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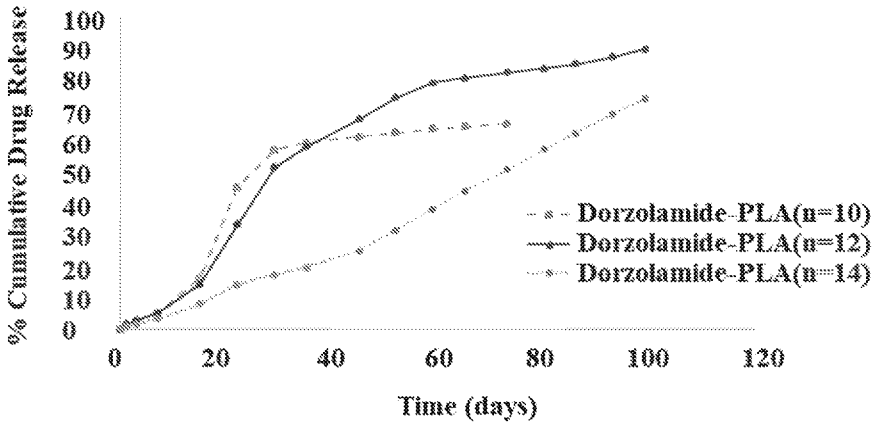



FIG. 36

**(57) Abstract:** The present invention provides new prodrugs of therapeutically active compounds, including oligomeric prodrugs, and compositions to treat medical disorders, for example glaucoma, a disorder or abnormality related to an increase in intraocular pressure (IOP), a disorder requiring neuroprotection, age-related macular degeneration, or diabetic retinopathy.

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# DRUGS AND COMPOSITIONS FOR THE TREATMENT OF OCULAR DISORDERS

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of provisional U.S. Application No. 62/475,802 filed March 23, 2017 and U.S. Application No. 62/598,933 filed December 14, 2017. The entirety of these applications are hereby incorporated by reference for all purposes.

## BACKGROUND

The eye is a complex organ with unique anatomy and physiology. The structure of the eye can be divided into two parts, the anterior and posterior. The cornea, conjunctiva, aqueous humor, iris, ciliary body and lens are in the anterior portion. The posterior portion includes the sclera, choroid, retinal pigment epithelium, neural retina, optic nerve and vitreous humor. The most important diseases affecting the anterior segment include glaucoma, allergic conjunctivitis, anterior uveitis and cataracts. The most prevalent diseases affecting the posterior segment of the eye are dry and wet age-related macular degeneration (AMD) and diabetic retinopathy.

Typical routes of drug delivery to the eye are topical, systemic, subconjunctival, intravitreal, punctal, intrasceral, transscleral, anterior or posterior sub-Tenon's, suprachoroidal, choroidal, subchoroidal, and subretinal.

To address issues of ocular delivery, a large number of types of delivery systems have been devised.These include conventional (solution, suspension, emulsion, ointment, inserts and gels); vesicular (liposomes, exosomes, niosomes, discomes and pharmacosomes); advanced materials (scleral plugs, gene delivery, siRNA and stem cells); and, controlled release systems (implants, hydrogels, dendrimers, iontophoresis, collagen shields, polymeric solutions, therapeutic contact lenses, cyclodextrin carriers, microneedles and microemulsions and particulates (microparticles and nanoparticles)).

Topical drops are the most widely used non-invasive routes of drug administration to treat anterior ocular diseases. However, a number of barriers exist to effective topical delivery, including tear turnover, nasolacrimal drainage, reflex blinking, and the barrier of the mucosal membrane. It is considered that less than 5% of topically applied dosages reach the deeper ocular tissue.

The patient may be required to instill topical drops up to four times a day. Indeed, certain patients, including corneal transplant recipients, require therapeutic doses of medications to be continuously maintained in the corneal tissues and some patients are required to endure lengthy and arduous dosing regimens that often involve up to hourly application. Each repeat dosing not only requires a further investment of a patient's time, but also increases the chance of irritation and non-compliance.

Drug delivery to the posterior area of the eye usually requires a different mode of administration from topical drops, and is typically achieved via an intravitreal injection, periocular injection or systemic administration. Systemic administration is not preferred given the ratio of volume of the eye to the entire body and thus unnecessary potential systemic toxicity. Therefore, intravitreal injections are currently the most common form of drug administration for posterior disorders. However, intravitreal injections also risk problems due to the common side effect of inflammation to the eye caused by administration of foreign material to this sensitive area, endophthalmitis, hemorrhage, retinal detachment and poor patient compliance.

Transscleral delivery with periocular administration is seen as an alternative to intravitreal injections, however, ocular barriers such as the sclera, choroid, retinal pigment epithelium, lymphatic flow and general blood flow compromise efficacy.

To treat ocular diseases, and in particular diseases of the posterior chamber, the drug must be delivered in an amount and for a duration to achieve efficacy. This seemingly straightforward goal is difficult to achieve in practice.

Examples of common drug classes used for ocular disorders include: prostaglandins, carbonic anhydrase inhibitors, receptor tyrosine kinase inhibitors (RTKIs), Rho kinase (ROCK) inhibitors, beta-blockers, alpha-adrenergic agonists, parasympathomimetics, epinephrine, and hyperosmotic agents.

Although a number of prostaglandin carboxylic acids are effective in treating eye disorders, for example, lowering intraocular pressure (IOP), their hydrophilic nature can lead to rapid clearance from the surface of the eye before effective therapy can be achieved. As a result, prostaglandins are dosed in the form of selected esters to allow entry to the eye and a "prolonged" residence. When in the eye, native esterase enzymes cleave the prostaglandin ester to release the active species. Despite this innovation, current drop administered prostaglandins, for example, latanoprost, bimatoprost, and travoprost, still require daily or several times daily dosing regimens

and may cause irritation or hyperemia to the eye in some patients. In addition, nearly half of patients on prostaglandin therapy for glaucoma require a second agent for control of IOP (Physician Drug and Diagnosis Audit (PDDA) from Verispan, L.L.C. January-June, 2003)

Carbonic anhydrase inhibitors (CAIs) are used as an alternative and sometimes in conjunction with prostaglandins to treat eye disorders. Unfortunately, compliancy issues can occur as these medications also require daily or dosing up to four times a day, and may also cause irritation or hyperemia to the eye in some patients.

Another potential avenue for the treatment of ocular disorders involves protecting neurons directly. Preliminary data on receptor tyrosine kinase inhibitors (RTKIs) and dual leucine zipper kinase inhibitors (DLKIs) suggests that instead of treating increasing ocular pressure, molecules such as Sunitinib and Crizotinib can prevent the nerve damage that is associated with it. Unfortunately, Sunitinib has had observed hepatotoxicity in both clinical trials and post-marketing clinical use.

References that describe treatments of ocular disorders and the synthesis of compounds related to treating ocular disorders include the following: Ongini et al., U.S. Pat. No. 8,058,467 titled “Prostaglandin derivatives”; Qlt Plug Delivery Inc, WO2009/035565 titled “Prostaglandin analogues for implant devices and methods”; Allergan Inc, U.S. Pat. No. 5,446,041 titled “Intraocular pressure reducing 11-acyl prostaglandins”; Upjohn Co., DE2263393 titled “9-O-Acylated prostaglandins F2a”; Shionogi & Co. patent publication 948,179 titled “Treatment for hypertension or glaucoma in eyes”; Ragactive, EP1329453 titled “Method for obtaining 4-(n-alkylamine)-5, 6-dihydro-4h-thieno-(2,3-b)-thiopyran-2-sulfonamide-7, 7-dioxides and intermediate products”; and American Cyanamid Co. GB844946 titled “2-(N-Substituted)acylamino-1,3,4-thiadiazole-5-sulfonamides”.

Other publications include Vallikivi, I., et al. (2005). "The modelling and kinetic investigation of the lipase-catalyzed acetylation of stereoisomeric prostaglandins." J. Mol. Catal. B: Enzym. 35(1-3): 62-69.; Parve, O., et al. (1999). "Lipase-catalyzed acylation of prostanoids." Bioorg. Med. Chem. Lett. 9(13): 1853-1858.; and Carmely, S., et al. (1980) "New prostaglandin (PGF) derivatives from the soft coral Lobophyton depressum" Tetrahedron Lett. 21(9): 875-878.

Patent applications that describe DLK inhibitors include: Zhejiang DTRM Biopharma Co., patent publication WO2014146486 titled “Three-level cyclic amine ALK kinase inhibitor for treating cancer”; Kyowa Hakko Kogyo Co., patent publication WO2005012257 titled “Indazole

Derivatives"; Genetech, patent publication WO2014177524 titled "C-linked heterocycloalkyl substituted pyrimidines and their uses", and patent publication WO2013174780 titled "Substituted dipyridylamines and uses thereof".

Patent applications that describe derivatives of prostaglandins include: Allergan, 5,767,154 titled "5-tran-prostaglandins of the F series and their use as ocular hypotensives", US5767154 titled "5-trans-prostaglandins of the F series and their use as ocular hypotensives"; Alcon Laboratories, EP0667160A2 titled "Use of certain prostaglandin analogues to treat glaucoma and ocular hypertension", EP667160 titled "Use of certain prostaglandin analogues to treat glaucoma and ocular hypertension; Asahi glass company and Santen Pharmaceutical Co., EP0850926A2 titled "Difluoroprostaglandin derivatives and their use"; Asahi Glass Co., JP2000080075 titled "Preparation of 15-deoxy-15,15-difluoroprostaglandins as selective and chemically-stable drugs", JP11255740 titled "Preparation of 15-deoxy-15-monofluoroprostaglandin derivatives", JP10087607 titled "Preparation of fluorine-containing prostaglandins as agents for inducing labor and controlling animal sexual cycle", WO9812175 titled "Preparation of fluorinated prostaglandin derivatives for treatment of glaucoma"; Santen Pharmaceutical Co., JP10259179 titled "Preparation of multi-substituted aryloxy-group containing prostaglandins and their use", EP850926 titled "Preparation of difluoroprostaglandin derivatives and their use for treatment of an eye disease".

Johns Hopkins University has filed a number of patents claiming formulations for ocular injections including WO2013/138343 titled "Controlled Release Formulations for the Delivery of HIF-1 Inhibitors", WO2013/138346 titled "Non-linear Multiblock Copolymer-drug Conjugates for the Delivery of Active Agents",WO2011/106702 titled "Sustained Delivery of Therapeutic Agents to an Eye Compartment", WO2016/025215 titled "Glucorticoid-loaded Nanoparticles for Prevention of Corneal Allograft Rejection and Neovascularization", WO2016/100392 titled "Sunitinib Formulations and Methods for Use Thereof in Treatment of Ocular Disorders", WO2016/100380 titled "Sunitinib Formulation and Methods for Use Thereof in Treatment of Glaucoma", WO2016/118506 titled "Compositions for the Sustained Release of Anti-Glaucoma Agents to Control Intraocular Pressure", WO2013/166385 titled "Nanocrystals, Compositions, and Methods that Aid Particle Transport in Mucus", WO2005/072710 titled "Drug and Gene Carrier Particles that Rapidly move Through Mucus Barriers,"WO2008/030557 titled "Compositions and Methods for Enhancing Transport through Mucus", WO2012/061703 titled "Compositions and

Methods Relating to Reduced Mucoadhesion," WO2012/039979 titled "Large Nanoparticles that Penetrate Tissue," WO2012/109363 titled "Mucus Penetrating Gene Carriers", WO2013/090804 titled "Biodegradable Stealth Nanoparticles Prepared by a Novel Self-Assembly Emulsification Method," WO2013/110028 titled "Nanoparticles Formulations with Enhanced Mucosal Penetration", and WO2013/166498 titled "Lipid-based Drug Carriers for Rapid Penetration through Mucus Linings".

GrayBug Vision, Inc. discloses prodrugs for the treatment of ocular therapy in US 2018-0036416, US 2018-0064823, US 2018-0028673, granted U.S. Patent 9,808,531 and PCT application WO2017/053638. Aggregating microparticles for ocular therapy are described in US 2017-0135960 and WO2017/083779.

U.S. Patent application 2010/227865 titled "Oligomer-Beta Blocker Conjugates" describes beta-blocker mono prodrugs.

The object of this invention is to provide additional compounds, compositions and methods to treat ocular disorders.

## SUMMARY

The present invention provides new prodrugs of therapeutically active compounds, including oligomeric prodrugs, and compositions thereof of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or composition thereof. In one embodiment, an active compound or its salt or composition, as described herein, is used to treat a medical disorder, for example glaucoma, a disorder mediated by carbonic anhydrase, a disorder mediated by a Rho-associated

kinase, a disorder mediated by a dual leucine zipper kinase, a disorder mediated by a tyrosine kinase inhibitor, a disorder mediated by VEGF, a disorder mediated by an α2 adrenergic receptor, a disorder or abnormality related to an increase in intraocular pressure (IOP), a disorder mediated by nitric oxide synthase (NOS), or a disorder requiring neuroprotection such as to regenerate/repair optic nerves. In one embodiment, the disorder is ocular. In another embodiment more generally, the disorder treated is allergic conjunctivitis, anterior uveitis, cataracts, dry or wet age-related macular degeneration (AMD), geographic atrophy, or diabetic retinopathy.

In one embodiment the compounds of the present invention have advantageous properties for ocular therapy. In one embodiment, the invention is a method for delivering an active drug to the eye that achieves a controlled release of the active material. This method optionally includes presenting the drug in a sustained delivery system such as a polymeric composition, a hydrophobic liquid, a hydrophobic solid, or a form of slow release reservoir or encapsulation. Often, ocular therapies are delivered to the eye in a form that is hydrophilic to be soluble in ocular fluid. In contrast in this invention, a hydrophobic prodrug of an active compound or a derivative thereof that can be delivered in a polymeric controlled delivery system is provided wherein the hydrophobic compound is more soluble within polymeric material than the ocular fluid, which slows release into ocular aqueous fluid.

In another embodiment, the compounds provided herein are designed to deliver two active compounds with the same, or instead different, but additive or synergistic mechanisms of action for ocular therapy to the eye.

In certain embodiments of the invention, at least one of the active therapeutic agents delivered in modified form is selected from a kinase inhibitor (for example, a tyrosine kinase inhibitor, a VEGF inhibitor, or a dual leucine zipper kinase inhibitor), a prostaglandin, an $\alpha_2$ adrenergic agonist, a carbonic anhydrase inhibitor, a beta blocker, or a Rho-associated kinase (ROCK) inhibitor. Non-limiting examples of active therapeutic agents include Sunitinib or a derivatized version of Sunitinib (for example, with a hydroxyl, amino, thio, carboxy, keto or other functional group instead of fluoro that can be used to covalently connect the hydrophobic moiety), pazopanib, axitinib, sorafenib, ponatinib, lenvatinib, vandetanib, cabozantinib, regorafenib, Latanoprost, dinoprost, travoprost, tafluprost, unoprostone, Timolol, Metipranolol, Brinzolamide, Dorzolamide, Acetazolamide, Methazolamide, Crizotinib, KW-2449, Tozasertib, bimatoprost, brimonidine, SR5834, and SR3677.

In one embodiment compounds of the invention can be used for the controlled administration of active compounds to the eye, over a period of at least two, three, four, five or six months or more in a manner that maintains at least a concentration in the eye that is effective for the disorder to be treated. In some embodiments, the prodrug is provided in a microparticle, microcapsule, vesicle, reservoir, or nanoparticle. In one embodiment, the drug is administered in a polymeric formulation that provides an advantageous release of compound. In one embodiment even the lowest concentration of release over the designated time period is at or above a therapeutically effective dose. In one embodiment, this is achieved by formulating a hydrophobic prodrug of the invention in a polymeric delivery material such as a polymer or copolymer that includes at least moieties of lactic acid, glycolic acid, propylene oxide or ethylene oxide. In a particular embodiment, the polymeric delivery system includes polylactide-co-glycolide, PLA or PGA with or without covalently attached or admixed polyethylene glycol. For example, the hydrophobic drug may be delivered in a mixture of PLGA and PLGA-PEG or PEG.

In certain embodiments, the prodrug of the present invention is delivered in a microparticle or nanoparticle that is a blend of two polymers, for example (i) a PLGA polymer or PLA polymer as described herein and (ii) a PLGA-PEG or PLA-PEG copolymer. In another embodiment, the microparticle or nanoparticle is a blend of three polymers, such as, for example, (i) a PLGA polymer; (ii) a PLA polymer; and, (iii) a copolymer of PLGA-PEG or PLA-PEG. In an additional embodiment, the microparticle or nanoparticle is a blend of (i) a PLA polymer; (ii) a PLGA polymer; (iii) a PLGA polymer that has a different ratio of lactide and glycolide monomers than the PLGA in (ii); and, (iv) a PLGA-PEG or PLA-PEG copolymer. Any ratio of lactide and glycolide in the PLGA can be used that achieves the desired therapeutic effect. In certain illustrative non-limiting embodiments, the ratio of PLA to PLGA by weight in a polymer blend as described is 77/22, 69/30, 49/50, 54/45, 59/40, 64/35, 69/30, 74/25, 79/20, 84/15, 89/10, 94/5, or 99/1.

In certain embodiments, a blend of three polymers that has (i) PLA (ii) PLGA (iii) PLGA with a different ratio of lactide and glycolide monomers than PLGA in (ii) wherein the ratio by weight is 74/20/5 by weight, 69/20/10 by weight, 69/25/5 by weight, or 64/20/15 by weight. In certain embodiments, the PLGA in (ii) has a ratio of lactide to glycolide of 85/15, 75/25, or 50/50. In certain embodiments the PLGA in (iii) has a ratio of lactide to glycolide of 85/15, 75/25, or 50/50.

In certain aspects, the drug may be delivered in a blend of PLGA or PLA and PEG-PLGA, including but not limited to (i) PLGA + approximately by weight 1% PEG-PLGA or (ii) PLA + approximately by weight 1% PEG-PLGA. In certain aspects, the drug may be delivered in a blend of (iii) PLGA/PLA + approximately by weight 1% PEG-PLGA. In certain embodiments, the blend of PLA, PLGA, or PLA/PGA with PLGA-PEG contains approximately from about 0.5% to about 10% by weight of a PEG-PLGA, from about 0.5% to about 5% by weight of a PEG-PLGA, from about 0.5% to about 4% by weight of a PEG-PLGA, from about 0.5% to about 3% by weight of a PEG-PLGA, from about 1.0% to about 3.0% by weight of a PEG-PLGA, from about 0.1% to about 10% of a PEG-PLGA, from about 0.1% to about 5% of a PEG-PLGA, from about 0.1% to about 1% PEG-PLGA, or from about 0.1% to about 2% PEG-PLGA.

In certain non-limiting embodiments, the ratio by weight percent of PLGA to PEG-PLGA in a two polymer blend as described is about 40/1, 45/1, 50/1, 55/1, 60/1, 65/1, 70/1, 75/1, 80/1, 85/1, 90/1, 95/1, 96/1, 97/1, 98/1, 99/1. The PLGA can be acid or ester capped. In non-limiting aspects, the drug can be delivered in a two polymer blend of PLGA75:25 4A + approximately 1% PEG-PLGA50:50; PLGA85:15 5A + approximately 1% PEG-PLGA5050; PLGA75:25 6E + approximately 1% PEG-PLGA50:50; or, PLGA50:50 2A + approximately 1% PEG-PLGA50:50.

In certain non-limiting embodiments, the ratio by weight percent of PLA/PLGA-PEG in a polymer blend as described is about 40/1, 45/1, 50/1, 55/1, 60/1, 65/1, 70/1, 75/1, 80/1, 85/1, 90/1, 95/1, 96/1, 97/1, 98/1, 99/1. The PLA can be acid capped or ester capped. In cetain aspects, the PLA is PLA 4.5A. In non-limiting aspects, the drug is delivered in a blend of PLA 4.5A + 1% PEG-PLGA.

The PEG segment of the PEG-PLGA may have, for example, in non-limiting embodiments, a molecular weight of at least about 1 kDa, 2 kDa, 3 kDa, 4 kDa, 5 kDa, 6 kDa, 7 kDa, 8 kDa, 9 kDa, or 10 kDa, and typically not greater than 10 kDa, 15 kDa, 20 kDa, or 50 kDa, or in some embodiments, 6 kDa, 7 kDa, 8 kDa, or 9kDa. In certain embodiment, the PEG segment of the PEG-PLGA has a molecular weight between about 3 kDa and about 7 kDa or between about 2 kDa and about 7 kDa. Non-limiting examples of the PLGA segment of the PEG-PLGA is PLGA50:50, PLGA75:25, or PLGA85:15. In one embodiment, the PEG-PLGA segment is PEG (5 kDa)-PLGA50:50.

When the drug is delivered in a blend of PLGA + PEG-PLGA, any ratio of lactide and glycolide in the PLGA or the PLGA-PEG can be used that achieves the desired therapeutic effect.

Non-limiting illustrative embodiments of the ratio of lactide/glycolide in the PLGA or PLGA-PEG are about 5/95, 10/90, 15/85, 20/80, 25/75, 30/70, 35/65, 40/60, 45/55, 50/50, 55/45, 60/40, 65/35, 70/30, 75/25, 80/20, 85/15, 90/10, or 95/5. In one embodiment, the PLGA is a block co-polymer, for example, diblock, triblock, multiblock, or star-shaped block. In one embodiment, the PLGA is a random co-polymer. In certain aspects, the PLGA is PLGA75:25 4A; PLGA85:15 5A; PLGA75:25 6E; or, PLGA50:50 2A.

In another embodiment, the polymer includes a polyethylene oxide (PEO) or polypropylene oxide (PPO). In certain aspects, the polymer can be a random, block, diblock, triblock or multiblock copolymer (for example, a polylactide, a polylactide-co-glycolide, polyglycolide or Pluronic). For injection into the eye, the polymer is pharmaceutically acceptable and typically biodegradable so that it does not have to be removed. As described in Example 9 and shown in Figure 32, Figure 33, Figure 34, and Figure 35, cumulative drug release of prodrugs of the invention occurs over a period of up to approximately 90 days. Drug release of brinzolamide-acetyl PLA (n=5) (18-3) as shown in Figure 32 is measured and occurs from day 0 to approximately day 90.

The decreased rate of release of the active material to the ocular compartment may result in decreased inflammation, which has been a significant side effect of ocular therapy to date.

It is also important that the decreased rate of release of the drug while maintaining efficacy over an extended time of up to 2, 3, 4, 5 or 6 months be achieved using a particle that is small enough for administration through a needle without causing significant damage or discomfort to the eye and not to give the illusion to the patient of black spots floating in the eye. This typically means the controlled release particle should be less than approximately 300, 250, 200, 150, 100, 50, 45, 40, 35, or 30 μm, such as less than approximately 30, 29, 28, 27, 26, 25, 24, 23, 22 21, or 20 μm. In one aspect, the particles do not agglomerate in vivo to form larger particles, but instead in general maintain their administered size and decrease in size over time.

The hydrophobicity of the conjugated drug can be measured using a partition coefficient (P; such as LogP in octanol/water), or distribution coefficient (D; such as Log D in octanol/water) according to methods well known to those of skill in the art. LogP is typically used for compounds that are substantially un-ionized in water and LogD is typically used to evaluate compounds that ionize in water. In certain embodiments, the conjugated derivatized drug has a LogP or LogD of greater than approximately 2.5, 3, 3.5, 4, 4.5, 5, 5.5 or 6. In other embodiments, the conjugated

derivatized drug has a LogP or LogD which is at least approximately 1, 1.5, 2, 2.5, 3, 3.5 or 4 LogP or LogD units, respectively, higher than the parent hydrophilic drug.

Compounds of Formula I, Formula II, and Formula III are prodrugs or derivatives of prostaglandins.

In certain embodiments, compounds of Formula I Formula II, and Formula III are hydrophobic prodrugs of prostaglandins.

Compound of Formula IV are single agent prodrugs of a prostaglandin and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

Compounds of Formula V, Formula VI, Formula V', and Formula VI' are single agent prodrug conjugates of a prostaglandin and one or more Timolol derivatives allowing for the release of both compounds in the eye. In one embodiment both compounds are released concurrently.

Compounds of Formula VII and Formula VIII are hydrophobic prodrugs of the $\alpha_2$ adrenergic agonist brimonidine.

In certain embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of a prostaglandin and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of a carbonic anhydrase inhibitor and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of a Rho kinase inhibitor and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of Sunitinib and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula IX and Formula IX' are single agent prodrug conjugates of a beta-blocker and brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula X, Formula XI, and Formula XII are single agent prodrug conjugates of a prostaglandin and a Sunitinib derivative allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula X, Formula XI, and Formula XII are single agent prodrug conjugates of brimonidine and a Sunitinib derivative allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula X, Formula XI, and Formula XII are single agent prodrug conjugates of Timolol and a Sunitinib derivative allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

Compounds of Formula X' are prodrugs or derivatives of Sunitinib.

In certain embodiments, compounds of Formula X' are hydrophobic prodrugs of Sunitinib.

In other embodiments, compounds of Formula XIII are single agent prodrug conjugates of Timolol and a prostaglandin derivative allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XIII are single agent prodrug conjugates of Timolol and Brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula XIV are hydrophobic prodrugs of the beta-blocker Timolol.

In alternative embodiments, compound of Formula XIV are pharmaceutically acceptable salts of hydrophobic prodrugs of the beta-blocker Timolol.

In certain embodiments, compounds of Formula XV, Formula XV', Fomula XV'', and Formula LIV are single agent prodrug conjugates of a prostaglandin and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XV, Formula XV', Fomula XV'', and Formula LIV are single agent prodrug conjugates of a carbonic anhydrase inhibitor and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XV, Formula XV', Fomula XV'', and Formula LIV are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XV, Formula XV', Fomula XV'', and Formula LIV are single agent prodrug conjugates of Brimonidine and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XV, Formula XV', Fomula XV'', and Formula LIV are single agent prodrug conjugates of Rho kinase inhibitors and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula XVI and Formula XVII are hydrophobic prodrugs of the beta-blocker Timolol.

In alternative embodiments, compounds of Formula XVI and Formula XVII are pharmaceutically acceptable hydrophobic prodrugs of the beta-blocker Timolol.

In certain embodiments, compounds of Formula XVII', Formula XVII'', and Formula XVII''' are hydrophobic prodrugs of Brimonidine.

In alternative embodiments, compounds of Formula XVII', Formula XVII'', and Formula XVII''', are pharmaceutically acceptable hydrophobic prodrugs of Brimonidine.

In certain embodiments, compounds of Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, and Formula XXI are single agent prodrug conjugates of a dual leucine zipper kinase and a prostaglandin allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, and Formula XXI are single agent prodrug conjugates of a dual leucine zipper kinase inhibitor and Brimonidine allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments. compounds of Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, and Formula XXI are single agent prodrug conjugates of a dual leucine zipper kinase inhibitor and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, and Formula XXI are single agent prodrug conjugates of a dual leucine zipper kinase inhibitor and Suntinib allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula XXII, Formula XXIII, Formula XXIV, Formula XXV, Formula XVI, and Formula XVII are single agent prodrug conjugates of a carbonic anhydride inhibitor and a prostaglandin allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXII, Formula XXIII, Formula XXIV, Formula XXV, Formula XVI, and Formula XVII are single agent prodrug conjugates of a carbonic anhydride inhibitor and a beta-blocker allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXII, Formula XXIII, Formula XXIV, Formula XXV, Formula XVI, and Formula XVII are single agent prodrug conjugates of a carbonic anhydride inhibitor and a dual leucine zipper kinase inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula XXVIII, Formula XXVIIIa, Formula XXIX, Formula XXIXa, Formula XXX, and Formula XXXa are single agent prodrug conjugates of a ROCK inhibitor and a prostaglandin allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXVIII, Formula XXVIIIa, Formula XXIX, Formula XXIXa, Formula XXX, and Formula XXXa are single agent prodrug conjugates of a ROCK inhibitor and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXVIII, Formula XXVIIIa, Formula XXIX, Formula XXIXa, Formula XXX, and Formula XXXa are single agent prodrug conjugates of a ROCK inhibitor and a carbonic anhydride inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXVIII, Formula XXVIIIa, Formula XXIX, Formula XXIXa, Formula XXX, and Formula XXXa are single agent prodrug conjugates

of a ROCK inhibitor and a dual leucine zipper kinase inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

Compounds of Formula XXXI, XXXII, and XXXIII are hydrophobic prodrugs of ROCK inhibitors.

In certain embodiments, compounds of Formula XXXIV are single agent prodrug conjugates of a prostaglandin and Metipranolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV are single agent prodrug conjugates of a carbonic anhydrase inhibitor and Metipranolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and Metipranolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV are single agent prodrug conjugates of Brimonidine and Metipranolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV are single agent prodrug conjugates of Timolol and Metipranolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

Compounds of Formula XXXV are hydrophobic prodrugs of Metipranolol.

In certain embodiments, compounds of Formula XXXIV and Formula XXXVIII are single agent prodrug conjugates of a prostaglandin and Levobunolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV and Formula XXXVIII are single agent prodrug conjugates of a carbonic anhydrase inhibitor and Levobunolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV and Formula XXXVIII are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and Levobunolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV and Formula XXXVIII are single agent prodrug conjugates of Brimonidine and Levobunolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XXXIV and Formula XXXVIII are single agent prodrug conjugates of Timolol and Levobunolol allowing release of both compounds in the eye.

Compounds of Formula XXXVII and Formula XXXIX are mono-prodrugs of a Levobunolol derivative.

In certain embodiments, compounds of Formula XL and Formula XLII are single agent prodrug conjugates of a prostaglandin and Carteolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XL and Formula XLII are single agent prodrug conjugates of a carbonic anhydrase inhibitor and Carteolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XL and Formula XLII are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and Carteolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XL and Formula XLII are single agent prodrug conjugates of Brimonidine and Carteolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XL and Formula XLII are single agent prodrug conjugates of Timolol and Carteolol allowing release of both compounds in the eye.

Compounds of Formula XLI and Formula XLII are mono-prodrugs of Carteolol.

In certain embodiments, compounds of Formula XLIV and Formula XLVI are single agent prodrug conjugates of a prostaglandin and Betaxolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XLIV and Formula XLVI are single agent prodrug conjugates of a carbonic anhydrase inhibitor and Betaxolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments compounds of Formula XLIV and Formula XLVI are single agent prodrug conjugates of dual leucine zipper kinase inhibitor and Betaxolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XLIV and Formula XLVI are single agent prodrug conjugates of Brimonidine and Betaxolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula XLIV and Formula XLVI are single agent prodrug conjugates of Timolol and Betaxolol allowing release of both compounds in the eye.

Compounds of Formula XLV and Formula XLVII are mono-prodrugs of Betaxolol.

Compounds of Formula XLVIII are bis-prodrugs of beta blockers.

Compounds of Formula XLIX are mono-prodrugs of beta blockers.

Compounds of Formula L are mono-prodrugs of the ROCK inhibitor SR5834.

Compounds of Formula LI are mono-prodrugs of the ROCK inhibitor SR3677.

In certain embodiments, compounds of Formula LII are prodrug conjugates of the ROCK inhibitor SR5834 and a prostaglandin allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LII are prodrug conjugates of the ROCK inhibitor SR5834 and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LII are prodrug conjugates of the ROCK inhibitor SR5834 and a carbonic anhydride inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LII are prodrug conjugates of the ROCK inhibitor SR5834 and a dual leucine zipper kinase inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In certain embodiments, compounds of Formula LIII are prodrug conjugates of the ROCK inhibitor SR3677 and a prostaglandin allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LIII are prodrug conjugates of the ROCK inhibitor SR3677 and Timolol allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LIII are prodrug conjugates of the ROCK inhibitor SR3677 and a carbonic anhydride inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

In alternative embodiments, compounds of Formula LIII are prodrug conjugates of the ROCK inhibitor SR3677 and a dual leucine zipper kinase inhibitor allowing release of both compounds in the eye. In one embodiment both compounds are released concurrently.

These compounds can be used to treat an ocular disorder in a host, for example a human, in need thereof. In one embodiment, a method for the treatment of such a disorder is provided that includes the administration of an effective amount of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or composition thereof, optionally in a pharmaceutically acceptable carrier, including a polymeric carrier, as described in more detail below.

Another embodiment is provided that includes the administration of an effective amount of an active compound or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier, including a polymeric carrier, to a host to treat an ocular or other disorder that can benefit from topical or local delivery. The therapy can be delivery to the anterior or posterior chamber of the eye. In specific aspects, the active compound is administered to treat a disorder of the cornea, conjunctiva, aqueous humor, iris, ciliary body, lens sclera, choroid, retinal pigment epithelium, neural retina, optic nerve or vitreous humor.

Any of the compounds described herein (Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX,

Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV) can be administered to the eye in a composition as described further herein in any desired form of administration, including via intravitreal, intrastromal, intracameral, sub-tenon, sub-retinal, retro-bulbar, peribulbar, suprachoroidal, choroidal, subchoroidal, conjunctival, subconjunctival, episcleral, posterior juxtascleral, circumcorneal, and tear duct injections, or through a mucus, mucin, or a mucosal barrier, in an immediate or controlled release fashion.

In any of the Formulas described herein (Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV) if the stereochemistry of a chiral carbon is not specifically designated in the Formula it is intended that the carbon can be used as an R enantiomer, an S enantiomer, or a mixture of enantiomers including a racemic mixture. Timolol as used Formula V, Formula VI, Formula V', Formula VI', Formula X, Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XVI, Formula XVII, Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXVIII, Formula XXVIIIa, Formula XXIX, Formula XXIXa, Formula

XXX, Formula XXXa, XXXIV, Formula XXXIV, Formula XXXVIII, Formula XL, Formula XLII, Formula LII, and Formula LII has (S)-stereochemistry as used in commercial Timolol maleate ophthalmic solutions, such as Istalol® and Timoptic®. On both U.S. FDA labels, Timolol maleate is described as a single enantiomer ((-)-1-(tert-butylamino) -3- [(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate) that "possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer." The (S)-enantiomer has CAS No. 26839-75-8 and the (R)-enantiomer has CAS No. 26839-76-9, but only the (S)-enantiomer is described as "Timolol". Likewise, compounds presented which are or are analogs of commercial products are provided in their approved stereochemistry for regulatory use, unless otherwise instructed.

In addition, moieties that have repetitive units, for example including but not limited to an oligomer of polylactic acid, polypropylene oxide, and polylactide-coglycolide that has a chiral carbon can be used with the chiral carbons all having the same stereochemistry, random stereochemistry, or ordered but different stereochemistry such as a block of S enantiomer units followed by a block of R enantiomer units in each oligomeric unit. In some embodiments lactic acid is used in its naturally occurring S enantiomeric form.

In certain embodiments, the conjugated active drug is delivered in a biodegradable microparticle or nanoparticle that has at least approximately 5, 7.5, 10, 12.5, 15, 20, 25 or 30% or more by weight conjugated active drug. In some embodiments, the biodegradable microparticle degrades over a period of time and in any event provides controlled delivery that lasts at least approximately 2 months, 3 months, 4 months, 5 months or 6 months or more. In some embodiments, the loaded microparticles are administered via subconjunctival or subchoroidal injection.

In certain embodiments, the conjugated active drug is delivered as the pharmaceutically acceptable salt form. Salt forms of a compound will exhibit distinctive solution and solid-state properties compared to their respective free base or free acid form, and for this reason pharmaceutical salts are used in drug formulations to improve aqueous solubility, chemical stability, and physical stability issues. Lipophilic salt forms of compounds, which have enhanced solubility in lipidic vehicles relative to the free acid or free base forms of compounds, are often advantageous in terms of pharmacological properties due in part to their low melting points. Lipophilic salt forms of compounds are used to increase aqueous solubility for oral and parenteral drug delivery, enhance permeation across hydrophobic barriers, and enhance drug loading in lipid-

based formulations. As discussed in Example 7, lipophilic salt forms of Timolol prodrugs were soluble in water and DMSO and as discussed in Example 9, the theoretical drug loading of Timolol salt forms was 13.8%. Figure 35 shows the drug release kinetics of salt forms of Timolol and irrespective of the salt, Timolol prodrugs were released within 25 days.

In all of the polymer moieties described in this specification, where the structures are depicted as block copolymers (for example, blocks of "x" followed by blocks of "y"), it is intended that the polymer can alternately be a random or alternating copolymer (for example, "x" and "y" are either randomly distributed or alternate). Unless stereochemistry is specifically indicated, each individual moiety of each oligomer that has a chiral center can be presented at the chiral carbon in (R) or (S) configuration or a mixture there of, including a racemic mixture.

Various Formulas below use R groups defined in other Formulas, each of which R group is meant to have the definition as presented in the first Formula that it was presented in unless explicitly changed by context.

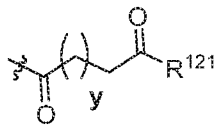
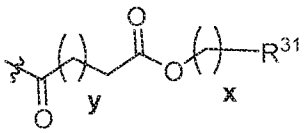
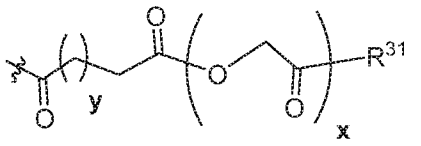
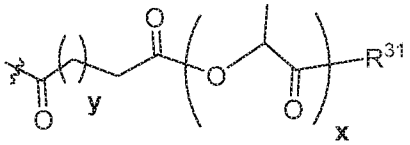
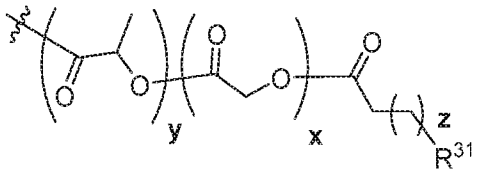
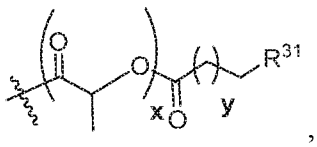
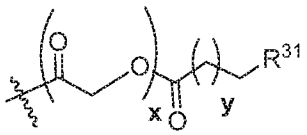
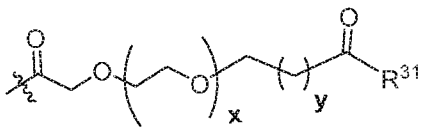
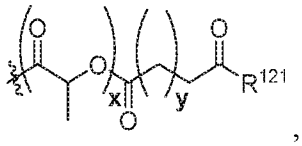
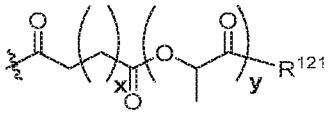
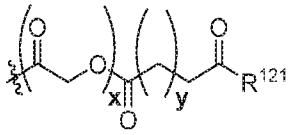
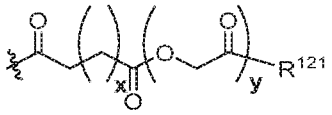
In most of the Formulas presented herein, the prodrugs are depicted as one or several active moieties covalently bound to or through a described prodrug moiety(ies) with a defined variable range of each of the active moiety and the prodrug moiety, typically through the use of descriptors n, m, o, x, y, z, u, v, w, x', y' or zz. As indicated below, these descriptors can independently have numerical ranges provided below, and in most embodiments, are typically within a smaller range, also as provided below. Each variable is independent such that any of the integers of one variable can be used with any of the integers of the other variable, and each combination is considered separately and independently disclosed, and set out below like this only for space considerations.

For example, n, m, and o can independently be any integer between 0 and 29 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29). In certain embodiments, n or m or o can independently be 0, 1, 2, 3, 4, 5, 6, 7 or 8, and in certain aspects, 1, 2, 3 or 4.

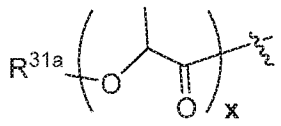
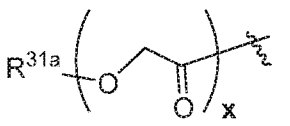
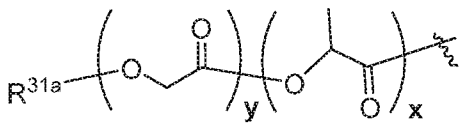
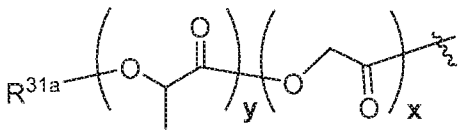
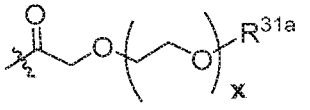
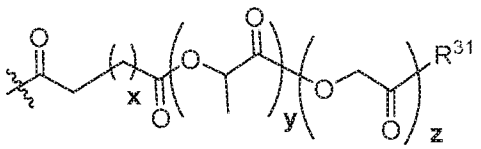
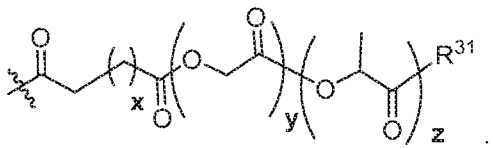
Likewise, x, y, and z can independently be any integer between 1 and 30 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30). In certain embodiments, x or y or z can independently be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 and in certain aspects, 1, 2, 3, 4, 5, or 6. In certain embodiments, x is 1, 2, 3, 4, 5, 6, 7, or 8. In certain embodiments, y is 1, 2, 3, 4, 5, 6, 7, or 8. In certain embodiments, x is 1, 2, 3, 4, 5, or 6. In certain embodiments, y is 1, 2, 3, 4, 5, or 6. In certain embodiments, z is 1, 2, 3, 4, 5, or 6. In certain

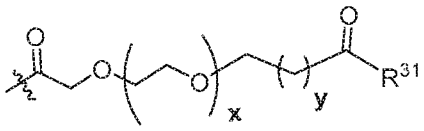
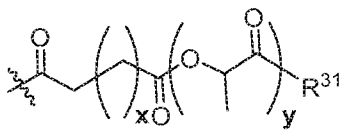
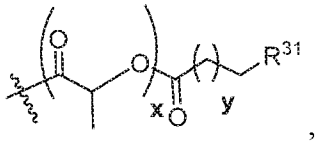
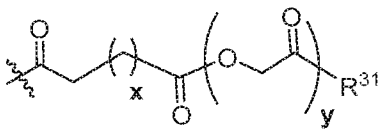
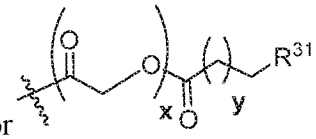
embodiments, y is 1, 2, or 3. In certain embodiments, x is 1, 2, or 3. In certain embodiments, x is an integer selected from 1, 2, 3, or 4 and y is 1. In certain embodiments, x is an integer selected from 1, 2, 3, or 4 and y is 2. In certain embodiments, x is in integer selected from 1, 2, 3, or 4 and y is 3.

Where x, y, or z is used in connection with a single atom, such as


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, or

, x, y, or z are typically independently 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12, and more typically 1, 2, 3, 4, 5 or 6, and even 1, 2, 3 or 4 or 1 or 2.

Where x, y, or z is used in connection with the monomeric residue in an oligomer, including for example but not limited to:


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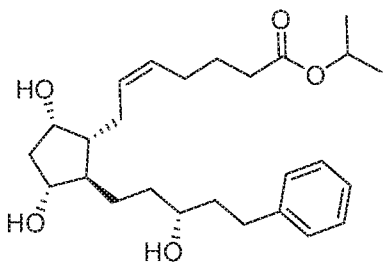
, or , then x, y or z is in some embodiments are independently 1, 2, 3, 4, 5, 6, 7 or 8, and even for example, 2, 4 or 6 residues.

Similarly, u, v, and w can independently be any integer between 0 and 29 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 ,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29) wherein u+v+w is 20 to 30 carbons. In certain embodiments, u or v or w can independently be 0, 1, 2, 3, 4, 5, 6, 7 or , and in certain aspects, 1, 2, 3 or 4.

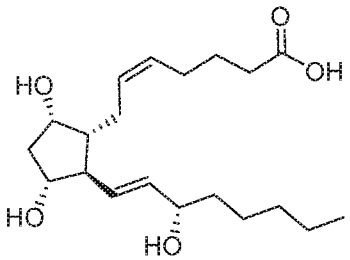
Also, x' and y' are independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and wherein if x' and y' are within the linker then x' and y' cannot both be 0. In some embodiments, x' and y' are independently 0, 1, 2, 3, 4, 5, 6 or 7, or even, 1, 2, 3, or 4.

The variable zz is selected from 1, 2, 3, 4, 5, or 6, and in some embodiments, 1, 2, 3 or 4, and in additional embodiments zz is selected from 7, 8, or 9. In additional embodiments, zz can be 0 if it results in a sufficiently stable compound.

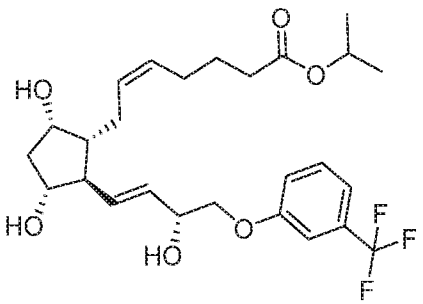
Non-limiting examples of Formula I and Formula II include at least hydrophobic prodrugs or derivatives of the following prostaglandins:



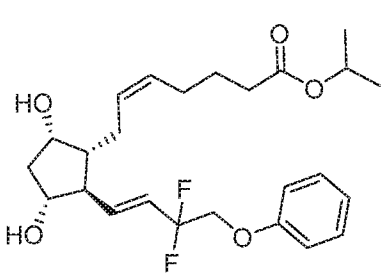
Latanoprost ,



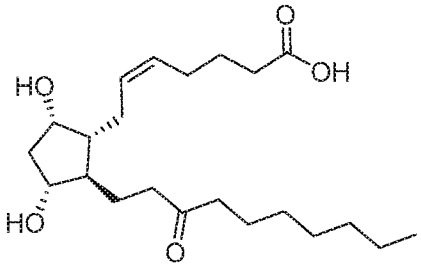
Dinoprost ,



Travoprost ,

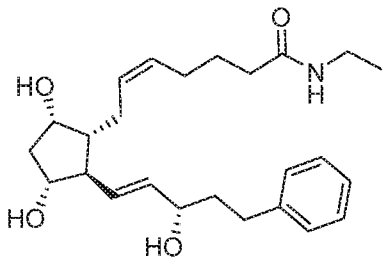


Tafluprost



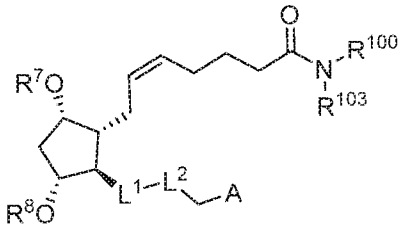
Unoprostone

and



Bimatoprost

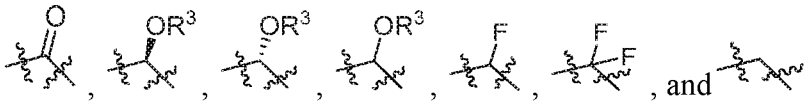
The disclosure provides a compound of Formula I:



(I)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$L^1$ is selected from: .

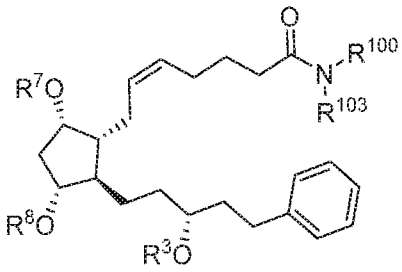
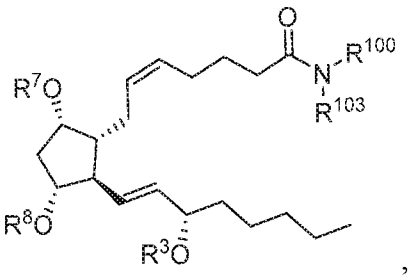
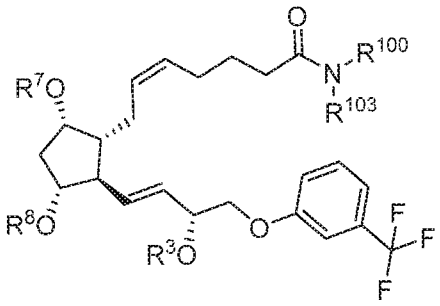
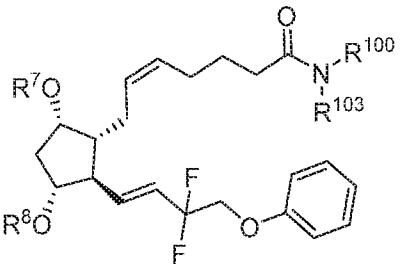
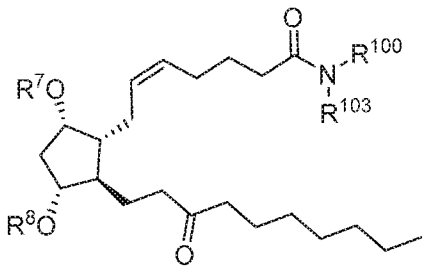
$L^2$ is selected from: .

A is selected from: H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy wherein each group can be optionally substituted with another desired substituent group which is pharmaceutically acceptable and sufficiently stable under the conditions of use, for example selected from $R^5$.

$R^{103}$ is selected from: H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy wherein each group can be optionally substituted with another desired substituent group which is pharmaceutically acceptable and sufficiently stable under the conditions of use, for example selected from $R^5$.

$R^3$ is selected from $-C(O)R^4$, $-C(O)A$, and hydrogen.

Non-limiting examples of Formula I include:


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, and

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$R^{100}$ is selected from:

(i) $C_1$-$C_{10}$alkyl, -$C_0$-$C_{10}$alkyl($C_3$-$C_7$cycloalkyl), heterocycle, –$C_0$-$C_{10}$alkyl($C_3$-$C_7$heterocycloalkyl), –aryl$C_0$-$C_{10}$alkyl, –heteroarylalkyl, -$C_0$-$C_{10}$alkyl$C_2$-$C_{10}$alkenyl, and $C_2$-$C_{10}$alkynyl;

(ii) an unsaturated fatty acid residue including but not limited the carbon fragment taken from linoleic acid (-$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$)), docosahexaenoic acid (–$(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid (-$(CH_2)_4(CHCHCH_2)_5CH_3$)), alpha-linolenic acid (–$(CH_2)_8(CHCHCH_2)_3CH_3$)) stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iii)–$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$,

–$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, -$C_{10}$-$C_{30}$alkenylalkynyl; and

(iv) $R^{50}$;

In one embodiment, –$C_{10}$-$C_{30}$ as used in the definition of $R^{100}$ is –$C_{12}$-$C_{28}$, –$C_{12}$-$C_{26}$, –$C_{12}$-$C_{24}$, –$C_{14}$-$C_{22}$, –$C_{14}$-$C_{20}$, –$C_{14}$-$C_{18}$, –$C_{14}$-$C_{16}$, or –$C_{12}$-$C_{14}$.

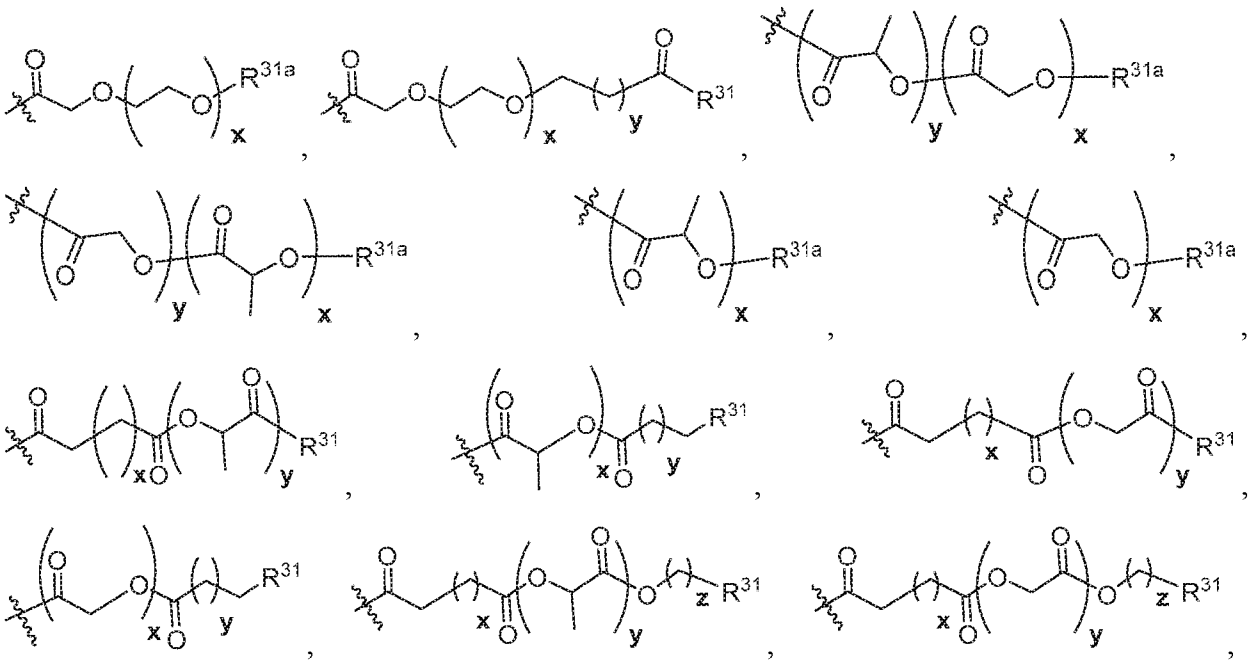
wherein in Formula I, $R^{100}$ can only be selected from (i), (ii), and (iii) above if at least one of $R^7$ and $R^8$, is selected to be $R^{50}$.

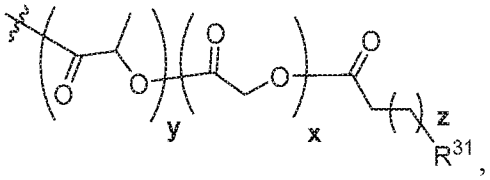
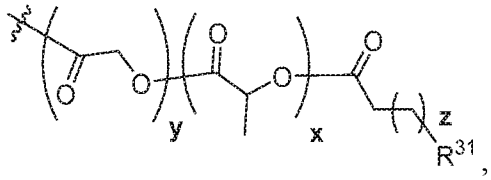
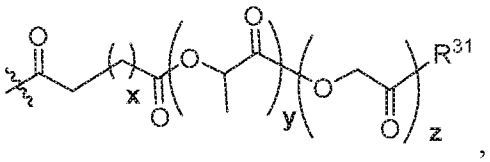
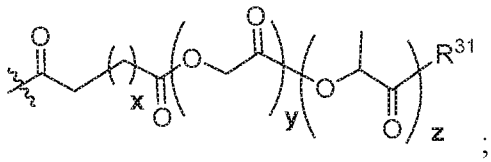
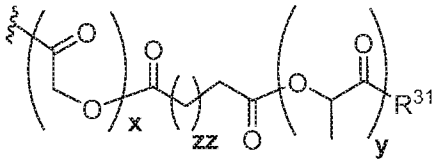
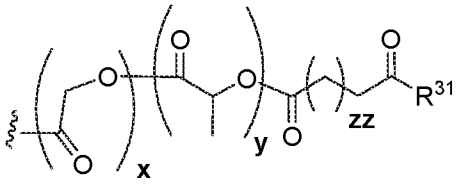
$R^5$ is selected from: halogen, hydroxyl, cyano, mercapto, amino, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -COOalkyl, and -CONH$_2$, each of which except halogen, cyano, and -Si(CH$_3$)$_3$ may be optionally substituted, for example with halogen, alkyl, aryl, heterocycle or heteroaryl if desired and if the resulting compound is stable and achieves the desired purpose, wherein the group cannot be substituted with itself, for example alkyl would not be substituted with alkyl;

$R^7$ and $R^8$, are independently selected from: -C(O)$R^4$, -C(O)A, hydrogen, and $R^{50}$;

$R^{50}$ is selected from carbonyl derivatives of polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, and other biodegradable polymers, each of which $R^{50}$ can be optionally capped or substituted with a $R^{31}$;

or $R^{50}$ is selected from:

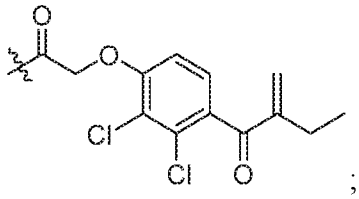


or $R^{50}$ is or ;

In some embodiments, the compound can be capped with hydrogen, or can be capped to create a terminal ester or ether. For example, the moiety can be capped with a terminal hydroxyl or carboxy which can be further derivatized to an ether or ester; and

$R^{31}$ is hydrogen, hydroxy, amino, A, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, orpolyethylene glycol;

$R^{31a}$ is hydrogen, A, -C(O)alkyl, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, stearoyl, or ;

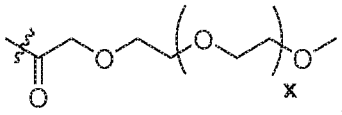
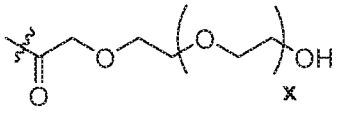
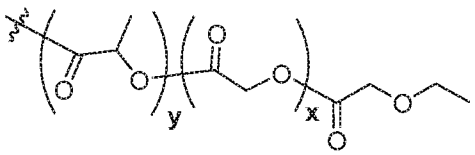
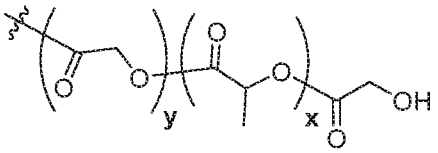
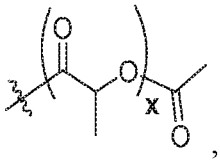
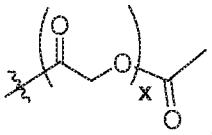
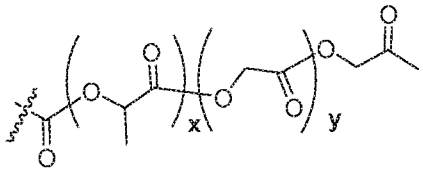
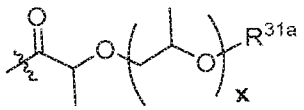
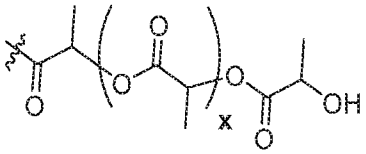
$R^4$ is selected from:

(i) $-C_{20}$-$C_{30}$alkyl$R^5$, $-C_{20}$-$C_{30}$alkenyl$R^5$, -$C_{20}$-$C_{30}$alkynyl$R^5$, -$C_{20}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{20}$-$C_{30}$alkyl, $-C_{20}$-$C_{30}$alkenyl, -$C_{20}$-$C_{30}$alkynyl, -$C_{20}$-$C_{30}$alkenylalkynyl;

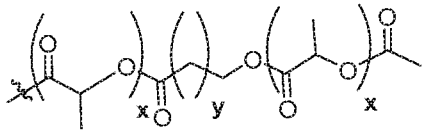
(ii) an unsaturated fatty acid residue containing at least 20 carbon atoms including but not limited to the carbon chains from docosahexaenoic acid ($-(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid ($-(CH_2)_4(CHCHCH_2)_5CH_3$)), docosatetraenoic acid, and nervonic acid, and wherein, if desired, each of which can be substituted with $R^5$.

x, y, and z can independently be any integer between 1 and 30 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30).

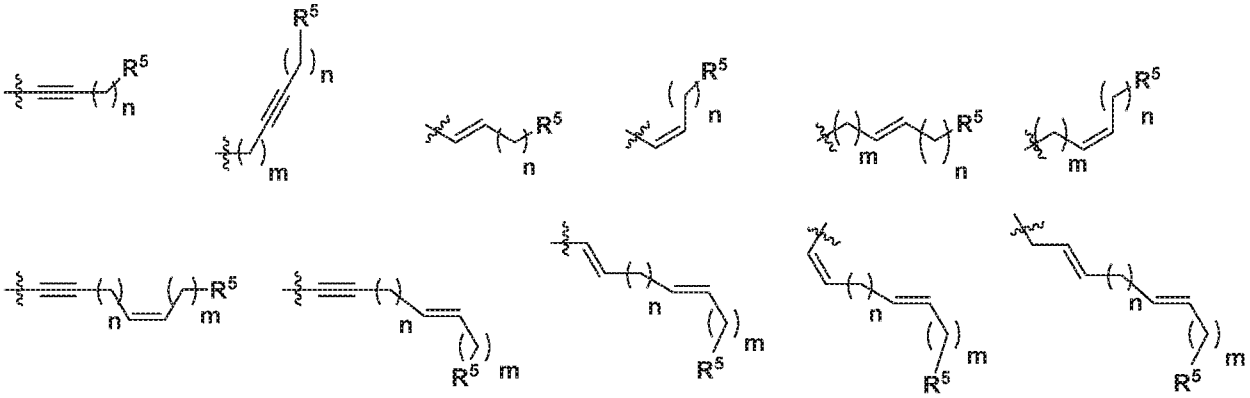
Non-limiting examples of $R^{50}$ include:

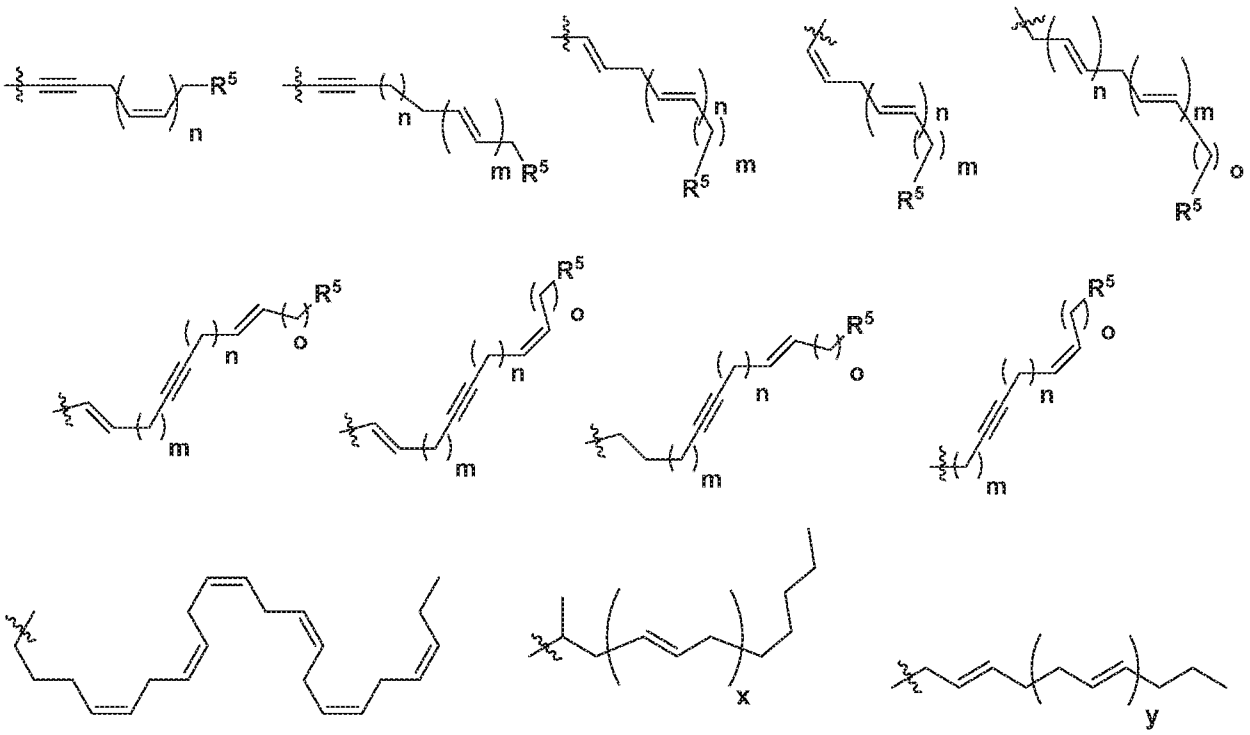

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Additional non-limiting examples of $R^{50}$ include:


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Non-limiting examples of $R^4$ include:



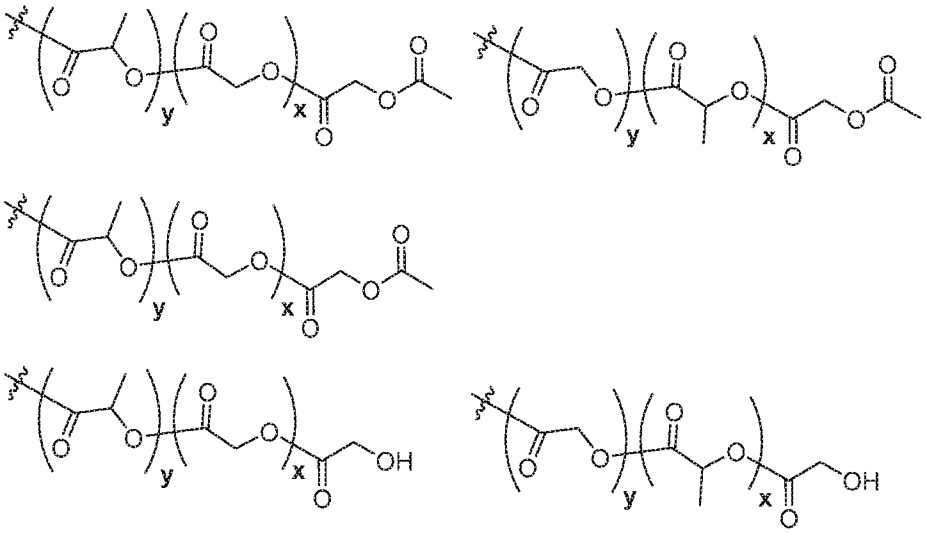


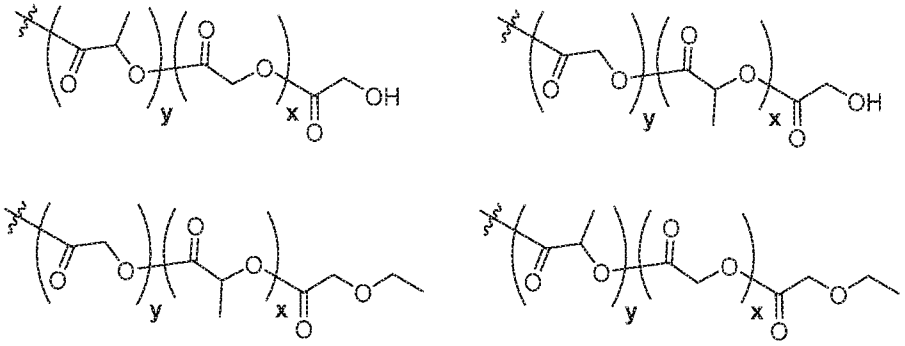
n, m, and o can independently be any integer between 0 and 29 (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 ,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29);

wherein as used in $R^4$ above n+m+o is 18 to 30 carbons;

In one embodiment x, y, and z are independently selected from the following ranges: 1 to 5, 6 to 11, 12 to 17, 18 to 23, and 24 to 30 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30).

Additional non-limiting examples of $R^{50}$ include:



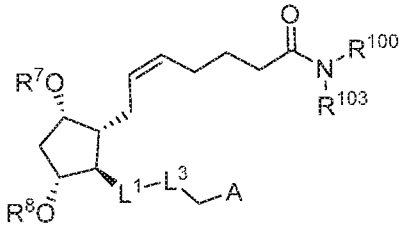


wherein x and y are as defined above.

In one embodiment $R^{100}$ is ethyl and $R^{103}$ is hydrogen.

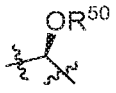
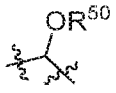
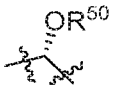
In one embodiment a compound of Formula I or Formula II is hydrolysable by an enzyme in vivo, such as an esterase.

The disclosure also provides a compound of Formula II:



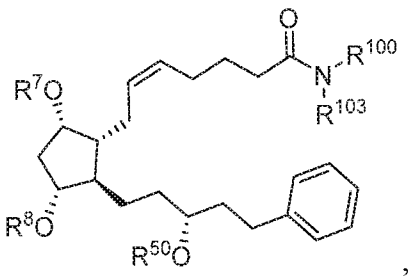
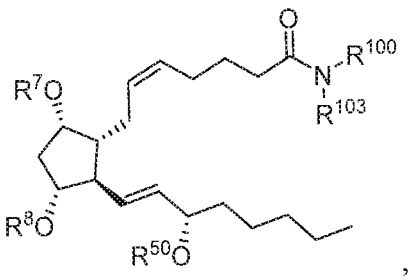
(II)

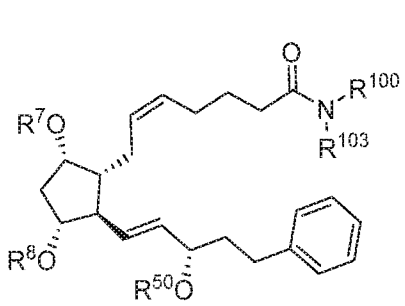
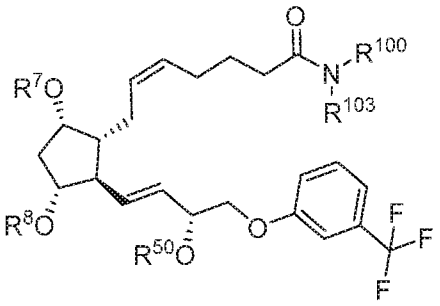
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$L^3$ is selected from: , , and ; and

wherein all other variables are as defined herein.

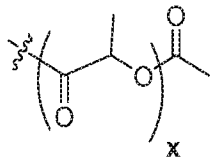
Non-limiting examples of Formula II include:

, ,

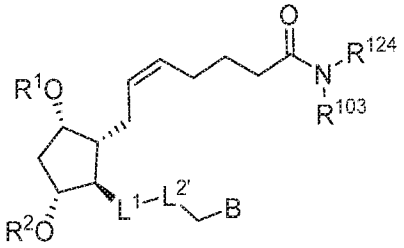
and .

In one embodiment, $R^{100}$ is ethyl and $R^{103}$ is hydrogen.

In one embodiment, $R^{50}$ is  .

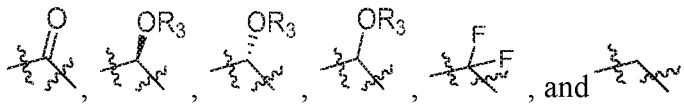
In one embodiment the disclosure provides a prodrug of a carbonic anhydrase inhibitor for ocular therapy, which can be released from a therapeutic, including a polymeric, delivery system while maintaining efficacy over an extended time such as up to 4, 5 or 6 months.

The disclosure provides a prostaglandin prodrug of Formula III:



(III),

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$L^{2'}$ is selected from:  ;

B is selected from: heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy wherein each group can be optionally substituted with another desired substituent group which is pharmaceutically acceptable and sufficiently stable under the conditions of use, for example selected from $R^5$; and

$R^1$, $R^2$, and $R^3$ are independently at each instance selected from: $-C(O)R^4$, C(O)A, and hydrogen,

wherein in Formula III, $R^1$ or $R^2$ is $-C(O)R^4$;

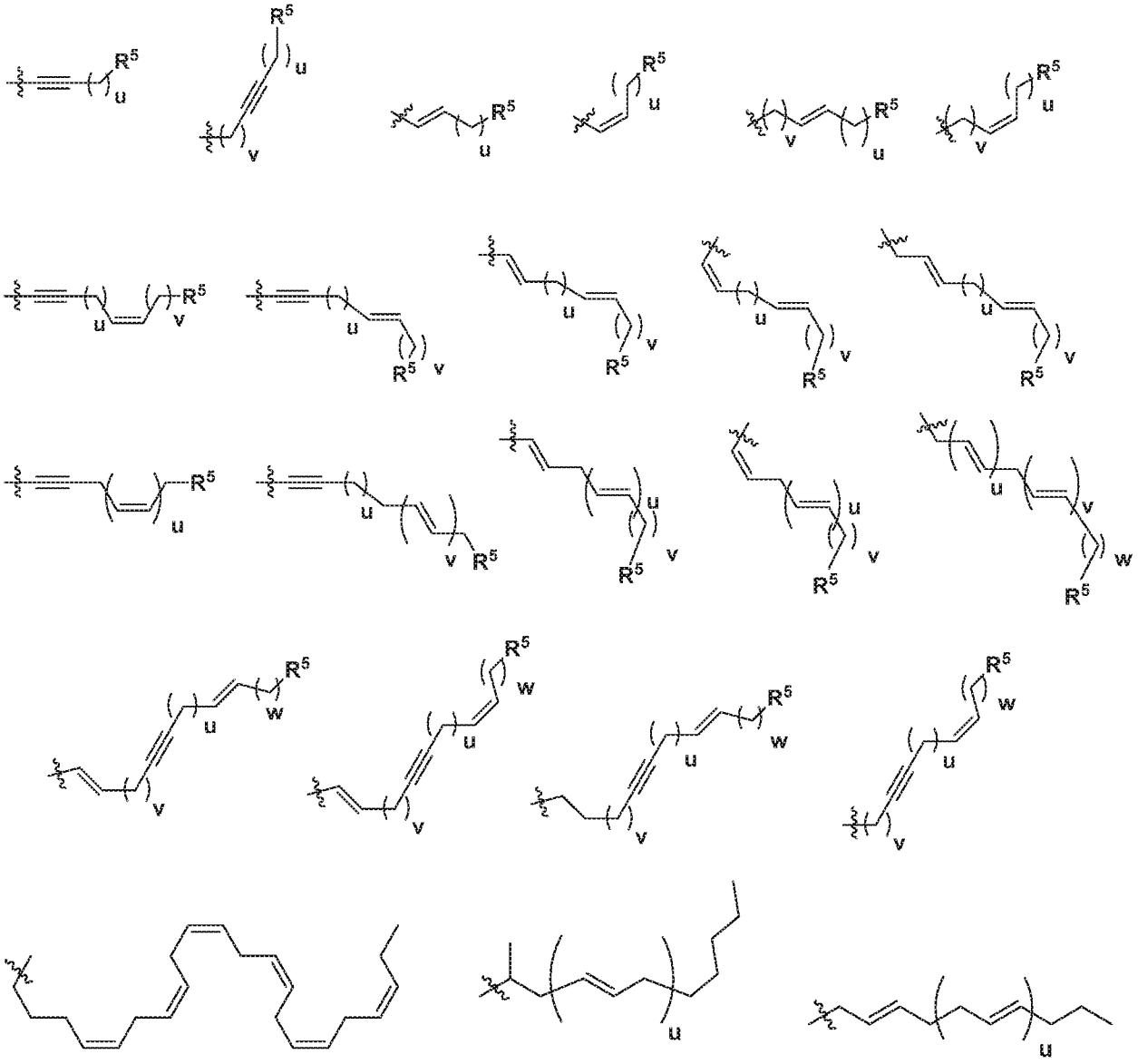
$R^{124}$ is selected from:

(i) an unsaturated fatty acid residue containing at least 22 carbon atoms including but not limited to the carbon chains from docosahexaenoic acid ($–(CH_2)_3(CHCHCH_2)_6CH_3$)), alpha-linolenic acid ($–(CH_2)_8(CHCHCH_2)_3CH_3$)), docosatetraenoic acid, and nervonic acid,

(ii) $–C_{22}$-$C_{30}$alkyl$R^5$, $–C_{22}$-$C_{30}$alkenyl$R^5$, -$C_{22}$-$C_{30}$alkynyl$R^5$, -$C_{22}$-$C_{30}$alkenylalkynyl$R^5$, $–C_{22}$-$C_{30}$alkyl, $–C_{22}$-$C_{30}$alkenyl, -$C_{22}$-$C_{30}$alkynyl, -$C_{22}$-$C_{30}$alkenylalkynyl;

and wherein, if desired, each $R^{124}$ can be substituted with $R^5$.

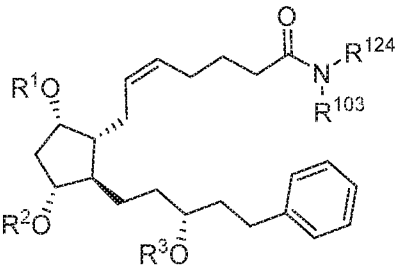
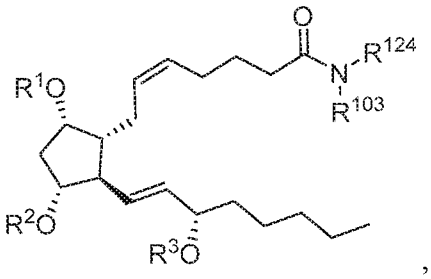
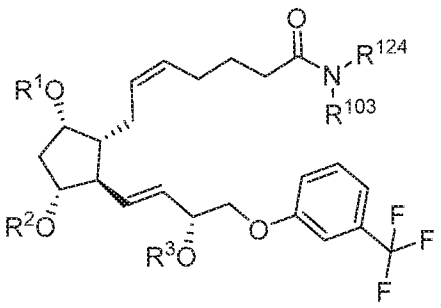
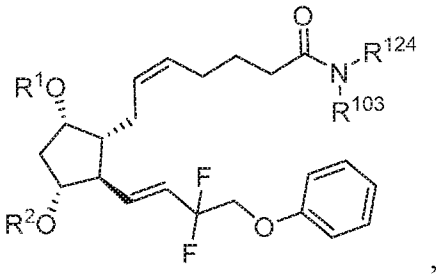
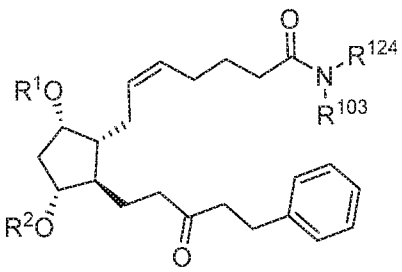
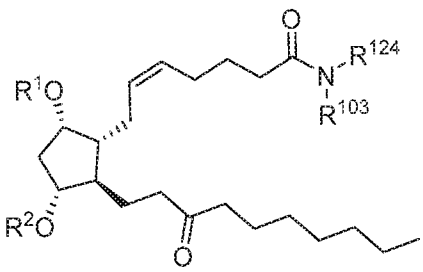
Non-limiting examples of $R^{124}$ include:



wherein u, v, and w can independently be any integer between 0 and 29 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17 ,18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29) wherein u+v+w is 20 to 30 carbons; and

wherein all other variables are as defined herein.

Non-limiting examples of Formula III include:


,

,

,

,

and

.

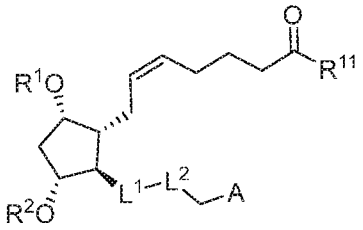
In one embodiment, $-C_{22}$-$C_{30}$ as used in the definition of $R^4$ is $-C_{22}$-$C_{28}$, $-C_{22}$-$C_{26}$, or $-C_{22}$-$C_{24}$.

While various structures are depicted as block copolymers (i.e., blocks of "x" followed by blocks of "y"), in some embodiments, the polymer can be a random or alternating copolymer ("x" and "y" are either randomly distributed or alternate).

In another embodiment a compound of Formula I, Formula II, or Formula III or a composition thereof is for use in the cosmetic enhancement of eyelash hair or eyebrow hair.

In another embodiment a compound of Formula I, Formula II, or Formula III or a composition thereof is used for the growth of eyelash or eyebrow hair.

The disclosure also provides a prodrug of Formula IV:



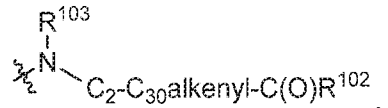
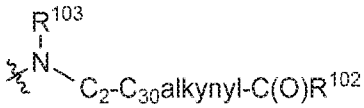
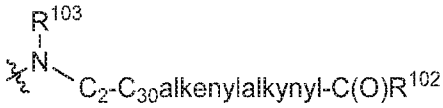
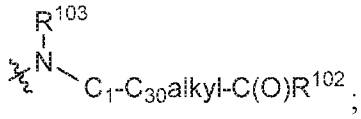
(IV)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{11}$ is selected from:

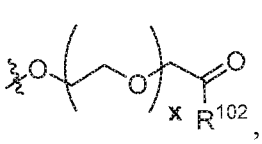
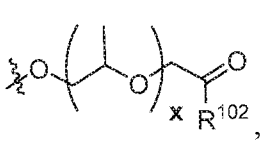
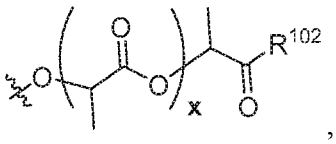
(i) $R^{102}$;

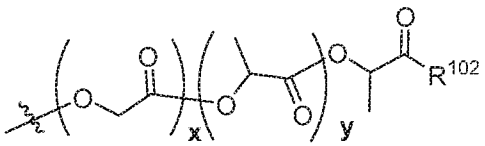
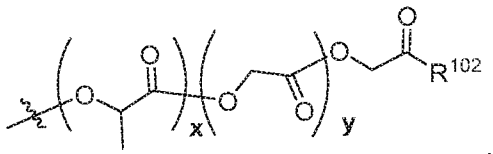
(ii) –NH-$C_2$-$C_{30}$alkenyl-C(O)$R^{102}$, -NH-$C_2$-$C_{30}$alkynyl-C(O)$R^{102}$, -NH-$C_2$-$C_{30}$alkenylalkynyl-C(O)$R^{102}$, -NH-$C_1$-$C_{30}$alkyl-C(O)$R^{102}$, -O-$C_2$-$C_{30}$alkenyl-C(O)$R^{102}$, -O-$C_2$-$C_{30}$alkynyl-C(O)$R^{102}$, -O-$C_2$-$C_{30}$alkenylalkynyl-C(O)$R^{102}$, and -O-$C_1$-$C_{30}$alkyl-C(O)$R^{102}$;

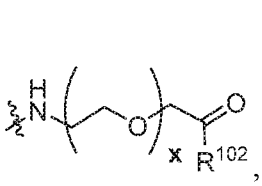
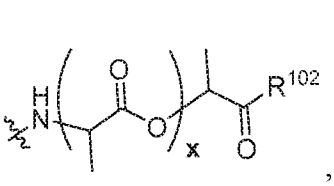
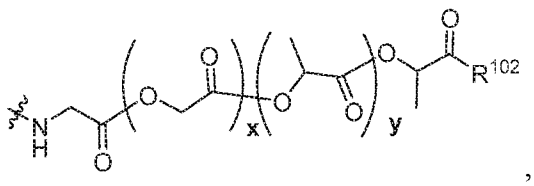
(iii) , ,  and ;

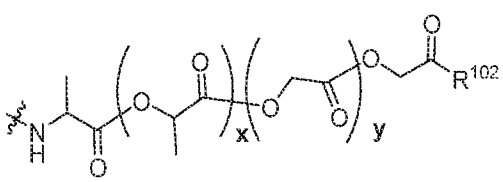
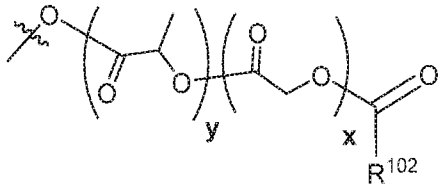
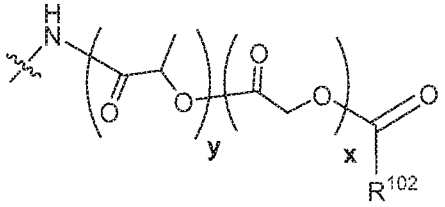
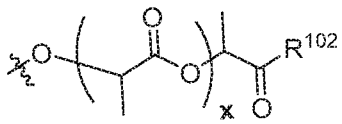
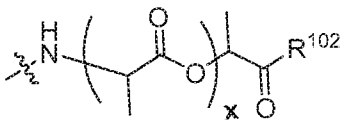
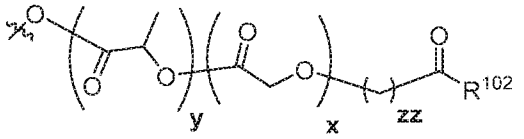
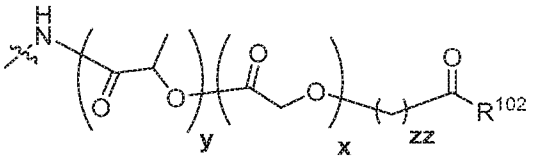
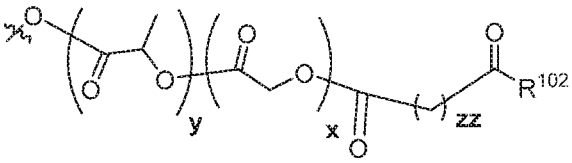
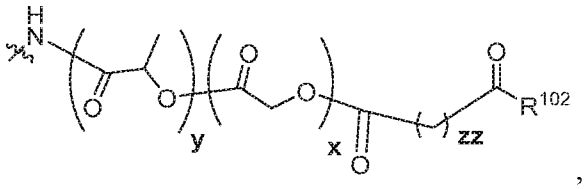
(iv) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, and poly(lactic-co-glycolic acid) capped with $R^{102}$

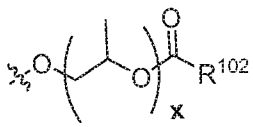
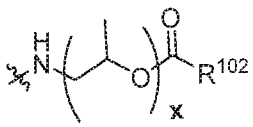
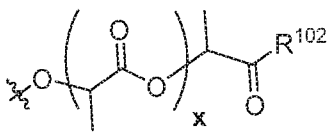
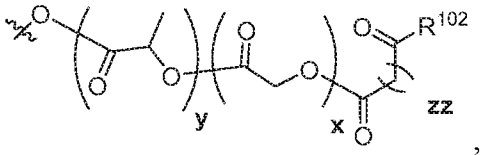
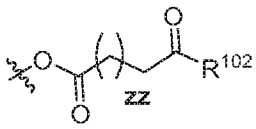
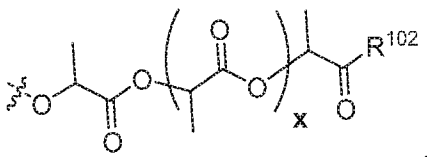
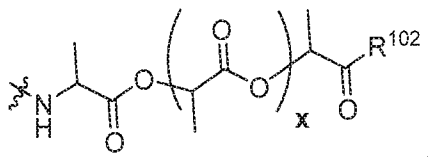
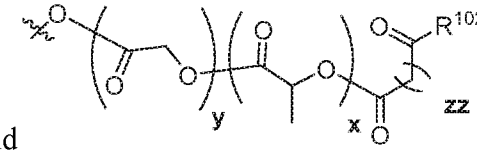
(v)

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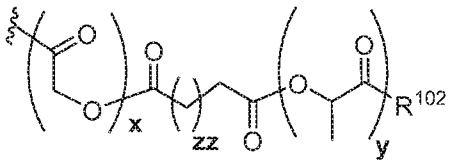
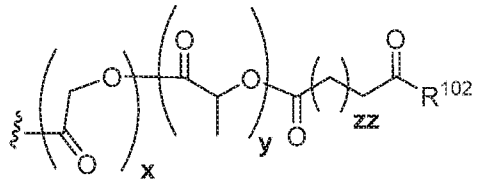
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, , ,

and ;

or $R^{11}$ is  or ;

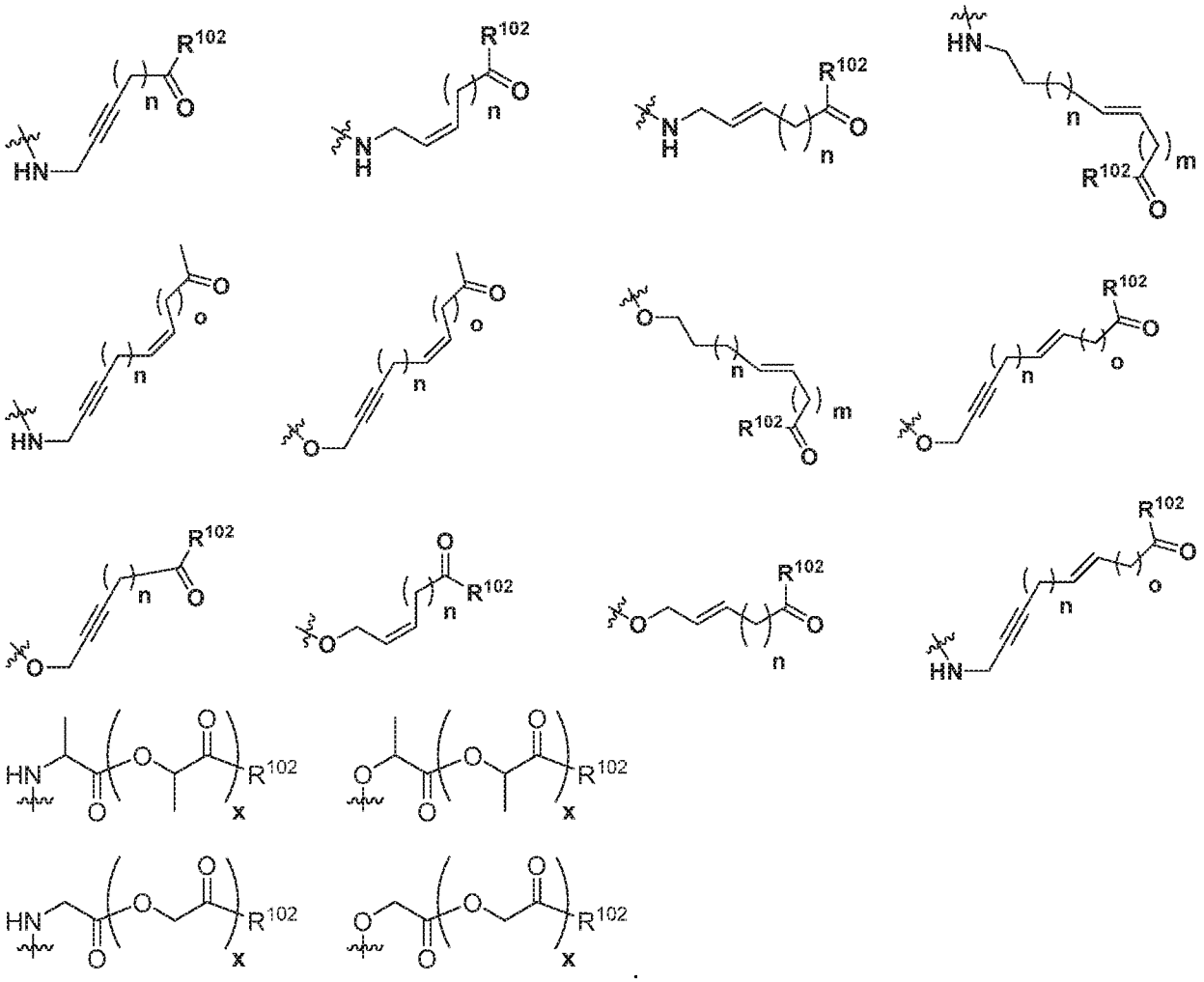
wherein $R^{11}$ can be further substituted with $R^5$ if valence permits, a stable compound is formed, and the resulting compound is pharmaceutically acceptable;

zz is selected from 1, 2, 3, 4, 5, or 6;

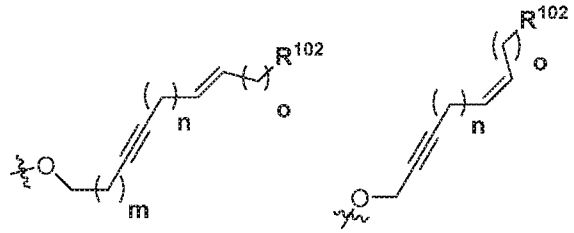
or zz is selected from at 7, 8, or 9;

or zz is 0 if the resulting compound is sufficiently stable.

Non-limiting examples of $R^{11}$ include:

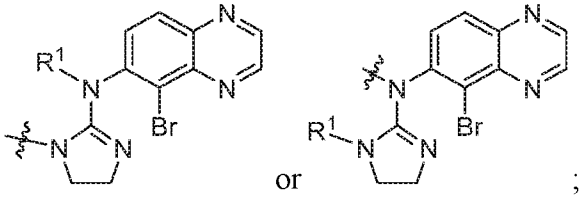


Additional non-limiting examples of $R^{11}$ include:

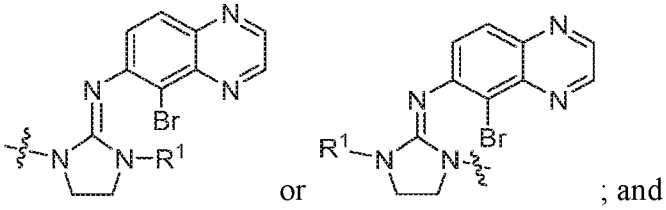


wherein n, m, o, x, and y are as defined above;

$R^{102}$ is



or $R^{102}$ is

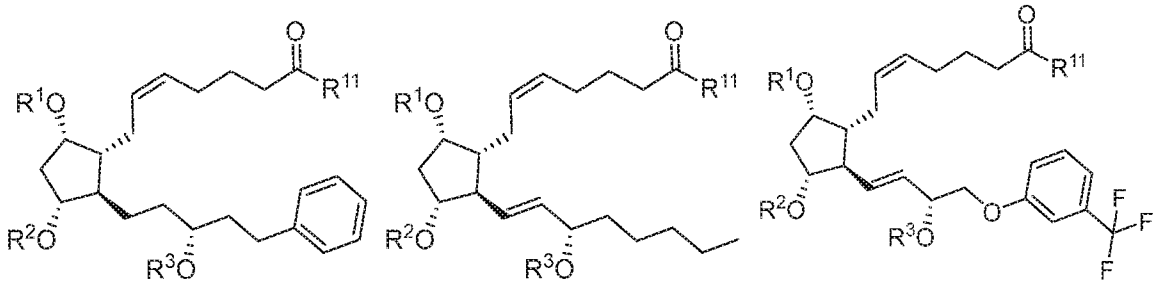


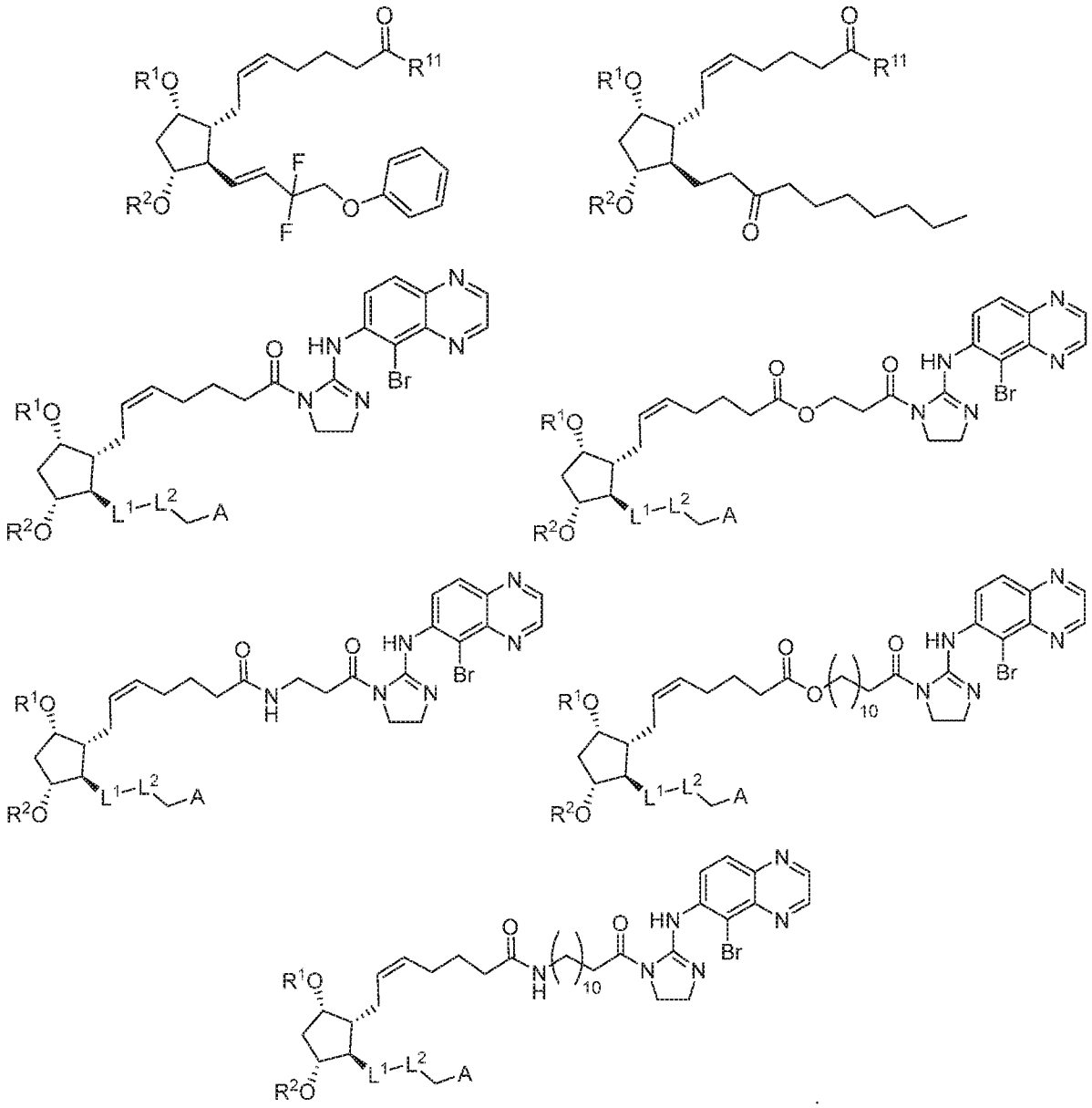
; and

wherein all other variables are as defined herein.

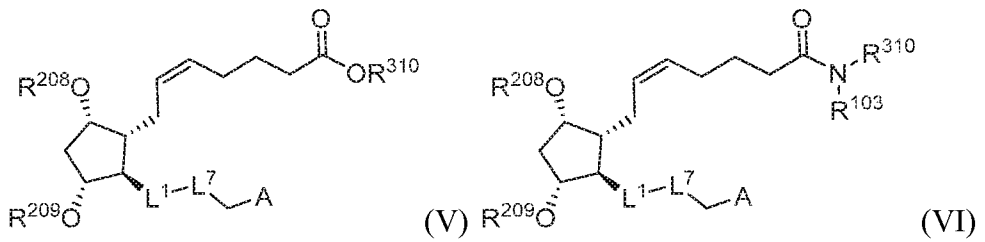
In various different embodiments, $-C_2$-$C_{30}$ as used in the definition of $R^{11}$ may be $-C_2$-$C_{28}$, $-C_4$-$C_{26}$, $-C_4$-$C_{24}$, $-C_6$-$C_{22}$, $-C_6$-$C_{20}$, $-C_8$-$C_{18}$, $-C_8$-$C_{16}$, $-C_8$-$C_{14}$, $-C_8$-$C_{12}$, $-C_8$-$C_{20}$, or $-C_6$-$C_{24}$

Non-limiting examples of Formula IV include:





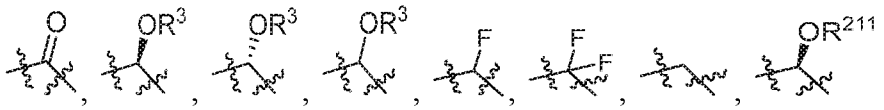
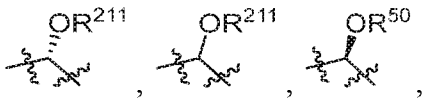
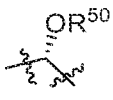
The disclosure also provides a compound of Formula V and VI:



(V) (VI)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{310}$ is alkyl or hydrogen;

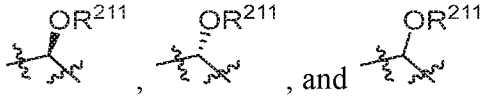
$L^7$ is selected from: , , and ;

$R^{208}$ and $R^{209}$ are independently selected from: $-C(O)R^{4b}$, -C(O)A, hydrogen, $R^{211}$, and $L^8$-$R^{212}$;

$R^{4b}$ is selected from:

(i) $-C_{10}$-$C_{30}$alkyl$R^5$, $-C_{10}$-$C_{30}$alkenyl$R^5$, $-C_{10}$-$C_{30}$alkynyl$R^5$, $-C_{10}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{10}$-$C_{30}$alkyl, $-C_{10}$-$C_{30}$alkenyl, $-C_{10}$-$C_{30}$alkynyl, -C10-$C_{30}$alkenylalkynyl;

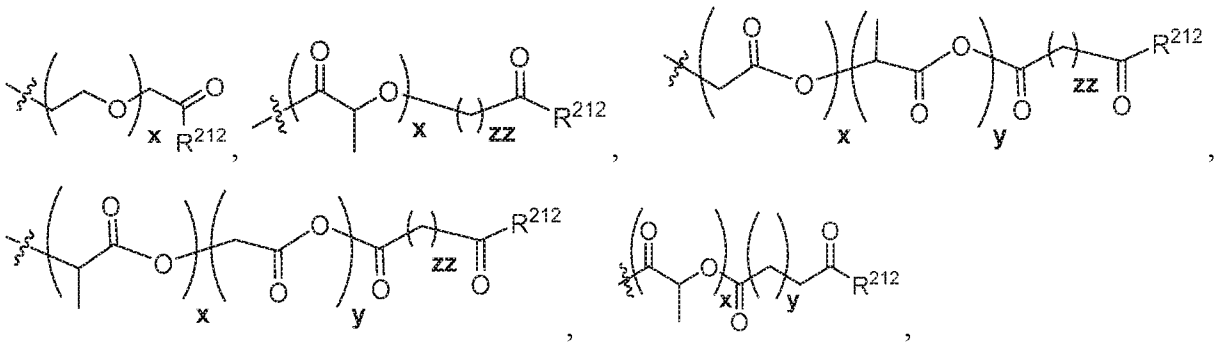
(ii) an unsaturated fatty acid residue including but not limited to the carbon chains from linoleic acid ($-(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$)), docosahexaenoic acid ($-(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid ($-(CH_2)_4(CHCHCH_2)_5CH_3$)), alpha-linolenic acid ($-(CH_2)_8(CHCHCH_2)_3CH_3$)) stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid or mead acid, and wherein, if desired, each of which can be substituted with $R^5$.

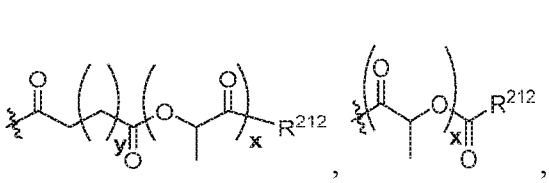
wherein either at least one of $R^{208}$ and $R^{209}$ is $R^{211}$ or $L^8$-$R^{212}$; or $L^7$ is selected from ;

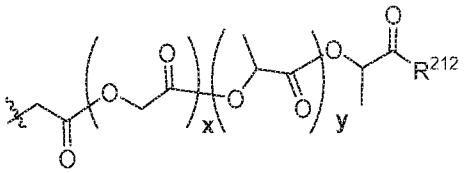
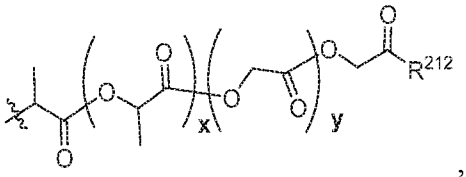
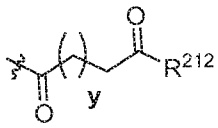
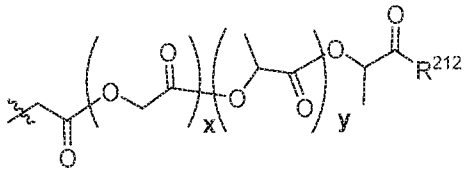
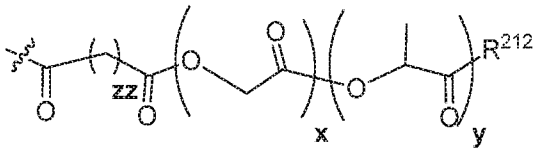
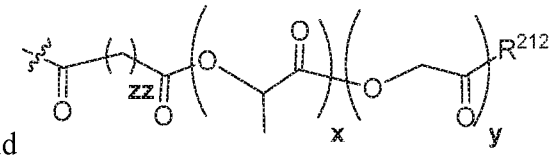
$L^8$ is -C(O)-alkyl-C(O)- or $L^8$ is –C(O)-alkenyl-C(O)-;

$R^{211}$ is selected from:

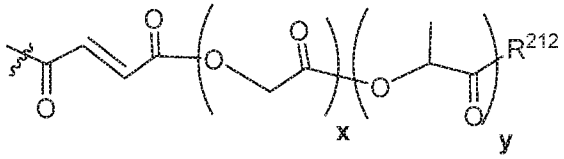
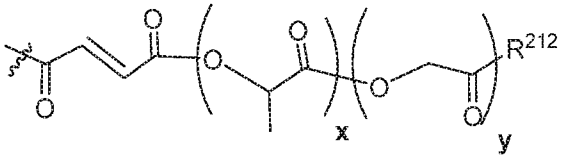
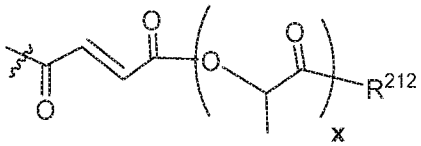
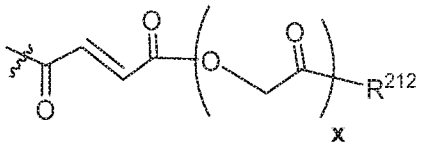
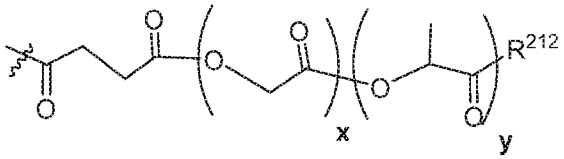
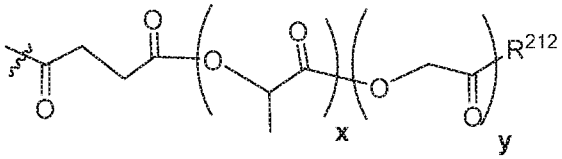
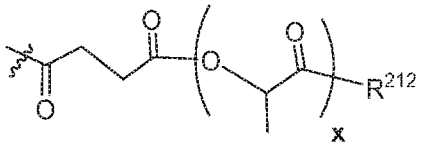
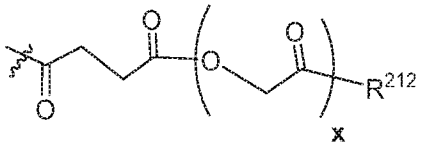
polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, a biodegradable polymer and poly(lactic-co-glycolic acid) each of which is optionally linked by a carbonyl and each is capped with $R^{212}$ including:

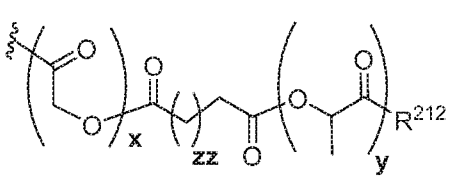
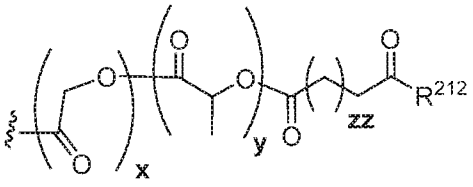



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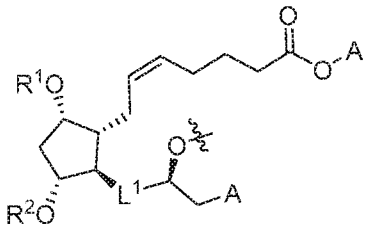
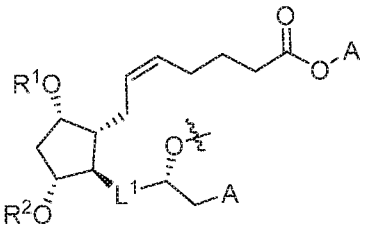
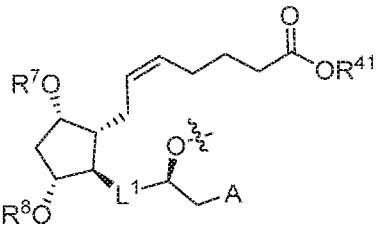
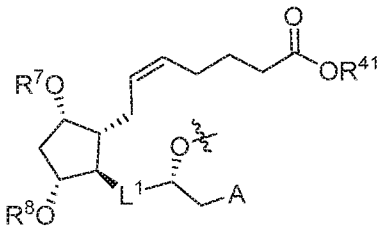
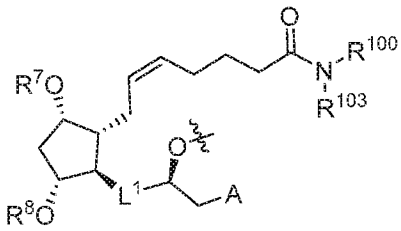
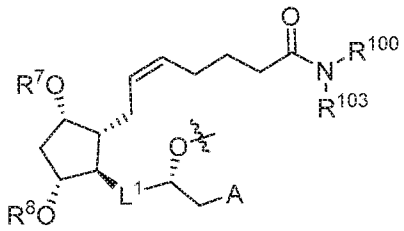
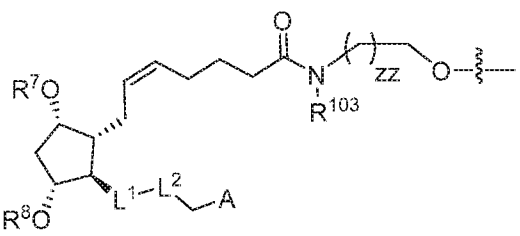
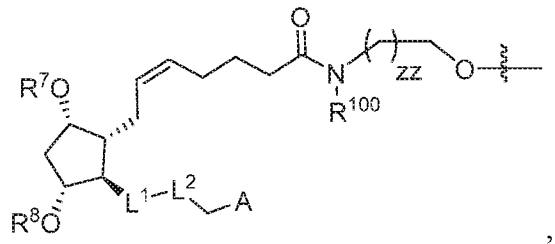
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or $R^{211}$ is selected from:

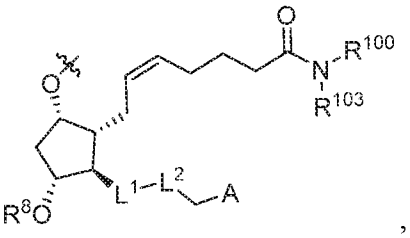
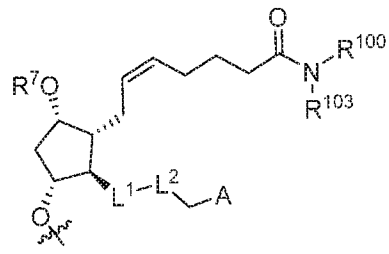
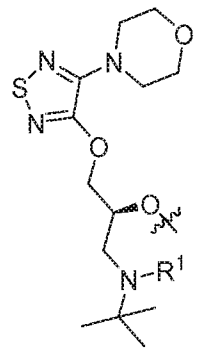

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or $R^{211}$ is

or

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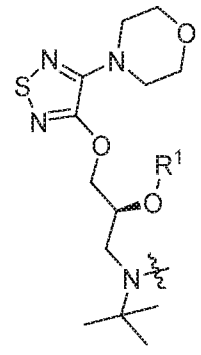
$R^{212}$ is selected from:

5

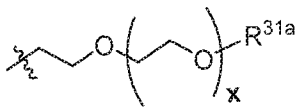
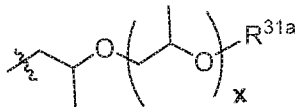
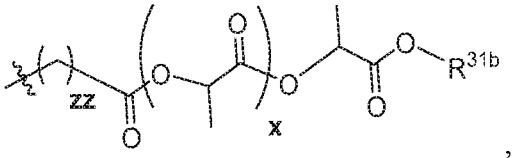
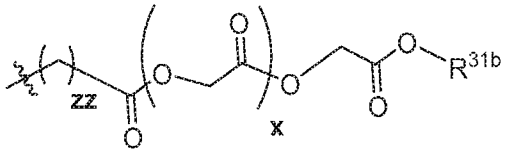
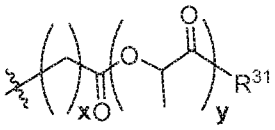
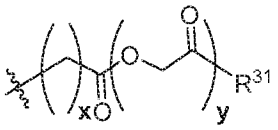




and



;

$R^{41}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, a polyamide, or other biodegradable polymer, , , , , , and , wherein in some embodiments a terminal hydroxy or carboxy group can be substituted to create an ether or ester;

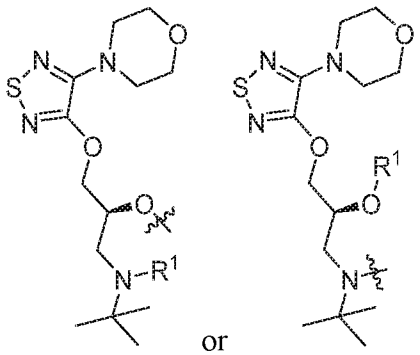
(ii) $-C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl;

(iii) an unsaturated fatty acid residue; and

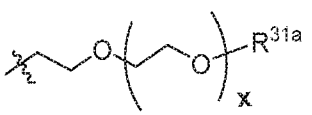
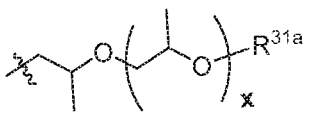
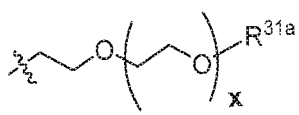
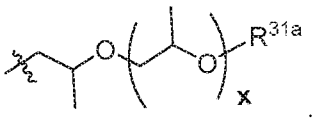
(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl; and

wherein all other variables are as defined herein.

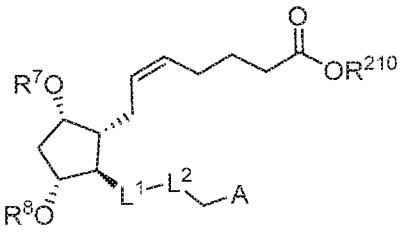
In one embodiment $R^{212}$ is

 or .

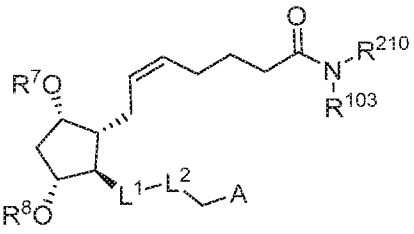
Non-limiting examples of $R^{41}$ include:

, , , and .

The disclosure also provides a compound of Formula V' and VI':



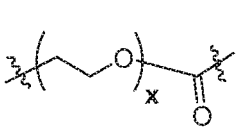
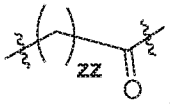
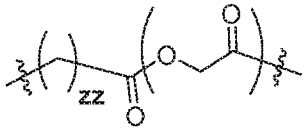
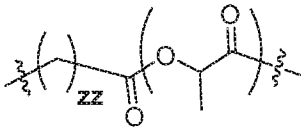
(V')



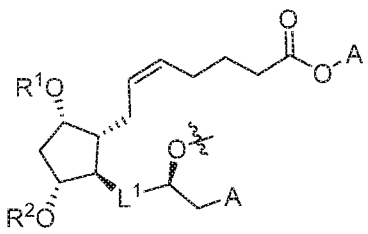
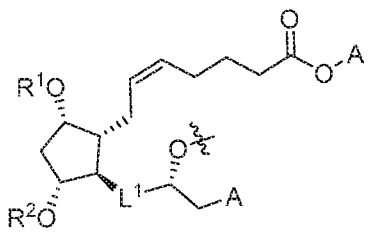
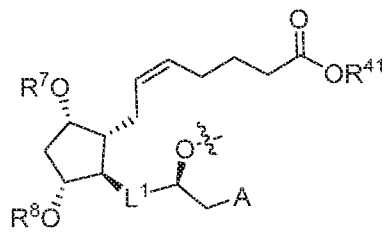
(VI')

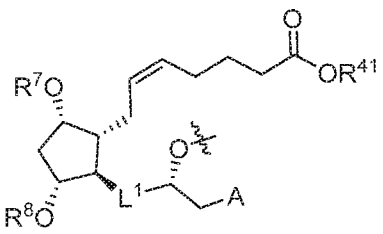
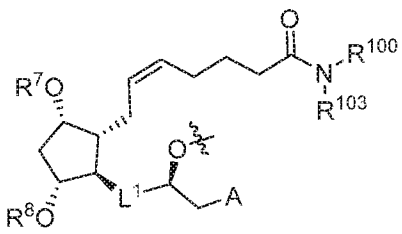
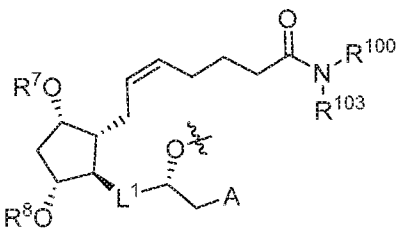
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

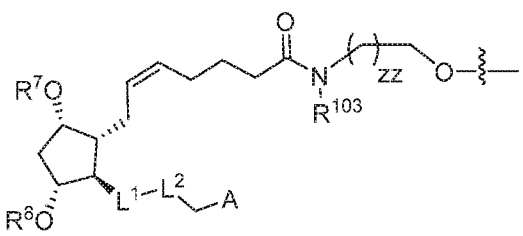
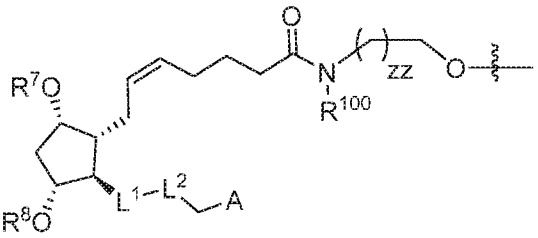
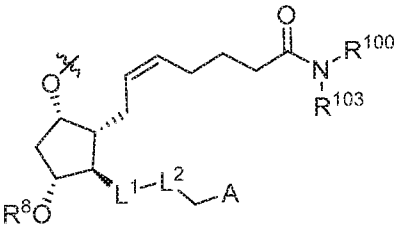
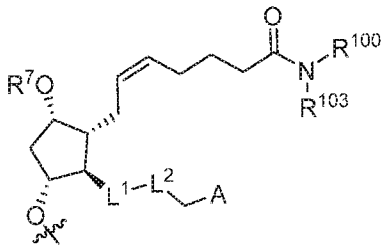
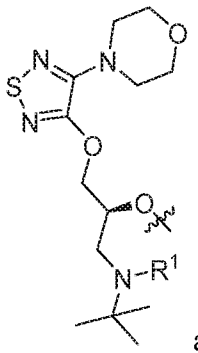
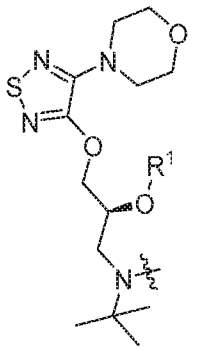
$R^{210}$ is $L^9$-$R^{212}$;

$L^9$ is selected from: , , , and ;

$R^{212}$ is selected from:

, , ,

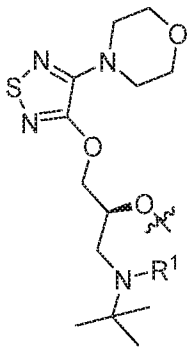
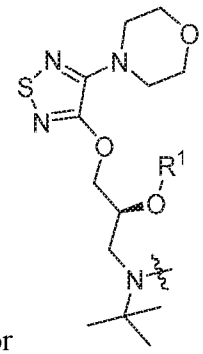
, , ,

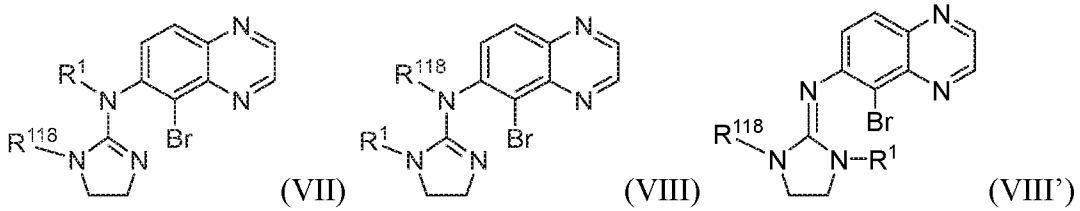
; and

wherein all other variables are as defined herein.

In one embodiment $R^{212}$ is


or

.

The disclosure also provides a prodrug of Formula VII, Formula VIII, or Formula VIII':



(VII) (VIII) (VIII')

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{118}$ is selected from:

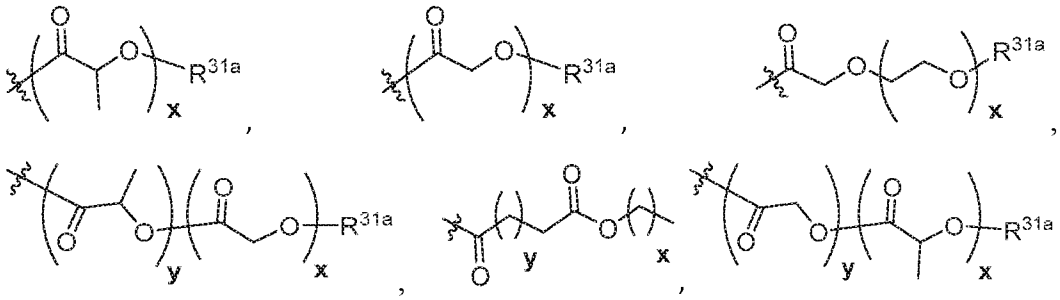
(i) $-C(O)C_5$-$C_{30}$alkyl$R^5$, $-C(O)C_2$-$C_{30}$alkenyl$R^5$, $-C(O)C_2$-$C_{30}$alkynyl$R^5$, $-C(O)C_4$-$C_{30}$alkenylalkynyl$R^5$, $-C(O)C_5$-$C_{30}$alkyl, $-C(O)C_2$-$C_{30}$alkenyl, $-C(O)C_2$-$C_{30}$alkynyl, and $-C(O)C_4$-$C_{30}$alkenylalkynyl;

(ii) $-C(O)(C_{1\text{-}30}$alkyl with at least one $R^5$ substituent on the alkyl chain), $-C(O)(C_{1\text{-}30}$alkenyl, with at least one $R^5$ substituent on the alkenyl chain), $-C(O)(C_{1\text{-}30}$alkynyl, with at least one $R^5$ substituent on the alkynyl chain), -(lactic acid)$_{1\text{-}20}C(O)C_{1\text{-}30}$alkyl, -(lactic acid)$_{1\text{-}10}C(O)C_{1\text{-}30}$alkyl, -(lactic acid)$_{4\text{-}20}C(O)C_{1\text{-}30}$alkyl, -(lactic acid)$_{1\text{-}20}C(O)C_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}C(O)C_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}C(O)OH$, -(lactic acid)$_{1\text{-}10}C(O)OH$, -(lactic acid)$_{4\text{-}20}C(O)OH$, -(lactic acid)$_{1\text{-}10}C(O)OH$, -(lactic acid)$_{4\text{-}10}C(O)OH$, -(lactide-co-glycolide)$_{1\text{-}10}C(O)C_{1\text{-}30}$alkyl, -(lactide-co-glycolide)$_{4\text{-}10}C(O)C_{1\text{-}30}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}C(O)C_{1\text{-}12}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}C(O)C_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}C(O)C_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}C(O)C_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}C(O)C_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}C(O)C_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}C(O)C_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}C(O)C_{4\text{-}10}$alkyl, and -(lactic acid)$_{1\text{-}10}C(O)C_{4\text{-}10}$alkyl;

(iii) an unsaturated fatty acid residue including but not limited to the carbonyl fragment taken from linoleic acid ($-(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$)), docosahexaenoic acid ($-(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid ($-(CH_2)_4(CHCHCH_2)_5CH_3$)), alpha-linolenic acid ($-(CH_2)_8(CHCHCH_2)_3CH_3$)), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid, each of which can be further optionally further substituted with $R^5$ (including for example a second $R^5$) if valence permits,

a stable compound is formed, and the resulting compound is pharmaceutically acceptable;

(iv) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, and other biodegradable polymers, each of which can be capped to complete the terminal valence or to create a terminal ether or ester; and

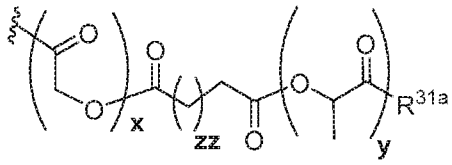
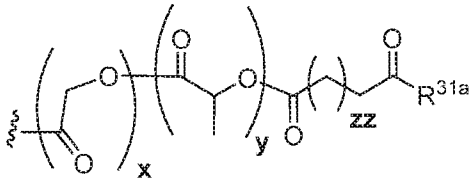
(v) 

;

or $R^{118}$ is selected from:

(vi) -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{4-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{4-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{4-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{4-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, (C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{2-10}$(C(O)CH(CH$_3$)O)$_{2-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-12}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-22}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{2-10}$(C(O)CH$_2$O)$_{2-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-12}$alkyl, and

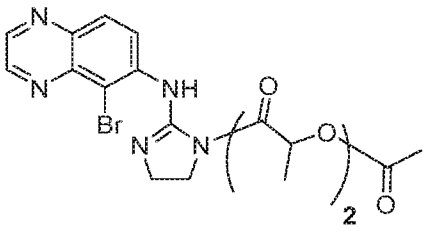
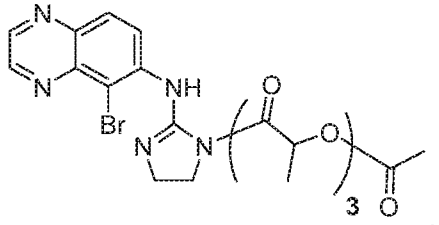
-(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-22}$alkyl;

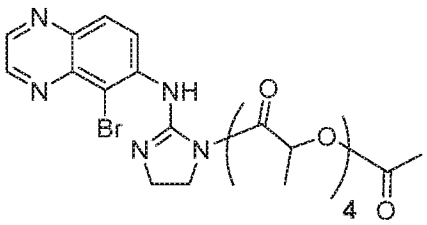
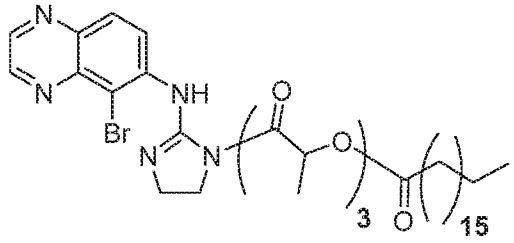
or $R^{118}$ is  or ;

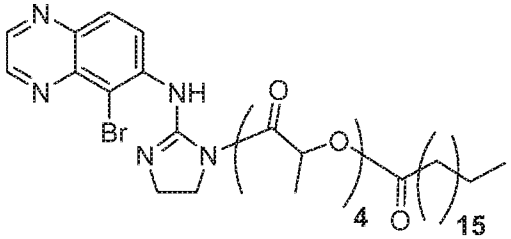
wherein all other variables are as defined herein.

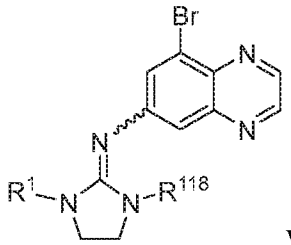
In various different embodiments, –C$_{10}$-C$_{30}$ as used in the definition of $R^{118}$ is –C$_{10}$-C$_{18}$, –C$_{10}$-C$_{16}$, –C$_{10}$-C$_{14}$, –C$_{10}$-C$_{12}$, –C$_{19}$-C$_{28}$, –C$_{19}$-C$_{26}$, –C$_{19}$-C$_{24}$, –C$_{19}$-C$_{22}$, –C$_{19}$-C$_{20}$, –C$_{20}$-C$_{28}$, –C$_{20}$-C$_{26}$, –C$_{20}$-C$_{24}$, –C$_{20}$-C$_{22}$, –C$_{22}$-C$_{28}$, –C$_{22}$-C$_{26}$, –C$_{22}$-C$_{24}$, or –C$_{26}$-C$_{28}$.

Non-limiting examples of Formula VII include:

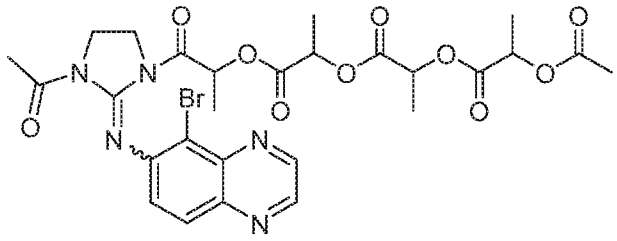
, ,

, , and

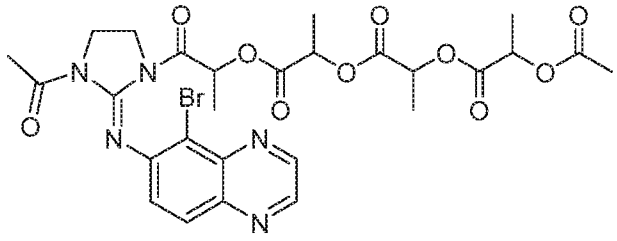
.

Compounds of Formula VIII' are drawn as  where the bond between the aromatic ring and the imidazole ring is drawn as a wavy line. In one embodiment, compounds of

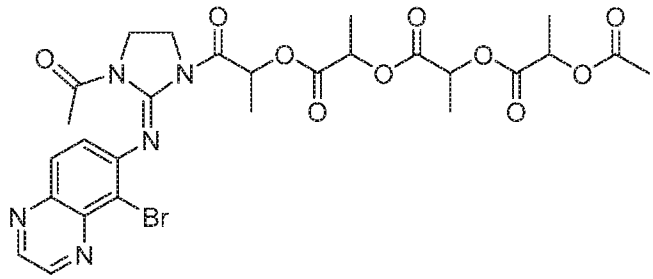
Formula VIII' are the Z isomer. In one embodiment, compounds of Formula VIII' are the E isomer. For example, Compound **115-1** is drawn as



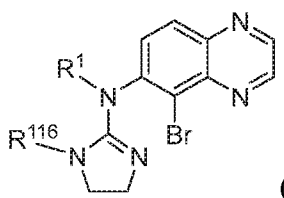
In one embodiment, Compound **115-1** is the Z isomer:



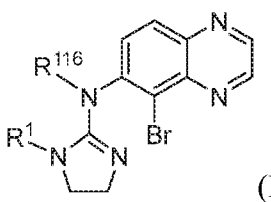
In one embodiment, Compound **115-1** is the E isomer:



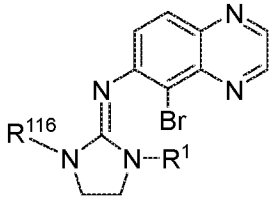
The disclosure also provides a prodrug of Formula IX, IX', or IX'':



(IX)



(IX')



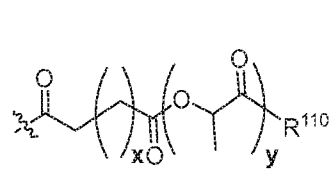
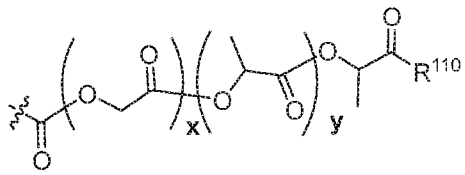
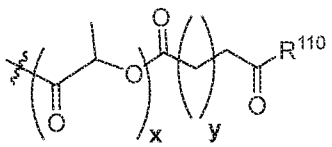
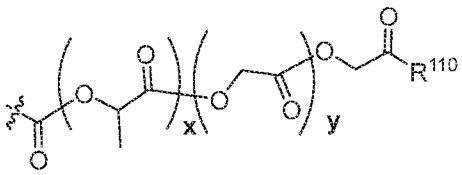
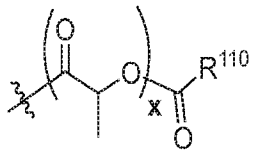
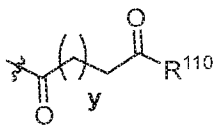
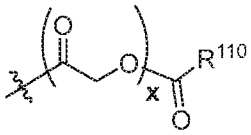
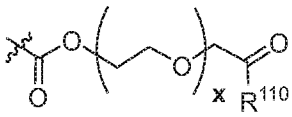
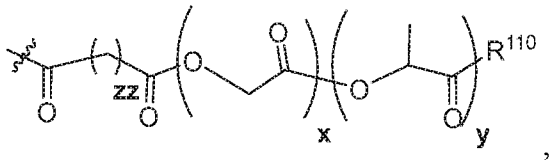
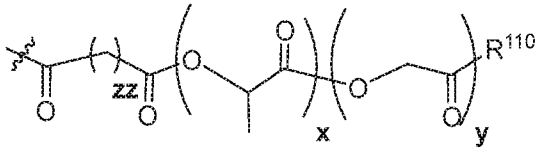
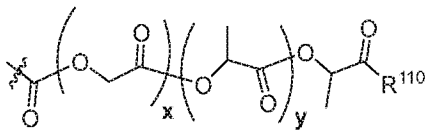
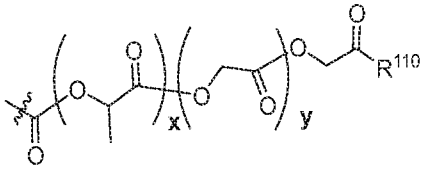
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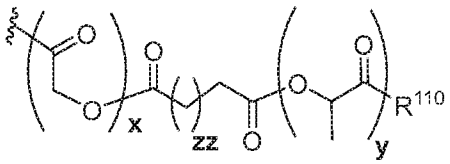
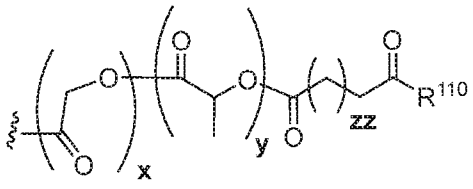
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{116}$ is selected from: $R^{117}$, alkyl, alkyloxy, acyl, polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, polyamide, or other biodegradable polymer, wherein each $R^{116}$ other than $R^{117}$ is substituted with at least one $L^4$-$R^{110}$;

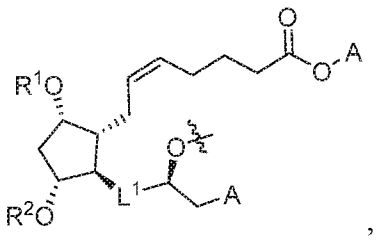
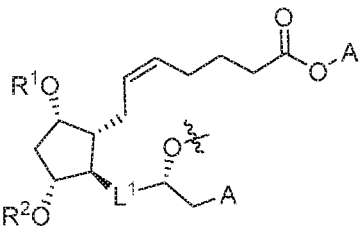
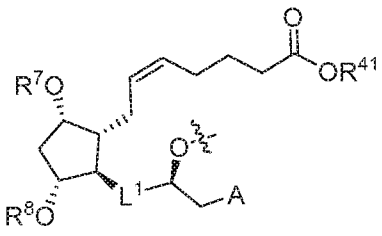
wherein $R^{116}$ can be further substituted with $R^5$ if valence permits, a stable compound is formed, and the resulting compound is pharmaceutically acceptable.

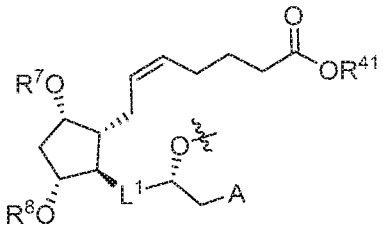
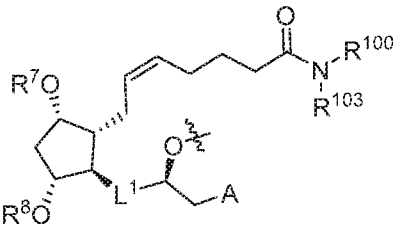
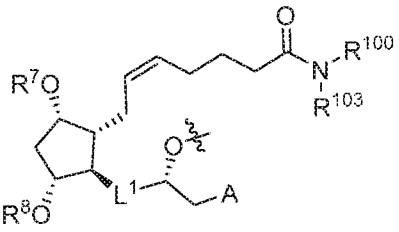
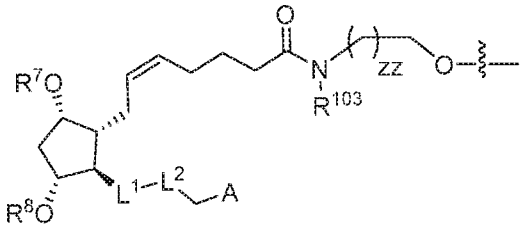
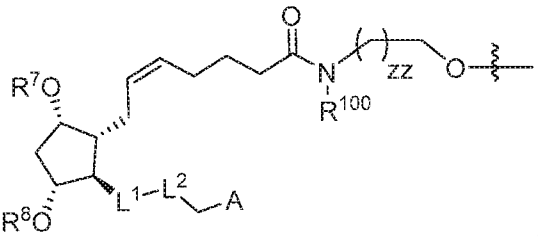
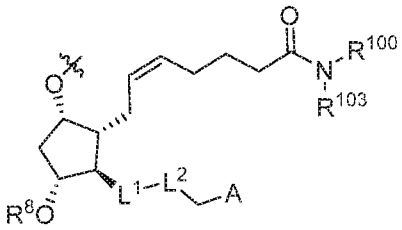
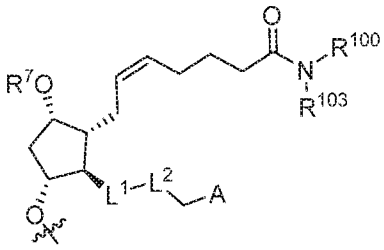
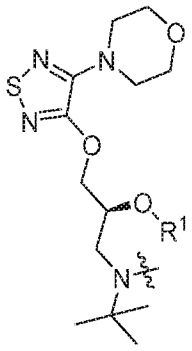
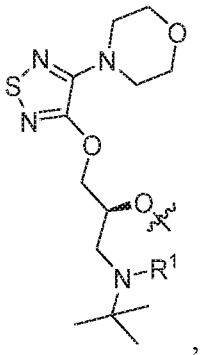
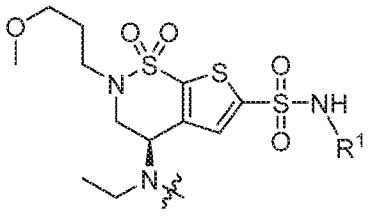
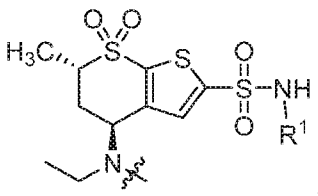
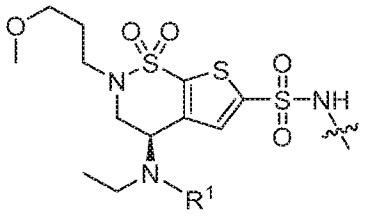
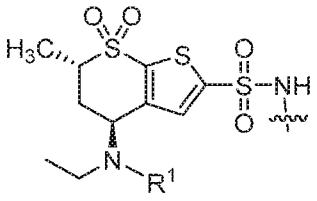
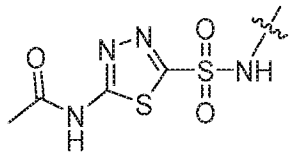
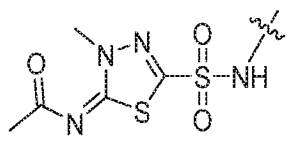
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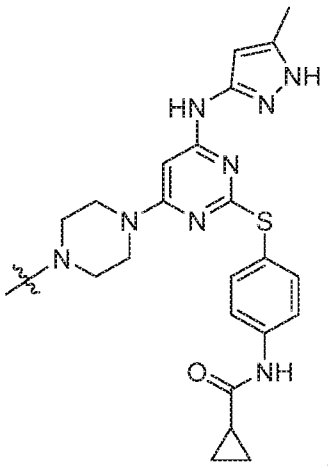
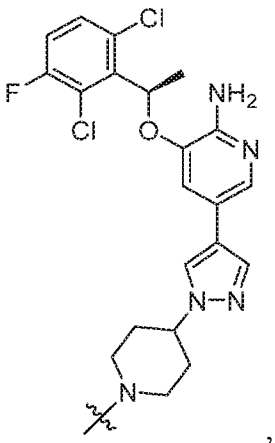
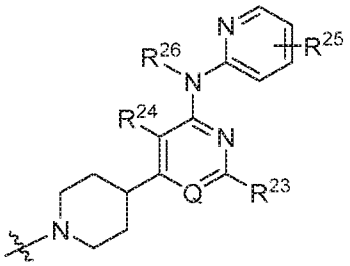
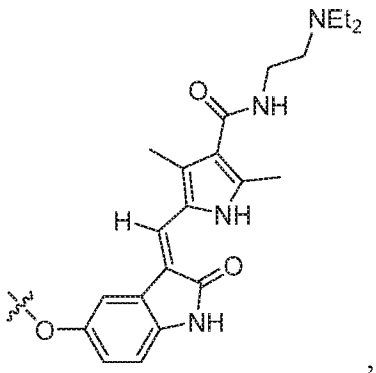
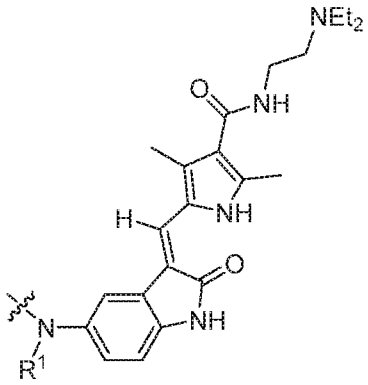
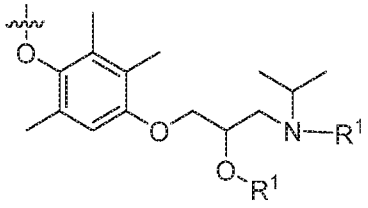
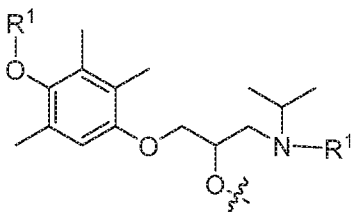
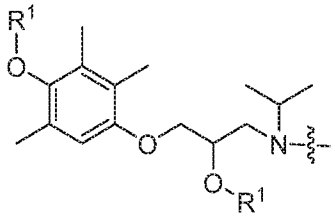
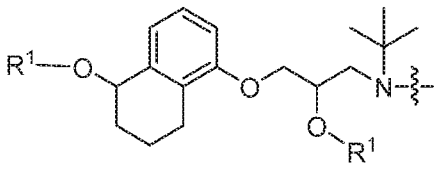
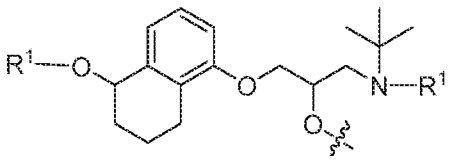
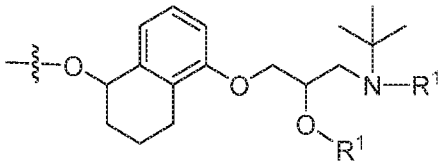
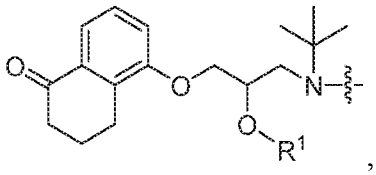
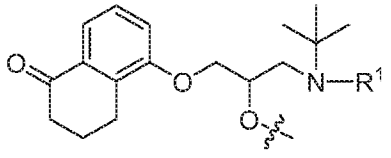
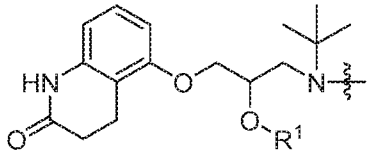

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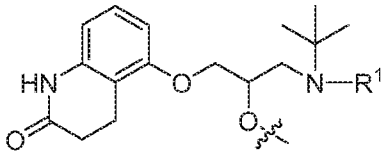
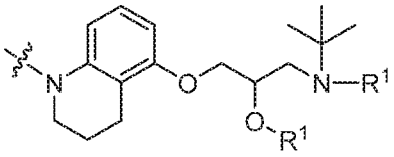
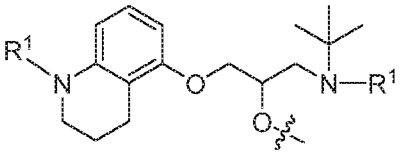
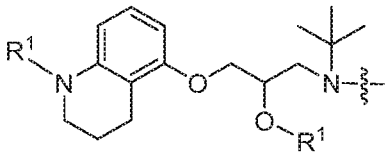
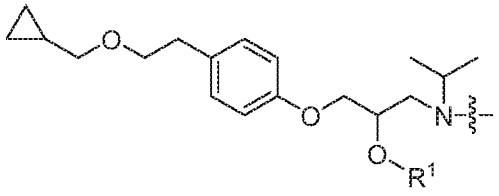
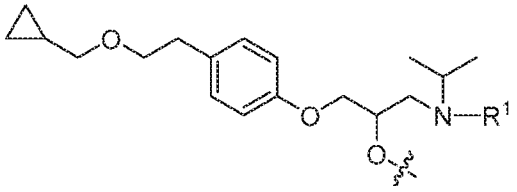
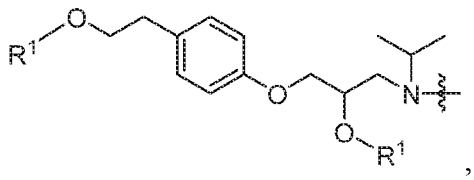
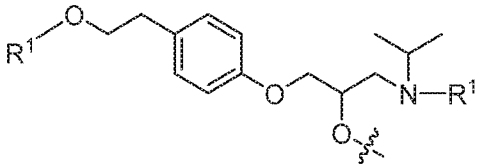
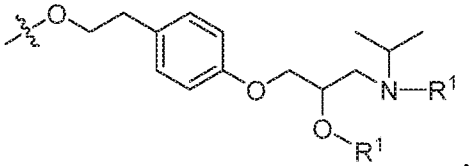
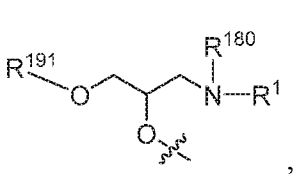
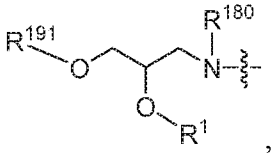
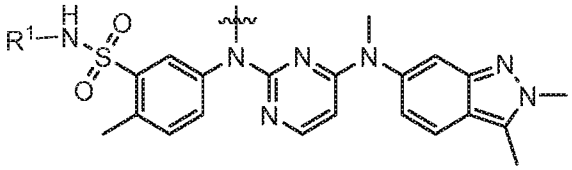
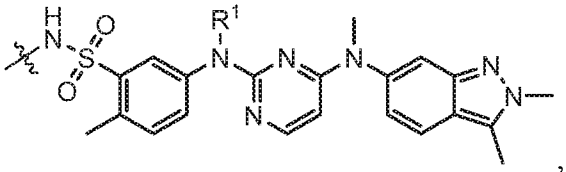
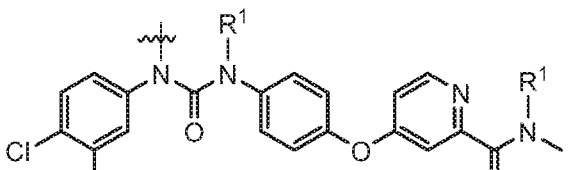
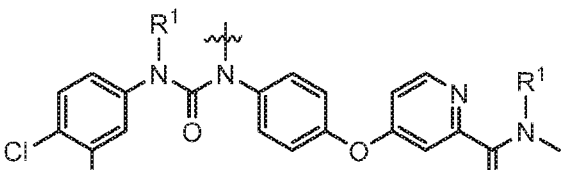
or $R^{117}$ is

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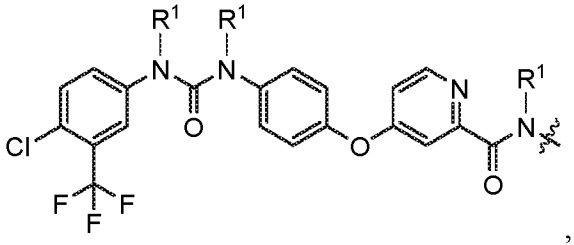
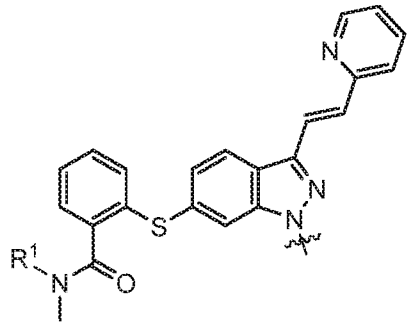
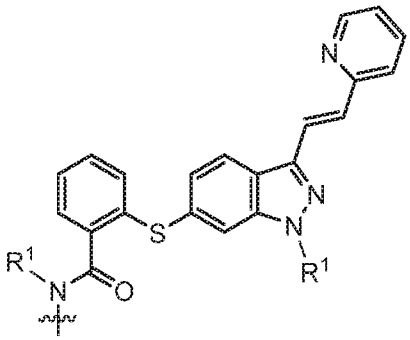
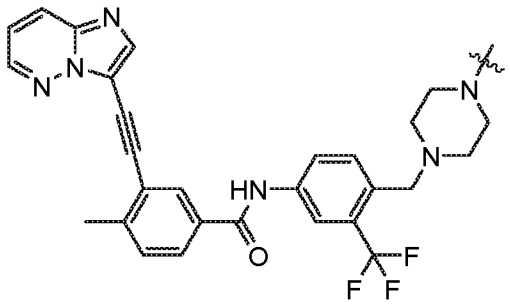
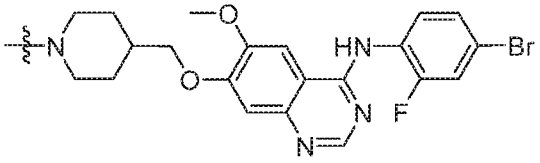
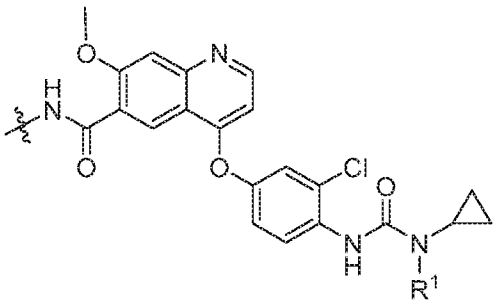
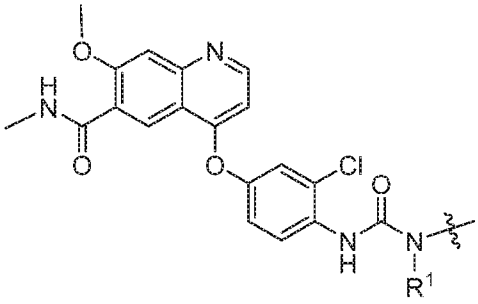
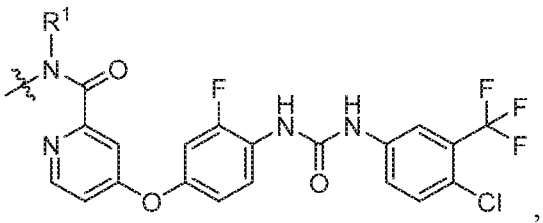
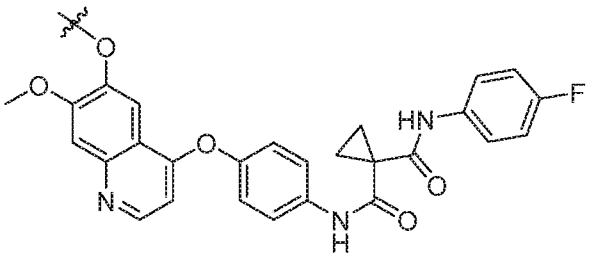
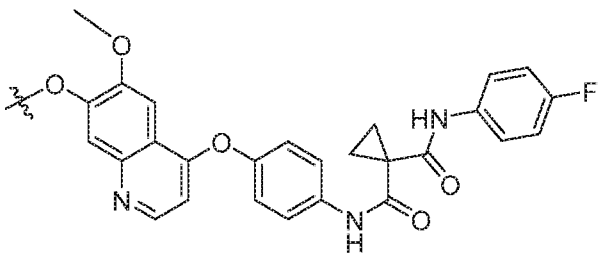
$R^{110}$ is selected from


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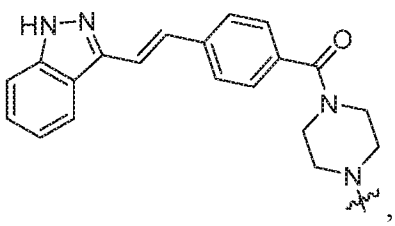
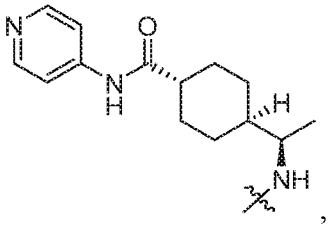
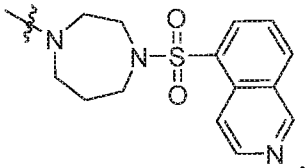
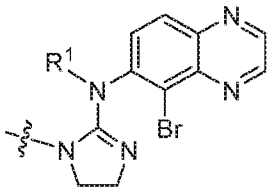
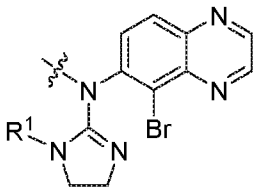
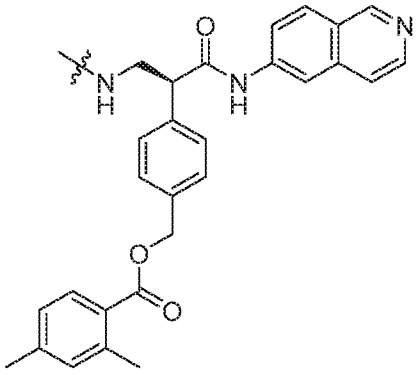

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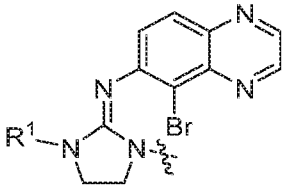
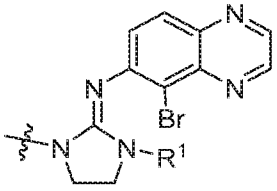

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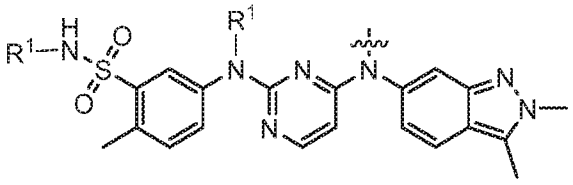

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and

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or $R^{110}$ is

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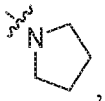
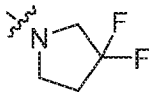
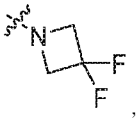
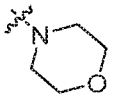

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$L^4$ is selected from: bond, alkyl, alkenyl, alkynyl, -C(O)-, -C(S)-, -NH-, -N(alkyl)-, -O-, and alkyl-C(O)-;

$R^{31b}$ is hydrogen, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polyethylene glycol, polylactic acid, polygylcolic acid, or stearoyl;

Q is selected from: N, CH, and $CR^{23}$;

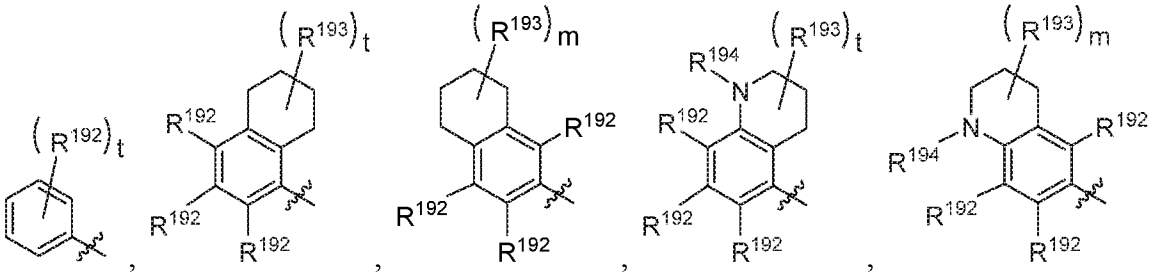
$R^{23}$, $R^{24}$, and $R^{25}$ are independently selected from: hydrogen, halogen, hydroxyl, cyano, mercapto, nitro, amino, aryl, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, $-S(O)_2$alkyl,

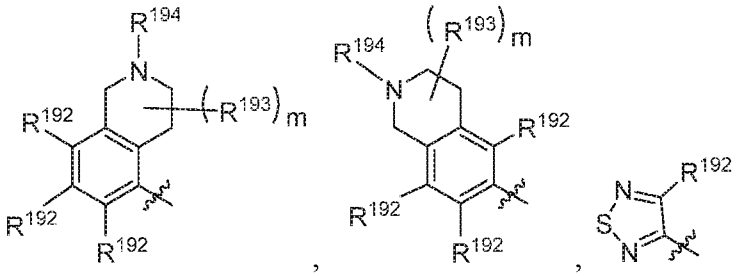
-S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -COOalkyl, -CONH$_2$, , , , and  each of which except halogen, nitro, and cyano, may be optionally substituted, for example with halogen, alkyl, aryl, heterocycle or heteroaryl;

$R^{26}$ is selected from H, C(O)A, -C$_0$-C$_{10}$alkyl$R^5$, -C$_2$-C$_{10}$alkenyl$R^5$, –C$_2$-C$_{10}$alkynyl$R^5$, -C$_2$-C$_{10}$alkenyl, and –C$_2$-C$_{10}$alkynyl;

$R^{180}$ is C$_1$-C$_6$ alkyl, acyl, or hydrogen;

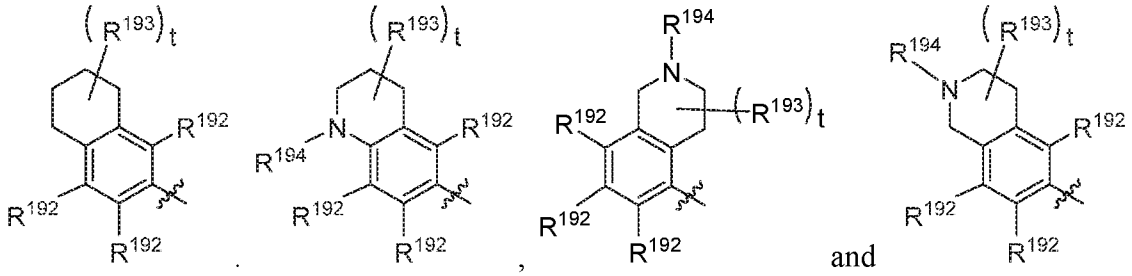
$R^{191}$ is selected from:





, and $R^{195}$;

or in an alternative embodiment, $R^{191}$ is selected from



;

t is independently selected from 0, 1, 2, 3, and 4;

$R^{192}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{192}$ is optionally substituted with a $R^{175}$ group;

$R^{193}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

or two $R^{193}$ groups with the carbon to which they are linked form a carbonyl group;

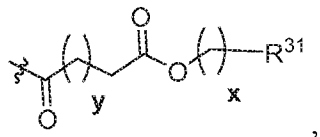
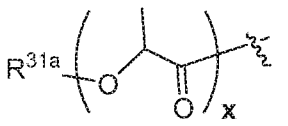
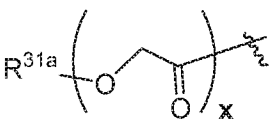
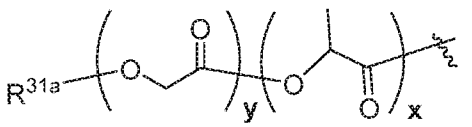
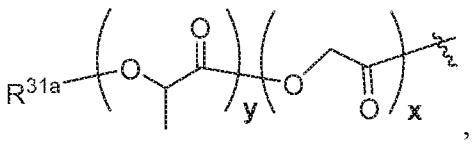
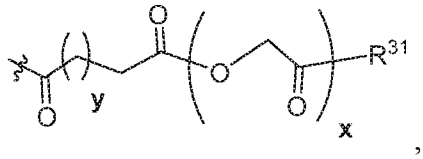
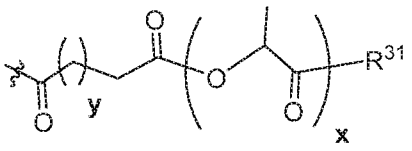
or two $R^{193}$ groups with the carbon(s) to which they are linked form a fused or spirocyclic ring;

$R^{194}$ is selected from alkyl, cycloalkyl, $R^{175}$, and acyl; and

$R^{195}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{195}$ is optionally substituted with 1, 2, 3, or 4 $R^{192}$ groups;

$R^{175}$ is selected from: C(O)A, $C(O)R^4$, and $R^{178}$;

$R^{178}$ is selected from:

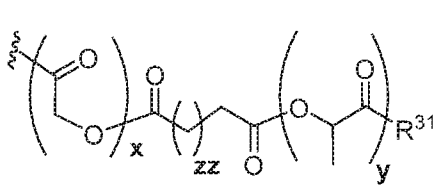
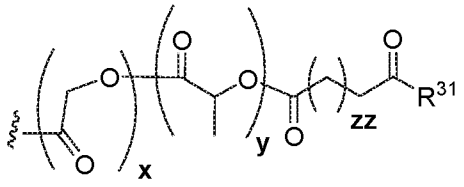
(i) carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , , , , , , , and other biodegradable polymer, wherein each $R^{178}$ is optionally substituted with $R^{31}$, and wherein each of $R^{178}$ with a terminal hydroxy or carboxy group can be substituted to create an ether or ester;

(ii) -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{4\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}20}$C(O)OH, -

(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, or -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl;

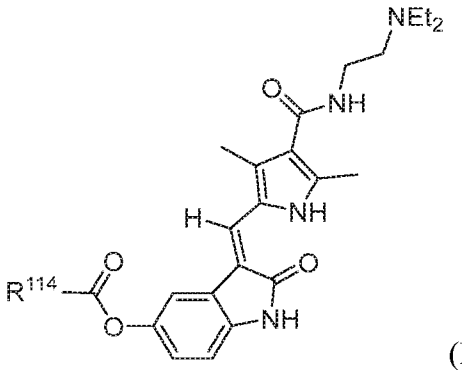
or $R^{178}$ is selected from:

(i) -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{4-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{4-20}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{1-20}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-20}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{4-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{4-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, (C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-10}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{2-10}$(C(O)CH(CH$_3$)O)$_{2-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{1-12}$alkyl, -(C(O)CH$_2$O)$_{1-10}$(C(O)CH(CH$_3$)O)$_{1-10}$C(O)C$_{4-22}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{2-10}$(C(O)CH$_2$O)$_{2-10}$C(O)C$_{1-30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-12}$alkyl, and -(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-22}$alkyl; and

or $R^{178}$ is  or ;

wherein all other variables are as defined herein.

