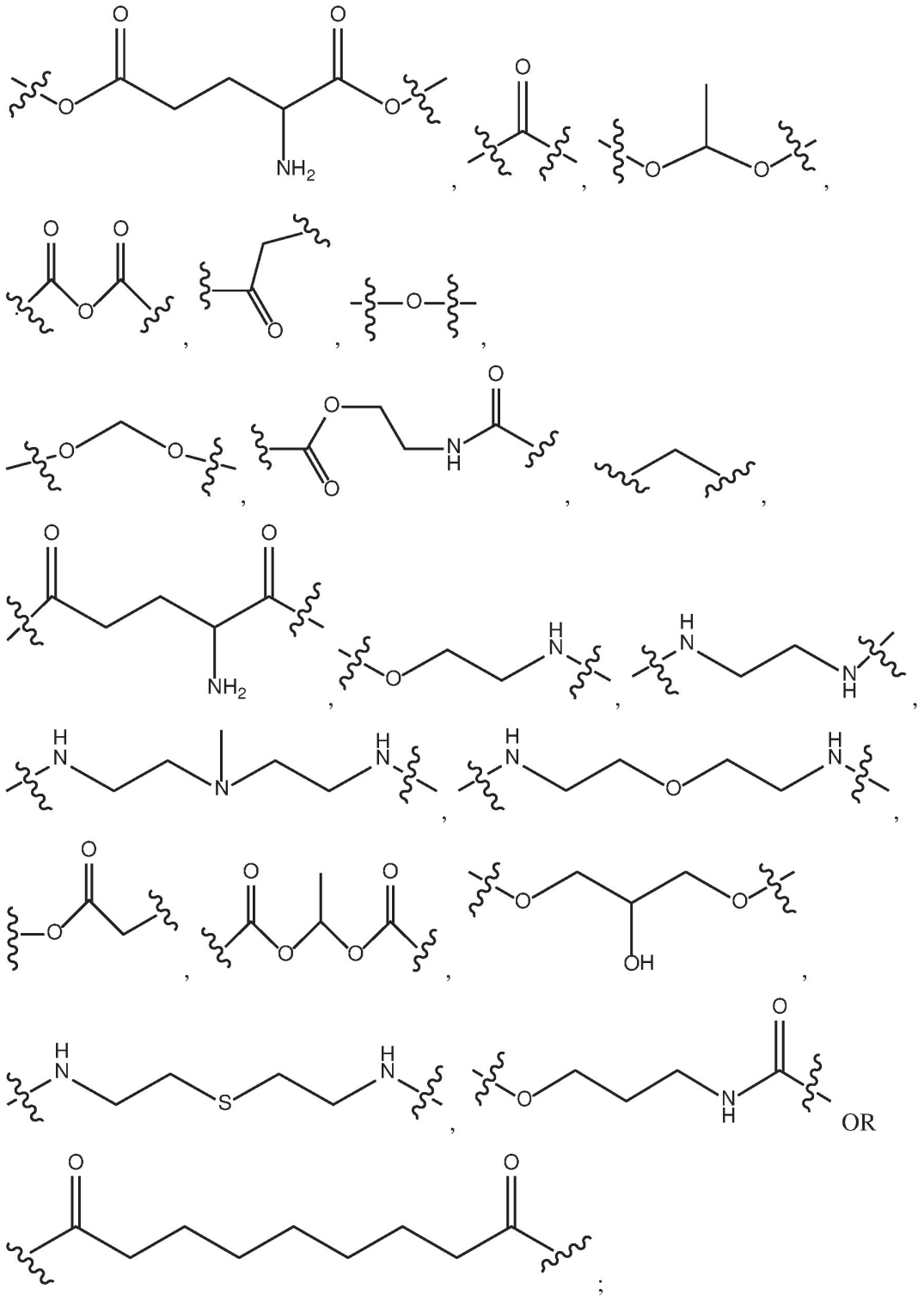
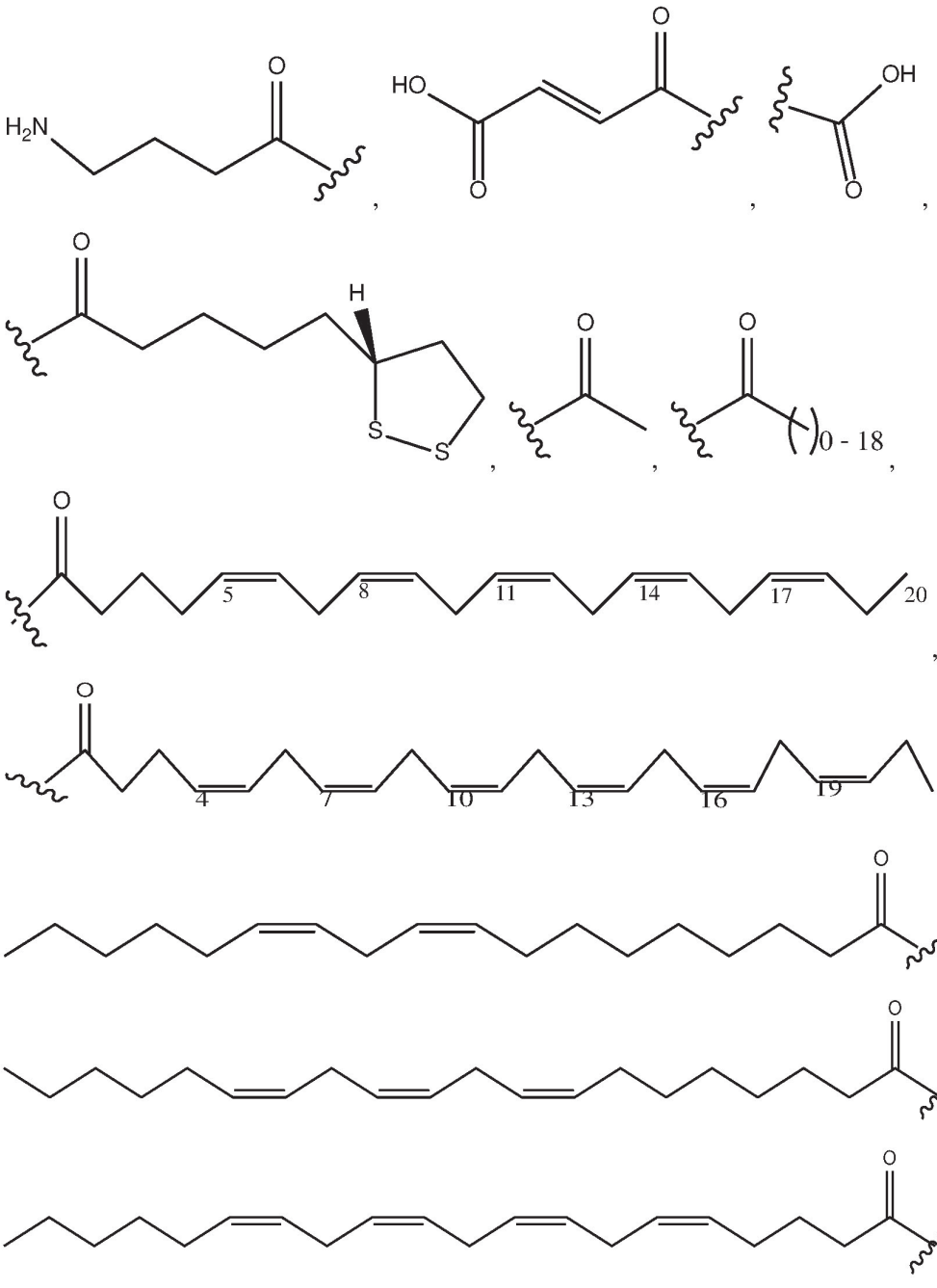
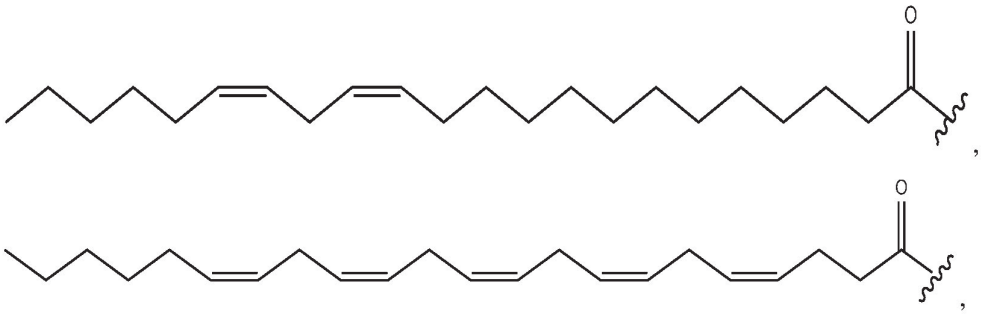
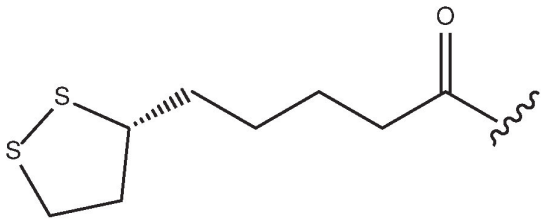
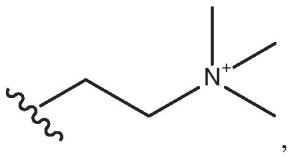


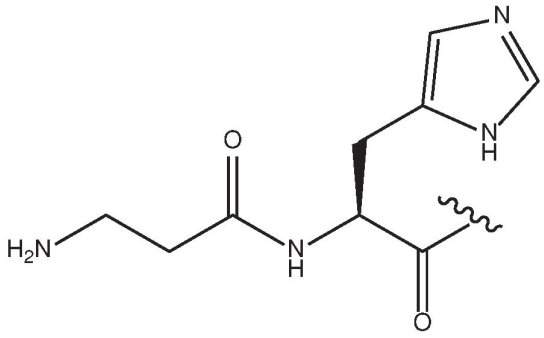
R^2 independently represents

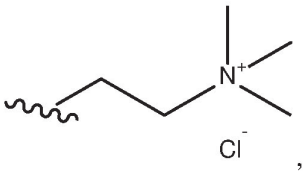


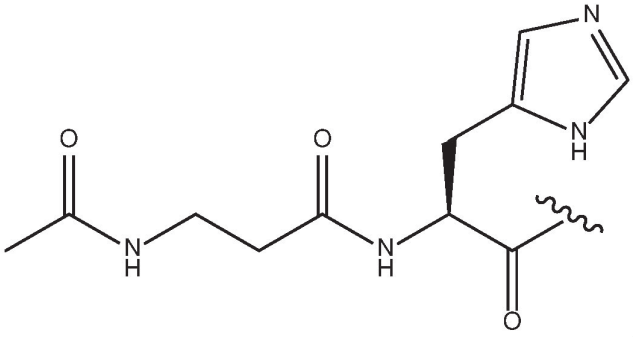


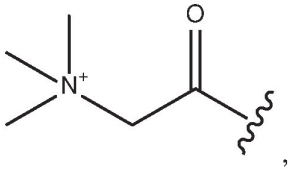


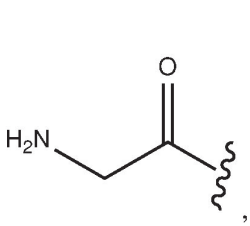


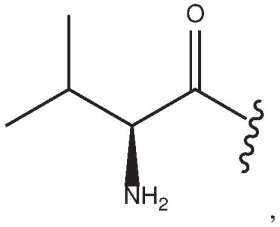


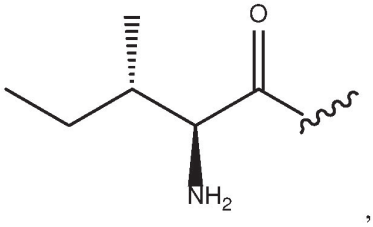


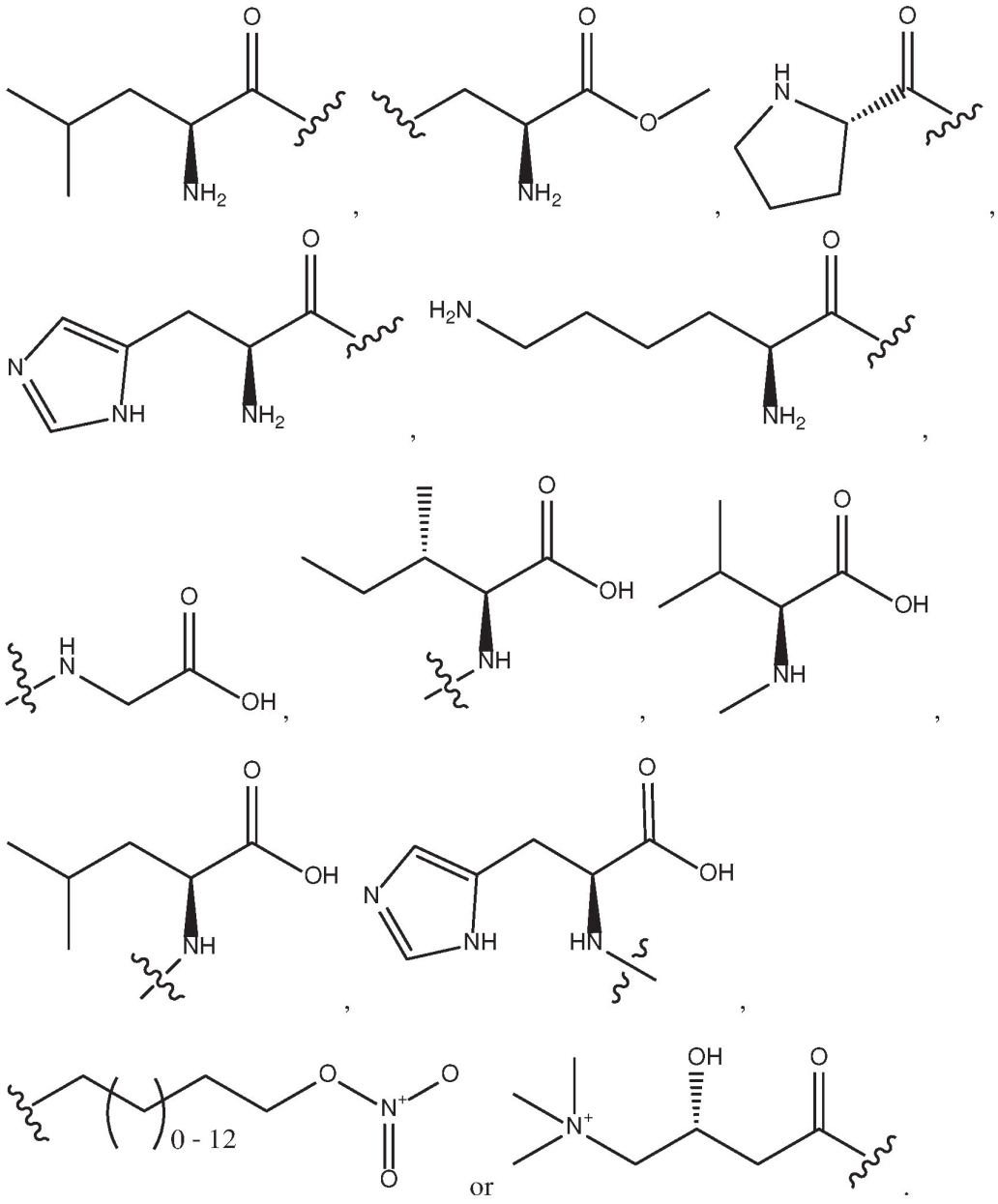






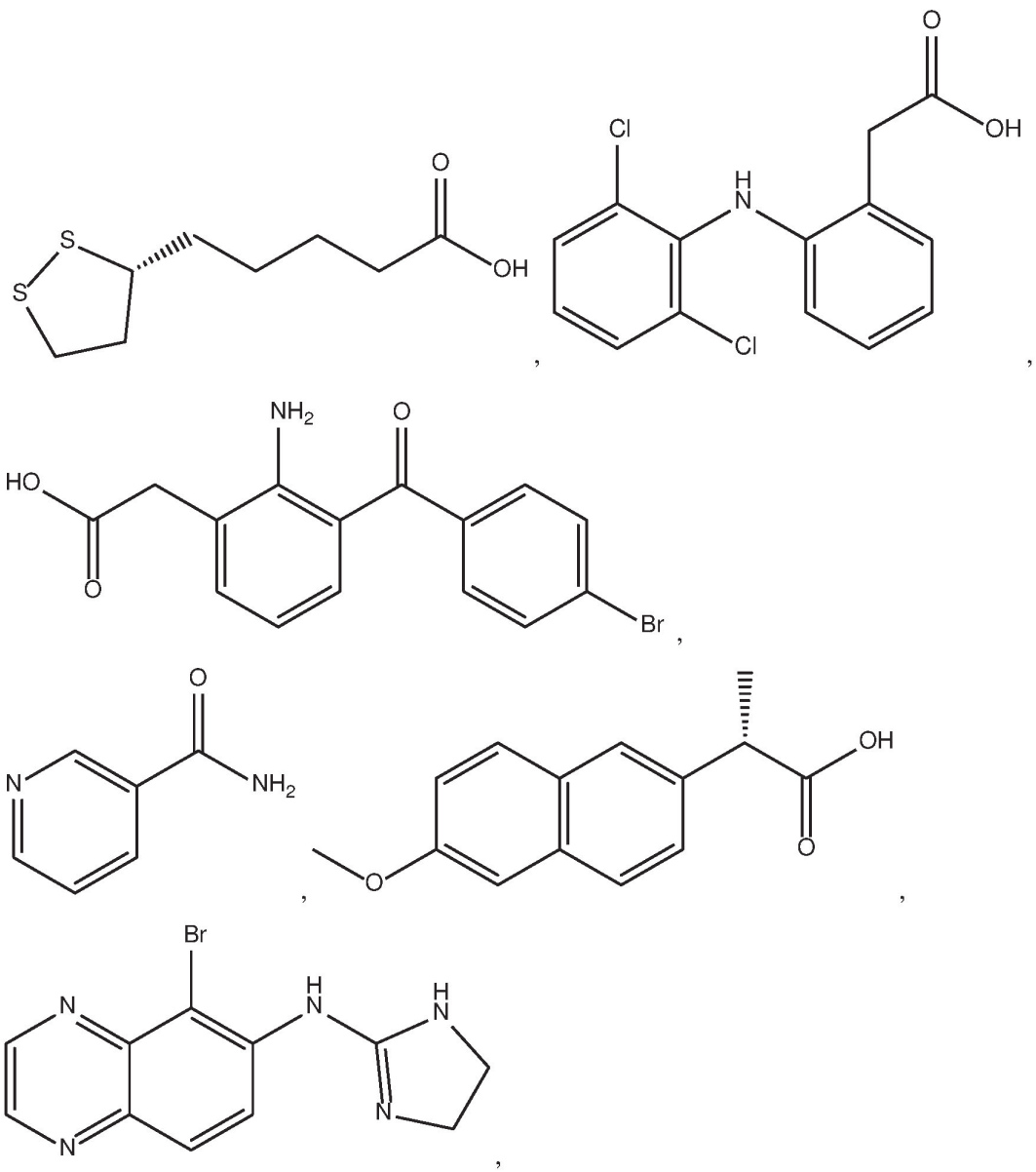






RH independently represents

NULL,

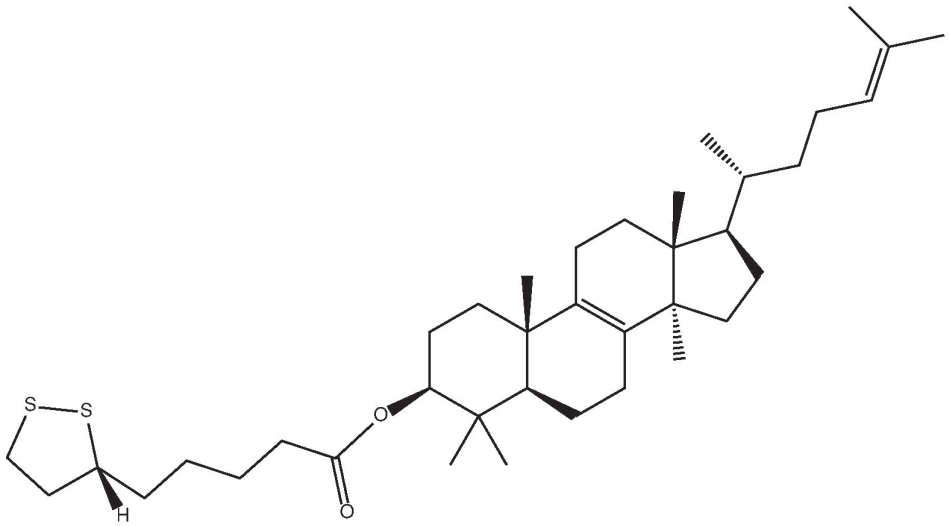


caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid,

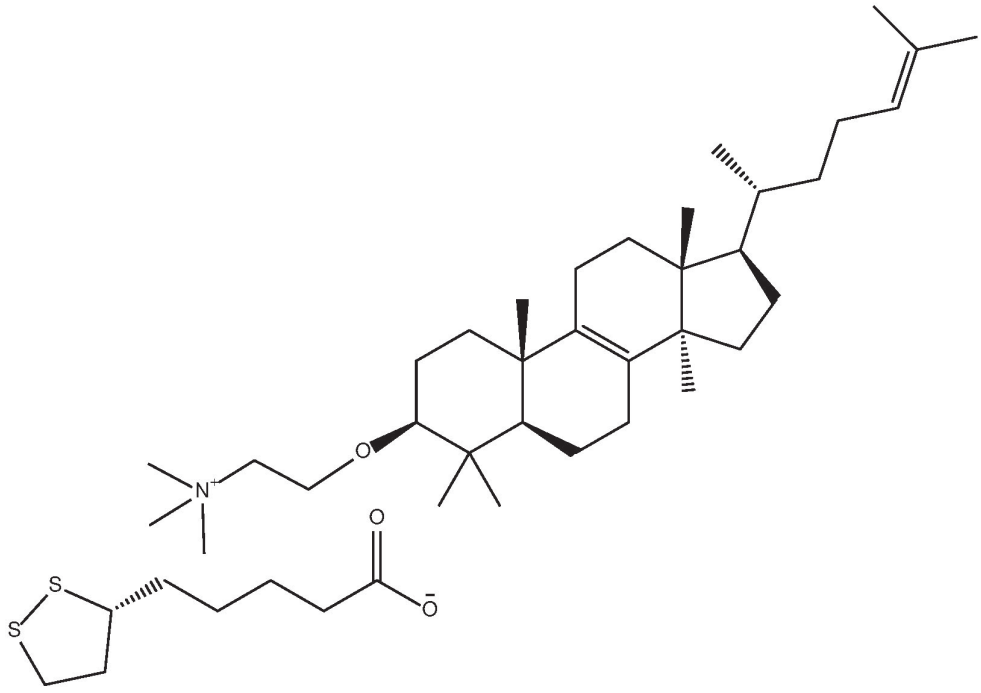
gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

[0050] The compositions are typically compounds in the forms of hydrates or solvates of 25-hydroxycholesterol derivative and a moiety [RH] containing compound selected [RH] in which the 25-hydroxycholesterol derivative is protonated / unprotonated based on the derivative functionality and the moiety [RH] of the pharmaceutically acceptable salt is at least in partially ionic form. In some instances, however, for example depending on the pH of the environment, the composition may be in the form of a mixture of 25-hydroxycholesterol derivative and a component represented by [RH]. The invention also provides pharmaceutical compositions comprising compositions of formula XVII and pharmaceutically acceptable excipients.

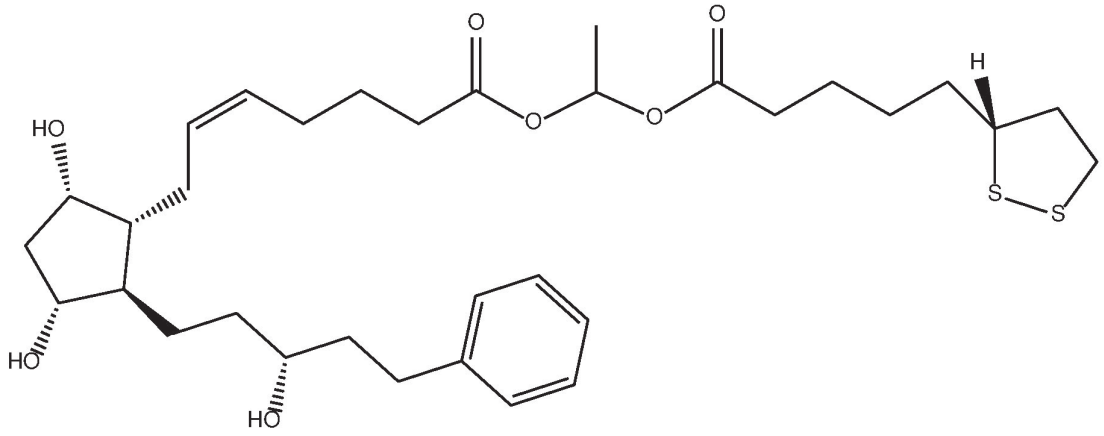
EXAMPLES OF COMPOUNDS OF FORMULAS:



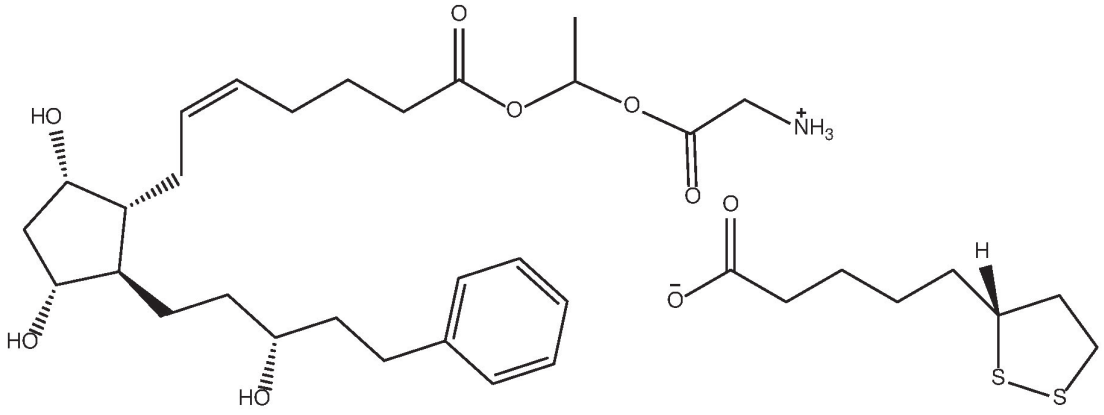
Formula 1-1



Formula 2-1



Formula 3-1



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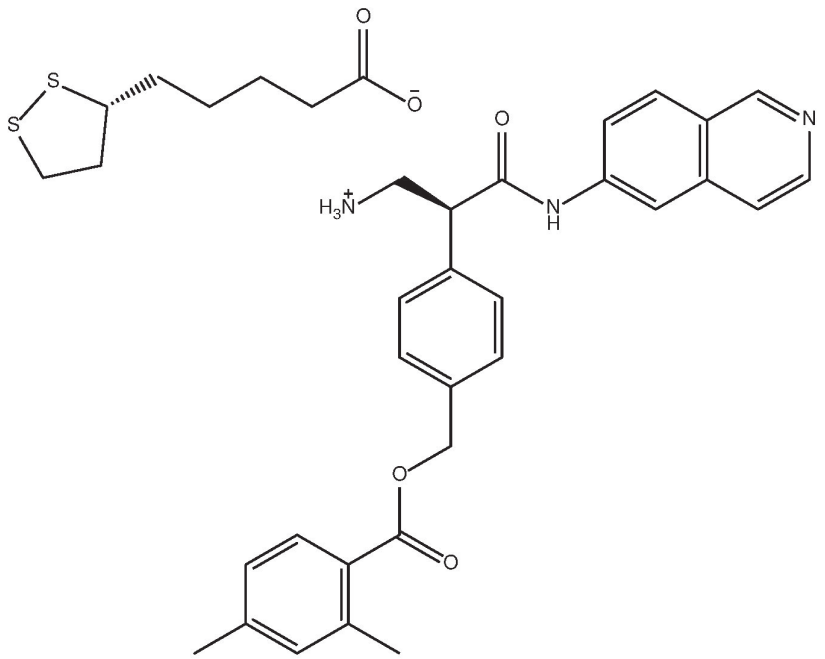
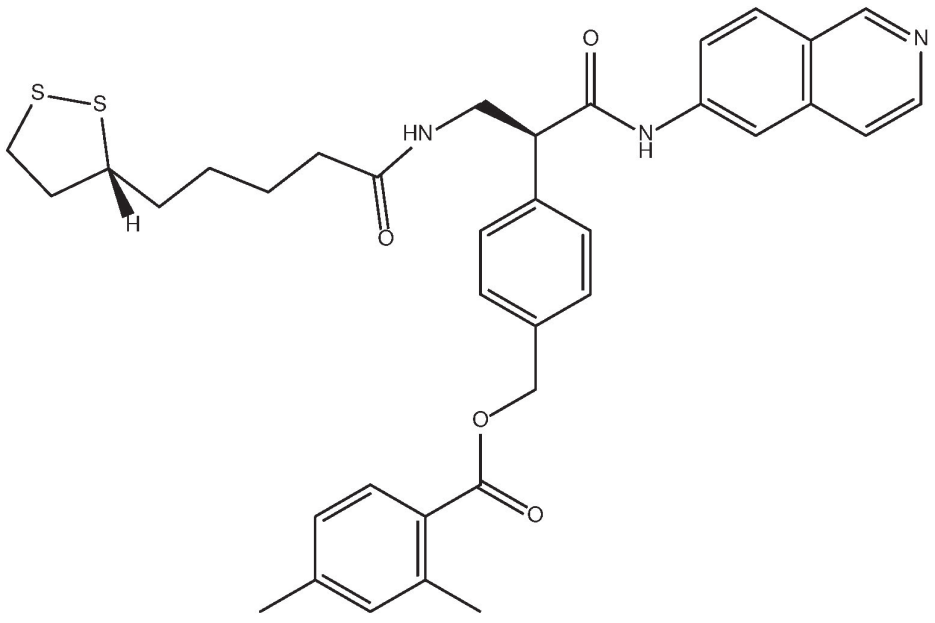
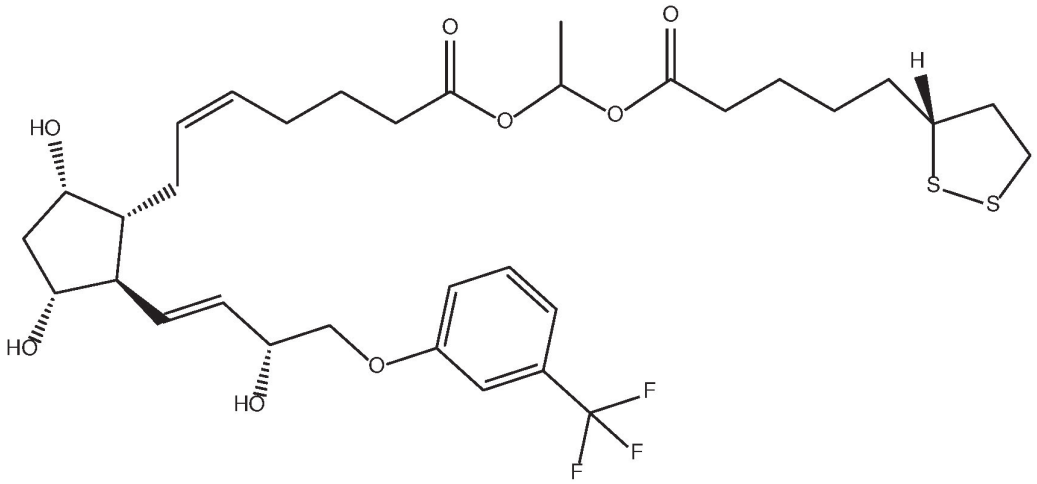


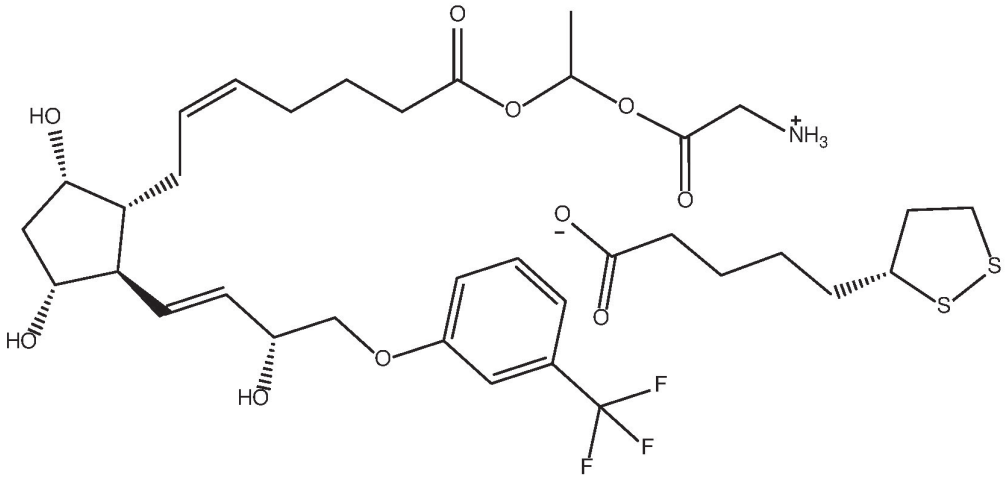
Formula 5-1



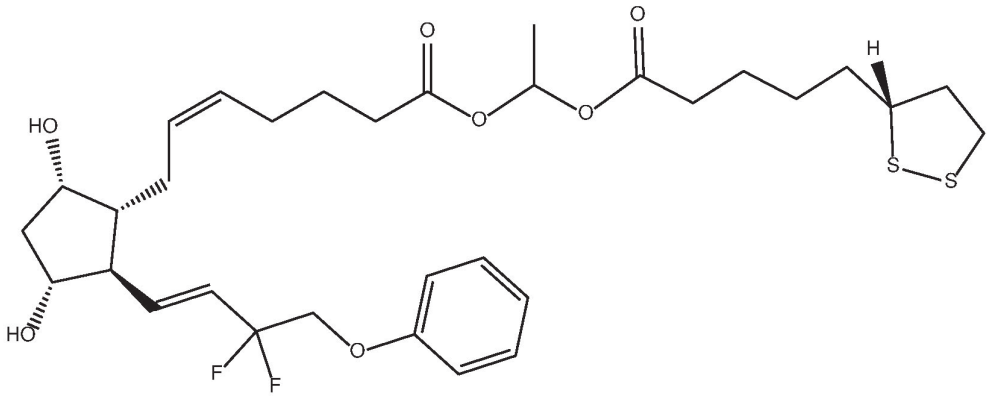
Formula 6-1



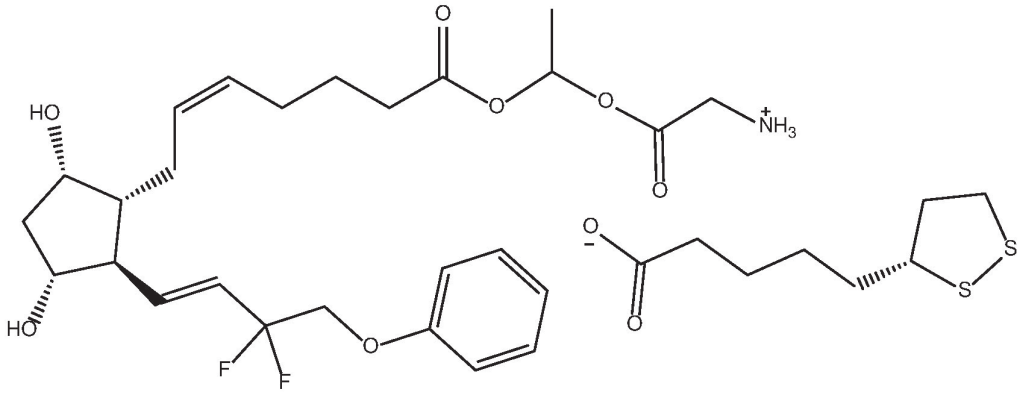
Formula 7-1



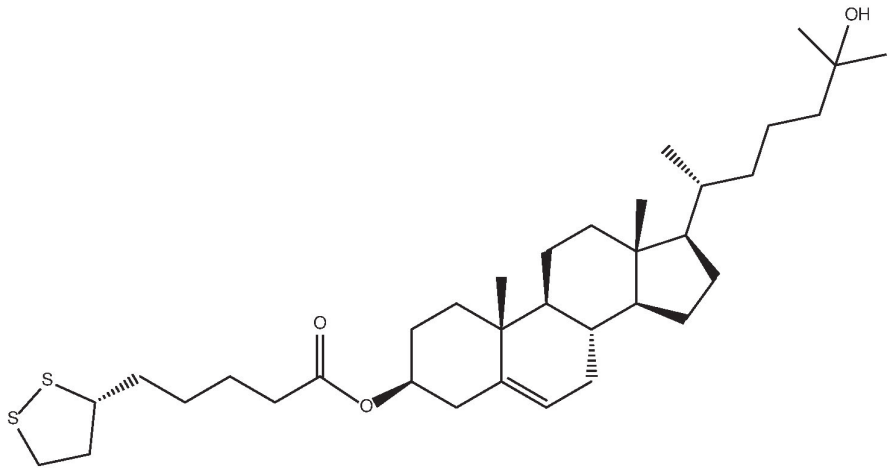
Formula 8-1



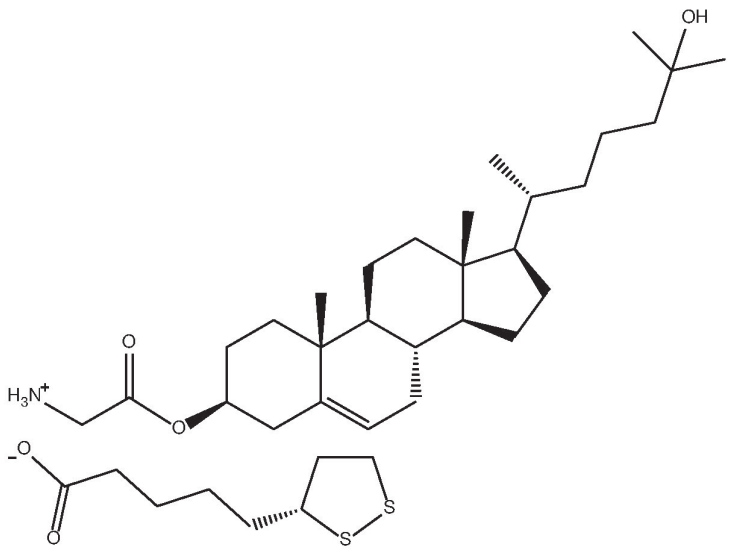
Formula 9-1



Formula 10-1



Formula 17-1



Formula 17-2

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0051] As used herein, the following terms and phrases shall have the meanings set forth below. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art.

[0052] Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers." Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Diastereomers are stereoisomers with opposite configuration at one or more chiral centers which are not enantiomers. Stereoisomers bearing one or more asymmetric centers that are non-superimposable mirror images of each other are termed "enantiomers." When a compound has an asymmetric center, for example, if a carbon atom is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center or centers and is described by the R- and S-sequencing rules of Cahn, lngold and Prelog, or by the manner in which the molecule rotates the plane of polarized light and

designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

[0053] As used herein, the term “metabolic condition” refers to an Inborn error of metabolism (or genetic metabolic conditions) are genetic disorders that result from a defect in one or more metabolic pathways; specifically, the function of an enzyme is affected and is either deficient or completely absent.

[0054] The term "polymorph" as used herein is art-recognized and refers to one crystal structure of a given compound.

[0055] The phrases “parenteral administration” and “administered parenterally” as used herein refer to modes of administration other than enteral and topical administration, such as injections, and include without limitation intravenous, intramuscular, intrapleural, intravascular, intrapericardial, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradennal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal and intrastemal injection and infusion.

[0056] A “patient,” “subject,” or “host” to be treated by the subject method may mean either a human or non-human animal, such as primates, mammals, and vertebrates.

[0057] The phrase “pharmaceutically acceptable” is art-recognized. In certain embodiments, the term includes compositions, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of mammals, human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0058] The phrase “pharmaceutically acceptable carrier” is art-recognized, and includes, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filler, diluent, solvent or encapsulating material involved in carrying or transporting any subject composition, from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of a subject composition and not injurious to the patient. In certain embodiments, a pharmaceutically acceptable carrier is non-pyrogenic. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and

sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0059] The term "prodrug" is intended to encompass compounds that, under physiological conditions, are converted into the therapeutically active agents of the present invention. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

[0060] The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

[0061] The term "predicting" as used herein refers to assessing the probability related diseases patient will suffer from abnormalities or complication and/or terminal platelet aggregation or failure and/or death (i.e. mortality) within a defined time window (predictive window) in the future. The mortality may be caused by the central nervous system or complication. The predictive window is an interval in which the subject will develop one or more of the said complications according to the predicted probability. The predictive window may be the entire remaining lifespan of the subject upon analysis by the method of the present invention.

[0062] The term "treating" is art recognized and includes preventing a disease, disorder or condition from occurring in an animal which may be predisposed to the disease, disorder and/or condition but has not yet been diagnosed as having it; inhibiting the disease, disorder or condition, e.g., impeding its progress; and relieving the disease, disorder, or condition, e.g., causing regression of the disease, disorder and/or condition. Treating the disease or condition includes ameliorating at least one symptom of the particular disease or condition, even if the underlying pathophysiology is not affected, such as treating Disorders of eyelid, lacrimal system and orbit, Disorders of conjunctiva , Disorders of sclera, cornea, iris and ciliary body , Cataract, Disorders of lens , Disorders of choroid and retina , Glaucoma , oGVHD, dry eye, Disorders of vitreous body and globe , Disorders of optic nerve and visual pathways , Visual disturbances and blindness , Presbyopia and other related diseases or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition.

[0063] The phrase "therapeutically effective amount" is an art-recognized term. In certain embodiments, the term refers to an amount of a solvate or hydrate or composition disclosed herein that produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. In certain embodiments, the term refers to that amount necessary or sufficient to eliminate or reduce medical symptoms for a period of time. The effective amount may vary depending on such factors as the disease or condition being treated, the particular targeted constructs being administered, the size of the subject, or the severity of the disease or condition. One of ordinary skill in the art may empirically determine the effective amount of a particular composition without necessitating undue experimentation.

[0064] In certain embodiments, the pharmaceutical compositions described herein are formulated in a manner such that said compositions will be delivered to a patient in a therapeutically effective amount, as part of a prophylactic or therapeutic treatment. The desired amount of the composition to be administered to a patient will depend on absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the hydrates or solvates and compositions from the subject compositions. It is to be noted that dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood

that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Typically, dosing will be determined using techniques known to one skilled in the art.

[0065] Additionally, the optimal concentration and/or quantities or amounts of any particular solvate or hydrate or composition may be adjusted to accommodate variations in the treatment parameters. Such treatment parameters include the clinical use to which the preparation is put, e.g., the site treated, the type of patient, e.g., human or non-human, adult or child, and the nature of the disease or condition.

[0066] In certain embodiments, the dosage of the subject compositions provided herein may be determined by reference to the plasma concentrations of the therapeutic composition or other encapsulated materials. For example, the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve from time 0 to infinity may be used.

[0067] When used with respect to a pharmaceutical composition or other material, the term "sustained release" is art-recognized. For example, a subject composition which releases a substance over time may exhibit sustained release characteristics, in contrast to a bolus type administration in which the entire amount of the substance is made biologically available at one time. For example, in particular embodiments, upon contact with body fluids including blood, spinal fluid, mucus secretions, lymph or the like, one or more of the pharmaceutically acceptable excipients may undergo gradual or delayed degradation (e.g., through hydrolysis) with concomitant release of any material incorporated therein, e.g., an therapeutic and/or biologically active solvate or hydrate and/or composition, for a sustained or extended period (as compared to the release from a bolus). This release may result in prolonged delivery of therapeutically effective amounts of any of the therapeutic agents disclosed herein.

[0068] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" are art-recognized, and include the administration of a subject composition, therapeutic or other material at a site remote from the disease being treated. Administration of an agent for the disease being treated, even if the agent is subsequently distributed systemically, may be termed "local" or "topical" or "regional" administration, other than directly into the central nervous system, e.g., by subcutaneous

administration, such that it enters the patient's system and, thus, is subject to metabolism and other like processes.

[0069] The present disclosure also contemplates prodrugs of the compositions disclosed herein, as well as pharmaceutically acceptable hydrates or solvates of said prodrugs.

[0070] This application also discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the composition of a compound of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may be formulated for systemic or topical or oral administration. The pharmaceutical composition may be also formulated for oral administration, oral solution, injection, subdermal administration, or transdermal administration. The pharmaceutical composition may further comprise at least one of a pharmaceutically acceptable stabilizer, diluent, surfactant, filler, binder, and lubricant.

[0071] In many embodiments, the pharmaceutical compositions described herein will incorporate the disclosed compounds and compositions (formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII) to be delivered in an amount sufficient to deliver to a patient a therapeutically effective amount of a compound of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII or composition as part of a prophylactic or therapeutic treatment. The desired concentration of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII or its pharmaceutical acceptable hydrates or solvates will depend on absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the hydrates or solvates and compositions from the subject compositions. It is to be noted that dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising

the administration of the compositions. Typically, dosing will be determined using techniques known to one skilled in the art.

[0072] Additionally, the optimal concentration and/or quantities or amounts of any particular compound of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may be adjusted to accommodate variations in the treatment parameters. Such treatment parameters include the clinical use to which the preparation is put, e.g., the site treated, the type of patient, e.g., human or non-human, adult or child, and the nature of the disease or condition.

[0073] The concentration and/or amount of any compound of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may be readily identified by routine screening in animals, e.g., rats, by screening a range of concentration and/or amounts of the material in question using appropriate assays. Known methods are also available to assay local tissue concentrations, diffusion rates of the hydrates or solvates or compositions, and local blood flow before and after administration of therapeutic formulations disclosed herein. One such method is microdialysis, as reviewed by T. E. Robinson et al., 1991, microdialysis in the neurosciences, Techniques, volume 7, Chapter 1. The methods reviewed by Robinson may be applied, in brief, as follows. A microdialysis loop is placed in situ in a test animal. Dialysis fluid is pumped through the loop. When compounds with formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII such as those disclosed herein are injected adjacent to the loop, released drugs are collected in the dialysate in proportion to their local tissue concentrations. The progress of diffusion of the hydrates or solvates or compositions may be determined thereby with suitable calibration procedures using known concentrations of hydrates or solvates or compositions.

[0074] In certain embodiments, the dosage of the subject compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or

formula XVII provided herein may be determined by reference to the plasma concentrations of the therapeutic composition or other encapsulated materials. For example, the maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve from time 0 to infinity may be used.

[0075] Generally, in carrying out the methods detailed in this application, an effective dosage for the compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII is in the range of about 0.00001 mg/kg/day to about 100 mg/kg/day in single or divided doses, for instance 0.01 mg/kg/day to about 50 mg/kg/day in single or divided doses. The compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may be administered at a dose of, for example, less than 0.0002 mg/kg/day, 0.0005 mg/kg/day, 1.0 mg/kg/day, 5 mg/kg/day, 10 mg/kg/day, 20 mg/kg/day, 30 mg/kg/day, or 40 mg/kg/day. Compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may also be administered to a human patient at a dose of, for example, between 0.000001 mg and 1000 mg, between 5 mg and 1010 mg, or less than 1.0, 9.0, 12.0, 20.0, 50.0, 75.0, 100, 300, 400, 500, 800, 1000, 2000, 5000 mg per day. In certain embodiments, the compositions herein are administered at an amount that is less than 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the compound of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII required for the same therapeutic benefit.

[0076] An effective amount of the compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII described herein refers to the amount of one of said hydrates or solvates or compositions which is capable of inhibiting or preventing a disease.

[0077] The compositions provided by this application may be administered to a subject in need of treatment by a variety of conventional routes of administration, including orally, topically, parenterally, e.g., intravenously, subcutaneously or intramedullary. Further, the compositions may be administered intranasally, as a rectal suppository, or using a "flash" formulation, i.e., allowing the medication to dissolve in the mouth without the need to use water. Furthermore, the compositions may be administered to a subject in need of treatment by controlled release dosage forms, site specific drug delivery, transdermal drug delivery, patch (active/passive) mediated drug delivery, by stereotactic injection, or in nanoparticles.

[0078] The compositions may be administered alone or in combination with pharmaceutically acceptable carriers, vehicles or diluents, in either single or multiple doses. Suitable pharmaceutical carriers, vehicles and diluents include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the compositions and the pharmaceutically acceptable carriers, vehicles or diluents are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as L-arginine, sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrates such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Appropriate materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof. The compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII,

formula XIII, formula XIV, formula XV, formula XVI, or formula XVII may also comprise enterically coated comprising of various excipients, as is well known in the pharmaceutical art.

[0079] For parenteral administration, solutions of the compositions may be prepared in (for example) sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solutions may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, the sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

[0080] The formulations, for instance tablets, may contain e.g. 10 to 100, 50 to 250, 150 to 500 mg, or 350 to 800 mg e.g. 10, 50, 100, 300, 500, 700, 800 mg of the compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII disclosed herein, for instance, compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII or pharmaceutical acceptable hydrates or solvates of a compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII.

[0081] Generally, a composition as described herein may be administered orally, or parenterally (e.g., intravenous, intramuscular, subcutaneous or intramedullary). Topical administration may also be indicated, for example, where the patient is suffering from gastrointestinal disorder that prevent oral administration, or whenever the medication is best applied to the surface of a tissue or organ as determined by the attending physician. Localized administration may also be indicated, for example, when a high dose is desired at the target tissue or organ. For buccal administration the active composition may take the form of tablets or lozenges formulated in a conventional manner.

[0082] The dosage administered will be dependent upon the identity of the eye disease; the type of host involved, including its age, health and weight; the kind of concurrent treatment, if any; the frequency of treatment and therapeutic ratio.

[0083] Illustratively, dosage levels of the administered active ingredients are: ocular, 0.0000001 mg/kg, intravenous, 0.000001 to about 200 mg/kg; intramuscular, 1 to about 500 mg/kg; orally, 5 to about 1000 mg/kg; intranasal instillation, 5 to about 1000 mg/kg; and aerosol, 5 to about 1000 mg/kg of host body weight.

[0084] Expressed in terms of concentration, an active ingredient can be present in the compositions of the present invention for localized use about the cutis, intranasally, pharyngolaryngeally, bronchially, intravaginally, rectally, or ocularly in a concentration of from about 0.000001 to about 50% w/w of the composition; preferably about 0.000001 to about 20% w/w of the composition; and for parenteral use in a concentration of from about 0.000005 to about 50% w/v of the composition and preferably from about 5 to about 20% w/v.

[0085] The compositions of the present invention are preferably presented for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions of suspensions, and oral solutions or suspensions and the like, containing suitable quantities of an active ingredient. For oral administration either solid or fluid unit dosage forms can be prepared.

[0086] As discussed above, the tablet core contains one or more hydrophilic polymers. Suitable hydrophilic polymers include, but are not limited to, water swellable cellulose derivatives, polyalkylene glycols, thermoplastic polyalkylene oxides, acrylic polymers, hydrocolloids, clays, gelling starches, swelling cross-linked polymers, and mixtures thereof. Examples of suitable water swellable cellulose derivatives include, but are not limited to, sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxyisopropylcellulose, hydroxybutylcellulose, hydroxyphenylcellulose, hydroxyethylcellulose (HEC), hydroxypentylcellulose, hydroxypropylethylcellulose, hydroxypropylbutylcellulose, and hydroxypropylethylcellulose, and mixtures thereof. Examples of suitable polyalkylene glycols include, but are not limited to, polyethylene glycol. Examples of suitable thermoplastic polyalkylene oxides include, but are not limited to, poly(ethylene oxide). Examples of suitable acrylic polymers include, but are not

limited to, potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, high-molecular weight crosslinked acrylic acid homopolymers and copolymers such as those commercially available from Noveon Chemicals under the tradename CARBOPOL™. Examples of suitable hydrocolloids include, but are not limited to, alginates, agar, guar gum, locust bean gum, kappa carrageenan, iota carrageenan, tara, gum arabic, tragacanth, pectin, xanthan gum, gellan gum, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, gum arabic, inulin, pectin, gelatin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan, and mixtures thereof. Examples of suitable clays include, but are not limited to, smectites such as bentonite, kaolin, and laponite; magnesium trisilicate; magnesium aluminum silicate; and mixtures thereof. Examples of suitable gelling starches include, but are not limited to, acid hydrolyzed starches, swelling starches such as sodium starch glycolate and derivatives thereof, and mixtures thereof. Examples of suitable swelling cross-linked polymers include, but are not limited to, cross-linked polyvinyl pyrrolidone, cross-linked agar, and cross-linked carboxymethylcellulose sodium, and mixtures thereof.

[0087] The carrier may contain one or more suitable excipients for the formulation of tablets. Examples of suitable excipients include, but are not limited to, fillers, adsorbents, binders, disintegrants, lubricants, glidants, release-modifying excipients, superdisintegrants, antioxidants, and mixtures thereof.

[0088] Suitable binders include, but are not limited to, dry binders such as polyvinyl pyrrolidone and hydroxypropylmethylcellulose; wet binders such as water-soluble polymers, including hydrocolloids such as acacia, alginates, agar, guar gum, locust bean, carrageenan, carboxymethylcellulose, tara, gum arabic, tragacanth, pectin, xanthan, gellan, gelatin, maltodextrin, galactomannan, pusstulan, laminarin, scleroglucan, inulin, whelan, rhamsan, zooglan, methylan, chitin, cyclodextrin, chitosan, polyvinyl pyrrolidone, cellulosics, sucrose, and starches; and mixtures thereof. Suitable disintegrants include, but are not limited to, sodium starch glycolate, cross-linked polyvinylpyrrolidone, cross-linked carboxymethylcellulose, starches, microcrystalline cellulose, and mixtures thereof.