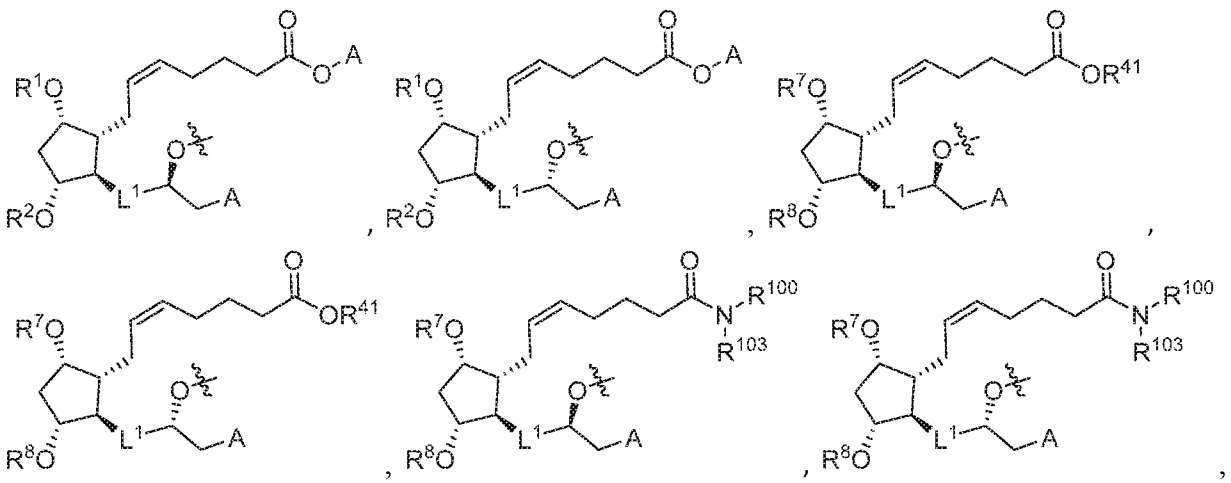
The disclosure also provides a prodrug of Formula X:

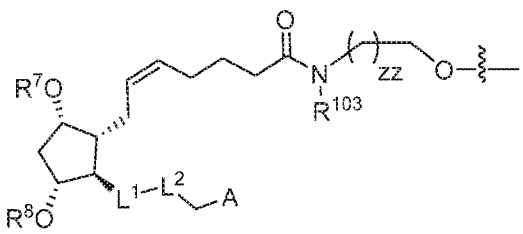
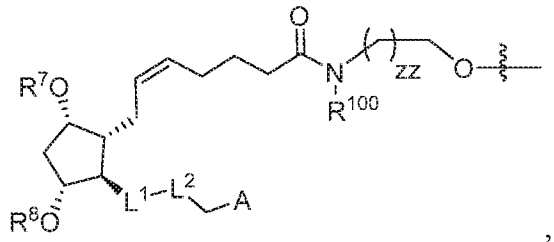
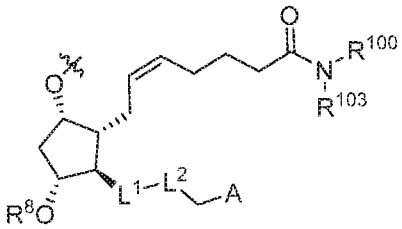
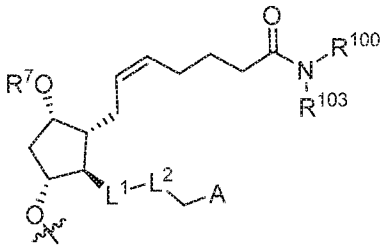
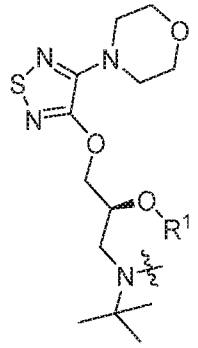
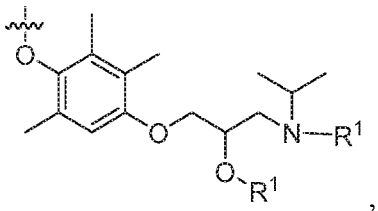
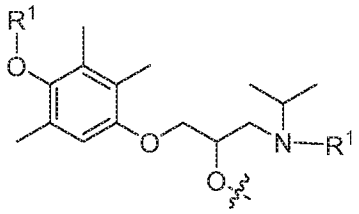
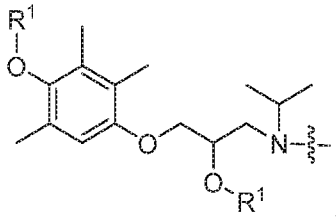
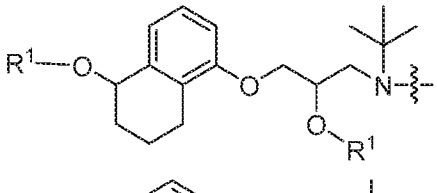
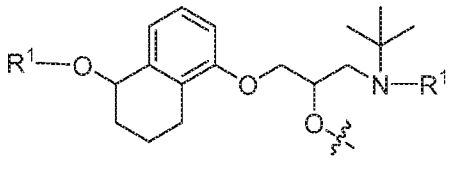
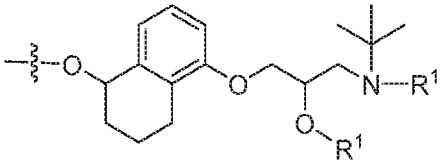
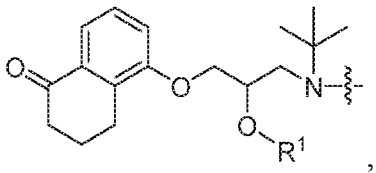
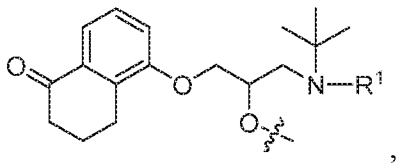
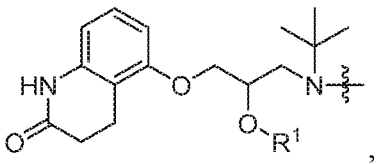
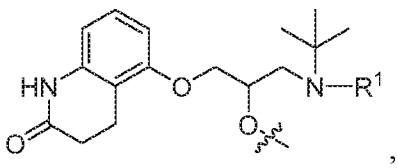
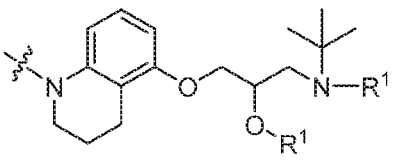
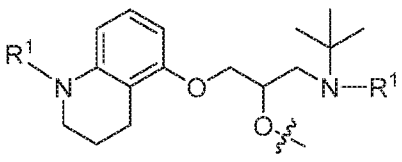


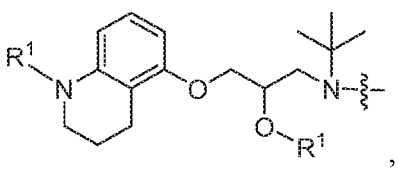
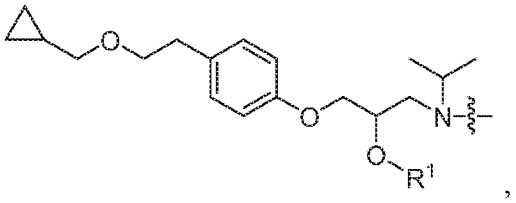
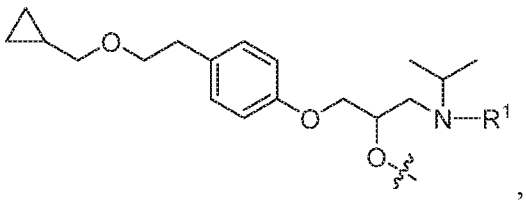
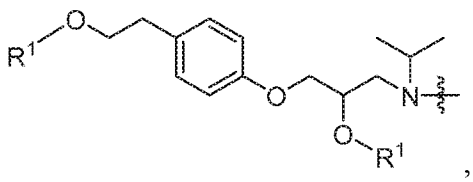
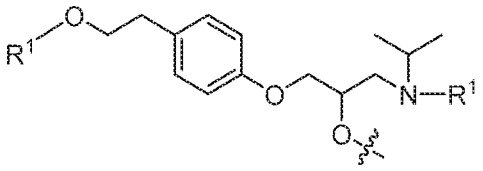
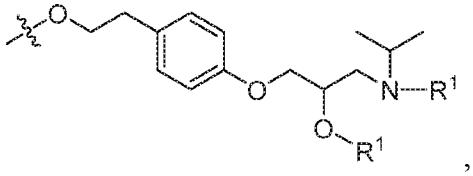
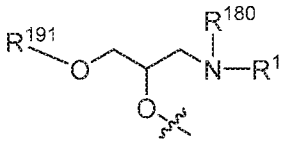
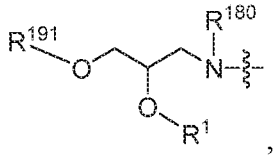
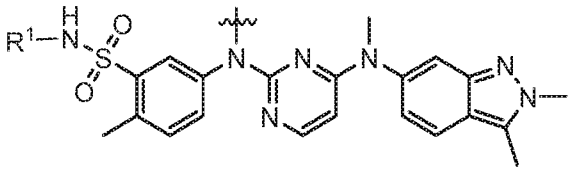
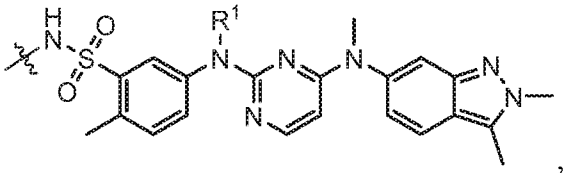
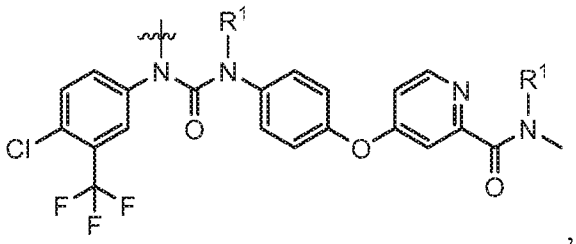
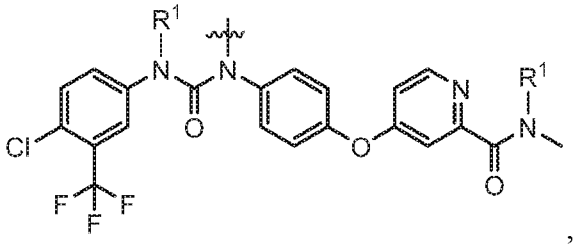
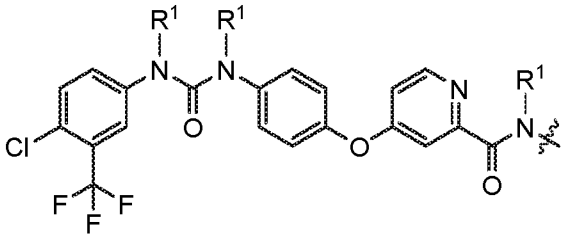
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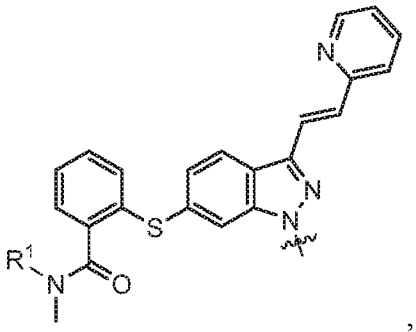
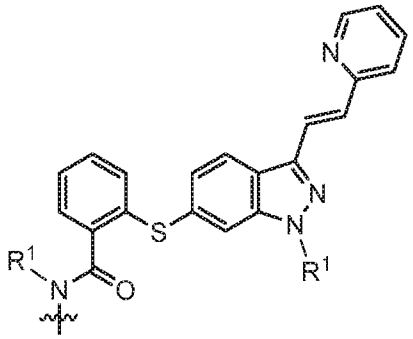
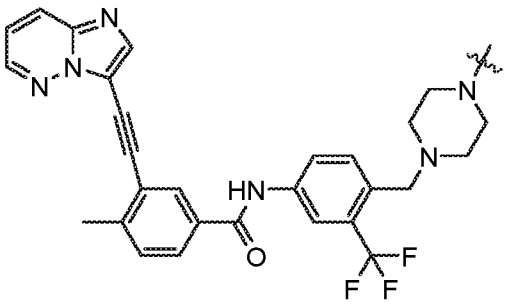
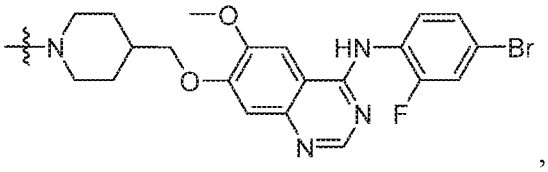
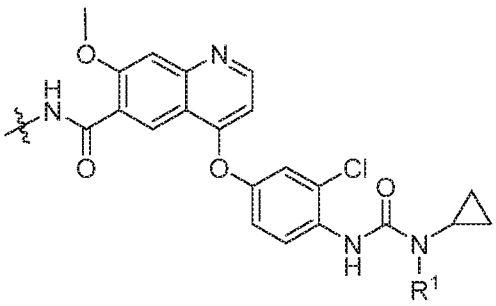
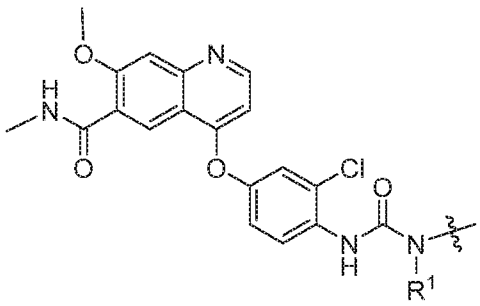
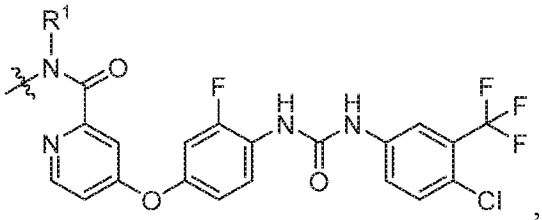
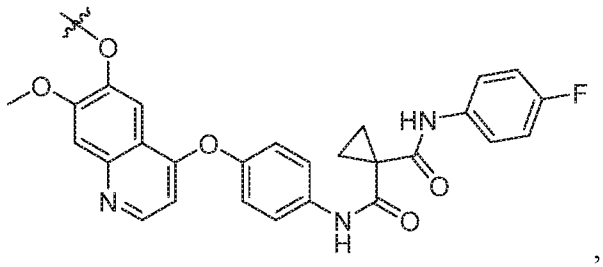
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof. This structure is related to Sunitinib (marketed in the form of the (-)-malic acid salt as SUTENT® by Pfizer, and previously known as SU11248), which is an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor that was approved by the FDA for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) on January 26, 2006. Sunitinib was the first cancer drug simultaneously approved for two different indications. Sunitinib inhibits cellular signaling by targeting multiple receptor tyrosine kinases (RTKs).These include all receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs), which play a role in both tumor angiogenesis and tumor cell proliferation. The simultaneous inhibition of these targets leads to both reduced tumor vascularization and cancer cell death, and, ultimately, tumor shrinkage. Sunitinib and derivatives thereof are described in U.S. Patent Nos. 7,211,600; 6,573,293; and 7,125,905, the entirety of which is incorporated by reference.

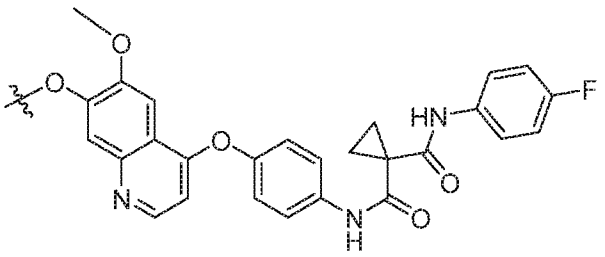
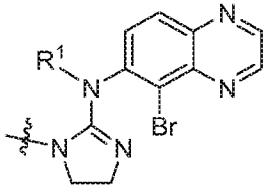
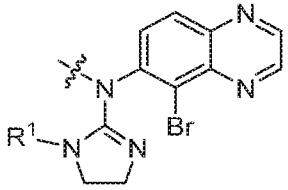
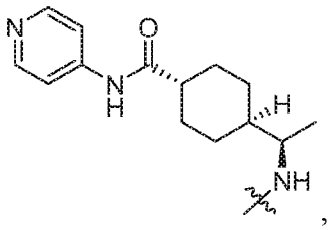
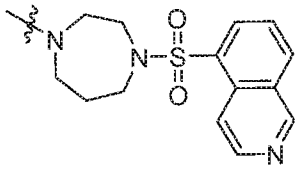
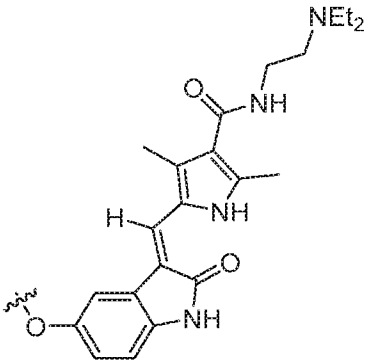
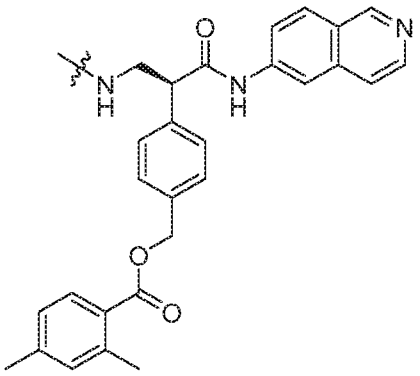
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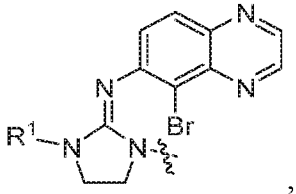
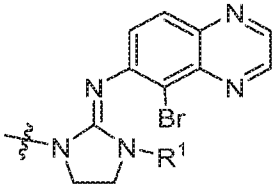
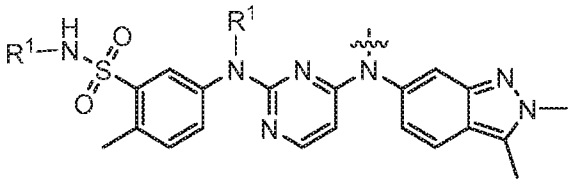



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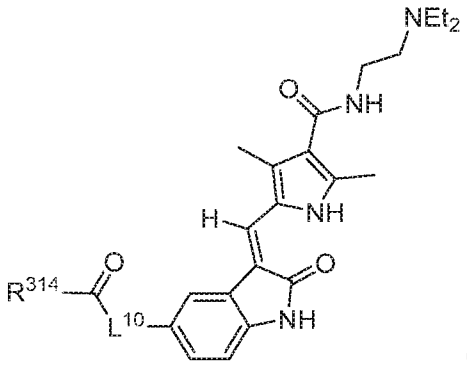
or $R^{114}$ is

,

, or

; and

wherein all other variables are as defined herein.

In one embodiment, $L^2$ is $L^{2'}$ wherein $L^{2'}$ is defined above.

In one embodiment, A is B wherein B is defined above.

In an alternative embodiment, the disclosure provides a prodrug of Formula X':



(X')

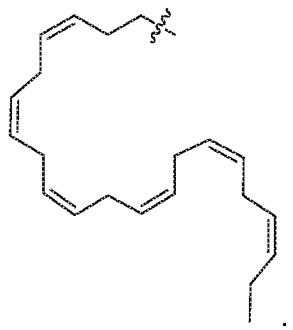
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof wherein

$L^{10}$ is -O-, -NH-, or –N(alkyl)-;

$R^{314}$ is an unsaturated fatty acid residue including but not limited to the carbon chains from linoleic acid (-$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$)), docosahexaenoic acid (–$(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid (–$(CH_2)_4(CHCHCH_2)_5CH_3$)), alphalinolenic acid (–$(CH_2)_8(CHCHCH_2)_3CH_3$)), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid, and wherein, if desired, each of which can be substituted with $R^5$; and

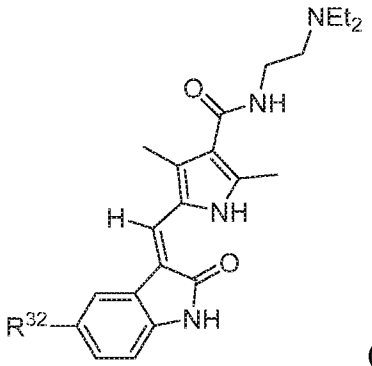
$R^5$ is defined above.

In one embodiment, $R^{314}$ is



.

The disclosure also provides a prodrug of Formula XI:



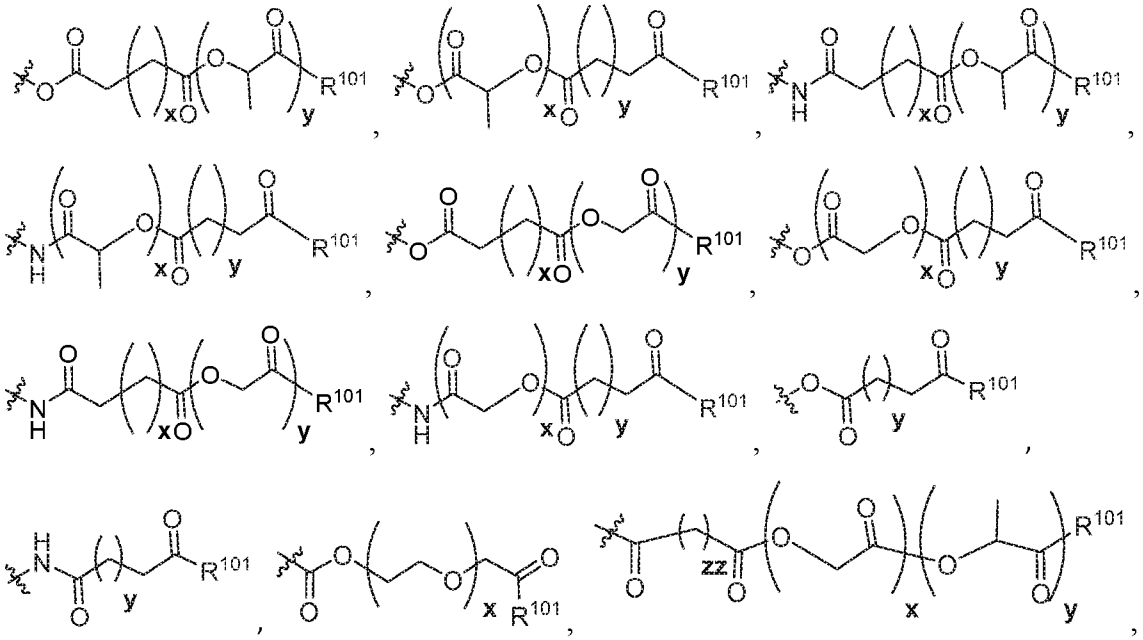
(XI)

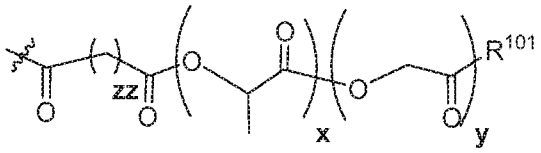
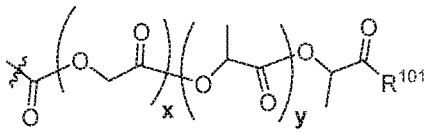
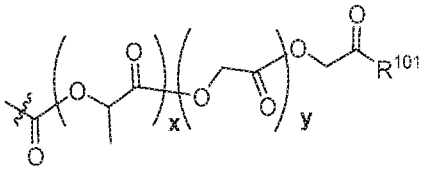
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

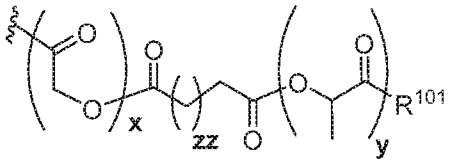
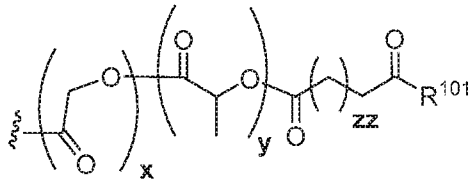
$R^{32}$ is selected from: $R^{35}$, alkyl, alkyloxy, acyl, polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, polyamide, or other biodegradable polymer, wherein each $R^{32}$ other than $R^{35}$ is substituted with at least one $L^4$-$R^{101}$;

wherein $R^{32}$ can be further substituted with $R^5$ if valence permits, a stable compound is formed, and the resulting compound is pharmaceutically acceptable.

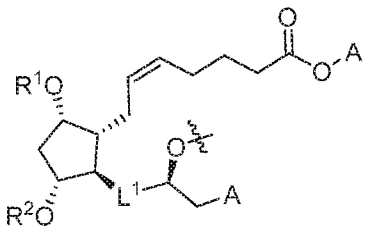
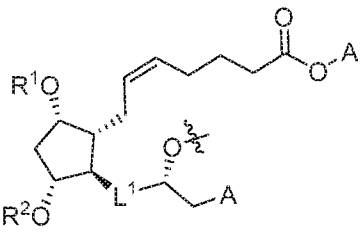
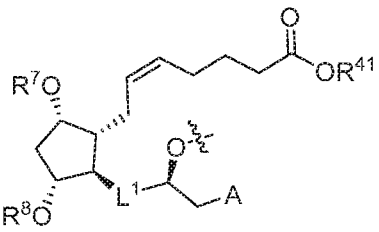
$R^{35}$ is selected from:

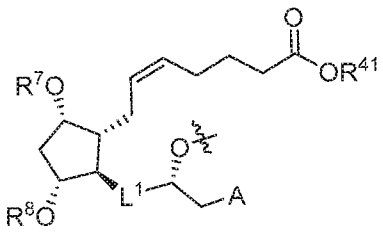
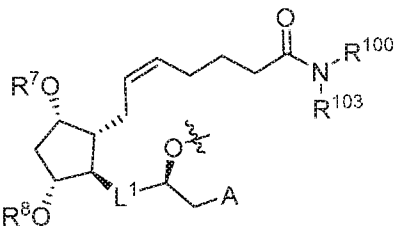
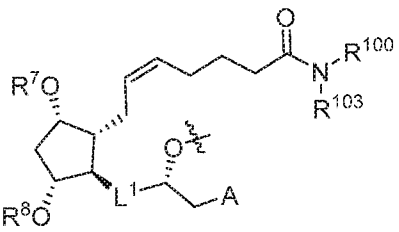


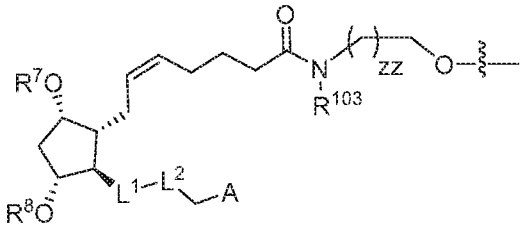
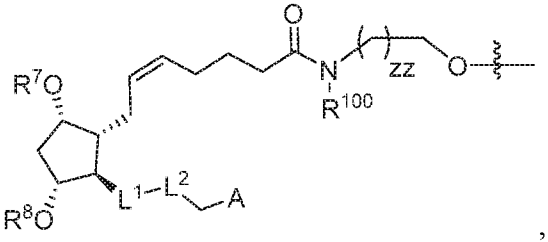

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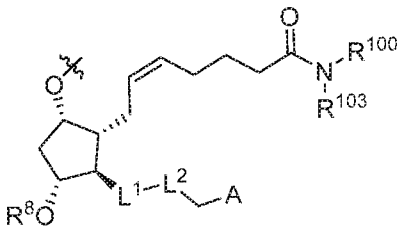
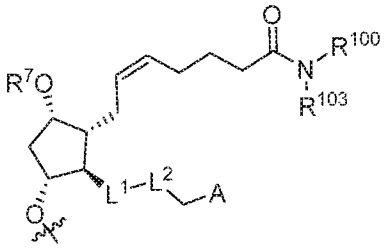
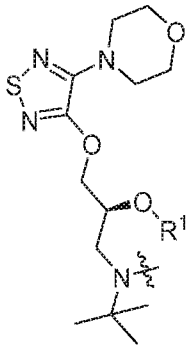
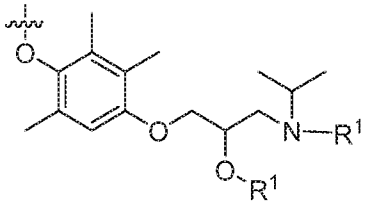
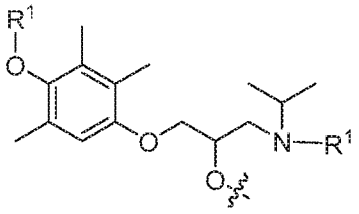
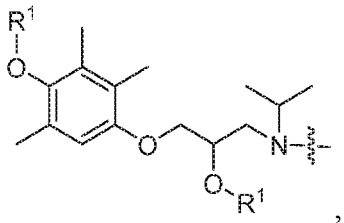
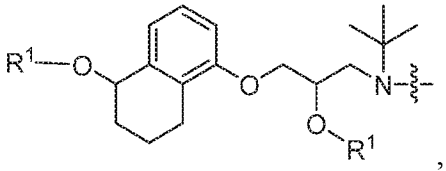
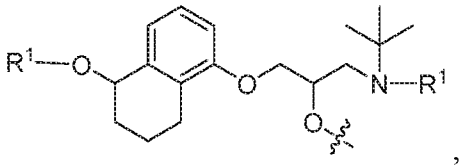
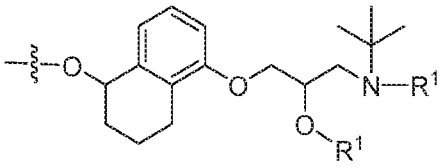
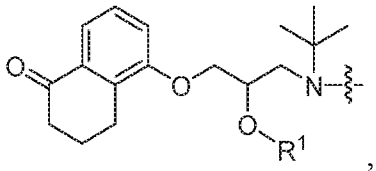
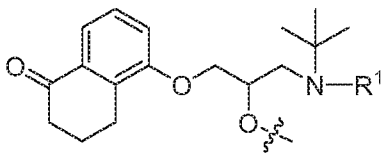
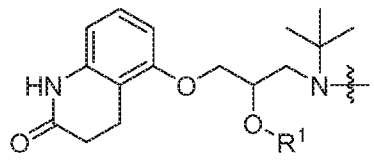
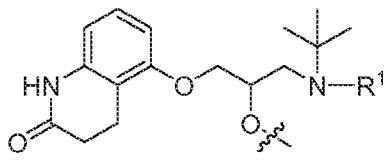
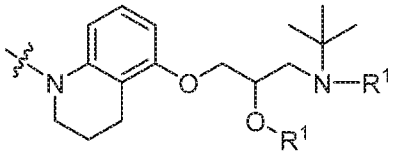
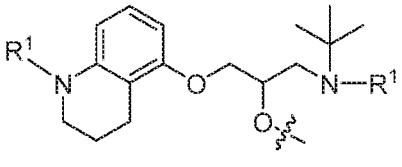
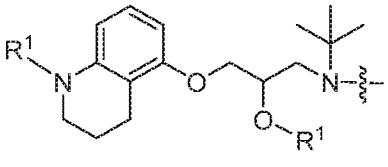
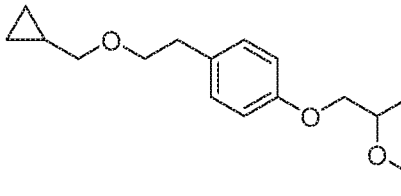
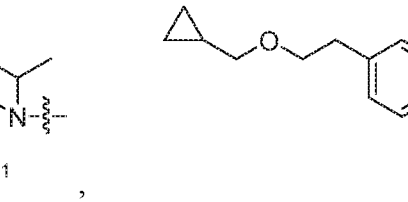
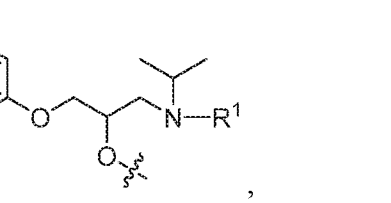
or $R^{35}$ is  or ;

$R^{101}$ is selected from


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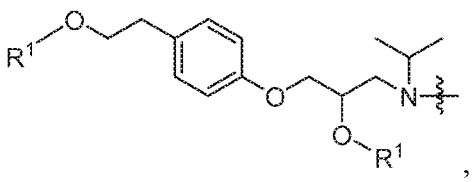
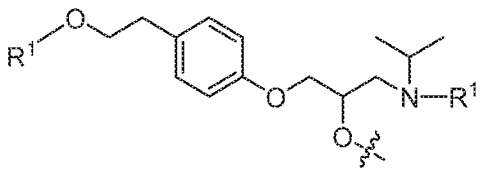
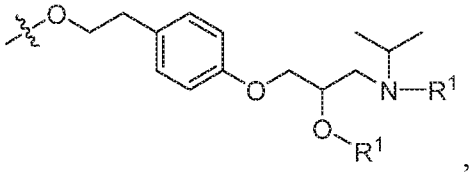
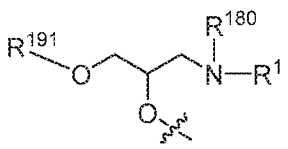
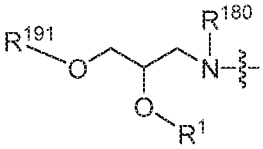
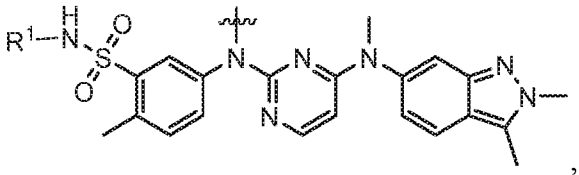
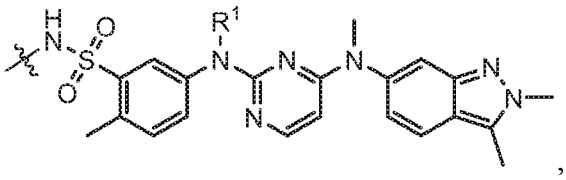
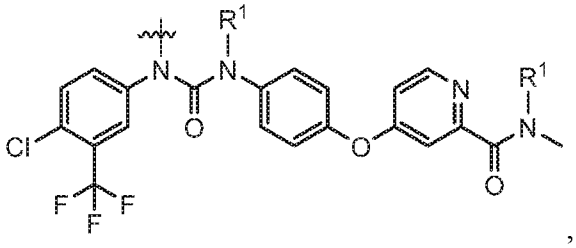
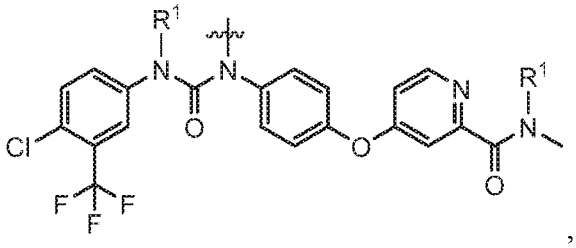
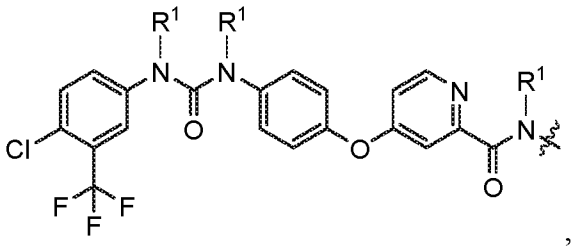
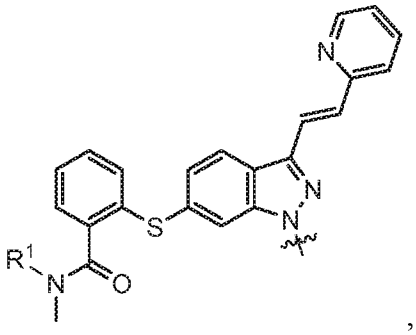
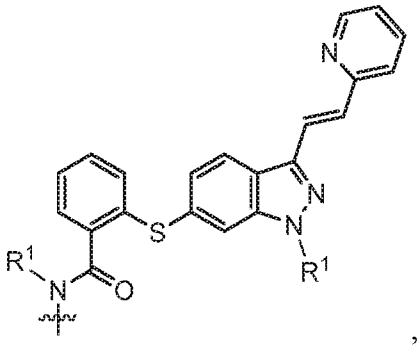
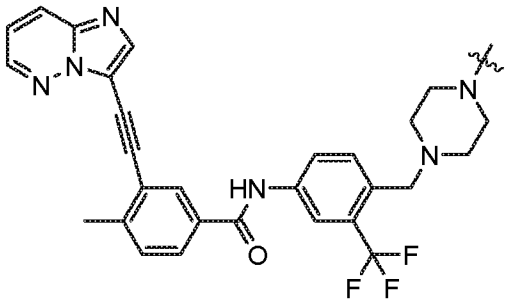

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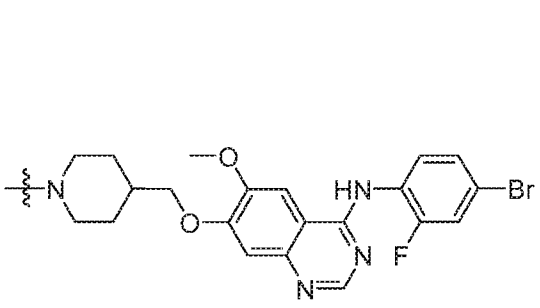
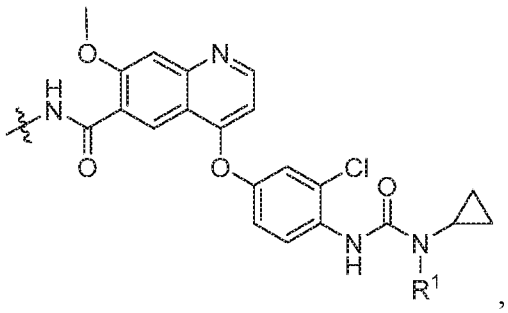
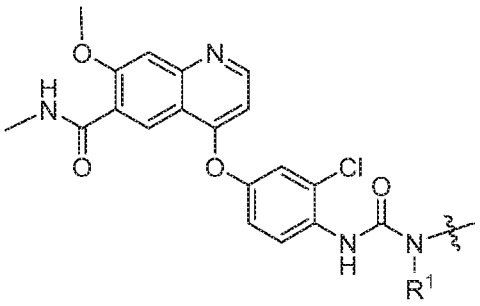
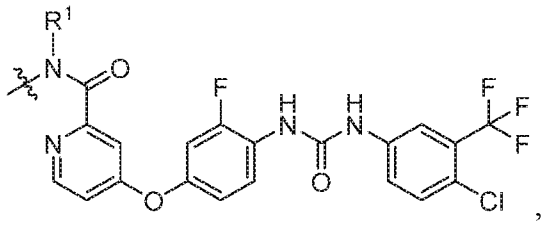
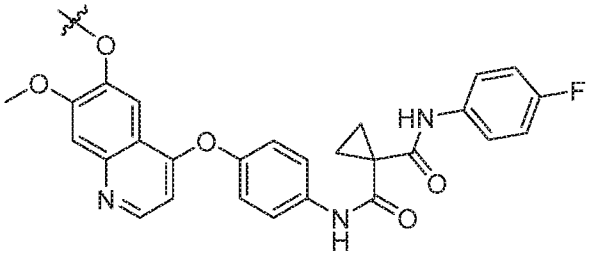
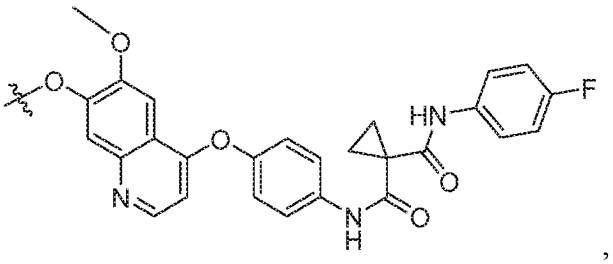
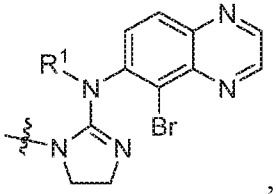
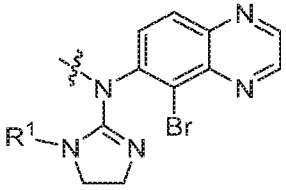
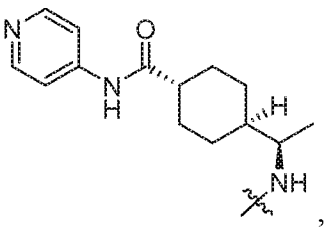
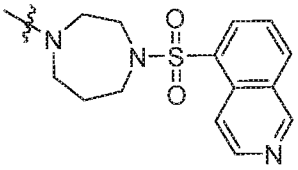
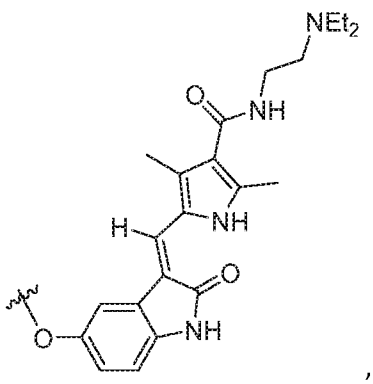
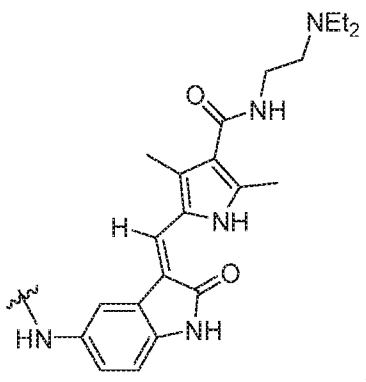
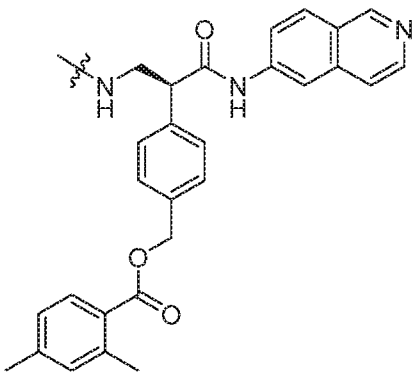

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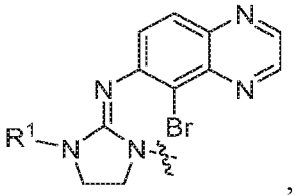
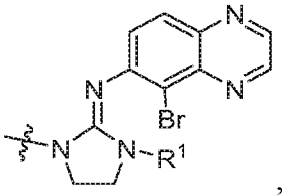
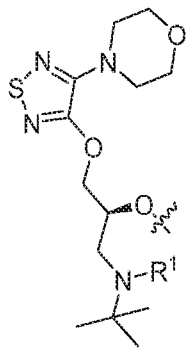

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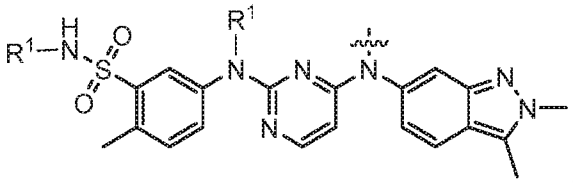
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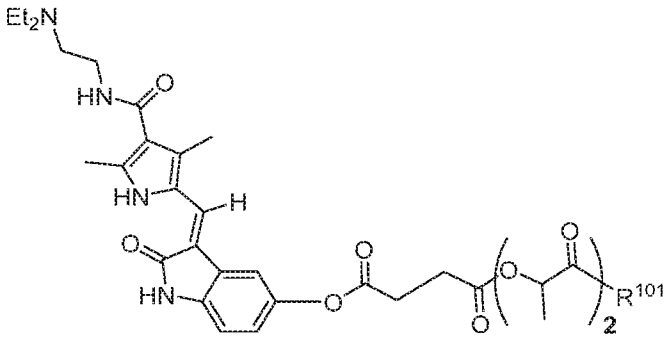

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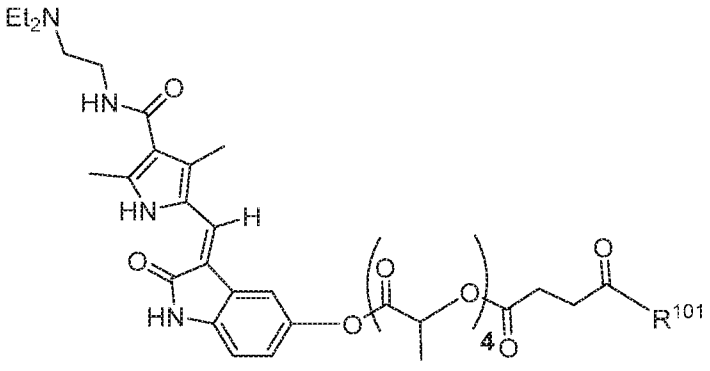
or $R^{101}$ is  ,  ,  or

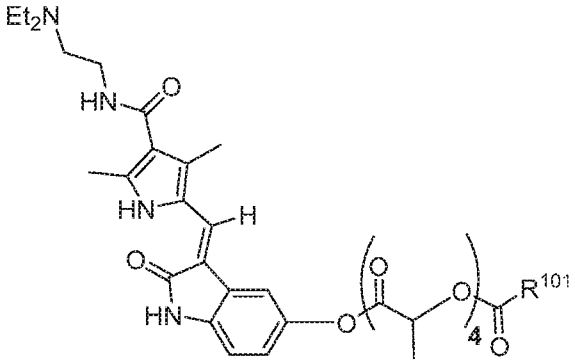
 ; and

wherein all other variables are as defined herein.

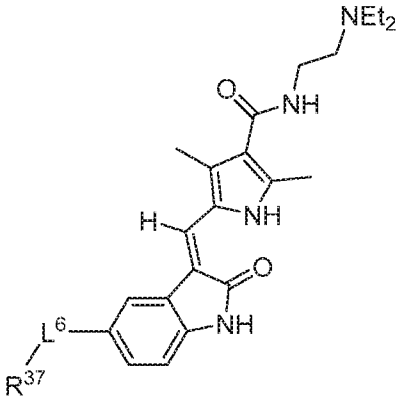
Non-limiting examples of Formula XI include



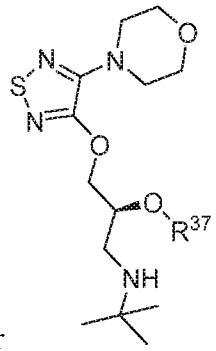
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The disclosure also provides a prodrug of Formula XII or Formula XIII:



(XII) or



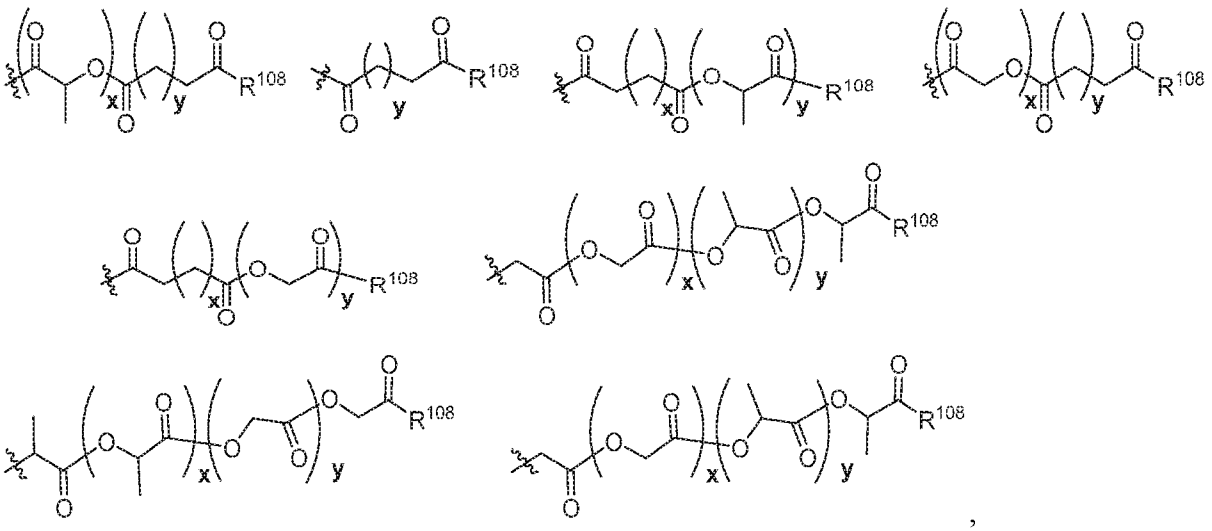
(XIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

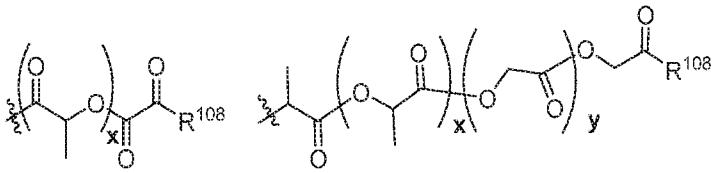
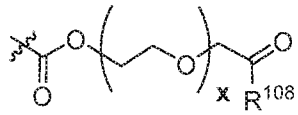
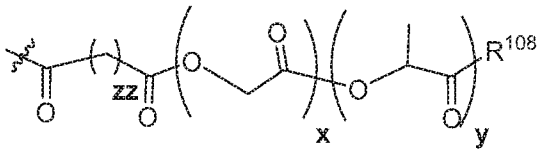
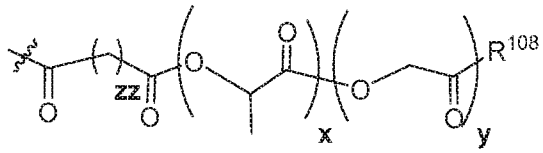
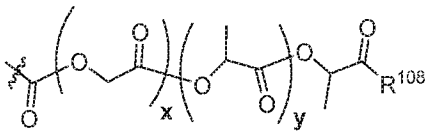
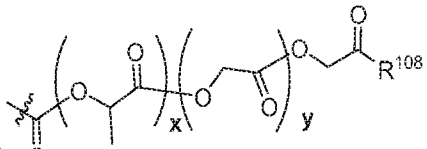
$R^{37}$ is selected from: $R^{38}$, polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, a polyamide, or other biodegradable polymer, wherein each $R^{37}$ other than $R^{38}$ is substituted with at least one $L^4$-$R^{108}$;

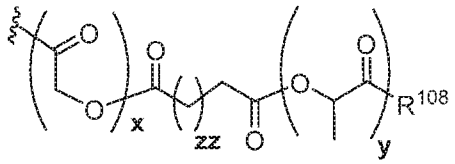
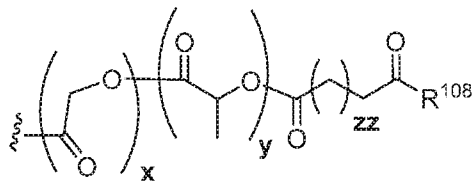
$L^6$ is selected from –O-, -NH-, -S-, -C(O)- and -OC(O)-;

$R^{38}$ is selected from:

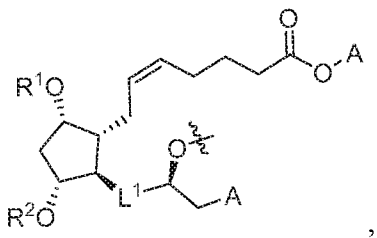
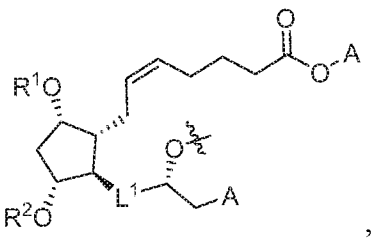
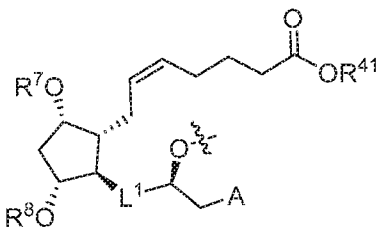
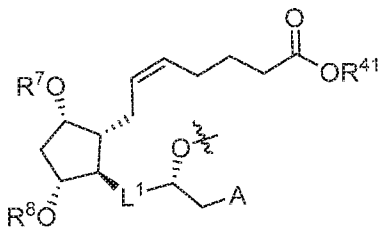
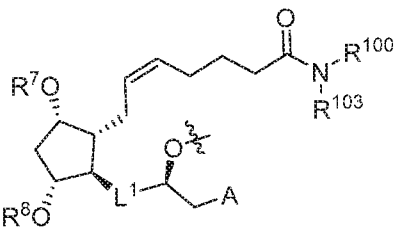
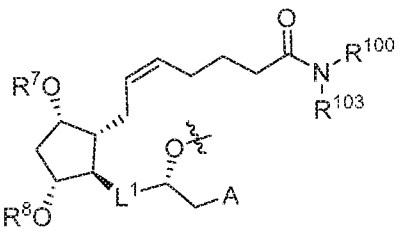
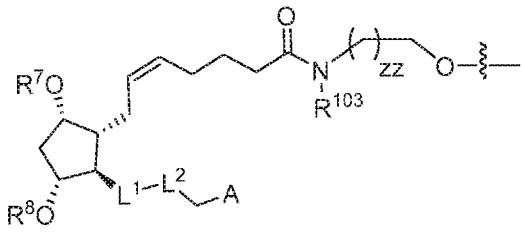
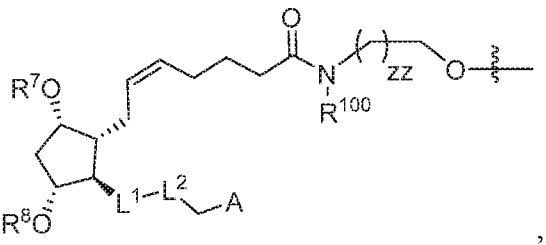


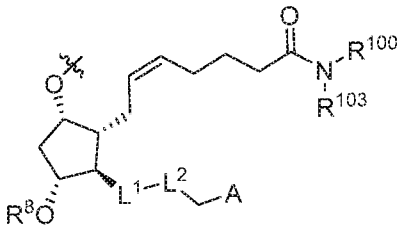
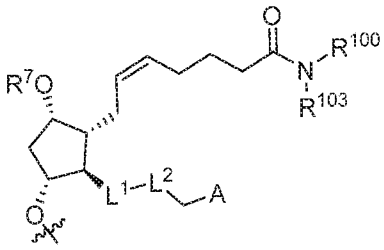
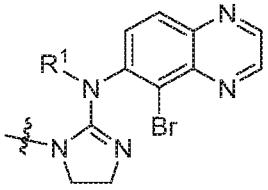
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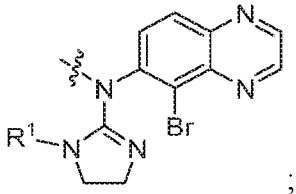






, and ; and

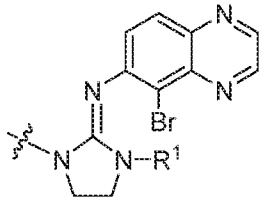
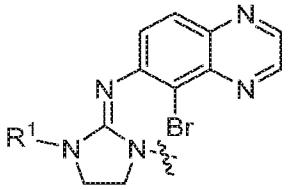


or $R^{38}$ is or ;

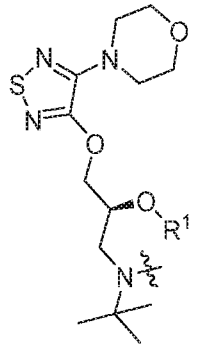
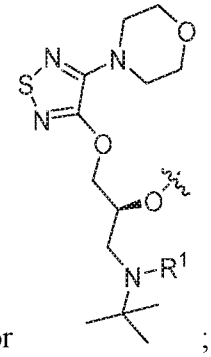
$R^{108}$ is selected from




, and

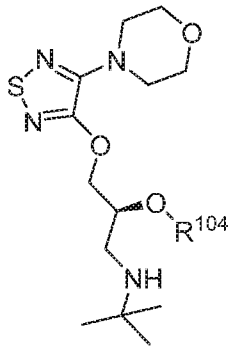

;

or $R^{108}$ is  or ;

or in an alternative embodiment, $R^{108}$ is  or ; and

wherein all other variables are as defined herein.

The disclosure also provides a prodrug of Formula XIV:


(XIV)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

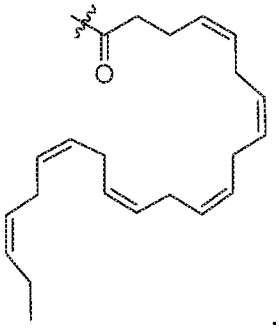
$R^{104}$ is selected from -C(O)$C_{17-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain), -C(O)($C_{10-30}$alkenyl, with at least one

$R^5$ substituent on the alkenyl chain), and -C(O)($C_{10-30}$alkynyl, with at least one $R^5$ substituent on the alkynyl chain);

wherein $R^5$ is defined above.

In one embodiment, $R^{104}$ is $-C(O)(CH_2)_{16}CH_3$.

In one embodiment, $R^{104}$ is



.

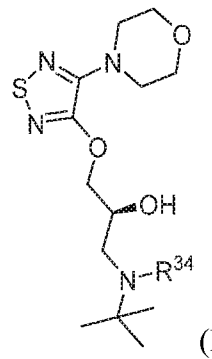
In one embodiment, a compound of Formula XIV is the pharmaceutically acceptable HCl salt.

In one embodiment, a compound of Formula XIV is the pharmaceutically acceptable maleic salt.

In one embodiment, a compound of Formula XIV is the pharmaceutically acceptable succinic salt.

In one embodiment, a compound of Formula XIV is the pharmaceutically acceptable fumaric salt.

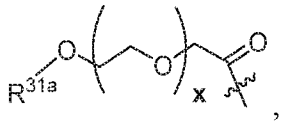
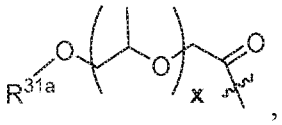
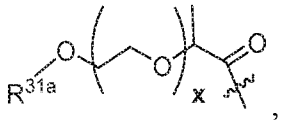
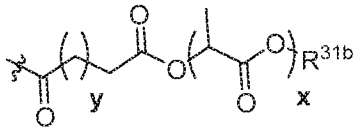
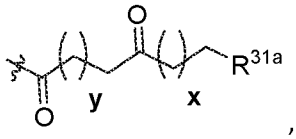
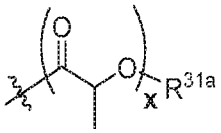
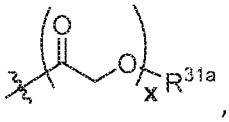
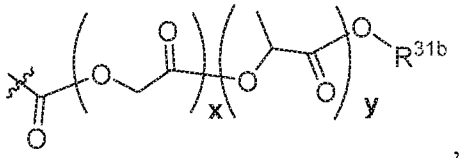
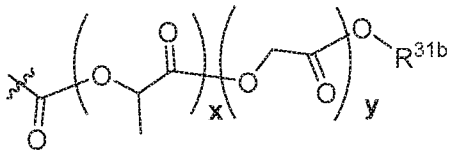
The disclosure also provides a prodrug of Formula XV:

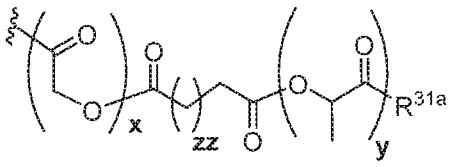
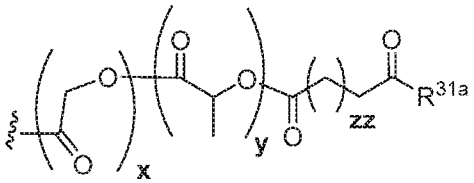


(XV)

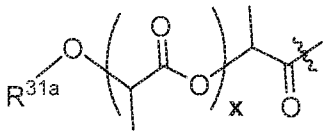
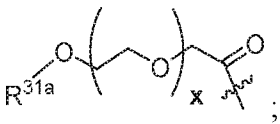
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

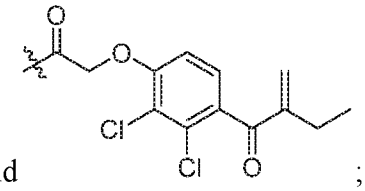
$R^{34}$ is selected from: acyl, $R^{36}$, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, and poly(lactic-co-

glycolic acid), a polyglycolic acid, a polyester, polyamide, , , , , , , , , and , or other biodegradable polymer, wherein each $R^{34}$ other than $R^{36}$ is substituted with at least one $L^4$-$R^{115}$;

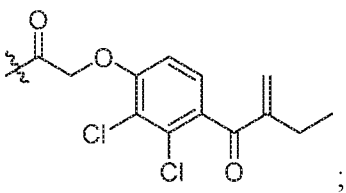
or $R^{34}$ is  or ;

In one embodiment $R^{34}$ is selected from:

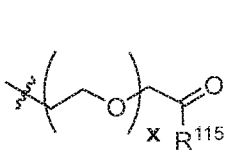
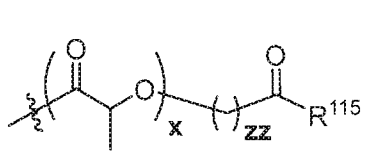
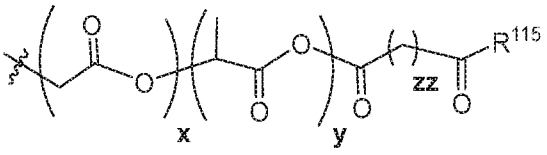
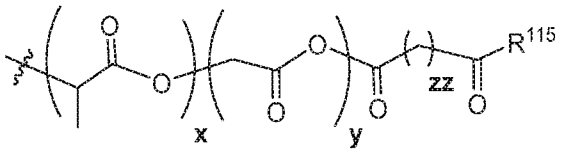
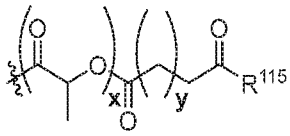
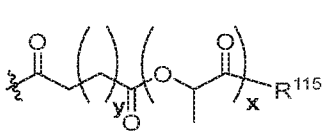
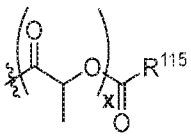
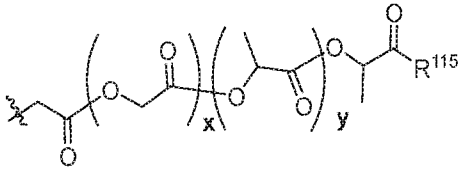
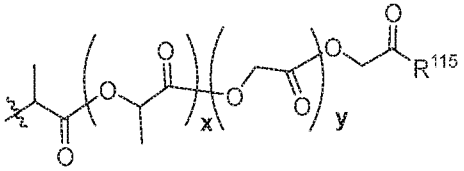
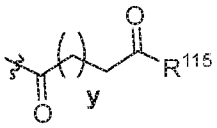
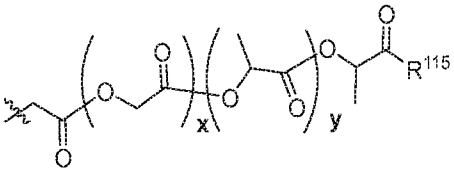
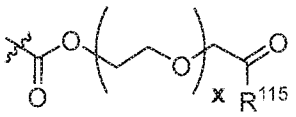
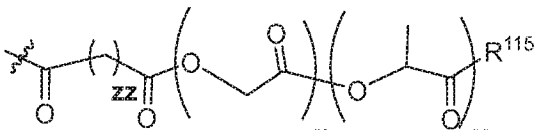
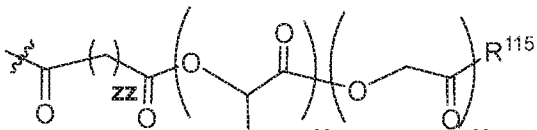
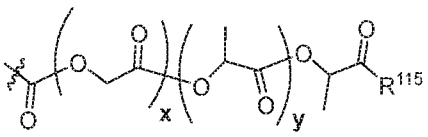
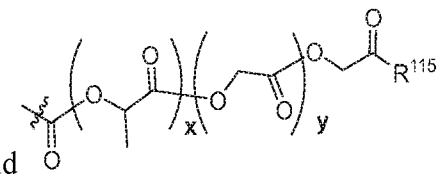
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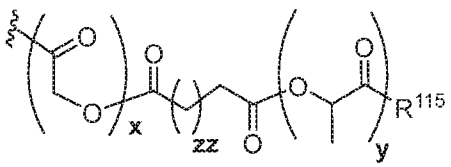
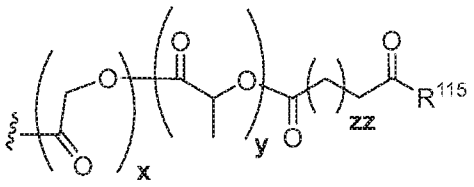
In one embodiment $R^{31a}$ is selected from -C(O)A, stearoyl, and ;

In an alternative embodiment, $R^{31b}$ is selected from -C(O)A, stearoyl, and

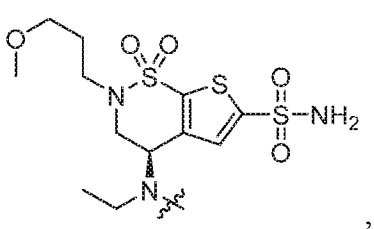
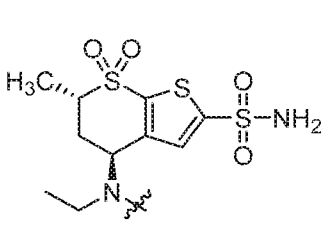
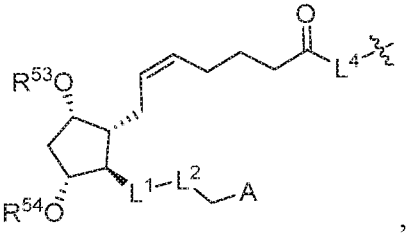
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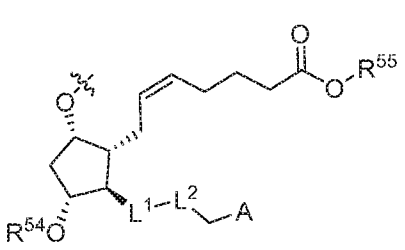
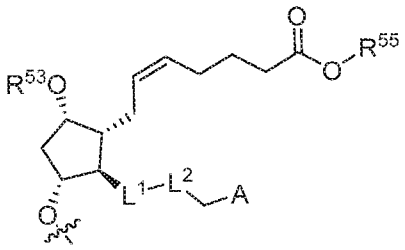
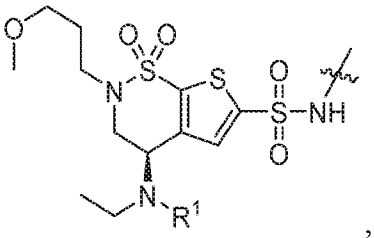
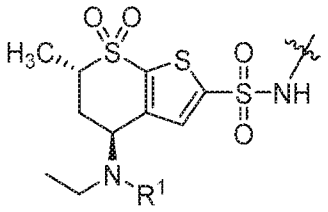
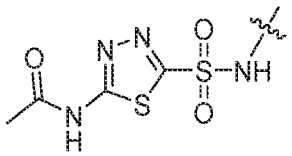
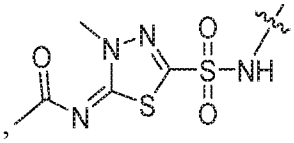
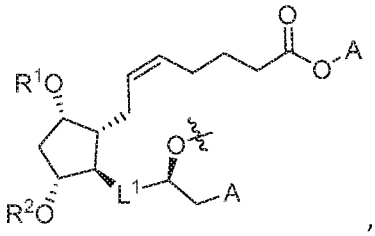
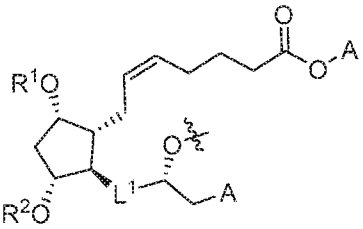
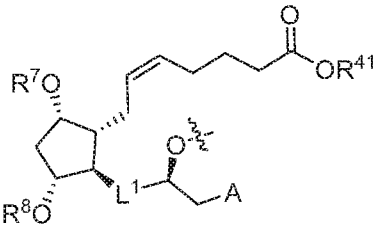
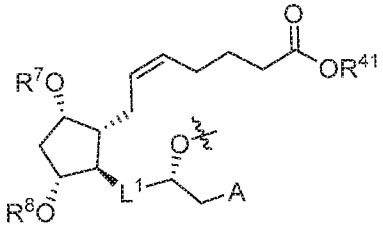
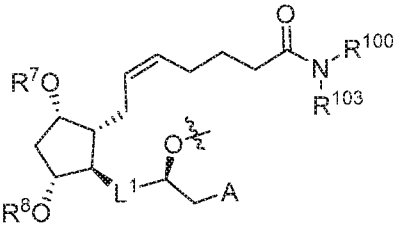
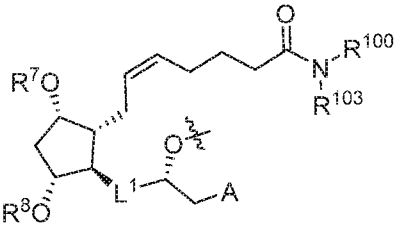
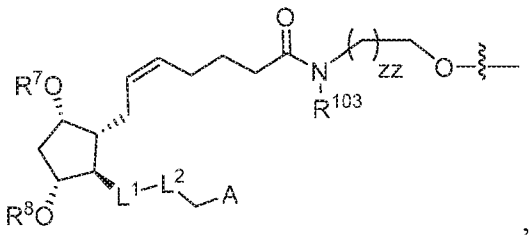
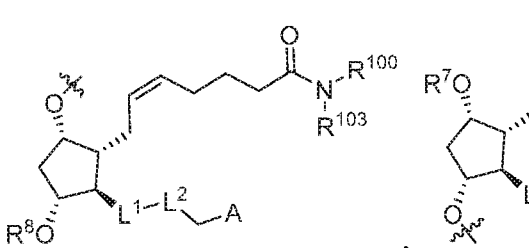
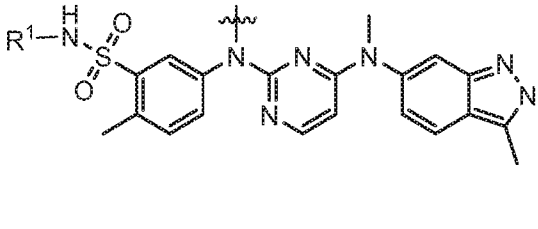
$R^{36}$ is selected from:


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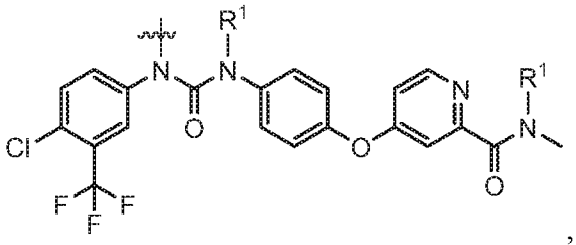
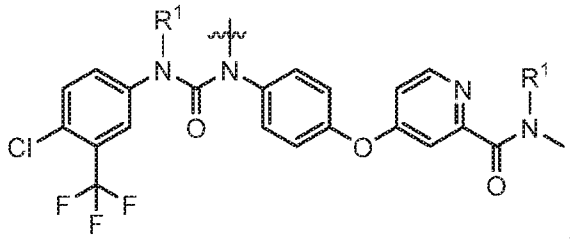
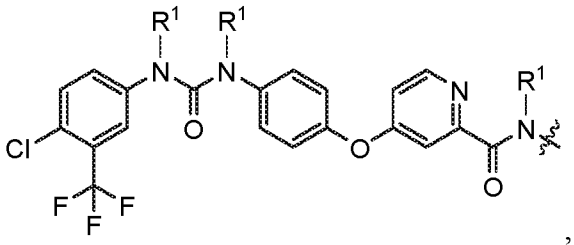
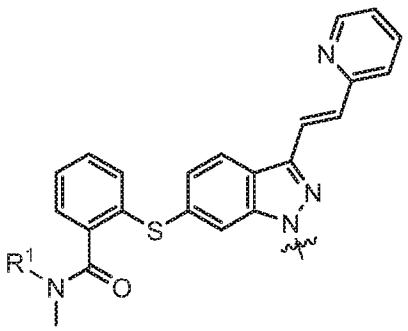
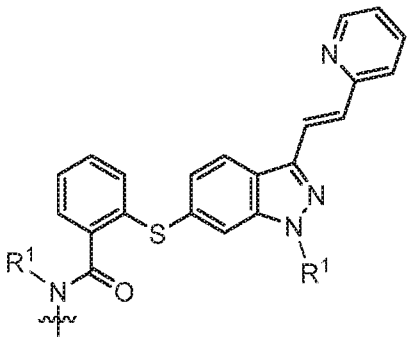
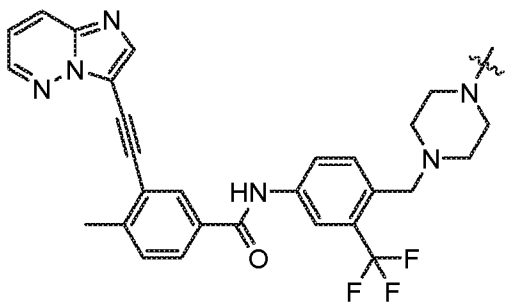
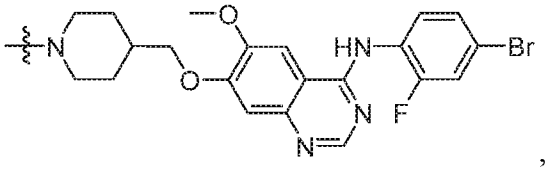
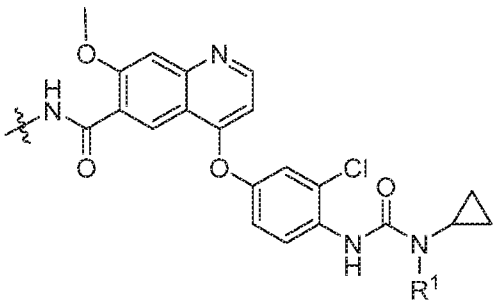
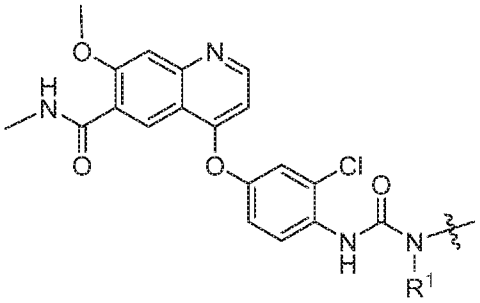
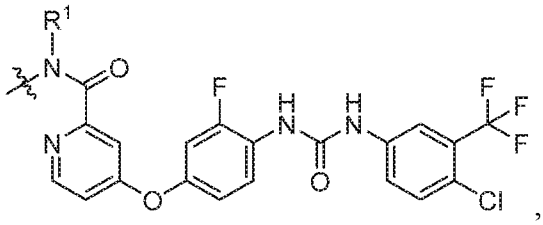
or $R^{36}$ is

or

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$R^{115}$ is selected from

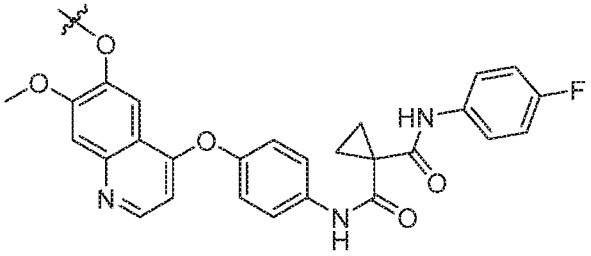
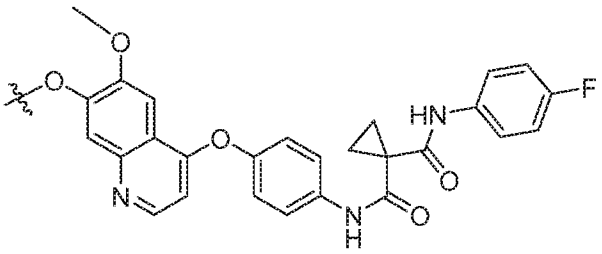
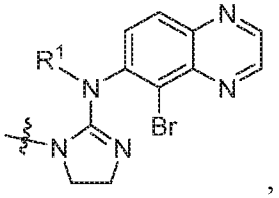
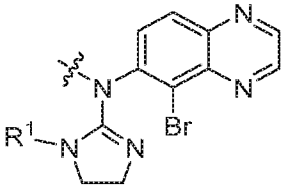
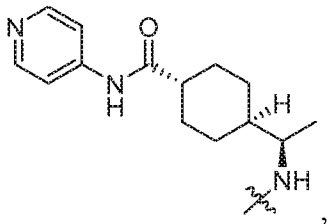
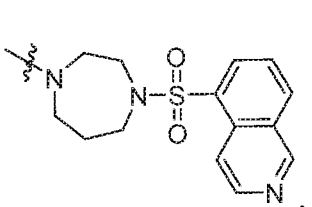
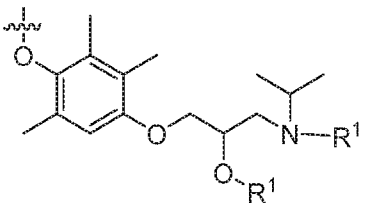
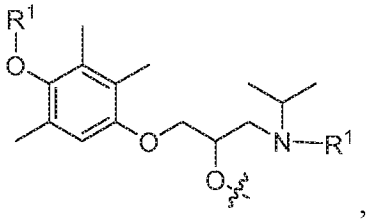
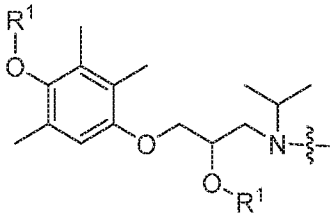
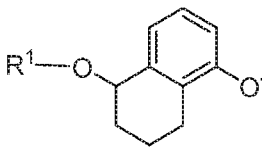
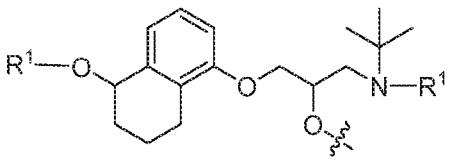
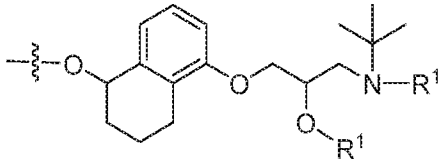
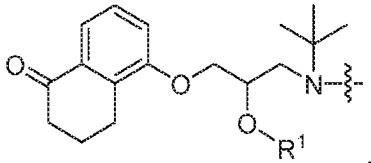
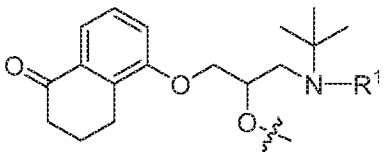
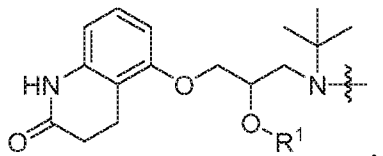
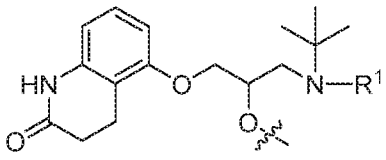
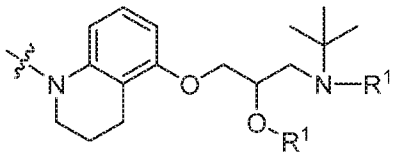
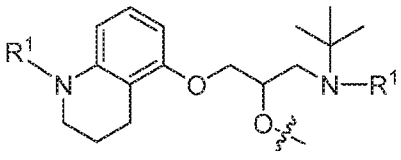

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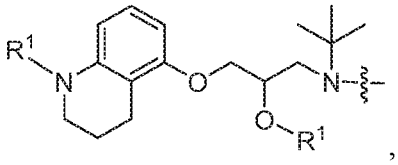
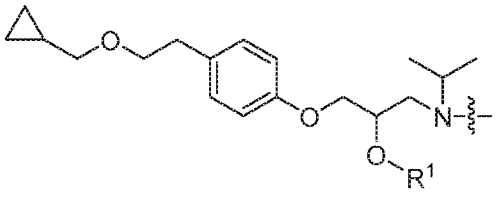
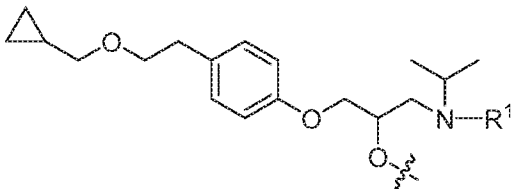
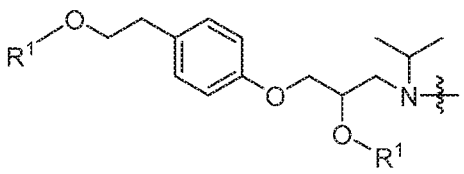
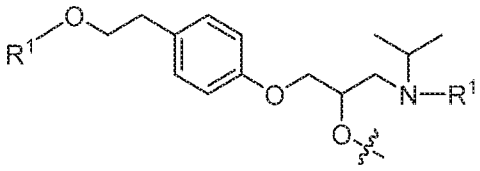
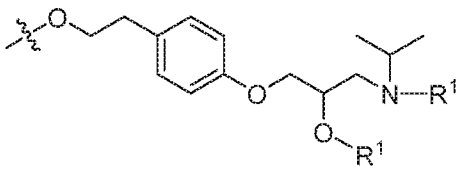
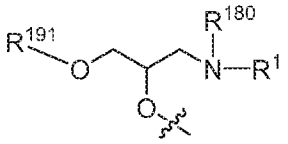
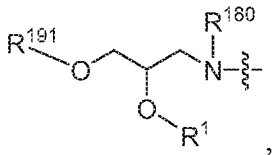
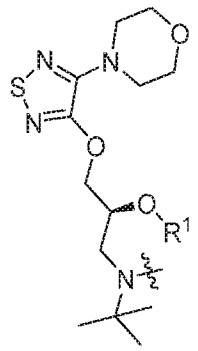
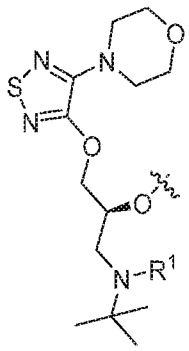
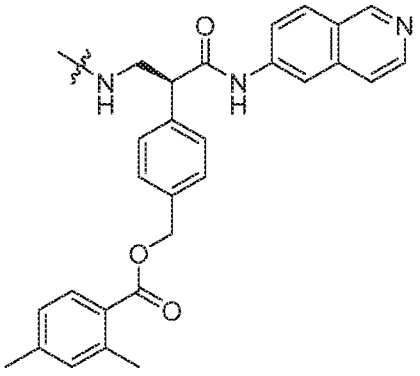
















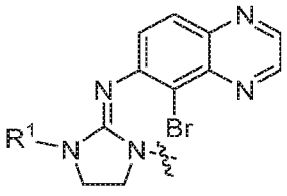
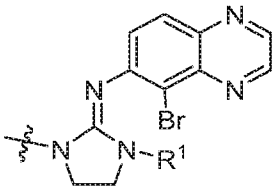


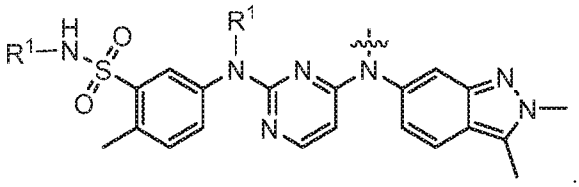

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and

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or $R^{115}$ is

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wherein

$R^{53}$ and $R^{54}$ are independently selected from $-C(O)R^4$, -C(O)A, and hydrogen; and

$R^{55}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, and poly(lactic-co-glycolic acid), polyglycolic acid, or a polyester, a polyamide, or other biodegradable polymer, wherein a terminal hydroxy or carboxy group can be substituted to create an ether or ester, respectively;

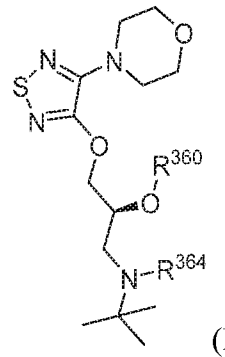
(ii) $-C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl;

(iii) an unsaturated fatty acid residue including but not limited the carbon fragment taken from linoleic acid (-$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$)), docosahexaenoic acid (–$(CH_2)_3(CHCHCH_2)_6CH_3$)), eicosapentaenoic acid (-$(CH_2)_4(CHCHCH_2)_5CH_3$)), alpha-linolenic acid (–$(CH_2)_8(CHCHCH_2)_3CH_3$)) stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl; and

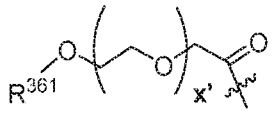
wherein all other variables are as defined herein.

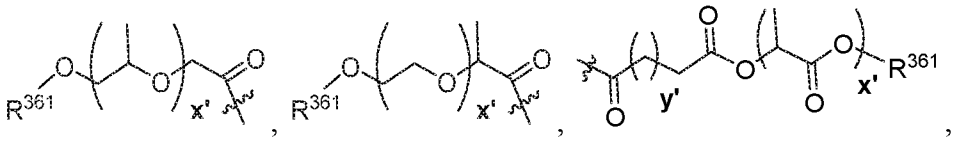
In an alternative embodiment, the disclosure also provides a prodrug of Formula XV'

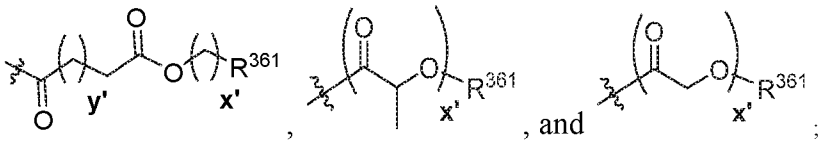


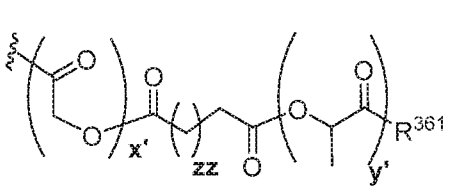
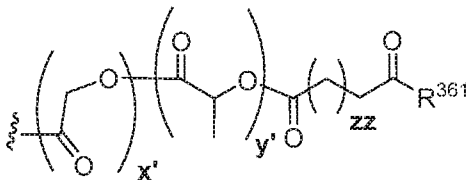
(XV')

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{364}$ is selected from: acyl, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, ,

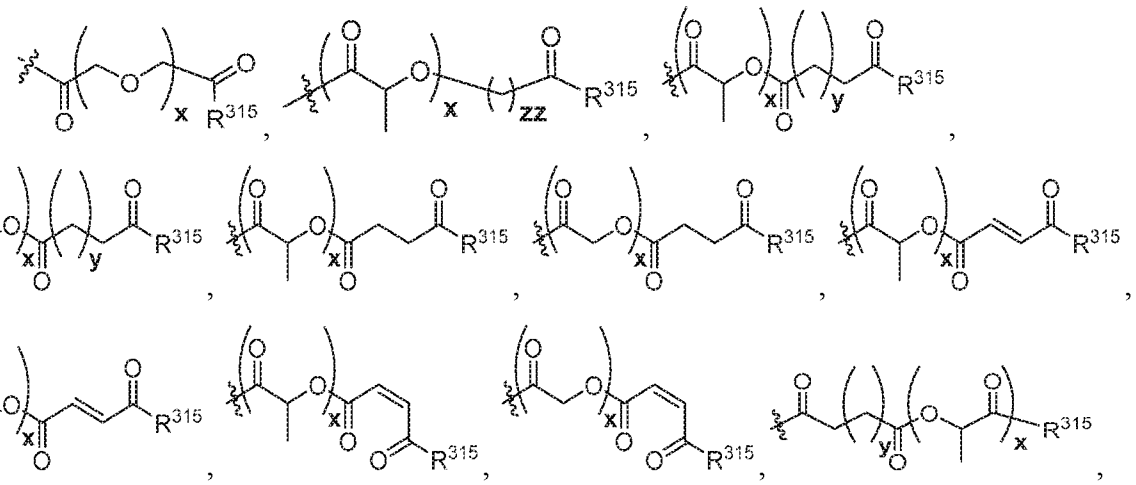
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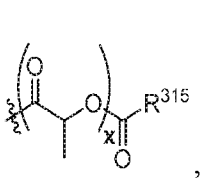
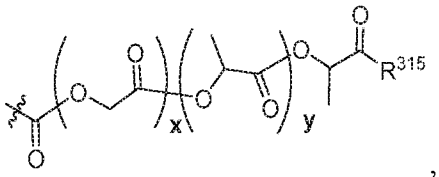
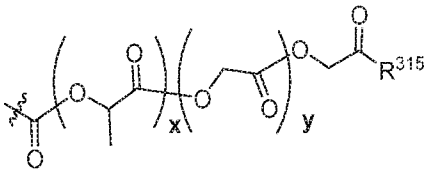
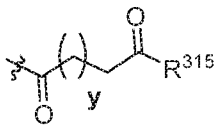
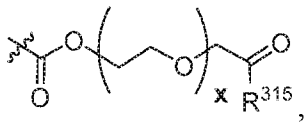
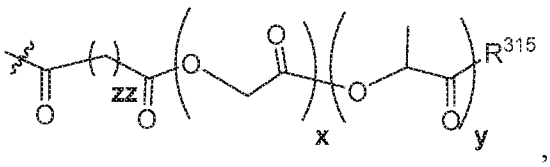
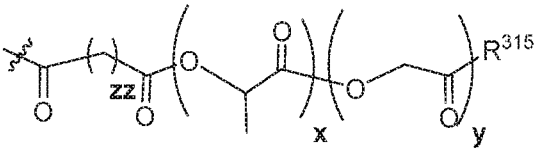
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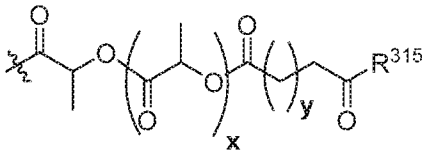
or $R^{364}$ is  or ;

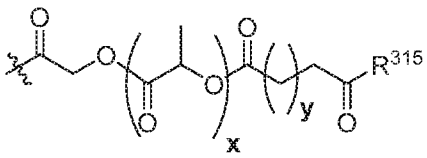
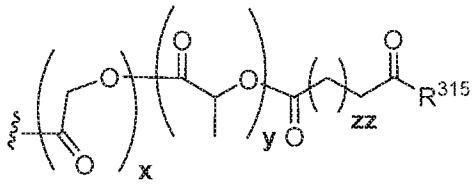
$R^{361}$ is selected from hydrogen, A, -C(O)alkyl, -C(O)A, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, and stearoyl;

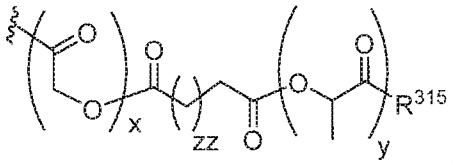
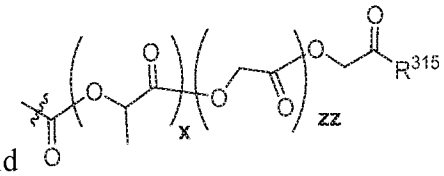
$R^{360}$ is selected from



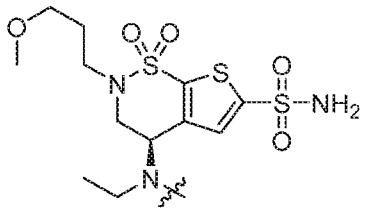
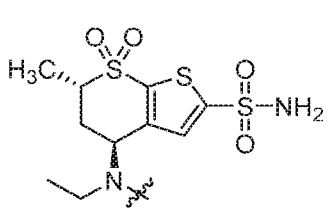
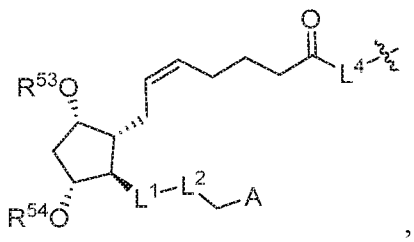

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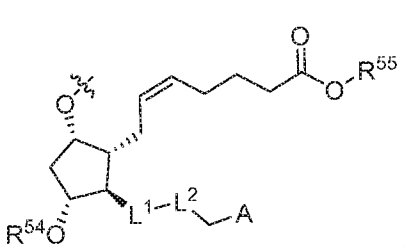
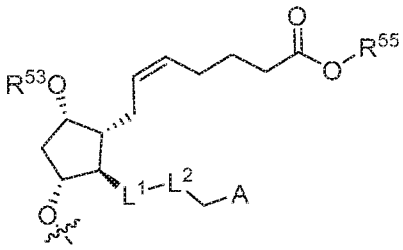
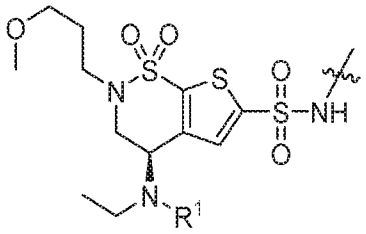
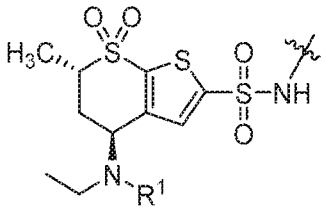
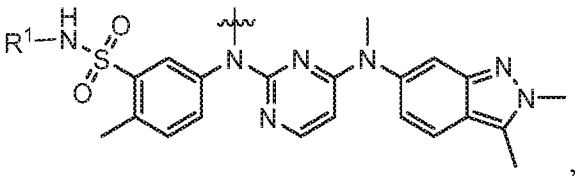
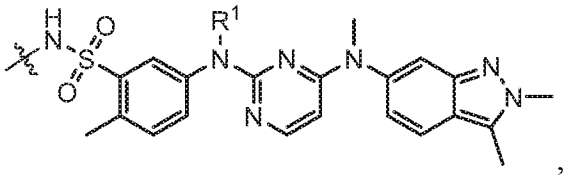
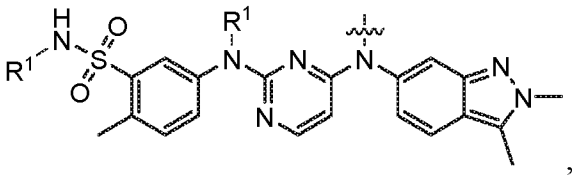
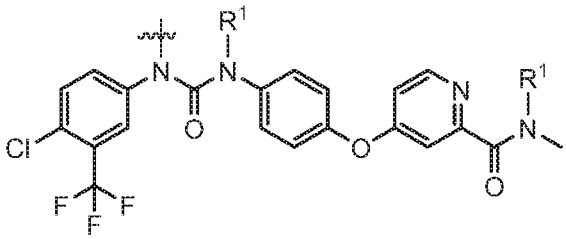
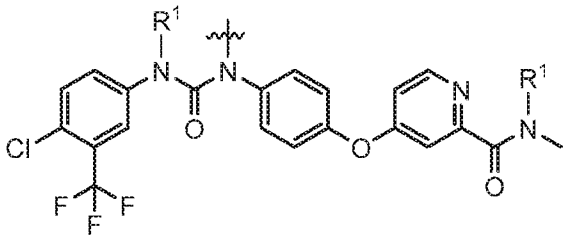
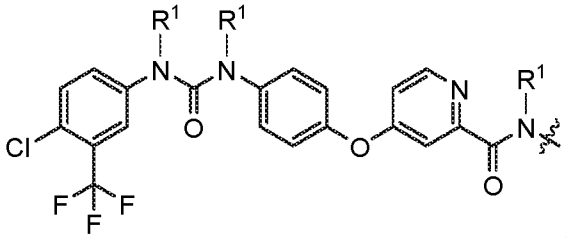
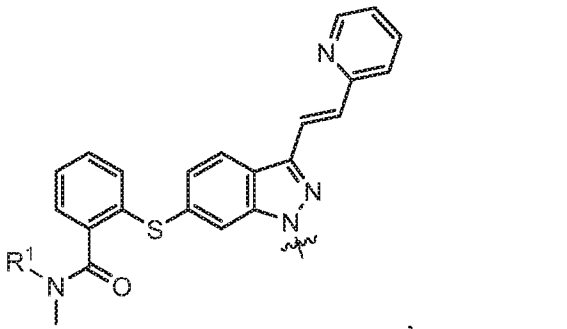
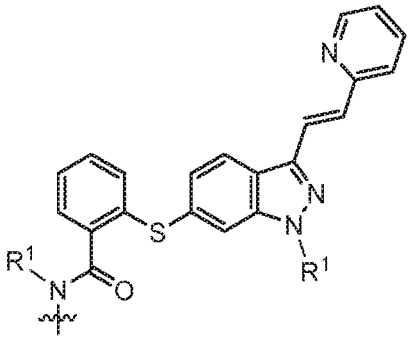
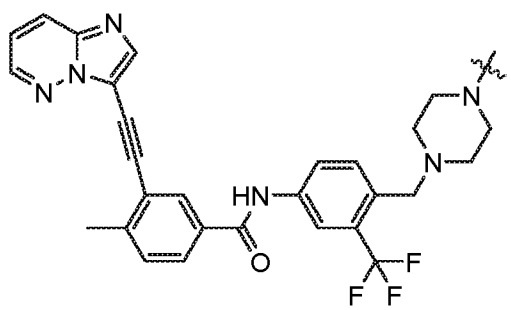
or $R^{360}$ is selected from

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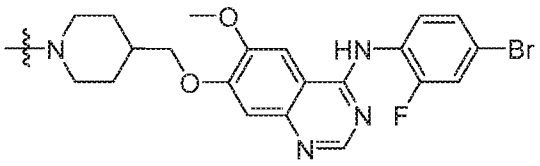
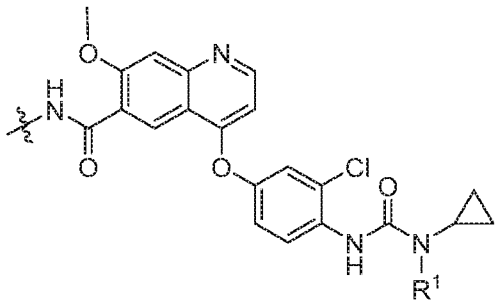
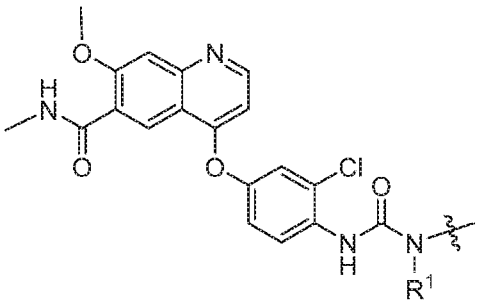
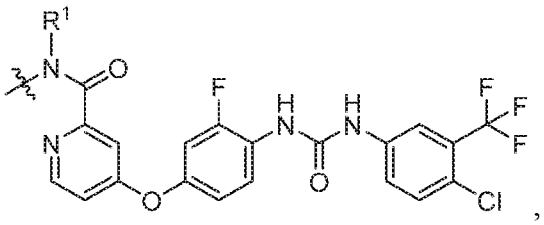
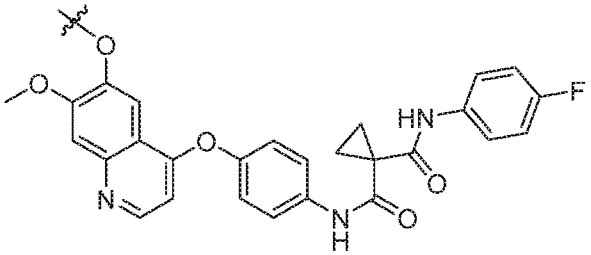
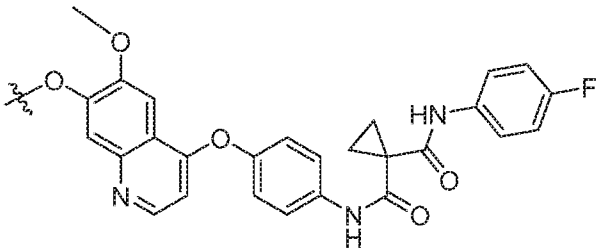
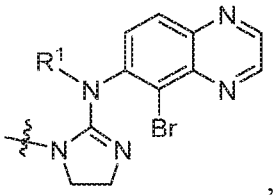
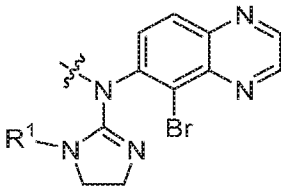
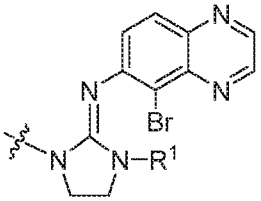
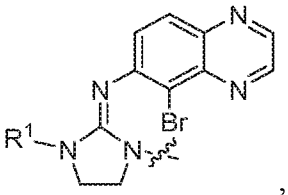
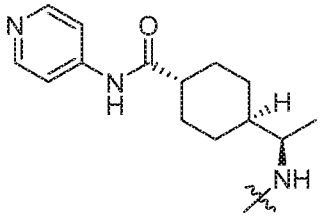
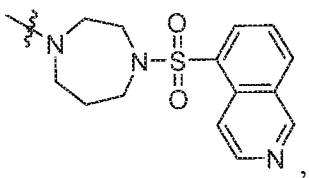
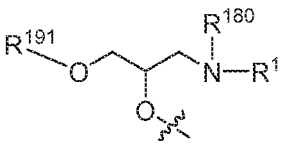
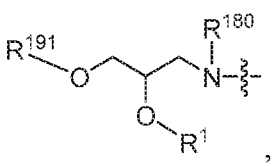
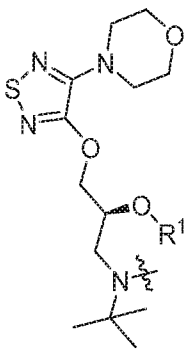
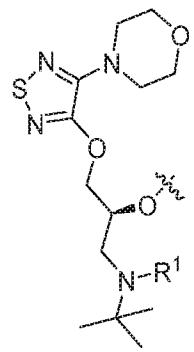
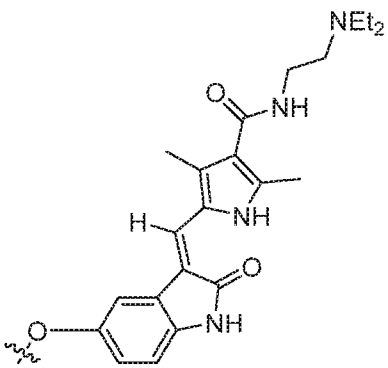

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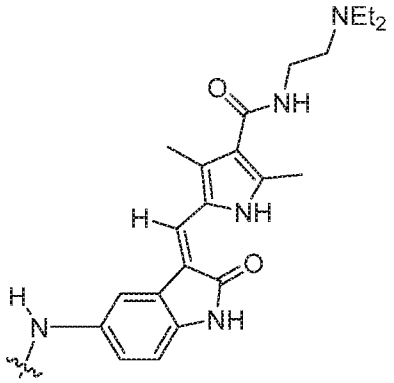
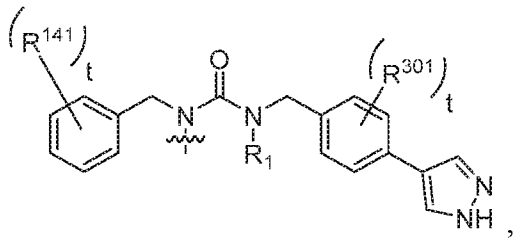
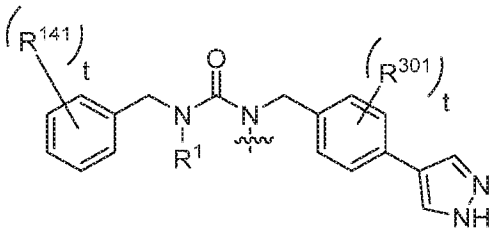
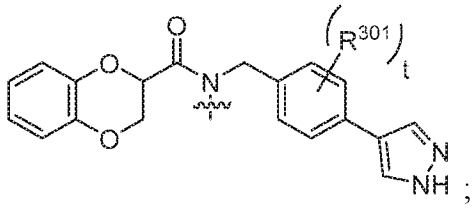

and

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$R^{315}$ is selected from


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x', and y' are independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and wherein if x' and y' are within the linker then x' and y' cannot both be 0;

$R^{141}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, and halogen;

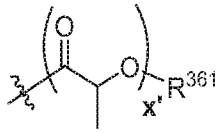
$R^{134}$ and $R^{135}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

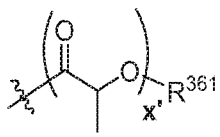
$R^{301}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, halogen, $-O(CH_2)_2NR^{334}R^{335}$, and $-N(CH_3)(CH_2)_2NR^{334}R^{335}$;

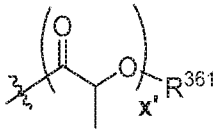
$R^{334}$ and $R^{335}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

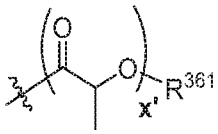
or $R^{334}$ and $R^{335}$ can together form a heterocycloalkyl; and

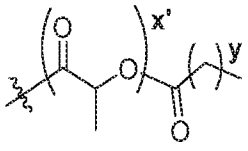
wherein all other variables are as defined herein.

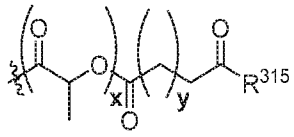
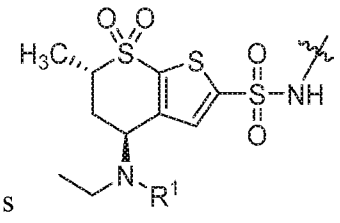
In one embodiment, $R^{364}$ is  and $R^{361}$ is –C(O)alkyl;

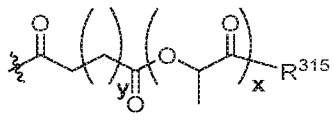
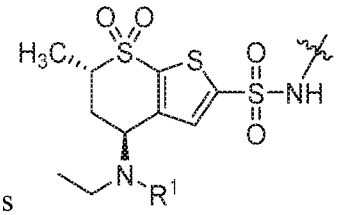
In one embodiment, $R^{364}$ is  and $R^{361}$ is –C(O)Me;

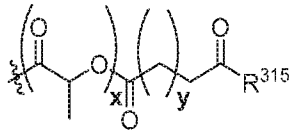
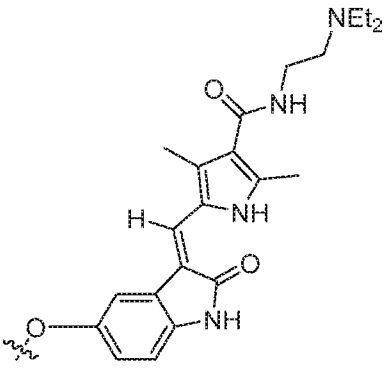
In one embodiment, $R^{364}$ is , $R^{361}$ is –C(O)Me, and x' is an integer between 1 and 6 (1, 2, 3, 4, 5, or 6);

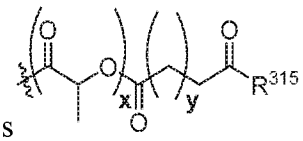
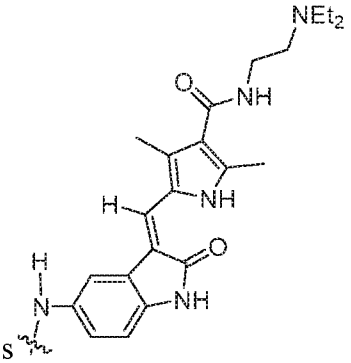
In one embodiment, $R^{364}$ is  and $R^{361}$ is stearoyl;

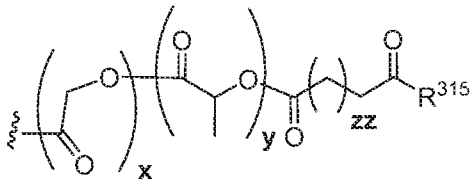
In one embodiment, $R^{364}$ is , x' is an integer between 1 and 6 (1, 2, 3, 4, 5, or 6), and y is 11 or 17, or in an alternative embodiment, y is 10 or 16.

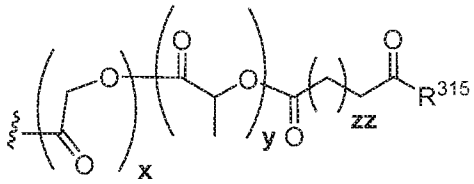
In one embodiment, $R^{360}$ is , $R^{315}$ is , and $R^1$ is hydrogen.

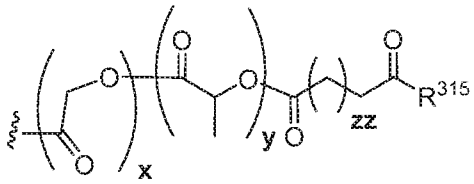
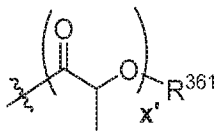
In one embodiment, $R^{360}$ is , $R^{315}$ is , and $R^1$ is hydrogen.

In one embodiment, $R^{360}$ is , $R^{315}$ is .

In one embodiment, $R^{360}$ is  and $R^{315}$ is .

In certain embodiments, $R^{360}$ is , x and y are independently selected from 1, 2, 3, 4, 5, or 6, and zz is 1, 2, or 3.

In certain embodiments, $R^{360}$ is , x and y are independently selected from 1, 2, or 3, and zz is 1, 2, or 3.

In certain embodiments, $R^{360}$ is , x and y are independently selected from 1, 2, or 3, zz is 1, 2, or 3, and $R^{360}$ is .

In certain embodiments, x' and x are 1 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 2 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 3 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 1 and y and y' are independently selected from 1, 2, or 3.

In certain embodiments, x' and x are 2 and y and y' are independently selected from 1, 2, or 3.

In certain embodiments, y' and y are 1 and x and x' are independently selected from 1, 2, 3, 4, 5, and 6.

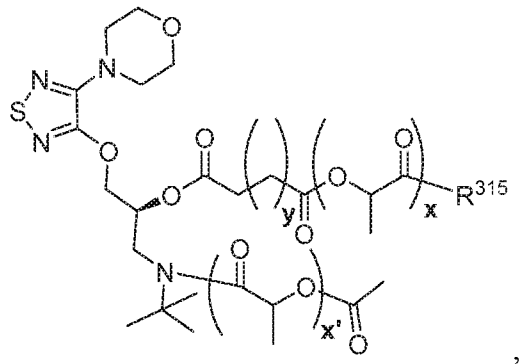
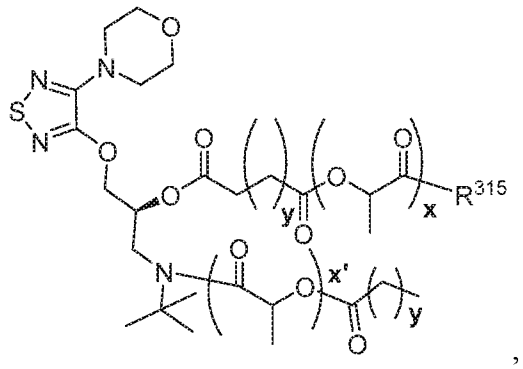
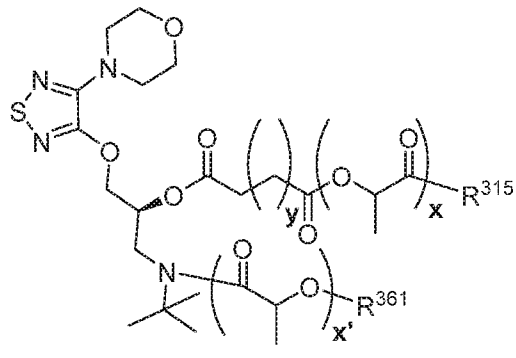
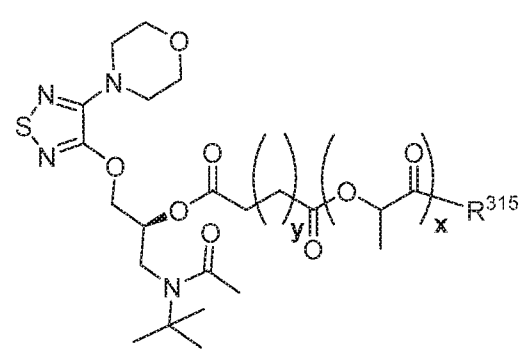
In certain embodiments, y' and y are 2 and x and x' are independently selected from 1, 2, 3, 4, 5, and 6.

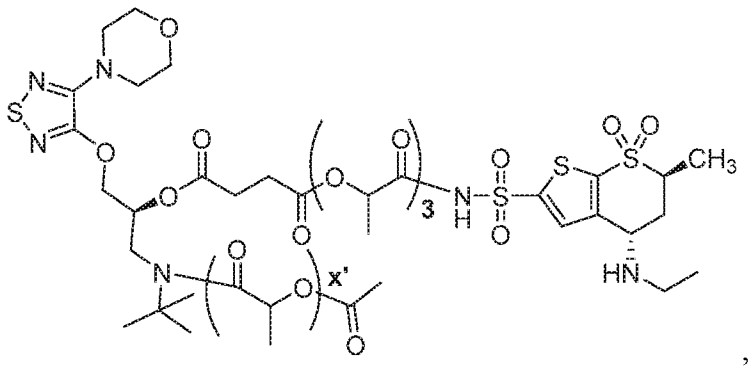
In certain embodiments, y' and y are 3 and x and x' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, y' and y are 1 and x and x' are independently selected from 1, 2, and 3.

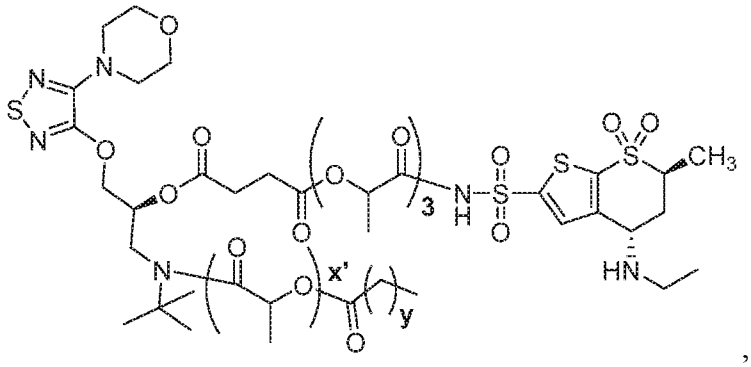
In certain embodiments, y' and y are 2 and x and x' are independently selected from 1, 2, and 3.

Non-limiting examples of compounds of Formula XV' include

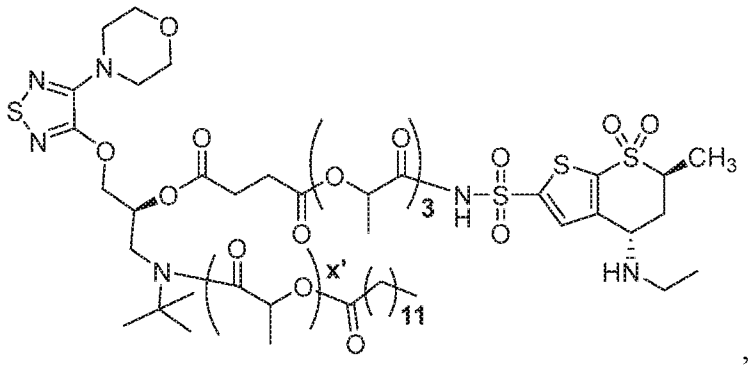

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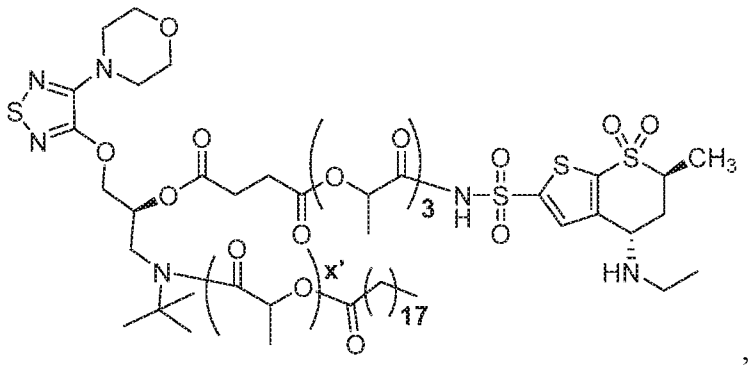
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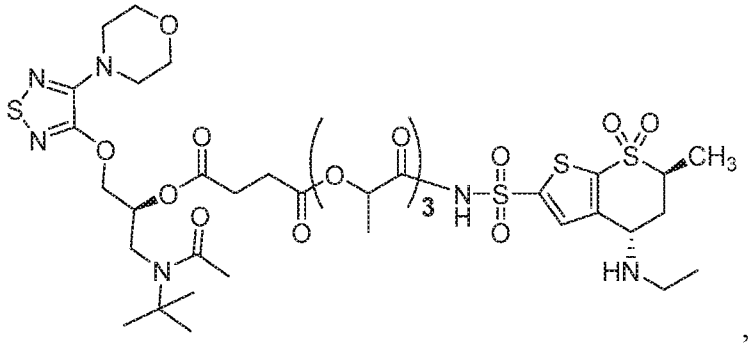


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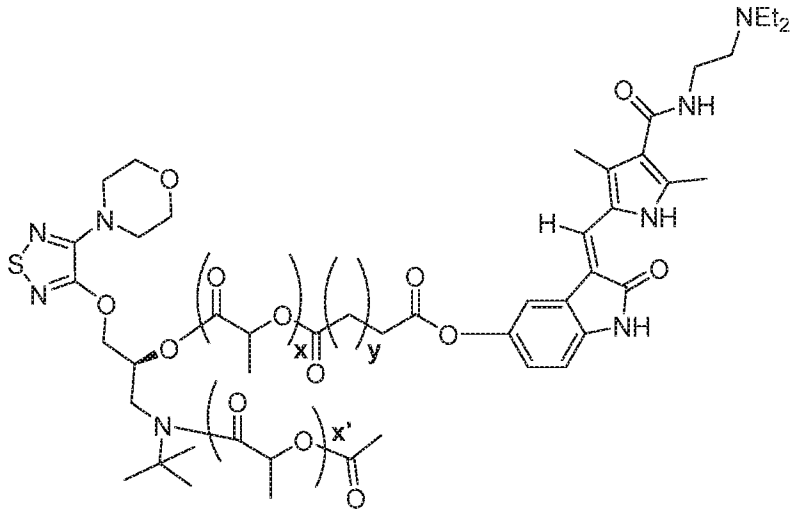


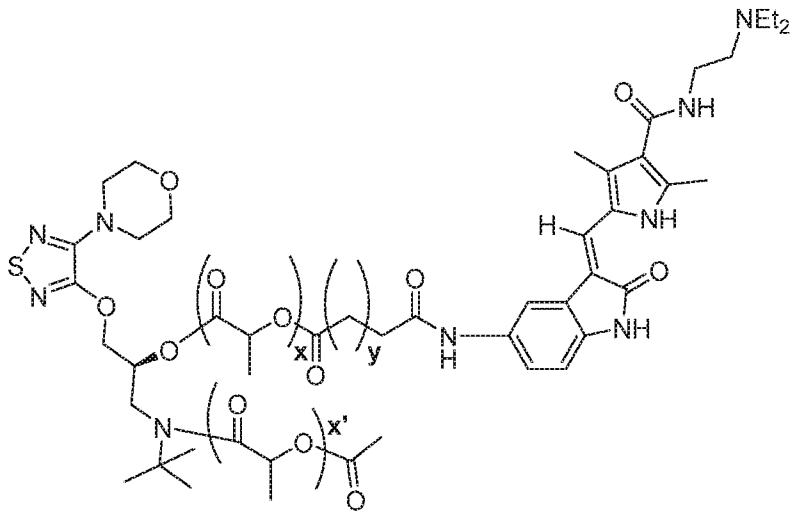
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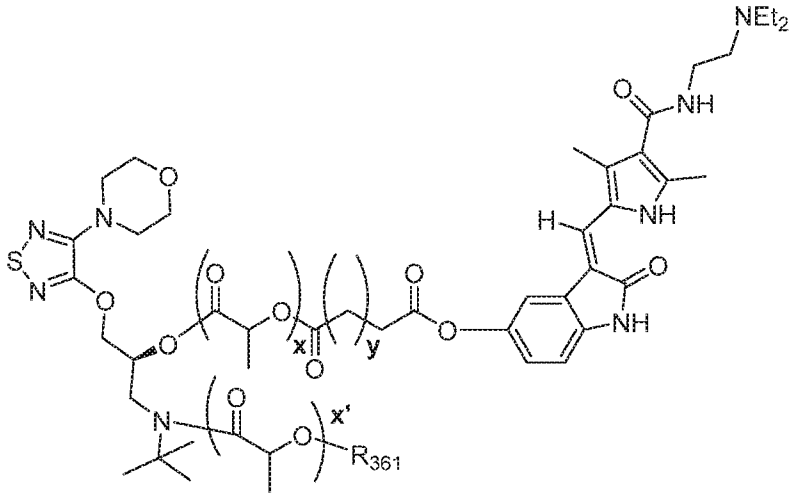
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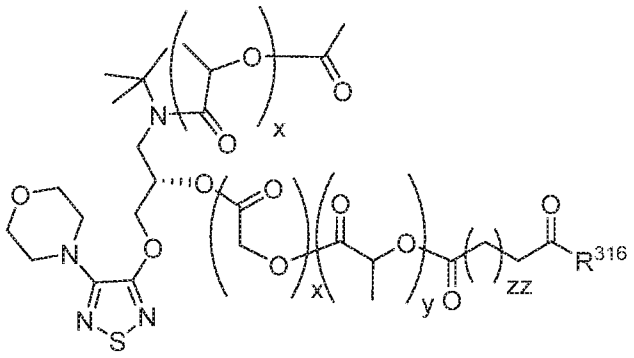
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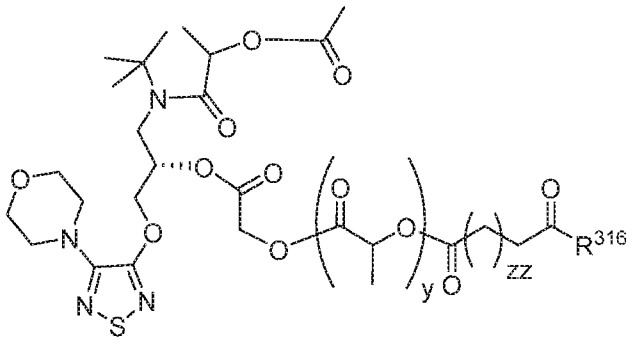


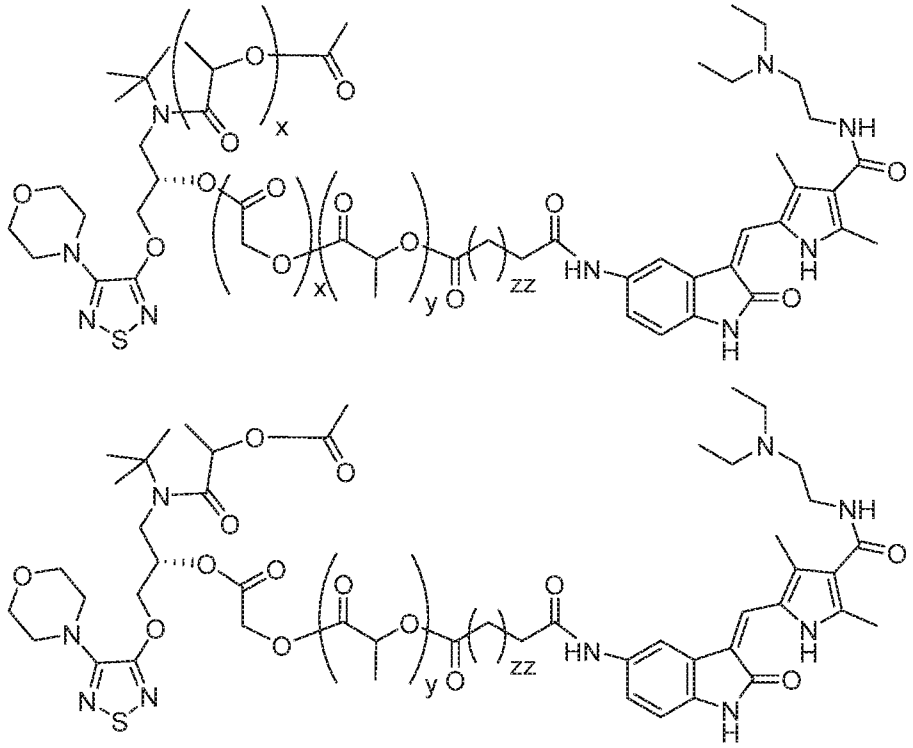




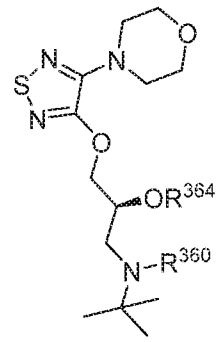
Additional non-limiting examples of compounds of Formula XV' include







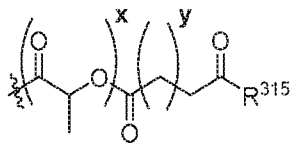
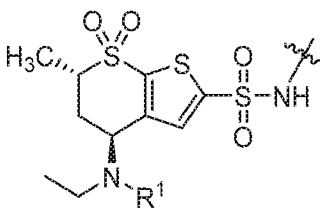
In an alternative embodiment, the disclosure also provides a prodrug of Formula XV'':

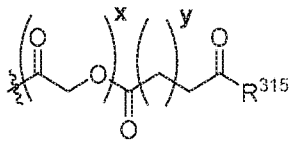
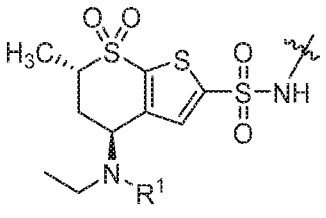


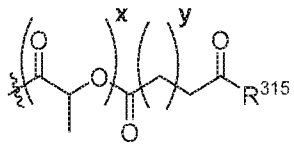
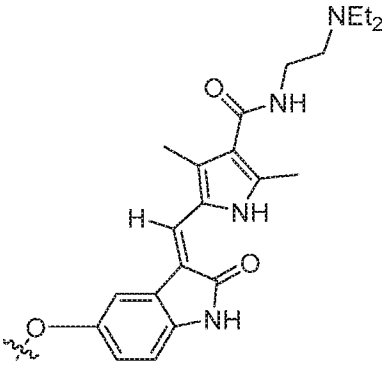
(XV'')

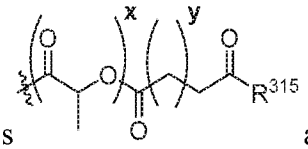
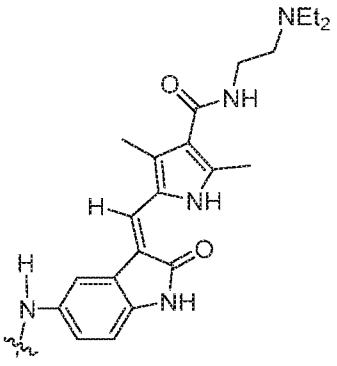
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

wherein $R^{360}$ and $R^{364}$ are defined above.

In one embodiment, $R^{360}$ is , $R^{315}$ is , and $R^1$ is hydrogen.

In one embodiment, $R^{360}$ is , $R^{315}$ is , and $R^1$ is hydrogen.

In one embodiment, $R^{360}$ is , $R^{315}$ is .

In one embodiment, $R^{360}$ is  and $R^{315}$ is .

In certain embodiments, x' and x are 1 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 2 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 3 and y and y' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, x' and x are 1 and y and y' are independently selected from 1, 2, or 3.

In certain embodiments, x' and x are 2 and y and y' are independently selected from 1, 2, or 3.

In certain embodiments, y' and y are 1 and x and x' are independently selected from 1, 2,

3, 4, 5, and 6.

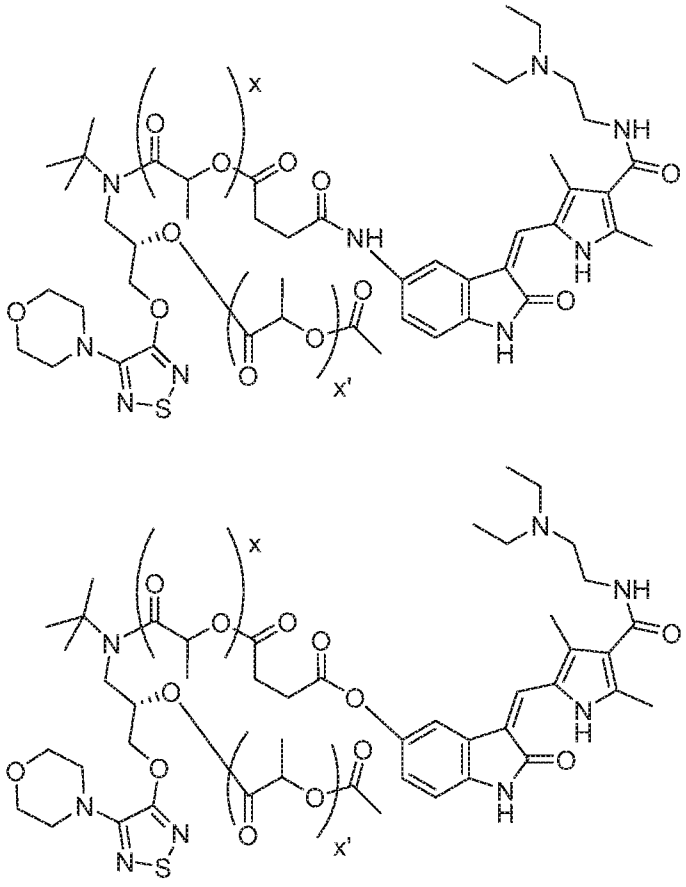
In certain embodiments, y' and y are 2 and x and x' are independently selected from 1, 2, 3, 4, 5, and 6.

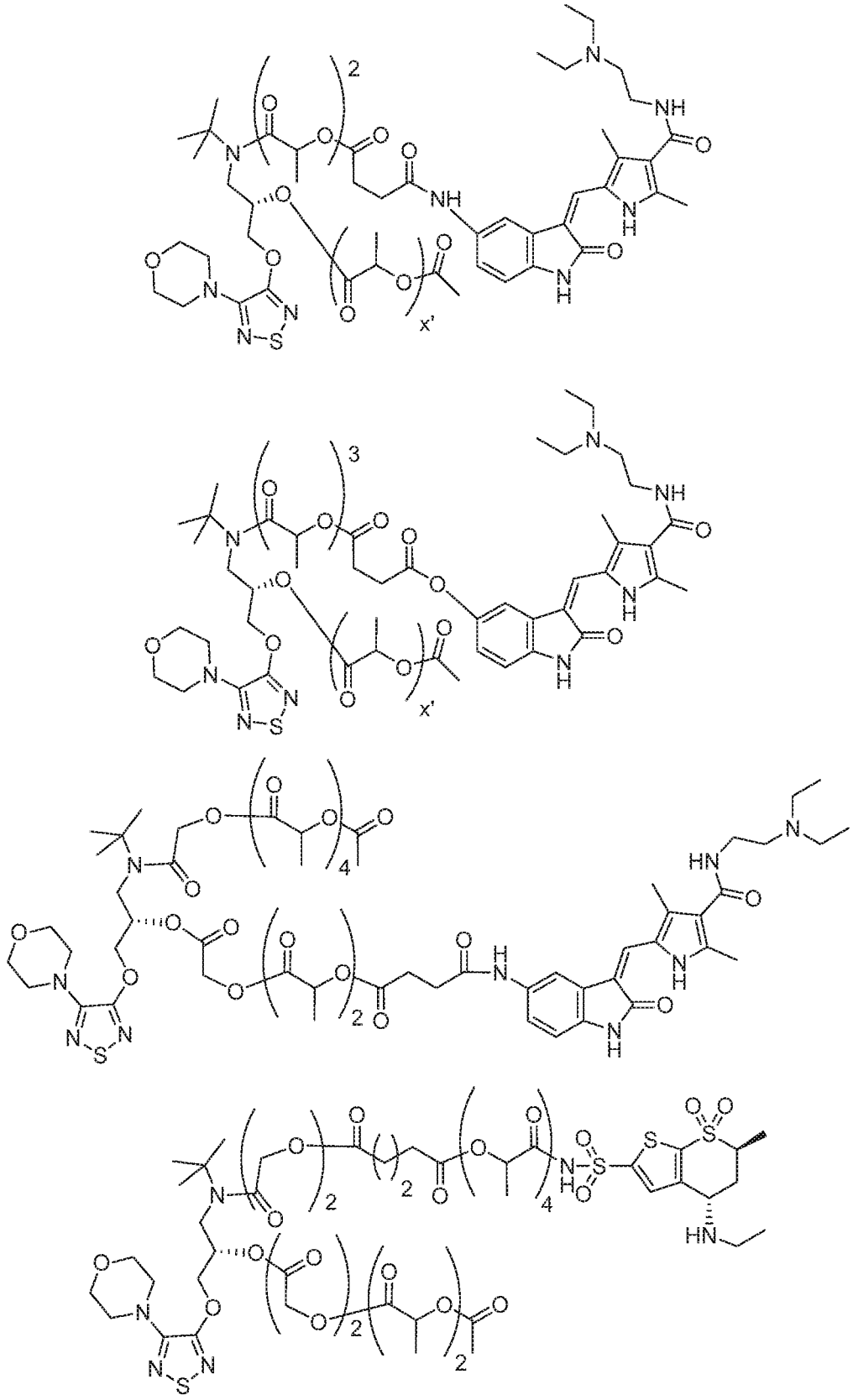
In certain embodiments, y' and y are 3 and x and x' are independently selected from 1, 2, 3, 4, 5, and 6.

In certain embodiments, y' and y are 1 and x and x' are independently selected from 1, 2, and 3.

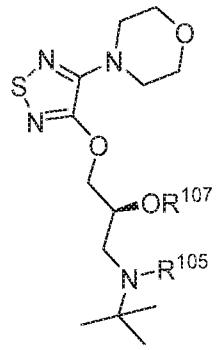
In certain embodiments, y' and y are 2 and x and x' are independently selected from 1, 2, and 3.

Non-limiting Examples of Compound of Formula XV'' include:





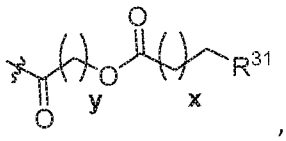
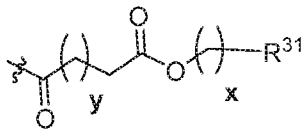
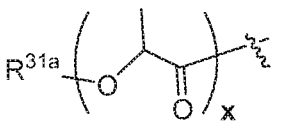
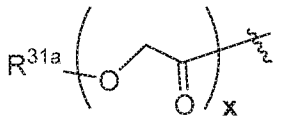
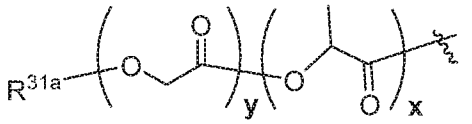
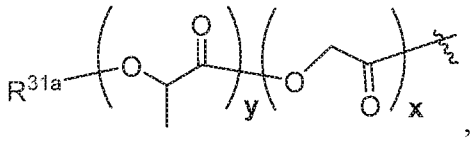
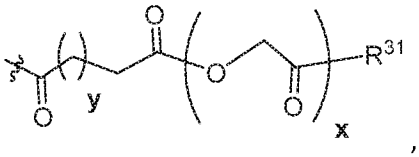
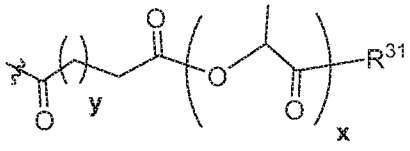
The disclosure also provides a prodrug of Formula XVI:



(XVI)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{105}$ is selected from:

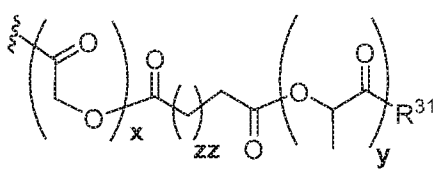
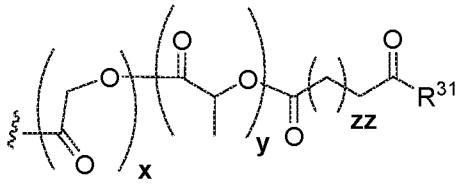
(i) , , , , , , , , and , and wherein each $R^{105}$ is optionally substituted with $R^{31}$;

(ii) -C(O)$C_{10-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain), -C(O)($C_{10-30}$alkenyl, with at least one $R^5$ substituent on the alkenyl chain) -C(O)($C_{10-30}$alkynyl, with at least one $R^5$ substituent on the alkynyl chain), -(lactic acid)$_{1-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH,

-(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{4\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, or -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl;

or $R^{105}$ is selected from:

(iii) -(C(O)CH$_2$O)$_{1\text{-}20}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}20}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH$_2$O)$_{4\text{-}20}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH(CH$_3$)O)$_{4\text{-}20}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}20}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}20}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}20}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}20}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, (C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH$_2$O)$_{2\text{-}10}$(C(O)CH(CH$_3$)O)$_{2\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, -(C(O)CH$_2$O)$_{1\text{-}10}$(C(O)CH(CH$_3$)O)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH(CH$_3$)O)$_{2\text{-}10}$(C(O)CH$_2$O)$_{2\text{-}10}$C(O)C$_{1\text{-}30}$alkyl, -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, and -(C(O)CH(CH$_3$)O)$_{1\text{-}10}$(C(O)CH$_2$O)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl;

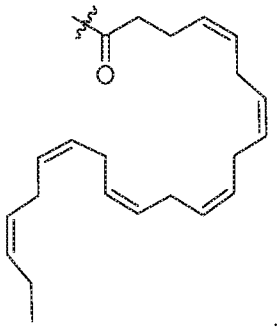
or $R^{105}$ is  or ;

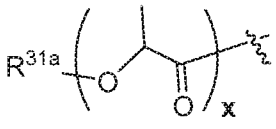
$R^{107}$ is selected from: hydrogen, -C(O)A, aryl, alkyl, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl; and

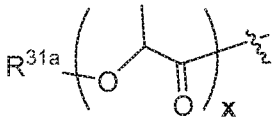
wherein all other variables are as defined herein.

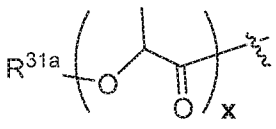
In one embodiment, $R^{105}$ is $-C(O)(CH_2)_{16}CH_3$.

In one embodiment, $R^{105}$ is

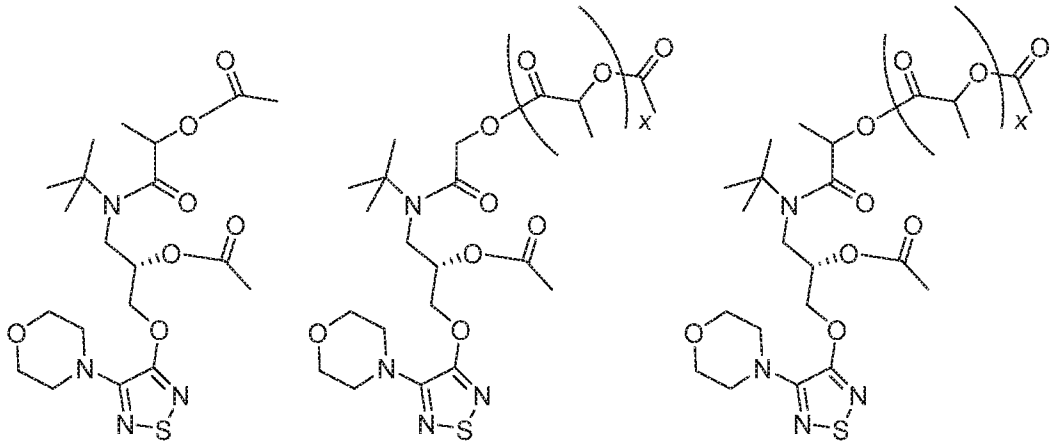


In an alternative embodiment, $R^{105}$ is , x is 1, and $R^{107}$ is –C(O)A.

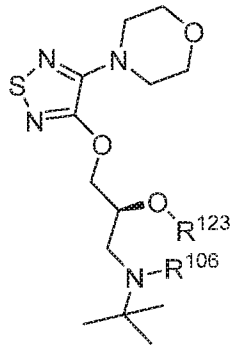
In an alternative embodiment, $R^{105}$ is  and $R^{31a}$ is -C(O)alkyl.

In an alternative embodiment, $R^{105}$ is  and $R^{31a}$ is -C(O)alkyl wherein alkyl is methyl.

Alternative non-limiting examples of Formula XVI include



The disclosure also provides a prodrug of Formula XVII:

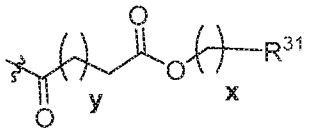
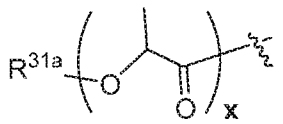
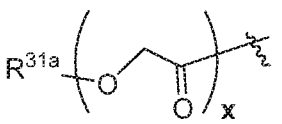


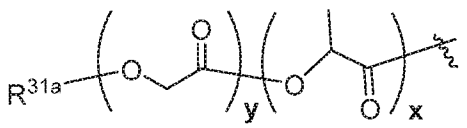
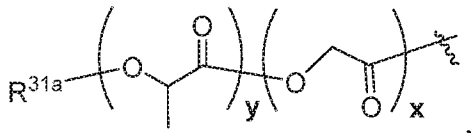
(XVII)

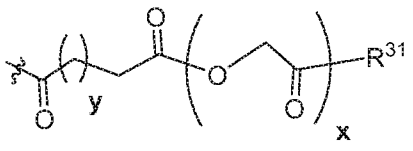
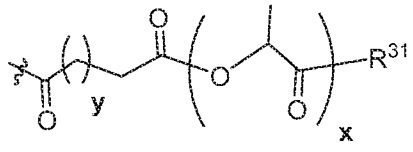
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{123}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide,

, , ,

, ,

, and , wherein

each $R^{123}$ is optionally substituted with $R^{31}$, and wherein each of $R^{123}$ with a terminal hydroxy or carboxy group can be substituted to create an ether or ester;

(ii) -C(O)$C_{17-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain), -C(O)($C_{10-30}$alkenyl, with at least one $R^5$ substituent on the alkenyl chain) -C(O)($C_{10-30}$alkynyl, with at least one $R^5$ substituent on the alkynyl chain), -(lactic acid)$_{1-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-22}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)$C_{1-22}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, or -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl;

or $R^{123}$ is selected from:

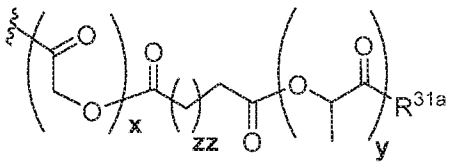
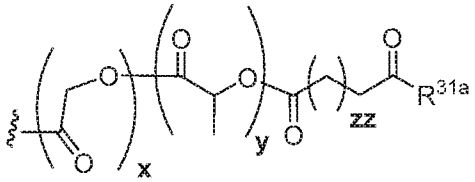
(iii) -(C(O)$CH_2$O)$_{1-20}$C(O)$C_{1-30}$alkyl, -(C(O)CH($CH_3$)O)$_{1-20}$C(O)$C_{1-30}$alkyl, -(C(O)$CH_2$O)$_{1-10}$C(O)$C_{1-30}$alkyl, -(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{1-30}$alkyl, -(C(O)$CH_2$O)$_{4-20}$C(O)$C_{1-30}$alkyl, -(C(O)CH($CH_3$)O)$_{4-20}$C(O)$C_{1-30}$alkyl, -(C(O)$CH_2$O)$_{1-20}$C(O)$C_{1-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-20}$C(O)$C_{1-10}$alkyl, -(C(O)$CH_2$O)$_{1-20}$C(O)$C_{4-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-20}$C(O)$C_{4-10}$alkyl, -(C(O)CH($CH_3$)O)$_{4-10}$C(O)$C_{1-10}$alkyl, -(C(O)$CH_2$O)$_{4-10}$C(O)$C_{1-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{1-10}$alkyl, -(C(O)$CH_2$O)$_{1-10}$C(O)$C_{1-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{4-10}$alkyl, (C(O)$CH_2$O)$_{1-10}$C(O)$C_{4-10}$alkyl, -(C(O)$CH_2$O)$_{1-10}$C(O)$C_{4-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{4-10}$alkyl, -(C(O)$CH_2$O)$_{1-10}$C(O)$C_{4-10}$alkyl, -(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{4-10}$alkyl, -(C(O)$CH_2$O)$_{1-10}$(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{1-30}$alkyl, -(C(O)$CH_2$O)$_{2-10}$(C(O)CH($CH_3$)O)$_{2-10}$C(O)$C_{1-30}$alkyl, -(C(O)$CH_2$O)$_{1-10}$(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{1-12}$alkyl, -(C(O)$CH_2$O)$_{1-10}$(C(O)CH($CH_3$)O)$_{1-10}$C(O)$C_{4-22}$alkyl,

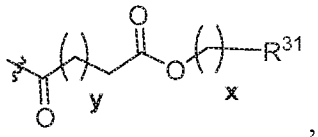
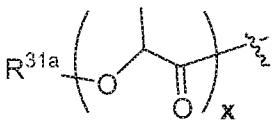
-(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-30}$alkyl,

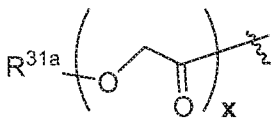
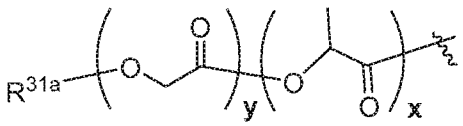
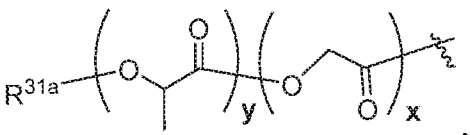
-(C(O)CH(CH$_3$)O)$_{2-10}$(C(O)CH$_2$O)$_{2-10}$C(O)C$_{1-30}$alkyl,

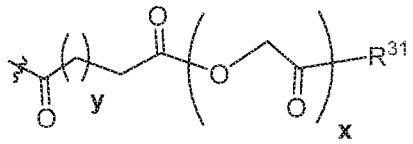
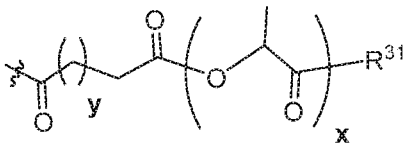
-(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{1-12}$alkyl, and

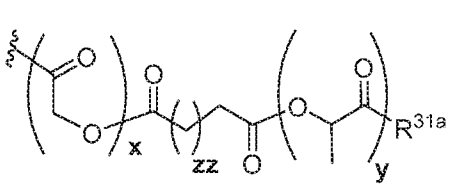
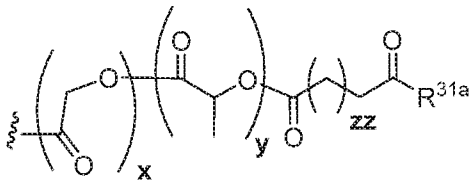
-(C(O)CH(CH$_3$)O)$_{1-10}$(C(O)CH$_2$O)$_{1-10}$C(O)C$_{4-22}$alkyl;

or R$^{123}$ is  or ;

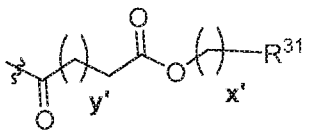
R$^{106}$ is selected from: , ,

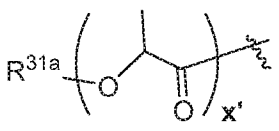
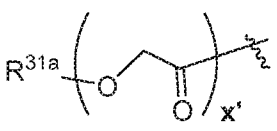
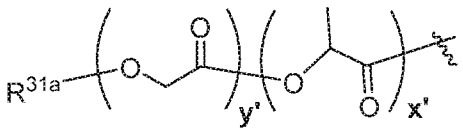
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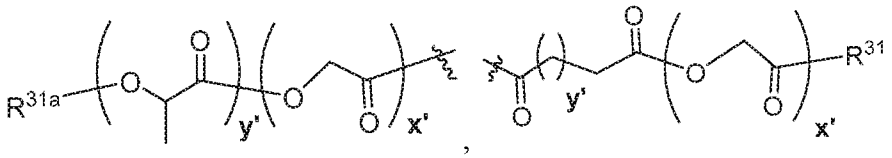
, , acyl, aryl, alkyl, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, and in one embodiment, R$^{106}$ is –C(O)(CH$_2$)$_{16}$CH$_3$; and

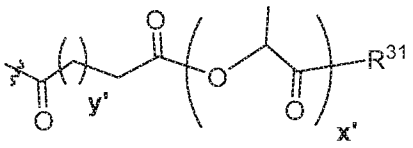
or R$^{106}$ is  or ;

wherein all other variables are as defined herein.

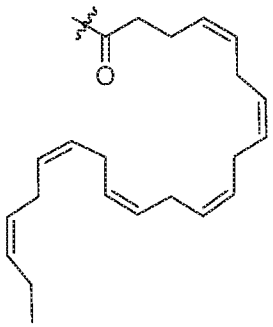
In an alternative embodiment, R$^{106}$ is selected form ,

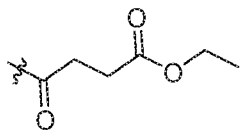
, , ,


, and

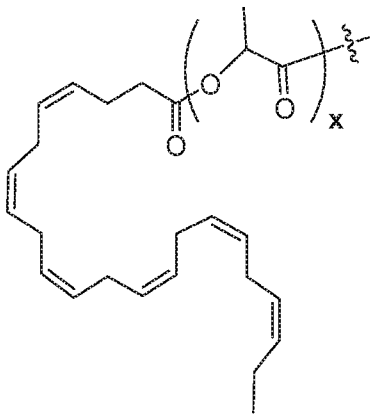

.

In one embodiment, $R^{123}$ is

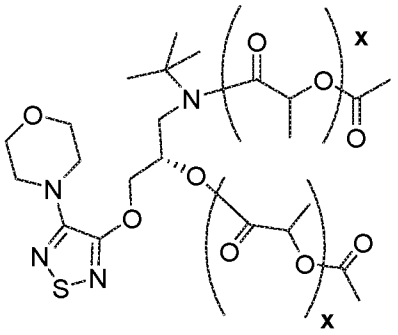

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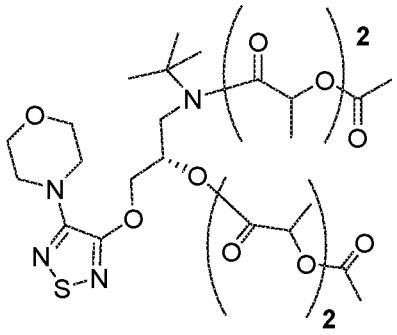
In one embodiment, $R^{123}$ is 
.

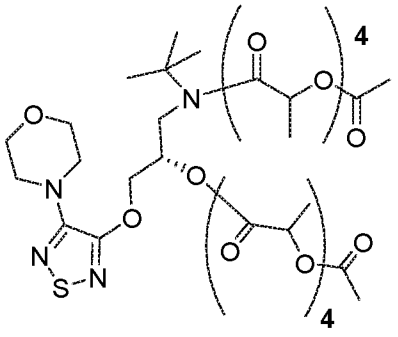
In an alternative embodiment, $R^{123}$ is

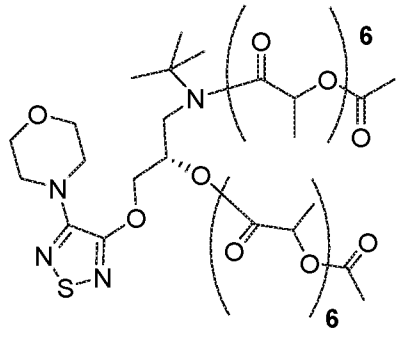

.

Non-limiting Examples of Formula XVII include



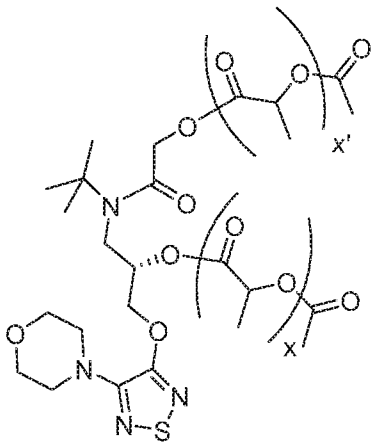
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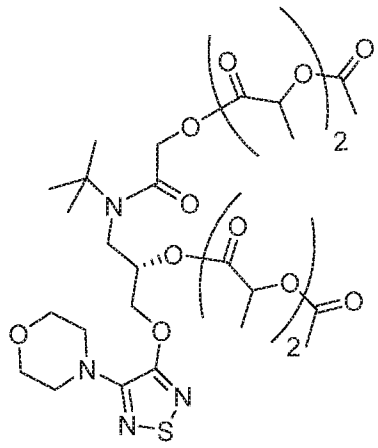
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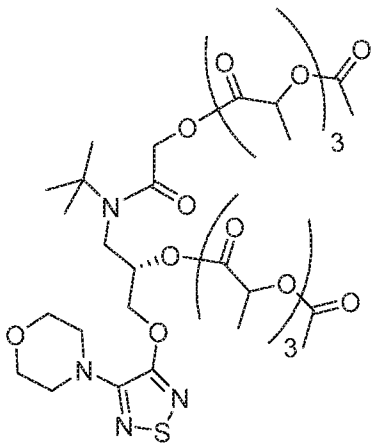
, and


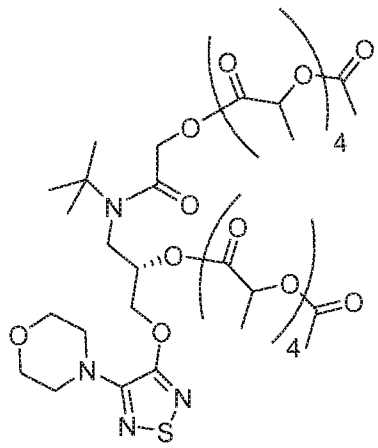
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Additional non-limiting Examples of Formula XVII include

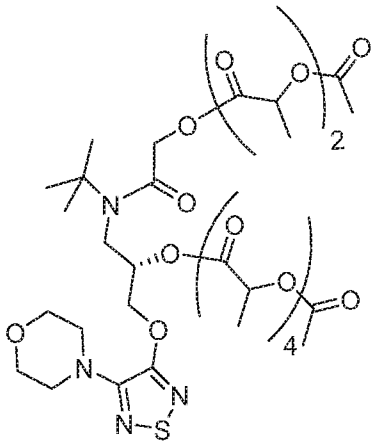


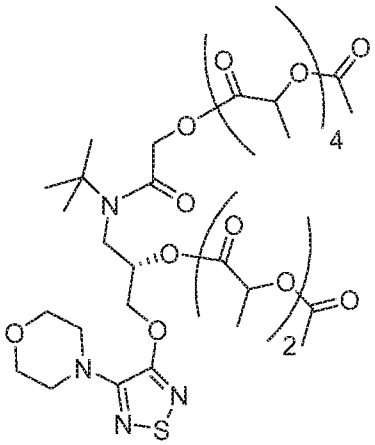


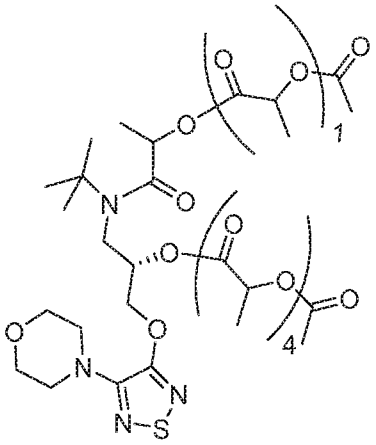


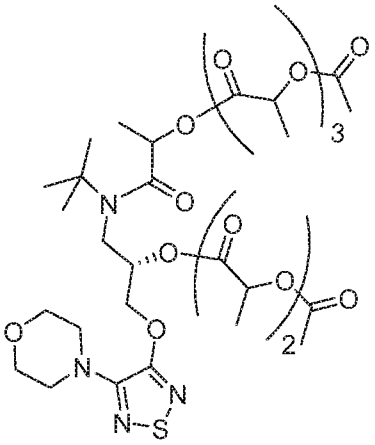


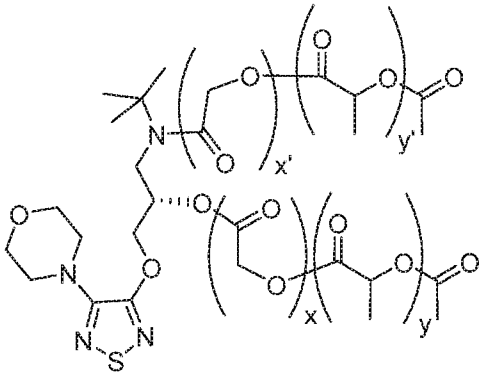

5

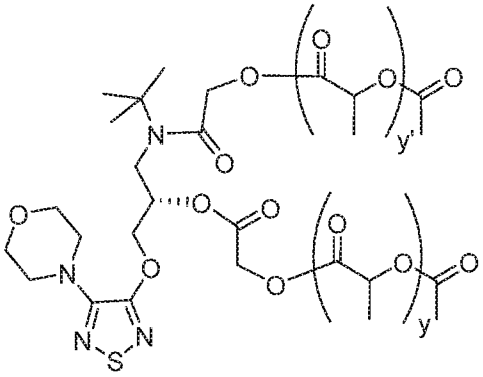


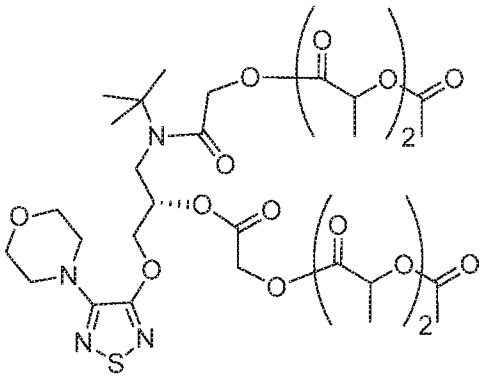


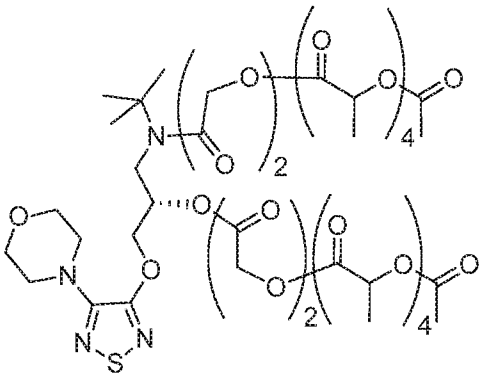




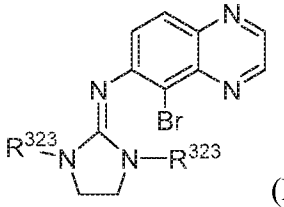




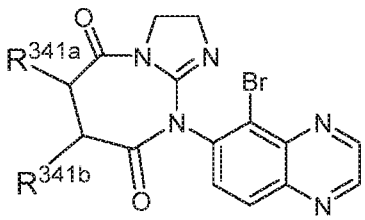




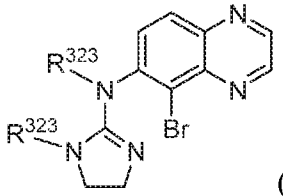
In an alternative embodiment, the disclosure also provides a prodrug of Formula XVII' XVII'', or XVII'''



(XVII')

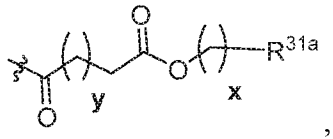
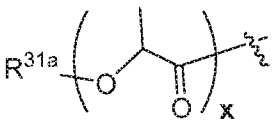
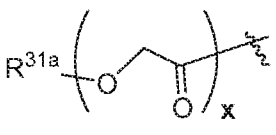
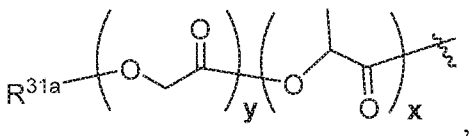
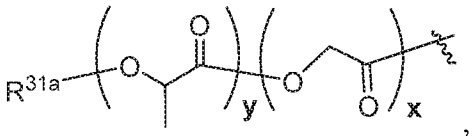
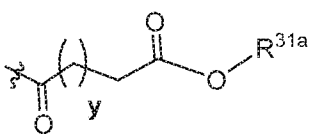
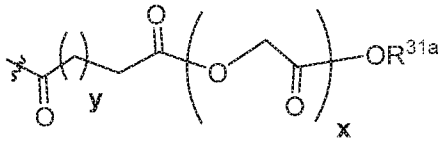
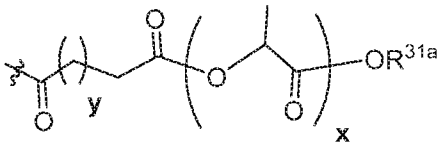


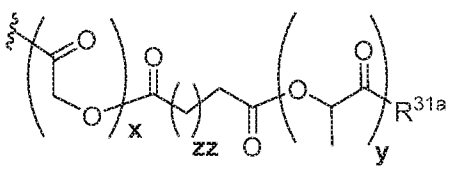
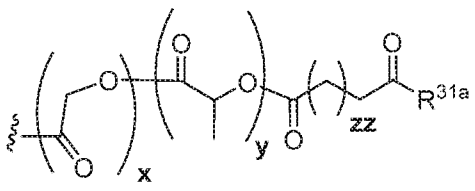
(XVII'')



(XVII''')

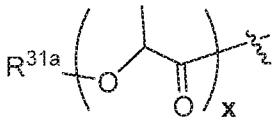
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

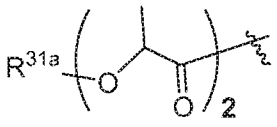
wherein $R^{323}$ is independently selected from polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , , , , , , , and ;

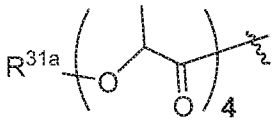
or $R^{323}$ is  or ;

$R^{341a}$ and $R^{341b}$ are independently selected from hydrogen and alkyl; and

wherein all other variables are as defined herein.

In one embodiment of Formula XVII', $R^{323}$ is  and $R^{31a}$ is –C(O)alkyl.

In one embodiment of Formula XVII', $R^{323}$ is  and $R^{31a}$ is –C(O)alkyl.

In one embodiment of Formula XVII', $R^{323}$ is  and $R^{31a}$ is –C(O)alkyl.

In one embodiment of Formula XVII'', $R^{341a}$ and $R^{341b}$ are hydrogen.

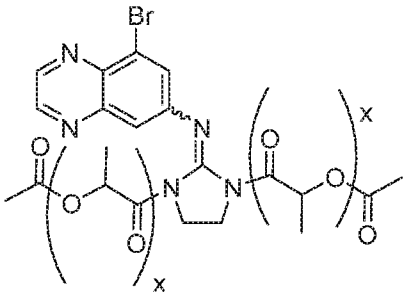
In one embodiment of Formula XVII'', $R^{341a}$ is hydrogen and $R^{341b}$ is methyl.

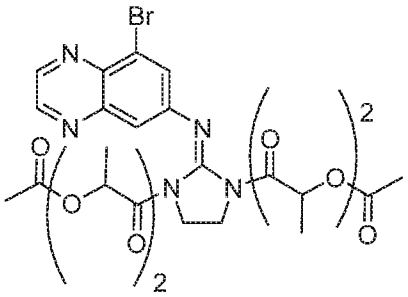
In one embodiment of Formula XVII'', $R^{341a}$ is methyl and $R^{341b}$ is hydrogen.

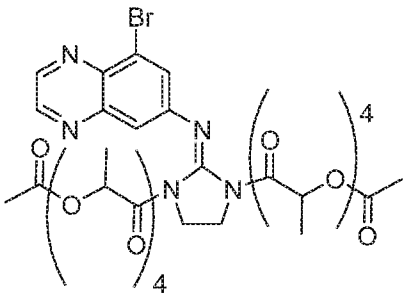
In one embodiment of Formula XVII'', Formula XVIII' is the malic salt.

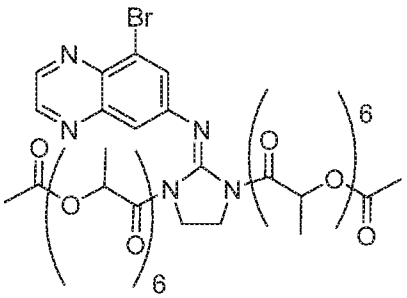
In one embodiment of Formula XVII'', Formula XVIII' is the maleate salt.

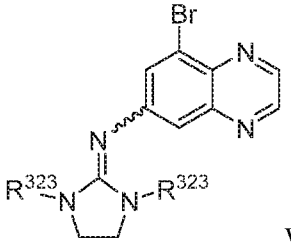
Non-limiting Examples of Formula XVII' include

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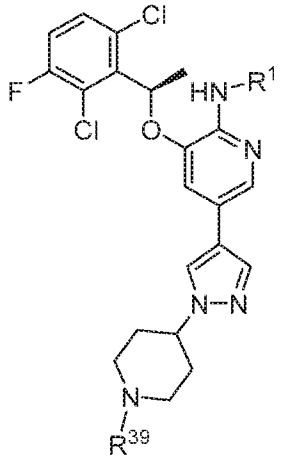
,

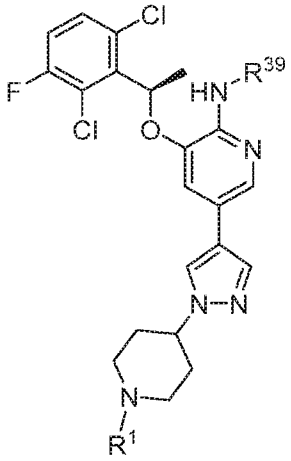
, and

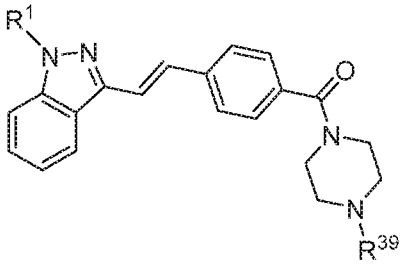
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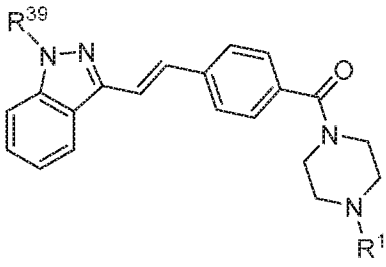
Compounds of Formula XVII' are drawn as  where the bond between the aromatic ring and the imidazole ring is drawn as a wavy line. In one embodiment, compounds of Formula XVII' are the Z isomer. In one embodiment, compounds of Formula XVII' are the E isomer.

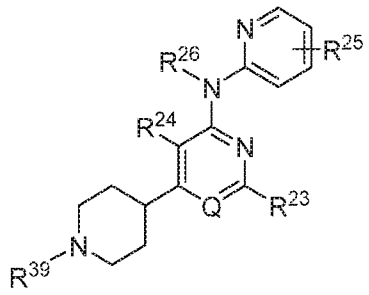
The disclosure also provides a prodrug of Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, and Formula XXI:

 (XVIII),

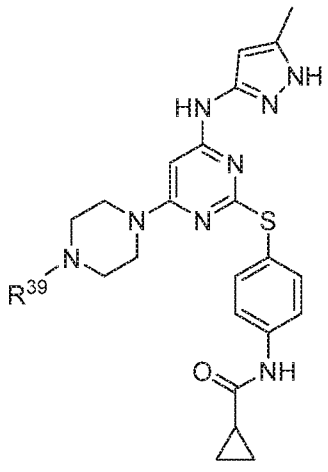
 (XVIII'),

 (XIX),

 (XIX'),



(XX),

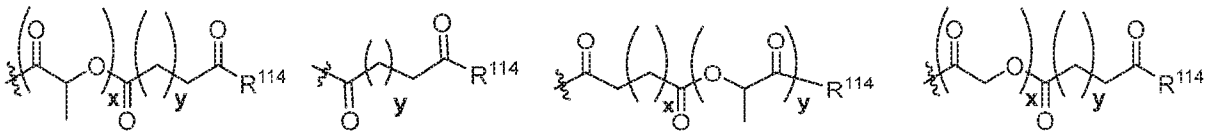


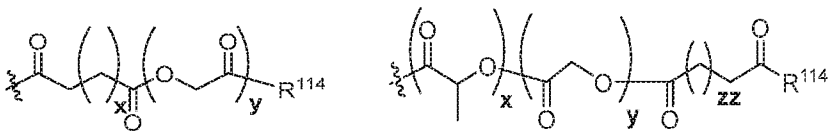
(XXI)

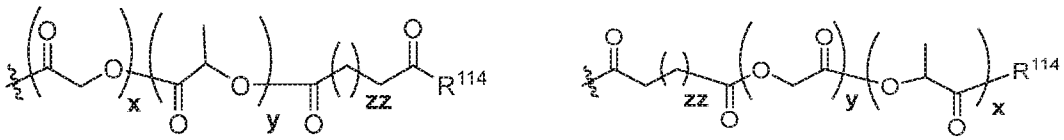
or a pharmaceutically acceptable salt thereof.

$R^{39}$ is selected from: $R^{40}$, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, and poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, polyamide, or other biodegradable polymer, wherein each $R^{39}$ other than $R^{40}$ is substituted with at least one $L^4$-$R^{114}$;

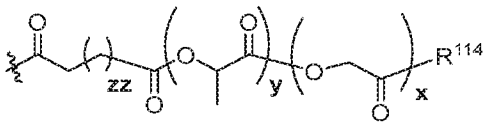
$R^{40}$ is selected from:





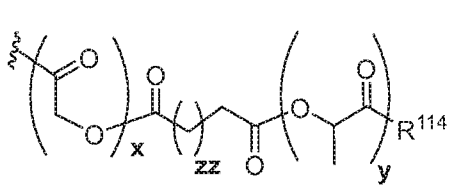


and

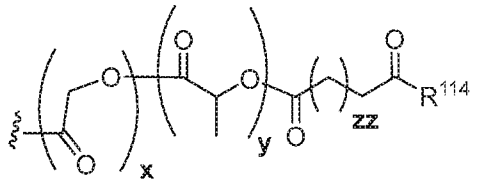


;

or $R^{40}$ is



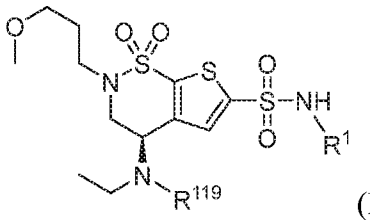
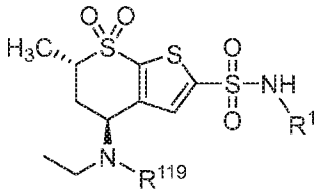
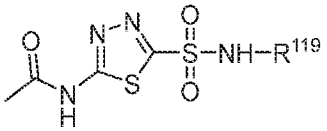
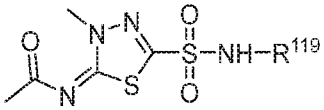
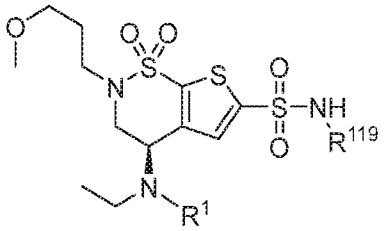
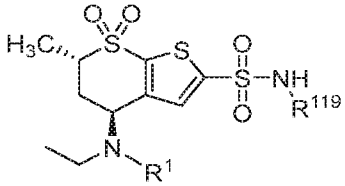
or



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wherein all other variables are as defined herein.

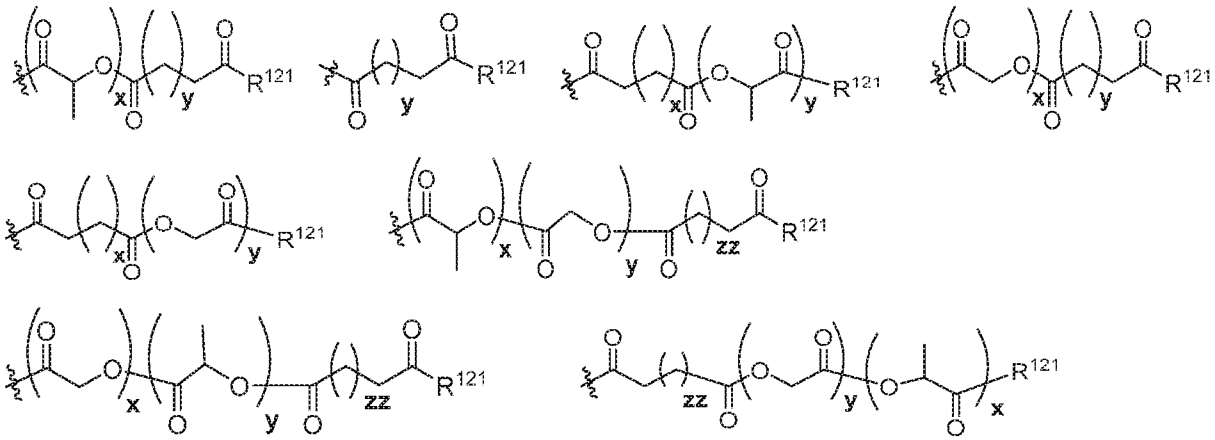
The disclosure also provides prodrugs of Formula XXII, Formula XXIII, Formula XXIV, Formula XXV, Formula XXVI, and Formula XXVII:

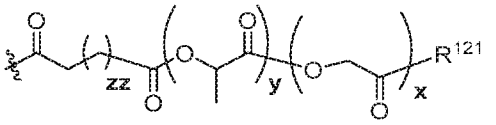
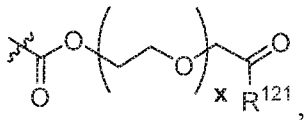

(XXII),

(XXIII),

(XXIV),

(XXV),

(XXVI), and

(XXVII),

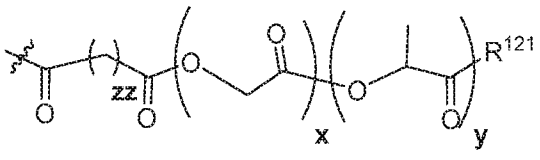
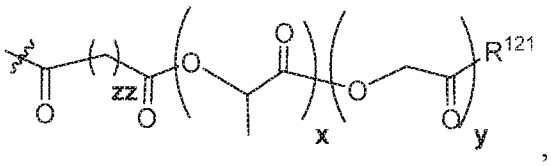
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

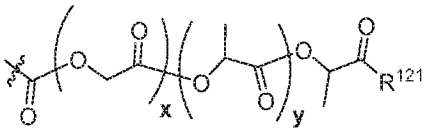
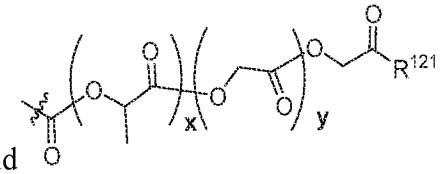
$R^{119}$ is selected from: acyl, $R^{120}$, polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, polyamide, or other biodegradable polymer, wherein each $R^{119}$ other than $R^{120}$ is substituted with at least one $L^4$-$R^{121}$;

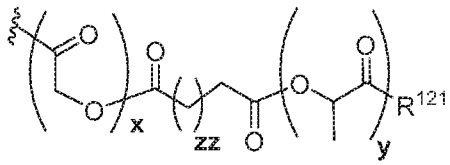
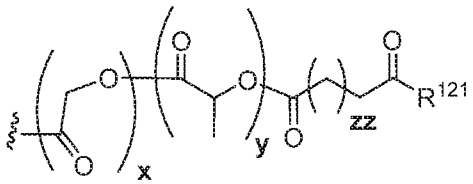
$R^{120}$ is selected from:



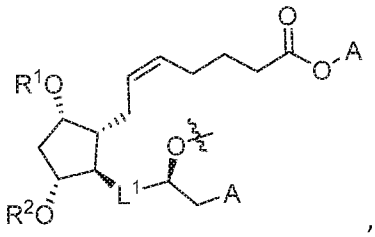
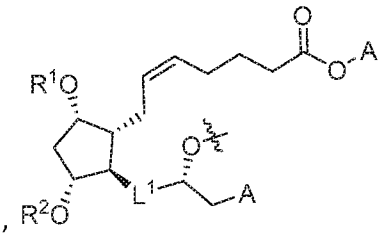
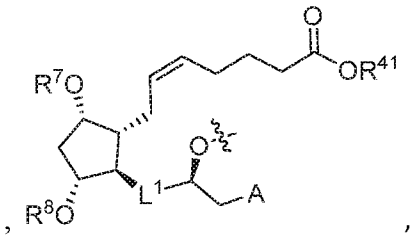


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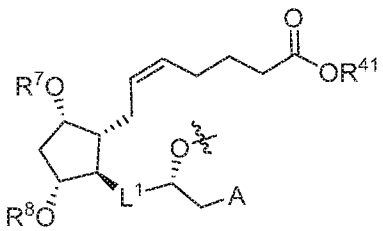
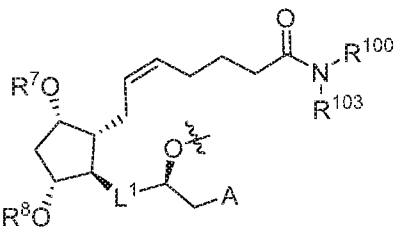
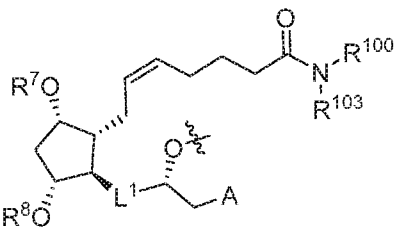

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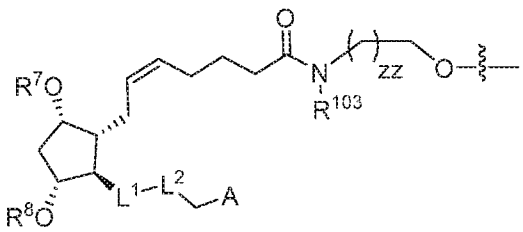
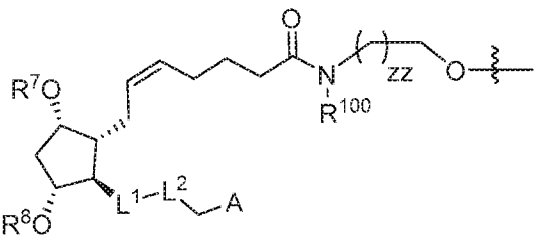

, and

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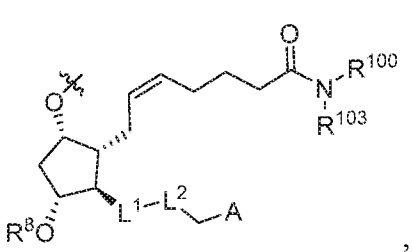
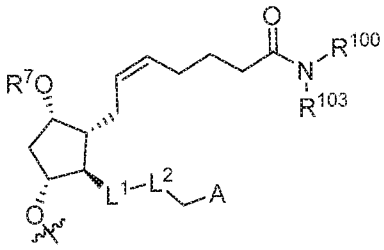
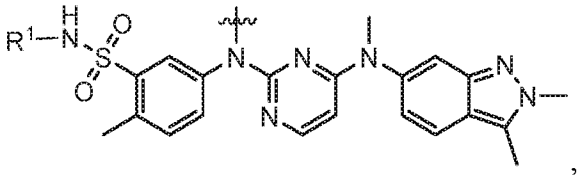
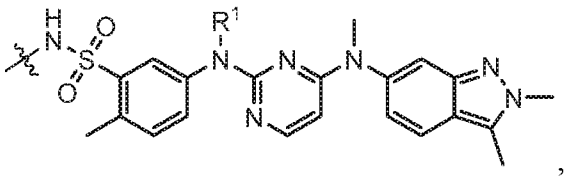
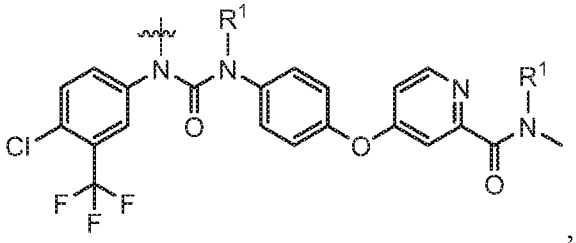
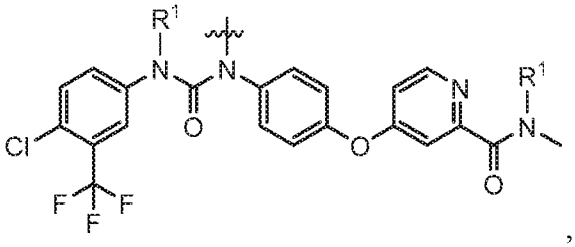
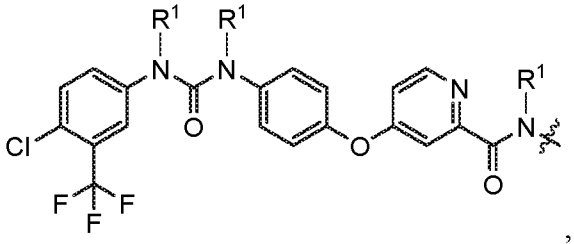
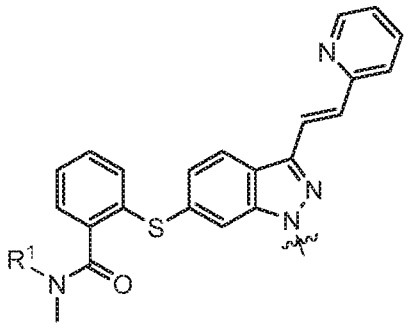
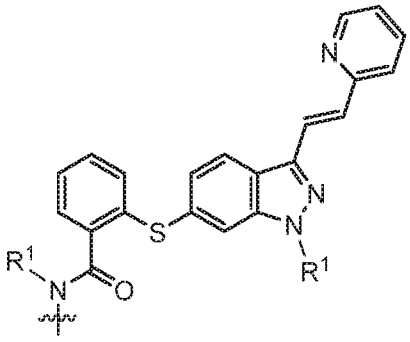
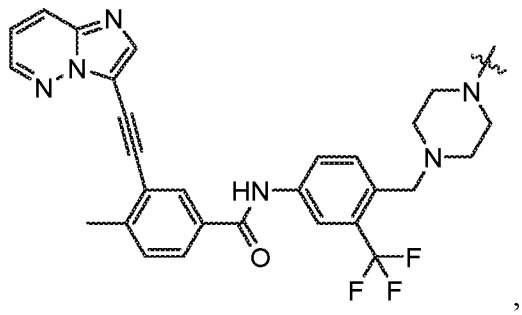
or $R^{120}$ is

or

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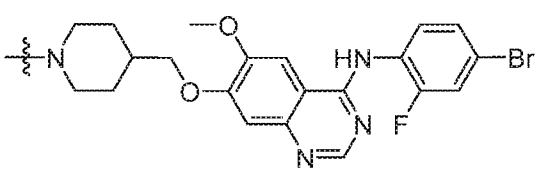
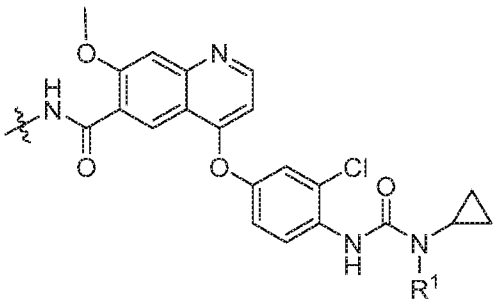
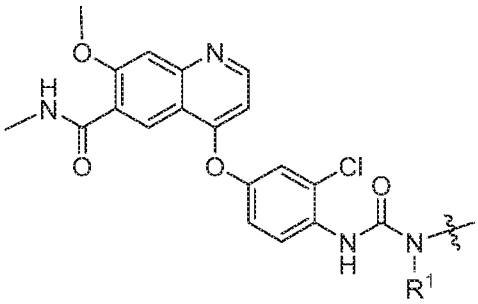
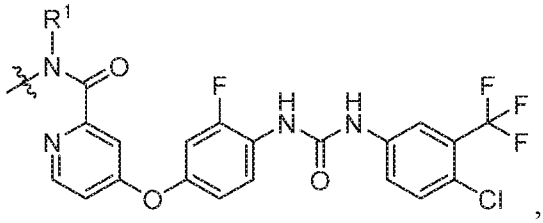
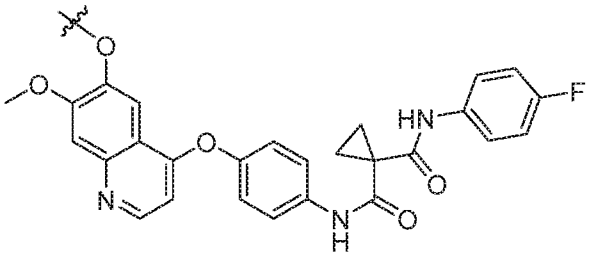
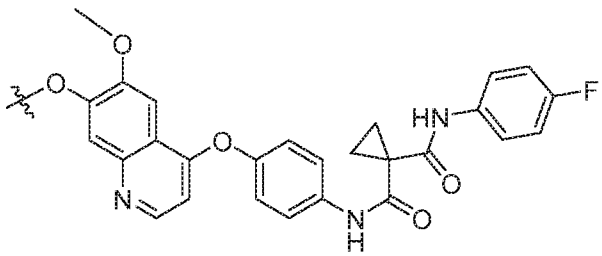
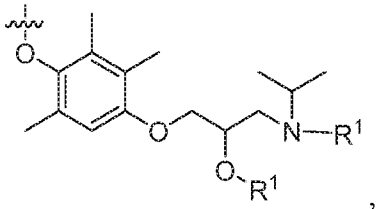
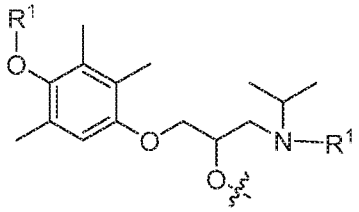
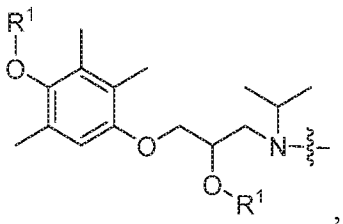
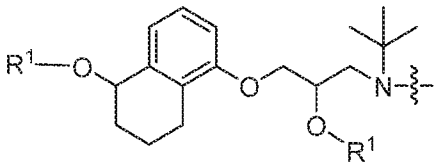
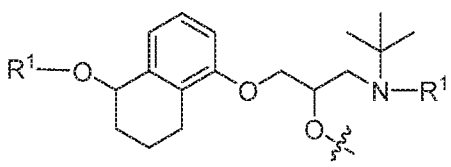
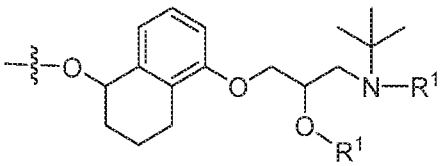
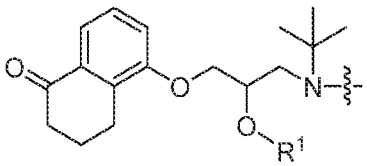
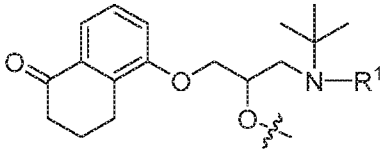
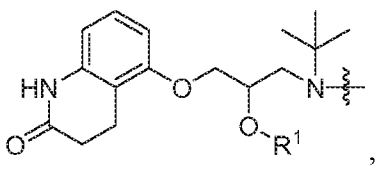
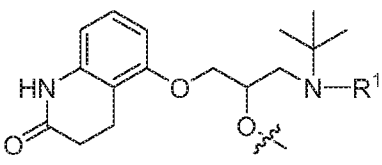
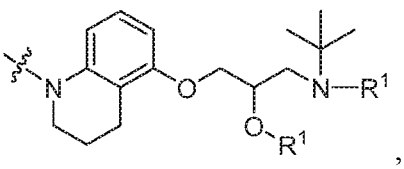
5 $R^{121}$ is selected from:


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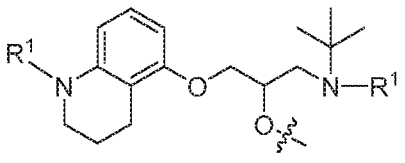
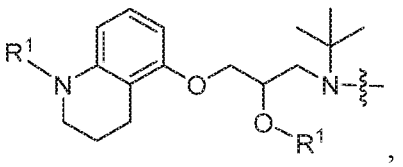
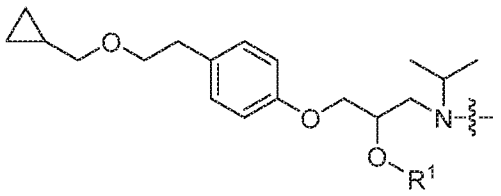
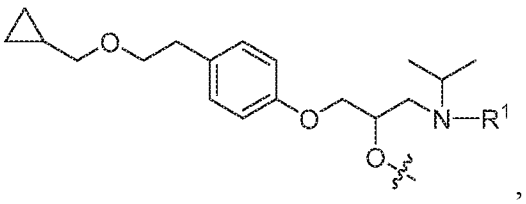
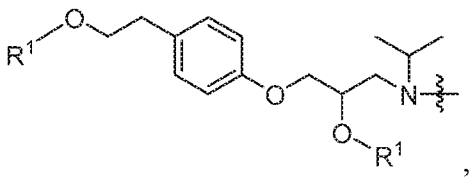
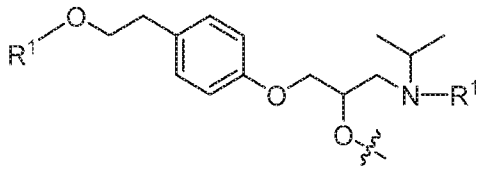
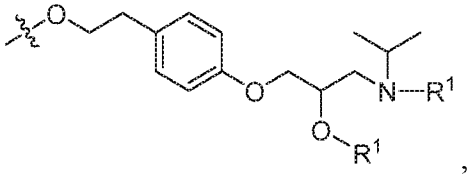
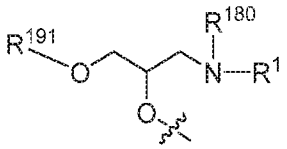
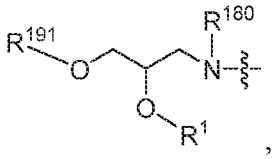
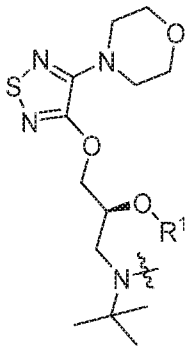
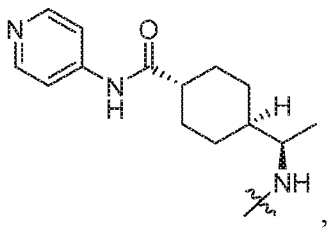
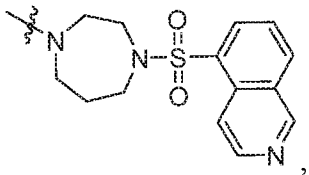
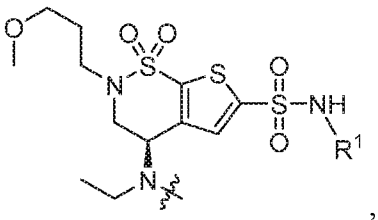

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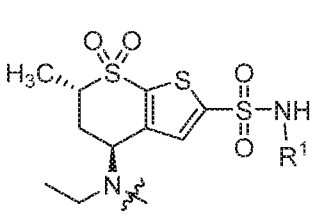
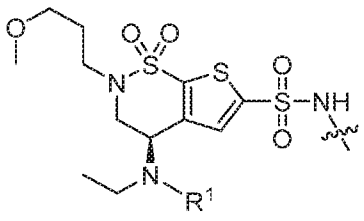
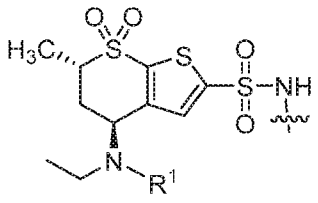
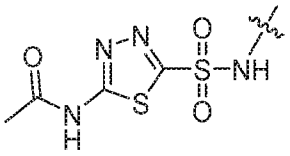
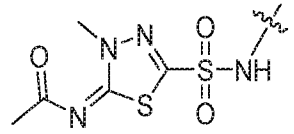
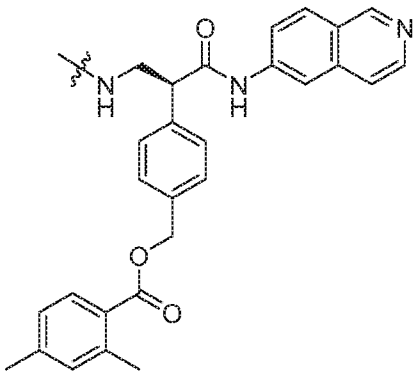

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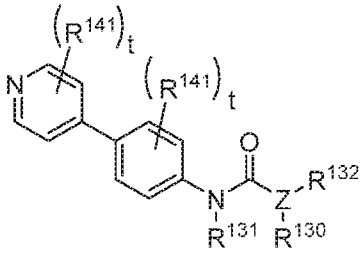
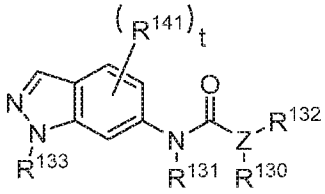
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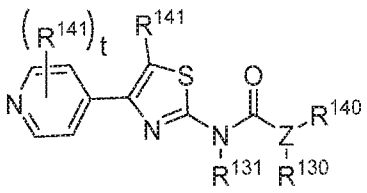
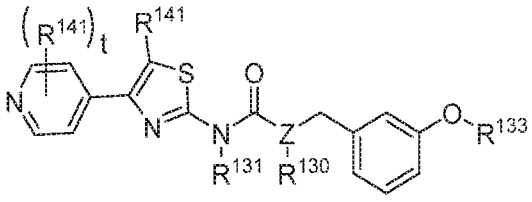

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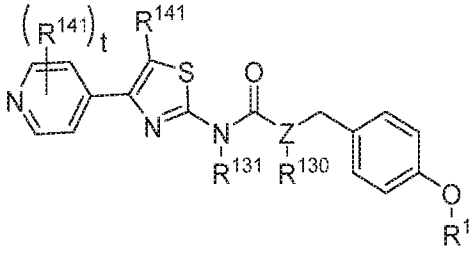

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wherein all other variables are as defined herein.

The disclosure also provides prodrugs of Formula XXVIII, XXIX, XXX, XXX' and XXX''


(XXVIII)

(XXIX)


(XXX)

(XXX')


(XXX'').

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

Z is $CR^{130}$ or N;

t is independently selected from 0, 1, 2, 3, and 4;

$R^{130}$, $R^{131}$, and $R^{133}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{136}$;

$R^{132}$ is selected from $R^{136}$, $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and alkylaryl, any of which can be optionally substituted with one or more of hydroxyl, -$CH_2$OH, -C(O)$NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxylalkoxy, haloalkoxy, heteroarylcarbonyl, heteroaryl, -$OCH_3$, -$OCF_3$, -$OCHF_2$, -$OCH_2F$, -$OSO_2CH_3$, tosyl, or halogen;

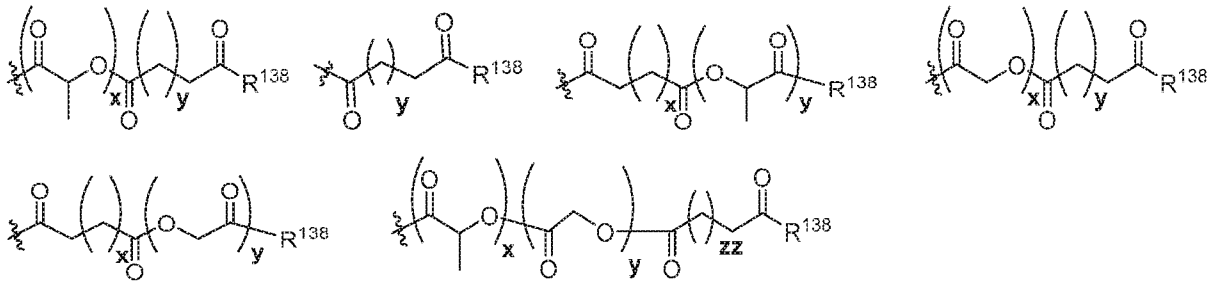
$R^{140}$ is selected from $R^{136}$, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, and aryl, any of which except hydrogen can be optionally substituted with one or more of hydroxyl, -$CH_2$OH, -C(O)$NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxylalkoxy, haloalkoxy, heteroarylcarbonyl, heteroaryl, -$OCH_3$, -$OCF_3$, -$OCHF_2$, -$OCH_2F$, -$OSO_2CH_3$, tosyl, or halogen;

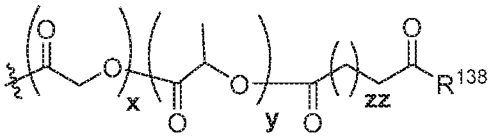
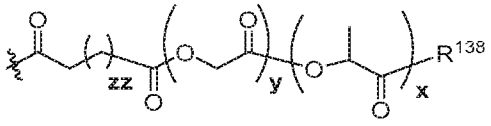
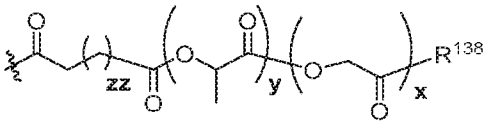
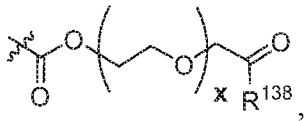
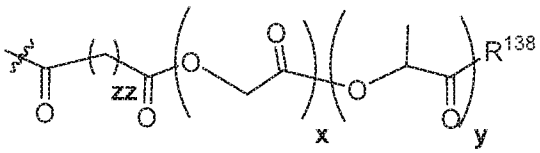
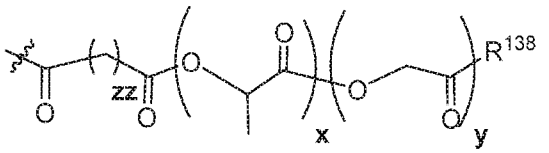
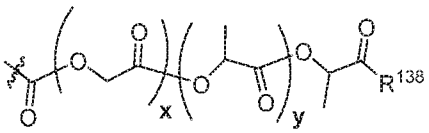
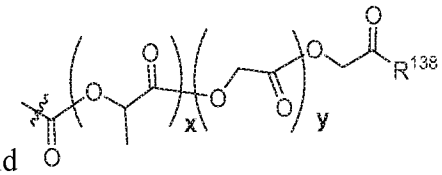
$R^{136}$ is selected from: $R^{137}$, acyl, alkyl, alkyloxy, polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), a polyglycolic acid, a polyester, polyamide, or other biodegradable polymer, wherein each $R^{136}$ other than $R^{137}$ is substituted with at least one $L^4$-$R^{138}$;

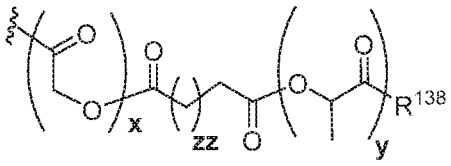
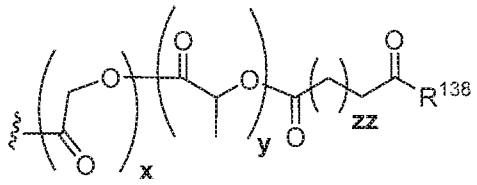
or $R^{136}$ is $L^4$-$R^{138}$ or $R^{138}$;

wherein at least one of $R^{130}$, $R^{131}$, and $R^{133}$ in Formula XXVIII, Formula XXIX, Formula XXX, Formula XXX' and Formula XXX'' is $R^{136}$;

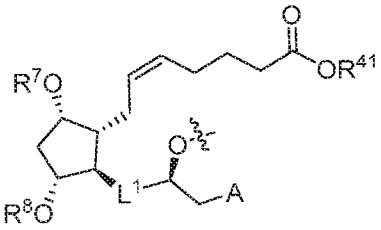
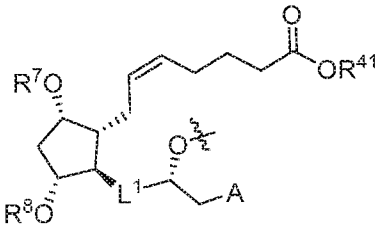
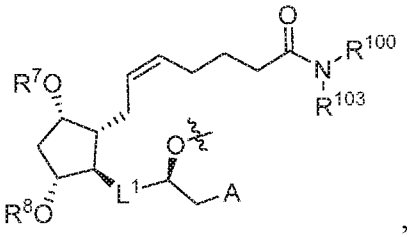
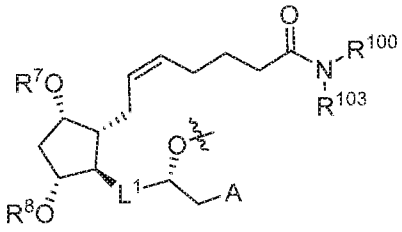
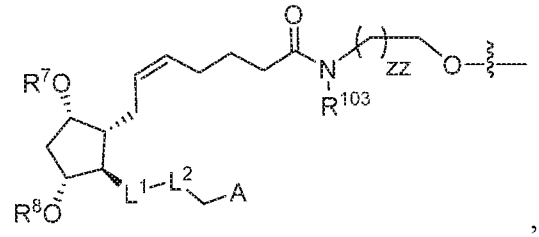
$R^{137}$ is selected from:

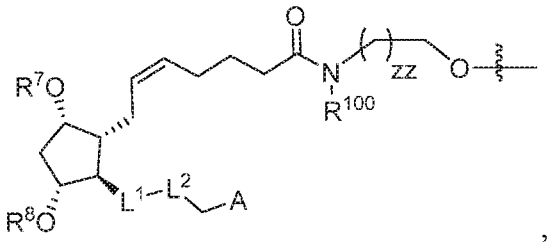
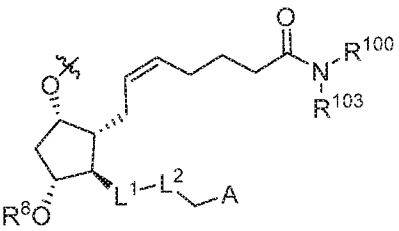
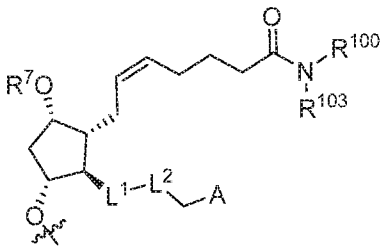
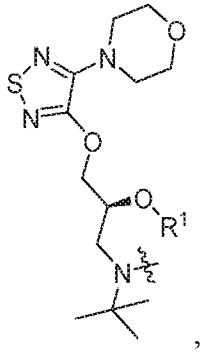
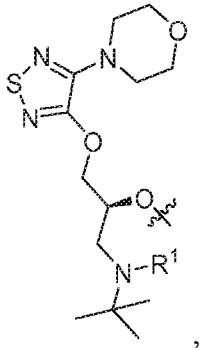
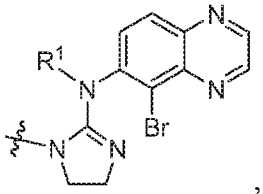
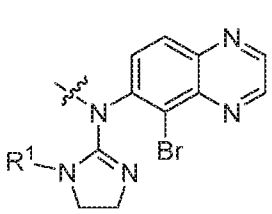
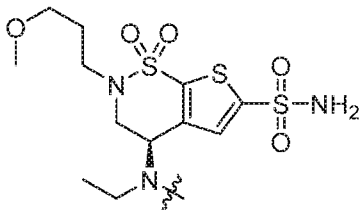
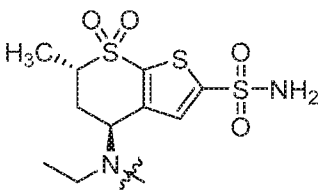
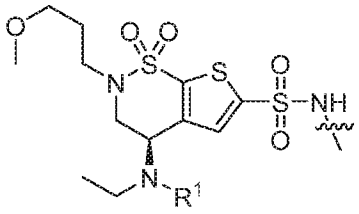
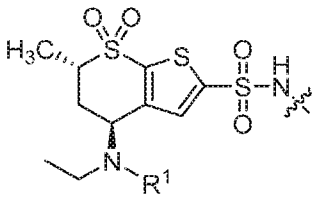
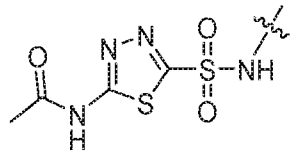
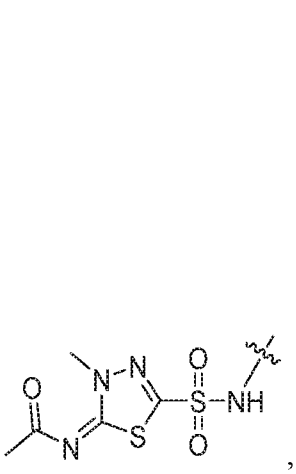
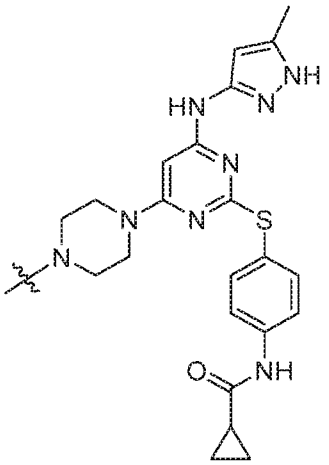
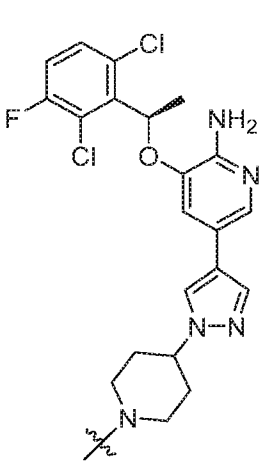


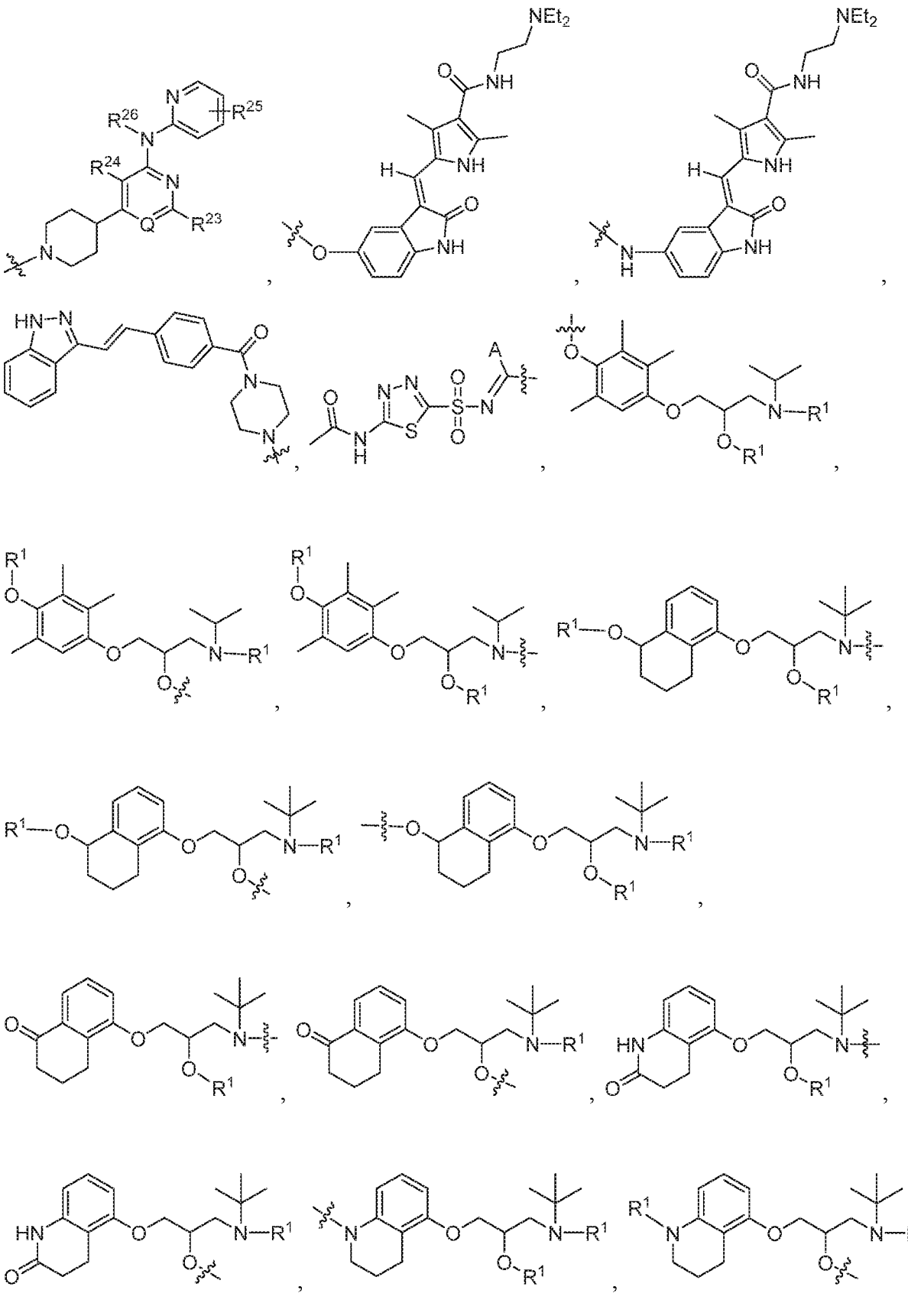




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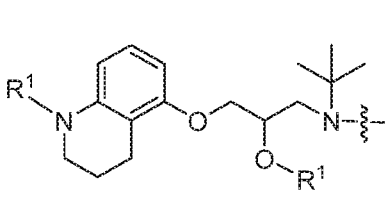
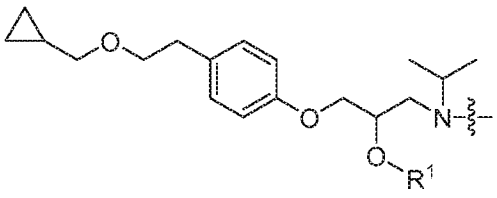
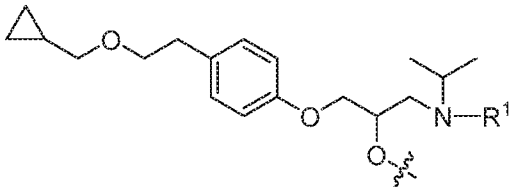
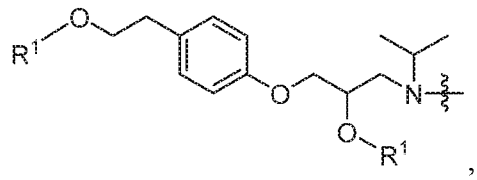
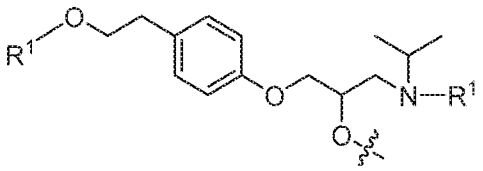
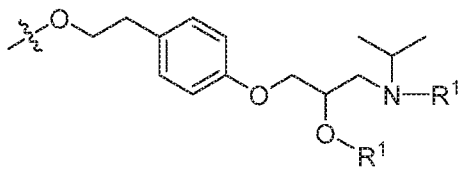
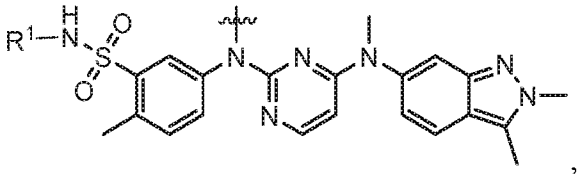
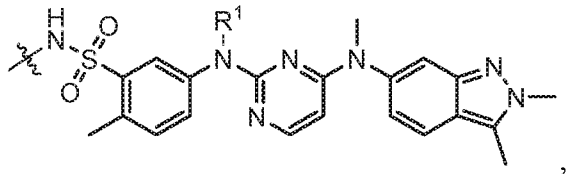
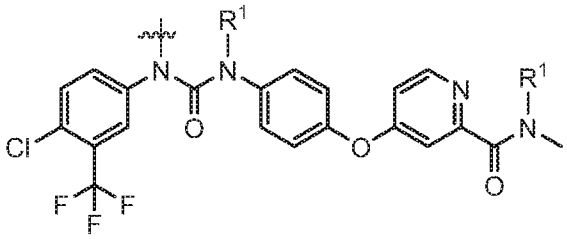
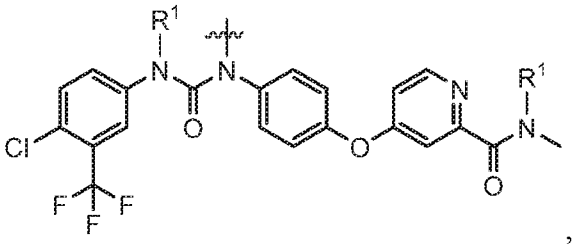
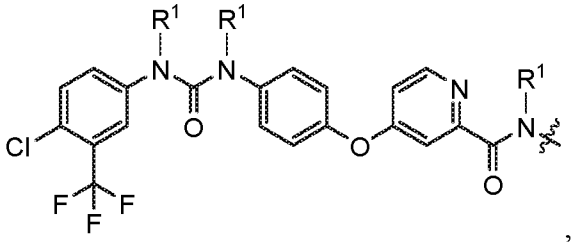
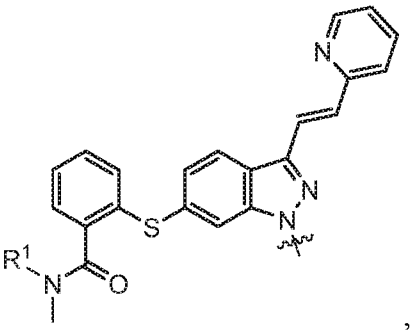
or $R^{137}$ is

or

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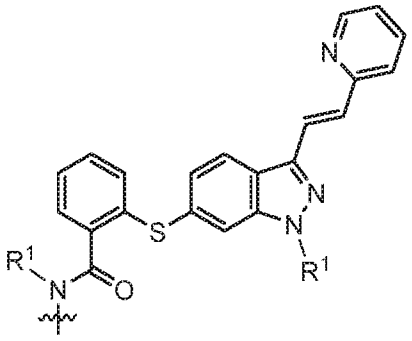
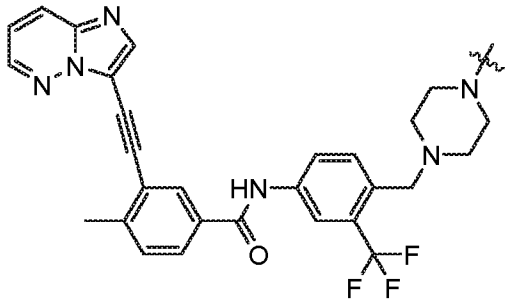
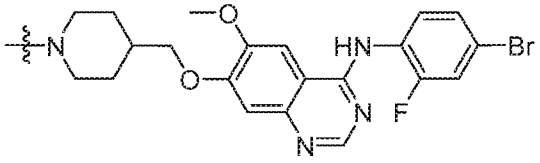
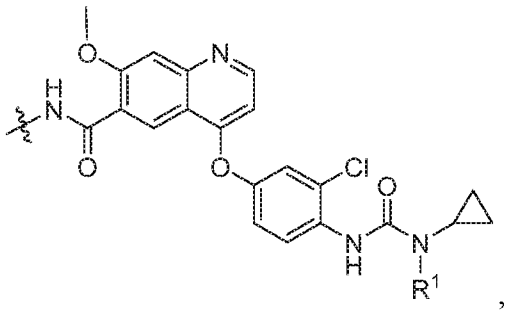
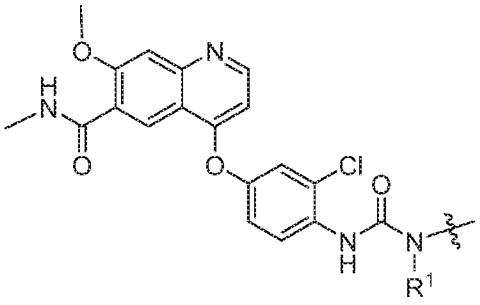
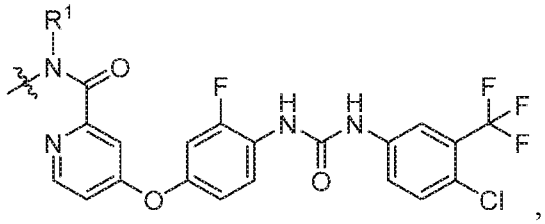
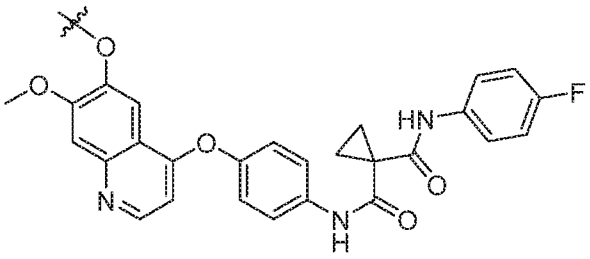
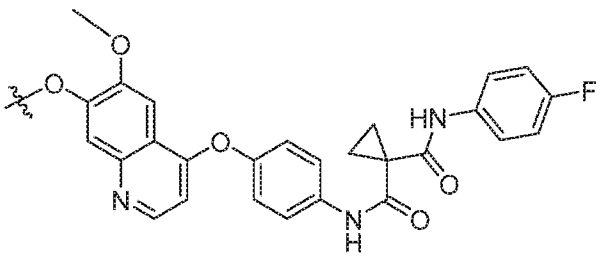
$R^{138}$ is selected from:


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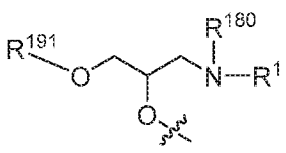
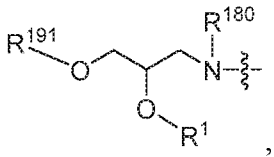
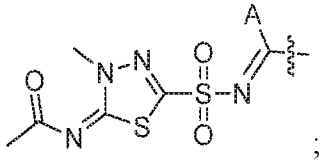

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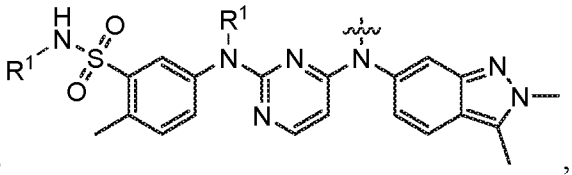
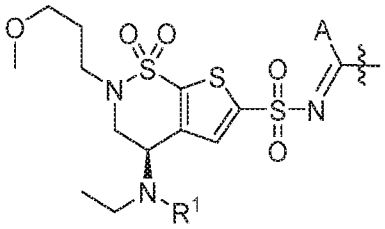
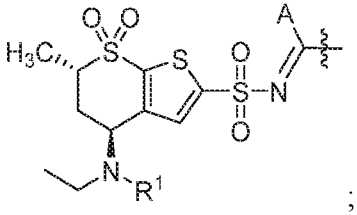


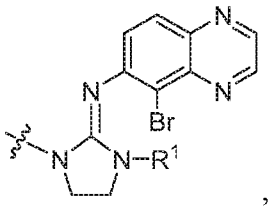
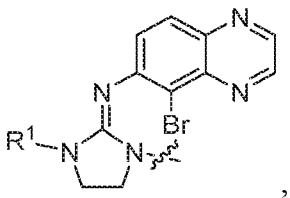
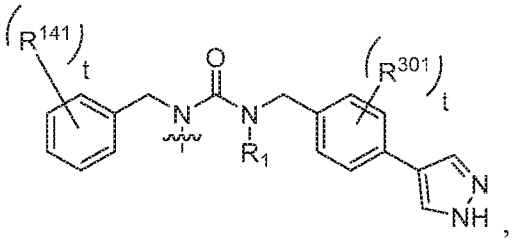
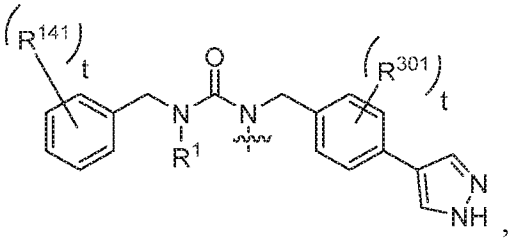
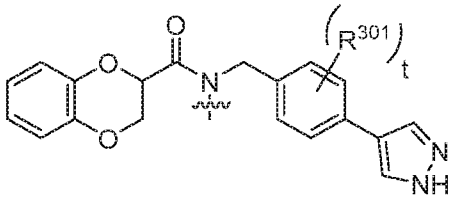

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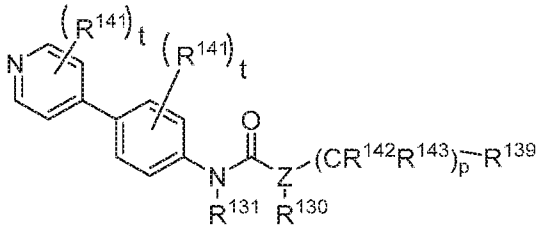

,

, and

;

or $R^{138}$ is  ,  ,  ;

Or in an alternative embodiment, $R^{138}$ is selected from  ,  ,  ,  , and  ; and

wherein all other variables are as defined herein.

In an alternative embodiment, Formula XXVIII is Formula XXVIIIa



(XXVIIIa)

wherein:

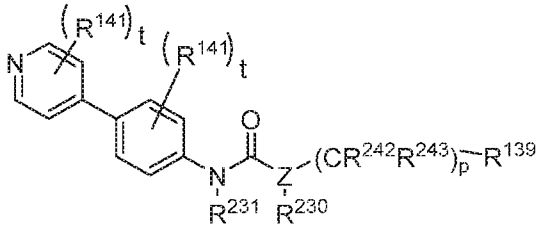
$R^{142}$ and $R^{143}$ are independently selected from H, -OH, acetyl, -C(O)$NH_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$cycloalkyl, hereterocycloalkyl, aryl, or heteroaryl, wherein any one of the $C_1$-$C_6$alkyl, $C_1$-$C_6$cycloalkyl, hereteroC$_1$-$C_6$cycloalkyl, aryl, or heteroaryl groups is optionally substituted with one or more of hydroxyl, -$CH_2$OH, -C(O)$NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkyl-O-$R^{136}$, alkoxy, alkylalkoxy, alkoxylalkoxy, heteroarylcarbonyl, heteroaryl, -$OCH_3$, -$OCF_3$, -$OCHF_2$, -$OCH_2F$;

$R^{139}$ is selected from cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, any of which is optionally substituted with one or more of hydroxyl, -$CH_2$OH, -C(O)$NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxylalkoxy, haloalkoxy, heteroarylcarbonyl, heteroaryl, -$OCH_3$, -$OCF_3$, -$OCHF_2$, -$OCH_2F$, -$OSO_2CH_3$, tosyl, or halogen;

p is 1, 2, or 3; and

wherein all other variables are as defined herein.

In an alternative embodiment, Formula XXVIII is Formula XXVIIIb



(XXVIIIb)

wherein:

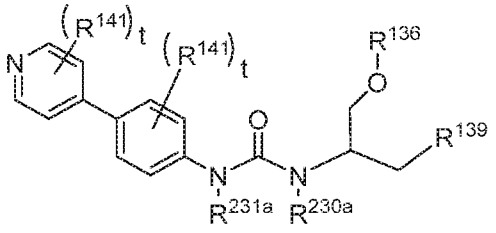
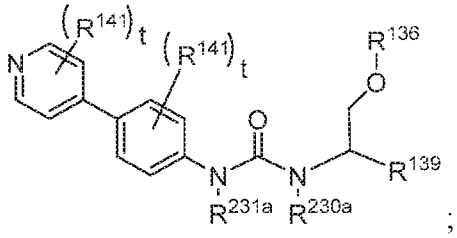
$R^{230}$ and $R^{231}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{136}$;

$R^{242}$ and $R^{243}$ are independently selected at each instance from H, -OH, acetyl, -C(O)$NH_2$, $C_1$-$C_6$alkyl, $C_1$-$C_6$cycloalkyl, hereterocycloalkyl, aryl, or heteroaryl, wherein any one of the $C_1$-$C_6$alkyl, $C_1$-$C_6$cycloalkyl, hereteroC$_1$-$C_6$cycloalkyl, aryl, or heteroaryl groups is optionally substituted with one or more substituents selected from hydroxyl, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkyl-O-$R^{136}$, -O-$R^{136}$, alkoxy, alkylalkoxy, alkoxylalkoxy, heteroarylcarbonyl, heteroaryl, -$OCH_3$, -$OCF_3$, -$OCHF_2$, -$OCH_2F$;

wherein at least one instance of $R^{230}$, $R^{231}$, $R^{242}$, or $R^{243}$ is $R^{136}$ or contains a O-$R^{136}$ substitutent; and

wherein all other variables are as defined herein.

In one embodiment the compound is:

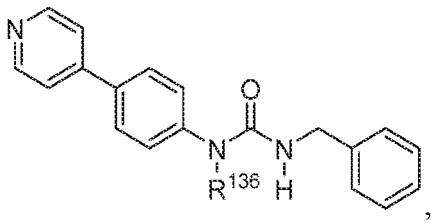
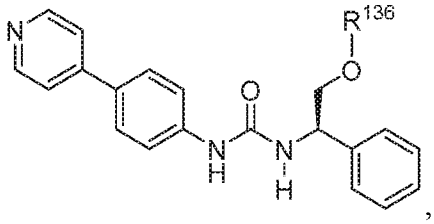
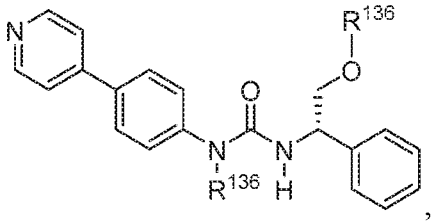
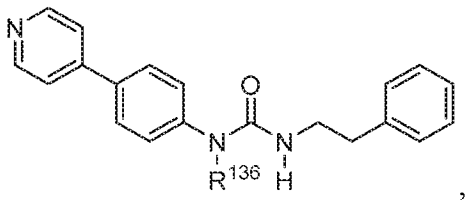
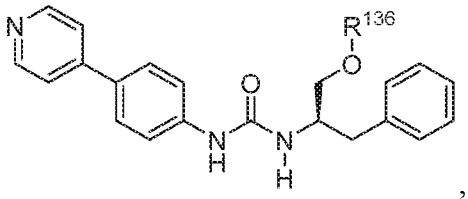
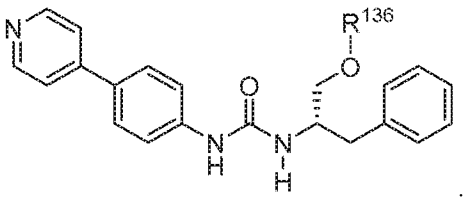

or

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wherein:

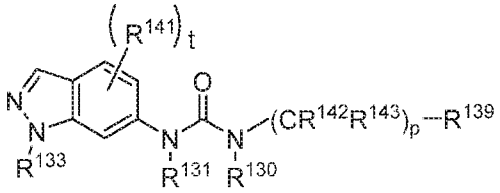
$R^{230a}$ and $R^{231a}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, and $C_1$-$C_{30}$heteroalkyl; and

wherein all other variables are as defined herein.

Non-limiting examples of Formula XXVIII include

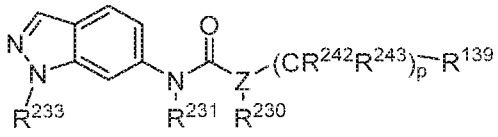

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In an alternative embodiment, Formula XXIX is Formula XXIXa


(XXIXa),

wherein all other variables are as defined herein.

In an alternative embodiment, Formula XXIX is Formula XXIXb



(XXIXb)

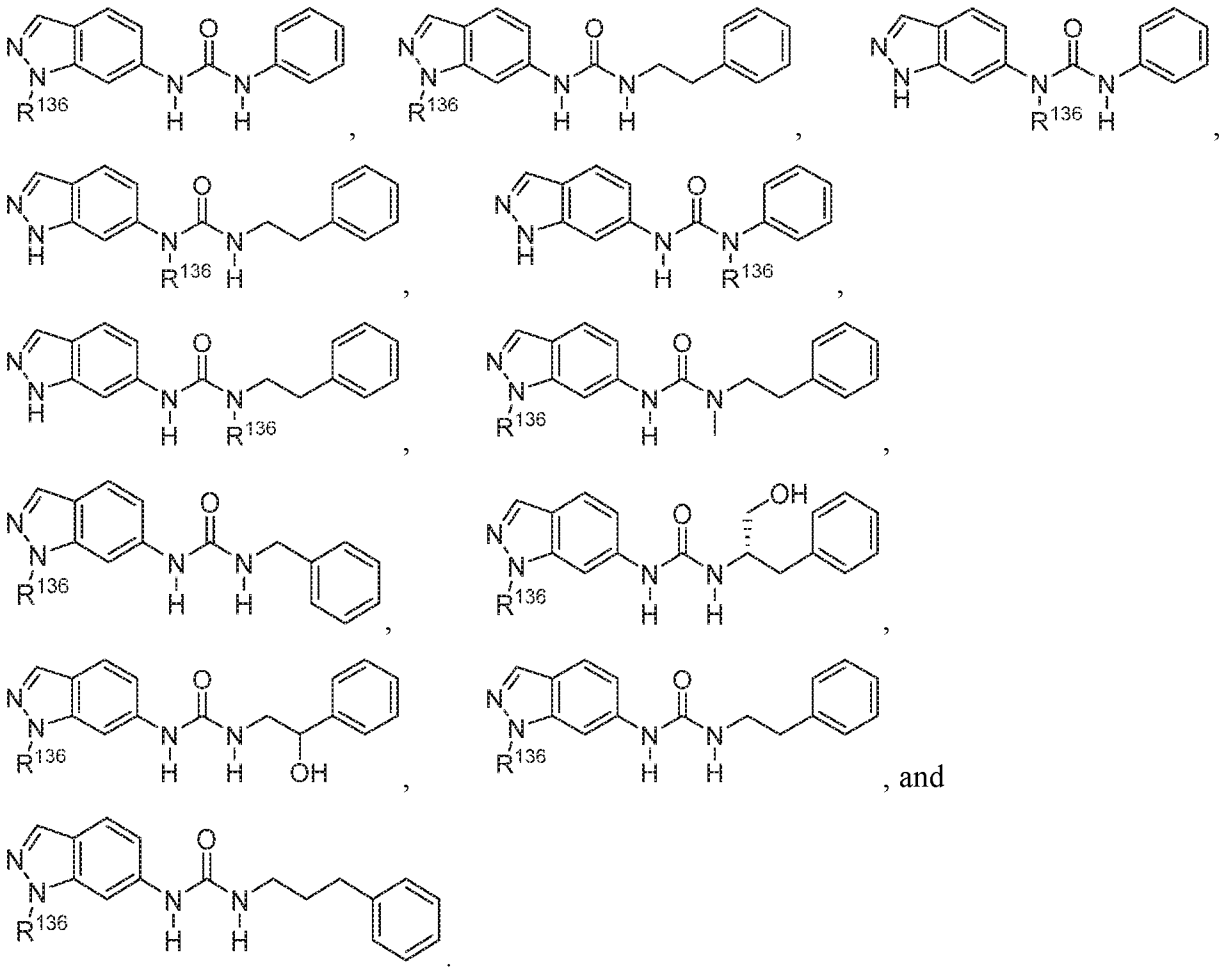
wherein:

$R^{230}$, $R^{231}$, and $R^{233}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{136}$;

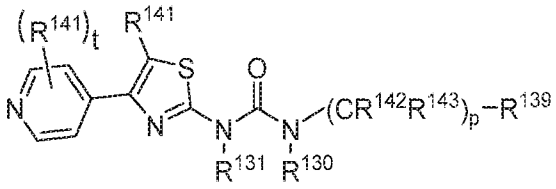
wherein at least one instance of $R^{230}$, $R^{231}$, $R^{233}$, $R^{242}$, or $R^{243}$ is $R^{136}$ or contains a O-$R^{136}$ substitutent;

wherein all other variables are as defined herein.

Non-limiting examples of Formula XXIX include



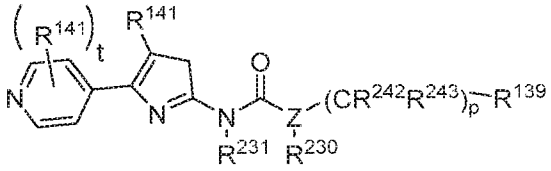
In an alternative embodiment, Formula XXX is Formula XXXa



(XXXa),

wherein all other variables are as defined herein.

In an alternative embodiment, Formula XXX is Formula XXXb

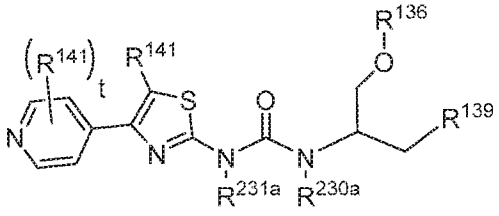


(XXXb)

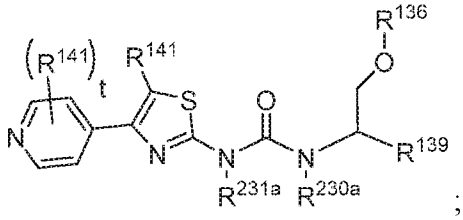
wherein at least one instance of $R^{230}$, $R^{231}$, $R^{242}$, or $R^{243}$ is $R^{136}$ or contains a O-$R^{136}$ substitutent; and

wherein all other variables are as defined herein.

In one embodiment the compound is:



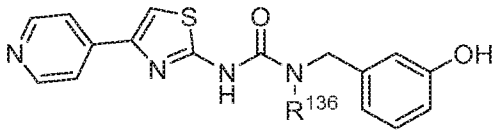
or



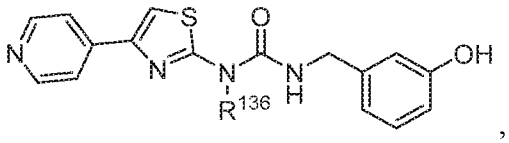
;

wherein all variables are as defined herein.

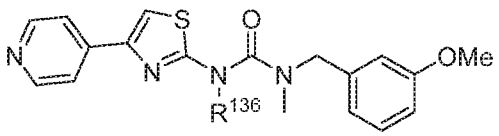
Non-limiting examples of Formula XXX include



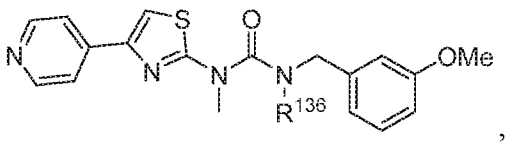
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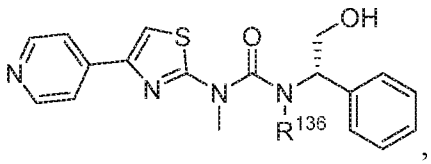
,



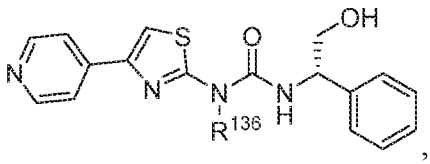
,



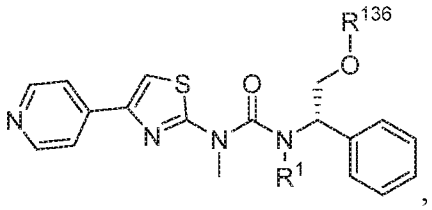
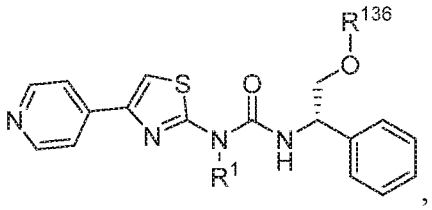
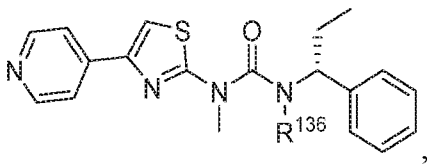
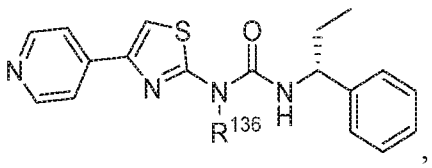
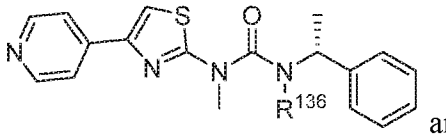
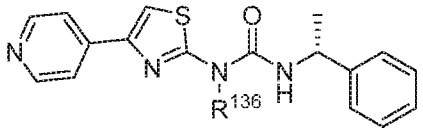
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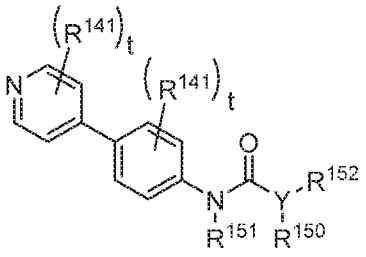
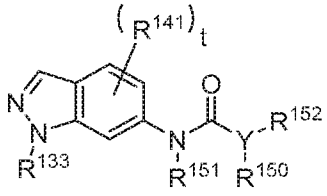
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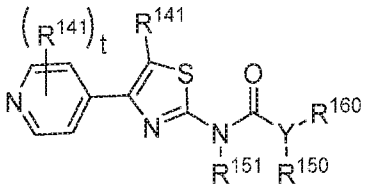


,


,

,

,

,

and

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The disclosure also provides prodrugs of Formula XXXI, XXXII, and XXXIII:


(XXXI)

(XXXII)


(XXXIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

Y is $CR^{150}$ or N;

$R^{150}$ and $R^{151}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{156}$;

in one embodiement the heteroalkyl contains at least one heteroatom in the chain, for example, an amine, carbonyl, carboxy, oxo, thio, phosphate, phosphonate, nitrogen, phosphorus, silicon, or boron atoms in place of a carbon atom. In one embodiment, the only heteroatom is oxygen. "Nonlimiting examples of heteroalkyl moieties are polyethylene glycol, polyalkylene

glycol, amide, polyamide, polylactide, polyglycolide, thioether, ether, alkyl-heterocycle-alkyl, -O-alkyl-O-alkyl, and alkyl-O-haloalkyl.

$R^{152}$ is selected from $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, aryl, heteroaryl, or alkylaryl, any of which can be optionally substituted with one or more of hydroxyl, $-CH_2OH$, $-C(O)NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxylalkoxy, haloalkoxy, heteroarylcarbonyl, heteroaryl, $-OCH_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OSO_2CH_3$, tosyl, or halogen;

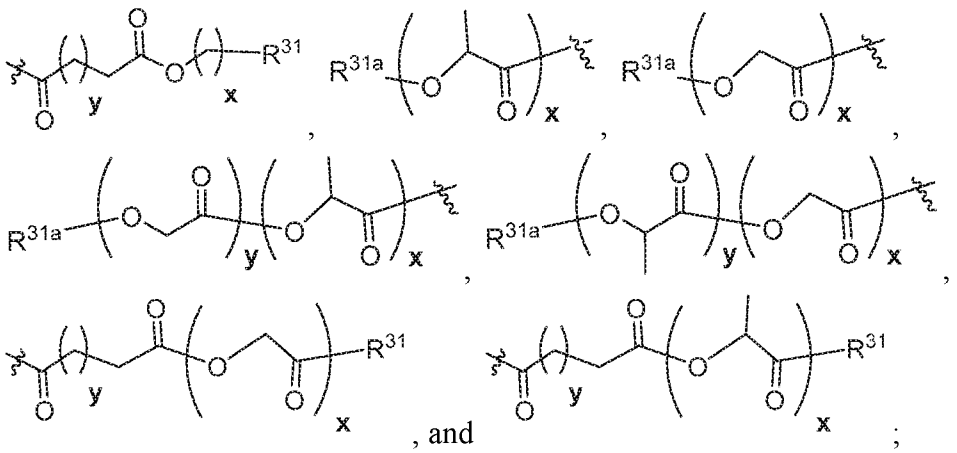
or $R^{151}$ and $R^{152}$ can together form a cycloalkyl or heterocycloalkyl;

$R^{160}$ is selected from H, $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, and aryl, any of which except hydrogen can be optionally substituted with one or more of hydroxyl, $-CH_2OH$, $-C(O)NH_2$, acetyl, carbonyl, alkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, any of which can be optionally substituted with one or more of hydroxyl, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxylalkoxy, haloalkoxy, heteroarylcarbonyl, heteroaryl, $-OCH_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2F$, $-OSO_2CH_3$, tosyl, or halogen; or $R^{151}$ and $R^{152}$ can together form a cycloalkyl or heterocycloalkyl;

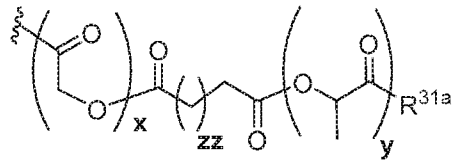
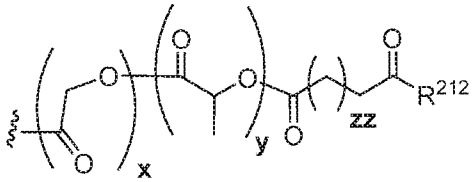
wherein at least one of $R^{150}$ and $R^{151}$ is $R^{156}$;

$R^{156}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid) polyglycolic acid, polyester, polyamide, and other biodegradable polymers, each of which can be capped to complete the terminal valence or to create a terminal ether or ester, in one embodiment the capping group is selected from $R^{31}$; and

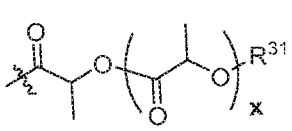
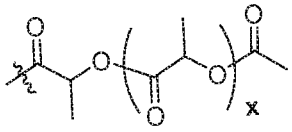
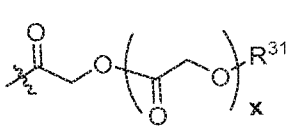
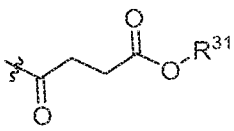
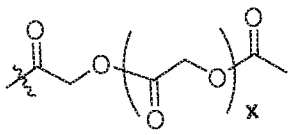
(ii) 

, and ;

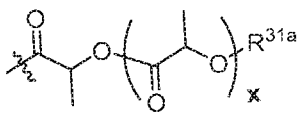
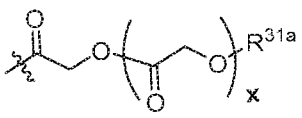
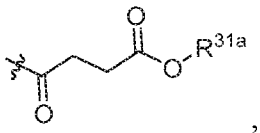
or $R^{156}$ is  or ;

wherein all other variables are as defined herein.

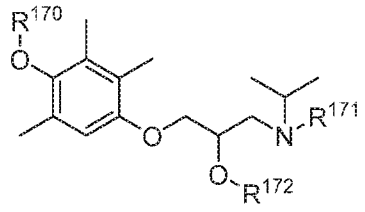
In one embodiment $R^{156}$ is selected from:

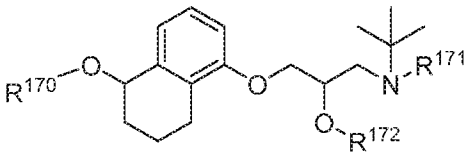
, , ,  and .

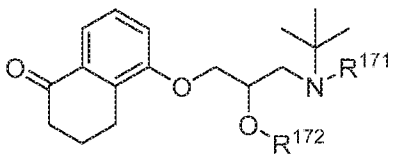
In one embodiment $R^{156}$ is selected from:

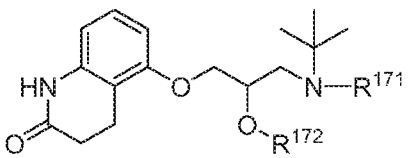
, , and ,

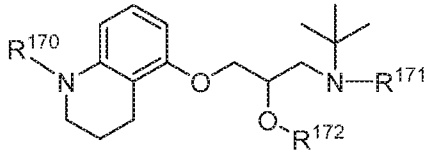
The disclosure also provides prodrugs of Formula XXXIV, Formula XXXVI, Formula XXXVIII, Formula XL, Formula XLII, Formula XLIV, Formula XLVI, and Formula XLVIII:

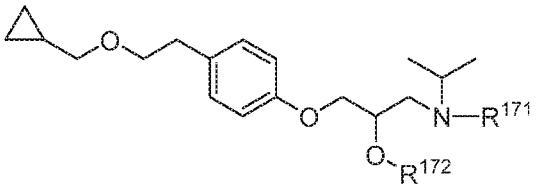
 (XXXIV)

 (XXXVI)

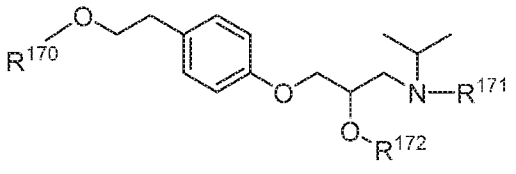
 (XXXVIII)

 (XL)

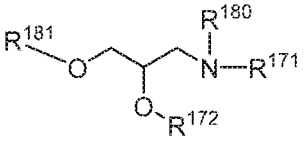
 (XLII)



(XLIV)



(XLVI)



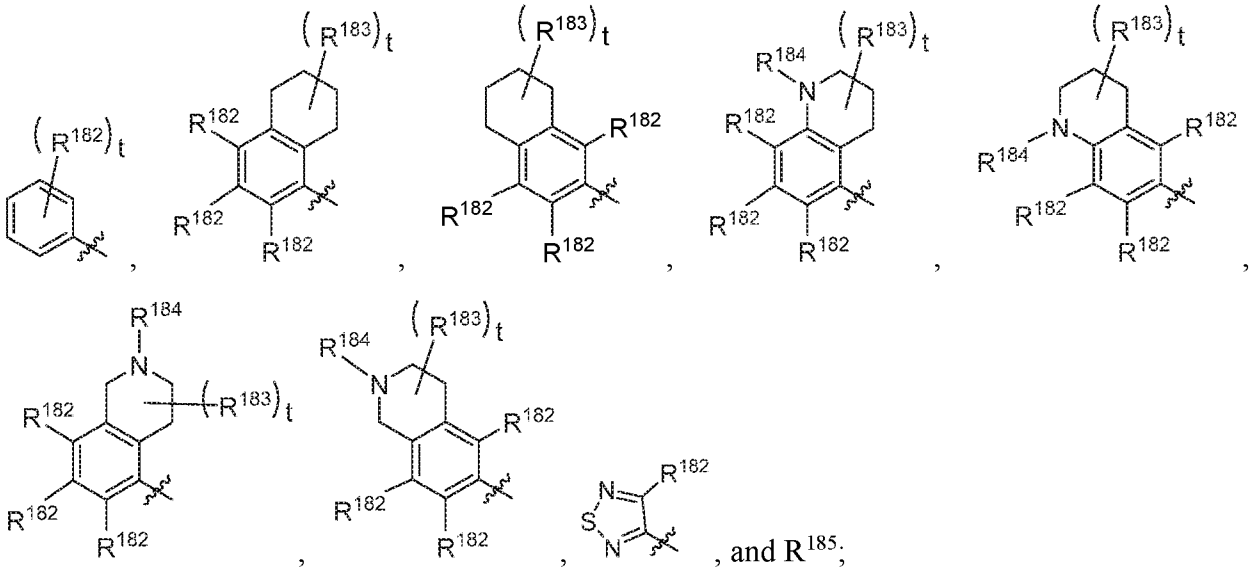
(XLVIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

$R^{170}$, $R^{171}$, and $R^{172}$ are independently selected from: $R^1$, $R^{173}$, acyl, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, or other biodegradable polymer, each of which $R^{170}$, $R^{171}$, and $R^{172}$ other than $R^{173}$ are optionally substituted with $L^8$-$R^{174}$;

wherein at least one of $R^{170}$, $R^{171}$, and $R^{172}$ is $R^{173}$ or substituted with $L^8$-$R^{174}$

$R^{181}$ is selected from:



, and $R^{185}$;

$R^{182}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{182}$ is optionally substituted with a $R^{170}$ group;

$R^{183}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

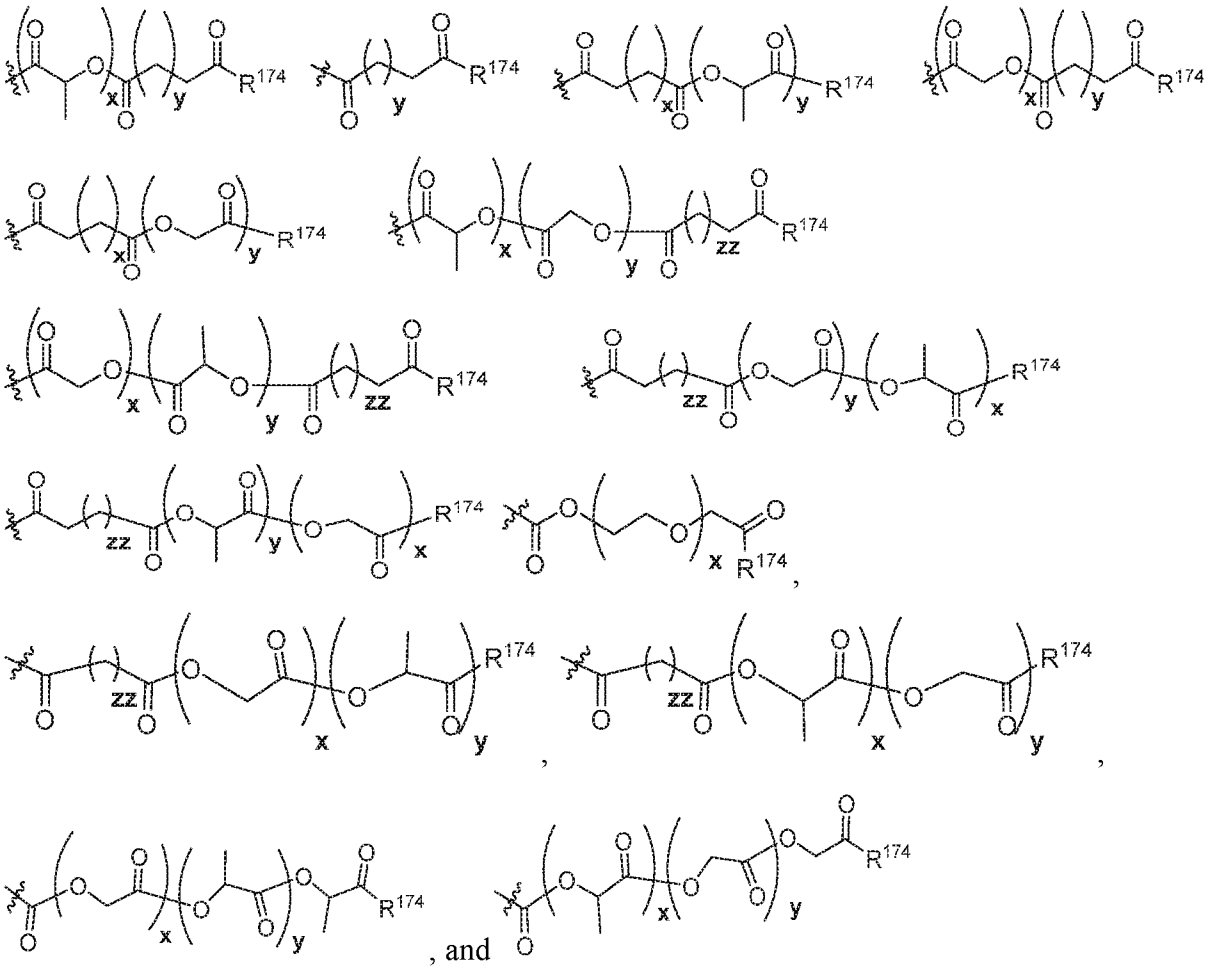
or two $R^{183}$ groups with the carbon to which they are linked form a carbonyl group;

or two $R^{183}$ groups with the carbon(s) to which they are linked form a fused or spirocyclic ring;

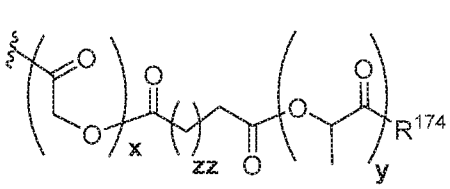
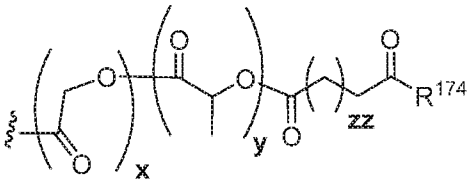
$R^{184}$ is selected from alkyl, cycloalkyl, $R^{170}$, and acyl;

$R^{185}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{185}$ is optionally substituted with 1, 2, 3, or 4 $R^{182}$ groups;

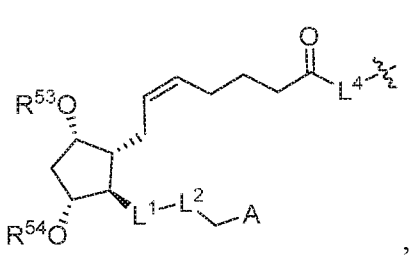
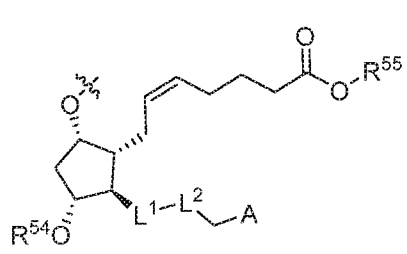
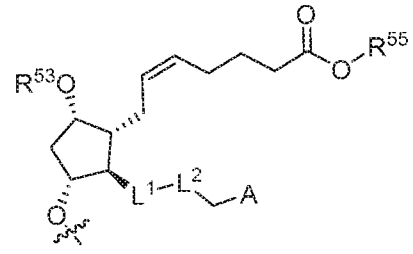
$R^{173}$ is selected from:

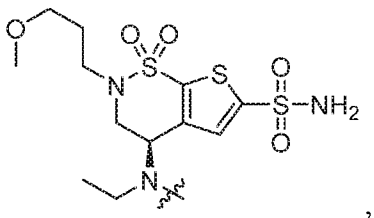
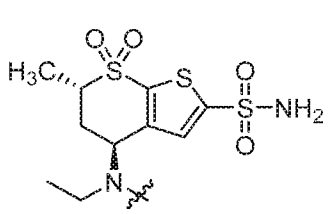
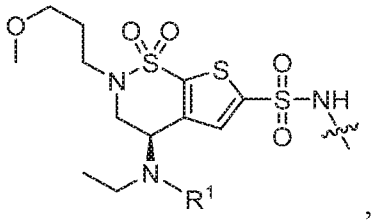


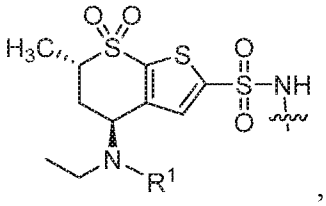
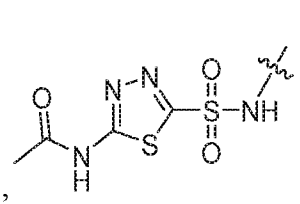
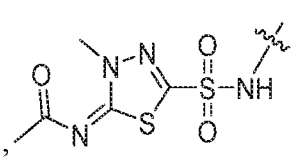
; and

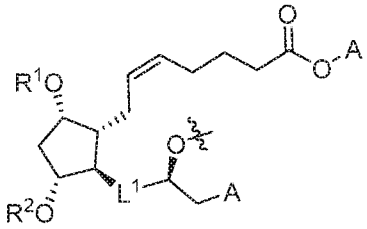
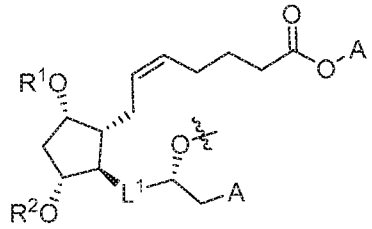
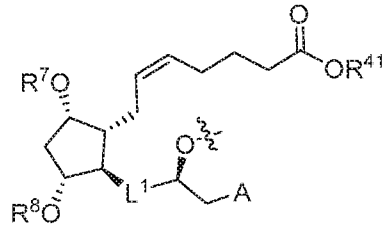
or $R^{173}$ is  or ;

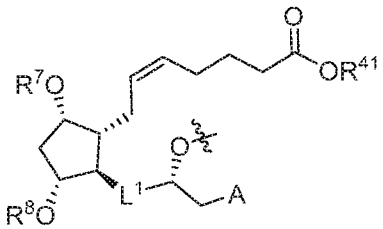
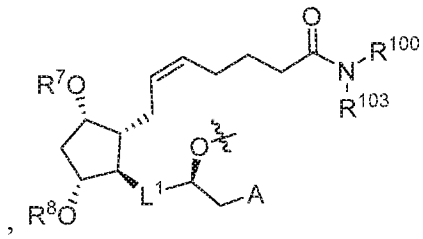
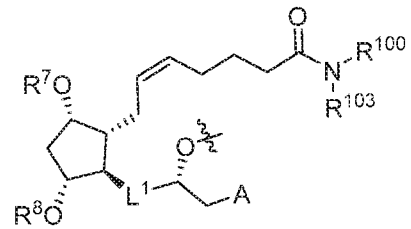
$R^{174}$ is selected from:

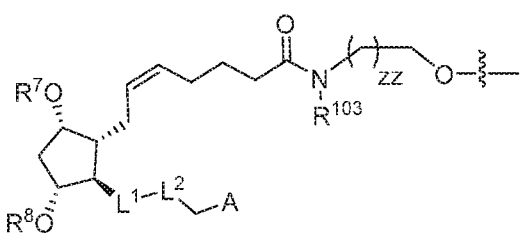
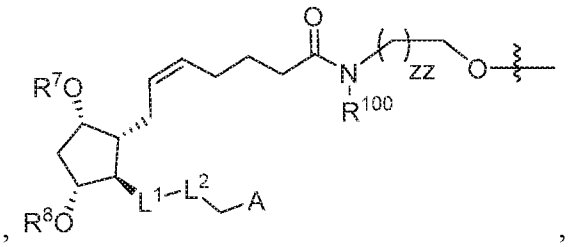
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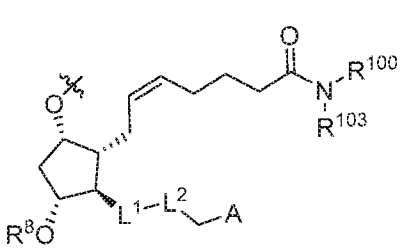
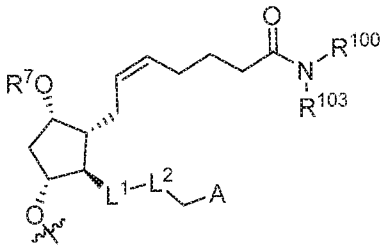
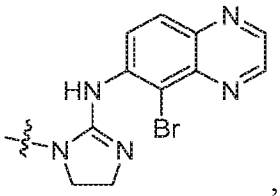
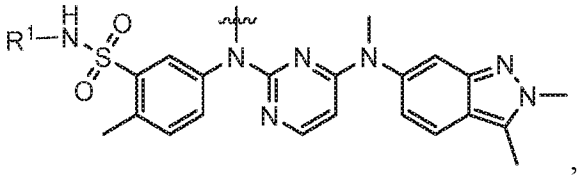
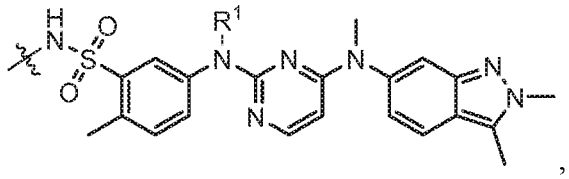
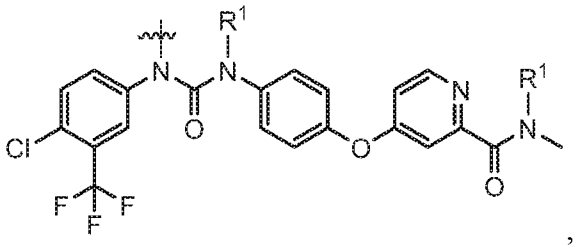
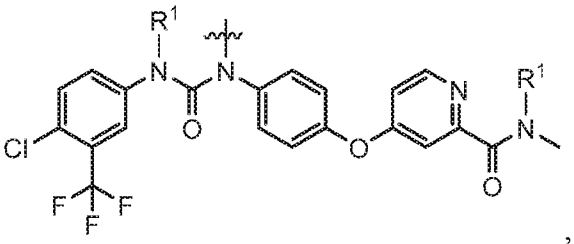
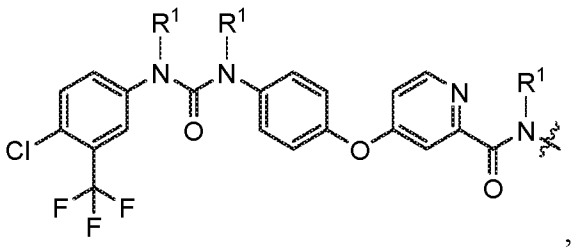
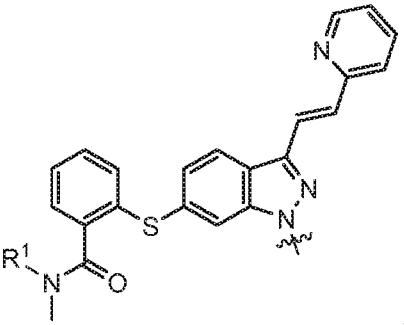
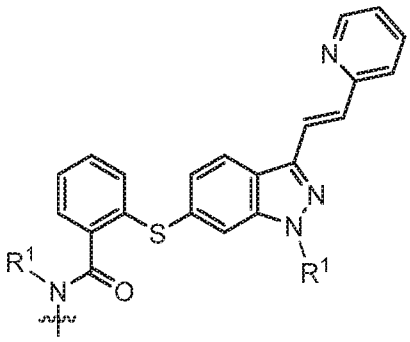
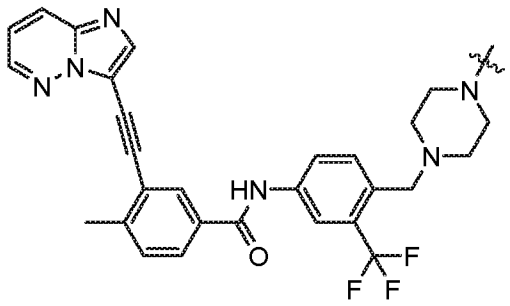
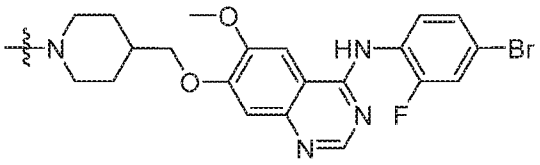
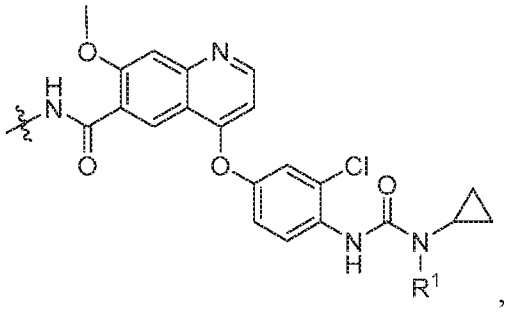
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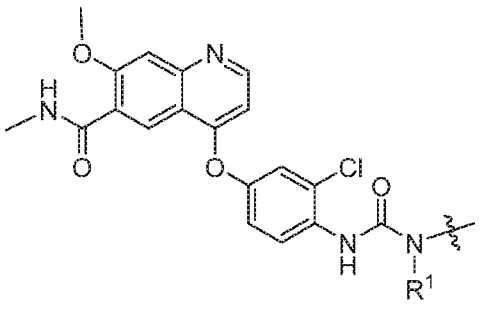
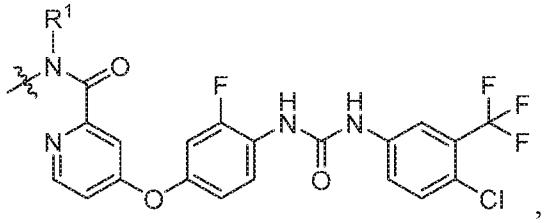
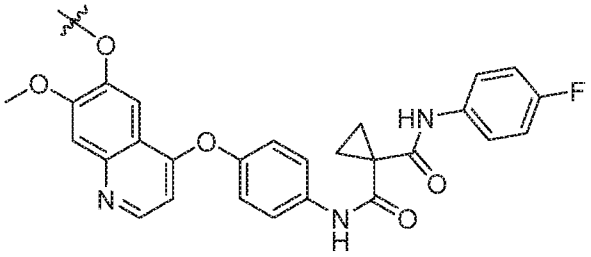
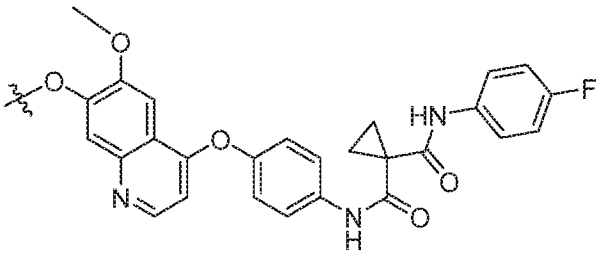
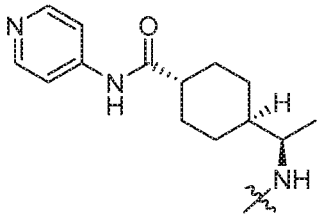
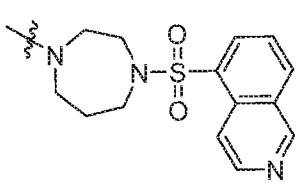
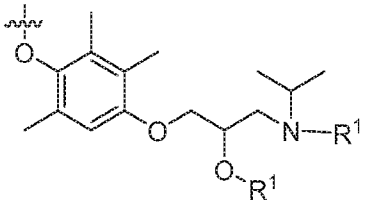
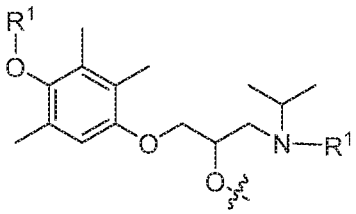
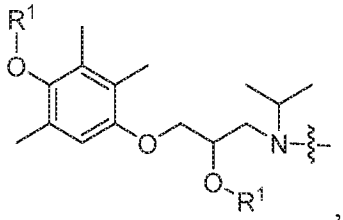
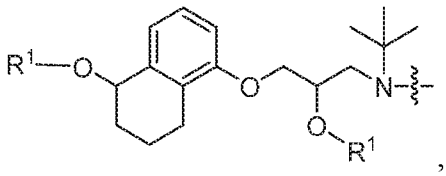
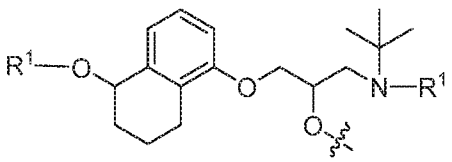
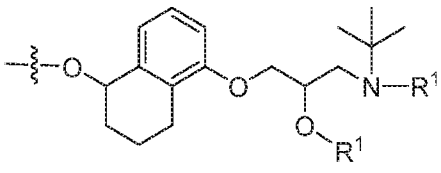
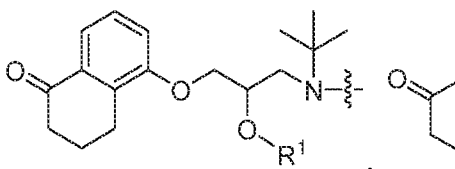
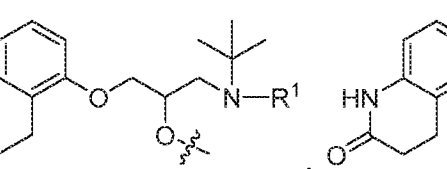
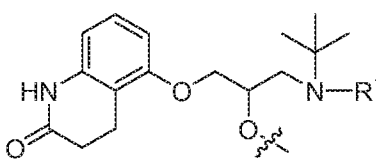
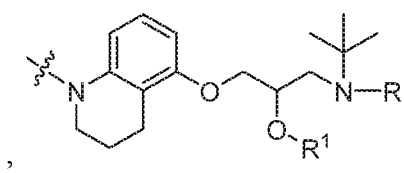
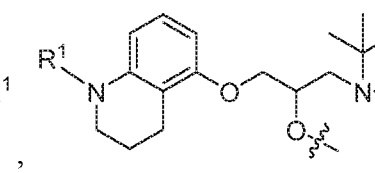
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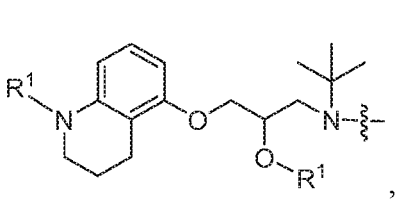
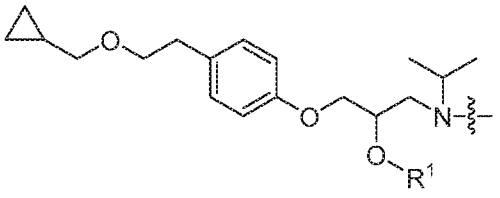
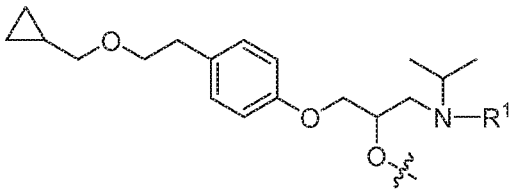
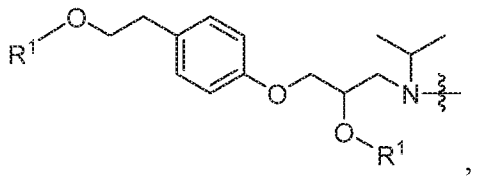
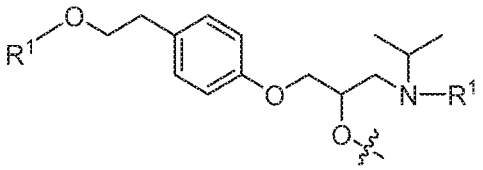
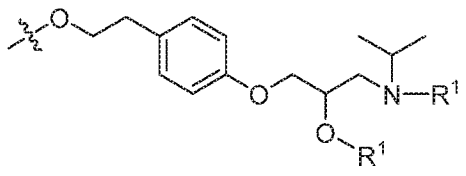
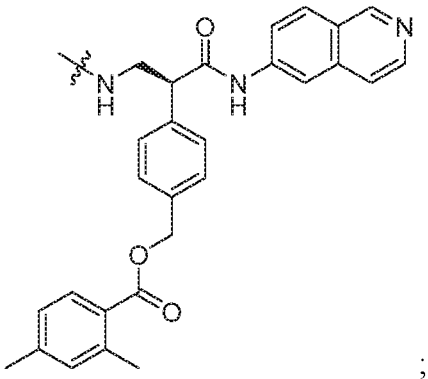

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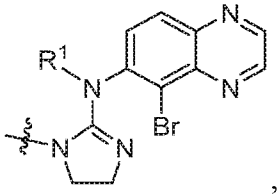
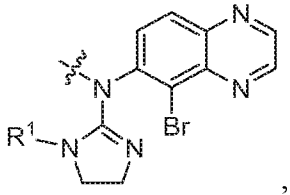
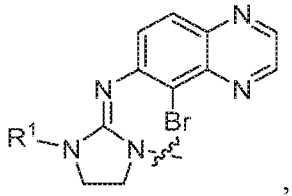
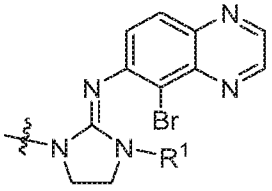
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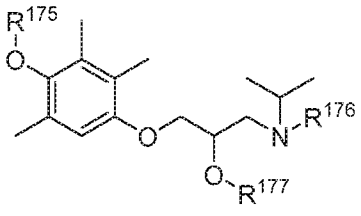

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or $R^{174}$ is

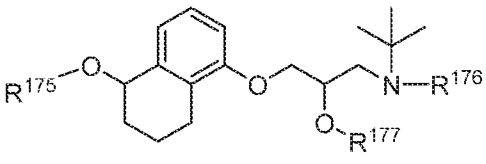

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wherein all other variables are as defined herein.

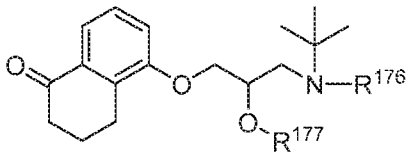
The disclosure also provides prodrugs of Formula XXXV, Formula XXXVII, Formula XXXIX, Formula XLI, Formula XLIII, Formula XLV, Formula XLVII, and Formula XLIX:



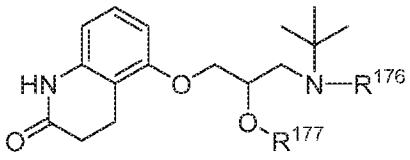
(XXXV)



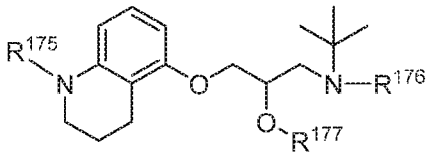
(XXXVII)



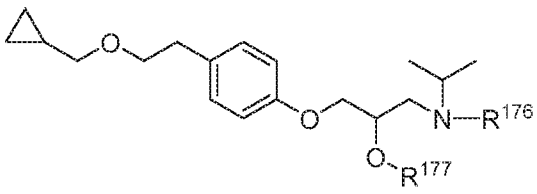
(XXXIX)



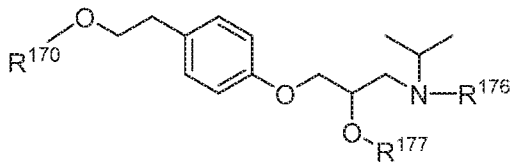
(XLI)



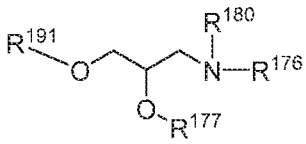
(XLIII)



(XLV)



(XLVII)



(XLIX)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof.

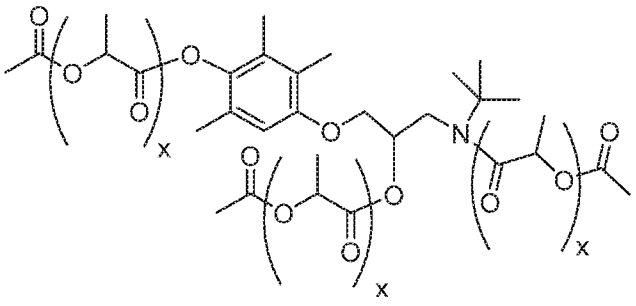
In some embodiments the compounds of Formula XXXIV to Formula XLIX can be used in the form of an R enantiomer, an S enantiomer, or a mixture of enantiomers including a racemic mixture.

In some embodiments the compounds of Formula XXXIV to Formula XLIX have the same stereochemistry as the corresponding commercial drug.

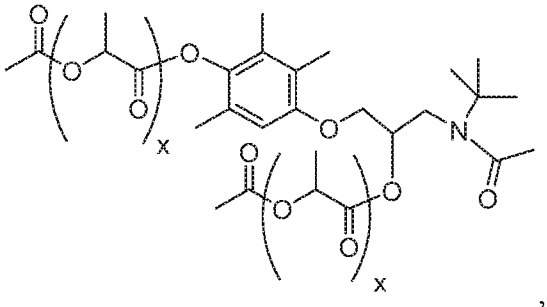
$R^{175}$, $R^{176}$, and $R^{177}$ are independently selected from: C(O)A, C(O)$R^4$, and $R^{178}$; wherein at least one of $R^{175}$, $R^{176}$, and $R^{177}$ is $R^{178}$; and

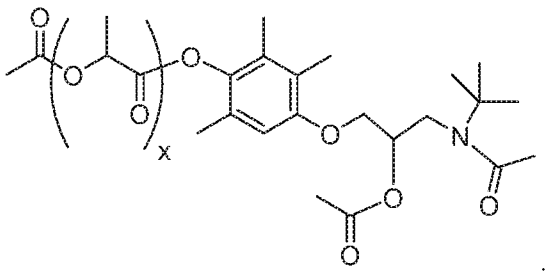
wherein all other variables are as defined herein.

Non-limiting examples of Formula XXXV include:



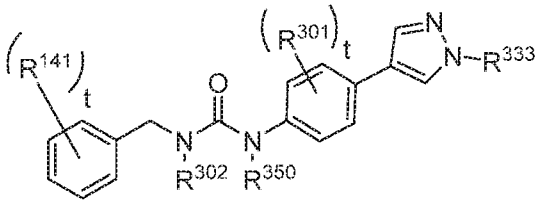
,



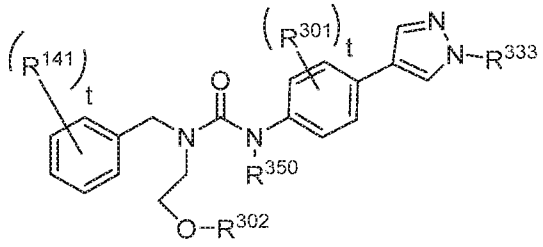


, and .

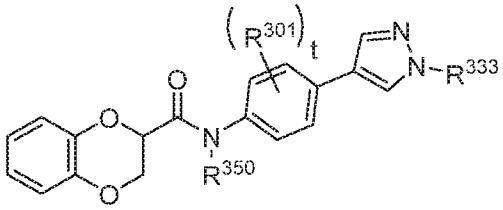
In an alternative embodiment, this disclosure provides prodrugs of Formula (L), (L'), and (LI):



(L)



(L')



(LI)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof

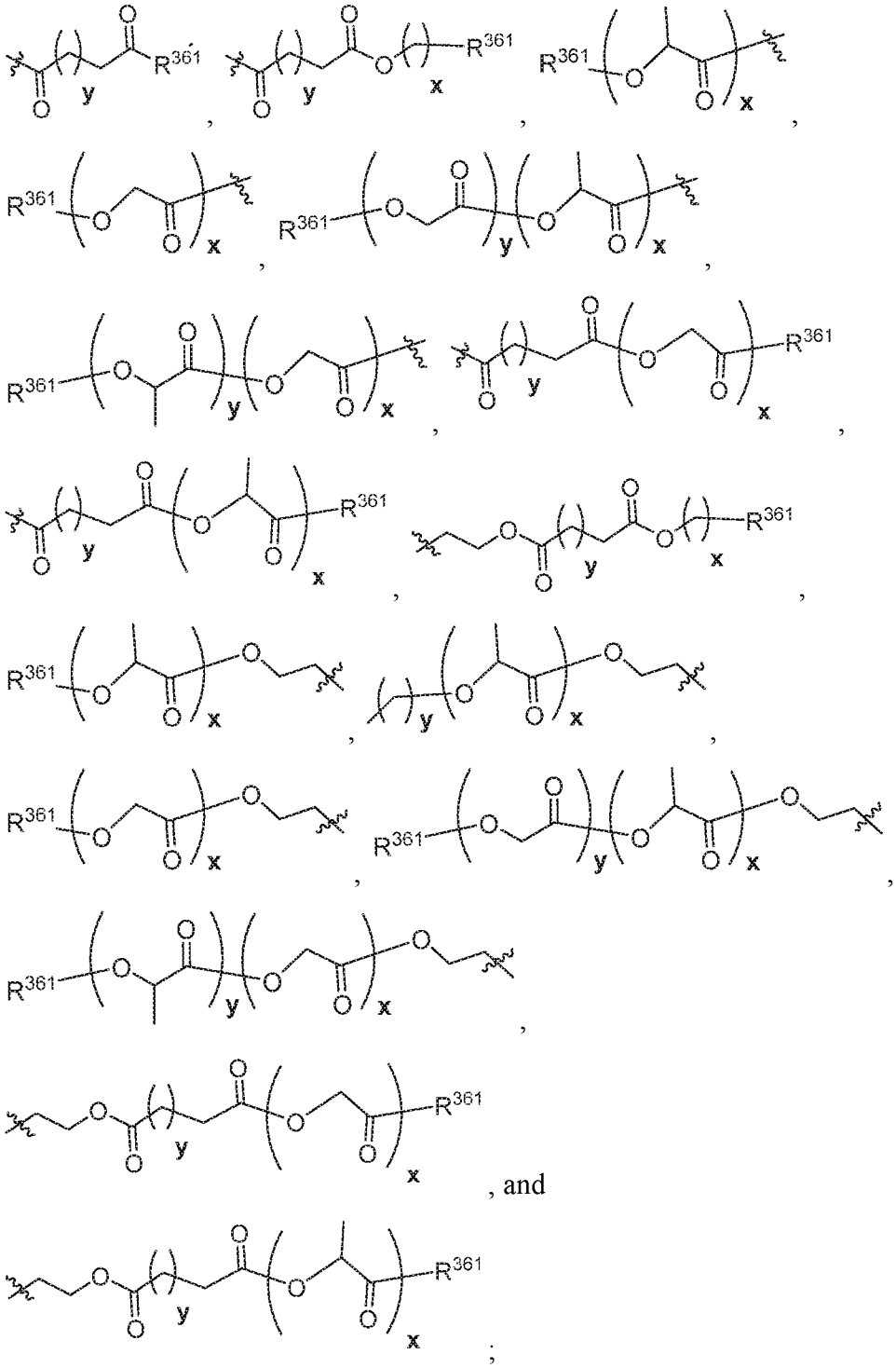
wherein

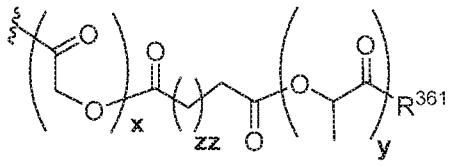
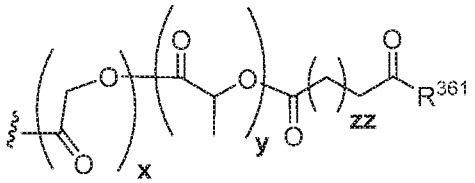
$R^{302}$ and $R^{333}$ are independently selected from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, $C_2$-$C_{30}$alkenyl, and $R^{356}$;

$R^{350}$ is selected from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, $C_2$-$C_{30}$alkenyl, and $R^{356}$;

$R^{356}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid) polyglycolic acid, polyester, polyamide, and other biodegradable polymers, each of which can be capped to complete the terminal valence or to create a terminal ether or ester;

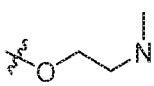
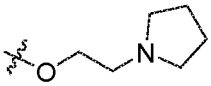
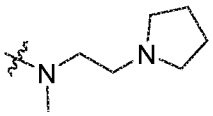
(ii) 
, and
;

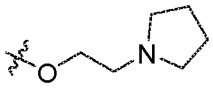
or $R^{356}$ is  or ;

wherein at least one of $R^{302}$, $R^{333}$ and $R^{350}$ is $R^{356}$; and

wherein all other variables are as defined herein.

In one embodiment, $R^{141}$ is $OCH_3$.

In one embodiment, $R^{301}$ is selected from $-N(CH_3)_2$, , , and .

In one embodiment, $R^{301}$ is .

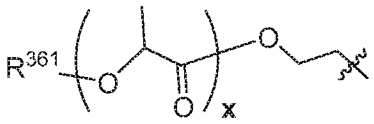
In one embodiment, $R^{301}$ is $-OCH_3$.

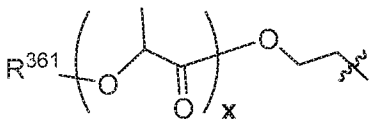
In one embodiment, $R^{301}$ is selected from F and Cl.

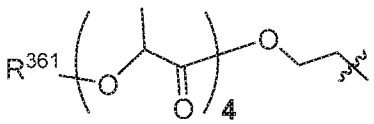
In one embodiment, $R^{350}$ is hydrogen.

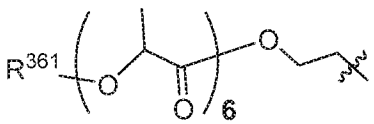
In one embodiment, $R^{350}$ is $CH_3$.

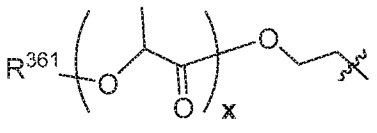
In one embodiment, $R^{350}$ is $CH_2H_5$.

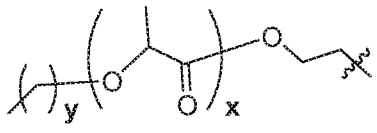
In one embodiment, $R^{356}$ is  and $R^{361}$ is $-C(O)CH_3$.

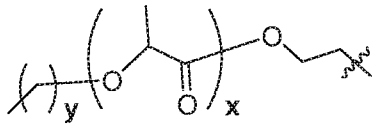
In one embodiment, $R^{356}$ is  and $R^{361}$ is stearoyl.

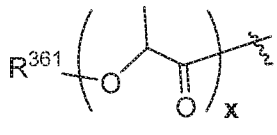
In one embodiment, $R^{356}$ is  and $R^{361}$ is $-C(O)CH_3$.

In one embodiment, $R^{356}$ is  and $R^{361}$ is $-C(O)CH_3$.

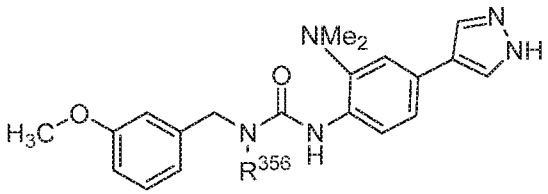
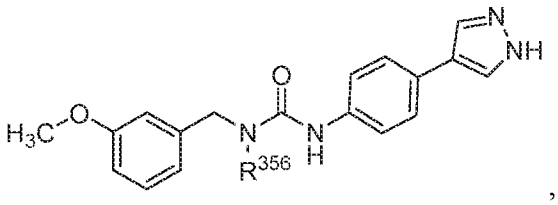
In one embodiment, $R^{356}$ is  and x is an integer between 1 and 6.

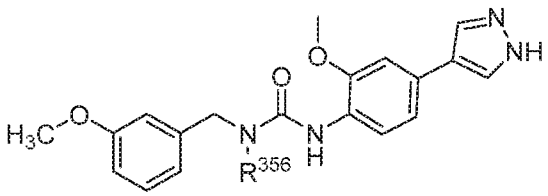
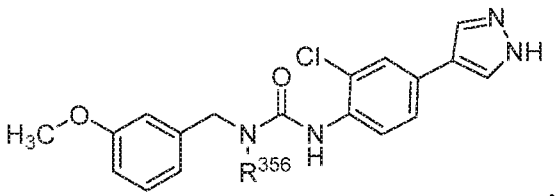
In one embodiment, $R^{356}$ is  and y is 11, or in an alternative embodiment, y is 10.

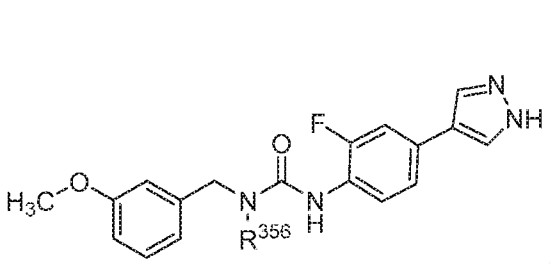
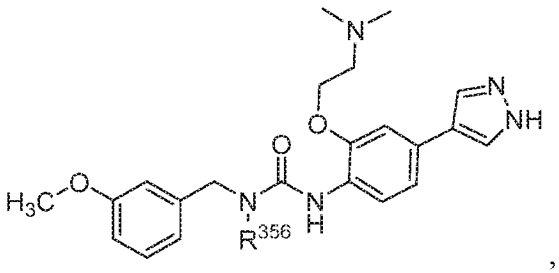
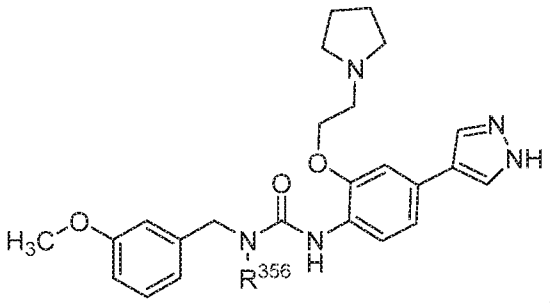
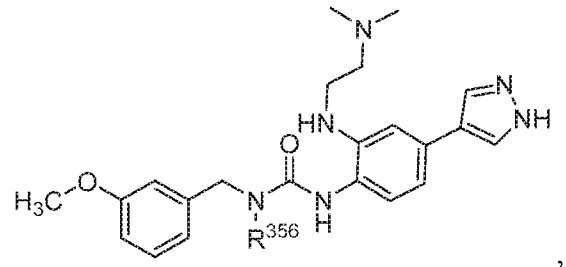
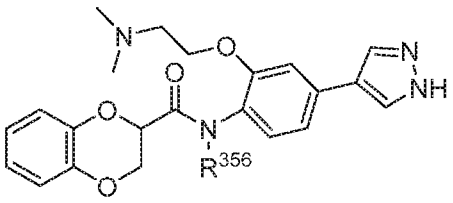
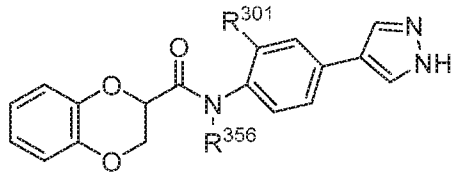
In one embodiment, $R^{356}$ is  and y is 17, or in an alternative embodiment, y is 16.

In one embodiment, $R^{333}$ is  and $R^{361}$ is -C(O)alkyl.

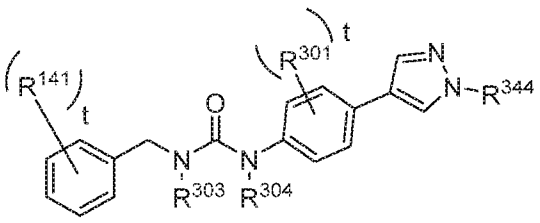
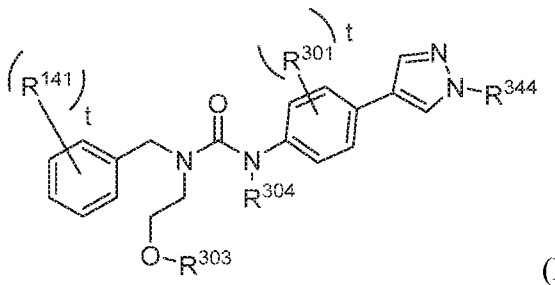
Non-limiting Examples of Formula L and Formula LI include

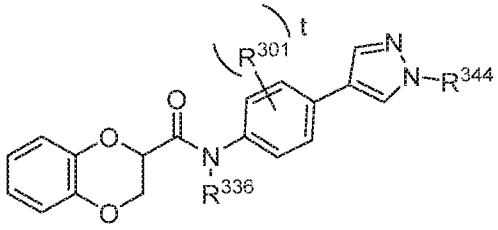
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, and

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In an alternative embodiment, this disclosure provides prodrugs of Formula (LII) and (LIII):


(LII)

(LII')


(LIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof

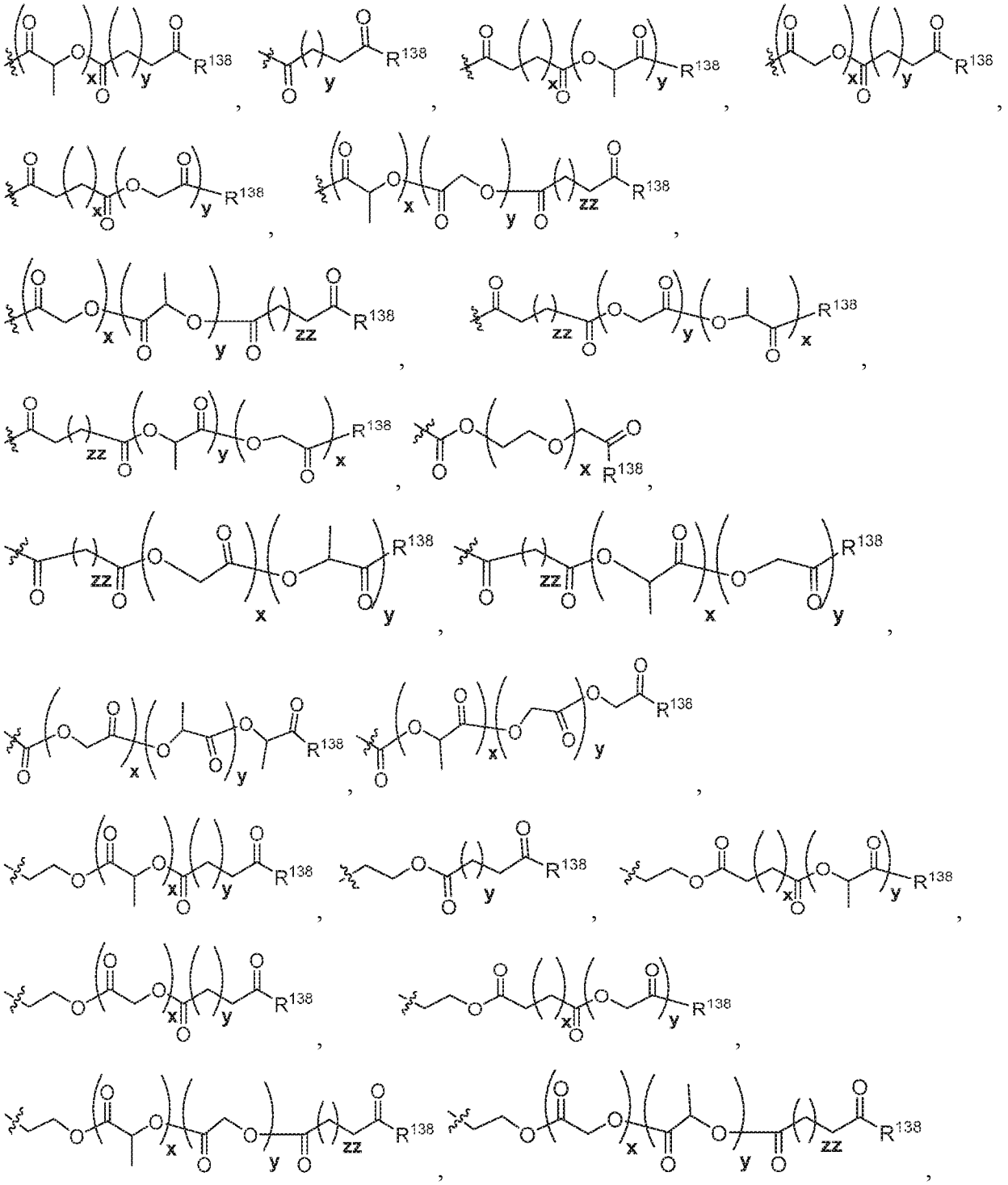
wherein

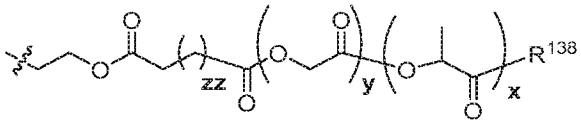
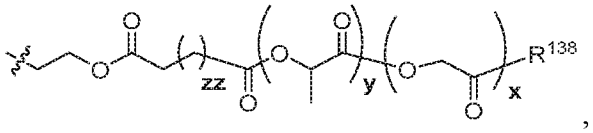
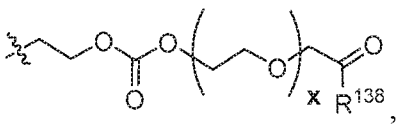
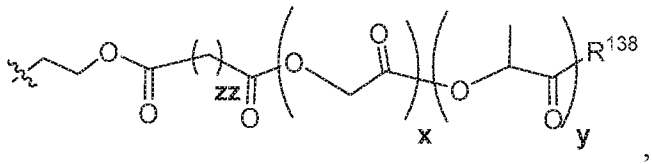
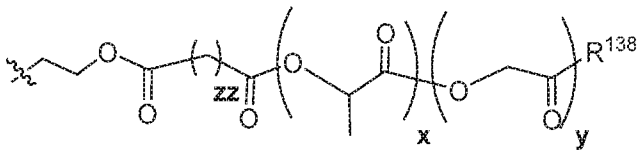
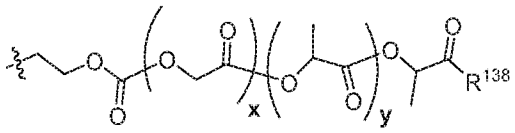
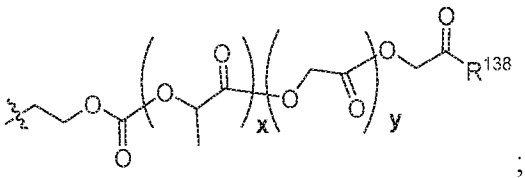
$R^{303}$, $R^{304}$, and $R^{344}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl,

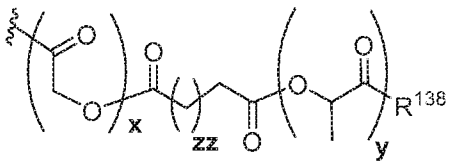
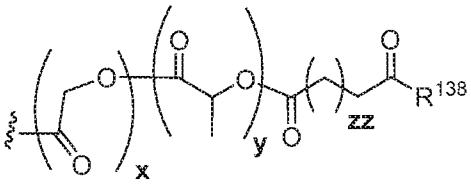
-C(O)$C_1$-$C_{30}$alkyl, $C_2$-$C_{30}$alkenyl, $C_1$-$C_{30}$heteroalkyl, and $R^{336}$;

wherein at least one of $R^{303}$, $R^{304}$, and $R^{344}$ is $R^{336}$;

$R^{336}$ is selected from:

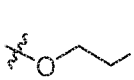
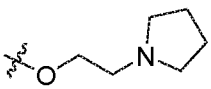
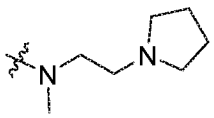


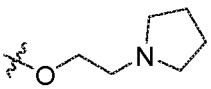

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, and

; and

or $R^{336}$ is

or

;

wherein all other variables are as defined herein.

In one embodiment, $R^{141}$ is $OCH_3$.

In one embodiment, $R^{301}$ is selected from $-N(CH_3)_2$,

,

, and

.

In one embodiment, $R^{301}$ is

.

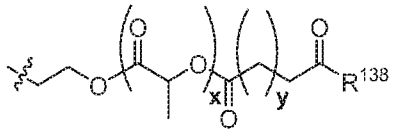
In one embodiment, $R^{301}$ is $-OCH_3$.

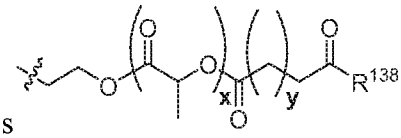
In one embodiment, $R^{301}$ is selected from F and Cl.

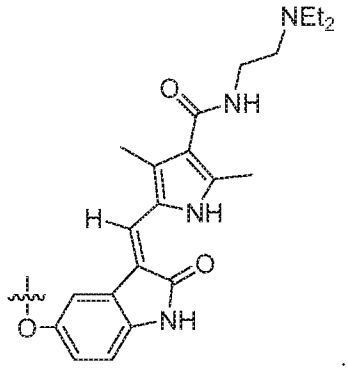
In one embodiment, $R^{304}$ is hydrogen.

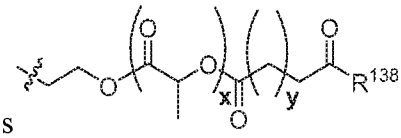
In one embodiment, $R^{304}$ is $CH_3$.

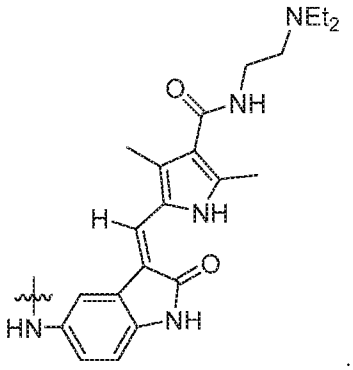
In one embodiment, $R^{304}$ is $CH_2H_5$.

In one embodiment, $R^{303}$ is .

In one embodiment, $R^{303}$ is  and $R^{138}$ is

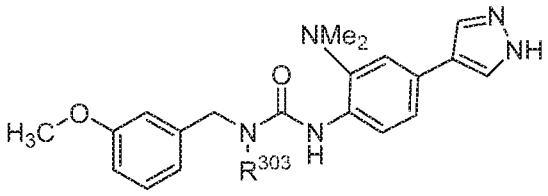
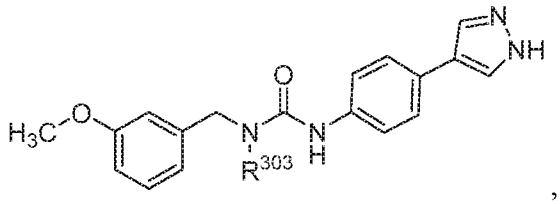
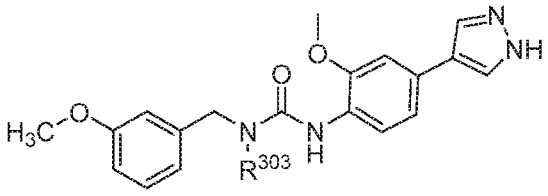
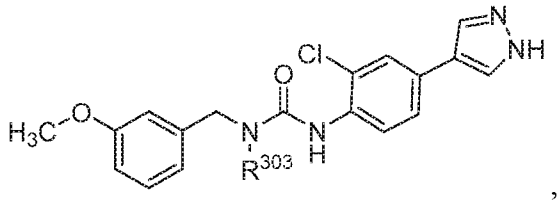
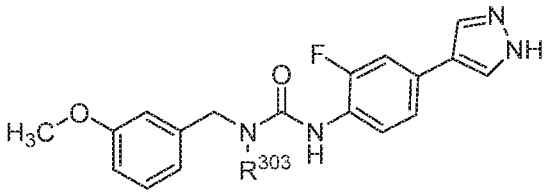
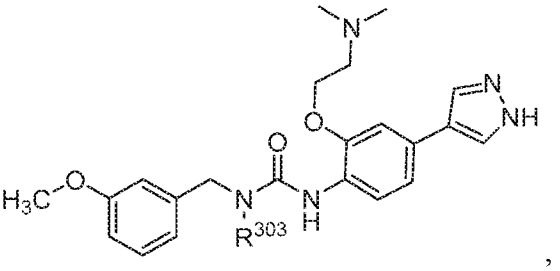
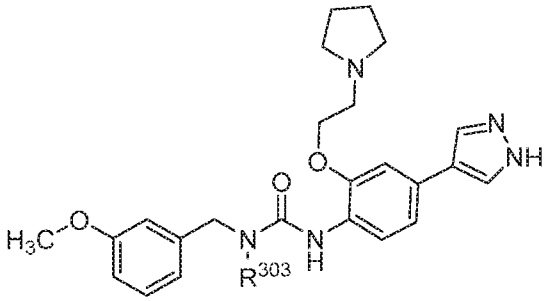
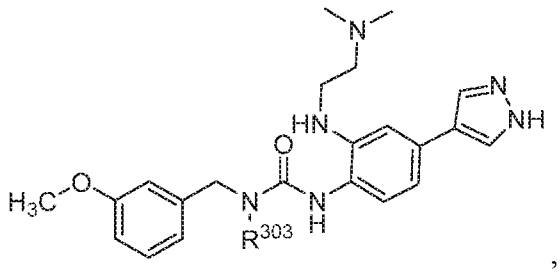
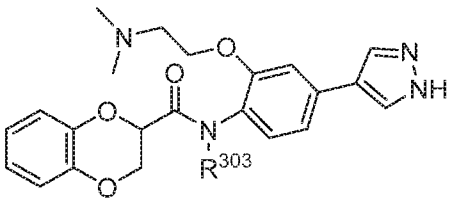
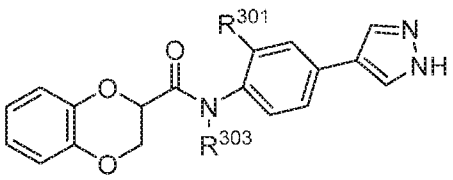
.