[0089] Suitable lubricants include, but are not limited to, long chain fatty acids and their hydrates or solvates, such as magnesium stearate and stearic acid, talc, glycerides waxes, and mixtures thereof. Suitable glidants include, but are not limited to, colloidal silicon dioxide.

Suitable release-modifying excipients include, but are not limited to, insoluble edible materials, pH-dependent polymers, and mixtures thereof.

[0090] Suitable insoluble edible materials for use as release-modifying excipients include, but are not limited to, water-insoluble polymers and low-melting hydrophobic materials, copolymers thereof, and mixtures thereof. Examples of suitable water-insoluble polymers include, but are not limited to, ethylcellulose, polyvinyl alcohols, polyvinyl acetate, polycaprolactones, cellulose acetate and its derivatives, acrylates, methacrylates, acrylic acid copolymers, copolymers thereof, and mixtures thereof. Suitable low-melting hydrophobic materials include, but are not limited to, fats, fatty acid esters, phospholipids, waxes, and mixtures thereof. Examples of suitable fats include, but are not limited to, hydrogenated vegetable oils such as for example cocoa butter, hydrogenated palm kernel oil, hydrogenated cottonseed oil, hydrogenated sunflower oil, and hydrogenated soybean oil, free fatty acids and their hydrates or solvates, and mixtures thereof. Examples of suitable fatty acid esters include, but are not limited to, sucrose fatty acid esters, mono-, di-, and triglycerides, glyceryl behenate, glyceryl palmitostearate, glyceryl monostearate, glyceryl tristearate, glyceryl trilaurylate, glyceryl myristate, GlycoWax-932, lauroyl macrogol-32 glycerides, stearoyl macrogol-32 glycerides, and mixtures thereof. Examples of suitable phospholipids include phosphotidyl choline, phosphotidyl serene, phosphotidyl enositol, phosphotidic acid, and mixtures thereof. Examples of suitable waxes include, but are not limited to, carnauba wax, spermaceti wax, beeswax, candelilla wax, shellac wax, microcrystalline wax, and paraffin wax; fat-containing mixtures such as chocolate, and mixtures thereof. Examples of super disintegrants include, but are not limited to, croscarmellose sodium, sodium starch glycolate and cross-linked povidone (crospovidone). In one embodiment the tablet core contains up to about 5 percent by weight of such super disintegrant.

[0091] Examples of antioxidants include, but are not limited to, tocopherols, ascorbic acid, sodium pyrosulfite, butylhydroxytoluene, butylated hydroxyanisole, edetic acid, and edetate hydrates or solvates, and mixtures thereof. Examples of preservatives include, but are not limited to, citric acid, tartaric acid, lactic acid, malic acid, acetic acid, benzoic acid, and sorbic acid, and mixtures thereof.

[0092] In one embodiment, the immediate release coating has an average thickness of at least 50 microns, such as from about 50 microns to about 2500 microns; e.g., from about 250 microns to about 1000 microns. In embodiment, the immediate release coating is typically compressed at a density of more than about 0.9 g/cc, as measured by the weight and volume of that specific layer.

[0093] In one embodiment, the immediate release coating contains a first portion and a second portion, wherein at least one of the portions contains the second pharmaceutically active agent. In one embodiment, the portions contact each other at a center axis of the tablet. In one embodiment, the first portion includes the first pharmaceutically active agent and the second portion includes the second pharmaceutically active agent.

[0094] In one embodiment, the first portion contains the first pharmaceutically active agent and the second portion contains the second pharmaceutically active agent. In one embodiment, one of the portions contains a third pharmaceutically active agent. In one embodiment one of the portions contains a second immediate release portion of the same pharmaceutically active agent as that contained in the tablet core.

[0095] In one embodiment, the outer coating portion is prepared as a dry blend of materials prior to addition to the coated tablet core. In another embodiment the outer coating portion is included of a dried granulation including the pharmaceutically active agent.

[0096] Formulations with different drug release mechanisms described above could be combined in a final dosage form containing single or multiple units. Examples of multiple units include multilayer tablets, capsules containing tablets, beads, or granules in a solid or liquid form. Typical, immediate release formulations include compressed tablets, gels, films, coatings, liquids and particles that can be encapsulated, for example, in a gelatin capsule. Many methods for preparing coatings, covering or incorporating drugs, are known in the art.

[0097] The immediate release dosage, unit of the dosage form, i.e., a tablet, a plurality of drug-containing beads, granules or particles, or an outer layer of a coated core dosage form, contains a therapeutically effective quantity of the active agent with conventional pharmaceutical excipients. The immediate release dosage unit may or may not be coated, and may or may not be admixed with the delayed release dosage unit or units (as in an encapsulated mixture of

immediate release drug-containing granules, particles or beads and delayed release drug-containing granules or beads).

[0098] Extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington—The Science and Practice of Pharmacy", 20th. Ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000). A diffusion system typically consists of one of two types of devices, reservoir and matrix, which are wellknown and described in die art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form.

[0099] An immediate release portion can be added to the extended release system by means of either applying an immediate release layer on top of the extended release core; using coating or compression processes or in a multiple unit system such as a capsule containing extended and immediate release beads.

[00100] Delayed release dosage formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in the acid environment of the stomach, but soluble in the neutral environment of small intestines. The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into either a tablet or capsule.

[00101] A pulsed release dosage form is one that mimics a multiple dosing profile without repeated dosing and typically allows at least a twofold reduction in dosing frequency as compared to the drug presented as a conventional dosage form (e.g., as a solution or prompt drug-releasing, conventional solid dosage form). A pulsed release profile is characterized by a time period of no release (lag time) or reduced release followed by rapid drug release.

[00102] Each dosage form contains a therapeutically effective amount of active agent. In one embodiment of dosage forms that mimic a twice daily dosing profile, approximately 30 wt. % to 70 wt. %, preferably 40 wt. % to 60 wt. %, of the total amount of active agent in the dosage form is released in the initial pulse, and, correspondingly approximately 70 wt. % to 3.0 wt. %, preferably 60 wt. % to 40 wt. %, of the total amount of active agent in the dosage form is released in the second pulse. For dosage forms mimicking the twice daily dosing profile, the

second pulse is preferably released approximately 3 hours to less than 14 hours, and more preferably approximately 5 hours to 12 hours, following administration.

[00103] Another dosage form contains a compressed tablet or a capsule having a drug-containing immediate release dosage unit, a delayed release dosage unit and an optional second delayed release dosage unit. In this dosage form, the immediate release dosage unit contains a plurality of beads, granules particles that release drug substantially immediately following oral administration to provide an initial dose. The delayed release dosage unit contains a plurality of coated beads or granules, which release drug approximately 3 hours to 14 hours following oral administration to provide a second dose.

[00104] For purposes of transdermal (e.g., topical) administration, dilute sterile, aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration), otherwise similar to the above parenteral solutions, may be prepared.

[00105] Methods of preparing various pharmaceutical compositions with a certain amount of one or more compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII or other active agents are known, or will be apparent in light of this disclosure, to those skilled in this art. For examples of methods of preparing pharmaceutical compositions, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995).

[00106] In addition, in certain embodiments, subject compositions of the present application maybe lyophilized or subjected to another appropriate drying technique such as spray drying. The subject compositions may be administered once, or may be divided into a number of smaller doses to be administered at varying intervals of time, depending in part on the release rate of the compositions and the desired dosage.

[00107] Formulations useful in the methods provided herein include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of a subject composition which may be combined with a carrier material to produce a single dose may vary depending upon the subject being treated, and the particular mode of administration.

[00108] Methods of preparing these formulations or compositions include the step of bringing into association subject compositions with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a subject composition with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00109] The compounds of formula I, formula II, formula III, formula IV, formula V, formula VI, formula VII, formula VIII, formula IX, forrmula X, formula XI formula XII, formula XIII, formula XIV, formula XV, formula XVI, or formula XVII described herein may be administered in inhalant or aerosol formulations. The inhalant or aerosol formulations may comprise one or more agents, such as adjuvants, diagnostic agents, imaging agents, or therapeutic agents useful in inhalation therapy. The final aerosol formulation may for example contain 0.005-90% w/w, for instance 0.005-50%, 0.005-5% w/w, or 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

[00110] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00111] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject

compositions, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, corn, peanut, sunflower, soybean, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[00112] Suspensions, in addition to the subject compositions, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol, and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00113] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable non-irritating carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax, or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the appropriate body cavity and release the encapsulated compound(s) and composition(s). Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

[00114] Dosage forms for transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. A subject composition may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required. For transdermal administration, the complexes may include lipophilic and hydrophilic groups to achieve the desired water solubility and transport properties.

[00115] The ointments, pastes, creams and gels may contain, in addition to subject compositions, other carriers, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of such substances. Sprays may additionally contain

customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00116] Methods of delivering a composition or compositions via a transdermal patch are known in the art. Exemplary patches and methods of patch delivery are described in US Patent Nos. 6,974,588, 6,564,093, 6,312,716, 6,440,454, 6,267,983, 6,239,180, and 6,103,275.

[00117] In another embodiment, a transdermal patch may comprise: a substrate sheet comprising a composite film formed of a resin composition comprising 100 parts by weight of a polyvinyl chloride-polyurethane composite and 2-10 parts by weight of a styrene-ethylene-butylene-styrene copolymer, a first adhesive layer on the one side of the composite film, and a polyalkylene terephthalate film adhered to the one side of the composite film by means of the first adhesive layer, a primer layer which comprises a saturated polyester resin and is formed on the surface of the polyalkylene terephthalate film; and a second adhesive layer comprising a styrene-diene-styrene block copolymer containing a pharmaceutical agent layered on the primer layer. A method for the manufacture of the above-mentioned substrate sheet comprises preparing the above resin composition molding the resin composition into a composite film by a calendar process, and then adhering a polyalkylene terephthalate film on one side of the composite film by means of an adhesive layer thereby forming the substrate sheet, and forming a primer layer comprising a saturated polyester resin on the outer surface of the polyalkylene terephthalate film.

[00118] Another type of patch comprises incorporating the drug directly in a pharmaceutically acceptable adhesive and laminating the drug-containing adhesive onto a suitable backing member, e.g. a polyester backing membrane. The drug should be present at a concentration which will not affect the adhesive properties, and at the same time deliver the required clinical dose.

[00119] Transdermal patches may be passive or active. Passive transdermal drug delivery systems currently available, such as the nicotine, estrogen and nitroglycerine patches, deliver small-molecule drugs. Many of the newly developed proteins and peptide drugs are too large to be delivered through passive transdermal patches and may be delivered using technology such as electrical assist (iontophoresis) for large-molecule drugs.

[00120] Iontophoresis is a technique employed for enhancing the flux of ionized substances through membranes by application of electric current. One example of an iontophoretic membrane is given in U.S. Pat. No. 5,080,646 to Theeuwes. The principal mechanisms by which iontophoresis enhances molecular transport across the skin are (a) repelling a charged ion from an electrode of the same charge, (b) electroosmosis, the convective movement of solvent that occurs through a charged pore in response the preferential passage of counter-ions when an electric field is applied or (c) increase skin permeability due to application of electrical current.

[00121] Ocular formulations include, but are not limited to, liquid formulations (e.g., solutions, suspensions) for topical administration as well as formulation for injection or ocular insert administration. Preferably, the ocular formulation is formulated for topical administration such as an eye drop, swab, ointment, gel, or mist (e.g, an aerosol or spray). In one embodiment, the formulation is an eye drop. For ocular formulations, the pharmaceutically acceptable excipients are selected to be compatible with, and suitable for, ocular use. Such excipients are well known in the art. In one embodiment, excipients may be selected to improve the solubility of the agent.

[00122] Exemplary excipients include, but are not limited to, buffers, tonicity agents, viscosity agents, preservatives, emulsifiers, salts, lubricants, polymers, solvents, and other known excipients for ocular pharmaceutical formulations. Appropriate amounts can be determined by one of ordinary skill in the art, but non-limiting exemplary amounts (in % by weight) are also provided below.

[00123] In one embodiment, the pharmaceutical composition includes one or more buffers to adjust or maintain the pH of the formulation. In one embodiment, the pH is near physiological pH (pH of tears is about 7). Thus, the pH of the formulation can be about 6 to about 8, about 6.5 to about 7.5, about 6.8 to about 7.2, about 7.1 to about 7.5, or about 7. In another embodiment, the pH is about 5.5. Thus, the pH of the formulation can be about 4 to about 7, about 4.5 to about 6, about 4.5 to about 5.5, about 5.5 to about 6.5, about 5 to about 6, about 5.25 to about 5.75, or about 5.5. Exemplary buffers include, but are not limited to, phosphate buffers (e.g., sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous), borate buffers, and HBSS (Hank's Balanced Salt Solution). In one embodiment, the buffer is a phosphate buffer. In another embodiment, the buffer is sodium phosphate monobasic monohydrate and/or sodium phosphate dibasic anhydrous. The buffer amount (amount of either

total buffer or a single buffer excipient) can be 0.1% to about 1.0%, about 0.2% to about 0.6%, about 0.05% to about 0.5%, about 0.25% to about 0.45%, or about 0.25%, about 0.43%, or about 0.7%. In one embodiment, the buffer is about 0.05% to about 0.5% (e.g., about 0.27%) sodium phosphate monobasic monohydrate and about 0.2% to about 0.6% (e.g., about 0.43%) sodium phosphate dibasic anhydrous.

[00124] In one embodiment, the pharmaceutical composition includes one or more tonicity agents. Although the formulation may be hypertonic or hypotonic, isotonic formulations are preferred (260-320 mOsm). Exemplary tonicity agents include, but are not limited to, sodium chloride. The tonicity agent amount can be about 0.1% to about 5%, about 0.1% to about 2%, about 0.1% to about 1%, about 0.25% to about 0.75%, about 0.2% to about 0.6%, or about 0.5%. In one embodiment, the tonicity agent is about 0.2% to about 0.6% (e.g., about 0.5%) sodium chloride.

[00125] In one embodiment the pharmaceutical composition includes one or more viscosity agents to increase the viscosity of the formulation. Exemplary viscosity agents include, but are not limited to, cellulosic agents (e.g., hydroxypropyl methylcellulose), polycarbophil, polyvinyl alcohol. In one embodiment, the viscosity agent is a cellulosic agent, e.g., hydroxypropyl methylcellulose. The viscosity agent amount can be about 0.1% to about 5%, about 0.1% to about 2%, about 0.1% to about 1%, about 0.1% to about 0.4%, or about 0.2%. In one embodiment, the viscosity agent is about 0.1% to about 0.4% (e.g., about 0.2%) hydroxypropyl methylcellulose.

[00126] In one embodiment, the pharmaceutical composition includes one or more preservatives to minimize microbial contamination or enhance shelf life. Exemplary preservatives include, but are not limited to, benzalkonium chloride (BAK), cetrimonium, chlorobutanol, edetate disodium (EDTA), polyquaternium-1 (Polyquad®), polyhexamethylene biguanide (PHMB), stabilized oxychloro complex (PURITE®), sodium perborate, and SofZia®. The preservative amount may be, e.g., less than about 0.02%, about 0.004% or less, or about 0.005% to about 0.01%.

[00127] In one embodiment, the pharmaceutical composition includes one or more stabilizers. Exemplary stabilizers include, but are not limited to, amino acids such as alanine. The stabilizer amount can be about 0.1% to about 5%, about 0.1% to about 2%, about 0.1% to about 1%,

about 0.25% to about 0.75%, about 0.2% to about 0.6%, or about 0.5%. In one embodiment, the stabilizer is about 0.2% to about 0.6% (e.g., about 0.5%) alanine.

[00128] In one embodiment, the pharmaceutical composition includes one or more emulsifiers. Exemplary emulsifiers include, but are not limited to, Polysorbate 80.

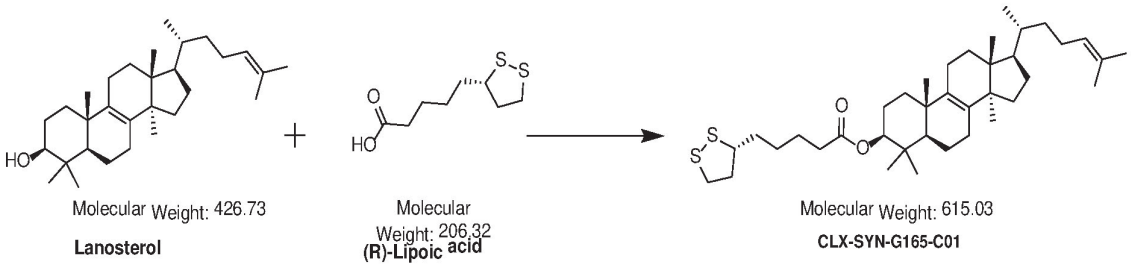
[00129] The compounds described herein can be used in combination with one another, with other active agents known to be useful in ocular disease, or with adjunctive agents that may not be effective alone, but may contribute to the efficacy of the active agent. For example, adjunctive agents might include one or more amino acids or choline (separate from the lipoic acid compound) to enhance the efficacy of the active agent. The combinations can be advantageous, e.g., in reducing metabolic degradation.

[00130] The term "co-administer" means to administer more than one active agent, such that the duration of physiological effect of one active agent overlaps with the physiological effect of a second active agent. In some embodiments, co-administration includes administering one active agent within 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, or 24 hours of a second active agent. Co-administration includes administering two active agents simultaneously, approximately simultaneously (e.g., within about 1, 5, 10, 15, 20, or 30 minutes of each other), or sequentially in any order. In some embodiments, co-administration can be accomplished by co-formulation, i.e., preparing a single pharmaceutical composition including both active agents. In other embodiments, the active agents can be formulated separately. In another embodiment, the active and/or adjunctive agents may be linked or conjugated to one another. In one embodiment, the pharmaceutical formulation includes a reducing agent-choline ester as the active agent and one or more pharmaceutical excipients selected from the group consisting of buffers, tonicity agents, and viscosity agents.

[00131] The pharmaceutical formulation may be packaged for administration by any means known in the art including, but not limited to, individual dose units or multi-dose units, e.g., dropper bottles. Multi-dose units may include, for example, about 1 mL to about 100 mL, about 1 mL to about 50 mL, about 1 mL to about 10 mL, about 2 mL to about 7 mL, or about 5 mL. An individual dose may be, e.g., 1-10 drops, 1-5 drops, or 2-3 drops, wherein each drop is about 5 to about 50 µl, about 10 to about 30 µl, or about 20 µl. Depending on the active agent concentration and the condition of the patient, doses may be administered.

Method of Synthesis

[00132] Scheme for Synthesis of CLX-SYN-G165-C01



: Details of the experiments performed for CLX-SYN-G165-C01

S. No	Name of the Raw Material	Qty	Unit	Mol. Wt.	mol	Vol
1.	Lanosterol	110	g	426.7	0.257	
2.	EDC.HCl	198	g	191.7	1.03	
3.	R- (+)-Lipoic acid	117	g	206.32	0.567	
4.	Triethylamine (TEA)	219	ml	101	1.54	
5.	4-Dimethylaminopyridine (DMAP)	9.4	g	122	0.077	
6.	Dichloromethane LR	1.65	L	-	-	15
7.	Amano lipase enzyme (Immmobilized on diatomite)	22	g	-	-	20%
8.	10% citric acid solution	1.65	L	-	-	15
9.	DM water (Lot-01)	0.55	L			5
10.	DM water (Lot-02)	0.55	L	-	-	5
11.	Saturated Brine solution	0.55	L	-	-	5

Process:

1. Charge DCM (1.65 L) into a 5 L RBF at 25-30° C
2. Charge R- (+)-Lipoic acid (117 g) and stir for 5-10 min at room temperature
3. Cool the reaction mixture to 0-5 °C
4. Charge EDC.HCl (198 g) at 0-5 °C and stir for 5 min
5. Charge TEA (219 ml) slowly over a period of 40 min
6. Stir for 15 min at 0-5 °C
7. Charge Lanosterol (110 g) followed by DMAP (9.4 g) and Amano Lipase PS *(immobilized on diatomite) (22g).*
8. Allow the reaction mixture to stir at 25-30 °C for 5 h
9. Completion of the reaction was monitored by HPLC and TLC [TLC System: Hexane: EtOAc:: 7:3]
10. The reaction mixture was filtered and washed the filter cake with dichloromethane
11. Lipase enzyme was recovered and stored at 2-8 °C
12. The filtrate was transferred to a 10 L separating funnel and washed with10% citric acid solution
13. The DCM layer was separated and washed with water (Lot -1 and Lot-2)
14. The DCM layer was washed with saturated brine solution
15. The DCM layer was dried over $NaSO_4$ and concentrated to obtain crude CLX-SYN-G165-C01 as yellow thick liquid

Crude yield: 175 g**,** Yellow viscous liquid

Purity by HPLC: 92.26%

Purification:

The crude product was purified by column chromatography [Silica gel 100-200 mesh, 5% EtOAc in hexane as eluent] to obtain CLX-SYN-G165-C01 as a gummy mass which was stirred in ethanol (500 ml) at rota vapor for 20-30 min at 25-30 °C to get CLX-SYN-G165-C01 as pale yellow solid. The solid was filtered and washed with ethanol (100 ml), suck dried for 1h. CLX-SYN-G165-C01 was further dried at hot air oven at 40-45 °C for 16 h.

Yield: 130 g, Pale yellow powder

% yield: 82

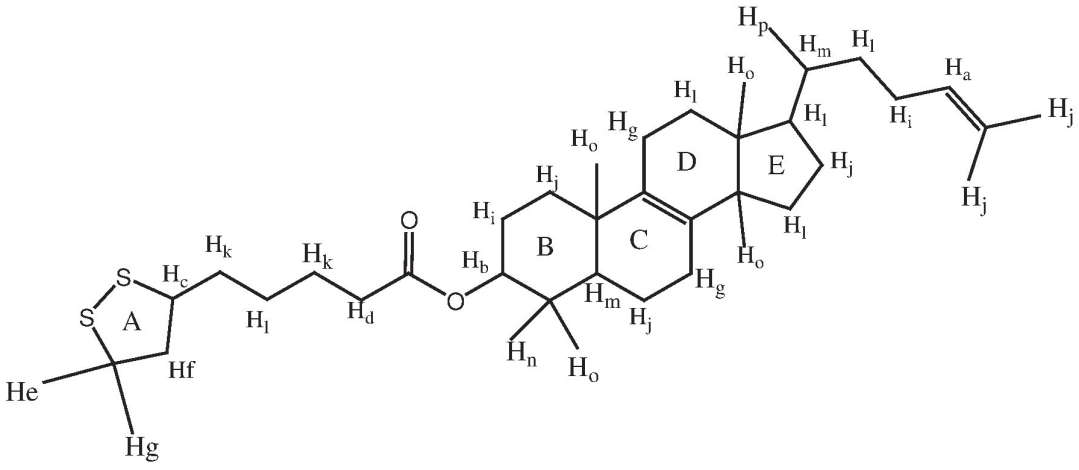
[00133] Structure characterization data:

MS: m/z 409 $[M+H-206]^+$ Loss of lipoic acid

IR (cm^{-1}): 2933, 1750, 1175

Position of the Functional group	Wave number (cm^{-1})
CH-Stretching of alkyl	2933
C=O Stretching of Ester	1750
CH-Bending of Alkyl	1371
C-O Stretching of Ester	1175

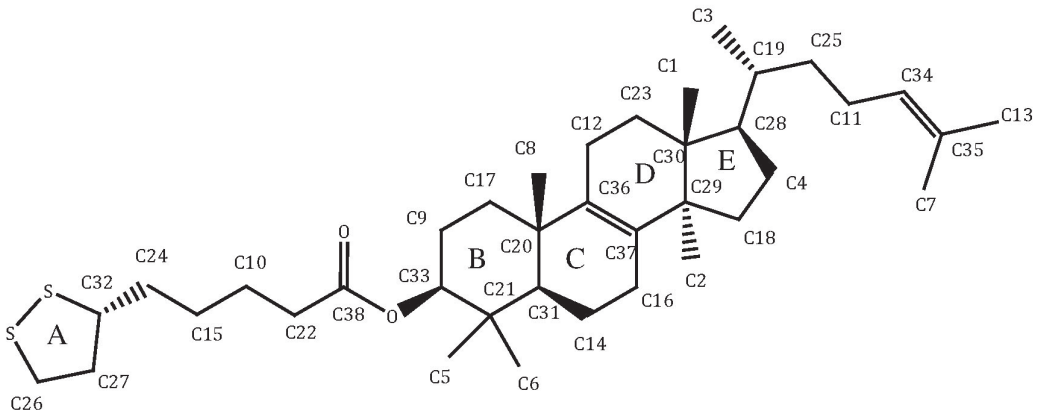
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 5.08 (t, 1H, H_a), 4.50 (dd, 1H, H_b), 3.55-3.58 (m, 1H, H_c), 3.08-3.21 (m, 2H, H_d), 2.42-2.50(m, 1H, H_e), 2.30 (t, 2H, H_f), 2.02-2.05 (m, 5H, H_g), 1.84-2.00(m, 4H, H_l), 1.68-1.82(m, 12H, H_j), 1.55-1.66(m, 4H, H_k), 1.28-1.53(m, 9H, H_l), 1.13-1.19 (t, 2H, H_m), 1.05-1.16 (m, 3H, H_n), 0.92-0.95(m, 12H, H_o), 0.68 (s, 3H, H_p)



Position of the proton	**Chemical shift, ppm**
CH Protons of alkene (H_a)	δ 5.08 (1H, t, $H_{a,}$)
CH Proton of ring B (H_b) attached to Lipoic acid	δ 4.50-4.52 (1H, dd, $H_{b,}$)
CH Proton of Lipoic acid ring A (H_c)	δ 3.55-3.58(1H, m, $H_{c,}$)
CH_2 Protons adjacent to carbonyl group of Lipoic acid (H_d)	δ 3.08-3.21 (2H, t, H_d)
CH Proton of Lipoic acid ring A (H_e)	δ 2.42-2.50 (1H, m, H_e)
Methylene proton of Lipoic acid ring A (H_f)	δ 2.30 (2H, t, H_f)
CH_2 proton of ring C, ring D and -CH proton of Lipoic acid ring A (H_g)	δ 2.02-2.05 (5H, m, H_g)
CH_2 proton of ring B (Hi), -CH_2 proton of side chain adjacent to olefin carbon	δ 1.84-2.00 (4H, m, Hi)
Dimethyl protons of side chain (Hj), methylene protons of ring B, ring C and ring E (Hj)	δ 1.68-1.82 (12H, m, Hj)
Methylene (-CH_2) protons of Lipoic acid (Hk)	δ 1.55-1.66(4H, m, Hk)
-CH_2 protons of ring D, ring E, lipoic acid, side chain and a -CH proton (tert-proton)of cyclopentane ring E (H_l)	δ 1.28-1.53 (9H, m, H_l)
Bridged methine proton between ring B and ring C plus tertiary proton of side chain (H_m)	δ 1.19 (2H, m, H_m)
CH_3 proton on ring B(H_n)	δ 1.10-1.16 (3H, s, H_n)
CH_3 proton on ring B, bridged -CH_3 between ring B	δ 0.87-0.95 (12H, s, H_o)

and C, bridged -CH_3 between ring D and E (H_o)	
CH_3 protons of side chain attached to cyclopentane ring (H_p)	δ 0.68(3H, s, H_p)

^{13}C NMR (100 MHz): 15.96, 16.84, 17.84, 18.33, 18.84, 19.39, 21.23, 24.45, 25.09, 25.13, 25.93, 26.58, 28.19, 28.40, 29.01, 31.03, 31.17, 34.79, 34.84, 35.46, 36.47, 36.56, 37.11, 38.07, 38.68, 40.43, 44.68, 50.01, 50.58, 50.71, 56.58, 80.99, 125.46, 131.11, 134.43, 134.71, 173.47



Solvent: $CDCl_3$

Position of the Carbon atom	**Chemical shift, ppm**
CH_3 bridged methyl group between ring D and E (C1)	δ 15.96
CH_3 bridged methyl group between ring D and E (C2)	δ 16.84
CH_3 carbon of alkane side chain (C3)	δ 17.84

CH_2 carbon of cyclopentane ring E (C4)	δ 18.33
CH_3 carbon on ring B (C5)	δ 18.44
CH_3 carbon on ring B (C6)	δ 19.39
CH_3 Carbon on alkane(C7)	δ 21.23
Bridged methyl (-CH_3) Carbon between ring B and C (C8)	δ 24.45
CH_2 of ring B (C9)	δ 25.09
CH_2 of alkane (C10)	δ 25.13
CH_2 Carbon on alkane(C11)	δ 25.93
CH_2 Carbon on ring D (C12)	δ 26.58
CH_3 Carbon of alkane (C13)	δ 28.19
CH_2 Carbon on ring C (C14)	δ 28.40
CH_2 of Lipoic acid (C15)	δ 29.01
CH_2 Carbon of ring C and ring B (C16-17)	δ 31.03
CH_2 Carbon of ring E (C18)	δ 31.17
CH-Carbon (tert-carbon) of side chain (C19)	δ 34.79
Bridged carbon between ring B and ring C (C20)	δ 34.84
Quaternary carbon of ring B (C21)	δ 35.46
-CH_2 of Lipoic acid adjacent to carbonyl group (C22)	δ 36.47
CH_2-Carbon of ring D (C23)	δ 36.56

CH_2 of Lipoic acid (C24)	δ 37.11
CH_2 Carbon of side chain (C25)	δ 38.07
Lipoic acid ring carbon (C26)	δ 38.68
Lipoic acid ring carbon (C27)	δ 40.43
tertiary carbon of cyclopentyl ring E (C28)	δ 44.68
Bridged carbon between ring D and ring E (C29)	δ 50.01
Bridged carbon between ring D and ring E (C30)	δ 50.58
Bridged carbon between ring B and ring C (C31)	δ 50.71
tertiary carbon of ring A (C32)	δ 56.58
-CH Carbon of ring B (C33)	δ 80.99
Olefin carbon of side chain (C34)	δ 125.46
Quaternary carbon of side chain (C35)	δ 131.11
Bridge carbon between ring D and ring E(C36)	δ 134.43
Bridge carbon between ring D and ring E (C37)	δ 134.71
-C=O of ester carbonyl carbon (C38)	δ 173.47

EQUIVALENTS

[00134] The present disclosure provides among other things compositions and methods for treating eye diseases and their complications. While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the systems and methods herein will become apparent to those skilled in the art upon review of this specification. The full scope of the claimed systems and methods should be

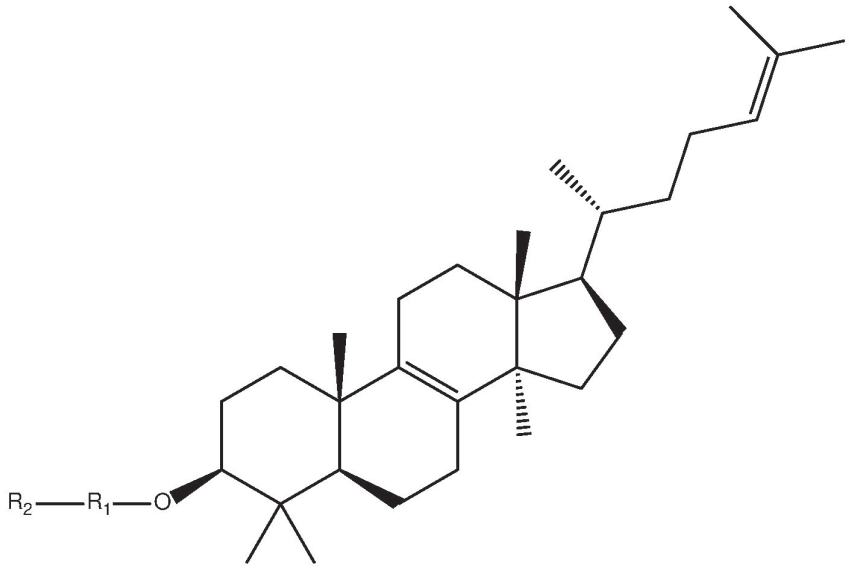
determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

INCORPORATION BY REFERENCE

[00135] All publications and patents mentioned herein, including those items listed above, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

STATEMENTS OF INVENTION

1. A compound of formula I

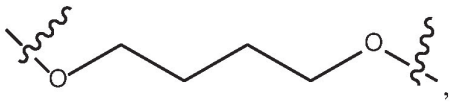


Formula I

and pharmaceutically acceptable hydrates, solvates, enantiomers, and stereoisomers thereof;

wherein,

R1 independently represents Null,



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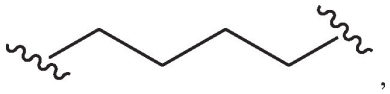

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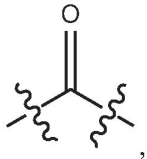

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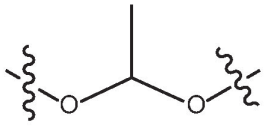

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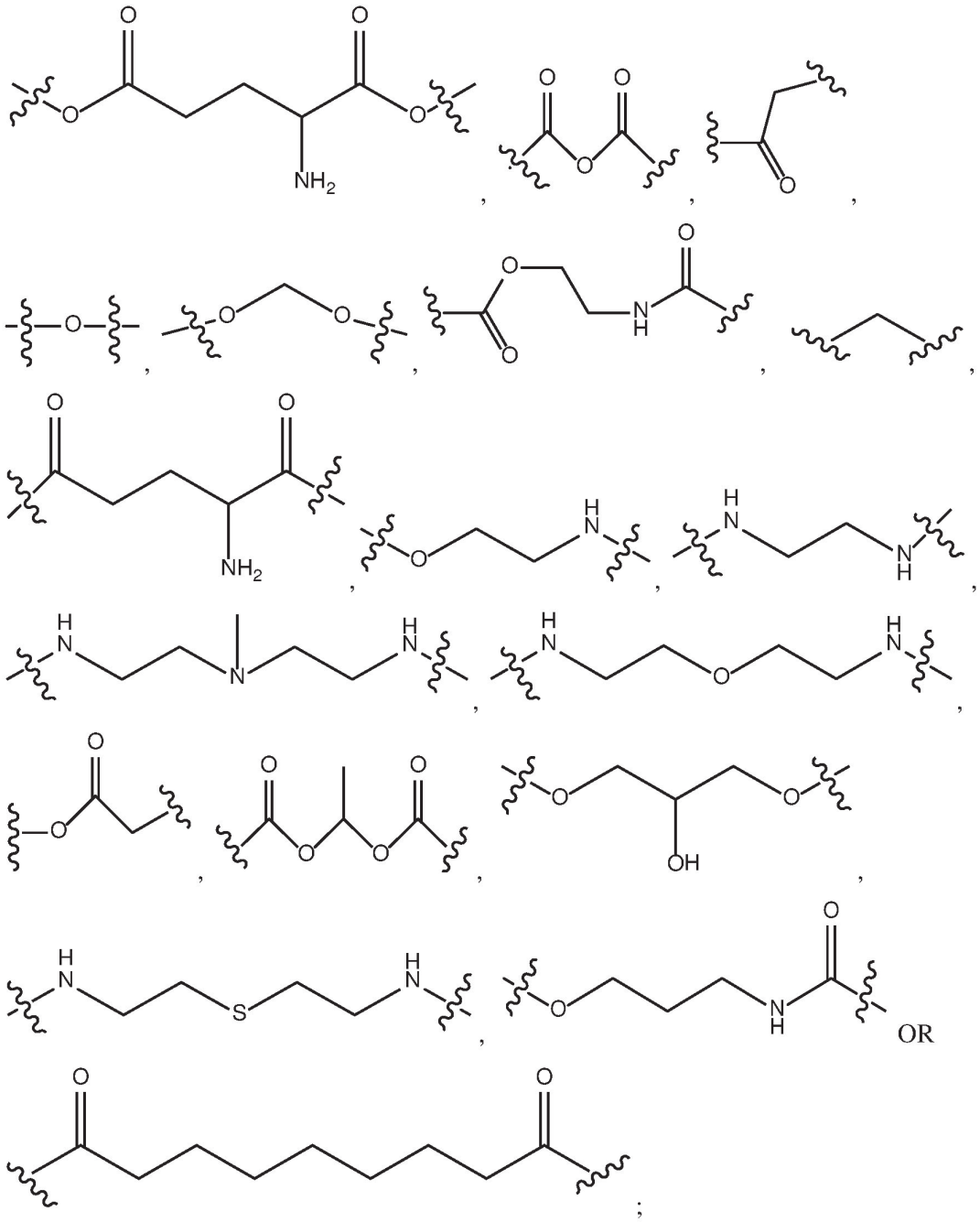
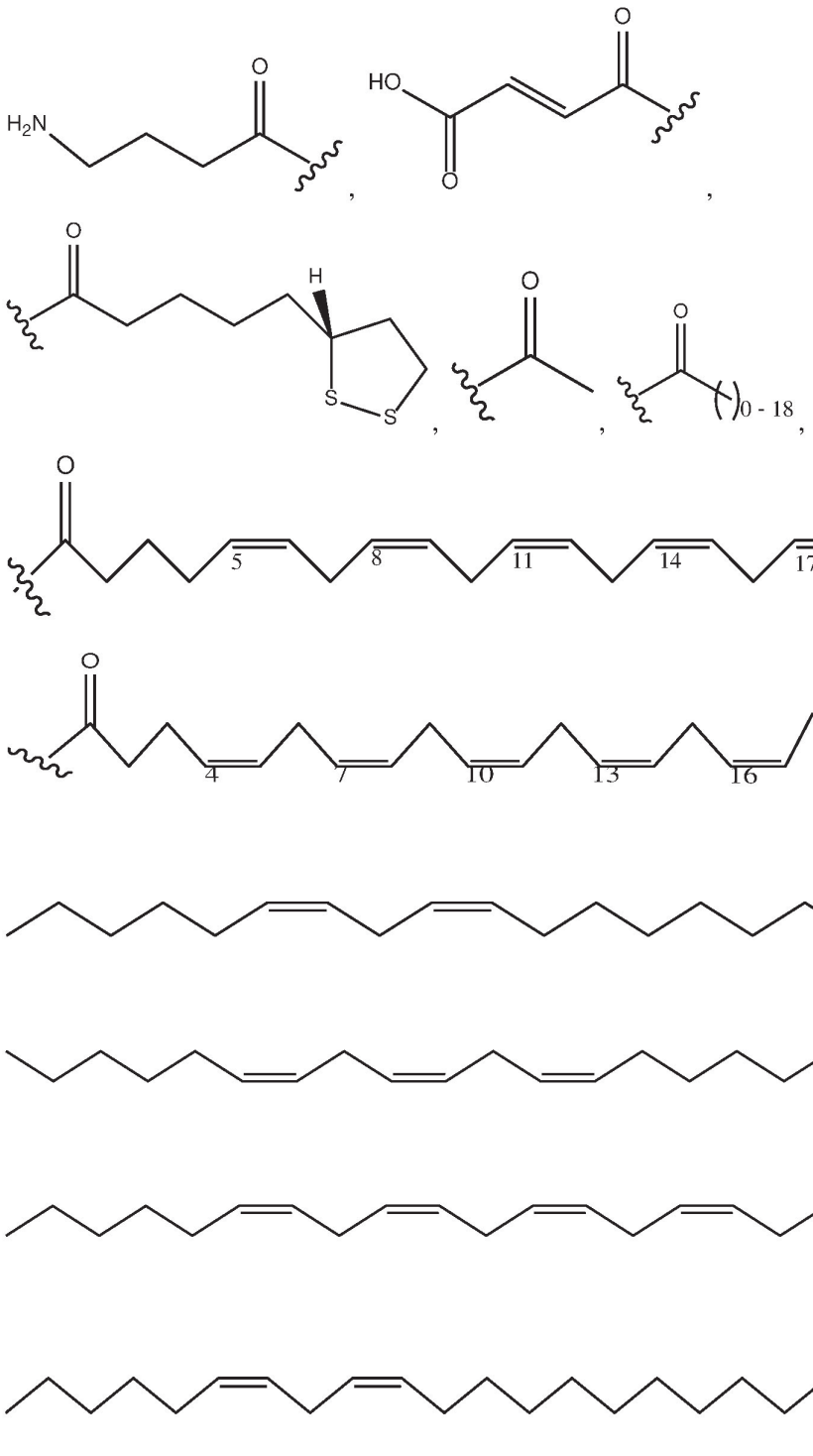
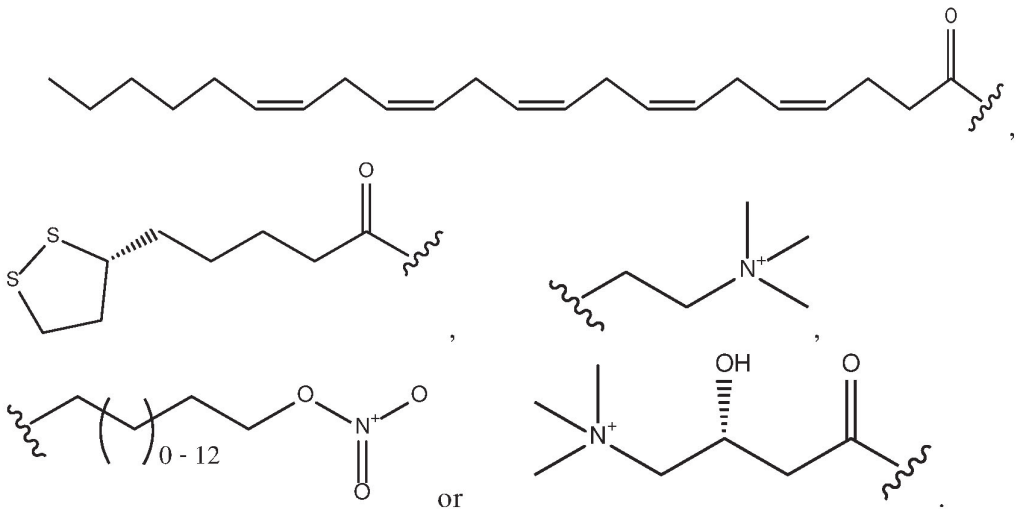


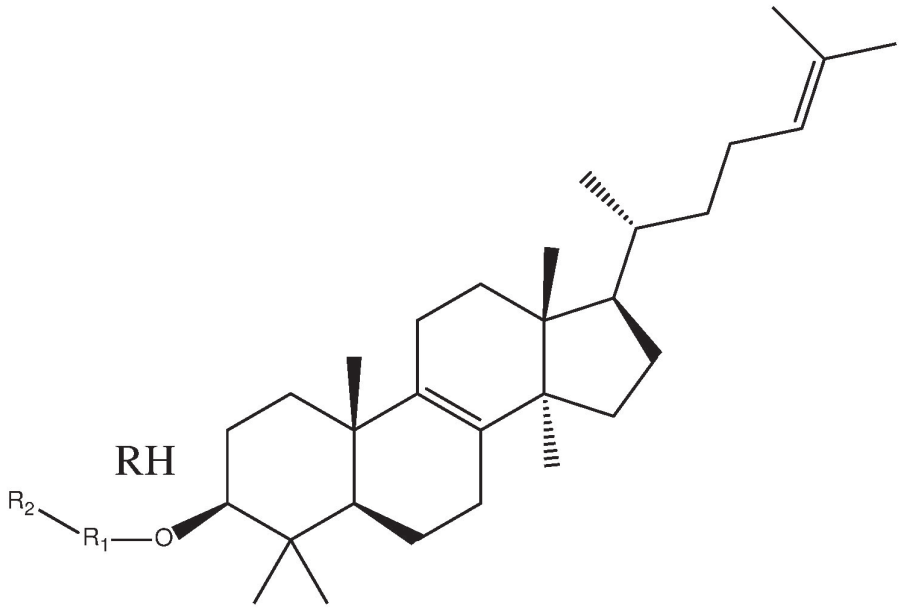
R_2 represents





or

2. A compound of formula II

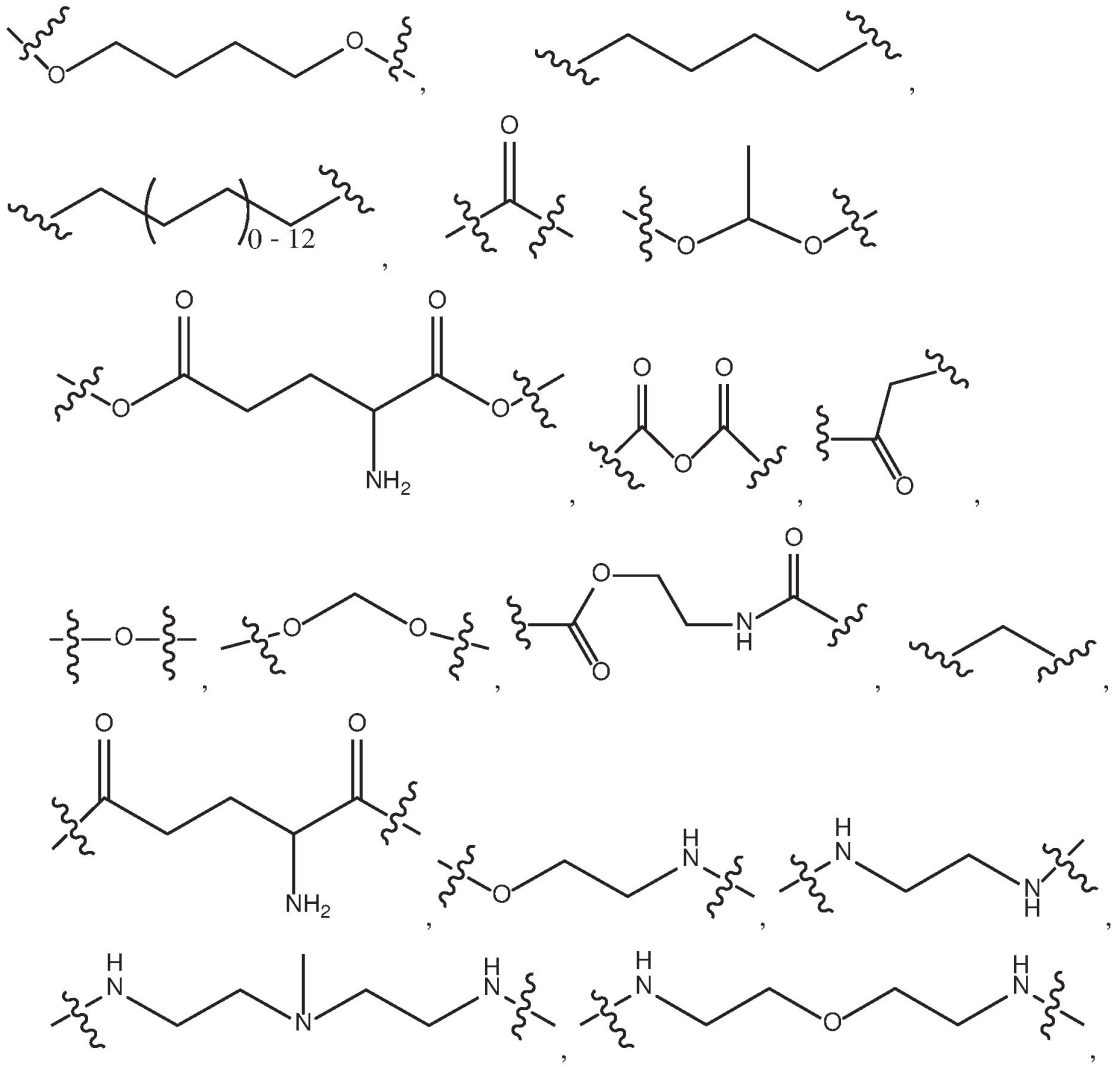


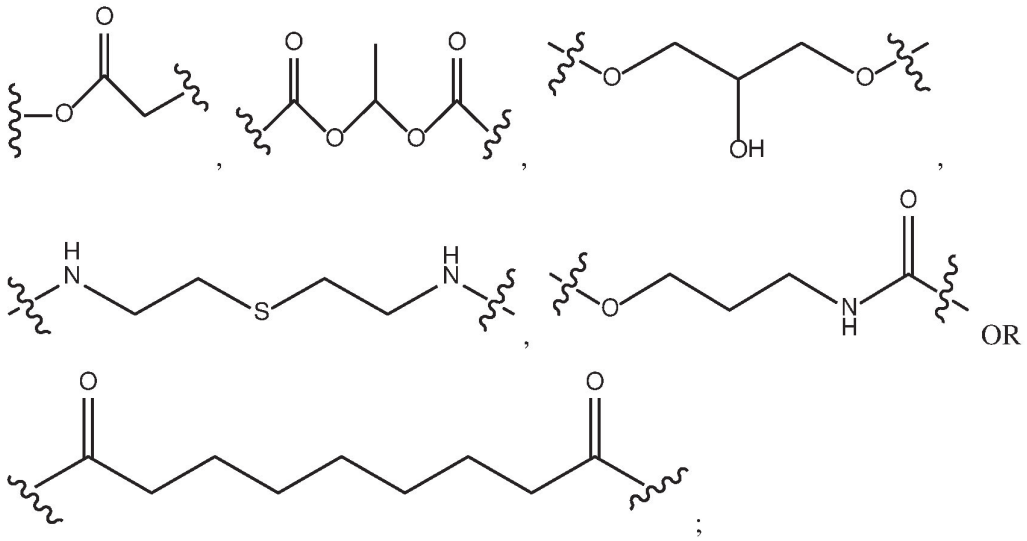
Formula II

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

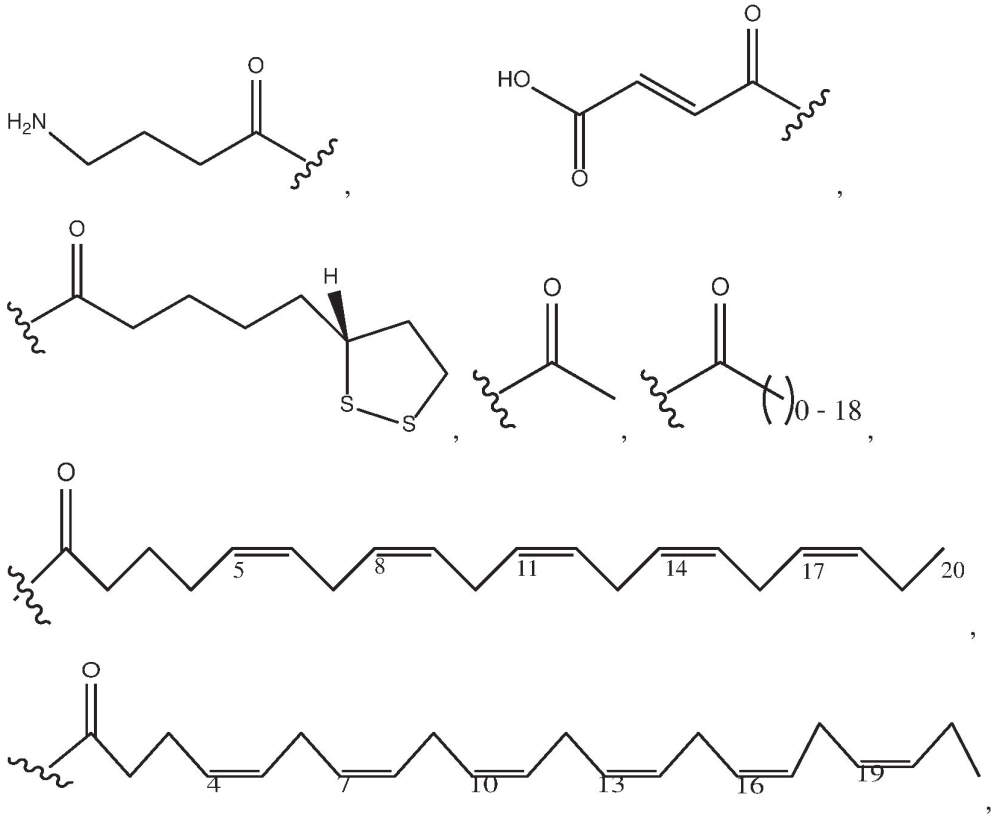
wherein,

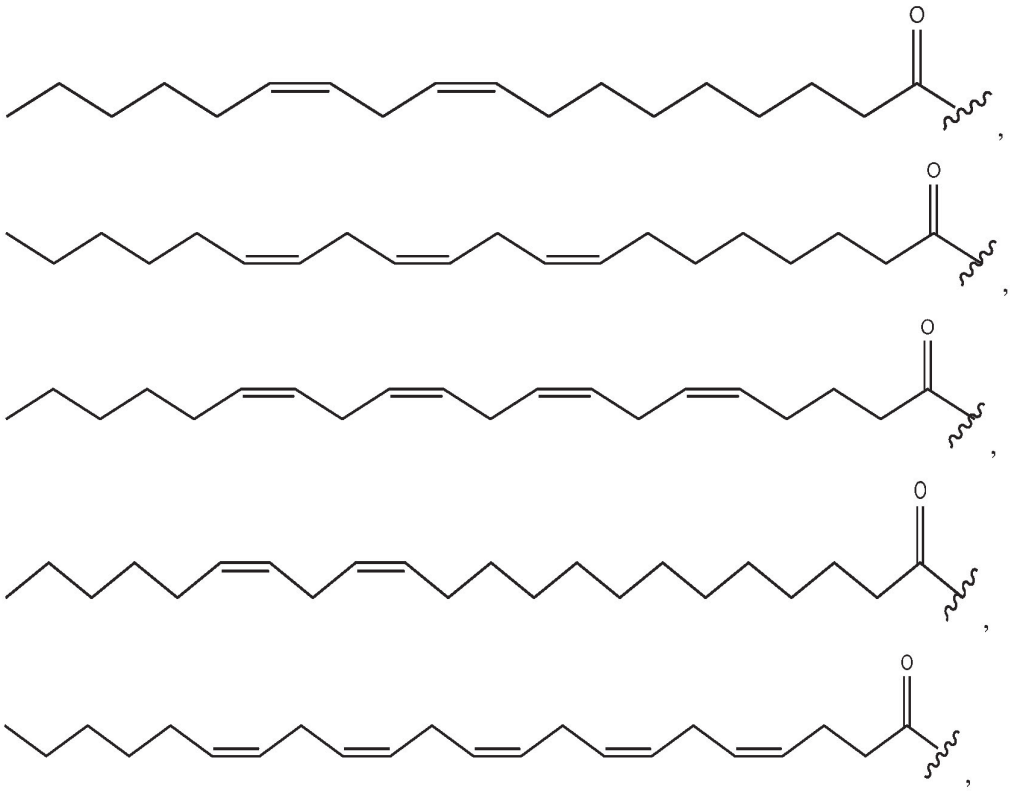
R1 represents Null,

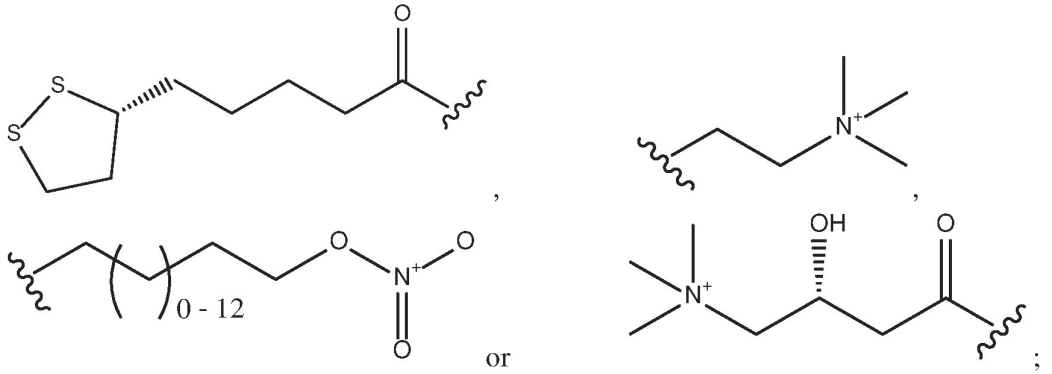




R_2 represents



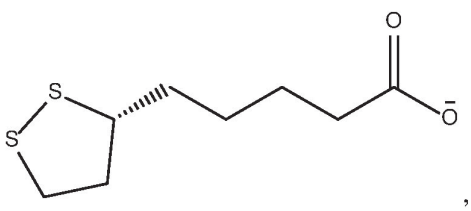
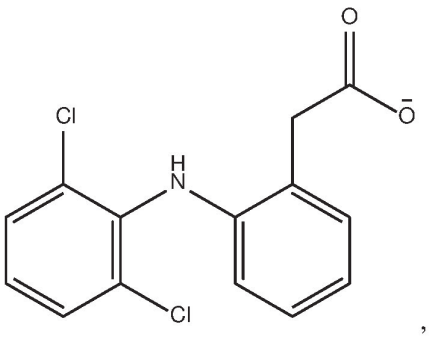
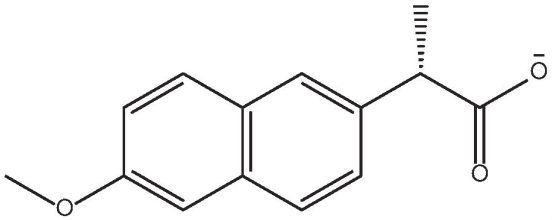
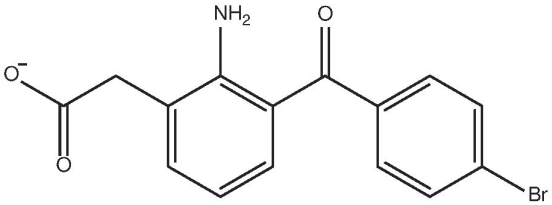
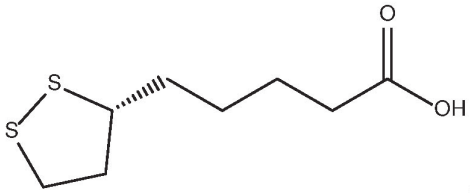
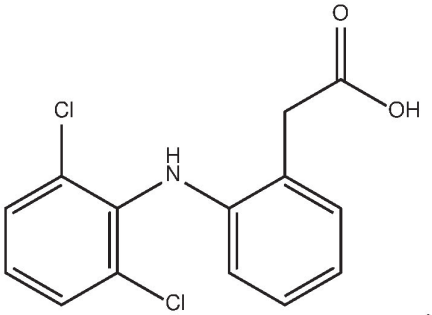
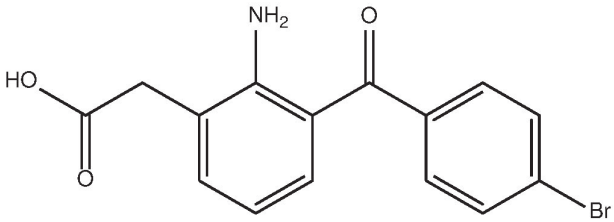
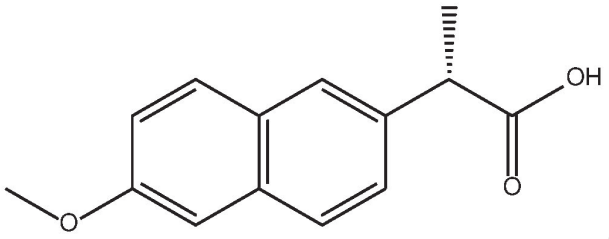




or

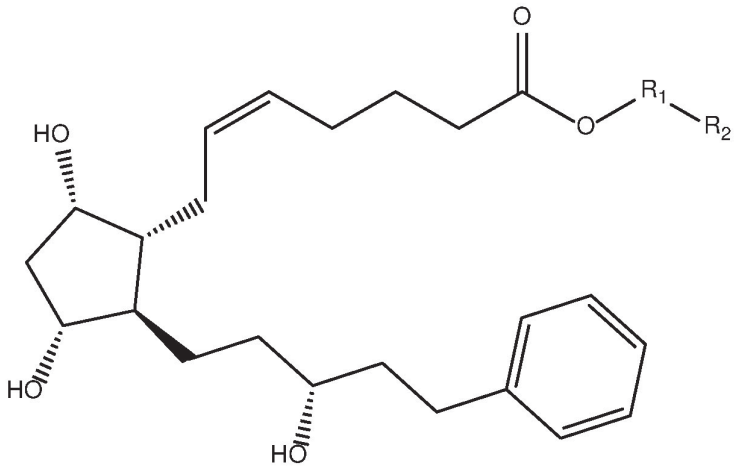
;