In one embodiment, $R^{303}$ is  and $R^{138}$ is

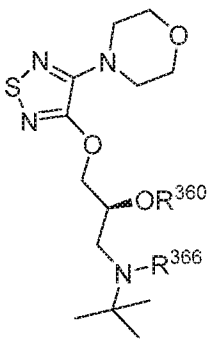
.

In a further embodiment, x is 2 and y is 2.

Non-limiting Examples of Formula LII and Formula LIII include


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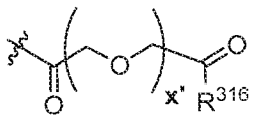
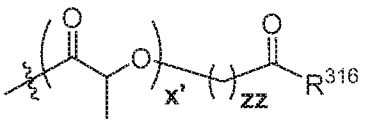
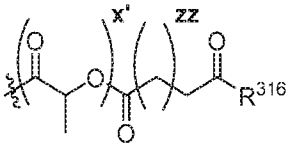
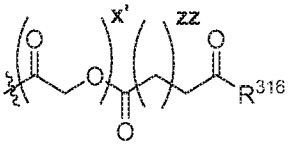
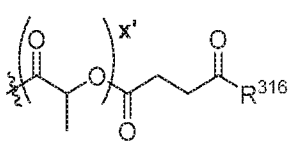
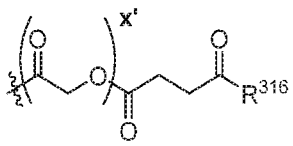
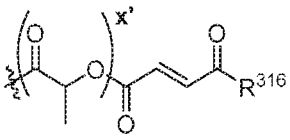
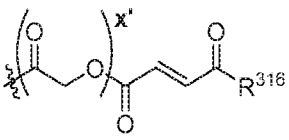
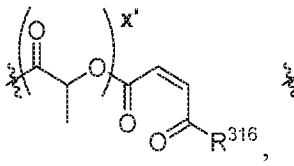
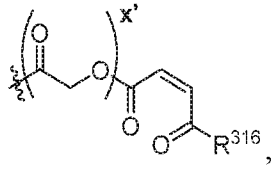
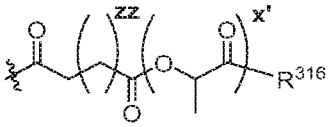
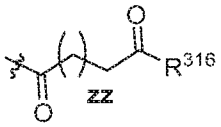
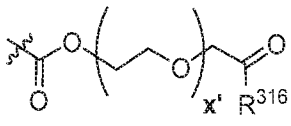
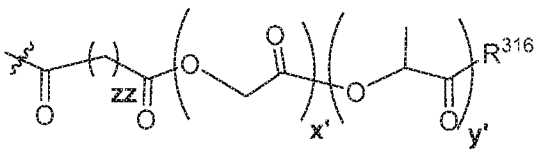
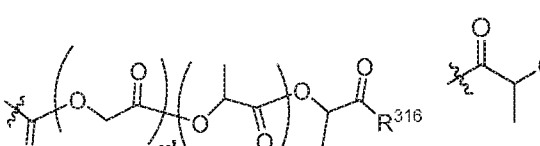
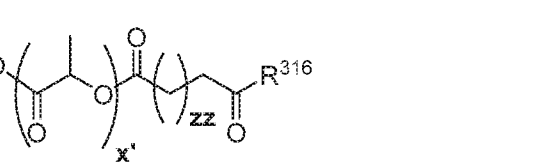
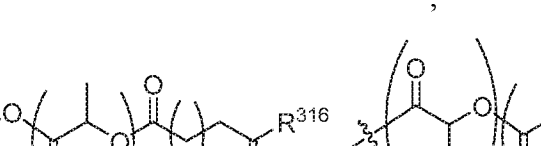
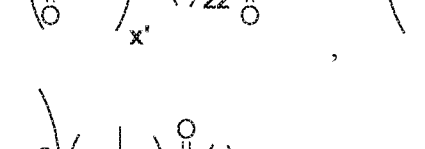
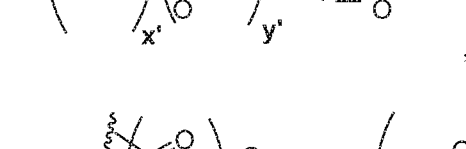
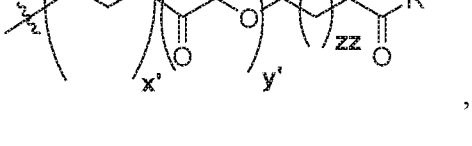
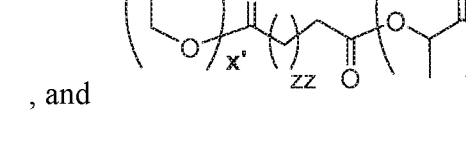
In an an alternative embodiment, this disclosure provides prodrugs of Formula (LIV):

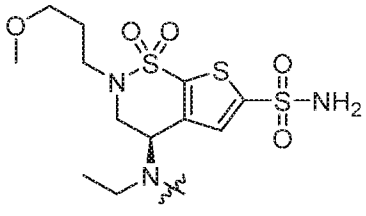
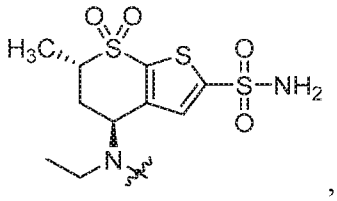
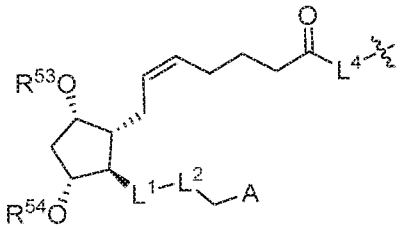
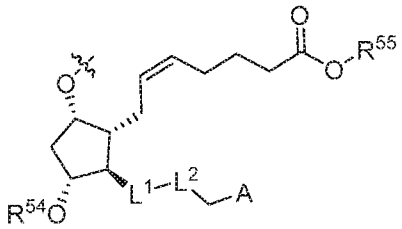
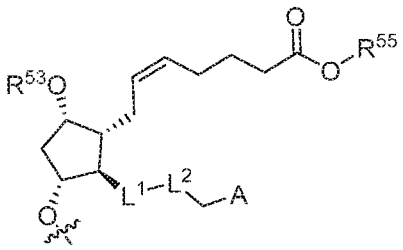
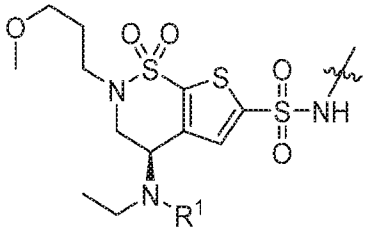
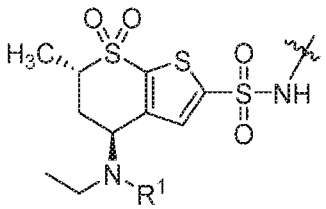
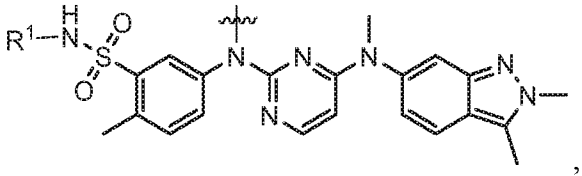
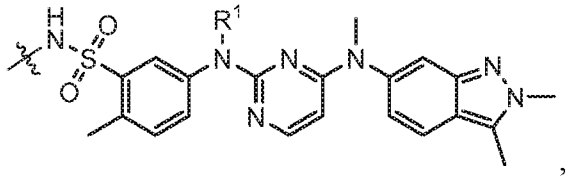
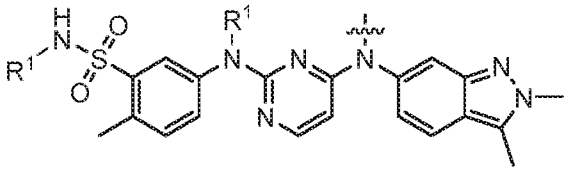
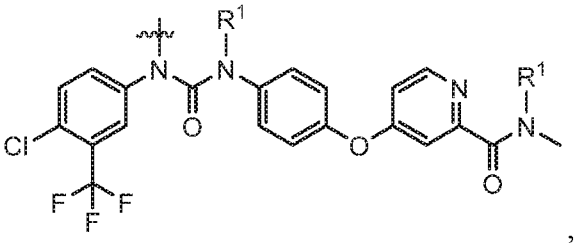
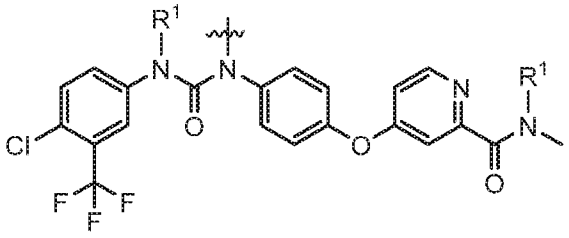
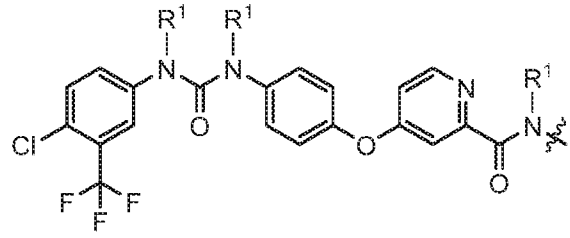


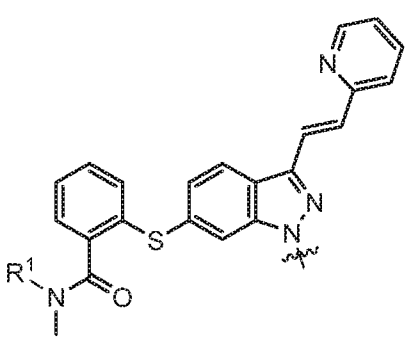
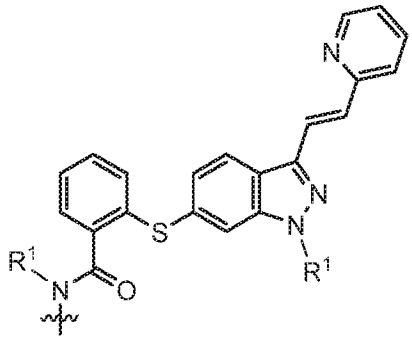
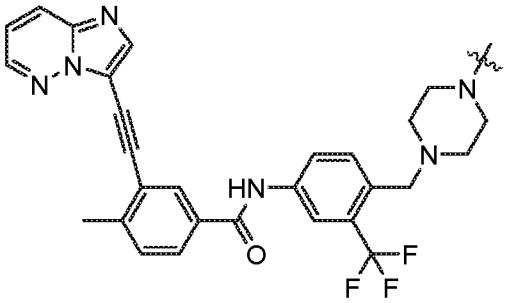
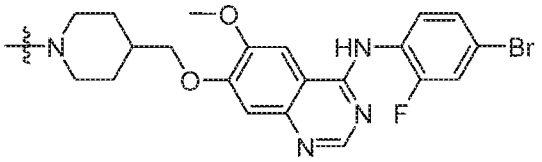
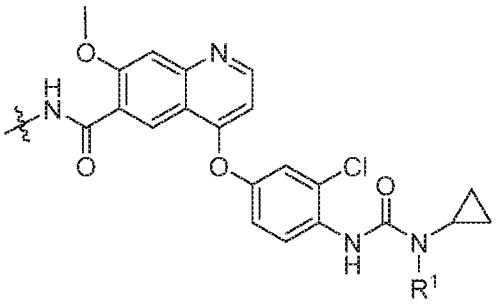
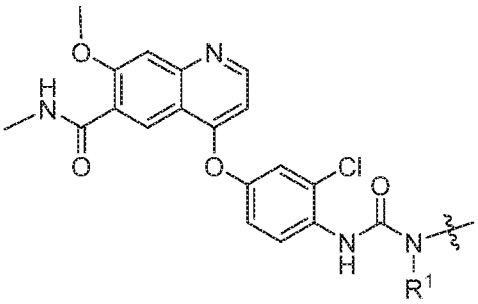
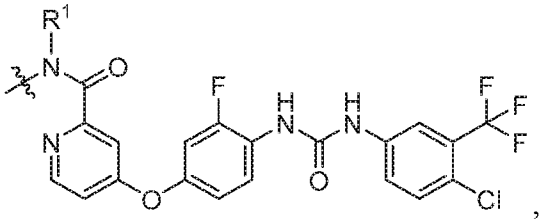
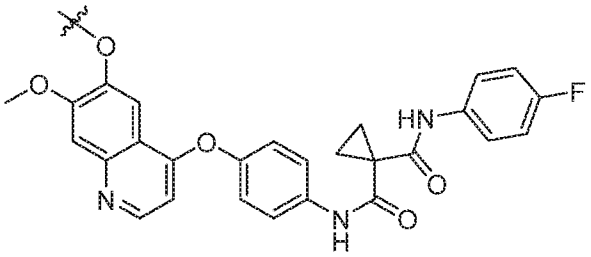
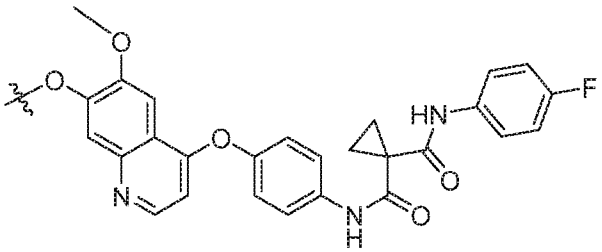
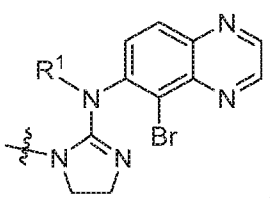
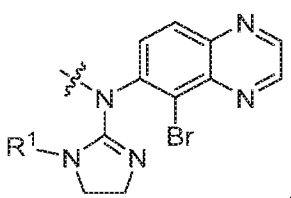
(LIV)

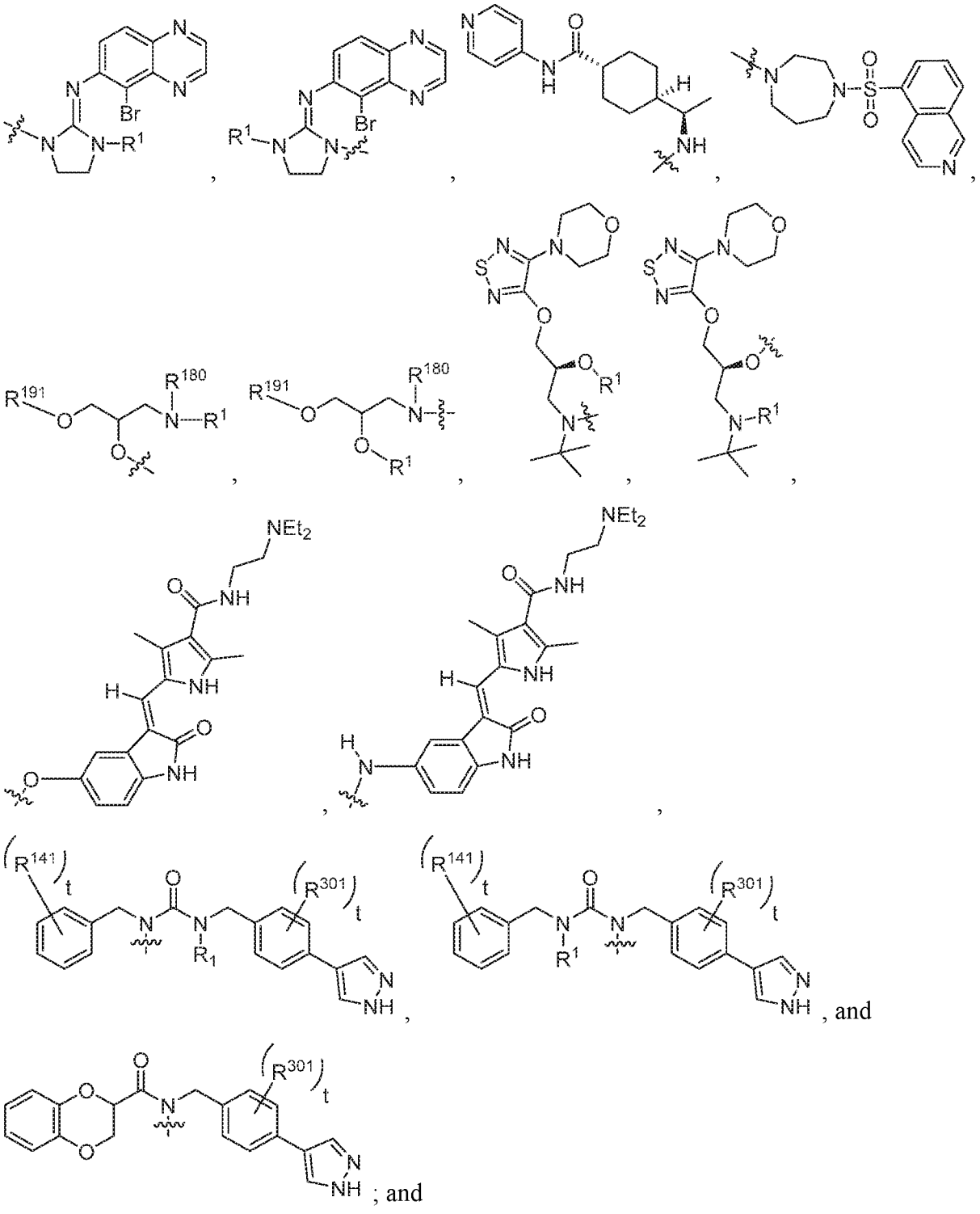
or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof

wherein

$R^{366}$ is selected from , , , , , , , , , , , , , , , , , , , , , , , , and ;

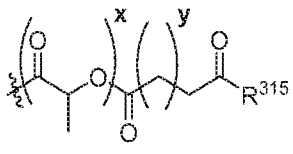
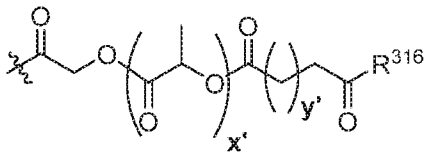
$R^{316}$ is selected from , , , , , , , , , , , , .

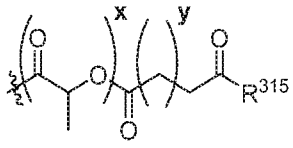
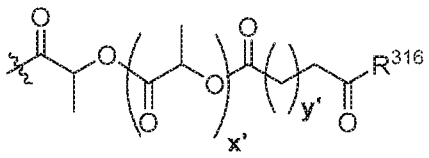

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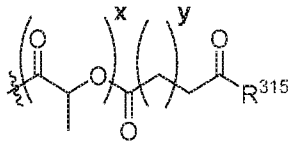


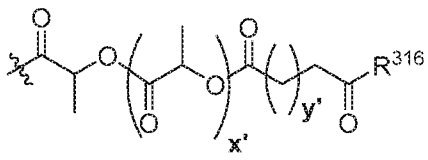
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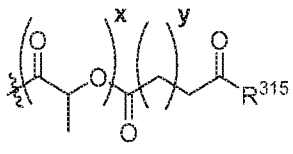
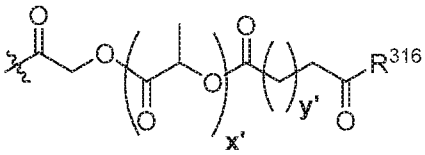
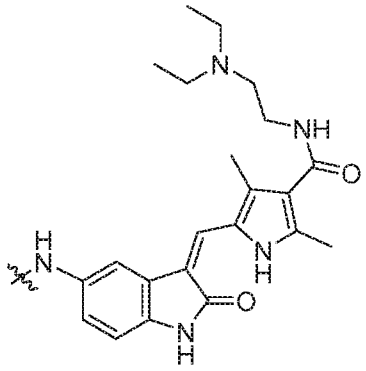
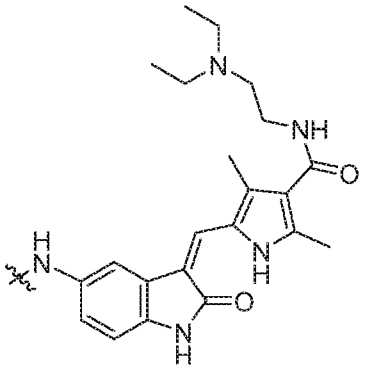
wherein all other variables are as defined herein.

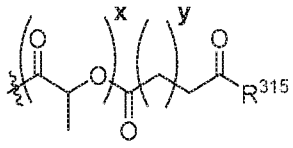
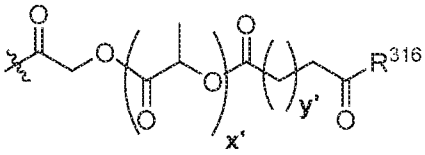
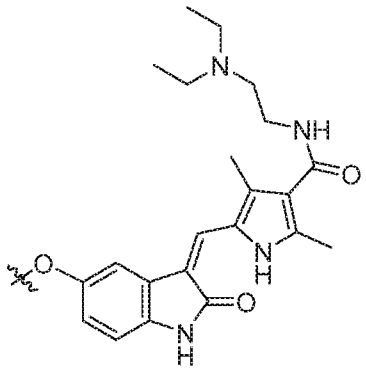
In one embodiment, $R^{360}$ is  and $R^{366}$ is .

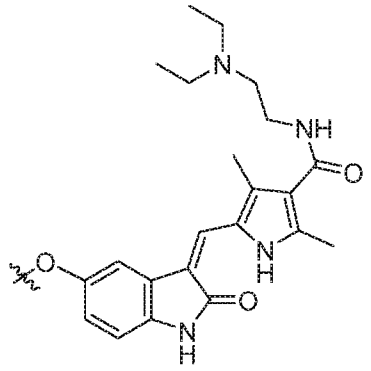
In one embodiment, $R^{360}$ is  and $R^{366}$ is .

In one embodiment, $R^{360}$ is , x is 1, 2, 3, or 4, and y is 1, 2, 3, or 4.

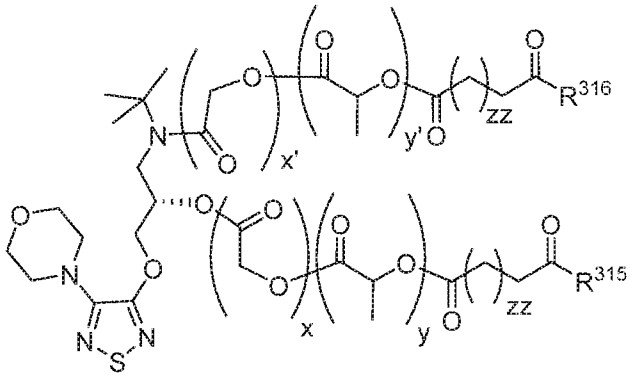
In one embodiment, $R^{366}$ is , and x' and y' are independently selected from an interger between 0 and 4.

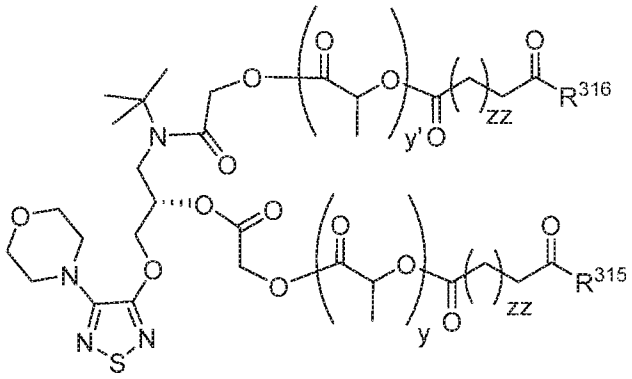
In one embodiment, $R^{360}$ is , $R^{366}$ , $R^{315}$ is , and $R^{316}$ is .

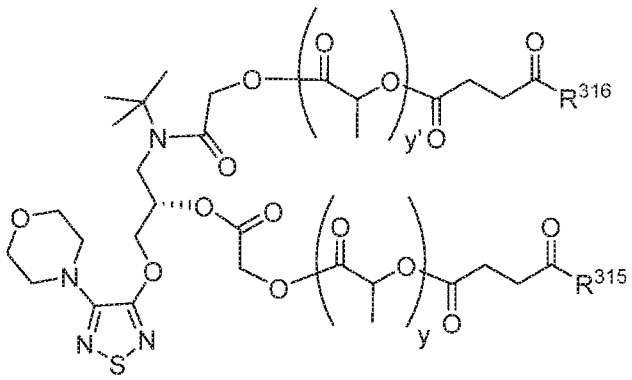
In one embodiment, $R^{360}$ is , $R^{366}$ is , $R^{315}$ is , and $R^{316}$ is



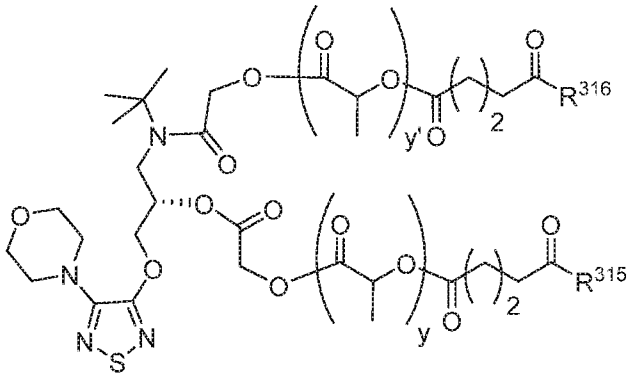
Non-limiting Examples of Compounds of Formula (LIV) include:

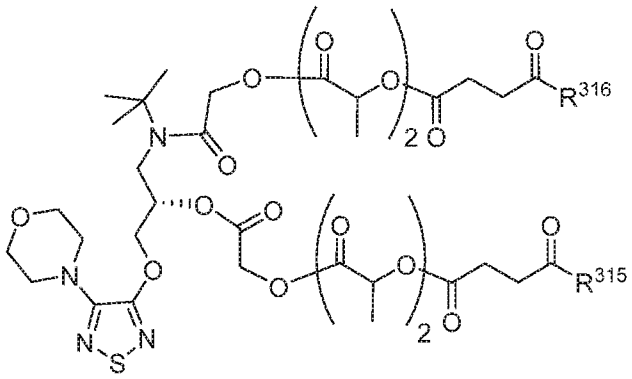


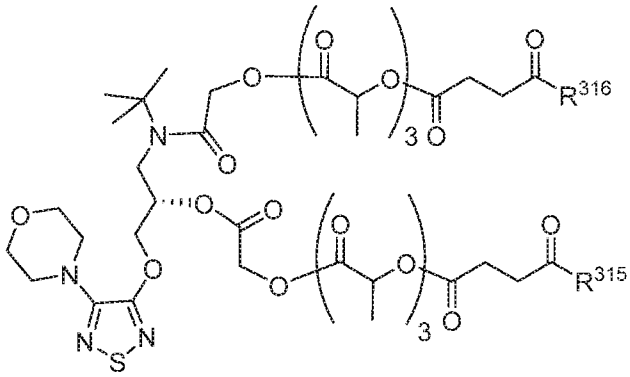


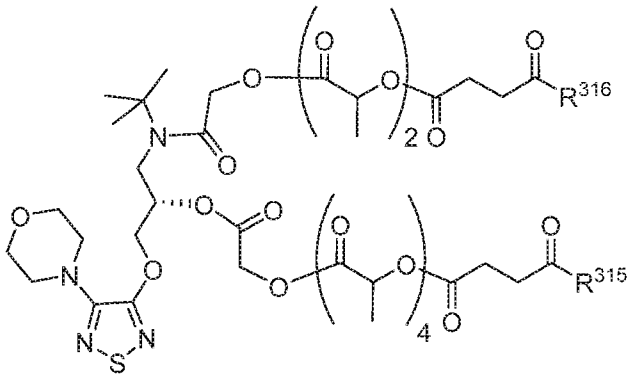


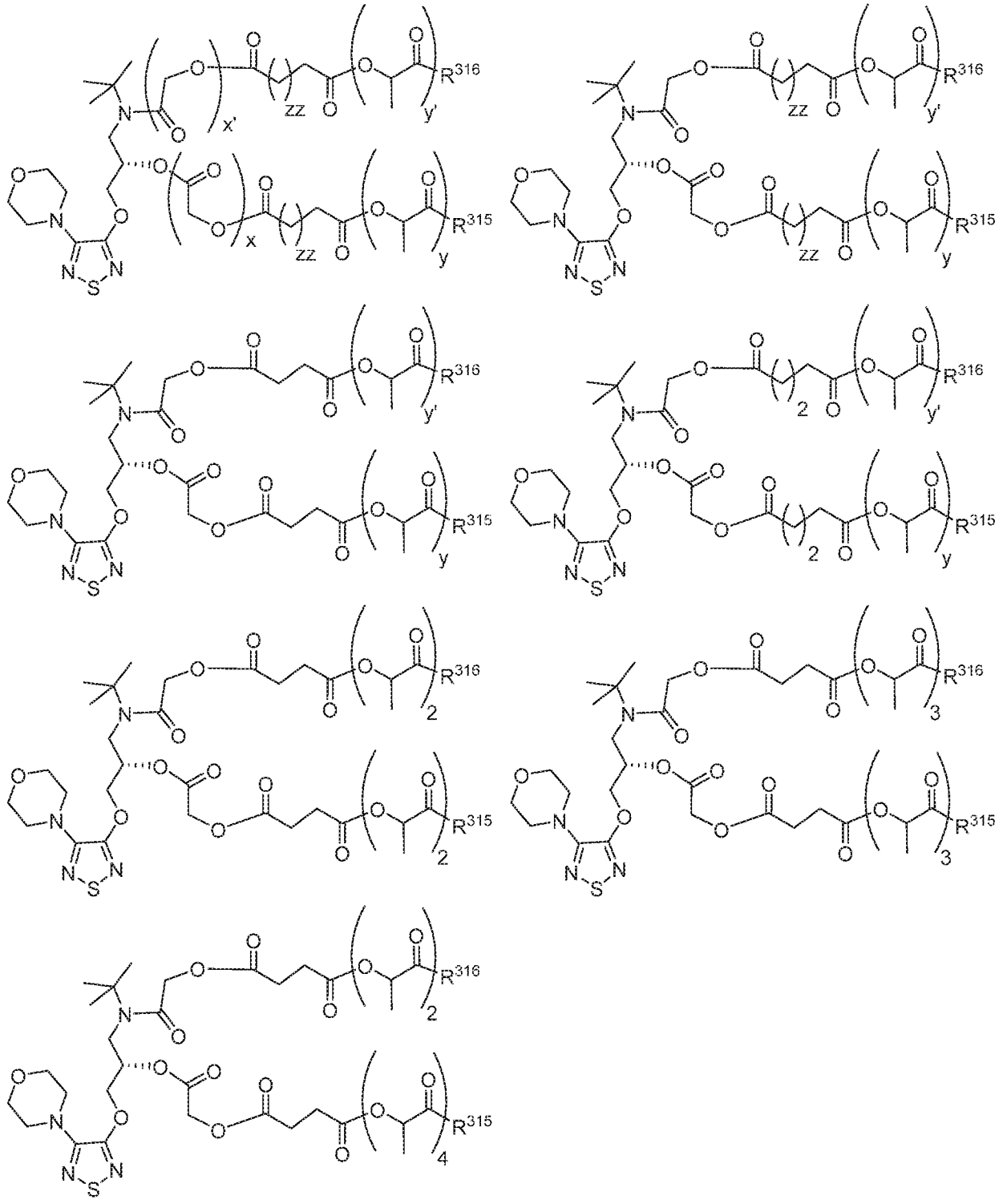
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In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, 3, 4, 5, or 6; y and y' are independently selected from 1, 2, 3, 4, 5, or 6; and zz in at least one instance is selected from 1, 2, or 3.

In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is selected from 1, 2, or 3.

In certain embodiments of Formula LIV, x and x' are independently selected selected from 1, 2, or 3; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is 1.

In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is 2.

In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is 3.

In certain embodiments of Formula LIV, x and x' are 1; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is selected from 1, 2, or 3.

In certain embodiments of Formula LIV, x and x' are 2; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is selected from 1, 2, or 3.

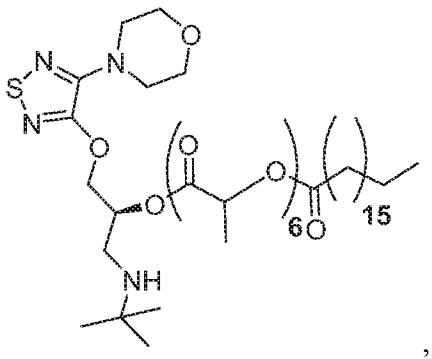
In certain embodiments of Formula LIV, x and x' are 3; y and y' are independently selected from 1, 2, or 3; and zz in at least one instance is selected from 1, 2, or 3.

In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are 1; and zz in at least one instance is selected from 1, 2, or 3.

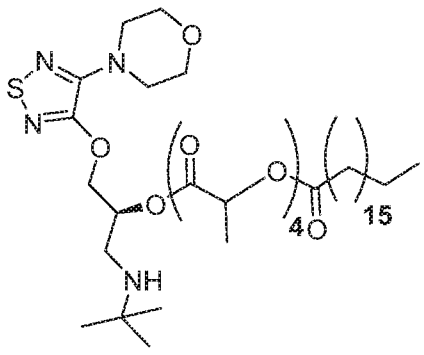
In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are 2; and zz in at least one instance is selected from 1, 2, or 3.

In certain embodiments of Formula LIV, x and x' are independently selected from 1, 2, or 3; y and y' are 3; and zz in at least one instance is selected from 1, 2, or 3.

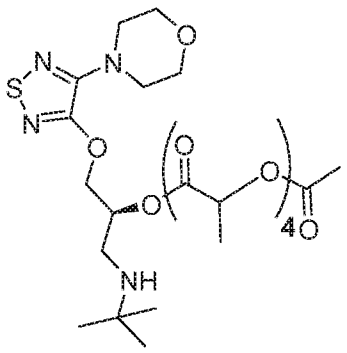
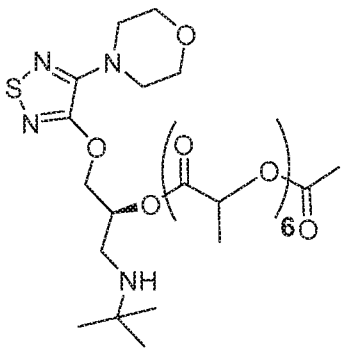
Additional compounds of the present invention include:



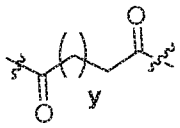
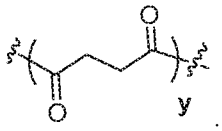

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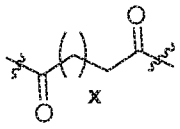
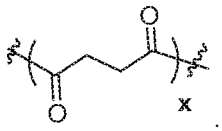



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and .

In one embodiment of any of the above formulas a  subunit is replaced with .

In one embodiment of any of the above formulas a  subunit is replaced with .

In an alternative embodiment, a  moiety in an R group that can be substituted with $R^5$ as defined herein is instead substituted with oxo to form .

Pharmaceutical compositions comprising a compound or salt of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI,

Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV together with a pharmaceutically acceptable carrier are also disclosed.

Methods of treating or preventing ocular disorders, including glaucoma, a disorder mediated by carbonic anhydrase, a disorder mediated by a Rho-associated kinase, a disorder mediated by a dual leucine zipper kinase, a disorder mediated by an α2 adrenergic receptor, a disorder mediated a disorder or abnormality related to an increase in intraocular pressure (IOP), a disorder mediated by nitric oxide synthase (NOS), a disorder requiring neuroprotection such as to regenerate/repair optic nerves, allergic conjunctivitis, anterior uveitis, cataracts, dry or wet age-related macular degeneration (AMD), geographic atrophy, or diabetic retinopathy are disclosed comprising administering a therapeutically effective amount of a compound or salt or Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV to a host, including a human, in need of such treatment.

In another embodiment, an effective amount of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI,

Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV is provided to decrease intraocular pressure (IOP) caused by glaucoma. In an alternative embodiment, the compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV be used to decrease intraocular pressure (IOP), regardless of whether it is associated with glaucoma.

In one embodiment, the disorder is associated with an increase in intraocular pressure (IOP) caused by potential or previously poor patient compliance to glaucoma treatment. In yet another embodiment, the disorder is associated with potential or poor neuroprotection through neuronal nitric oxide synthase (NOS). The active compound or its salt or prodrug provided herein may thus dampen or inhibit glaucoma in a host, by administration of an effective amount in a suitable manner to a host, typically a human, in need thereof.

Methods for the treatment of a disorder associated with glaucoma, increased intraocular pressure (IOP), and optic nerve damage caused by either high intraocular pressure (IOP) or neuronal nitric oxide synthase (NOS) are provided that includes the administration of an effective amount of a compound Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula

XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier are also disclosed.

Methods for the treatment of a disorder associated with age-related macular degeneration (AMD) and geographic atrophy are provided that includes the administration of an effective amount of a compound Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt thereof, optionally in a pharmaceutically acceptable carrier are also disclosed.

Methods for treatment of a disorder mediated by a carbonic anhydrase are provided to treat a patient in need thereof wherein a prodrug of a carbonic anhydrase inhibitor as described herein is provided.

Methods for treatment of a disorder mediated by a Rho-associated kinase are provided to treat a patient in need thereof wherein a prodrug of a Rho-associated kinase inhibitor as described herein is provided.

Methods for treatment of a disorder mediated by a beta-blocker are provided to treat a patient in need thereof wherein a prodrug of a beta blocker as described herein is provided.

Methods for treatment of a disorder mediated by a dual leucine zipper kinase are provided to treat a patient in need thereof wherein a prodrug of a dual leucine zipper kinase inhibitor as described herein is provided.

Methods for treatment of a disorder mediated by a $\alpha_2$ adrenergic are provided to treat a patient in need thereof also disclosed wherein a prodrug of a $\alpha_2$ adrenergic agonist as described herein is provided.

The present invention includes at least the following features:

(a) a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein, or a pharmaceutically acceptable salt or prodrug thereof (each of which and all subgenuses and species thereof are considered individually and specifically described);

(b) a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI,

Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein, or a pharmaceutically acceptable salt or prodrug thereof, for use in treating or preventing an ocular disorder as further described herein;

(c) a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein, or a pharmaceutically acceptable salt or prodrug thereof for use in treating or preventing disorders related to an ocular disorder such as glaucoma, a disorder mediated by carbonic anhydrase, a disorder or abnormality related to an increase in intraocular pressure (IOP), a disorder mediated by nitric oxide synthase (NOS), a disorder requiring neuroprotection such as to regenerate/repair optic nerves, allergic conjunctivitis, anterior uveitis, cataracts, dry or wet age-related macular degeneration (AMD), geographic atrophy or diabetic retinopathy;

(d) use of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII,

Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for use in treating or preventing glaucoma and disorders involving increased intraocular pressure (IOP) or nerve damage related to either IOP or nitric oxide synthase (NOS) and other disorders described further herein;

(e) use of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or prodrug thereof in the manufacture of a medicament for use in treating or preventing age-related macular degeneration (AMD) and other disorders described further herein;

(f) a process for manufacturing a medicament intended for the therapeutic use for treating or preventing glaucoma and disorders involving nerve damage related to both (IOP) and nitric oxide synthase (NOS) and other disorders described further herein characterized in that a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII,

Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein is used in the manufacture;

(g) a pharmaceutical formulation comprising an effective host-treating amount of the a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or prodrug thereof together with a pharmaceutically acceptable carrier or diluent;

(h) a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula

XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein in substantially pure form, (e.g., at least 90 or 95%);

(i) processes for the manufacture of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or a pharmaceutically acceptable salt or prodrug thereof; and

(j) processes for the preparation of therapeutic products including drug delivery agents that contain an effective amount a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula

XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV as described herein.

## BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph depicting the stability of Timolol-maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-maleate as a percentage of the total amount of Timolol-maleate.

FIG. 2 is a graph depicting the percentage of Timolol-acetyl PLA (n=1) maleate (**44-2**) that is degraded to parent Timolol maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded of Timolol-acetyl PLA (n=1) maleate (**44-2**) as a percentage of the total amount of Timolol-maleate.

FIG. 3 is a graph depicting the percentage of Timolol-stearyl PLA (n=1) maleate (**38-2**) that is degraded to parent Timolol maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-stearyl PLA (n=1) maleate (**38-2**) as a percentage of the total amount of Timolol-maleate.

FIG. 4 is a graph depicting the percentage of Timolol-stearyl PLA (n=1) HCl (**39-1**) that is degraded to parent Timolol maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-stearyl PLA (n=1) HCl (**39-1**) as a percentage of the total amount of Timolol-maleate.

FIG. 5 is a graph depicting the percentage of Timolol-acetyl PLA (n=4) maleate (**45-2**) that is degraded to parent Timolol maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-acetyl PLA (n=4) maleate (**45-2**) as a percentage of the total amount of Timolol-maleate.

FIG. 6 is a graph depicting the percentage of Timolol-stearyl PLA (n=4) maleate (**40-2**) that is degraded to parent Timolol maleate (**35-1**) over the course of 8 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-stearyl PLA (n=4) maleate (**40-2**) as a percentage of the total amount of Timolol-maleate.

FIG. 7 is a graph depicting the percentage of Timolol-O-Boc-N-acetate (**37-2**) that is degraded to parent Timolol maleate (**35-1**) over the course of 3.5 days as described in Example 8. The x-axis represents time measured in days and the y-axis represents the amount of undegraded Timolol-O-Boc-N-acetate (**37-2**) as a percentage of the total amount of Timolol-maleate.

FIG. 8 is a graph measuring the stability of Timolol-O-linoleic acid maleate (**70-1**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. Over the course of 4 days, the prodrug exhibited steady generation of the parent Timolol. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 9 is a graph measuring the stability of N-acyl-Timolol-PLA (n=2)-stearate (**65-1**) over 8 hours at 37 °C as described in Example 8. The concentration of **65-1** does not decreases as the prodrug is resistant to hydrolysis. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 10 is a graph measuring the stability of N-acyl-Timolol-PLA (n=2)-DHA (**102-1**) as the prodrug degrades to N-acyl-Timolol-PLA (n=1)-DHA and parent Timolol at 37 °C as described in Example 8. Over the course of 8 days, the prodrug exhibited steady generation of the intermediate N-acyl-Timolol-PLA (n=1)-DHA and slow hydrolysis to parent Timolol. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 11 is a graph measuring the stability of N-acyl-Timolol-PLA (n=2) (**48-1**) as the prodrug degrades to N-acyl-Timolol-PLA (n=1) (**47-1**) and parent Timolol at 37 °C as described in Example 8. Over the course of 8 days, the prodrug exhibited steady generation of the

intermediate (**47-1**) and slow hydrolysis to parent Timolol. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 12 is a graph measuring the stability of Timolol-bis-N-acetyl-PLA(n=2) (**118-1**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 13 is a graph measuring the stability of Timolol-bis-N-acetyl-PLA(n=4) (**119-6**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 14 is a graph measuring the stability of of Timolol-bis-N-acetyl-PLA(n=4)-O-ethyl succinate (**120-1**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 15 is a graph measuring the stability of of Timolol-bis-N-acetyl-PLA(n=2)-O-ethyl-succinate (**117-6**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 16 is a graph measuring the stability of of Timolol-bis-N-acetyl-PLA(n=4)-O-acetyl PLA(n=2) (**229**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 17 is a graph measuring the stability of of Timolol-bis-N-acetyl-PLA(n=2)-O-acetyl PLA(n=4) (**230**) as the prodrug degrades to parent Timolol at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 18A is a graph measuring the stability of dorzolamide-stearyl PLA (n=8) as the prodrug degrades to dorzolamide-PLA (n=4), dorzolamide-PLA (n=2), and dorzolamide-PLA (n=1) at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 18B is a graph measuring the stability of dorzolamide-stearyl PLA (n=12) (**13-2**) as the prodrug degrades to dorzolamide-PLA (n=4), dorzolamide-PLA (n=2), and dorzolamide-PLA

(n=1) at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 18C is a graph measuring the stability of dorzolamide-stearyl PLA (n=14) (**14-2**) as the prodrug degrades to dorzolamide-PLA (n=4), dorzolamide-PLA (n=2), and dorzolamide-PLA (n=1) at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 19A is a graph measuring the stability of dorzolamide-Acetyl PLA (n=10) as the prodrug degrades to dorzolamide-PLA (n=2), dorzolamide-PLA (n=1), and parent dorzolamide at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 19B is a graph measuring the stability of dorzolamide-acetyl PLA (n=12) as the prodrug degrades to dorzolamide-PLA (n=4), dorzolamide-PLA (n=2), dorzolamide-PLA (n=1), and parent dorzolamide at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 20 is a graph measuring the stability of dorzolamide-acetyl PLA (n=14) as the prodrug degrades to dorzolamide-PLA (n=4), dorzolamide-PLA (n=2), dorzolamide-PLA (n=1), and parent dorzolamide at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 21 is a graph measuring the stability of Brimonidine-acetyl PLA(n=4) (**27-2**) as the prodrug degrades to Brimonidine-PLA (n=2) and parent Brimonidine at 37 °C as described in Example 8. The x-axis is the time measured in hours and the y-axis is intensity measured as area under the curve (AUC).

FIG. 22 is a graph measuring the stability of Brimonidine-acetyl PLA(n=8) (**109-1**) as the prodrug degrades to parent Brimonidine at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 23 is a graph measuring the stability of Brimonidine-bis-acetyl PLA(n=2) (**111-4**) as the prodrug degrades to parent Brimonidine at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 24 is a graph measuring the stability of Brimonidine-acetyl PLA(n=2)-N-Acetate (**114-4**) as the prodrug degrades to parent Brimonidine at 37 °C as described in Example 8. The x-

axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 25 is a graph measuring the stability of Brimonidine-acetyl PLA(n=4)-N-Acetate (**115-1**) as the prodrug degrades to parent Brimonidine at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 26 is a graph measuring the stability of Brimonidine-bis-acetyl PLA(n=4) (**116-1**) as the prodrug degrades to parent Brimonidine at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 27 is a graph measuring the stability of SR5834-acetyl PLA(n=4) (**88-3**) as the prodrug degrades to parent SR5834 at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 28 is a graph measuring the stability of SR5834-bis-acetyl PLA(n=4) (**113-1**) as the prodrug degrades to parent SR5834 at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 29 is a graph measuring the stability of RKI-H-1y-acetyl PLA(n=4) (**90-3**) as the prodrug degrades to parent RKI-H-1y at 37 °C as described in Example 8. The x-axis is the time measured in days and the y-axis is intensity measured as area under the curve (AUC).

FIG. 30A is a graph measuring the stability of Timolol-Dorzolamide prodrug (**58-2**) over 5 hours at 37 °C as described in Example 8. The concentration of **58-2** decreases as the prodrug cleaves to afford free Timolol and Dorzolamide linked with 1-3 PLA moieties (Dorzolamide Prodrug). The x-axis is the time measured in hours and the y-axis is intensity measured as area under the curve (AUC).

FIG. 30B is a graph measuring the stability of Timolol-Dorzolamide prodrug (**64-4**) over 25 hours at 37 °C as described in Example 8. The concentration of **64-4** decreases as the prodrug cleaves to afford free Timolol and Dorzolamide linked with 1-3 PLA moieties (Dorzolamide Prodrug 1 and Dorzolamide Prodrug 2). Prodrug **64-4** cleaves to afford the active moieties in less

than 5 hours. The x-axis is the time measured in hours and the y-axis is intensity measured as area under the curve (AUC).

FIG. 31A is a light microscopy image at 40X magnification of particles encapsulating Brinzolamide-acetyl PLA (n=5) (**18-3**) as described in Example 9. Particles were found to be spherical in nature.

FIG. 31B is a light microscopy image at 40X magnification of particles encapsulating Dorzolamide-acetyl PLA (n=5) as described in Example 9. Particles were found to be spherical in nature.

FIG. 31C is a light microscopy image at 40X magnification of particles encapsulating Latanoprost-acetyl PLA (n=5) as described in Example 9. Particles were found to be spherical in nature.

FIG. 31D is a light microscopy image at 40X magnification of particles encapsulating Timolol-acetyl PLA (n=5) (**45-2**) as described in Example 9. Particles were found to be spherical in nature.

FIG. 32 is a graph depicting the drug release kinetics of Brinzolamide-acetyl PLA (n=5) from particles prepared with a polymer concentration of 140 mg/mL and 200 mg/mL over the course of 100 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 33 is a graph comparing the drug release kinetics of Brinzolamide-acetyl PLA (n=5) (**18-3**), Dorzolamide-acetyl PLA (n=5), and Latanoprost-acetyl PLA (n=5) over the course of 100 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 34 is a graph comparing the drug release kinetics of Brinzolamide PLA (n=4) and Dorzolamide PLA (n=4) over the course of 60 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 35 is a graph comparing the drug release kinetics of Timolol stearyl PLA (n=4) maleate (**40-2**), Timolol stearyl PLA (n=4) HCl (**41-2**), and Timolol acetyl PLA (n=4) (**45-2**) over the course of 25 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 36 is a graph comparing the drug release kinetics of Dorzolamide-PLA(n=10), Dorzolamide-PLA (n=12), and Dorzolamide-PLA (n=14) encapsulated in PLGA7525 4A particles over the course of 100 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 37 is a graph comparing the drug release kinetics of Dorzolamide-PLA(n=10), Dorzolamide-PLA (n=12), and Dorzolamide-PLA (n=14) encapsulated in PLA 4.5A/PLGA8515 5A particles over the course of 100 days as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 38 is a graph comparing the drug release kinetics of Timolol-stearyl PLA (n=4) maleate (**40-2**), Timolol-stearyl PLA (n=4) HCl (**41-2**), and Timolol-acetyl PLA (n=4) maleate (**45-2**) as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 39 is a graph comparing the drug release kinetics of bis-Timolol prodrugs Timolol-succinic acid-Timolol-maleate (**76-4**), Timolol-glutaric acid-Timolol-maleate (**77-1**), and Timolol-fumurate-Timolol-maleate (**78-1**) to mono-Timolol prodrugs Timolol-O-laurylfumurate-maleate and Timolol-O-stearylfumurate-maleate as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 40 is a graph comparing the drug release kinetics of Timolol-bis-Acetyl PLA(n=4) (**119-6**) from particles generated from different blends of PLA and PLGA polymers as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 41 is a graph comparing the drug release kinetics of Timolol-Bis-N-Acetyl-PLA (n=4)-O-Acetyl PLA (n=2) (**229**) from particles with varying polymer blends as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 42 is a graph comparing the drug release kinetics of Timolol-Bis-N-Acetyl-PLA (n=2)-O-Acetyl PLA (n=4) (**230**) from particles with varying polymer blends as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 43 is a graph of the drug release kinetics of Brimonidine-PLA(n=4)-N-acetate (**115-1**) from particles with 15, 20 and 30% theoretical drug loading as described in Example 9. The x-

axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 44 is a graph of the drug release kinetics of SR5834 from particles of different polymer blends as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 45 is a graph comparing the drug release kinetics of SR5834 and SR5834-Acetyl PLA(n=4) (**88-3**) from PLGA7525 4A microparticles as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 46 is a graph of the drug release kinetics of native RKI-H-1y from particles of different polymer blends as described in Example 9. The x-axis represents time measured in days and the y-axis represents cumulative drug release measured in percent.

FIG. 47 is a graph comparing the actual drug-loading and the target drug-loading of Timolol-Dorzolamide prodrug **58-2** as described in Example 8. As the target drug-loading increases from 15% to 30%, the actual drug-loading initially increases and then begins to decline. The x-axis is target drug-loading measured in percent and the y-axis is actual drug-loading measured in percent.

FIG. 48 is an image of microspheres with a target drug-loading of 30% Timolol-Dorzolamide prodrug **58-2**. As described in Example 8, as the target drug-loading exceeds 20%, the drug tends to disrupt the physical integrity of the polymer matrix.

FIGS. 49A and 49B are graphs comparing the percent release of free Timolol (FIG. 16A) and Dorzolamide linked with PLA moieties (FIG. 16B) that is released from microparticles encapsulating Timolol-Dorzolamide prodrug **58-2**. Prodrug **58-2** was encapsulated in microparticles with fast degrading polymer matrices (PLGA 5050 4A) and slow-degrading polymer matrices (PLA 4A and PLFA 7525 8E) as described in Example 8. The x-axis is time measured in days and the y-axis is accumulative release measured in percent.

FIG. 50 is a graph of measuring the percent release of free Timolol and Dorzolamide linked with PLA moieties that is released from microparticles encapsulating Timolol-Dorzolamide

prodrug **58-2** at a target drug-loading of 15%. As described in Example 8, a lag period of about 10 days was observed.

FIG. 51 is a graph of measuring the percent release of free Timolol and Dorzolamide linked with PLA moieties that is released from microparticles encapsulating Timolol-Dorzolamide prodrug **58-2** at a target drug-loading of 20%. As described in Example 8, no lag period in release was observed.

FIG. 52A is an image of microsphere encapsulating Timolol-Dorzolamide prodrug **58-2** at a target drug-loading of 20% as described in Example 8. Small pores were observed at the microsphere surface.

FIG. 52B is an image of microspheres encapsulating Timolol-Dorzolamide prodrug **58-2** at a target drug-loading of 15% as described in Example 8. Microspheres have smooth surface with minimal pores at the surface.

FIG. 53 is the synthesis of compound **76-4**, a bis-prodrug of the beta-blocker Timolol.

FIG. 54 is the synthesis of 1-ethoxy-1-oxopropan-2-yl 2-((2-((2-hydroxypropanoyl)oxy)propanoyl)oxy)propanoate (**F25-7**). In the first reaction (**I**), 1-ethoxy-1-oxopropan-2-yl 2-hydroxypropanoate (F25-2) is generated and in the second reaction (**II**), 2-((2-((tert-butyldiphenylsilyl)oxy)propanoyl)oxy)propanoic acid is generated (**F25-5**). Finally, **F25-2** and **F25-5** are combined in the third reaction (**III**) to afford **F25-7**, a PLA derivative used in the synthesis of mono- and bis-prodrugs. **F25-1** was converted to **F25-2** on a 32 g scale and formation of compound **F25-2** was confirmed by LC-MS. Compound **F25-2** was isolated on a 49.5 g scale(Crude). **F25-2** to was converted to **F25-3** on a 49.5 g scale and the formation of compound **F25-3** was confirmed by NMR and LC-MS. Compound **F25-3** on a 29.5 g scale. F25-4 was converted to **F25-5** on a 12.5 g scale and formation of compound **F25-5** was confirmed by NMR and LC-MS. Compound **F25-5** was isolated on a 27.5 g scale. Compound **F25-5** was converted to **F25-6** on a 27.5 g scale and formation of **F25-6** was confirmed by NMR and LC-MS. Compound **F25-6** was isolated on a 10.5 g scale.

FIG. 55 is the synthesis of the ROCK inhibitor SR5834. SR5832 is synthesized by first generating (1-(tert-butoxycarbonyl)-1H-pyrazol-4-yl)boronic acid as an intermediate.

FIG. 56 is the synthesis of PLA derivative, 2,5,8,11-tetramethyl-4,7,10,13-tetraoxo-3,6,9,12-tetraoxatetradecanoic acid (**F27-6**). Compound **F27-1** was converted to **F27-2** on a 35 g scale and formation of compound **F27-2** was confirmed by NMR and LC-MS. Compound **F27-2**

was isolated on a 39 g scale. Compound **F27-2** was converted to **F27-3** on a 39 g scale and formation of compound **F27-3** was confirmed by NMR and MS. Compound **F27-3** was isolated on a 21.5 g scale. Compound **F27-4** was converted to **F27-5** on a 21.5 g scale and formation of compound **F27-5** was confirmed by NMR and LC-MS. Compound **F27-5** was isolated on a 26 g scale. Compound **F27-5** was converted to **F27-6** on a 26 g scale and formation of compound F27-6 was confirmed by NMR and MS. Compound **F27-6** was isolated on a 19.5 g scale.

FIG. 57 is the synthesis of ROCK inhibitor RKI-H-1y.

FIG. 58 is the synthesis of ROCK inhibitor compound **90-1** via a coupling reaction of the PLA derivative **F27-6** and ROCK inhibitor RKI-H-1y. Compound **91-1** is synthesized in a similar manner.

FIG. 59 is the synthesis of compound **101-3**, a bis-prodrug of a ROCK inhibitor and Brimonidine.

FIG. 60 is the synthesis of compound **108-1**, a Sunitinib derivative.

FIG. 61 is the synthesis of compound compound **F32-6**, a Brimonidine mono-prodrug. Compound **F32-1** was converted to **F32-2** on a 14.0 g scale. Formation of compound **F32-2** was confirmed by NMR and LC-MS and compound **F32-2** was isolated on a 4.8 g scale. Compound **F32-2** was converted to **F32-4** on a 4.8 g scale. Formation of compound **F32-4** was confirmed by NMR and LC-MS and compound **F32-4** was isolated on a 8.2 g scale. Compound **F32-4** was converted to **F32-5** on a 8.2 g scale. Formation of compound **F32-5** was confirmed by NMR and LC-MS and compound **F32-6** was isolated on a 5.7 g scale.

FIG. 62 is the synthesis of compound **110-1**, a Brimonidine derivative.

FIG. 63 is the synthesis of compound **117-6**, a Timolol mono-prodrug.

FIG. 64 is the synthesis of compound **118-1**, a Timolol mono-prodrug. Compound **119-6** is synthesized in a similar manner.

FIG. 65 is the synthesis of compound **120-1**, a Timolol mono-prodrug.

## DETAILED DESCRIPTION

### I. TERMINOLOGY

The presently disclosed subject matter may be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Indeed, many modifications and other embodiments of the presently disclosed subject matter will come to mind for one skilled

in the art to which the presently disclosed subject matter pertains having the benefit of the teachings presented in the descriptions included herein. Therefore, it is to be understood that the presently disclosed subject matter is not to be limited to the specific embodiments disclosed and that modifications and other embodiments are intended to be included within the scope of the disclosed subject matter.

Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

Compounds are described using standard nomenclature. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

The compounds in any of the Formulas described herein include enantiomers, mixtures of enantiomers, diastereomers, cis/trans isomers, tautomers, racemates and other isomers, such as rotamers, as if each is specifically described.

The compounds in any of the Formulas may be prepared by chiral or asymmetric synthesis from a suitable optically pure precursor or obtained from a racemate or mixture of enantiomers or diastereomers by any conventional technique, for example, by chromatographic resolution using a chiral column, TLC or by the preparation of diastereoisomers, separation thereof and regeneration of the desired enantiomer or diastereomer. *See*, *e.g.*, "Enantiomers, Racemates and Resolutions," by J. Jacques, A. Collet, and S.H. Wilen, (Wiley-Interscience, New York, 1981); S.H. Wilen, A. Collet, and J. Jacques, *Tetrahedron*, 2725 (1977); E.L. Eliel *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and S.H. Wilen *Tables of Resolving Agents and Optical Resolutions* 268 (E.L. Eliel ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972, *Stereochemistry of Organic Compounds*, Ernest L. Eliel, Samuel H. Wilen and Lewis N. Manda (1994 John Wiley & Sons, Inc.), and *Stereoselective Synthesis A Practical Approach*, Mihály Nógrádi (1995 VCH Publishers, Inc., NY, NY).

The terms “a” and “an” do not denote a limitation of quantity, but rather denote the presence of at least one of the referenced item. Recitation of ranges of values are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the

specification as if it were individually recited herein. The endpoints of all ranges are included within the range and are independently combinable. All methods described herein can be performed in a suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of examples, or exemplary language (e.g., "such as"), is intended merely to better illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed.

The present invention includes compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV and the use of compounds with at least one desired isotopic substitution of an atom, at an amount above the natural abundance of the isotope, i.e., enriched. Isotopes are atoms having the same atomic number but different mass numbers, i.e., the same number of protons but a different number of neutrons.

Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine, and chlorine, such as $^{2}H$, $^{3}H$, $^{11}C$, $^{13}C$, $^{14}C$, $^{15}N$, $^{18}F$ $^{31}P$, $^{32}P$, $^{35}S$, $^{36}CI$, $^{125}I$ respectively. The invention includes isotopically modified compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula

XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

By way of general example and without limitation, isotopes of hydrogen, for example, deuterium ($^2H$) and tritium ($^3H$) may be used anywhere in described structures that achieves the desired result. Alternatively or in addition, isotopes of carbon, e.g., $^{13}C$ and $^{14}C$, may be used. In one embodiment, the isotopic substitution is deuterium for hydrogen at one or more locations on the molecule to improve the performance of the drug, for example, the pharmacodynamics, pharmacokinetics, biodistribution, half-life, stability, AUC, $T_{max}$, $C_{max}$, etc. For example, the deuterium can be bound to carbon in a location of bond breakage during metabolism (an α-deuterium kinetic isotope effect) or next to or near the site of bond breakage (a β-deuterium kinetic isotope effect).

Isotopic substitutions, for example deuterium substitutions, can be partial or complete. Partial deuterium substitution means that at least one hydrogen is substituted with deuterium. In certain embodiments, the isotope is 90, 95 or 99% or more enriched at any location of interest. In one embodiment deuterium is 90, 95 or 99% enriched at a desired location.

In one embodiment, the substitution of a hydrogen atom for a deuterium atom can be provided in any of A, $L^1$, or $L^2$. In one embodiment, the substitution of a hydrogen atom for a deuterium atom occurs within an R group selected from any of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^7$, $R^8$, $R^{11}$, $R^{16}$, $R^{17}$, $R^{23}$, $R^{24}$, $R^{25}$, $R^{26}$, $R^{31}$, $R^{32}$, $R^{34}$, $R^{35}$ $R^{36}$ $R^{37}$ $R^{38}$ $R^{39}$ $R^{40}$, $R^{41}$, $R^{50}$, $R^{100}$, $R^{101}$, $R^{102}$ $R^{103}$ $R^{104}$, $R^{105}$, $R^{106}$, $R^{107}$, $R^{108}$, $R^{110}$, $R^{114}$, $R^{116}$, $R^{117}$, $R^{118}$, $R^{119}$, $R^{120}$, $R^{121}$, $R^{123}$, $R^{124}$, $R^{130}$, $R^{131}$, $R^{132}$, $R^{133}$, $R^{134}$, $R^{135}$, $R^{136}$, $R^{137}$, $R^{138}$, $R^{139}$, $R^{140}$, $R^{141}$, $R^{142}$, $R^{143}$, $R^{150}$, $R^{151}$, $R^{152}$, $R^{153}$, $R^{156}$, $R^{160}$, $R^{170}$, $R^{171}$, $R^{172}$, $R^{173}$, $R^{174}$, $R^{175}$, $R^{176}$, $R^{177}$, $R^{178}$, $R^{182}$, $R^{183}$, $R^{192}$, $R^{193}$, $R^{194}$, $R^{208}$, $R^{209}$, $R^{210}$, $R^{211}$, $R^{212}$, $R^{301}$, $R^{302}$, $R^{303}$, $R^{304}$, $R^{334}$, $R^{335}$, $R^{336}$, and $R^{356}$. For example, when any of R groups are, or contain for example through substitution, methyl, ethyl, or methoxy, the alkyl residue may be deuterated (in non-limiting embodiments, $CD_3$, $CH_2CD_3$, $CD_2CD_3$, $CDH_2$, $CD_2H$, $CD_3$, $CHDCH_2D$, $CH_2CD_3$, $CHDCHD_2$, $OCDH_2$, $OCD_2H$, or $OCD_3$ etc.

The compound of the present invention may form a solvate with a solvent (including water). Therefore, in one embodiment, the invention includes a solvated form of the active compound. The term "solvate" refers to a molecular complex of a compound of the present invention (including salts thereof) with one or more solvent molecules. Examples of solvents are water, ethanol, dimethyl sulfoxide, acetone and other common organic solvents. The term "hydrate" refers to a molecular complex comprising a compound of the invention and water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent may be isotopically substituted, *e.g.* $D_2O$, $d_6$-acetone, $d_6$-DMSO. A solvate can be in a liquid or solid form.

A dash ("-") is defined by context and can in addition to its literary meaning indicate a point of attachment for a substituent. For example, -(C=O)$NH_2$ is attached through carbon of the keto (C=O) group. A dash ("-") can also indicate a bond within a chemical structure. For example -C(O)-$NH_2$ is attached through carbon of the keto group which is bound to an amino group ($NH_2$).

An equal sign ("=") is defined by context and can in addition to its literary meaning indicate a point of attachment for a substituent wherein the attachment is through a double bond. For example, =$CH_2$ represents a fragment that is doubly bonded to the parent structure and consists of one carbon with two hydrogens bonded in a terminal fashion. =$CHCH_3$ on the other hand represents a fragment that is doubly bonded to the parent structure and consists of two carbons. In the above example it should be noted that the stereoisomer is not delineated and that both the cis and trans isomer are independently represented by the group.

The term “substituted”, as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a moiety selected from the indicated group, provided that the designated atom's normal valence is not exceeded. For example, when the substituent is oxo (i.e., =O), then in one embodiment, two hydrogens on the atom are replaced. When an oxo group replaces two hydrogens in an aromatic moiety, the corresponding partially unsaturated ring replaces the aromatic ring. For example a pyridyl group substituted by oxo is a pyridone. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates.

A stable compound or stable structure refers to a compound with a long enough residence time to either be used as a synthetic intermediate or as a therapeutic agent, as relevant in context.

"Alkyl" is a straight chain saturated aliphatic hydrocarbon group. In certain embodiments, the alkyl is $C_1$-$C_2$, $C_1$-$C_3$, $C_1$-$C_6$, or $C_1$-$C_{30}$ (i.e., the alkyl chain can be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 carbons in length). The specified ranges as used herein indicate an alkyl group with length of each member of the range described as an independent species. For example, the term $C_1$-$C_6$ alkyl as used herein indicates a straight alkyl group having from 1, 2, 3, 4, 5, or 6 carbon atoms and is intended to mean that each of these is described as an independent species. For example, the term $C_1$-$C_4$alkyl as used herein indicates a straight or branched alkyl group having from 1, 2, 3, or 4 carbon atoms and is intended to mean that each of these is described as an independent species. When $C_0$-$C_n$ alkyl is used herein in conjunction with another group, for example, ($C_3$-$C_7$cycloalkyl)$C_0$-$C_4$ alkyl, or –$C_0$-$C_4$alkyl($C_3$-$C_7$cycloalkyl), the indicated group, in this case cycloalkyl, is either directly bound by a single covalent bond ($C_0$alkyl), or attached by an alkyl chain in this case 1, 2, 3, or 4 carbon atoms. Alkyls can also be attached via other groups such as heteroatoms as in –O-$C_0$-$C_4$alkyl($C_3$-$C_7$cycloalkyl). Alkyls can be further substituted with alkyl to make branched alkyls. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, *tert*-pentyl, neopentyl, n-hexyl, 2-methylpentane, 3-methylpentane, 2,2-dimethylbutane and 2,3-dimethylbutane. In one embodiment, the alkyl group is optionally substituted as described above.

"Alkenyl" is a straight chain aliphatic hydrocarbon group having one or more carbon-carbon double bonds each of which is independently either cis or trans that may occur at a stable point along the chain. In one embodiment, the double bond in a long chain similar to a fatty acid has the stereochemistry as commonly found in nature. Non-limiting examples are $C_2$-$C_{30}$alkenyl, $C_{10}$-$C_{30}$alkenyl (i.e., having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 carbons), and $C_2$-$C_4$alkenyl. The specified ranges as used herein indicate an alkenyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Examples of alkenyl include, but are not limited to, ethenyl and propenyl. Alkenyls can be further substituted with alkyl to make branched alkenyls. In one embodiment, the alkenyl group is optionally substituted as described above.

"Alkynyl" is a straight chain aliphatic hydrocarbon group having one or more carbon-carbon triple bonds that may occur at any stable point along the chain, for example, $C_2$-$C_8$alkynyl or $C_{10}$-$C_{30}$alkynyl (i.e., having 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21,

22, 23, 24, 25, 26, 27, 28, 29, or 30 carbons). The specified ranges as used herein indicate an alkynyl group having each member of the range described as an independent species, as described above for the alkyl moiety. Alkynyls can be further substituted with alkyl to make branched alkynyls. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl. In one embodiment, the alkynyl group is optionally substituted as described above.

"Alkylene" is a bivalent saturated hydrocarbon. Alkylenes, for example, can be a 1 to 8 carbon moiety, 1 to 6 carbon moiety, or an indicated number of carbon atoms, for example $C_1$-$C_4$alkylene, $C_1$-$C_3$alkylene, or $C_1$-$C_2$alkylene.

"Alkenylene" is a bivalent hydrocarbon having at least one carbon-carbon double bond. Alkenylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example $C_2$-$C_4$alkenylene.

"Alkynylene" is a bivalent hydrocarbon having at least one carbon-carbon triple bond. Alkynylenes, for example, can be a 2 to 8 carbon moiety, 2 to 6 carbon moiety, or an indicated number of carbon atoms, for example $C_2$-$C_4$alkynylene.

"Alkenylalkynyl" in one embodiment is a bivalent hydrocarbon having at least one carbon-carbon double bond and at least one carbon-carbon triple bond. It will be recognized to one skilled in the art that the bivalent hydrocarbon will not result in hypervalency, for example, hydrocarbons that include -C=C≡C-C or -C≡C≡C-C, and must be stable. Alkenylalkynyls, for example, can be a 4 to 8 carbon moiety, 4 to 6 carbon moiety, or an indicated number of carbon atoms, for example $C_4$-$C_6$alkenylalkynyls.

"Alkoxy" is an alkyl group as defined above covalently bound through an oxygen bridge (-O-). Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, 2-butoxy, t-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, n-hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly an "alkylthio" or a "thioalkyl" group is an alkyl group as defined above with the indicated number of carbon atoms covalently bound through a sulfur bridge (-S-). In one embodiment, the alkoxy group is optionally substituted as described above.

"Alkenyloxy" is an alkenyl group as defined covalently bound to the group it substitutes by an oxygen bridge (-O-).

"Amide" or "carboxamide" is $-C(O)NR^aR^b$ wherein $R^a$ and $R^b$ are each independently selected from hydrogen, alkyl, for example, $C_1$-$C_6$alkyl, alkenyl, for example, $C_2$-$C_6$alkenyl, alkynyl, for example, $C_2$-$C_6$alkynyl, $-C_0$-$C_4$alkyl($C_3$-$C_7$cycloalkyl), $-C_0$-$C_4$alkyl($C_3$-$C_7$heterocycloalkyl), $-C_0$-$C_4$alkyl(aryl), and $-C_0$-$C_4$alkyl(heteroaryl); or together with the nitrogen to which they are bonded, $R^a$ and $R^b$ can form a $C_3$-$C_7$heterocyclic ring. In one embodiment, the $R^a$ and $R^b$ groups are each independently optionally substituted as described above.

"Carbocyclic group", "carbocyclic ring", or "cycloalkyl" is a saturated or partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. A carbocyclic group typically contains 1 ring of 3 to 7 carbon atoms or 2 fused rings each containing 3 to 7 carbon atoms. Cycloalkyl substituents may be pendant from a substituted nitrogen or carbon atom, or a substituted carbon atom that may have two substituents can have a cycloalkyl group, which is attached as a spiro group. Examples of carbocyclic rings include cyclohexenyl, cyclohexyl, cyclopentenyl, cyclopentyl, cyclobutenyl, cyclobutyl and cyclopropyl rings. In one embodiment, the carbocyclic ring is optionally substituted as described above. In one embodiment, the cycloalkyl is a partially unsaturated (i.e., not aromatic) group containing all carbon ring atoms. In another embodiment, the cycloalkyl is a saturated group containing all carbon ring atoms. In another embodiment, a carbocyclic ring comprises a caged carbocyclic group. In one embodiment, a carbocyclic ring comprises a bridged carbocyclic group. An example of a caged carbocyclic group is adamantane. An example of a bridged carbocyclic group includes bicyclo[2.2.1]heptane (norbornane). In one embodiment, the caged carbocyclic group is optionally substituted as described above. In one embodiment, the bridged carbocyclic group is optionally substituted as described above.

"Hydroxyalkyl" is an alkyl group as previously described, substituted with at least one hydroxyl substituent.

"Halo" or "halogen" indicates independently any of fluoro, chloro, bromo, and iodo.

"Aryl" indicates aromatic groups containing only carbon in the aromatic ring or rings. In one embodiment, the aryl groups contain 1 to 3 separate or fused rings and is 6 to about 14 or 18 ring atoms, without heteroatoms as ring members. When indicated, such aryl groups may be further substituted with carbon or non-carbon atoms or groups. Such substitution may include fusion to a 4 to 7-membered saturated cyclic group that optionally contains 1 or 2 heteroatoms independently chosen from N, O, B, and S, to form, for example, a 3,4-methylenedioxyphenyl group. Aryl groups

include, for example, phenyl and naphthyl, including 1-naphthyl and 2-naphthyl. In one embodiment, aryl groups are pendant. An example of a pendant ring is a phenyl group substituted with a phenyl group. In one embodiment, the aryl group is optionally substituted as described above. In one embodiment, aryl groups include, for example, dihydroindole, dihydrobenzofuran, isoindoline-1-one and indolin-2-one that can be optionally substituted.

The term "heterocycle," or "heterocyclic ring" as used herein refers to a saturated or a partially unsaturated (i.e., having one or more double and/or triple bonds within the ring without aromaticity) carbocyclic radical of 3 to about 12, and more typically 3, 5, 6, 7 to 10 ring atoms in which at least one ring atom is a heteroatom selected from nitrogen, oxygen, phosphorus, silicon, boron and sulfur, the remaining ring atoms being C, where one or more ring atoms is optionally substituted independently with one or more substituents described above. A heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 4 heteroatoms selected from N, O, P, and S) or a bicycle having 5 to 10 ring members (4 to 9 carbon atoms and 1 to 6 heteroatoms selected from N, O, P, and S), for example: a bicyclo [4,5], [5,5], [5,6], or [6,6] system. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W. A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. Spiro moieties are also included within the scope of this definition. Examples of a heterocyclic group wherein 1 or 2 ring carbon atoms are substituted with oxo (=O) moieties are pyrimidinonyl and 1,1-dioxo-thiomorpholinyl. The heterocycle groups herein are optionally substituted independently with one or more substituents described herein.

"Heteroaryl" indicates a stable monocyclic aromatic ring which contains from 1 to 3, or in some embodiments from 1 to 2, heteroatoms chosen from N, O, and S, with remaining ring atoms being carbon, or a stable bicyclic or tricyclic system containing at least one 5- to 7-membered aromatic ring which contains from 1, 2, 3, or 4, or in some embodiments from 1 or 2, heteroatoms chosen from N, O, B, and S, with remaining ring atoms being carbon. In one embodiment, the only heteroatom is nitrogen. In one embodiment, the only heteroatom is oxygen. In one embodiment, the only heteroatom is sulfur. Monocyclic heteroaryl groups typically have from 5 to 7 ring atoms.

In some embodiments bicyclic heteroaryl groups are 9- to 10-membered heteroaryl groups, that is, groups containing 9 or 10 ring atoms in which one 5- to 7-member aromatic ring is fused to a second aromatic or non-aromatic ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, these heteroatoms are not adjacent to one another. In one embodiment, the total number of S and O atoms in the heteroaryl group is not more than 2. In another embodiment, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Heteroaryl groups are optionally substituted independently with one or more substituents described herein.

"Heterocycloalkyl" is a saturated ring group. It may have, for example, 1, 2, 3, or 4 heteroatoms independently chosen from N, S, and O, with remaining ring atoms being carbon. In a typical embodiment, nitrogen is the heteroatom. Monocyclic heterocycloalkyl groups typically have from 3 to about 8 ring atoms or from 4 to 6 ring atoms. Examples of heterocycloalkyl groups include morpholinyl, piperazinyl, piperidinyl, and pyrrolinyl.

The term "esterase" refers to an enzyme that catalyzes the hydrolysis of an ester. As used herein, the esterase can catalyze the hydrolysis of prostaglandins described herein. In certain instances, the esterase includes an enzyme that can catalyze the hydrolysis of amide bonds of prostaglandins.

A "dosage form" means a unit of administration of an active agent. Examples of dosage forms include tablets, capsules, injections, suspensions, liquids, emulsions, implants, particles, spheres, creams, ointments, suppositories, inhalable forms, transdermal forms, buccal, sublingual, topical, gel, mucosal, and the like. A "dosage form" can also include an implant, for example an optical implant.

A "pharmaceutical composition" is a composition comprising at least one active agent, such as a compound or salt of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula

XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV and at least one other substance, such as a pharmaceutically acceptable carrier. "Pharmaceutical combinations" are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat any disorder described herein.

A "pharmaceutically acceptable salt" includes a derivative of the disclosed compound in which the parent compound is modified by making inorganic and organic, non-toxic, acid or base addition salts thereof. The salts of the present compounds can be synthesized from a parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salt can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting a free base form of the compound with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are typical, where practicable.

Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, conventional non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like.

Additional non-limiting examples of salts include 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, adipic acid, aspartic acid, benzenesulfonic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, cyclamic acid, dodecylsulfuric acid,

ethane-1,2-disulfonic acid, ethanesulfonic acid, formic acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutaric acid, glycerophosphoric acid, hippuric acid, isobutyric acid, lactobionic acid, lauric acid, malonic acid, mandelic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, nitric acid, oleic acid, palmitic acid, pyroglutamic acid, sebacic acid, thiocyanic acid, and undecylenic acid. Lists of additional suitable salts may be found, e.g., in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., p. 1418 (1985).

The term "carrier" refers to a diluent, excipient, or vehicle with which an active compound is provided.

A "patient" or "host" or "subject" is typically a human, however, may be more generally a mammal. In an alternative embodiment it can refer to for example, a cow, sheep, goat, horses, dog, cat, rabbit, rat, mice, fish, bird and the like.

A "prodrug" as used herein, means a compound which when administered to a host *in vivo* is converted into a parent drug. As used herein, the term "parent drug" means the active form of the compounds that renders the biological effect to treat any of the disorders described herein, or to control or improve the underlying cause or symptoms associated with any physiological or pathological disorder described herein in a host, typically a human. Prodrugs can be used to achieve any desired effect, including to enhance properties of the parent drug or to improve the pharmaceutic or pharmacokinetic properties of the parent. Prodrug strategies exist which provide choices in modulating the conditions for *in vivo* generation of the parent drug, all of which are deemed included herein. Non-limiting examples of prodrug strategies include covalent attachment of removable groups, or removable portions of groups, for example, but not limited to acylation, phosphorylation, phosphonylation, phosphoramidate derivatives, amidation, reduction, oxidation, esterification, alkylation, other carboxy derivatives, sulfoxy or sulfone derivatives, carbonylation or anhydride, among others. In certain aspects of the present invention, at least one hydrophobic group is covalently bound to the parent drug to slow release of the parent drug in vivo.

A "therapeutically effective amount" of a pharmaceutical composition/combination of this invention means an amount effective, when administered to a patient, to provide a therapeutic benefit such as an amelioration of symptoms of the selected disorder, typically an ocular disorder In certain aspects, the disorder is glaucoma, a disorder mediated by carbonic anhydrase, a disorder or abnormality related to an increase in intraocular pressure (IOP), a disorder mediated by nitric

oxide synthase (NOS), a disorder requiring neuroprotection such as to regenerate/repair optic nerves, allergic conjunctivitis, anterior uveitis, cataracts, dry or wet age-related macular degeneration (AMD) or diabetic retinopathy.

"y-linolenic acid" is gamma-linolenic acid.

The term "polymer" as used herein includes oligomers.

## II. DETAILED DESCRIPTION OF THE ACTIVE COMPOUNDS

In certain embodiments, compounds for ocular delivery are provided that are lipophilic monoprodrugs of, for example, Timolol, Metipranolol, Levobunolol, Carteolol, Betaxolol, Brinzolamide, Dorzolamide, acetazolamide, Methazolamide, Brimonidine, apraclonidine, Sunitinib, Latanoprost, dinoprost, travoprost, tafluprost, unoprostone, SR8165, SR5834, axitinib, bosutinib, neratinib, Crizotinib, Tozasertib, lestautinib, foretinib, TAE-684, KW-2449, Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, pazopanib, axitinib, sorafenib, ponatinib, lenvatinib, vandetanib, cabzantinib, or regorafenib, covalently linked to a biodegradable oligomer, as described in more detail herein.

In various embodiments, two biologically active compounds are covalently linked (optionally with a biodegradable linker(s), for example, that includes a linking ester, amide, etc. bond as exemplifed throughout this specification in detail, e.g., —""linked through to"--) for ocular combination therapy. In some embodiments, the bis-prodrug is in a biodegradable polymeric delivery system, such as a biodegradable microparticle or nanoparticle, for controlled delivery. In one embodiment, a β-blocker (for example, Timolol, Metipranolol, Levobunolol, Carteolol or Betaxolol) is covalently linked to a carbonic anhydrase inhibitor (for example, Brinzolamide, Dorzolamide, acetazolamide or Methazolamide). In another embodiment, an α-agonist (for example Brimonidine or apraclonidine) is covalently linked to a β-blocker (for example, Timolol, Metipranolol, Levobunolol, Carteolol or Betaxolol). Alternatively, an α-agonist (for example Brimonidine or apraclonidine) is covalently linked to a carbonic anhydrase inhibitor (for example, Brinzolamide, Dorzolamide, Acetazolamide or Methazolamide). This invention includes the specific combination of each of the named actives with each other named active in the bis-prodrug, as if each combination were individually described (and is only written like this for efficiency of space).

In yet another embodiment, a Rho associated kinase inhibitor (for example Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, or SR5834) (ROCK inhibitor) is covalently linked to a β-blocker (for example, Timolol, Metipranolol, Levobunolol, Carteolol or Betaxolol). In yet another embodiment, a ROCK inhibitor (for example Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, or SR5834) is covalently linked to a carbonic anhydrase inhibitor (for example, Brinzolamide, Dorzolamide, acetazolamide or Methazolamide). In yet another embodiment, ROCK inhibitor (for example Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, SR5834, or fasudil) is covalently linked to an α-agonist (for example Brimonidine or apraclonidine). Alternatively, a neuroprotectant DLK inhibitor (for example, Sunitinib, SR8165, axitinib, bosutinib, neratinib, Crizotinib, Tozasertib, lestautinib, foretinib or TAE-684) is covalently linked to a ROCK inhibitor (for example Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, or SR5834). In alternative embodiments, a ROCK inhibitor can be selected for these embodiments selected from those disclosed in Pireddu, et. al., "Pyridylthiazole-based urease as inhibitors of Rho associated protein kinases (ROCK 1 and 2)" *Med. Chem. Comm.* 2012, 3, 699; Patel, et al., "Identification of novel ROCK inhibitors with anti-migratory and anti-invasive activities" *Oncogene* 2014, 33, 550-555; Patel, et al, "RKI-1447 is a potent inhibitor of the Rho-Associated ROCK Kinase with anti-Invasive and Antitumor Activities in Breast Cancer" *Cancer Research*, online July 30, 2012, 5025-5033); Yin et al., "Discovery of Potent and Selective Urea-Based ROCK Inhibitors and Their Effects on Intraocular Pressure in Rats" *ACS Med. Chem. Lett.* 2010, 1, 175-179; or, Mei, et al. "Discovery of potent and selective urea-based ROCK inhibitors: Exploring the inhibitor's potency and ROCK2/PKA selectivity by 3D-QSAR, molecular docking and molecular dynamics simulations" *Bioorganic & Medicinal Chemistry* 2015, 23, 2505-2517. See also U.S. Patent Nos. 9,221,808 and 9,409,868, herein incorporated in their entirety by reference. Again, this invention includes the specific combination of each of the named actives with each other named active in the bis-prodrug, as if each combination were individually (and is only written like this for efficiency of space).

In other embodiments, a small molecule VEGF inhibitor (for example, pazopanib, axitinib, sorafenib, ponatinib, lenvatinib, vandetanib, cabzantinib, or regorafenib) is covalently linked to a ROCK inhibitor (for example Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, or SR5834), a β-blocker (for example, as named above), an α-

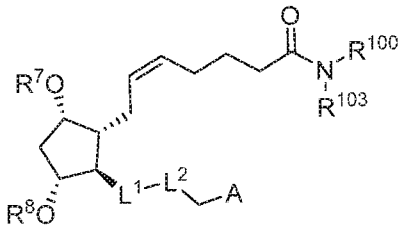
agonist (for example, as named above), a carbonic anhydrase inhibitor (for example, as named above), a prostaglandin (for example Latanoprost, dinoprost, travoprost, tafluprost or unoprostone), or a neuroprotective DLK inhibitor such as SR8165, axitinib, bosutinib, neratinib, Crizotinib, toazaertib, lestautinib, foretinib, TAE-684 or KW-2449. As above, this invention includes the specific combination of each of the named actives with each other named active in the bis-prodrug, as if each combination were individually (and is only written like this for efficiency of space).

In specific embodiments, Sunitinib is covalently linked to one of the β-blockers named above. In another embodiment, Sunitinib is covalently linked to a carbonic acid inhibitor named above. Alternatively, Sunitinib is covalently linked to an α-agonist above. In certain embodiments, Sunitinib is covalently linked to a prostaglandin (for example Latanoprost, dinoprost, travoprost, tafluprost or unoprostone). Alternatively, instead of Sunitinib, a TKI neuroprotectant DLK inhibitor such as SR8165, axitinib, bosutinib, neratinib, Crizotinib, Tozasertib, lestautinib, foretinib, TAE-684 or KW-2449 is covalently linked to a β-blocker, an α-agonist, ROCK inhibitor, a carbonic anhydrase inhibitor, VEGR inhibitor or prostaglandin, as named above. Again, this invention includes the specific combination of each of the named actives with each other named active in the bis-prodrug, as if each combination were individually (and is only written like this for efficiency of space).

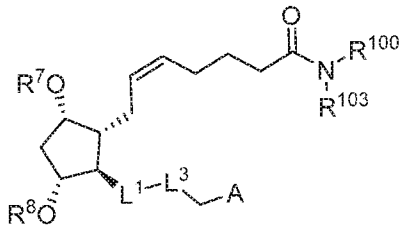
In other various embodiments, the biologically active compound as described herein for ocular therapy is covalently linked (optionally with a biodegradable linker(s) that include a linking ester, amide, etc. bond as exemplifed throughout this specification in detail) to a second same biologically active compound, to create a biodegradable dimer for ocular combination therapy. The dimer is more lipophilic and thus will enhance the controlled delivery of the active compound over time, in particular in a polymeric delivery system, for example, when administered in a hydrophilic intravitreal fluid of the eye. Biologically active compounds that can be dimerized with a biodegradable linker for use in a biodegradable polymeric composition include, but are not limited to, Timolol, Metipranolol, Levobunolol, Carteolol, Betaxolol, Brinzolamide, Dorzolamide, acetazolamide, Methazolamide, Brimonidine, apraclonidine, Sunitinib, Latanoprost, dinoprost, travoprost, tafluprost, unoprostone, SR8165, axitinib, bosutinib, neratinib, Crizotinib, Tozasertib, lestautinib, foretinib, TAE-684, KW-2449, Y-27637, AMA0076, AR-13324, RKI-1447, RKI-1313, Wf536, CID 5056270, K-115, fasudil, SR5834, pazopanib, axitinib, sorafenib,

ponatinib, lenvatinib, vandetanib, cabzantinib, or regorafenib. Methods to dimerize these compounds with a biolodegradable linker are exemplifed throughout this specification.

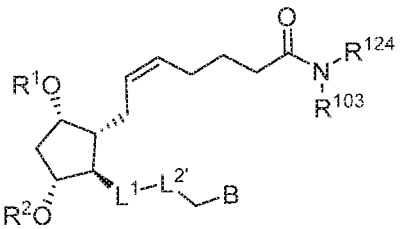
According to the present invention, compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV are provided:



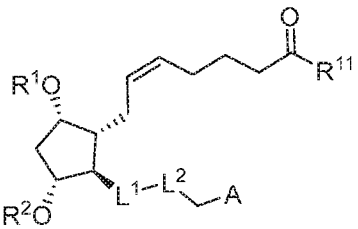
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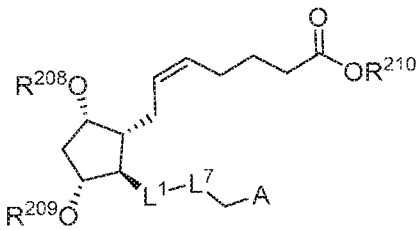
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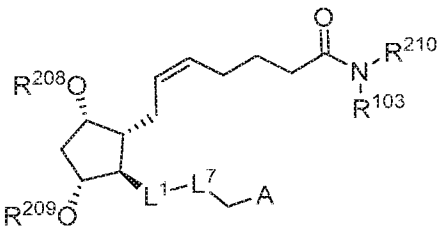
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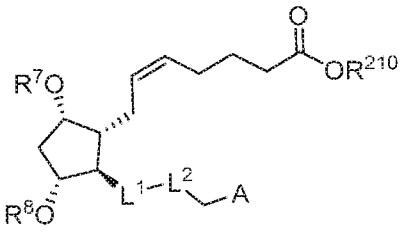
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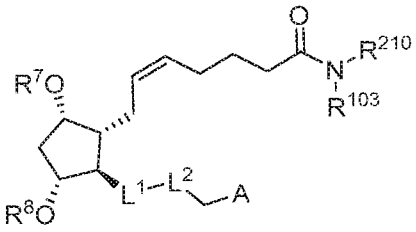
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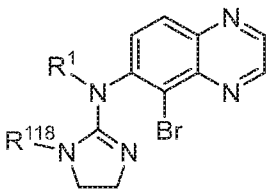
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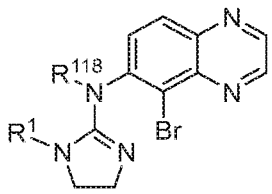
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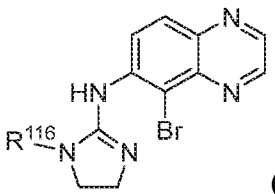
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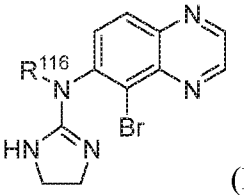
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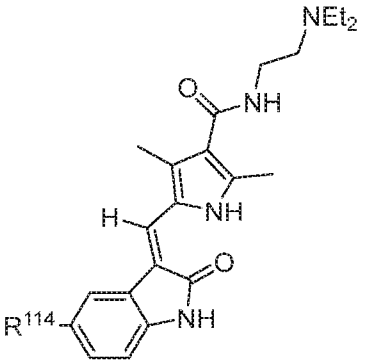
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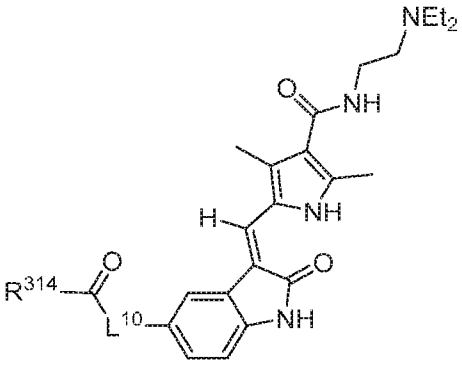
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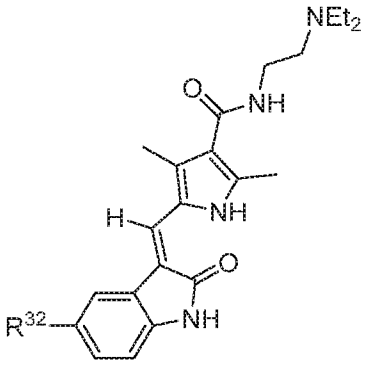
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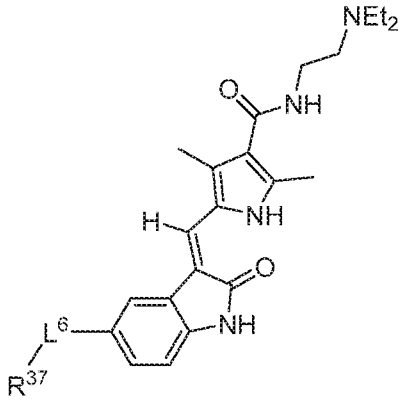
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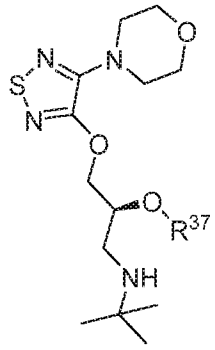
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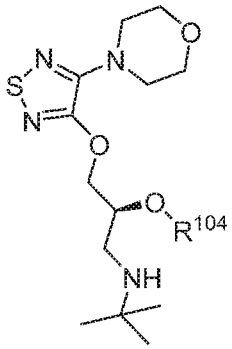
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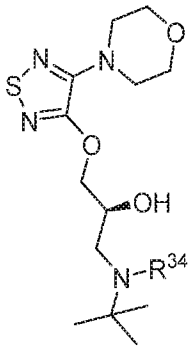
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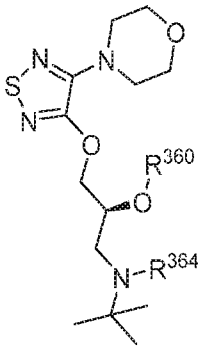
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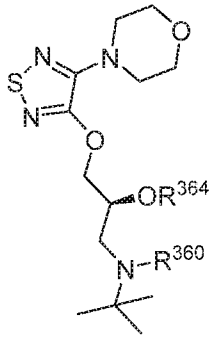
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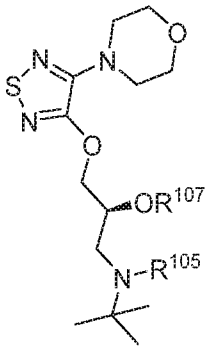
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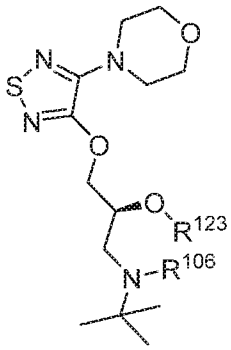
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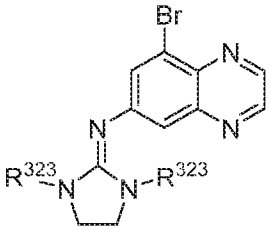
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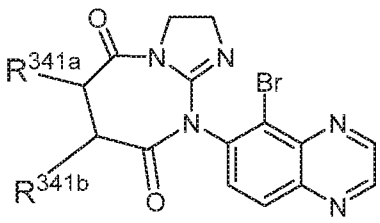
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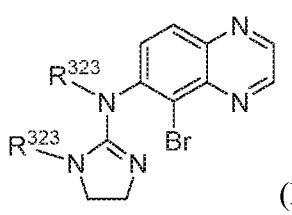
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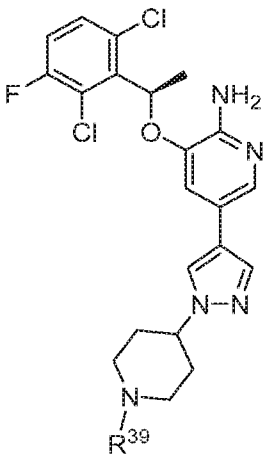
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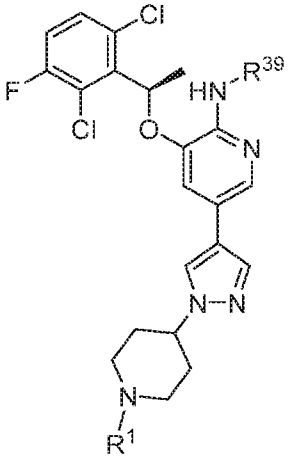
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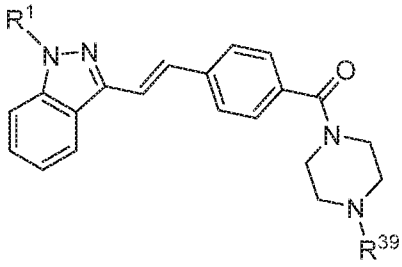
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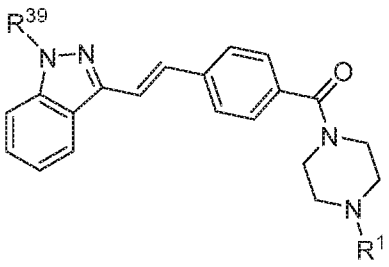
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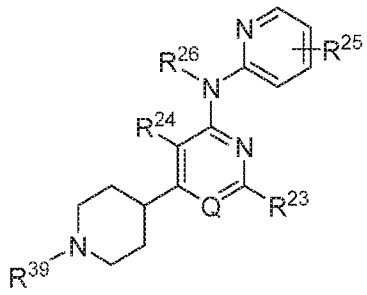
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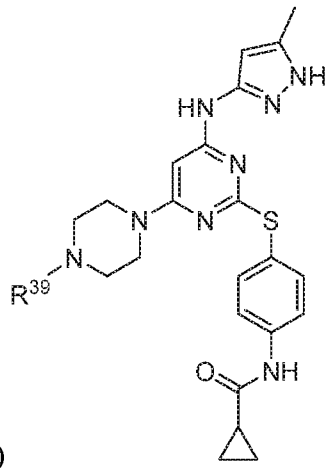
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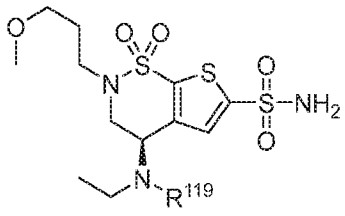
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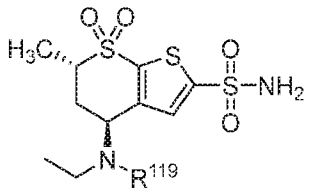
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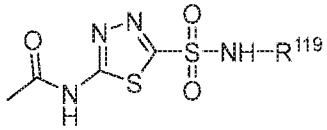
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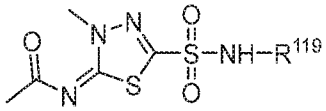
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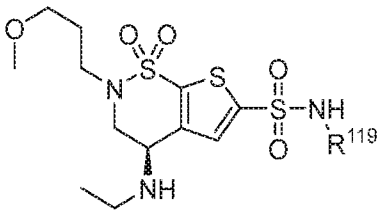
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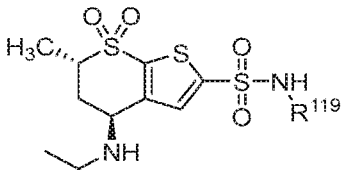
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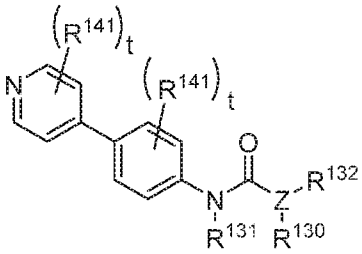
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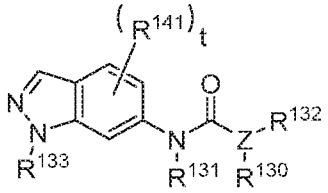
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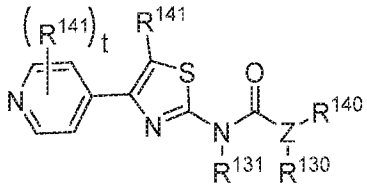
(XXVII)



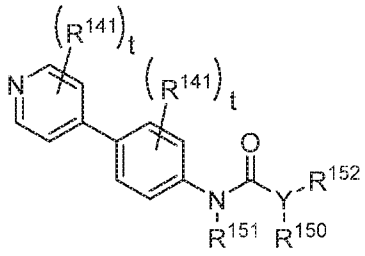
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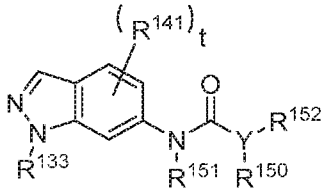
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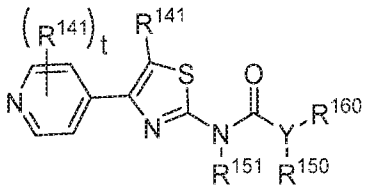
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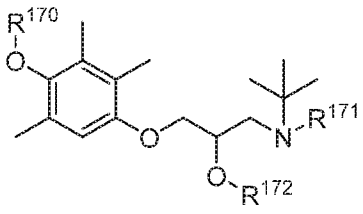
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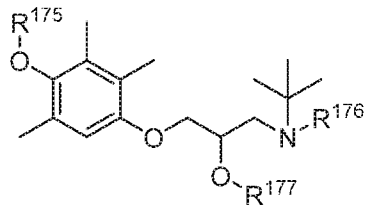
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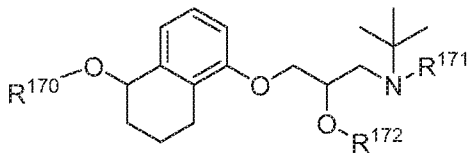
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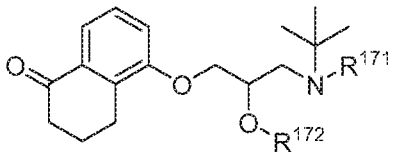
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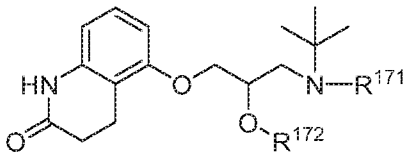
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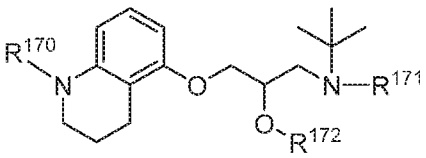
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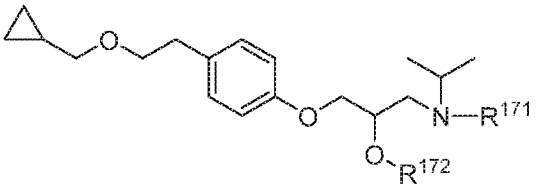
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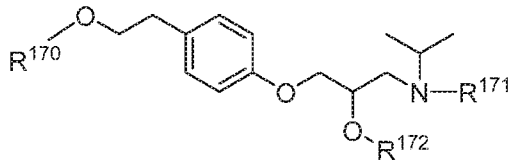
(XL)



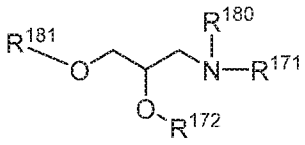
(XLII)



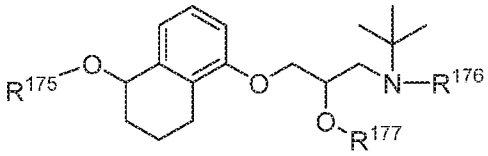
(XLIV)



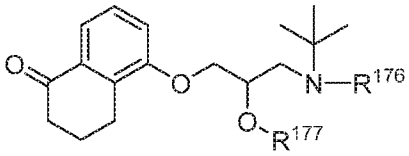
(XLVI)



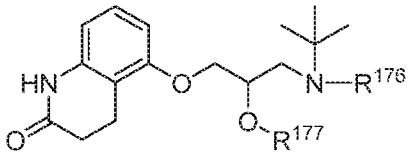
(XLVIII)



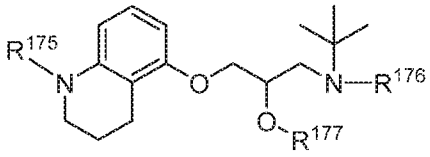
(XXXVII)



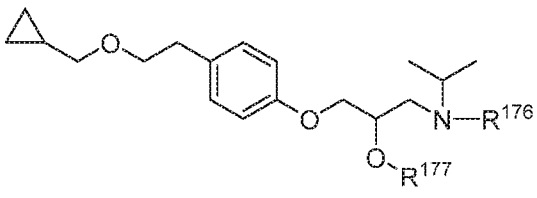
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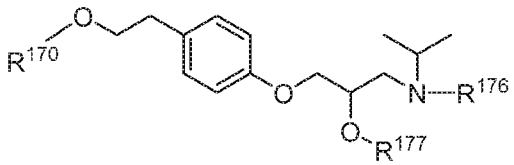
(XLI)



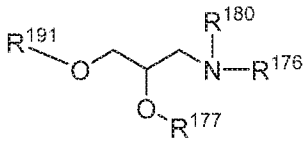
(XLIII)



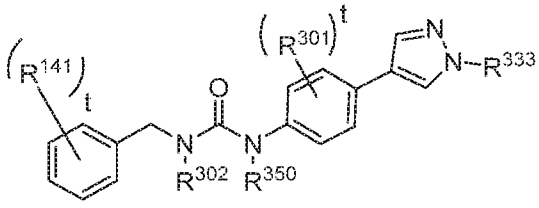
(XLV)



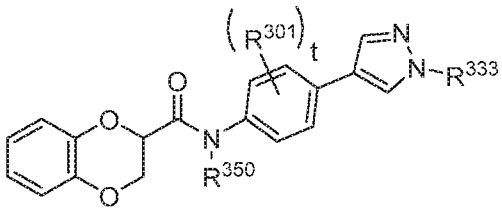
(XLVII)



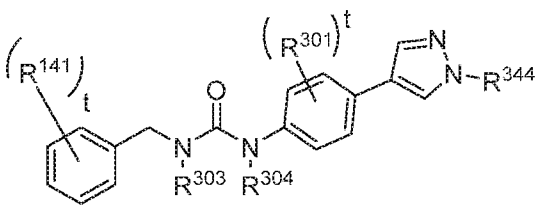
(XLIX)



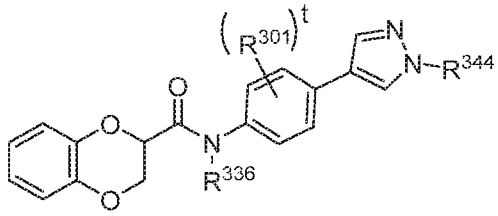
(L)



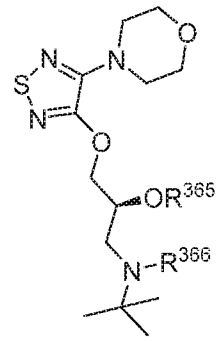
(LI)



(LII)



(LIII)



(LIV)

as well as the pharmaceutically acceptable salts and compositions thereof. Formula I, Formula II, and Formula III can be considered a prostaglandin covalently bound to a hydrophobic moiety through an ester or amide linkage that may be metabolized in the eye to afford the parent prostaglandin. Formula IV can be considered a prostaglandin covalently bound to Brimonidine through either a direct bond or a connecting fragment bound to both species that may be metabolized in the eye to afford the parent prostaglandin and Brimonidine. Formula V, Formula V', Formula VI, and Formula VI' can be considered a prostaglandin covalently bound to Timolol through either a direct bond or a connecting fragment bound to both species that may be metabolized in the eye to afford the parent prostaglandin and one, two, or three moieties of Timolol per prostaglandin. Formula VII and Formula VIII can be considered Brimonidine covalently bound to a hydrophobic moiety through an amide linkage that may be metabolized in the eye to afford Brimonidine. Formula IX and IX' can be considered Brimonidine covalently bound to a prostaglandin, Timolol, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford Brimonidine as well as either prostaglandin, Timolol, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula X can be considered a derivative of Sunitinib covalently bound to either a prostaglandin, Brimonidine, or Timolol through an ester or amide linkage that may be metabolized in the eye to afford the parent Sunitinib derivative as well as either a prostaglandin, Brimonidine, or Timolol. Formula X' can be considered a derivative of Sunitinib covalently bound to a hydrophobic moiety through an ester or amide linkage that may be metabolized in the eye to

afford the parent Sunitinib. Formula XI can be considered a derivative of Sunitinib covalently bound to either a prostaglandin, Brimonidine, or Timolol through an ester or amide linkage that may be metabolized in the eye to afford the parent Sunitinib derivative as well as either a prostaglandin, Brimonidine, or Timolol. Formula XII can be considered a derivative of Sunitinib covalently bound to either a prostaglandin, Brimonidine, or Timolol through an ester or amide linkage that may be metabolized in the eye to afford the parent Sunitinib derivative as well as either a prostaglandin, Brimonidine, or Timolol. Formula XIII can be considered Timolol covalently bound to either a prostaglandin or Brimonidine that may be metabolized in the eye to afford Timolol as well as either a prostaglandin or Brimonidine. Formula XIV can be considered Timolol covalently bound to a hydrophobic moiety through an ester linkage that may be metabolized in the eye to afford the Timolol. Formula XV, Formula XV', Formula XV'' and Formula LIV can be considered Timolol covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase that may be metabolized in the eye to afford Timolol as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XVI can be considered Timolol covalently bound to a hydrophobic moiety through an ester linkage that may be metabolized in the eye to afford Timolol. Formula XVII can be considered Timolol covalently bound to a hydrophobic moiety through an ester linkage that may be metabolized in the eye to afford Timolol. Formula XVIII and Formula XVIII' can be considered Crizotinib covalently bound to either a prostaglandin, Brimonidine, or Timolol through a connecting fragment bound to both species that may be metabolized in the eye to release Crizotinib as well as either either a prostaglandin, Brimonidine, or Timolol. Formula XIX and Formula XIX' can be considered KW-2449 covalently to either a prostaglandin, Brimonidine, or Timolol through a connecting fragment bound to both species that may be metabolized in the eye to release KW-2449 as well as a prostaglandin, Brimonidine, or Timolol. Formula XX can be considered an active DLK inhibitor covalently bound to either a prostaglandin, Brimonidine, or Timolol through a connecting fragment bound to both species that may be metabolized in the eye to release the active DLK inhibitor as well as a prostaglandin, Brimonidine, or Timolol. Formula XXI can be considered a derivative of Tozasertib covalently bound to either a prostaglandin, Brimonidine, or Timolol through a connecting fragment bound to both species that may be metabolized in the eye to release Tozasertib as well as a prostaglandin, Brimonidine, or Timolol. Formula XXII can be considered Brinzolamide covalently bound to a prostaglandin

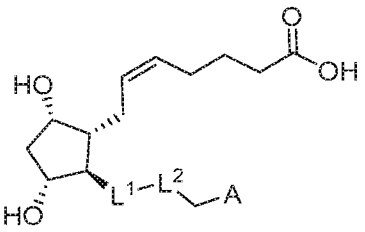
through a connecting fragment bound to both species that may be metabolized in the eye to afford Brinzolamide and a prostaglandin. Formula XXIII can be considered Dorzolamide covalently bound to a prostaglandin through a connecting fragment bound to both species that may be metabolized in the eye to afford Dorzolamide and a prostaglandin. Formula XXIV can be considered Acetazolamide covalently bound to a prostaglandin through a connecting fragment bound to both species that may be metabolized in the eye to afford Acetazolamide and a prostaglandin. Formula XXV can be considered Methazolamide covalently bound to a prostaglandin through a connecting fragment bound to both species that may be metabolized in the eye to afford Methazolamide and a prostaglandin. Formula XXVI can be considered Brinzolamide covalently bound to a prostaglandin through a connecting fragment bound to both species that may be metabolized in the eye to afford Brinzolamide and a prostaglandin. Formula XXVII can be considered Dorzolamide covalently bound to a prostaglandin through a connecting fragment bound to both species that may be metabolized in the eye to afford Dorzolamide and a prostaglandin. Formula XXVIII can be considered an active ROCK inhibitor covalently bound to either a prostaglandin, Brimonidine, Timolol, a carbonic anhydrase inhibitor, a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to release the active ROCK inhibitor. Formula XXIX can be considered an active ROCK inhibitor covalently bound to either a prostaglandin, Brimonidine, Timolol, a carbonic anhydrase inhibitor, a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to release the active ROCK inhibitor. Formula XXX can be considered an active ROCK inhibitor covalently bound to either a prostaglandin, Brimonidine, Timolol, a carbonic anhydrase inhibitor, a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to release the active ROCK inhibitor. Formula XXXI can be considered a ROCK inhibitor covalently bound to a hydrophobic moiety through an amide linkage that may be metabolized in the eye to afford the parent ROCK inhibitor. Formula XXXII can be considered a ROCK inhibitor covalently bound to a hydrophobic moiety through an amide linkage to both species that may be metabolized in the eye to afford the parent ROCK inhibitor. Formula XXXIII can be considered a ROCK inhibitor covalently bound to a hydrophobic moiety through an amide linkage bound to both species that may be metabolized in the eye to afford the parent ROCK inhibitor. Formula XXXIV can be considered Metipranolol covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper

kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford Metipranolol as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XXXV can be considered a Metipranolol covalently bound to a hydrophobic moiety through an amide or ester linkage that may be metabolized in the eye to afford Metipranolol. Formula XXXIV and Formula XXXVIII can be considered Levobunolol covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford Levobunolol as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XXXVII and Formula XXXIX can be considered Levobunolol covalently bound to a hydrophobic moiety through an amide or ester linkage that may be metabolized in the eye to afford Levobunolol. Formula XL and Formula XLII can be considered Carteolol covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford Carteolol as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XLI and Formula XLII can be considered Carteolol covalently bound to a hydrophobic moiety through an amide or ester linkage that may be metabolized in the eye to afford Carteolol. Formula XLIV and Formula XLVI can be considered Betaxolol covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford Betaxolol as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XLV and Formula XLVII can be considered Carteolol covalently bound to a hydrophobic moiety through an amide or ester linkage that may be metabolized in the eye to afford Betaxolol. Formula XLVIII can be considered a beta-blocker covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford the beta-blocker as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula XLIX can be considered a beta-blocker covalently bound to a hydrophobic moiety through an amide or ester linkage that may be metabolized in the eye to afford the beta-blocker. Formula L can be considered SR5834 covalently bound to a hydrophobic moiety through an amide or amine linkage that may be metabolized in the eye to afford SR5834. Formula

LI can be considered SR3677 covalently bound to a hydrophobic moiety through an amide or amine linkage that may be metabolized in the eye to afford SR3677. Formula LII can be considered SR5834 covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford SR5834 as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase. Formula LIII LII can be considered SR3677 covalently bound to a prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase through a connecting fragment bound to both species that may be metabolized in the eye to afford SR3677 as well as either prostaglandin, Brimonidine, a carbonic anhydrase inhibitor, or a duel leucine zipper kinase.

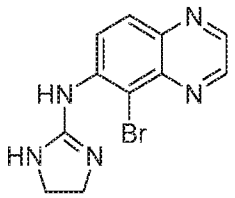
In one embodiment, the compound is a treatment for glaucoma, and therefore can be used as an effective amount to treat a host in need of glaucoma treatment. In another embodiment, the compound acts through a mechanism other than those associated with glaucoma to treat a disorder described herein in a host, typically a human.

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active carboxylic acid compound. Thus, when a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula VI, Formula V', or Formula VI' is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release the parent free acid compound:



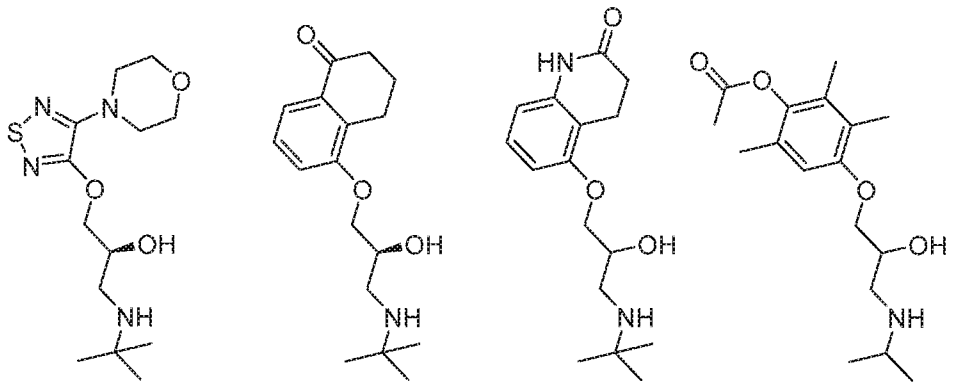

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The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active imidazole compound. Thus when a compound of Formula VII, Formula VIII, Formula IX, Formula IX', Formula XVII', Formula XVII'', or Formula XVII''' is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release Brimonidine.

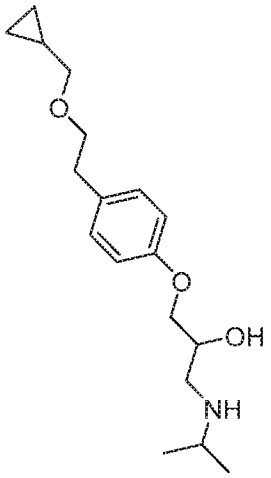


Brimonidine

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active beta-blockers Timolol, Metipranolol, Levobunolol, Carteolol, or Betaxolol. Thus when a compound of Formula III, Formula IV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, or Formula LIV is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release Timolol. When a compound of Formula XXXIV or Formula XXXV is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release Metipranolol. When a compound of Formula XXXVI or Formula XXXVIII is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release Levobunolol. When a compound of Formula XL or Formula XLII is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release careolol. When a compound of Formula XLIV or Formula XLVI is administered to a mammalian subject, typically a human, the amide or ester modifications may be cleaved to release Betaxolol.

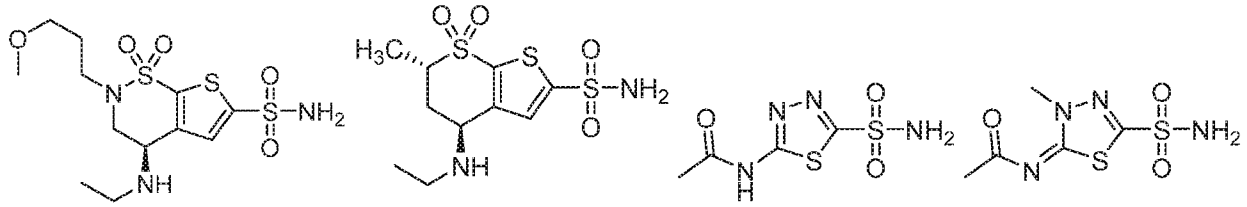


Timolol Levobunolol Carteolol Metipranolol



Betaxolol

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active sulfonamide compound. Thus when a compound of Formula XII or Formula XXIV is administered to a mammalian subject, typically a human, the amide or sulfonamide modification may be cleaved to release Brinzolamide. When a compound of Formula XXIII or Formula XXVII is administered to a mammalian subject, typically a human, the amide or sulfonamide modification may be cleaved to release Dorzolamide. When a compound of Formula XXIV is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release Acetazolamide. When a compound of Formula XXV is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release Methazolamide.

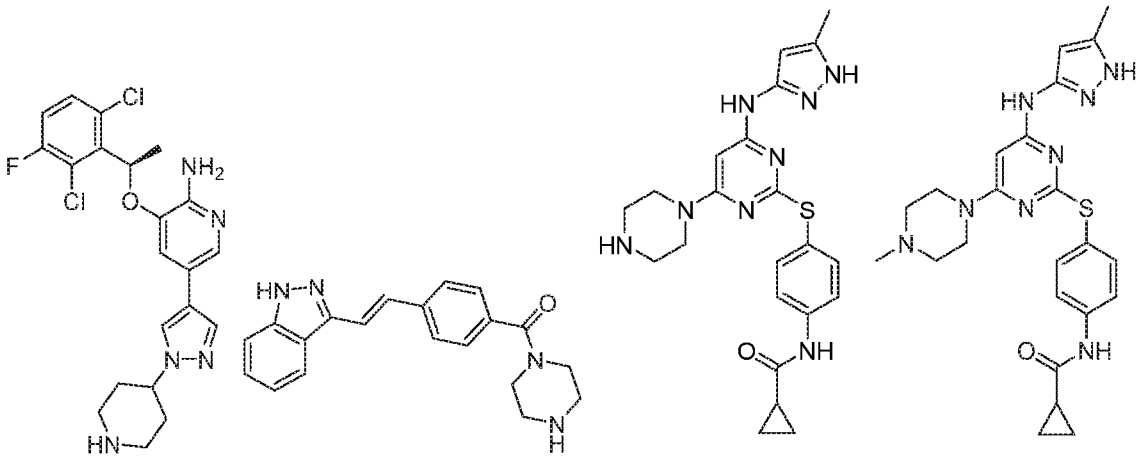


Brinzolamide Dorzolamide Acetazolamide Methazolamide

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to form the active Sunitinib derivative and an active carboxylic acid or an active sulfonamide compound. Thus when a compound of Formula X, Formula X', Formula XI, or Formula XII is administered to a mammalian subject, typically a human, the prodrug may be

cleaved to release the parent Sunitinib derivative. The active Sunitinib derivative is a phenol compound that has been demonstrated in the literature to be an active RTKI (Kuchar, M., et al. (2012). "Radioiodinated Sunitinib as a potential radiotracer for imaging angiogenesis-radiosynthesis and first radiopharmacological evaluation of 5-[125I]Iodo-Sunitinib." Bioorg Med Chem Lett 22(8): 2850-2855. Formulations of Sunitinib for the treatment of ocular disorders and glaucoma have been described in WO2016/100392 and WO2016/100380, respectively.

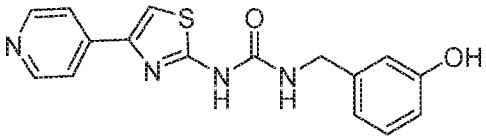
The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to release the active DLK inhibitor. Thus when a compound of Formula XVIII or Formula XVIII' is administered to a mammalian subject, typically a human, the amide bond may be cleaved to release Crizotinib. When a compound of Formula XIX or XIX' is administered to a mammalian subject, typically a human, the amide bond may be cleaved to release KW-2449. When a compound of Formula XX is administered to a mammalian subject, typically a human, the amide bond may be cleaved to release a piperidino DLK inhibitor. When a compound of Formula XXI is administered to a mammalian subject, typically a human, the amide bond may be cleaved to release a Tozasertib derivative.



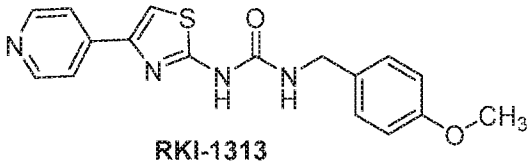

Crizotinib KW-2449 Tozasertib derivative Tozasertib

The compounds, as described herein, may include, for example, prodrugs, which are hydrolysable to release the active ROCK inhibitor. Thus when a compound of Formula XXX or XXXIII is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release RKI-1447 or RKI-1313. When a compound of Formula XXIX or XXXII is administered to a mammalian subject, typically a human, the amide modifications may be cleaved

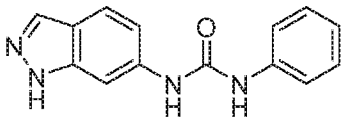
to release RKI-11 or RKI-18. When a compound of Formula L or LII is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release SR5834 (1-(2-hydroxyethyl)-1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]urea), RKI-H-1y (1-(2-hydroxyethyl)-1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)-2-[2-(pyrrolidin-1-yl)ethoxy]phenyl]urea), or RKI-1y (3-(4-(1H-pyrazol-4-yl)-2-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-1-ethyl-1-(3-methoxybenzyl)urea). When a compound of Formula LI or Formula LIII is administered to a mammalian subject, typically a human, the amide modifications may be cleaved to release SR3677.



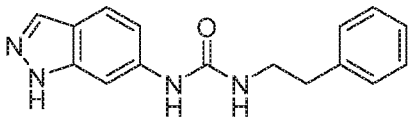
RKI-1447



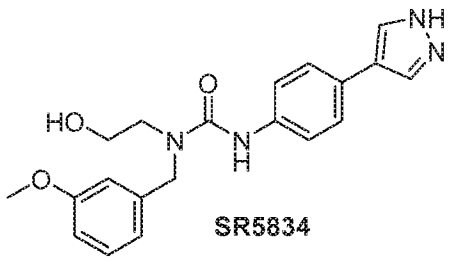
RKI-1313



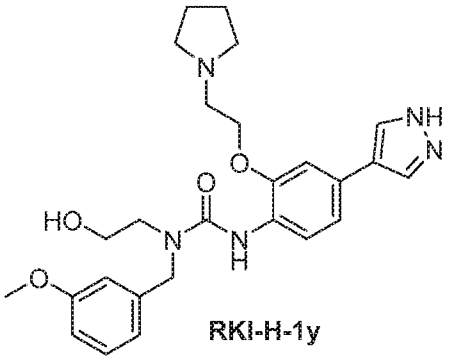
RKI-11



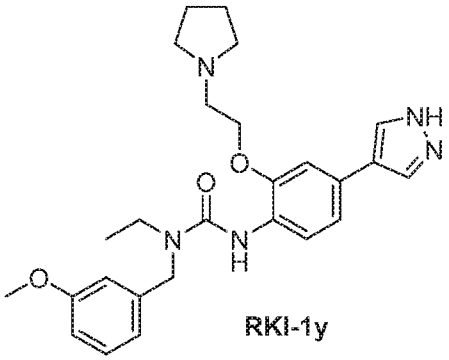
RKI-18



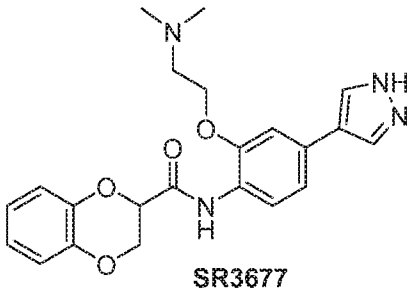
SR5834



RKI-H-1y



RKI-1y



SR3677

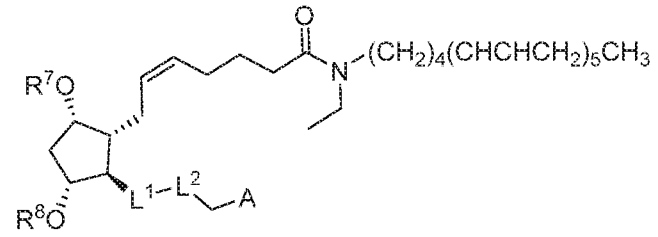
The amides and esters of commercial prostaglandins are believed to act as prodrugs in the eye, in that the ester or amide form, is hydrolyzed by an endogenous ocular enzyme, releasing the parent compound as a free acid which is the active pharmacologic agent. However, this also releases a potentially toxic and potentially irritating small aliphatic alcohol, for example, isobutanol into the eye. While effective in reducing intraocular pressure, most drugs currently in use, including Latanoprost, bimatoprost, travoprost, may cause a significant level of eye irritation in some patients.

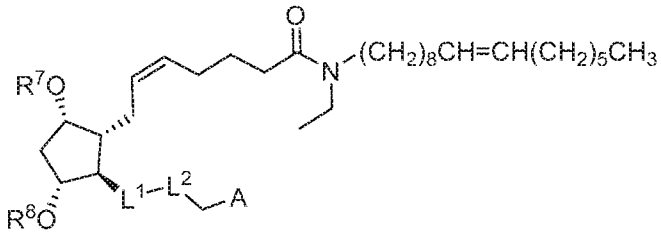
In addition to the foregoing, the isopropyl esters of prostaglandins, for example, Latanoprost and fluprostenol, are highly viscous, glassy oils, which can be difficult to handle and to formulate into ophthalmic solutions. In addition, these compounds can be prone to the retention of potentially toxic process solvents. The higher alkyl esters or amides of prostaglandins can be easier to handle and may not release as irritating of an alcohol or amine upon hydrolysis.

In addition to the irritation caused by the prostaglandins themselves, and particularly the naturally-occurring and synthetic prostaglandins of the type presently on the market, the preservatives typically used in ophthalmic solutions are known to potentially irritate a percentage of the population. Thus, despite the fact that the prostaglandins represent an important class of potent therapeutic agents for the treatment of glaucoma, the unwanted side effects of these drugs, particularly ocular irritation and inflammation, may limit patient use and can be related to patient withdrawal from the use of these drugs. The higher alkyl esters and amides of prostaglandins as disclosed herein, can be less irritating to patients yet therapeutically effective.

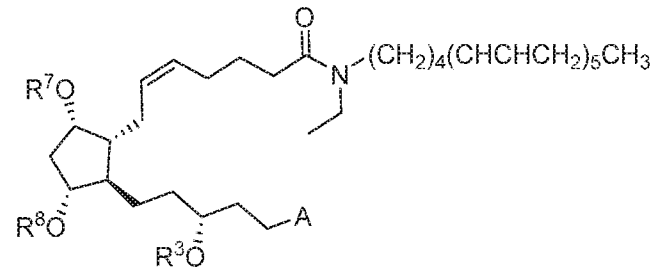
Non-limiting examples of compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XVI, Formula XVII, Formula XVII', Formula XVII'',

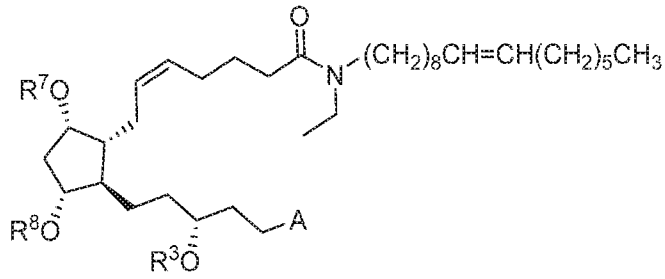
Formula XVII'", Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, or Formula LIII with variations in the variables e.g., $L^1$, $L^2$, $R^1$-$R^{27}$, and A, are illustrated below. The disclosure includes all combinations of these definitions so long as a stable compound results.

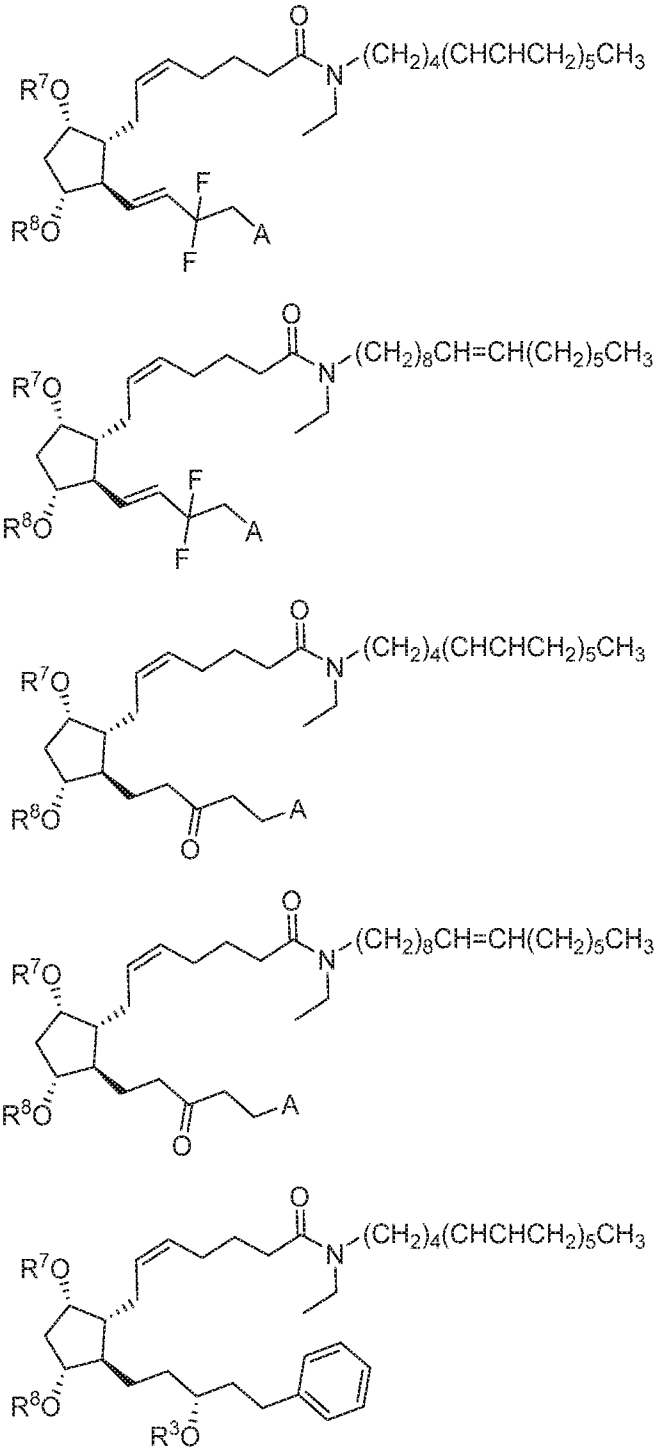




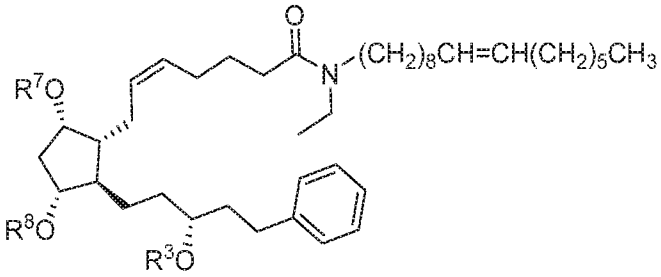
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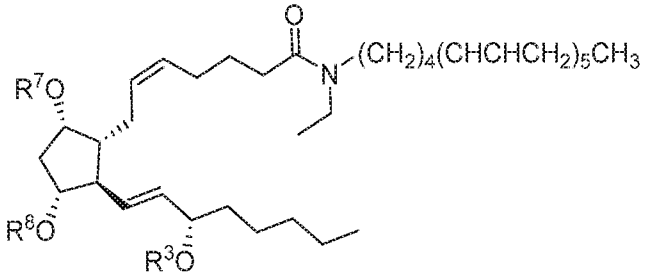


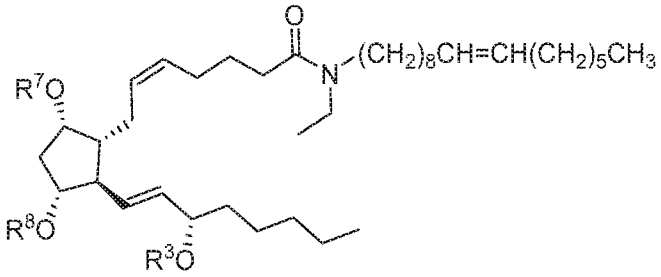


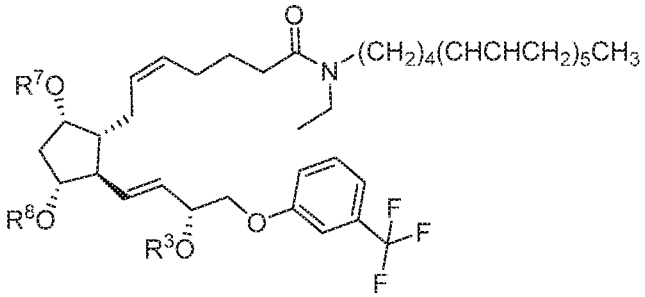


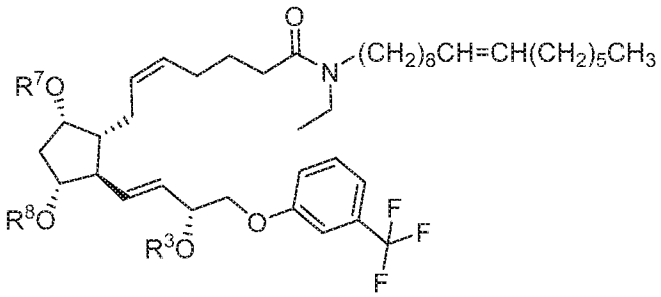
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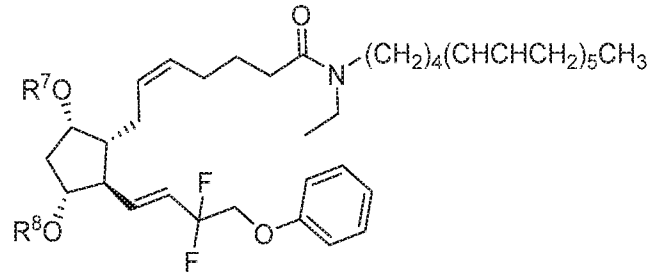


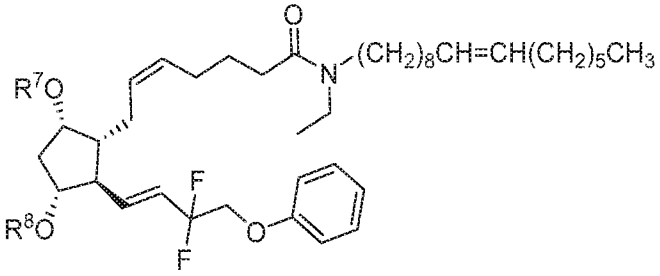


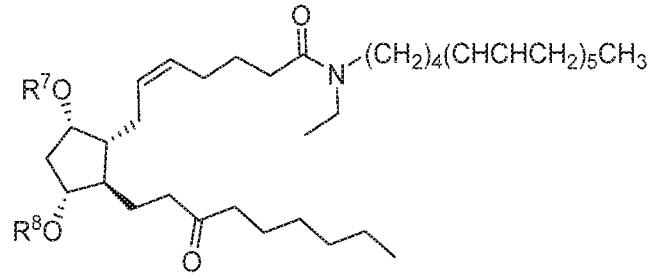


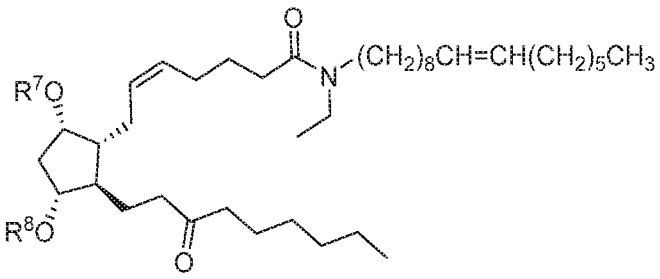


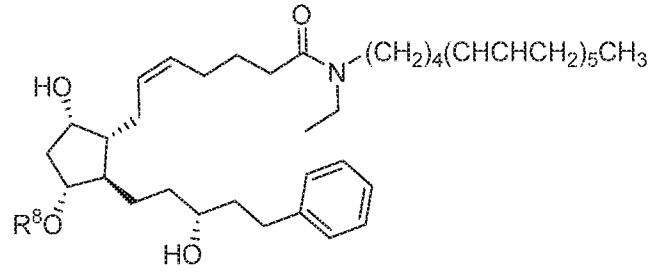
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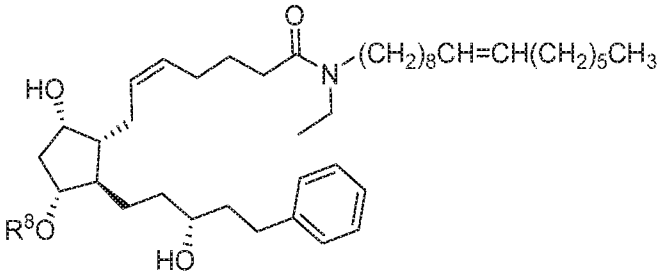


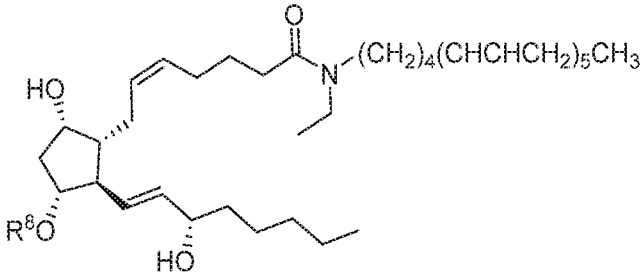


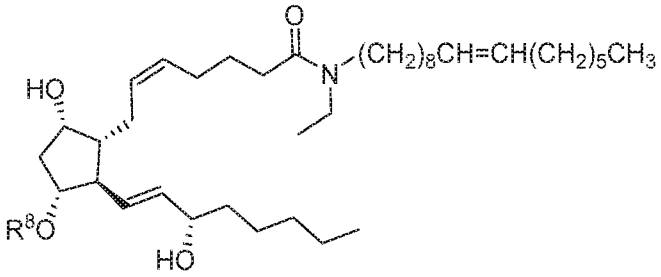


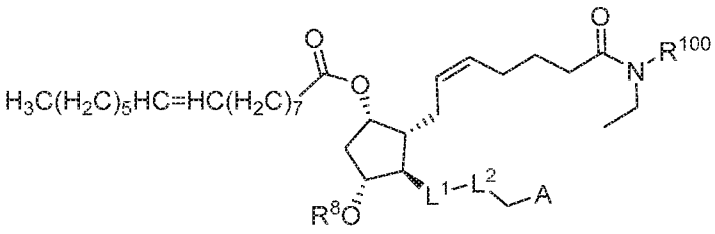


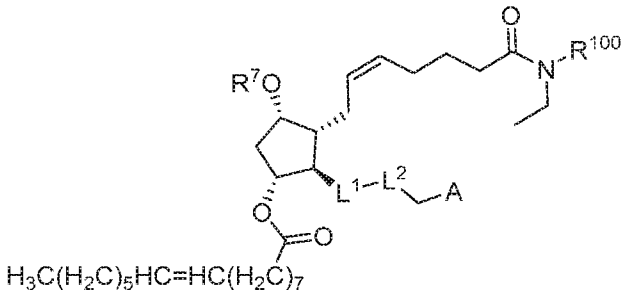
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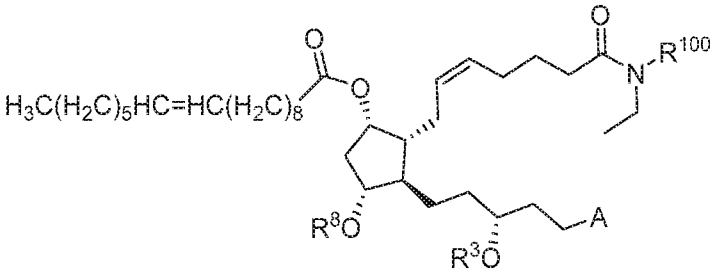


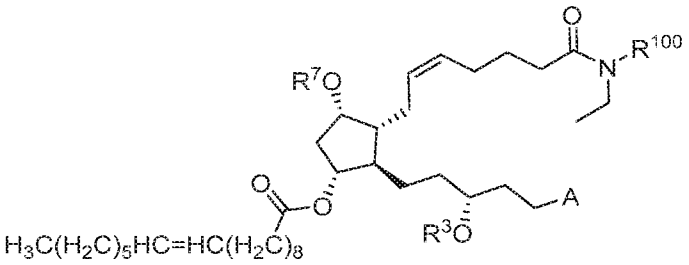


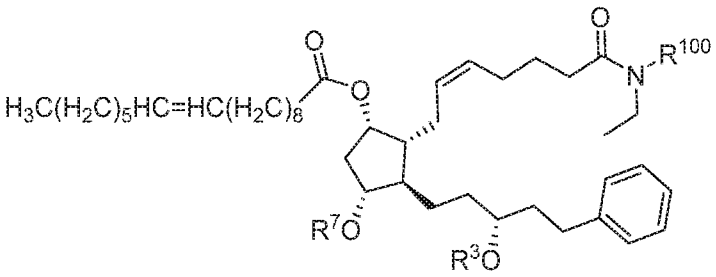


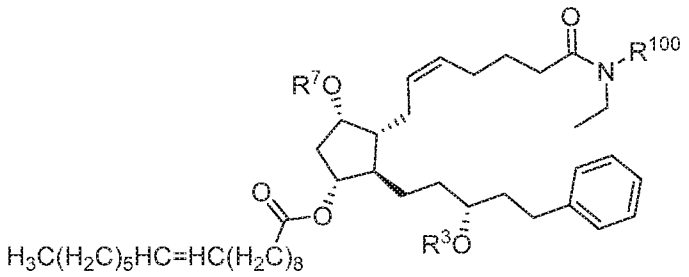


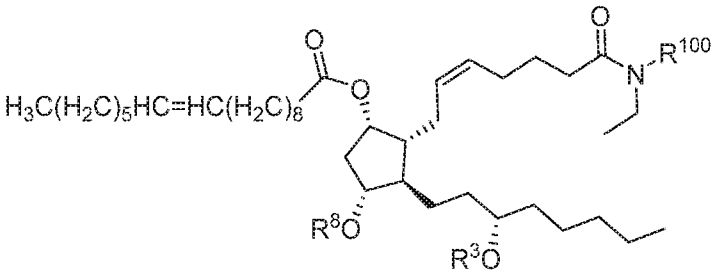




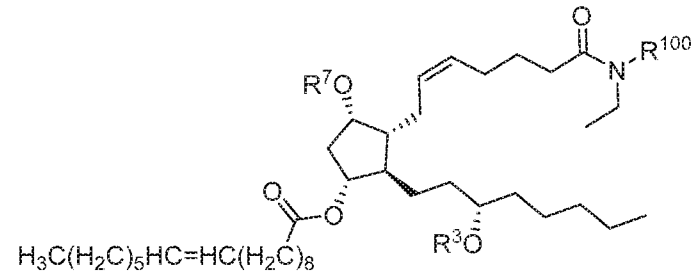


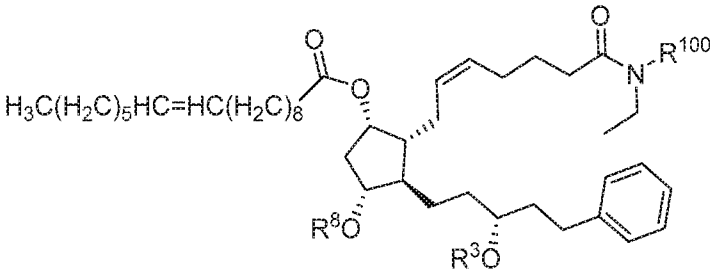


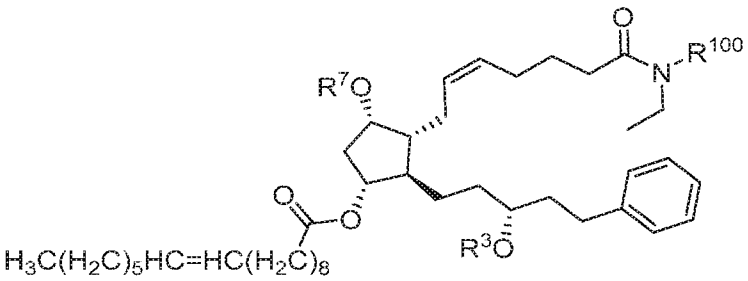


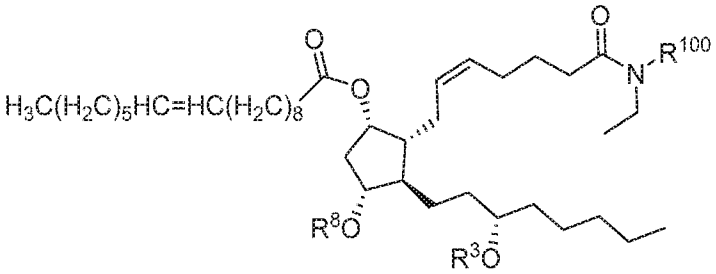


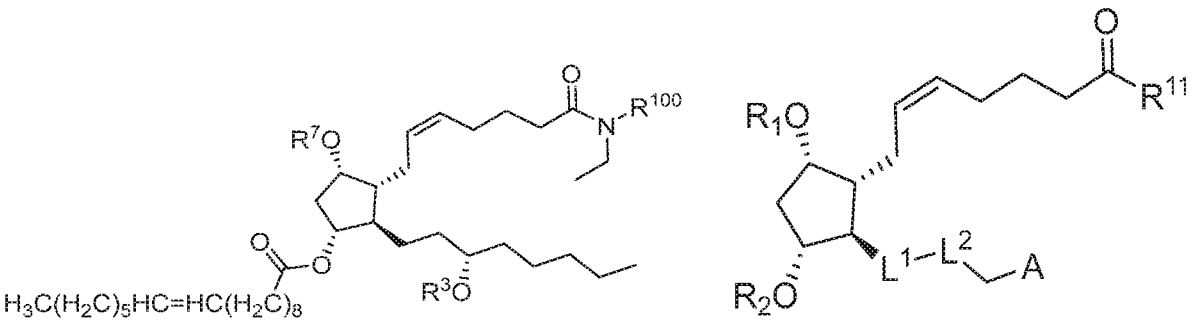
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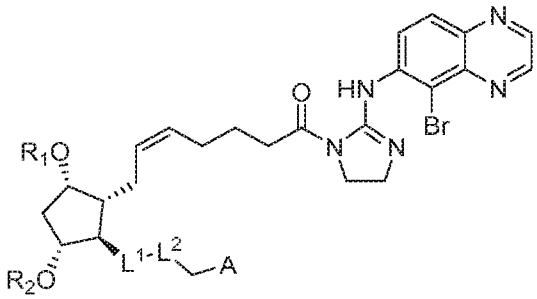


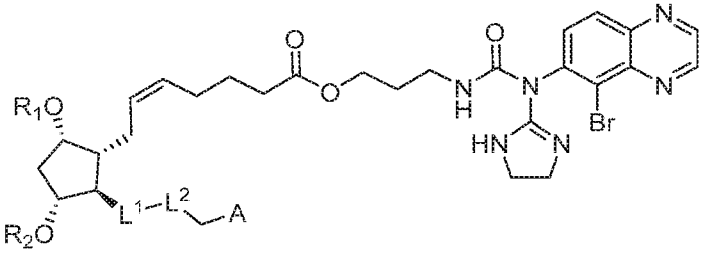


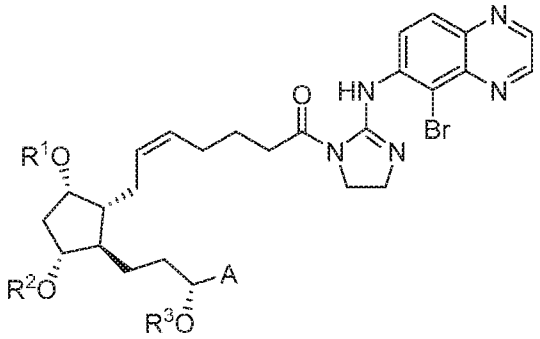


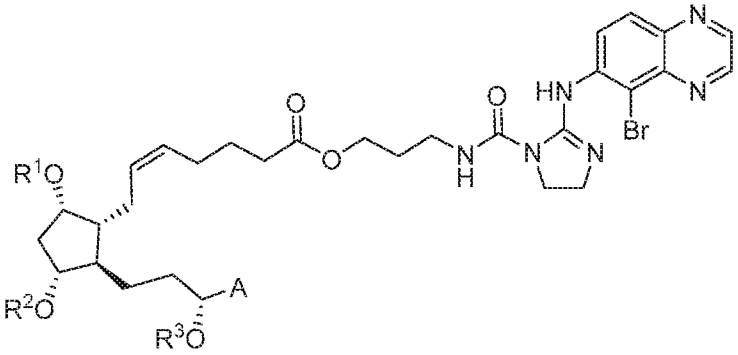


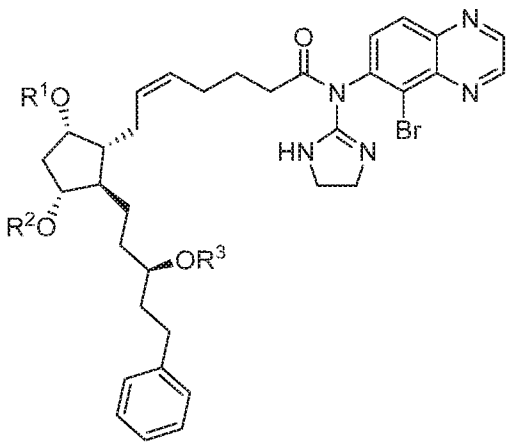


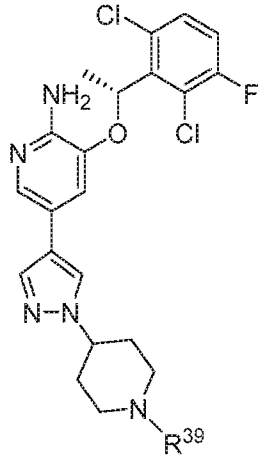


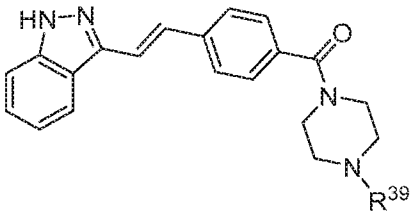


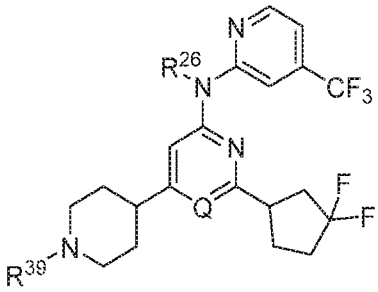


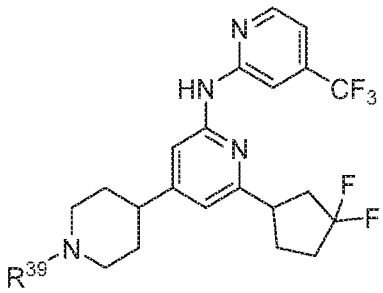


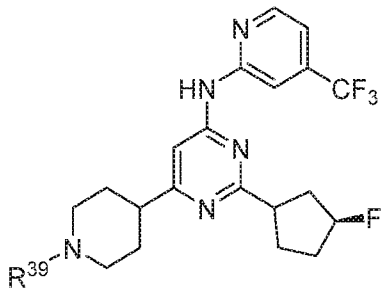


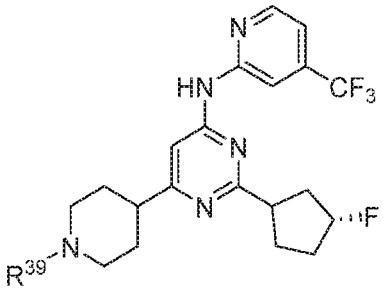


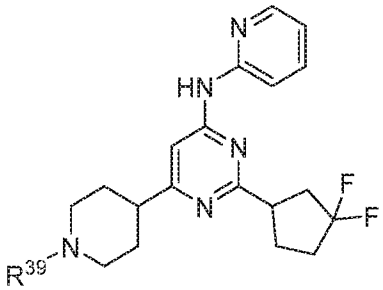


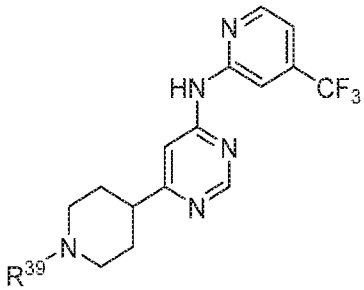


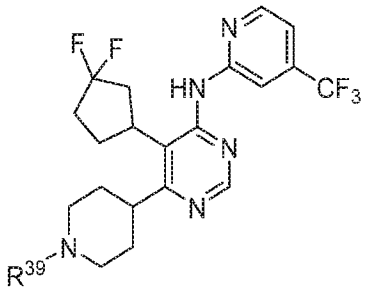


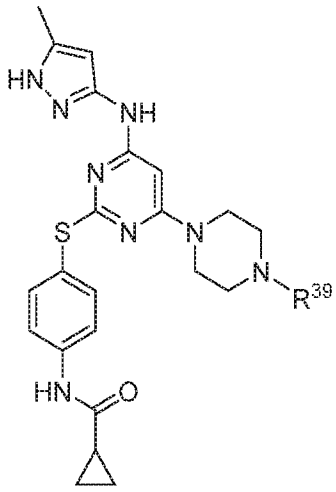




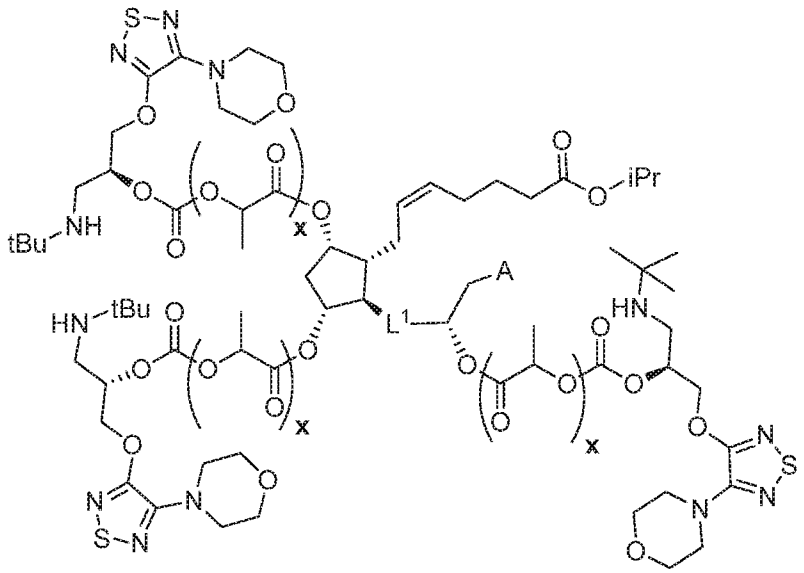


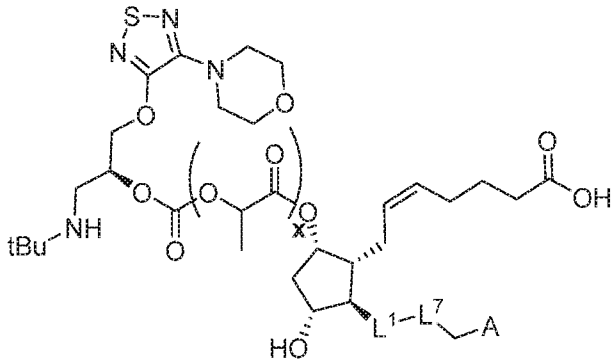


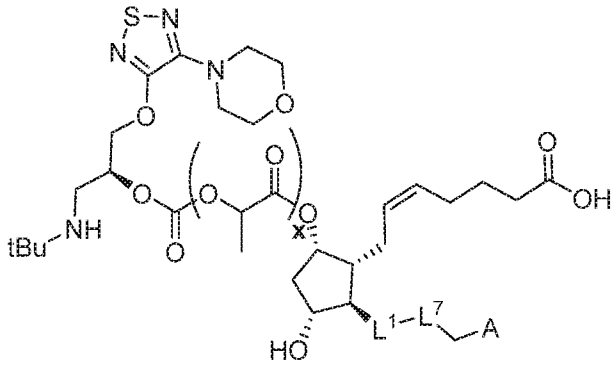


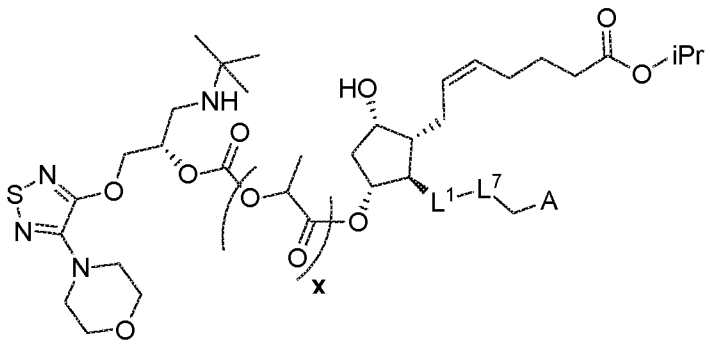


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**Embodiments of x and y**

In embodiments provided herein, each of the below is considered individually and specifically described.

In one embodiment x is 1 and y is 1.

In one embodiment x is 1 and y is 2.

In one embodiment x is 1 and y is 3.

In one embodiment x is 1 and y is 4.

In one embodiment x is 1 and y is 5.

In one embodiment x is 1 and y is 6.

In one embodiment x is 1 and y is 7.

In one embodiment x is 1 and y is 8.

In one embodiment x is 2 and y is 1.

In one embodiment x is 2 and y is 2.

In one embodiment x is 2 and y is 3.

In one embodiment x is 2 and y is 4.

In one embodiment x is 2 and y is 5.

In one embodiment x is 2 and y is 6.

In one embodiment x is 2 and y is 7.

In one embodiment x is 2 and y is 8.

In one embodiment x is 3 and y is 1.

In one embodiment x is 3 and y is 2.

In one embodiment x is 3 and y is 3.

In one embodiment x is 3 and y is 4.

In one embodiment x is 3 and y is 5.

In one embodiment x is 3 and y is 6.

In one embodiment x is 3 and y is 7.

In one embodiment x is 3 and y is 8.

In one embodiment x is 4 and y is 1.

In one embodiment x is 4 and y is 2.

In one embodiment x is 4 and y is 3.

In one embodiment x is 4 and y is 4.

In one embodiment x is 4 and y is 5.

In one embodiment x is 4 and y is 6.

In one embodiment x is 4 and y is 7.

In one embodiment x is 4 and y is 8.

In one embodiment x is 5 and y is 1.

In one embodiment x is 5 and y is 2.

In one embodiment x is 5 and y is 3.

In one embodiment x is 5 and y is 4.

In one embodiment x is 5 and y is 5.

In one embodiment x is 5 and y is 6.

In one embodiment x is 5 and y is 7.

In one embodiment x is 5 and y is 8.

In one embodiment x is 6 and y is 1.

In one embodiment x is 6 and y is 2.

In one embodiment x is 6 and y is 3.

In one embodiment x is 6 and y is 4.

In one embodiment x is 6 and y is 5.

In one embodiment x is 6 and y is 6.

In one embodiment x is 6 and y is 7.

In one embodiment x is 6 and y is 8.

In one embodiment x is 7 and y is 1.

In one embodiment x is 7 and y is 2.

In one embodiment x is 7 and y is 3.

In one embodiment x is 7 and y is 4.

In one embodiment x is 7 and y is 5.

In one embodiment x is 7 and y is 6.

In one embodiment x is 7 and y is 7.

In one embodiment x is 7 and y is 8.

In one embodiment x is 8 and y is 1.

In one embodiment x is 8 and y is 2.

In one embodiment x is 8 and y is 3.

In one embodiment x is 8 and y is 4.

In one embodiment x is 8 and y is 5.

In one embodiment x is 8 and y is 6.

In one embodiment x is 8 and y is 7.

In one embodiment x is 8 and y is 8.

## III. PHARMACEUTICAL PREPARATIONS

One embodiment provides compositions including the compounds described herein. In certain embodiments, the composition includes a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV in combination with a pharmaceutically acceptable carrier, excipient or diluent. In one embodiment, the composition is a pharmaceutical composition for treating an eye disorder or eye disease. Non-limiting exemplary eye disorder or disease treatable with the composition includes age related macular degeneration, alkaline erosive keratoconjunctivitis, allergic conjunctivitis, allergic keratitis, anterior uveitis, Behcet's disease, blepharitis, blood-aqueous barrier disruption, chorioiditis, chronic uveitis, conjunctivitis, contact lens-induced keratoconjunctivitis, corneal abrasion, corneal trauma, corneal ulcer, crystalline retinopathy, cystoid macular edema,

dacryocystitis, diabetic keratophathy, diabetic macular edema, diabetic retinopathy, dry eye disease, dry age-related macular degeneration, geographic atrophy, eosinophilic granuloma, episcleritis, exudative macular edema, Fuchs' Dystrophy, giant cell arteritis, giant papillary conjunctivitis, glaucoma, glaucoma surgery failure, graft rejection, herpes zoster, inflammation after cataract surgery, iridocorneal endothelial syndrome, iritis, keratoconjunctiva sicca, keratoconjunctival inflammatory disease, keratoconus, lattice dystrophy, map-dot-fingerprint dystrophy, necrotic keratitis, neovascular diseases involving the retina, uveal tract or cornea, for example, neovascular glaucoma, corneal neovascularization, neovascularization resulting following a combined vitrectomy and lensectomy, neovascularization of the optic nerve, and neovascularization due to penetration of the eye or contusive ocular injury, neuroparalytic keratitis, non-infectious uveitisocular herpes, ocular lymphoma, ocular rosacea, ophthalmic infections, ophthalmic pemphigoid, optic neuritis, panuveitis, papillitis, pars planitis, persistent macular edema, phacoanaphylaxis, posterior uveitis, post-operative inflammation, proliferative diabetic retinopathy, proliferative sickle cell retinopathy, proliferative vitreoretinopathy, retinal artery occlusion, retinal detachment, retinal vein occlusion, retinitis pigmentosa, retinopathy of prematurity, rubeosis iritis, scleritis, Stevens- Johnson syndrome, sympathetic ophthalmia, temporal arteritis, thyroid associated ophthalmopathy, uveitis, vernal conjunctivitis, vitamin A insufficiency-induced keratomalacia, vitreitis, and wet age-related macular degeneration.

Compounds of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV or its salt, can be delivered by any method known for ocular delivery. Methods include but are not limited to conventional (solution, suspension, emulsion, ointment, inserts and gels); vesicular (liposomes, niosomes, discomes and

pharmacosomes), particulates (microparticles and nanoparticles), advanced materials (scleral plugs, gene delivery, siRNA and stem cells); and controlled release systems (implants, hydrogels, dendrimers, iontoporesis, collagen shields, polymeric solutions, therapeutic contact lenses, cyclodextrin carriers, microneedles and microemulsions).

In certain aspects, a delivery system is used including but not limited to the following; i) a degradable polymeric composition; ii) a non-degradable polymeric composition; (iii) a gel, including, a hydrogel; (iv) a depot; (v) a particle containing a core; vi) a surface-coated particle; vii) a multi-layered polymeric or non-polymeric or mixed polymeric and non-polymeric particle; viii) a polymer blend and/or ix) a particle with a coating on the surface of the particle. The polymers can include, for example, hydrophobic regions. In some embodiments, at least about 30, 40 or 50% of the hydrophobic regions in the coating molecules have a molecular mass of least about 2 kDa. In some embodiments, at least about 30, 40 or 50% of the hydrophobic regions in the coating molecules have a molecular mass of least about 3 kDa. In some embodiments, at least about 30, 40 or 50% of the hydrophobic regions in the coating molecules have a molecular mass of least about 4 kDa. In some embodiments, at least about 30, 40 or 50% of the hydrophobic regions in the coating molecules have a molecular mass of least about 5 kDa. In certain embodiments, up to 5, 10, 20, 30, 40, 50, 60, 70, 80, 90 or even 95% or more of a copolymer or polymer blend consists of a hydrophobic polymer or polymer segment. In some embodiments, the polymeric material includes up to 2, 3, 4, 5, 6, 7, 8, 9, or 10% or more hydrophilic polymer. In one embodiment, the hydrophobic polymer is a polymer or copolymer of lactic acid or glycolic acid, including PLGA. In one embodiment, the hydrophilic polymer is polyethylene glycol. In certain embodiments a triblock polymer such as a Pluronic is used. The drug delivery system can be suitable for administration into an eye compartment of a patient, for example by injection into the eye compartment. In some embodiments, the core includes a biocompatible polymer. As used herein, unless the context indicates otherwise, “drug delivery system”, “carrier”, and “particle composition” can all be used interchangeably. In a typical embodiment this delivery system is used for ocular delivery.

The particle in the drug delivery system can be of any desired size that achieves the desired result. The appropriate particle size can vary based on the method of administration, the eye compartment to which the drug delivery system is administered, the therapeutic agent employed and the eye disorder to be treated, as will be appreciated by a person of skill in the art in light of

the teachings disclosed herein. For example, in some embodiments the particle has a diameter of at least about 1 nm, or from about 1 nm to about 50 microns. The particle can also have a diameter of, for example, from about 1 nm to about 15, 16, 17, 18, 19, 2, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 microns; or from about 10 nm to about less than 30, 35, 40, 45 or 50 microns; or from about 10 nm to about less than 28 microns; from about 1 nm to about 5 microns; less than about 1 nm; from about 1 nm to about 3 microns; or from about 1 nm to about 1000 nm; or from about 25 nm to about 75 nm; or from about 20 nm to less than or about 30 nm; or from about 100 nm to about 300 nm. In some embodiments, the average particle size can be about up to 1 nm, 10 nm, 25 nm, 30 nm, 50 nm, 150 nm, 200 nm, 250 nm, 300 nm, 350 nm, 400 nm, 450 nm, 500 nm, 550 nm, 600 nm, 650 nm, 700 nm, 750 nm, 800 nm, 850 nm, 900 nm, 950 nm, 1000 nm, or more. In some embodiments, the particle size can be about 100 microns or less, about 50 microns or less, about 30 microns or less, about 10 microns or less, about 6 microns or less, about 5 microns or less, about 3 microns or less, about 1000 nm or less, about 800 nm or less, about 600 nm or less, about 500 nm or less, about 400 nm or less, about 300 nm or less, about 200 nm or less, or about 100 nm or less. In some embodiments, the particle can be a nanoparticle or a microparticle. In some embodiments, the drug delivery system can contain a plurality of sizes particles. The particles can be all nanoparticles, all microparticles, or a combination of nanoparticles and microparticles.

When delivering the active material in a polymeric delivery composition, the active material can be distributed homogeneously, heterogeneously, or in one or more polymeric layers of a multi-layered composition, including in a polymer coated core or a bare uncoated core.

In some embodiments, the drug delivery system includes a particle comprising a core. In some embodiments a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX,

Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV can be present in the core in a suitable amount, e.g., at least about 1% weight (wt), at least about 5% wt, at least about 10% wt, at least about 20% wt, at least about 30% wt, at least about 40% wt, at least about 50% wt, at least about 60% wt, at least about 70% wt, at least about 80% wt, at least about 85% wt, at least about 90% wt, at least about 95% wt, or at least about 99% wt of the core. In one embodiment, the core is formed of 100% wt of the pharmaceutical agent. In some cases, the pharmaceutical agent may be present in the core at less than or equal to about 100% wt, less than or equal to about 90% wt, less than or equal to about 80% wt, less than or equal to about 70% wt, less than or equal to about 60% wt, less than or equal to about 50% wt, less than or equal to about 40% wt, less than or equal to about 30% wt, less than or equal to about 20% wt, less than or equal to about 10% wt, less than or equal to about 5% wt, less than or equal to about 2% wt, or less than or equal to about 1% wt. Combinations of the above-referenced ranges are also possible (e.g., present in an amount of at least about 80% wt and less than or equal to about 100% wt). Other ranges are also possible.

In embodiments in which the core particles comprise relatively high amounts of a pharmaceutical agent (e.g., at least about 50% wt of the core particle), the core particles generally have an increased loading of the pharmaceutical agent compared to particles that are formed by encapsulating agents into polymeric carriers. This is an advantage for drug delivery applications, since higher drug loadings mean that fewer numbers of particles may be needed to achieve a desired effect compared to the use of particles containing polymeric carriers.

In some embodiments, the core is formed of a solid material having a relatively low aqueous solubility (i.e., a solubility in water, optionally with one or more buffers), and/or a relatively low solubility in the solution in which the solid material is being coated with a surface-altering agent. For example, the solid material may have an aqueous solubility (or a solubility in a coating solution) of less than or equal to about 5 mg/mL, less than or equal to about 2 mg/mL, less than or equal to about 1 mg/mL, less than or equal to about 0.5 mg/mL, less than or equal to about 0.1 mg/mL, less than or equal to about 0.05 mg/mL, less than or equal to about 0.01 mg/mL, less than or equal to about 1 μg /mL, less than or equal to about 0.1 μg /mL, less than or equal to about 0.01 μg /mL, less than or equal to about 1 ng /mL, less than or equal to about 0.1 ng /mL, or less than or equal to about 0.01 ng /mL at 25 °C. In some embodiments, the solid material may have an aqueous solubility (or a solubility in a coating solution) of at least about 1 pg/mL, at least about 10 pg/mL, at least about 0.1 ng/mL, at least about 1 ng/mL, at least about 10 ng/mL, at least about

0.1 μg/mL, at least about 1 μg/mL, at least about 5 μg/mL, at least about 0.01 mg/mL, at least about 0.05 mg/mL, at least about 0.1 mg/mL, at least about 0.5 mg/mL, at least about 1.0 mg/mL, at least about 2 mg/mL. Combinations of the above-noted ranges are possible (e.g., an aqueous solubility or a solubility in a coating solution of at least about 10 pg/mL and less than or equal to about 1 mg/mL). Other ranges are also possible. The solid material may have these or other ranges of aqueous solubilities at any point throughout the pH range (e.g., from pH 1 to pH 14).

In some embodiments, the core may be formed of a material within one of the ranges of solubilities classified by the U.S. Pharmacopeia Convention: e.g., very soluble: > 1,000 mg/mL; freely soluble: 100- 1,000 mg/mL; soluble: 33-100 mg/mL; sparingly soluble: 10-33 mg/mL; slightly soluble: 1-10 mg/mL; very slightly soluble: 0.1-1 mg/mL; and practically insoluble: <0.1 mg/mL.

Although a core may be hydrophobic or hydrophilic, in many embodiments described herein, the core is substantially hydrophobic. "Hydrophobic" and "hydrophilic" are given their ordinary meaning in the art and, as will be understood by those skilled in the art, in many instances herein, are relative terms. Relative hydrophobicities and hydrophilicities of materials can be determined by measuring the contact angle of a water droplet on a planar surface of the substance to be measured, e.g., using an instrument such as a contact angle goniometer and a packed powder of the core material.

In some embodiments, the core particles described herein may be produced by nanomilling of a solid material (e.g., a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV) in the presence of one or more stabilizers/surface- altering agents. Small particles of a solid material may require the

presence of one or more stabilizers/surface-altering agents, particularly on the surface of the particles, in order to stabilize a suspension of particles without agglomeration or aggregation in a liquid solution. In some such embodiments, the stabilizer may act as a surface-altering agent, forming a coating on the particle.

In a wet milling process, milling can be performed in a dispersion (e.g., an aqueous dispersion) containing one or more stabilizers (e.g., a surface-altering agent), a grinding medium, a solid to be milled (e.g., a solid pharmaceutical agent), and a solvent. Any suitable amount of a stabilizer/surface-altering agent can be included in the solvent. In some embodiments, a stabilizer/surface-altering agent may be present in the solvent in an amount of at least about 0.001% (wt or % weight to volume (w:v)), at least about 0.01 , at least about 0.1 , at least about 0.5, at least about 1, at least about 2, at least about 3, at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 10, at least about 12, at least about 15, at least about 20, at least about 40, at least about 60, or at least about 80% of the solvent. In some cases, the stabilizer may be present in the solvent in an amount of about 100% (e.g., in an instance where the stabilizer/surface-altering agent is the solvent). In other embodiments, the stabilizer may be present in the solvent in an amount of less than or equal to about 100, less than or equal to about 80, less than or equal to about 60, less than or equal to about 40, less than or equal to about 20, less than or equal to about 15, less than or equal to about 12, less than or equal to about 10, less than or equal to about 8, less than or equal to about 7%, less than or equal to about 6%, less than or equal to about 5%, less than or equal to about 4%, less than or equal to about 3%, less than or equal to about 2%, or less than or equal to about 1% of the solvent. Combinations of the above-referenced ranges are also possible (e.g., an amount of less than or equal to about 5% and at least about 1% of the solvent). Other ranges are also possible. The particular range chosen may influence factors that may affect the ability of the particles to penetrate mucus such as the stability of the coating of the stabilizer/surface-altering agent on the particle surface, the average thickness of the coating of the stabilizer/surface-altering agent on the particles, the orientation of the stabilizer/surface-altering agent on the particles, the density of the stabilizer/surface altering agent on the particles, stabilizer/drug ratio, drug concentration, the size and polydispersity of the particles formed, and the morphology of the particles formed.

The compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X,

Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV (or salt thereof) may be present in the solvent in any suitable amount. In some embodiments, the pharmaceutical agent (or salt thereof) is present in an amount of at least about 0.001% (wt% or % weight to volume (w:v)), at least about 0.01%, at least about 0.1%, at least about 0.5%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 10%, at least about 12%, at least about 15%, at least about 20%, at least about 40%, at least about 60%, or at least about 80% of the solvent. In some cases, the pharmaceutical agent (or salt thereof) may be present in the solvent in an amount of less than or equal to about 100%, less than or equal to about 90%, less than or equal to about 80%, less than or equal to about 60%, less than or equal to about 40%, less than or equal to about 20%, less than or equal to about 15%, less than or equal to about 12%, less than or equal to about 10%, less than or equal to about 8%, less than or equal to about 7%, less than or equal to about 6%, less than or equal to about 5%, less than or equal to about 4%, less than or equal to about 3%, less than or equal to about 2%, or less than or equal to about 1% of the solvent. Combinations of the above-referenced ranges are also possible (e.g., an amount of less than or equal to about 20% and at least about 1% of the solvent). In some embodiments, the pharmaceutical agent is present in the above ranges but in w:v.

The ratio of stabilizer/surface-altering agent to pharmaceutical agent (or salt thereof) in a solvent may also vary. In some embodiments, the ratio of stabilizer/surface-altering agent to pharmaceutical agent (or salt thereof) may be at least 0.001 : 1 (weight ratio, molar ratio, or w:v ratio), at least 0.01 : 1, at least 0.01 : 1, at least 1 : 1, at least 2: 1, at least 3: 1, at least 5: 1, at least 10: 1, at least 25: 1, at least 50: 1, at least 100: 1, or at least 500: 1. In some cases, the ratio of stabilizer/surface-altering agent to pharmaceutical agent (or salt thereof) may be less than or equal to 1000: 1 (weight ratio or molar ratio), less than or equal to 500: 1, less than or equal to 100: 1,

less than or equal to 75: 1, less than or equal to 50: 1, less than or equal to 25: 1, less than or equal to 10: 1, less than or equal to 5: 1, less than or equal to 3: 1, less than or equal to 2: 1, less than or equal to 1 : 1, or less than or equal to 0.1 : 1.

Combinations of the above-referenced ranges are possible (e.g. , a ratio of at least 5: 1 and less than or equal to 50: 1). Other ranges are also possible.

Stabilizers/surface-altering agents may be, for example, polymers or surfactants. Examples of polymers are those suitable for use in coatings, as described in more detail below. Non-limiting examples of surfactants include L-a-phosphatidylcholine (PC), 1,2-dipalmitoylphosphatidycholine (DPPC), oleic acid, sorbitan trioleate, sorbitan mono-oleate, sorbitan monolaurate, polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate, natural lecithin, oleyl polyoxyethylene ether, stearyl polyoxyethylene ether, lauryl polyoxyethylene ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil, glyceryl monolaurate, corn oil, cotton seed oil, and sunflower seed oil. Derivatives of the above-noted compounds are also possible. Combinations of the above- noted compounds and others described herein may also be used as surface- altering agents in the inventive particles. As described herein, in some embodiments a surface-altering agent may act as a stabilizer, a surfactant, and/or an emulsifier. In some embodiments, the surface altering agent may aid particle transport in mucus.

It should be appreciated that while in some embodiments the stabilizer used for milling forms a coating on a particle surface, which coating renders particle mucus penetrating, in other embodiments, the stabilizer may be exchanged with one or more other surface-altering agents after the particle has been formed. For example, in one set of methods, a first stabilizer/surface-altering agent may be used during a milling process and may coat a surface of a core particle, and then all or portions of the first stabilizer/surface- altering agent may be exchanged with a second stabilizer/surface-altering agent to coat all or portions of the core particle surface. In some cases, the second stabilizer/surface-altering agent may render the particle mucus penetrating more than the first stabilizer/surface-altering agent. In some embodiments, a core particle having a coating including multiple surface- altering agents may be formed.

In other embodiments, core particles may be formed by a precipitation technique. Precipitation techniques (e.g., microprecipitation techniques, nanoprecipitation techniques) may involve forming a first solution comprising a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV and a solvent, wherein the material is substantially soluble in the solvent. The solution may be added to a second solution comprising another solvent in which the material is substantially insoluble, thereby forming a plurality of particles comprising the material. In some cases, one or more surface-altering agents, surfactants, materials, and/or bioactive agents may be present in the first and/or second solutions. A coating may be formed during the process of precipitating the core (e.g., the precipitating and coating steps may be performed substantially simultaneously). In other embodiments, the particles are first formed using a precipitation technique, following by coating of the particles with a surface- altering agent.

In some embodiments, a precipitation technique may be used to form particles (e.g., nanocrystals) of a salt of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII,

Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV. Generally, a precipitation technique involves dissolving the material to be used as the core in a solvent, which is then added to a miscible anti-solvent with or without excipients to form the core particle. This technique may be useful for preparing particles of pharmaceutical agents that are soluble in aqueous solutions (e.g., agents having a relatively high aqueous solubility). In some embodiments, pharmaceutical agents having one or more charged or ionizable groups can interact with a counter ion (e.g., a cation or an anion) to form a salt complex.

As described herein, in some embodiments, a method of forming a core particle involves choosing a stabilizer that is suitable for both nanomilling and for forming a coating on the particle and rendering the particle mucus penetrating. For example, as described in more detail below, it has been demonstrated that 200-500 nm nanoparticles of a model compound pyrene produced by nanomilling of pyrene in the presence of Pluronic® F127 resulted in particles that can penetrate physiological mucus samples at the same rate as well- established polymer-based MPP. Interestingly, it was observed that only a handful of stabilizers/surface- altering agents tested fit the criteria of being suitable for both nanomilling and for forming a coating on the particle that renders the particle mucus penetrating, as described in more detail below.

## IV. DESCRIPTION OF POLYMERIC DELIVERY MATERIALS

The particles of the drug delivery system can include a biocompatible polymer. As used herein, the term "biocompatible polymer" encompasses any polymer than can be administered to a patient without an unacceptable adverse effect to the patient.

Examples of biocompatible polymers include but are not limited to polystyrenes; poly(hydroxy acid); poly(lactic acid); poly(glycolic acid); poly(lactic acid-co-glycolic acid); poly(lactic-co-glycolic acid); poly(lactide); poly(glycolide); poly(lactide-co-glycolide); polyanhydrides; polyorthoesters; polyamides; polycarbonates; polyalkylenes; polyethylenes; polypropylene; polyalkylene glycols; poly(ethylene glycol); polyalkylene oxides; poly(ethylene oxides); polyalkylene terephthalates; poly(ethylene terephthalate); polyvinyl alcohols; polyvinyl ethers; polyvinyl esters; polyvinyl halides; poly(vinyl chloride); polyvinylpyrrolidone; polysiloxanes; poly(vinyl alcohols); poly(vinyl acetate); polyurethanes; co-polymers of polyurethanes; derivativized celluloses; alkyl cellulose; hydroxyalkyl celluloses; cellulose ethers;

cellulose esters; nitro celluloses; methyl cellulose; ethyl cellulose; hydroxypropyl cellulose; hydroxy-propyl methyl cellulose; hydroxybutyl methyl cellulose; cellulose acetate; cellulose propionate; cellulose acetate butyrate; cellulose acetate phthalate; carboxylethyl cellulose; cellulose triacetate; cellulose sulfate sodium salt; polymers of acrylic acid; methacrylic acid; copolymers of methacrylic acid; derivatives of methacrylic acid; poly(methyl methacrylate); poly(ethyl methacrylate); poly(butylmethacrylate); poly(isobutyl methacrylate); poly(hexylmethacrylate); poly(isodecyl methacrylate); poly(lauryl methacrylate); poly(phenyl methacrylate); poly(methyl acrylate); poly(isopropyl acrylate); poly(isobutyl acrylate); poly(octadecyl acrylate); poly(butyric acid); poly(valeric acid); poly(lactide-co-caprolactone); copolymers of poly(lactide-co-caprolactone); blends of poly(lactide-co-caprolactone); hydroxyethyl methacrylate (HEMA); copolymers of HEMA with acrylate; copolymers of HEMA with polymethylmethacrylate (PMMA); polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA); acrylate polymers/copolymers; acrylate/carboxyl polymers; acrylate hydroxyl and/or carboxyl copolymers; polycarbonate-urethane polymers; silicone-urethane polymers; epoxy polymers; cellulose nitrates; polytetramethylene ether glycol urethane; polymethylmethacrylate-2-hydroxyethylmethacrylate copolymer; polyethylmethacrylate-2-hydroxyethylmethacrylate copolymer; polypropylmethacrylate-2-hydroxyethylmethacrylate copolymer; polybutylmethacrylate-2-hydroxyethylmethacrylate copolymer; polymethylacrylate-2-hydroxyethylmethacrylate copolymer; polyethylacrylate-2-hydroxyethylmethacrylate copolymer; polypropylacrylate-2-hydroxymethacrylate copolymer; polybutylacrylate-2-hydroxyethylmethacrylate copolymer; copolymermethylvinylether maleicanhydride copolymer; poly (2-hydroxyethyl methacrylate) polymer/copolymer; acrylate carboxyl and/or hydroxy copolymer; olefin acrylic acid copolymer; ethylene acrylic acid copolymer; polyamide polymers/copolymers; polyimide polymers/copolymers; ethylene vinylacetate copolymer; polycarbonate urethane; silicone urethane; polyvinylpyridine copolymers; polyether sulfones; polygalactin, poly-(isobutyl cyanoacrylate), and poly(2-hydroxyethyl-L-glutamine); polydimethyl siloxane; poly(caprolactones); poly(ortho esters); polyamines; polyethers; polyesters; polycarbamates; polyureas; polyimides; polysulfones; polyacetylenes; polyethyeneimines; polyisocyanates; polyacrylates; polymethacrylates; polyacrylonitriles; polyarylates; and combinations, copolymers and/or mixtures of two or more of any of the foregoing. In some cases, the particle includes a hydrophobic material and at least one bioactive agent. In certain

embodiments, the hydrophobic material is used instead of a polymer. In other embodiments, the hydrophobic material is used in addition to a polymer.

An active compound as described herein can be physically mixed in the polymeric material, including in an interpenetrating polymer network or can be covalently bound to the polymeric material

Linear, non-linear or linear multiblock polymers or copolymers can be used to form nanoparticles, microparticles, and implants (e.g., rods, discs, wafers, etc.) useful for the delivery to the eye. The polymers can contain one or more hydrophobic polymer segments and one or more hydrophilic polymer segments covalently connected through a linear link or multivalent branch point to form a non-linear multiblock copolymer containing at least three polymeric segments. The polymer can be a conjugate further containing one or more therapeutic, prophylactic, or diagnostic agents covalently attached to the one or more polymer segments. By employing a polymer- drug conjugate, particles can be formed with more controlled drug loading and drug release profiles. In addition, the solubility of the conjugate can be controlled so as to minimize soluble drug concentration and, therefore, toxicity.

The one or more hydrophobic polymer segments, independently, can be any biocompatible hydrophobic polymer or copolymer. In some cases, the one or more hydrophobic polymer segments are also biodegradable. Examples of suitable hydrophobic polymers include polyesters such as polylactic acid, polyglycolic acid, or polycaprolactone, polyanhydrides, such as polysebacic anhydride, and copolymers thereof. In certain embodiments, the hydrophobic polymer is a polyanhydride, such as polysebacic anhydride or a copolymer thereof. The one or more hydrophilic polymer segments can be any hydrophilic, biocompatible, non-toxic polymer or copolymer. The hydrophilic polymer segment can be, for example, a poly(alkylene glycol), a polysaccharide, poly(vinyl alcohol), polypyrrolidone, a polyoxyethylene block copolymer (PLURONIC®) or a copolymers thereof. In preferred embodiments, the one or more hydrophilic polymer segments are, or are composed of, polyethylene glycol (PEG).

WO 2016/100380A1 and WO 2016/100392 A1 describe certain Sunitinib delivery systems, which can also be used in the present invention to deliver Sunitinib or another active agent provided by the current invention, and as described further herein. For example, WO 2016/100380A1 and WO 2016/100392 A1 describe that a polymeric Sunitinib drug formulation can be prepared by: (i) dissolving or dispersing Sunitinib or its salt in an organic solvent optionally

with an alkaline agent; (ii) mixing the solution/dispersion of step (i) with a polymer solution that has a viscosity of at least about 300 cPs (or perhaps at least about 350, 400, 500, 600, 700 or 800 or more cPs); (iii) mixing the drug polymer solution/dispersion of step (ii) with an aqueous non-acidic or alkaline solution (for example at least approximately a pH of 7, 8, or 9 and typically not higher than about 10) optionally with a surfactant or emulsifier, to form a solvent-laden Sunitinib encapsulated microparticle, (iv) isolating the microparticles. When Sunitinib malate or another pharmaceutically acceptable salt of Sunitinib is used, it was reported that it may be useful to include the alkaline agent in the organic solvent. However, when Sunitinib free base is used, then it was reported that adding an acid to the organic solvent can improve drug loading of the microparticle. Examples were provided demonstrating that polyesters such as PLGA, PEG-PLGA( PLA) and PEG-PLGA/PLGA blend microparticles display sustained release of Sunitinib or its analog or pharmaceutically acceptable salt. The PCT references describe that polymer microparticles composed of PLGA and PEG covalently conjugated to PLGA ($M_w$ 45 kDa) (PLGA45k-PEG5k) loaded with Sunitinib malate were prepared using a single emulsion solvent evaporation method. Loading improvement was achieved by increasing the alkalinity of Sunitinib malate in solution, up to 16.1% with PEG-PLGA, which could be further increased by adding DMF, compared to only 1% with no alkaline added. Sunitinib malate loading was further increased by increasing the pH of the aqueous solution as well as the polymer solution. Still further significant increases in Sunitinib malate loading in the microparticles was achieved by increasing polymer concentration or viscosity. It was reported in these PCT applications that the loading of Sunitinib can be increased by increasing the alkalinity of the Sunitinib in solution during encapsulation. This can be achieved by selection of the solvent, adding alkalizing agents to the solvent, or including alkaline drugs with the Sunitinib. Examples of compounds that can be added for this purpose include solvents or solvent additives such as dimethylacetamide (DMA), DMTA, triethylamine (TEA), aniline, ammonium, and sodium hydroxide, drugs such as Vitamin B4, caffeine, alkaloids, nicotine, the analgesic morphine, the antibacterial berberine, the anticancer compound vincristine, the antihypertension agent reserpine, the cholinomimetic galantamine, the anticholinergic agent atropine, the vasodilator vincamine, the antiarrhythmia compound quinidine, the antiasthma therapeutic ephedrine, and the antimalarial drug quinine. Surfactants include anionic, cationic and non-ionic surfactants, such as, but not limited to, polyvinyl alcohol, F-127, lectin, fatty acids, phospholipids, polyoxyethylene sorbitan fatty acid derivatives, tocopherols and

castor oil. The PCTs also reported that drug loading in the particle is significantly affected by the acid value. For example, raising the pH by addition of alkaline significantly increases the amount of Sunitinib malate incorporated. Loading also can be increased by changing the water phase pH. For example, when water phase (such as PBS) pH is raised from 6.8 to 7.4. Drug loading can also be increased by increasing both polymer and drug concentration, polymer molecular weight. The preferred aqueous pH is higher than 6 and lower than 10, more for example between pH 6 and 8. According to WO 2016/100380A1 and WO 2016/100392 A1, polymer concentration and viscosity can affect encapsulation efficiency. For example, it was reported that for the same formulation composition (99% PLGA 75:25 4A and 1% PLGA-PEG (PEG MW 5 Kd, PLGA MW ~ 45 Kd)) at different polymer concentrations in dichloromethane (DCM), the encapsulation efficiency increases to over 50% at 100 mg/mL polymer concentration. The dynamic viscosity of this polymer solution in DCM, prior to mixing with Sunitinib malate solution in DMSO, is estimated to be around 350 cPs. The preferred minimal viscosity of polymer solution in DCM is about 350 cPs. In a preferred embodiment, the polymer concentration in DCM is 140 mg/mL, which is approximately 720 cPs by calculation. Particles made of 99% PLGA 7525 6E and 1% PLGA-PEG (PEG MW 5 Kd, PLGA MW ~ 45 Kd) can have a polymer concentration in DCM ranging from 100-200 mg/mL. Since PLGA 7525 6E is a polymer with higher Mw than that of PLGA 7525 4A, the polymer solution in DCM is more viscous with a dynamic viscosity of about 830 cPs. Drug loading is also significantly affected by the method of making and the solvent used. For example, S/O/W single emulsion method will yield a higher loading than O/W single emulsion method even without control the acid value. In addition, W/O/W double emulsions have been shown to significantly improve drug loading of less hydrophobic salt forms over single O/W emulsions. The ratio of continuous phase to dispersed phase can also significantly alter the encapsulation efficiency and drug loading by modulation of the rate of particle solidification. The rate of polymer solidification with the evaporation of solvent affects the degree of porosity within microparticles. A large CP:DP ratio results in faster polymer precipitation, less porosity, and higher encapsulation efficiency and drug loading. However, decreasing the rate of evaporation of the solvent during particle preparation can also lead to improvements in drug loading of highly polar compounds. As the organic phase phase evaporates, highly polar compounds within the organic phase is driven to the surface of the particles resulting in poor encapsulation and drug loading. By decreasing the

rate of solvent evaporation by decreasing the temperature or rate of stirring, encapsulation efficiency and % drug loading can be increased for highly polar compounds.

These technologies can be used by one of skill in the art to deliver any of the active compounds as described generally in this specification.

U.S. Patent No. 8,889,193 and PCT/US2011/026321 disclose, for example, a method for treating an eye disorder in a patient in need thereof, comprising administering into the eye, for example, by intravitreal injection into the vitreous chamber of the eye, an effective amount of a drug delivery system which comprises: (i) a microparticle including a core which includes the biodegradable polymer polylactide-co-glycolide; (ii) a coating associated with the core which is non-covalently associated with the microparticle particle; wherein the coating molecule has a hydrophilic region and a hydrophobic region, and wherein the hydrophilic region is polyethylene glycol; and (iii) a therapeutically effective amount of a therapeutic agent, wherein the drug delivery system provides sustained release of the therapeutic agent into the vitreous chamber over a period of time of at least three months; and wherein the vitreous chamber of the eye exhibits at least 10% less inflammation or intraocular pressure than if the particle were uncoated. In certain embodiments, the microparticle can be about 50 or 30 microns or less. The delivery system described in U.S. Patent No. 8,889,193 and PCT/US2011/026321 can be used to deliver any of the active agents described herein.

In some embodiments, the drug delivery systems contain a particle with a coating on the surface, wherein the coating molecules have hydrophilic regions and, optionally, hydrophobic regions,

The drug delivery system can include a coating. The coating can be disposed on the surface of the particle, for example by bonding, adsorption or by complexation. The coating can also be intermingled or dispersed within the particle as well as disposed on the surface of the particle.

The homogeneous or heterogenous polymer or polymeric coating can be, for example, polyethylene glycol, polyvinyl alcohol (PVA), or similar substances. The coating can be, for example, vitamin E-PEG 1k or vitamin E-PEG 5k or the like. Vitamin E-PEG 5k can help present a dense coating of PEG on the surface of a particle. The coating can also include nonionic surfactants such as those composed of polyalkylene oxide, e.g., polyoxyethylene (PEO), also referred to herein as polyethylene glycol; or polyoxypropylene (PPO), also referred to herein as polypropylene glycol (PPG), and can include a copolymer of more than one alkylene oxide.

The polymer or copolymer can be, for example, a random copolymer, an alternating copolymer, a block copolymer or graft copolymer.

In some embodiments, the coating can include a polyoxyethylene-polyoxypropylene copolymer, e.g., block copolymer of ethylene oxide and propylene oxide. (i.e., poloxamers). Examples of poloxamers suitable for use in the present invention include, for example, poloxamers 188, 237, 338 and 407. These poloxamers are available under the trade name Pluronic® (available from BASF, Mount Olive, N.J.) and correspond to Pluronic® F-68, F-87, F-108 and F-127, respectively. Poloxamer 188 (corresponding to Pluronic® F-68) is a block copolymer with an average molecular mass of about 7,000 to about 10,000 Da, or about 8,000 to about 9,000 Da, or about 8,400 Da. Poloxamer 237 (corresponding to Pluronic® F-87) is a block copolymer with an average molecular mass of about 6,000 to about 9,000 Da, or about 6,500 to about 8,000 Da, or about 7,7000 Da. Poloxamer 338 (corresponding to Pluronic® F-108) is a block copolymer with an average molecular mass of about 12,000 to about 18,000 Da, or about 13,000 to about 15,000 Da, or about 14,600 Da. Poloxamer 407 (corresponding to Pluronic® F-127) is a polyoxyethylene-polyoxypropylene triblock copolymer in a ratio of between about $E_{101}P_{56}E_{101}$ to about $E_{106}P_{70}E_{106}$, or about $E_{101}P_{56}E_{101}$, or about $E_{106}P_{70}E_{106}$, with an average molecular mass of about 10,000 to about 15,000 Da, or about 12,000 to about 14,000 Da, or about 12,000 to about 13,000 Da, or about 12,600 Da. For example, the NF forms of poloxamers or Pluronic® polymers can be used.

In some embodiments, the polymer can be, for example Pluronic® P103 or Pluronic® P105. Pluronic® P103 is a block copolymer with an average molecular mass of about 3,000 Da to about 6,000 Da, or about 4,000 Da to about 6,000 Da, or about 4,950 Da. Pluronic® P105 is a block copolymer with an average molecular mass of about 5,000 Da to about 8,000 Da, or about 6,000 Da to about 7,000 Da, or about 6,500 Da.

In some embodiments, the polymer can have an average molecular weight of about 9,000 Da or greater, about 10,000 Da or greater, about 11,000 Da or greater or about 12,000 Da or greater. In exemplary embodiments, the polymer can have an average molecular weight of from about 10,000 to about 15,000 Da, or about 12,000 to about 14,000 Da, or about 12,000 to about 13,000 Da, or about 12,600 Da. In some embodiments, the polymer can be selected from Pluronic® P103, P105, F-68, F-87, F-108 and F-127, from Pluronic® P103, P105, F-87, F-108 and F-127, or from Pluronic® P103, P105, F-108 and F-127, or from Pluronic® P103, P105 and F-127. In some

embodiments, the polymer can be Pluronic® F-127. In representative embodiments, the polymer is associated with the particles. For example, the polymer can be covalently attached to the particles. In representative embodiments, the polymer comprises polyethylene glycol, which is covalently attached to a selected polymer, yielding what is commonly referred to as a PEGylated particle.

In some embodiments, a coating is non-covalently associated with a core particle. This association can be held together by any force or mechanism of molecular interaction that permits two substances to remain in substantially the same positions relative to each other, including intermolecular forces, dipole-dipole interactions, van der Waals forces, hydrophobic interactions, electrostatic interactions and the like. In some embodiments, the coating is adsorbed onto the particle. According to representative embodiments, a non-covalently bound coating can be comprised of portions or segments that promote association with the particle, for example by electrostatic or van der Waals forces. In some embodiments, the interaction is between a hydrophobic portion of the coating and the particle. Embodiments include particle coating combinations which, however attached to the particle, present a hydrophilic region, e.g. a PEG rich region, to the environment around the particle coating combination. The particle coating combination can provide both a hydrophilic surface and an uncharged or substantially neutrally-charged surface, which can be biologically inert.

Suitable polymers for use according to the compositions and methods disclosed herein can be made up of molecules having hydrophobic regions as well as hydrophilic regions. Without wishing to be bound by any particular theory, when used as a coating, it is believed that the hydrophobic regions of the molecules are able to form adsorptive interactions with the surface of the particle, and thus maintain a non-covalent association with it, while the hydrophilic regions orient toward the surrounding, frequently aqueous, environment. In some embodiments the hydrophilic regions are characterized in that they avoid or minimize adhesive interactions with substances in the surrounding environment. Suitable hydrophobic regions in a coatings can include, for example, PPO, vitamin E and the like, either alone or in combination with each other or with other substances. Suitable hydrophilic regions in the coatings can include, for example, PEG, heparin, polymers that form hydrogels and the like, alone or in combination with each other or with other substances.

Representative coatings according to the compositions and methods disclosed herein can include molecules having, for example, hydrophobic segments such as PPO segments with molecular weights of at least about 1.8 kDa, or at least about 2 kDa, or at least about 2.4 kDa, or at least about 2.8 kDa, or at least about 3.2 kDa, or at least about 3.6 kDa, or at least about 4.0 kDa, or at least about 4.4 kDa, or at least about 4.8 kDa or at least about 5.2 kDa, or at least 5.6 kDa, or at least 6.0 kDa, or at least 6.4 kDa or more. In some embodiments, the coatings can have PPO segments with molecular weights of from about 1.8 kDa to about 10 kDa, or from about 2 kDa to about 5 kDa, or from about 2.5 kDa to about 4.5 kDa, or from about 2.5 kDa to about 3.5 kDa, or from about 3.0 kDa to about 5.0 kDa, or from about 3.0 kDa to about 6.0 kDa, or from about 4 kDa to about 6 kDa, or from 4.0 kDa to about 7.0 kDa. In some embodiments, at least about 10%, or at least about 25%, or at least about 50%, or at least about 75%, or at least about 90%, or at least about 95%, or at least about 99% or more of the hydrophobic regions in these coatings have molecular weights within these ranges. In some embodiments, the coatings are biologically inert. Compounds that generate both a hydrophilic surface and an uncharged or substantially neutrally-charged surface can be biologically inert.

Representative coatings according to the compositions and methods disclosed herein can include molecules having, for example, hydrophobic segments such as PEG segments with molecular weights of at least about 1.8 kDa, or at least about 2 kDa, or at least about 2.4 kDa, or at least about 2.8 kDa, or at least about 3.2 kDa, or at least about 3.6 kDa, or at least about 4.0 kDa, or at least about 4.4 kDa, or at least about 4.8 kDa, or at least about 5.2 kDa, or at least 5.6 kDa, or at least 6.0 kDa, or at least 6.4 kDa or more. In some embodiments, the coatings can have PEG segments with molecular weights of from about 1.8 kDa to about 10 kDa, or from about 2 kDa to about 5 kDa, or from about 2.5 kDa to about 4.5 kDa, or from about 2.5 kDa to about 3.5 kDa. In some embodiments, at least about 10%, or at least about 25%, or at least about 50%, or at least about 75%, or at least about 90%, or at least about 95%, or at least about 99% or more of the hydrophobic regions in these coatings have molecular weights within these ranges. In some embodiments, the coatings are biologically inert. Compounds that generate both a hydrophilic surface and an uncharged or substantially neutrally-charged surface can be biologically inert.

Representative coatings according to the compositions and methods disclosed herein can include molecules having, for example, segments such as PLGA segments with molecular weights of at least about 4 kDa, or at least about 8 kDa, or at least about 12 kDa, or at least about 16 kDa,

or at least about 20 kDa, or at least about 24 kDa, or at least about 28 kDa, or at least about 32 kDa, or at least about 36 kDa, or at least about 40 kDa, or at least about 44 kDa, of at least about 48 kDa, or at least about 52 kDa, or at least about 56 kDa, or at least about 60 kDa, or at least about 64 kDa, or at least about 68 kDa, or at least about 72 kDa, or at least about 76 kDa, or at least about 80 kDa, or at least about 84 kDa, or at least about 88 kDa or more. In some embodiments, at least about 10%, or at least about 25%, or at least about 50%, or at least about 75%, or at least about 90%, or at least about 95%, or at least about 99% or more of the regions in these coatings have molecular weights within these ranges. In some embodiments, the coatings are biologically inert. Compounds that generate both a hydrophilic surface and an uncharged or substantially neutrally-charged surface can be biologically inert.

In some embodiments, s coating can include, for example, one or more of the following: anionic proteins (e.g., bovine serum albumin), surfactants (e.g., cationic surfactants such as for example dimethyldioctadecyl-ammonium bromide), sugars or sugar derivatives (e.g., cyclodextrin), nucleic acids, polymers (e.g., heparin), mucolytic agents, N-acetylcysteine, mugwort, bromelain, papain, clerodendrum, acetylcysteine, bromhexine, carbocisteine, eprazinone, mesna, ambroxol, sobrerol, domiodol, letosteine, stepronin, tiopronin, gelsolin, thymosin β4, dornase alfa, neltenexine, erdosteine, various DNases including rhDNase, agar, agarose, alginic acid, amylopectin, amylose, beta-glucan, callose, carrageenan, cellodextrins, cellulin, cellulose, chitin, chitosan, chrysolaminarin, curdlan, cyclodextrin, dextrin, ficoll, fructan, fucoidan, galactomannan, gellan gum, glucan, glucomannan, glycocalyx, glycogen, hemicellulose, hydroxyethyl starch, kefiran, laminarin, mucilage, glycosaminoglycan, natural gum, paramylon, pectin, polysaccharide peptide, schizophyllan, sialyl lewis x, starch, starch gelatinization, sugammadex, xanthan gum, xyloglucan, L-phosphatidylcholine (PC), 1,2-dipalmitoylphosphatidycholine (DPPC), oleic acid, sorbitan trioleate, sorbitan monooleate, sorbitan monolaurate, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monooleate, natural lecithin, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, polyoxyethylene (4) lauryl ether, block copolymers of oxyethylene and oxypropylene, synthetic lecithin, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, isopropyl myristate, glyceryl monooleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, polyethylene glycol 400, cetyl pyridinium chloride, benzalkonium chloride, olive oil,

glyceryl monolaurate, corn oil, cotton seed oil, sunflower seed oil, lecithin, oleic acid, sorbitan trioleate, and combinations of two or more of any of the foregoing.

A particle-coating combinations can be made up of any combination of particle and coating substances disclosed or suggested herein. Examples of such combinations include, for example, polystyrene-PEG, or PLGA-Pluronic® F-127.

In one aspect of the present invention, an effective amount of an active compound as described herein is incorporated into a nanoparticle, *e.g.* for convenience of delivery and/or extended release delivery. The use of materials in nanoscale provides one the ability to modify fundamental physical properties such as solubility, diffusivity, blood circulation half-life, drug release characteristics, and/or immunogenicity. These nanoscale agents may provide more effective and/or more convenient routes of administration, lower therapeutic toxicity, extend the product life cycle, and ultimately reduce health-care costs. As therapeutic delivery systems, nanoparticles can allow targeted delivery and controlled release.

In another aspect of the present invention, the nanoparticle or microparticle is coated with a surface agent that facilitates passage of the particle through mucus. Said nanoparticles and microparticles have a higher concentration of surface agent than has been previously achieved, leading to the unexpected property of extremely fast diffusion through mucus. The present invention further comprises a method of producing said particles. The present invention further comprises methods of using said particles to treat a patient.

A number of companies have developed microparticles for treatment of eye disorders that can be used in conjunction with the present invention. For example, Allergan has disclosed a biodegradable microsphere to deliver a therapeutic agent that is formulated in a high viscosity carrier suitable for intraocular injection or to treat a non-ocular disorder (see U.S. publication 2010/0074957 and U.S. publication 2015/0147406). In one embodiment, the '957 application describes a biocompatible, intraocular drug delivery system that includes a plurality of biodegradable microspheres, a therapeutic agent, and a viscous carrier, wherein the carrier has a viscosity of at least about 10 cps at a shear rate of 0.1/second at 25 °C. Allergan has also disclosed a composite drug delivery material that can be injected into the eye of a patient that includes a plurality of microparticles dispersed in a media, wherein the microparticles contain a drug and a biodegradable or bioerodible coating and the media includes the drug dispersed in a depot-forming material, wherein the media composition may gel or solidify on injection into the eye (see WO

2013/112434 A1, claiming priority to January 23, 2012). Allergan states that this invention can be used to provide a depot means to implant a solid sustained drug delivery system into the eye without an incision. In general, the depot on injection transforms to a material that has a viscosity that may be difficult or impossible to administer by injection. In addition, Allergan has disclosed biodegradable microspheres between 40 and 200 μm in diameter, with a mean diameter between 60 and 150 μm that are effectively retained in the anterior chamber of the eye without producing hyperemia, see, US 2014/0294986. The microspheres contain a drug effective for an ocular condition with greater than seven day release following administration to the anterior chamber of the eye. The administration of these large particles is intended to overcome the disadvantages of injecting 1-30 μm particles which are generally poorly tolerated.

In another embodiment any of the above delivery systems can be used to facilitate or enhance delivery through mucus.

Common techniques for preparing particles include, but are not limited to, solvent evaporation, solvent removal, spray drying, phase inversion, coacervation, and low temperature casting. Suitable methods of particle formulation are briefly described below. Pharmaceutically acceptable excipients, including pH modifying agents, disintegrants, preservatives, and antioxidants, can optionally be incorporated into the particles during particle formation.

**Solvent Evaporation**

In this method, the drug (or polymer matrix and one or more Drugs) is dissolved in a volatile organic solvent, such as methylene chloride. The organic solution containing the drug is then suspended in an aqueous solution that contains a surface active agent such as poly(vinyl alcohol). The resulting emulsion is stirred until most of the organic solvent evaporated, leaving solid nanoparticles. The resulting nanoparticles are washed with water and dried overnight in a lyophilizer. Nanoparticles with different sizes and morphologies can be obtained by this method.

Drugs which contain labile polymers, such as certain polyanhydrides, may degrade during the fabrication process due to the presence of water. For these polymers, the following two methods, which are performed in completely anhydrous organic solvents, can be used.

**Solvent Removal**

Solvent removal can also be used to prepare particles from drugs that are hydrolytically unstable. In this method, the drug (or polymer matrix and one or more Drugs) is dispersed or dissolved in a volatile organic solvent such as methylene chloride. This mixture is then suspended

by stirring in an organic oil (such as silicon oil) to form an emulsion. Solid particles form from the emulsion, which can subsequently be isolated from the supernatant. The external morphology of spheres produced with this technique is highly dependent on the identity of the drug.

In one embodiment a compound of the present invention is administered to a patient in need thereof as particles formed by solvent removal. In another embodiment the present invention provides particles formed by solvent removal comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by solvent removal comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by solvent removal comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by solvent removal can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by solvent removal are formulated into a tablet but the tablet is uncoated.

**Spray Drying**

In this method, the drug (or polymer matrix and one or more Drugs) is dissolved in an organic solvent such as methylene chloride. The solution is pumped through a micronizing nozzle driven by a flow of compressed gas, and the resulting aerosol is suspended in a heated cyclone of air, allowing the solvent to evaporate from the micro droplets, forming particles. Particles ranging between 0.1-10 microns can be obtained using this method.

In one embodiment a compound of the present invention is administered to a patient in need thereof as a spray dried dispersion (SDD). In another embodiment the present invention provides a spray dried dispersion (SDD) comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the SDD comprises a compound of the present invention and an additional therapeutic agent. In a further embodiment the SDD comprises a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described spray dried dispersions can be coated to form a coated tablet. In an alternative embodiment the spray dried dispersion is formulated into a tablet but is uncoated.

**Phase Inversion**

Particles can be formed from drugs using a phase inversion method. In this method, the drug (or polymer matrix and one or more Drugs) is dissolved in a "good" solvent, and the solution is poured into a strong non solvent for the drug to spontaneously produce, under favorable conditions, microparticles or nanoparticles. The method can be used to produce nanoparticles in a wide range of sizes, including, for example, about 100 nanometers to about 10 microns, typically possessing a narrow particle size distribution.

In one embodiment a compound of the present invention is administered to a patient in need thereof as particles formed by phase inversion. In another embodiment the present invention provides particles formed by phase inversion comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by phase inversion comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by phase inversion comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by phase inversion can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by phase inversion are formulated into a tablet but the tablet is uncoated.

**Coacervation**

Techniques for particle formation using coacervation are known in the art, for example, in GB-B-929 406; GB-B-929 40 1; and U.S. Patent Nos. 3,266,987, 4,794,000, and 4,460,563. Coacervation involves the separation of a drug (or polymer matrix and one or more Drugs )solution into two immiscible liquid phases. One phase is a dense coacervate phase, which contains a high concentration of the drug, while the second phase contains a low concentration of the drug. Within the dense coacervate phase, the drug forms nanoscale or microscale droplets, which harden into particles. Coacervation may be induced by a temperature change, addition of a non-solvent or addition of a micro-salt (simple coacervation), or by the addition of another polymer thereby forming an interpolymer complex (complex coacervation).

In one embodiment a compound of the present invention is administered to a patient in need thereof as particles formed by coacervation. In another embodiment the present invention provides particles formed by coacervation comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the

particles formed by coacervation comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by coacervation comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by coacervation can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by coacervation are formulated into a tablet but the tablet is uncoated.

**Low Temperature Casting**

Methods for very low temperature casting of controlled release microspheres are described in U.S. Patent No. 5,019,400 to Gombotz *et al.* In this method, the drug (or polymer matrix and Sunitinib) is dissolved in a solvent. The mixture is then atomized into a vessel containing a liquid non-solvent at a temperature below the freezing point of the drug solution which freezes the drug droplets. As the droplets and non-solvent for the drug are warmed, the solvent in the droplets thaws and is extracted into the non-solvent, hardening the microspheres.

In one embodiment a compound of the present invention is administered to a patient in need thereof as particles formed by low temperature casting. In another embodiment the present invention provides particles formed by low temperature casting comprising a compound of the present invention and one or more pharmaceutically acceptable excipients as defined herein. In another embodiment the particles formed by low temperature casting comprise a compound of the present invention and an additional therapeutic agent. In a further embodiment the particles formed by low temperature casting comprise a compound of the present invention, an additional therapeutic agent, and one or more pharmaceutically acceptable excipients. In another embodiment any of the described particles formed by low temperature casting can be formulated into a tablet and then coated to form a coated tablet. In an alternative embodiment the particles formed by low temperature casting are formulated into a tablet but the tablet is uncoated.

## V. CONTROLLED RELEASE OF THERAPEUTIC AGENT

The rate of release of the therapeutic agent can be related to the concentration of therapeutic agent dissolved in polymeric material. In many embodiments, the polymeric composition includes non-therapeutic agents that are selected to provide a desired solubility of the therapeutic agent. The selection of polymer can be made to provide the desired solubility of the therapeutic agent in

the matrix, for example, a hydrogel may promote solubility of hydrophilic material. In some embodiments, functional groups can be added to the polymer to increase the desired solubility of the therapeutic agent in the matrix. In some embodiments, additives may be used to control the release kinetics of therapeutic agent, for example, the additives may be used to control the concentration of therapeutic agent by increasing or decreasing solubility of the therapeutic agent in the polymer so as to control the release kinetics of the therapeutic agent. The solubility may be controlled by including appropriate molecules and/or substances that increase and/or decrease the solubility of the dissolved from of the therapeutic agent to the matrix. The solubility of the therapeutic agent may be related to the hydrophobic and/or hydrophilic properties of the matrix and therapeutic agent. Oils and hydrophobic molecules and can be added to the polymer to increase the solubility of hydrophobic treatment agent in the matrix.

Instead of or in addition to controlling the rate of migration based on the concentration of therapeutic agent dissolved in the matrix, the surface area of the polymeric composition can be controlled to attain the desired rate of drug migration out of the composition. For example, a larger exposed surface area will increase the rate of migration of the active agent to the surface, and a smaller exposed surface area will decrease the rate of migration of the active agent to the surface. The exposed surface area can be increased in any number of ways, for example, by any of castellation of the exposed surface, a porous surface having exposed channels connected with the tear or tear film, indentation of the exposed surface, protrusion of the exposed surface. The exposed surface can be made porous by the addition of salts that dissolve and leave a porous cavity once the salt dissolves. In the present invention, these trends can be used to decrease the release rate of the active material from the polymeric composition by avoiding these paths to quicker release. For example, the surface area can be minimized, or channels avoided.

Further, an implant may be used that includes the ability to release two or more drugs in combination, for example, the structure disclosed in U.S. Patent No. 4,281,654 (Shell), for example, in the case of glaucoma treatment, it may be desirable to treat a patient with multiple prostaglandins or a prostaglandin and a cholinergic agent or an adrenergic antagonist (beta blocker), for example, Alphagan (Allegan, Irvine, CA, USA), or a prostaglandin and a carbonic anhydrase inhibitor.

In addition, drug impregnated meshes may be used, for example, those disclosed in U.S. Patent Application Publication No. 2002/0055701 or layering of biostable polymers as described

in U.S. Patent Application Publication No. 2005/0129731. Certain polymer processes may be used to incorporate drug into the devices, as described herein, for example, so-called "self-delivering drugs" or Polymer Drugs (Polymerix Corporation, Piscataway, NJ, USA) are designed to degrade only into therapeutically useful compounds and physiologically inert linker molecules, further detailed in U.S. Patent Application Publication No. 2005/0048121 (East), hereby incorporated by reference in its entirety. Such delivery polymers may be employed in the devices, as described herein, to provide a release rate that is equal to the rate of polymer erosion and degradation and is constant throughout the course of therapy. Such delivery polymers may be used as device coatings or in the form of microspheres for a drug depot injectable (for example, a reservoir described herein). A further polymer delivery technology may also be adapted to the devices, as described herein, for example, that described in U.S. Patent Application Publication No. 2004/0170685 (Carpenter), and technologies available from Medivas (San Diego, CA, USA).

VI. PROCESS OF PREPARATION OF COMPOUNDS OF Formula I, Formula II, Formula III, Formula IV, Formula V, Formula V', Formula VI, Formula VI', Formula VII, Formula VIII, Formula IX, Formula IX', Formula X, Formula X', Formula XI, Formula XII, Formula XIII, Formula XIV, Formula XV, Formula XV', Formula XV'', Formula XVI, Formula XVII, Formula XVII', Formula XVII'', Formula XVII''', Formula XVIII, Formula XVIII', Formula XIX, Formula XIX', Formula XX, Formula XXI, Formula XXII, Formula XXIII, Formula XXIV, Formula XV, Formula XVI, Formula XVII, Formula XVIII, Formula XXIX, Formula XXX, Formula XXXI, Formula XXXII, Formula XXXIII, Formula XXXIV, Formula XXXV, Formula XXXVI, Formula XXXVII, Formula XXXVIII, Formula XXXIX, Formula XL, Formula XLI, Formula XLII, Formula XLIII, Formula XLIV, Formula XLV, Formula XLVI, Formula XLVII, Formula XLVIII, Formula XLIX, Formula L, Formula LI, Formula LII, Formula LIII, or Formula LIV.

ABBREVIATIONS

| | |
|---|---|
| CAN | Acetonitrile |
| Ac | Acetyl |
| $Ac_2O$ | Acetic anhydride |

| | |
|---|---|
| AcOEt, EtOAc | ethyl acetate |
| AcOH | Acetic acid |
| $Boc_2O$ | di-*tert*-butyl dicarbonate |
| Bu | Butyl |
| CAN | Ceric ammonium nitrate |
| CBz | Carboxybenzyl |
| CDI | Carbonyldiimidazole |
| $CH_3OH$, MeOH | Methanol |
| CsF | Cesium fluoride |
| CuI | Cuprous iodide |
| DCM, $CH_2Cl_2$ | Dichloromethane |
| DIEA, DIPEA | *N*,*N*-diisopropylethylamine |
| DMA | *N*,*N*-dimethylacetamide |
| DMAP | 4-Dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| DMS | Dimethyl sulfide |
| DMSO | Dimethylsulfoxide |
| DPPA | Diphenyl phosphoryl azide |
| EDCI | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide |
| Et | Ethyl |
| $Et_3N$, TEA | Triethylamine |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| HATU | 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium3-oxide hexafluorophosphate |
| HCl | Hydrochloric acid |
| HOBT | Hydroxybenzotriazole |
| *i*Bu, *i*-Bu, *i*soBu | Isobutyl |
| *i*Pr, *i*-Pr, *iso*Pr | Isopropyl |
| *i*$Pr_2$NEt | *N*,*N*-diisopropylethylamine |
| $K_2CO_3$ | Potassium carbonate |
| $K_2CO_3$ | Potassium carbonate |
| LiOH | Lithium hydroxide |

| | |
|---|---|
| Me | Methyl |
| MeI | Methyl iodide |
| Ms | Mesyl |
| MsCl | Mesylchloride |
| MTBE | Methyl tbutylether |
| $Na_2SO_4$ | Sodium sulfate |
| NaCl | Sodium chloride |
| NaH | Sodium hydride |
| $NaHCO_3$ | Sodium bicarbonate |
| NBS | *N*-bromo succinimide |
| NCS | *N*-chloro succinimide |
| $NEt_3$ | Trimethylamine |
| NMP | *N*-Methyl-2-pyrrolidone |
| PCC | Pyridinium chlorochromate |
| Pd $(OAc)_2$ | Palladium acetate |
| $Pd(dppf)Cl_2$ | [1,1′-Bis(diphenylphosphino) ferrocene]dichloropalladium(II) |
| $Pd(PPh_3)_2Cl_2$ | Bis(triphenylphosphine)palladium(II) dichloride |
| $Pd(PPh_3)_4$ | Tetrakis(triphenylphosphine)palladium(0) |
| Pd/C | Palladium on carbon |
| $Pd_2(dba)_3$ | Tris(dibenzylideneacetone)dipalladium(0) |
| PMB | 4-Methoxybenzyl ether |
| $PPh_3$ | Triphenylphosphine |
| Pr | Propyl |
| Py, py | Pyridine |
| RT | Room temperature |
| TBAF | Tetra-n-butylammonium fluoride |
| TBAT | Tetrabutylammonium difluorotriphenylsilicate |
| tBu, t-Bu | Tertbutyl |
| tBuOK | Potassium tert-butoxide |
| TEA | Trimethylamine |
| $Tf_2O$ | Trifluoromethanesulfonic anhydride |
| TFA | Trifluoroacetic acid |

| | |
|---|---|
| THF | Tetrahydrofuran |
| TMS | Trimethylsilane |
| TMSBr | Bromotrimethylsilane |
| $t_R$ | Retention time |
| Troc | 2,2,2-Trichlorethoxycarbonyl chloride |
| $Zn(CN)_2$ | Zinc cyanide |

General Methods

All nonaqueous reactions were performed under an atmosphere of dry argon or nitrogen gas using anhydrous solvents. The progress of reactions and the purity of target compounds were determined using one of the two liquid chromatography (LC) methods listed below. The structure of starting materials, intermediates, and final products was confirmed by standard analytical techniques, including NMR spectroscopy and mass spectrometry.

The compounds described herein can be prepared by methods known by those skilled in the art. In one non-limiting example the disclosed compounds can be made by the schemes below.

Compounds of the present invention with stereocenters may be drawn without stereochemistry for convenience. One skilled in the art will recognize that pure enantiomers and diastereomers can be prepared by methods known in the art. Examples of methods to obtain optically active materials include at least the following.

i) Physical separation of crystals—a technique whereby macroscopic crystals of the individual enantiomers are manually separated. This technique can be used if crystals of the separate enantiomers exist, i.e., the material is a conglomerate, and the crystals are visually distinct;

ii) Simultaneous crystallization—a technique whereby the individual enantiomers are separately crystallized from a solution of the racemate, possible only if the latter is a conglomerate in the solid state;

iii) Enzymatic resolutions—a technique whereby partial or complete separation of a racemate by virtue of differing rates of reaction for the enantiomers with an enzyme;

iv) Enzymatic asymmetric synthesis—a synthetic technique whereby at least one step of the synthesis uses an enzymatic reaction to obtain an enantiomerically pure or enriched synthetic precursor of the desired enantiomer;

v) Chemical asymmetric synthesis—a synthetic technique whereby the desired enantiomer is synthesized from an achiral precursor under conditions that produce asymmetry (i.e., chirality) in the product, which may be achieved using chiral catalysts or chiral auxiliaries;

vi) Diastereomer separations—a technique whereby a racemic compound is reacted with an enantiomerically pure reagent (the chiral auxiliary) that converts the individual enantiomers to diastereomers. The resulting diastereomers are then separated by chromatography or crystallization by virtue of their now more distinct structural differences and the chiral auxiliary later removed to obtain the desired enantiomer;

vii) First- and second-order asymmetric transformations—a technique whereby diastereomers from the racemate equilibrate to yield a preponderance in solution of the diastereomer from the desired enantiomer or where preferential crystallization of the diastereomer from the desired enantiomer perturbs the equilibrium such that eventually in principle all the material is converted to the crystalline diastereomer from the desired enantiomer. The desired enantiomer is then released from the diastereomer;

viii) Kinetic resolutions—this technique refers to the achievement of partial or complete resolution of a racemate (or of a further resolution of a partially resolved compound) by virtue of unequal reaction rates of the enantiomers with a chiral, non-racemic reagent or catalyst under kinetic conditions;

ix) Enantiospecific synthesis from non-racemic precursors—a synthetic technique whereby the desired enantiomer is obtained from non-chiral starting materials and where the stereochemical integrity is not or is only minimally compromised over the course of the synthesis;

x) Chiral liquid chromatography—a technique whereby the enantiomers of a racemate are separated in a liquid mobile phase by virtue of their differing interactions with a stationary phase (including via chiral HPLC). The stationary phase can be made of chiral material or the mobile phase can contain an additional chiral material to provoke the differing interactions;

xi) Chiral gas chromatography—a technique whereby the racemate is volatilized and enantiomers are separated by virtue of their differing interactions in the gaseous mobile phase with a column containing a fixed non-racemic chiral adsorbent phase;

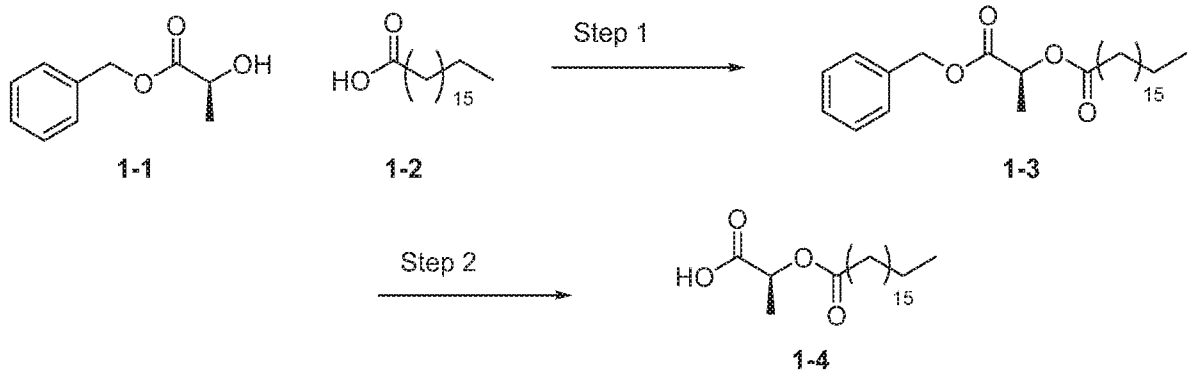
xii) Extraction with chiral solvents—a technique whereby the enantiomers are separated by virtue of preferential dissolution of one enantiomer into a particular chiral solvent;

xiii) Transport across chiral membranes—a technique whereby a racemate is placed in contact with a thin membrane barrier. The barrier typically separates two miscible fluids, one containing the racemate, and a driving force such as concentration or pressure differential causes preferential transport across the membrane barrier. Separation occurs as a result of the non-racemic chiral nature of the membrane that allows only one enantiomer of the racemate to pass through.

xiv) Simulated moving bed chromatography, is used in one embodiment. A wide variety of chiral stationary phases are commercially available.

**Example 1. Synthesis of PLA linkers**

**Scheme 1: Synthesis of Octadecanoic acid (*S*)-1-carboxy-ethyl ester (1-4):**



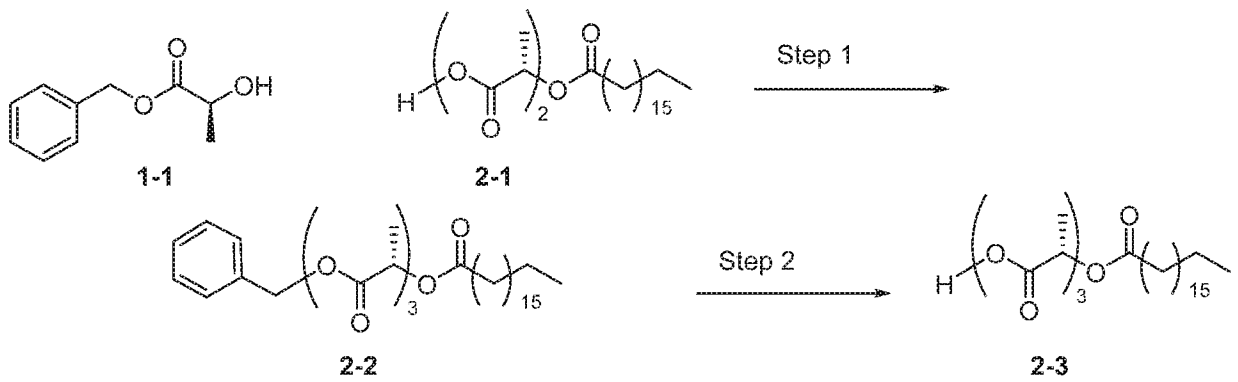

1-1 1-2 1-3 1-4

**Step-1**: **Preparation of Octadecanoic acid (*S*)-1-benzyloxycarbonyl-ethyl ester (1-2):** To a solution of octadecanoic acid (**1-2**, 14.2 g, 50.00 mmol) in dichloromethane (100 mL) was added EDC.HCl (15.9 g, 83.20 mmol), (*S*)-2-hydroxy-propionic acid benzyl ester (**1-1**, 10.0 g, 55.50 mmol) and 4-dimethylaminopyridine (680 mg, 5.5 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (750 mL), extracted with dichloromethane (800 X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% ethyl acetate in hexane) to obtain product **1-3** as a colorless liquid (13 g, 53 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.39 – 7.32 (m, 5H), 5.14 (s, 2H), 5.04 (q, *J* = 7.2 Hz, 1H), 2.32 (t, 2H), 1.51-1.47 (m, 2H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.22 (bs, 28H), 0.84 (t, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 445.1

**Step-2**: **Preparation of Octadecanoic acid (*S*)-1-carboxy-ethyl ester (1-4):** To a 250 mL autoclave vessel, a solution of octadecanoic acid (*S*)-1-benzyloxycarbonyl-ethyl ester (**1-3**,13 g, 27.86 mmol) in methanol (70 mL) and 10% Pd/C (2.6 g, 50% wet) were added at 25-30 °C. The

reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed. Then volatiles were evaporated under reduced pressure to obtain product **1-4** as an off white solid (7.5 g, 78 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 12.25 (s, 1H), 4.86 (q, *J* = 7.2 Hz, 1H), 2.31 (t, 2H), 1.53-1.49 (m, 2H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.23 (bs, 28H), 0.84 (t, *J* = 7.2 Hz, 3H); MS m/z $(M-H)^-$ 355.4

**Scheme 2: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (2-3):**

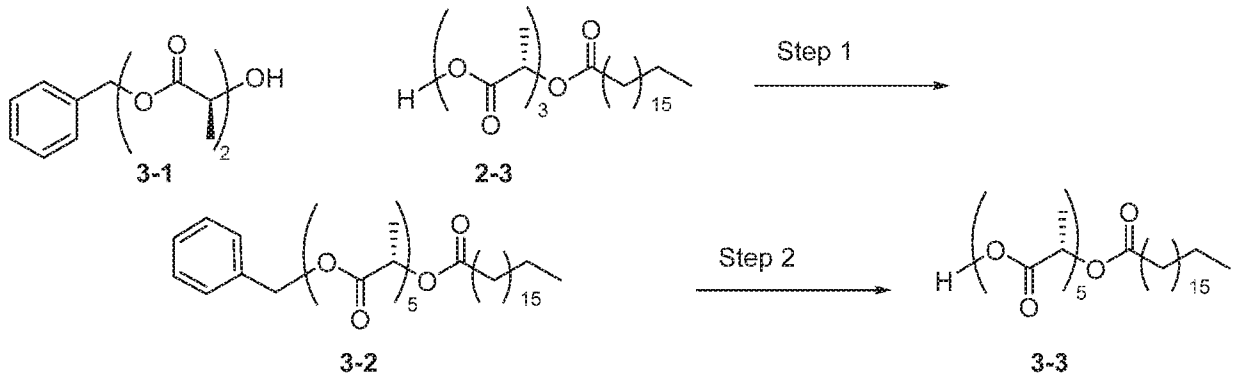



**Step-1**: **Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1- benzyloxycarbonyl -ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (2-2):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (**2-1**, 16.6 g, 41.66 mmol) in dichloromethane (50 mL) was added EDC.HCl (10.6 g, 55.54 mmol), (*S*)-2-hydroxy-propionic acid benzyl ester (**1-1**, 5 g, 27.77 mmol) and 4-dimethylaminopyridine (338 mg, 2.77 mmol) and at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (250 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% ethyl acetate in hexane) to obtain product **2-2** as a colorless liquid (11 g, 70 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.40 – 7.32 (m, 5H),5.20-5.14 (m, 4H), 5.05 (q, *J* = 7.2 Hz, 1H), 2.33 (t, 2H), 1.52-1.47 (m, 2H), 1.45-1.40 (m, 9H), 1.22 (bs, 28H), 0.86 (t, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 590.79, $(M+NH_4)^+$ 609

**Step-2**: **Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (2-3):** To a 100 mL autoclave vessel, a solution of octadecanoic acid (*R*)-1-[(*R*)-1-((*R*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**2-2**, 11 g,

19.57 mmol) in methanol (60 mL) and 10% Pd/C (2.2 g, 50% wet) was added at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed and the volatiles were evaporated under reduced pressure to obtain product **2-3** as a white solid (7.7 g, 83 %).

**Scheme 3: Synthesis of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (3-3):**



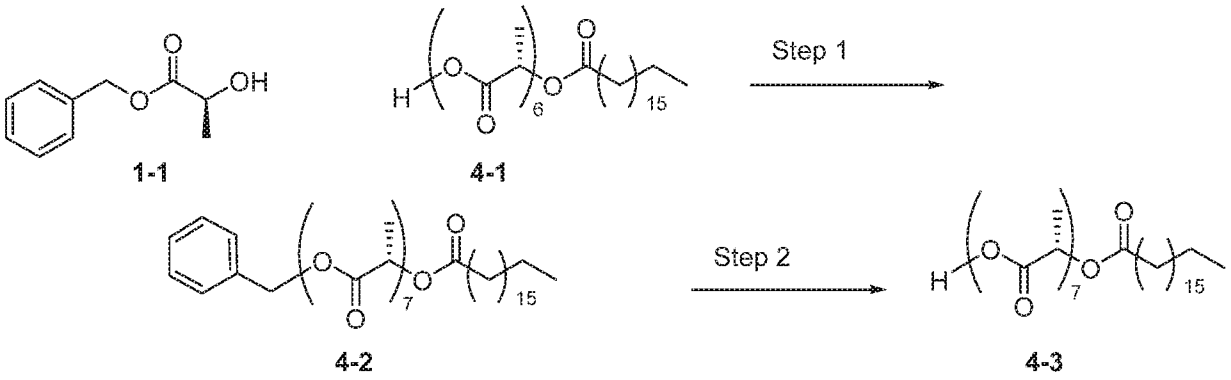

**Step-1**: **Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (3-2):** To a solution of octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**2-3**, 8.92 g, 17.85 mmol) in dichloromethane (30 mL) was added EDC.HCl (4.54 g, 23.8 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester (**3-1**, 3 g, 11.90 mmol) and 4-dimethylaminopyridine (145 mg, 1.19 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% ethyl acetate in hexane) to obtain product **3-2** as a colorless liquid (6.2 g, 71 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.38 – 7.34 (m, 5H), 5.21-5.15 (m, 6H), 5.05 (q, *J* = 7.2 Hz, 1H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.51-1.39 (m, 17H), 1.27 (bs, 28H), 0.86 (t, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 736, $(M+NH_4)^+$ 754

**Step-2**: **Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (3-3):**

To a 100 mL autoclave vessel, a solution of octadecanoic acid (*R*)-1-[(*R*)-1-((*R*)

-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**3-2**, 6.2 g, 19.57 mmol) in methanol (60 mL) and 20% Pd/C (1.24 g, 50% wet) were added at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed and the volatiles were evaporated under reduced pressure to obtain product **3-3** as a white solid (4.2 g, 77 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.23-5.14 (m, 3H), 5.05 (q, *J* = 7.2 Hz, 1H), 4.98 (q, *J* = 7.2 Hz, 1H), 2.32 (m, 2H), 1.53-1.39 (m, 17H), 1.23 (bs, 28H), 0.84 (t, *J* = 7.2 Hz, 3H); MS m/z (M-H)$^-$ 643.9

**Scheme 4: Synthesis of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (4-3):**

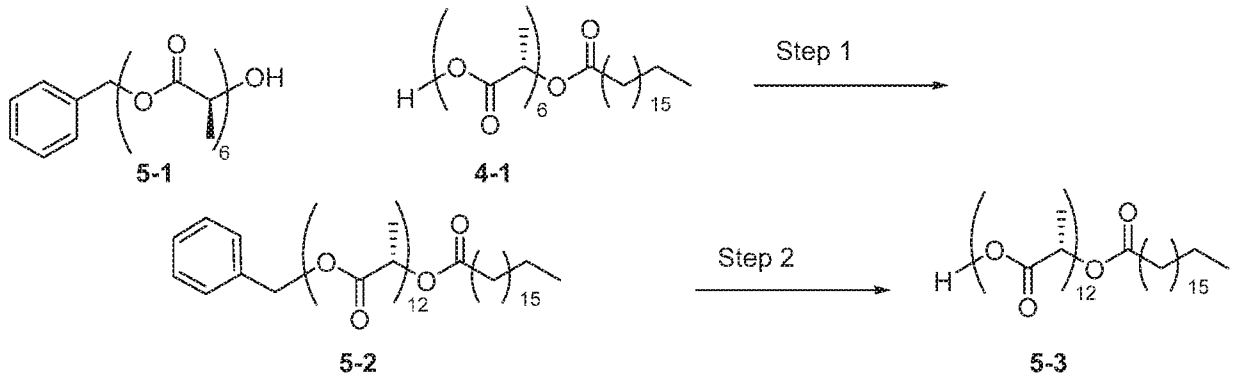



**Step-1: Preparation of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (4-2):** To a solution of octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**4-1**, 11.9 g, 16.66 mmol) in dichloromethane (50 mL) was added EDC.HCl (4.2 g, 22.22 mmol), (*S*)-2-hydroxy-propionic acid benzyl ester (**1-1**, 2.0 g, 11.11 mmol) and 4-dimethylaminopyridine (135 mg, 1.11 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (5% ethyl acetate in hexane) to obtain

product **4-2** as a colorless liquid (7.1 g, 73 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.38 – 7.34 (m, 5H),5.20-5.15 (m, 8H), 5.05 (q, *J* = 7.2 Hz, 1H), 2.35-2.31 (m, 2H), 1.50-1.39 (m, 23H), 1.24 (bs, 28H), 0.86 (t, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 879.9; $(M+NH_4)^+$ 897

**Step-2**: **Preparation of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (4-3):** To a 100 mL autoclave vessel, a solution of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]- ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**4-2**, 7.1 g, 8.08 mmol) in methanol (20 mL) and 10% Pd/C (1.42 g, 50% wet) were added at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed and the volatiles were evaporated under reduced pressure to obtain product **4-3** as a colorless low melting solid (4.8 g, 75 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.25-5.12 (m, 2H), 5.05 (q, *J* = 7.2 Hz, 1H), 4.97 (q, *J* = 7.2 Hz, 1H), 2.33 (m, 2H), 1.52-1.39 (m, 23H), 1.23 (bs, 28H), 0.85 (t, *J* = 7.2 Hz, 3H); MS m/z $(M-H)^-$ 787.1

**Scheme 5: Synthesis of Compound 5-3:**

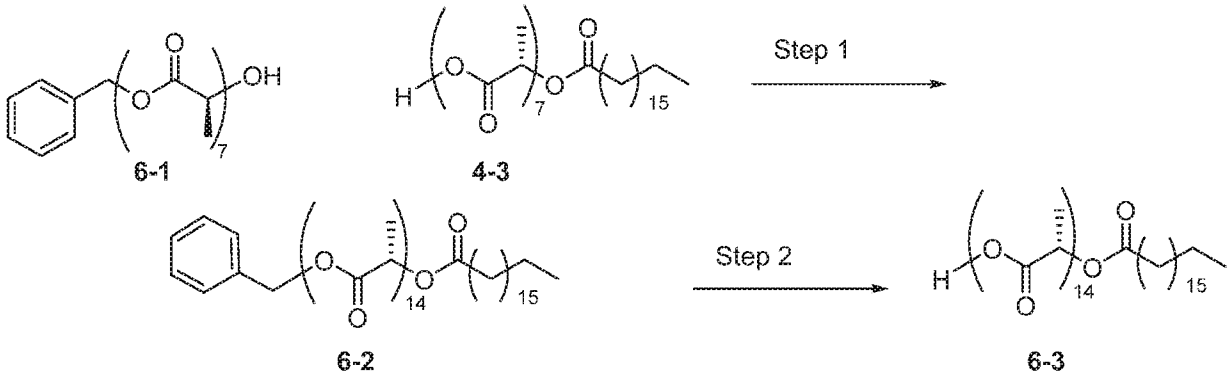



**Step-1**: **Preparation of Compound 5-2:** To a solution of octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**4-1**, 3.9 g, 5.55mmol) in dichloromethane (15 mL) was added EDC.HCl (1.4 g, 7.40 mmol), (*R*)-2-hydroxy-propionic acid (*R*)-1-((*R*)-1-{(*R*)-1-[(*R*)-1-((*R*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (**5-1**, 2.0 g, 3.70 mmol) and 4-dimethylaminopyridine (45 mg, 0.37 mmol) at 0°C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The

resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (6% ethyl acetate in hexane) to obtain product **5-2** as a pale yellow liquid 3.1 g (67 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.37 – 7.35 (m, 5H),5.21-5.15 (m, 13H), 5.05 (q, *J* = 7.2 Hz, 1H), 2.35-2.31 (m, 2H), 1.47-1.41 (m, 38H), 1.24 (bs, 28H), 0.86 (t, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 1240.3; $(M+NH_4)^+$ 1257.3

**Step-2**: **Preparation Compound 5-3:** To a 100 mL autoclave vessel, a solution of compound (**5-2**, 3.1 g, 2.50 mmol) in methanol (20 mL) and 20% Pd/C (0.62 g, 50% wet) were added at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed and the volatiles were evaporated under reduced pressure to obtain product **5-3** as a off white solid (2.3 g, 80 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 13.11 (bs, 1H), 5.23-5.17 (m, 10H), 5.09-4.95 (m, 2H), 1.47-1.40 (m, 36 H), 1.23 (bs, 32 H), 0.82 (t, *J* = 8.8 Hz, 3H), 2.35-2.31 (m, 2H), 1.47-1.41 (m, 38H), 1.24 (bs, 28H), 0.86 (t, *J* = 7.2 Hz, 3H) ; MS m/z $(M+H)^+$ 1240.3; $(M+NH_4)^+$ 1257.3

**Scheme 6: Synthesis of Compound 6-3:**




**Step-1: Preparation of Compound 6-2:** To a solution of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**4-3**, 6.75 g, 8.57 mmol) in dichloromethane (40 mL) was added EDC.HCl (2.18 g, 11.43 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**6-1**, 3.5 g, 5.71

mmol) and 4-dimethylaminopyridine (69 mg, 0.57 mmol) at 0°C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (250 mL), extracted with dichloromethane (350 X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (6% ethyl acetate in hexane) to obtain product **6-2** as a pale yellow liquid (6.2 g, 78 %).

**Step-2**: **Preparation Compound 6-3:** To a 250 mL autoclave vessel, a solution of compound **6-2**, 6.2 g, 4.48 mmol) in methanol (60 mL) and 20% Pd/C (1.24 g, 50% wet) were added at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 $kg/cm^2$) over a period of 2 hours. After completion of the reaction, the reaction mixture was filtered through celite bed and the volatiles were evaporated under reduced pressure to obtain product **6-3** as an off white solid (4.2 g, 72 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 13.20 (s, 1H), 5.23-5.15 (m, 12H), 5.08-4.97 (m, 2H), 2.33 t, $J$ = 7.2 Hz, 2H), 1.50-1.41 (m, 44H), 1.23 (bs, 28H), 0.85 (t, $J$ = 7.2 Hz, 3H); MS m/z $(M-H)^-$ 1147.7

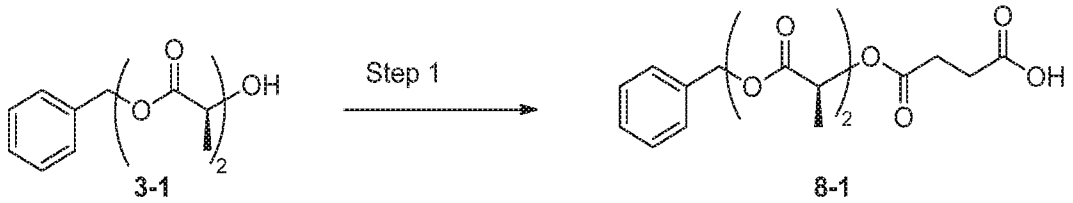
**Scheme 7: Synthesis of Succinic acid mono-((*S*)-1-benzyloxycarbonyl-ethyl) ester (7-1):**




1-1 7-1

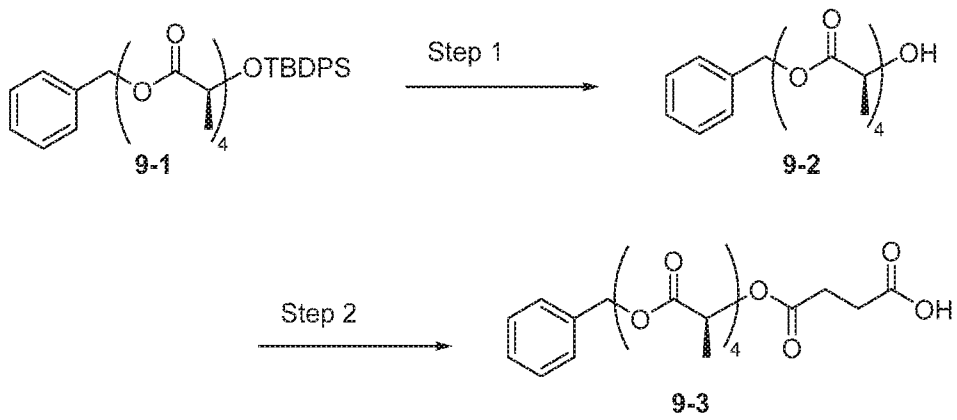
**Step-1: Preparation of Succinic acid mono-((*S*)-1-benzyloxycarbonyl-ethyl) ester (7-1):** To a solution of succinic acid (6.56 g, 55.55 mmol) in dichloromethane (50 mL) was added EDC.HCl (15.9 g, 83.33 mmol), hydroxybenzotriazole (0.766 g, 5.55 mmol), (*S*)-2-Hydroxy-propionic acid benzyl ester (**1-1**, 5.0 g, 27.77 mmol) and 4-dimethylaminopyridine (338 mg, 2.77 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mixture was quenched with water (150 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (30% ethyl acetate in hexane) to obtain **7-1** as a pale yellow liquid (1.0 g, 71 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 12.25 (bs, 1H), 7.38 – 7.33 (m, 5H), 5.15 (s, 2H), 5.05 (q, $J$ = 7.2 Hz, 1H), 2.58-2.46 (m, 4H), 1.40 (d, $J$ = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 281.6

**Scheme 8: Synthesis of Succinic acid mono-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl] ester (8-1):**




**Step-1: Preparation of Succinic acid mono-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl] ester (8-1):** To a solution of succinic acid (5.6 g, 47.61 mmol) in dichloromethane (60 mL) was added EDC.HCl (13.6 g, 71.4 mmol), hydroxybenzotriazole (0.697 g, 4.76 mmol), (*S*)-2-hydroxy-propionic acid benzyl ester (**3-1**, 6.0 g, 23.80 mmol) and 4-dimethylaminopyridine (290 mg, 2.38 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mixture was quenched with water (250 mL), extracted with dichloromethane (400X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (35% ethyl acetate in hexane) to obtain **8-1** as a pale, yellow liquid 4.3 g (51 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 12.24 (bs, 1H), 7.38 – 7.33 (m, 5H), 5.16-5.15 (m, 3H), 5.04 (q, *J* = 7.2 Hz, 1H), 2.57-2.45 (m, 4H), 1.40 (d, *J* = 7.2 Hz, 3H), 1.35 (d, J=7.2 Hz, 3H)

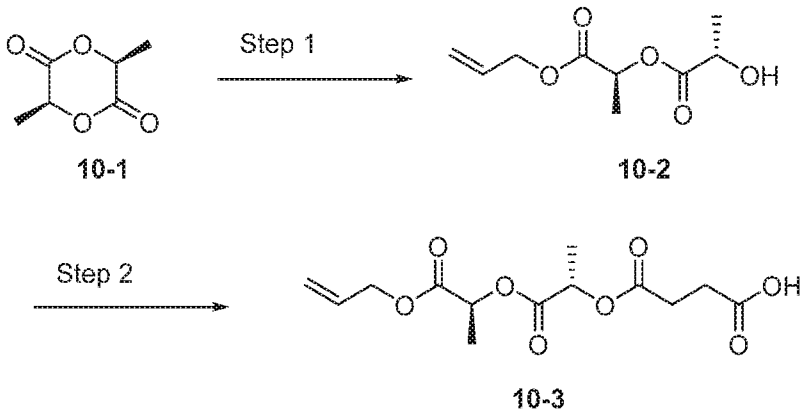
**Scheme 9: Synthesis of Succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethox ycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (9-3):**



**Step-1: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (9-2):** To a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**9-1**, 14 g, 22.05 mmol) in tetrahydrofuran (1400 mL) was added tetra-*n*-butylammonium fluoride (33.08 mL, 1.0 M, 33.08 mmol) and acetic acid (1.98 g, 33.08 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel column chromatography (20% ethyl acetate in hexane) to afford product **9-2** as colorless liquid (4.7 g, 53%). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.40 – 7.33 (m, 5H), 5.47 (d, *J* = 7.2 Hz, 1H), 5.20-5.07 (m, 5H), 4.22-4.177 (m, 1H), 1.46-1.39 (m, 9H), 1.26 (d, J=7.2 Hz, 3H); MS m/z $(M+H)^+$ 396.8

**Step-2: Preparation of Succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (9-3):** To a solution of succinic acid (2.8 g, 23.71 mmol) in dichloromethane (50 mL) was added EDC.HCl (6.79 g, 35.55 mmol), hydroxybenzotriazole (0.327 g, 2.37 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **9-2**, 4.7 g, 11.85 mmol) and 4-dimethylaminopyridine (144 mg, 1.18 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mixture was quenched with water (250 mL), extracted with dichloromethane (500X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (40% ethyl acetate in hexane) to obtain product **9-3** as a pale yellow liquid (3.1 g, 53 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 12.24 (bs, 1H), 7.38 – 7.35 (m, 5H), 5.21-5.15 (m, 5H), 5.05 (q, *J* = 7.2 Hz, 1H), 2.7-2.5 (m, 4H), 1.46-1.40 (m, 12H); MS m/z $(M-H)^-$ 494.6

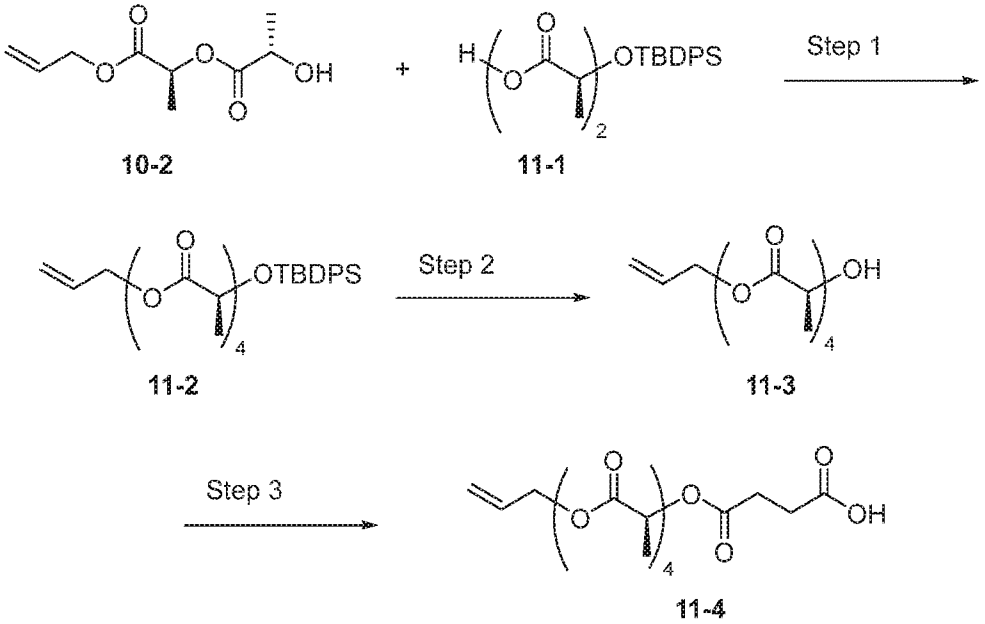
**Scheme 10: Synthesis of Succinic acid mono-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl] ester (10-3):**




**Step-1: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-allyloxycarbonyl-ethyl ester (10-2):** To a solution of (3*S*,6*S*)-3,6-dimethyl-[1,4]dioxane-2,5-dione **10-1**, 5.0 g, 34.72 mmol) in toluene (100 mL) was added allyl alcohol (2.24 mL, 32.98 mmol) and camphorsulfonic acid (0.8 g, 3.47 mmol) at 25-30 °C. The reaction mixture was allowed to stir at 80 °C over a period of 16 hours. The resulting reaction mixture was diluted with ethyl acetate (800 mL) and washed with water (2 X 400 mL). The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column chromatography (5% methanol in dichloromethane) to obtain product **10-2** as a pale yellow liquid (3.6 g, 51%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.93-5.87 (m, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 5.34-5.21 (m, 2H), 5.07 (q, *J* = 7.2 Hz, 1H), 4.62-4.60 (d, *J* = 7.2 Hz, 1H), 4.22-4.18 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.28 (d, *J* = 7.2 Hz, 3H); MS m/z $(M+H)^+$ 203.0

**Step-2: Preparation of Succinic acid mono-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl] ester (10-3):** To a solution of (*S*)-2-hydroxy-propionic acid (*S*)-1-allyloxycarbonyl-ethyl ester **10-2**, 3.6 g, 17.82 mmol) in dichloromethane (40 mL) was added 4-dimethylaminopyridine (338 mg, 2.77 mmol) and dihydro-furan-2,5-dione (3.2 g, 32.07 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 16 hours. The resulting reaction mixture was quenched with water (150 mL), extracted with dichloromethane (250X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in dichloromethane) to obtain product **10-3** as a pale yellow liquid (2.9 g, 53 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 12.25 (bs, 1H), 5.94-5.84 (m, 1H), 5.33-5.04 (m, 4H), 4.61 (m, 2H) 2.66-2.54 (m, 4H), 1.41(m, 6H); $(M+H)^+$ 302.9 $(M+NH_4)^+$ 319.9

**Scheme 11: Synthesis of Succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (11-4):**




**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (11-2):** To a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester **11-1**, 2.75 g, 6.43 mmol) in dichloromethane (10 mL) was added EDC.HCl (1.88 g, 9.88 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-allyloxycarbonyl-ethyl ester **10-2**, 1.0 g, 4.94 mmol) and 4-dimethylaminopyridine (59 mg, 0.49 mmol) at 0°C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (150X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% ethyl acetate in hexane) to obtain product **11-2** as a colorless liquid (1.8 g, 62 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.61-7.39 (m, 10H), 5.92-5.85 (m, 1H), 5.32-5.13 (m, 4H), 4.95 (q, *J* = 6.8 Hz, 1H), 4.61-4.59 (m, 2H), 4.29 (q, *J* = 6.8 Hz, 1H), 1.5-1.4 (m, 6H), 1.35-1.28 (m, 6H) 1.02 (s, 9H); MS m/z $(M+H)^+$ 585.7, $(M+NH_4)^+$ 602.7

**Step-2: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (11-3):** To a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-

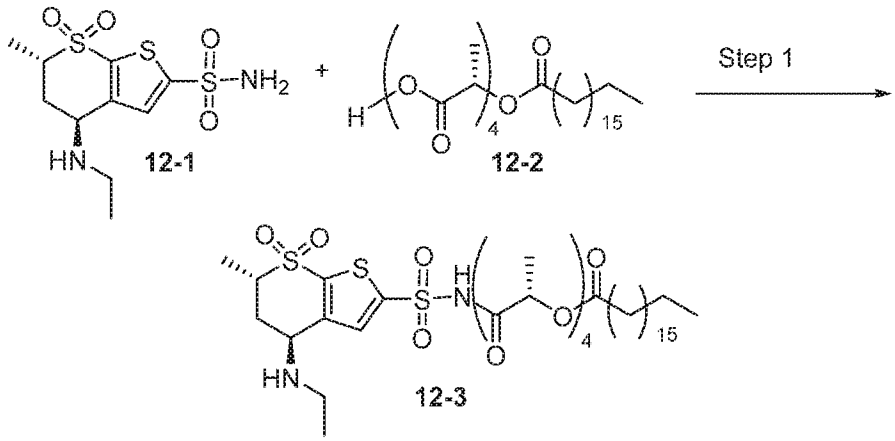
ethoxycarbonyl]-ethyl ester **11-2**, 2.0 g, 3.42 mmol) in tetrahydrofuran (20 mL) was added tetra-*n*-butylammonium fluoride (5.1 mL, 1.0 M, 5.13 mmol) and acetic acid (0.30 g, 5.13 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour at 0 °C. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel column chromatography (18% ethyl acetate in hexane) to afford product **11-3** as a colorless liquid (0.6 g, 50%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.93-5.86 (m, 1H), 5.48 (d, *J* = 6.4 Hz, 1H), 5.34-5.09 (m, 5H), 4.62-4.60 (m, 2H), 4.20 (q, *J* = 6.4 Hz, 1H), 1.48-1.40 (m, 9H), 1.29-1.25 (m, 3H); MS m/z $(M+H)^+$ 347.7, $(M+NH_4)^+$ 364.7

**Step-3: Preparation of Succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (11-4):** To a solution of (*S*)-2-hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **11-3**, 0.6 g, 1.73 mmol) in dichloromethane (6 mL) was added 4-dimethylaminopyridine (42 mg, 0.34 mmol) and dihydro-furan-2,5-dione (0.31 g, 3.11 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 16 hours. The resulting reaction mixture was quenched with water (50 mL), extracted with dichloromethane (150 X 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in dichloromethane) to obtain product **11-4** as a colorless liquid (0.4 g, 51 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.93-5.86 (m, 1H), 5.34-5.04 (m, 6H), 4.62-4.60 (m, 2H), 2.60-2.44 (m, 4H), 1.47-1.42 (m, 12H); MS m/z $(M-H)^-$ 445.5.

**Example 2. Synthesis of Mono-Prodrugs**

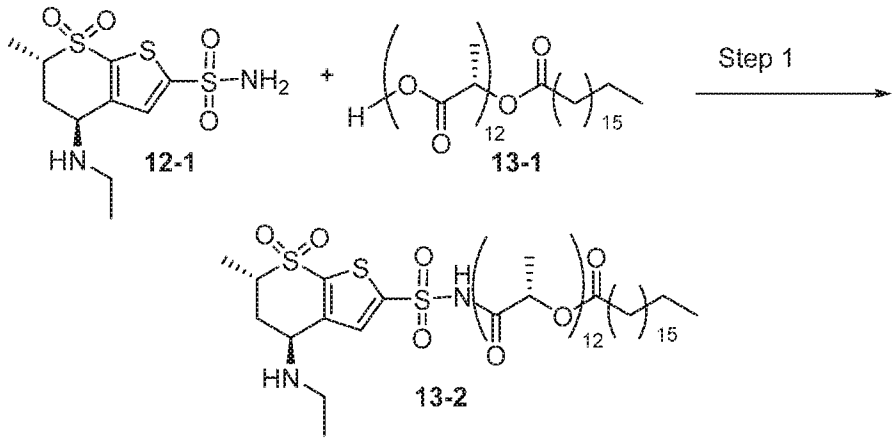
***Synthesis of Dorzolamide Mono-Prodrugs***

**Scheme 12: Synthesis of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-2-(4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (12-3):**



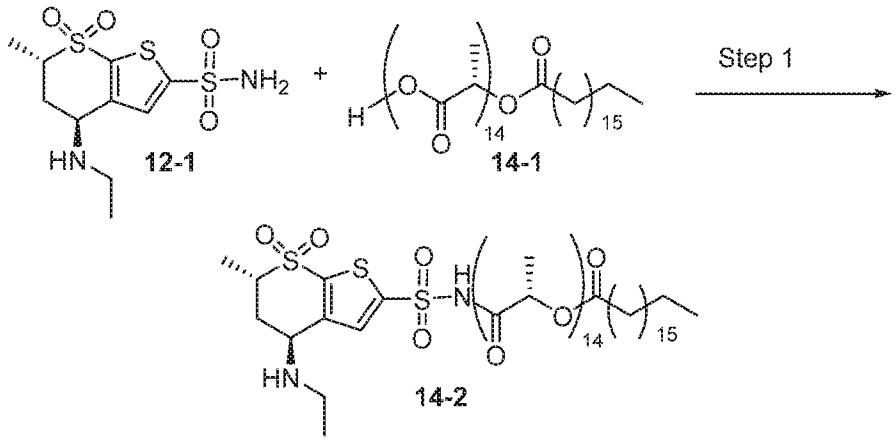

**Step-1: Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-2-(4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (12-3):** To a solution of Dorzolamide (**12-1**, 0.3 g, 0.83 mmol) in dichloromethane (3 mL) was added *N*,*N*-diisopropylethylamine (0.3 mL, 1.66 mmol) at 0 °C. After 30 minutes, octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**12-2**, 0.715 g, 1.25 mmol), EDC.HCl (0.317 g, 1.66 mmol) and 4-dimethylaminopyridine (0.01 g, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (250X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% methanol in DCM) to obtain product **12-3** as an off-white solid (0.3 g, 41%). $^1$H-NMR (400 MHz, DMSO-d6 with TFA) δ 8.85 (m, 2H), 8.14 (s, 1H), 5.2-5.1 (m, 2H), 5.1-4.9 (m, 2H), 4.75-4.65 (m, 1H), 4.15-4.0 (m. 1H), 3.30-2.9 (m, 2H), 2.7-2.4 (m, 2H), 2.30 (t, 2H), 1.55-1.3 (m, 17H), 1.3-1.1 (m, 31H), m, 0.85-0.75 (m, 3H); MS *m/z* $[M+H]^+$ 880.3.

**Scheme 13: Synthesis of Compound 13-2:**




**Step-1: Preparation of Compound 13-2:** To a solution of Dorzolamide (**12-1**, 0.25 g, 0.69 mmol) in dichloromethane (2.5 mL) was added *N,N*-diisopropylethylamine (0.25 mL, 1.38 mmol) at 0 °C. After 30 minutes, compound **13-1** (1.03 g, 0.89 mmol), EDC.HCl (0.263 g, 1.38 mmol) and 4-dimethylaminopyridine (0.008 g, 0.07 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (250X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3.5% methanol in DCM) to obtain **13-2** as an off-white solid 0.35 g (34.6%). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.43 (bs, 1H), 5.26-5.15 (m, 9H), 5.15-5.0 (m, 2H), 4.79 (q, 1H), 3.95-3.8 (m. 2H), 2.6-2.4 (m, 2H), 2.33 (t, 2H), 1.55-1.38 (m, 33H), 1.38-1.15 (m, 38H), 1.15-0.95 (m, 3H), 0.83 (t, 3H); MS *m/z* $[M+H]^+$ 1456.5.

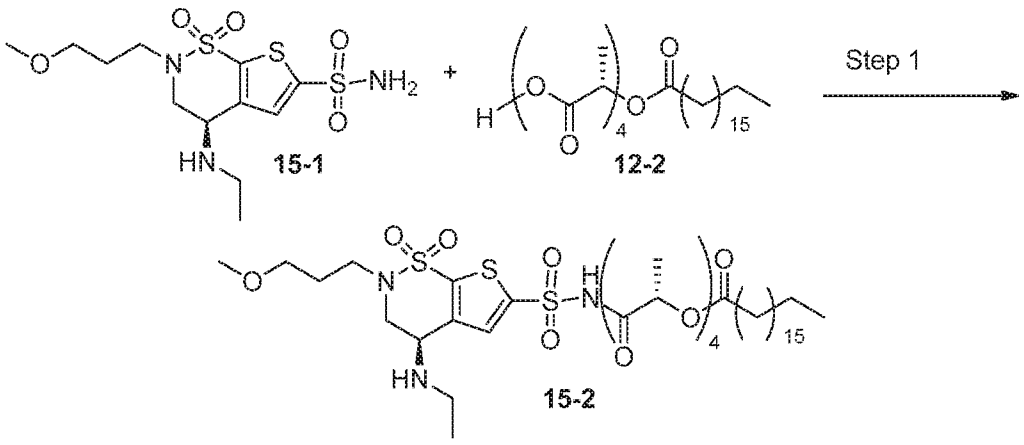
**Scheme 14: Synthesis of Compound 14-2:**



**Step-1: Preparation of Compound 14-2:** To a solution of Dorzolamide (**12-1**, 0.25 g, 0.69 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.25 mL, 1.38 mmol) at 0 °C. After 30 minutes, compound **14-1** (1.168 g, 0.9 mmol), EDC.HCl (0.263 g, 1.38 mmol) and 4-dimethylaminopyridine (0.008 g, 0.07 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (250X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in DCM) to obtain **14-2** as an off-white solid (0.15 g, 13.6%). $^1$H-NMR (400 MHz, DMSO-d6 with TFA) δ 9.0-8.75 (m, 2H), 8.13 (s, 1H), 5.24-5.1 (m, 12H), 5.03 (q, 2H), 4.97 (q, 2H), 4.73-4.65 (m, 1H), 4.15-4.0 (m. 1H), 2.7-2.4 (m, 2H), 2.33 (t, 2H), 1.6-1.3 (m, 47H), 1.3-1.1 (m, 31H), 0.81 (t, 3H).

***Synthesis of Brinzolamide Mono-Prodrugs***

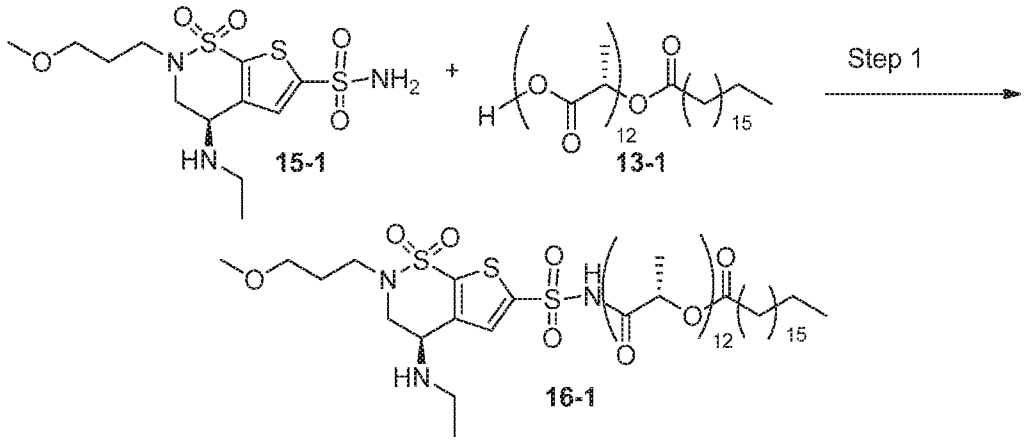
**Scheme 15: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (15-2):**




**Step-1: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-**

**sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (15-2):** To a solution of Brinzolamide (**15-1**, 0.3g, 0.78 mmol) and octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**12-2**, 0.671 g, 1.17 mmol) in dichloromethane (3 mL) was added EDC.HCl (0.298 g, 1.56 mmol), 4-dimethylaminopyridine (9 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (250 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) to obtain product **15-2** as an off white solid (0.2 g, 27.3 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.9 (m, 2H), 7.89 (s, 1H), 5.21-5.01 (m, 3H), 4.90-4.79 (m, 2H), 4.13-3.99 (m, 2H), 3.42-3.31 (m, 3H), 3.24-3.0 (m, 6H), 2.33 (t, 2H), 1.83 (quintet, 2H), 1.57-1.37 (m, 11H), 1.34-1.15 (m, 31H), 0.83 (t, 3H). MS *m/z* $[M+H]^+$ 939.1.

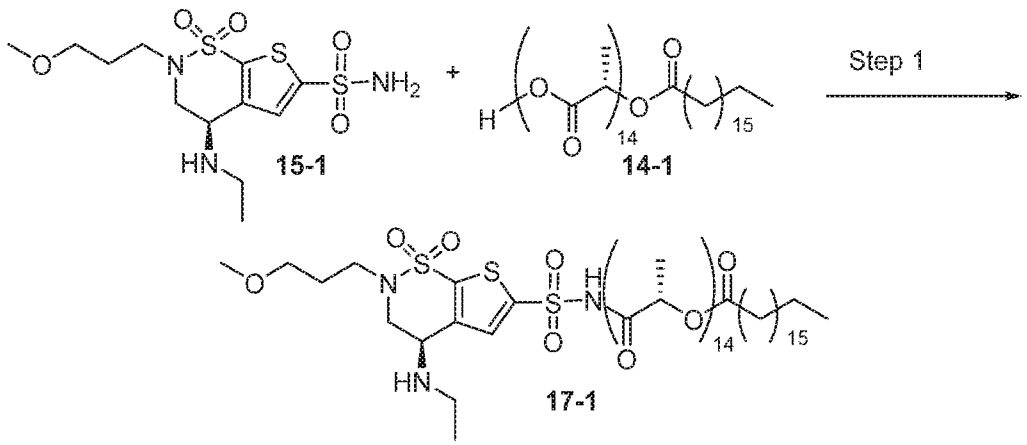
**Scheme 16: Synthesis of Compound 16-1:**




**Step-1: Preparation of Compound 16-1:** To a solution of Brinzolamide (**15-1**, 0.3g, 0.78 mmol) and compound (**13-1**, 1.165 g, 1.01 mmol) in dichloromethane (3 mL) was added EDC.HCl (0.298 g, 1.56 mmol) and 4-dimethylaminopyridine (9 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (250 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in

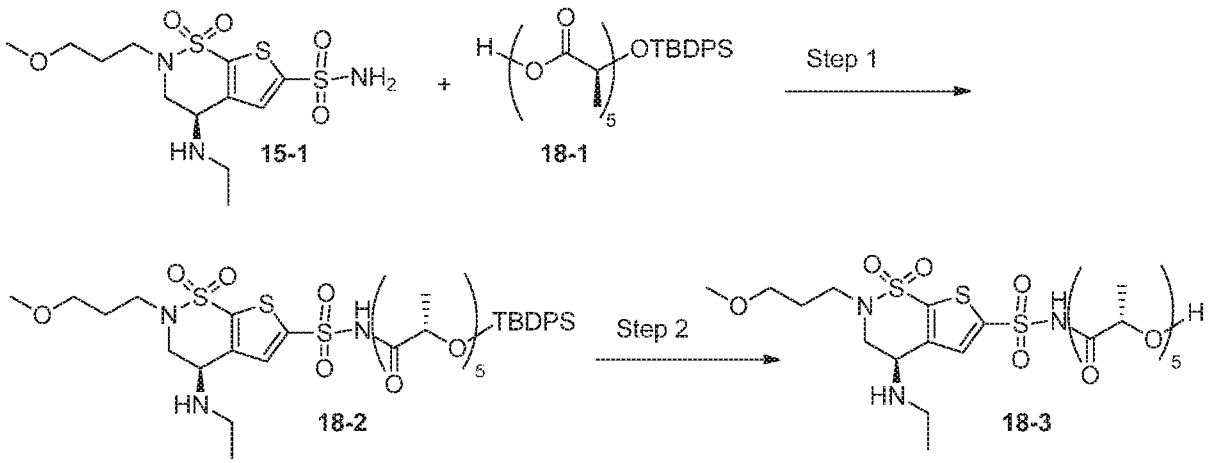
DCM) to obtain **16-1** as an off white solid (0.2 g, 19.4 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.9 (m, 2H), 7.84 (bs, 1H), 5.25-5.0 (m, 11H), 5.14-4.89-4.75 (m, 2H), 4.1-3.9 (m, 2H), 3.41-3.32 (m, 3H), 3.24-3.0 (m, 6H), 2.35-2.25 (m, 2H), 1.82 (quintet, 2H), 1.55-1.39 (m, 32H), 1.34-1.16 (m, 34H), 0.83 (t, 3H). MS *m/z* $[M+H]^+$ 1515.7.

**Scheme 17: Synthesis of compound 17-1:**




**Step-1: Preparation of Compound 17-1:** To a solution of Brinzolamide (**15-1**, 0.25g, 0.65 mmol) and compound (**14-1**, 1.18 g, 9.1 mmol) in dichloromethane (2.5 mL) was added EDC.HCl (0.248 g, 1.3 mmol) and 4-dimethylaminopyridine (8 mg, 0.06 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (250 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% methanol in DCM) to obtain crude **17-1**, which was further purified by preparative HPLC to afford **17-1** as an off white solid (0.08 g, 8 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.9 (m, 2H), 7.79 (s, 1H), 5.25-5.15 (m, 11H), 5.14-5.01 (m, 2H), 4.89-4.73 (m, 2H), 4.1-3.9 (m, 2H), 3.41-3.30 (m, 3H), 3.24-3.0 (m, 6H), 2.33 (t, 2H), 1.81 (quintet, 2H), 1.54-1.37 (m, 39H), 1.36-1.15 (m, 34H), 0.82 (t, 3H). MS *m/z* $[M+H]^+$ 1658.4.

**Scheme 18: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (18-3):**

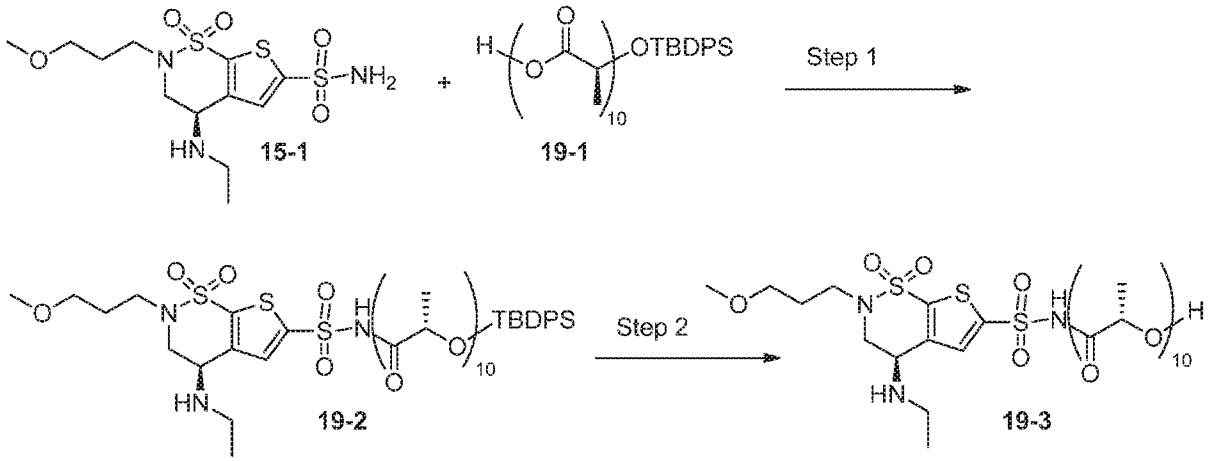



**Step-1: Preparation of compound 18-2:** To a solution of Brinzolamide (**15-1**, 0.8 g, 2.09 mmol) and (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid, (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**18-1**, 1.933 g, 3.13 mmol) in dichloromethane (8 mL) was added EDC.HCl (0.798 g, 4.18 mmol) and 4-dimethylaminopyridine (25 mg, 0.21 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (300 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% methanol in DCM) to obtain product **18-2** as an off-white solid (1.4 g, 68.6 %). 1H NMR (400 MHz, DMSO-d6) δ 7.64 – 7.57 (m, 4H), 7.53 – 7.37 (m, 6H), 5.11 (dq, *J* = 34.1, 7.0 Hz, 2H), 4.94 (q, *J* = 7.0 Hz, 2H), 4.29 (q, *J* = 6.7 Hz, 1H), 4.03 (bs, 1H), 3.74 (s, 2H), 3.45 – 3.34 (m, 3H), 3.22 (m, 2H), 1.80 (m, *J* = 6.8 Hz, 2H), 1.46 (dd, *J* = 10.1, 7.0 Hz, 7H), 1.38 – 1.20 (m, 18H), 1.02 (s, 14H). MS m/z (M+H) 983.2

**Step-2: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(S)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (18-3):** To a solution of compound **18-2** (1.4 g, 1.42 mmol) in tetrahydrofuran (14 mL) was added tetra butyl ammonium fluoride (2.13 mL, 1.0M, 2.13 mmol) and acetic acid (0.128 ml, 2.13 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 12 hours. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified

through silica gel column chromatography (5% methanol in ethyl acetate) to afford product **18-3** as an off white solid (500 mg, 47%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.8 (m, 2H), 7.76 (bs, 1H), 5.45 (d, 1H), 5.19-5.03 (m, 3H), 4.79 (q, 1H), 4.18 (quintet, 1H), 4.1-3.95 (m, 2H), 3.40-3.28 (m, 3H), 3.21-2.9 (m, 6H), 1.80 (quintet, 2H), 1.48-1.39 (m, 9H), 1.29-1.22 (m, 6H), 1.16 (t, 3H). MS *m/z* $[M+H]^+$ 744.6.

**Scheme 19: Synthesis of Compound 19-3:**

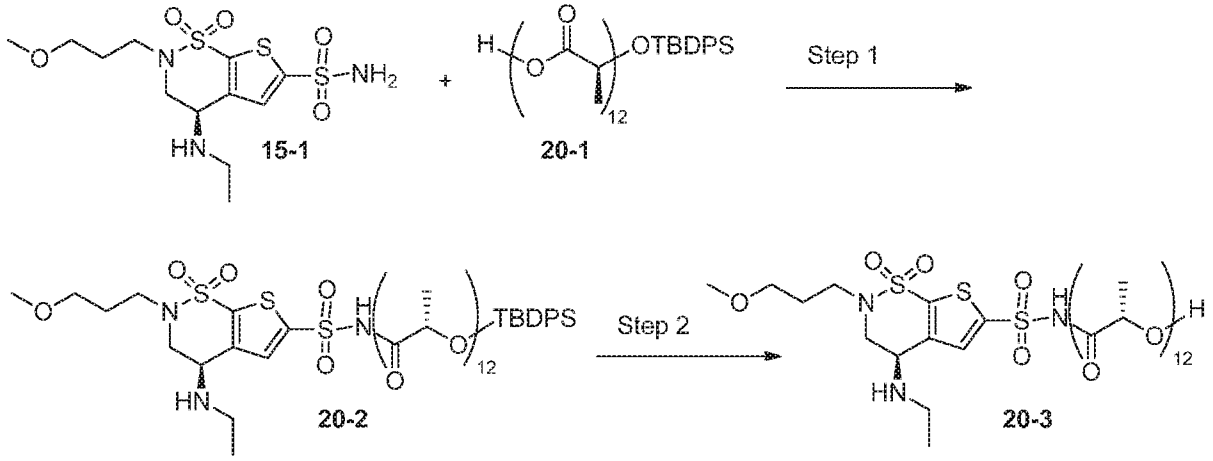



**Step-1: Preparation of Compound 19-2:** To a solution of Brinzolamide (**15-1**, 0.35 g, 0.91 mmol) and (2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-[(tertbutyldiphenylsilyl)oxy]propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoic acid (**19-1**, 1.33 g, 1.36 mmol) in dichloromethane (3.5 mL) was added EDC.HCl (0.348 g, 1.82 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4.5% methanol in DCM) to obtain product **19-2** as an off-white solid (0.54 g, 44.3 %). 1H NMR (400 MHz, DMSO-d6) δ 7.61 – 7.59 (m, 4H), 7.48-7.39 (m, 6H), 5.22-5.15 (m, 6H), 5.08 (q, *J* = 7.2 Hz, 1H), 4.94

(q, *J* = 7.2 Hz, 1H), 4.79 (q, *J* = 7.2 Hz, 2H), 3.40-3.33 (m, 4H), 3.22 (s, 2H), 1.48 – 1.40 (m, 21H), 1.33 - 1.29 (m, 16H), 1.01 (s, 10H). MS m/z $(M+H)^+$ 1343.0

**Step-2: Preparation compound 19-3:** To a solution of compound (**19-2**, 0.54 g, 0.4 mmol) in tetrahydrofuran (5.4 mL) was added tetra butyl ammonium fluoride (0.8 mL, 1.0M, 0.8 mmol) and acetic acid (0.048 ml, 0.8 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 12 hours. The resulting reaction mixture was concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (5.5% methanol in ethyl acetate) and further purified by preparative HPLC to obtain **19-3** as an off white solid (55 mg, 12.5 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.9 (m, 2H), 7.82 (s, 1H), 5.76 (s, 1H), 5.48 (d, 1H), 5.25-5.05 (m, 7H), 4.9-4.77 (m, 2H), 4.21 (quintet, 1H), 4.13-3.98 (m, 2H), 3.45-3.35 (m, 3H), 3.24-3.0 (m, 6H), 1.82 (quintet, 2H), 1.50-1.41 (m, 24H), 1.33-1.25 (m, 6H), 1.24 (t, 3H). MS *m/z* $[M+H]^+$ 1105.0.

**Scheme 20: Synthesis of Compound 20-3:**



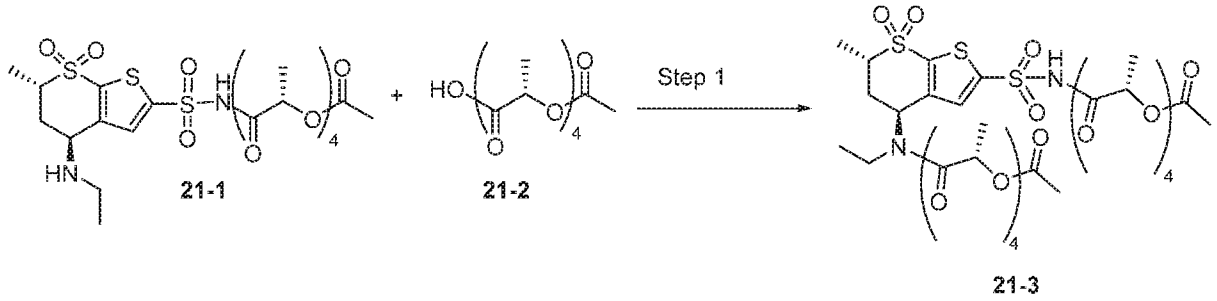

**Step-1: Preparation of Compound 20-2:** To a solution of Brinzolamide (**15-1**, 0.35 g, 0.91 mmol) and (2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2*S*)-2-{[(2S)-2-{[(2*S*)-2-[(*tert*-butyldiphenylsilyl)oxy]propanoyl]oxy}propanoyl]oxy} propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}p ropanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoic acid (**20-1**, 1.53 g, 1.36 mmol) in dichloromethane (3.5 mL) was added EDC.HCl (0.348 g, 1.82 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at

25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) to obtain product **20-2** as an off-white solid (1 g, 74 %).

**Step-2: Preparation of Compound 20-3:** To a solution of compound **20-2** (1 g, 0.67 mmol) in tetrahydrofuran (10 mL) was added tetra butyl ammonium fluoride (1.34 mL, 1.0M, 1.34 mmol) and acetic acid (0.08 ml, 1.34 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 12 hours. The resulting reaction mixture was concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in ethyl acetate) and further purified by preparative HPLC to obtain product **20-3** as an off white solid (120 mg, 14.3 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.2-8.9 (m, 2H), 7.73 (s, 1H), 5.73 (s, 1H), 5.44 (d, 1H), 5.25-5.15 (m, 9H), 5.15-5.02 (m, 2H), 4.81-4.73 (m, 2H), 4.17 (quintet, 1H), 4.1-3.9 (m, 2H), 3.48-3.29 (m, 3H), 3.24-2.952 (m, 6H), 1.80 (quintet, 2H), 1.50-1.40 (m, 30H), 1.30-1.22 (m, 6H), 1.18 (t, 3H). MS *m/z* $[M+H]^+$ 1248.9.0.

***Synthesis of Bis-PLA-Dorzolamide Mono-Prodrugs***

**Scheme 21: Synthesis of Compound 21:**

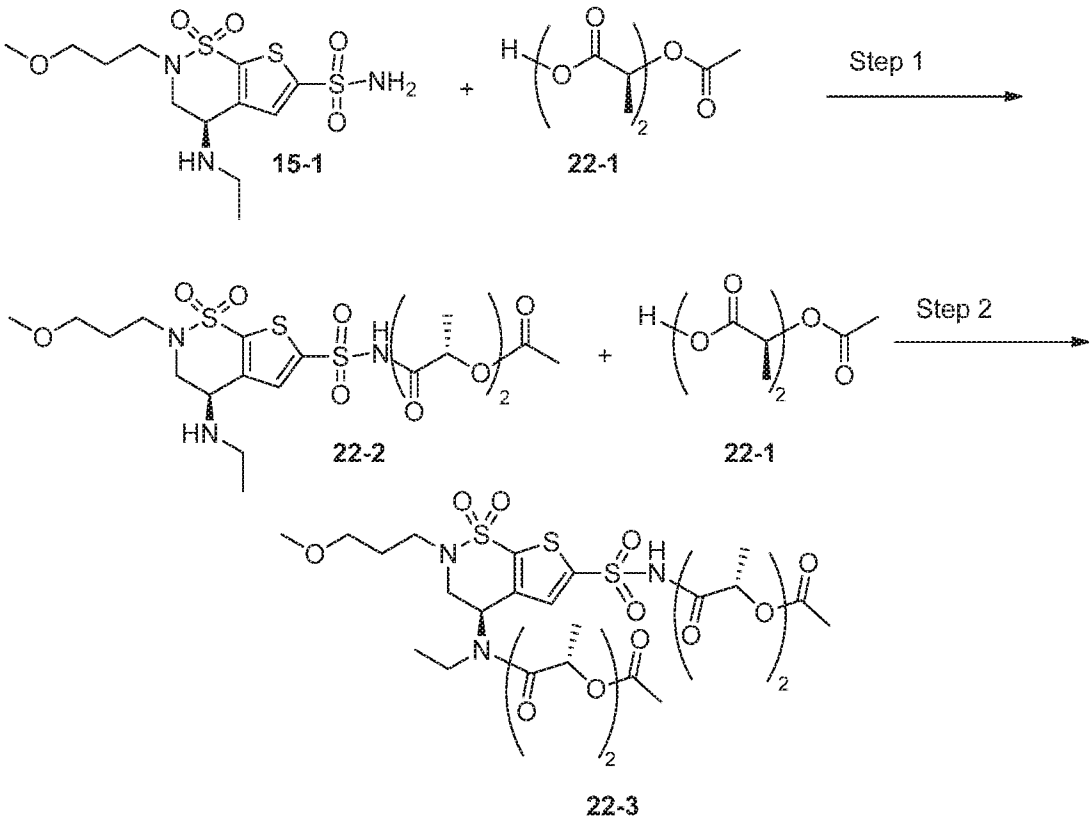



**Step-1: Preparation of Compound 21-3:** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**21-2**, 0.636 g, 1.83 mmol) in dichloromethane (8 mL) was added triethyamine (0.5 ml, 3.66 mmol), ethyl chloroformate (0.25 ml, 2.44mmol), (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (*S*)-1-{(*S*)-2-[(*S*)-4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethylester (**27-1**, 0.8 g, 1.22

mmol), 4-dimethylaminopyridine (14.8 mg, 0.12 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC. The recovered solid was washed with water and dried to obtain product **27-3** as an off white solid (60 mg, 5 %). $^1$H-NMR (400 MHz, DMSO-d6) (2 rotamers observed) δ 7.33 and 7.02 (2s, 1H), 5.9-5.0 (m,7H), 4.77 (q, 1H), 3.77 (t, 1H), 3.5-3.0 (m, 2H), 2.8-2.3 (m, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 1.55-1.2 (m, 27H), 1.16 and 0.97 (2t, 3H); MS *m/z* $(M-H)^-$ 984.2.

***Synthesis of Bis-PLA-Brinzolamide Mono-Prodrugs***

**Scheme 22: Synthesis of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[4-{[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-ethyl-amino}-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethyl ester (22-3):**

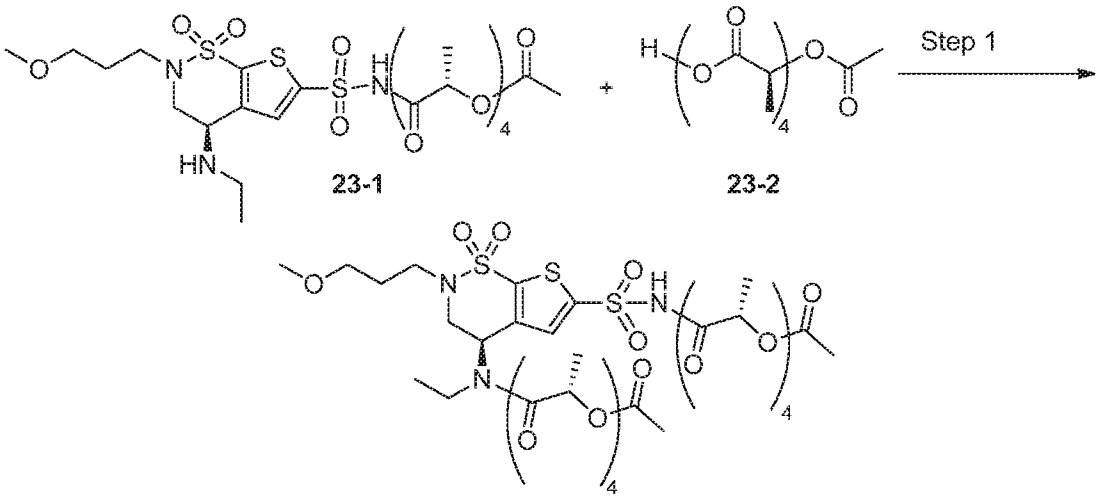



**Step-1: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-**

**methyl-2-oxo-ethyl ester (22-2):** To a solution of Brinzolamide (**15-1**, 1 g, 2.61 mmol) and (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (**22-1**, 0.797 g, 3.91 mmol) in dichloromethane (10 mL) was added EDC.HCl (0.997 g, 5.22 mmol) and 4-dimethylaminopyridine (32 mg, 0.26 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (150X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (3% methanol in DCM) to obtain product **22-2** as an off white solid (550 mg, 37 %). $^1$H NMR (400 MHz, DMSO-d6) δ 7.57 (s, 1H), 5.06 – 4.89 (m, 1H), 4.78 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.38 (q, *J* = 6.4 Hz, 4H), 3.25 – 3.10 (m, 3H), 2.09 – 2.03 (m, 2H), 2.05 (s, 2H), 1.85 – 1.77 (m, 2H), 1.48 – 1.36 (m, 4H), 1.29 (dd, *J* = 7.0, 4.0 Hz, 3H), 1.09 (dd, *J* = 7.2, 4.5 Hz, 2H). MS m/z $(M+H)^+$ 570.0.

**Step-2: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[4-{[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-ethyl-amino}-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1lambda*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethyl ester (22-3):** To a solution of (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (**22-1**, 0.294 g, 1.44 mmol) in dichloromethane (5.5 mL) was added triethyamine (0.394 ml, 2.88 mmol), ethyl chloroformate (0.252 ml, 2.4mmol), (*S*)-2-acetoxy-propionic acid (*S*)-2-[4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethyl ester (**22-2**, 0.550 g, 0.96 mmol), and 4-dimethylaminopyridine (11.7 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200 X2 mL). The dichloromethane was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC to obtain product **22-3** as an off white solid (75 mg, 10 %). $^1$H-NMR (400 MHz, DMSO-d6) δ (2 rotamers observed) δ 7.63 and 7.29 (2s, 1H), 5.9-4.8 (m, 4H), 4.2-2.6 (m, 12H), 2.09-2.03 (4s, 6H), 1.88-1.78 (m, 2H), 1.48-0.8 (m, 15H), MS *m/z* $(M-H)^-$ 755.8.

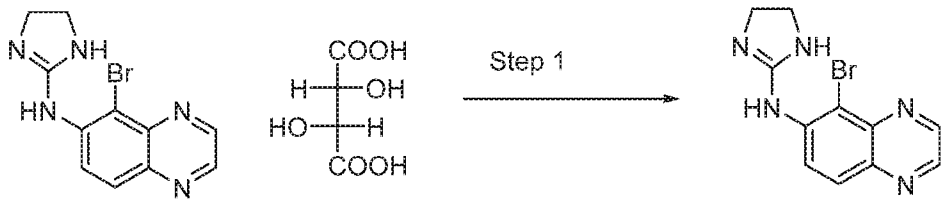
**Scheme 23: Synthesis of Compound 23-3:**




**Step-1: Preparation of Compound 23-3:** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**23-2**, 0.439 g, 1.26 mmol) in dichloromethane (6 mL) was added triethyamine (0.34 ml, 2.52 mmol), ethyl chloroformate (0.17 ml, 1.68 mmol), (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (*S*)-1-{(*S*)-2-[(S)-4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (**23-1**, 0.6 g, 0.84 mmol), and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC to obtain product **23-3** as an off white solid (50 mg, 5.7 %). $^1$H-NMR (400 MHz, DMSO-d6) δ (2 rotamers observed) δ 7.63 and 7.26 (2s, 1H), 5.9-4.8 (m, 8H), 4.2-2.6 (m, 12H), 2.07 (s, 6H), 1.81 (q, 2H), 1.55-0.9 (m, 27H), MS *m/z* $(M-H)^-$ 1044.1.

***Synthesis of Brimonidine Mono-Prodrugs***

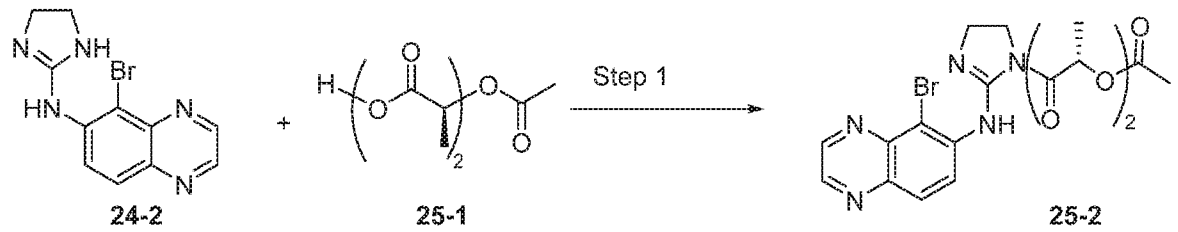
**Scheme 24: Synthesis of Free Brimonidine (24-2):**




24-1 24-2

**Step-1: Preparation of Free Brimonidine (24-2):** To a solution of Brimonidine tartarate (**24-1**, 5g, 11.3mmol) in water (50 ml) was added NaOH pellets (1.13 g, 28.27 mmol) slowly at 0 °C. The reaction mixture was allowed to stir at 0-5 °C over a period of 15 minutes. The resulting reaction mass was filtered and the collected solid was dried under high vacuum to obtain product **24-2** as a pale yellow solid (2 g, 60 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.85 (d, J = 2 Hz, 1H), 8.69 (d, J = 2 Hz, 1H), 7.83 (d, J = 9 Hz, 1H), 7.56 (d, J = 9 Hz, 1H), 6.56 (s, 2H), 3.50 (s, 4H). MS *m/z* $[M+H]^+$ 292.1/294.1.

**Scheme 25: Synthesis of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (25-2):**

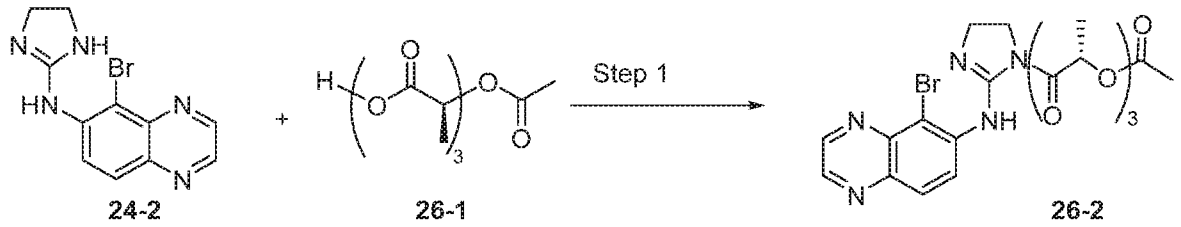



24-2 25-1 25-2

**Step-1: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (25-2):** To a solution of Brimonidine (**24-2**, 0.25 g, 0.85 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.31 mL, 1.7 mmol) at 0 °C. After 30 minutes, (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (**25-1**, 0.433 g, 2.12 mmol), EDC.HCl (0.487 g, 2.55 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon

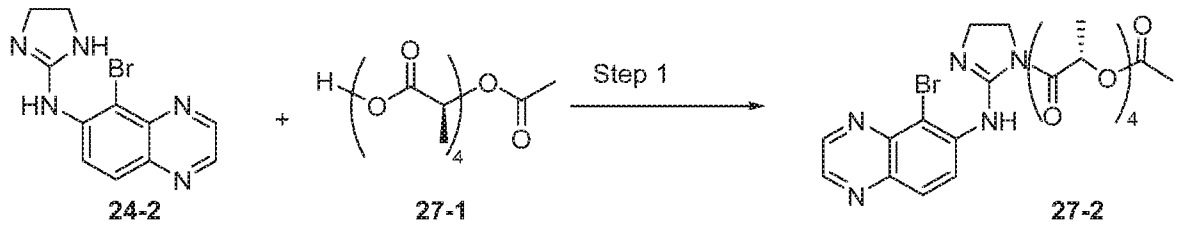
evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in DCM) and further purified by prep-HPLC to obtain product **25-2** as a pale yellow solid (60 mg, 14.7 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 7.29 (s, 1H), 6.53 (q, 1H), 5.05 (q, 1H), 3.96-3.84 (m, 2H), 3.44-3.34 (m, 2H), 2.06 (s, 3H), 1.63 (d, 3H), 1.47 (d, 3H). MS *m/z* $[M+H]^+$ 480.3.

**Scheme 26: Synthesis of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (26-2):**




**Step-1: Preparation of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (26-2):** To a solution of Brimonidine (**24-2**, 0.25 g, 0.85 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.31 mL, 1.7 mmol) at 0 °C. After 30 minutes, (*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (**26-1**, 0.586 g, 2.12 mmol), EDC.HCl (0.487 g, 2.55 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in DCM) to obtain product **26-2** as a pale yellow solid (100 mg, 21.7%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, *J* = 2 Hz, 1H), 8.85 (d, *J* = 2 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.30 (s, 1H), 6.52 (q, 1H), 5.18 (q, 1H), 5.0 (q, 1H), 3.96-3.83 (m, 2H), 3.45-3.34 (m, 2H), 2.06 (s, 3H), 1.64 (d, 3H), 1.50 (d, 3H), 1.44 (d, 3H). MS *m/z* $[M+H]^+$ 551.2.

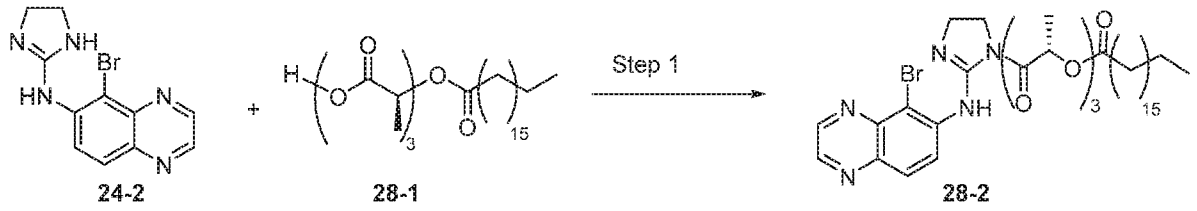
**Scheme 27: Synthesis of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (27-2):**




24-2 27-1 27-2

**Step-1: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (27-2):** To a solution of Brimonidine (**24-2**, 0.25 g, 0.85 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.31 mL, 1.7 mmol) at 0 °C. After 30 minutes, ((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**27-1**, 0.739 g, 2.12 mmol), EDC.HCl (0.487 g, 2.55 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2.5% methanol in DCM) to obtain product **27-2** as a pale yellow solid (100 mg, 18.9%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, *J* = 2 Hz, 1H), 8.85 (d, *J* = 2 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.30 (s, 1H), 6.52 (q, 1H), 5.23-5.15 (m, 2H), 5.04 (q, 1H), 3.95-3.83 (m, 2H), 3.45-3.34 (m, 2H), 2.06 (s, 3H), 1.64 (d, 3H), 1.50 (d, 3H), 1.48 (d, 3H), 1.42 (d, 3H). MS *m/z* $[M+H]^+$ 622.9.

**Scheme 28: Synthesis of Octadecanoic acid (*R*)-1-((*R*)-1-{(*R*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (28-2):**

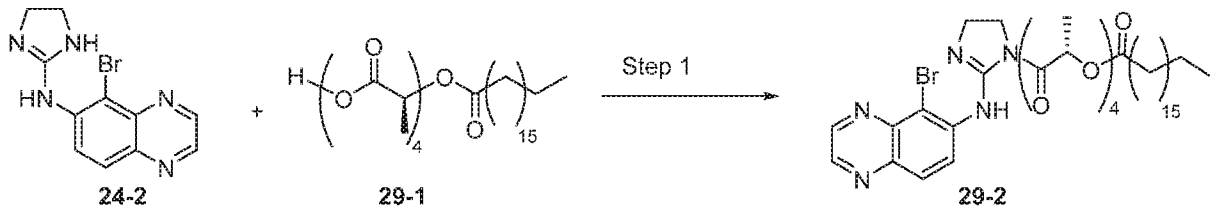



24-2 28-1 28-2

**Step-1: Preparation of Octadecanoic acid (*R*)-1-((*R*)-1-{(*R*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-**

**ethyl ester (28-2):** To a solution of Brimonidine (**24-2**, 0.25 g, 0.85 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.31 mL, 1.7 mmol) at 0 °C. After 30 minutes, octadecanoic acid (*R*)-1-[(*R*)-1-((*R*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**28-1**, 1.062 g, 2.12 mmol), EDC.HCl (0.487 g, 2.55 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100 X2 mL). The dichloromethane was dried over sodium sulfate, filtered sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (40% ethyl acetate in hexane) to obtain product **28-2** as a pale yellow solid (100 mg, 15%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.59 (d, *J* = 9 Hz, 1H), 7.29 (s, 1H), 6.52 (q, 1H), 5.17 (q, 1H), 5.06 (q, 1H), 3.95-3.84 (m, 2H), 3.44-3.34 (m, 2H), 2.32 (t, 2H), 1.63 (d, 3H), 1.52-1.38 (m, 14H), 1.30-1.14 (m, 28H), 0.83 (t, 3H). MS *m/z* $[M+H]^+$ 775.2.

**Scheme 29: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (29-2):**



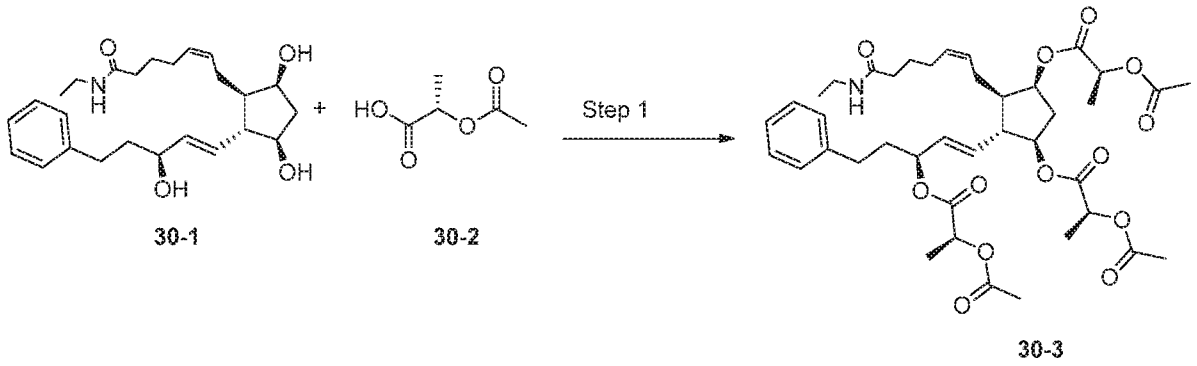

**Step-1: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (29-2):**

To a solution of Brimonidine (**24-2**, 0.25 g, 0.85 mmol) in dichloromethane (2.5 mL) was added *N*,*N*-diisopropylethylamine (0.31 mL, 1.7 mmol) at 0 °C. After 30 minutes, octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**29-1**, 1.212 g, 2.12 mmol), EDC.HCl (0.487 g, 2.55 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and

concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (37% ethyl acetate in hexane) to obtain product **29-2** as a pale yellow solid 220 mg (30%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, *J* = 2 Hz, 1H), 8.84 (d, *J* = 2 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.59 (d, *J* = 9 Hz, 1H), 7.29 (s, 1H), 6.52 (q, 1H), 5.24-5.16 (m, 2H), 5.05 (q, 1H), 3.94-3.83 (m, 2H), 3.44-3.34 (m, 2H), 2.33 (t, 2H), 1.63 (d, 3H), 1.54-1.44 (m, 8H), 1.41 (d, 3H), 1.30-1.14 (m, 28H), 0.83 (t, 3H). MS *m/z* $[M+H]^+$ 847.4.

***Synthesis of Tris-PLA-Bimatoprost Prodrugs (Compounds of Formula II)***

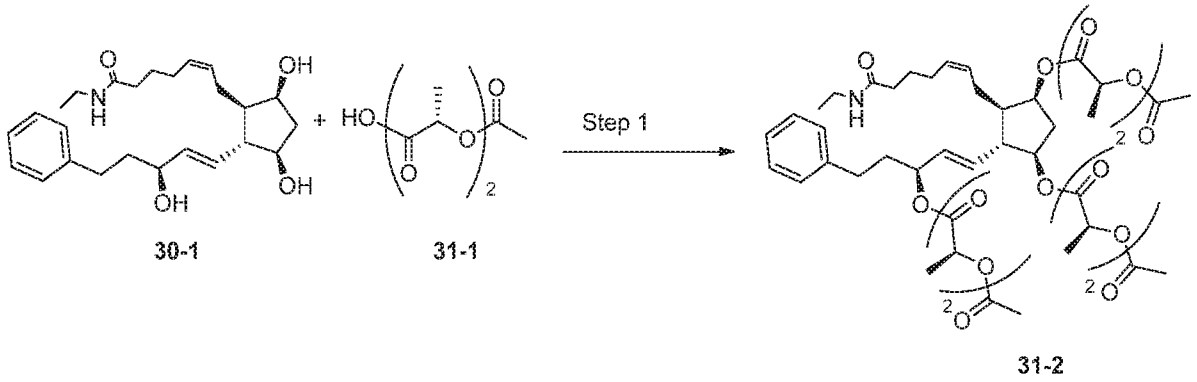
**Scheme 30: Synthesis of (*S*)-2-Acetoxy-propionic acid (1*S*,2*R*,3*R*,4*R*)-4-((*S*)-2-acetoxy-propionyloxy)-3-[(*E*)-(*S*)-3-((*S*)-2-acetoxy-propionyloxy)-5-phenyl-pent-1-enyl]-2-((*Z*)-6-ethylcarbamoyl-hex-2-enyl)-cyclopentyl ester (30-3):**




**Step-1: Preparation of (*S*)-2-Acetoxy-propionic acid (1*S*,2*R*,3*R*,4*R*)-4-((*S*)-2-acetoxy-propionyloxy)-3-[(*E*)-(*S*)-3-((*S*)-2-acetoxy-propionyloxy)-5-phenyl-pent-1-enyl]-2-((*Z*)-6-ethylcarbamoyl-hex-2-enyl)-cyclopentyl ester (30-3):** To a solution of bimatoprost (**30-1**, 0.1 g, 0.24 mmol) and (*S*)-2-acetoxy-propionic acid (**30-2**, 0.19 g, 1.44 mmol) in dichloromethane (1 mL) was added EDC.HCl (0.367g, 1.92mol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (50X4 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (50% ethyl acetate in hexane) to obtain product **30-3** as a colorless wax (130 mg, 72 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.69 (t, 1H), 7.30-7.23 (m, 2H), 7.20-7.12 (m, 3H), 5.66-5.56 (m, 2H), 5.36-5.22 (m, 2H), 5.21-5.13 (m, 1H), 5.05-4.85 (m, 5H), 3.02 (quintet, 2H),

2.65-2.5 (m, 2H), 2.08 (s, 6H), 2.07-1.78 (m, 13H), 1.52-1.32 (m, 13H), 0.97 (t, 3H); MS *m/z* $[M+H-AcOCH(Me)COOH]^+$ 626.6, $(M+Formate)^-$ 802.9.