RH independently represents

132

3. A compound of formula III

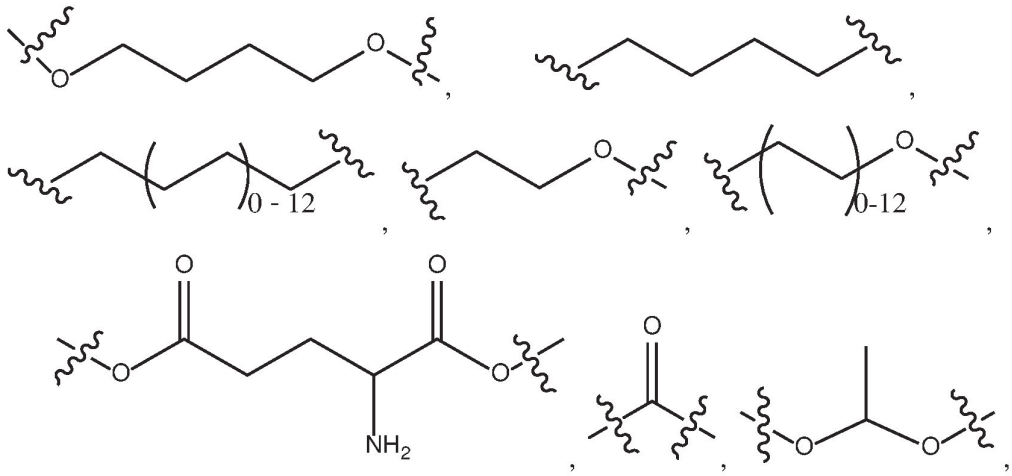


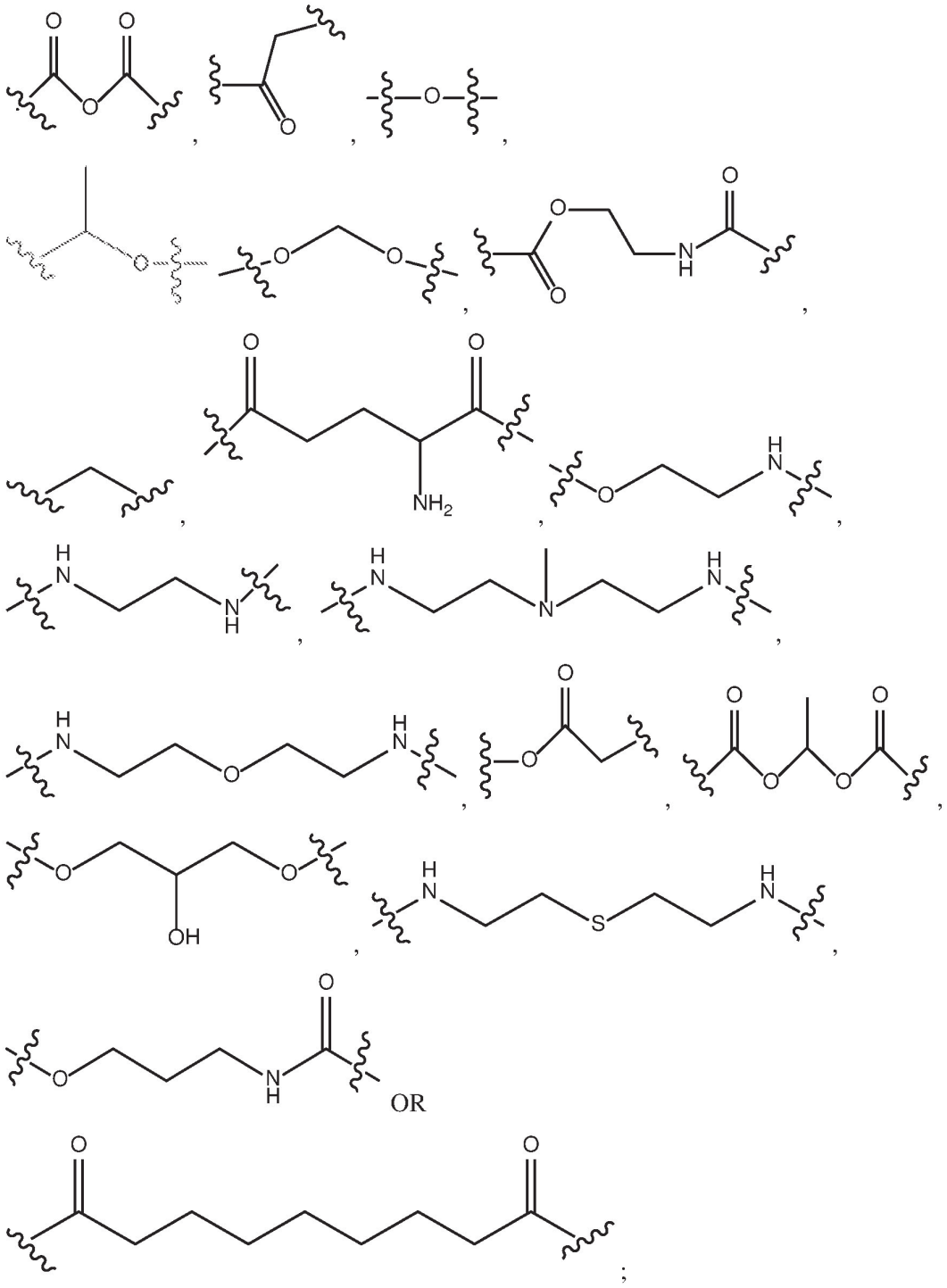
Formula III

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

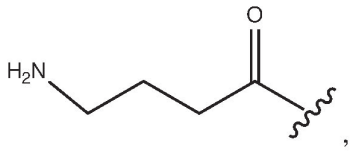
wherein,

R1 represents Null,





R_2 represents



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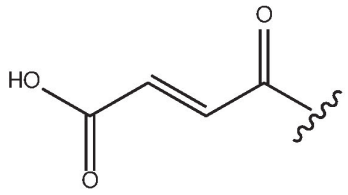

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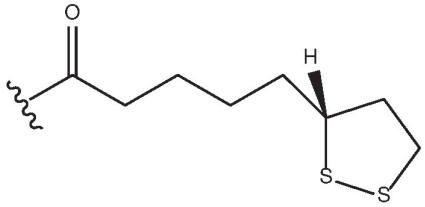

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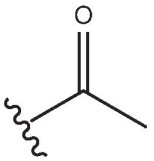

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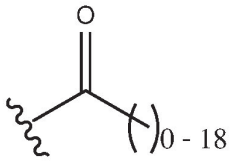

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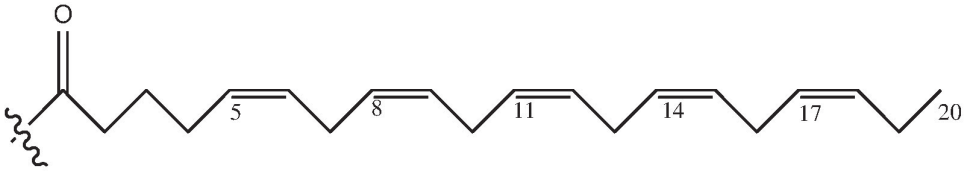

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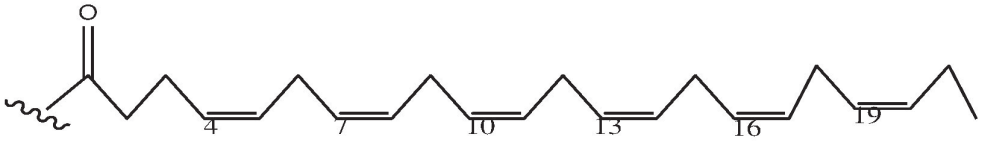

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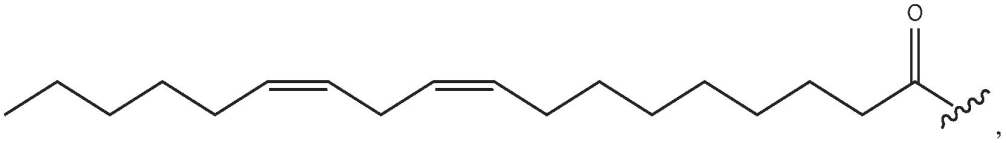

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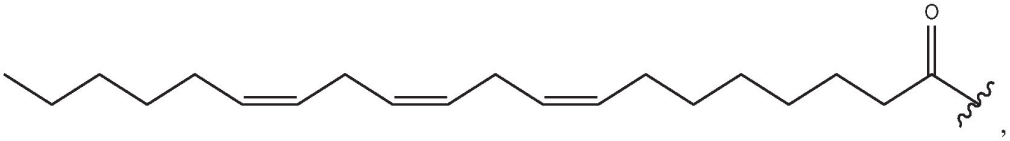

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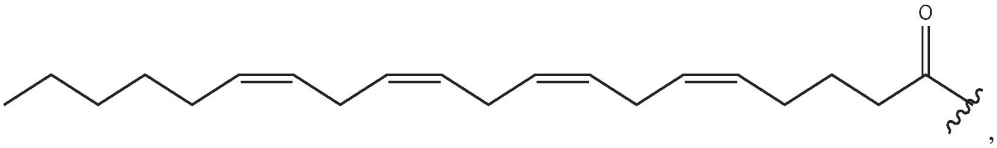

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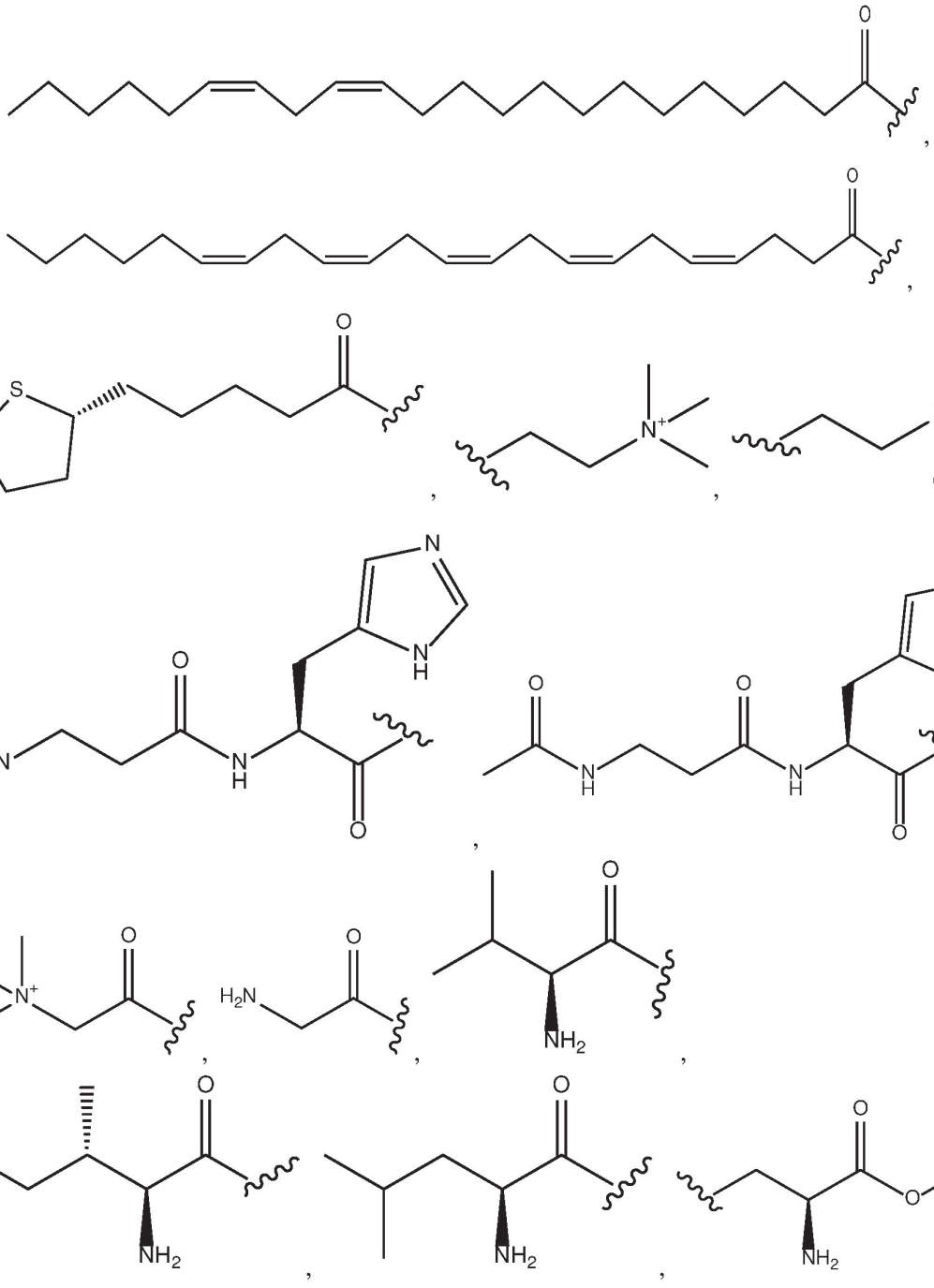
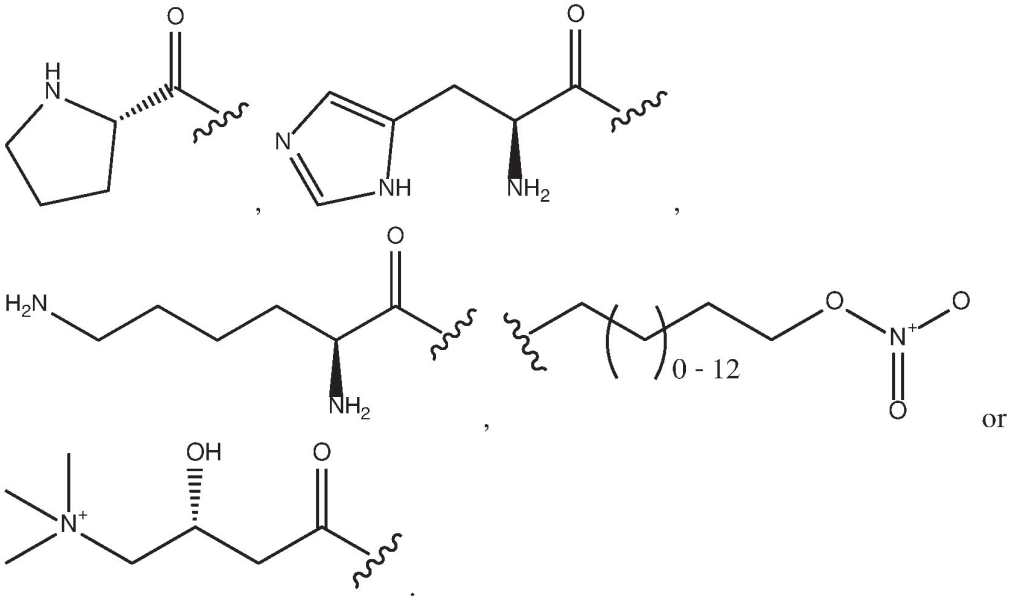
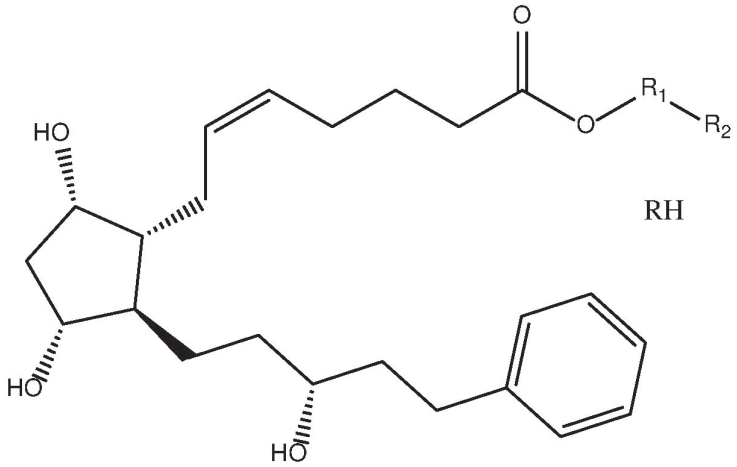

O
S
S
N+
Cl-
N
H
H2N
NH2



or

4. A compound of formula IV



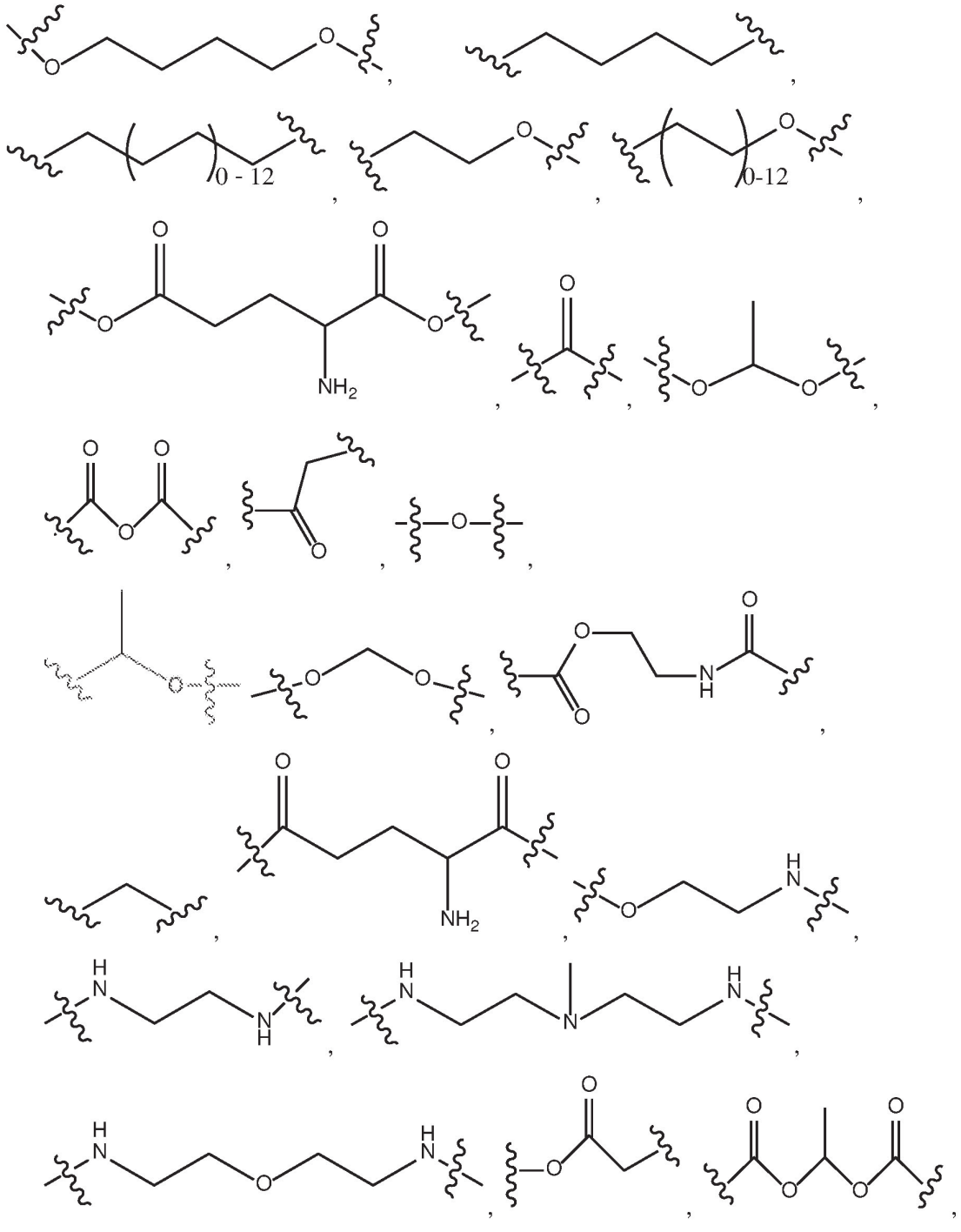
RH

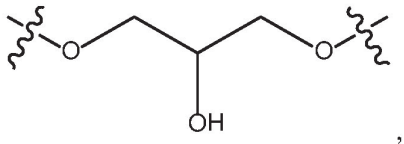
Formula IV

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof

wherein,

R^1 represents Null,


O
0 - 12
0-12
NH2
H
N



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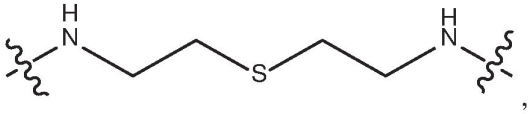

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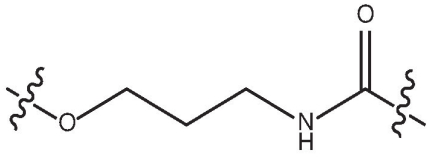
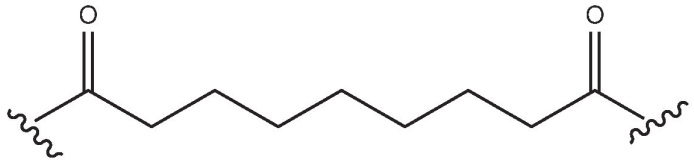
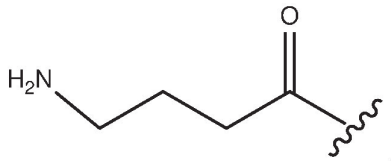




;

R_2 represents



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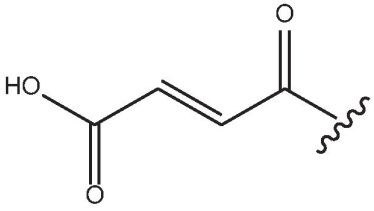

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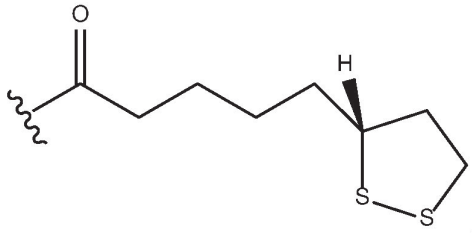

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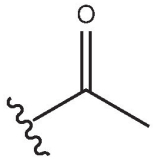

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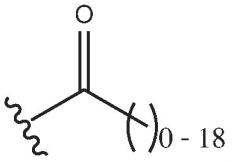

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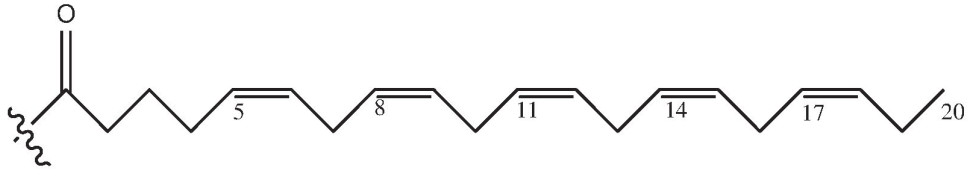

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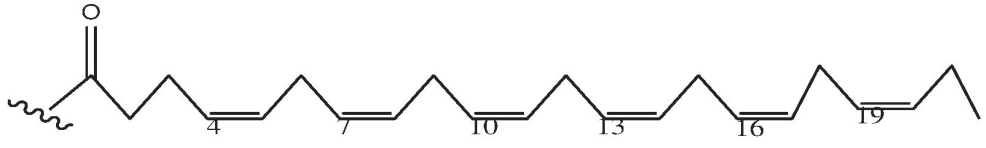

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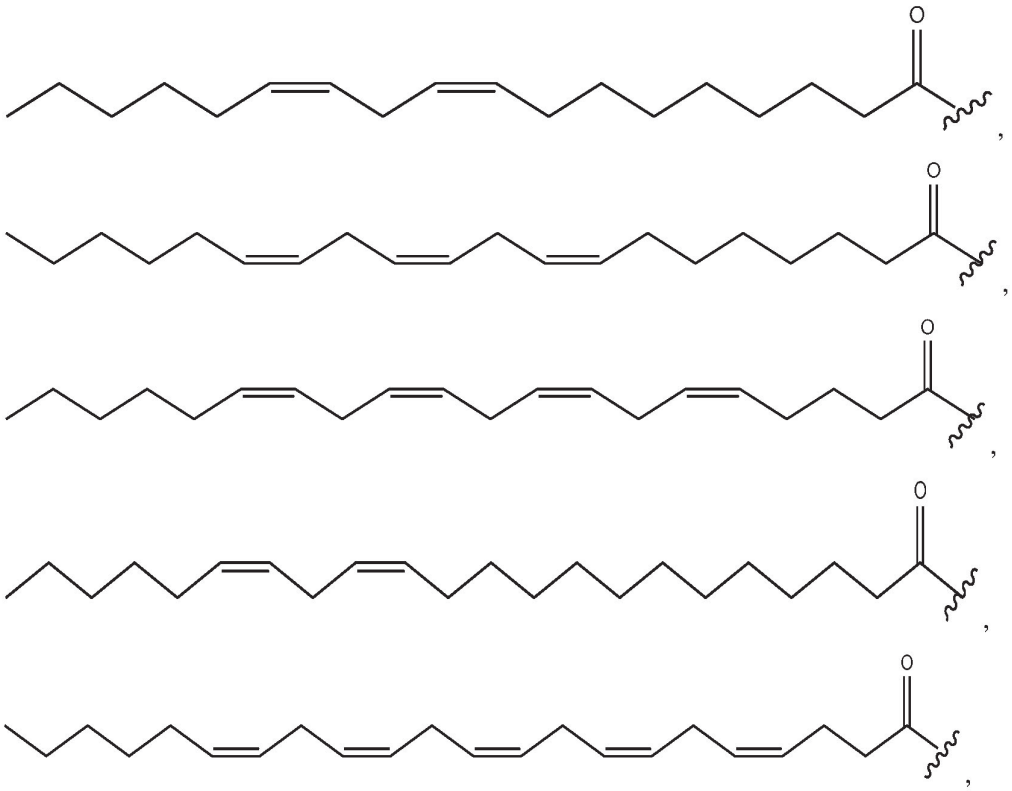
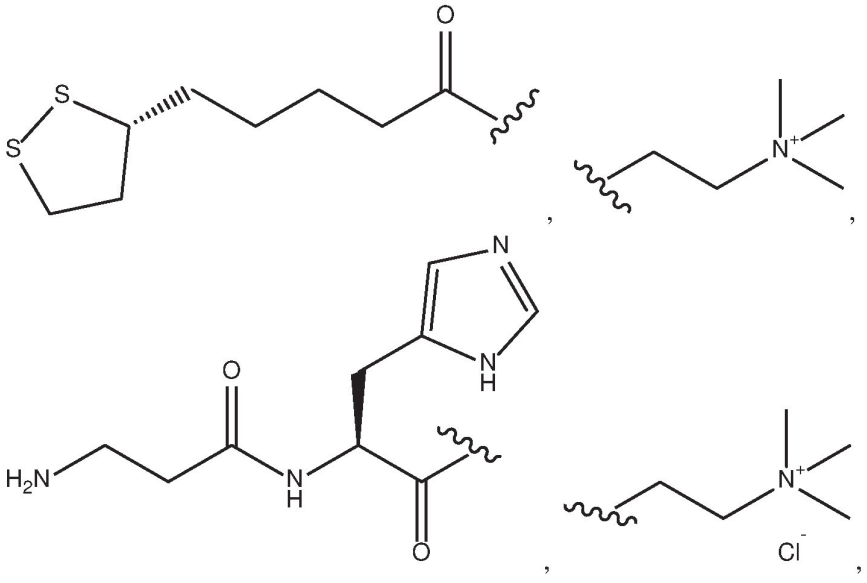
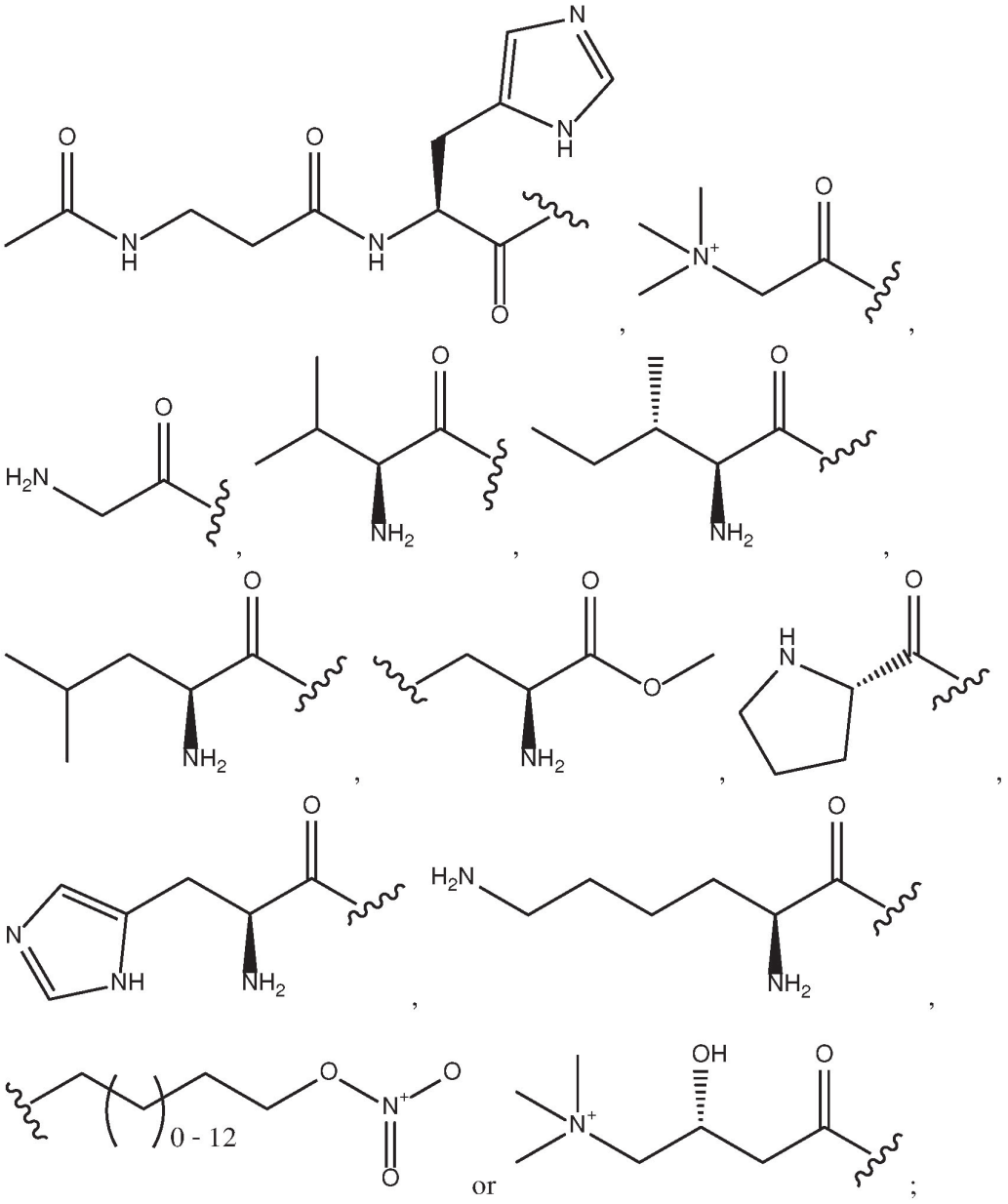
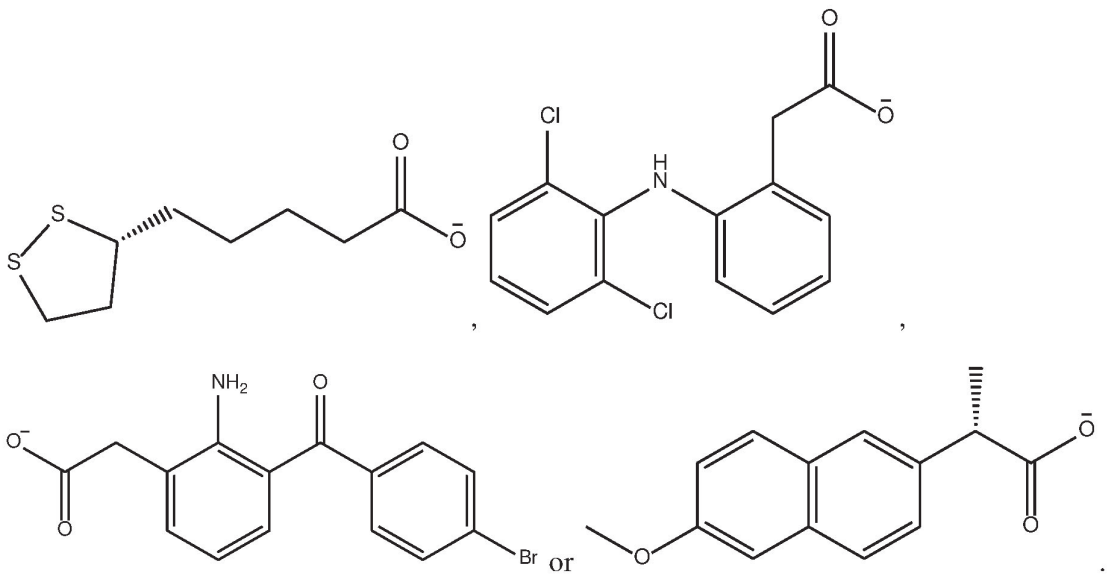


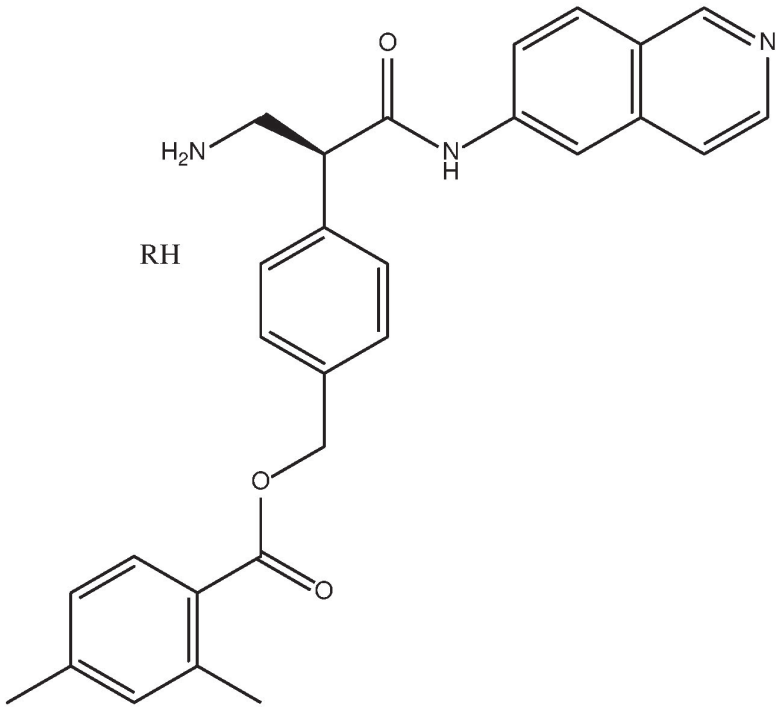




RH represents



5. A compound of formula V

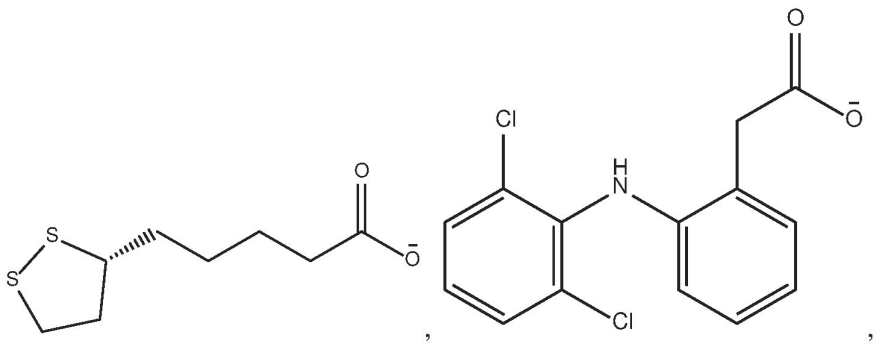


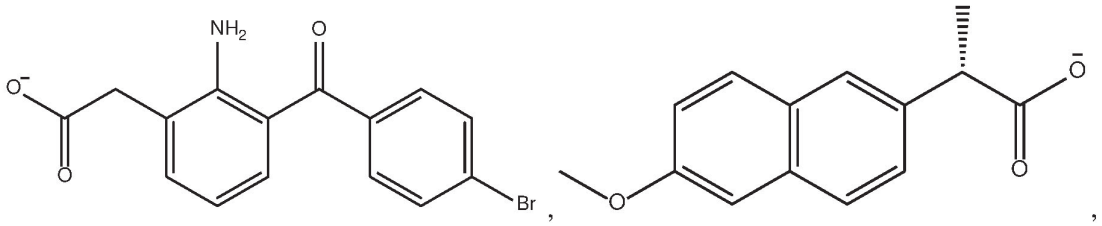
Formula V

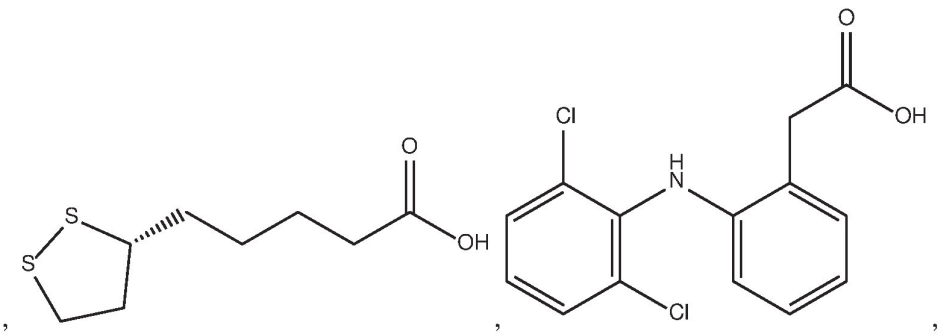
and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

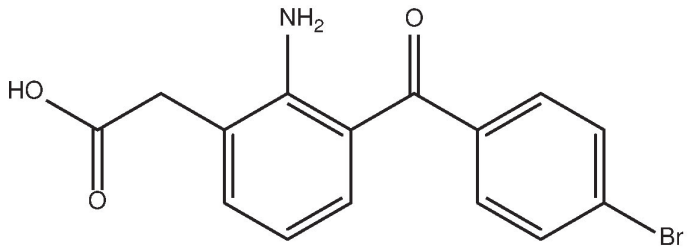
wherein,

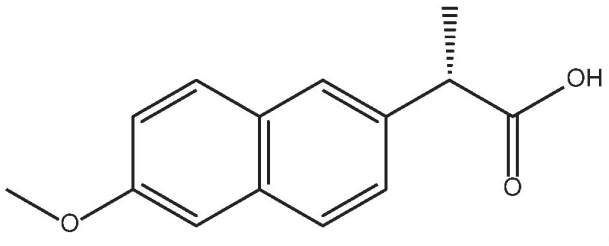
RH represents









or 

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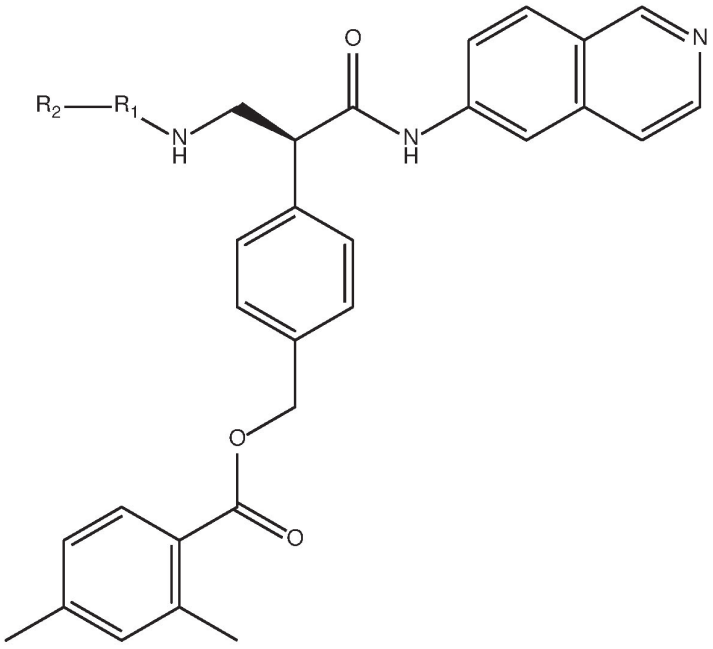
6. A compound of formula VI

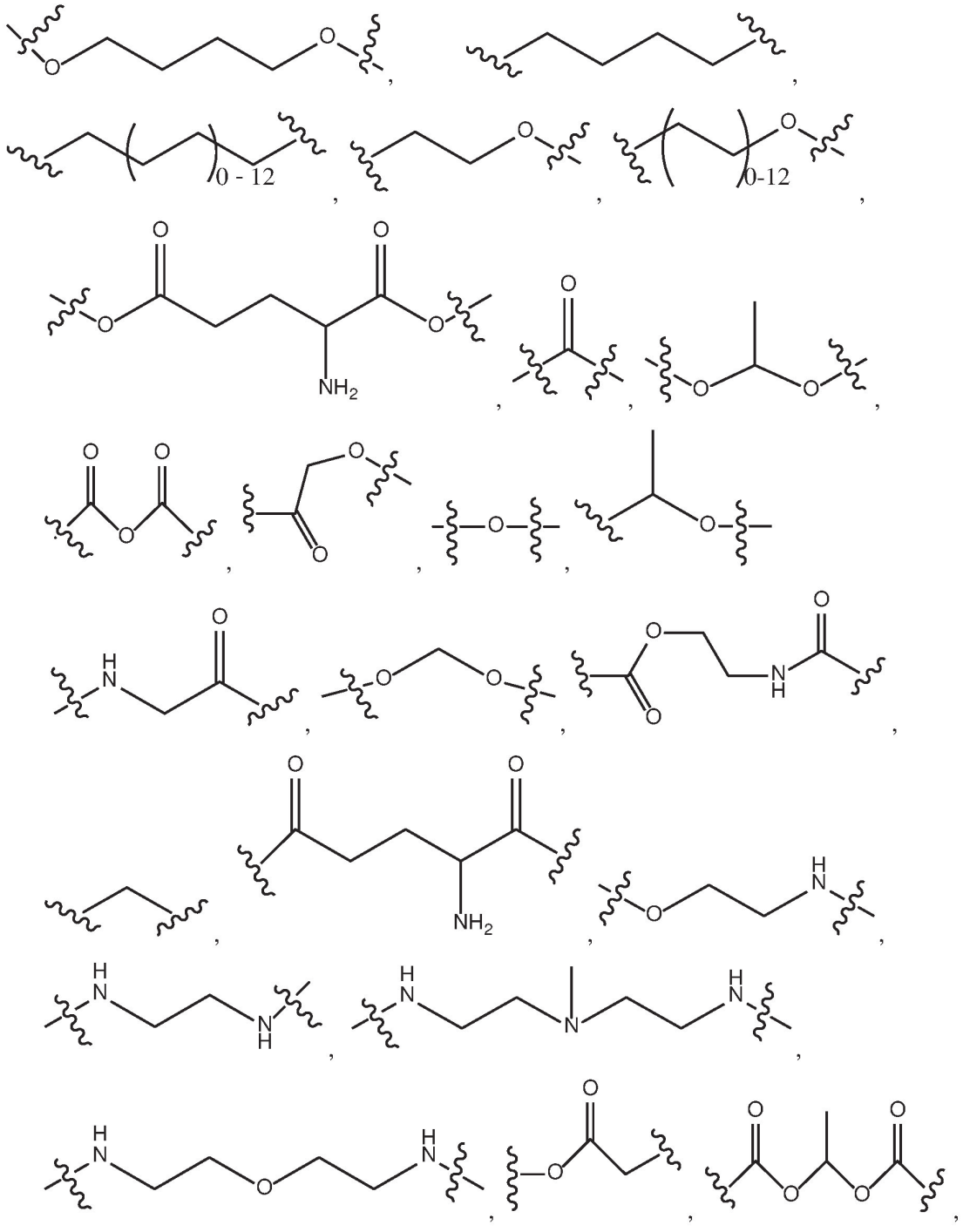


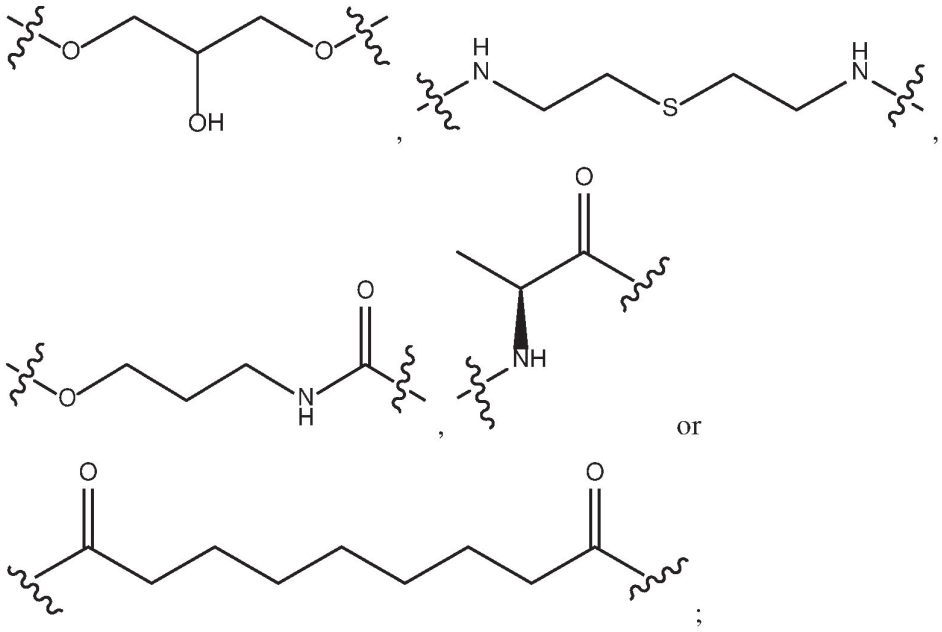
Formula VI

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R^1 represents Null,

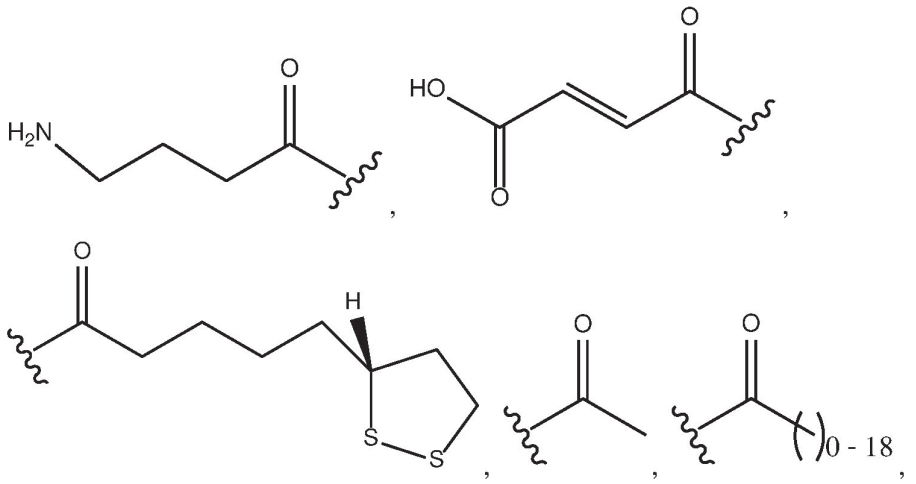

O
0 - 12
0-12
NH2
H
N



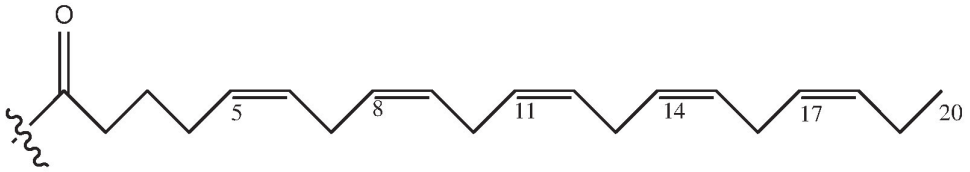
or

;

R_2 represents



0 - 18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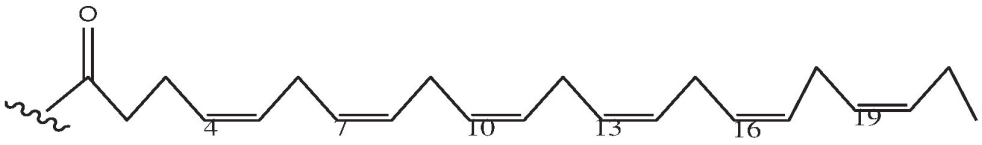
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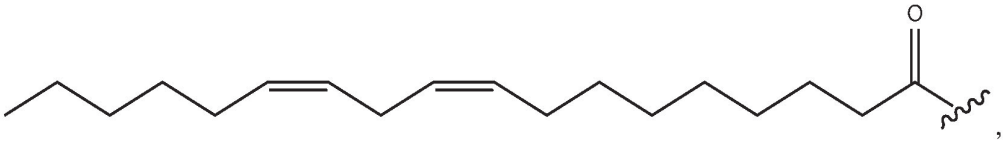
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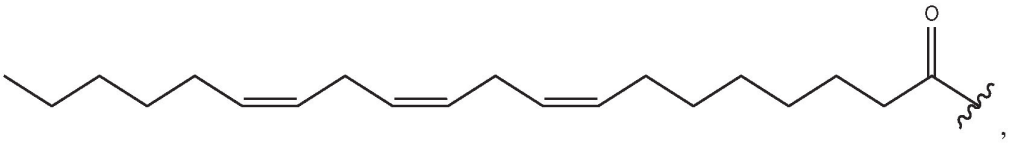
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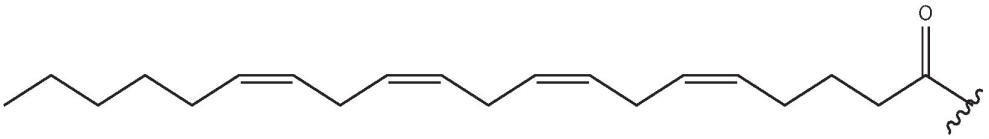
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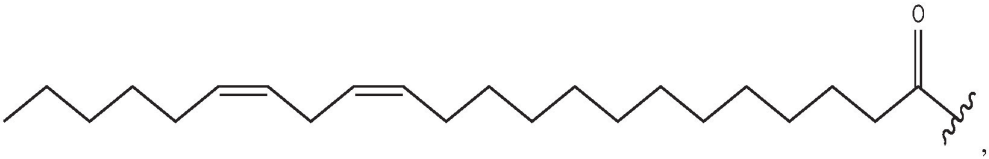
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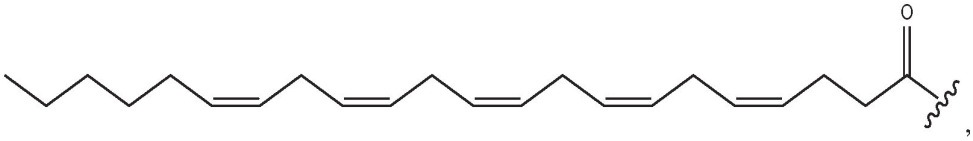
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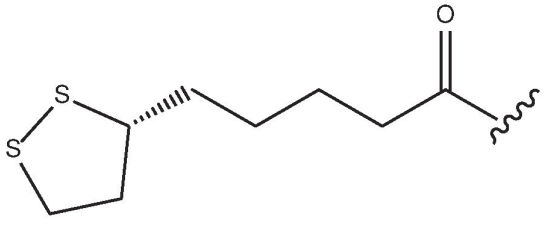
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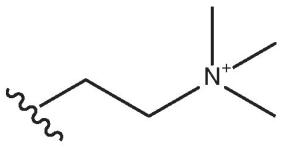
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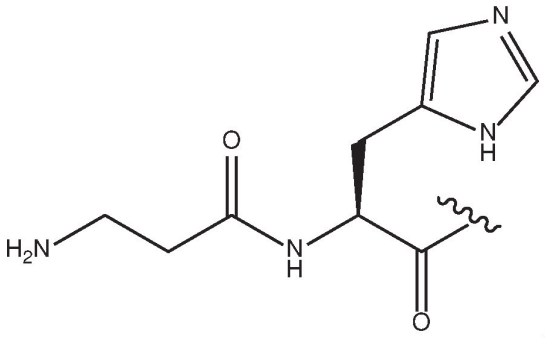
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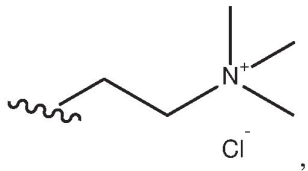
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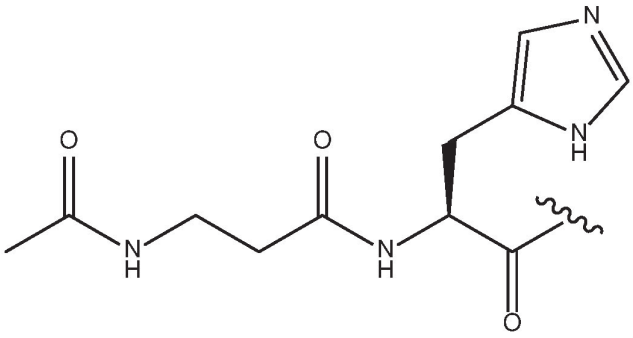
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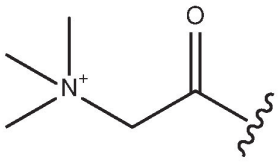
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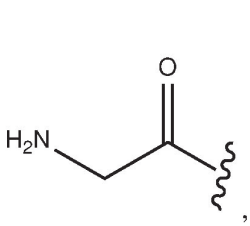
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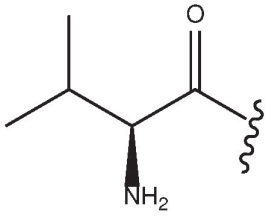
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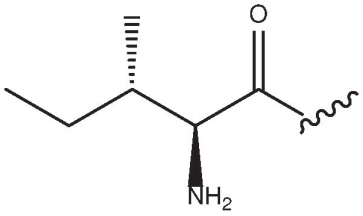
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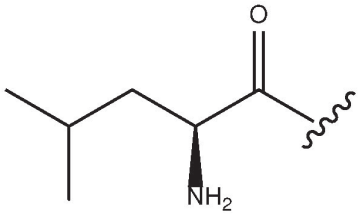
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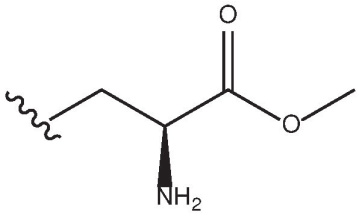
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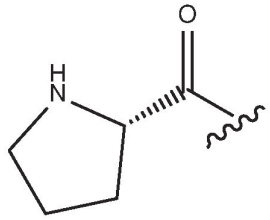
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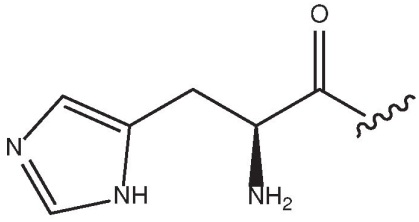
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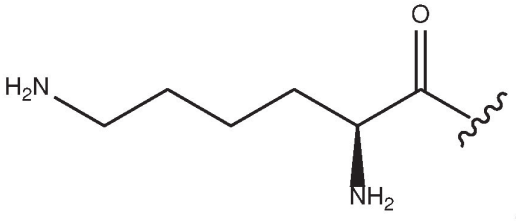
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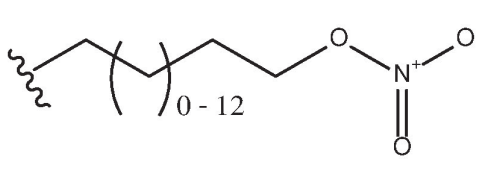

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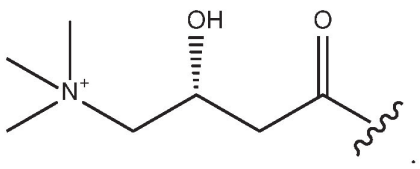

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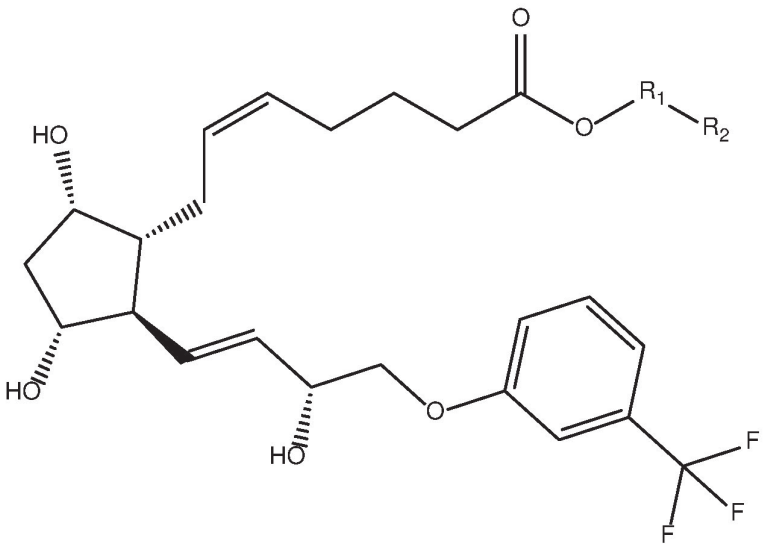
7. A compound of formula VII

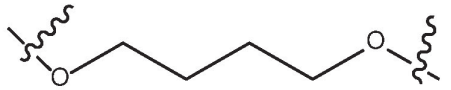


Formula VII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R^1 represents Null,



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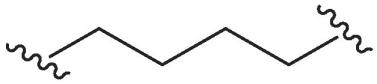
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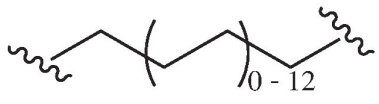

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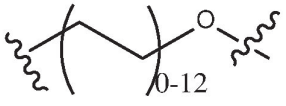

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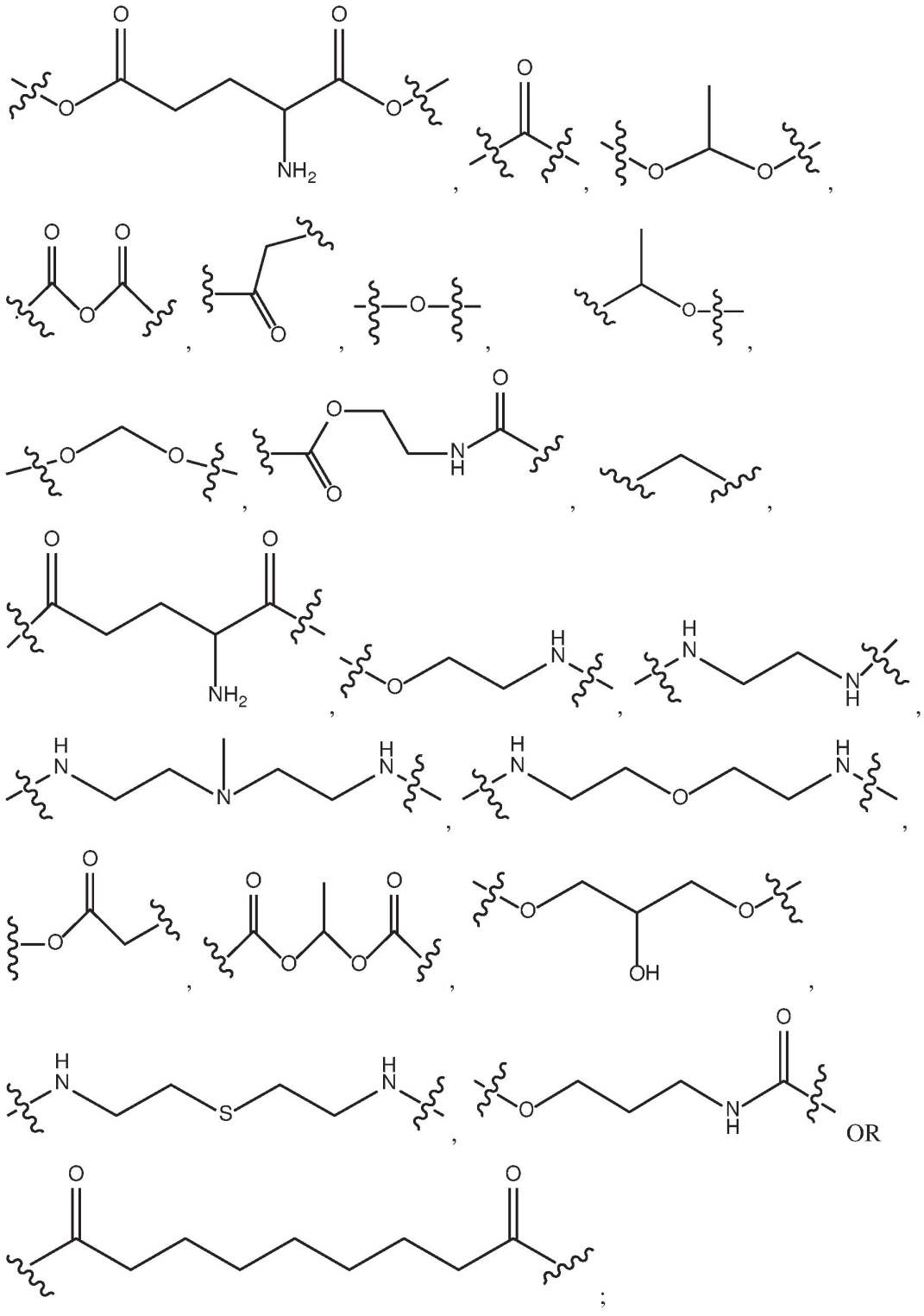
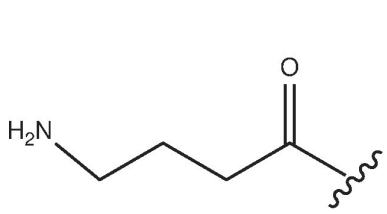


R_2 represents



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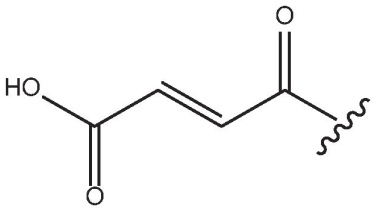

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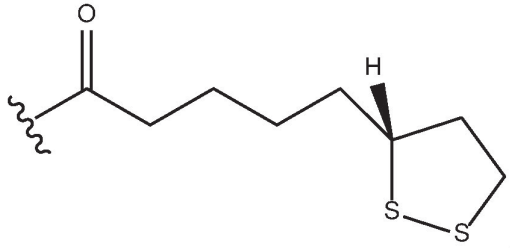

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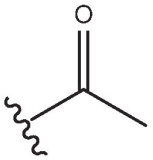

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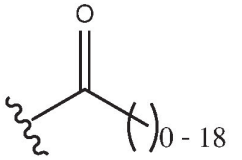

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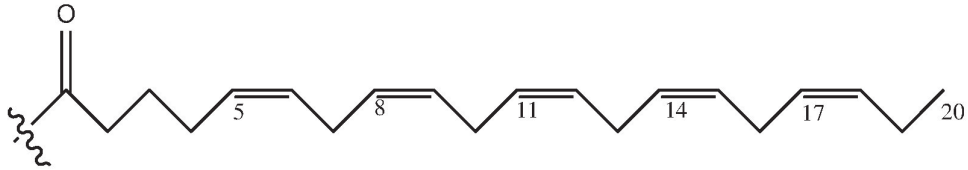

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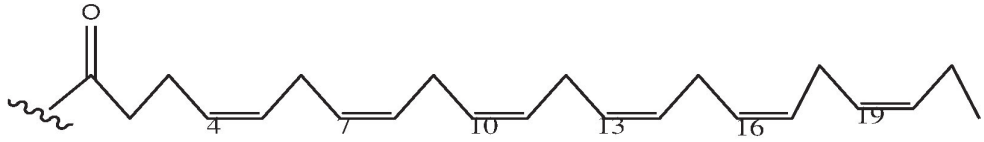

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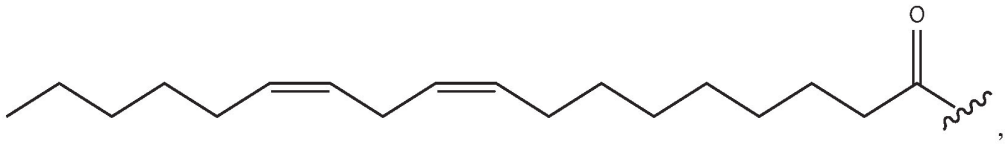

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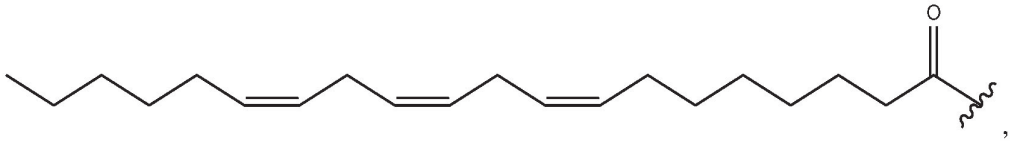

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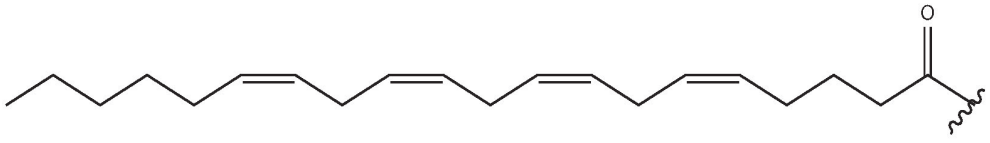

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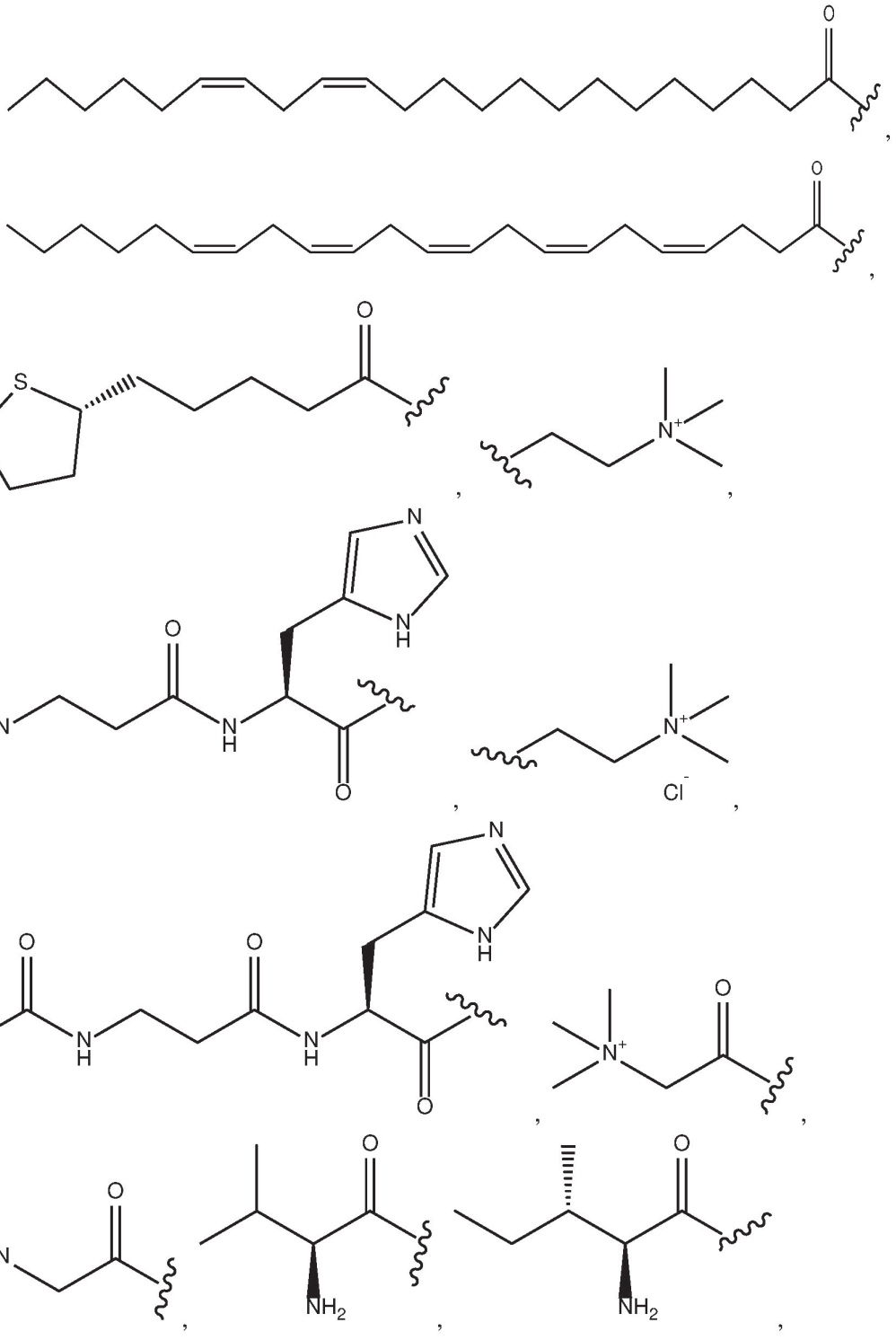
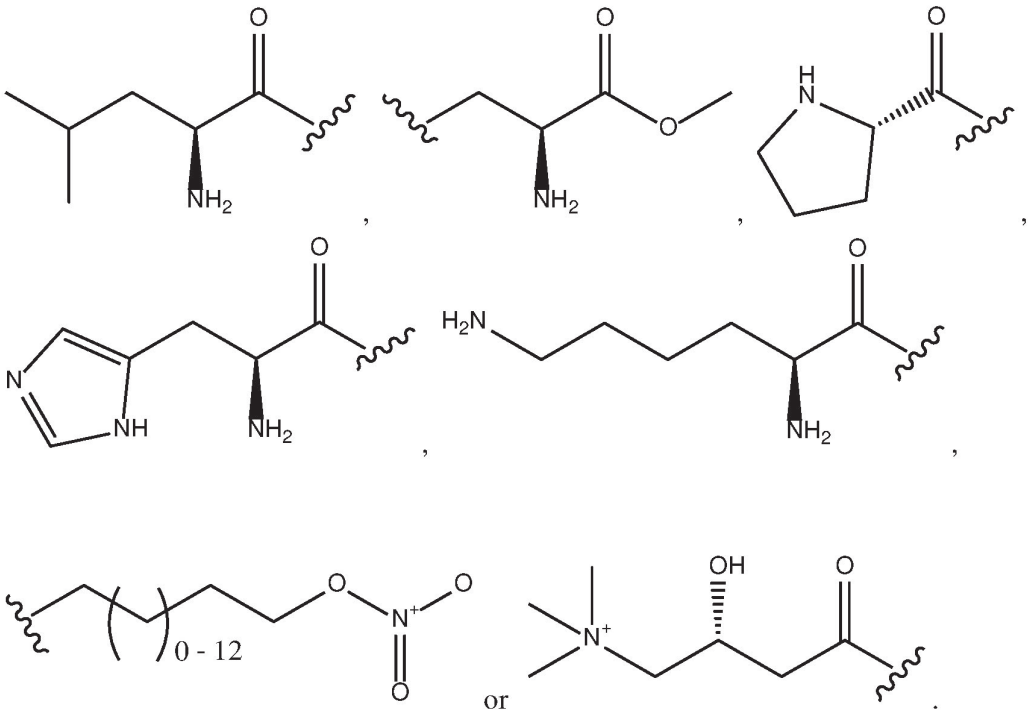
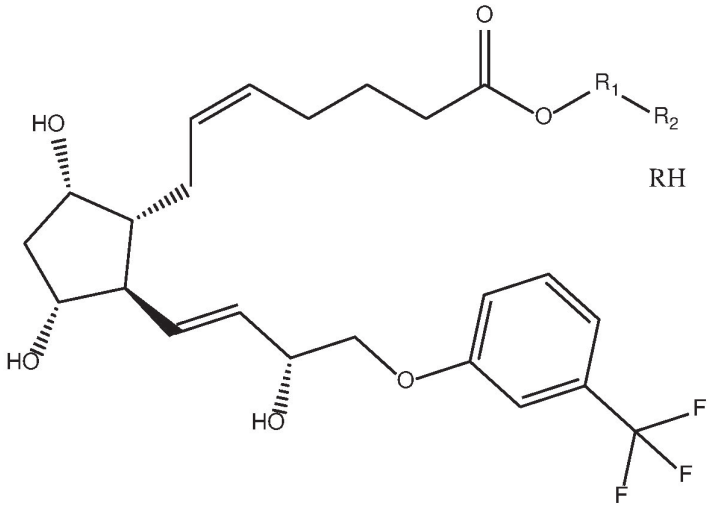




8. A compound of formula VIII

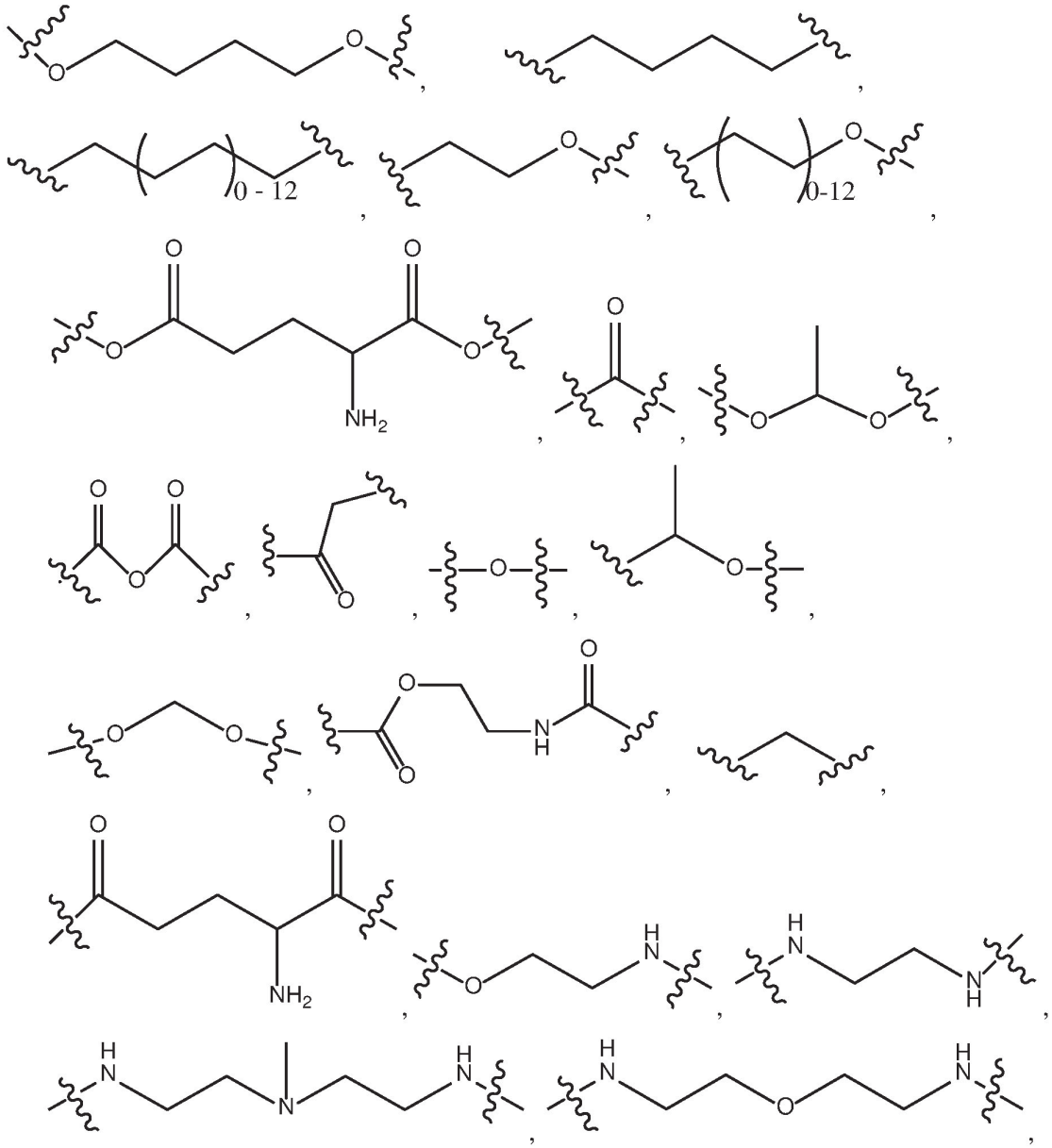


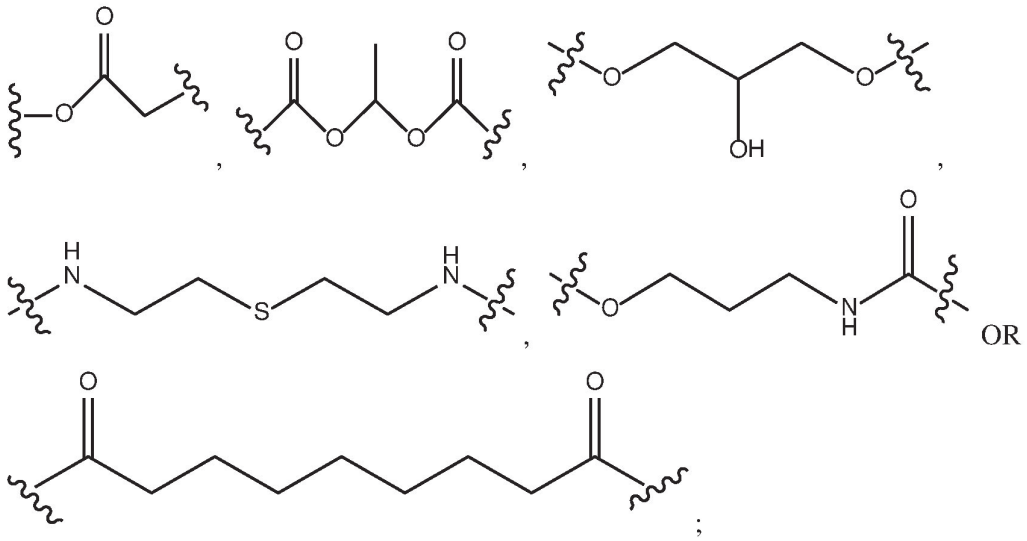
Formula VIII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

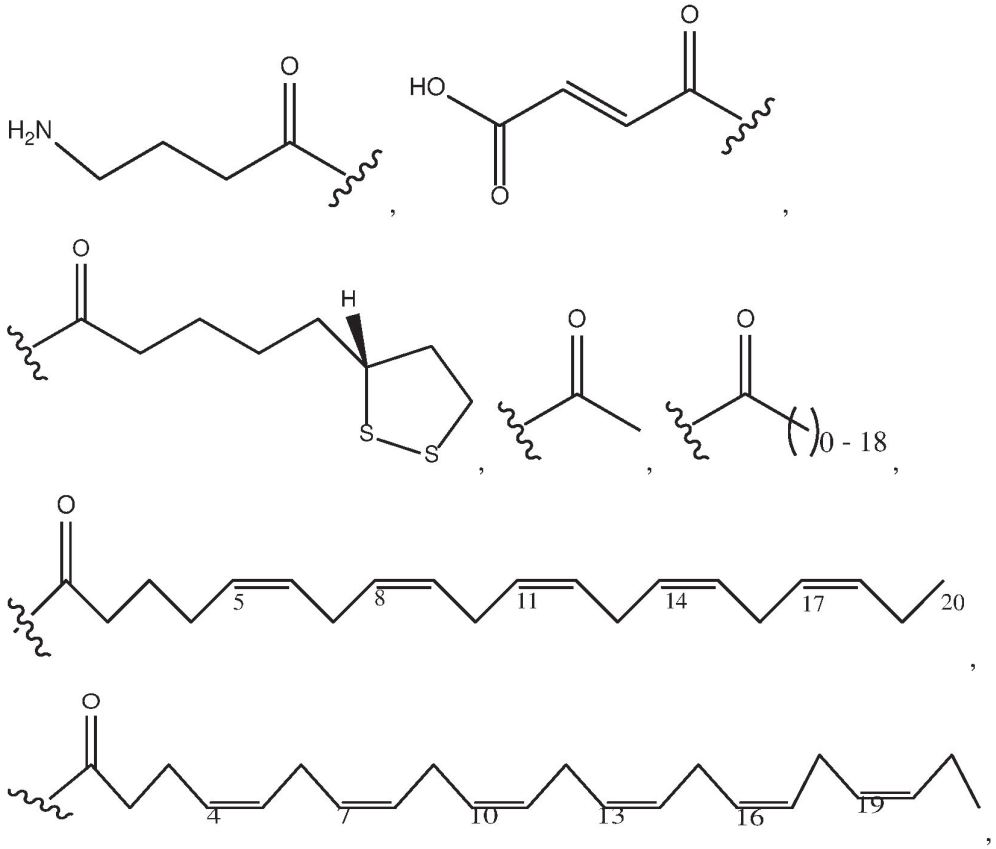
wherein,

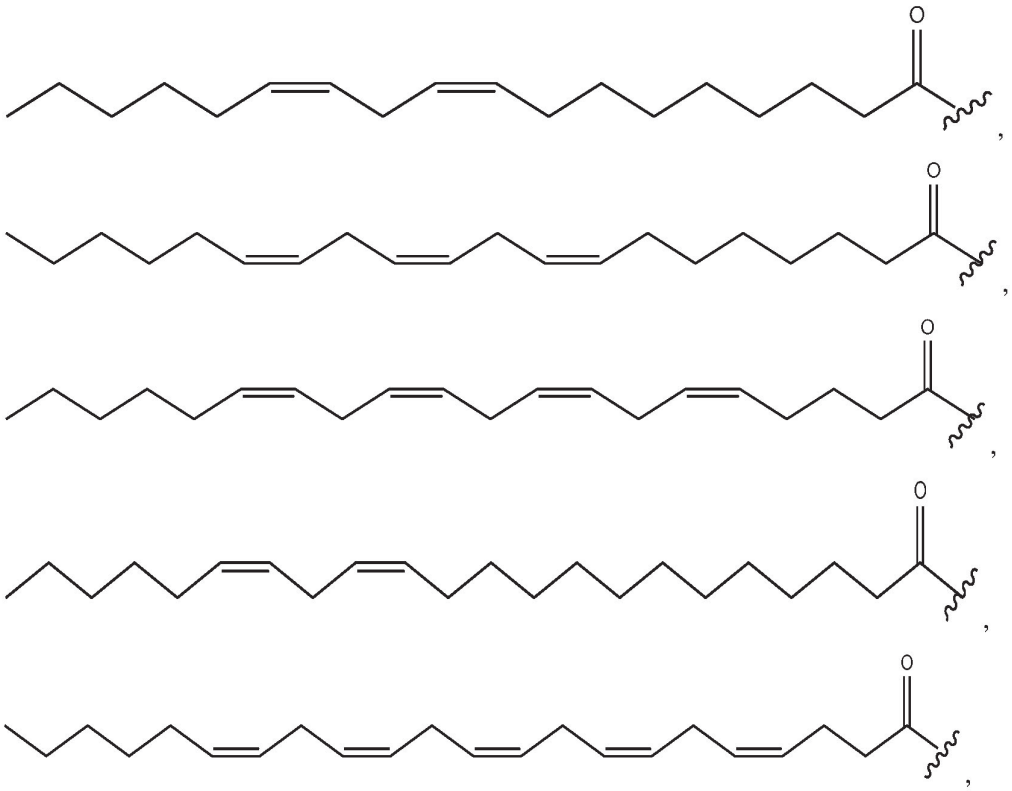
R^1 represents Null,





R_2 represents

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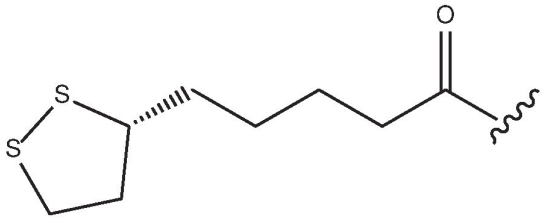
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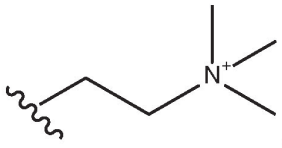
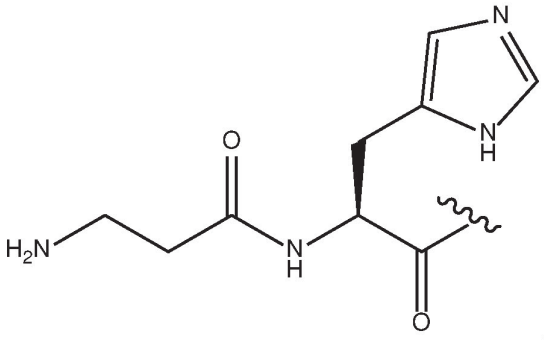

N+


N
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H2N
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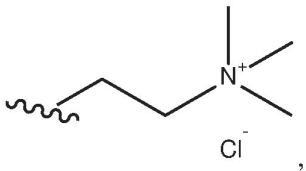
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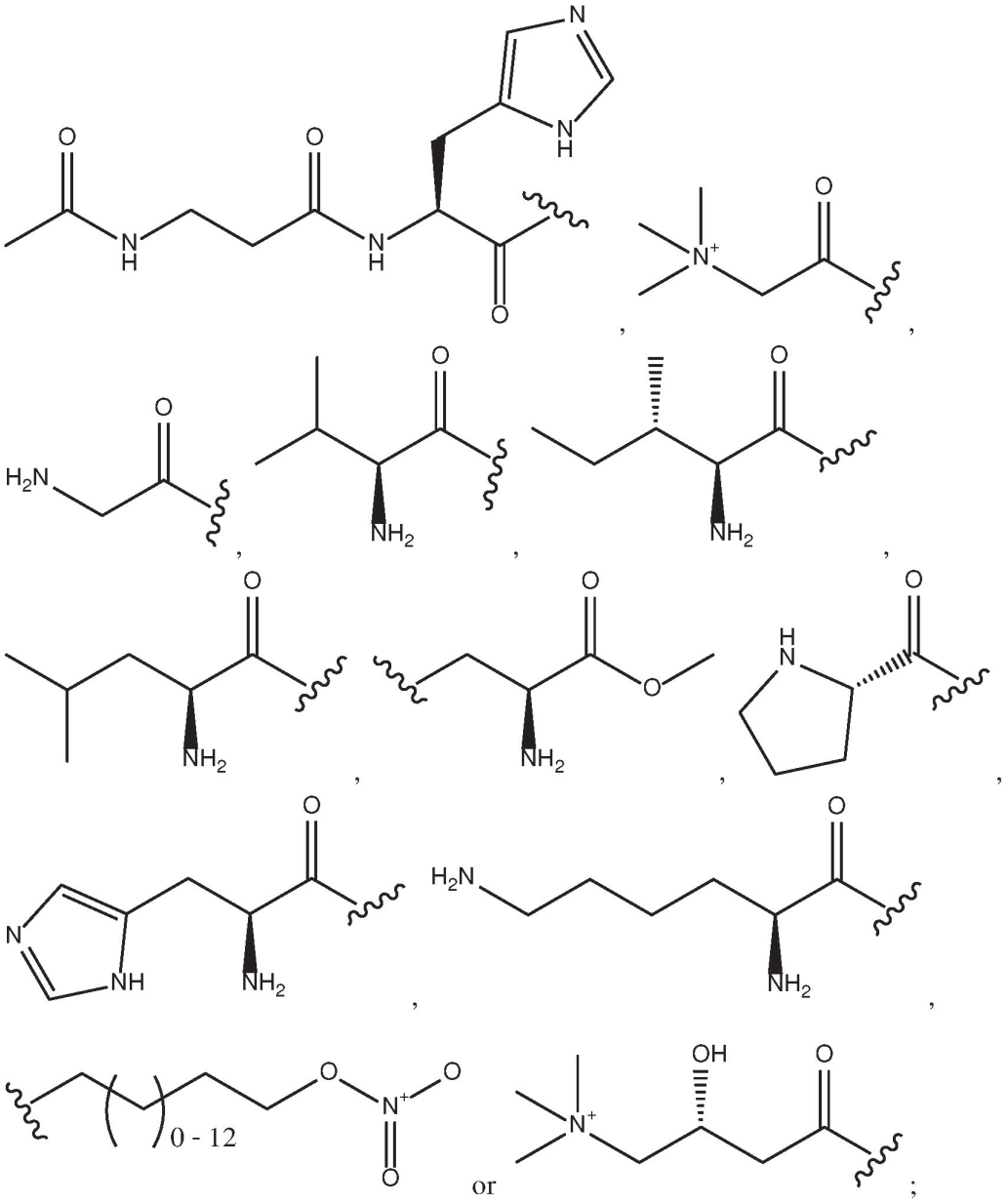
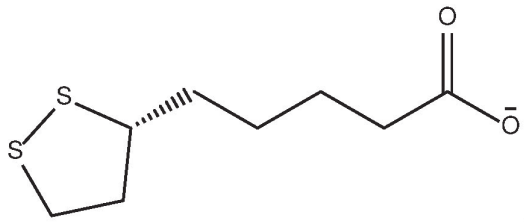
Cl-



RH represents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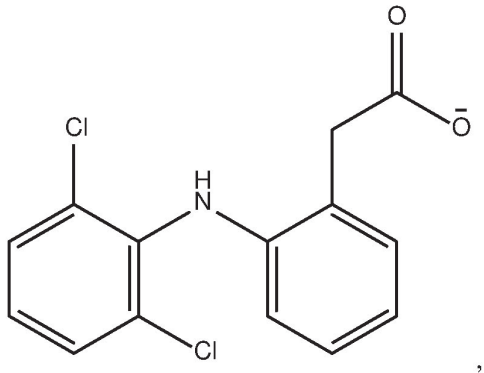
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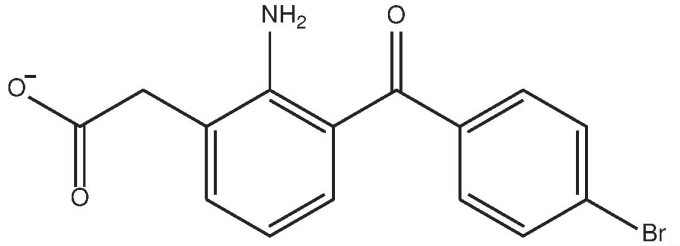
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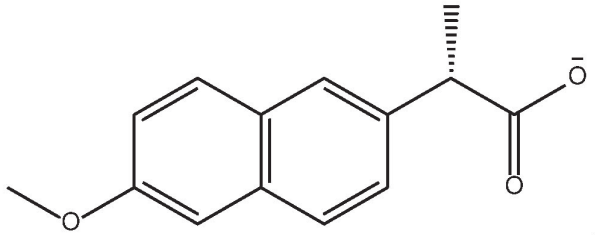
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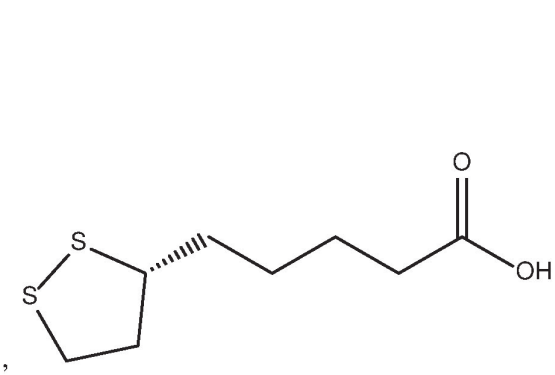
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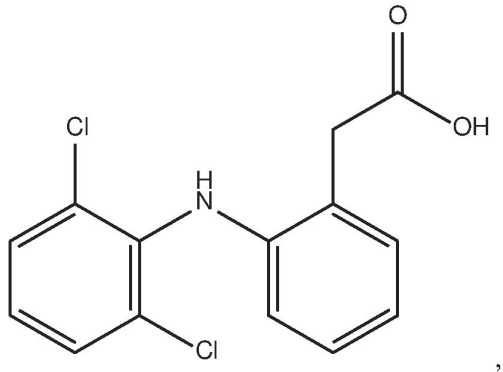
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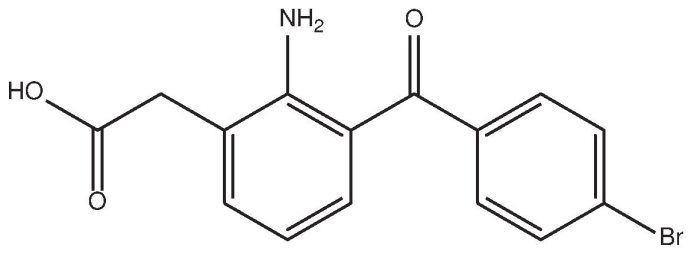
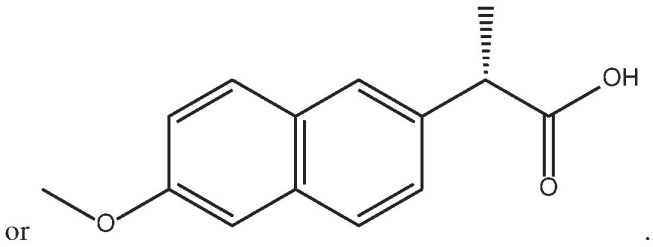
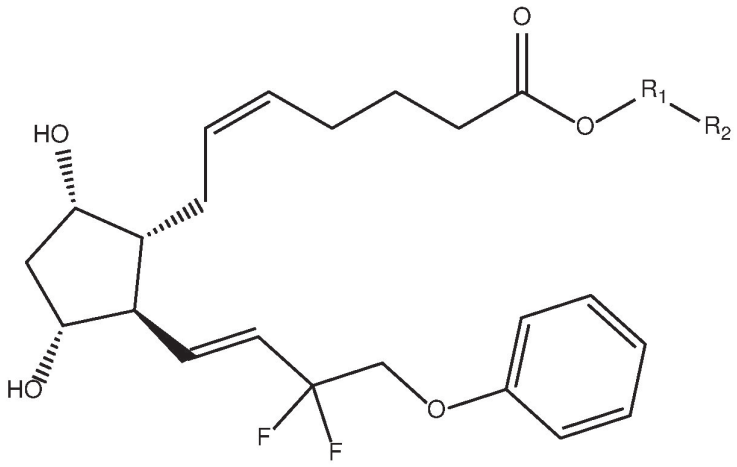




or .