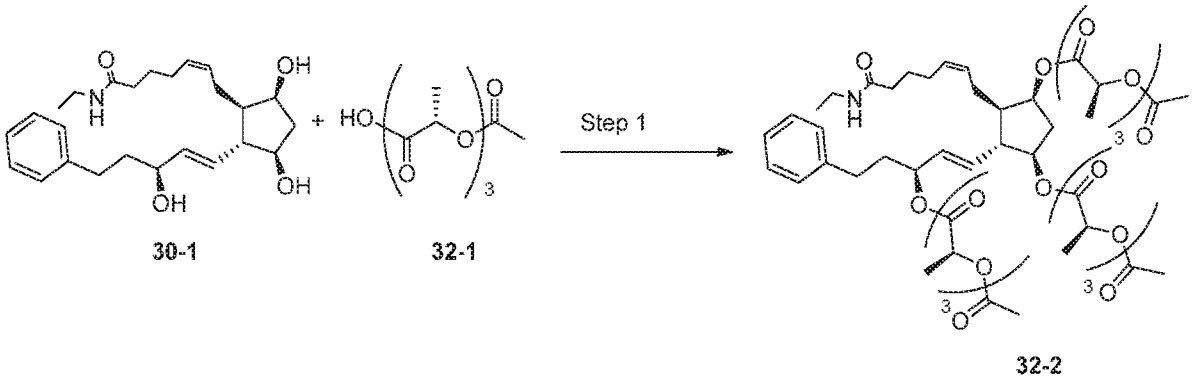
**Scheme 31: Synthesis of compound 31-2:**




30-1 31-1 31-2

**Step-1: Preparation of compound 31-2:** To a solution of bimatoprost (**30-1**, 0.1 g, 0.24 mmol) and (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (**31-1**, 0.294 g, 1.44 mmol) in dichloromethane (1 mL) was added EDC.HCl (0.367 g, 1.92 mol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (50 X4 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (55% ethyl acetate in hexane) to obtain product **31-2** as a colorless wax (120 mg, 52 %). $^1$H-NMR (400 MHz, DMSO-d$_6$) δ 7.69 (t, 1H), 7.30-7.23 (m, 2H), 7.21-7.13 (m, 3H), 5.67-5.52 (m, 2H), 5.36-5.22 (m, 2H), 5.21-5.14 (m, 1H), 5.14-4.98 (m, 7H), 4.94-4.86 (m, 1H), 3.02 (quintet, 2H), 2.63-2.5 (m, 2H), 2.09-1.78 (m, 19H), 1.52-1.32 (m, 22H), 0.97 (t, 3H); MS *m/z* $[M+H]^+$ 975.0, $[M+H-AcOCH(Me)COOCH(Me)COOH]^+$ 770.9, $[M+Formate]^-$ 1019.3.

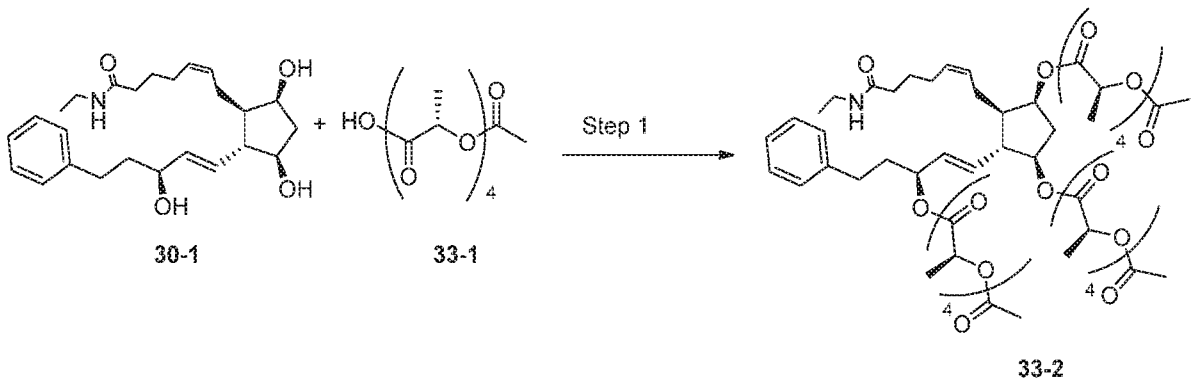
**Scheme 32: Synthesis of compound 32-2:**




30-1 32-1 32-2

**Step-1: Preparation of compound 32-2:** To a solution of bimatoprost (**30-1**, 0.1 g, 0.24 mmol) and (*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (**32-1**, 0.397 g, 1.44 mmol) in dichloromethane (1 mL) was added EDC.HCl (0.367g, 1.92mol) and 4-dimethylaminopyridine (9 mg, 0.07 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (50 X4 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (52% ethyl acetate in hexane) to obtain product **32-2** as a colorless wax (120 mg, 42 %). $^1$H-NMR (400 MHz, DMSO-d$_6$) δ 7.69 (t, 1H), 7.30-7.23 (m, 2H), 7.21-7.13 (m, 3H), 5.65-5.55 (m, 2H), 5.36-4.98 (m, 13H), 4.95-4.86 (m, 1H), 3.02 (quintet, 2H), 2.63-2.5 (m, 2H), 2.06 (s, 9H), 2.05-1.78 (m, 10H), 1.52-1.33 (m, 31H), 0.97 (t, 3H); MS *m/z* $[M+H]^+$ 1191.2, $[M+H\text{-}AcOCH(Me)\ COOCH(Me)COOCH(Me)COOH]^+$ 915.2, $[M+Formate]^-$ 1235.7.

**Scheme 33: Synthesis of Compound 33-2:**

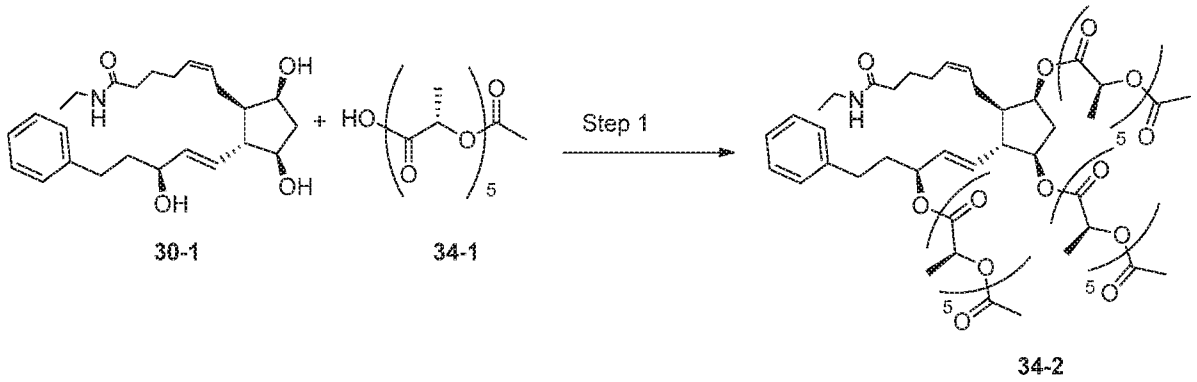



30-1 33-1 33-2

**Step-1: Preparation of Compound 33-2:** To a solution of bimatoprost (**30-1**, 0.2 g, 0.48 mmol) and (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic

acid (**33-1**, 1.002 g, 2.88 mmol) in dichloromethane (2 mL) was added EDC.HCl (0.733 g, 3.84 mol) and 4-dimethylaminopyridine (17 mg, 0.14 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (50% ethyl acetate in hexane) to obtain product **33-2** as a colorless wax (320 mg, 47 %). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.68 (t, 1H), 7.30-7.23 (m, 2H), 7.21-7.13 (m, 3H), 5.65-5.54 (m, 2H), 5.37-5.00 (m, 16H), 4.95-4.86 (m, 1H), 3.01 (quintet, 2H), 2.62-2.5 (m, 2H), 2.06 (s, 9H), 2.05-1.78 (m, 10H), 1.51-1.34 (m, 40H), 0.97 (t, 3H); MS *m/z* $[M+H]^+$ 1407.4, $[M+H-AcOCH(Me)COOCH(Me)COOCH(Me)COOCH(Me)COOH]^+$ 1059.6.

**Scheme 34: Synthesis of Compound 34-2:**

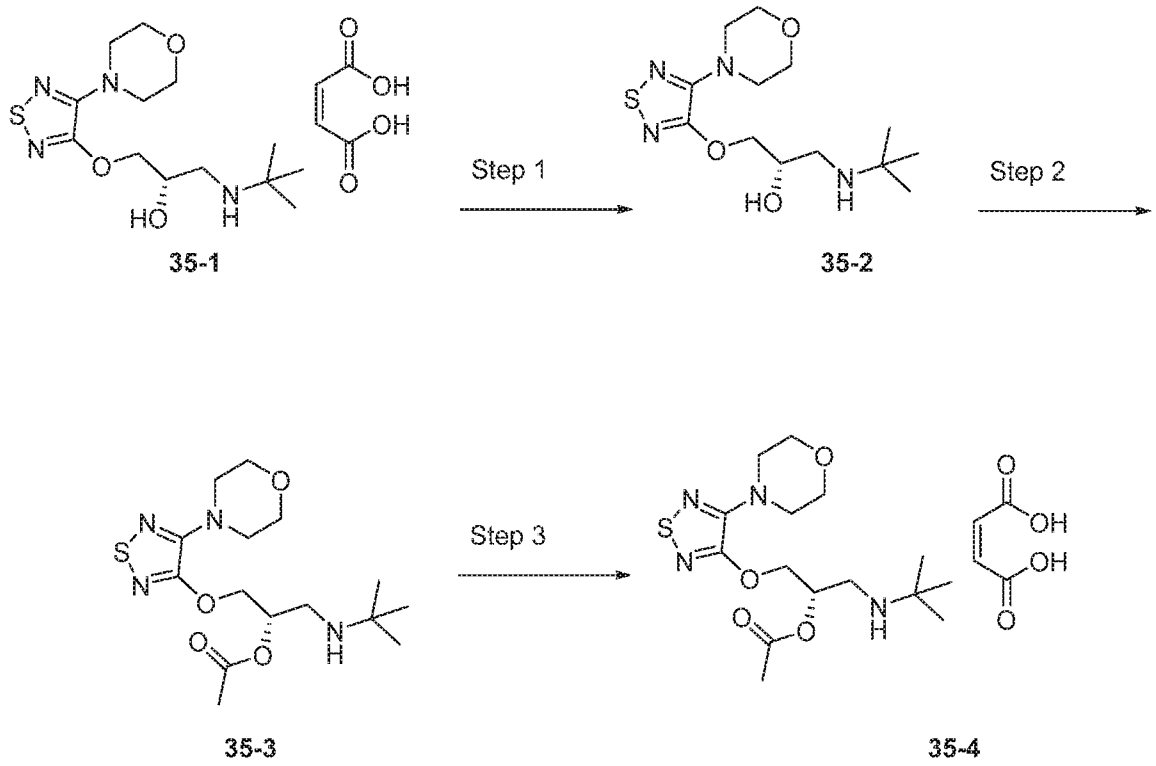



**Step-1: Preparation of compound 34-2:** To a solution of bimatoprost (**30-1**, 0.15 g, 0.36 mmol) and (*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionic acid (**34-1**, 0.907 g, 2.16 mmol) in dichloromethane (1.5 mL) was added EDC.HCl (0.55 g, 2.88 mol) and 4-dimethylaminopyridine (13 mg, 0.11 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200 X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (50% ethyl acetate in hexane) to obtain product **34-2** as a colorless wax (350 mg, 59 %). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 7.68 (t, 1H), 7.30-7.23 (m, 2H), 7.21-7.14 (m, 3H), 5.66-5.52 (m, 2H), 5.37-4.99 (m, 19H), 4.95-4.86 (m, 1H), 3.01 (quintet, 2H), 2.62-2.5 (m, 2H), 2.06

(s, 9H), 2.05-1.78 (m, 10H), 1.51-1.35 (m, 49H), 0.97 (t, 3H); MS *m/z* [M+H-AcOCH(Me)COOCH(Me)COOCH(Me)COOCH(Me)CO-OCH(Me)COOH]$^+$ 1203.4.

***Synthesis of Timolol Mono-Prodrugs***

**Scheme 35: Synthesis of Acetic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (35-4):**



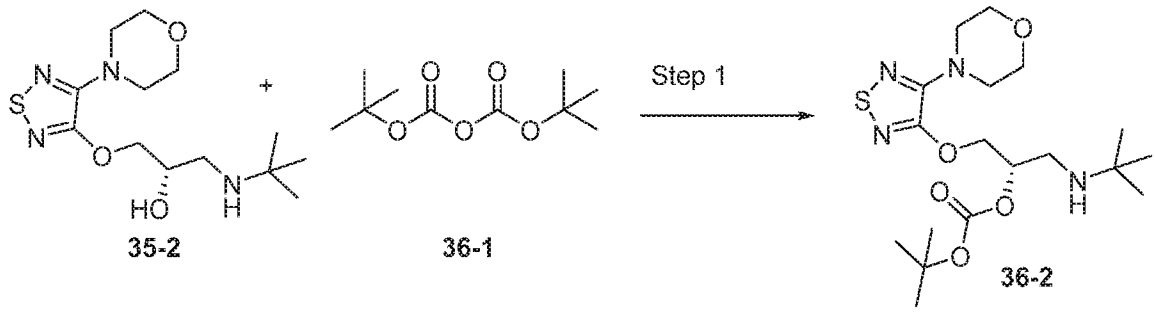

**Step-1: Preparation of Free-Timolol (35-2):** To a solution of Timolol maleate (**35-1**, 1.6 g, 4.60 mmol) in water (16 mL) was added NaOH pellets (0.46 g, 11.5 mmol) slowly at 0 °C. The reaction mixture was allowed to stir at 0-5 °C over a period of 15 minutes. The resulting reaction mixture was diluted with dichloromethane (500 mL) and washed with water (2 X200 mL). The product obtained upon evaporation of volatiles afforded **35-2** as a colorless liquid (1.0 g, 85 %). $^1$H NMR (400 MHz, DMSO-d6) δ 5.01 (bs, 1H), 4.39 (dd, *J* = 4.0 Hz, *J* = 10.5 Hz 2H), 4.29 (dd, *J* = *6.*4 Hz, *J* = 10.5 Hz 2H), 3.88-3.78 (m, 1H), 3.74-3.66 (m, 4H), 3.50-3.40 (m, 4H), 2.6-2.5 (m, 2H), 1.4 (bs, 1H), 1.00 (s, 9H) ; MS m/z (M+H)$^+$ 317.6.

**Step-2: Preparation of Acetic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (35-3):** To a solution of Timolol (**35-2**, 1.0 g, 3.16 mmol)

in dichloromethane (10 mL) was added acetic anhydride (0.8 mL, 7.90 mmol) and 4-dimethylaminopyridine (0.077 g, 0.316 mmol) at 0° C. The reaction mixture was stirred at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (200 mL), extracted with dichloromethane (2 X 200 mL) and dried over sodium sulfate. The dried solution was filtered and volatiles were evaporated under reduced pressure to obtain product **35-3** as an off-white solid (1.2 g, 80%).

**Step-3: Preparation of Acetic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (35-4):** To a solution of acetic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (**35-3**, 1.2 g, 2.52 mmol) in acetone (6 mL) was added maleic acid (0.264 g, 2.27 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **35-4** as white solid (0.3 g, 21%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.57 (bs, 1H), 8.29 (bs, 1H), 6.02 (s, 2H), 5.45-5.35 (m, 1H), 4.66 (dd, 1H), 4.45 (dd, 1H), 3.72-3.65 (m, 4H), 3.48-3.29 (m, 5H), 3.25-3.12 (m, 1H), 2.08 (s, 3H), 1.29 (s, 9H). MS *m/z* $[M+H]^+$ 359.1.

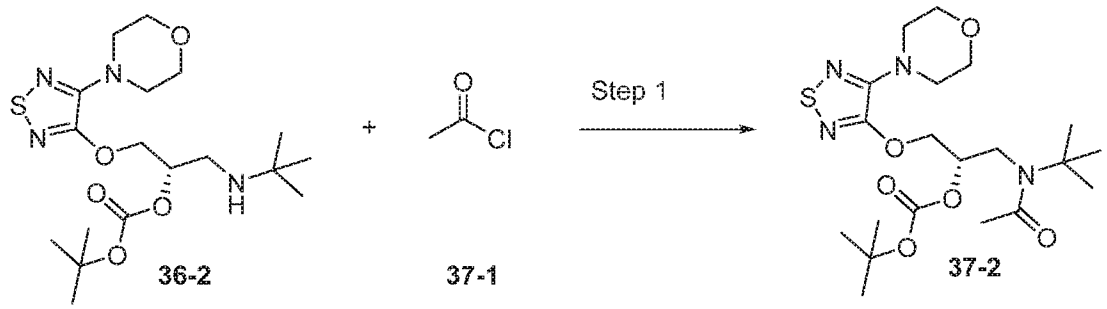
**Scheme 36: Synthesis of Carbonic acid tert-butyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-mor pholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (36-2):**




**Step-1: Preparation of Carbonic acid tert-butyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (36-2):** To a solution of Timolol (**35-2**, 4.0 g, 12.65 mmol) in dichloromethane (40 mL) was added di-tert-butyl dicarbonate (**36-1**, 4.36 mL, 18.99 mmol) and 4-dimethylaminopyridine (0.155 g, 1.26 mmol) at 0° C. The reaction mixture stirred at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (300 mL), extracted with dichloromethane (2 X 500 mL) and dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% methanol in dichloromethane) to

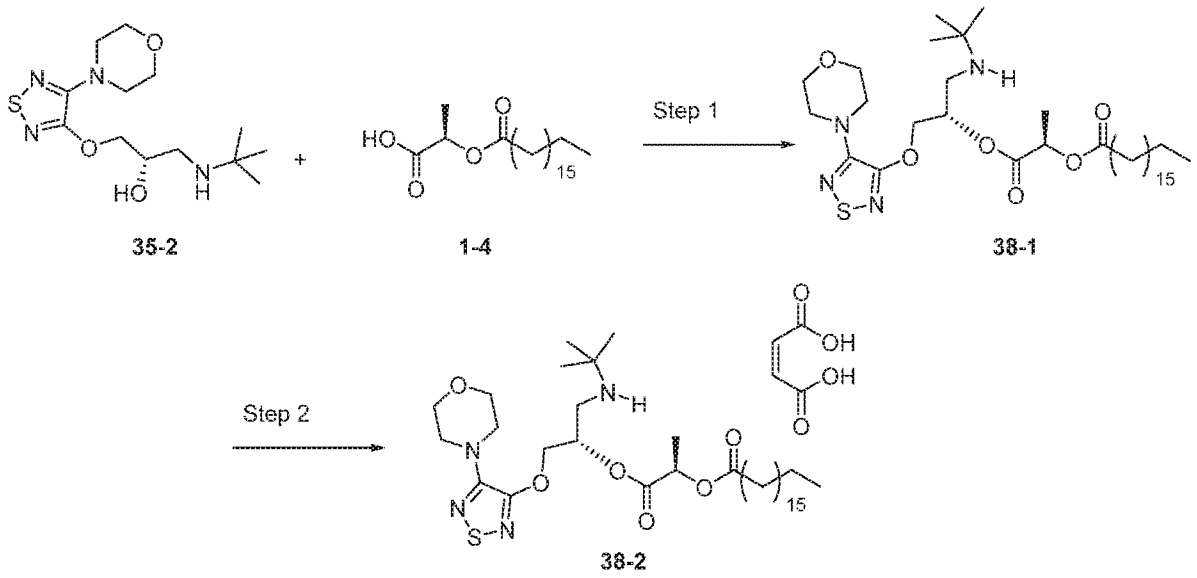
obtain product **36-2** as a colorless liquid (0.7 g, 58 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 4.94-4.85 (m, 1H), 4.64 (dd, 1H), 4.46 (dd, 1H), 3.69-3.63 (m, 4H), 3.43-3.38 (m, 4H), 2.72-2.63 (m, 2H), 1.40 (s, 9H), 0.97 (s, 9H). MS *m/z* $[M+H]^+$ 417.1.

**Scheme 37: Synthesis of Carbonic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester *tert*-butyl ester (37-2):**




**Step-1: Preparation of Carbonic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester *tert*-butyl ester (37-2):** To a solution of carbonic acid *tert*-butyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-mor pholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (**36-2**, 0.6 g, 1.44 mmol) in dichloromethane (6 mL) was added *N,N*-diisopropylethylamine (0.7 mL, 4.32 mmol) and acetyl chloride (**37-1**, 0.11 mL, 3.60 mmol) at 0° C. The reaction mixture stirred at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (200 mL), extracted with dichloromethane (2X200 mL) and dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (25% ethyl acetate in hexane) to obtain product **37-2** as a colorless liquid (0.24 g, 36%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.22-5.14 (m, 1H), 4.60 (dd, 1H), 4.44 (dd, 1H), 3.70-3.61 (m, 6H), 3.41-3.35 (m, 4H), 2.05 (s, 3H), 1.37 (s, 9H), 1.33 (s, 9H). MS *m/z* $[M+H]^+$ 459.2.

**Scheme 38: Synthesis of Octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester maleate (38-2):**

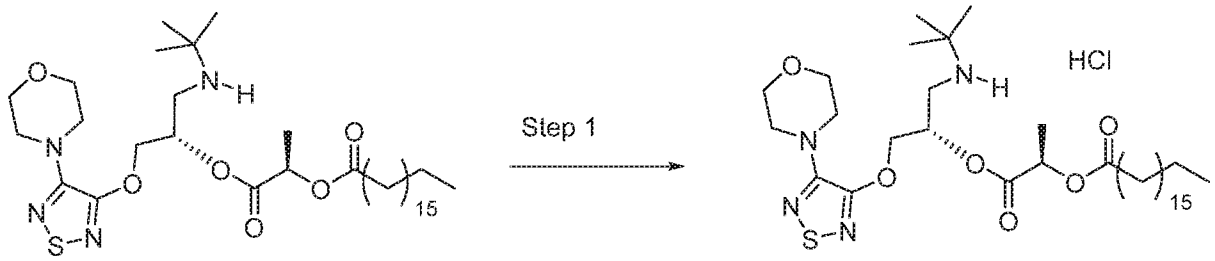



**Step-1: Preparation of Octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (38-1):** To a solution of octadecanoic acid (*R*)-1-carboxy-ethyl ester (**1-4**, 0.84 g, 2.36 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.604 g, 3.16 mmol), Timolol (**35-2**, 0.5 g, 1.57 mmol) and 4-dimethylaminopyridine (19 mg, 0.157 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The reaction was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (25% ethyl acetate in hexane) to obtain product **38-1** as colorless liquid (0.7 g, 70%).

**Step-2: Preparation of Octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester maleate (38-2):** To a solution of octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (**38-1**, 0.5 g, 0.763 mmol) in acetone (2.5 mL) was added maleic acid (0.08 g, 0.687 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting mixture was filtered and the solid was dried under reduced pressure to give product **38-2** as white solid (0.45 g, 77%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.57 (bs, 1H), 8.41 (bs, 1H), 6.02 (s, 2H), 5.51-5.42 (m, 1H),

5.18 (q, 1H), 4.67 (dd, 1H), 4.49 (dd, 1H), 3.73-3.62 (m, 4H), 3.48-3.12 (m, 6H), 2.32 (t, 2H), 1.50 (quintet, 2H), 1.40 (d, 3H), 1.35-1.15 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 656.1.

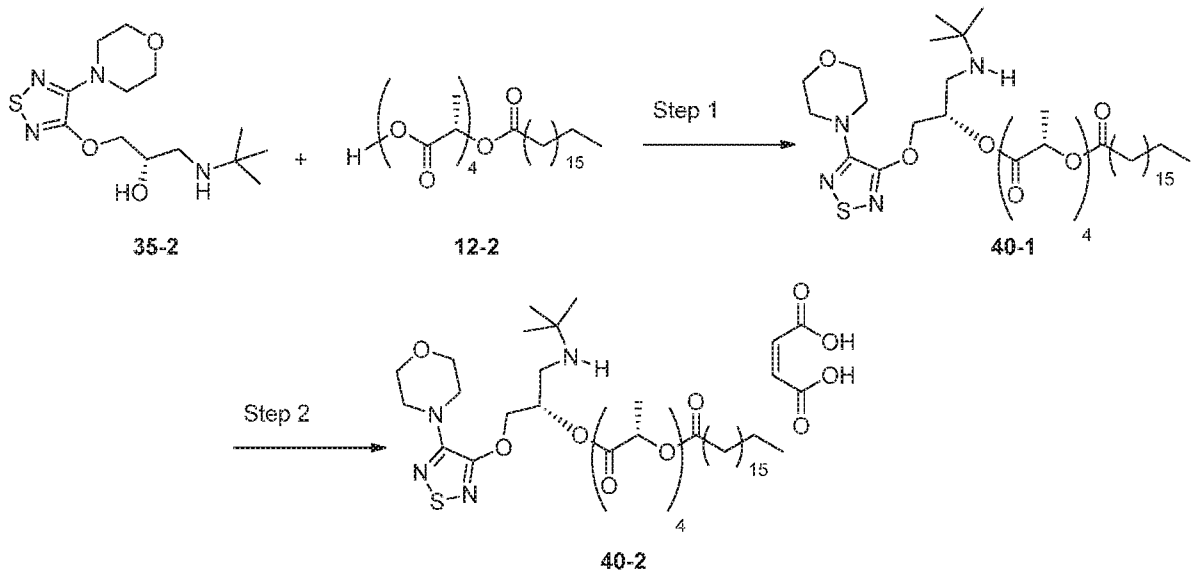
**Scheme 39: Synthesis of Octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester hydrochloride (39-1):**




38-1 39-1

**Step-1: Preparation of Octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester hydrochloride (39-1):** To a solution of octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (**38-1**, 0.2 g, 0.305 mmol) in dioxane (0.4 mL) was added 4M HCl in dioxane (0.15 mL, 0.61 mmol) at 0 °C. The mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting mixture was concentrated under reduced pressure to give product **39-1** as waxy solid (0.15 g, 71%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.18 (bs, 1H), 8.82 (bs, 1H), 5.53-5.46 (m, 1H), 5.23 (q, 1H), 4.69 (dd, 1H), 4.51 (dd, 1H), 3.74-3.63 (m, 4H), 3.48-3.3 (m, 5H), 3.25-3.12 (m, 1H), 2.33 (t, 2H), 1.51 (quintet, 2H), 1.37 (d, 3H), 1.35-1.15 (m, 37H), 0.83 (t, 3H). MS *m/z* $[M+H]^+$ 656.0.

**Scheme 40: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester maleate (40-2):**

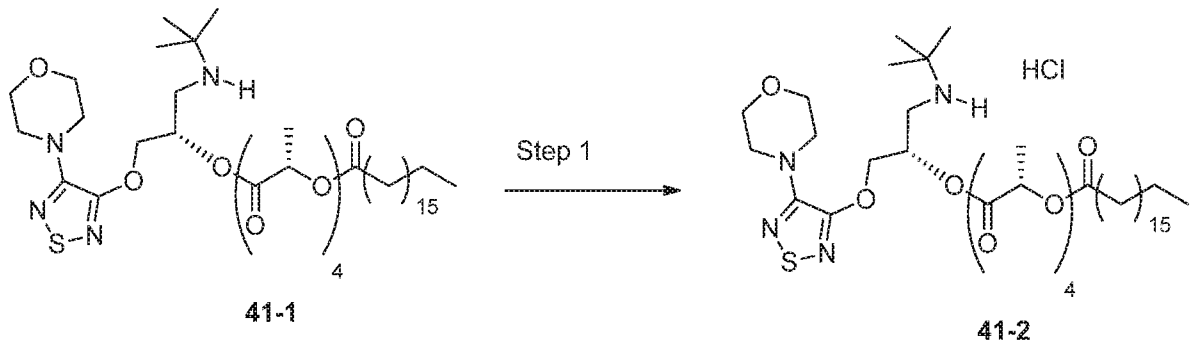



**Step-1: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (40-1):** To a solution of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**12-2**, 1.62 g, 2.84 mmol) in dichloromethane (6 mL) was added EDC.HCl (0.725 g, 3.79 mmol), Timolol (**35-2**, 0.6 g, 1.89 mmol) and 4-dimethylaminopyridine (23 mg, 0.189 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200 X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (25% ethyl acetate in hexane) to obtain product **40-1** as colorless liquid (1.0 g, 62%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.23–5.11 (m, 3H), 515-5.07 (m, 2H), 4.62 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.46 (dd, *J* = 11.6, 7.4 Hz, 1H), 3.67 (t, *J* = 4.7 Hz, 4H), 3.40 (s, 4H), 2.71 (s, 2H),2.33-2.30 (m, 3H), 1.48–1.36 (m, 12H), 1.23 (s, 32H), 1.00 (s, 9H), 0.89–0.77 (m, 3H) ; MS m/z (M+H) 872.1

**Step-2: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester maleate (40-2):** To a solution of octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-

ethyl ester (**40-1**, 0.8 g, 0.918 mmol) in acetone (4 mL) was added maleic acid (0.095 g, 0.826 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was filtered and dried under reduced pressure to give product **40-2** as waxy solid (0.8 g, 88%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.7-8.3 (m, 2H), 6.04 (s, 2H), 5.55-5.44 (m, 1H), 5.27 (q, 1H), 5.25-5.13 (m, 2H), 5.06 (q, 1H), 4.68 (dd, 1H), 4.49 (dd, 1H), 3.73-3.64 (m, 4H), 3.48-3.15 (m, 6H), 2.33 (t, 2H), 1.56-1.38 (m, 14H), 1.32-1.14 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 872.1.

**Scheme 41: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester hydrochloride (40-1):**

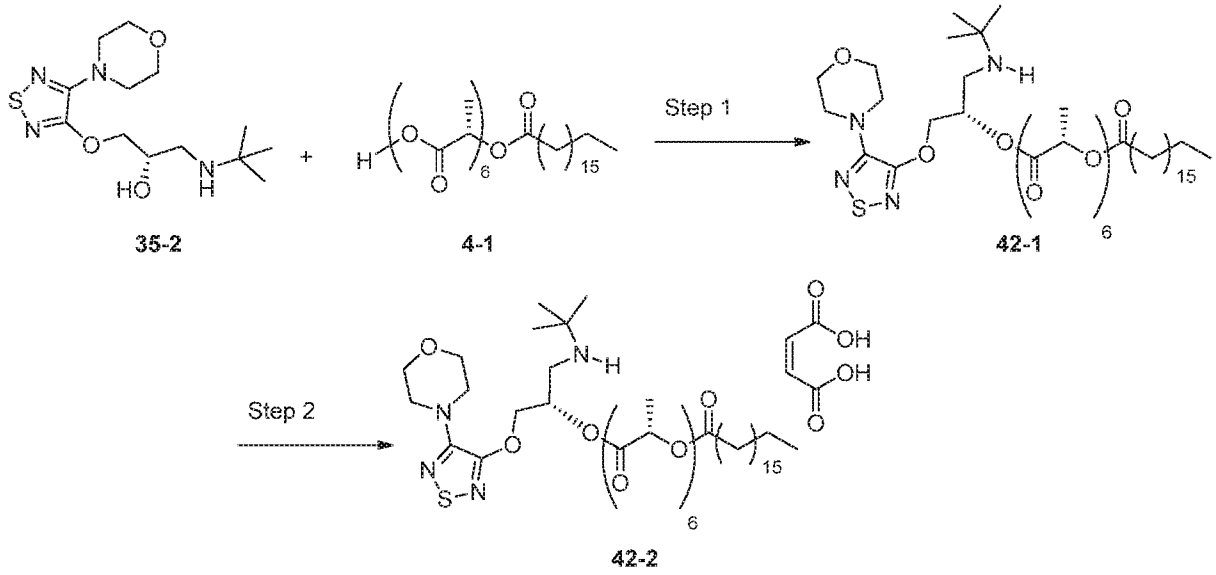



41-1 41-2

**Step-1: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester hydrochloride (41-2):** To a solution of octadecanoic acid (*R*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethylester (**40-1**, 0.2 g, 0.229 mmol) in dioxane (0.4 mL) was added 4M HCl in dioxane (0.11 mL, 0.459 mmol) at 0 °C. The mixture was allowed to stir at room temperature over a period of 20 minutes and concentrated under reduced pressure to afford product **40-2** as waxy solid (0.15 g, 71%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.09 (bs, 1H), 8.80 (bs, 1H), 5.56-5.47 (m, 1H), 5.32 (q, 1H), 5.22-5.13 (m, 2H), 5.05 (q, 1H), 4.68 (dd, 1H), 4.50 (dd, 1H), 3.72-3.64 (m, 4H), 3.48-3.32 (m, 5H), 3.26-3.12 (m, 1H), 2.33 (t, 2H), 1.56-1.38 (m, 14H), 1.32-1.14 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 872.2.

**Scheme 42: Synthesis of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-**

**ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester maleate (42-2):**

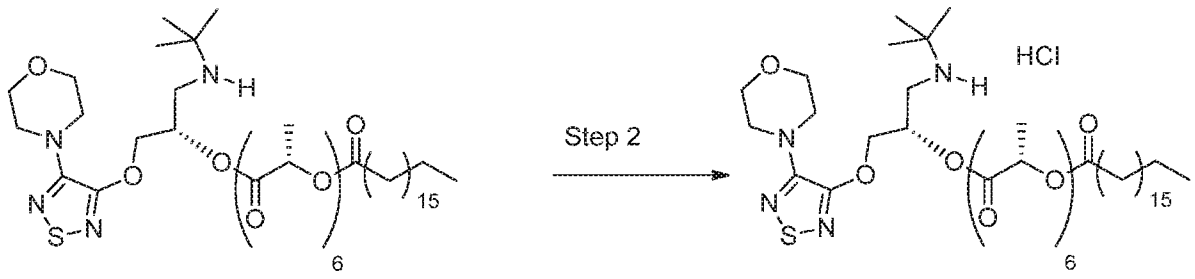



**Step-1: Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (42-1):** To a solution of octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (**4-1**, 1.69 g, 2.37 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.603 g, 3.16 mmol), Timolol (**35-2**, 0.5 g, 1.58 mmol) and 4-dimethylaminopyridine (19 mg, 0.158 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The reaction was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (25% ethyl acetate in hexane) to obtain product **42-1** as colorless liquid (0.7 g, 43%).

**Step-2: Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester maleate (42-2):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-

ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (**42-1**, 0.5 g, 0.492 mmol) in acetone (2.5 mL) was added maleic acid (0.051 g, 0.443 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to afford product **42-2** as waxy solid (0.45 g, 81%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.7-8.3 (m, 2H), 6.11 (s, 2H), 5.54-5.44 (m, 1H), 5.29 (q, 1H), 5.24-5.13 (m, 4H), 5.06 (q, 1H), 4.68 (dd, 1H), 4.49 (dd, 1H), 3.73-3.62 (m, 4H), 3.5-3.1 (m, 6H), 2.33 (t, 2H), 1.56-1.38 (m, 20H), 1.35-1.15 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 1016.2.

**Scheme 43: Synthesis of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester hydrochloride (43-1):**

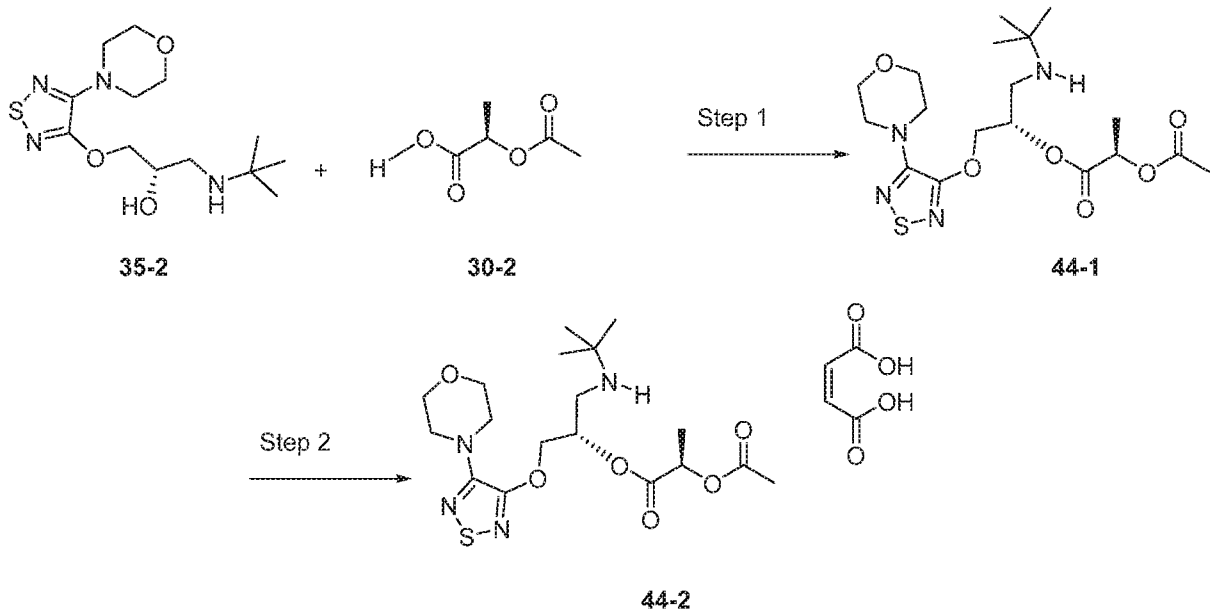



42-1 43-1

**Step-1: Preparation of Octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester hydrochloride (43-1):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (**42-1**, 0.2 g, 0.196 mmol) in dioxane (0.4 mL) was added 4M HCl in dioxane (0.095 mL, 0.393 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **43-1** as a waxy solid (0.15 g, 72%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.06 (bs, 1H), 8.77 (bs, 1H), 5.56-5.46 (m, 1H), 5.32 (q, 1H), 5.24-5.13 (m, 4H), 5.04 (q,

1H), 4.69 (dd, 1H), 4.51 (dd, 1H), 3.73-3.64 (m, 4H), 3.48-3.32 (m, 5H), 3.26-3.12 (m, 1H), 2.33 (t, 2H), 1.56-1.38 (m, 20H), 1.38-1.14 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 1016.3.

**Scheme 44: Synthesis of (*R*)-2-Acetoxy-propionic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (44-2):**




35-2 30-2 44-1

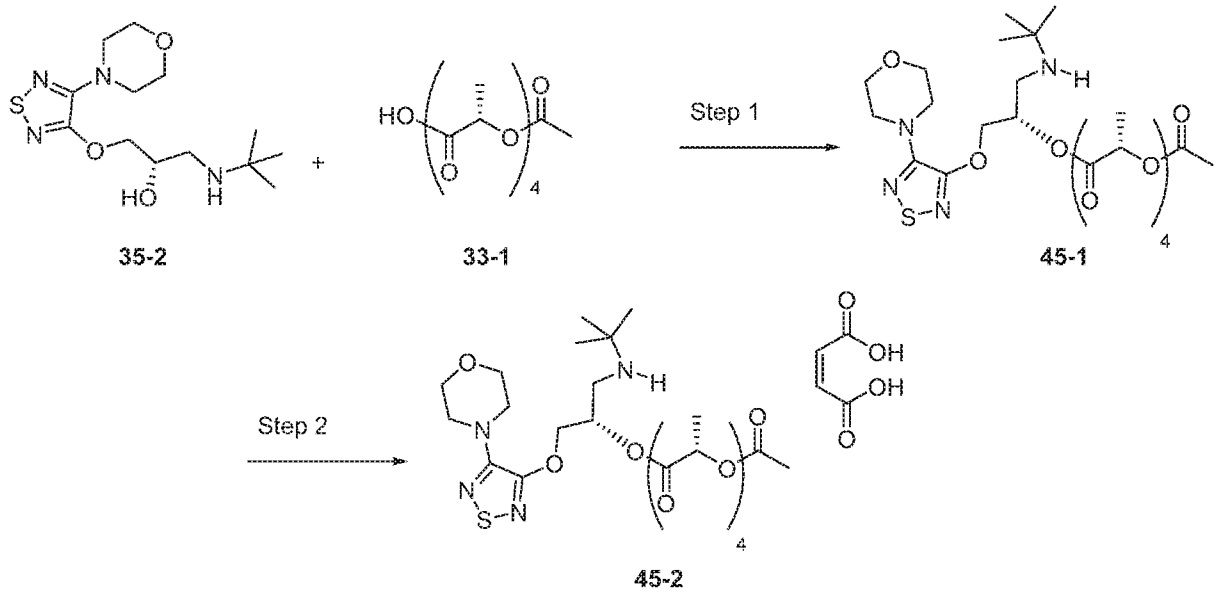
44-2

**Step-1: Preparation of (*R*)-2-Acetoxy-propionic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (44-1):** To a solution of (*R*)-2-acetoxy-propionic acid (**30-2**, 0.63 g, 4.74 mmol) in dichloromethane (10 mL) was added EDC.HCl (1.2 g, 6.32 mmol), Timolol (**35-2**, 1.0 g, 3.16 mmol) and 4-dimethylaminopyridine (38 mg, 0.316 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (30% ethyl acetate in hexane) to obtain product **44-1** as colorless liquid (0.3 g, 26%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.20-4.12 (m, 1H), 4.96 (q, *J* = 7.0 Hz, 1H), 4.63 (dd, 1H), 4.50 (dd, 1H), 3.73–3.64 (m, 4H), 3.43–3.38 (m, 4H), 2.76 – 2.68 (m, 2H), 2.04 (s, 3H), 1.35 (d, *J* = 7.0 Hz, 3H), 1.00 (s, 9H); MS m/z $(M+H)^+$ 431.6

**Step-2: Preparation of (*R*)-2-Acetoxy-propionic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (44-2):**

To a solution of (*R*)-2-acetoxy-propionic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (**44-1**, 0.3 g, 0.697 mmol) in acetone (1.5 mL) was added maleic acid (0.072 g, 0.627 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting suspension was filtered and the collected solid was dried under reduced pressure to give product **44-2** as white solid (0.32 , 84%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.58 (bs, 1H), 8.39 (bs, 1H), 6.02 (s, 2H), 5.52-5.41 (m, 1H), 5.18 (q, 1H), 4.67 (dd, 1H), 4.50 (dd, 1H), 3.72-3.62 (m, 4H), 3.48-3.31 (m, 5H), 3.29-3.12 (m, 1H), 2.08 (s, 3H), 1.40 (d, 3H), 1.28 (s, 9H). MS *m/z* $[M+H]^+$ 431.6.

**Scheme 45: Synthesis of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxy carbonyl]-ethyl ester maleate (45-2):**

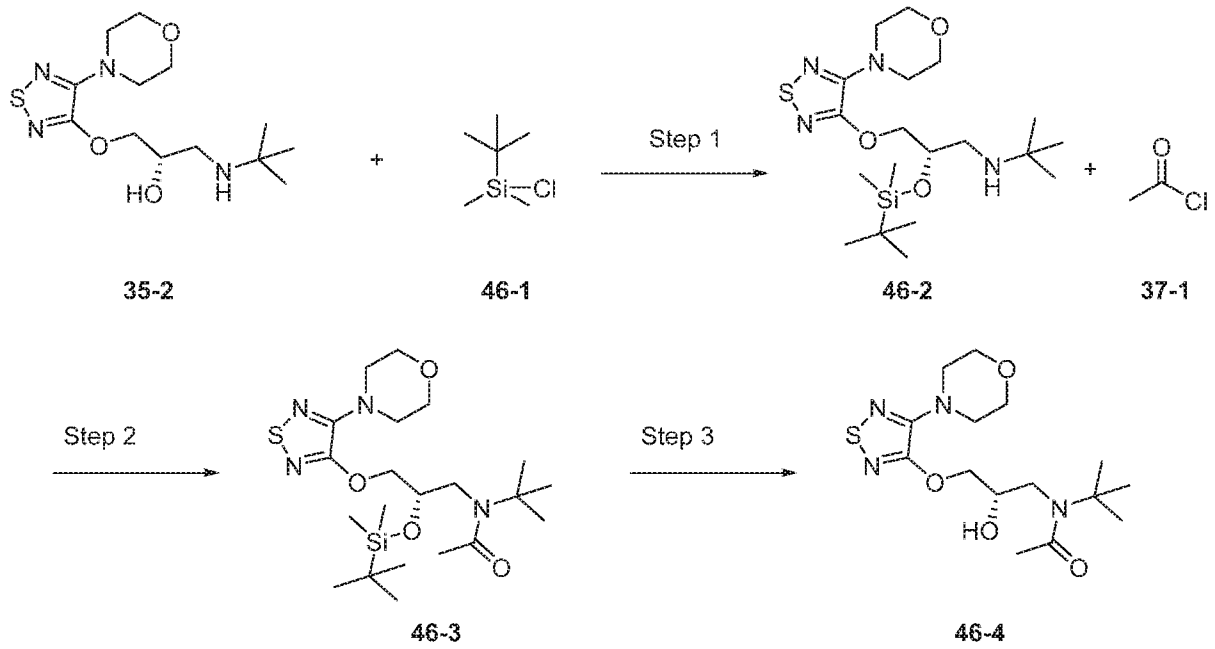



**Step-1: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-[(S)-1-(tert-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (45-1):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**33-1**, 3.3 g, 9.49 mmol) in dichloromethane (20 mL) was added EDC.HCl (2.41 g, 12.65 mmol), Timolol (**35-2**, 2.0 g, 6.32 mmol) and 4-dimethylaminopyridine (77 mg, 0.632 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (400X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles

was purified through silica gel (230-400) column (40% ethyl acetate in hexane) to obtain product **45-1** as colorless liquid 1.2 g (29%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.24–4.99 (m, 5H), 4.62 (dd, 1H), 4.47 (dd, 1H), 3.70-3.64 (m, 4H), 3.45-3.38 (m, 4H), 2.76-2.66 (m, 2H), 2.06 (s, 3H), 1.50-1.37 (m, 12H), 1.00 (s, 9H); MS m/z $(M+H)^+$ 647.6

**Step-2: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxy carbonyl]-ethyl ester maleate (45-2):** To a solution of (*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxy carbonyl]-ethyl ester (**45-1,** 1.2 g, 1.85 mmol) in acetone (6 mL) was added maleic acid (0.193 g, 1.66 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **45-2** as white solid (1.3 g, 92%).

**Scheme 46: Synthesis of *N*-*tert*-Butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (46-4):**



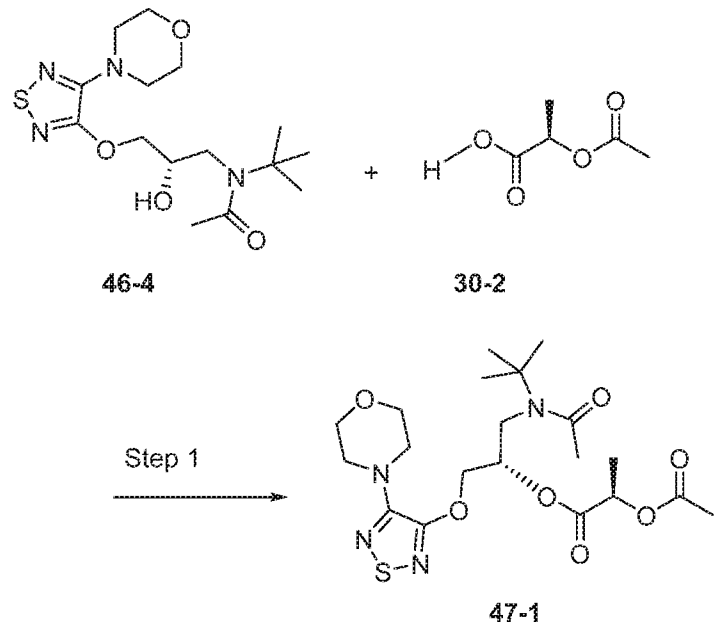

**Step-1: Preparation of *tert*-Butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine (46-2):** To a solution of Timolol (**35-2**, 5 g, 15.8

mmol) in dimethylformamide (50 mL) was added imidazole (2.69 g, 39.0 mmol) and TBDMS-Cl (2.86 mL, 18.9 mmol) at 0° C. The reaction mixture was stirred at room temperature over period of 12 hours and the resulting reaction mixture was removed under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (2% isopropyl alcohol in chloroform) to obtain product **46-2** as a colorless liquid (4 g, 58.8 %). $^1$H NMR (400 MHz, DMSO-d6) δ 4.49-4.36 (m, 2H), 4.03 (bs, 1H), 3.74-3.63 (m, 4H), 3.51–3.35 (m, 4H), 2.65-2.5 (m, 2H), 1.23 (bs, 1H), 1.01 (s, 9H), 0.84 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); MS m/z $(M+H)^+$ 431.7

**Step-2: Preparation of *N*-*tert*-Butyl-*N*-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (46-3):** To a solution of *tert*-butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine (**46-2**, 4 g, 9.29 mmol) in chloroform (40 mL) was added triethylamine (1.9 ml, 13.93 mmol) and acetyl chloride (**37-1**, 0.99 mL, 13.93 mmol) at 0° C. The reaction mixture was stirred at 25-30 °C over a period of 12 hours, quenched with water (100 mL) and extracted with dichloromethane (2X200 mL). The dichloromethane was dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain product **46-3** as a colorless liquid (3.3 g, 75 %). $^1$H NMR (400 MHz, DMSO-d6) δ 4.40 (dd, 1H), 4.32 (dd, 1H), 4.26-4.18 (m, 1H), 3.74-3.64 (m, 4H), 3.6 – 3.35 (m, 6H), 2.08 (s, 2H), 1.83 (s, 9H), 0.82 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ; MS m/z (M+H) 473.7

**Step-3: Preparation of *N*-*tert*-Butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (46-4):** To a solution of *N*-*tert*-butyl-*N*-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-3**, 3.3 g, 6.98 mmol) in tetrahydrofuran (33 mL) was added tetra butyl ammonium fluoride (10.4 mL, 1.0 M, 10.47 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel column chromatography (60 % ethyl acetate in hexane) to afford product **46-4** as an off white solid (1.3 g, 52%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.46 (d, $J$ = 5.3 Hz, 1H), 4.36–4.23 (m, 2H), 4.03-3.97 (m, 1H), 3.72-3.66 (m, 4H), 3.46–3.37 (m, 6H), 2.06 (s, 3H), 1.38 (s, 9H) ; MS m/z $(M+H)^+$ 359.6.

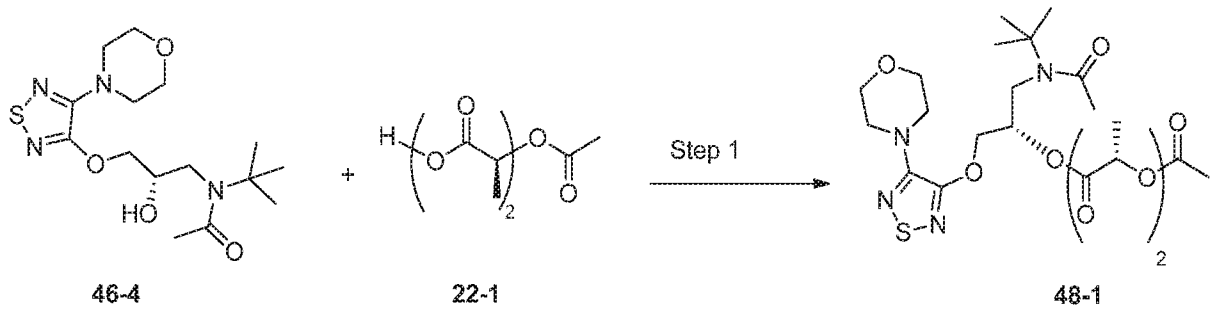
**Scheme 47: Synthesis of (*R*)-2-Acetoxy-propionic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (47-1):**




46-4 30-2 47-1

**Step-1: Preparation of (*R*)-2-Acetoxy-propionic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (47-1):** To a solution of (R)-2-acetoxy-propionic acid (**30-2**, 0.166 g, 1.26 mmol) in dichloromethane (3 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.312 g, 1.51 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4** ,0.3 g, 0.84 mmol ) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (100X3 mL) The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (60% ethylacetate in hexane) to obtain product **47-1** as a colorless wax 250 mg (63 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.44-5.32 (m, 1H), 4.96 (q, 1H), 4.56 (dd, 1H), 4.41 (dd, 1H), 3.82-3.60 (m, 6H), 3.43-3.34 (m, 4H), 2.08 (s, 3H), 2.02 (s, 3H), 1.38-1.30 (m, 12H). MS *m/z* $[M+H]^+$ 473.6.

**Scheme 48: Synthesis of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (48-1):**

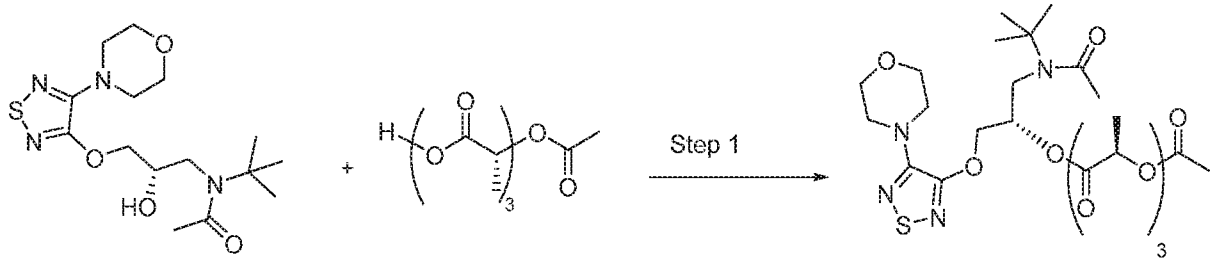



46-4 22-1 48-1

**Step-1: Preaparation of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid (*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (48-1):**

To a solution of (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (**22-1**, 0.086 g, 0.42 mmol) in dichloromethane (1 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.104 g, 0.5 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.1 g, 0.28 mmol ) and 4-dimethylaminopyridine (4 mg, 0.03 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (50X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (63% ethyl acetate in hexane) to obtain product **48-1** as a colorless wax (100 mg, 66 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.48-5.40 (m, 1H), 5.09-5.00 (m, 2H), 4.56 (dd, 1H), 4.41 (dd, 1H), 3.79-3.63 (m, 6H), 3.42-3.34 (m, 4H), 2.09 (s, 3H), 2.04 (s, 3H), 1.43-1.35 (m, 6H), 1.34 (s, 9H). MS *m/z* $[M+H]^+$ 545.5.

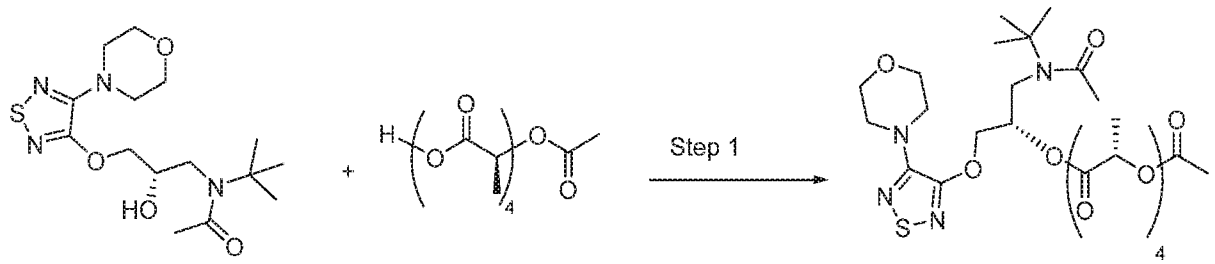
**Scheme 49: Synthesis of (*R*)-2-((*R*)-2-Acetoxy-propionyloxy)-propionic acid (*R*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (49-1):**




46-4 26-1 49-1

**Step-1: Preaparation of (*R*)-2-((*R*)-2-Acetoxy-propionyloxy)-propionic acid (*R*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (49-1):** To a solution of (*R*)-2-[(*R*)-2-((*R*)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (**26-3**, 0.114 g, 0.42 mmol) in dichloromethane (1 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.104 g, 0.5 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.1 g, 0.28 mmol ) and 4-dimethylaminopyridine (4 mg, 0.03 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (50X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (62% ethyl acetate in hexane) to obtain product **49-1** as a colorless wax (110 mg, 63.9 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.48-5.39 (m, 1H), 5.20 (q, 1H), 5.09-4.94 (m, 2H), 4.55 (dd, 1H), 4.42 (dd, 1H), 3.79-3.62 (m, 6H), 3.41-3.36 (m, 4H), 2.10 (s, 3H), 2.06 (s, 3H), 1.44 (d, 3H), 1.39-1.33 (m, 15H). MS *m/z* $[M+H]^+$ 617.6.

**Scheme 50: Synthesis of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*R*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (50-1):**

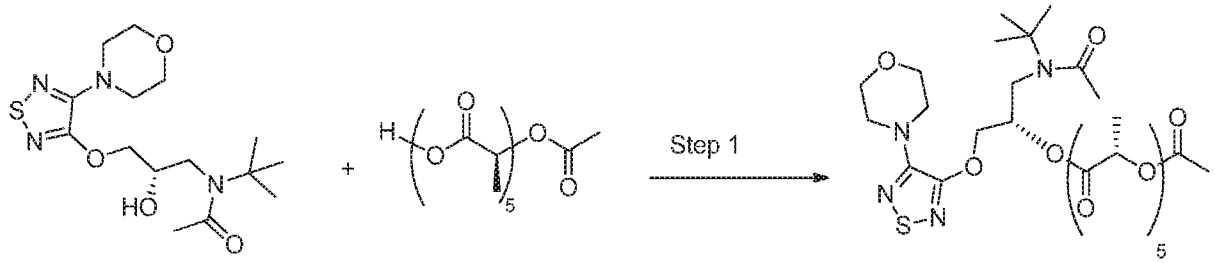



46-4 27-1 50-1

**Step-1: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-[(*S*)-1-[(acetyl-tert-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (50-1):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**27-1**, 0.318 g, 0.91 mmol) in dichloromethane (2.5 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.226 g, 1.09 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide

(**46-4**, 0.25 g, 0.61 mmol) and 4-dimethylaminopyridine (7 mg, 0.06 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (50 mL) and extracted with dichloromethane (100X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (60% ethyl acetate in hexane) to obtain product **50-1** as a colorless wax (170 mg, 40.4 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.48-5.39 (m, 1H), 5.21 (q, 1H), 5.14 (q, 1H), 5.09-5.00 (m, 2H), 4.55 (dd, 1H), 4.42 (dd, 1H), 3.80-3.62 (m, 6H), 3.41-3.35 (m, 4H), 2.08 (s, 3H), 2.06 (s, 3H), 1.44-1.34 (m, 12H), 1.33 (s, 9H). MS *m/z* $[M+H]^+$ 689.8.

**Scheme 51: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-[(*S*)-1-[(*tert*-butyl-formyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (51-1):**

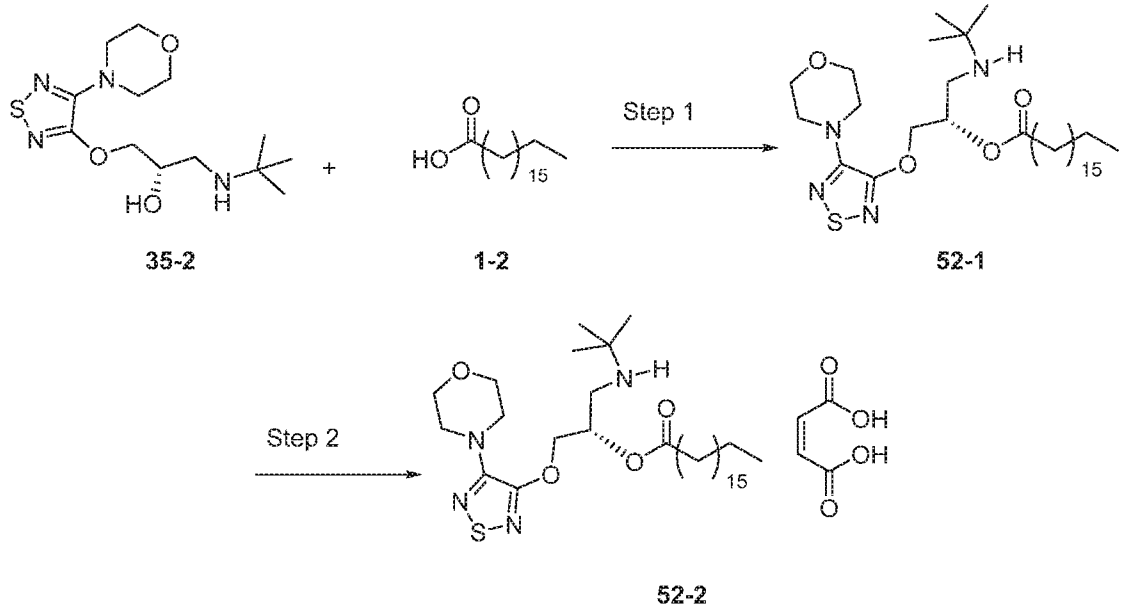



46-4 34-1 51-1

**Step-1: Preaparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-[(*S*)-1-[(*tert*-butyl-formyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (51-1):** To a solution of (*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionic acid (**34-1**, 0.529 g, 1.26 mmol) in dichloromethane (3 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.312 g, 1.51 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.3 g, 0.84 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (100 X 3 mL). The dichloromethane extract was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (55% ethyl acetate in hexane) to obtain product **51-1** as a colorless wax (230 mg, 36.6 %). $^1$H-NMR (400 MHz, DMSO-

d6) δ 5.49-5.40 (m, 1H), 5.25-5.12 (m, 3H), 5.09-5.00 (m, 2H), 4.55 (dd, 1H), 4.42 (dd, 1H), 3.79-3.62 (m, 6H), 3.41-3.35 (m, 4H), 2.08 (s, 3H), 2.07 (s, 3H), 1.47-1.34 (m, 15H), 1.34 (s, 9H). MS *m/z* $[M+H]^+$ 761.9.

**Scheme 52: Synthesis of Octadecanoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (52-2):**

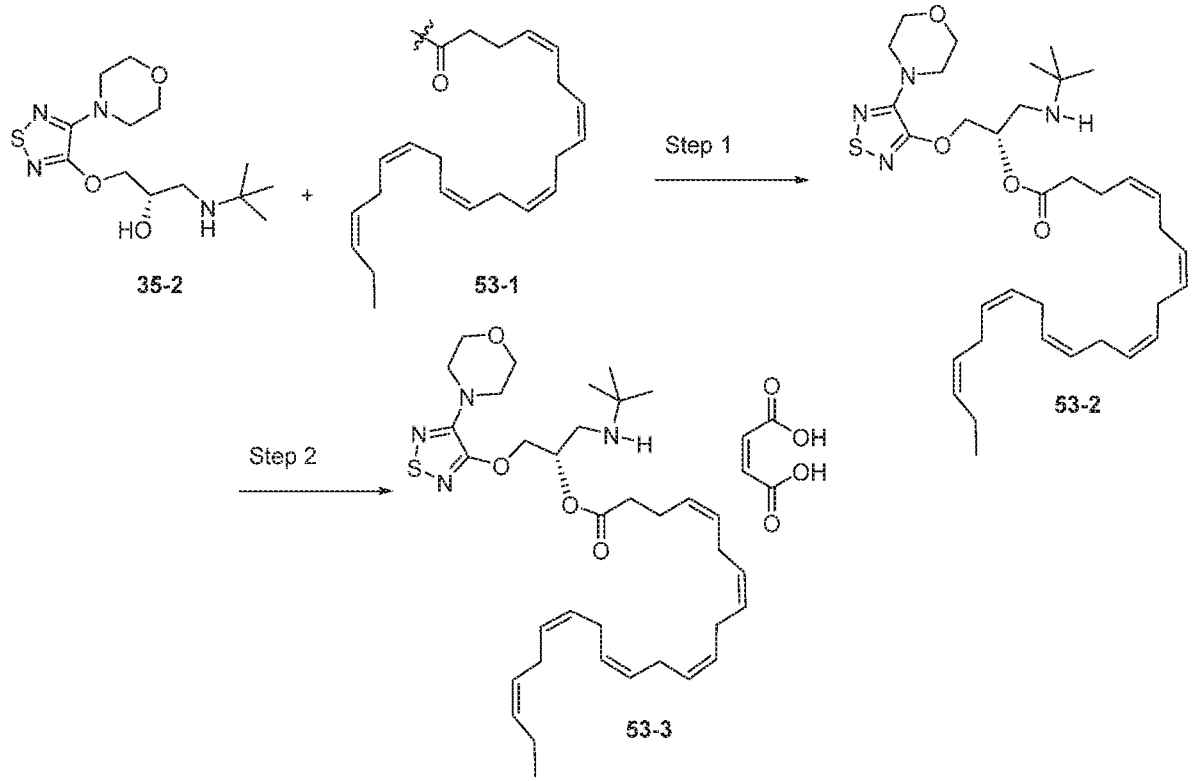



**Step-1: Preparation of Octadecanoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (52-1):** To a solution of stearic acid (**1-2**, 0.674 g, 2.37 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.603 g, 3.16 mmol), Timolol (**35-2**, 0.5 g, 1.58 mmol) and 4-dimethylaminopyridine (19 mg, 0.16 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (35% ethyl acetate in hexane) to obtain product **52-1** as a colorless wax (500 mg, 54%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.18–5.15 (m, 1H), 4.59 (dd, 1H), 4.47 (dd, 1H), 3.68 (t, 4H), 3.46-3.33 (4, 4H), 2.71-2.64 (m, 2H), 2.29-2.22 (m, 2H), 1.7-1.4 (m, 3H), 1.3-1.1 (m, 28H), 1.00 (s, 9H) 0.82 (t, 3H); MS m/z $(M+H)^+$ 583.7

**Step-2: Preparation of Octadecanoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester maleate (52-2):** To a solution of octadecanoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (**52-1**, 0.5

g, 0.86 mmol) in acetone (2.5 mL) was added maleic acid (95 mg, 0.82 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was filtered to afford product **52-2** as a white solid (0.55 g, 91%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.56 (bs, 1H), 8.31 (bs, 1H), 6.02 (s, 2H), 5.46-5.36 (m, 1H), 4.65 (dd, 1H), 4.48 (dd, 1H), 3.72-3.63 (m, 4H), 3.48-3.12 (m, 6H), 2.33 (t, 2H), 1.51 (quintet, 2H), 1.31-1.13 (m, 37H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 583.8.

**Scheme 53: Synthesis of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethylester maleate (53-3):**

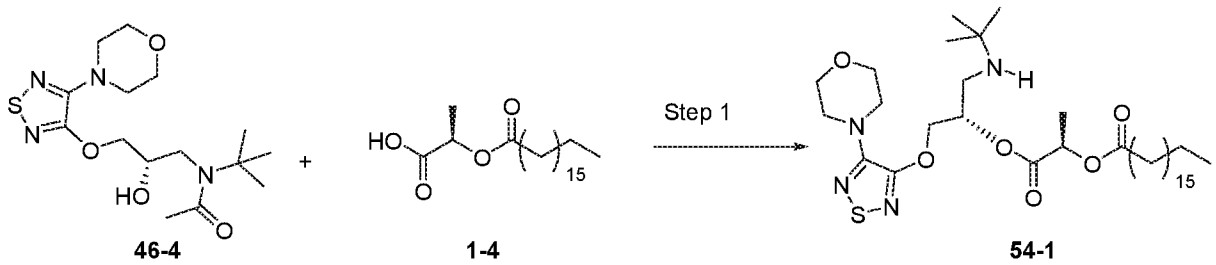



**Step-1: Preparation of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-(tert-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (53-2):** To a solution of docosahexaenoic acid (**53-1**, 0.519 g, 2.37 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.603 g, 3.16 mmol), Timolol (**35-2**, 0.5 g, 1.58 mmol) and 4-dimethylaminopyridine (19 mg, 0.16 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon

evaporation of volatiles was purified through silica gel (230-400) column (30% ethyl acetate in hexane) to obtain product **53-2** as a colorless wax (280 mg, 28%). $^1$H NMR (400 MHz, DMSO-d6) δ 5.41-5.22 (m, 12H), 5.18–5.06 (m, 1H), 4.62 (dd, 1H), 4.46 (dd, Hz, 1H), 3.70-3.63 (m, 4H), 3.47–3.31 (m, 6H), 2.87–2.73 (m, 10H), 2.71-2.66 (m, 2H), 2.38–2.22 (m, 4H), 2.09–1.96 (m, 2H), 0.96 (s, 9H), 0.91 (t, 3H). ; MS m/z $(M+H)^+$ 627.7

**Step-2: Preaparation of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethylester maleate (52-3):** To a solution of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (**53-2**, 0.28 g, 0.45 mmol) in acetone (1.4 mL) was added maleic acid (46 mg, 0.4 mmol) at 0 °C. The mixture was allowed to stir at room temperature over a period of 20 minutes and was filtered to give product **53-3** as an off white low melting solid (0.27 g, 80%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.58 (bs, 1H), 8.33 (bs, 1H), 6.07 (s, 2H), 5.46-5.21 (m, 13H), 4.65 (dd, 1H), 4.48 (dd, 1H), 3.71-3.65 (m, 4H), 3.46-3.13 (m, 6H), 2.85-2.72 (m, 10H), 2.40 (t, 2H), 2.34-2.24 (m, 2H), 2.01 (quintet, 2H), 1.30 (s, 9H), 0.91 (t, 3H). MS *m/z* $[M+H]^+$ 627.7.

**Scheme 54: Synthesis of Octadecanoic acid (*R*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (54-1):**

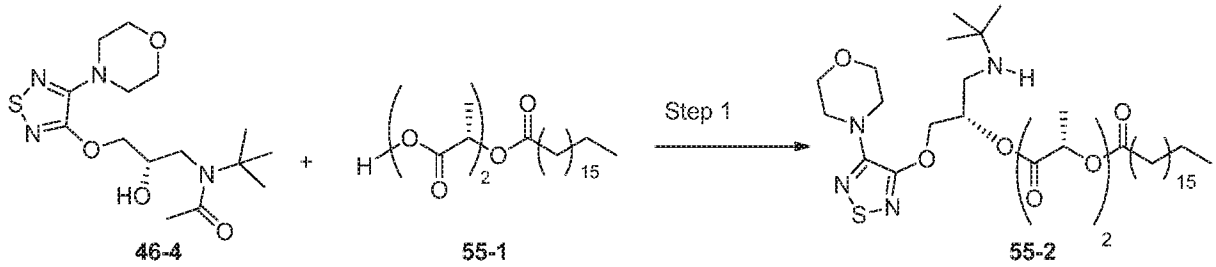



46-4 1-4 54-1

**Step-1: Preparation of Octadecanoic acid (*R*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethyl ester (54-1):** To a solution of octadecanoic acid (*R*)-1-carboxy-ethyl ester (**1-4**, 1.024 g, 1.47 mmol) in dichloromethane (3.5 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.363 g, 1.76 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.35 g, 0.98 mmol ) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour, quenched with water (100 mL) and extracted with dichloromethane (100X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of

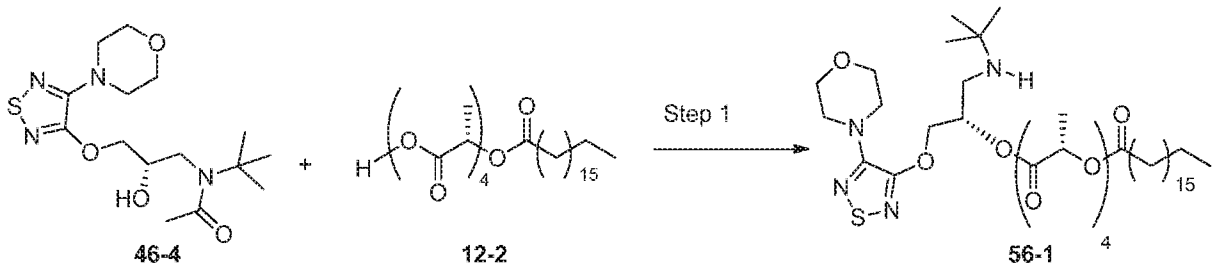
volatiles was purified through silica gel (230-400) column (30% ethyl acetate in hexane) to obtain product **54-1** as a colorless wax (280 mg, 41 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.44-5.36 (m, 1H), 4.97 (q, 1H), 4.53 (dd, 1H), 4.41 (dd, 1H), 3.78-3.61 (m, 6H), 3.45-3.36 (m, 4H), 2.30 (t, 2H), 2.08 (s, 3H), 1.5-1.15 (m, 42H) 0.84 (t, 3H). MS *m/z* $[M+H]^+$ 697.8.

**Scheme 55: Synthesis of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (55-2):**




**Step-1: Preparation of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-tert-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (55-1):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (**55-1**, 0.539 g, 1.26 mmol) in dichloromethane (3 mL) was added *N*,*N*'-dicyclohexylcarbodiimide (0.312 g, 1.51 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.3 g, 0.84 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (100X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (35% ethyl acetate in hexane) to obtain product **55-2** as an colorless wax (300 mg, 46 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.47-5.37 (m, 1H), 5.09-5.01 (m, 2H), 4.55 (dd, 1H), 4.41 (dd, 1H), 3.78-3.62 (m, 6H), 3.42-3.35 (m, 4H), 2.30 (t, 2H), 2.08 (s, 3H), 1.55-1.15 (m, 45H) 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 770.1.

**Scheme 56: Synthesis of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (56-1):**

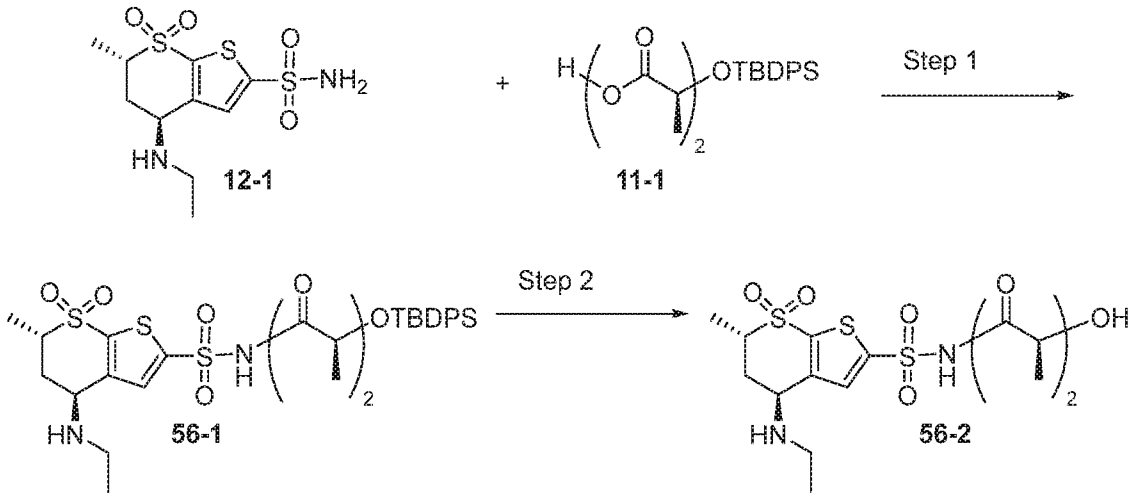



**Step-1: Preparation of Octadecanoic acid (*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (56-1):** To a solution of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**12-2**, 0.721 g, 1.26 mmol) in dichloromethane (3 mL) was added *N,N'*-dicyclohexylcarbodiimide (0.312 g, 1.51 mmol), N-tert-butyl-N-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**46-4**, 0.3 g, 0.84 mmol ) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (100 X 3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (32% ethyl acetate in hexane) to obtain product **56-1** as a colorless wax (300 mg, 39 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.46-5.39 (m, 1H), 5.22 (q, 1H), 5.13 (q, 1H), 5.08-5.01 (m, 2H), 4.55 (dd, 1H), 4.41 (dd, 1H), 3.80-3.64 (m, 6H), 3.41-3.36 (m, 4H), 2.33 (t, 2H), 2.08 (s, 3H), 1.55-1.18 (m, 51H) 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 914.3.

## Example 3. Synthesis of Bis-Prodrugs

***Synthesis of Dorzolamide-Timolol Bis-Prodrugs***

**Scheme 56: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethyl ester (56-2):**




**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethyl ester (56-1):**

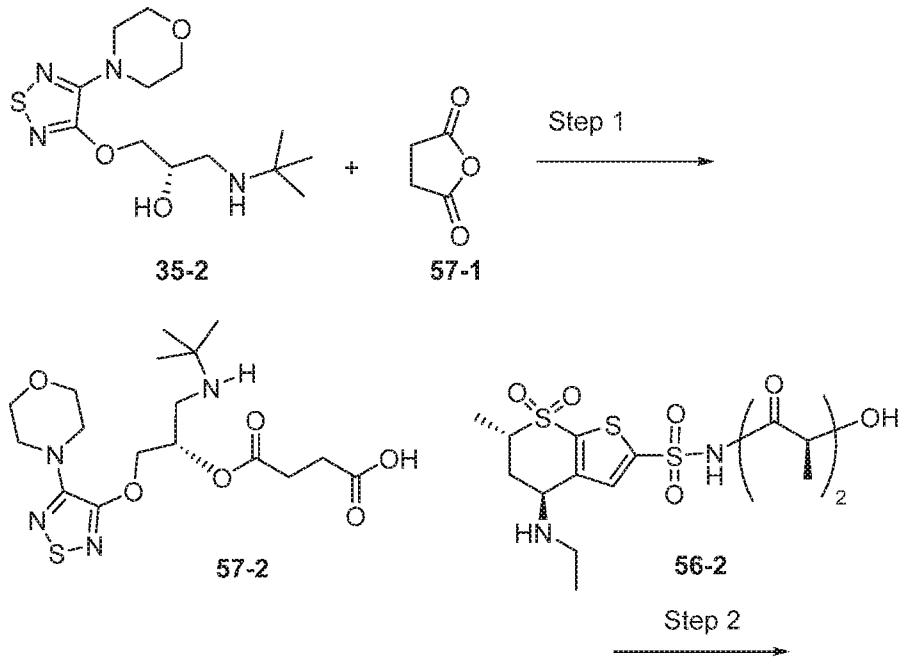
To a solution of Dorzolamide (**12-1**, 1.2 g, 3.33 mmol) in dichloromethane (12 mL) was added *N*,*N*-diisopropylethylamine (1.2 mL, 6.66 mmol) at 0 °C. After 30 minutes, (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester (**11-4,** 2.0 g, 5.01 mmol), EDC.HCl (1.27 g, 6.68 mmol) and 4-dimethylaminopyridine (0.04 g, 0.033 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (6% methanol in DCM) to obtain product **56-1** as a pale yellow solid (1.4 g, 60 %).

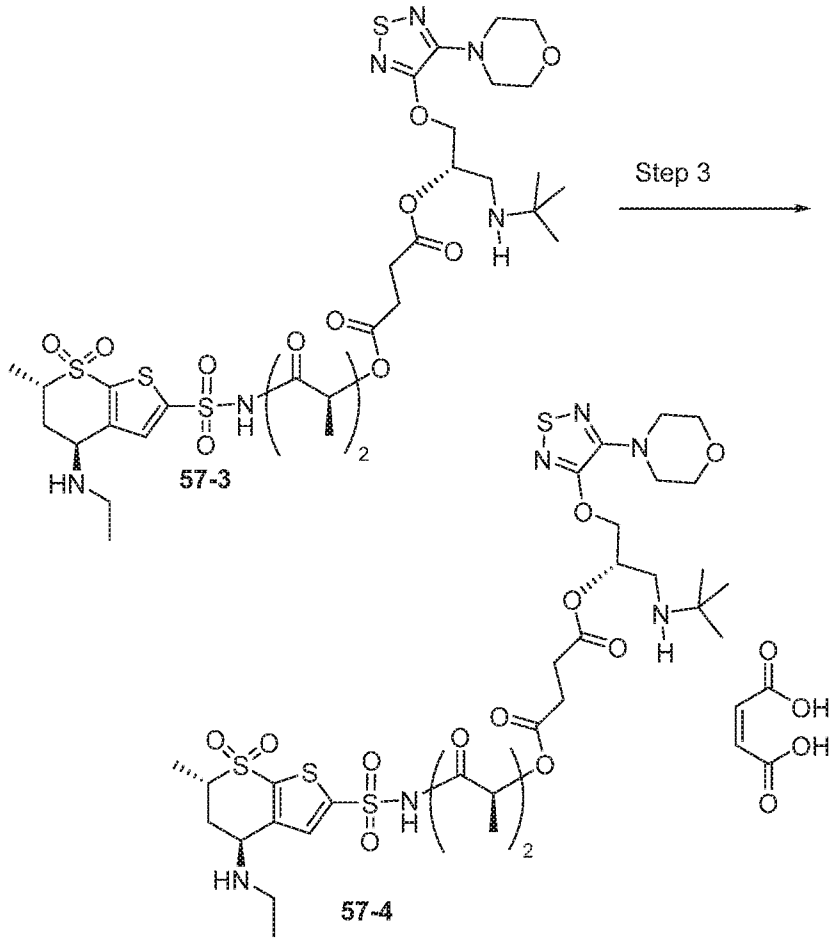
**Step-2:Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethyl ester (56-2):**

To a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[ethyl-((4*S*,6*S*)-6-methyl-7,7-dioxo-2-sulfamoyl-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-4-yl)-carbamoyl]-ethyl ester (**56-1**, 1.4 g, 1.98 mmol) in tetrahydrofuran (15 mL) was added tetra butyl ammonium fluoride (2.97 mL, 1.0 M, 2.97 mmol) and acetic acid (0.17 g, 2.97 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 12 hours. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon

evaporation of the volatiles was purified through silica gel column chromatography (4% methanol in ethyl acetate) to give product **56-2** as an off white solid (850 mg, 92%).

**Scheme 57: Synthesis of compound 57-4:**






**Step-1: Preparation of Succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (57-2):** To a solution of (*S*)-1-*tert*-butylamino-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propan-2-ol (**35-2**, 1.0 g, 3.16 mmol) in dichloromethane (10 mL) was added dihydro-furan-2,5-dione (**57-1**, 0.35 g, 3.48 mmol) and 4-dimethylaminopyridine (0.039 g, 0.31 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 hours. The resulting reaction mixture was concentrated under reduced pressure to give product **57-2** as an off white solid (800 mg, 61%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.25-5.14 (m, 1H), 4.60 (dd, 1H), 4.46 (dd, 1H), 3.72-3.64 (m, 4H), 3.46-3.36 (m, 4H), 2.84-2.74 (m, 2H), 2.51–2.36 (m, 4H), 1.05 (s, 9H). MS m/z (M+H) 417.8.

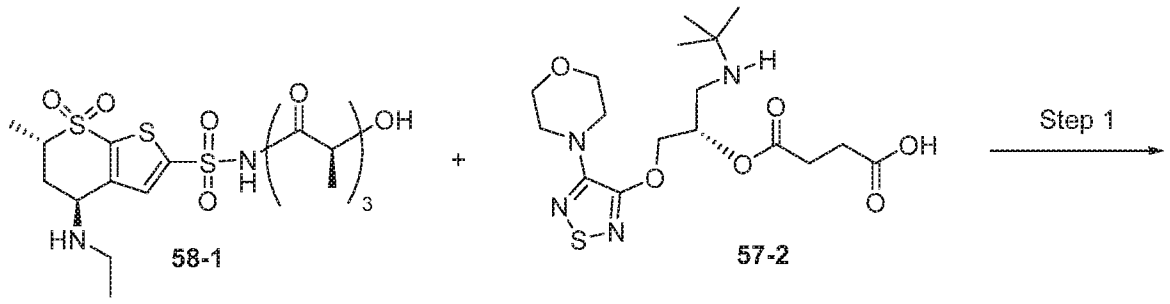
**Step-2: Preparation of Compound 57-3:** To a solution of succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (**57-2**, 0.71 g, 1.70 mmol) in dichloromethane (5 mL) were added EDC.HCl (0.4 g, 2.13 mmol), ((S)-2-hydroxy-propionic acid (*S*)-2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-

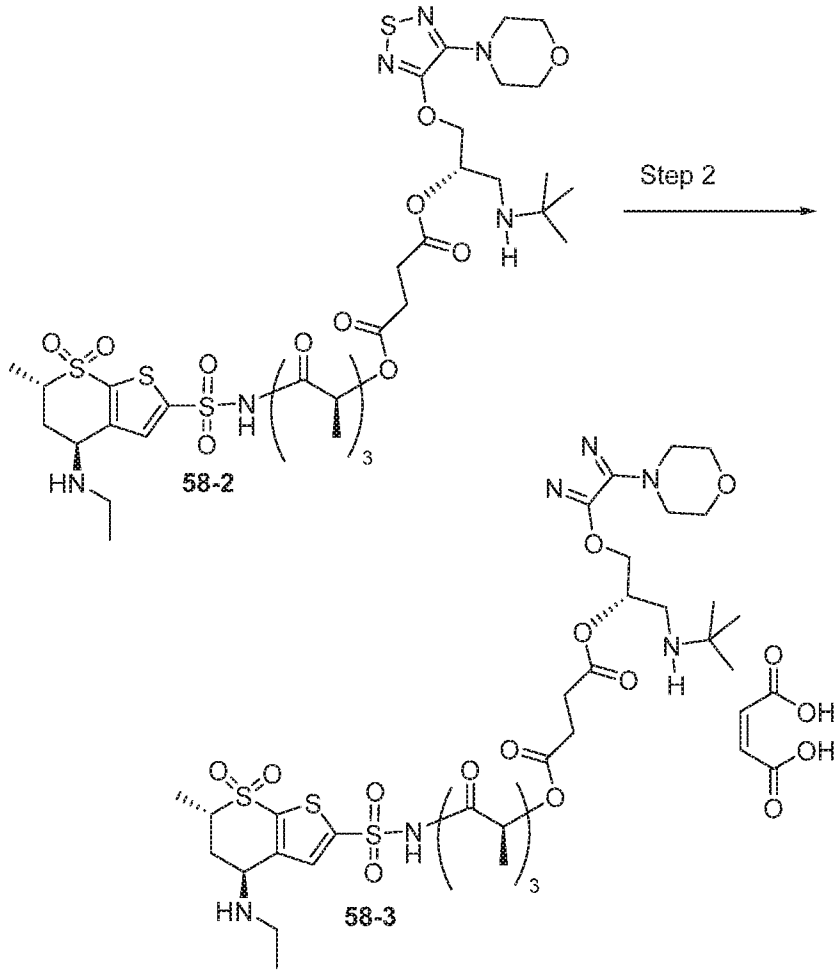
thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethyl ester (**56-2**, 0.5 g, 1.06 mmol) and 4-dimethylaminopyridine (13 mg, 0.106 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (6% methanol in DCM) to obtain product **57-3** as an off white solid (0.3 g, 33%). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.40 (s, 1H), 5.43-5.34 (m, 1H), 4.96 (q, *J* = 7 Hz, 1H), 4.79 (q, *J* = 7 Hz, 1H), 4.62 (dd, 1H), 4.48 (dd, 1H), 3.95-4.84 (m, 1H), 3.71-3.65 (m, 4H), 3.42-3.34 (m, 6H), 2.69-2.5 (m, 6H), 2.4-2.2 (m, 2H), 1.44 (d, *J* = 7.0 Hz, 3H), 1.36–1.15 (m, 16H), 1.04 (t, 3H). MS m/z (M-H)$^-$ 866.1.

**Step-3: Preparation of compound 57-4:** To a solution of compound **57-3** (0.3 g, 0.346 mmol) in acetone (1.5 mL) was added maleic acid (36 mg, 0.311 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **57-4** as an off white solid (0.32 g, 94%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.75 (bs, 2H), 8.55 (bs, 1H), 8.28 (bs, 1H), 7.70 (s, 1H), 6.06 (s, 2H, Maleate), 5.46-5.36 (m, 1H), 4.96 (q, 1H), 4.80 (q, 1H), 4.66-4.58 (m, 2H), 4.48 (dd, 1H), 4.00-3.91 (m, 1H), 3.71-3.65 (m, 4H), 3.5-3.1 (m, 7H), 3.07-2.95 (m, 1H), 2.7-2.5 (m, 6H), 1.45 (d, 3H), 1.37 (d, 3H), 1.32-1.25 (m, 12H), 1.21 (t, 3H). MS *m/z* [M-H]$^-$ 866.2.

**Scheme 58**

**Synthesis of Compound 58-3:**





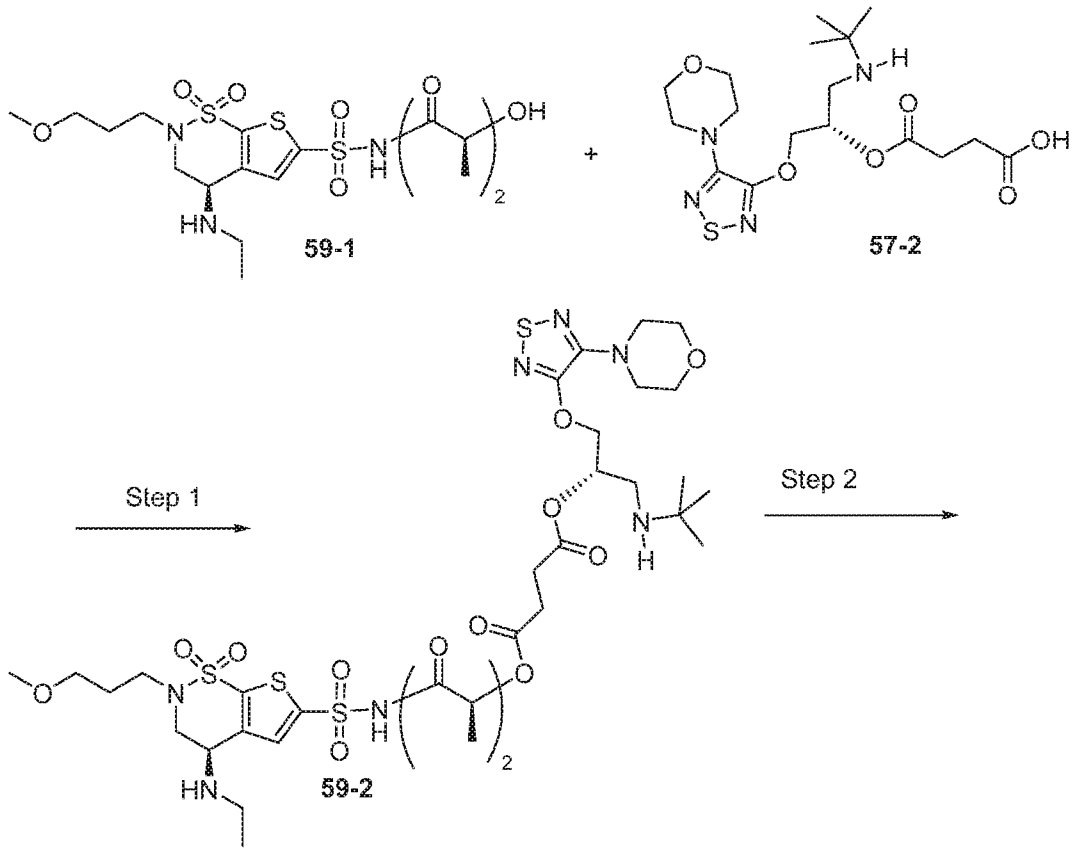

**Step-1: Preparation of Compound 58-2:** To a solution of succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (**57-2**, 0.61 g, 1.48 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.353 g, 1.85 mmol), 2-hydroxy-propionic acid 1-[2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7λ*6*-thieno[2,3-b]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethoxycarbonyl]-ethyl ester (**58-1**, 0.5 g, 0.92 mmol) and 4-dimethylaminopyridine (11 mg, 0.092 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) to obtain product **58-2** as an off white solid (0.1 g, 11%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.55 (bs, 1H), 8.4 (bs, 1H), 7.40 (bs, 1H), 5.45-5.33 (m, 1H), 5.10-5.01 (m, 2H), 4.79 (q, 1H), 4.66–4.58 (dd, 1H), 4.48 (dd, 1H), 3.94-3.82 (m, 2H), 3.71-3.64 (m, 4H), 3.47-3.35 (m,

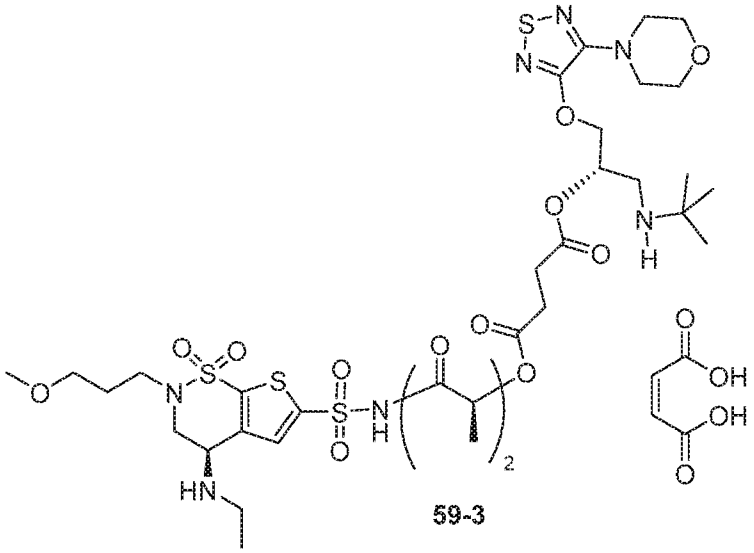
6H), 3.25-3.10 (m, 2H), 2.75-2.58 (m, 4H), 2.4-2.2 (m, 2H), 1.48 (d, 3H), 1.42 (d, 3H), 1.33-1.15 (m, 15H), 1.04 (t, 3H). MS *m/z* [M-H]$^-$ 938.2.

**Step-2: Preparation of Compound 58-3:** To a solution of compound **58-2** (0.1 g, 0.106 mmol) in acetone (1 mL) was added maleic acid (11 mg, 0.095 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **58-3** as an off white solid (0.1 g, 92%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.75 (bs, 2H), 8.54 (bs, 1H), 8.29 (bs, 1H), 7.70 (s, 1H), 6.08 (s, 2H, Maleate), 5.46-5.36 (m, 1H), 5.11-5.01 (m, 2H), 4.81 (q, 1H), 4.66-4.56 (m, 2H), 4.48 (dd, 1H), 4.01-3.91 (m, 1H), 3.71-3.64 (m, 4H), 3.5-3.1 (m, 7H), 3.09-2.95 (m, 1H), 2.7-2.5 (m, 6H), 1.49 (d, 3H), 1.41 (d, 3H), 1.37 (d, 3H), 1.32-1.25 (m, 12H), 1.21 (t, 3H). MS *m/z* [M-H]$^-$ 938.2.

***Synthesis of Brinzolamide-Timolol Bis-Prodrugs***

**Scheme 59: Synthesis of compound 59-3:**





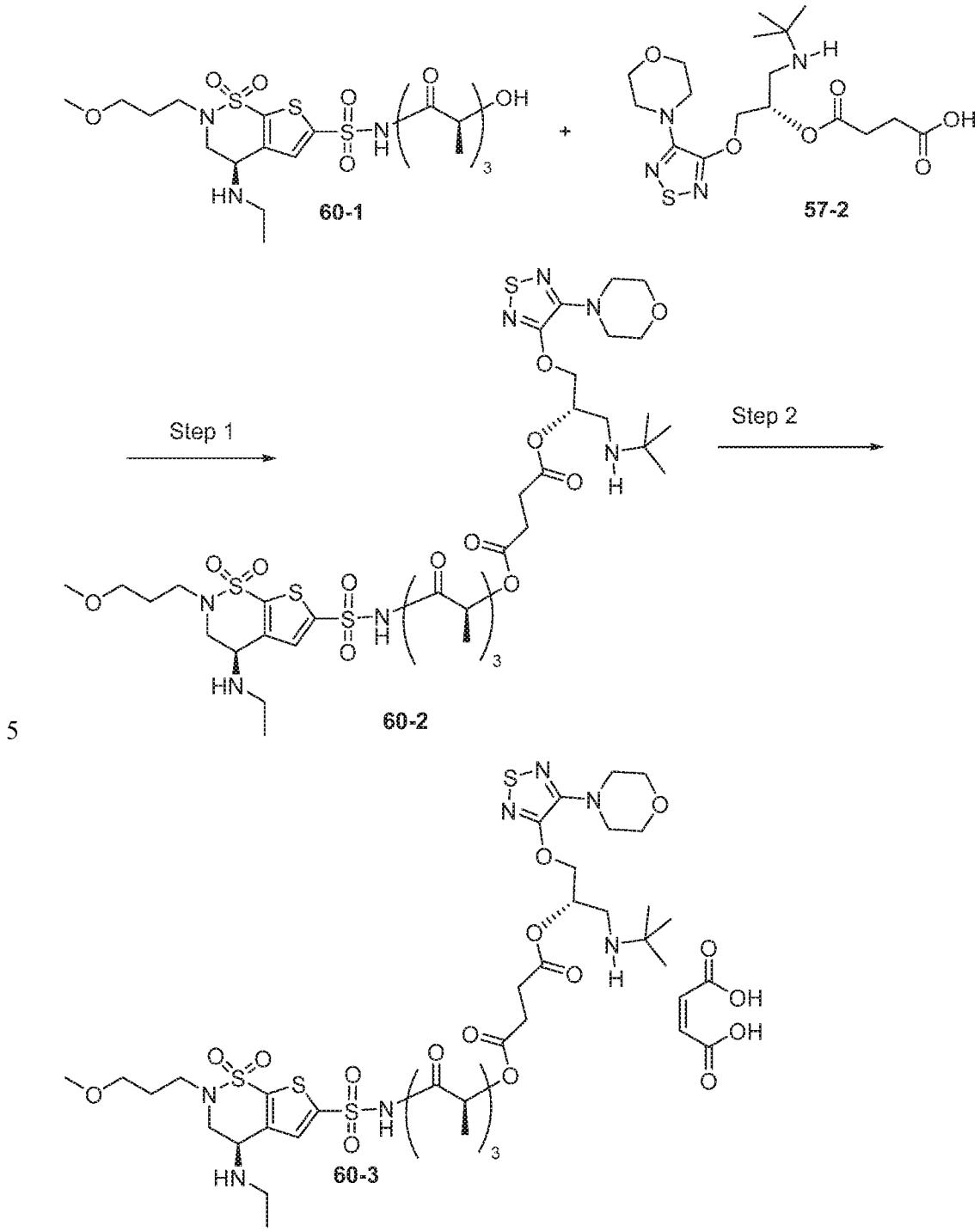
59-3

**Step-1: Preparation of Compound 59-2:** To a solution of succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (**57-2**, 0.506 g, 1.22 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.29 g, 1.59 mmol), 2-hydroxy-propionic acid 2-[(*R*)-4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethyl ester (**59-1**, 0.4 g, 0.76 mmol) and 4-dimethylaminopyridine (10 mg, 0.012 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) to obtain product **59-2** as an off white solid (0.15 g (21%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.55 (bs, 1H), 8.29 (bs, 1H), 7.48 (s, 1H), 5.46-5.34 (m, 1H), 4.96 (q, 1H), 4.79 (q, 1H), 4.63 (dd, 1H), 4.48 (dd, 1H), 4.11-3.98 (m, 1H), 3.81-3.65 (m, 6H), 3.5-3.3 (m, 8H), 3.3-3.08 (m, 5H), 2.75–2.5 (m, 6H), 1.79 (quintet, 2H), 1.44 (d, 3H), 1.35–1.1 (m, 13H), 1.01 (t, 3H). MS m/z $(M+H)^+$ 926.8

**Step-2: Preparation of Compound 59-3:** To a solution of compound **59-2** (0.15 g, 0.161 mmol) in acetone (1 mL) was added maleic acid (17 mg, 0.145 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 10 minutes. The resulting reaction mixture was concentrated under reduced pressure to give product **59-3** as an off white solid (0.16 g, 94%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.1 (bs, 2H), 8.56 (bs, 1H), 8.29 (bs, 1H), 7.79 (s, 1H), 6.09 (s, 2H, Maleate), 5.46-5.36 (m, 1H), 4.96 (q, 1H), 4.86-4.77 (m, 2H), 4.62 (dd, 1H), 4.48 (dd, 1H),

4.11-3.96 (m, 1H), 3.71-3.65 (m, 4H), 3.5-3.3 (m, 8H), 3.3-3.0 (m, 7H), 2.73-2.59 (m, 4H), 1.89-1.77 (m, 2H), 1.45 (d, 3H), 1.32-1.25 (m, 12H), 1.21 (t, 3H). MS *m/z* $[M+H]^+$ 926.8.

**Scheme 60: Synthesis of Compound 60-3:**

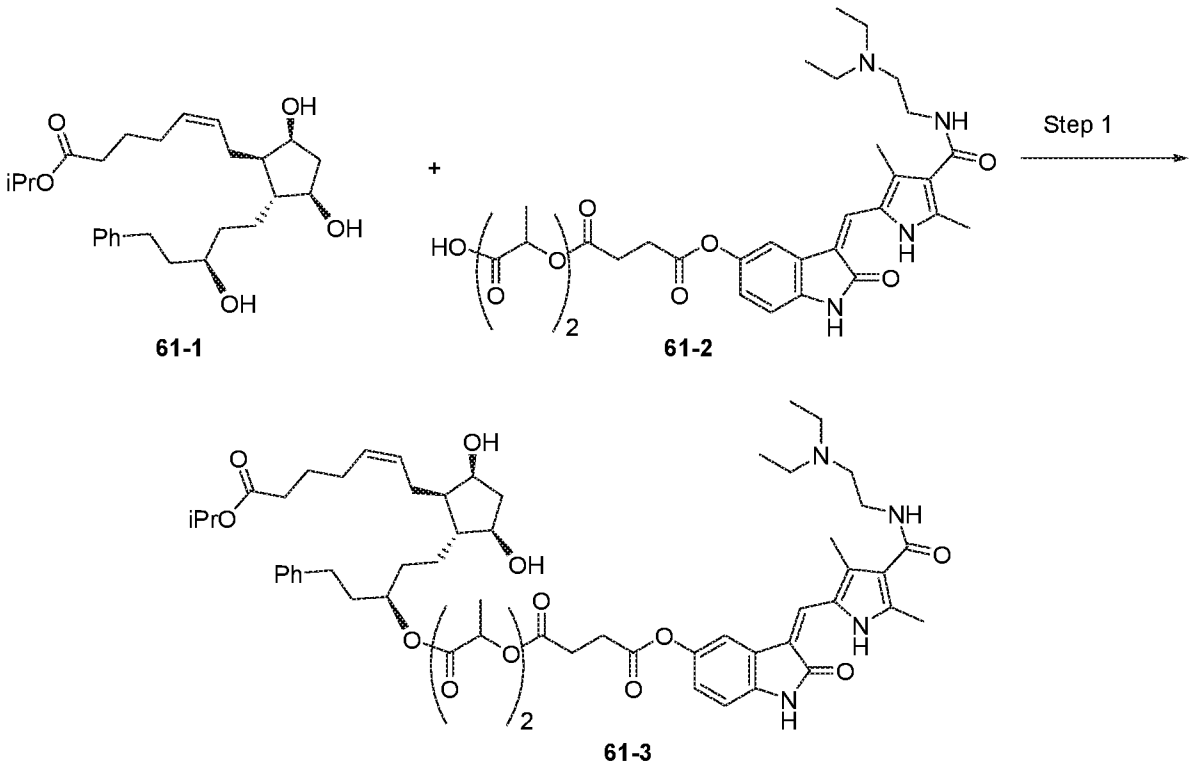


**Step-1: Preparation of Compound 60-2:** To a solution of succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (**57-2**, 0.66 g, 1.60 mmol) in dichloromethane (6 mL) was added EDC.HCl (0.382 g, 2.0 mmol), 2-hydroxy-propionic acid 1-{2-[(*R*)-4-ethylamino-2-(3-methoxy-propyl)-1,1-dioxo-1,2,3,4-tetrahydro-1λ*6*-thieno[3,2-e][1,2]thiazine-6-sulfonylamino]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (**60-1**, 0.6 g, 1.00 mmol) and 4-dimethylaminopyridine (12 mg, 0.010 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) to obtain product **60-2** as an off white solid (0.13 g, 19%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.56 (bs, 1H), 8.27 (bs, 1H), 7.49 (bs, 1H), 5.40 (bs, 1H), 5.09-5.01 (m, 2H), 4.79 (q, 1H), 4.62 (dd, 1H), 4.48 (dd, 1H), 4.11-3.98 (m, 1H), 3.82-3.66 (m, 6H), 3.48–3.32 (m, 8H), 3.25–3.08 (m, 5H), 2.74–2.5 (m, 6H), 1.80 (quintet, 2H), 1.47 (d, 3H), 1.41 (d, 3H), 1.32–1.18 (m, 13H), 1.02 (t, 3H). MS m/z $(M+H)^+$ 999.1.

**Step-2: Preparation of Compound 60-3:** To a solution of compound **60-2** (0.13 g, 0.161 mmol) in acetone (1 mL) was added maleic acid (17 mg, 0.145 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to afford product **60-3** as an off white solid (0.135 g, 93%). $^1$H-NMR (400 MHz, DMSO-d6) δ 9.1 (bs, 2H), 8.59 (bs, 1H), 8.33 (bs, 1H), 7.78 (s, 1H), 6.05 (s, 2H, Maleate), 5.46-5.36 (m, 1H), 5.11-5.01 (m, 2H), 4.85-4.75 (m, 2H), 4.62 (dd, 1H), 4.48 (dd, 1H), 4.12-3.94 (m, 2H), 3.72-3.65 (m, 4H), 3.5-3.3 (m, 8H), 3.25-2.95 (m, 7H), 2.73-2.59 (m, 4H), 1.89-1.79 (m, 2H), 1.49 (d, 3H), 1.41 (d, 3H), 1.33-1.25 (m, 12H), 1.19 (t, 3H). MS *m/z* $[M+H]^+$ 999.1.

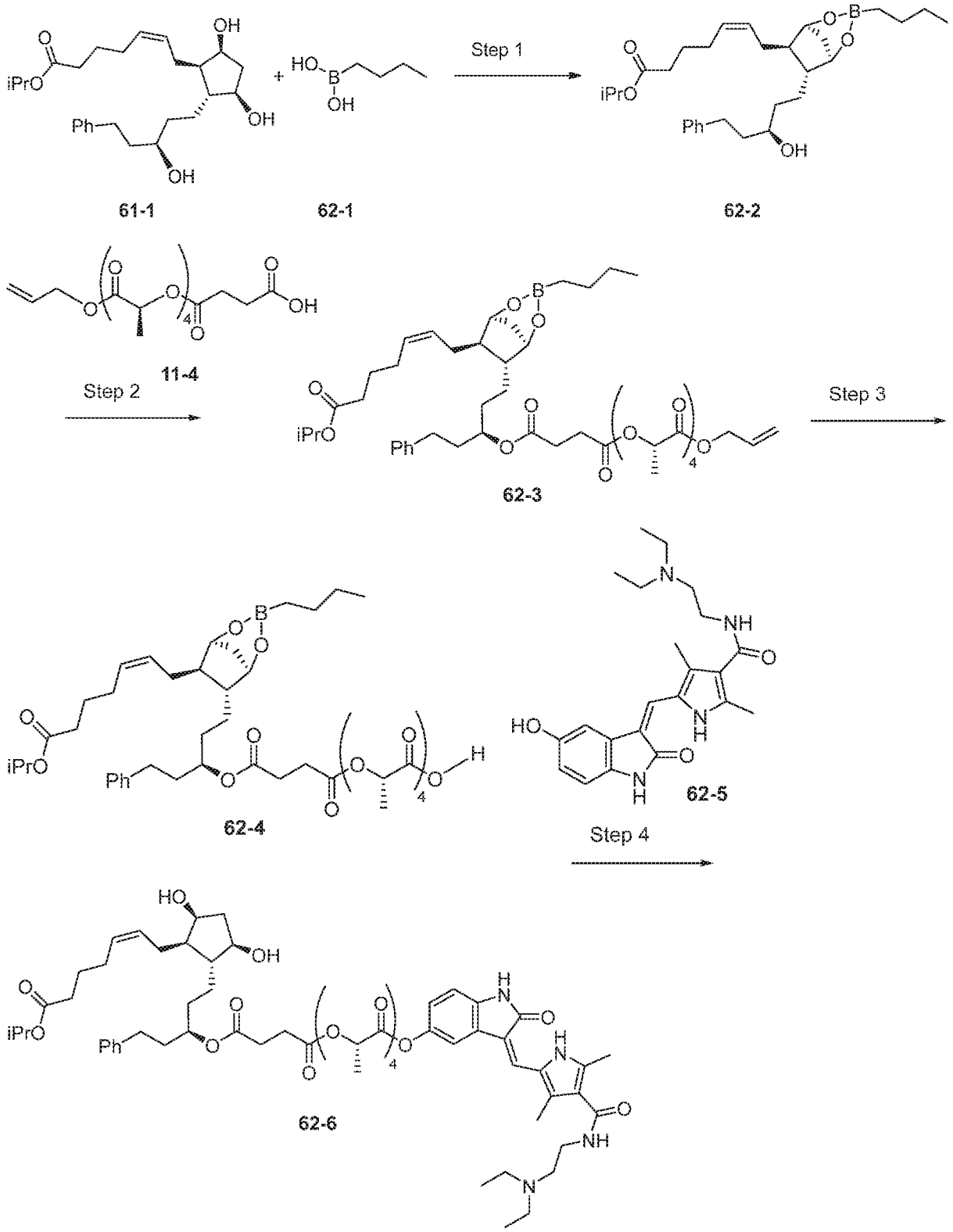
***Synthesis of Latanoprost:Sunitinib Bis-Prodrugs (Compounds of Formula VII)***

**Scheme 61: Synthesis of Compound 61-1:**




**Step-1: Preparation of Compound 61-1:** To a solution of (2*S*)-2-{[(2*S*)-2-[(4-{[(3*Z*)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1*H*-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1*H*-indol-5-yl]oxy}-4-oxobutanoyl)oxy]propanoyl]oxy}propanoic acid (**61-1**, 0.3 g, 0.462 mmol) in dichloromethane (6 mL) was added EDC.HCl (0.132 g, 0.694 mmol), Latanoprost (**61-2**, 0.1 g, 0.231 mmol) and 4-dimethylaminopyridine (3 mg, 0.023 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (4% methanol in DCM) and further purified by preparative-HPLC to obtain product **61-3** as pale yellow solid (0.05 g, 20%). $^1$H-NMR (400 MHz, DMSO-d$_6$) δ 13.67 (s, 1H), 10.94 (s, 1H), 8.19 (s, 1H, formate), 7.67 (s, 1H), 7.59 (s, 1H), 7.48 (t, 1H), 7.30-7.21 (m, 2H), 7.20-7.10 (m, 3H), 6.90-6.78 (m, 2H), 5.5-4.7 (m, 6H), 4.6 (bs, 1H), 4.4 (bs, 1H), 3.9-3.3 (m, 4H), 2.9-2.5 (m, 12H), 2.44 (s, 3H), 2.40 (s, 3H), 2.25-1.8 (m, 7H), 1.7-1.1 (m, 17H), 1.13 (d, 6H), 0.98 (t, 6H). MS *m/z* $(M+H)^+$ 1056.4, $(M+2H)^{++}$ 641.6.

**Scheme 62: Synthesis of compound 62-6:**




**Step-1: Preparation of isopropyl (Z)-7-((1R,5S,6R,7R)-3-butyl-7-((R)-3-hydroxy-5-phenylpentyl)-2,4-dioxa-3-borabicyclo[3.2.1]octan-6-yl)hept-5-enoate (62-2):** To a solution of

Latanoprost (**61-1**, 3.0 g, 6.94 mmol) in anhydrous dichloromethane (30 mL) was added *n*-butylboronic acid (**62-1**, 0.778 g, 7.63 mmol). The mixture was heated at 45 °C for 1 hour under a nitrogen atmosphere. Solvent was removed and the residue was dried *in vacuo*. Additional anhydrous dichloromethane was added and removed *in vacuo* for an additional 3 hours. The residue was further heated in anhydrous dichloromethane at 45 °C for 16 hours and the solvent was removed under reduced pressure to obtain product **62-2** as a colorless oil (2.8 g, 80%). $^1$H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H), 7.25-7.17 (m, 3H), 5.52-5.37 (m, 2H), 5.01 (quintet, 1H), 4.33-4.28 (m, 1H), 4.08-4.04 (m, 1H), 3.68-3.60 (m, 1H), 2.86-2.76 (m, 1H), 2.73-2.63 (m, 1H), 2.31–2.21 (m, 4H), 2.16-2.09 (m, 2H), 1.96-1.91 (m, 1H), 1.82-1.47 (m, 9H), 1.43-1.22 (m, 12H), 0.88 (t, 3H), 0.67 (t, 2H).

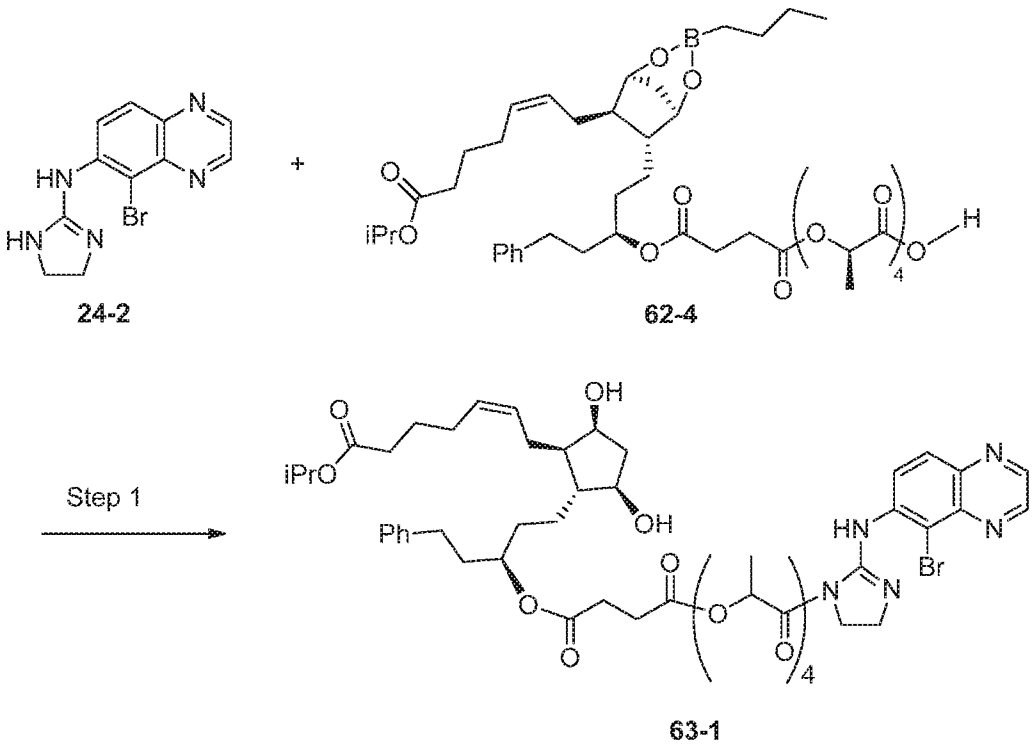
**Step-2: Preparation of (62-3):** To a solution of succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (**11-4**, 3.58 g, 8.02 mmol) in dichloromethane (20 mL) was added *N,N'*-diisopropylcarbodiimide (1.26 mL, 8.02 mmol), (*Z*)-7-[(1*S*,5*R*,6*R*,7*R*)-3-butyl-7-((*R*)-3-hydroxy-5-phenyl-pentyl)-2,4-dioxa-3-bora-bicyclo[3.2.1]oct-6-yl]-hept-5-enoic acid isopropyl ester (**62-2**, 2.0 g, 4.01 mmol) and 4-dimethylaminopyridine (48 mg, 0.40 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400) column (30% ethyl acetate in hexane) to obtain product **62-3** as colorless liquid (2.5 g, 67%).

**Step-3: Preparation of (62-4):** To a solution succinic acid (*R*)-1-{(*R*)-1-[(*R*)-1-((*R*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (*R*)-3-[(1*R*,5*S*,6*R*,7*R*)-3-butyl-7-((*Z*)-6-isopropoxycarbonyl-hex-2-enyl)-2,4-dioxa-3-bora-bicyclo[3.2.1]oct-6-yl]-1-phenethyl-propyl ester (**62-3**, 2.5 g, 2.69 mmol) in tetrahydrofuran (25 mL) was added tetrakis(triphenylphosphine)palladium (0.31 g, 0.269 mmol) and pyrrolidine (0.22 mL, 2.56 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 hours. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel column chromatography (8% methanol in dichloromethane) to afford product **62-4** as colorless liquid (1.2 g, 52%).

**Step-4: Preparation of Compound 62-6:** To a solution of succinic acid (*R*)-3-[(1*R*,5*S*,6*R*,7*R*)-3-butyl-7-((*Z*)-6-isopropoxycarbonyl-hex-2-enyl)-2,4-dioxa-3-bora-bicyclo[3.2.1]oct-6-yl]-1-phenethyl-propyl ester (*R*)-1-{(*R*)-1-[(*R*)-1-((*R*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (**62-4**, 0.45 g, 0.505 mmol) in dichloromethane (4 mL) was added *N*,*N*-diisopropylethylamine (0.12 mL, 0.631 mmol) at 0 °C. After 5 minutes, EDC.HCl (0.12 g, 0.631 mmol), 5-hydroxy Sunitinib (**62-5**, 0.125 g, 0.315 mmol) and 4-dimethylaminopyridine (4 mg, 0.031 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X3 mL). The dichloromethane was dried over sodium sulfate, filtered concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified was purified by preparative HPLC to obtain product **62-6** as a reddish yellow solid (40 mg, 10 %). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ 13.74 (s, 1H), 11.01 (s, 1H), 7.8-7.6 (m, 3H), 7.29-7.22 (m, 2H), 7.19-7.12 (m, 3H), 6.92-6.81 (m, 2H), 5.5-4.7 (m, 8H), 4.48 (d, 1H), 4.26, (d, 1H), 3.9-3.8 (m, 1H), 3.6-3.5 (m, 1H), 3.3-3.1 (m, 2H), 2.7-2.4 (m, 18H), 2.3-1.9 (m, 7H), 1.8-1.3 (m, 23H), 1.3-1.0 (m, 12H). MS *m/z* $[M+H]^+$ 1200.9

***Synthesis of a Latanoprost:Brimonidine Bis-Prodrug***

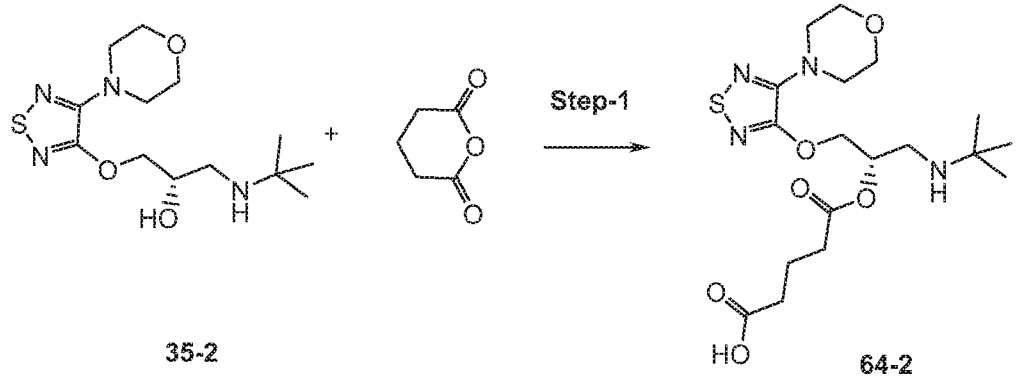
**Scheme 63: Synthesis of compound 63-1:**




**Step-1: Preparation of Compound 63-1:** To a solution of succinic acid 1-{1-[1-(1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxy-carbonyl}-ethyl ester (*R*)-3-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-((*Z*)-6-isopropoxycarbonyl-hex-2-enyl)-cyclopentyl]-1-phenethyl-propyl ester (**62-4**, 0.31 g, 0.385 mmol) in dichloromethane (3 mL) was added triethylamine (0.086 ml, 0.64 mmol), ethyl chloroformate (0.053 ml, 0.51 mmol), Brimonidine (**24-2**, 0.075 g, 0.256 mmol) and 4-dimethylaminopyridine (3 mg, 0.025 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL) and extracted with dichloromethane (200X2 mL). The dichloromethane was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC to obtain product **63-1** as a pale yellow solid (50 mg, 12 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, *J* = 2 Hz, 1H), 8.84 (d, *J* = 2 Hz, 1H), 7.99 (d, *J* = 9 Hz, 1H), 7.59 (d, *J* = 9 Hz, 1H), 7.30-7.21 (m, 3H), 7.19-7.12 (m, 3H), 6.52 (q, 1H), 5.51-5.39 (m, 1H), 5.31-5.22 (m, 1H), 5.18 (q, 1H), 5.12 (q, 1H), 5.06 (q, 1H), 4.90-4.83 (m, 2H), 4.48 (d, 1H), 4.25 (d, 1H), 3.96-3.82 (m, 3H), 3.73-3.63 (m, 1H), 3.45-3.34 (m, 2H), 2.69-2.5 (m, 6H), 2.21 (t, 2H), 2.15-2.06 (m, 1H), 2.05-1.93 (m, 4H), 1.81-1.72 (m, 2H), 1.67-1.29 (m, 20H), 1.23-1.09 (m, 7H). MS *m/z* $[M-H]^-$ 1094.2.

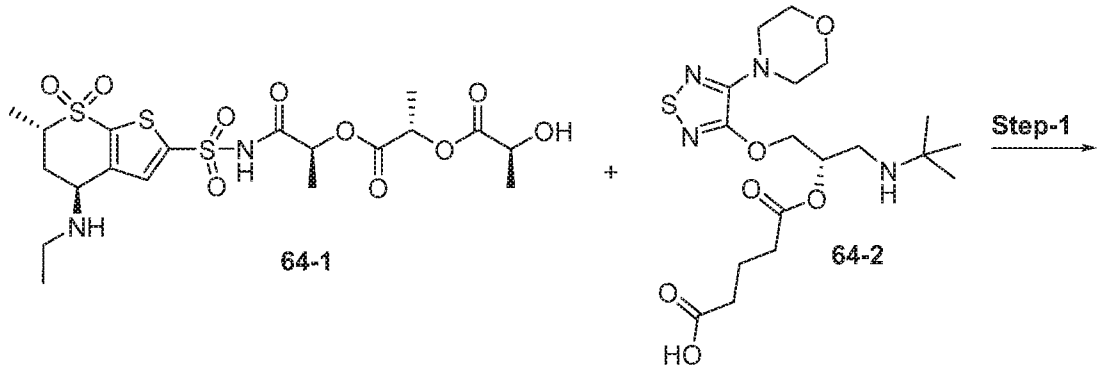
**Example 4: Synthetic Examples to describe Select Compounds of the Present Invention**

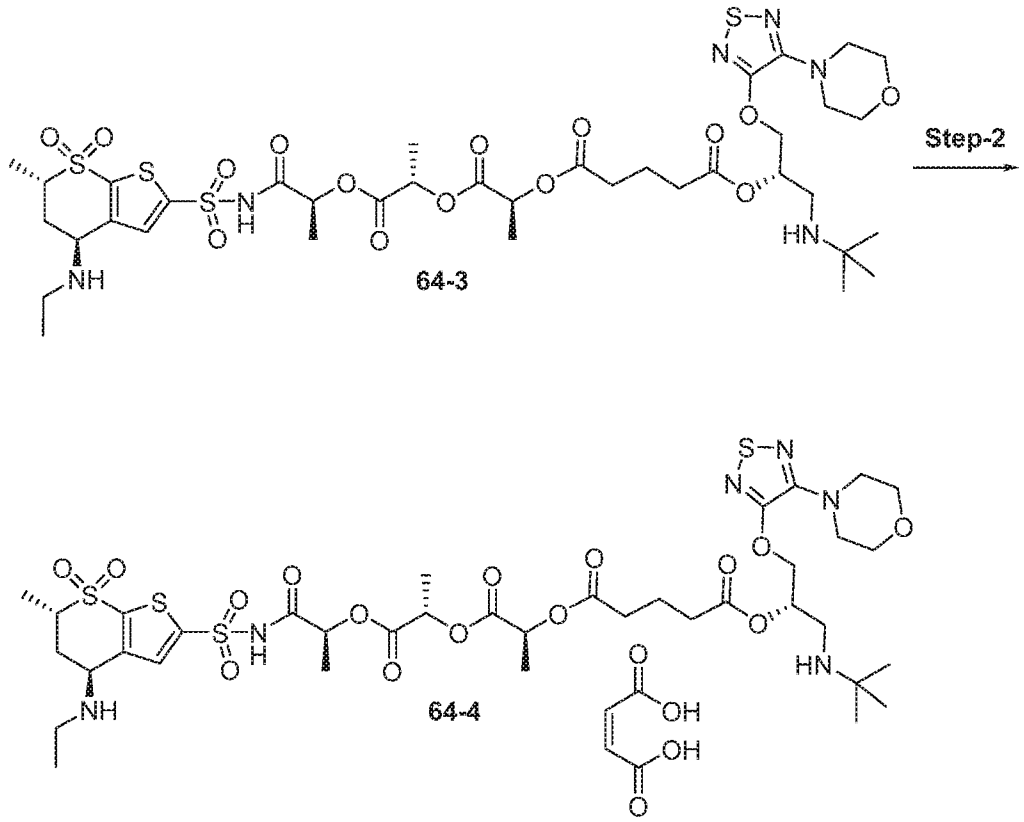
**Scheme 64. Synthesis of Pentanedioic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (64-2):**




**Step 1: Pentanedioic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (64-2):** To a solution of (*S*)-1-*tert*-butylamino-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propan-2-ol **35-2** (2.0 g, 6.32 mmol) in dichloromethane (20 mL) were added dihydro-pyran-5,6-dione (0.86 g, 7.59 mmol) and 4-dimethylaminopyridine (0.079 g, 0.62 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 h. The resulting reaction mixture was concentrated under reduced pressure to afford product **64-2** as an off white solid 2.0 g (73%).

**Scheme 65. Synthesis of Timolol-*O*-glutarate-PLA(n=3)-Dorzolamide maleate salt (64-4):**






**Step 1: Preparation of Timolol-*O*-glutarate-PLA(n=3)-Dorzolamide (64-3):**

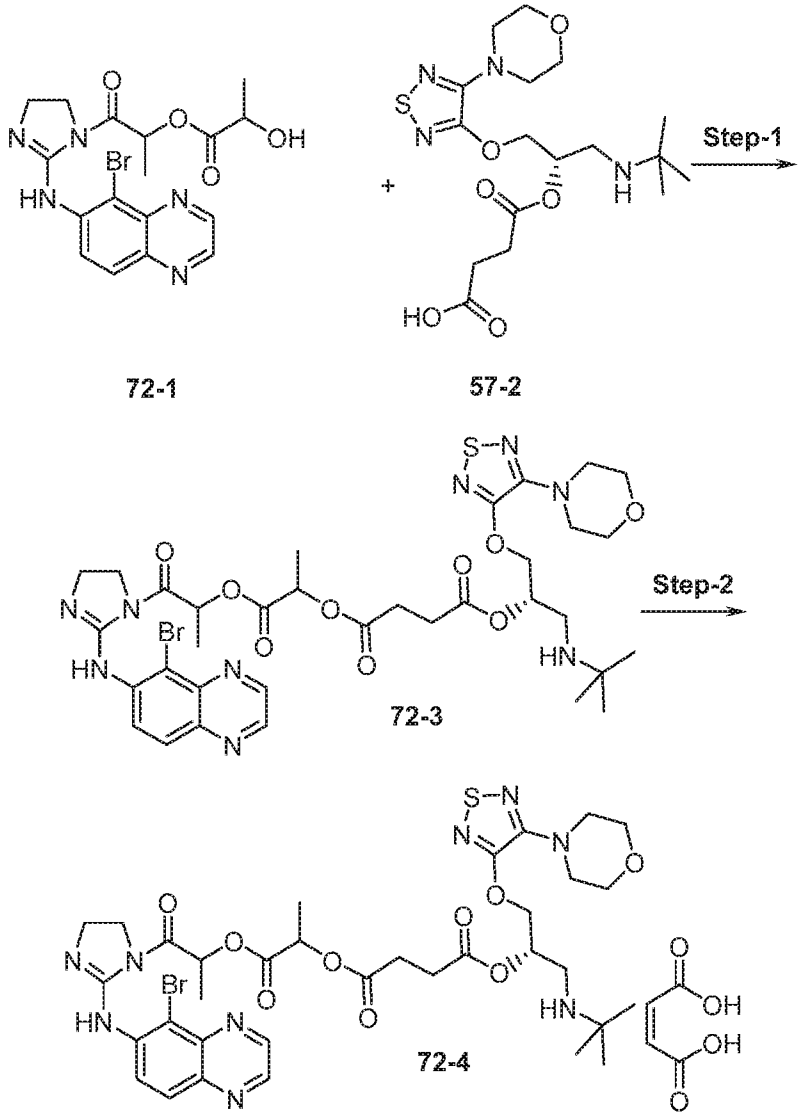
To a solution of pentanedioic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester **64-1** (0.61 g, 1.48 mmol) in dichloromethane (5 mL) was added EDC.HCl (0.35 g, 1.85 mmol), (S)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-2-((4*S*,6*S*)-4-ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7lambda*6*-thieno[2,3-*b*]thiopyran-2-sulfonylamino)-1-methyl-2-oxo-ethoxycarbonyl]-ethyl ester **64-2** (0.50 g, 0.92 mmol) and 4-dimethylaminopyridine (11 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (4% methanol in DCM) to obtain product **64-3** as an off white solid 0.1 g (11%).

**Step 2: Preparation of Timolol-*O*-glutarate-PLA(n=3)-Dorzolamide maleate salt (64-4):**

To a solution of Timolol-*O* -glutarate-PLA(n=3)-Dorzolamide **64-3** (0.1 g, 0.10 mmol) in acetone (1 mL) was added maleic acid (11 mg, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was

concentrated under reduced pressure and dried under vacuum to give product **64-4** as an off white solid 0.1 g (92%).

**Scheme 66: Synthesis of Maleate salt of Succinic acid 1-{2-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (72-4):**

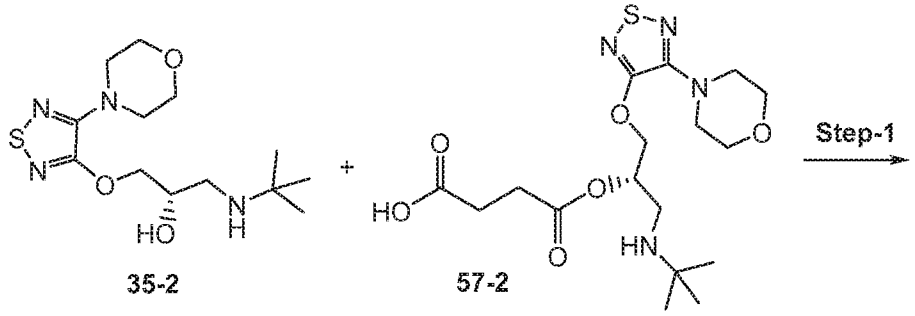



**Step 1: Preparation of Succinic acid 1-{2-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (72-3):** To a solution of Succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5] thiadiazol-3-yloxy)-ethyl] ester **57-2** (4.29 g, 10.32 mmol) in dichloromethane (30 mL) was added EDC·HCl (2.62 g, 13.75mmol), 2-hydroxy-propionic acid 2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-

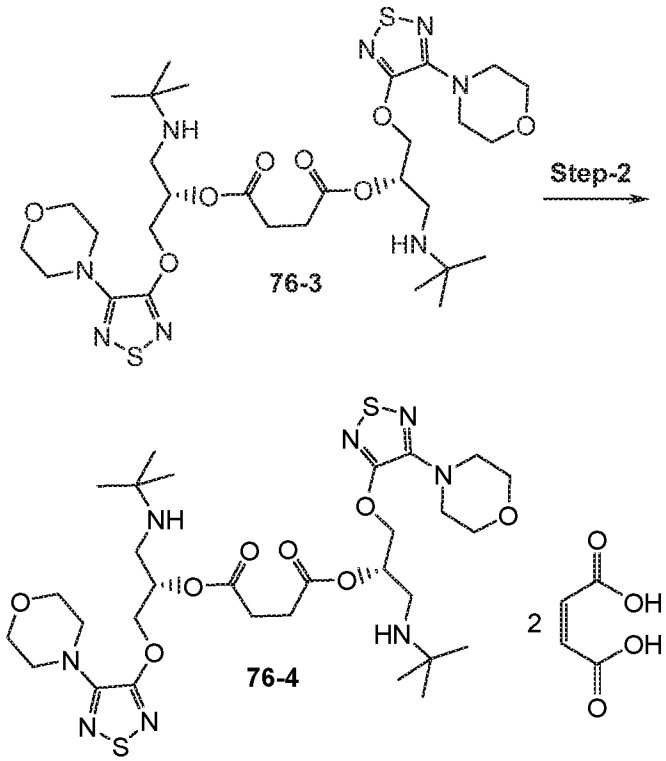
imidazol-1-yl]-1-methyl-2-oxo-ethyl ester **72-1** (3 g, 6.88 mmol), and 4-dimethylaminopyridine (0.083 g, 0.688 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (300 mL), extracted with dichloromethane (300 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (3% 2-propanol in DCM) to obtain product **72-3** as a pale green solid 1.0 g (17%).

**Step 2: Preparation of Maleate salt of Succinic acid 1-{2-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (72-4):** To a solution of Succinic acid 1-{2-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester **72-3** (1 g, 1.19 mmol) in acetone (5 mL) was added maleic acid (0.125 g, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure and dried under vacuum to give product **72-4** as a pale green solid 1.0 g (89%).

**Scheme 67: Synthesis of Maleate salt of Succinic acid bis-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (76-4):**




35-2 57-2

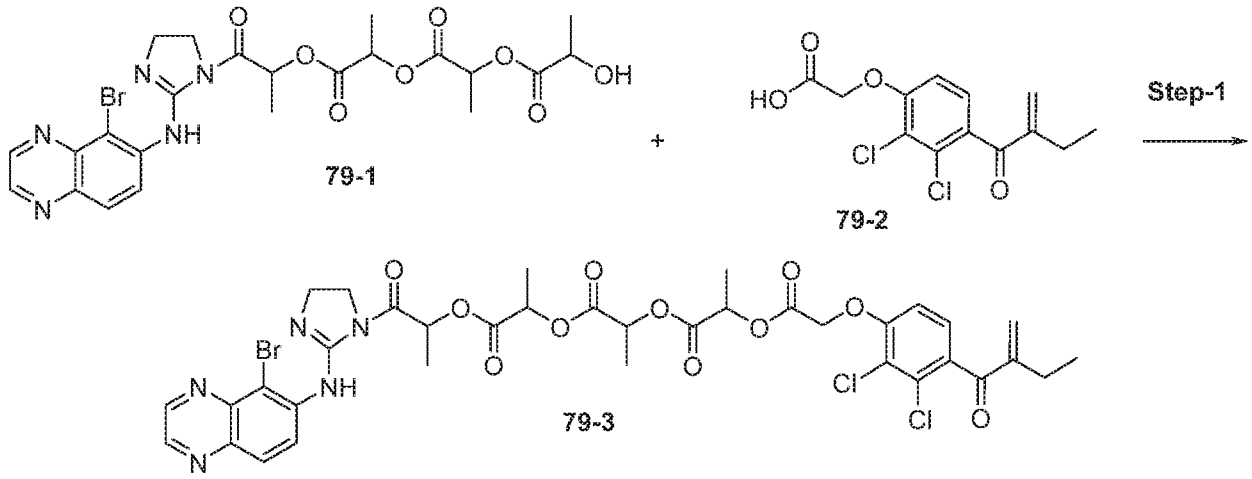



**Step 1: Preparation of Succinic acid bis-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (76-3):** To a solution of Succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester **57-2** (7.24 g, 17.4 mmol) in dichloromethane (50 mL) was added EDC·HCl (4.53 g, 23.7 mmol), (*S*)-1-*tert*-Butylamino-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propan-2-ol **35-2** (5 g, 15.8 mmol), and 4-dimethylaminopyridine (0.19g, 1.582 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (200 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (40-50% ethyl acetate in hexane) to obtain product **76-3** as a colorless liquid 4.1 g (36%).

**Step 2: Preparation of Maleate salt of Succinic acid bis-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester (76-4):** To a solution of Succinic acid bis-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl] ester **76-3** (4.1 g, 5.74 mmol) in acetone (20 mL) was added maleic acid (0.559 g, 5.16 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 20 minutes. The

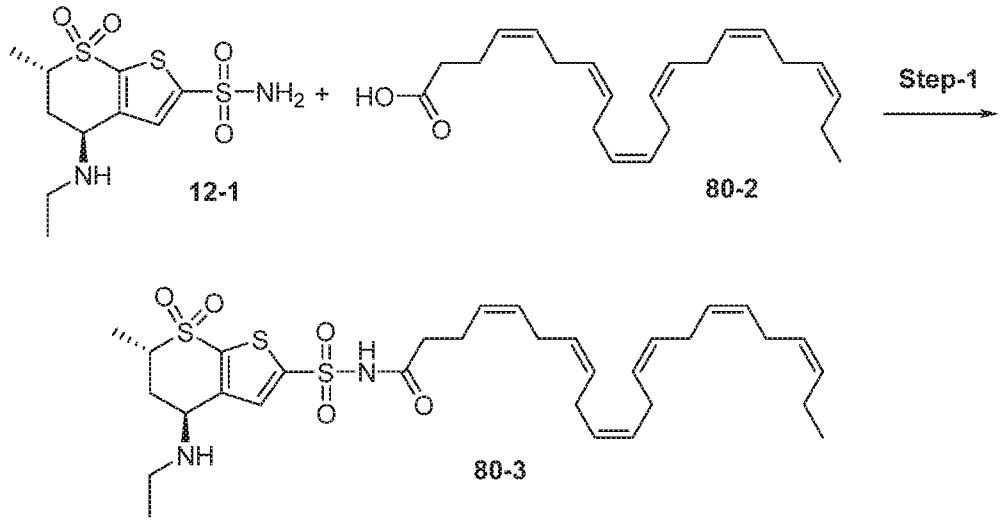
resulting reaction mixture was concentrated under reduced pressure to afford product **76-4** as a white solid 3 g (63%).

**Scheme 68: Synthesis of 2-[2-(2-{2-[2,3-dichloro-4-(2-Methylene-butyryl)-phenoxy]-acetoxy}-propionyloxy)-propionyloxy]-propionic acid 2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (79-3):**



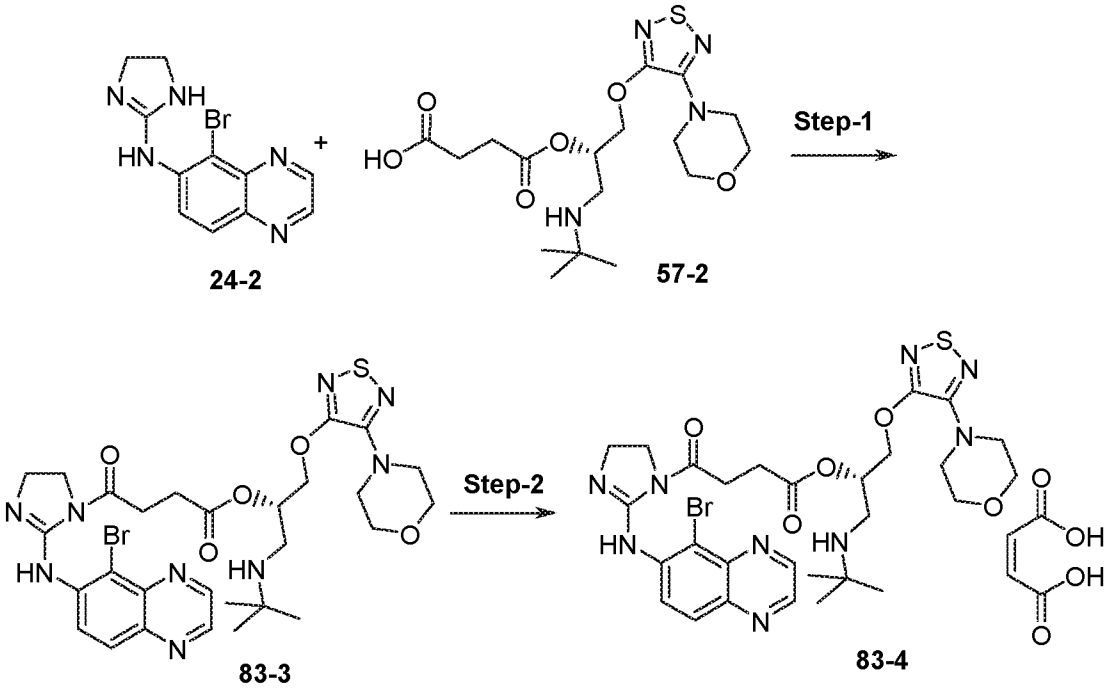

**Step 1: Preparation of 2-[2-(2-{2-[2,3-Dichloro-4-(2-methylene-butyryl)-phenoxy]-acetoxy}-propionyloxy)-propionyloxy]-propionic acid 2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (79-3):** To a solution of ethacrynic acid **79-2** (2.44 g, 8.06 mmol) in dichloromethane (40 mL) was added EDC·HCl (1.92 g, 10.08 mmol), 2-hydroxy-propionic acid 1-(1-{2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester **79-1** (3.9 g, 6.72 mmol) and 4-dimethylaminopyridine (0.082g, 0.672 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (200 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (12-15% ethyl acetate in dichloromethane) to obtain product **79-3** as a pale green solid 2.0 g (35%).

**Scheme 69: Synthesis of (4*S*,6*S*)-4-Ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7lambda*6*-thieno[2,3-*b*]thiopyran-2-sulfonic acid ((4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoyl)-amide (80-3):**




**Step 1: Preparation of (4*S*,6*S*)-4-Ethylamino-6-methyl-7,7-dioxo-4,5,6,7-tetrahydro-7lambda*6*-thieno[2,3-*b*]thiopyran-2-sulfonic acid ((4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-docosa-4,7,10,13,16,19-hexaenoyl)-amide (80-3):** To a solution of Dorzolamide **12-1** (3.0 g, 8.35 mmol) in dichloromethane (30 mL) was added *N*,*N*-diisopropylethylamine (3.07 mL,16.6 mmol) at 0 °C. After 30 minutes, (4*Z*,7*Z*,10*Z* ,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid **80-2** (3.5 g, 10.8 mmol), EDC·HCl (2.38 g, 12.5 mmol), benzotriazol-1-ol (0.23 g, 1.66 mmol) and 4-dimethylaminopyridine (0.1 g, 0.83 mmol) were added at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (400 mL), extracted with dichloromethane (300 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (2% methanol in DCM) to obtain product **80-3** as off white low melting solid 2.5 g (95%).

**Scheme 70: Synthesis of Maleate salt of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5] thiadiazol-3-yloxy)-ethyl ester (83-4):**

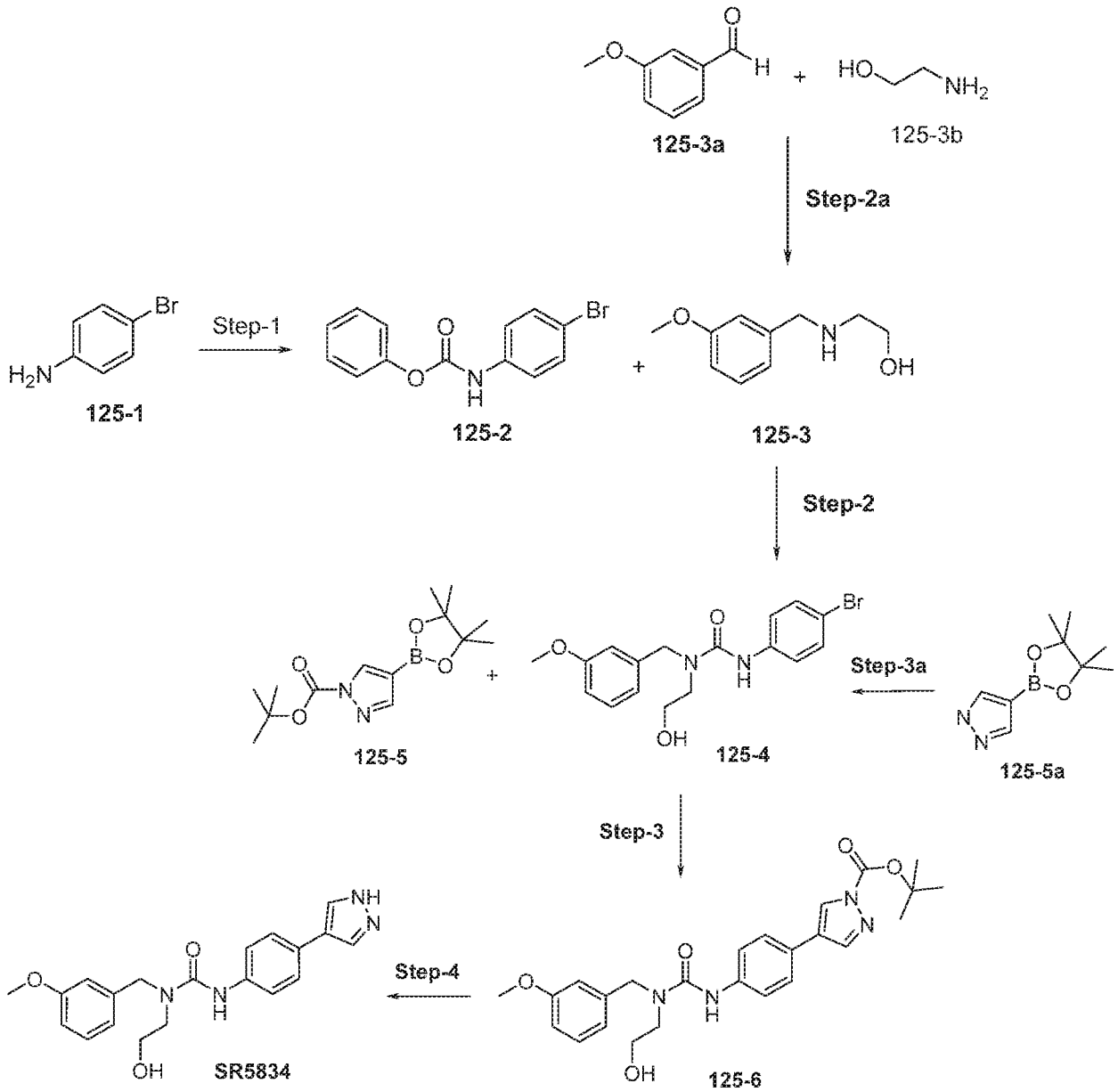



**Step 1: Preparation of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester (83-3):** To a solution of Succinic acid mono-[(*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5] thiadiazol-3-yloxy)-ethyl] ester **57-2** (8.54 g, 20.5 mmol) in dichloromethane (40 mL) was added EDC·HCl (5.232 g, 27.3 mmol), Brimonidine **24-2** (4 g, 13.6 mmol), and 4-dimethylaminopyridine (0.167g, 1.36 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (250 mL), extracted with dichloromethane (250 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (3% 2-propanol in dichloromethane) to obtain product **83-3** as a pale yellow solid 3.0 g (31%).

**Step 2: Preparation of maleate salt of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5] thiadiazol-3-yloxy)-ethyl ester (83-4):** To a solution of 4-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-(*tert*-butylamino-methyl)-2-(4-morpholin-4-yl-[1,2,5] thiadiazol-3-yloxy)-ethyl ester **83-3** (3 g, 4.34 mmol) in acetone (15 mL) was added maleic acid (0.45 g, 3.91 mmol) at 0 °C. The reaction mixture was allowed to stir at room

temperature over a period of 20 minutes. The resulting reaction mixture was concentrated under reduced pressure to afford product **83-4** as a pale yellow solid 3 g (85%).

**Scheme 71: Synthesis of 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-urea (SR5834):**




**Step 1: Preparation of (4-Bromo-phenyl)-carbamic acid phenyl ester (125-2):** To a solution of 4-bromo aniline **125-1** (50 g, 290 mmol) in dichloromethane (500 mL) was added *N*,*N*-diisopropylethylamine (148 mL, 871 mmol) followed by phenyl chloroformate (40.3 mL, 319 mmol) over a period of 30 min at 0 °C. The reaction mixture was allowed to stir at 25 °C for 2 h.

After the complete conversion of starting material as detected by TLC, the reaction mixture was concentrated completely under reduced pressure to give the crude **125-2** as light brown oil which was used in the next step without further purification.

**Step 2a: Preparation of 2-(3-Methoxy-benzylamino)-ethanol (38-3):** To a solution of 3-methoxy-benzaldehyde **125-3a** (30 g, 220 mmol) in methanol (300 mL) was added 2-amino-ethanol **125-3b** (13.45 g, 220 mmol). After stirring at room temperature for 15 min, the solution was cooled to 0 °C prior to the addition of sodium borohydride (4.16 g, 110 mmol). The resulting solution was stirred at room temperature for 1 h. After quenching with water (100 mL), methanol was removed under reduced pressure and the resulting aqueous phase was diluted with water (500 mL), extracted with 10 % methanol in dichloromethane (2 x 500 mL). The combined extracts were dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to give **125-3** as yellow oil 22 g (55%).

**Step 2: Preparation of 3-(4-Bromo-phenyl)-1-(2-hydroxy-ethyl)-1-(3-methoxy-benzyl)-urea (125-4):** To a solution of (4-bromo-phenyl)-carbamic acid phenyl ester (**125-2**) (83 g, 284 mmol) in dimethyl sulfoxide (415 mL) was added *N*,*N*-diisopropylethylamine (96.6 mL, 568 mmol) followed by 2-(3-Methoxy-benzylamino)-ethanol **125-3** (51.47 g, 284 mmol) at 25 °C. The reaction mixture was stirred for 1 h at 65 °C. The reaction mixture was cooled to 25 °C, diluted with water (2 L) and extracted with ethyl acetate (2 x 830 mL). The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by recrystallization using 10% ethyl acetate in hexane to give **125-4** as an off white solid 71.14 g (66%).

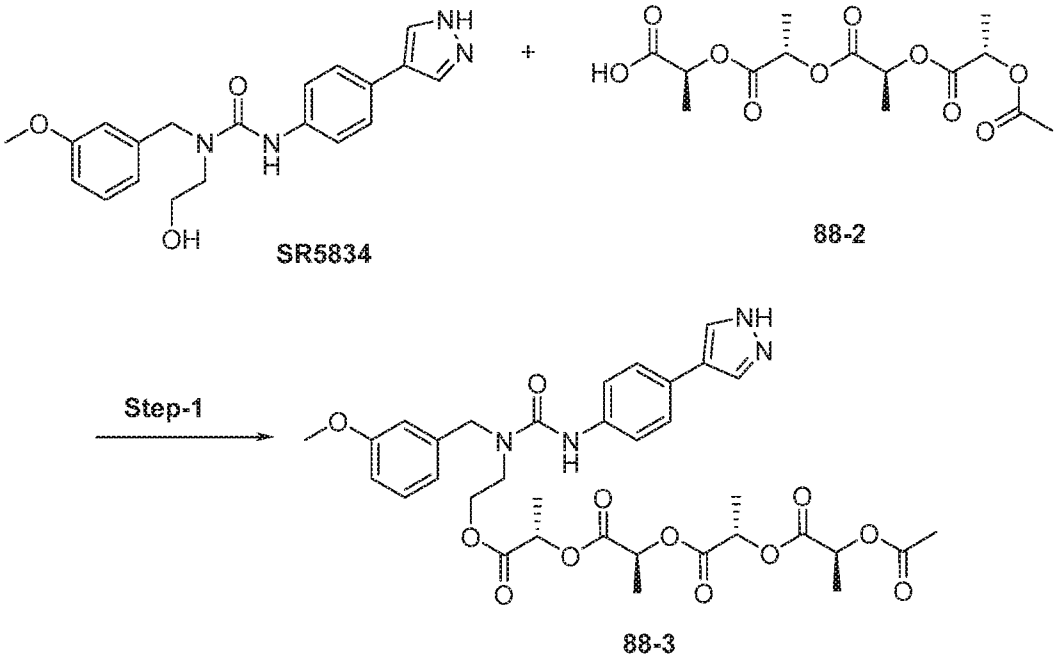
**Step 3a: Preparation of 4-(4,4,5,5-Tetramethyl-[1,3,2] dioxaborolan-2-yl)-pyrazole-1-carboxylic acid *tert*-butyl ester (125-5):** To a solution of 4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-2-yl)-1H-pyrazole **125-5a** (100 g, 515 mmol) in *N*, *N*-dimethylformamide (500 mL, 5V) was added 4-dimethylaminopyridine (8.8 g, 72 mmol) followed by BOC anhydride (118 mL, 515 mmol) drop wise at 0 °C. The reaction mixture was stirred for 16 h at 25 °C. The reaction mixture was quenched with chilled water (2.5 L). The solid precipitate was collected by filtration and dried under vacuum to give ester **125-5** as a white solid 99 g (65%).

**Step 3: Preparation of 4-{4-[3-(2-Hydroxy-ethyl)-3-(3-methoxy-benzyl)-ureido]-phenyl}-pyrazole-1-carboxylic acid *tert*-butyl ester (125-6):** 3-(4-bromo-phenyl)-1-(2-hydroxy-ethyl)-1-(3-methoxy-benzyl)-urea **125-4** (25 g, 65 mmol) and 4-(4,4,5,5-tetramethyl-[1,3,2] dioxaborolan-

2-yl)-pyrazole-1-carboxylic acid *tert*-butyl ester **38-5** (29 g, 98 mmol) and potassium carbonate (27.3 g, 197 mmol) were dissolved in degassed 5:1 dioxane/$H_2O$ (300 mL). $Pd(PPh_3)_4$ (7.6 g, 6.5 mmol) was then added under argon and the mixture was heated at 110 °C for 1 h. After cooling to room temperature, the mixture was diluted with water (500 mL) and extracted with ethyl acetate (500 x 2 mL). The combined organic extracts were washed with brine (500 mL), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give crude **125-6** as a pale brown liquid which was used in the next step without further purification.