9. A compound of formula IX

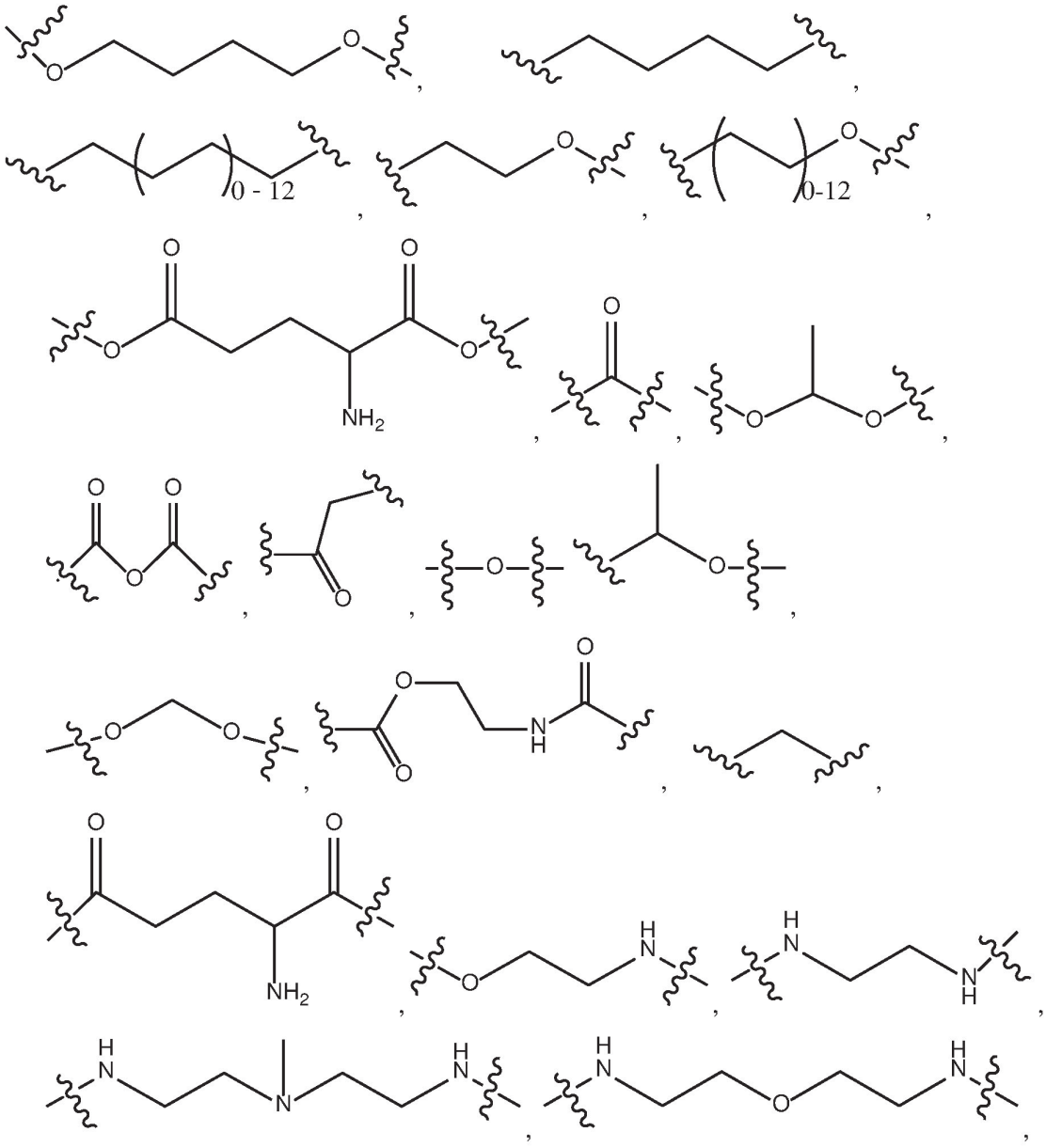


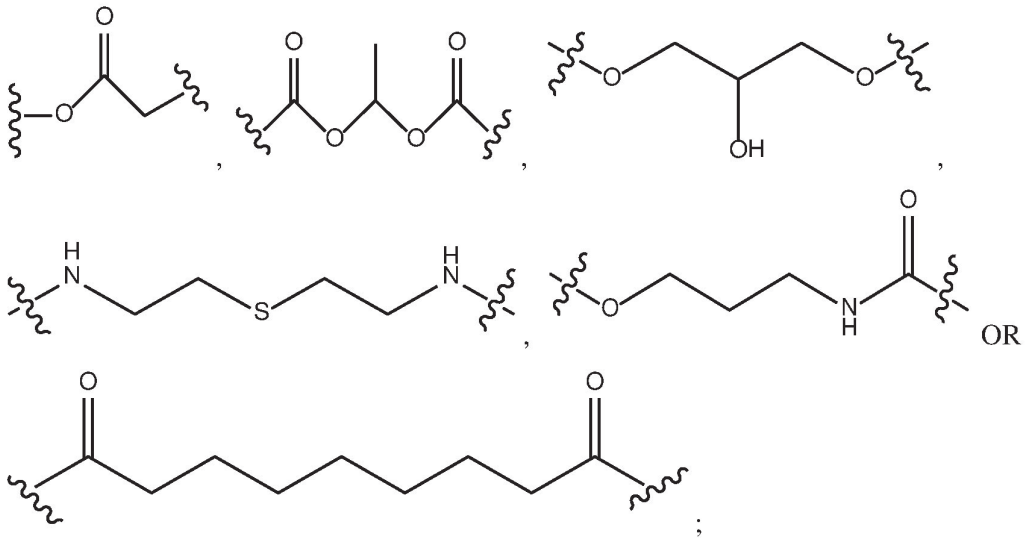
Formula IX

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R^1 represents Null,


O
0 - 12
0-12
NH2
H
N



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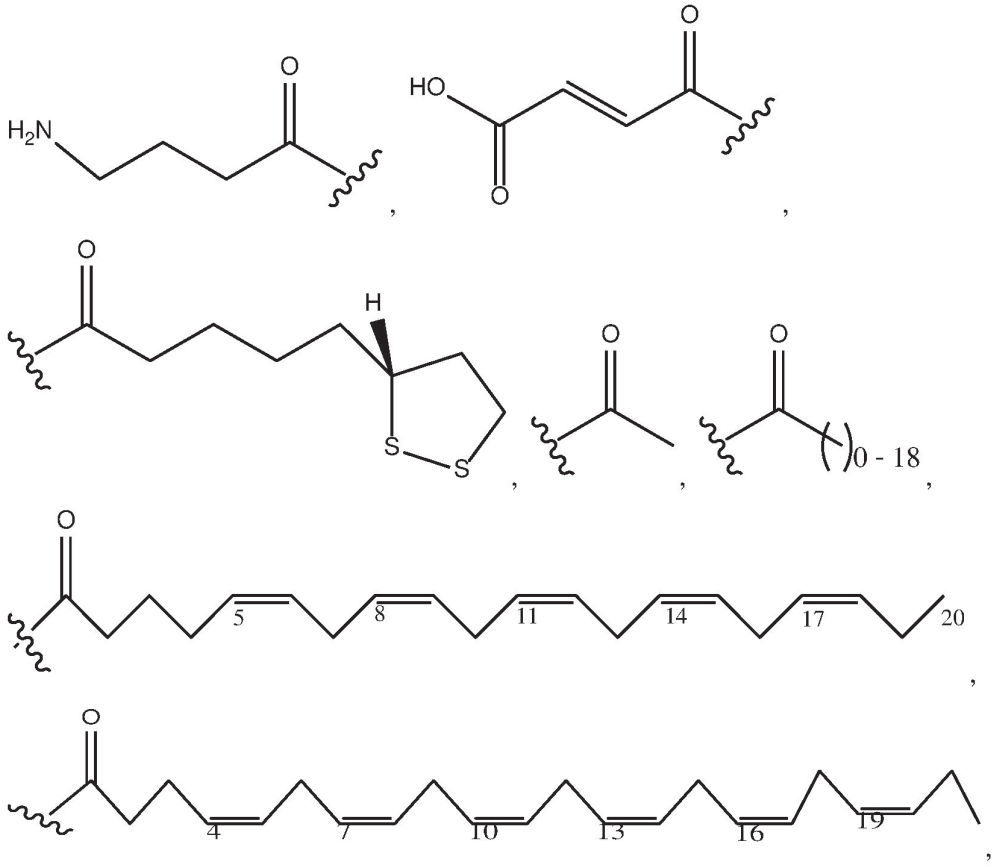

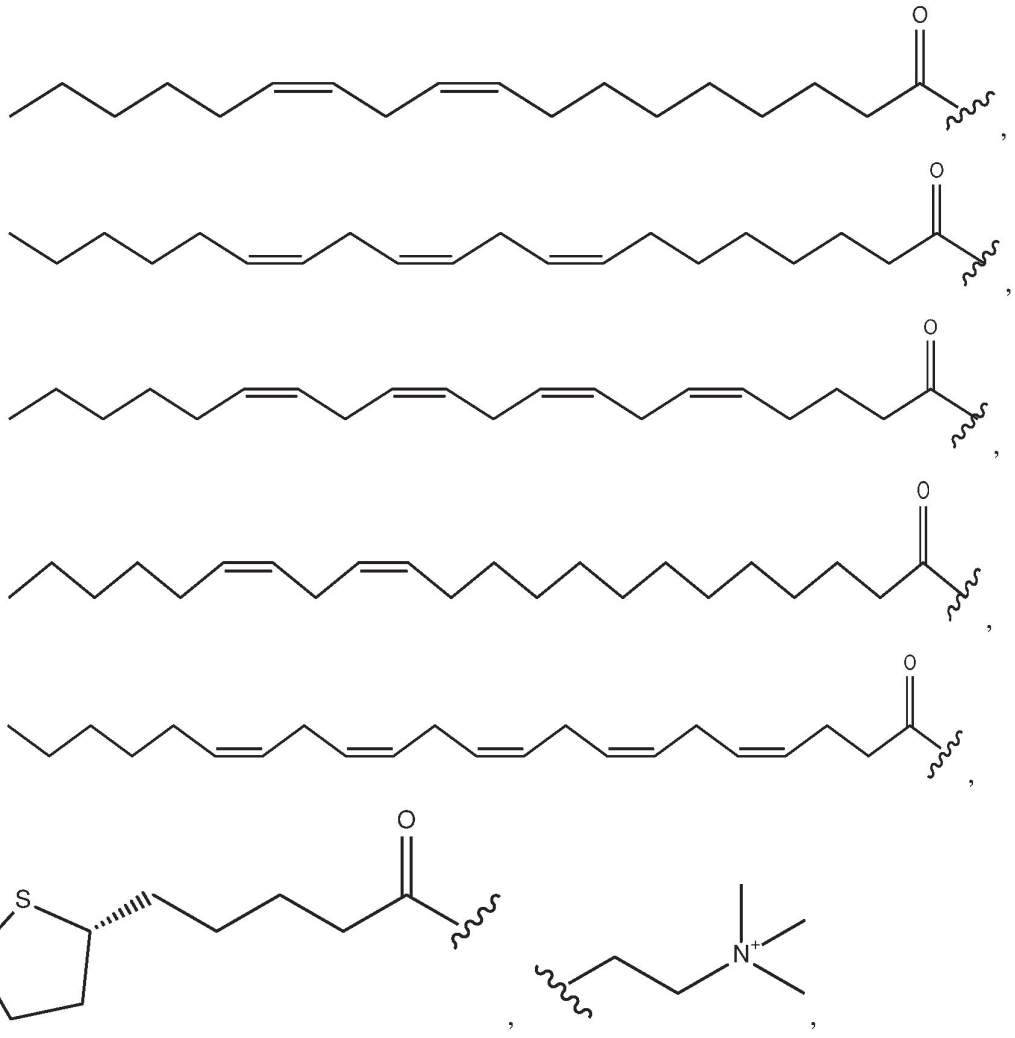
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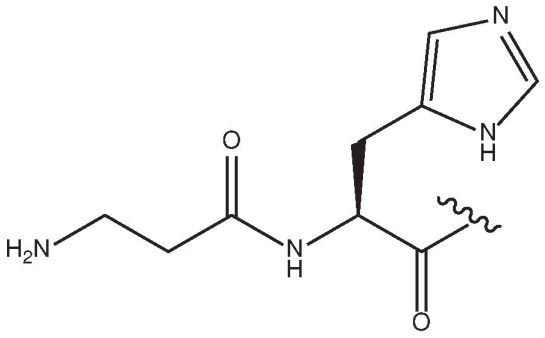
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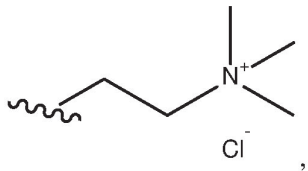
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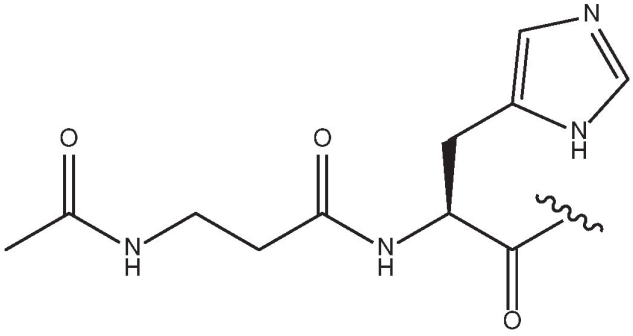
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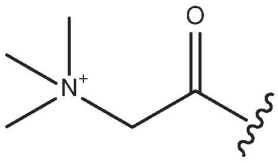
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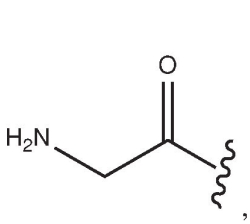
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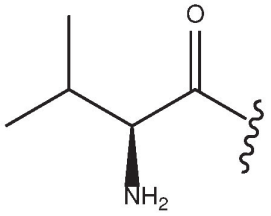
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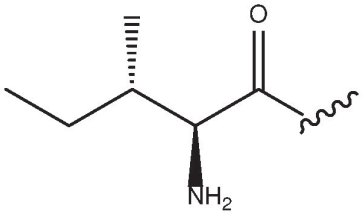
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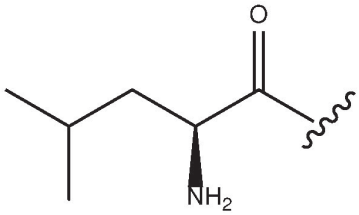
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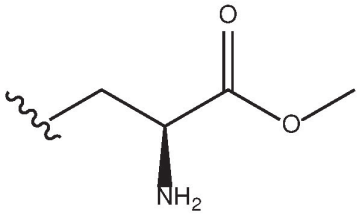
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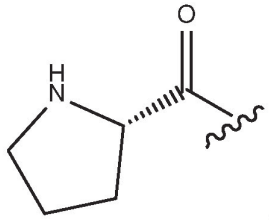
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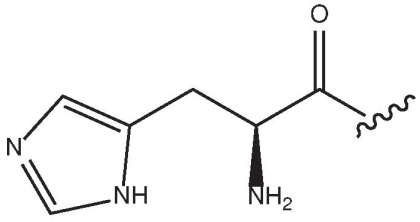
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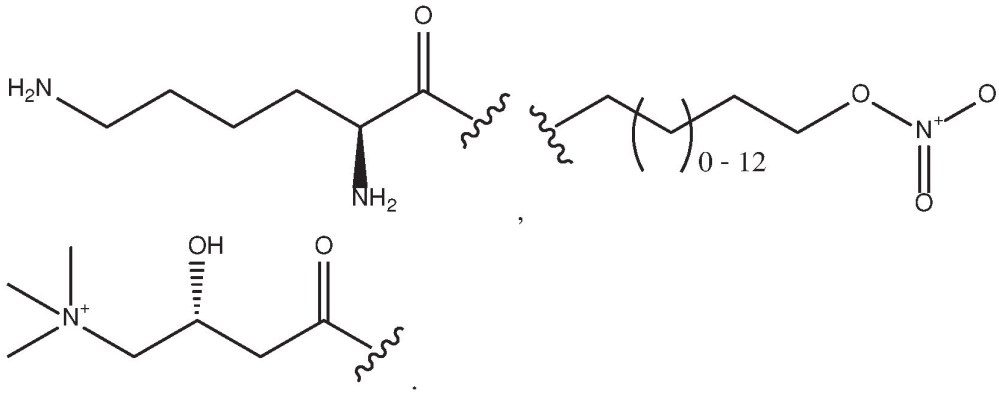
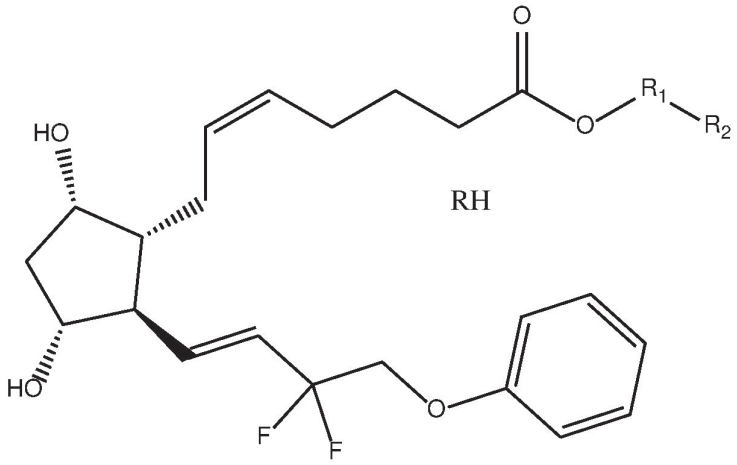


or

10. A compound of formula X

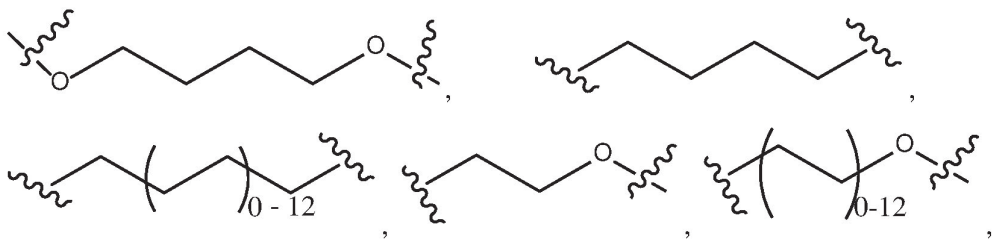


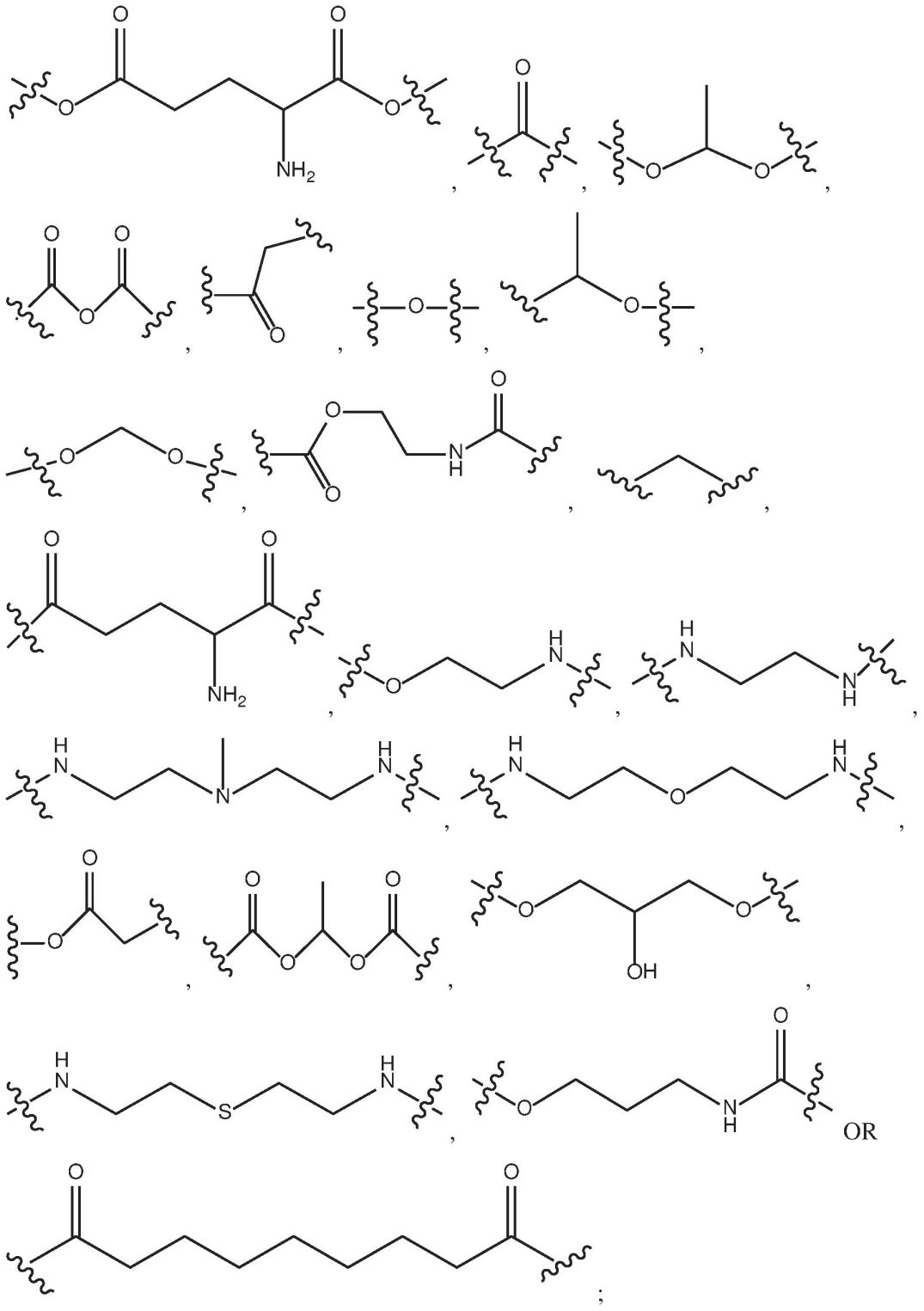
Formula X

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

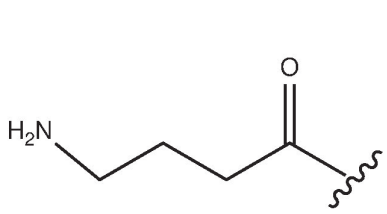
wherein,

R^1 represents Null,





R_2 represents



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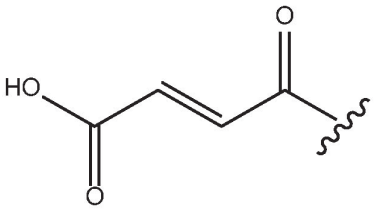

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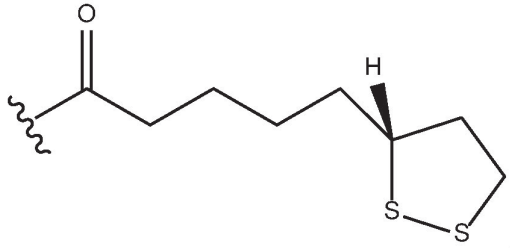

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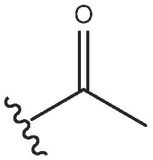

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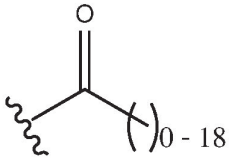

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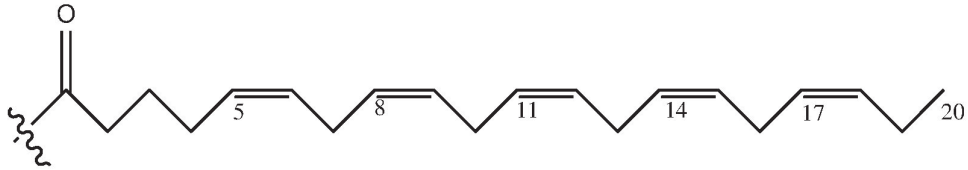

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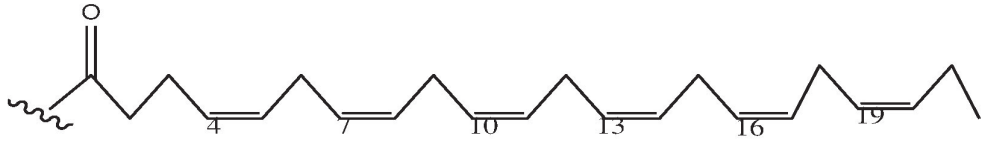

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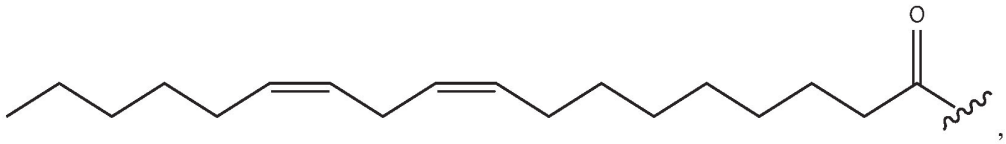

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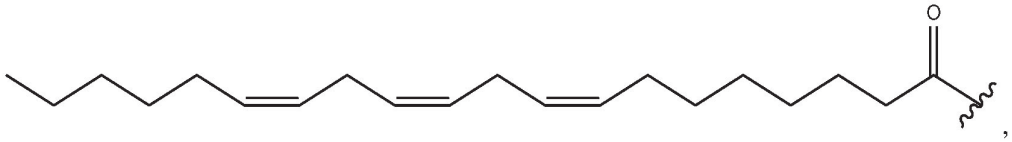

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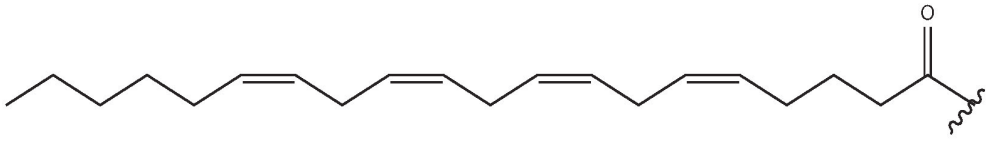

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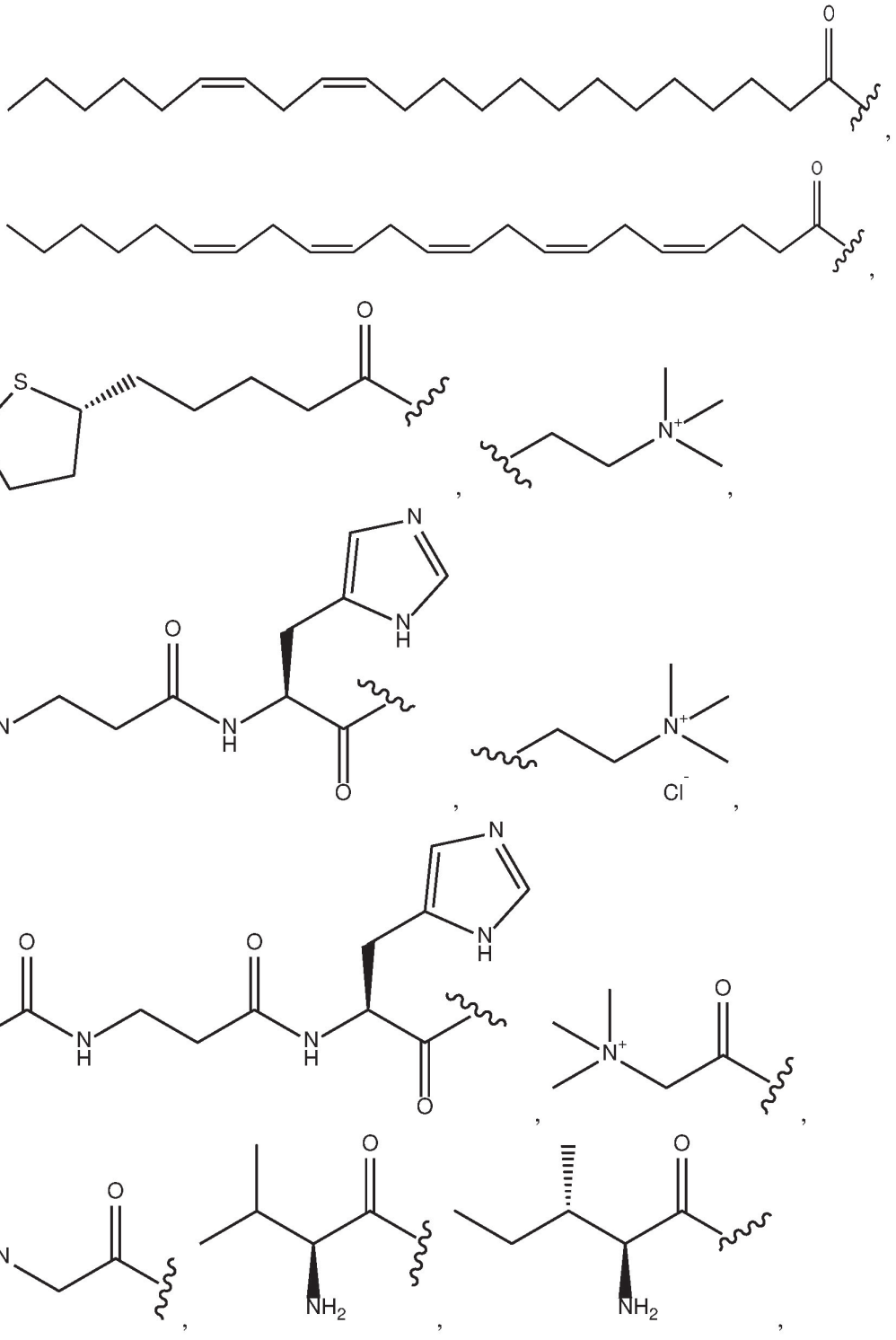

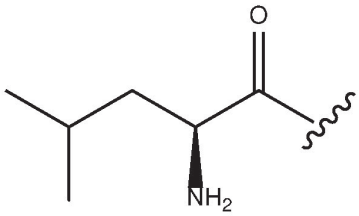

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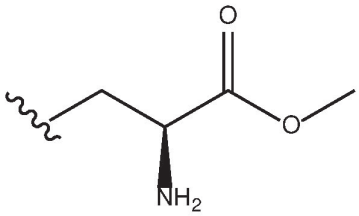

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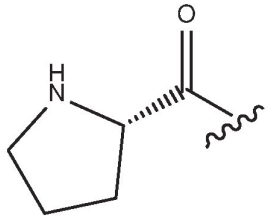

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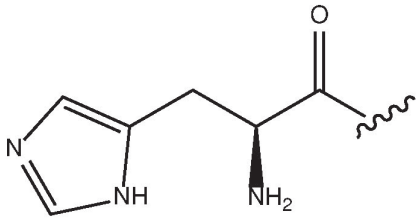

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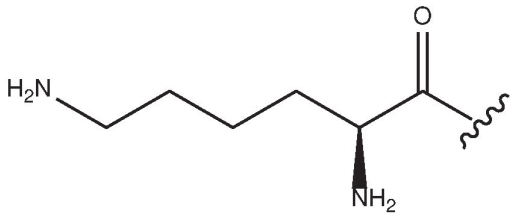

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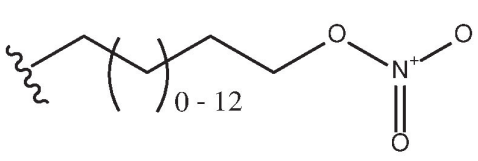

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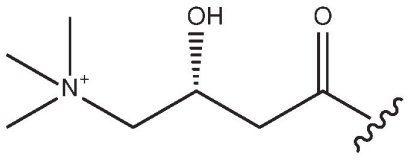
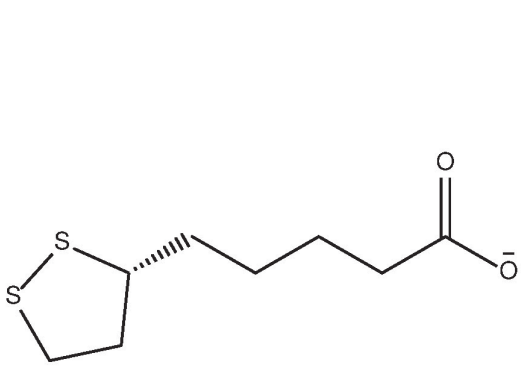


;

RH represents



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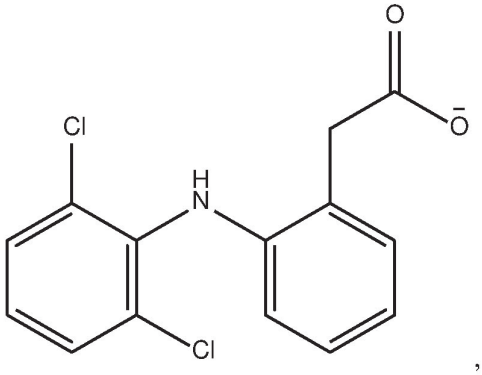

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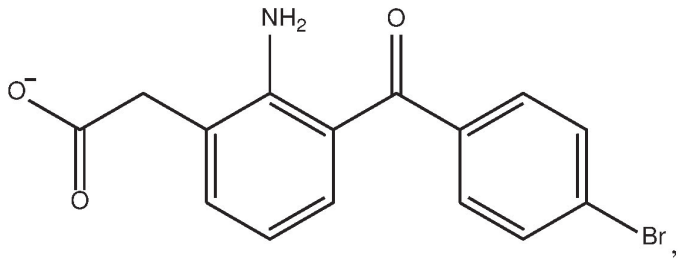

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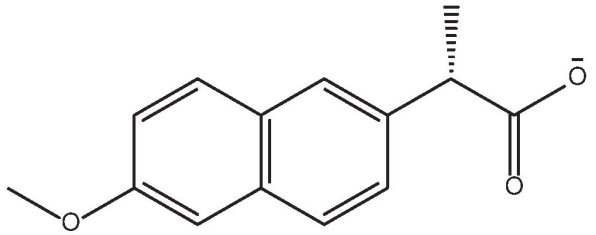

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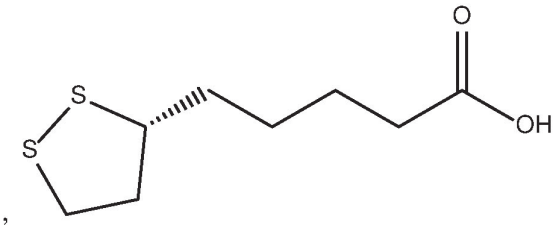

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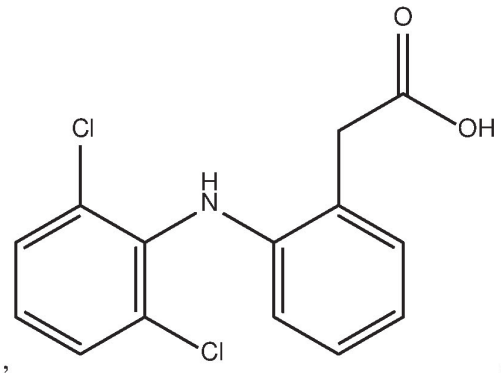

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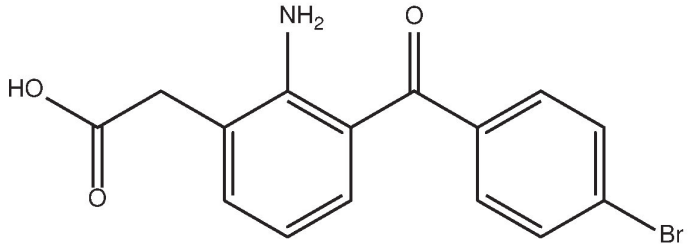
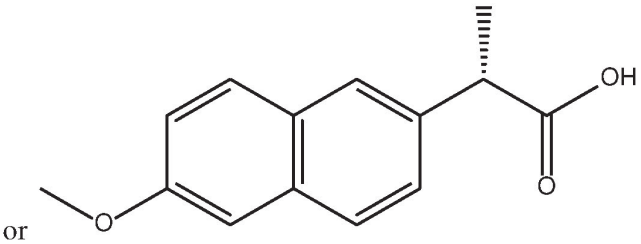
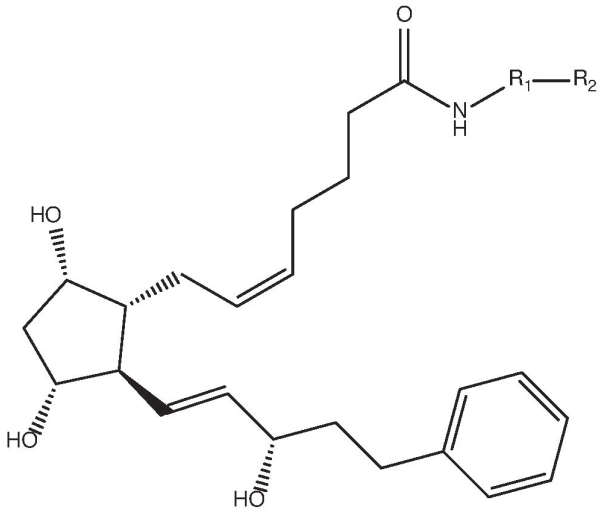




or .

11. A compound of formula XI

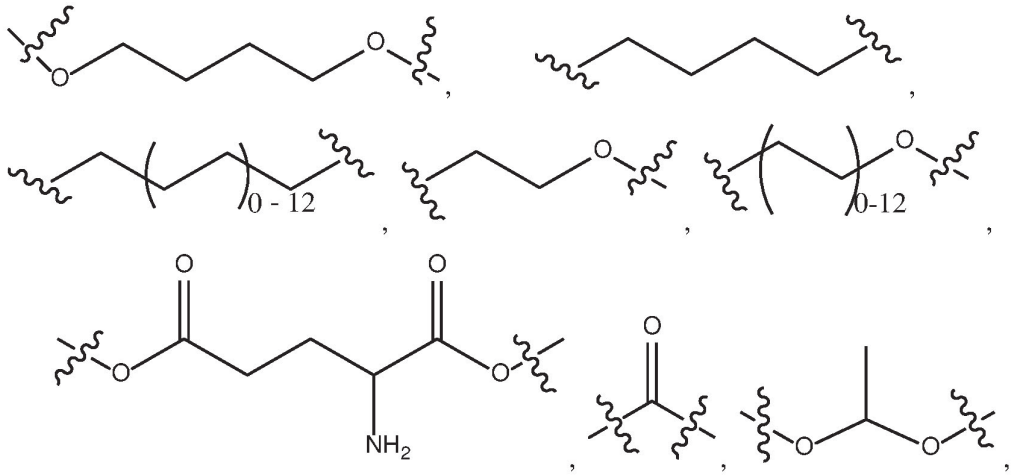


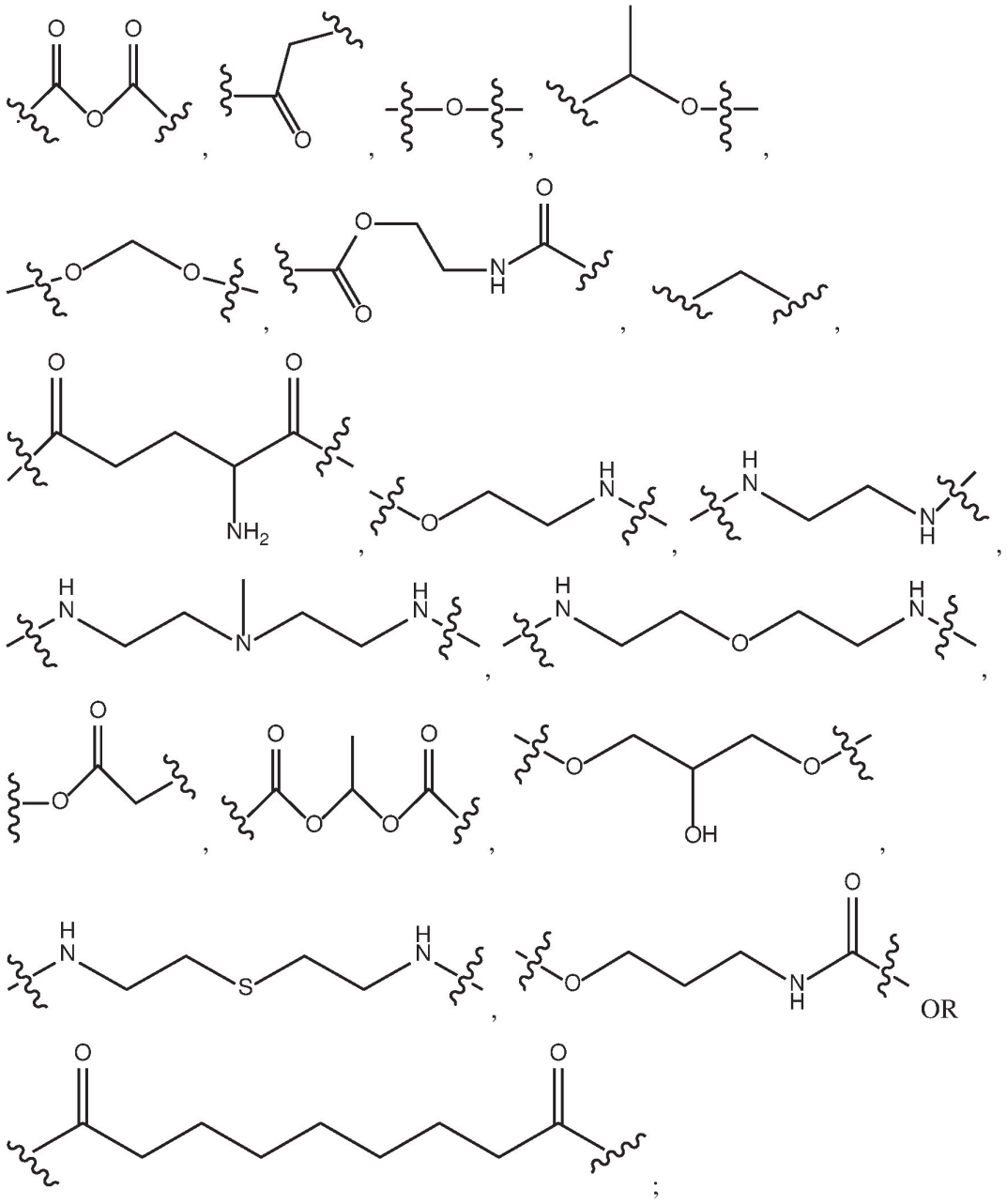
Formula XI

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

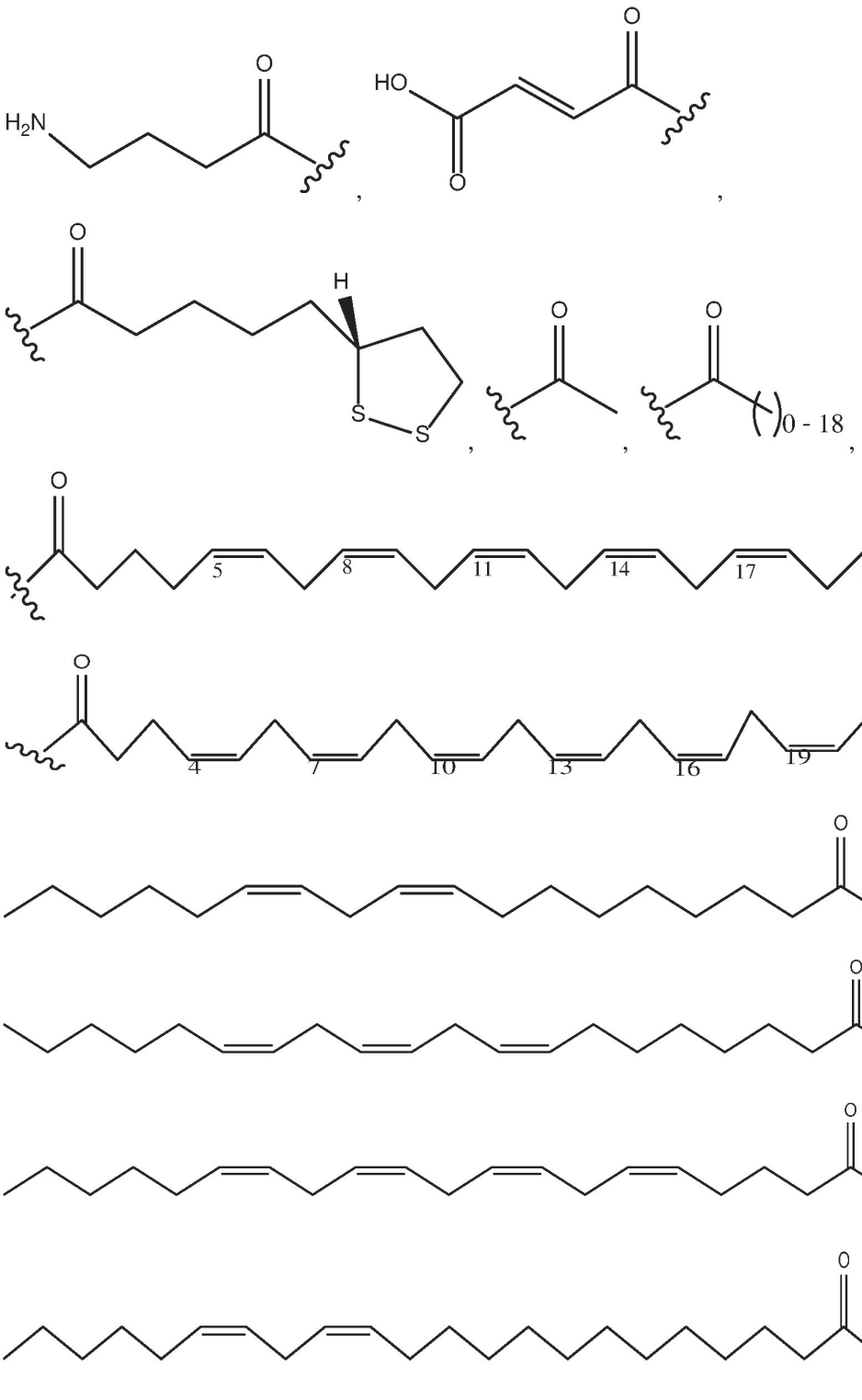
wherein,

R^1 represents Null,





R_2 represents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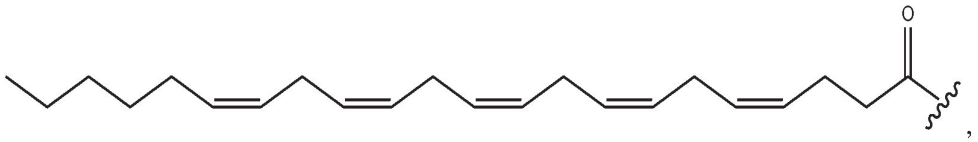
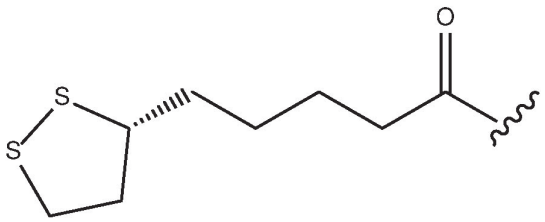
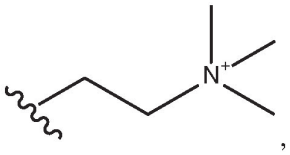
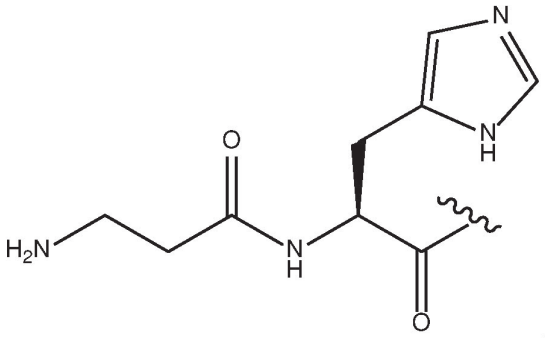
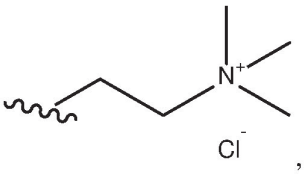
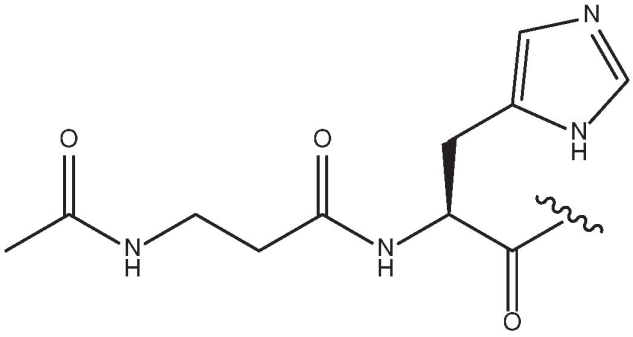
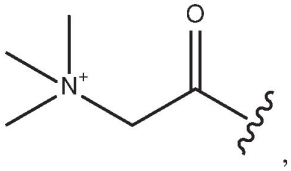
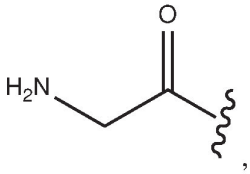
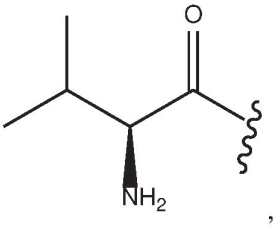
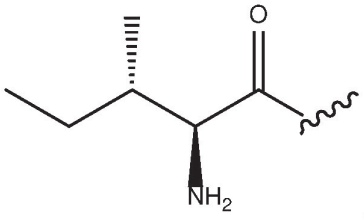
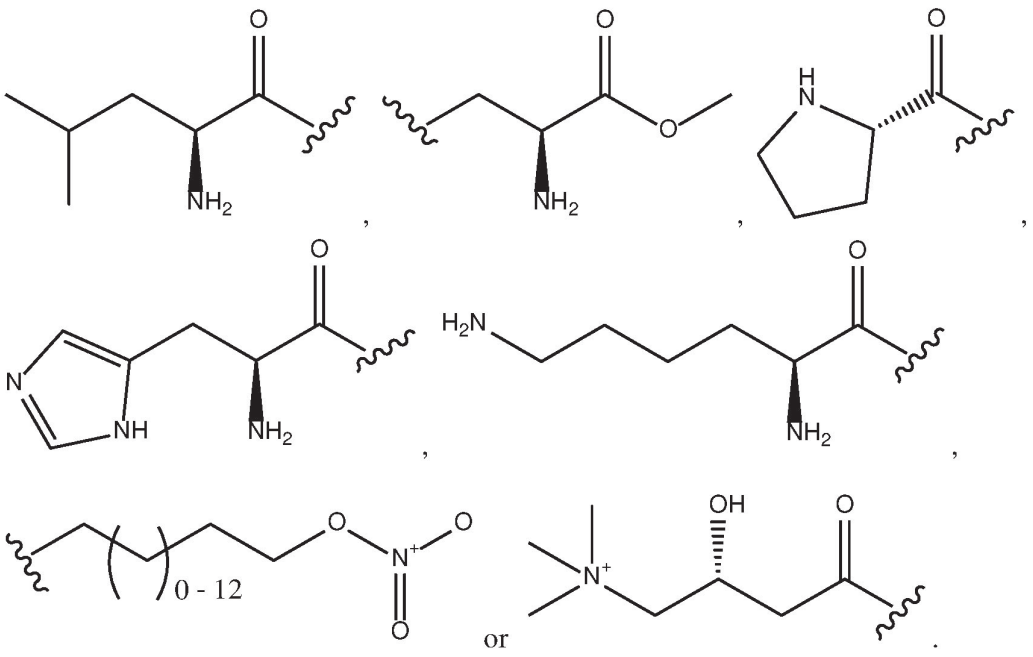
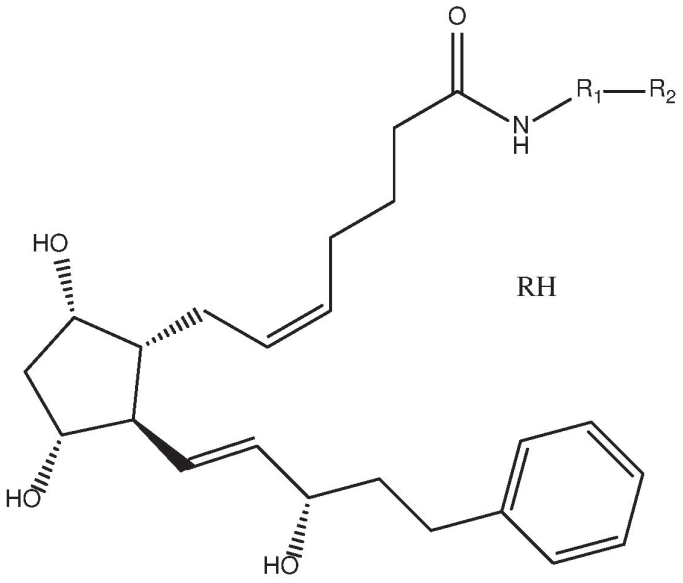













12. A compound of formula XII

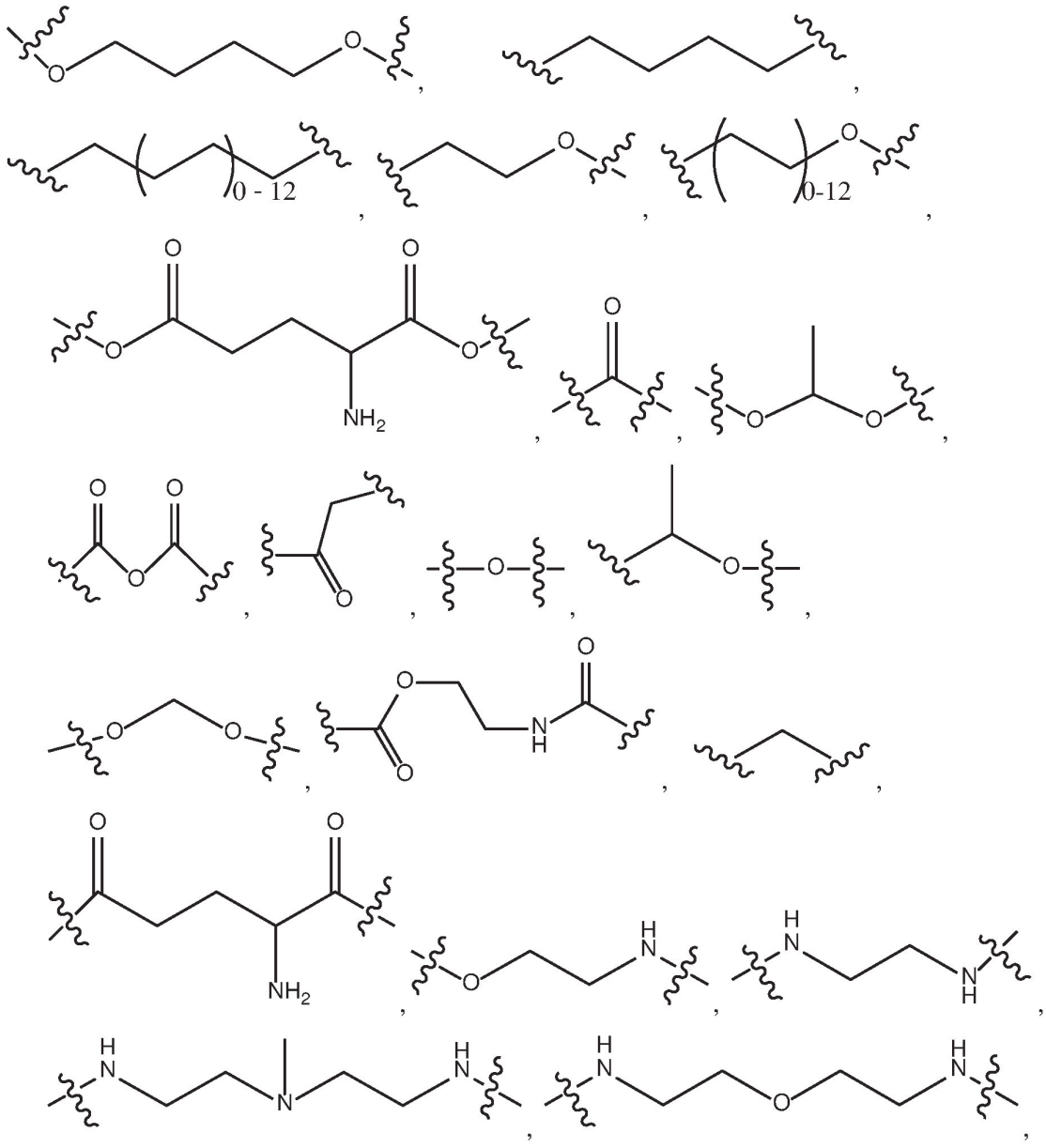


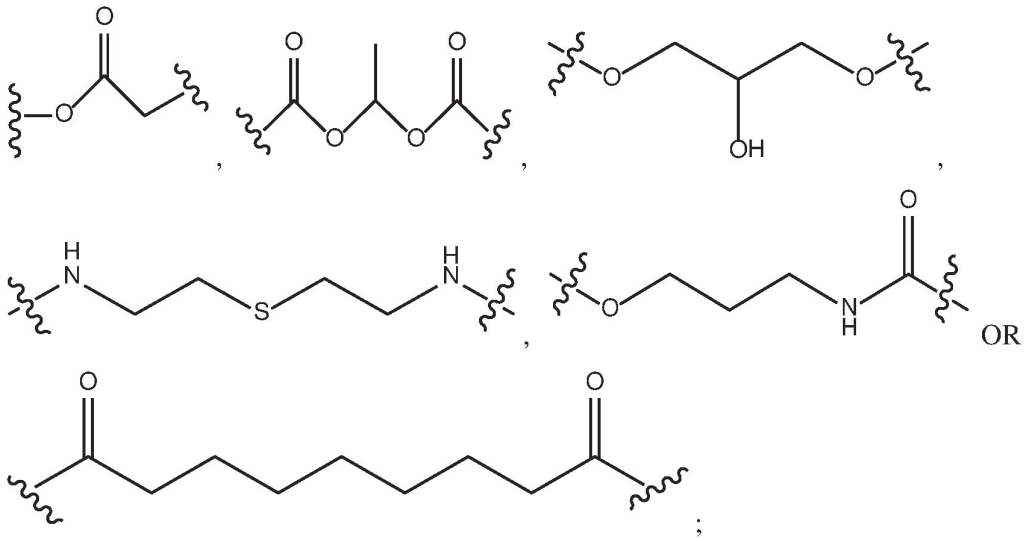
Formula XII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

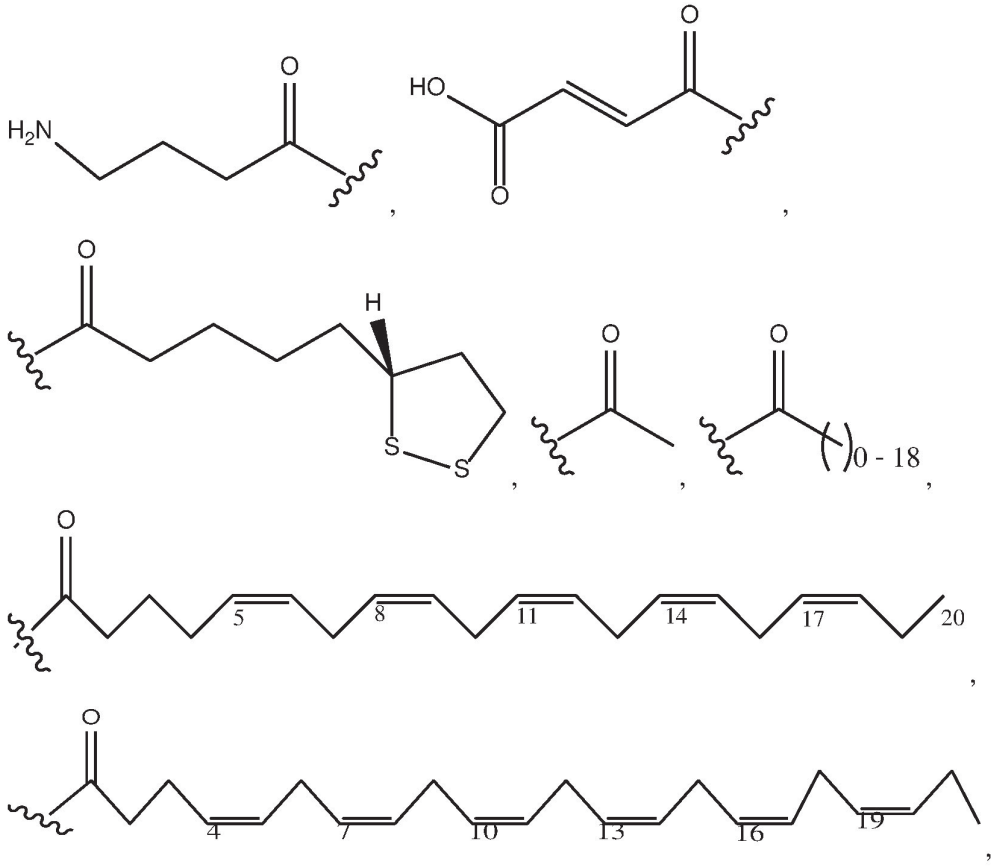
wherein,

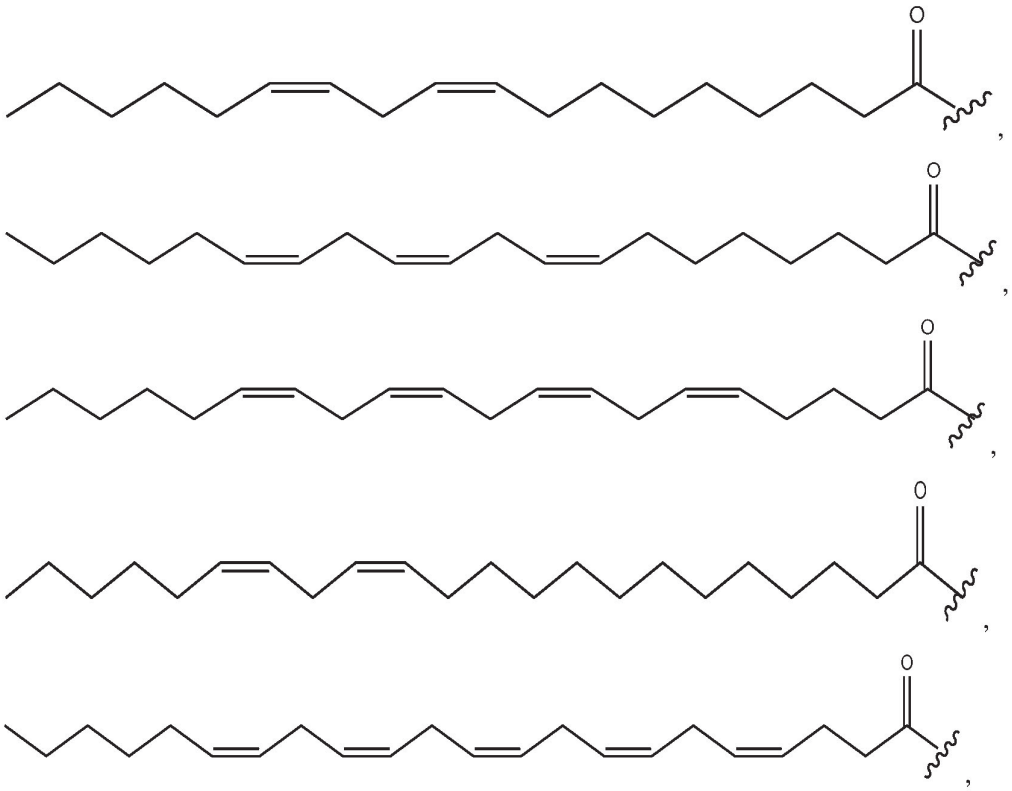
R^1 represents Null,

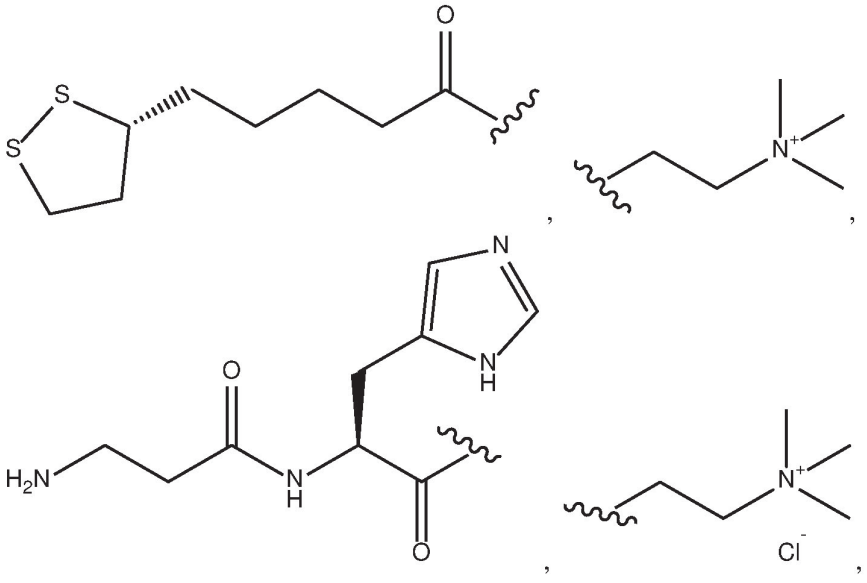


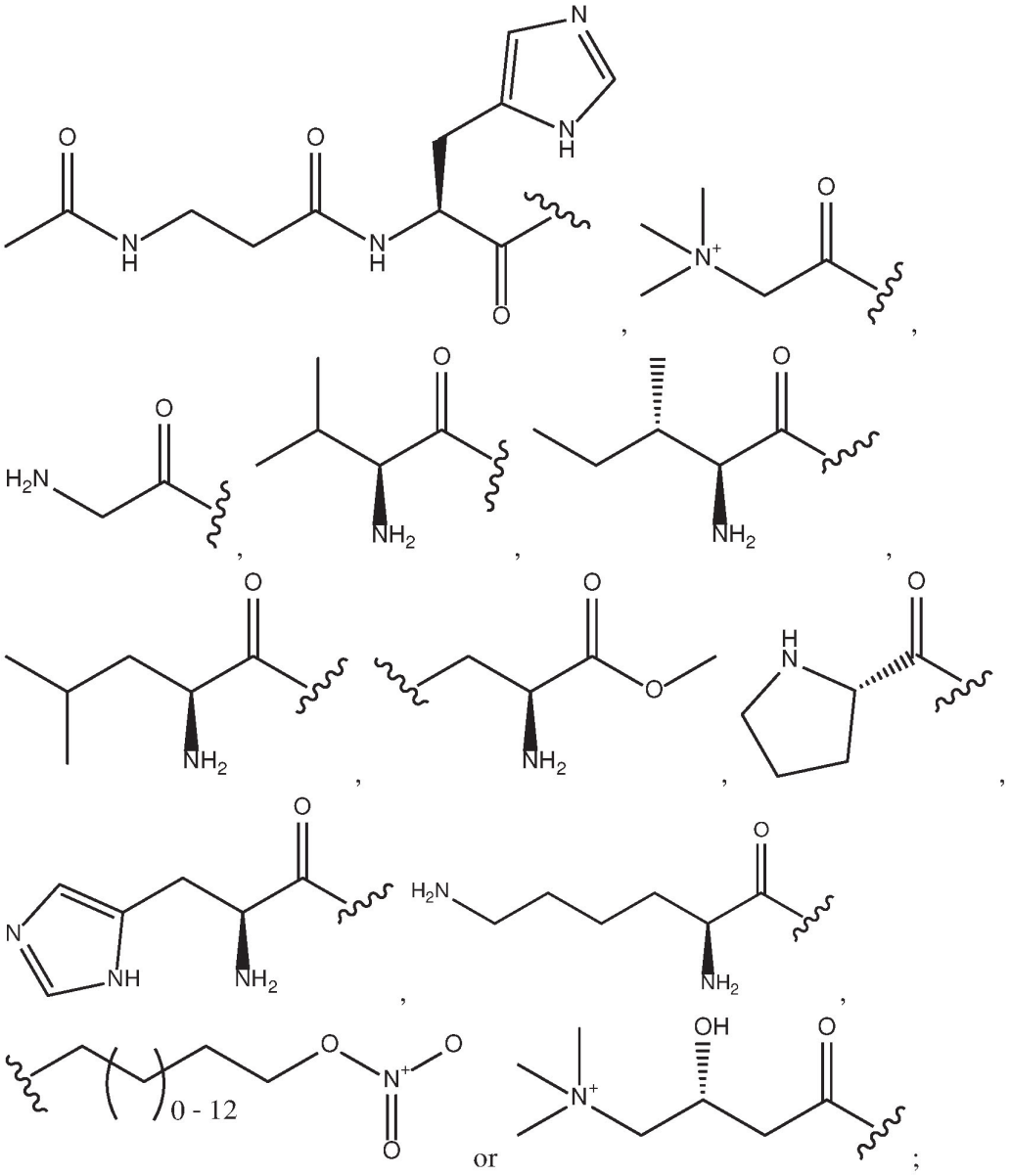


R_2 represents

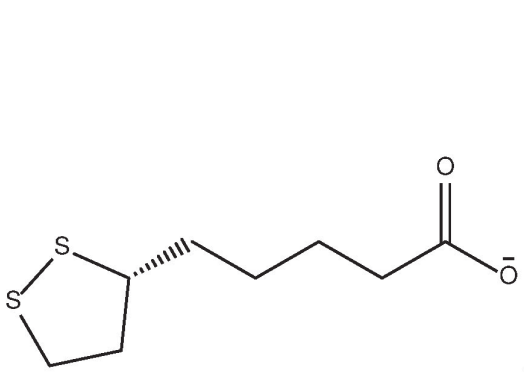
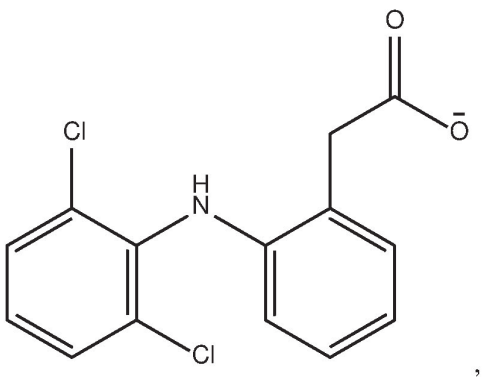
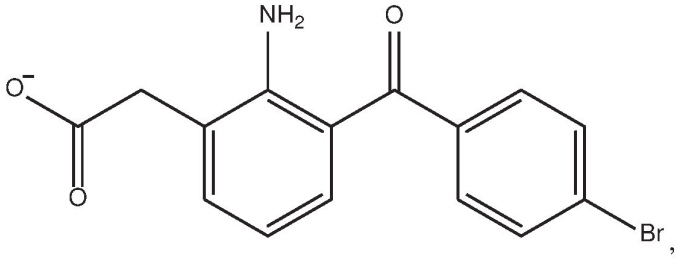
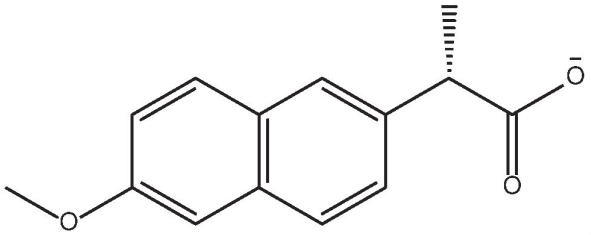
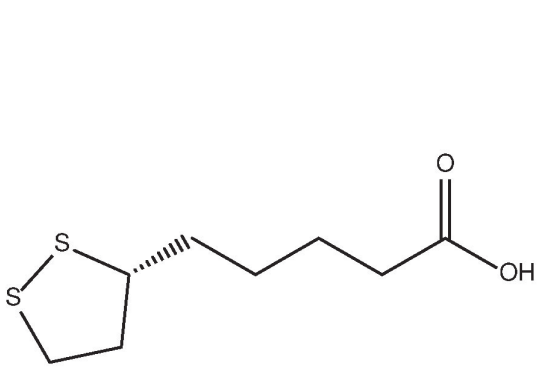
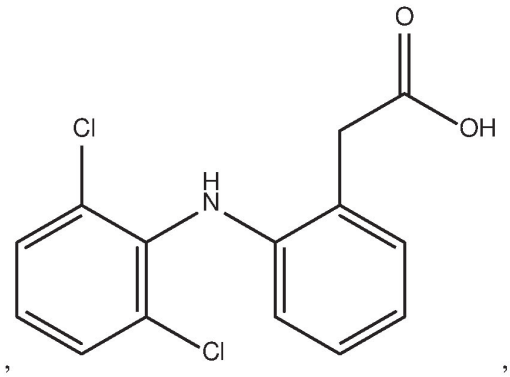


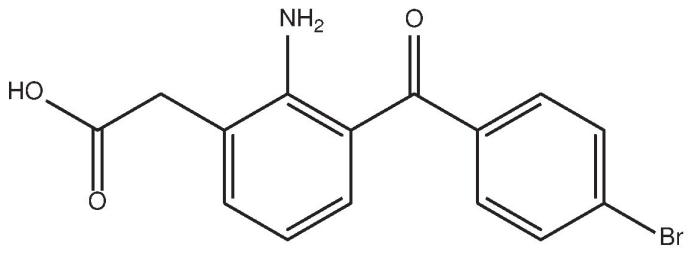


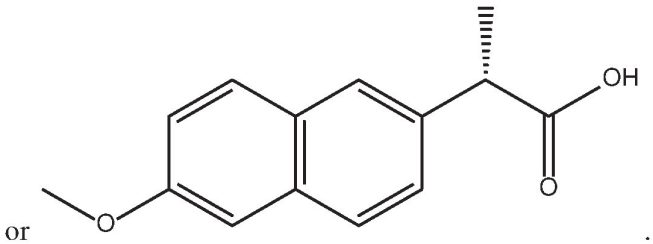




RH represents

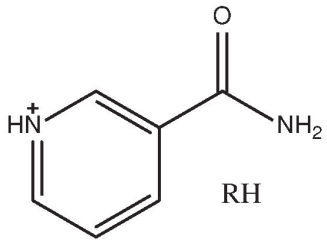











or .

13. A compound of formula XIII

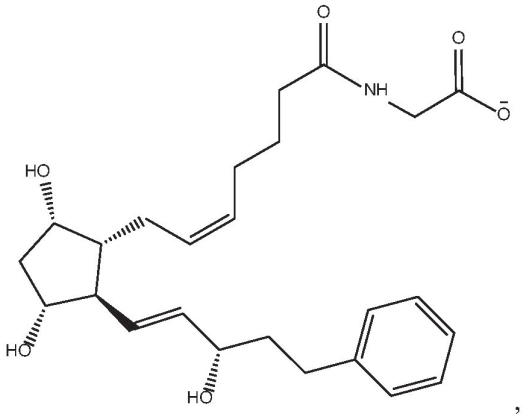


Formula XIII

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

RH independently represents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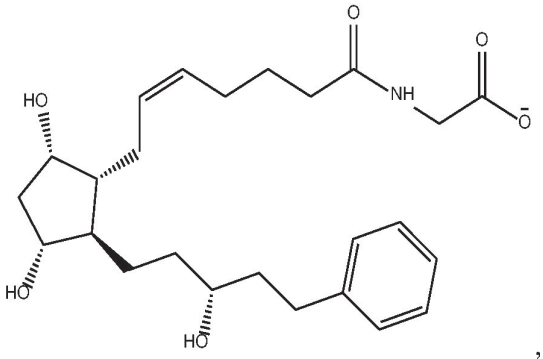
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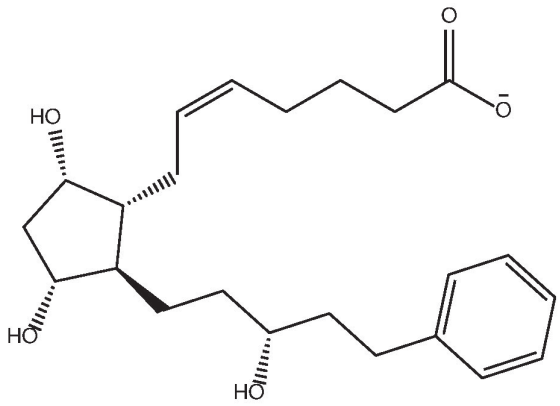
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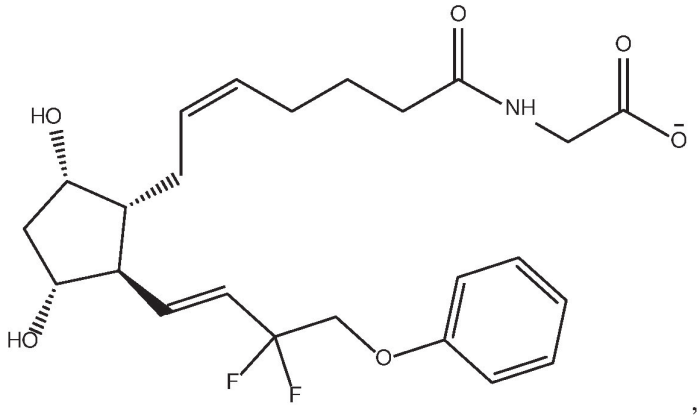
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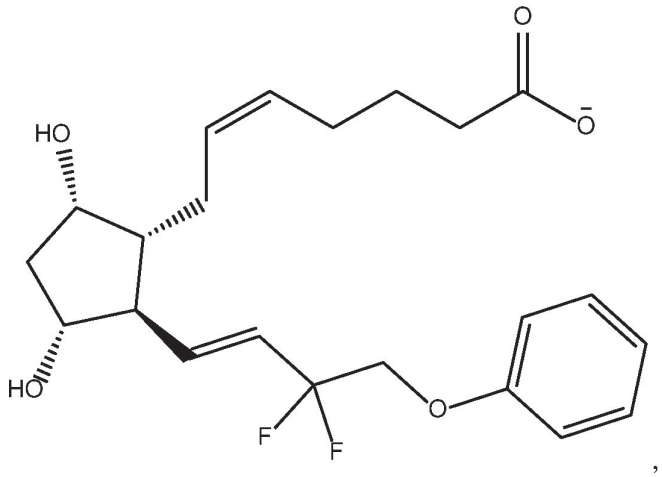

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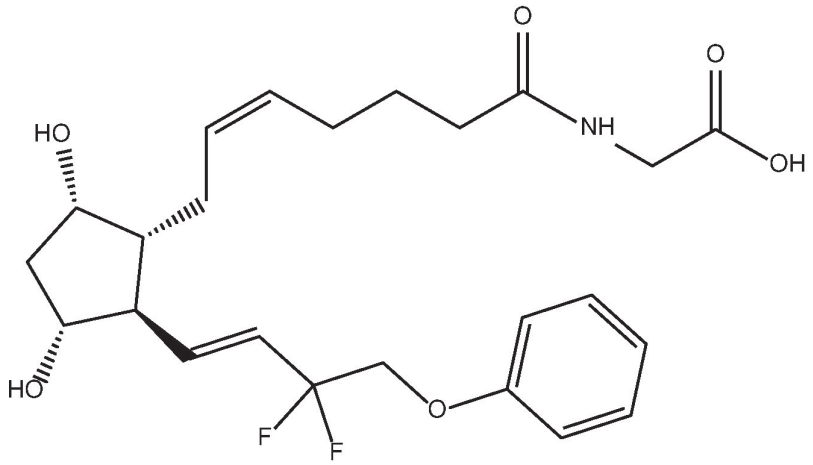
OR



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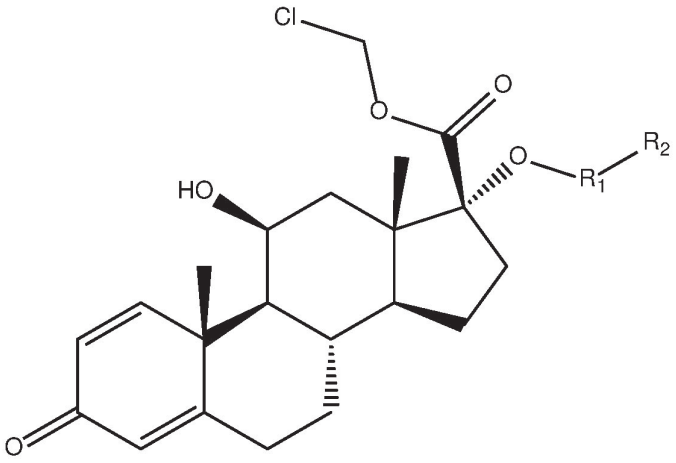
14. A compound of formula XIV



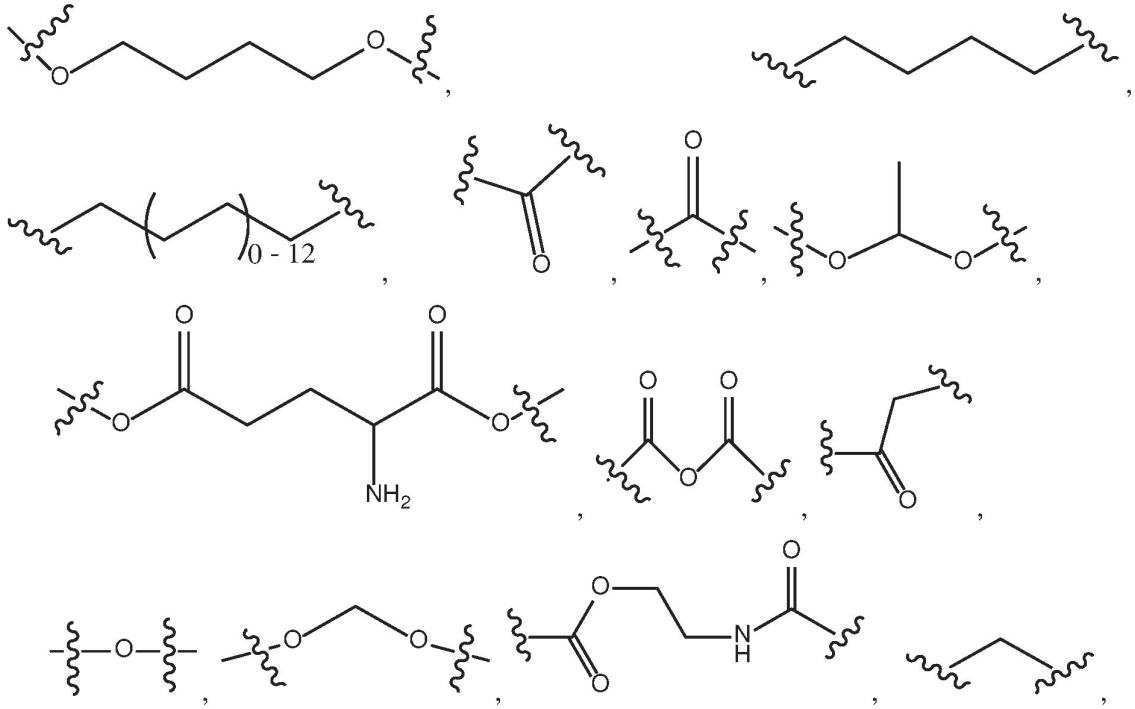
RH

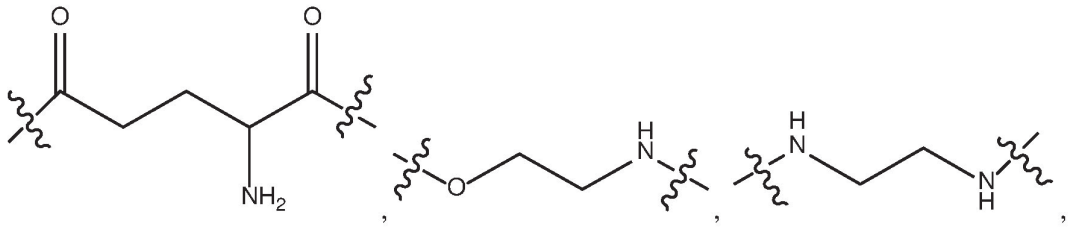
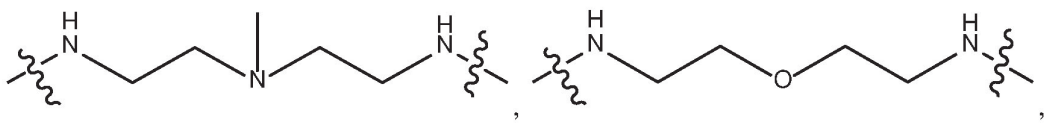
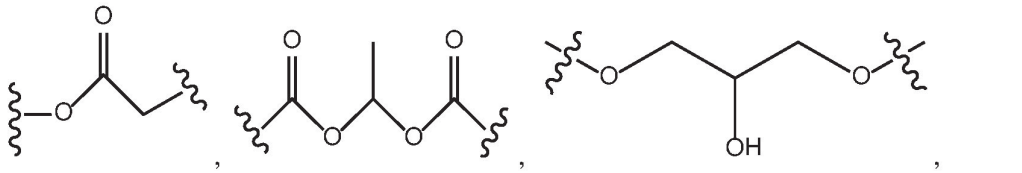
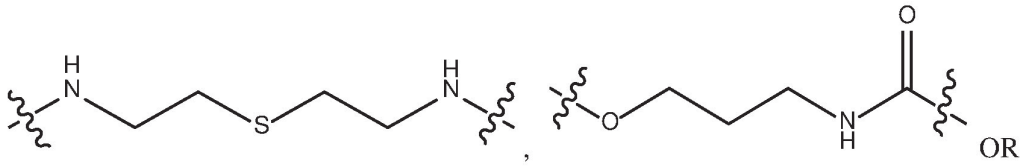
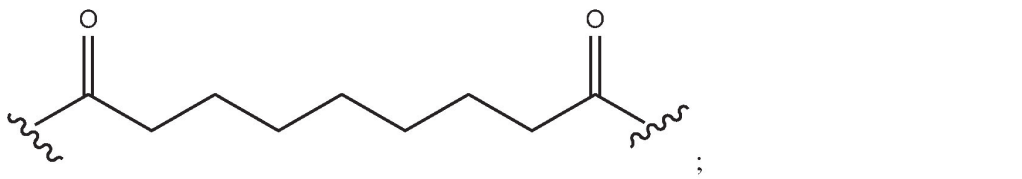
Formula XIV

and pharmaceutically acceptable hydrates, solvates, enantiomers, and stereoisomers thereof; wherein,

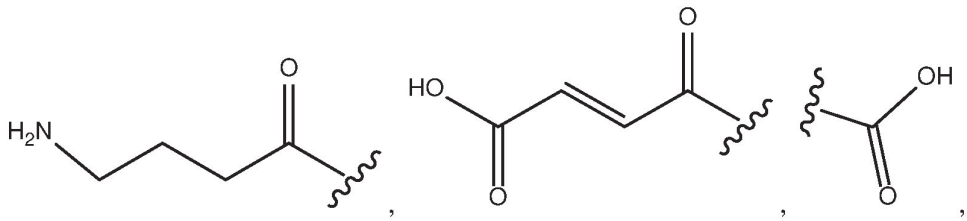
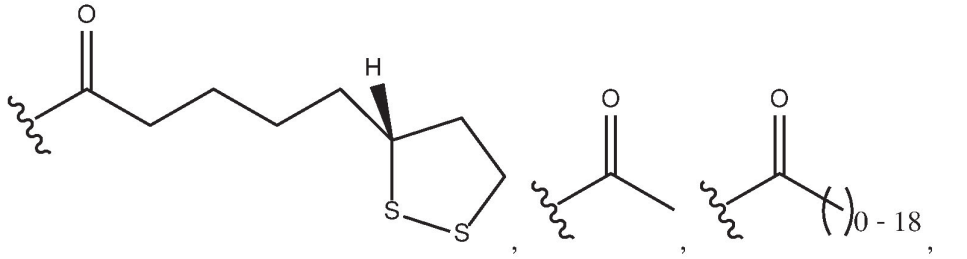
R^1 independently represents

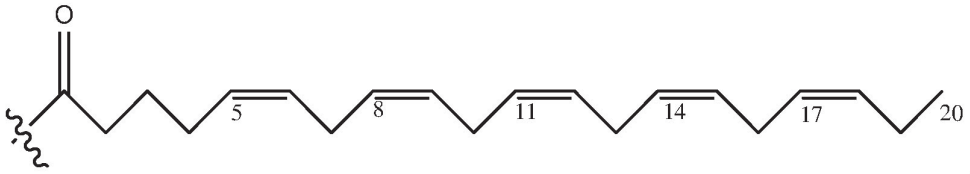
NULL,



R^2 independently represents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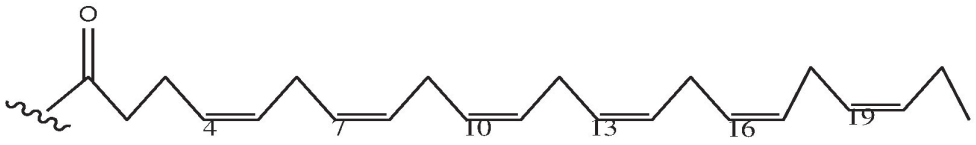
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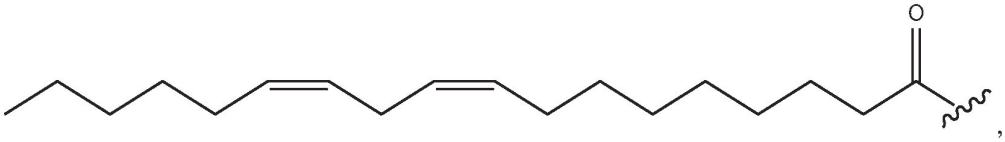
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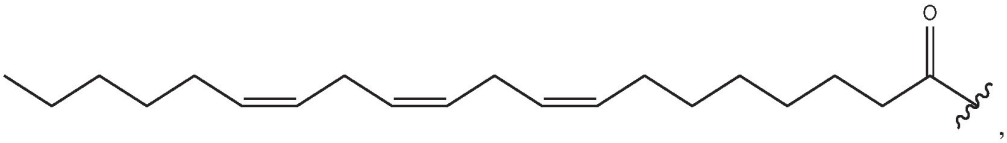
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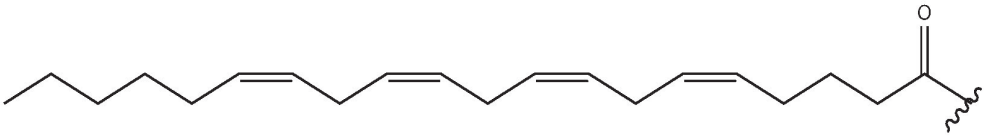
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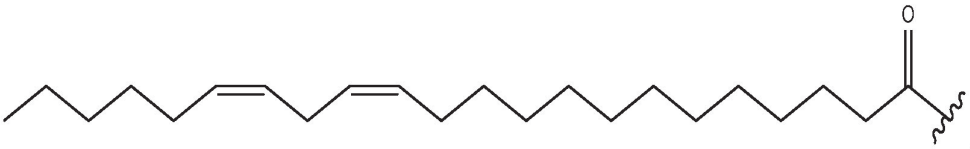
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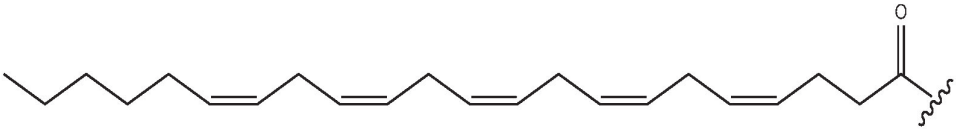
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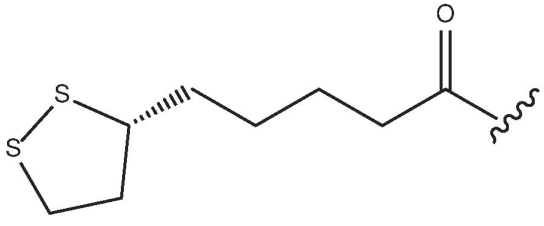
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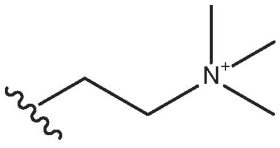
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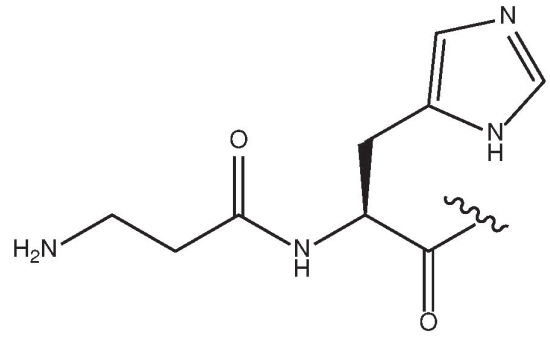
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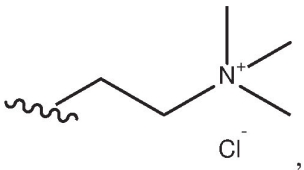
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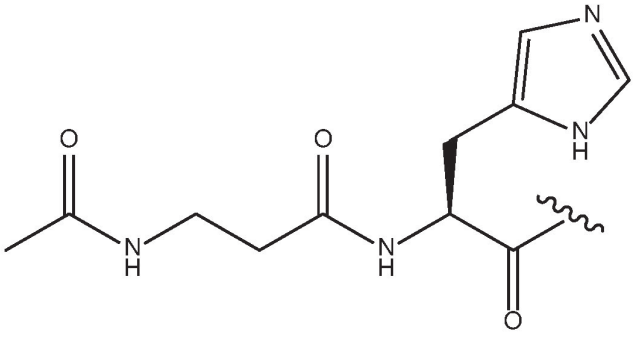
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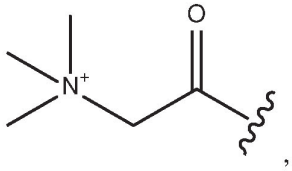
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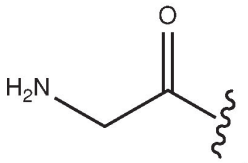
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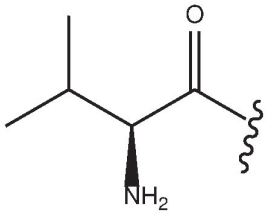
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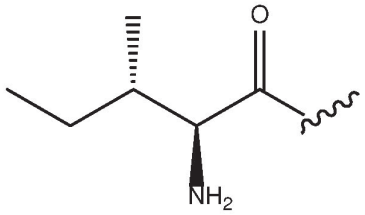
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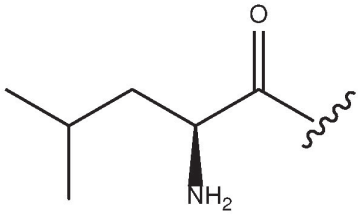
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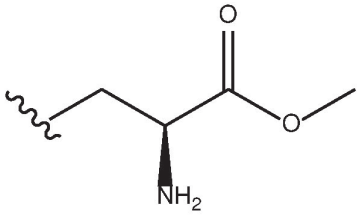
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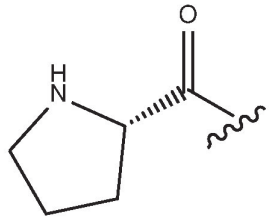
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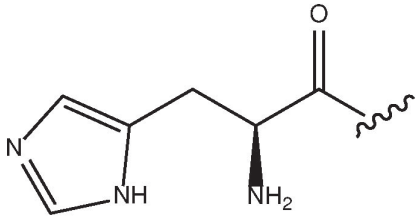
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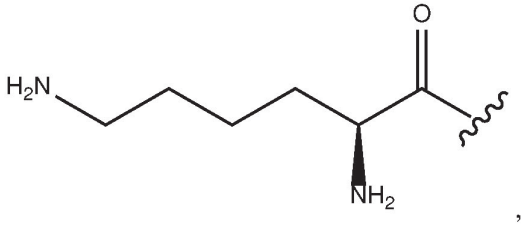
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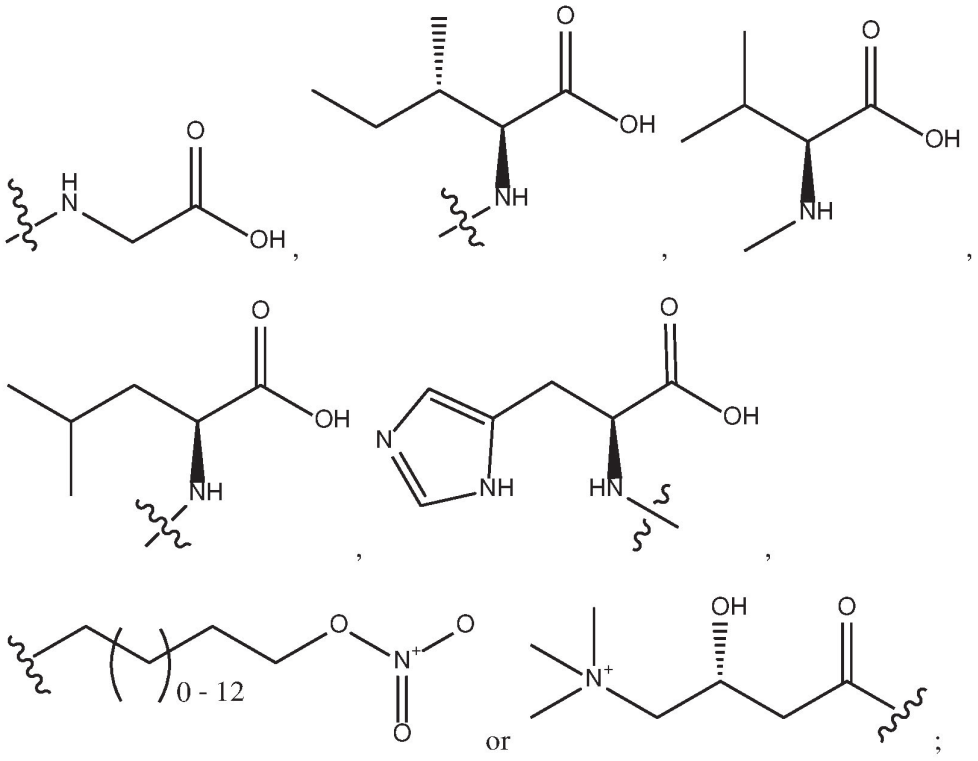

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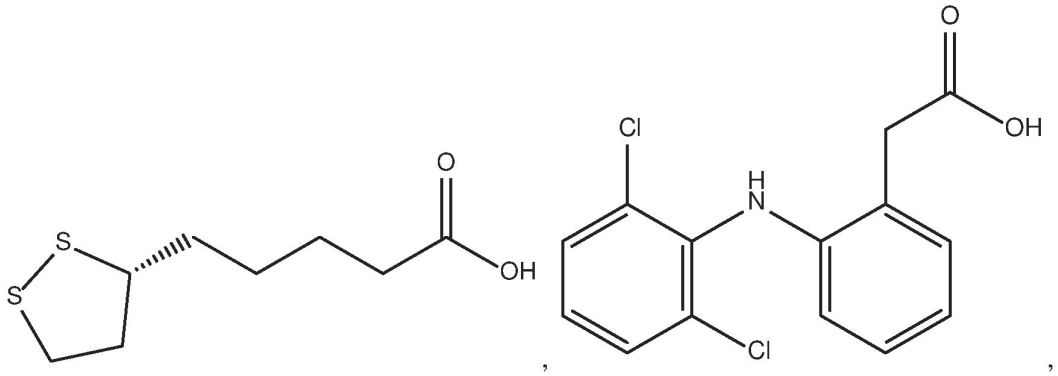

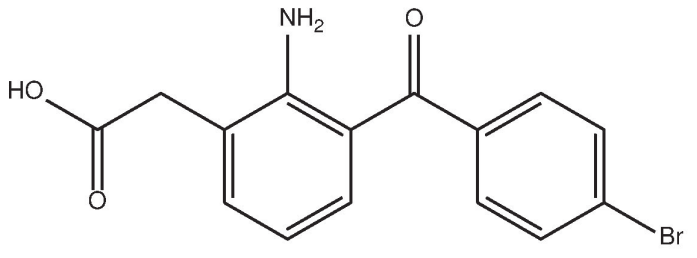

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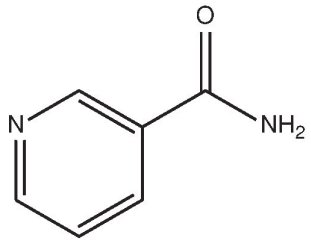

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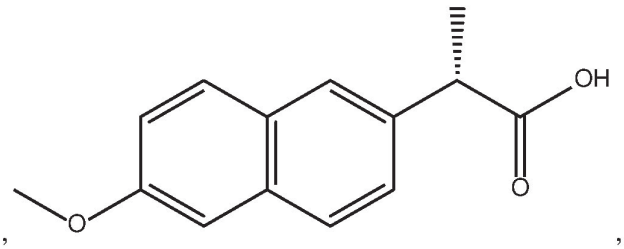

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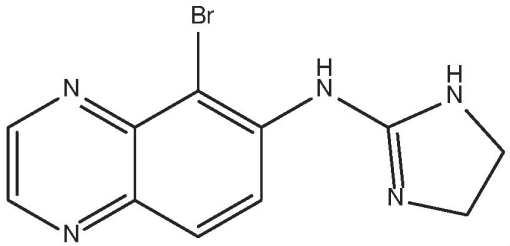
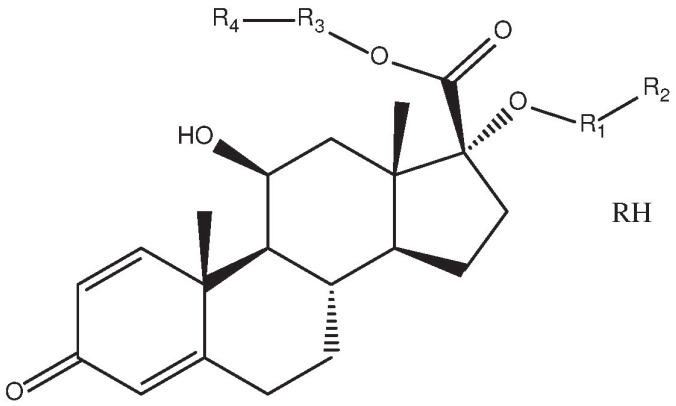


,

caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, acid,

alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

15. A compound of formula XV



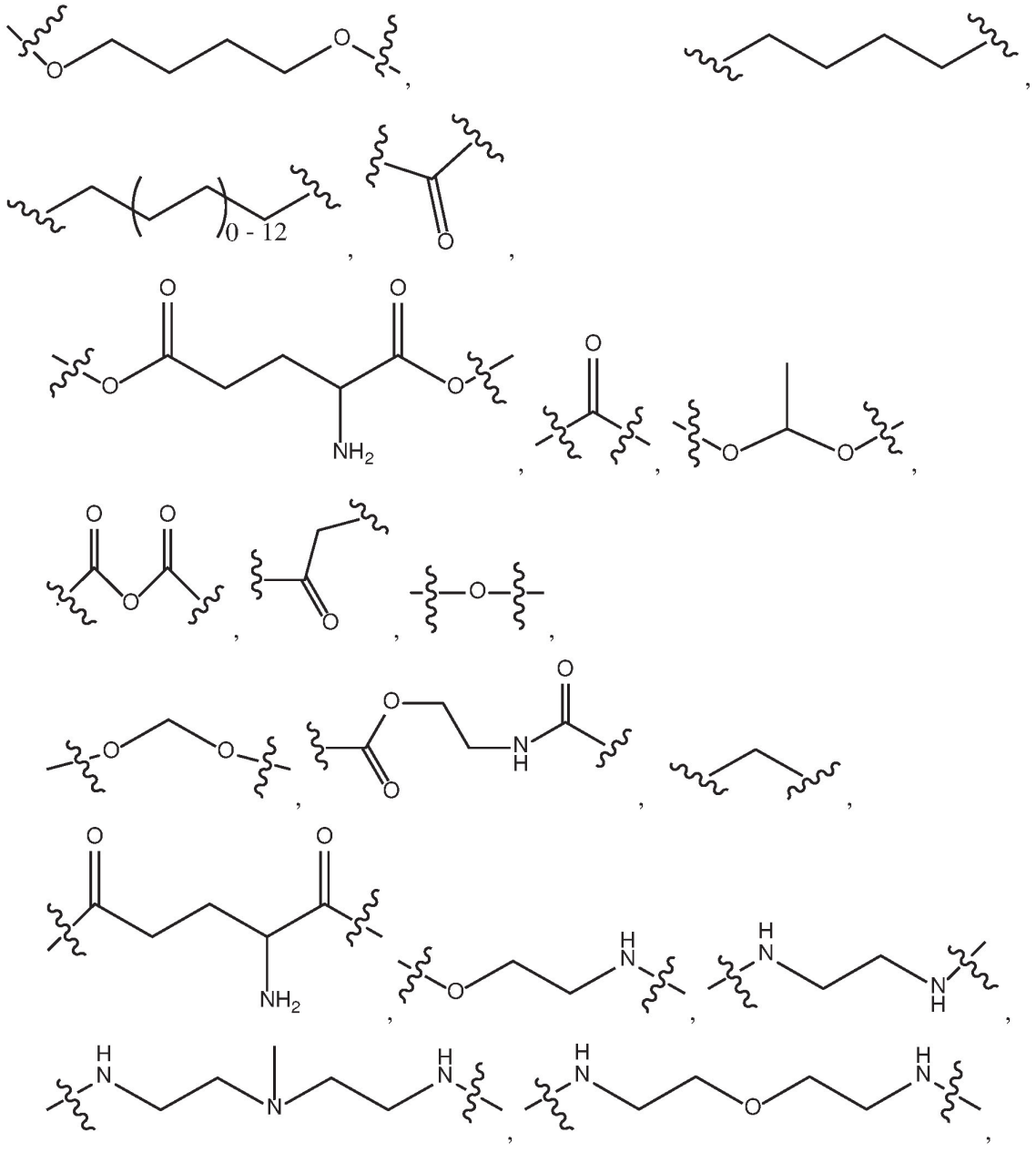
Formula XV

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R^1, R^3 independently represents

NULL,


O
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0 - 12
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NH2
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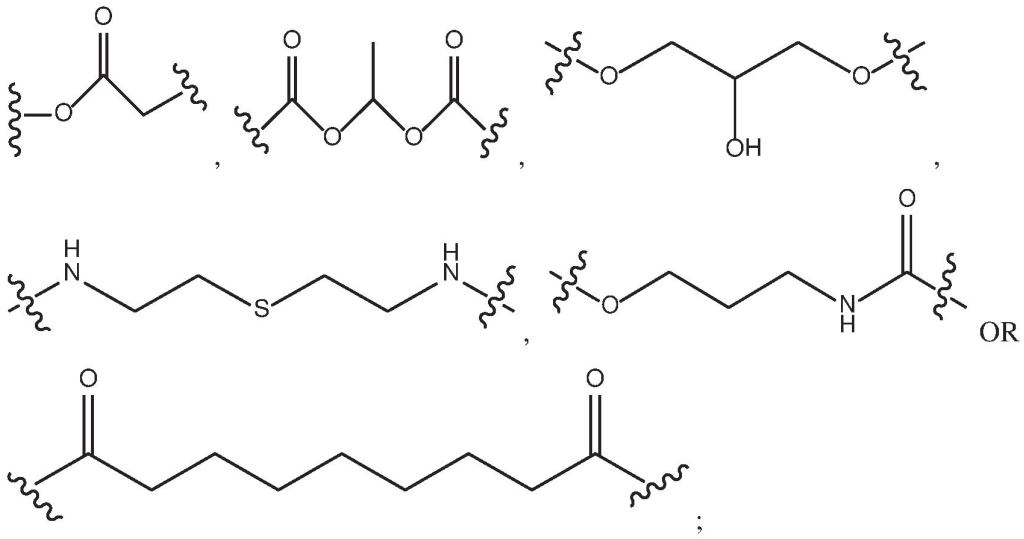
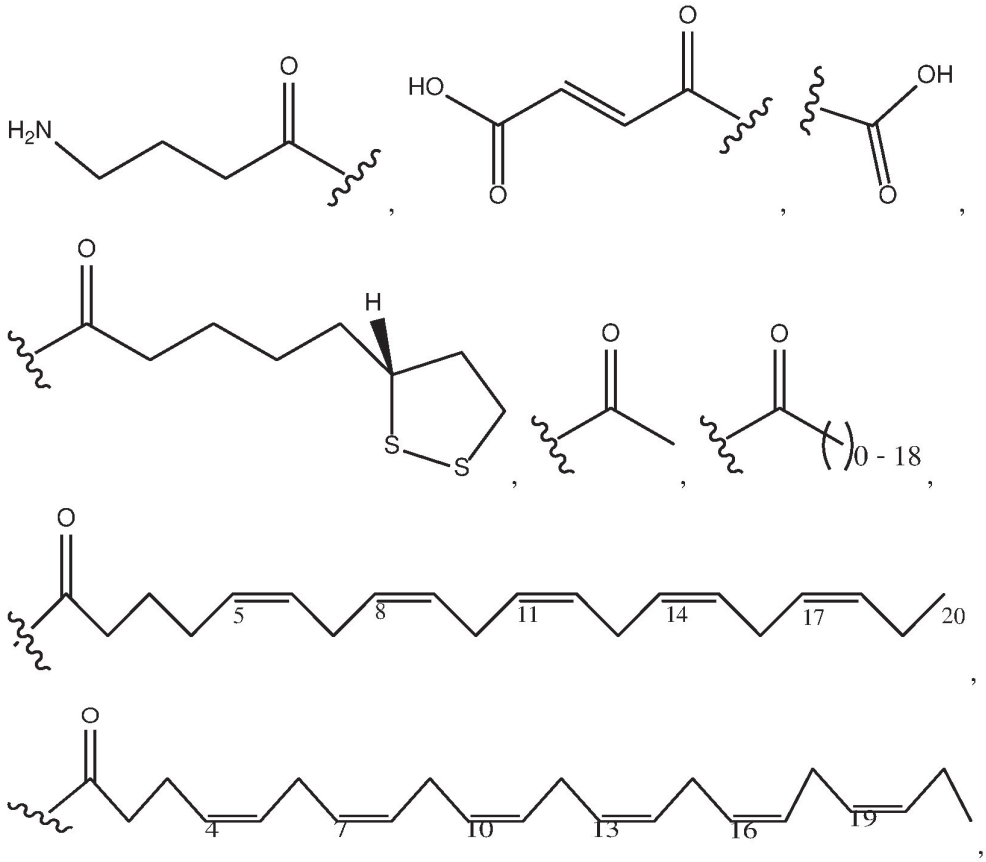
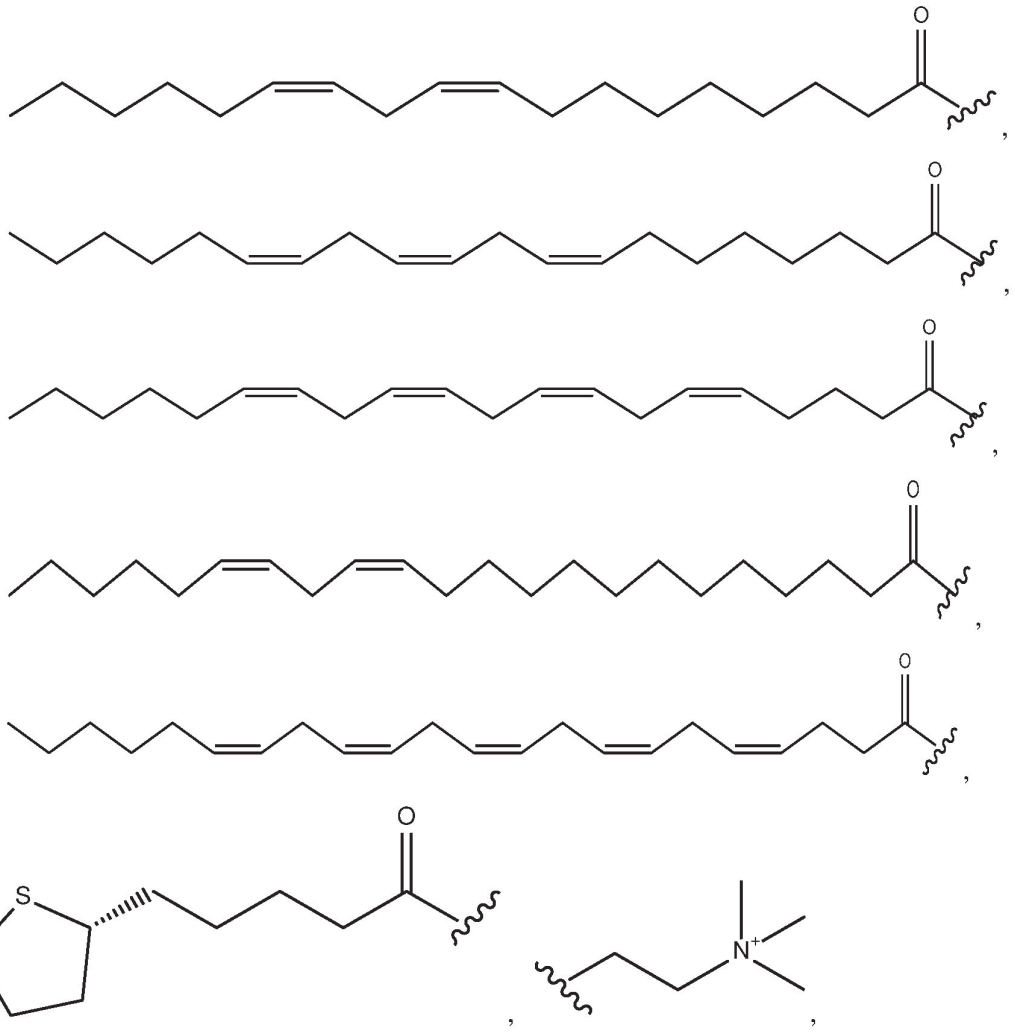