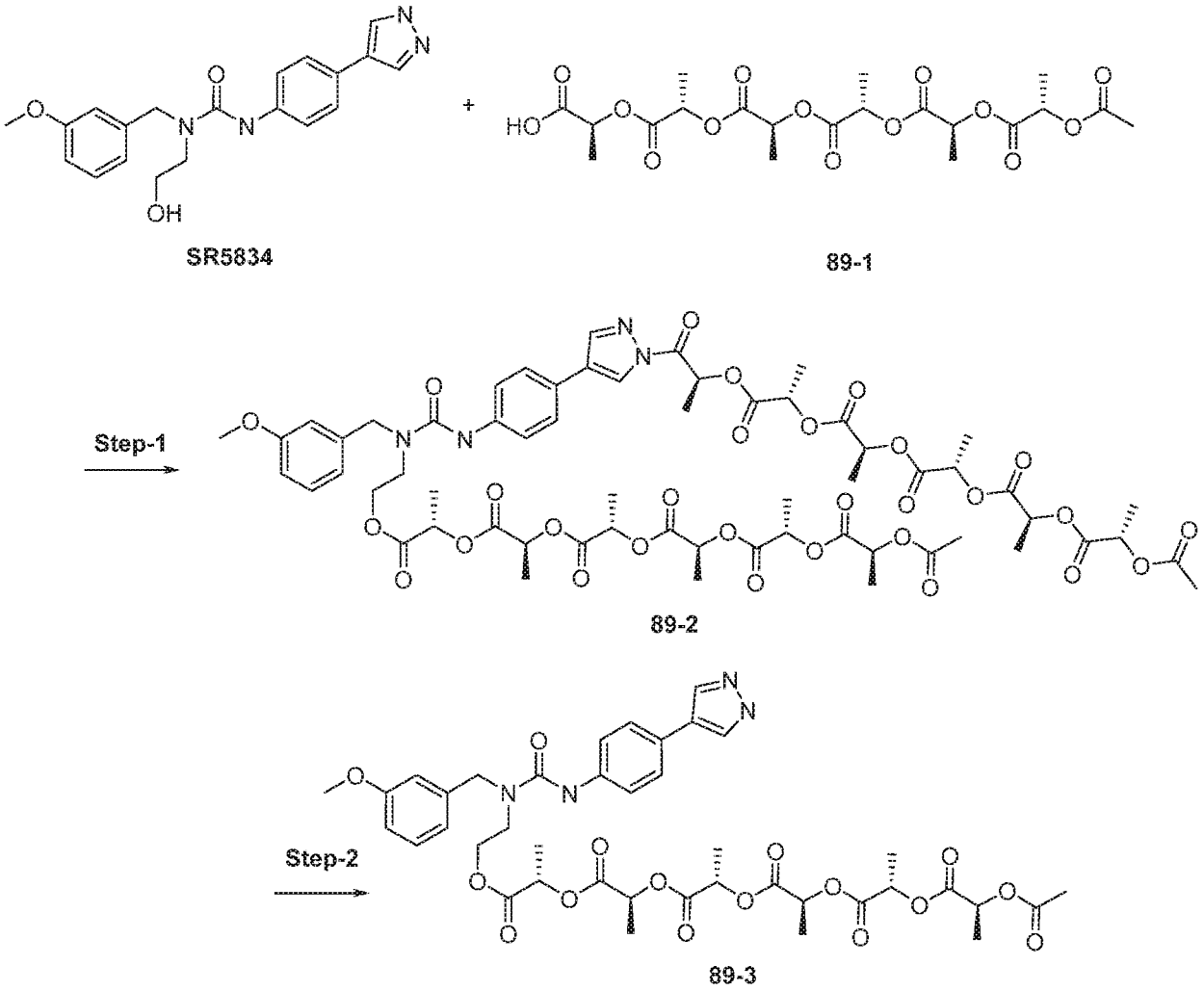
**Step 4: Preparation of 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-urea (SR5834):** To a solution of (4-bromo-phenyl)-carbamic acid phenyl ester **125-6** (30 g, 64 mmol) in 1,4-dioxane (150 mL) was added 4N hydrochloric acid in 1,4-dioxane (60 mL) dropwise at 0 °C. The reaction mixture was stirred for 1 h at 65 °C. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was then recrystallized using dichloromethane to afford **SR5834** as an off white solid 8 g.

**Scheme 72: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid 2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethyl ester (88-3):**



**Step 1: Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid 2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethyl ester (88-3):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **88-2** (1.56 g, 4.5 mmol) in dichloromethane (30 mL) were added EDC·HCl (0.78 g, 4.0 mmol), 1-(2-hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-urea **SR8543** (1.5 g, 4.0 mmol) and 4-dimethylaminopyridine (50 mg, 0.40 mmol) at 25 °C. The resulting reaction mixture was stirred at 25 °C for 48 hours. After the complete conversion of starting material as detected by TLC. The reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by silica gel (60-120 mesh) column chromatography (40-50 % ethyl acetate in hexane) to give **88-31** as a yellow solid 500 mg (18%).

**Scheme 73: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-[(*S*)-1-(2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (89-3):**

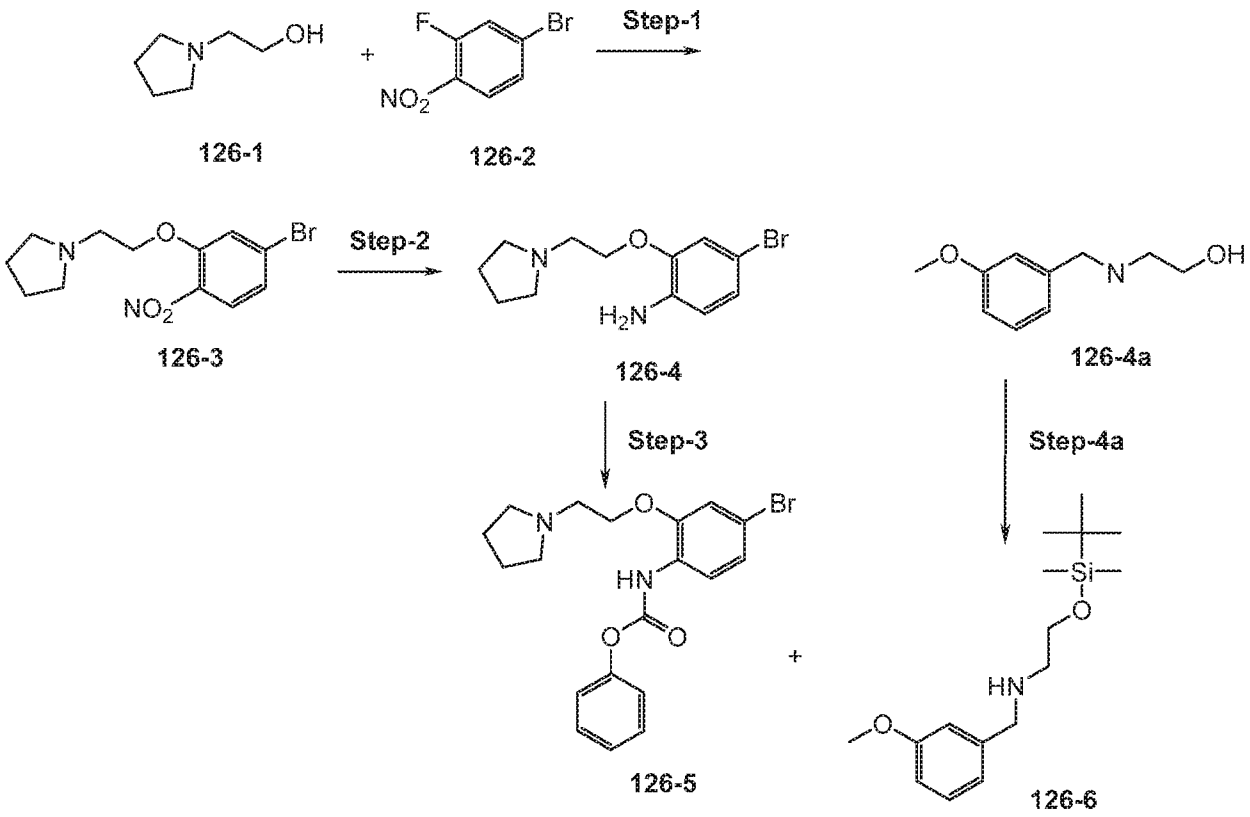


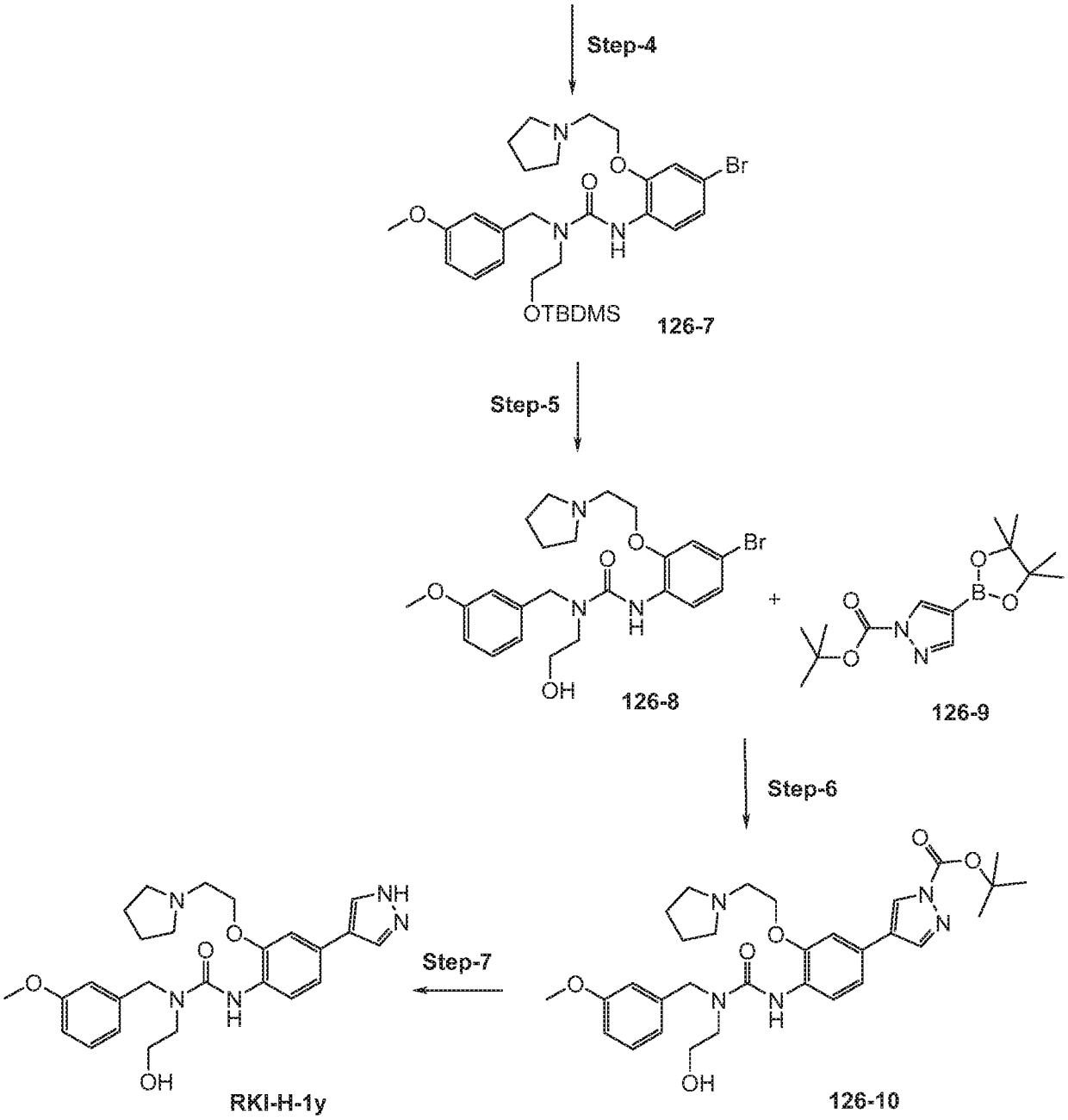

**Step 1: Preparation of SR5834-Bis-PLA(n=6)-OAc (89-2):** To a solution of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid **89-1** (1.6 g, 3.4 mmol) in dichloromethane (32 mL) were added EDC·HCl (0.65 g, 3.4 mmol), 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-urea **SR5834** (500 mg, 1.3 mmol) and 4-dimethylaminopyridine (17 mg, 0.13 mmol) at 0 °C. The resulting reaction mixture was stirred at 25 °C for 16 hours. After the complete conversion of starting material as detected by TLC, the reaction mixture was quenched with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure to give crude **89-2** as a thick colorless oil 1.8 g.

**Step 2: Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-[(*S*)-1-(2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (89-3):**

A solution of **89-2** (1.8 g, 1.189 mmol) in a mixture of water, ethanol and dichloromethane taken in the ratio (1:1:0.1, 10 V) was stirred at 25 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated completely to remove ethanol, diluted with water (20 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure and purified by silica gel (60 -120 mesh) column chromatography (40-50 % ethyl acetate in hexane) to obtain **89-3** as a white solid 700 mg (70%).

**Scheme 74: Synthesis of 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-urea (RKI-H-1y):**






**Step 1: Preparation of 1-[2-(5-Bromo-2-nitro-phenoxy)-ethyl]-pyrrolidine (126-3):** To a solution of 4-bromo-2-fluoro-1-nitro-benzene **126-2** (38 g, 172 mmol) in *N*,*N*-dimethyl formamide (380 mL) was added cesium carbonate (168.83 g, 518 mmol) followed by 2-pyrrolidin-1-yl-ethanol **126-1** (22.18 g, 190 mmol) drop-wise at 0 °C. The reaction mixture was stirred at 25 °C for 16 h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with ice water (3.8 L). The solid precipitate was collected by filtration and dried

over vacuum. The solid obtained was further suspended in hexane (190 mL) and stirred for 15 min, filtered and dried to obtain **126-3** as a yellow solid 41.9 g (77 %).

**Step 2: Preparation of 4-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenylamine (126-4):** To a solution of 1-[2-(5-bromo-2-nitro-phenoxy)-ethyl]-pyrrolidine **126-3** (38 g, 120 mmol) in ethyl acetate (380 mL) was added stannous chloride (114 g, 602 mmol) portion wise at 0 °C. The reaction mixture was stirred for 6 h at 25 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with 10% sodium hydroxide solution and extracted with 10% methanol in dichloromethane (2 x 500 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain **126-4** as a pale brown solid 23.8 g (69%).

**Step 3: Preparation of [4-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-carbamic acid phenyl ester (126-5):** To a solution of 4-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenylamine **126-4** (9 g, 31 mmol) in dichloromethane (90 mL) was added *N,N*-diisopropylethylamine (16.1 mL, 94 mmol) followed by phenyl chloroformate (4.38 mL, 34 mmol) over a period of 5 min at 0 °C. The reaction mixture was stirred for 2 h slowly raising the temperature to 25 °C. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was concentrated completely under reduced pressure to give crude **126-5** as a pale yellow liquid which was used in the next step without further purification.

**Step 4a: Preparation of 2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(3-methoxy-benzyl)-amine (126-6)** To a solution of 2-(3-Methoxy-benzylamino)-ethanol **126-4a** (32.8 g, 181 mmol) in dichloromethane (328 mL) was added imidazole (24.6 g, 362 mmol) followed by tertiary butyl dimethyl silyl chloride (29.86 g, 199 mmol) portion wise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with water (1000 mL) and extracted with dichloromethane (2 x 1000 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to give **126-6** as a pale yellow liquid 50 g (93%).

**Step 4: Preparation of 3-[4-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-(2-[*tert*-butyl dimethylsilyl)oxy]ethyl)-1-(3-methoxy-benzyl)-urea (126-7):** To a solution of [4-bromo-2-(2-pyrrolidin-1-yl-ethoxy)phenyl]-carbamic acid phenyl ester **126-5** (12 g, 29 mmol) in dimethyl sulphoxide (60 mL) was added *N,N*-diisopropylamine (10 mL, 59 mmol) followed by [2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-(3-methoxy-benzyl)-amine **126-6** (8.74 g, 29 mmol) at 25 °C.

The reaction mixture was stirred at 65 °C for 1h. The reaction mixture was cooled to 25 °C, diluted with water (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was dried over sodium sulfate, concentrated under reduced pressure to give crude **126-7** as pale brown liquid which was used in the next step without further purification.

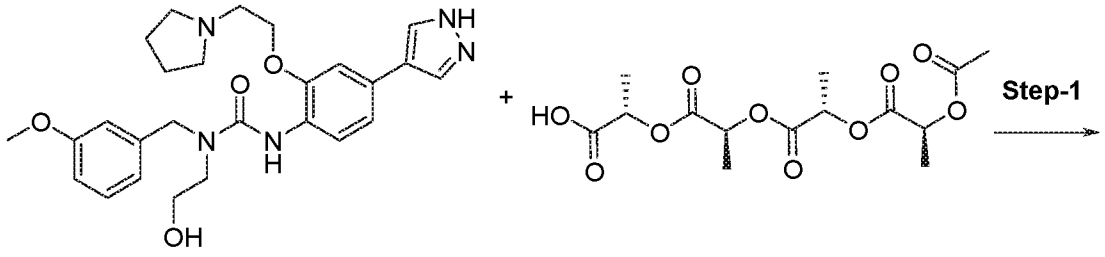
**Step 5: Preparation of 3-[4-Bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-(2-hydroxy-ethyl)-1-(3-methoxy-benzyl)-urea (126-8):** To a solution of 3-[4-bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-(2-[*tert*-butyl dimethylsilyl)oxy]ethyl)-1-(3-methoxy-benzyl)-urea **126-7** (14 g, 23 mmol) in tetrahydrofuran (140 mL) was added tetrabutyl ammonium fluoride (27.5 mL, 1.0M, 27 mmol) drop-wise at 0 °C and the reaction mixture was stirred at 25 °C for 1h. The reaction mixture was diluted with water (500 mL) and extracted with ethyl acetate (2 x 500 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was recrystallized with methanol at 0 °C. The resultant solid was filtered and dried over high vacuum to give **126-8** as an off white solid 5 g (53%).

**Step 6: Preparation of 4-[4-[3-(2-Hydroxy-ethyl)-3-(3-methoxy-benzyl)-ureido]-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrazole-1-carboxylic acid *tert*-butyl ester (126-10):** 3-[4-bromo-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-1-(2-hydroxy-ethyl)-1-(3-methoxy-benzyl)-urea **126-8** (40 g, 81 mmol) and 4-(4,4,5,5-Tetramethyl-[1,3,2] dioxaborolan-2-yl)-pyrazole-1-carboxylic acid *tert*-butyl ester **126-5** (31 g, 105 mmol), and potassium carbonate (33.6 g, 243 mmol) were dissolved in degassed 5:1 dioxane/$H_2O$ (400 mL). $Pd(PPh_3)_4$ (9.4 g, 8.1 mmol) was then added under argon and the mixture was heated at 110 °C for 1 h. After cooling to room temperature, the mixture was diluted with water (1000 mL) and extracted with ethyl acetate (1000 mL x 2). The combined organic extracts were washed with brine (1000 mL), dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure to give crude **126-10** as a pale brown liquid which was used in the next step without further purification.

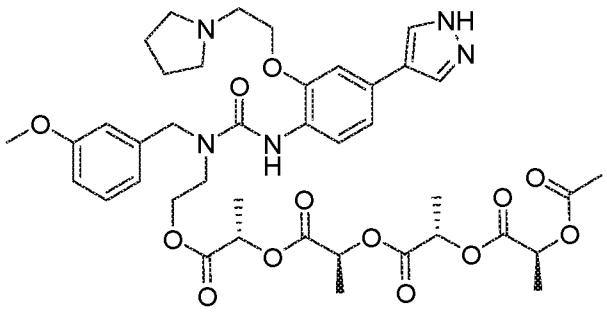
**Step 7: Preparation of 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-urea (RKI-H-1y):** To a solution of 4-[4-[3-(2-hydroxy-ethyl)-3-(3-methoxy-benzyl)-ureido]-3-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-pyrazole-1-carboxylic acid *tert*-butyl ester **126-10** (45 g, 77 mmol) in methanol (450 mL) was added 4N hydrochloric acid in 1,4-dioxane (90 mL) drop-wise at 0 °C. The reaction mixture was stirred at 25 °C 1h. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was diluted with

water (1000 mL) and washed with ethyl acetate (2 x 1000 mL). Aqueous layer was neutralized (pH = 10) using sodium bicarbonate and extracted with 10% methanol in dichloromethane (2 x 1000 mL). The combined organic layer was dried over sodium sulfate and concentrated under reduced pressure to give **RKI-H-1y** as an off white solid 18 g (48%).

**Scheme 75: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid 2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-ethyl ester (90-2):**




**RKI-H-1y** **90-1**

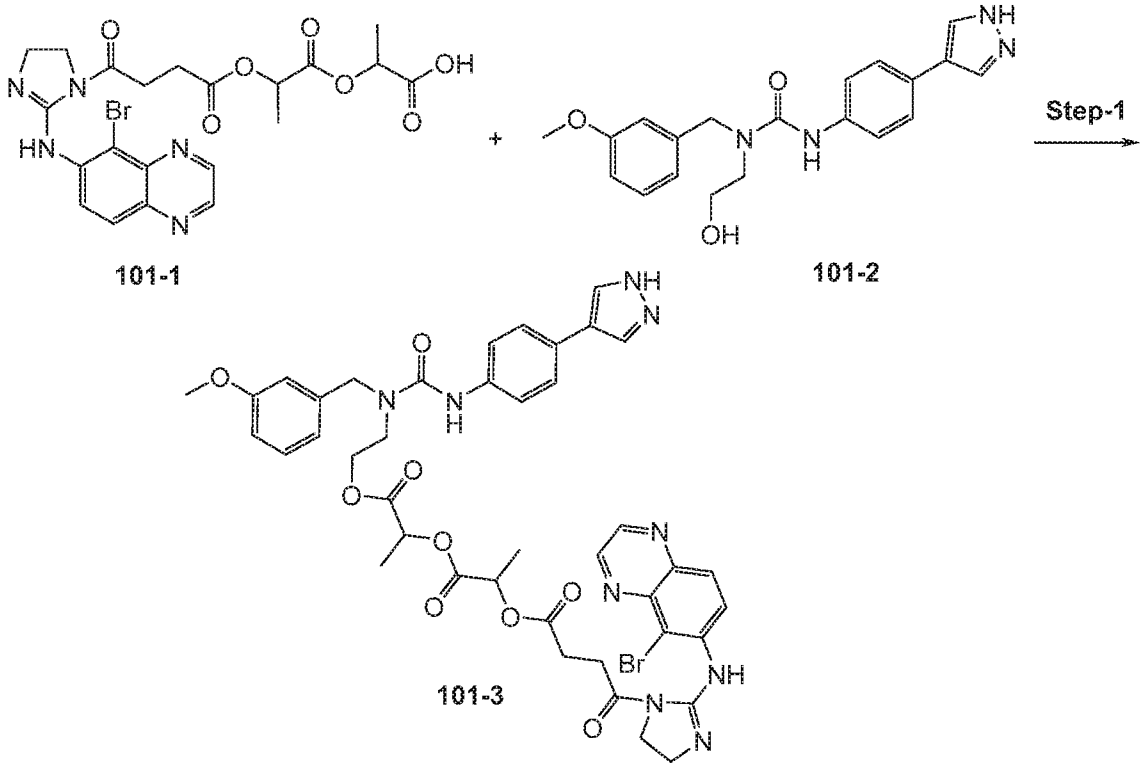


**90-2**

**Step 1: Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid 2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-ureido}-ethyl ester (90-2):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **90-1** (3.12 g, 2.710 mmol) in dichloromethane (13 mL) was added EDC·HCl (1.3 g, 6.776 mmol) followed by 4-dimethyl amino pyridine (33 mg, 0.217 mmol) at 0 °C. After 5 min 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-2-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-urea **RKI-H-1y** (1.3 g, 2.710 mmol) was added and resulting reaction mixture was stirred at 25 °C for 4 days. The progress of the reaction was monitored by TLC and LCMS. The reaction mixture was quenched with water (250 mL) and extracted with dichloromethane (2 x 300 mL). The combined organic

layer was dried over sodium sulfate, concentrated under reduced pressure and purified by combi-flash column to give **90-2** as an off white solid 300 mg (14%).

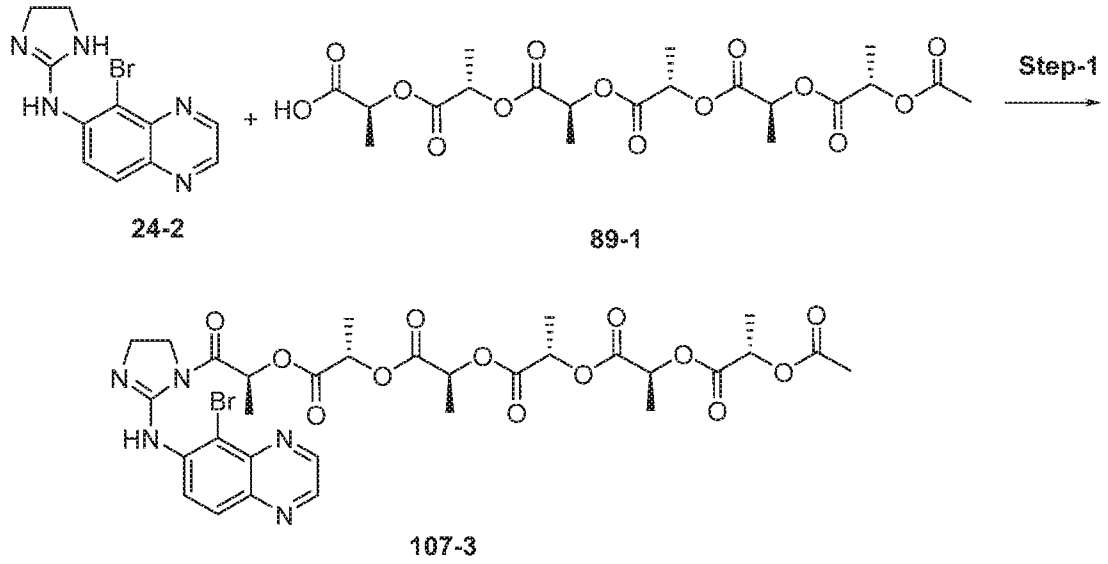
**Scheme 76: Synthesis of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid 1-[1-(2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (101-3):**




**Step 1: Preparation of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid 1-[1-(2-{1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-ureido}-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (101-3):** To a solution of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid 1-(1-carboxy-ethoxycarbonyl)-ethyl ester **101-1** (0.615 g, 1.14 mmol) in dichloromethane (10 mL) was added EDC·HCl (0.273 g, 1.43 mmol), 1-(2-Hydroxy-ethyl)-1-(3-methoxy-benzyl)-3-[4-(1*H*-pyrazol-4-yl)-phenyl]-urea **101-2** (0.35 g, 0.95 mmol), and 4-dimethylaminopyridine (0.01 g, 0.09 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 16 hours. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (100 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained

upon evaporation of volatiles was purified through preparative HPLC to obtain product **101-3** as a pale yellow solid 60 mg (7%).

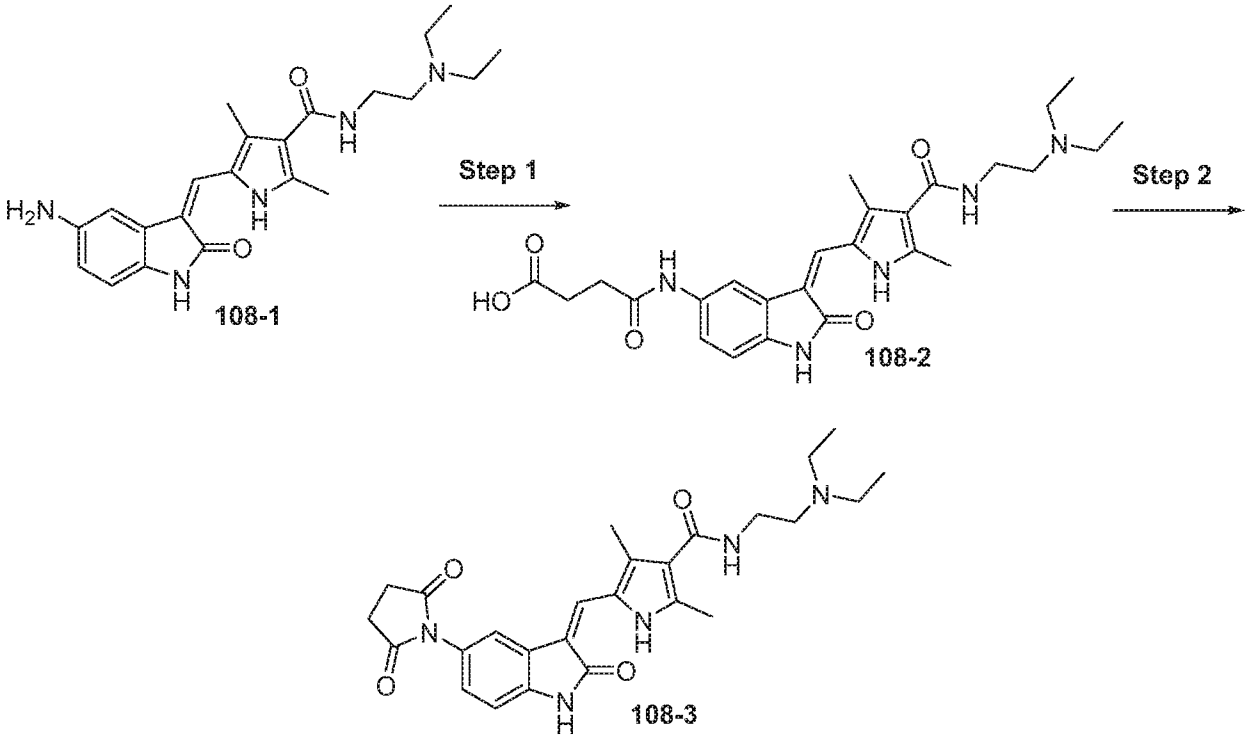
**Scheme 77: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (107-3):**




**Step 1: Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (107-3):**

To a solution of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid **89-1** (5.56 g, 11.3 mmol) in dimethyl sulfoxide (30 mL) were added EDC·HCl (2.55 g, 13.3 mmol), benzotriazol-1-ol (0.28 g, 2.05 mmol), Brimonidine **24-2** (3 g, 10.2 mmol) and 4-dimethylaminopyridine (0.125 g, 1.02 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mass was quenched with water (400 mL), extracted with dichloromethane (500 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (45% ethyl acetate in hexane) to obtain product **107-3** as a pale yellow solid 2.4g (30.5%).

**Scheme 78: Synthesis of 5-[5-(2,5-Dioxo-pyrrolidin-1-yl)-2-oxo-1,2-dihydro-indol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (108-3):**

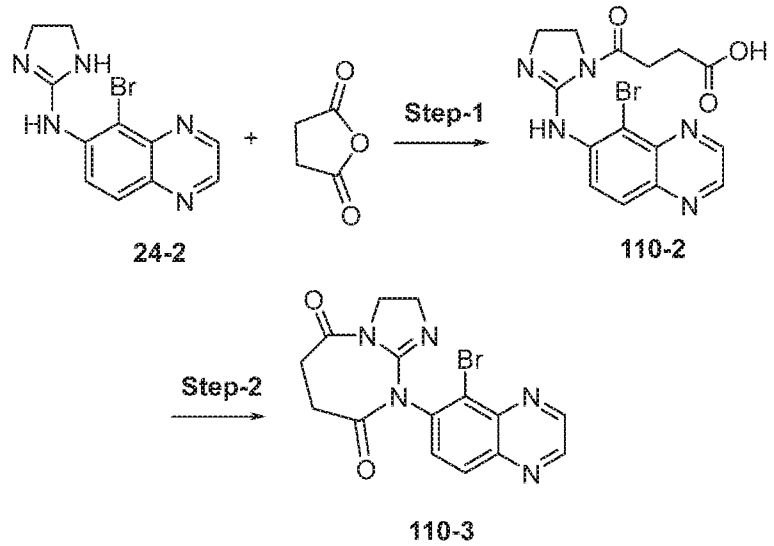



**Step 1: Preparation of *N*-{3-[1-[4-(2-Diethylamino-ethylcarbamoyl)-3,5-dimethyl-1*H*-pyrrol-2-yl]-meth-(*Z*)-ylidene]-2-oxo-2,3-dihydro-1*H*-indol-5-yl}-succinamic acid (108-2):** To a solution of 5-[5-Amino-2-oxo-1,2-dihydro-indol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide **108-1** (7.0 g, 17.7 mmol) in dichloromethane (70 mL) were added dihydro-furan-2,5-dione (1.94 g, 19.49 mmol) and 4-dimethylaminopyridine (0.21 g, 1.77 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 16 h. The resulting reaction mixture was concentrated under reduced pressure to give product **108-2** as a brown solid 4.4 g (50%).

**Step 2: Preparation of 5-[5-(2,5-Dioxo-pyrrolidin-1-yl)-2-oxo-1,2-dihydro-indol-(3*Z*)-ylidenemethyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide (108-3):** To a solution of *N*-{3-[1-[4-(2-Diethylamino-ethylcarbamoyl)-3,5-dimethyl-1*H*-pyrrol-2-yl]-meth-(*Z*)-ylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl}-succinamic acid **108-2** (2.3 g, 4.65 mmol) in *N*,*N*-dimethylformamide (23 mL) were added *N*,*N*-diisopropylethylamine (1.28 mL, 6.97 mmol), HATU (2.1 g, 5.58 mmol), 4-dimethylaminopyridine (0.057 g, 0.46 mmol) at 0 °C. The

reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mass was quenched with water (100 mL), extracted with ethyl acetate (200 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was washed with diethyl ether (20 x 2 mL) to obtain product **108-3** as a pale yellow solid 1.2 g (54%).

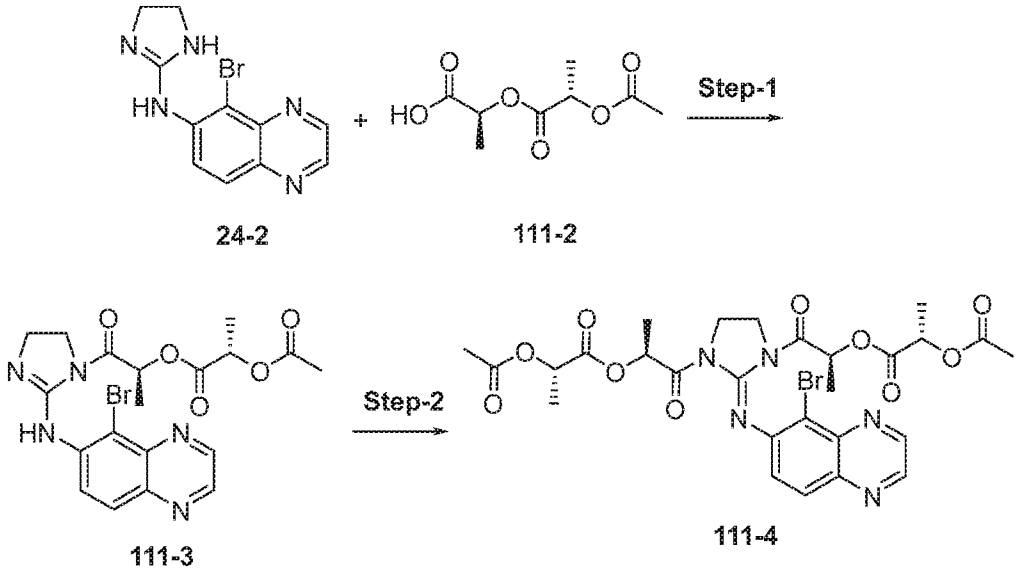
**Scheme 79: Synthesis of 9-(5-Bromo-quinoxalin-6-yl)-2,6,7,9-tetrahydro-3*H*-imidazo[1,2-*a*][1,3]diazepine-5,8-dione (110-3):**




**Step 1: Preparation of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (110-2):** To a solution Brimonidine **24-2** (2 g, 6.84 mmol) in dimethyl sulfoxide (20 mL) were added dihydro-furan-2,5-dione (0.89 g, 8.90 mmol) and 4-dimethylaminopyridine (83 mg, 0.68 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 hours. The resulting reaction mixture was quenched with ice cold water and stirred for 10 min. The solid precipitate was filtered and dried under vacuum to obtain product **110-2** as yellow solid 1.8 g (67%).

**Step 2: Preparation of 9-(5-Bromo-quinoxalin-6-yl)-2,6,7,9-tetrahydro-3*H*-imidazo[1,2-*a*][1,3]diazepine-5,8-dione (110-3):** To a solution of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid **110-2** (4 g, 10.20 mmol) in *N*,*N*-dimethylformamide (20 mL) were added *N*,*N*-diisopropylethylamine (2.82 mL, 15.30 mmol), HATU (5.04 g, 13.20 mmol), 4-dimethylaminopyridine (124 mg, 1.02 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mixture was quenched with ice cold water and stirred for 10 min. The solid precipitate was filtered and dried under vacuum obtain product as **110-3** as an off white solid 2 g (52%).

**Scheme 80: Synthesis of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[3-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-2-(5-bromo-quinoxalin-6-ylimino)-imidazolidin-1-yl]-1-methyl-2-oxo-ethyl ester (111-4):**



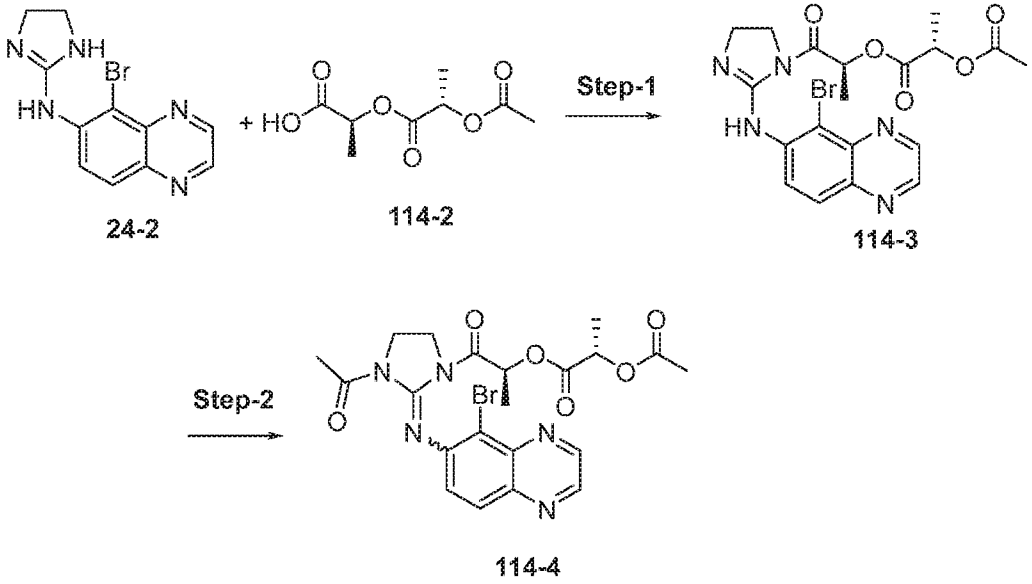

24-2 111-2 111-3 111-4

**Step 1: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (111-3):** To a solution of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid **111-2** (0.433 g, 2.12 mmol) in dimethyl sulfoxide were added EDC·HCl (0.487 g, 2.55 mmol), Brimonidine **24-2** (0.25 g, 0.85 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (50 mL), extracted with ethyl acetate (100 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **111-3** as a pale yellow solid 250 mg (62%).

**Step 2: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[3-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-2-(5-bromo-quinoxalin-6-ylimino)-imidazolidin-1-yl]-1-methyl-2-oxo-ethyl ester (111-4):** To a solution of (*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionic acid **111-2** (1.92 g, 9.41 mmol) in dichloromethane (20 mL) were added oxalyl chloride (0.96 mL, 11.29 mmol) and *N*,*N*-dimethylformamide (0.3 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 min. Concentrated the reaction mixture to dryness under

nitrogen, diluted with dichloromethane (45 mL), was added triethylamine (1.92 mL, 14.11 mmol) followed by (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester **111-3** (4.5 g, 9.41 mmol) and 4-dimethylaminopyridine (0.114 g, 0.94 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 hours. The resulting reaction mass was quenched with water (200 mL), extracted with ethyl acetate (200 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure and washed with ether (30 mL x 2) to obtain product **111-4** as an off white solid 4.0 g (64%).

**Scheme 81: Synthesis of (*S*)-2-Acetoxy-propionic acid (*S*)-2-{3-acetyl-2-[(*Z*)-5-bromo-quinoxalin-6-ylimino]-imidazolidin-1-yl}-1-methyl-2-oxo-ethyl ester (114-4):**




24-2 114-2 114-3 114-4

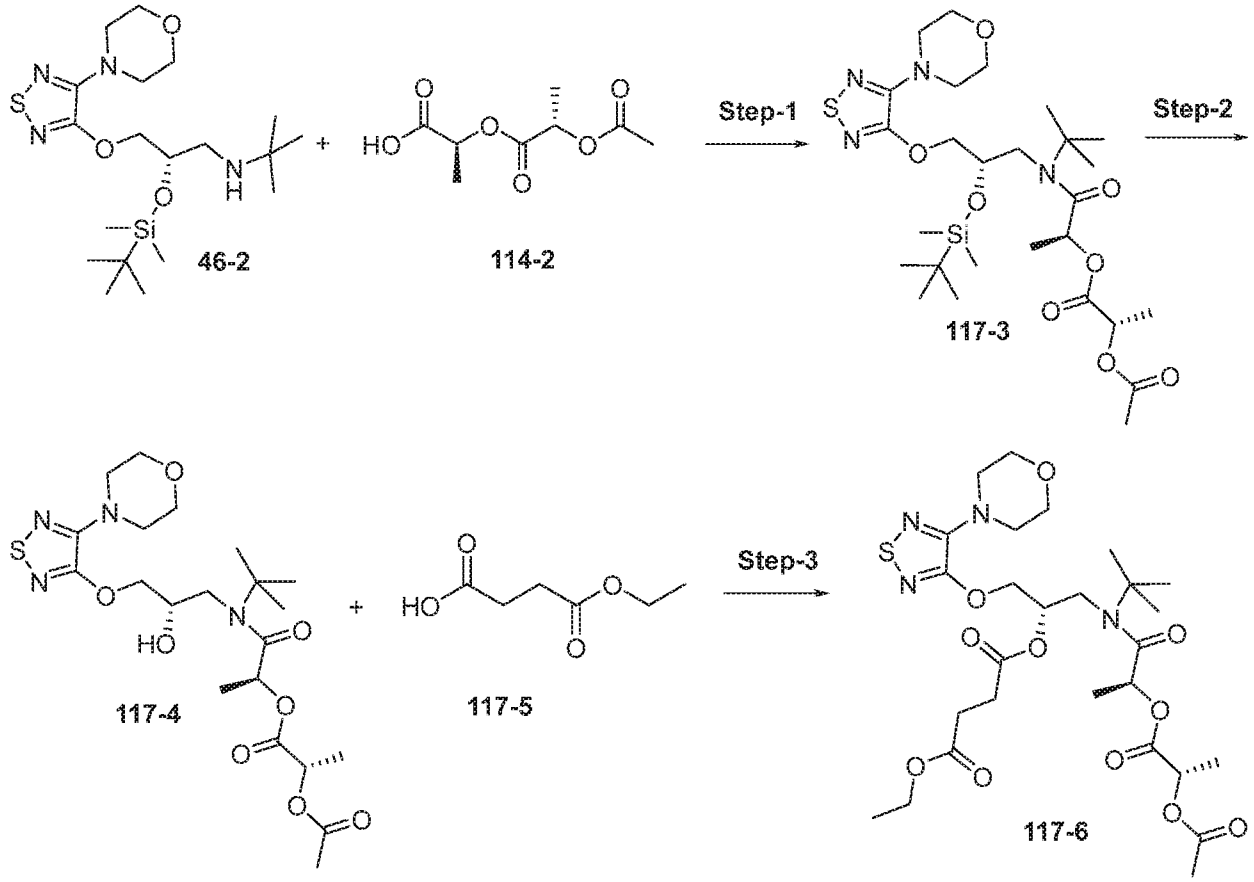
**Step 1: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (114-3):**

To a solution of (*S*)-2-((*S*)-2- Acetoxy-propionyloxy)-propionic acid **114-2** (0.433 g, 2.12 mmol), in dimethyl sulfoxide (2.5 mL) were added EDC·HCl (0.487 g, 2.55 mmol), Brimonidine **24-2** (0.25 g, 0.85 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (50 mL), extracted with dichloromethane (100 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **114-3** as a pale yellow solid 250 mg (62%).

**Step 2: (*S*)-2-Acetoxy-propionic acid (*S*)-2-{3-acetyl-2-[(*Z*)-5-bromo-quinoxalin-6-ylimino]-imidazolidin-1-yl}-1-methyl-2-oxo-ethyl ester (114-4):**

To a solution of (*S*)-2-Acetoxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester **114-3** (1 g, 2.09 mmol) in dichloromethane (20 mL) were added triethylamine (1.47 ml, 10.40 mmol), acetyl chloride (0.22 mL, 3.1 mmol) and 4-dimethylaminopyridine (0.025 g, 0.20 mmol) at 0 °C. The reaction mixture stirred at 25-30 °C over a period of 1 h. The resulting reaction mixture was quenched with water (200 mL), extracted with dichloromethane (2 x 250 mL) and dried over sodium sulfate. Then volatiles were evaporated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **114-4** as an off white solid 0.6 g.

**Scheme 82: Synthesis of Succinic acid (*S*)-1-({[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-*tert*-butyl-amino}-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester ethyl ester (117-6):**



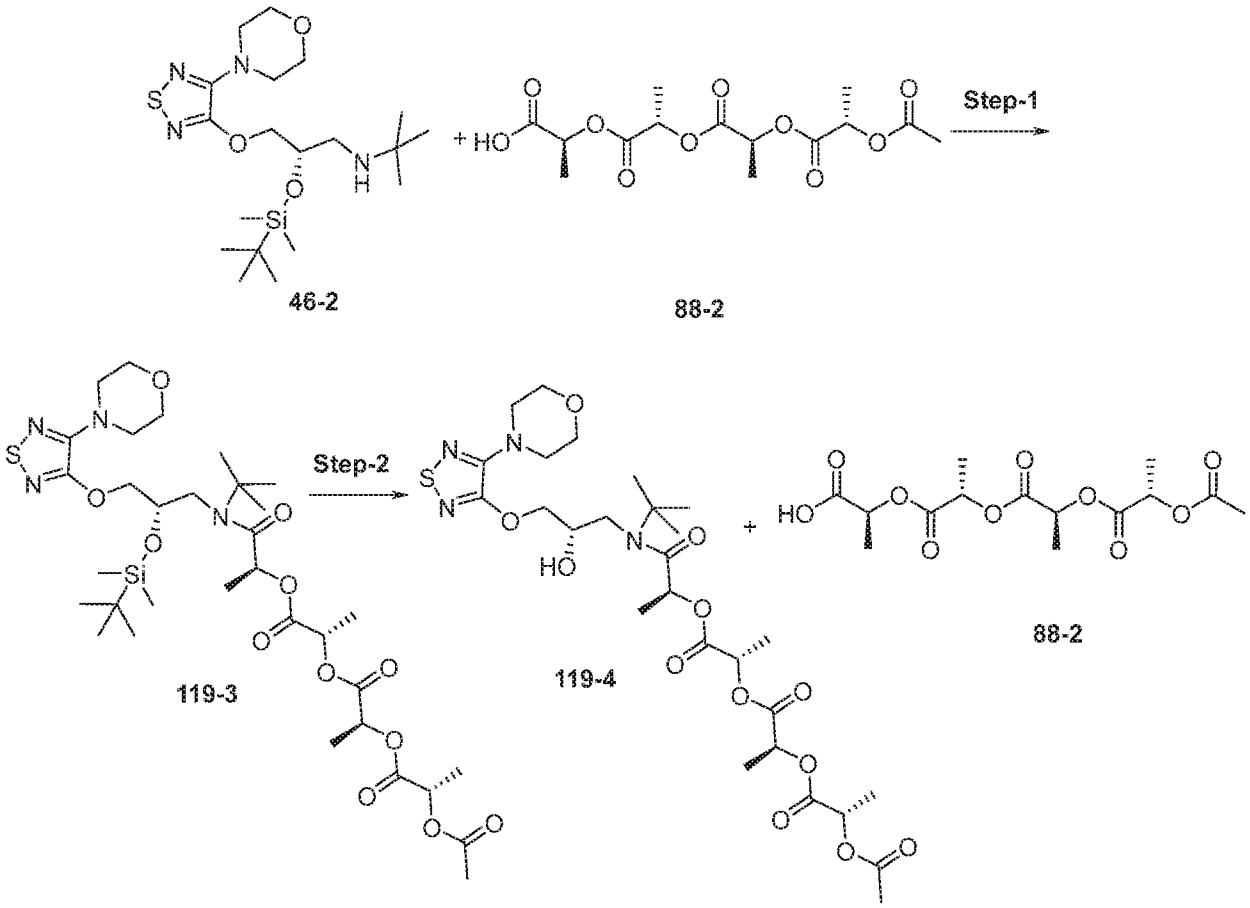
**Step 1: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (117-3):** To a solution of (*S*)-2-((S)-2-Acetoxy-propionyloxy)-propionic acid **114-2** (9.47 g, 46.4 mmol) in dichloromethane (100 mL) was added oxalyl chloride (5.97 mL, 69.6 mmol) and *N*,*N*-dimethylformamide (0.2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 minutes. The reaction mixture was concentrated to dryness under nitrogen, diluted with dichloromethane (100 mL), and *N*,*N*-diisopropylethylamine (17.1 mL, 92.8 mmol) followed by *tert*-Butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine **46-2** (10 g, 23.2 mmol) and 4-dimethylaminopyridine (0.02 g, 2.3 mmol) was added at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mass was quenched with water (500 mL), extracted with dichloromethane (500 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (12% ethyl acetate in hexane) to obtain product **117-3** as colorless liquid 5.0 g (34%).

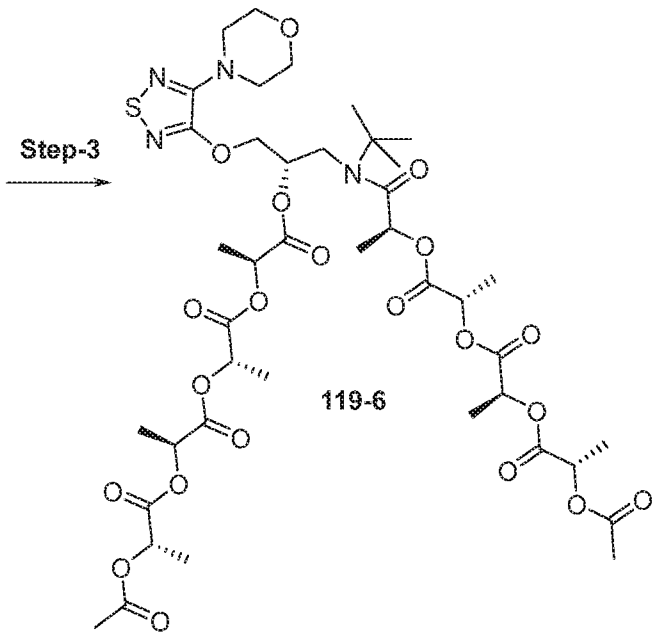
**Step 2: Preparation of (*S*)-2-Acetoxy-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (117-4):** To a solution of 2-Acetoxy-propionic acid 1-{*tert*-butyl-[(*S*)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester **117-3** (5.0 g, 8.1 mmol) in tetrahydrofuran (50 mL) was added tetra butyl ammonium fluoride (12.1 mL, 1.0 M, 12.1 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (25% ethyl acetate in hexane) to give product **117-4** as an colorless wax 1.3 g (31%).

**Step 3: Preparation of Succinic acid (*S*)-1-({[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyl]-*tert*-butyl-amino}-methyl)-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethyl ester ethyl ester (117-6):** To a solution of Succinic acid monoethyl ester **117-5** (0.5 g, 3.50 mmol) in dichloromethane (15 mL) was added DCC (0.73 g, 3.58 mmol), (*S*)-2-Acetoxy-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester **117-4** (1.2 g, 2.38 mmol) and 4-dimethylaminopyridine (0.029 g, 0.23

mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (25% ethyl acetate in hexane) to obtain product **117-6** as colorless wax 0.8 g (52%).

**Scheme 83: Synthesis of Timolol-Bis-PLA(n=4)-OAc (119-6):**





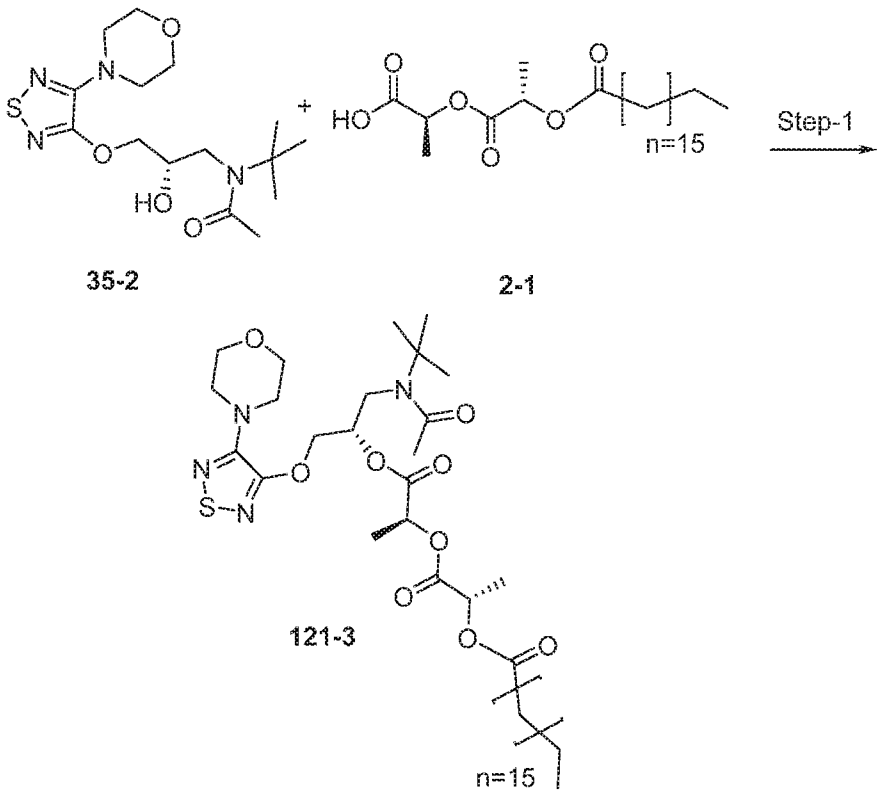

**Step 1: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (119-3):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **88-2** (14.5 g, 41.7 mmol) in dichloromethane (100 mL) was added oxalyl chloride (4.5 mL, 52.2 mmol) and *N*,*N*-dimethylformamide (0.2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 minutes. The reaction mixture was concentrated to dryness under nitrogen, diluted with dichloromethane (100 mL), and *N*,*N*-diisopropylethylamine (13.4 mL, 73.1 mmol) followed by *tert*-Butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine **46-2** (9 g, 20.8 mmol) and 4-dimethylaminopyridine (0.25 g, 2.0 mmol) was added at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mass was quenched with water (500 mL), extracted with dichloromethane (500 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (16% ethyl acetate in hexane) to obtain product **119-3** as colorless wax 8.0 g (50%).

**Step 2: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (119-4):** To a solution of (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-

propionyloxy]-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester **119-3** (7.0 g, 9.2 mmol) in tetrahydrofuran (70 mL) was added tetra butyl ammonium fluoride (14 mL, 1.0 M, 13.8 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (25% ethyl acetate in hexane) to give product **119-4** as a colorless wax 1.2 g (20%).

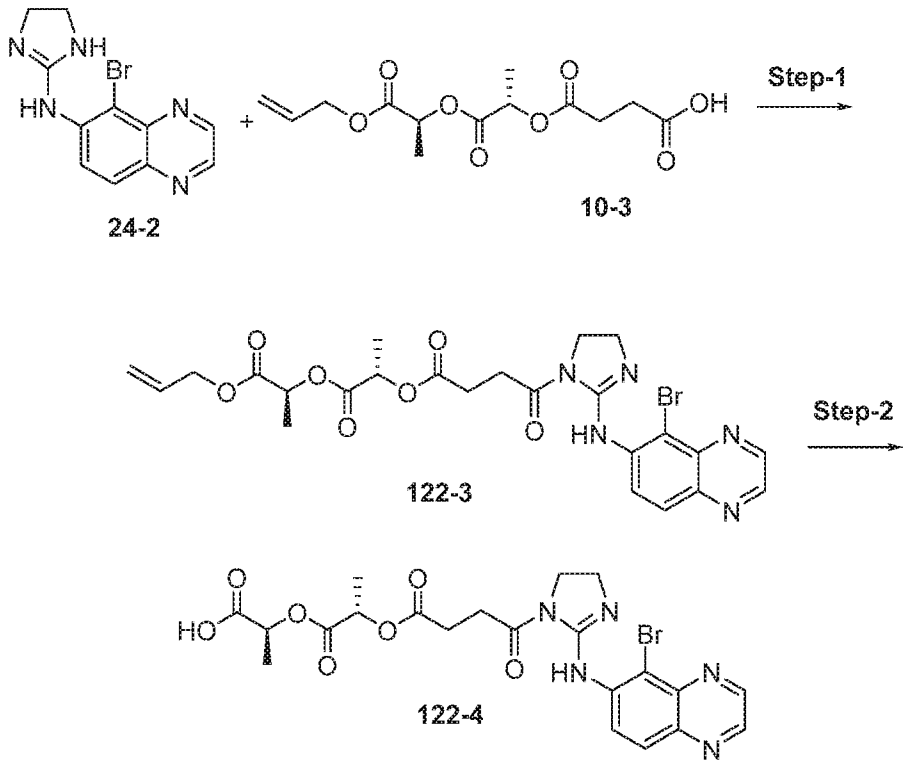
**Step 3: Preparation of Timolol-Bis-PLA(n=4)-OAc (119-6):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **88-2** (0.8 g, 2.5 mmol) in dichloromethane (10 mL) was added DCC (0.63 g, 3.0 mmol), (*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (*S*)-1-{*tert*-butyl-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester **119-4** (1.1 g, 1.7 mmol) and 4-dimethylaminopyridine (0.02 g, 0.17 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through combi-flash column chromatography (45% ethyl acetate in hexane) to obtain product **119-6** as colorless wax 0.7 g (42%).

**Scheme 84: Synthesis of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (121-3):**




**Step 1: Synthesis of Octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-[(acetyl-*tert*-butyl-amino)-methyl]-2-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (121-3):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester **2-1** (0.3 g, 0.83 mmol) in dichloromethane (6 mL) was added DCC (0.31 g, 1.50 mmol), *N*-*tert*-butyl-*N*-[(*S*)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide **35-2** (0.53g, 1.25 mmol) and 4-dimethylaminopyridine (0.01 g, 0.08mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (50 mL), extracted with dichloromethane (50 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (60% ethyl acetate in hexane) to obtain product **121-3** as a thick oil 0.3 g (95 %).

**Scheme 85: Synthesis of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (122-4):**




**Step 1: Preparation of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl ester (122-3):**

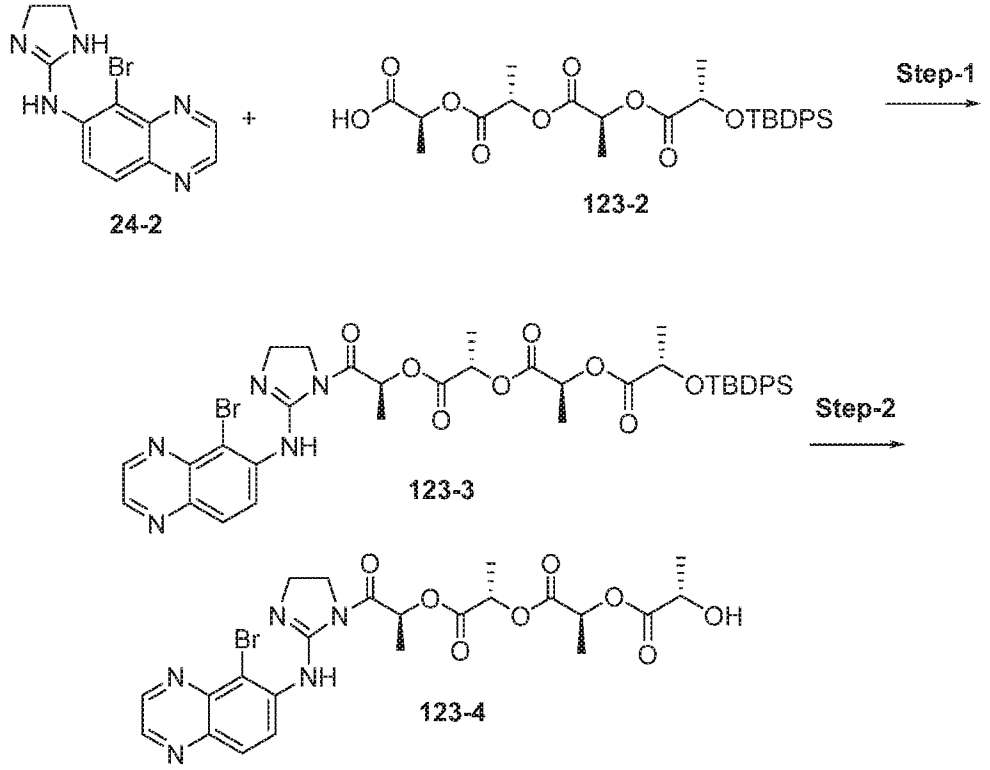
To a solution of Succinic acid mono-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl] ester **10-3** (4.6 g, 15.4 mmol) in dimethyl sulfoxide (30 mL) was added EDC·HCl (3.5 g, 18.4 mmol), benzotriazol-1-ol (0.28 g, 2.05 mmol), Brimonidine **24-2** (3g, 10.2 mmol) and 4-dimethylaminopyridine (0.12 g, 1.02 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mass was quenched with water (400 mL), extracted with dichloromethane (500 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (50% ethyl acetate in hexane) to obtain product **122-3** as a pale yellow solid 4.2g (70%).

**Step 2: Preparation of 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (122-4):**

To a solution 4-[2-(5-Bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-4-oxo-butyric acid (*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl ester **122-3** (4 g, 6.94mmol) in tetrahydrofuran (40 mL) were added tetrakis (triphenylphosphine) palladium (0.8 g, 0.69 mmol)

and pyrrolidine (0.6 mL, 6.59 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 2 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (8% isopropyl alcohol in dichloromethane) to give product **122-4** as a greenish solid 2.3 g (62%).

**Scheme 86: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (123-4):**

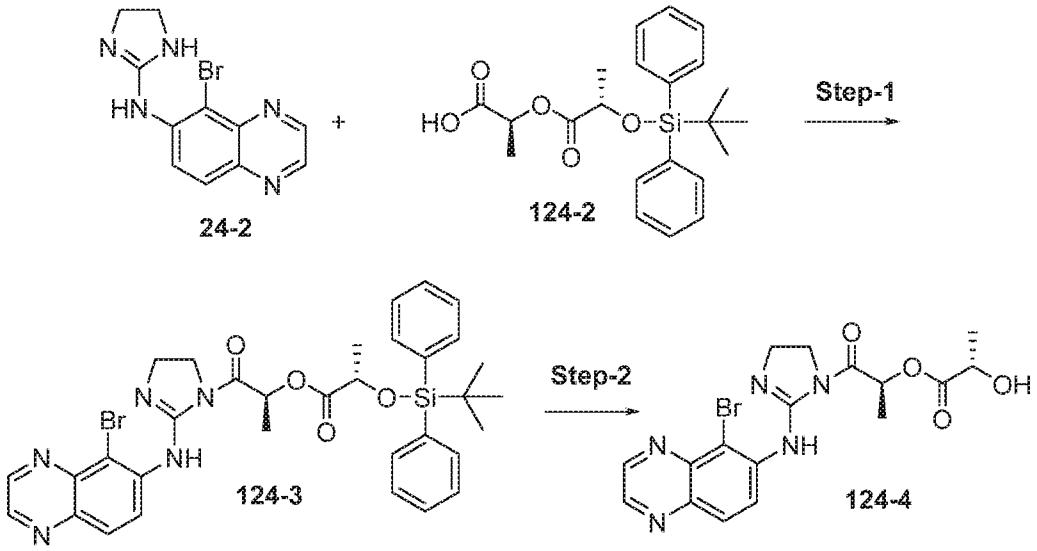



**Step 1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (123-3):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **3-2** (11.1 g, 20.5 mmol) in dimethyl sulfoxide (20 mL) was added *N*,*N*-diisopropylethylamine (6 mL, 34.2 mmol), EDC·HCl (5.2 g, 27.3 mmol), benzotriazol-1-ol (0.37 g, 2.73 mmol), Brimonidine **24-2** (4 g, 13.60 mmol) and 4-dimethylaminopyridine (0.16 g, 1.36 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (400 mL), extracted with dichloromethane

(500 x 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **123-3** as a pale yellow solid 9.5g (84%).

**Step 2: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (123-4):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-{(*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester **123-3** (8.0 g, 9.77 mmol) in tetrahydrofuran (80 mL) was added tetra butyl ammonium fluoride (14.6 mL, 1.0 M, 14.60 mmol) and acetic acid (0.85 mL, 14.60 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 3 hours. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (2% 2-propanol in DCM) to give product **123-4** as a pale yellow solid 4.0 g (70%).

**Scheme 87: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (124-4):**

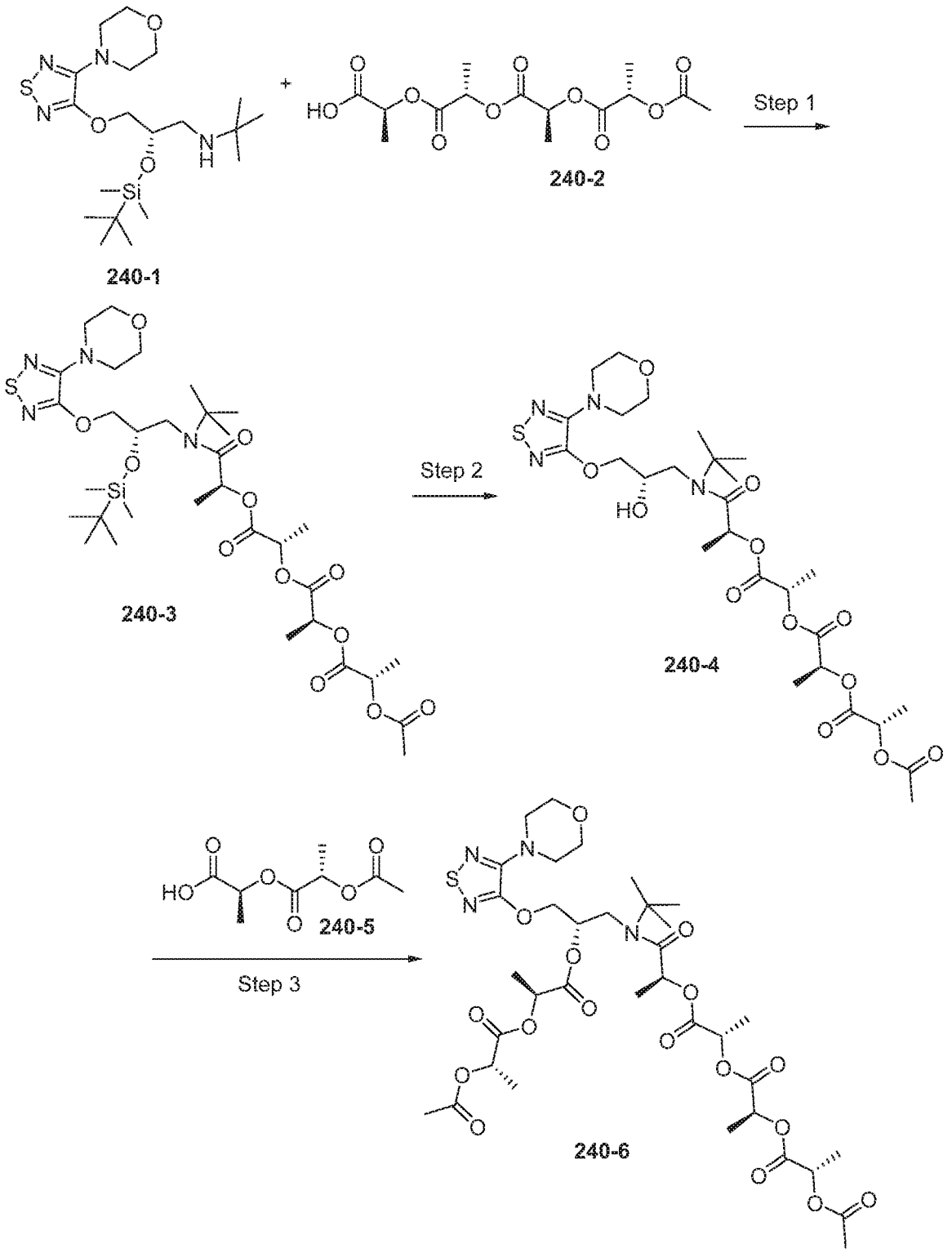



**Step 1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (124-3):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester **124-2** (24.6 g, 61.6 mmol) in dimethyl sulfoxide (120 mL) was added EDC·HCl (14.12 g,

73.9 mmol), Brimonidine **24-2** (12 g, 41.09 mmol) and 4-dimethylaminopyridine (0.5 g, 4.19 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (300 mL), extracted with ethyl acetate (500 X 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **124-3** as a pale yellow solid 11.8 g (42%).

**Step 2: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester (124-4):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethyl ester **124-3** (11.8 g, 18.20 mmol) in tetrahydrofuran (118 mL) was added tetra butyl ammonium fluoride (36.4 mL, 1.0 M, 36.47 mmol) and acetic acid (2.2 mL, 36.47 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 3 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (2% 2-propanol in DCM) to give product **124-4** as pale yellow solid 3 g (37%).

**Scheme 88: Synthesis of compound 240-6:**




**Step-1: Preparation of (S)-2-[(S)-2-((S)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (S)-1-{tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (240-3):** To a solution of (S)-2-

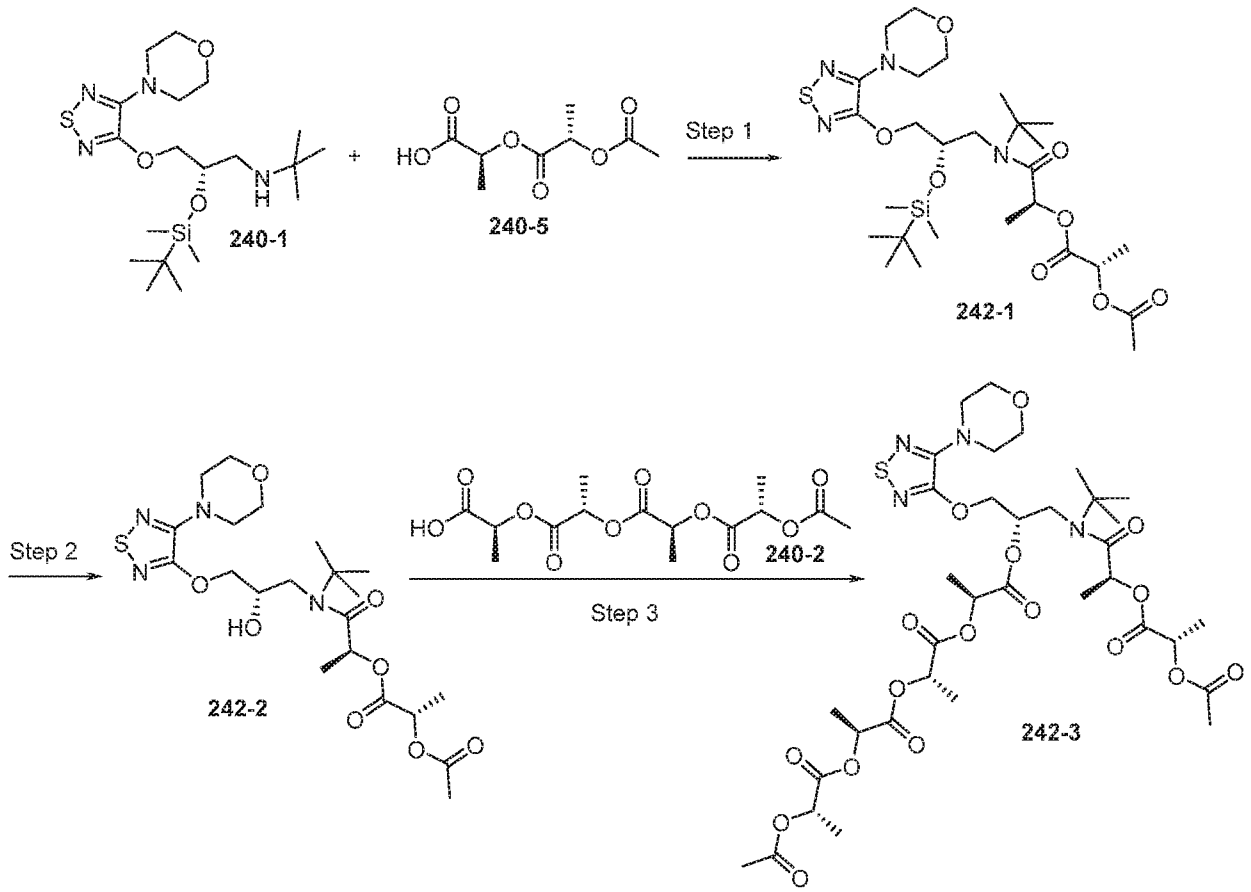
{(S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (**240-2**, 14.5 g, 41.7 mmol) in dichloromethane (100 mL) was added oxalyl chloride (4.5 mL, 52.2 mmol) and N,N-dimethylformamide (0.2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 minutes. The reaction was concentrated to dryness under nitrogen atmosphere, diluted with dichloromethane (100 mL), N,N-diisopropylethylamine (13.4 mL, 73.1 mmol) was added followed by tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine (**240-1**, 9 g, 20.8 mmol) and 4-dimethylaminopyridine (0.25 g, 2.0 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was quenched with water (500 mL), extracted with dichloromethane (2 X 500 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (16% ethyl acetate in hexane) to give **240-3** as a colorless wax (8.0 g, 50%).

**Step-2: Preparation of (S)-2-[(S)-2-((S)-2-Acetoxy-propionyloxy)-propionyloxy]-propionic acid (S)-1-{tert-butyl-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (240-4):** To a solution of (S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (S)-1-{tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (**240-3**, 7.0 g, 9.2 mmol) in tetrahydrofuran (70 mL) was added tetrabutylammonium fluoride (14 mL, 1.0 M, 13.8 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure, and the crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (25 % ethyl acetate in hexane) to give **240-4** as a colorless wax (1.2 g, 20%).

**Step-3: Preparation of (2S)-1-{[(2S)-1-[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-(acetyloxy) propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}-N-tert-butylpropanamido]-3-{[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy}propan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (240-6):** To a solution of **240-5** (0.85 g, 4.18 mmol) in dichloromethane (15 mL) were added DCC (0.95 g, 4.64 mmol), (S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)-propionyloxy]-propionic acid (S)-1-{tert-butyl-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (**240-4**, 1.5 g, 2.32 mmol) and 4-

dimethylaminopyridine (28 mg, 0.23 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (100 mL), extracted with dichloromethane (250 X 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (25% ethyl acetate in hexane) to give **240-6** as a colorless wax (0.75 g, 38%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.25-4.92 (m, 5H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.45-3.3 (m, 4H), 2.06 (s, 3H), 2.05 (s, 3H), 1.5-1.35 (m, 18H), 1.35 (s, 9H). MS *m/z* $[M+Na]^+$ 856.3.

**Scheme 89: Synthesis of 242-3**




**Step-1: Preparation of (S)-2-Acetoxy-propionic acid (S)-1-{tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (242-1):** To a solution of (S)-2-((S)-2-acetoxy-propionyloxy)-propionic acid (**240-5**, 9.47 g, 46.4 mmol) in dichloromethane (100 mL) were added oxalyl chloride (5.97 mL, 69.6 mmol) and N,N-dimethylformamide (0.2 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 minutes. The reaction mixture was concentrated to dryness

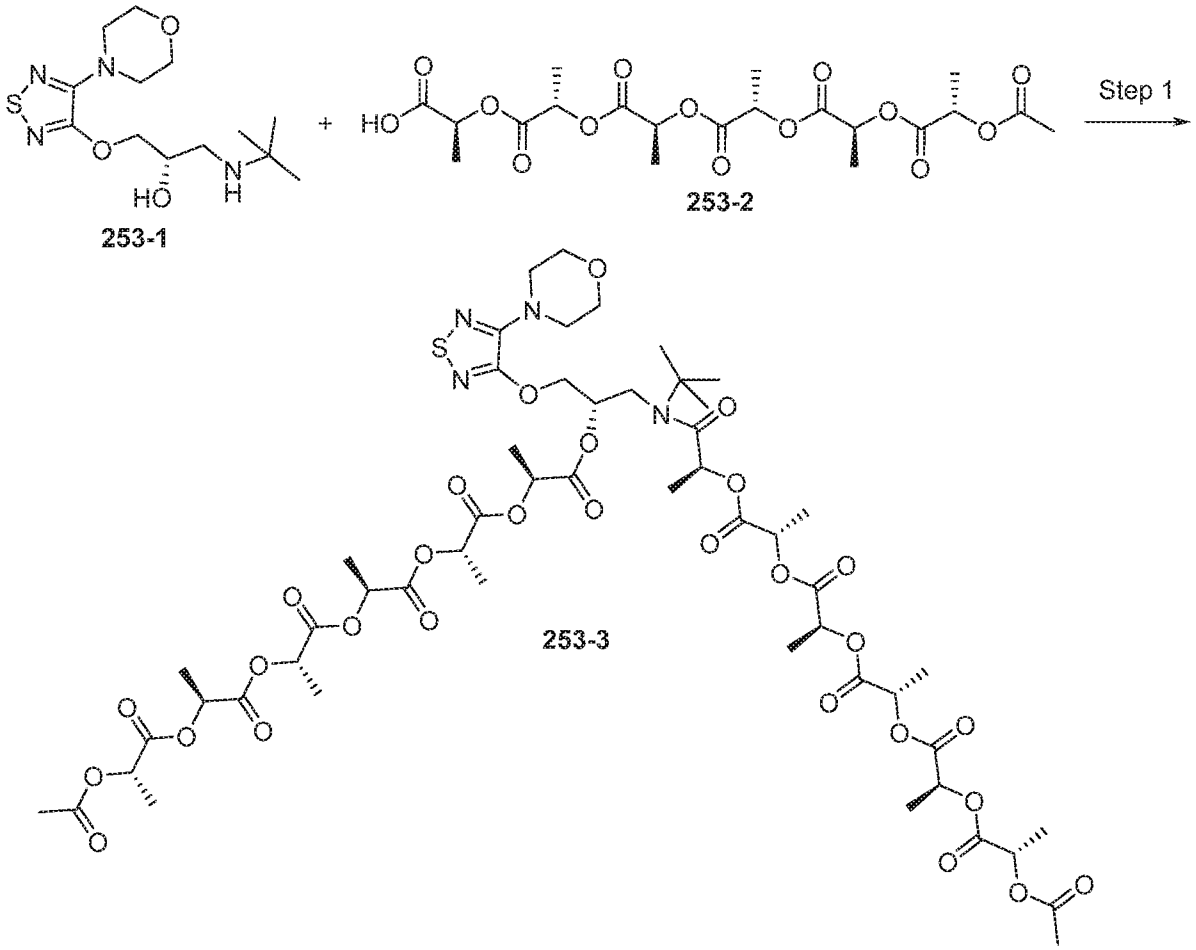
under nitrogen and diluted with dichloromethane (100 mL). N,N-diisopropylethylamine (17.1 mL, 92.8 mmol) was added followed by tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine (**240-1**, 10 g, 23.2 mmol) and 4-dimethylaminopyridine (0.02 g, 2.3 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was quenched with water (500 mL), extracted with dichloromethane (2 X 500 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (12% ethyl acetate in hexane) to give **242-1** as a colorless liquid (5.0 g, 34%).

**Step-2: Preparation of (S)-2-Acetoxy-propionic acid (S)-1-{tert-butyl-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (242-2):** To a solution of 2-acetoxy-propionic acid 1-{tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (**242-1**, 5.0 g, 8.1 mmol) in tetrahydrofuran (50 mL), was added tetrabutylammonium fluoride (12.1 mL, 1.0 M, 12.1 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure, and the crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (25 % ethyl acetate in hexane) to give **242-2** as a colorless wax (1.3 g, 31%).

**Step-3: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-[(2S)-2-{[(2S)-2-(acetyloxy)propanoyl] oxy}-N-tert-butylpropanamido]-3-{[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy} propan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (242-3):** To a solution of **240-2** (1.99 g, 5.72 mmol) in dichloromethane (16 mL) were added DCC (1.31 g, 6.36 mmol), (S)-2-acetoxy-propionic acid (S)-1-{tert-butyl-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-carbamoyl}-ethyl ester (**242-2**, 1.6 g, 3.18 mmol) and 4-dimethylaminopyridine (39 mg, 0.32 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (100 mL), extracted with ethyl acetate (100 X 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (25% ethyl acetate in hexane) to give **242-3** as a colorless wax (0.75 g,

28%). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.23-5.01 (m, 5H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.47-3.3 (m, 4H), 2.05 (s, 3H), 2.03 (s, 3H), 1.5-1.35 (m, 18H), 1.34 (s, 9H). MS *m/z* $[M+Na]^+$ 856.5.

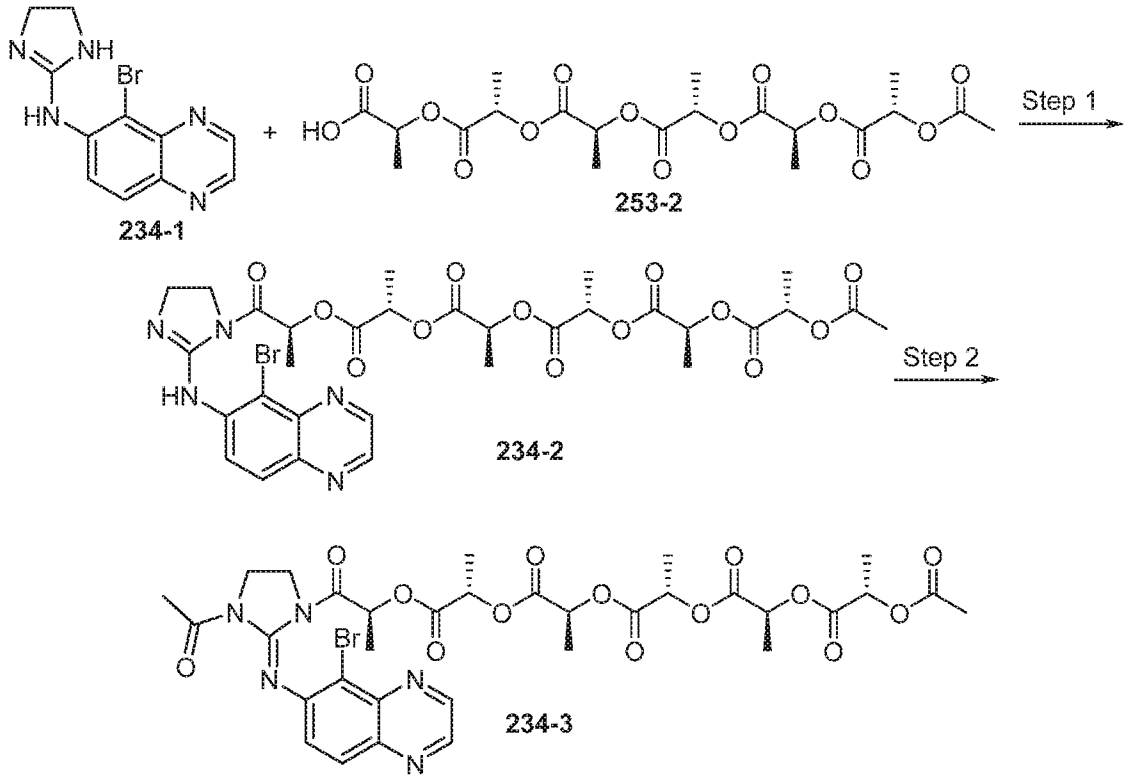
**Scheme 90: Synthesis of 253-3**




**Step-1: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-(acetyloxy)propanoyl]oxy}propanoyl]oxy} propanoyl] oxy} propanoyl]oxy}propanoyl]oxy}-N-tert-butylpropanamido]-3-{[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy}propan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (253-3):** To a solution of (S)-2-[(S)-2-((S)-2-{(S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)- propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid (**253-2**, 2.72 g, 5.53 mmol) in dichloromethane (30 mL) were added oxalyl chloride (0.54 mL, 6.32 mmol) and N,N-dimethylformamide (0.1 mL) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 30 minutes. The reaction mixture was

concentrated to dryness under nitrogen and diluted with dichloromethane (20 mL). N,N-diisopropylethylamine (1.38 mL, 7.9 mmol) was added followed by timolol (**253-1**, 0.5 g, 1.58 mmol) and 4-dimethylaminopyridine (0.02 g, 0.16 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was quenched with water (150 mL), extracted with ethyl acetate (300 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (40% ethyl acetate in hexane) to give partially pure **253-3** as a colorless wax. The waxy residue was further purified by preparative HPLC and lyophilized to obtain pure product **253-3** as a colorless wax (350 mg, 17 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.3-5.0 (m, 11H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.45-3.3 (m, 4H), 2.07 (s, 6H), 1.5-1.35 (m, 36H), 1.33 (s, 9H). MS *m/z* $[M+NH_4]^+$ 1284.3.

**Scheme 91**: **Synthesis of 234-3**

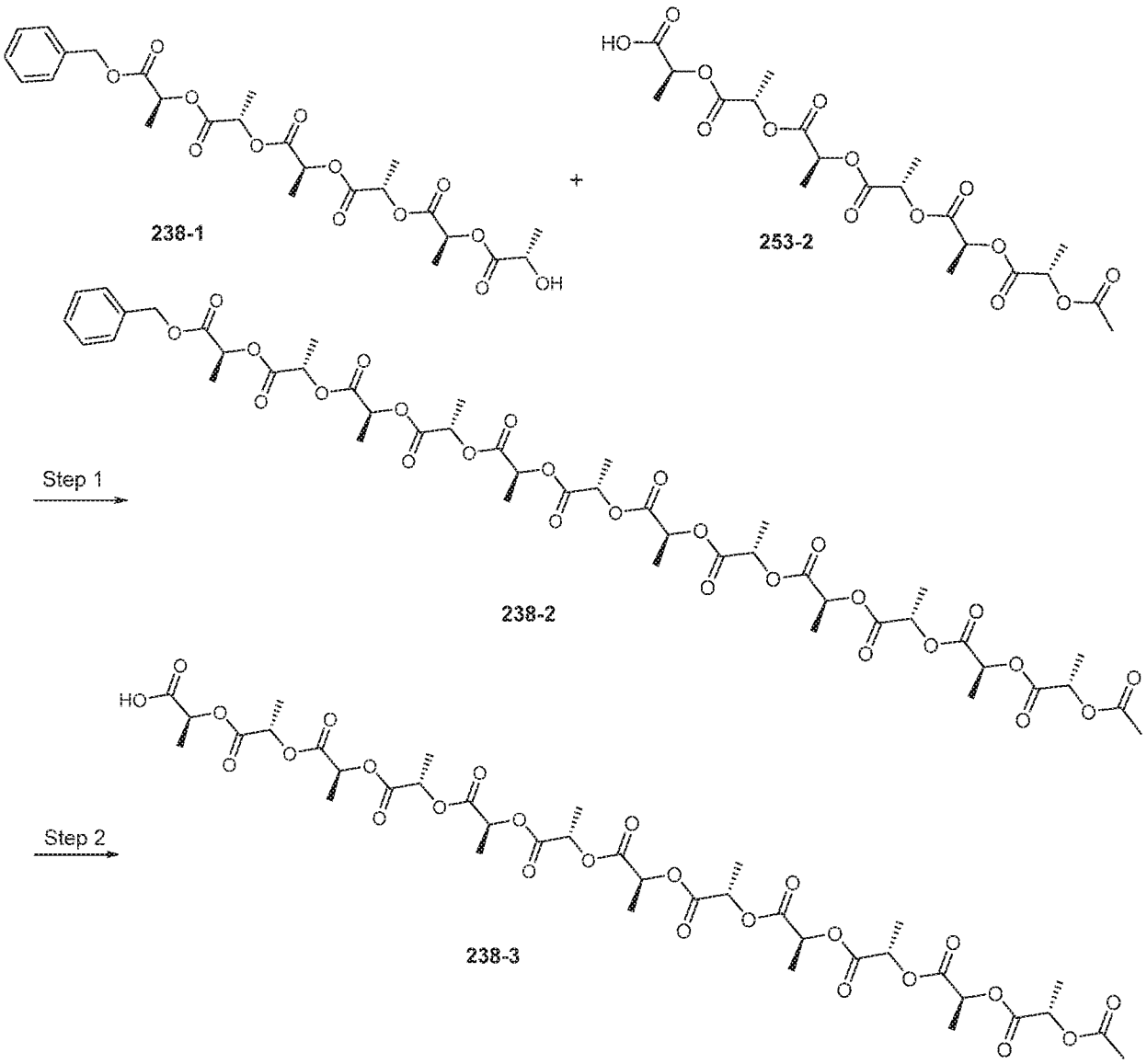


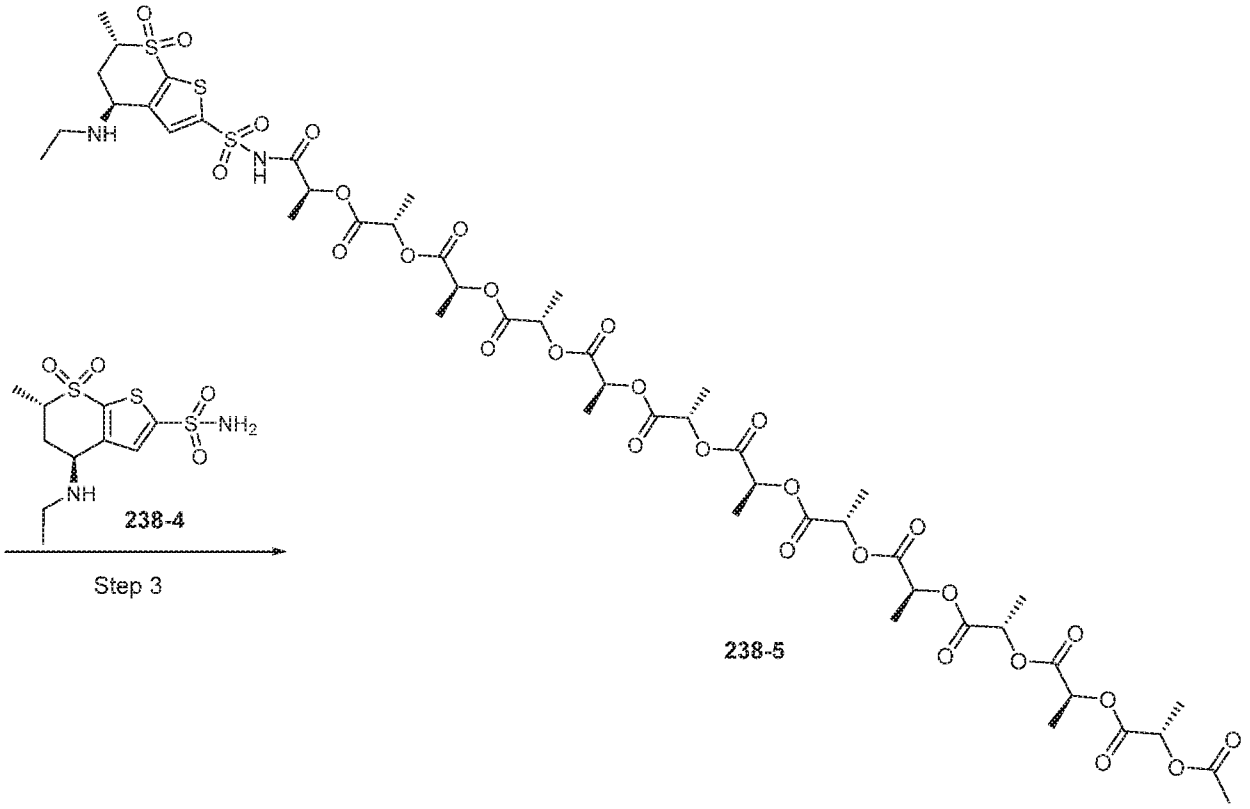

**Step-1: Preparation of (S)-2-{(S)-2-[(S)-2-((S)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (S)-1-{(S)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (234-2):** To a solution of (S)-2-[(S)-2-((S)-2-{(S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-

propionyloxy)-propionyloxy]-propionic acid (**253-2**, 5.5 g, 11.1 mmol) in dichloromethane (60 mL) were added EDC.HCl (1.89 g, 12.2 mmol), hydroxybenzotriazole (0.68 g, 5.08 mmol), brimonidine (**234-1**, 3.0 g, 10.1 mmol) and 4-dimethylaminopyridine (125 mg, 1.01 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (250 mL), extracted with ethyl acetate (400 X 2 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (40% Ethyl acetate in Hexane) to give **234-2** as a pale yellow solid (2.4 g, 30%).

**Step-2: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-[(2Z)-3-acetyl-2-[(5-bromoquinoxalin-6-yl)imino]imidazolidin-1-yl]-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (234-3):** To a solution of (S)-2-{(S)-2-[(S)-2-((S)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (S)-1-{(S)-2-[2-(5-bromo-quinoxalin-6-ylamino)-4,5-dihydro-imidazol-1-yl]-1-methyl-2-oxo-ethoxycarbonyl}-ethyl ester (**234-2**, 6.5 g, 8.47 mmol) in dichloromethane (65 mL) were added triethylamine (3.67 mL, 25.41 mmol), acetyl chloride (1.21 mL, 16.95 mmol) and 4-dimethylaminopyridine (103 mg, 0.84 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (200 mL), extracted with ethyl acetate (2 X 200 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (70% Ethyl acetate in Hexane) to give **234-3** as a pale yellow solid (3.0 g, 43%). $^1$H-NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 6.3-6.1 (m, 1H), 5.24-5.14 (m, 4H), 5.02 (q, 1H), 4.15-3.85 (m, 4H), 2.06 (s, 6H), 1.55-1.37 (m, 18H). MS *m/z* $[M+H]^+$ 808.6.

**Scheme 92**: **Synthesis of 238-5**


238-1
253-2
Step 1
238-2
Step 2
238-3




**Step-1: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}

(230-400 mesh) column chromatography (17% ethyl acetate in hexane) to obtain product **238-2** as a colorless liquid (2.3 g, 62%).

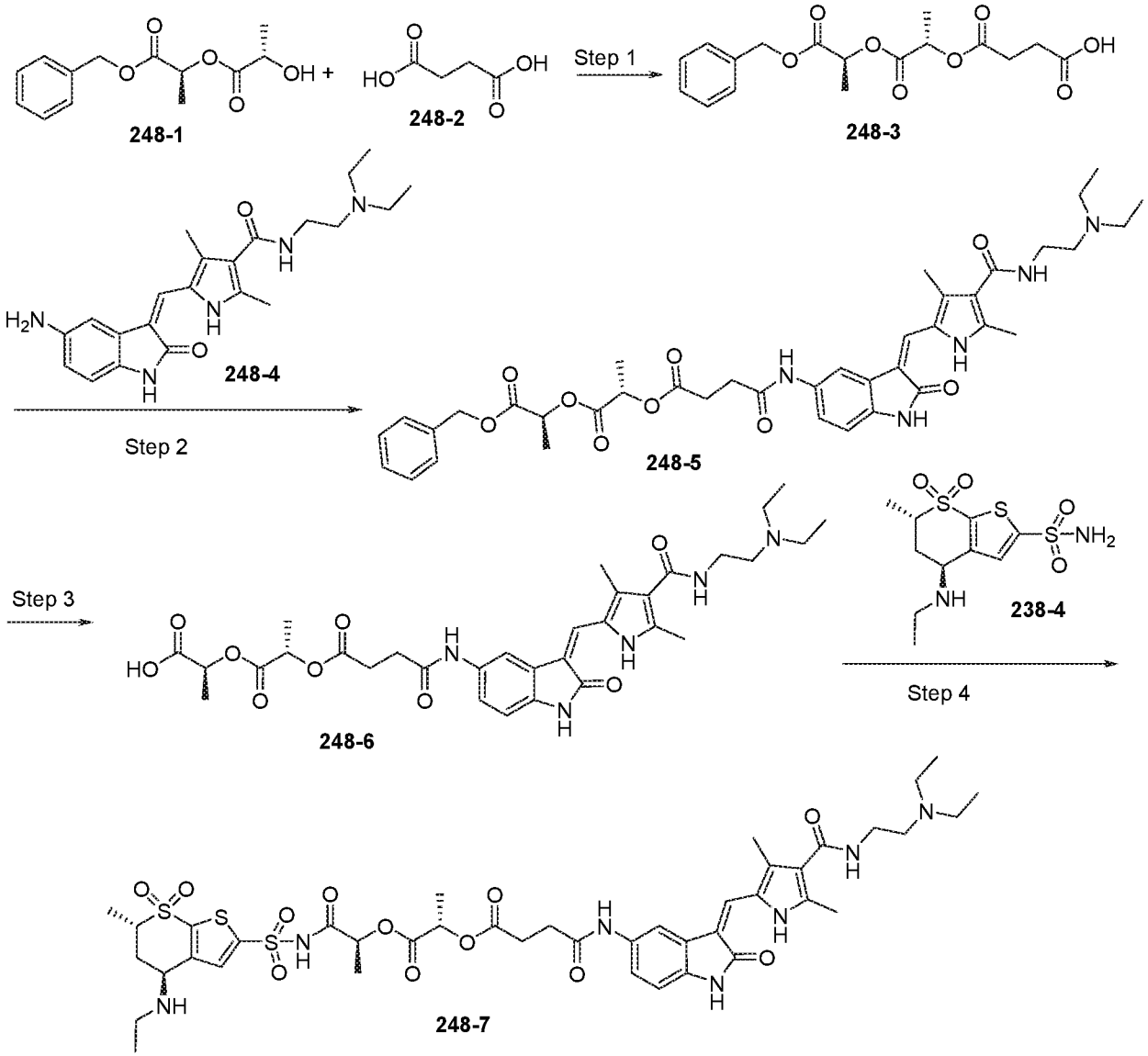
**Step-2: Preparation of (2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-(acetyloxy)propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoic acid (238-3):** To a Parr hydrogenation vessel was added a solution of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (**238-2**, 2.3 g, 2.26 mmol) in methanol (30 mL) and 10% Pd/C (0.57 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 $kg/cm^2$) over a period of 1 hour. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under reduced pressure to obtain **238-3** as a wax (1.4 g, 70%).

**Step-3: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-[(1S)-1-({[(2S,4S)-4-(ethylamino)-2-methyl-1,1-dioxo-2H,3H,4H-1λ⁶-thieno[2,3-b]thiopyran-6-yl]sulfonyl}carbamoyl)ethoxy]-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl (2S)-2-(acetyloxy)propanoate (238-5):**

To a suspension of dorzolamide (**238-4**, 0.38 g, 1.0 mmol) in dichloromethane (6 mL) was added N,N-diisopropylethylamine (0.38 mL, 2.11 mmol) at 0 °C, and the reaction was stirred for 30 minutes. Then (2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-(acetyloxy)propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoic acid (**238-3**, 1.39 g, 1.37 mmol), EDC.HCl (0.30 g, 1.58 mmol), hydroxybenzotriazole (0.029 g, 0.021 mmol) and 4-dimethylaminopyridine (0.012 g, 0.010 mmol) were added at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mass was quenched with water (100 mL), extracted with ethyl acetate (3 X 150 mL), dried over

sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (100% ethyl acetate ) to obtain product **238-5** as an off white solid (550 mg, 42 %). $^1$H-NMR (400 MHz, DMSO-d6) δ 7.37 (s, 1H), 5.26-5.13 (m, 9H), 5.13-5.00 (m, 2H), 4.79 (q, 1H), 3.94-3.75 (m, 2H), 2.7-2.5 (m, 2H), 2.32-2.2 (m, 2H), 2.07 (s, 3H), 1.51-1.38 (m, 33H), 1.35-1.25 (m, 6H), 1.02 (t, 3H); MS *m/z* $(M+H)^+$ 1232.4.

**Scheme 93: Synthesis of 248-7**




**Step-1**

**Preparation 4-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-4-oxobutanoic acid (248-3):** To a solution of succinic acid (**248-2**, 28 g, 237 mmol) in

dichloromethane (300 mL) was added N,N-diisopropylethylamine (52 mL, 295 mmol), EDC.HCl (56.9 g, 295 mmol), hydroxybenzotriazole (3.2 g, 23 mmol), 2-hydroxy-propionic acid 1-benzyloxycarbonyl-ethyl ester (**248-1**, 30 g, 118 mmol) and 4-dimethylaminopyridine (1.45 g, 11 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mixture was quenched with water (300 mL), extracted with dichloromethane (2 X 200 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column (35% ethyl acetate in hexane) to obtain product **248-3** as a colorless liquid (25 g, 65%).

**Step-2: Preparation of (2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (248-5):**

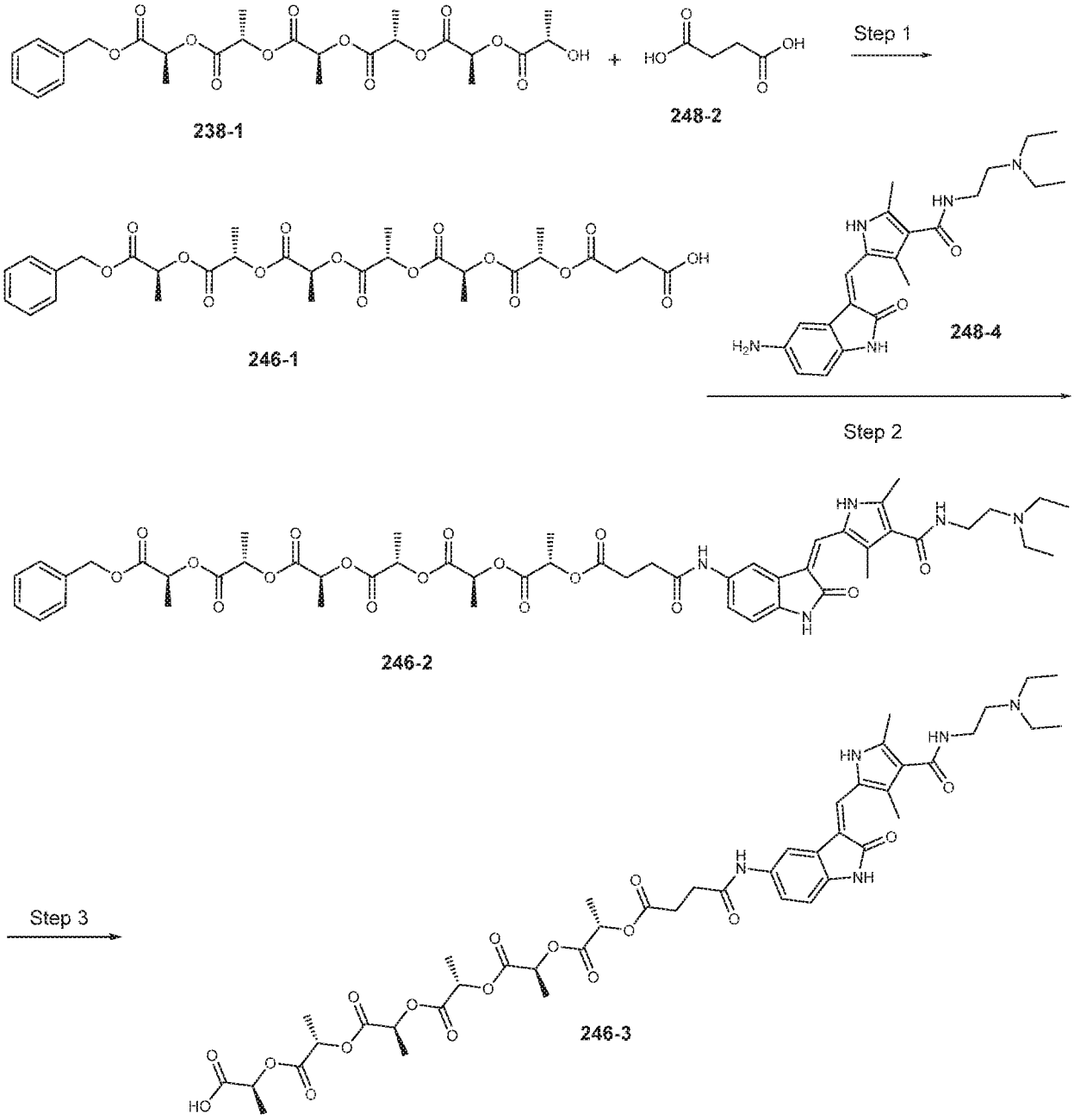
To a solution of succinic acid mono-[1-(1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl] ester (**248-3**, 10.4 g, 19 mmol) in N,N-dimethylformamide (100 mL) were added N,N-diisopropylethylamine (6.8 mL, 39 mmol), HATU (11.2 g, 29 mmol) and 5-amino sunitinib (**248-4**, 10 g, 19 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 3 hours. The resulting reaction mixture was quenched with water (500 mL), extracted with dichloromethane (2 X 250 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by recrystallization using ethyl acetate/diethyl ether to obtain product **248-5** as a reddish brown solid (11 g, 76%).

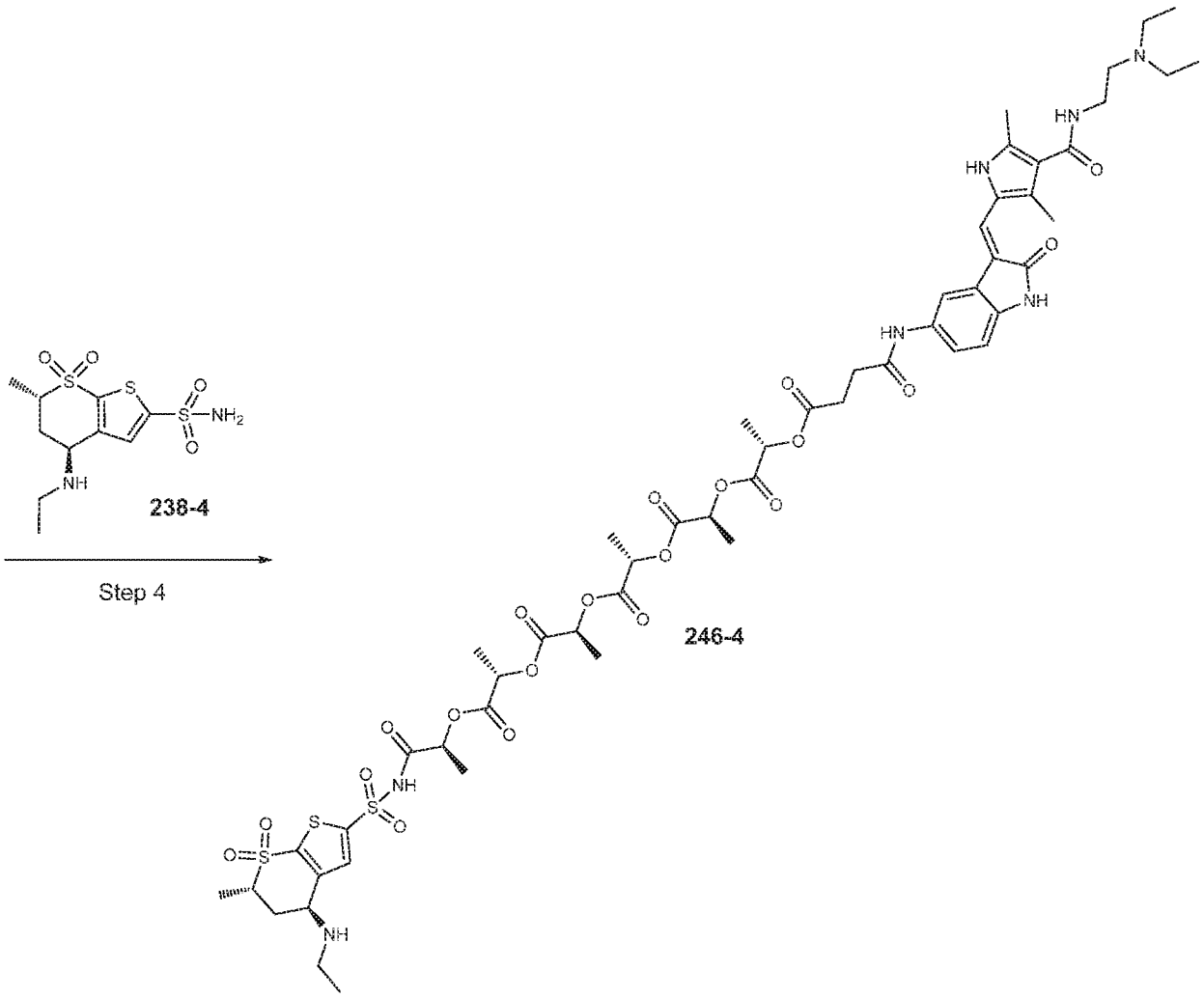
**Step-3: Preparation of (2S)-2-{[(2S)-2-[(3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoyl)oxy]propanoyl]oxy}propanoic acid (248-6):** To a 100 mL autoclave vessel were added a solution of N-{3-[1-[4-(2-diethylamino-ethylcarbamoyl)-3,5-dimethyl-1H-pyrrol-2-yl]-meth-(Z)-ylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl}-succinamic acid 1-(1-benzyl oxy carbonyl-ethoxycarbony l)-ethyl ester (**248-5**, 11 g, 15 mmol) in a mixture of methanol (220 mL) and dichloromethane (22 mL) followed by 10% Pd/C (2.2 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (1 $kg/cm^2$) over a period of 30 minutes. After completion of the reaction, the reaction mixture was filtered through a celite bed. Then volatiles were evaporated under reduced pressure to obtain product **248-6** as a reddish orange solid (8.4 g, 87%).

**Step-4: Preparation of (2S)-1-[(1S)-1-({[(2S,4S)-4-(ethylamino)-2-methyl-1,1-dioxo-2H,3H,4H-1λ⁶-thieno[2,3-b]thiopyran-6-yl]sulfonyl}carbamoyl)ethoxy]-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (248-7):** To a suspension of dorzolamide (**238-4**, 300 mg, 0.833 mmol) in dichloromethane (6 mL) was added N,N-diisopropylethylamine (0.2 mL, 1.333 mmol) at 0 °C and stirred for 30 minutes. Then (2S)-2-{[(2S)-2-[(3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoyl)oxy]propanoyl]oxy}propanoic acid (**248-6**, 533 mg, 0.833 mmol), EDC.HCl (255 mg, 1.333 mmol), hydroxybenzotriazole (23 mg, 0.166 mmol) and 4-dimethylaminopyridine (10 mg, 0.083 mmol) were added at 0° C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (50 mL), extracted with dichloromethane (3 X 50 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC and lyophilized to obtain the monoformate salt of product **248-7** as an orange solid (197 mg, 25 %)) $^1$H-NMR (400 MHz, DMSO-d6) δ 13.71 (s, 1H), 10.87 (s, 1H), 9.88 (s, 1H), 8.14 (s, 1H), 7.94 (d, $J$ = 2 Hz, 1H), 7.69 (t, 1H), 7.5-7.4 (m, 2H), 7.17 (dd, $J$ = 2 Hz, $J$ = 8 Hz, 1H), 6.81 (d, $J$ = 8 Hz, 1H), 4.99 (q, 1H), 4.80 (q, 1H), 4.1-3.8 (m, 2H), 3.5-3.4 (m, 2H), 3.1-2.95 (m, 6H), 2.8-2.5 (m, 6H), 2.46 (s, 3H), 2.42 (s, 3H), 2.4-2.2 (m, 2H), 1.46 (d, 3H), 1.4-1.3 (m, 6H), 1.16 (t, 6H), 1.06 (t, 3H); MS $m/z$ $[M+H]^+$ 947.4.

**Scheme 94**

**Synthesis of 246-4**






**Step-1: Preparation of 4-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-4-oxobutanoic acid (246-1):** To a solution of succinic acid (**248-2**, 3.01 g, 25.5 mmol) in dichloromethane (60 mL) was added N,N-diisopropylethylamine (5.1 mL, 27.7 mmol), EDC.HCl (5.3 g, 27.7 mmol), hydroxybenzotriazole (0.30 g, 2.2 mmol), (S)-2-hydroxy-propionic acid (S)-1-((S)-1-{(S)-1-[(S)-1-((S)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (**238-1**, 6 g, 11 mmol) and 4-dimethylaminopyridine (0.135 g, 1.1 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was quenched with water (200 mL), extracted with dichloromethane (2 X 200 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon

evaporation of volatiles was purified through silica gel (230-400 mesh) column (2-5% methanol in DCM) to obtain product **246-1** as a colorless liquid (4.7 g, 66%).

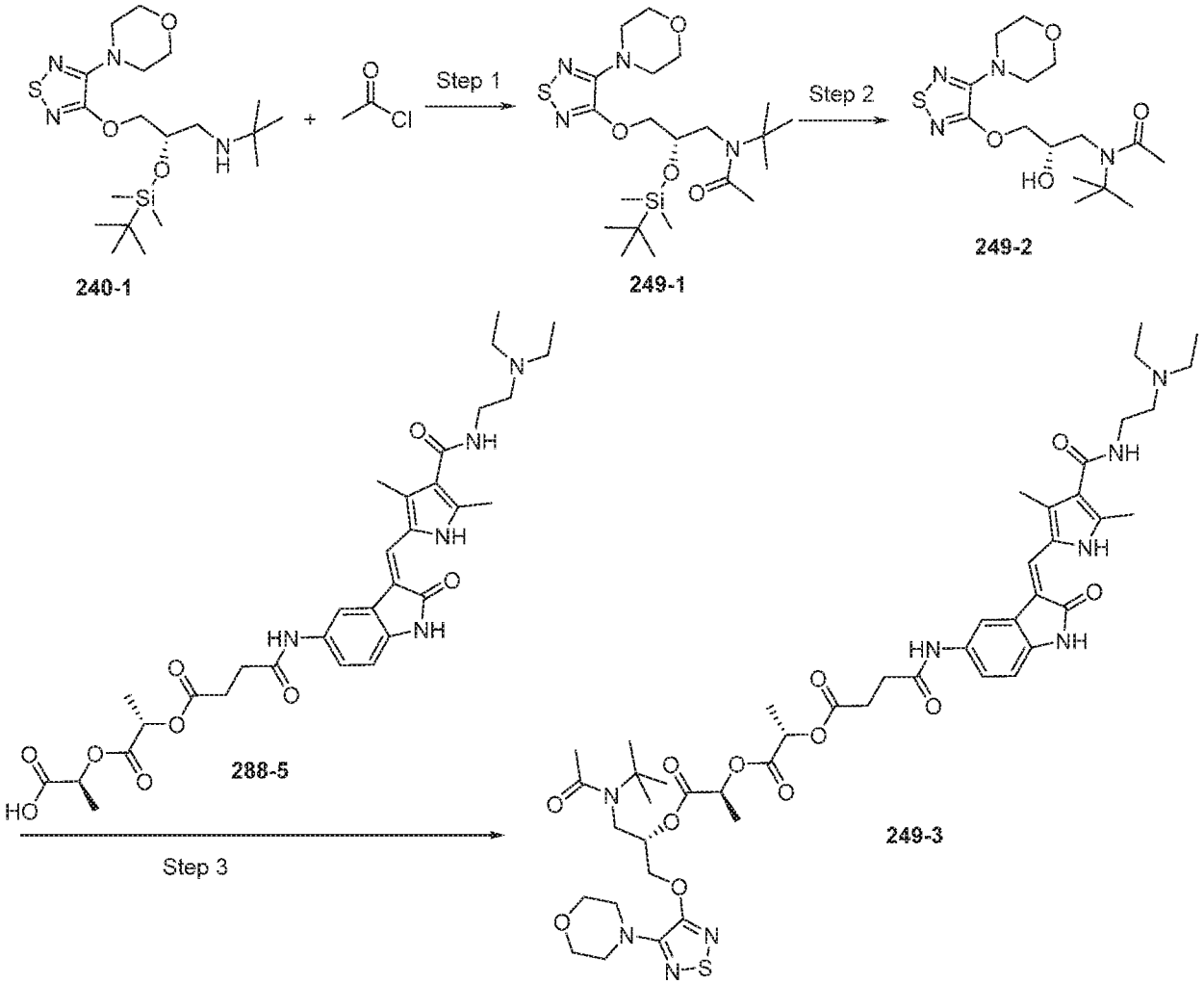
**Step-2: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (246-2):** To a solution of 4-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-4-oxobutanoic acid (**246-1**, 4.59 g, 7.17 mmol) in N,N-dimethylformamide (25 mL) were added N,N-diisopropylethylamine (1.76 mL, 9.56 mmol), HATU (2.72 g, 7.17 mmol) and 5-amino sunitinib (**248-4**, 1.89 g, 4.78 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 hour. The resulting reaction mixture was quenched with water (100 mL), extracted with dichloromethane (2 X 250 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by recrystallization using ethyl acetate/diethyl ether and hexane to obtain **246-2** as a reddish brown solid (3.3 g, 67%).

**Step-3: Preparation of (2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-{[(2S)-2-[(3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoyl)oxy]propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoyl]oxy}propanoic acid (246-3):** To a Parr hydrogenation vessel were added a solution of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-(benzyloxy)-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (**246-2**, 3.3 g, 3.2 mmol) in a combination of methanol (27 mL) and dichloromethane (3 mL) followed by 10% Pd/C (0.33 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (1 kg/cm2) over a period of 30 minutes. After completion of the reaction, the reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to obtain **246-3** as a reddish orange solid (2.5 g, 83%).

**Step-4: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-{[(2S)-1-[(1S)-1-({[(2S,4S)-4-(ethylamino)-2-methyl-1,1-dioxo-2H,3H,4H-1λ⁶-thieno[2,3-b]thiopyran-6-yl]sulfonyl}carbamoyl)ethoxy]-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (246-4):** To a suspension of dorzolamide (**238-4**, 750 mg, 2.0 mmol) in dichloromethane (10 mL) was added N,N-diisopropylethylamine (0.61 mL, 3.3 mmol) at 0 °C and stirred for 30 minutes. Then **246-3** (2.5 g, 2.7 mmol), EDC.HCl (635 mg, 3.3 mmol), hydroxybenzotriazole (57 mg, 0.41 mmol) and 4-dimethylaminopyridine (25 mg, 0.20 mmol) were added at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 hours. The resulting reaction mixture was concentrated under reduced pressure and slurried with water (10 mL), and the resulting precipitate was collected by filtration. The crude compound was further purified by preparative HPLC and lyophilized to obtain the monoformate salt of **246-4** as an orange solid (900 mg, 36%). $^1$H-NMR (400 MHz, DMSO-d6) δ 13.71 (s, 1H), 10.86 (s, 1H), 9.88 (s, 1H), 8.14 (s, 1H), 7.94 (d, $J$ = 2 Hz, 1H), 7.68 (t, 1H), 7.5-7.4 (m, 2H), 7.17 (dd, $J$ = 2 Hz, $J$ = 8 Hz, 1H), 6.81 (d, $J$ = 8 Hz, 1H), 5.25-5.0 (m, 5H), 4.79 (q, 1H), 4.1-3.8 (m, 2H), 3.55-3.4 (m, 2H), 3.15-2.9 (m, 6H), 2.8-2.5 (m, 6H), 2.46 (s, 3H), 2.41 (s, 3H), 2.4-2.2 (m, 2H), 1.55-1.4 (m, 15H), 1.36-1.24 (m, 6H), 1.16 (t, 6H), 1.06 (t, 3H); MS *m/z* $[M+H]^+$ 1235.6, $[M+2H]^{2+}$ 619.8.

**Scheme 95**

**Synthesis of 249-3**



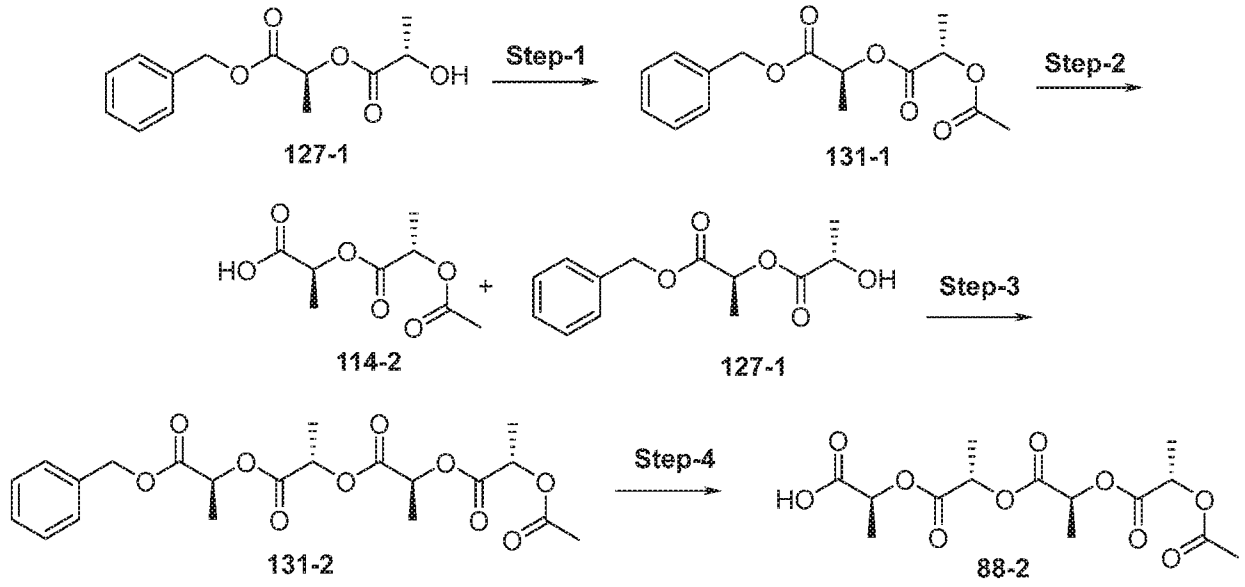

**Step-1: Preparation of N-tert-Butyl-N-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (249-1):** To a solution of tert-butyl-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-amine (**240-1**, 4 g, 9.29 mmol) in chloroform (40 mL) were added triethylamine (1.9 ml, 13.93 mmol) and acetyl chloride (0.99 mL, 13.93 mmol) at 0° C. The reaction mixture was stirred at 25-30 °C over a period of 12 hours. The resulting reaction mixture was quenched with water (100 mL), extracted with dichloromethane (2 X 200 mL) and dried over sodium sulfate. The volatiles were evaporated under reduced pressure to obtain product **249-1** as a colorless liquid (3.3 g, 75%).

**Step-2: Preparation of N-tert-butyl-N-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (249-2):** To a solution of N-tert-butyl-N-[(S)-2-(tert-butyl-dimethyl-silanyloxy)-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide (**249-1**, 3.3 g, 6.98 mmol) in tetrahydrofuran (33 mL) was added tetrabutylammonium fluoride (10.4 mL, 1.0 M, 10.47 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 hour. The resulting reaction mixture was concentrated under reduced pressure. The crude product obtained upon evaporation of the volatiles was purified through silica gel (60-120 mesh) column chromatography (60 % ethyl acetate in hexane) to give product **249-2** as an off white solid (1.3 g, 52%).

**Step-3: Preparation of (2S)-1-{[(2S)-1-{[(2S)-1-(N-tert-butylacetamido)-3-{[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy}propan-2-yl]oxy}-1-oxopropan-2-yl]oxy}-1-oxopropan-2-yl 3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoate (249-3):** The mixture of (2S)-2-{[(2S)-2-[(3-{[(3Z)-3-[(4-{[2-(diethylamino)ethyl]carbamoyl}-3,5-dimethyl-1H-pyrrol-2-yl)methylidene]-2-oxo-2,3-dihydro-1H-indol-5-yl]carbamoyl}propanoyl)oxy]propanoyl]oxy}propanoic acid (**288-5**, 3.48 g, 5.45 mmol ) and N-tert-butyl-N-[(S)-2-hydroxy-3-(4-morpholin-4-yl-[1,2,5]thiadiazol-3-yloxy)-propyl]-acetamide **25-4** (**249-2**, 1.5 g, 4.19 mmol ) was stripped with N,N-dimethylformamide (3 x 15 mL). The residue was brought up in N,N-dimethylformamide (15 mL) and dried molecular sieves (4A°), EDC.HCl (1.2 g, 6.28 mmol), hydroxybenzotriazole (0.11 g, 0.83 mmol) and 4-dimethylaminopyridine (0.05 g, 0.42 mmol) were added at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 16 hours. The resulting reaction mixture was diluted with ethyl acetate (100 mL) and filtered to remove insoluble material. The filtrate was washed with water (2 X 50 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified by preparative HPLC and lyophilized to obtain product **249-3** as an orange solid (250 mg, 6%). $^1$H-NMR (400 MHz, DMSO-d6) δ 13.64 (s, 1H), 10.84 (s, 1H), 9.87 (s, 1H), 7.89 (d, $J$ = 2 Hz, 1H), 7.47 (t, 1H), 7.43 (s, 1H), 7.21 (dd, $J$ = 2 Hz, $J$ = 8 Hz, 1H), 6.81 (d, $J$ = 8 Hz, 1H), 5.48-5.36 (m, 1H), 5.12-4.97 (m, 2H), 4.54 (dd, 1H), 4.41 (dd, 1H), 3.8-3.6 (m, 6H), 3.5-3.3 (m, 6H), 2.7-2.5 (m, 8H), 2.44 (s, 3H), 2.39 (s, 3H), 2.09 (s, 3H), 1.5-1.3 (m, 15H), 0.99 (t, 6H); MS $m/z$ $[M+H]^+$ 981.4.

**Example 5. Synthetic Examples to Describe Linker Moieties Utilized Above**

**Scheme 96: Synthesis of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (88-2):**




**Step-1**: **Preparation of (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid benzyl ester (131-1):** To a solution of (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (5 g, 19.84 mmol) in dichloromethane (50 mL) was added 4-dimethylaminopyridine (0.24 g, 1.98 mmol) and acetic anhydride (2.8 mL, 29.76 mmol) at 0 °C. The reaction mixture stirred at 25-30 °C over a period of 3 h. The resulting reaction mixture was quenched with water (200 mL), extracted with ethyl acetate (2 x 200 mL) and dried over sodium sulfate. The volatiles were evaporated under reduced pressure to obtain product **131-1** as a pale yellow liquid (7.3 g, 73%).

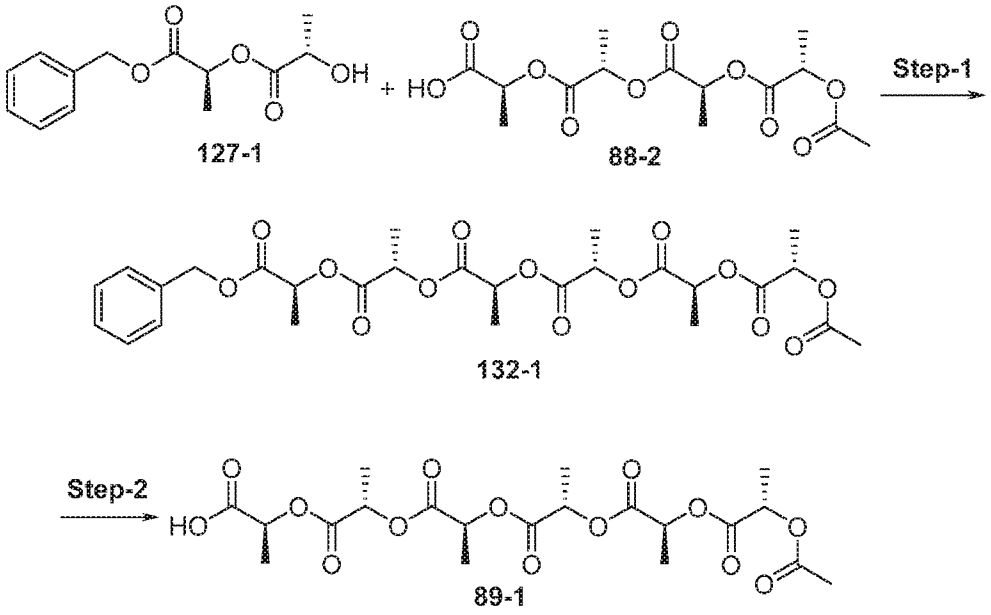
**Step-2**: **Preparation of (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid (114-2):** To a 250 mL autoclave vessel were added a solution of (*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionic acid benzyl ester **131-1** (7.3 g, 24.82) in methanol (40 mL) and 10% Pd/C (1.5 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. Then volatiles were evaporated under reduced pressure to obtain product **114-2** as a pale yellow liquid 4.4 g (81%).

**Step-3**: **Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid benzyl ester (131-2):** To a solution of (*S*)-2-((*S*)-2-acetoxy-

propionyloxy)-propionic acid **114-2** (4.3 g, 20.83 mmol) and (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (3.5 g, 13.88 mmol) in dichloromethane (50 mL) were added EDC·HCl (5.3g, 27.76 mmol), 4-dimethylaminopyridine (169 mg, 1.38 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200X3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (8% ethyl acetate in hexane) to obtain product **131-2** as a pale yellow liquid 2.2 g (36%).

**Step-4**: **Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (88-2):** To a 100 mL autoclave vessel were added a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid benzyl ester **131-2** (2.2 g, 5.08 mmol) in methanol (15 mL) and 10% Pd/C (0.45 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to give **88-2** as a pale yellow liquid 1.1 g (65%).

**Scheme 97: Synthesis of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid (89-1):**

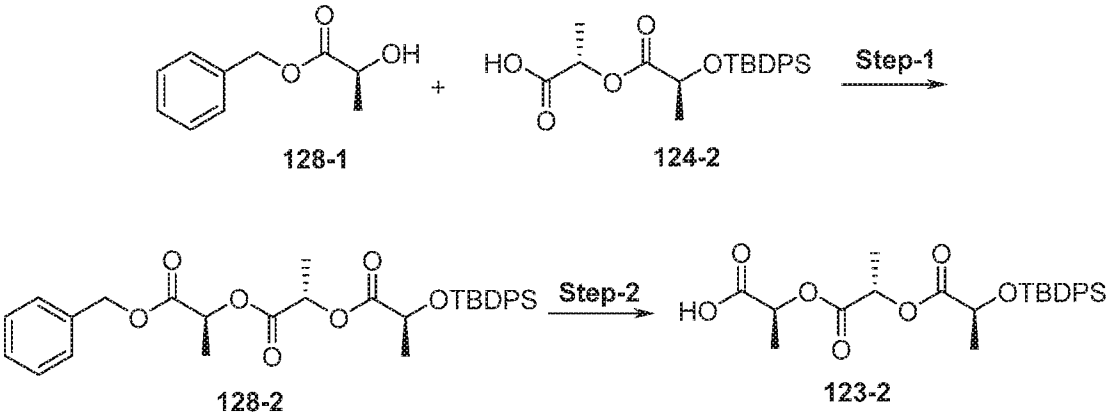



**Step-1**: **Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid benzyl ester**

**(132-1):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **88-2** (12.4 g, 35.71 mmol) and (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (6.0 g, 23.80 mmol) in dichloromethane (60 mL) were added EDC·HCl (9.09 g, 47.60 mmol), 4-dimethylaminopyridine (290 mg, 2.38 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (200 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (6% ethyl acetate in hexane) to obtain product **132-1** as a pale yellow liquid 8.3 g (60%).

**Step-2: Preparation of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid (89-1):** To a 250 mL autoclave vessel were added a solution of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid benzyl ester **132-1** (8.3 g, 14.26 mmol) in methanol (50 mL) and 10% Pd/C (1.65 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. Then volatiles were evaporated under reduced pressure to obtain product **89-1** as a pale yellow liquid 5.7 g (81%).

**Scheme 98: Synthesis of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (123-2):**

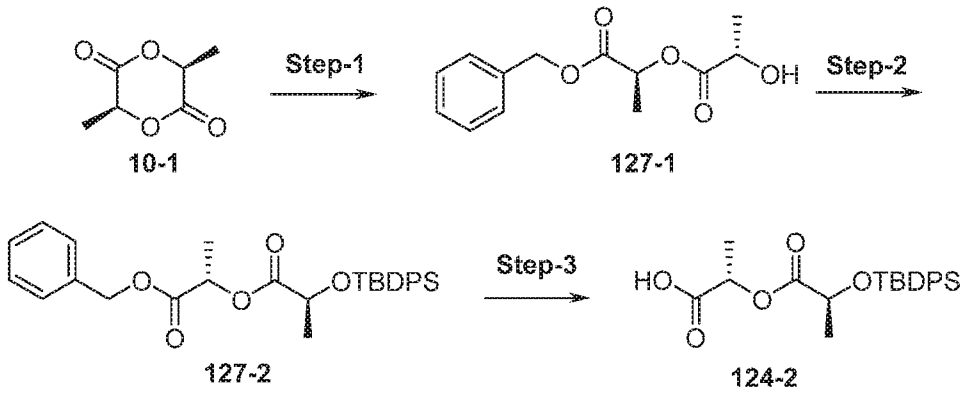



**Step-1: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl ester (128-2):** To a solution of (*S*)-2-(*tert*-Butyl-

diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester **124-2** (5.17 g, 7.22 mmol) in dichloromethane (10 mL) were added EDC·HCl (2.12 g, 11.11 mmol), (*S*)-2-hydroxy-propionic acid benzyl ester **128-1** (1 g, 5.55 mmol) and 4-dimethylaminopyridine (670 mg, 0.55 mmol) at 0 °C. The reaction mixture was allowed to stir at ambient temperature over a period of 1 h. Resulting reaction mixture was diluted with ethyl acetate (300 mL) and washed with water (2 x 50 mL). The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (3% ethyl acetate in hexane) to give product **128-2** as a colorless liquid 4.3g (88%).

**Step-2: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (123-2):** To a 100 mL autoclave vessel were added a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl ester **128-2** (7.0 g, 12.45) in methanol (40 mL) and 10% Pd/C (1.4 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (10% methanol in dichloromethane) to obtain product **123-2** as a pale yellow liquid 5.8 g (94%).

**Scheme 99: Synthesis of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester (124-2):**



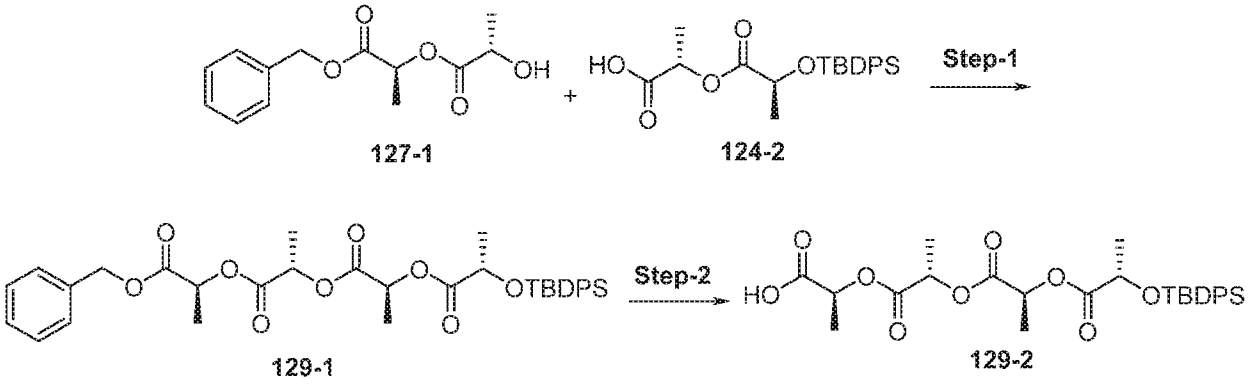

**Step-1: Preparation of (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester (127-1):** To a solution of (3*S*,6*S*)-3,6-dimethyl-[1,4]dioxane-2,5-dione **10-1** (5.0 g, 34.72 mmol) in toluene (100 mL) was added benzyl alcohol (3.2 mL, 31.72 mmol) and camphor sulfonic acid

(0.8 g, 3.47 mmol) at 25-30 °C. The reaction mixture was allowed to stir at 80 °C over a period of 2 hours and the resulting reaction mixture was diluted with ethyl acetate (800 mL) and washed with water (2 x 400 mL). The crude product obtained upon evaporation of volatiles was purified through preparative HPLC to obtain product **127-1** as a pale yellow liquid 5.5 g (63%).

**Step-2: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1 benzyloxycarbonyl-ethyl ester (127-2):** To a solution of (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (0.1 g, 0.23 mmol) in dichloromethane (5 mL) were added triethylamine (0.23 mL, 1.61 mmol), TBDPS-Cl (0.43 mL, 1.618 mmol) and catalytic amount of 4-dimethylaminopyridine at 0 °C. The reaction mixture was stirred at room temperature over period of 8 h. Resulting reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). Then volatiles were evaporated under reduced pressure to obtain product **127-2** as a colorless liquid 200 mg (74%).

**Step-3: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester (124-2):** To a 100 mL autoclave vessel were added a solution of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-2** (1.5 g) in methanol (20 mL) and 10% Pd/C (0.3 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (10% methanol in dichloromethane) to obtain product **124-2** as colorless liquid 700 mg (58%).

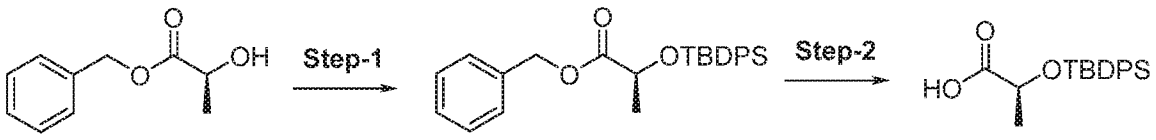
**Scheme 100: Synthesis of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (129-2):**



**Step-1: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (129-1):** To a solution of (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (6.0 g, 33.2 mmol) and (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester **124-2** (17.3 g, 7.77 mmol) in dichloromethane (60 mL) were added EDC·HCl (8.2 g, 43.2 mmol), 4-dimethylaminopyridine (405 mg, 3.3 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (250 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (10% methanol in dichloromethane) to obtain product **129-1** as a pale yellow liquid 5.8 g (94%).

**Step-2: Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (129-2):** To a 100 mL autoclave vessel were added a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **129-1** (700 mg, 1.10 mmol) in methanol (10 mL) and 10% Pd/C (140 mg, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (60-120 mesh) column chromatography (10% methanol in dichloromethane) to obtain product **129-2** as a pale yellow liquid 420 mg (78%).

**Scheme 101: Synthesis of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (130-2):**




128-1 130-1 130-2

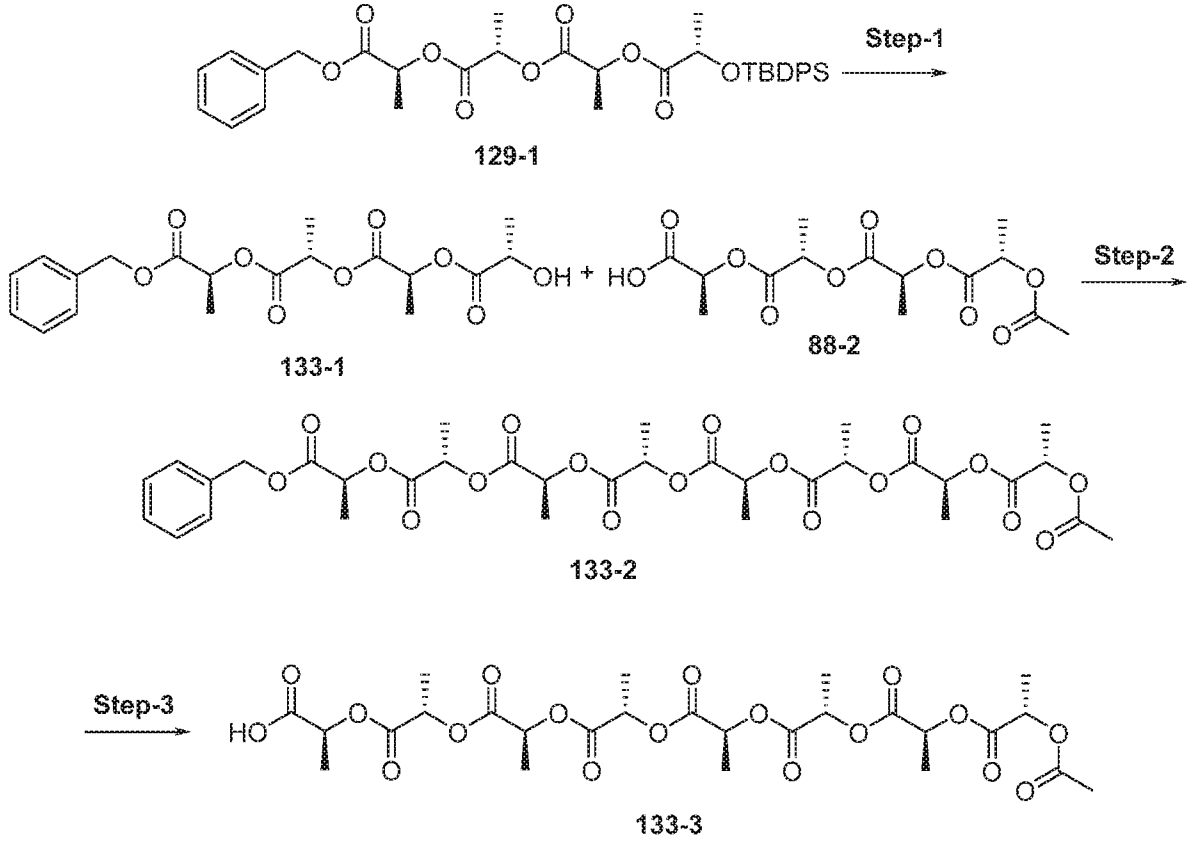
**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid benzyl ester (130-1):** To a solution of (*S*)-2-hydroxy-propionic acid benzyl ester **128-1** (5 g, 27.77 mmol) in dichloromethane (50 mL) were added triethylamine (7.8 mL, 55.55 mmol), TBDPS-Cl (14.6 mL, 55.55 mmol) and catalytic amount of 4-dimethylaminopyridine at 0 °C. The reaction mixture was stirred at room temperature over period of 8 h. Resulting reaction mixture was quenched with

water (200 mL) and extracted with ethyl acetate (2 x 150 mL). Then volatiles were evaporated under reduced pressure to obtain product **130-1** as a pale yellow liquid 8.2 g (70%).

**Step-2**: **Preparation of (*S*)-2-(*tert*-butyl-diphenyl-silanyloxy)-propionic acid (130-2):**

To a 250 mL autoclave vessel were added a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid benzyl ester **130-1** (8.2 g, 19.61 mmol) in methanol (50 mL) and 10% Pd/C (1.6 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to obtain product **130-2** as a pale yellow liquid 4.9 g (76 %).

**Scheme 102: Synthesis of (*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionic acid (133-3):**



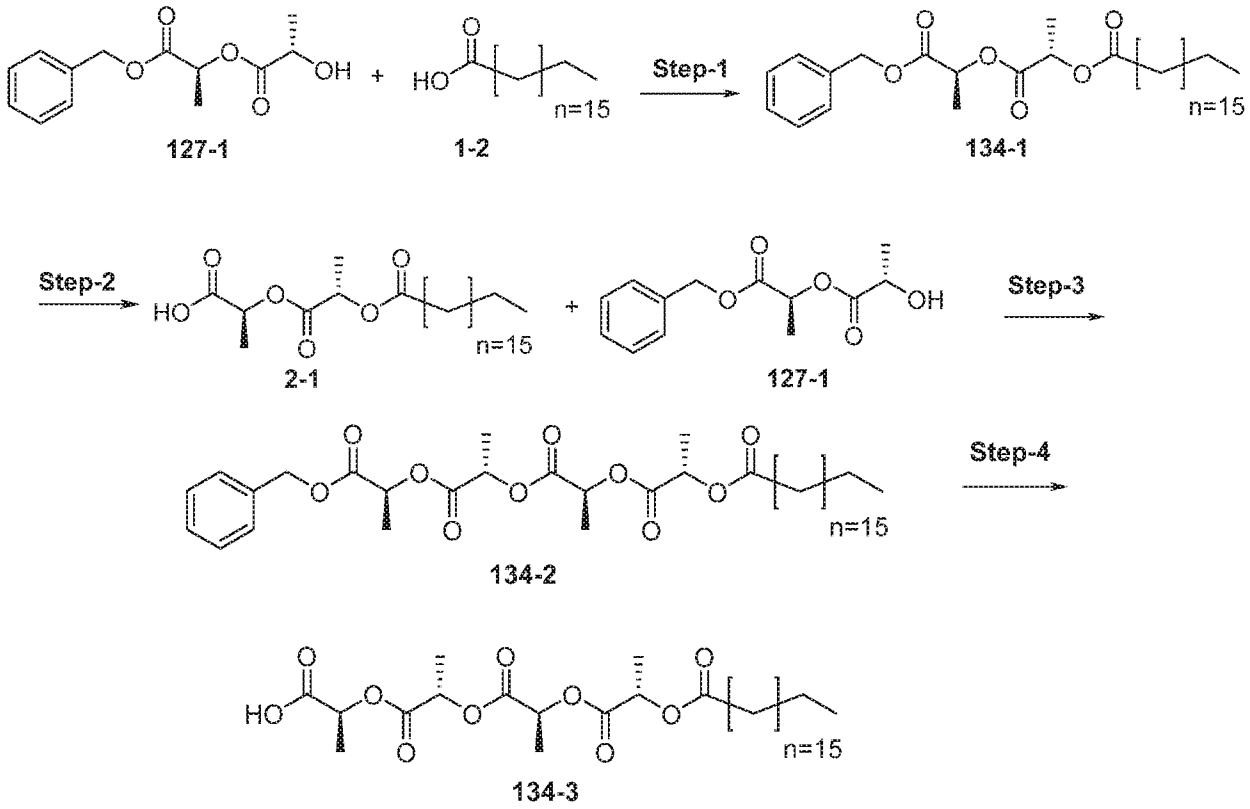

**Step-1**: **Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (129-1):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **129-1** (2.0 g, 31.54 mmol) in tetrahydrofuran (20 mL) were added

tetra butyl ammonium fluoride (4.73 mL, 1.0M, 47.31 mmol) and acetic acid (2.86 g, 47.31 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (13% ethyl acetate in hexane) to give product **133-1** as a colorless liquid 1.3 g (41.9%).

**Step-2. Preparation of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (133-2):** To a solution of (*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionic acid **88-2** (1.315 g, 3.78 mmol) and (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **133-1** (1.0 g, 2.52 mmol) in dichloromethane (10 mL) were added EDC·HCl (0.866 g, 4.53 mmol), 4-dimethylaminopyridine (31 mg, 0.25 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (300 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (12% ethyl acetate in hexane) to obtain product **133-2** as a pale yellow liquid 1.2 g (65%).

**Step-3: Preparation of (*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionic acid (133-3):** To a 250 mL autoclave vessel were added a solution of (*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-{(*S*)-2-[(*S*)-2-((*S*)-2-Acetoxy-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionyloxy]-propionyloxy}-propionyloxy)-propionic acid **133-2** (1.2 g, 2.06 mmol) in methanol (12 mL) and 10% Pd/C (0.3 g, 10% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to give **133-3** as a pale yellow liquid 0.8 g (76%).

**Scheme 103: Synthesis of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxy carbonyl]-ethoxycarbonyl}-ethyl ester (134-3):**




**Step-1**: **Preparation of octadecanoic acid (*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl ester (134-1):** To a solution of octadecanoic acid **1-2** (23.4 g, 82.53 mmol) and (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (16.0 g, 63.49 mmol) in dichloromethane (160 mL) were added EDC·HCl (24.2 g, 126.90 mmol), 4-dimethylaminopyridine (770 mg, 6.34 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (500 mL), extracted with dichloromethane (500 X 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (2% ethyl acetate in hexane) to obtain product **134-1** as a pale yellow liquid 18 g (55%).

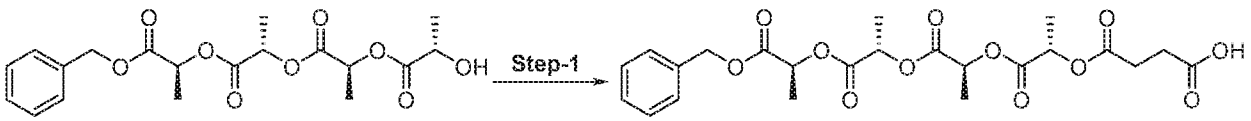
**Step-2**: **Preparation of octadecanoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (2-1):** To a 500 mL autoclave vessel were added a solution of octadecanoic acid (S)-1-((S)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethyl ester **134-1** (18 g, 34.74 mmol) in methanol (90 mL) and 10% Pd/C (3.6 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the

reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to obtain product **2-1** as a colorless low melting solid 12.5 g (84%).

**Step-3**: **Preparation of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (134-2):** To a solution of octadecanoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester **2-1** (10.2 g, 23.80 mmol) and (*S*)-2-hydroxy-propionic acid (*S*)-1-benzyloxycarbonyl-ethyl ester **127-1** (4.0 g, 15.87 mmol) in dichloromethane (40 mL) were added EDC·HCl (6.06 g, 31.74 mmol), hydroxybenzotriazole (428 mg, 3.17 mmol) and 4-dimethylaminopyridine (193 mg, 1.58 mmol) and at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (500 mL), extracted with dichloromethane (500 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (3% ethyl acetate in hexane) to obtain product **134-2**as a pale yellow liquid 6.1 g (58%).

**Step-4**: **Preparation of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxy carbonyl]-ethoxycarbonyl}-ethyl ester (134-3):** To a 250 mL autoclave vessel were added a solution of octadecanoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester **134-2** (6.1 g, 9.21 mmol) in methanol (40 mL) and 10% Pd/C (1.2 g, 50% wet) at 25-30 °C. The reaction mixture was stirred at room temperature under hydrogen pressure (5 kg/cm$^2$) over a period of 2 h. After completion of the reaction, the reaction mixture was filtered through a celite bed. The volatiles were evaporated under reduced pressure to obtain product **134-3** as a colorless low melting solid 4.5 g (85%).

**Scheme 104: Synthesis of succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (135-1):**

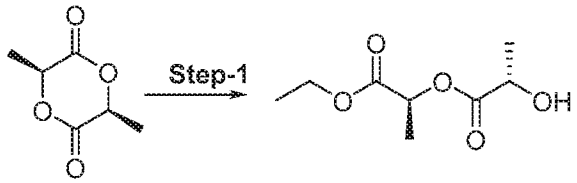



133-1 135-1

**Step-1: Preparation of succinic acid mono-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl) ester (135-1):** To a solution of succinic acid (2.8 g, 23.71 mmol) in dichloromethane (50 mL) were added EDC·HCl (6.79 g, 35.55 mmol), hydroxybenzotriazole (0.327 g, 2.37 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-

[(*S*)-1-((*S*)-1-benzyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **133-1** (4.7 g, 11.85 mmol) and 4-dimethylaminopyridine (144 mg, 1.18 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mixture was quenched with water (250 mL), extracted with dichloromethane (500 x 3 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (40% ethyl acetate in hexane) to obtain product **135-1** as a pale yellow liquid 3.1 g (53%).

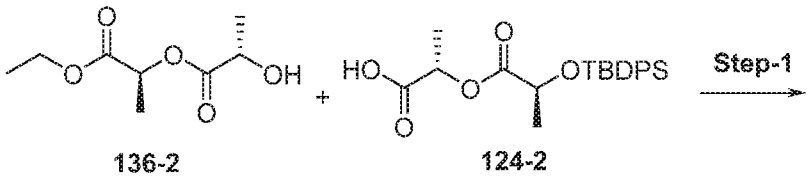
**Scheme 105: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-ethoxycarbonyl-ethyl ester (133-2):**



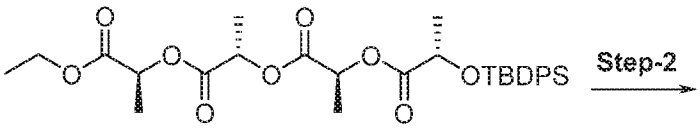

10-1 136-2

**Step-1: Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-ethoxycarbonyl-ethyl ester (136-2):** To a solution of (3*S*,6*S*)-3,6-dimethyl-[1,4]dioxane-2,5-dione **10-1** (5.0 g, 34.72 mmol) in toluene (100 mL) was added ethanol (1.92 mL, 31.98 mmol) and camphor sulfonic acid (0.8 g, 3.47 mmol) at 25-30 °C. The reaction mixture was allowed to stir at 80 °C over a period of 2 h. The resulting reaction mixture was diluted with ethyl acetate (800 mL) and washed with water (2 x 200 mL). The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (13% ethyl acetate in hexane) to obtain product **136-2** as a colorless liquid 6.6 g (60%).

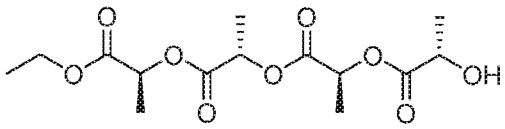
**Scheme 106: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (137-2):**




136-2 124-2




137-1



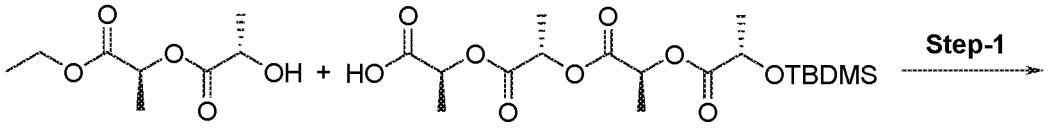

137-2

**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (137-1):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-carboxy-ethyl ester **124-2** (5.4 g, 13.68 mmol) in dichloromethane (60 mL) was that added EDC·HCl (3.0 g, 15.78 mmol), (*S*)-2-Hydroxy-propionic acid (S)-1-ethoxycarbonyl-ethyl ester (2.0 g, 10.52 mmol) and 4-dimethylaminopyridine (0.12 g, 1.05 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (250 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (3% ethyl acetate in hexane) to obtain product **137-1** as a colorless liquid 4.2 g (70%).

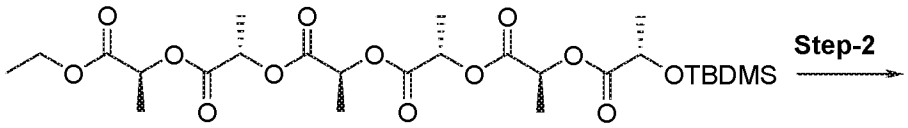
**Step-2**: **Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester (137-2):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **137-1** (4 g, 6.99 mmol) in tetrahydrofuran (40 mL) was added tetra butyl ammonium fluoride (10.49 mL, 1.0M, 10.49 mmol) and acetic acid (0.63 g, 10.49 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column

chromatography (12% ethyl acetate in hexane) to give product **137-2** as a colorless liquid 1.0 g (43%).