R^2 , R^4 independently represents

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O
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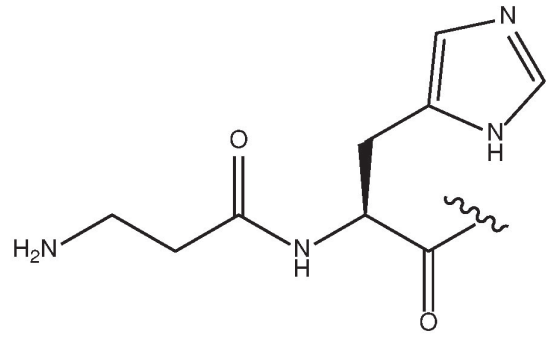
O
O
S
S
N+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N
H
O
H_2N
N
H
O
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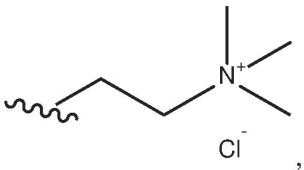
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Cl^-
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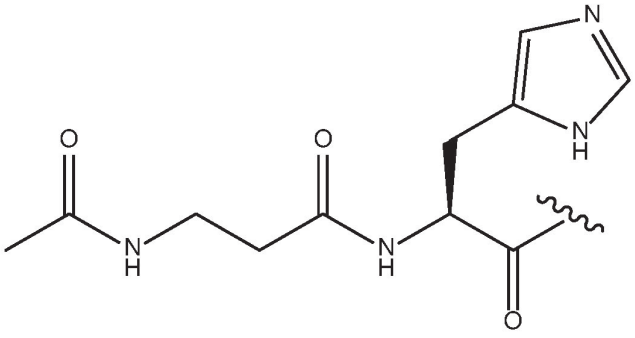
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N
H
O
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O
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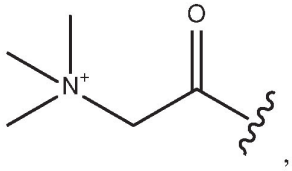
N^+
O
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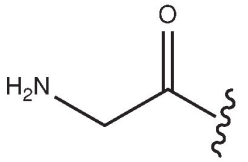
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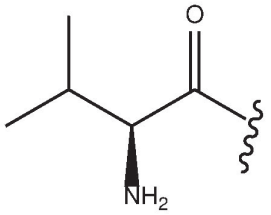
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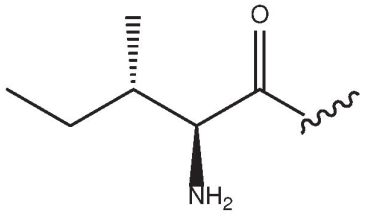
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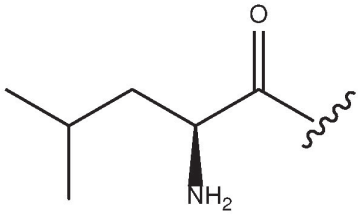
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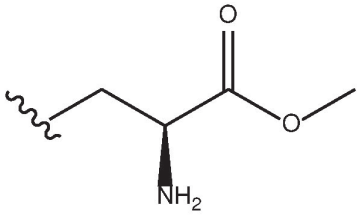
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O
NH_2
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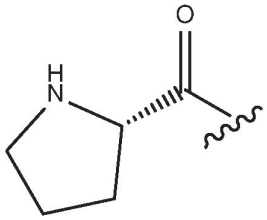
H
N
O
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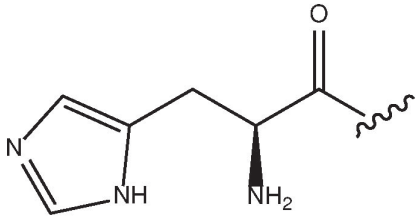
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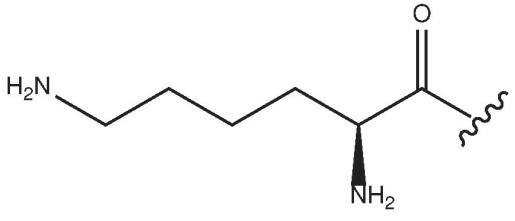
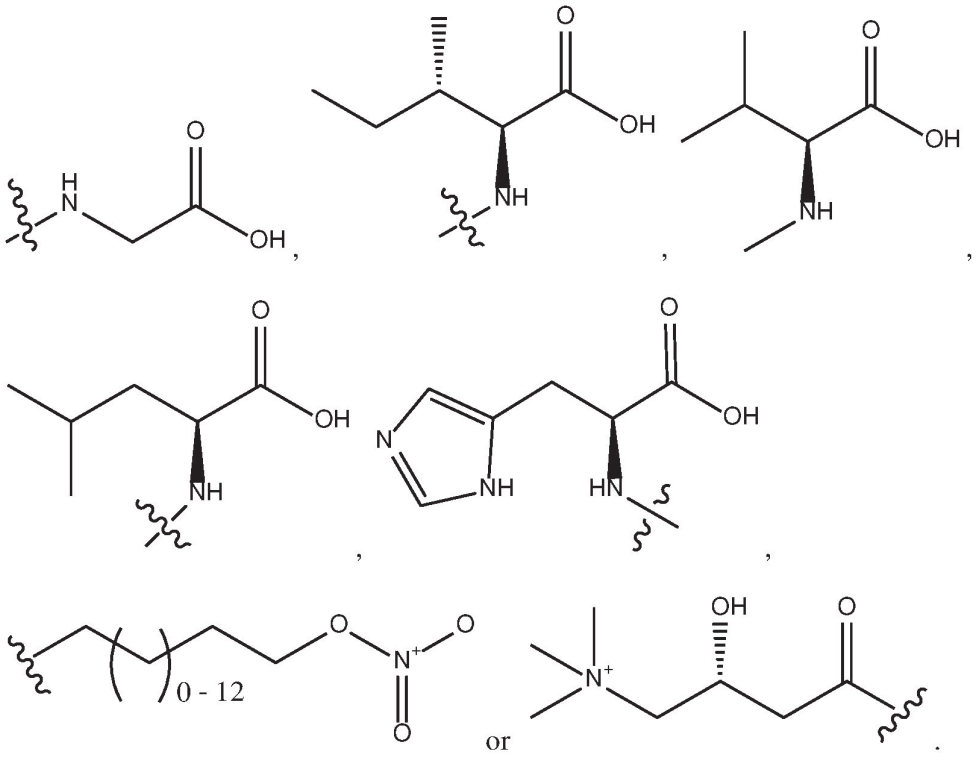
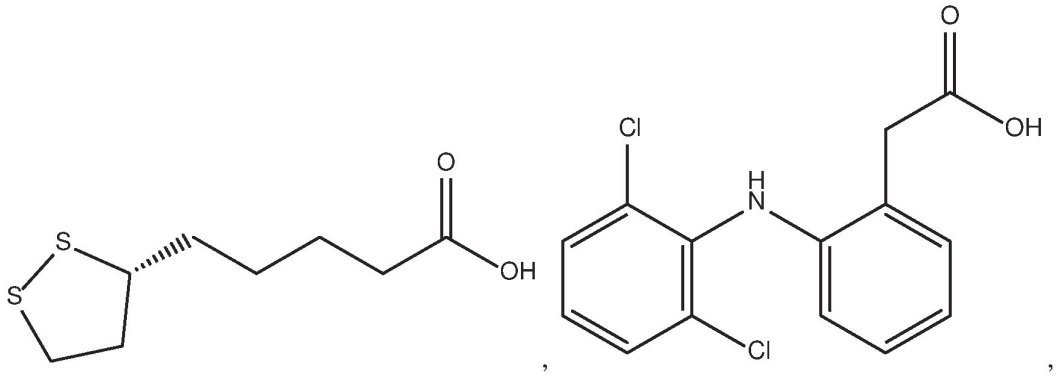
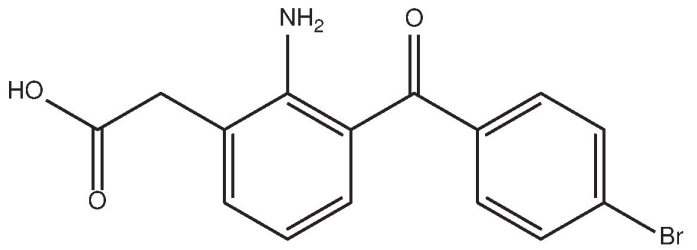
N
NH
NH_2
,

H_2N
O
NH_2
,



RH independently represents

NULL,





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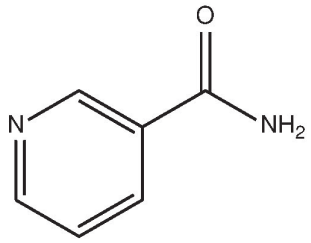

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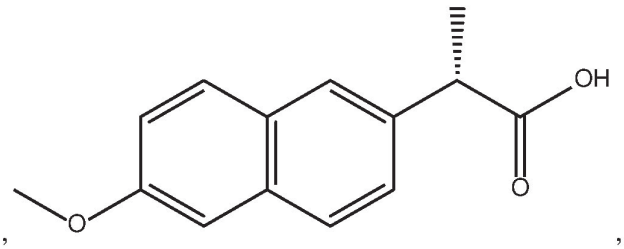

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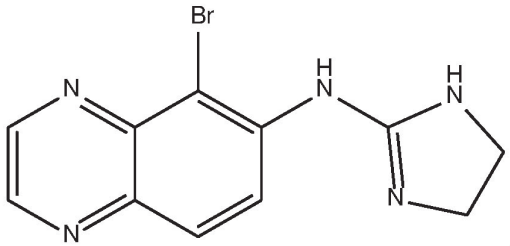
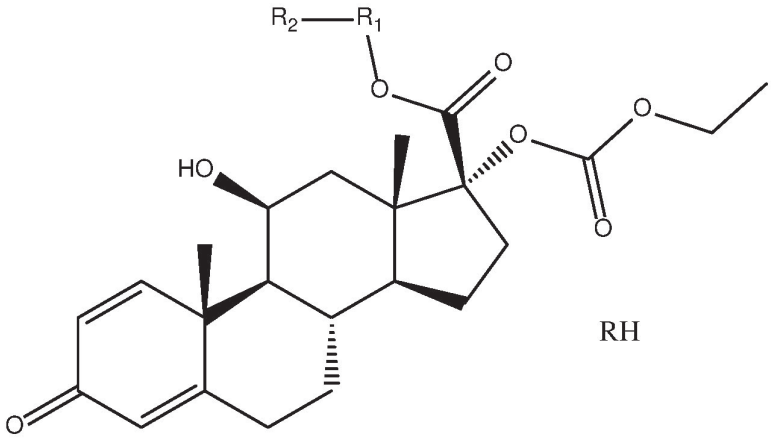


,

caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, lauric

acid, alpha lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

16. A compound of formula XVI



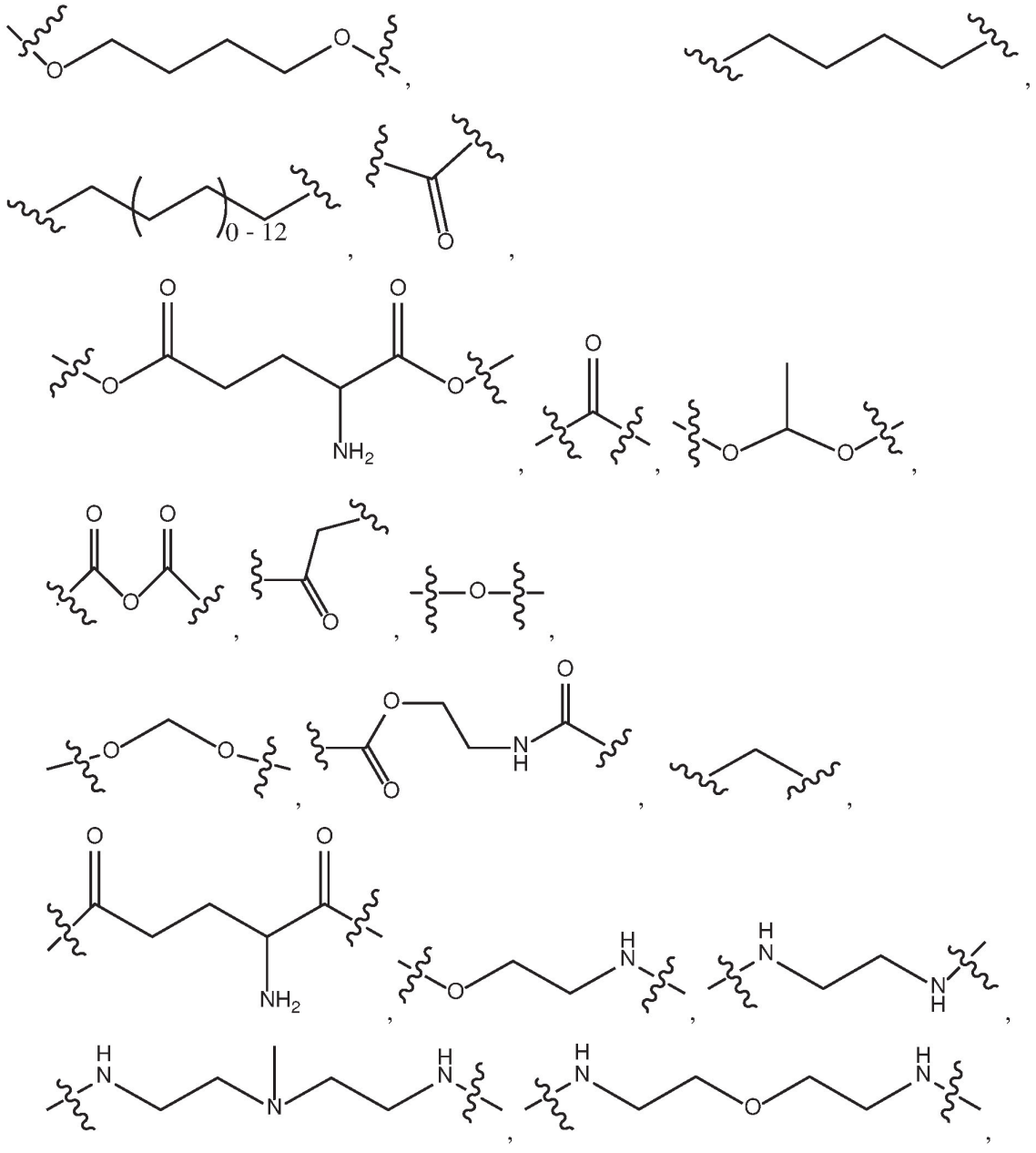
Formula XVI

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R^1 independently represents

NULL,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NH2
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NH2
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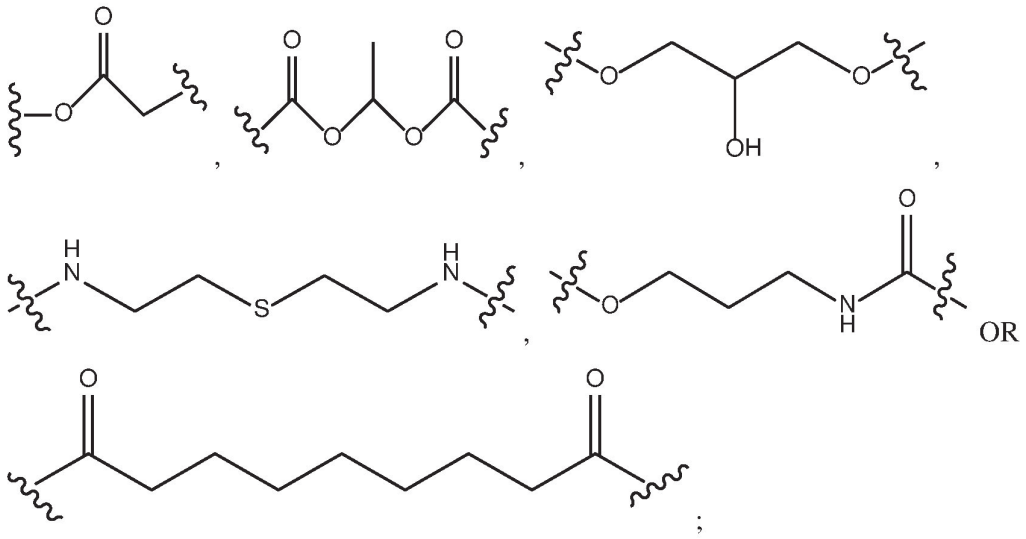
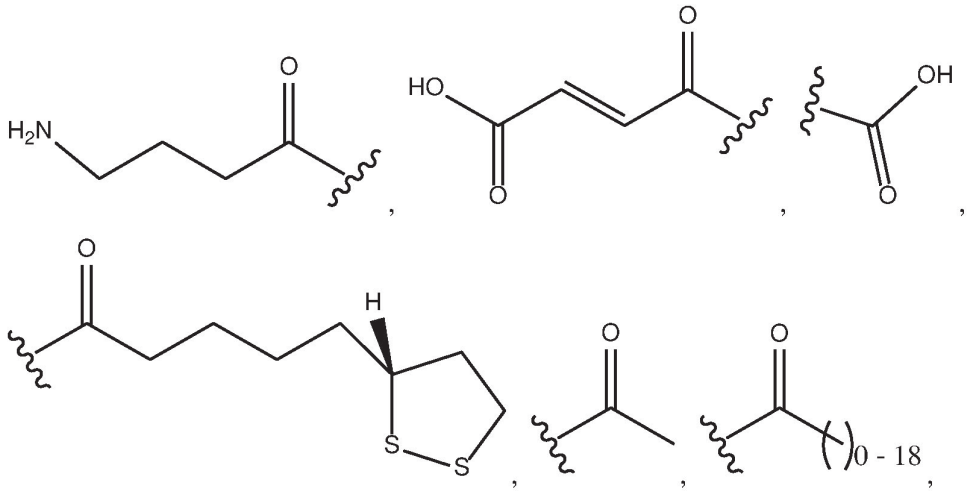
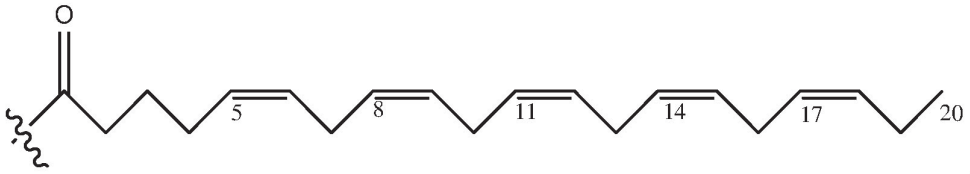


R^2 independently represents

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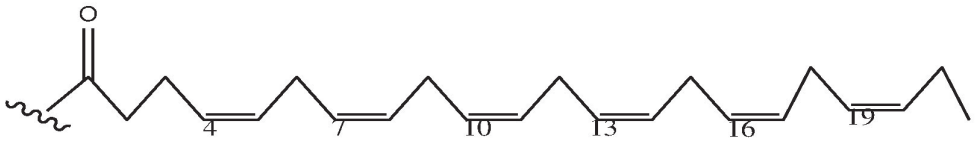
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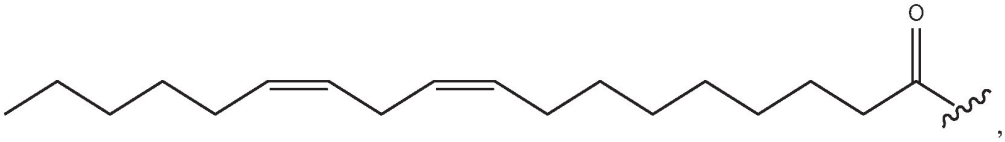
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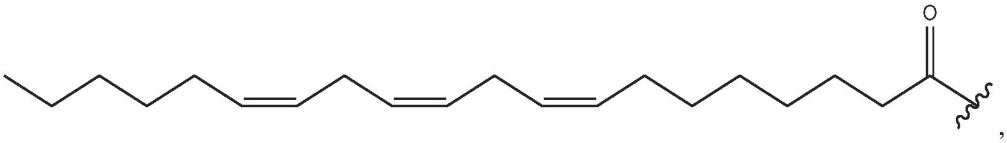
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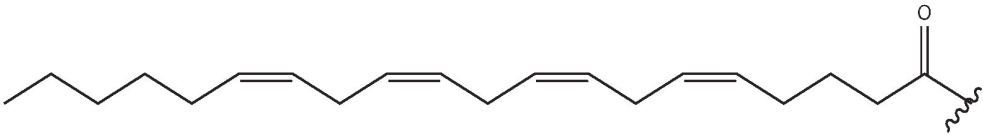
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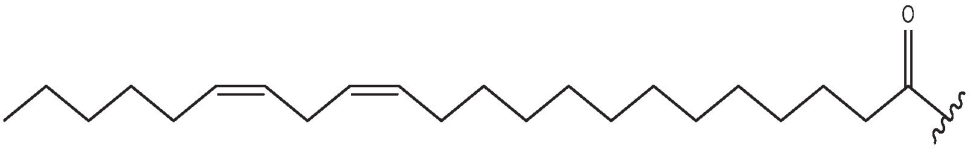
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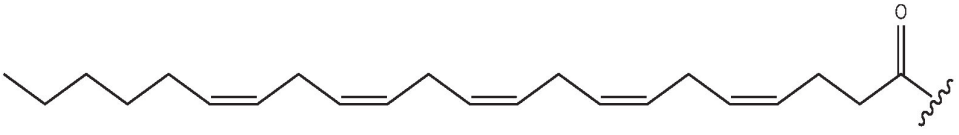
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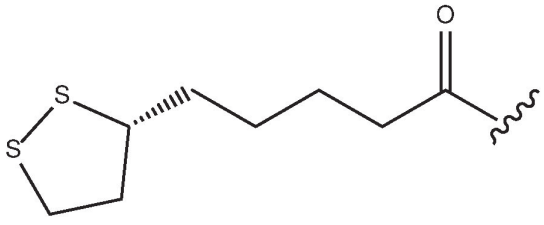
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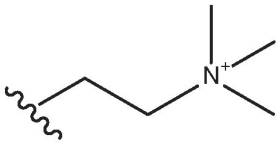
N+
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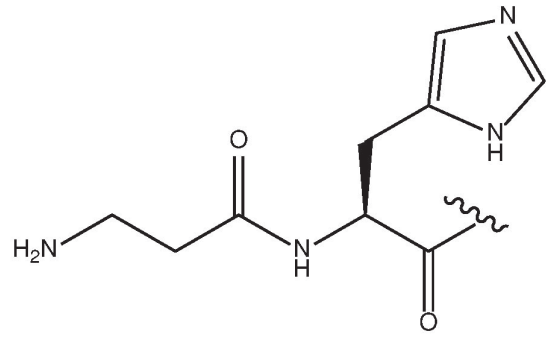
N
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H
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H_2N
N
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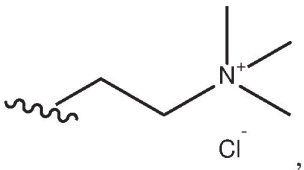
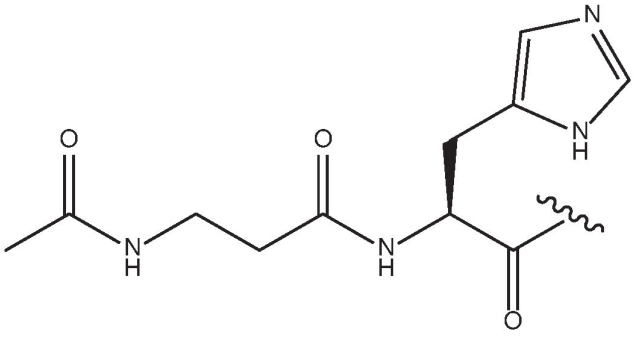

N^+
Cl^-
,

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N
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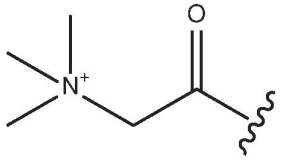
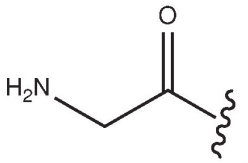
O
N
H
N
H
O
,

N^+
O
,

H_2N
O
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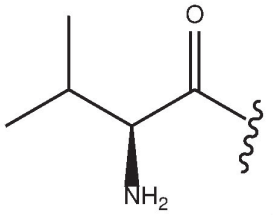
O
NH_2
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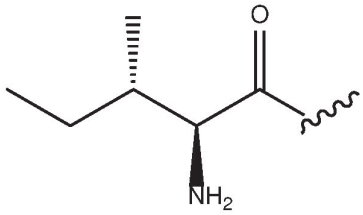
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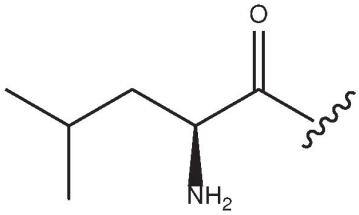
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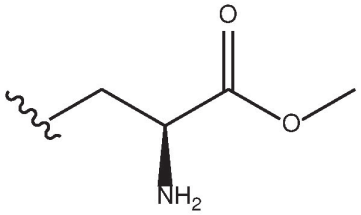
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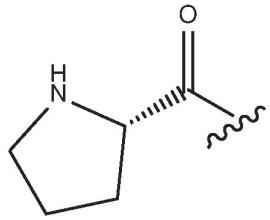
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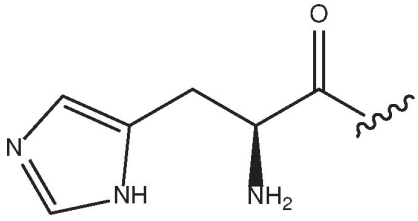
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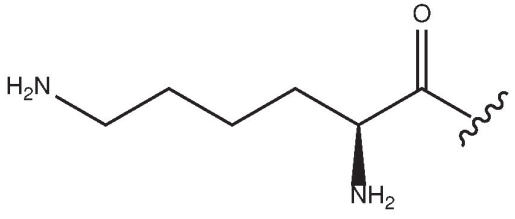
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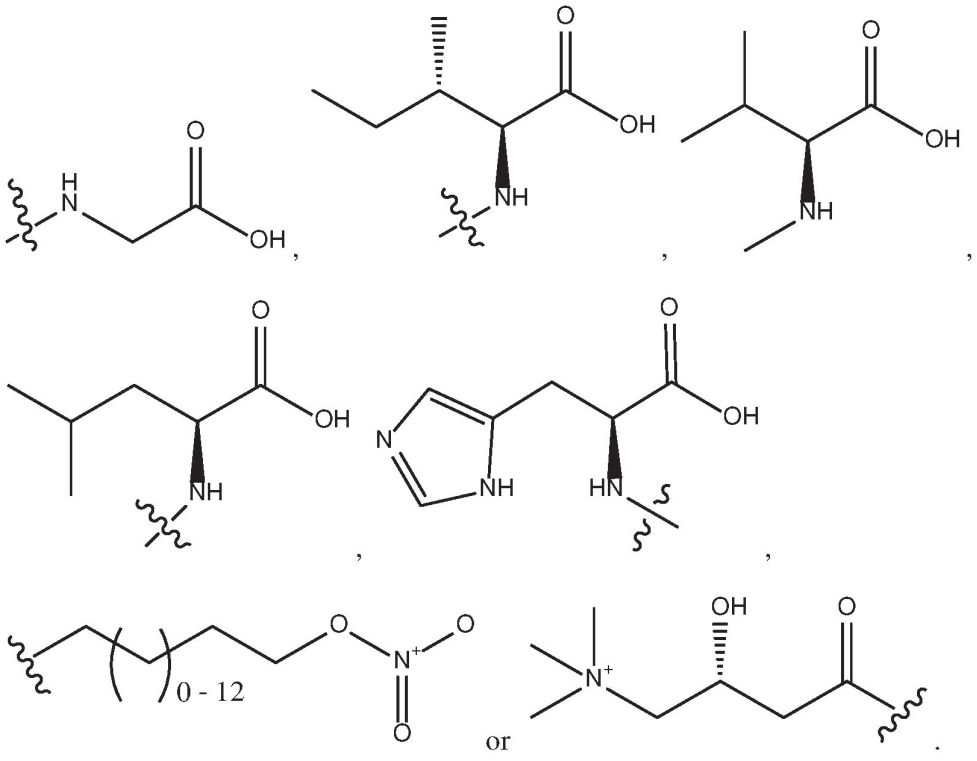

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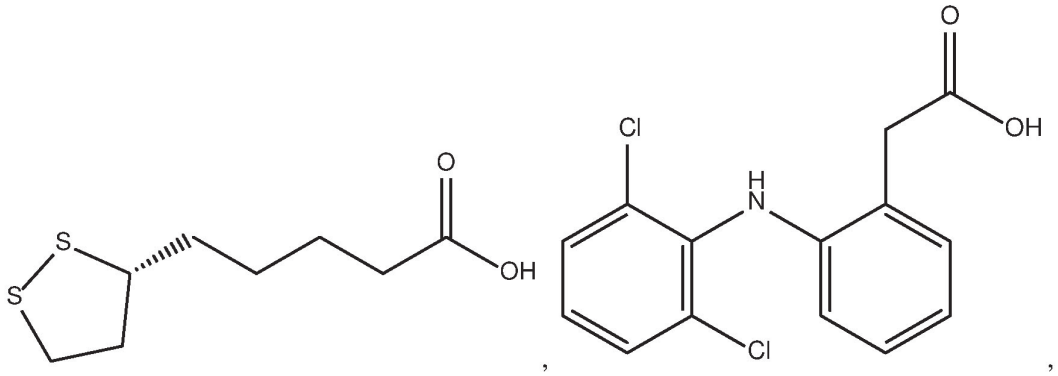

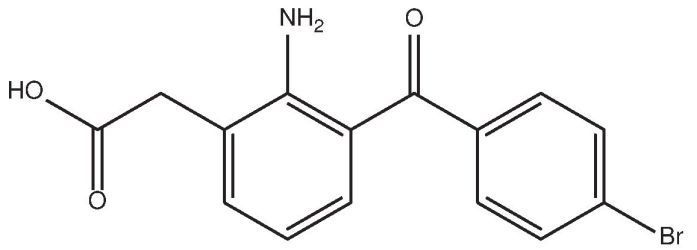

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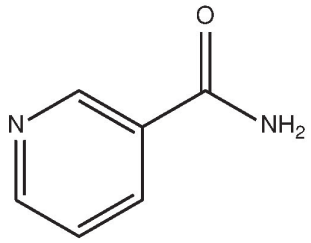

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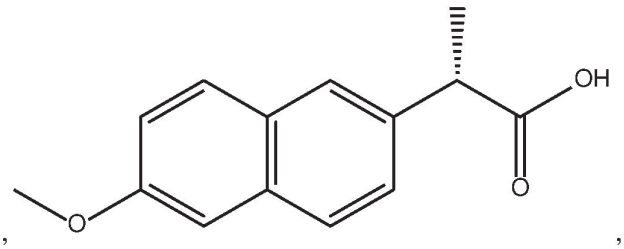

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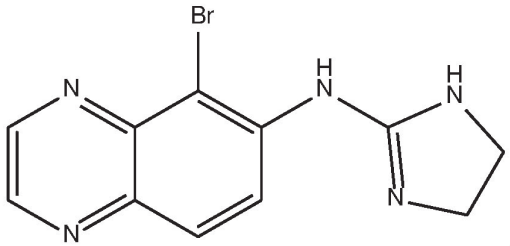

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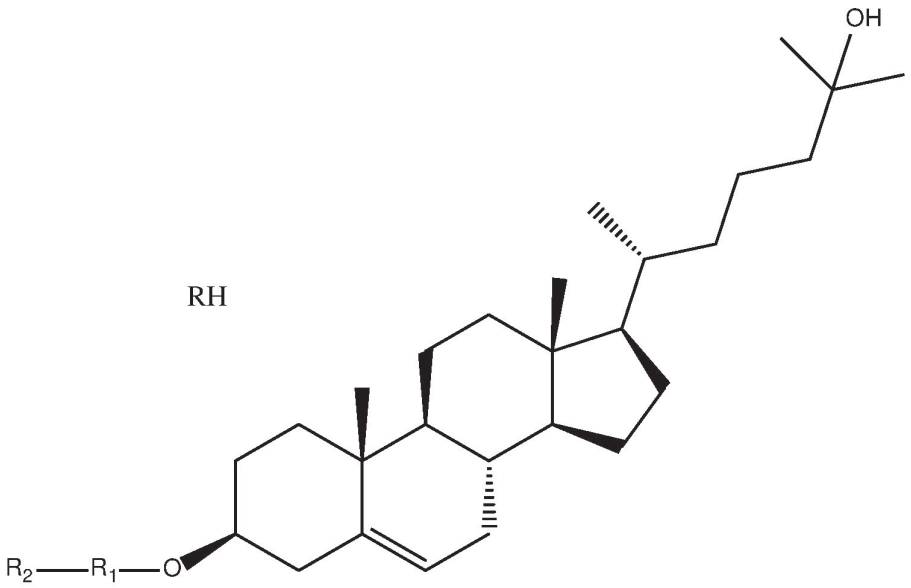
caprylic acid, 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-hydroxyethanesulfonic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, adipic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid (decanoic acid), caproic acid (hexanoic acid), carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid , glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, proprionic acid, pyroglutamic acid, salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, toluenesulfonic acid, undecylenic acid, omega 3 fatty acids, omega 6 fatty acids, n-acetyl cysteine (nac), furoate, methyl furoate, ethyl furoate, aminocaproic acid, caprilic acid, alpha

lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

17. A compound of formula XVII



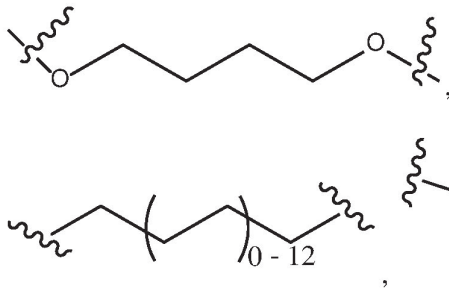
Formula XVII

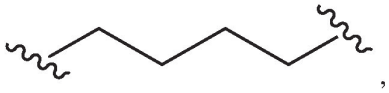
and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

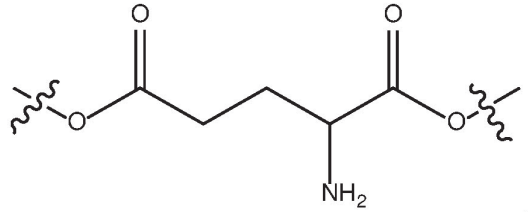
wherein,

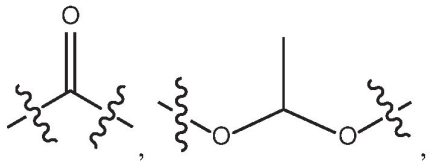
R^1 independently represents

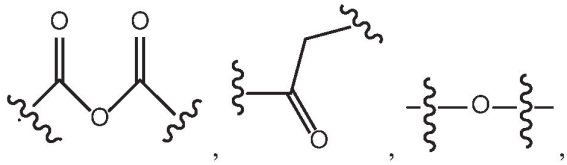
NULL,

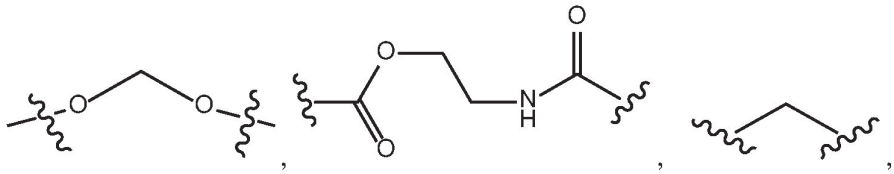


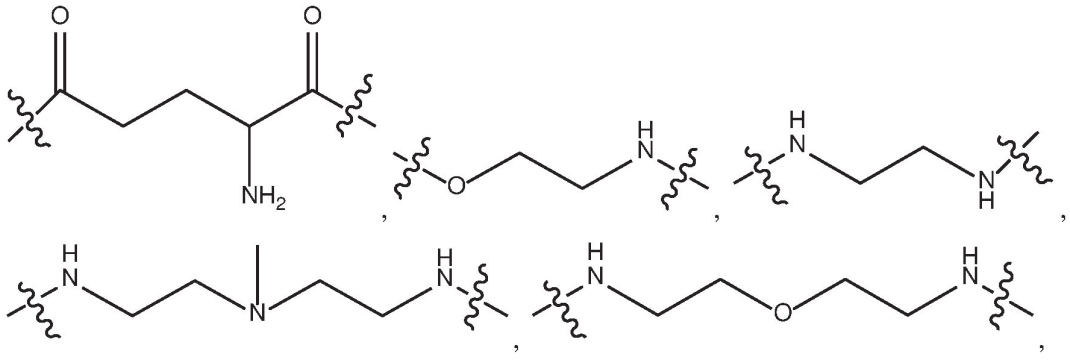


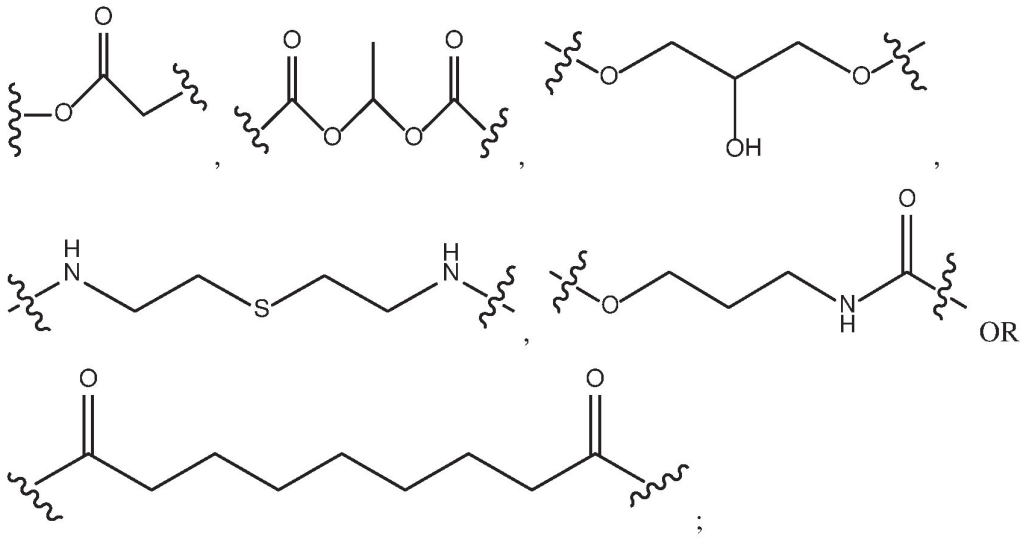












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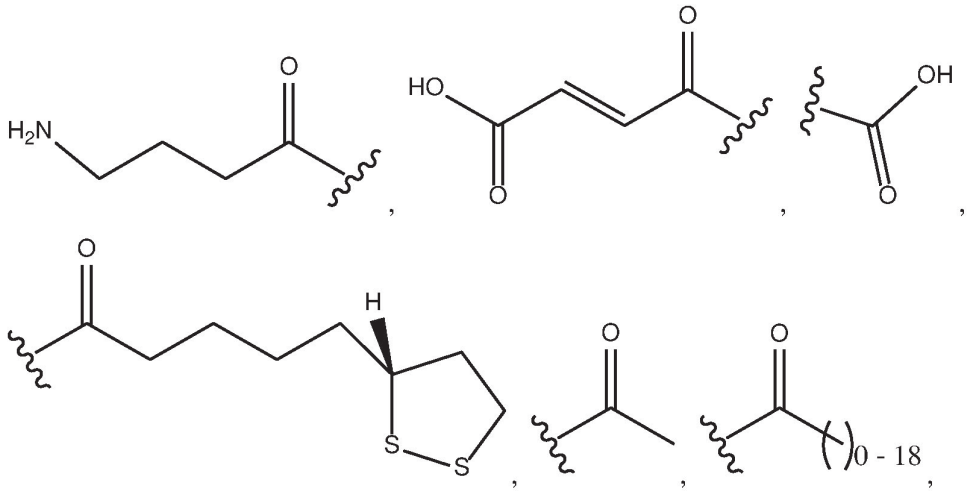

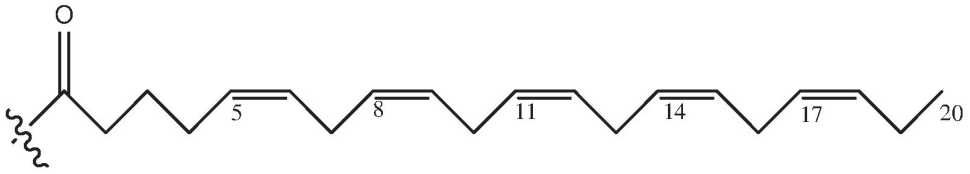
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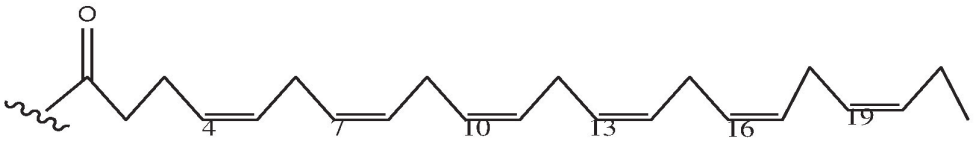
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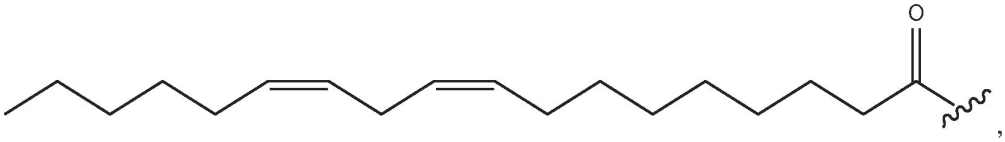
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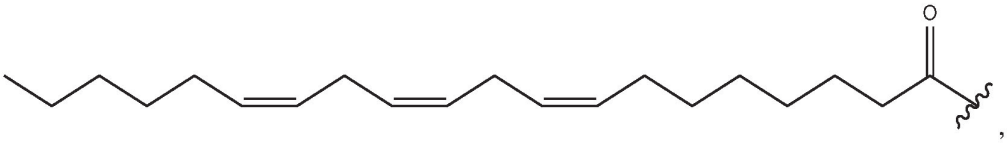
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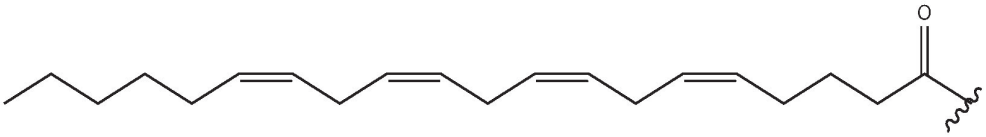
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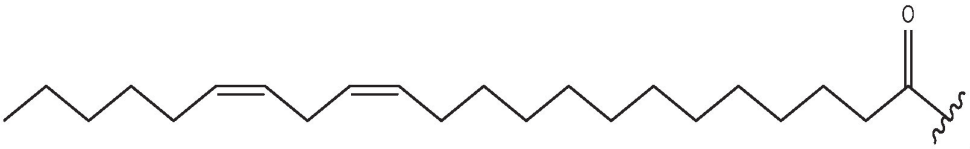
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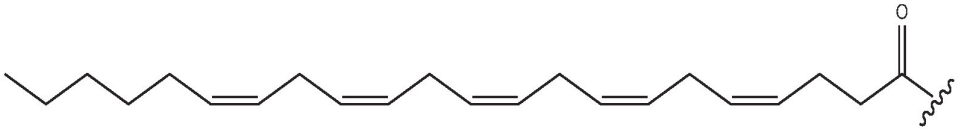
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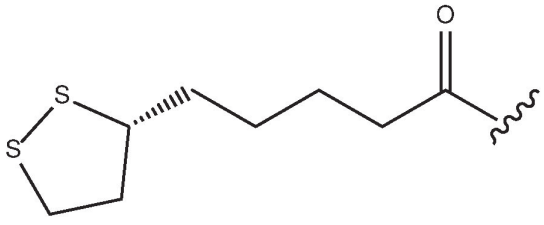
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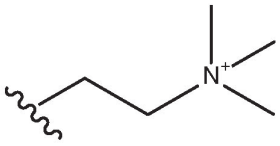
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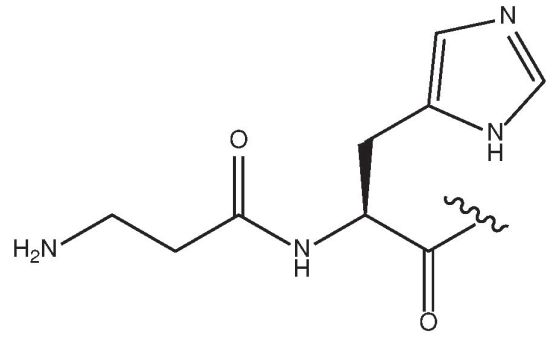
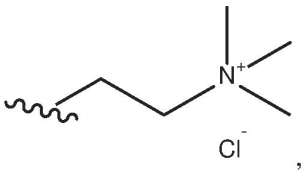
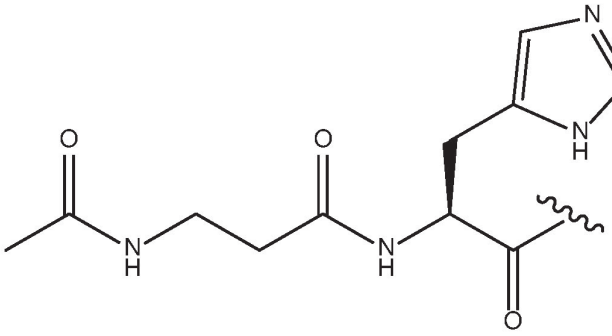
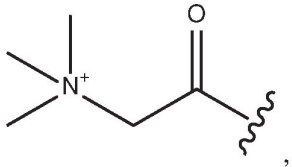
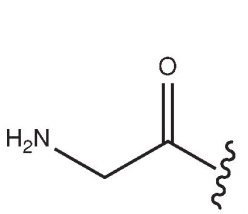
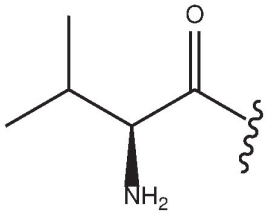
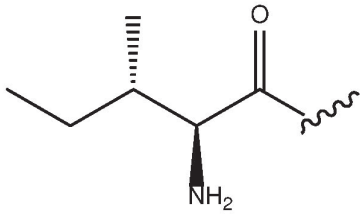
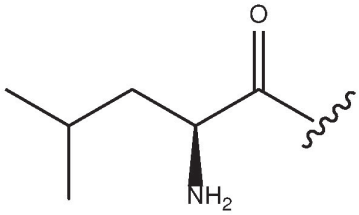
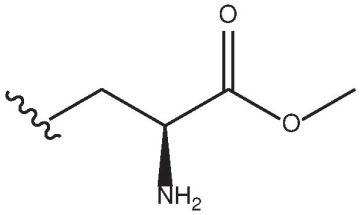
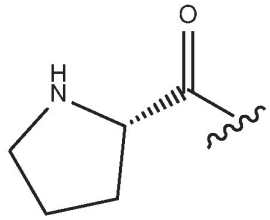
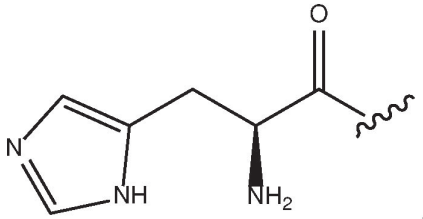
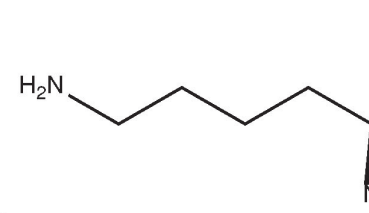
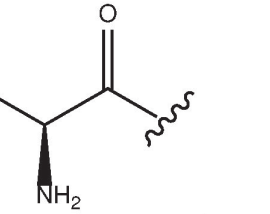

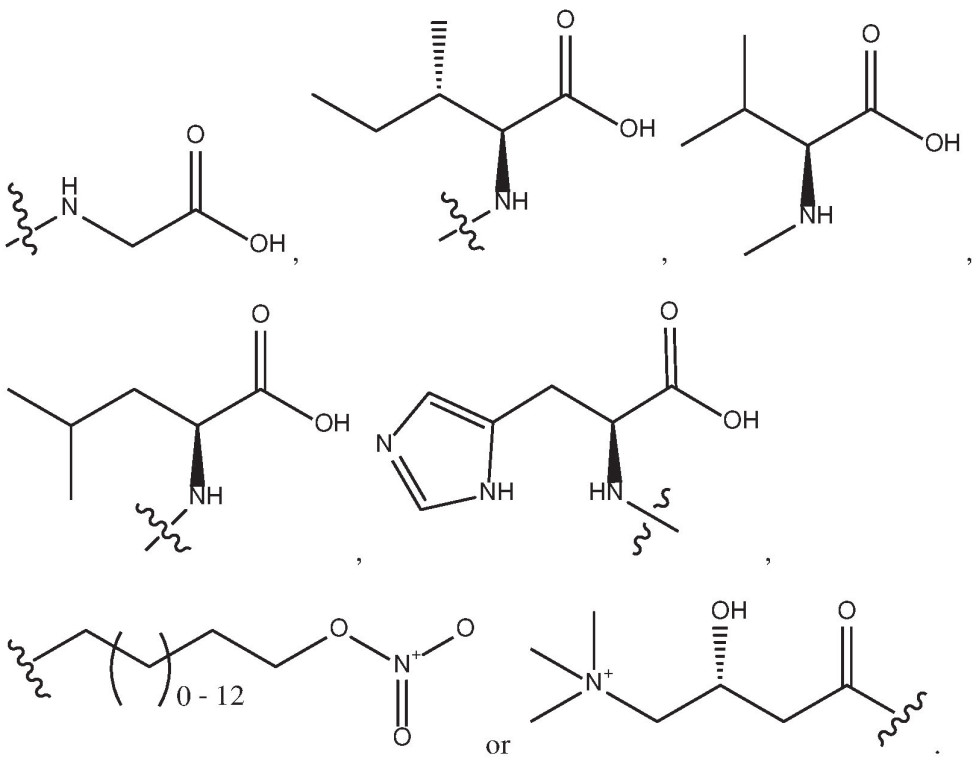

RH independently represents

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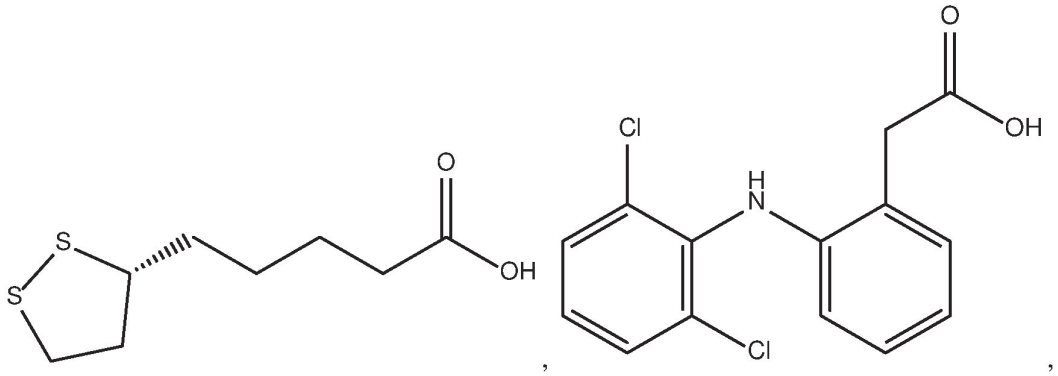

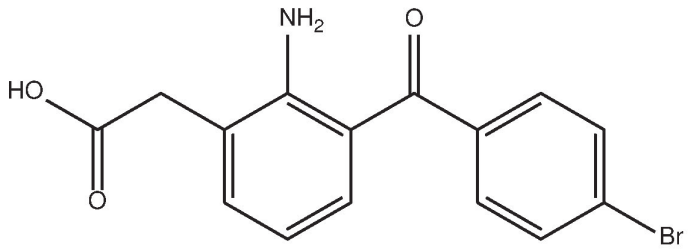

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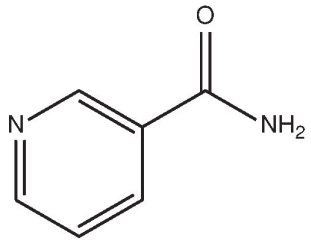

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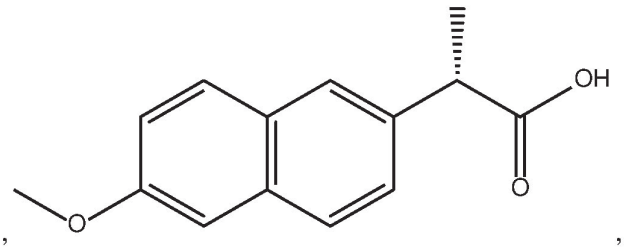

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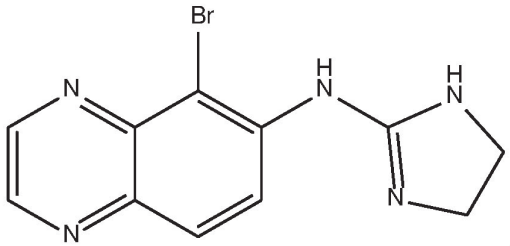

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lipoic acid, R-lipoic acid, myristic acid, myristoleic acid, palmitoleic acid, phospholipids, phosphatidylcholine, oleic acid, elaidic acid, linoleic acid, linolenic acid, menthol, retinoic acid, vitamin A, retinol, linolelaidic acid, arachidonic acid, retinal, isotretinoin, curcumin, tretinoin, α-carotene β-carotene retinol, d2 ergosterol, ergocalciferol, 7-dehydrocholesterol, cholecalciferol, 25-hydroxycholecalciferol, calcitriol (1,25-dihydroxycholecalciferol), calcitroic acid, d4 dihydroergocalciferol, alfacalcidol, dihydrotachysterol, calcipotriol, tacalcitol, paricalcitol, tocopherol, naphthoquinone, phylloquinone (k1), menaquinones (k2), menadione (k3), menadiol (k4), thiamine, acefurtiamine, allithiamine, benfotiamine, fursultiamine, octotiamine, prosultiamine, sulbutiamine, riboflavin, niacin, nicotinamide, pantothenic acid, dexpanthenol, pantethine, pyridoxine, pyridoxal phosphate, pyridoxamine, pyritinol, biotin, folic acid, dihydrofolic acid, folinic acid, levomefolic acid, adenosylcobalamin, cyanocobalamin, hydroxocobalamin, methylcobalamin, choline, or dehydroascorbic acid, 1-docosanol.

18. A Pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.
19. The pharmaceutical composition of claim 18, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
20. The pharmaceutical composition of claim 19, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
21. A Pharmaceutical composition comprising a compound of claim 2, and a pharmaceutically acceptable carrier.
22. The pharmaceutical composition of claim 21, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

23. The pharmaceutical composition of claim 22, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
24. A Pharmaceutical composition comprising a compound of claim 3, and a pharmaceutically acceptable carrier.
25. The pharmaceutical composition of claim 24, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, topical administration, injection, ocular, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
26. The pharmaceutical composition of claim 25, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
27. A Pharmaceutical composition comprising a compound of claim 4, and a pharmaceutically acceptable carrier.
28. The pharmaceutical composition of claim 27, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection,subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
29. The pharmaceutical composition of claim 28, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
30. A Pharmaceutical composition comprising a compound of claim 5, and a pharmaceutically acceptable carrier.
31. The pharmaceutical composition of claim 30, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, topical administration, ocular, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
32. The pharmaceutical composition of claim 31, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
33. A Pharmaceutical composition comprising a compound of claim 6, and a pharmaceutically acceptable carrier.
34. The pharmaceutical composition of claim 33, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, topical administration,

ocular, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

35. The pharmaceutical composition of claim 34, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

36. A Pharmaceutical composition comprising a compound of claim 7, and a pharmaceutically acceptable carrier.

37. The pharmaceutical composition of claim 36, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

38. The pharmaceutical composition of claim 37, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

39. A Pharmaceutical composition comprising a compound of claim 8, and a pharmaceutically acceptable carrier.

40. The pharmaceutical composition of claim 39, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

41. The pharmaceutical composition of claim 40, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

42. A Pharmaceutical composition comprising a compound of claim 9, and a pharmaceutically acceptable carrier.

43. The pharmaceutical composition of claim 42, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

44. The pharmaceutical composition of claim 43, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

45. A Pharmaceutical composition comprising a compound of claim 10, and a pharmaceutically acceptable carrier.

46. The pharmaceutical composition of claim 45, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, topical administration, injection, subdermal, ocular, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

47. The pharmaceutical composition of claim 46, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

48. A Pharmaceutical composition comprising a compound of claim 11, and a pharmaceutically acceptable carrier.

49. The pharmaceutical composition of claim 48, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

50. The pharmaceutical composition of claim 49, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

51. A Pharmaceutical composition comprising a compound of claim 12, and a pharmaceutically acceptable carrier.

52. The pharmaceutical composition of claim 51, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

53. The pharmaceutical composition of claim 52, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

54. A Pharmaceutical composition comprising a compound of claim 13, and a pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 54, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

56. The pharmaceutical composition of claim 55, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

57. A Pharmaceutical composition comprising a compound of claim 14, and a pharmaceutically acceptable carrier.

58. The pharmaceutical composition of claim 57, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

59. The pharmaceutical composition of claim 58, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

60. A Pharmaceutical composition comprising a compound of claim 15, and a pharmaceutically acceptable carrier.

61. The pharmaceutical composition of claim 60, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

62. The pharmaceutical composition of claim 61, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

63. A Pharmaceutical composition comprising a compound of claim 16, and a pharmaceutically acceptable carrier.

64. The pharmaceutical composition of claim 63, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal

spray, oral spray rectal administration, buccal administration or transmucosal administration.

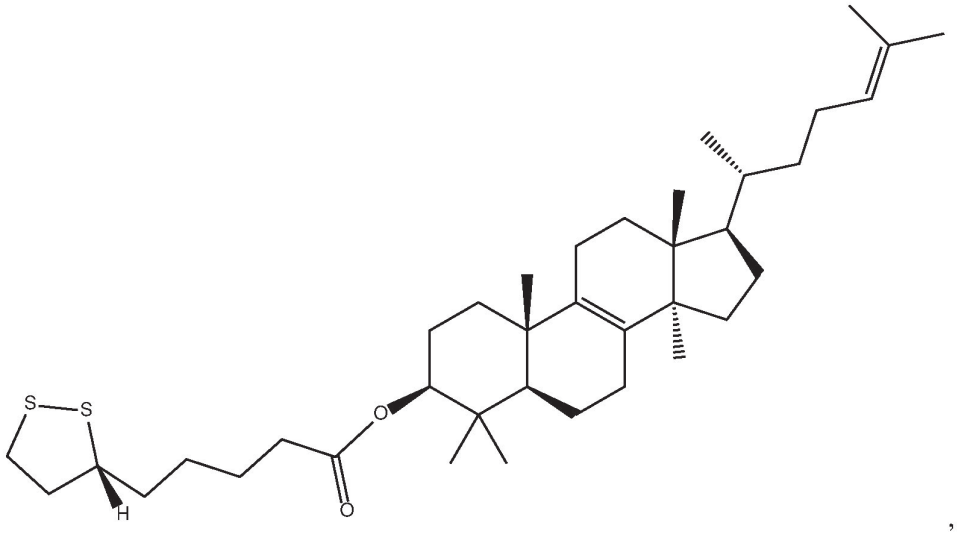
65. The pharmaceutical composition of claim 64, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

66. A Pharmaceutical composition comprising a compound of claim 17, and a pharmaceutically acceptable carrier.

67. The pharmaceutical composition of claim 66, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.

68. The pharmaceutical composition of claim 67, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.

69. A compound of the structure:



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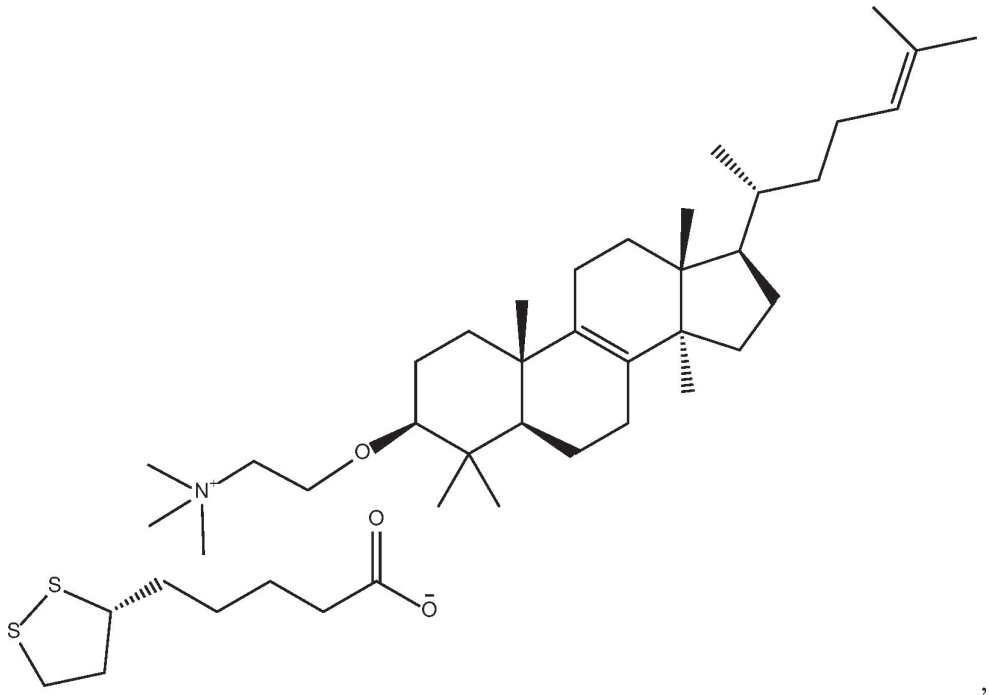
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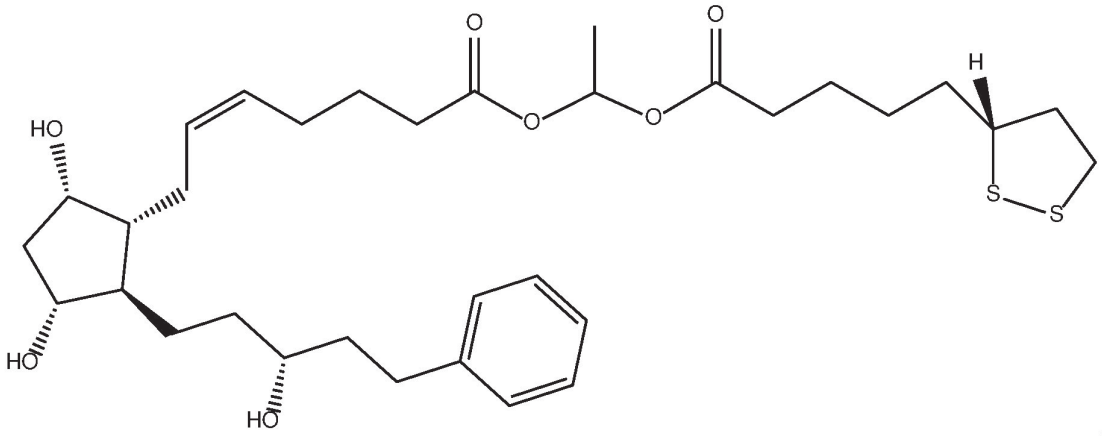
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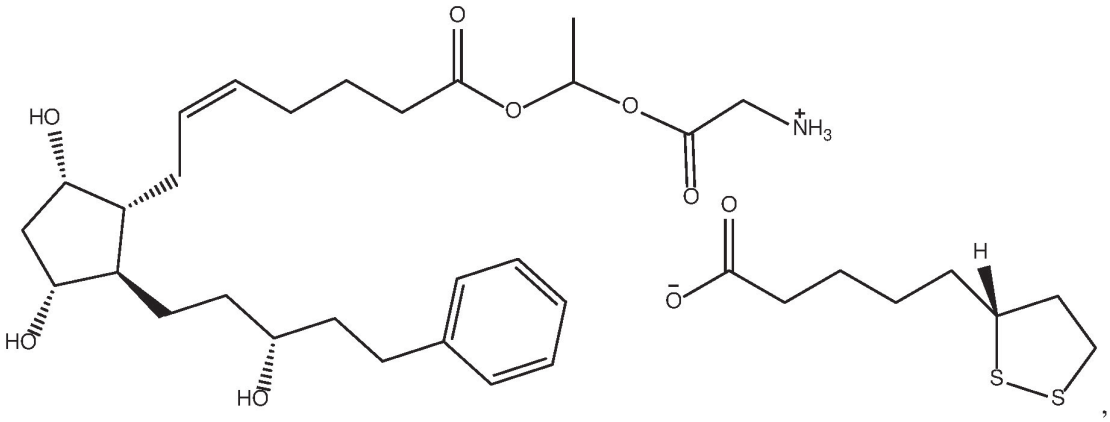
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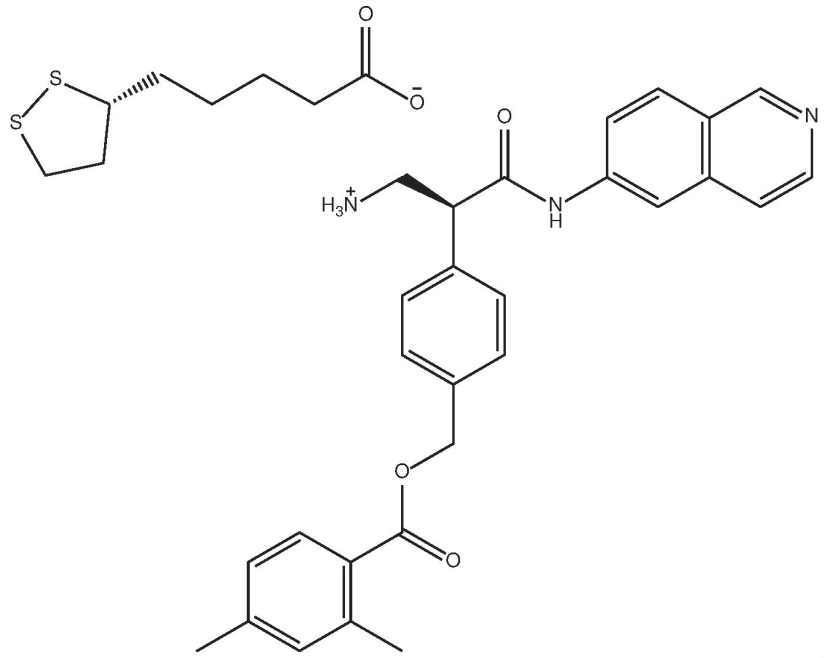
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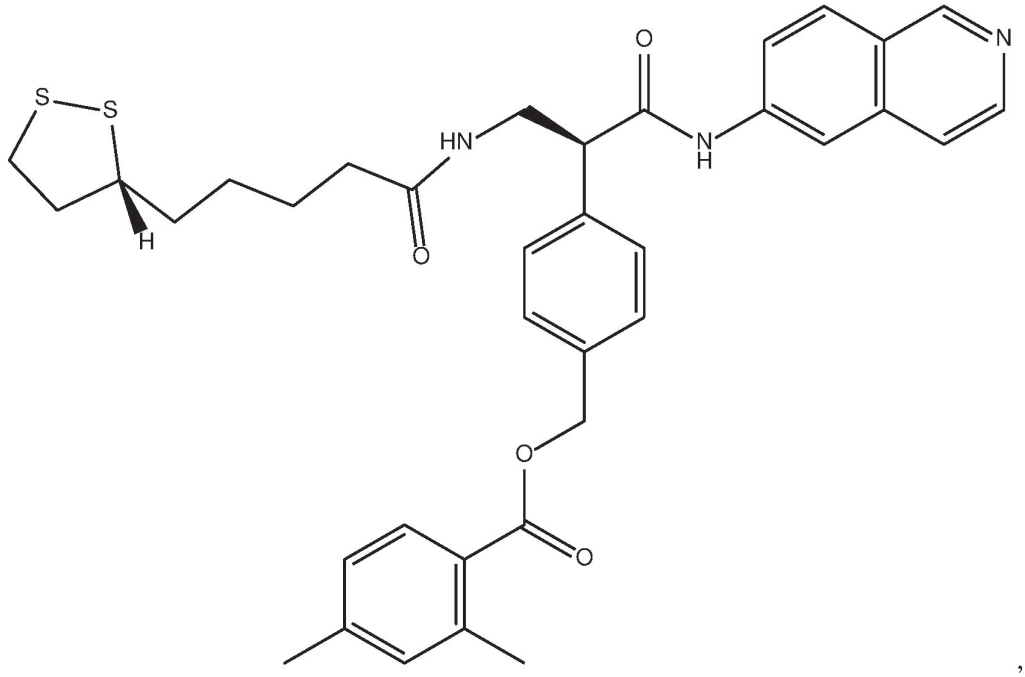
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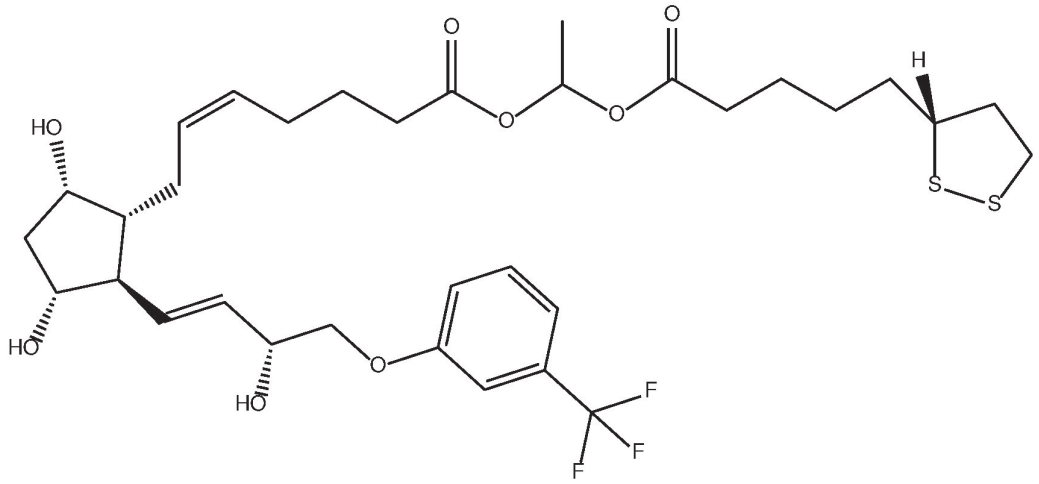
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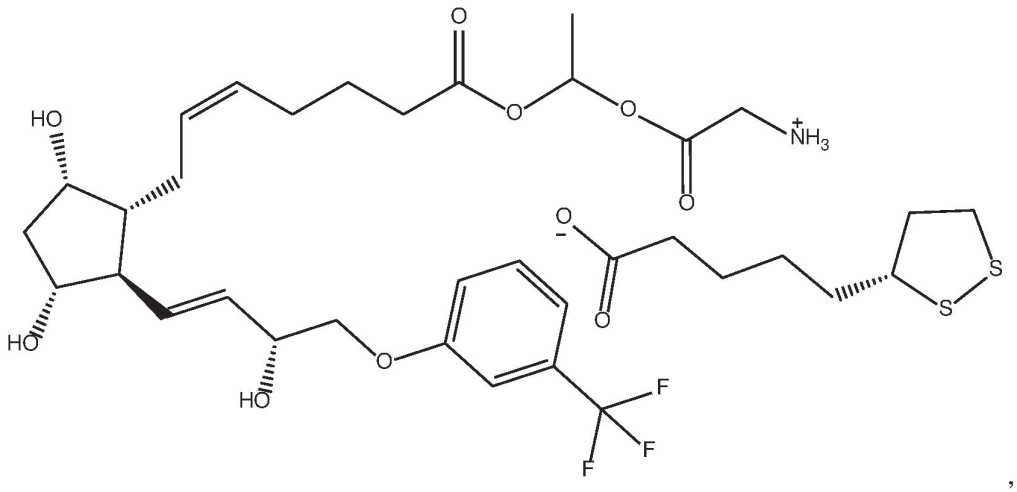

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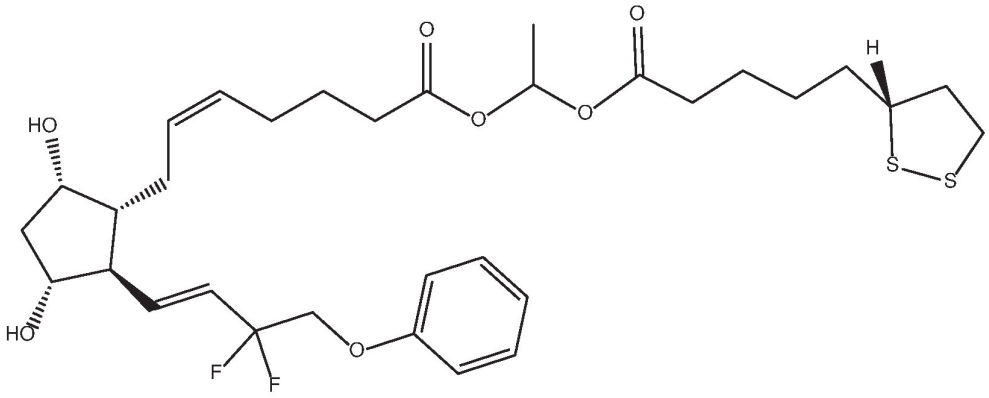

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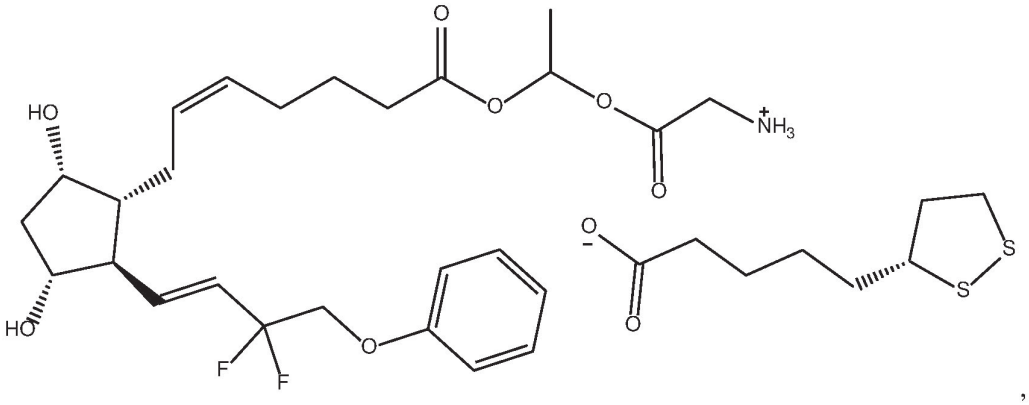

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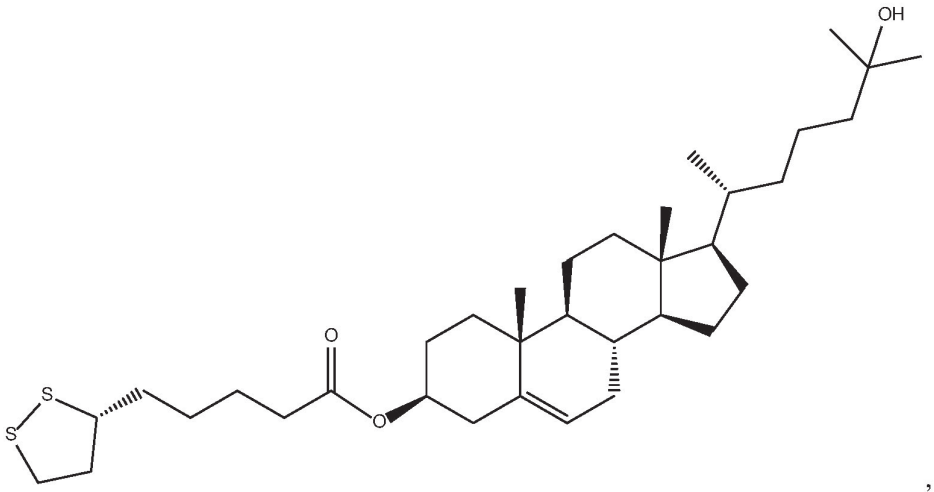
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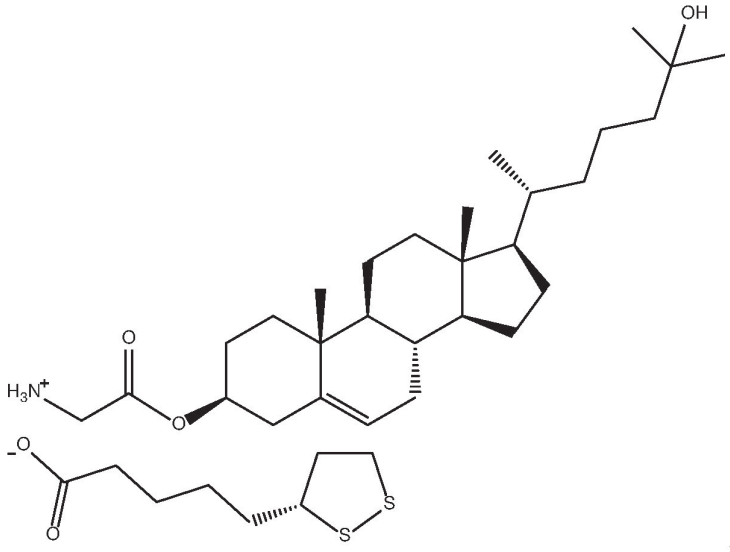
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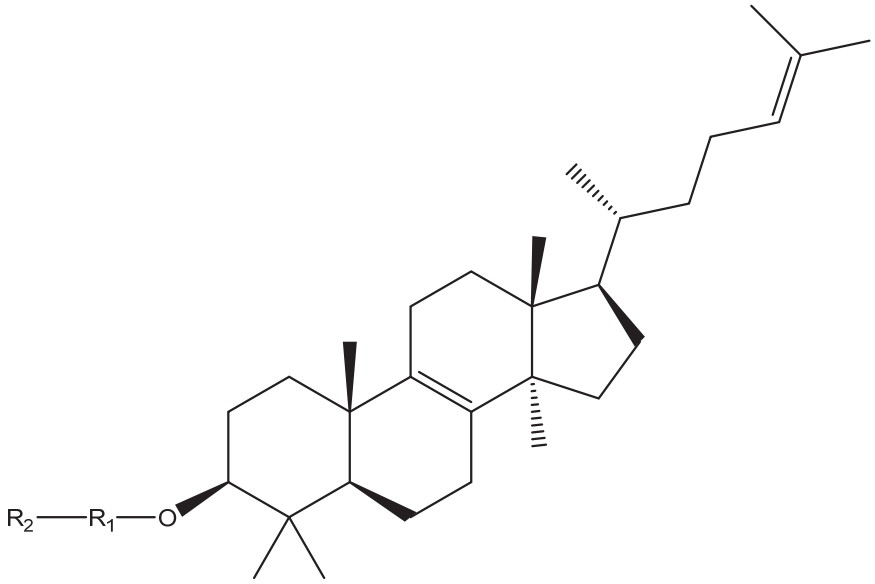
We Claims:

The invention Claimed is:

1. A compound of formula I

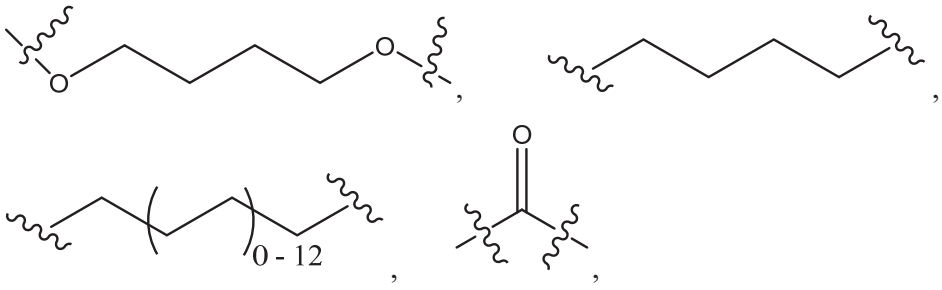


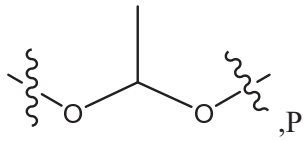
Formula I

and pharmaceutically acceptable hydrates, solvates, enantiomers, and stereoisomers thereof;

wherein,

R1 independently represents Null,

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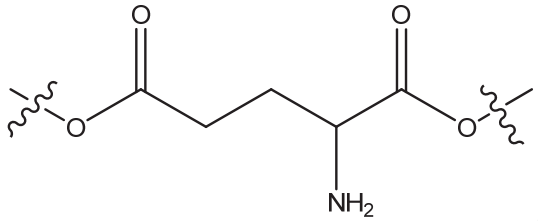
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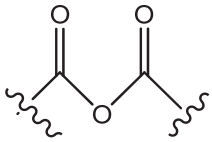
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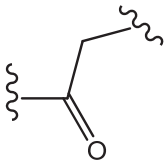
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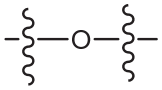
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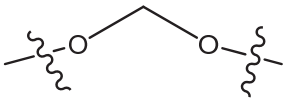
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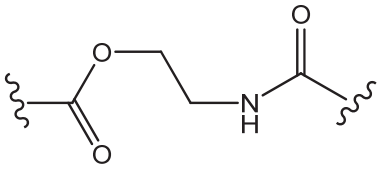
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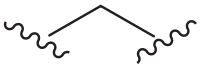
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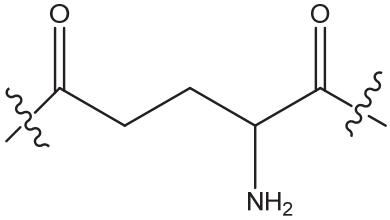
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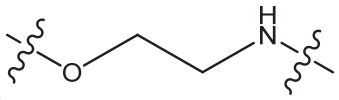
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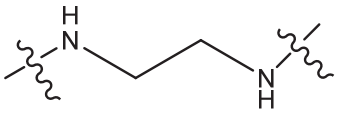
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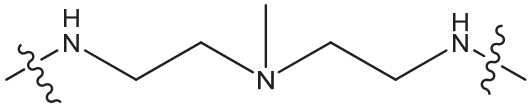
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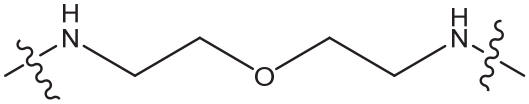
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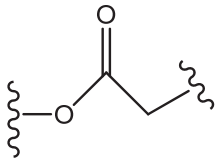
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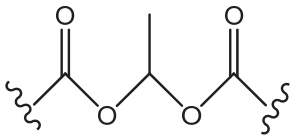
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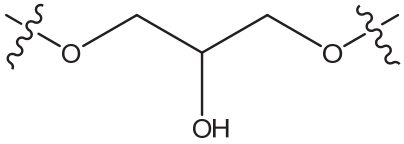
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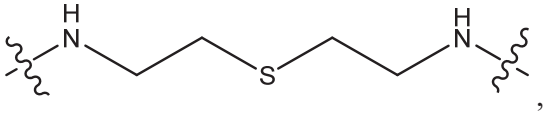
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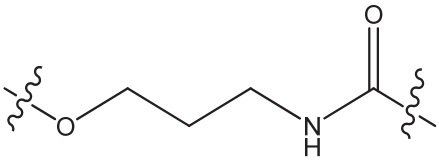
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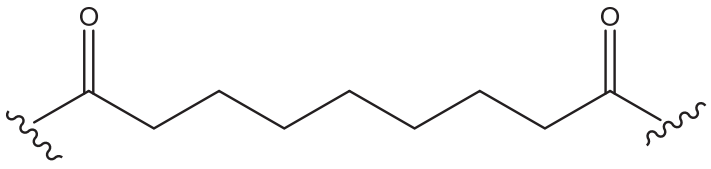

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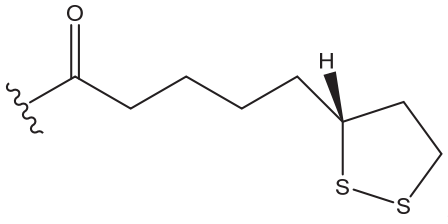

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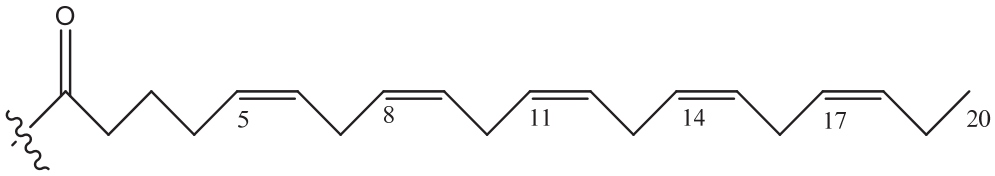

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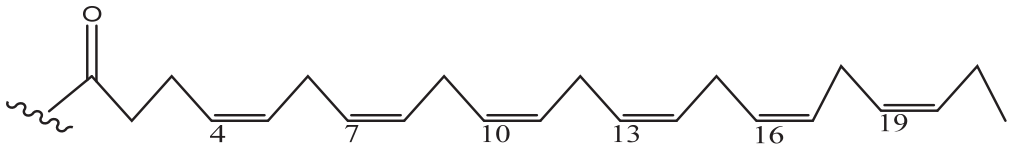

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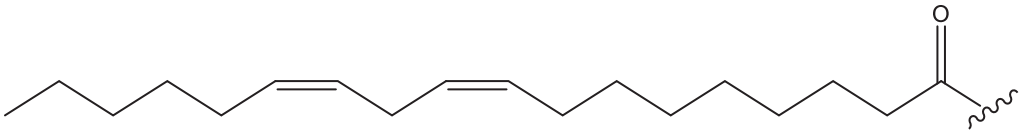

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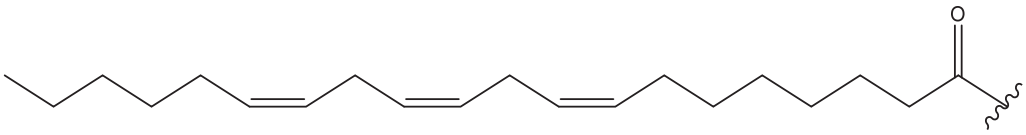

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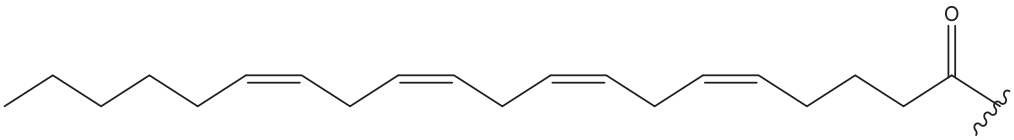

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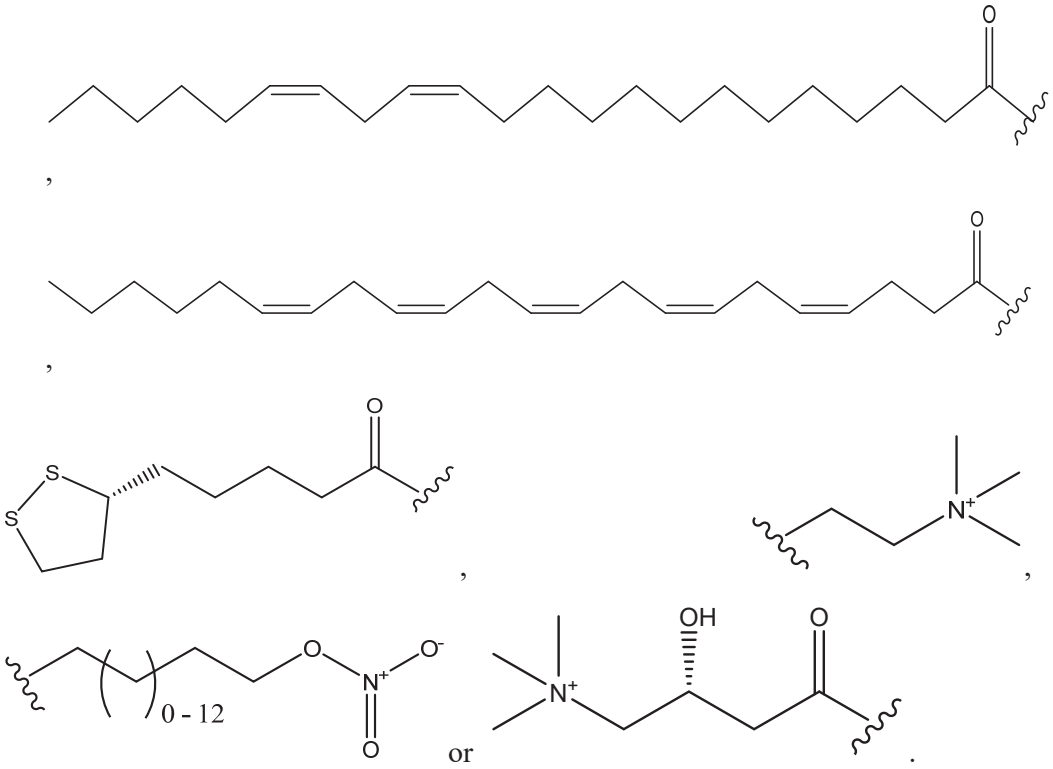
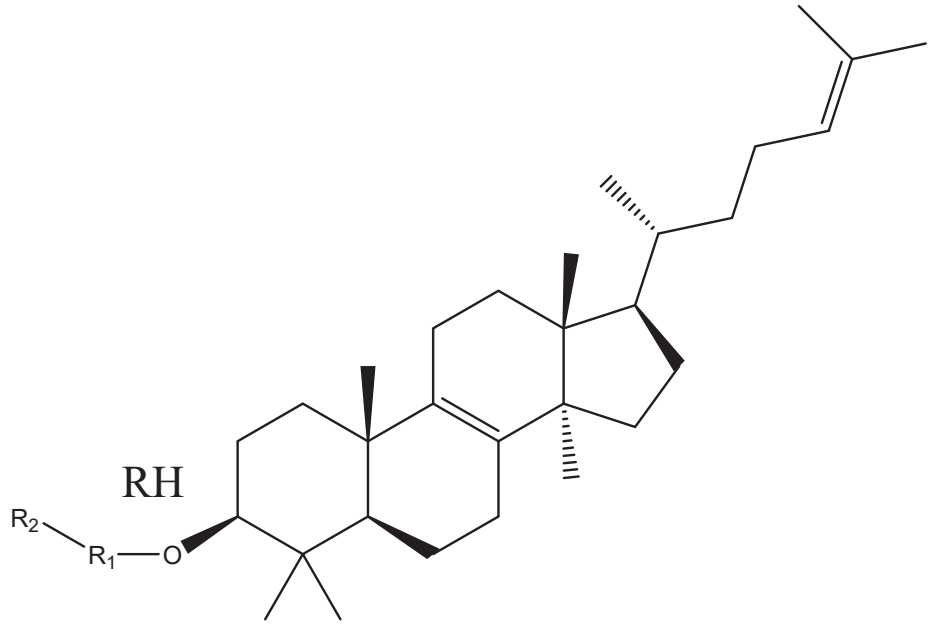


2. A compound of formula II

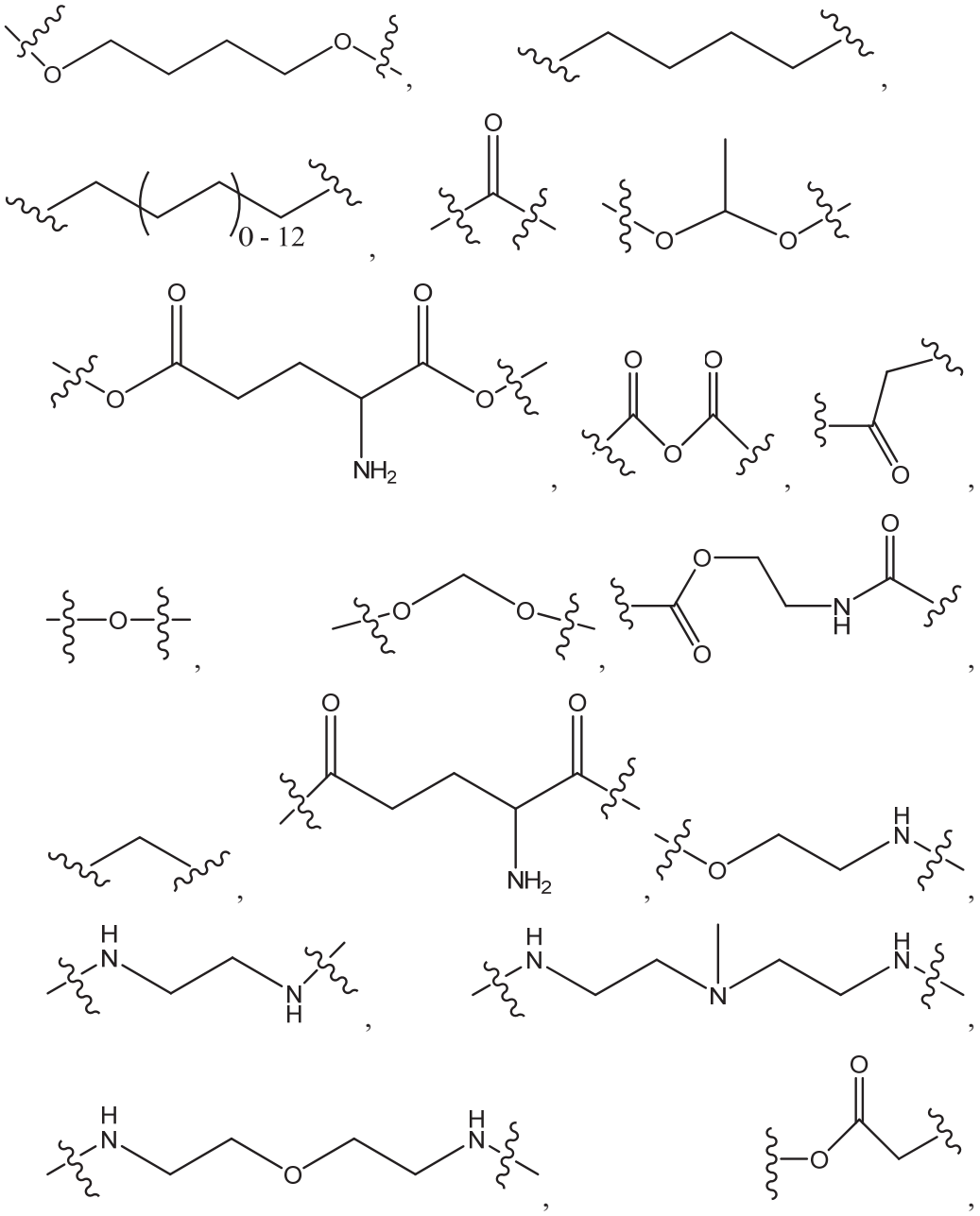


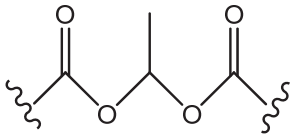
Formula II

and pharmaceutically acceptable hydrates, solvates, prodrugs, enantiomers, and stereoisomers thereof;

wherein,

R1 represents Null,

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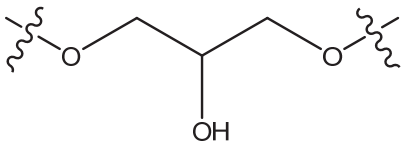
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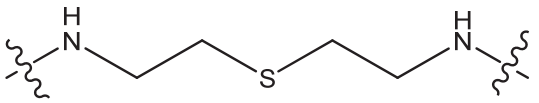
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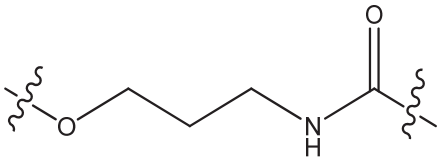
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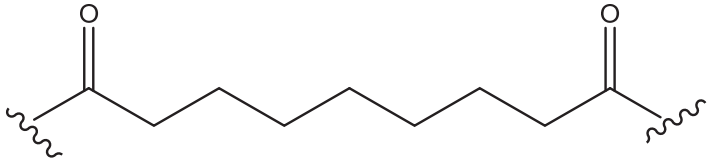
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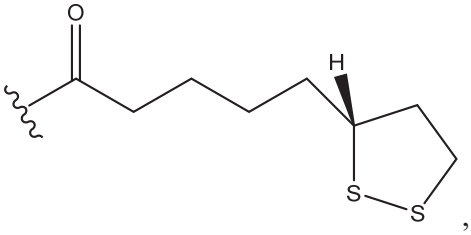
R_2 represents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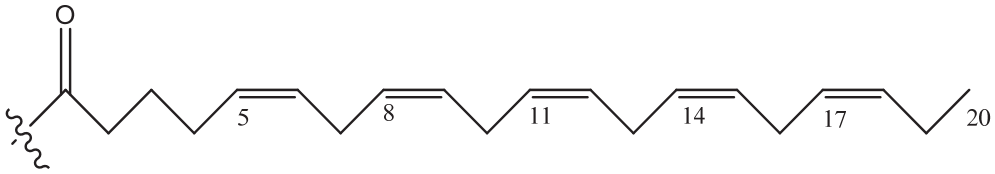
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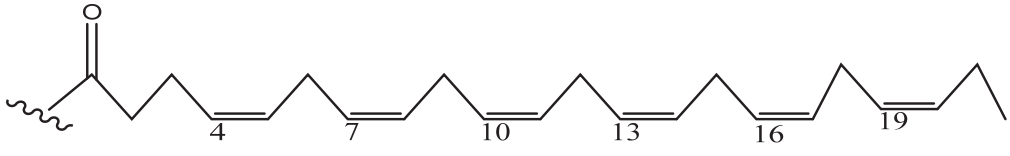
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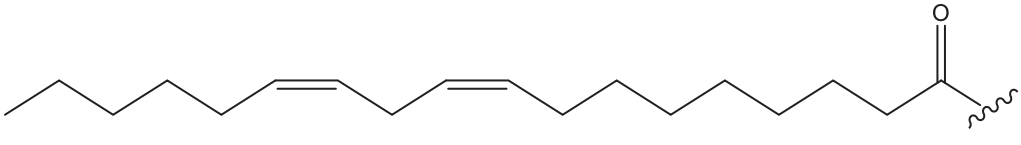
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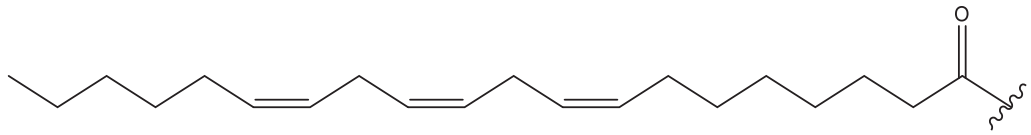

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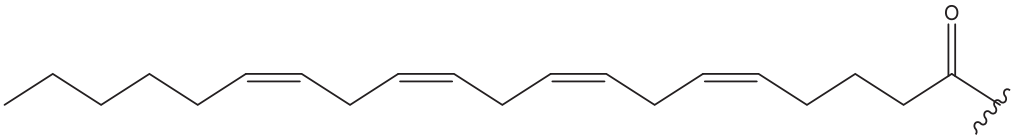

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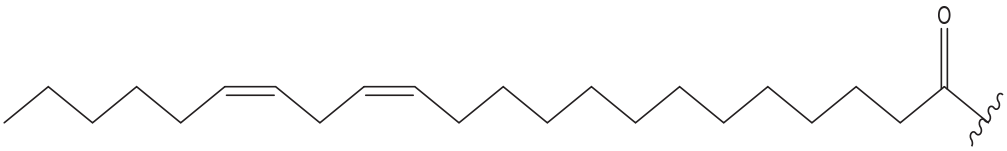

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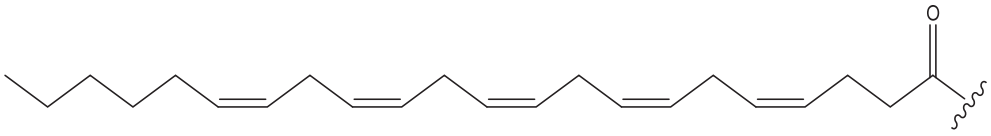

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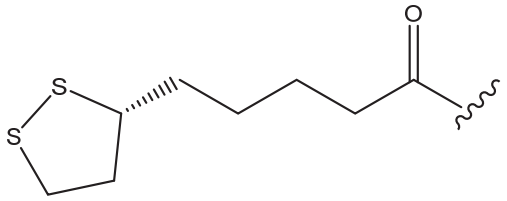

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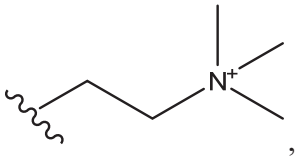

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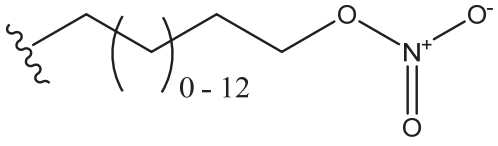

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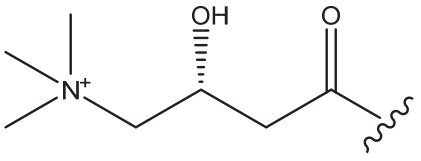

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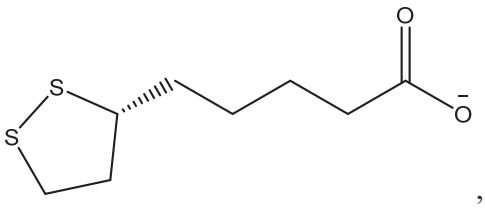
RH independently represents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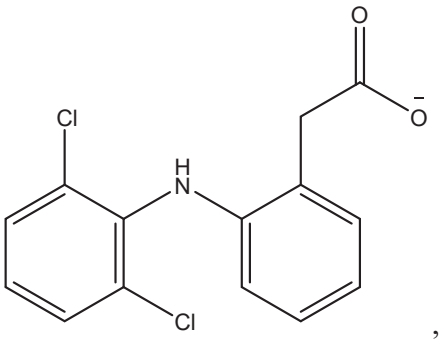
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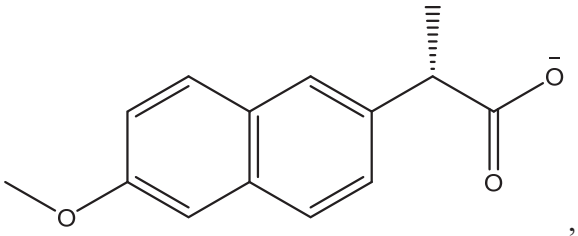
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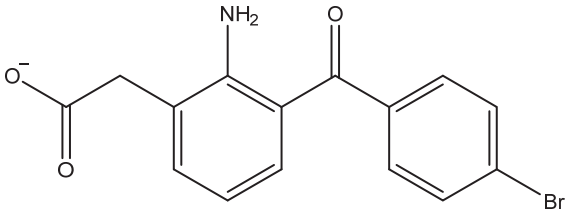
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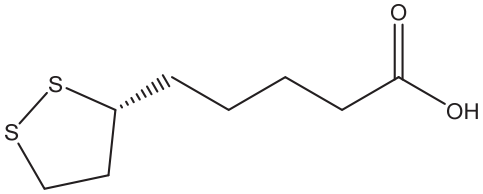
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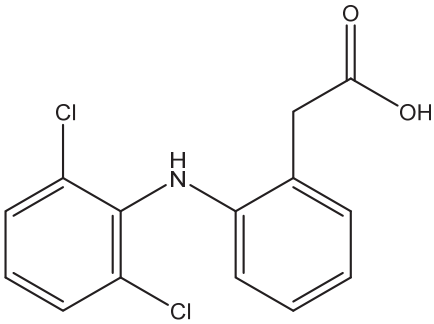
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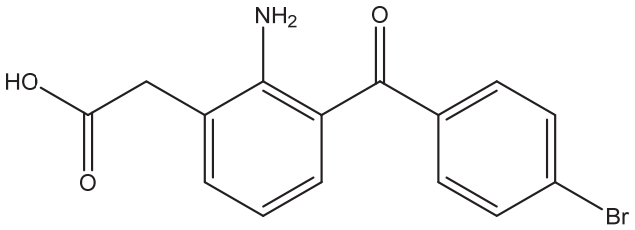

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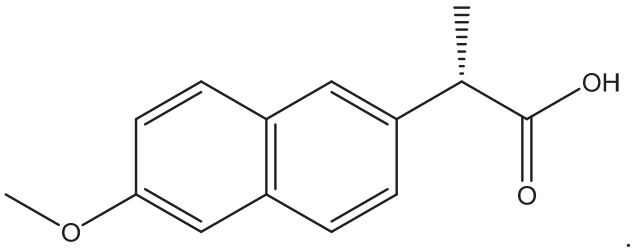

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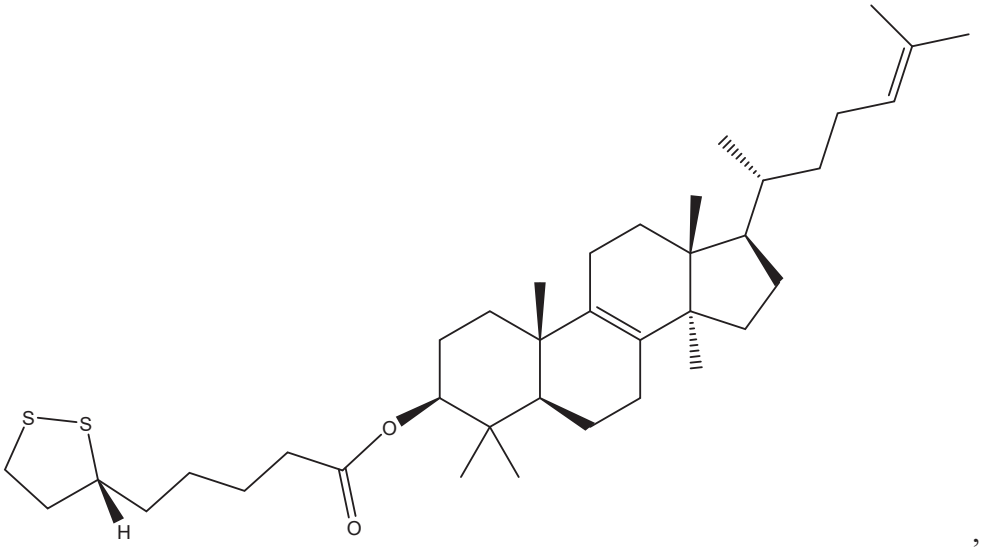
3. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable carrier.
4. The pharmaceutical composition of claim 18, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
5. The pharmaceutical composition of claim 19, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
6. A pharmaceutical composition comprising a compound of claim 2, and a pharmaceutically acceptable carrier.
7. The pharmaceutical composition of claim 21, wherein said pharmaceutical composition is formulated for oral administration, parenteral administration, ocular, topical administration, injection, subdermal, transdermal administration, oral solution, nasal spray, oral spray rectal administration, buccal administration or transmucosal administration.
8. The pharmaceutical composition of claim 22, are formulated for the treatment of glaucoma, presbyopia, IOP, cataract, dry eye and oGVHD.
9. A compound of the structure: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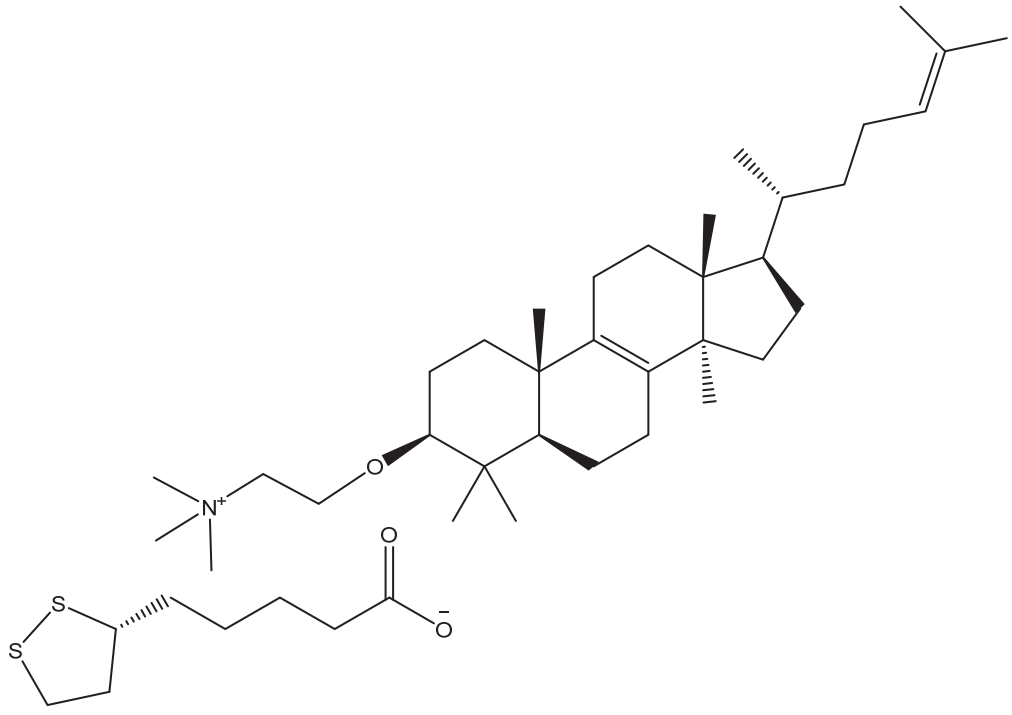
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