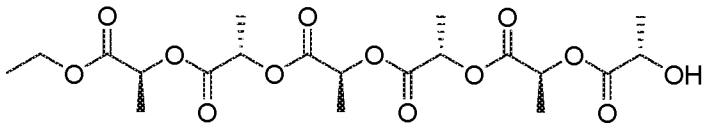
**Scheme 107: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (138-2):**




136-2 129-2




138-1

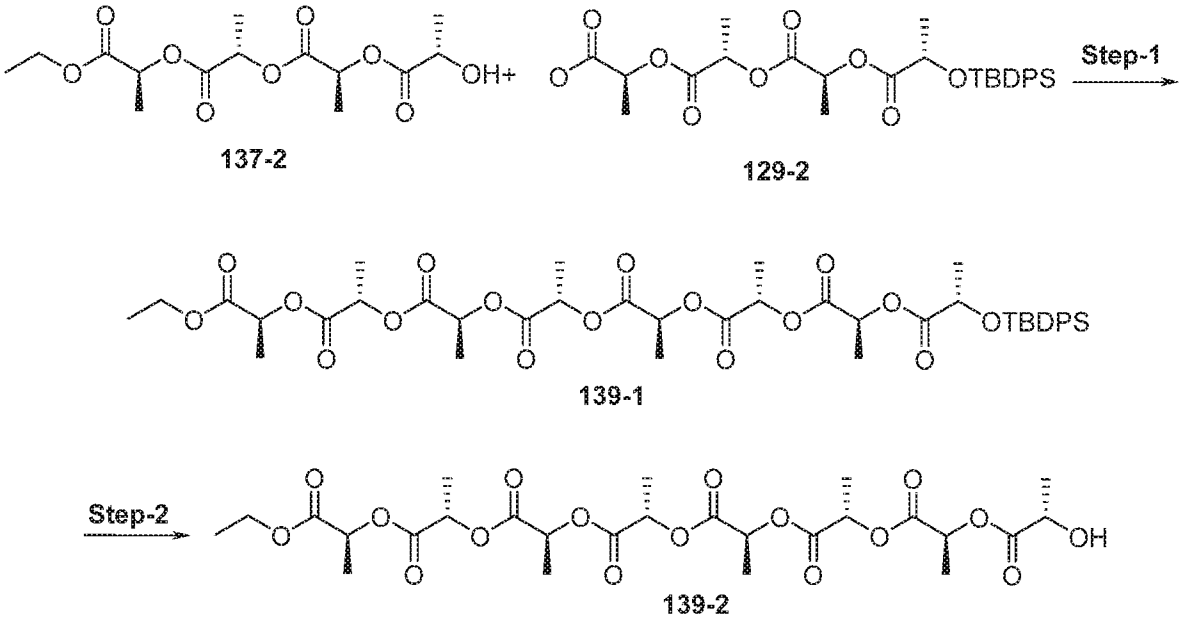



138-2

**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (138-1):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **129-2** (7.44 g, 13.68 mmol) in dichloromethane (20 mL) was added EDC·HCl (2.411 g, 12.62 mmol), (S)-2-Hydroxy-propionic acid (S)-1-ethoxycarbonyl-ethyl ester (2 g, 10.52 mmol) **136-2** and 4-dimethylaminopyridine (128 mg, 1.05 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (200 mL), extracted with dichloromethane (250 x 2 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (5% ethyl acetate in hexane) to obtain product **138-1** as a colorless liquid 6.0 g (79%).

**Step-2 Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester (15-2):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethyl ester **138-1** (7 g, 9.78 mmol) in tetrahydrofuran (70 mL) were added tetra butyl ammonium fluoride (14.64 mL, 1.0M, 14.66 mmol) and acetic acid (0.88 g, 14.66 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (14% ethyl acetate in hexane) to give product **138-2** as a colorless liquid 3.0 g (64%).

**Scheme 108: Synthesis of (*S*)-2-Hydroxy-propionic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (139-2):**

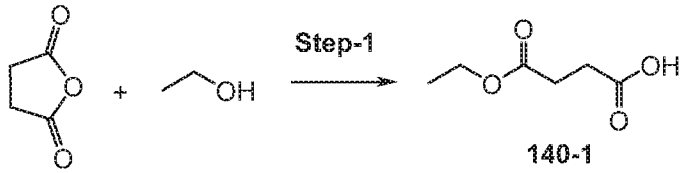



**Step-1: Preparation of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (139-1):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **129-2** (17.78 g, 32.69 mmol) in dichloromethane (84

mL) were added EDC·HCl (7.2 g, 37.72 mmol), (*S*)-2-Hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethyl ester **137-2** (8.4 g, 25.15 mmol) and 4-dimethylaminopyridine (0.30 g, 2.51 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 1 h. The resulting reaction mass was quenched with water (500 mL), extracted with dichloromethane (250 x 4 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (8% ethyl acetate in hexane) to obtain product **139-1** as a colorless liquid 10.0 g (47.6%).

**Step-2**: **Preparation of (*S*)-2-Hydroxy-propionic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (139-2):** To a solution of (*S*)-2-(*tert*-Butyl-diphenyl-silanyloxy)-propionic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-ethoxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester **139-1** (10.0 g, 11.63 mmol) in tetrahydrofuran (100 mL) were added tetra butyl ammonium fluoride (17.44 mL, 1.0M, 17.44 mmol) and acetic acid (0.88 g, 17.44 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (14% ethyl acetate in hexane) to give product **139-2** as a colorless liquid 4.5 g (62%).

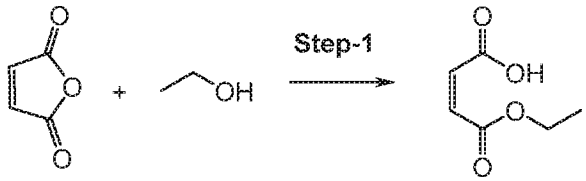
**Scheme 109: Synthesis of Succinic acid monoethyl ester (140-1):**




140-1

**Step-1: Preparation of Succinic acid monoethyl ester (140-1):** A solution of dihydro-furan-2,5-dione (20 g, 20 mmol) in ethanol (100 mL) was allowed to stir at 80 °C over a period of 16 h. The resulting reaction mixture was directly concentrated under reduced pressure. The residue was diluted with DCM (600 mL) and washed with saturated sodium bicarbonate solution (300 mL). The aqueous layer was separated from organic, acidified with 1.5N HCl (pH = 2) and extracted with DCM (300 x 2 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain product **140-1** as a colorless liquid 11.5 g (39.3%).

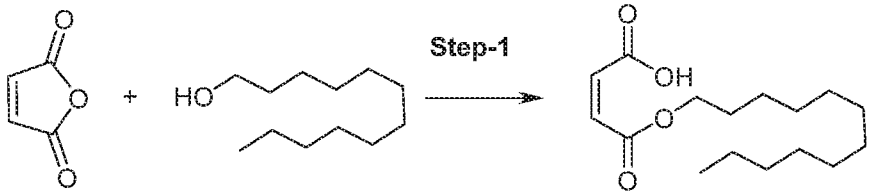
**Scheme 110: Synthesis of (*Z*)-But-2-enedioic acid monoethyl ester (141-1):**




141-1

**Step-1: Preparation of (*Z*)-But-2-enedioic acid monoethyl ester (141-1):** A solution of furan-2,5-dione (5 g, 51.02 mmol) in ethanol (50 mL) was allowed to stir at 100 °C over a period of 16 h. The resulting reaction mixture was directly concentrated under reduced pressure. Then residue was diluted with DCM (450 mL) and washed with saturated sodium bicarbonate solution (200 mL). The aqueous layer was separated from organic, acidified with 1.5N HCl (pH =2) and extracted with DCM (150 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain product **141-1** as a colorless liquid 3.3 g (45.2%).

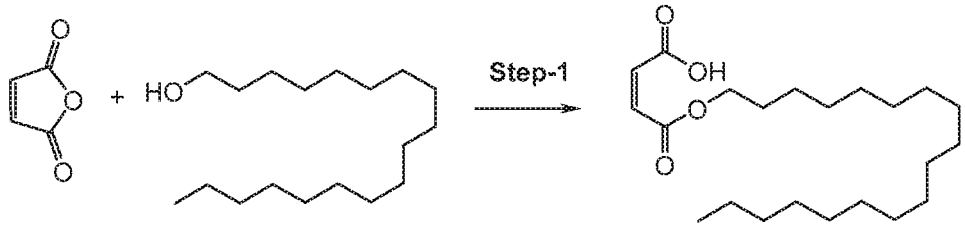
**Scheme 103: Synthesis of (*Z*)-But-2-enedioic acid monododecyl ester (142-1):**




142-1

**Step-1: Preparation of (*Z*)-But-2-enedioic acid monododecyl ester (142-1):** To a solution of dodecan-1-ol (1.0 g, 5.37 mmol) in toluene (10 mL) was added furan-2,5-dione (0.526 g, 5.37 mmol) at 25-30 °C. The resulting mixture was allowed to stir at 100 °C over a period of 16 h. The reaction mixture was diluted with ethyl acetate (300 mL) and basified (pH = 10) with sodium hydroxide solution (100 mL). The aqueous layer was separated from organic, acidified with 1.5N HCl (pH = 2), extracted with ethyl acetate (100 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to obtain product **142-1** as a white solid 1.1 g (73%).

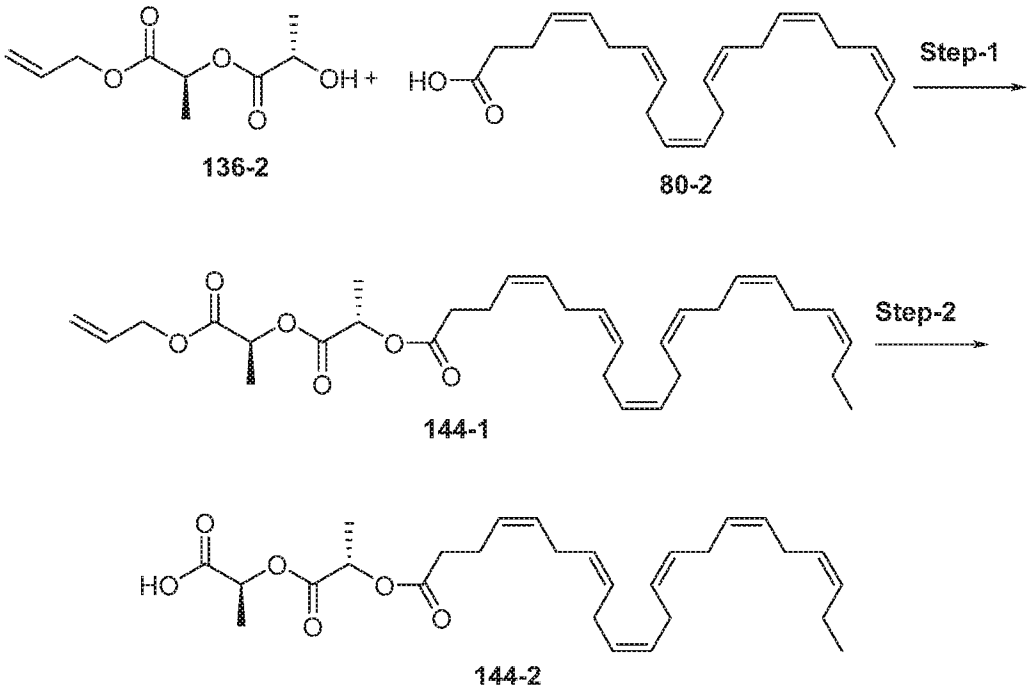
**Scheme 111: Synthesis of (*Z*)-But-2-enedioic acid monooctadecyl ester (143-1):**




143-1

**Step-1**: **Preparation of (*Z*)-But-2-enedioic acid monooctadecyl ester (143-1):** To a solution of octadecan-1-ol (1.0 g, 3.70 mmol) in toluene (10 mL) was added furan-2,5-dione (0.362 g, 3.70 mmol) at 25-30 °C. The resulting mixture was allowed to stir at 100 °C over a period of 16 h. The reaction mixture was diluted with ethyl acetate (300 mL) and basified (pH = 10) with sodium hydroxide solution (100 mL). That aqueous layer was separated from organic, acidified with 1.5N HCl (pH = 2), extracted with ethyl acetate (100 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure to obtained product **143-1** as a white solid 0.8 g (58.8%).

**Scheme 112: Synthesis of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (144-2):**




136-2

80-2

144-1

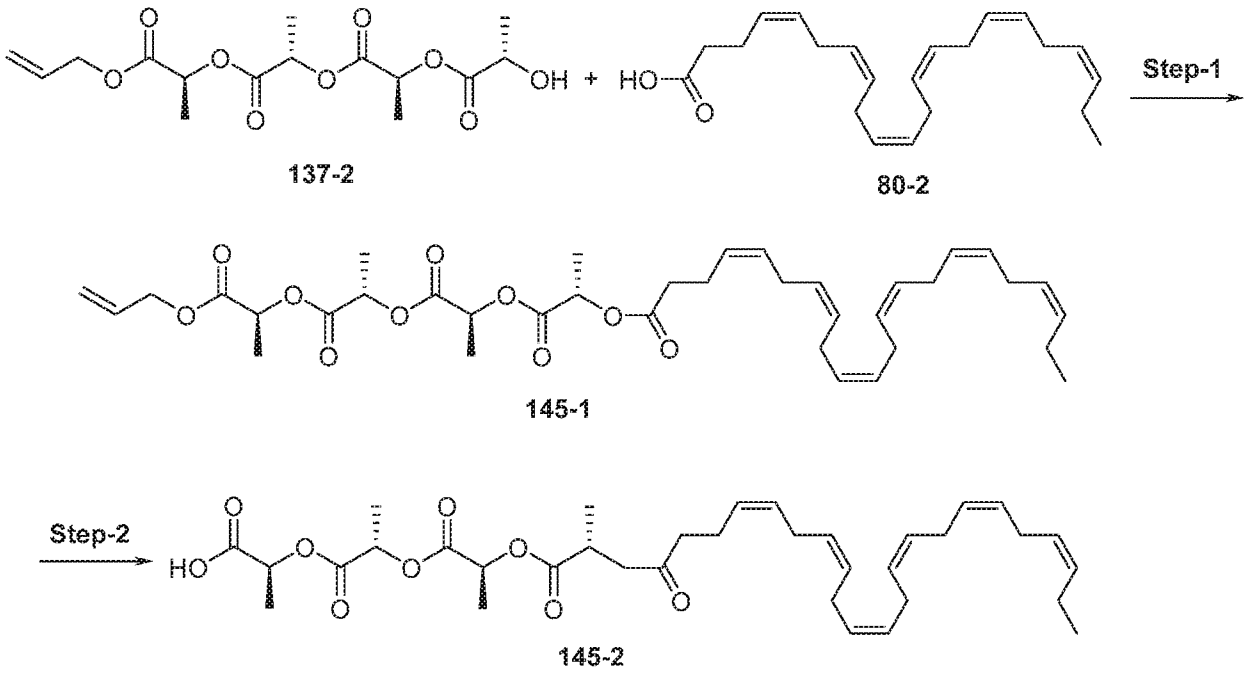
144-2

**Step-1: Preparation of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl ester (144-1):** To a solution of (4Z,7Z,10Z,13Z,16Z,19Z)-Docosa-4,7,10,13,16,19-hexaenoic acid **80-2** (3.11 g, 9.47 mmol) in dichloromethane (15 mL) were added EDC·HCl (2.26 g, 11.83 mmol), (*S*)-2-Hydroxy-propionic

acid (*S*)-1-allyloxycarbonyl-ethyl ester **(13-1)** (1.5 g, 7.89 mmol) and 4-dimethylaminopyridine (96 mg, 0.79 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (250 x 2 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (4% ethyl acetate in hexane) to obtain product **144-1** as a brown liquid 1.5 g (37%).

**Step-2: Preparation of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethyl ester (144-2):** To a solution of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethyl ester **80-2** (1.5 g, 2.92 mmol) in tetrahydrofuran (15 mL) were added palladium tetrakis (0.338 g, 0.29 mmol) and pyrrolidine (0.19 g, 2.77 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure and crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (2% methanol in dichloromethane) to give **144-2** as a brown wax 0.5 g (36%).

**Scheme 113: Synthesis of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (145-2):**



**Step-1: Preparation (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (145-1):** To a solution of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid **80-2** (1.14 g, 3.7 mmol) in dichloromethane (10 mL) were added DCC (0.893 g, 4.33 mmol), (*S*)-2-hydroxy-propionic acid (*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxy carbonyl]-ethyl ester **137-2** (1.0 g, 2.89 mmol) and 4-dimethylaminopyridine (35 mg, 0.29 mmol) at 0 °C. The reaction mixture was allowed to stir at 25-30 °C over a period of 2 h. The resulting reaction mass was quenched with water (100 mL), extracted with dichloromethane (100 x 3 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product obtained upon evaporation of volatiles was purified through silica gel (230-400 mesh) column chromatography (5% ethyl acetate in hexane) to obtain product **145-1** as a brown liquid 0.9 g (47.6%).

**Step-2: Preparation of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-carboxy-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester (145-2):** To a solution of (4*Z*,7*Z*,10*Z*,13*Z*,16*Z*,19*Z*)-Docosa-4,7,10,13,16,19-hexaenoic acid (*S*)-1-{(*S*)-1-[(*S*)-1-((*S*)-1-allyloxycarbonyl-ethoxycarbonyl)-ethoxycarbonyl]-ethoxycarbonyl}-ethyl ester **145-1** (0.9 g, 1.37 mmol) in tetrahydrofuran (9 mL) were added palladium tetrakis (0.162 g, 0.14 mmol) and pyrrolidine (0.09 g, 1.3 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature over a period of 1 h. The resulting reaction mixture was concentrated under reduced pressure. The crude product obtained upon evaporation of the volatiles was purified through silica gel (230-400 mesh) column chromatography (2% MeOH in DCM) to give product **145-2** as a brown wax 0.4 g (46%).

## Example 6. Analytical Method Development for Select Compounds

### *Analytical Method Development for Timolol Prodrugs*

*Determination of Maximal Absorptive Wavelength*

Timolol maleate (**35-1**) and prodrugs of Timolol were dissolved in DMSO at a concentration of 100 µg/mL. The samples were scanned at a wavelength range of 200-800 nm using a Genesys 105 UV-VIS spectrophotometer (Thermo Scientific). Maximum absorption wavelength was 298 nm.

*HPLC Method for Timolol and PLA-conjugated Timolol*

Chromatographic separation of native Timolol and its PLA conjugated derivatives was achieved using an Agilent 1260 Infinity HPLC equipped with a diode array and a multiple wavelength

detector with an XTERRA C8 column (5µm, 4.6mm x 150mm) as the stationary phase. The gradient separation method is outlined in Table 1A. The analysis was performed at an injection volume of 40 µL, a flow rate of 0.8 mL/min and a detection wavelength of 298 nm at 25 °C. Retention times for Timolol and PLA-conjugated compounds are illustrated in Table 1B.

**Table 1A. HPLC Gradient Method for Separation of Timolol Derivatives**

| Time (min) | A (water + 0.1% FA) | B (MeCN+0.1% FA) |
|---|---|---|
| 0 | 95 | 5 |
| 4 | 5 | 95 |
| 5 | 5 | 95 |
| 5.5 | 95 | 5 |
| 9 | 95 | 5 |

**Table 1B. Relative Retention Times of Timolol and Derivatives**

| PLA Repeat Units | Timolol RRT (min) |
|---|---|
| Parent | 4.27 |
| Acetyl, n=1 | 4.64 |
| Acetyl, n=4 | 4.83 |
| Stearyl, n=1 | 5.78 |
| Stearyl, n=4 | 5.94 |
| Stearyl, n=6 | 6.27 |

n = the number of LA repeat units conjugated to the parent compound.

***Analytical Method Development for ROCK Inhibitor Prodrugs***

Chromatographic separation of SR5834 and RKI-H-1y and their prodrugs was achieved using an Agilent 1260 Infinity HPLC with an XTERRA C8 column (5µm, 4.6mm x 150mm) as the stationary phase and a gradient method utilizing acetonitrile and water as the mobile phase. The gradient separation method is outlined in **Table 2**. The analysis was performed at an injection volume of 10 µL, a flow rate of 0.8 mL/min and a detection wavelength of 270 nm at 25 °C.

**Table 2. HPLC Gradient Method for separation of Rock Inhibitor Prodrugs**

| Time (min) | A (water + 0.1% FA) | B (MeCN+0.1% FA) |
|---|---|---|
| 0 | 95 | 5 |
| 4 | 20 | 80 |
| 5 | 5 | 95 |
| 5.5 | 95 | 5 |

7 95 5

**Example 7. Determination of Drug Solubility**

For each test, approximately 5-10 mg was transferred to a 10 mL glass vial. Aqueous or organic solvent was added to each vial to achieve an overall concentration of 50 mg/mL. After vortexing aggressively for 2-3 minutes and sonicating in a bath sonicator for 5 minutes, undissolved drug was spun down at 1200 rpm for 5 minutes to generate a pellet. The supernatant was collected and filtered through a 0.2 μm nylon syringe filter into HPLC vials for drug content analysis. Drug concentration was determined by comparing against a standard calibration curve.

Drug solubility in aqueous and organic solvent can inform on the potential for said drug to be encapsulated within microparticles and its release kinetics once it has been encapsulated. Herein, drug solubility was evaluated to better predict and select compounds that may be amenable to particle encapsulation. The solubility of PLA-Brinzolamide monoprodrugs, PLA-Dorzolamide monoprodrugs, Tris-PLA Latanoprost prodrugs, Sunitinib-related prodrugs, Brimonidine monoprodrugs, Timolol monoprodrugs, and bisprodrugs are shown in **Table 3A** and **Table 3B**.

All prodrugs of Brimonidine, rock inhibitors, and bifunctional conjugates of Sunitinib exhibited low aqueous solubility and high organic solubility (less than 1 mg/mL in aqueous solution and greater than 50 mg/mL in DMSO), respectively.

Solubility of Timolol prodrugs was controlled by a number of parameters including the linker, the terminal end-group, the number of PLA repeat units, and the salt form. Increasing PLA repeat units enhanced hydrophobicity of the compound, resulting in a decrease in the aqueous solubility. The aqueous solubility of Timolol-stearyl PLA(n=4) (**41-2**) decreased from greater than 50 mg/mL to 6.25 when the PLA repeat units was increased from n=4 (compound **41-2**) to n=6, (compound **43-1**) respectively. In general, HCL salts of the Timolol-prodrugs was more water soluble than the maleate salt forms.

**Table 3A. Solubility of Mono-prodrugs and Bifunctional Prodrugs**

| | | Solubility | | |
|---|---|---|---|---|
| | Compound Name | Water | DMSO | DCM |
| Brinzolamide Parent | Brinzolamide | <1.0 | >50 | <7.5 |
| | Brinzolamide-PLA (n=5) **(18-3)** | <25 | >50 | >50 |
| | Brinzolamide-PLA (n=10) **(19-3)** | <1.0 | >50 | >50 |

| | | | | |
|---|---|---|---|---|
| | Brinzolamide-PLA (n=12) **(20-2)** | <1.0 | >50 | >50 |
| | Brinzolamide-Stearyl PLA (n=4) **(15-2)** | <1.0 | >50 | - |
| | Brinzolamide-Stearyl PLA (n=6) | <0.1 | >50 | - |
| | Brinzolamide-Stearyl PLA (n=8) | <0.1 | >50 | - |
| | Brinzolamide-Stearyl PLA (n=12) **(16-1)** | <0.1 | >50 | - |
| | Brinzolamide-Stearyl PLA (n=14) **(17-1)** | <0.1 | >50 | - |
| Dorzolamide Parent | Dorzolamide | >50 | <1.0 | <1.0 |
| PLA-Dorzolamide Mono Prodrugs | Dorzolamide-PLA (n=1) | >50 | <1.0 | - |
| | Dorzolamide-Stearyl PLA(n=4) **(12-3)** | <0.1 | >50 | >50 |
| | Dorzolamide-Stearyl PLA(n=6) | <0.1 | >50 | >50 |
| | Dorzolamide-Stearyl PLA(n=8) | <0.1 | >50 | >50 |
| | Dorzolamide-Stearyl PLA(n=12) **(13-2)** | <1.0 | >50 | >50 |
| | Dorzolamide-Stearyl PLA(n=14) **(14-2)** | <1.0 | >50 | >50 |
| Latanoprost Parent | Latanoprost | <1.0 | >50 | >50 |
| Tris-PLA Latanoprost Prodrugs | Latanoprost-Acetyl PLA (n=6) | <1.0 | <50 | - |
| Sunitinib Related Prodrugs | 5-Amino Sunitinib | <1.0 | >50 | - |
| | Acetyl PLA(n=2)-5-hydroxy Sunitinib | >50 | >50 | - |
| | Acetyl PLA(n=3)-5-hydroxy Sunitinib | >50 | >50 | - |
| | Acetyl PLA(n=4)-5-hydroxy Sunitinib | >50 | >50 | - |
| | Acetyl PLA(n=5)-5-hydroxy Sunitinib | >10 | >50 | - |
| | 5-hydroxy Sunitinib-PLA(n=3)-Etacrynic acid | <1.0 | >50 | - |
| Brimonidine Mono Prodrugs | Brimonidine-PLA(n=2)-Acetate **(25-2)** | <1.0 | >50 | - |
| | Brimonidine-PLA(n=3)-Acetate **(26-2)** | <1.0 | >50 | - |
| | Brimonidine-PLA(n=4)-Acetate **(27-2)** | <1.0 | >50 | - |
| | Brimonidine-PLA(n=3)-Stearate **(28-2)** | <1.0 | >50 | - |
| | Brimonidine-PLA(n=4)-Stearate **(29-2)** | <1.0 | >50 | - |
| | Brimonidine-Acetyl PLA(n=8) **(109-1)** | <0.1 | >50 | - |
| | Brimonidine-Bis-Acetyl PLA(n=2) **(111-4)** | <1.0 | >50 | - |
| | Brimonidine-Acetyl PLA(n=2)-N-acetate **(114-4)** | 1.0 | 100 | - |
| | Brimonidine-Acetyl PLA(n=4)-N-acetate **(115-1)** | <0.2 | 100 | - |
| | Brimonidine-Bis-Acetyl PLA (n=4) **(116-1)** | <0.003 | 100 | - |
| Timolol Mono Prodrugs | Timolol-O-Acetate Maleate **(35-4)** | <1.0 | >50 | - |
| | Timolol-O-Boc **(36-2)** | <1.0 | >50 | - |
| | Timolol-O-Boc-N-Acetate **(37-2)** | <1.0 | >50 | - |
| | Timolol-Acetyl PLA(n=1) Maleate **(44-2)** | <1.0 | >50 | - |
| | Timolol-Stearyl PLA(n=1) Maleate **(38-2)** | <1.0 | >50 | - |
| | Timolol-Stearyl PLA(n=1) HCL **(39-1)** | <25 | >50 | - |
| | Timolol-Acetyl PLA(n=4) Maleate **(45-2)** | <1.0 | >50 | - |
| | Timolol-Stearyl PLA(n=4) Maleate **(40-2)** | <1.0 | >50 | - |
| | Timolol-Stearyl (n=4) HCL **(41-2)** | >50 | >50 | - |

| | | | | |
|---|---|---|---|---|
| | Timolol-Stearyl (n=6) Maleate **(42-2)** | <1.0 | >50 | - |
| | Timolol-Stearyl (n=6) HCL **(43-1)** | 6.25 | >50 | - |

**Table 3B. Solubility Data of Additional Mono-prodrugs and Bifunctional Prodrugs**

| | | Solubility | | |
|---|---|---|---|---|
| | Compound Name | Water | DMSO | DCM |
| Brinzolamide Parent | Brinzolamide | <1.0 | >50 | <7.5 |
| PLA-Brinzolamide Prodrugs | Brinzolamide (n=1) | >50 | >50 | >50 |
| Dorzolamide Parent | Dorzolamide | >50 | <1.0 | <1.0 |
| PLA-Dorzolamide Prodrugs | Dorzolamide-PLA (n=5) | <1.0 | >50 | >50 |
| | Dorzolamide-PLA(n=10) | <0.1 | >50 | >50 |
| | Dorzolamide-PLA(n=12) | <0.1 | >50 | >50 |
| | Dorzolamide-PLA(n=14) | <0.1 | >50 | >50 |
| | Dorzolamide-DHA **(80-3)** | <1.0 | >100 | >50 |
| Timolol Mono Prodrugs | Timolol-DHA Maleate **(53-3)** | <1.0 | >100 | - |
| | *N*-Acyl-Timolol-PLA (n=1) Stearate **(65-1)** | <1.0 | >100 | - |
| | *N*-Acyl-Timolol-PLA (n=2) Stearate **(66-1)** | <1.0 | >100 | - |
| | *N*-Acyl-Timolol-PLA (n=4) Stearate **(67-1)** | <1.0 | 70 | - |
| | *N*-Acyl-Timolol-DHA **(68-1)** | <1.0 | >100 | - |
| | *N*-Acyl-Timolol-PLA (n=2) DHA | <1.0 | >100 | |
| | *N*-Acyl-Timolol-PLA (n=4) DHA | <1.0 | >50 | |
| | *N*-Acyl-Timolol-PLA (n=4) **(69-1)** | <6.3 | >100 | |
| | Timolol-O-Linoleic Acid-Maleate **(70-1)** | <0.01 | >50 | - |
| | Timolol-O-Linoleic Acid-HCl **(71-1)** | >25 | >50 | - |
| | Timolol-Bis-Acetyl-PLA (n=2) **(118-1)** | <0.1 | >50 | - |
| | Timolol-Bis-Acetyl-PLA (n=4) **(119-1)** | <0.00005 | >50 | - |
| | Timolol-Bis-N-Acetyl-PLA (n=4)-O-Ethyl-succinate **(120-1)** | <1.0 | >50 | - |
| | Timolol-Bis-N-Acetyl-PLA (n=4)-O-Acetyl PLA (n=2) **(229)** | <0.006 | >50 | - |
| | Timolol-Bis-N-Acetyl-PLA (n=2)-O-Acetyl PLA (n=4) **(230)** | <0.007 | >50 | - |
| Timolol Bis Prodrugs | Timolol-Sebacic Acid-Timolol Maleate **(75-1)** | <1.0 | >100 | |
| | Timolol-Succinic Acid-Timolol Maleate **(76-4)** | >6.25 | >100 | |
| | Timolol-Glutaric Acid-Timolol Maleate **(77-1)** | <1.0 | >100 | |
| | Timolol-Fumurate-Timolol Maleate **(78-1)** | <1.0 | >100 | |
| | Timolol-Bis-N-Acetyl-PLA (n=2)-O-Ethyl-succinate **(117-6)** | <1.0 | >50 | - |
| Rock Inhibitor Mono Prodrugs | RKI-1y | <1.0 | >100 | - |
| | RKI-H-1y | <1.0 | >100 | - |
| | SR5834 | <1.0 | >100 | - |

| | | | |
|---|---|---|---|
| SR5834-Acetyl PLA(n=4) (**88-3**) | <0.001 | >50 | - |
| SR5834-Bis-Acetyl PLA(n=4) (**113-1**) | <1.0 | 50 | - |
| RKI-H-ly-Acetyl PLA (n=4) (**90-3**) | <0.3 | >100 | - |

**Example 8.** ***In vitro*** **Stability of Prodrugs**

Prodrugs of interest were dissolved in PBS (pH 7) containing 10 % DMSO (v/v) at a concentration of 0.1 mg/mL. The samples were incubated at 37 °C or 50 °C to simulate physiological and accelerated degradation conditions, respectively. At various time points, 500 µL of the solution was collected, filtered through a 0.2 µm nylon syringe filter and analyzed by RP-HPLC.

***In vitro Stability of Timolol NCEs***

The degradation kinetics of Timolol maleate (**Figure 1**) and prodrugs of Timolol (**Figure 2, Figure 3, Figure 4, Figure 5, and Figure 6**) was evaluated. Rapid degradation to the parent compound was observed for Timolol prodrugs with O-PLA(n)-O-Acetyl functionalization in a 1% Tween/PBS buffer solution at 37 °C (**Figure 2, Figure 3**). Within less than one hour, 100% conversion to the parent compound was observed. In addition, esters with alkoxy substitutes in the alpha position were more labile than alkyl acids. In comparison, O-PLA(n)-O-stearyl prodrugs of Timolol (**Figure 1**, **Figure 6**) were significantly more stable than their acetylated forms, with 100% conversion to the parent compound within 24 hours after incubation. Timolol prodrugs with O-Boc-N-Acetyl functionalization were very stable and resistant to hydrolysis with greater than 75% of the prodrug remaining in solution after 1 week of incubation (**Figure 7**). In addition, the rate of hydrolysis was independent of salt form (**Figure 3** vs. **Figure 4**).

The degradation kinetics of N-acyl Timolol prodrugs was evaluated. Linoleic acid prodrug of Timolol (**70-1**) degraded steadily over the 4-day period, releasing parent Timolol in a linear rate (**Figure 8**). As shown in **Figure 9**, acyl-Timolol-PLA (n=2) stearate (**65-1**) was resistant to hydrolysis and failed to release the parent over the course of the study. Without wishing to be bound by any one therory, the long stearate chain serves to protect the prodrug from degradation. In contrast, *N*-Acyl-Timolol-PLA(n=2)-DHA (**102-1**) (**Figure 10**) exhibited steady generation of intermediate degradants and slow hydrolysis to the parent compound. A similar trend was observed for *N*-acyl-Timolol-PLA(n=2) (**48-1**) (**Figure 11**). Timolol-bis-N-acetyl PLA(n=2) (**118-1**) (**Figure 12**) degraded slightly faster than a Timolol-bis-N-acetyl PLA(n=4) (**119-6**) (**Figure 13**)

as the number of intermediate processes leading to the release of free Timolol is less. In contrast Timolol-bis-N-acetyl-PLA(n=4)-O-ethyl-succinate (**120-1**) (**Figure 14**) degraded to free Timolol incompletely by day 13. Timolol-bis-N-acetyl-PLA(n=2)-O-ethyl-succinate (**117-6**) (**Figure 15**) degraded to free Timolol faster, yet by day 13 only approximately 50% of the polymer was hydrolyzed to release free Timolol. Bis prodrugs of Timolol wherein the -N and -O functional groups were modified with PLA polymers exhibited rapid hydrolysis of the polymer generating intermediates and releasing free Timolol in a linear rate (**Figure 16 and Figure 17**).

***In vitro Stability of Dorzolamide NCEs***

Stearyl capped prodrugs were more stable and less prone to ester hydrolysis than acetylated prodrugs (**Figure 18A, Figure 18B, and Figure 18C**) and LA units were hydrolyzed in pairs (**Figure 19A, Figure 19B,** and **Figure 20**).

***In vitro stability of prodrugs of Brimonidine NCEs***

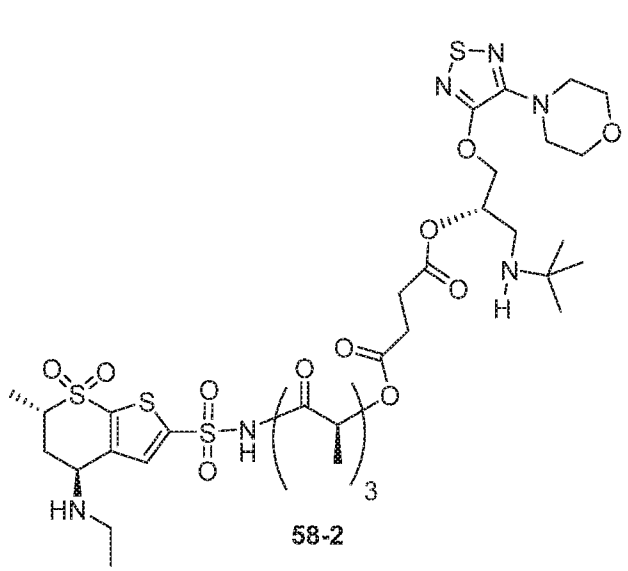
Prodrugs of Brimonidine rapidly hydrolyze to release the parent compound in aqueous solution under physiological conditions. All compounds tested exhibit rapid degradation to the parent compound at one day followed by a more prolonged phase of hydrolysis to the parent (**Figure 21, Figure 22, Figure 23, Figure 24,** and **Figure 25**). The rate of degradation back to the parent decreased with increasing number of lactide units on the polymer linker. In addition, the kinetics of degradation to the parent compound was slowed further by the conjugation of Bis-PLA (**Figure 26**).

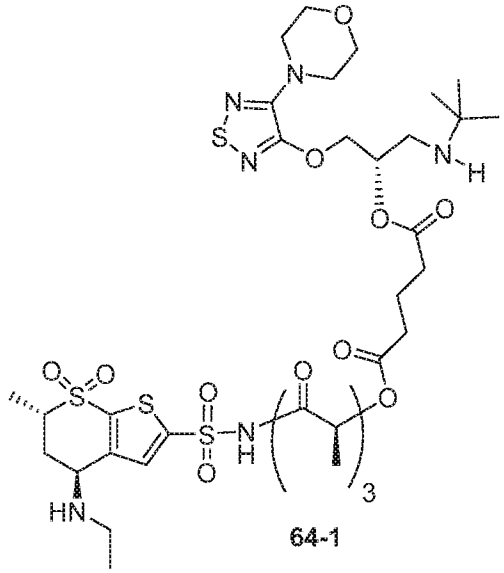
***In vitro stability of prodrugs of Rock Inhibitors***

Evaluation of the stability and kinetics of degradation of the prodrug revealed rapid hydrolysis of the polymer and degradation to the parent drug for all prodrugs of rock inhibitors tested (**Figure 27, Figure 28, and Figure 29**). The bis-modified prodrug (**Figure 28**) exhibited comparably rapid degradation of the primary prodrug; however, the rate of generation of the parent was half of that observed in prodrugs modified at one functional site.

***In vitro Stability of Timolol-Dorzolamide bi-functional prodrugs***

Timolol-succinate-$(PLA)_3$-Dorzolamide (**58-2**) was prepared as shown in Scheme 58 and Timolol-glutarate-$(PLA)_3$-Dorzolamide (**64-4**) was prepared as shown in Scheme 64.




Timolol-Dorzolamide bi-functional prodrugs were dissolved in a mixture of DMSO and PBS and incubated at 37 °C. The solution was aliquoted and analyzed by HPLC at pre-determined time points. Timolol-Dorzolamide bi-functional prodrugs were stable for about 3 hours as evidenced by the significant reduction of prodrug peaks in HPLC after 2-3 hours (**Figure 30A** and **Figure 30B**). Timolol parent drug was detected as the bi-functional prodrug degraded, whereas Dorzolamide appeared in the form of prodrugs, i.e., Dorzolamide linked with 1-3 PLA units.

**Example 9. Encapsulation of conjugates in polymer microparticles**

**Materials**

poly(D,L-lactic-co-glycolic acid (PLGA, 75:25 lactic acid to glycolic acid ratio, 4A, Evonik)

poly(D,L-lactic-co-glycolic acid (PLGA, 50:50 lactic acid to glycolic acid ratio)-poly(ethylene glycol)5000

poly(D,L-lactide, 4A, Evonik)

poly vinyl alcohol (Mr ~25K, 88% hydrolyzed, Polysciences)

D-α-tocopherol poly(ethylene glycol)$_{1000}$ succinate (Sigma Aldrich)

Phosphate-buffered saline (pH 7.4)

Ultrapure cell culture grade water

All other chemicals were A.C.S. reagent grade (VWR)

***Microparticle preparation***

Microparticles containing prodrugs of Brinzolamide, Dorzolamide, Timolol, Latanoprost or bimatoprost were formulated using an oil-in-water solvent evaporation microencapsulation method. The polymer was initially dissolved in a water immiscible organic solvent to which dissolved drug was added. Briefly, PLGA (LA:GA=75:25, 4A) or PLA (140-200 mg/mL) and $PLGA_{50/50}$-$PEG_{5k}$ (1.4-2 mg/mL) was dissolved in 2 mL of methylene chloride. The prodrug (13.8-50% theoretical loading) was dissolved in 1 mL of DMSO or ethyl acetate after vigorous vortexing and ultrasonication in a bath sonicator and added to the polymer solution. The aqueous phase consisted of 200 mL of PBS or water with 1 % PVA or D-α-tocopherol poly(ethylene glycol)$_{1000}$ succinate as a surfactant to stabilize the emulsification. The aqueous phase was mixed at 5000 rpms using a Silverson L5A-M benchtop mixer. The dispersed phase was rapidly added to the aqueous phase and allowed to mix at 5000 rpms for 1 minute to generate an oil-in-water emulsion and disperse the materials as droplets. The organic solution was allowed to evaporate under constant stirring at 500 rpms for 2 hours under ambient temperatures or at 4° C in an ice bath. The particle suspension was allowed to settle for 30 min, after which the solution was decanted and remaining particles were collected, suspended in distilled deionized water, and washed 3 times using water via centrifugation at 1000 rpms for 5 minutes to remove any residual solvent. The pellet was collected and lyophilized overnight.

***Particle Size***

Particle size and size distribution was determined using a Beckman Coulter Multsizer IV with a 100 μm diameter aperture based on a sample size of at least 50,000 counts. Particle size was expressed as volume-weighted mean diameters. Briefly, 2-5 mg of particles were suspended in 1 mL of double distilled water and added to a beaker containing 100 mL of ISOTON II solution. Measurements were obtained once the coincidence of particles reached 6-10 %. **Table 5 and Table 8** outlines the size and size distribution of the microparticles generated for each test compound. Particle size can vary depending upon a number of variables including polymer concentration, mixing-speed, mixing-time, dispersed/aqueous phase ratio, etc. Particles were formulated with volume-weighted mean diameters ranging from approximately 19 μm to 34 μm depending on the formulation parameters.

***Drug Loading***

To determine the % drug loading (DL), 10 mg of particles was weighed into a glass scintillation vial and dissolved with 10 mL of MeCN:water(1:1, v/v). The solution was filtered

through a 0.2 μm nylon syringe filter and the drug content was determined by RP-HPLC referenced against a standard calibration curve. The drug loading results are presented in Table 5 and **Table 8**. All particles generated at ambient temperature with 1 % PVA in the aqueous phase exhibited low drug loading regardless of the encapsulated drug (<1.0 % DL), but results in Table 8 suggest that loading is influenced by the presence of the functional group on the terminal lactate. Loading of acetylated test compounds was approximately 5-fold higher than those with uncapped hydroxyl on the terminal lactate units (0.14 vs. 1.00 and 0.22 vs. 0.98 %, respectively for Brinzolamide and Dorzolamide).

Loading was also dependent on the rate of solidification of the particles and the surfactant used in the emulsification process. Preparing particles at 4 °C and with D-α-tocopherol poly(ethylene glycol)$_{1000}$ succinate to stabilize the emulsification resulted in significant enhancement in drug loading. For example, % DL of Brinzolamide-acetyl PLA (n=5) (**18-3**) was 0.73 % when particles were formulated at room temperature using 1 % PVA as the surfactant compared to 7.39 % when particles were formulated at 4 °C using D-α-tocopherol poly(ethylene glycol)$_{1000}$ succinate as the surfactant. In addition, increasing polymer concentration also resulted in an increase in %DL. Brinzolamide-acetyl PLA (n=5) (38-1) content increased from 7.39% to 8.89 % when the polymer concentration increased from 140 mg/mL to 200 mg/mL, respectively.

Increased theoretical loading (% drug mass/polymer mass) in the dispersed phase can increase %DL within the formed particles. This is evidenced in the case of Timolol bis prodrugs (**Table 6 and Table 7**) and Brimonidine prodrugs (**Table 4 and Table 5)**.

**Table 4. Polymer, Polymer concentration, and percent theoretical loading of prodrugs of Brinzolamide, Dorzolamide, Latanoprost, and Brimonidine encapsulated microparticles**

| Compound Name | Backbone Polymer | Polymer Conc (mg/mL) | % Theoretical Loading |
|---|---|---|---|
| Brinzolamide-PLA (n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Brinzolamide-PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Brinzolamide-PLA(n=4) | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Brinzolamide-Acetyl PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Brinzolamide-Acetyl PLA(n=5) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |

| | | | |
|---|---|---|---|
| Brinzolamide-Acetyl PLA(n=5) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Brinzolamide-Acetyl PLA(n=5) | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Brinzolamide-Acetyl PLA(n=5) | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Brinzolamide-Acetyl PLA(n=5) | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Dorzolamide-PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Dorzolamide-PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Dorzolamide-PLA(n=4) | PLA 4.5A+ 1% PEG-PLGA5050 | 180 | 13.8 |
| Dorzolamide-PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Dorzolamide-Acetyl PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Dorzolamide-Acetyl PLA(n=5) | PLGA7525 4A + 1% PEG-PLGA5050 | 140 | 13.8 |
| Dorzolamide-Acetyl PLA(n=5) | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Dorzolamide-Acetyl PLA(n=5) | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Dorzolamide-PLA(n=10) | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=10) | 77/22 (PLA 4.5A/PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=12) | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=12) | 77/22 (PLA 4.5A/PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=14) | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=14) | 77/22 (PLA 4.5A/PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 140 | 13.8 |
| Latanoprost-Acetyl PLA(n=4) | PLA + 1% PEG-PLGA5050 | 180 | 13.8 |
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 200 | 13.8 |

| | | | |
|---|---|---|---|
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 200 | 15 |
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 200 | 30 |
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 200 | 50 |
| Latanoprost-Acetyl PLA(n=4) | PLGA + 1% PEG-PLGA5050 | 200 | 40 |
| Latanoprost-tris Acetyl PLA(n=6) | PLGA + 1% PEG-PLGA5050 | 200 | 13.8 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | PLGA8515 5A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | PLGA8515 5A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 200 | 15.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 200 | 20.0 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 200 | 30.0 |

**Table 5. Formulation parameters and physicochemical properties of prodrugs of Brinzolamide, Dorzolamide, Latanoprost, and Brimonidine encapsulated microparticles**

| Compound Name | Surfactant | Formulation Temp | Mean Particle Size (μm) | SD | %DL |
|---|---|---|---|---|---|
| Brinzolamide-PLA (n=4) | A | RT | 25.8 | 7.48 | 0.14 |

| | | | | | |
|---|---|---|---|---|---|
| Brinzolamide-PLA(n=4) | B | ice bath | 27.56 | 8.51 | 8.11 |
| Brinzolamide-PLA(n=4) | B | ice bath | 25.76 | 8.18 | 8.05 |
| Brinzolamide-Acetyl PLA(n=4) | A | RT | 24.9 | 8.27 | 1.01 |
| Brinzolamide-Acetyl PLA(n=5) | A | RT | 23.58 | 7.73 | 0.156 |
| Brinzolamide-Acetyl PLA(n=5) | B | ice bath | 26.5 | 7.98 | 7.39 |
| Brinzolamide-Acetyl PLA(n=5) | B | ice bath | 27.4 | 7.86 | 8.89 |
| Brinzolamide-Acetyl PLA(n=5) | B | ice bath | 27.12 | 10.3 | 9.09 |
| Brinzolamide-Acetyl PLA(n=5) | A | ice bath | 26.38 | 8.92 | 10.5 |
| Dorzolamide-PLA(n=4) | A | RT | 26.83 | 8.53 | 0.22 |
| Dorzolamide-PLA(n=4) | B | ice bath | 28.42 | 9.34 | 8.28 |
| Dorzolamide-PLA(n=4) | B | ice bath | 26.22 | 8.15 | 8.34 |
| Dorzolamide-PLA(n=4) | A | ice bath | 27.89 | 9.18 | 7.98 |
| Dorzolamide-Acetyl PLA(n=4) | A | RT | 26.4 | 8.94 | 0.98 |
| Dorzolamide-Acetyl PLA(n=5) | A | RT | 23.14 | 8.06 | 0.991 |
| Dorzolamide-Acetyl PLA(n=5) | B | ice bath | 19.7 | 9.45 | 8.71 |
| Dorzolamide-Acetyl PLA(n=5) | A | ice bath | 30.37 | 11.2 | 10.1 |
| Dorzolamide-PLA(n=10) | A | RT | 26.59 | 18.4 | 15.3 |
| Dorzolamide-PLA(n=10) | A | RT | 24.37 | 13.6 | 11.8 |
| Dorzolamide-PLA(n=12) | A | RT | 28.73 | 11.0 | 11.7 |
| Dorzolamide-PLA(n=12) | A | RT | 24.14 | 10.5 | 12.5 |
| Dorzolamide-PLA(n=14) | A | RT | 25. | 13.3 | 14.7 |
| Dorzolamide-PLA(n=14) | A | RT | 24.76 | 10.2 | 13.6 |
| Latanoprost-Acetyl PLA(n=4) | A | RT | 28.1 | 8.58 | 0.53 |
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 32.16 | 11.3 | 3.1 |
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 27.78 | 8.12 | 8.59 |
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 27.86 | 8.81 | 8.57 |
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 27.46 | 8.08 | 21.15 |
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 32.12 | 10.6 | 36.4 |

| | | | | | |
|---|---|---|---|---|---|
| Latanoprost-Acetyl PLA(n=4) | A | ice bath | 30.92 | 10.3 | 30.98 |
| Latanoprost-tris Acetyl PLA(n=6) | B | ice bath | 26.44 | 9.18 | 3.57 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | A | RT | 23.9 | 9.38 | 4.54 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | A | RT | 29.31 | 9.45 | 4.83 |
| Brimonidine-Acetyl PLA(n=2)-N-Acetate (**114-4**) | A | RT | 22.67 | 9.18 | 3.81 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | A | RT | 22.59 | 8.16 | 12.7 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | C | RT | 24.57 | 8.55 | 13.72 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | C | RT | 32.1 | 12.5 | 14.72 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | C | RT | 24.15 | 7.09 | 13.37 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | C | RT | 22.61 | 7.10 | 18.72 |
| Brimonidine-Acetyl PLA(n=4)-N-Acetate (**115-1**) | C | RT | 24.1 | 7.04 | 27.49 |

Surfactant- A) 1% PVA in PBS; B) 1% alpha-tocopherol-$PEG_{1k}$-succinate in PBS; C) 1% PVA in $H_2O$.

**Table 6. Backbone polymer, Polymer concentration, and percent theoretical loading of PLA-Timolol, ROCK Inhibitors, and bifunctional prodrug encapsulated microparticles**

| Compound Name | Backbone Polymer | Polymer Conc (mg/mL) | % Theoretical Loading |
|---|---|---|---|
| Timolol-stearyl PLA (n=4) maleate **(40-2)** | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) maleate **(40-2)** | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) maleate **(40-2)** | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) HCL **(41-2)** | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) HCL **(41-2)** | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) HCL **(41-2)** | PLGA8515 5A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) HCL **(41-2)** | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 13.8 |

| | | | |
|---|---|---|---|
| Timolol-Acetyl PLA (n=4) maleate **(45-2)** | PLGA7525 4A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-stearyl PLA (n=4) HCL **(41-2)** | PLGA5050 2A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-Acetyl PLA (n=4) maleate **(45-2)** | PLA 4.5A + 1% PEG-PLGA5050 | 200 | 13.8 |
| Timolol-Succinic acid-Timolol Maleate (**76-4**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Glutaric acid-Timolol Maleate (**77-1**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Fumarate-Timolol Maleate (**78-1**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 64/20/15 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 20.0 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 30.0 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) (**229**) | PLA 4.5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) (**229**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) (**229**) | 64/20/15 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) (**230**) | PLA 4.5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) (**230**) | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |

| | | | |
|---|---|---|---|
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) (**230**) | 64/20/15 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 69/30 (PLA 4.5A/PLGA7525 6E) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 77/22 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 74/20/5 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 69/20/10 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | PLGA7525 6E + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 74/20/5 (PLA 4.5A/PLGA7525 4A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | 69/20/10 (PLA 4.5A/PLGA7525 4A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | PLGA8515 5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834 | PLA 4.5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| SR5834-PLA(n=4) | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | 69/30 (PLA 4.5A/PLGA7525 6E) + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | 69/30 (PLA 4.5A/PLGA7525 8E) + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | 69/30 (PLA 4.5A/PLGA8515 5A) + 1% PEG-PLGA5050 | 260 | 15.0 |

| | | | |
|---|---|---|---|
| RKI-H-1y malate | 69/25/5 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A) + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | PLGA7525 6E + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | PLGA8515 5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| RKI-H-1y malate | PLA 4.5A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Hydroxy-1y-Acetyl PLA(n=4) (**90-3**) | PLGA7525 4A + 1% PEG-PLGA5050 | 260 | 15.0 |
| Dorzolamide-PLA(n=4)-succinate-5-hydroxy-Sunitinib | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |
| Brinzolamide-PLA(n=4)-succinate-5-hydroxy-Sunitinib | PLA 4.5A + 1% PEG-PLGA5050 | 180 | 13.8 |

PLGA$^{x}$ (85:15 lactic acid to glycolic acid ratio, 5A, Evonik)
PLGA$^{y}$ (50:50 lactic acid to glycolic acid ratio, 2A, Evonik)

**Table 7. Formulation parameters and physicochemical properties of PLA-Timolol prodrugs and bifunctional prodrugs**

| Compound Name | Surfactant | Formula-tion Temp | Mean Particle Size (μm) | SD | %DL |
|---|---|---|---|---|---|
| Timolol-stearyl PLA (n=4) maleate (**40-2**) | 1% PVA in PBS | ice bath | 34.17 | 12.1 | 10.18 |
| Timolol-stearyl PLA (n=4) maleate (**40-2**) | 1% PVA in PBS | RT | 31.51 | 11 | 12.7 |
| Timolol-stearyl PLA (n=4) maleate (**40-2**) | 1% PVA in PBS | ice bath | 34.74 | 12.9 | 12.13 |
| Timolol-stearyl PLA (n=4) HCL (**41-2**) | 1% PVA in PBS | RT | 33.12 | 12 | 12.09 |
| Timolol-stearyl PLA (n=4) HCL (**41-2**) | 1% PVA in PBS | ice bath | 36.2 | 12.8 | 11.09 |
| Timolol-stearyl PLA (n=4) HCL (**41-2**) | 1% PVA in PBS | RT | 34.03 | 11.9 | 12.6 |
| Timolol-stearyl PLA (n=4) HCL (**41-2**) | 1% PVA in PBS | RT | 27.99 | 8.13 | 12.26 |
| Timolol-Acetyl PLA (n=4) maleate (**45-2**) | 1% PVA in PBS | RT | 31.2 | 11.7 | 10.63 |
| Timolol-stearyl PLA (n=4) HCL (**41-2**) | 1% PVA in PBS | RT | 25.33 | 8.77 | 12.51 |

| | | | | | |
|---|---|---|---|---|---|
| Timolol-Acetyl PLA (n=4) maleate **(45-2)** | 1% PVA in PBS | RT | 27.85 | 8.23 | 8.76 |
| Timolol-Succinic acid-Timolol-Maleate (**76-4**) | 1% PVA in PBS | RT | 28.74 | 11.0 | 7.45 |
| Timolol-Glutaric acid-Timolol-Maleate (**77-1**) | 1% PVA in PBS | RT | 27.29 | 11.0 | 7.94 |
| Timolol-Fumarate-Timolol-Maleate (**78-1**) | 1% PVA in PBS | RT | 27.45 | 10.3 | 9.61 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 1% PVA in $H_2O$ | RT | 26.52 | 8.46 | 6.8 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 1% PVA in $H_2O$ | RT | 28.0 | 8.47 | 7.38 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 1% PVA in $H_2O$ | RT | 29.27 | 7.84 | 10.41 |
| Timolol-Bis-Acetyl PLA(n=4) (**119-6**) | 1% PVA in $H_2O$ | RT | 28.17 | 7.97 | 13.10 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) | 1% PVA in $H_2O$ | RT | 28.17 | 7.52 | 13.36 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) | 1% PVA in $H_2O$ | RT | 27.29 | 8.25 | 14.06 |
| Timolol-Bis-N-Acetyl PLA(n=4)-O-Acetyl PLA(n=2) | 1% PVA in $H_2O$ | RT | 26.87 | 8.05 | 13.4 |
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) | 1% PVA in $H_2O$ | RT | 28.24 | 7.62 | 12.65 |
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) | 1% PVA in $H_2O$ | RT | 27.31 | 8.33 | 16.33 |
| Timolol-Bis-N-Acetyl PLA(n=2)-O-Acetyl PLA(n=4) | 1% PVA in $H_2O$ | RT | 27.6 | 8.29 | 12.6 |
| SR5834 | 1% PVA in PBS | RT | 25.28 | 7.9 | 7.19 |
| SR5834 | 1% PVA in PBS | RT | 23.91 | 7.91 | 6.31 |
| SR5834 | 1% PVA in PBS | RT | 24.21 | 7.8 | 6.81 |
| SR5834 | 1% PVA in PBS | RT | 23.71 | 7.7 | 6.22 |
| SR5834 | 1% PVA in PBS | RT | 22.24 | 7.83 | 6.56 |

| | | | | | |
|---|---|---|---|---|---|
| SR5834 | 1% PVA in PBS | RT | 27.23 | 8.73 | 7.69 |
| SR5834 | 1% PVA in PBS | RT | 22.86 | 7.90 | 6.29 |
| SR5834 | 1% PVA in PBS | RT | 22.74 | 7.53 | 6.54 |
| SR5834 | 1% PVA in PBS | RT | 25.07 | 7.66 | 6.89 |
| SR5834 | 1% PVA in PBS | RT | 24.3 | 7.41 | 6.36 |
| SR5834-PLA(n=4) | 1% PVA in PBS | RT | 30.41 | 10.5 | 12.88 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 24.25 | 8.23 | 17.31 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 25.43 | 8.15 | 16.91 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 26.42 | 7.98 | 17.17 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 24.52 | 8.80 | 17 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 29.42 | 10.1 | 17.03 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 27.42 | 9.94 | 16.95 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 26.93 | 10.4 | 17.17 |
| RKI-H-1y malate | 1% PVA in PBS | RT | 25.35 | 8.94 | 17.48 |
| Hydroxy-1y-Acetyl PLA(n=4) (**90-3**) | 1% PVA in PBS | RT | 23.76 | 8.48 | 12.84 |
| Dorzolamide-PLA(n=4)-succinate-5-hydroxy-Sunitinib | 1% PVA in PBS | RT | 26.91 | 10.8 | 11.62 |
| Brinzolamide-PLA(n=4)-succinate-5-hydroxy-Sunitinib | 1% PVA in PBS | RT | 33.83 | 11.5 | 8.47 |

Surfactant: A) 1% PVA in PBS

***Particle Morphology***

Particle morphology was assessed using a Nikon Eclipse TS-100 light microscope. Briefly, 3-5 mg of particles were suspended in 1 mL of water. A volume of 10 uL of the particle suspension was transferred onto a glass slide and imaged directly. In general, particles were found to be spherical in morphology (**Figure 31A**, **Figure 31B**, **Figure 31C**, and **Figure 31D**).

***Drug Release***

In vitro drug release kinetics were evaluated in a release medium of PBS and 1% Tween 20 (pH 7.4). Briefly, 10 mg of particles were transferred to glass scintillation vials and 4 mL of the release medium was added to suspend the particles. Samples were prepared in duplicate. The particles were mixed by gentle vortexing and incubated on an orbital shaker at 150 rpm at 37 °C. At various time points, 3 mL of release media was collected and analyzed for drug content and 3 mL of fresh media was added to replace the sample that was collected. Collected release samples were frozen and stored at -80 °C until analysis for drug content. The collected samples were filtered through a 0.2 μm syringe filter and analyzed by RP-HPLC.

**Figure 32** illustrates the cumulative release profile for particles with polymer concentrations of 140 mg/mL and 200 mg/mL encapsulating Brinzolamide-acetyl PLA (n=5). The cumulative release profiles of both formulations exhibited relatively low initial burst release (0.65 % and 0.32 % released at 3 hours, respectively). However, by day 3, particles prepared with a higher polymer concentration exhibited significantly slower burst release than particles prepared at 140 mg/mL concentration (2.85 % vs. 4.92 %, respectively). By day 42, particles prepared at a polymer concentration of 140 mg/mL had released 87.6 % of the drug whereas particles prepared at a concentration of 200 mg/mL had released only 80.7%. Thus, by increasing the polymer concentration from 140 mg/mL to 200 mg/mL, the burst and overall rate of release of Brinzolamide-Acetyl PLA (n=5) from the particles was decreased. Without wishing to be bound to any one therory, the rate of release of Brinzolamide-acetyl PLA (n=5) may be attributed to its high hydrophobicity and hydrophobic interactions between the drug and the polymer matrix. Increasing the hydrophobocity of the polymer by selecting a higher LA:GA ratio of polymer or PLA may further decrease the rate of release.

In vitro release profiles of Brinzolamide-acetyl PLA (n=5), Dorzolamide-acetyl PLA (n=5) and Latanoprost-acetyl PLA (n=5) are shown in **Figure 33**. The release kinetics of acetylated Brinzolamide and Dorzolamide with five LA repeat units were comparable. The release kinetics for Brinzolamide-acetyl PLA (n=5) and Dorzolamide-acetyl PLA (n=5) was significantly faster than Latanoprost-acetyl PLA (n=5); approximately 75.3% of Dorzolamide-acetyl PLA (n=5) was released after 37 days compared to 54.3 % for Latanoprost-acetyl PLA (n=5). Without wishing to be bound to any one therory, this may be attributed to the differences in hydrophobicity between CAIs and Latanoprost. Burst release was also significantly higher for Dorzolamide-acetyl PLA

(n=5) than Latanoprost-acetyl PLA (n=5). At 3 hours, approximately 1.20 % of Dorzolamide-acetyl PLA (n=5) had been released compared to 0.55 % for Latanoprost-acetyl PLA (n=5).

Release kinetics for uncapped Brinzolamide-PLA(n=4) and Dorzolamide-PLA(n=4) is illustrated in **Figure 34.** A cursory evaluation of the release kinetics between acetylated vs non-acetylated carbonic anhydrase inhibiting NCEs reveal acetylation of the terminal lactate unit significantly decreased the release kinetics of the NCE from the microparticles. For example, approximately 97% of Dorzolamide-Acetyl PLA(n=5) was released by day 63 whereas approximately 99% of non-acetylated Dorzolamide-PLA(n=4) was released by day 37, respectively. Without wishing to be bound to any one therory, this may be attributed to the large difference in aqueous solubility between the acetylated compounds (low aqueous solubility) and the un-acetylated compounds (high aqueous solubility).

Increasing the number of PLA repeat units on the Dorzolamide prodrug resulted in a significant increase in the duration of release (**Figure 36 and Figure 37**).

Analysis of the cumulative release profile of prodrug derivatives of Timolol (**Figure 35 and Figure 38**) revealed that the nature of the endcap group on the terminal lactate unit has an effect on the release kinetics of the NCE. Particles encapsulating Timolol-Stearyl PLA(n=4) maleate (**40-2**) were found to release the NCE at a much slower rate than particles encapsulating Timolol-Acetyl PLA(n=4) maleate (**45-2**). The rate of release was independent of the salt form. For Timolol, endcapping the terminal lactide with a stearyl chain decreased the rate of drug release over acetylation of the terminal lactide (**Figure 38**). Comparative evaluation of blended particles with the same polymer composition encapsulating 5 different mono and bis prodrugs of Timolol (**Figure 39**) revealed only minor differences between the release rates of the 5 particle formulations. Thus, release rate is not solely dictated by the physicochemical properties of the linker but rather must be attributed to a combination of parameters that may include linker type and site of linker conjugation.

The effect of polymer composition including monomer ratio and molecular weight, polymer end-groups (ester or acid), inherent viscosity and polymer blend ratios on particle degradation and drug release kinetics was evaluate and illustrated in **Figure 40**. The rate of particle degradation was slowed and drug release was prolonged when the mole % of DL-lactide over glycolide was increased. By incorporating polymers with different monomer ratios (i.e. PLA, PLGA8515, PLGA525, PLGA5050; wherein 8515 refers to 85% DL-lactide and 15% glycolide)

into the particles, it is possible to fine-tune the degradation rate of the particles to achieve a linear rate of drug release from the particles to minimize burst or lag and to extend the duration of release. End-group modification of the polymer from the acid form to the ester form exhibited a similar effect at slowing particle degradation and drug release. Interestingly, blending a number of different polymers with different monomer ratios, end groups and molecular weights enabled optimization of release kinetics to achieve a linear 3-6 month release profile. Based on the current evidence, the 78/22(PLA 5A/PLGA8515 4.5A) and 65/20/15(PLA 4A/PLGA6515 4.5A/PLGA5050 4A) polymer blends generated ideal particles for a 3-6 month linear release formulation for Timolol-bis-Acetyl-PLA(n=4) (**119-6**) (**Figure 40**). Particles of 100% PLA 4.5A and 77/22(PLA 4.5A/PLGA8515 5A) blends exhibited comparable slow release of encapsulated Timolol-Bis-N-acetyl-PLA (n=4)-O-acetyl PLA (n=2) (**229**) in comparison to particles comprised of 65/20/15(PLA 4A/PLGA6515 4.5A/PLGA5050 4A) polymer blends (**Figure 41**). This trend was mirrored for particles encapsulating Timolol-Bis-N-acetyl-PLA (n=2)-O-acetyl PLA (n=4) (**230**) (**Figure 42**).

As evidenced in **Figure 43**, a correlation between % theoretical loading and drug release rate can be observed for Brimonidine-Acetyl PLA(n=4)-N-acetate (**115-1**). Increasing the amount of drug loaded into the particles resulted in an increase in the rate of drug release.

Evaluation of particle formulations of SR5834 composed of different polymer blends revealed three formulations that exhibit sustained release for a period of 90 days (**Figure 44**). Modification of the rock inhibitor into a prodrug via facile conjugation to Acetyl-PLA(n=4) (compound **88-3**) did not result in any significant effect on the release kinetics (**Figure 45**). Similarly, sustained release formulations for RKI-H-1y was prepared with varying copolymer compositions and blends (**Figure 46**).

The microparticle compositions described herein have demonstrated the potential to load and release one or more prodrugs for the management of elevated intraocular pressure for a prolonged period (>1 month).

***Encapsulation of Timolol-Dorzolamide prodrugs in polymeric microspheres and concurrent dual drug release from prodrug-loaded microspheres***

Timolol-Dorzolamide bi-functional prodrugs **58-2** and **64-4** were encapsulated in polymeric microspheres using w/o emulsion, solvent evaporation techniques described in Example 9. Prodrugs were successfully encapsulated into microspheres with drug loading between 10-20

w/w%. Various formulation parameters, such as target drug loading, polymer concentration, formulation temperature, polymer composition, disperse phase and continuous phase ratio, etc., were investigated to optimize drug loading.

Target drug loading has a direct impact on the actual drug loading. Actual drug loading first increased with target drug loading and then reduced after target drug loading exceeded 20%. (**Figure 47**). Without being bound to any one theory, the initial positive correlation between actual drug loading and target drug loading is probably due to more drug being added to the system and thus encapsulated. However, as the target drug loading exceeds 20%, the excessive drug disrupts the physical integrity of the polymer matrix and yields a low drug loading due to drug leakage. This is evidenced by the highly porous structure of the microspheres. (**Figure 48**)

Parent Timolol and Dorzolamide prodrugs (Dorzolamide linked with 1-3 PLA units) were released concurrently from the bi-functional prodrug-loaded microspheres. Two important factors that impacted drug release kinetics, namely polymer composition and target drug loading, are described below.

(i) Polymer composition vs. release kinetics

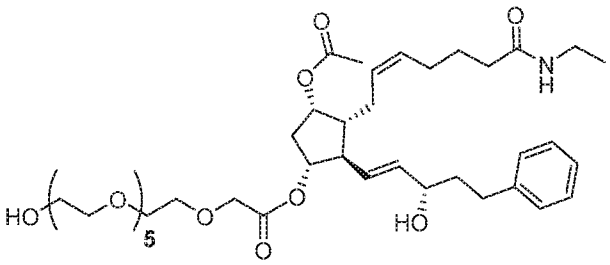
Different polymer compositions were investigated to encapsulate Timolol-succinate-PLA (n=3)-Dorzolamide (**58-2**). When a fast-degrading polymer (PLGA50:50 4A) was incorporated into the polymer matrix, the drug release rate was increased. When the microspheres were composed of slow-degrading polymers (e.g., PLA 4A and PLGA75:25 8E), the drug release rates were reduced. (**Figure 49A** and **Figure 49B**).

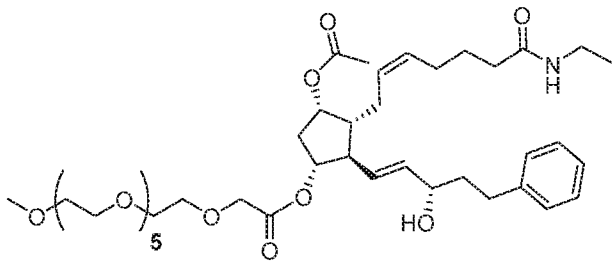
(ii) Drug loading vs. release kinetics

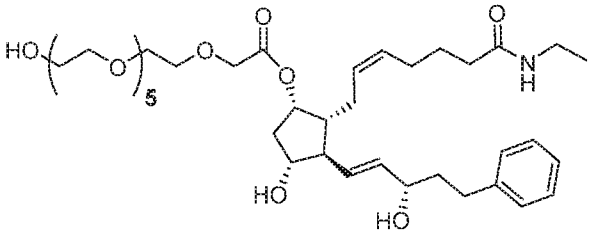
Drug release from polymeric microspheres usually exhibit a lag period where minimal amount of drugs are released in the first few days or even weeks of the study. This is usually undesirable in clinical applications when initial patient response is required because the drug released in this period may not reach therapeutic effective level.

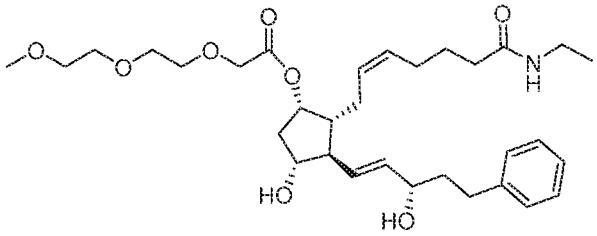
A lag period of about 10 days was observed for microspheres with a target drug loading of 15%. (**Figure 50**) However, when the target drug loading was increased to 20%, no lag period was observed. (**Figure 51**). Without wishing to be bound to any one theory, this is probably due to the slightly porous structure of the microspheres caused by the higher target drug loading. (**Figure 52A** and **Figure 52B**)

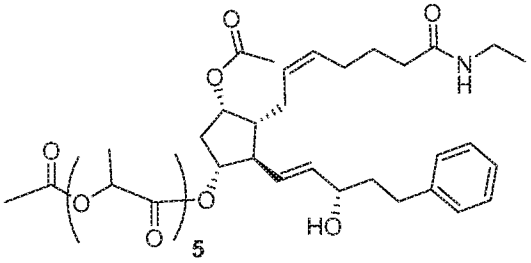
**Example 10. Non-limiting examples of Compounds of Formula I**

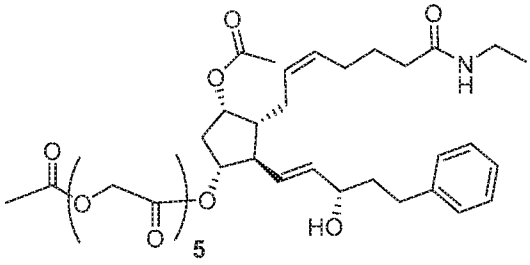


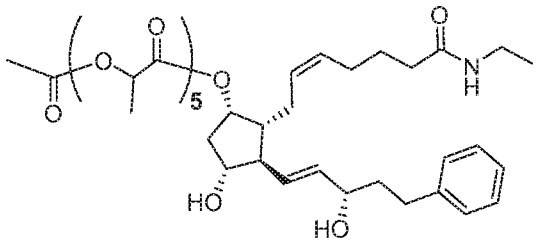


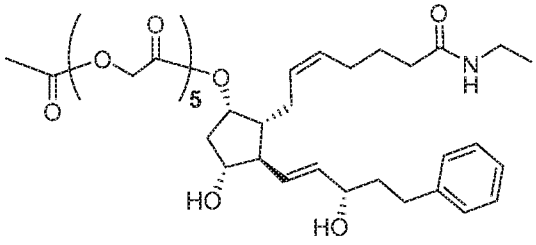


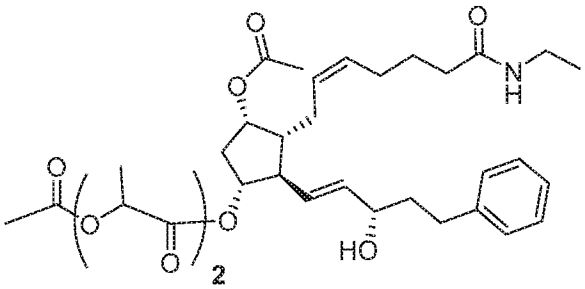


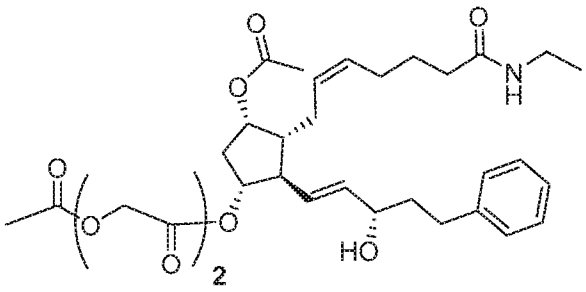


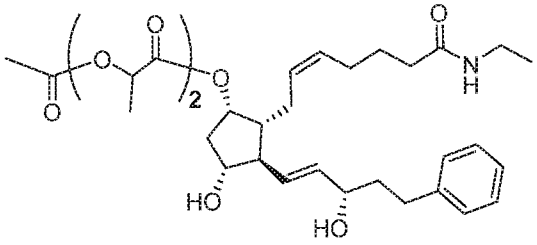


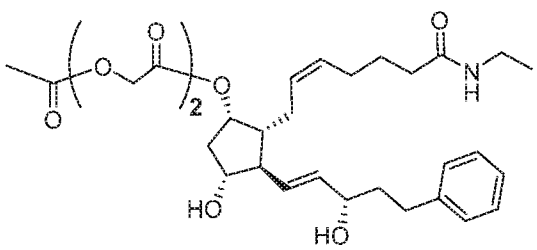


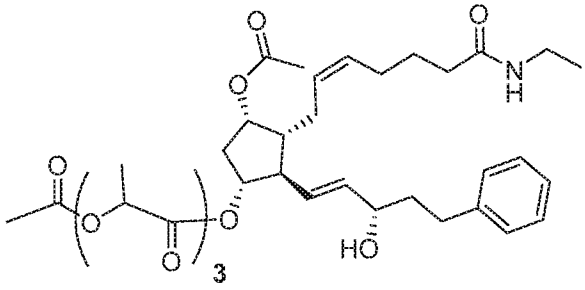


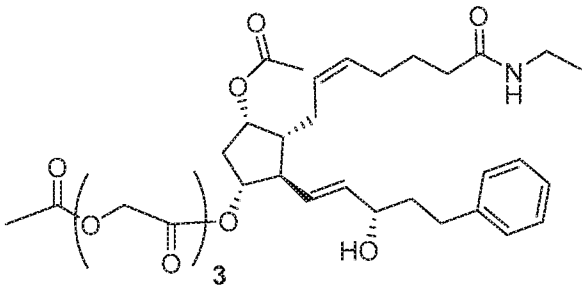


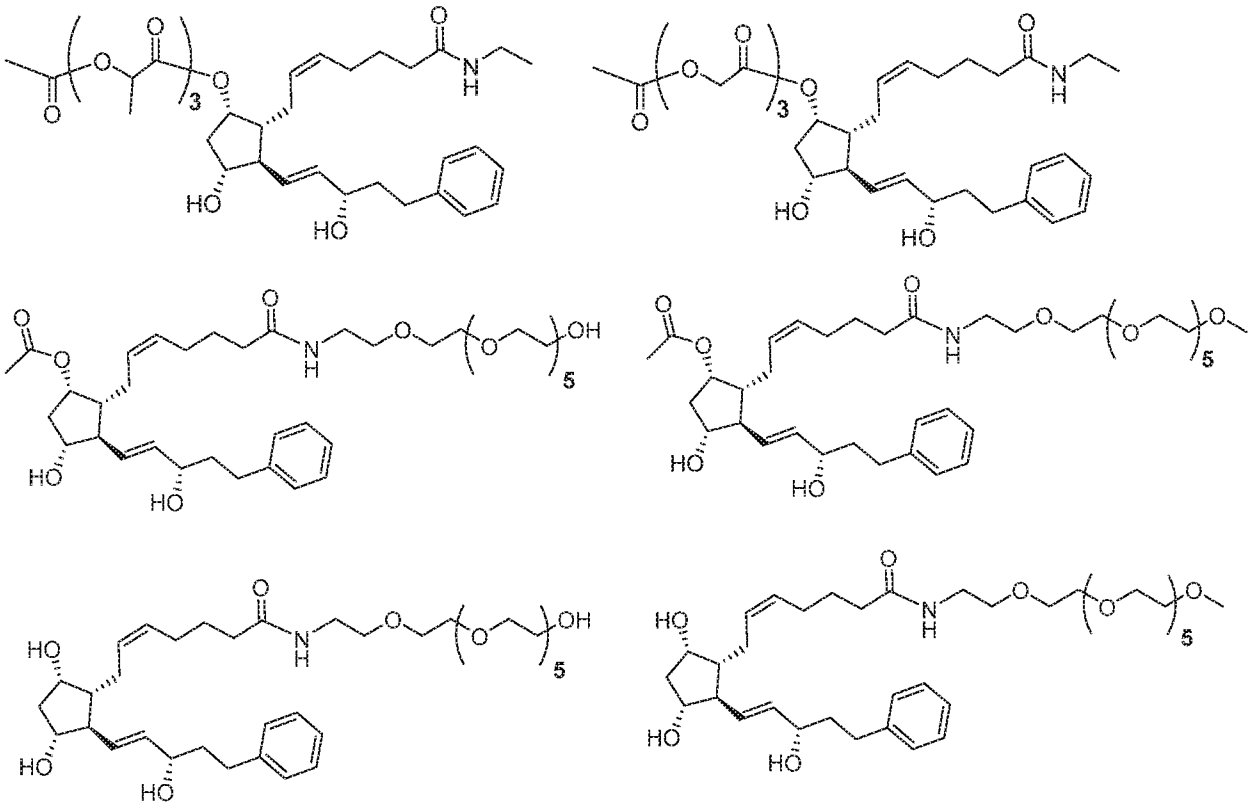




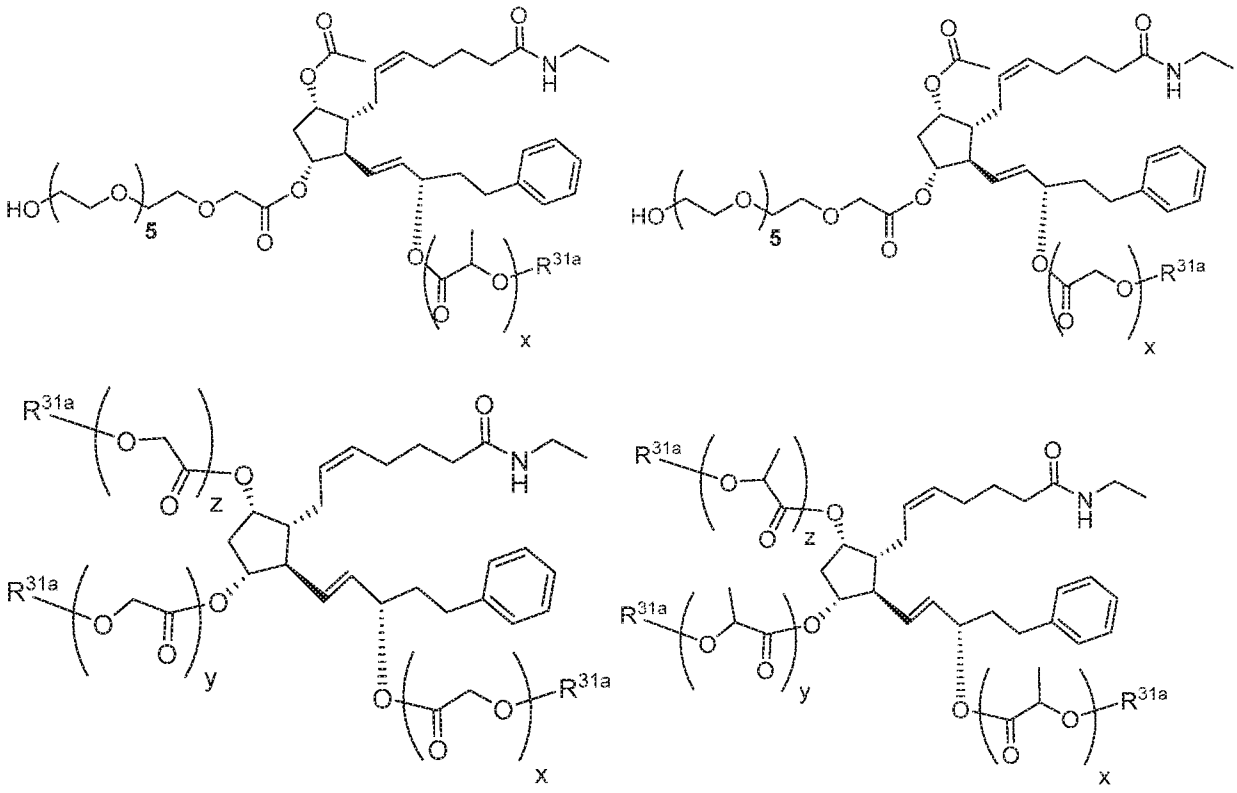


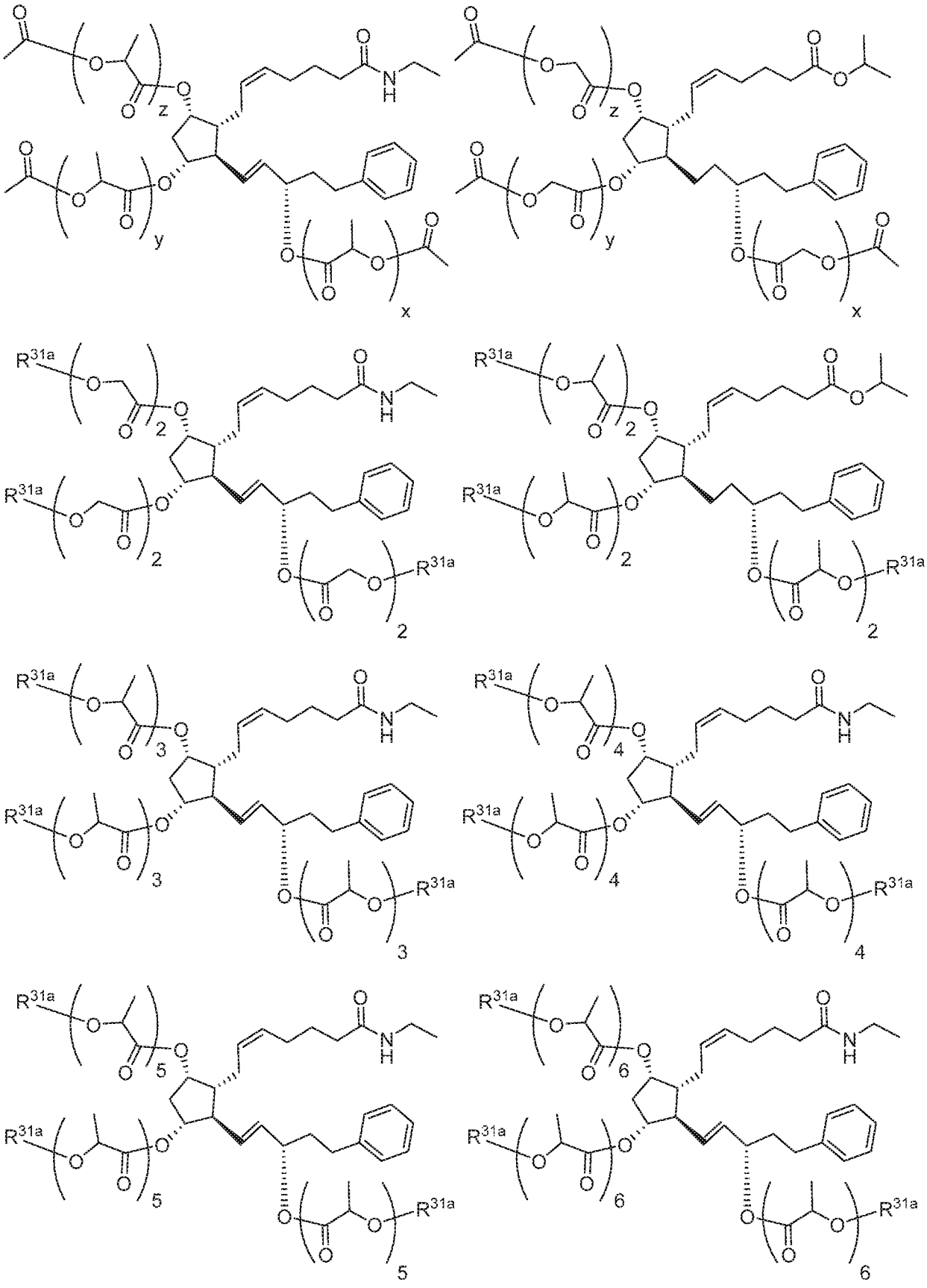




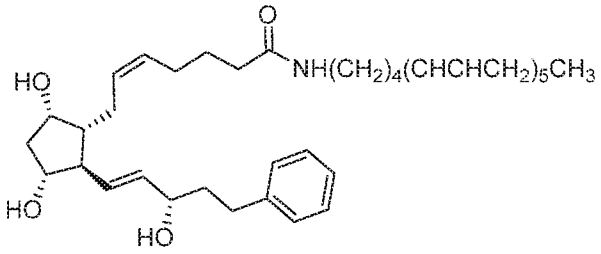


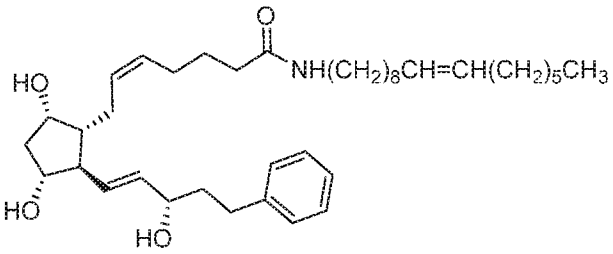
**Example 11. Non-limiting examples of Compounds of Formula II**

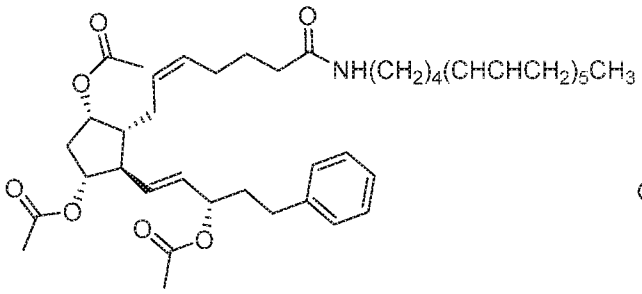


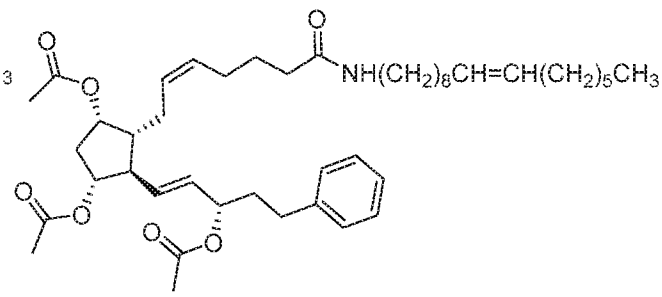


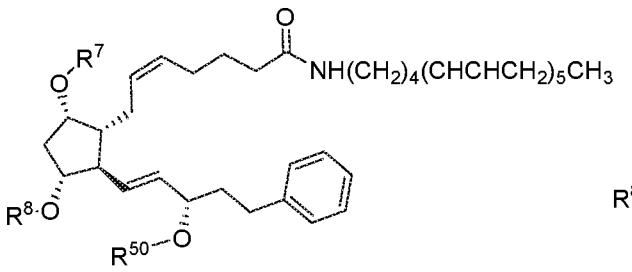
**Example 12. Non-limiting examples of Compounds of Formula III**

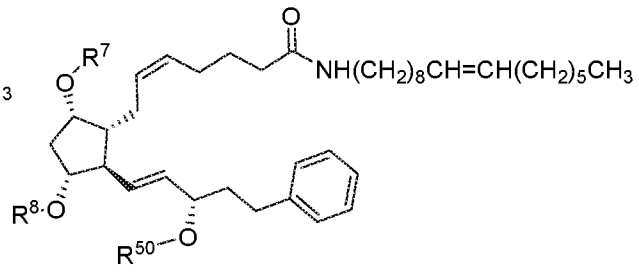


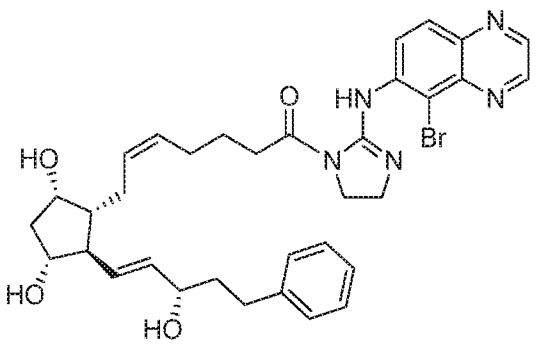



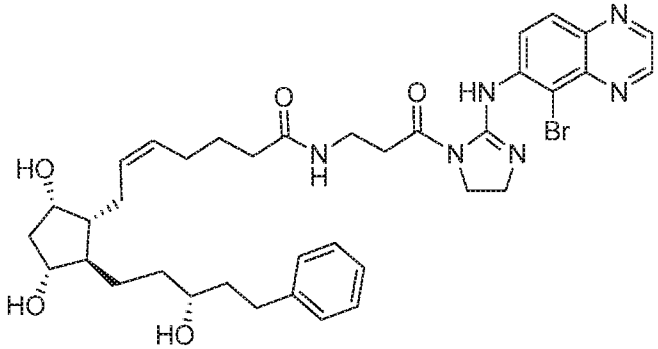



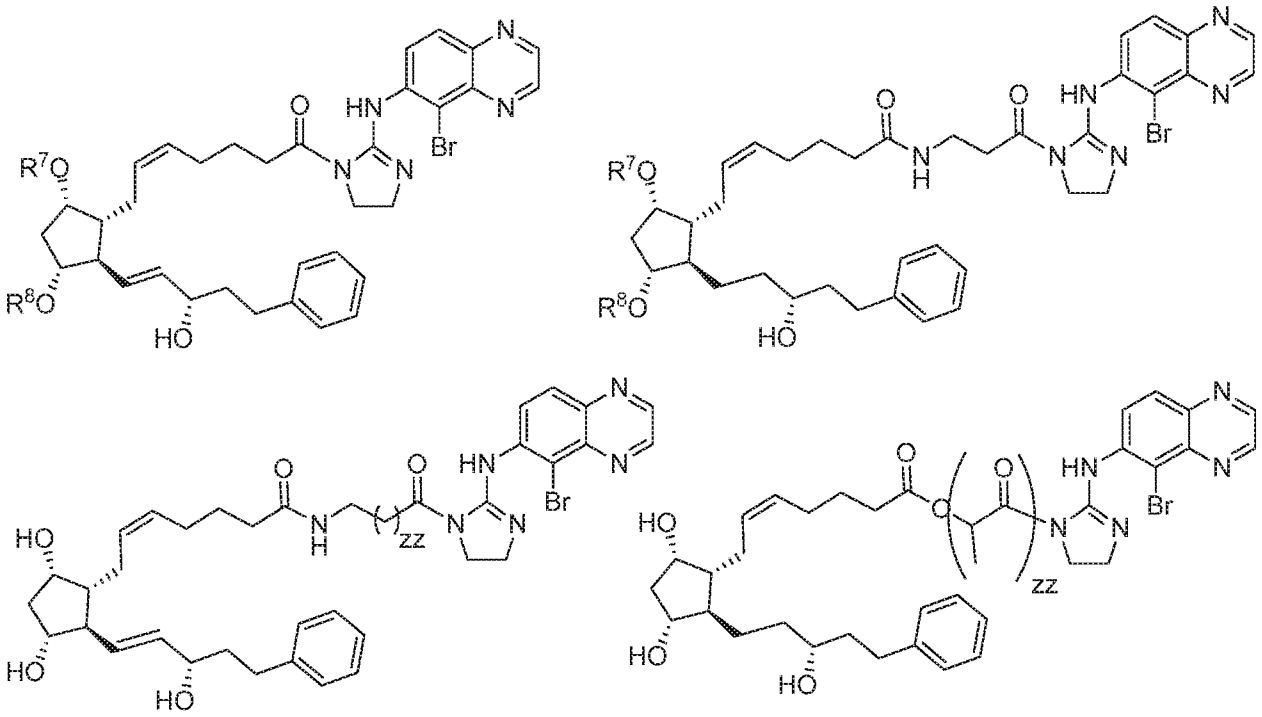



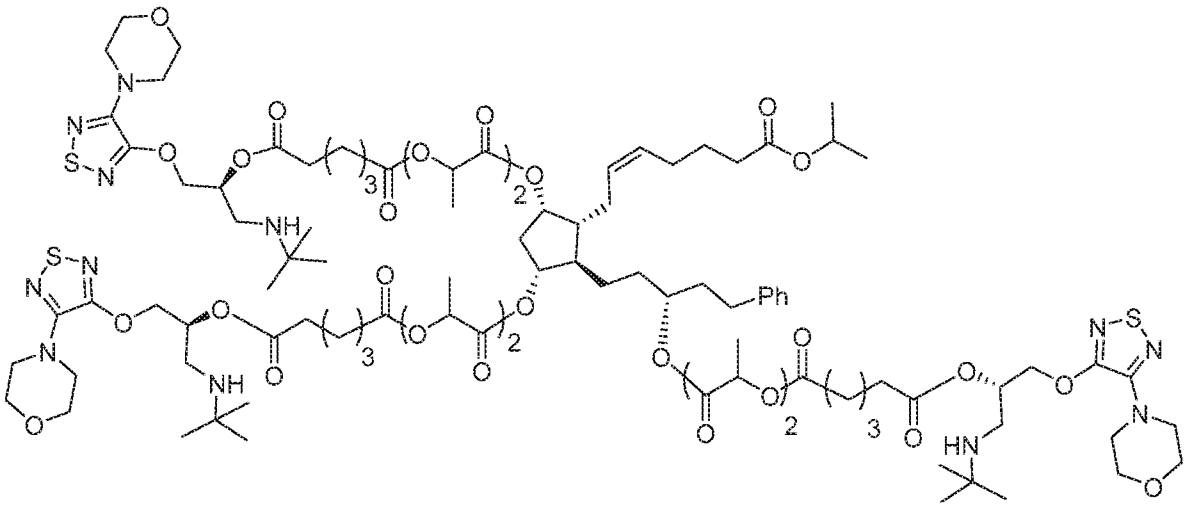

**Example 13. Non-limiting examples of Compounds of Formula IV**

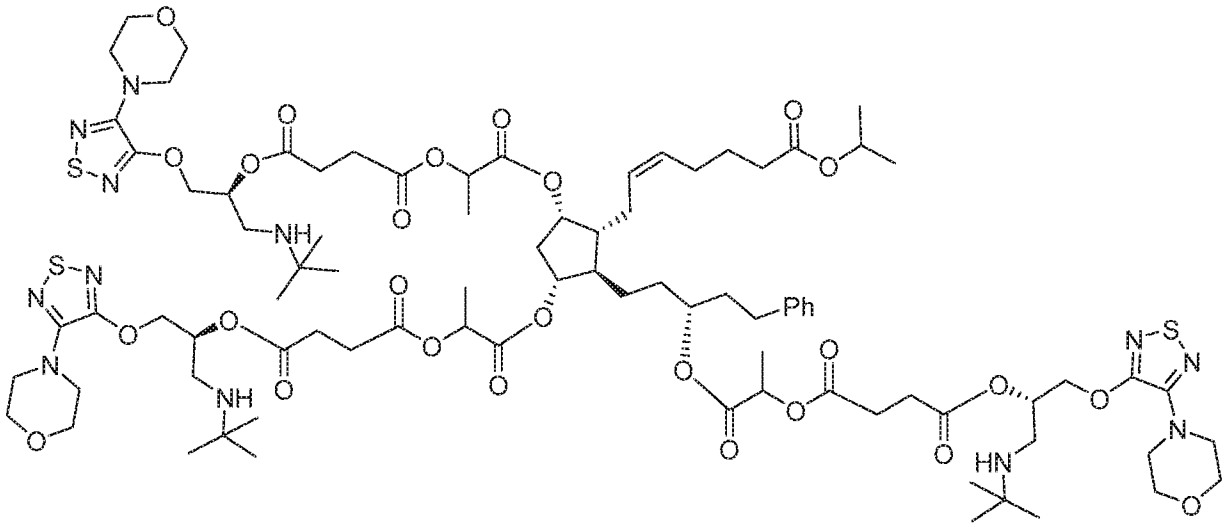


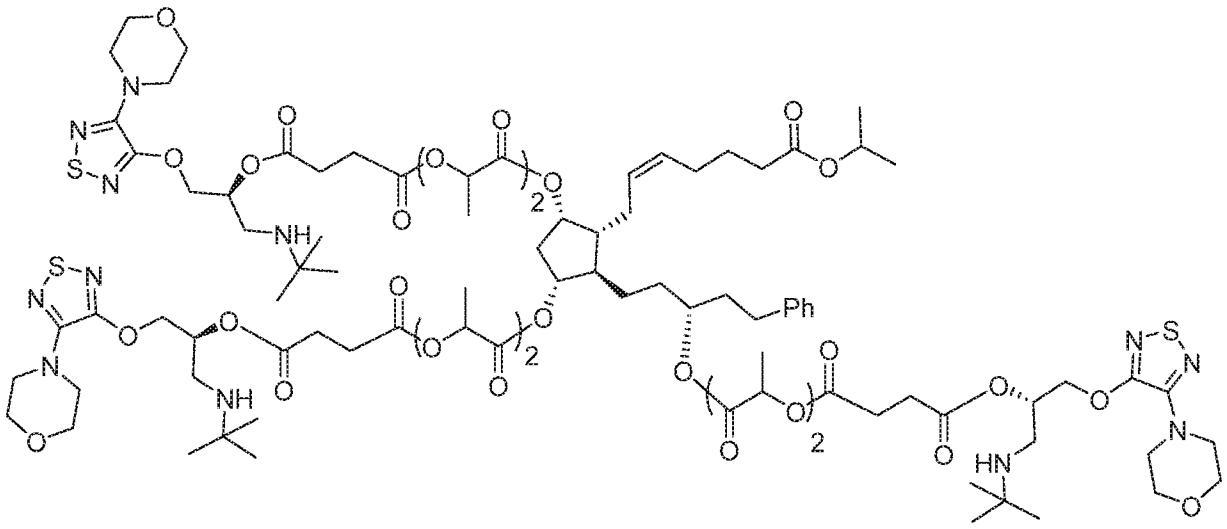



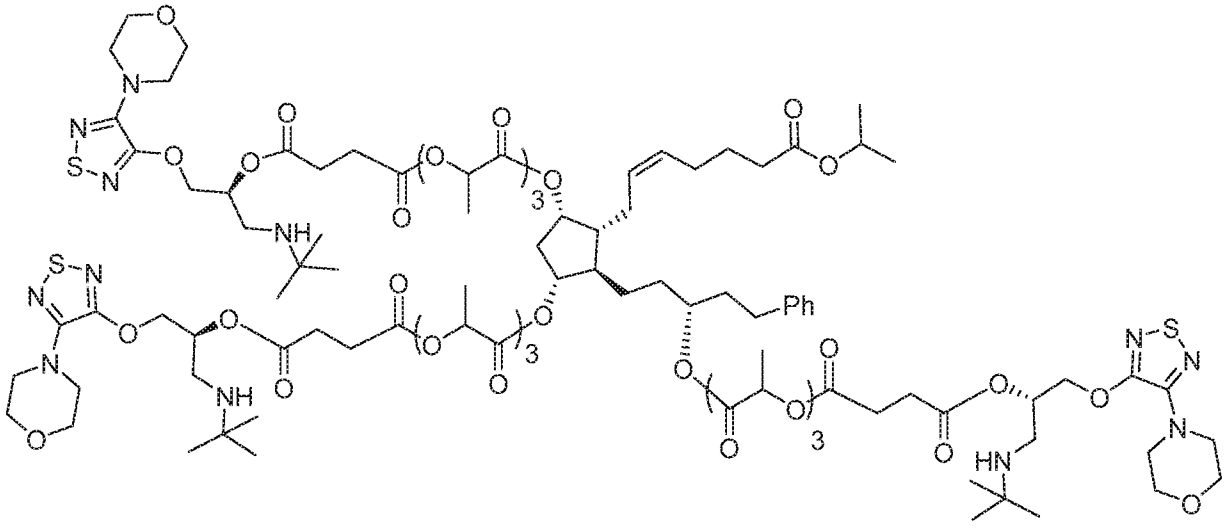


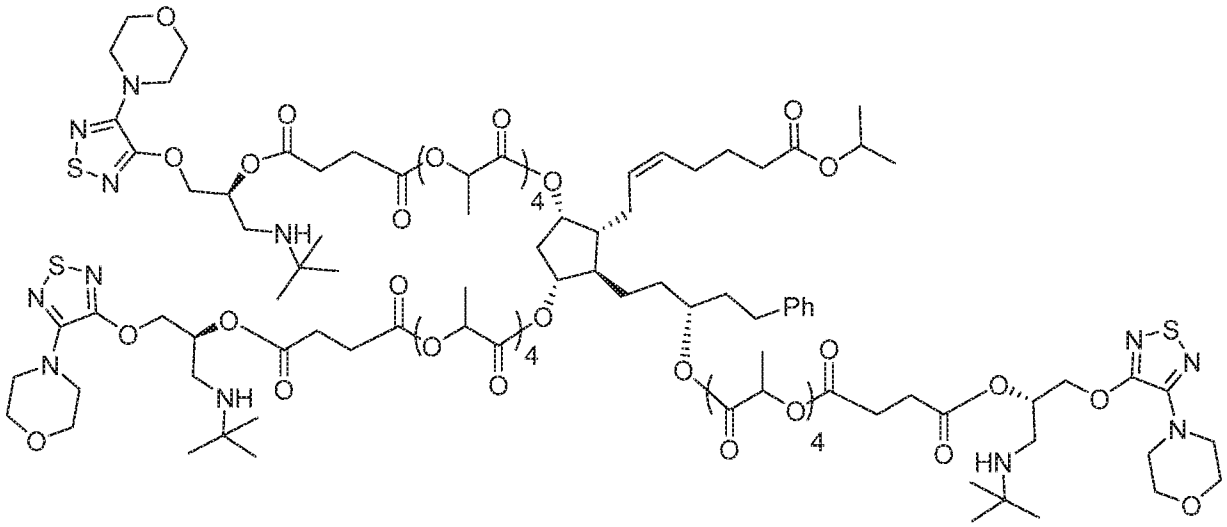
**Example 14. Non-limiting Examples of Formula V and VI**

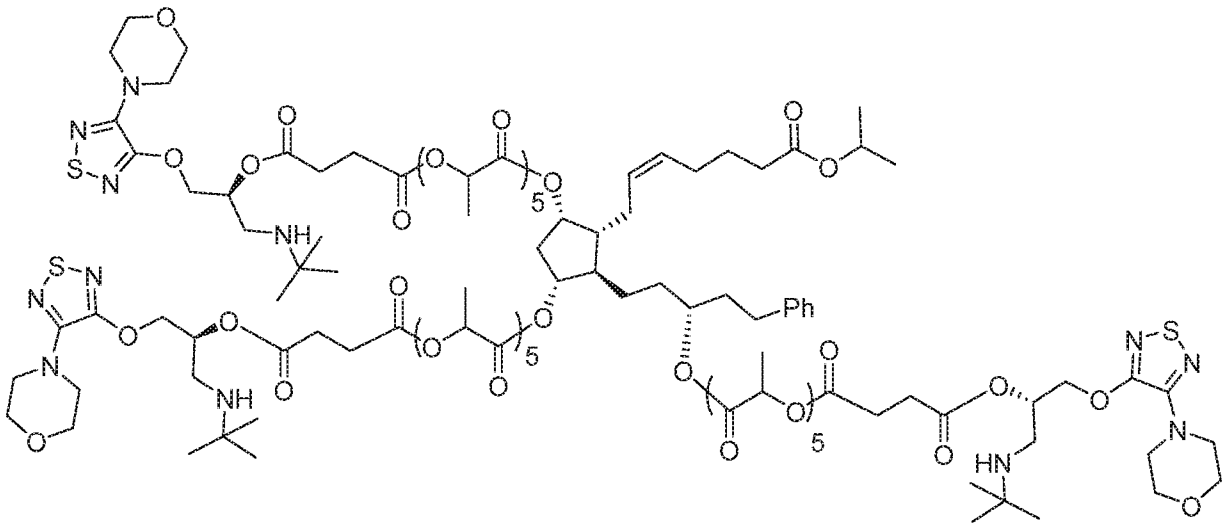


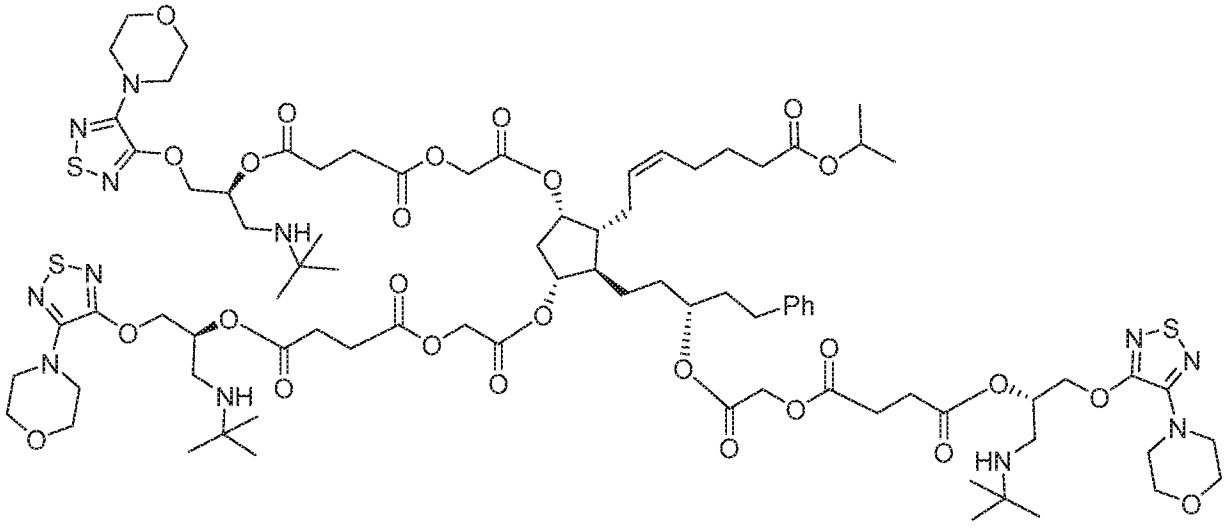


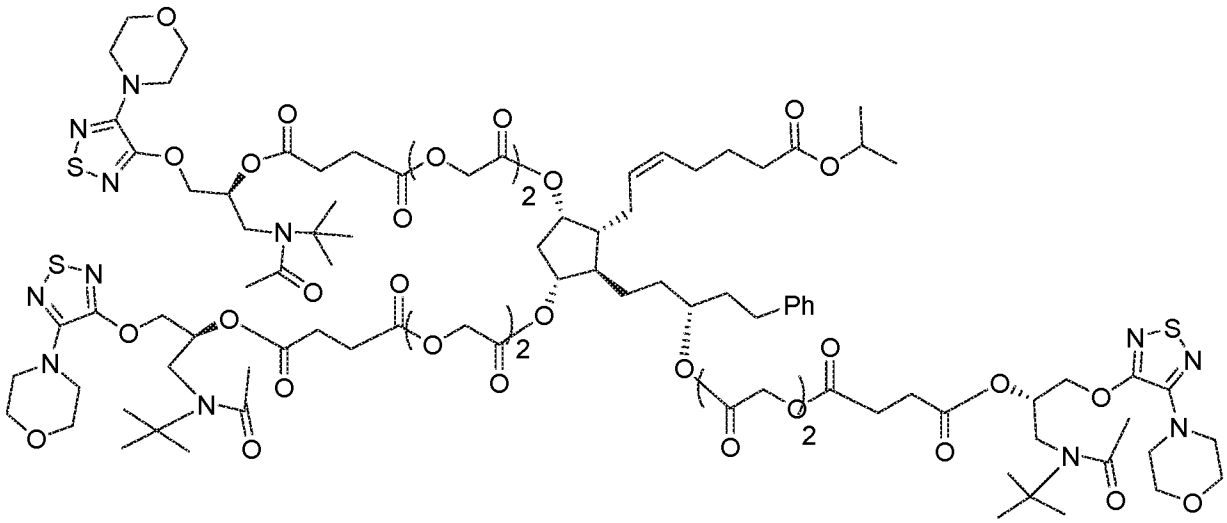


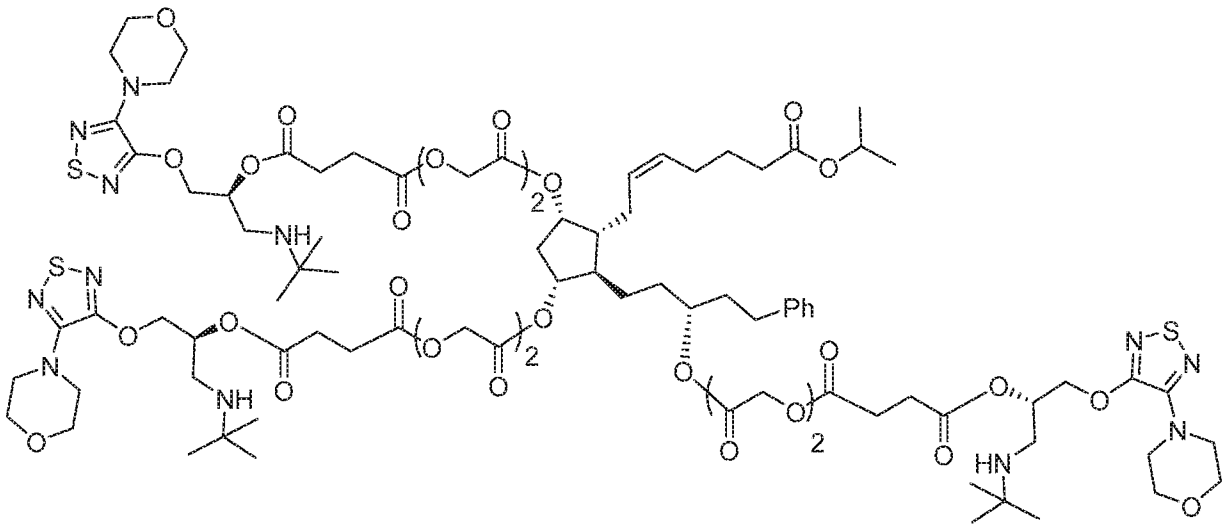


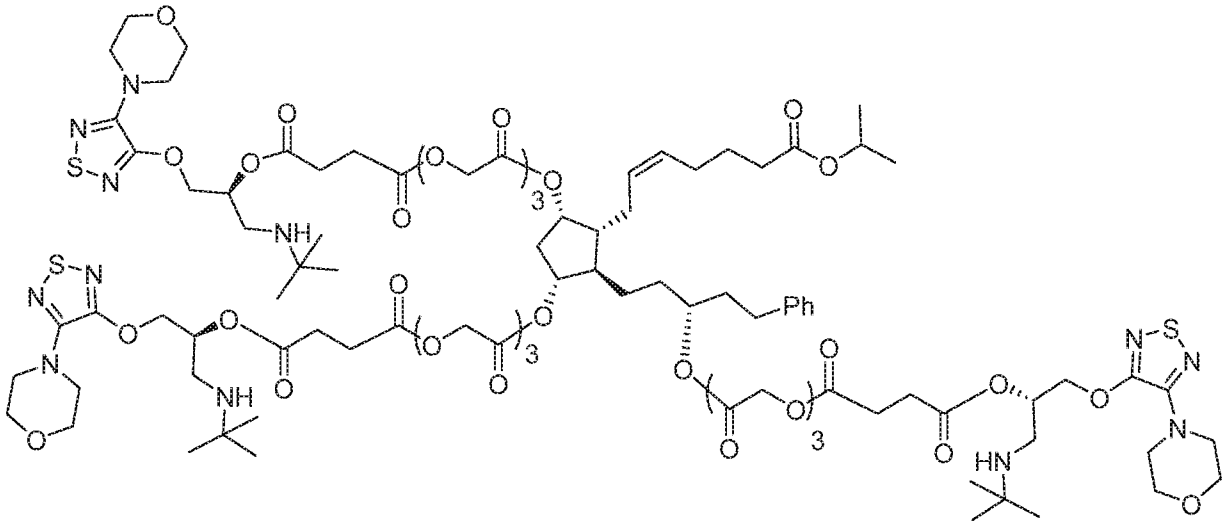


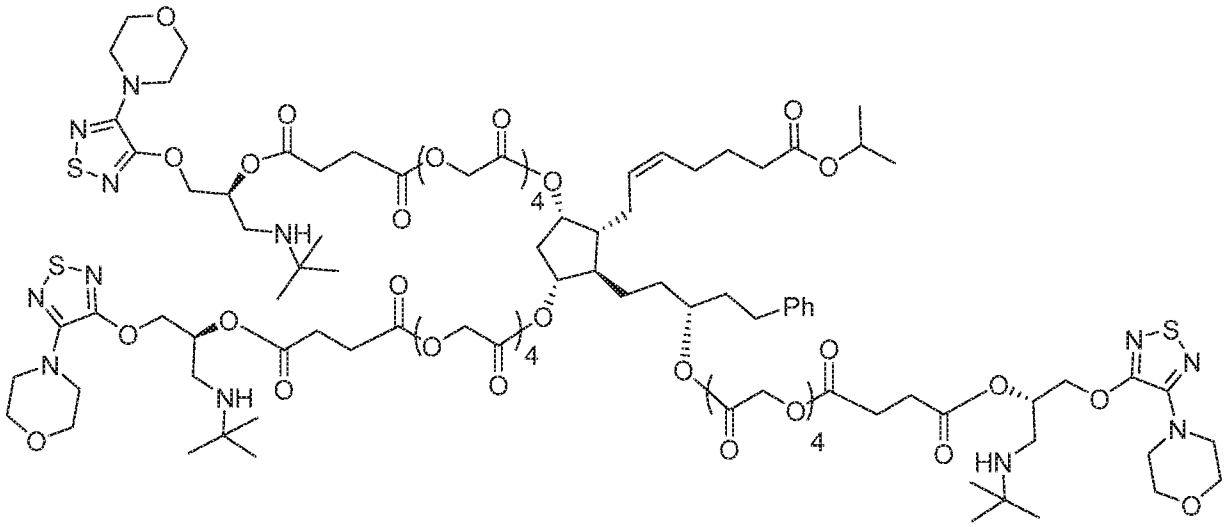


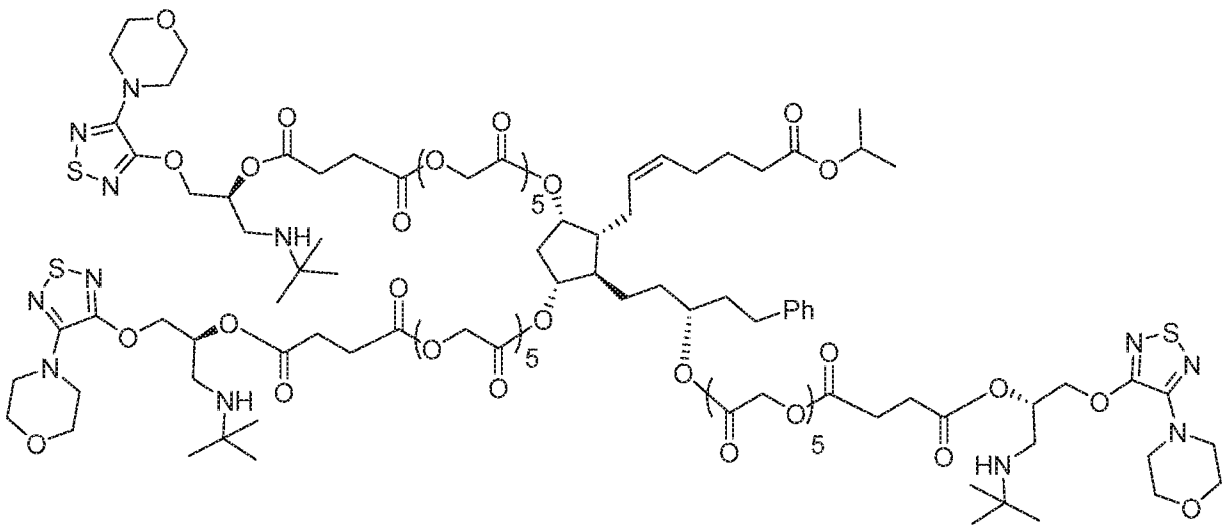


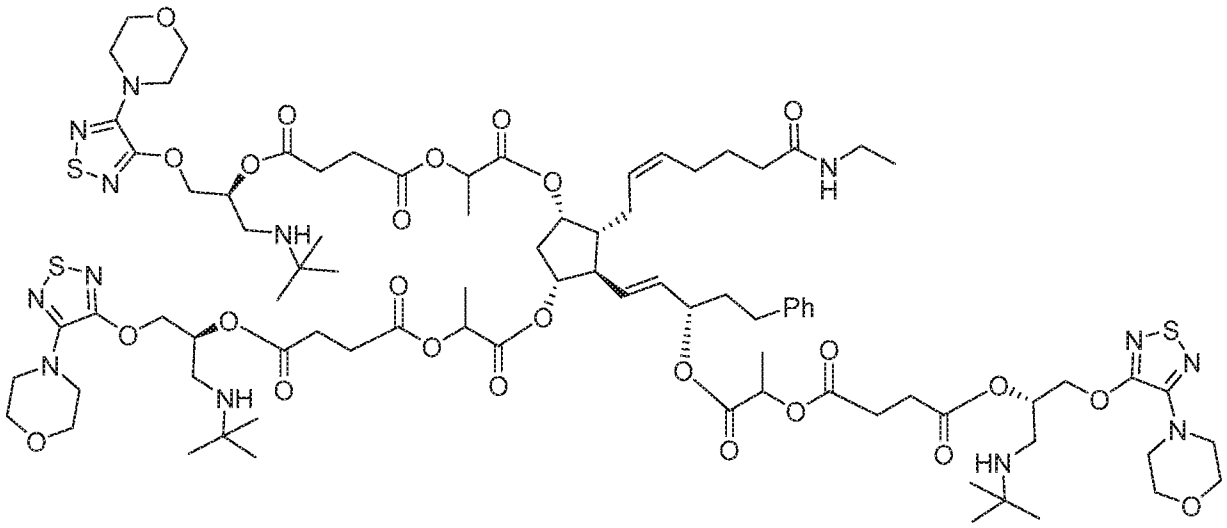


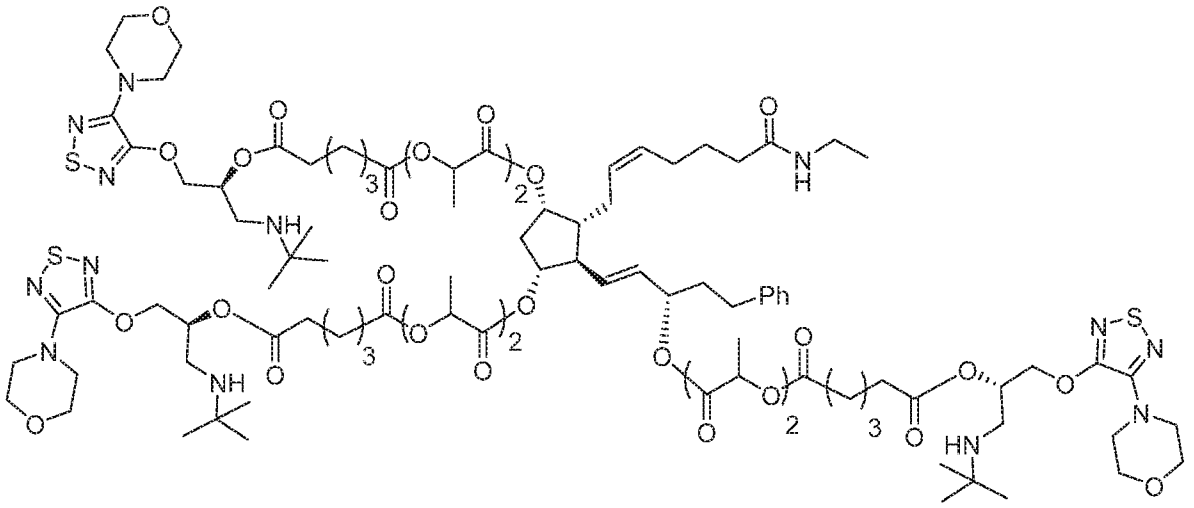


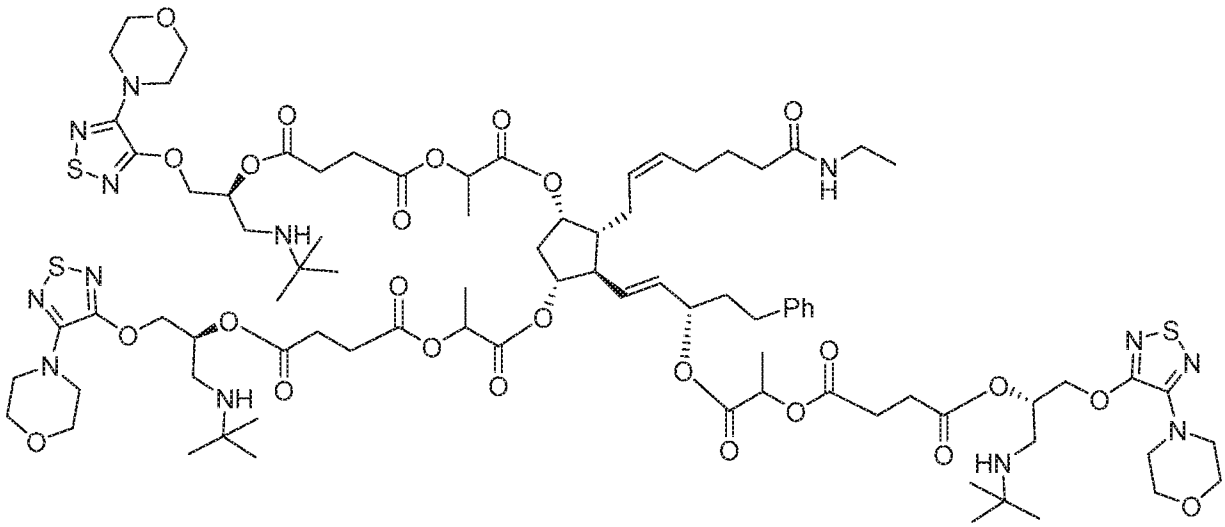


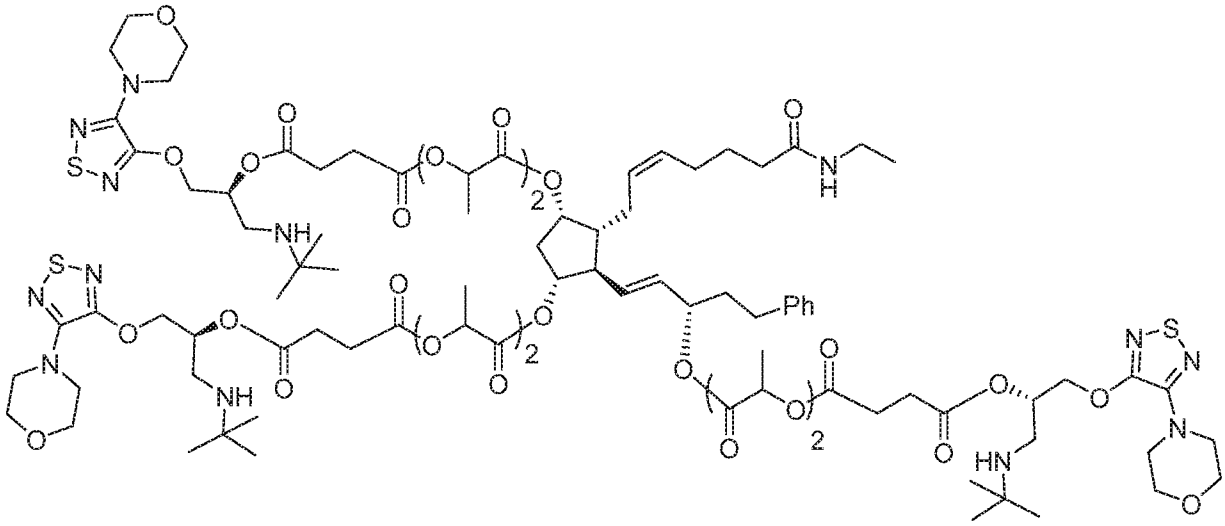


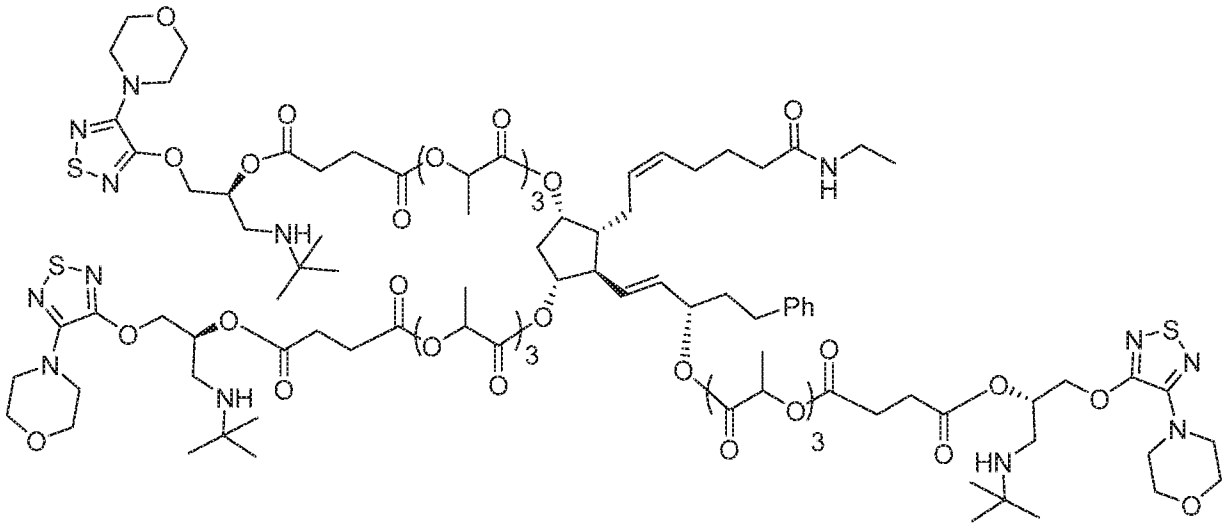


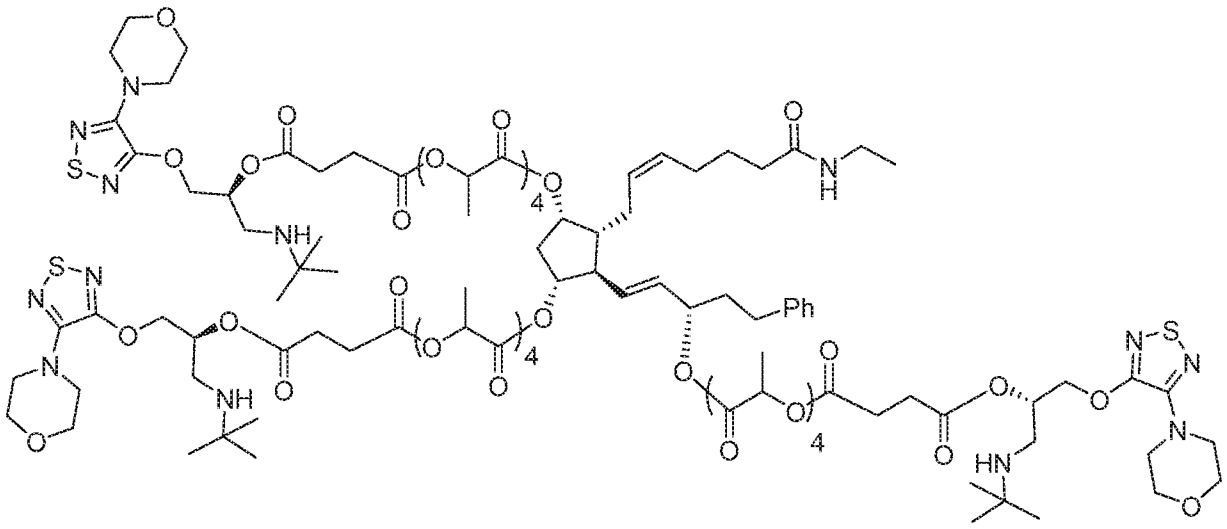


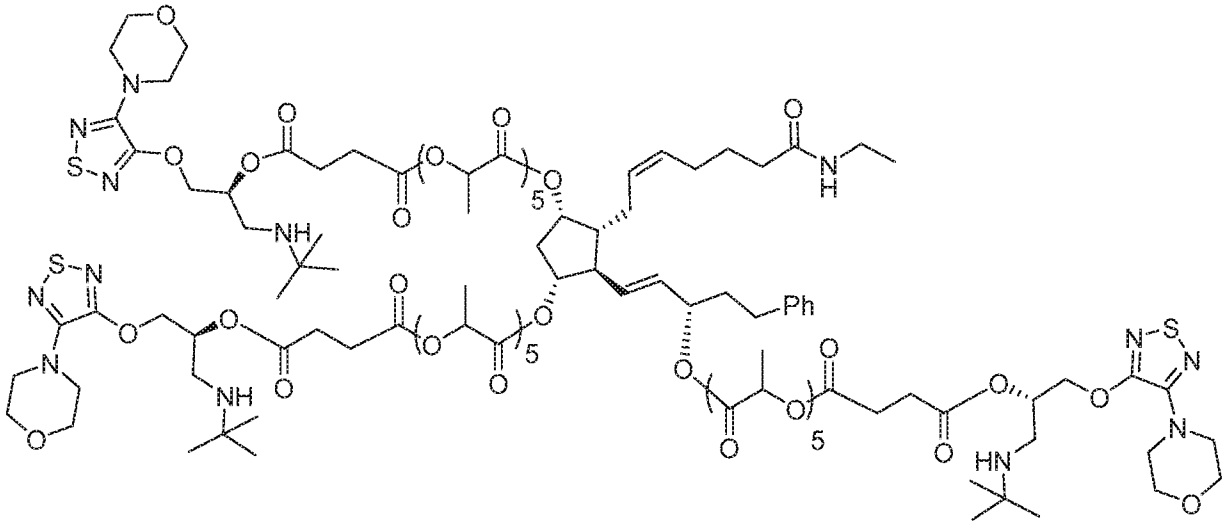


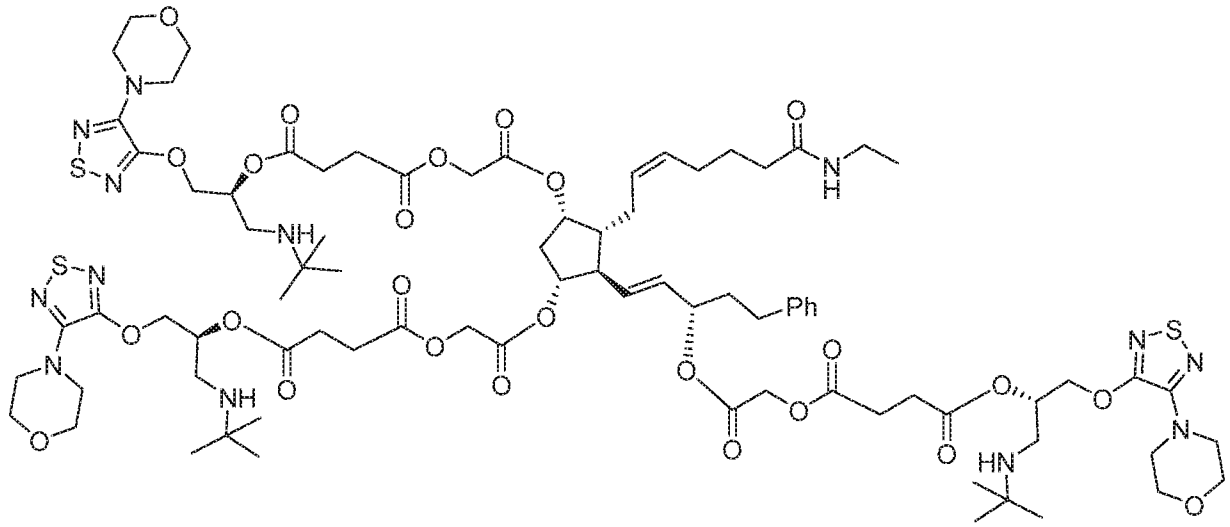


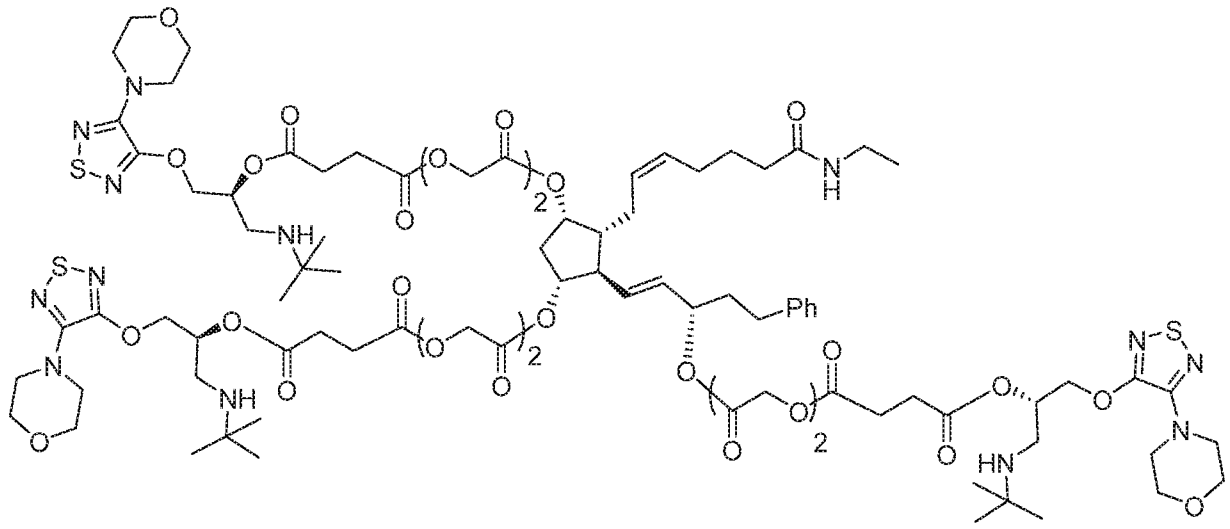


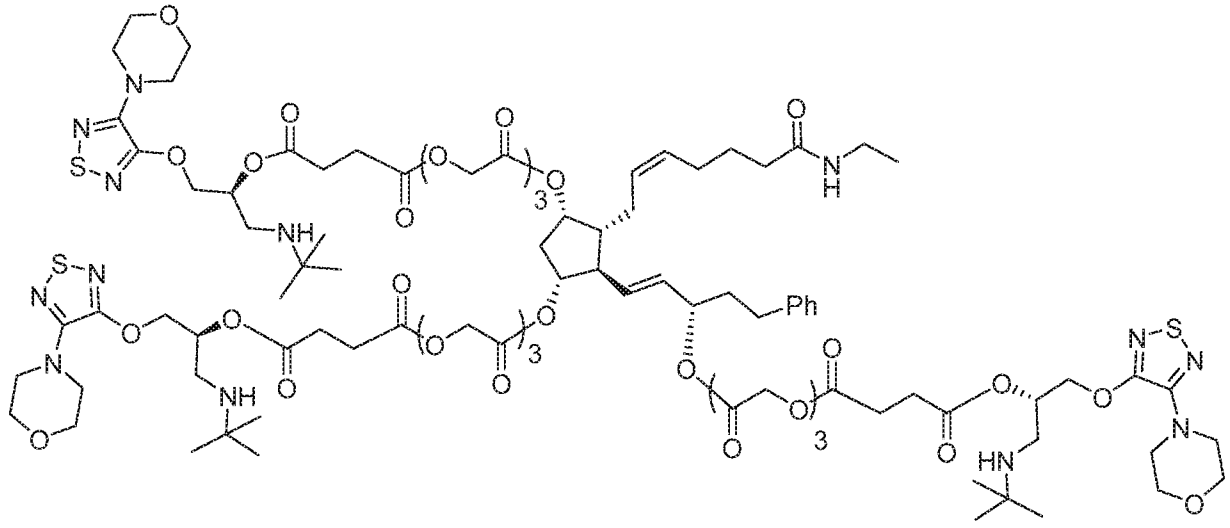


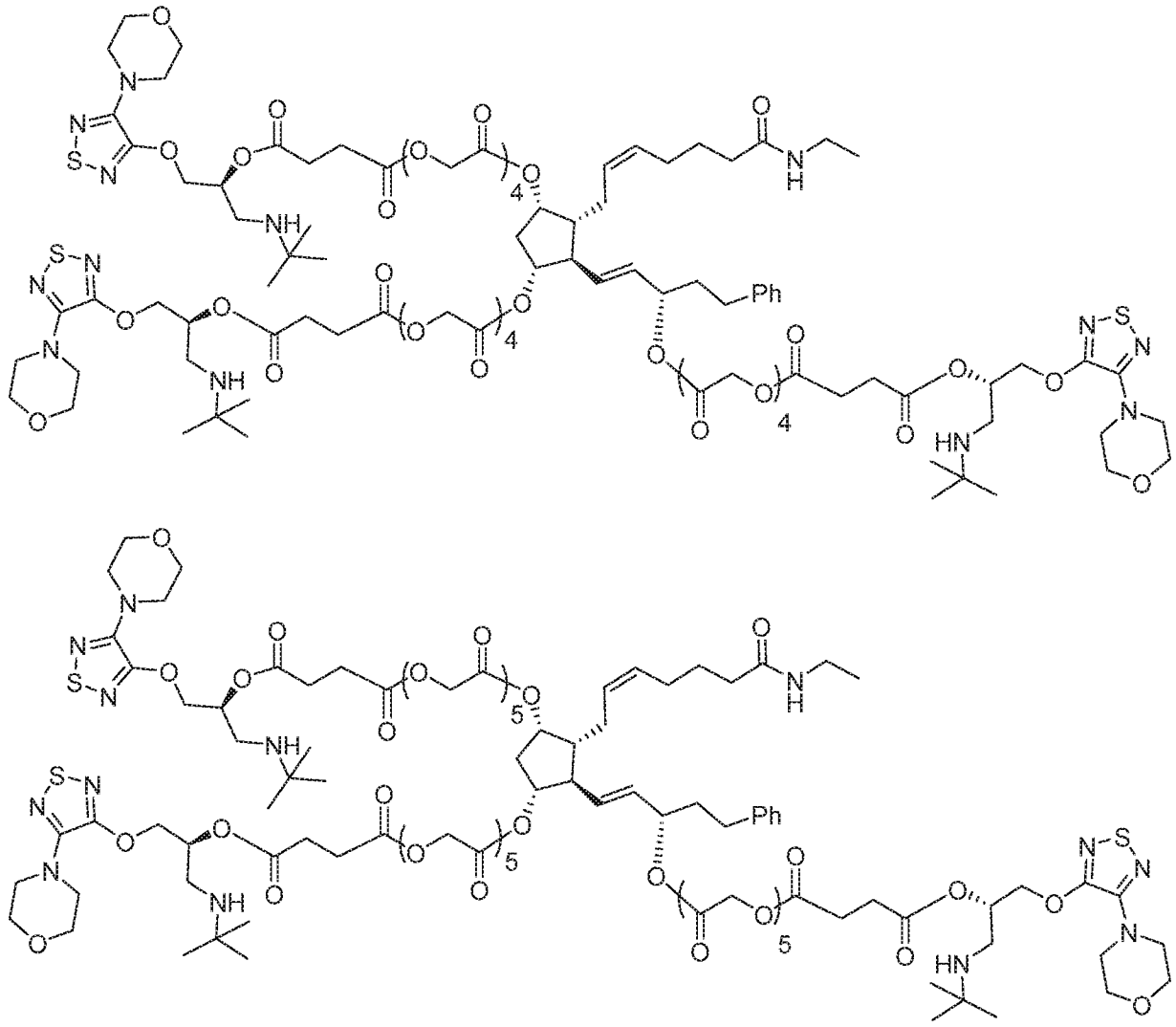




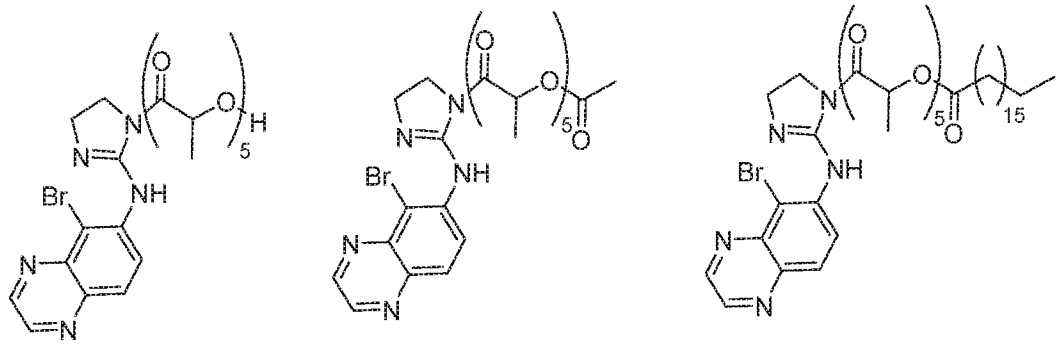


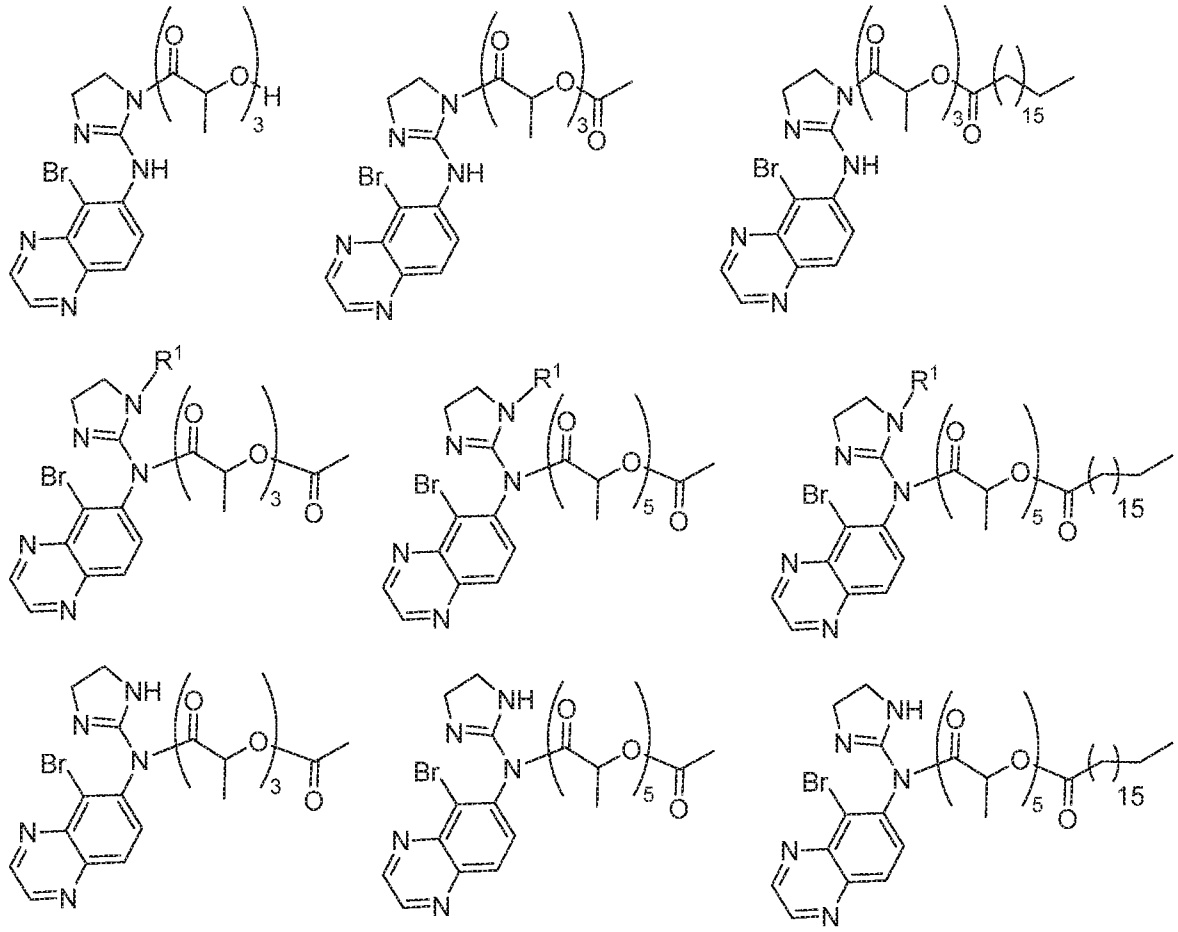




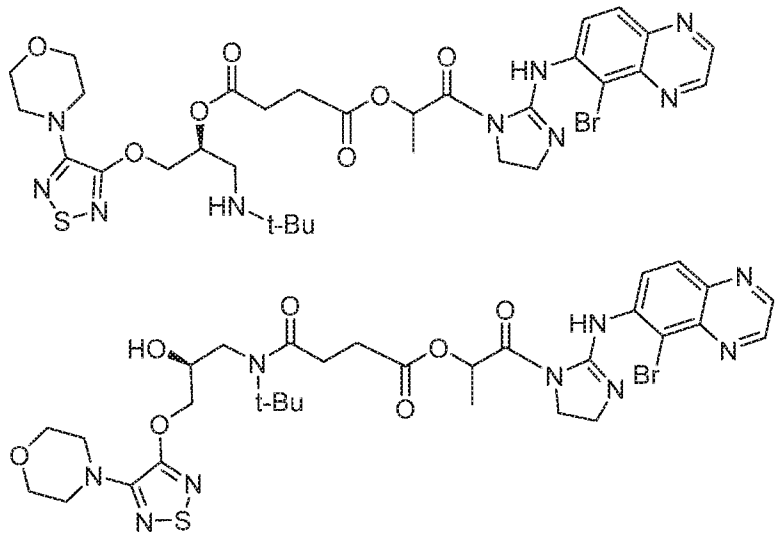


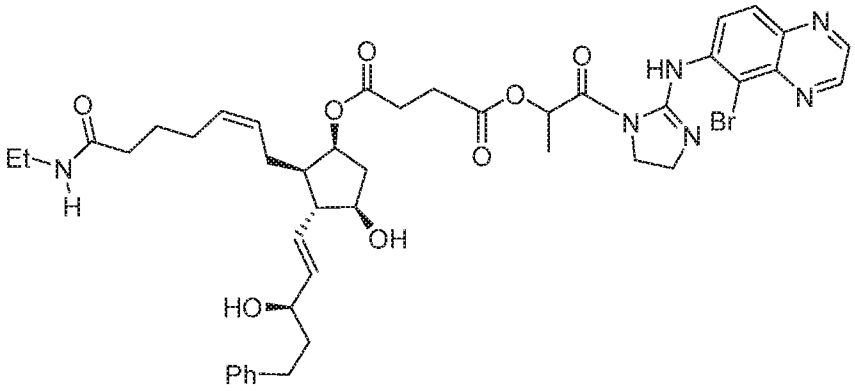
**Example 15. Non-limiting Examples of Formula VII and VIII**

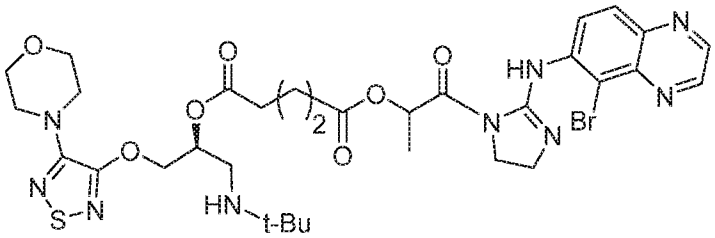


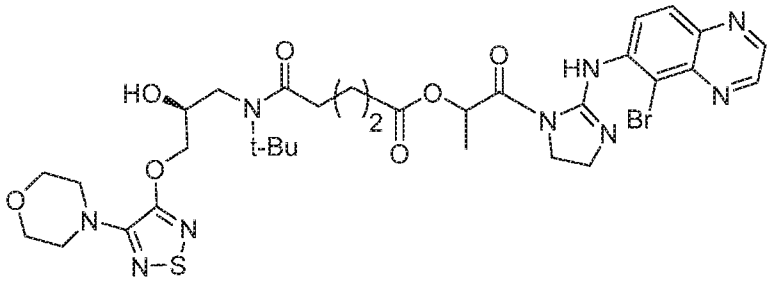


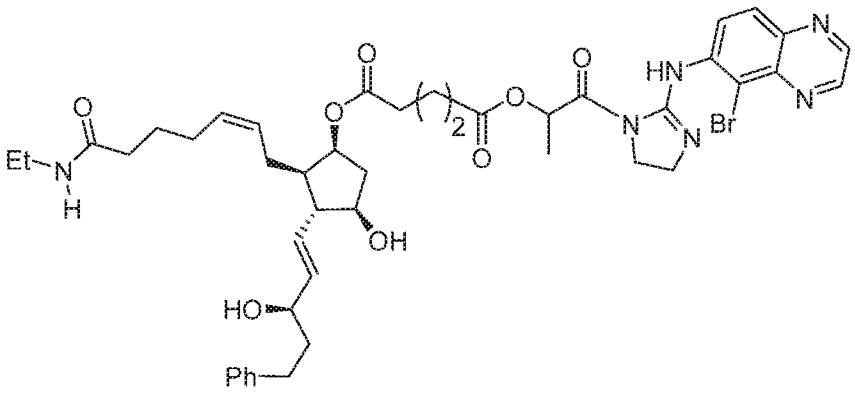
**Example 16. Non-limiting Examples of Formula IX and IX'**

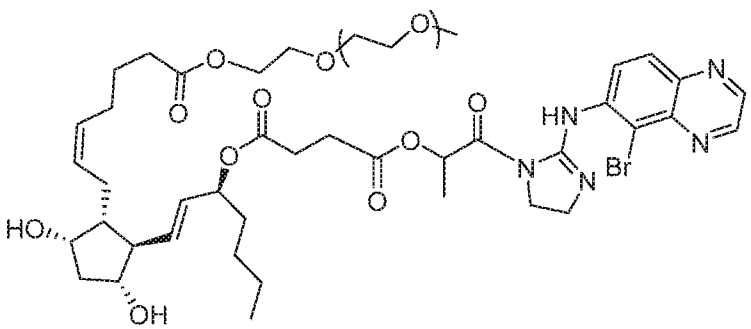


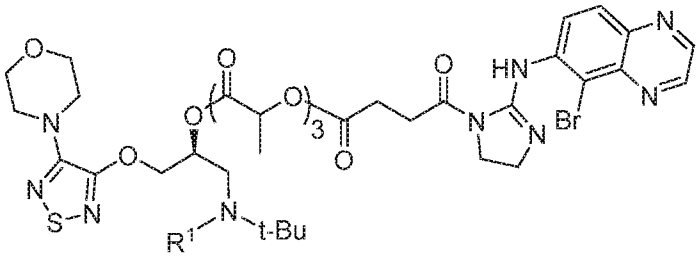


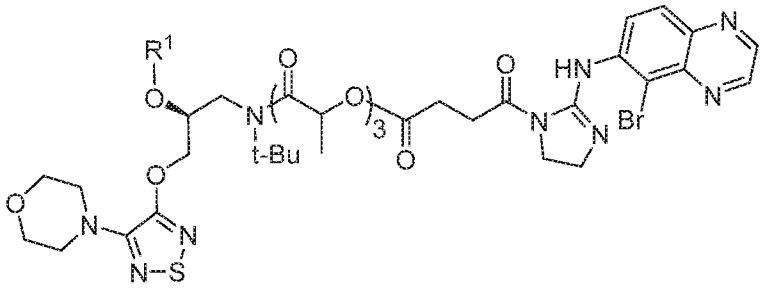


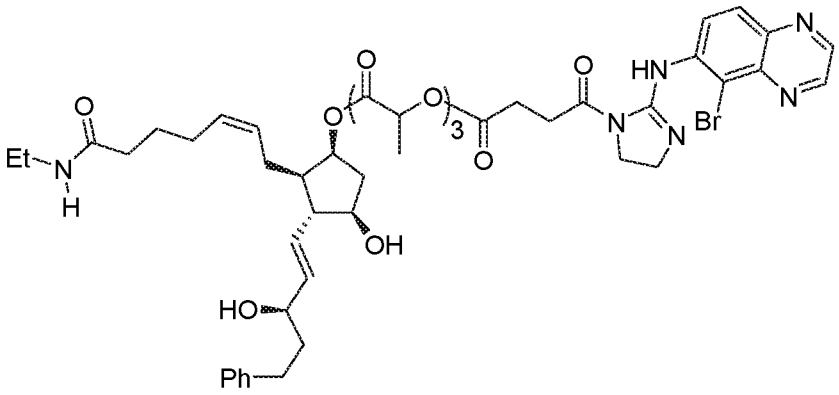


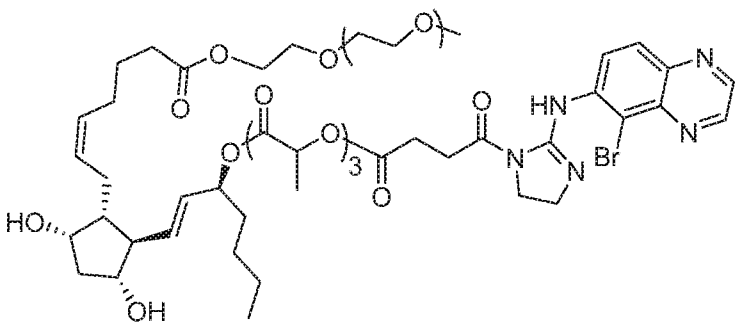


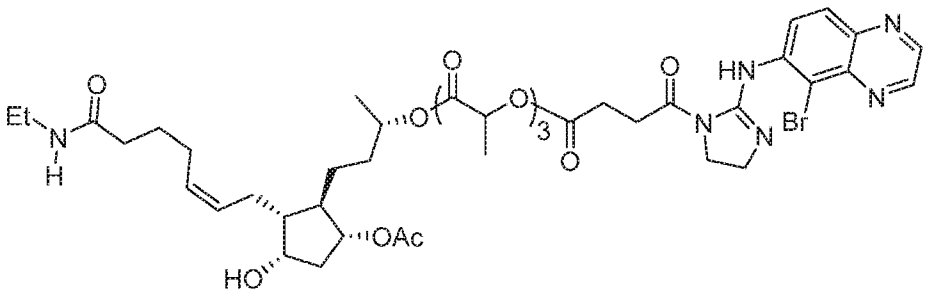


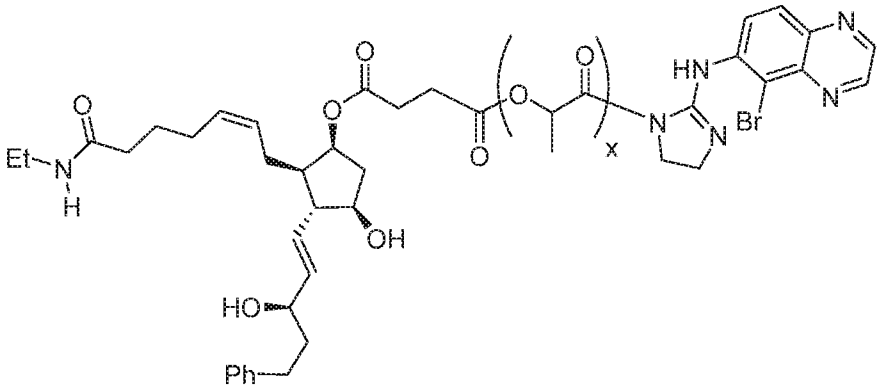




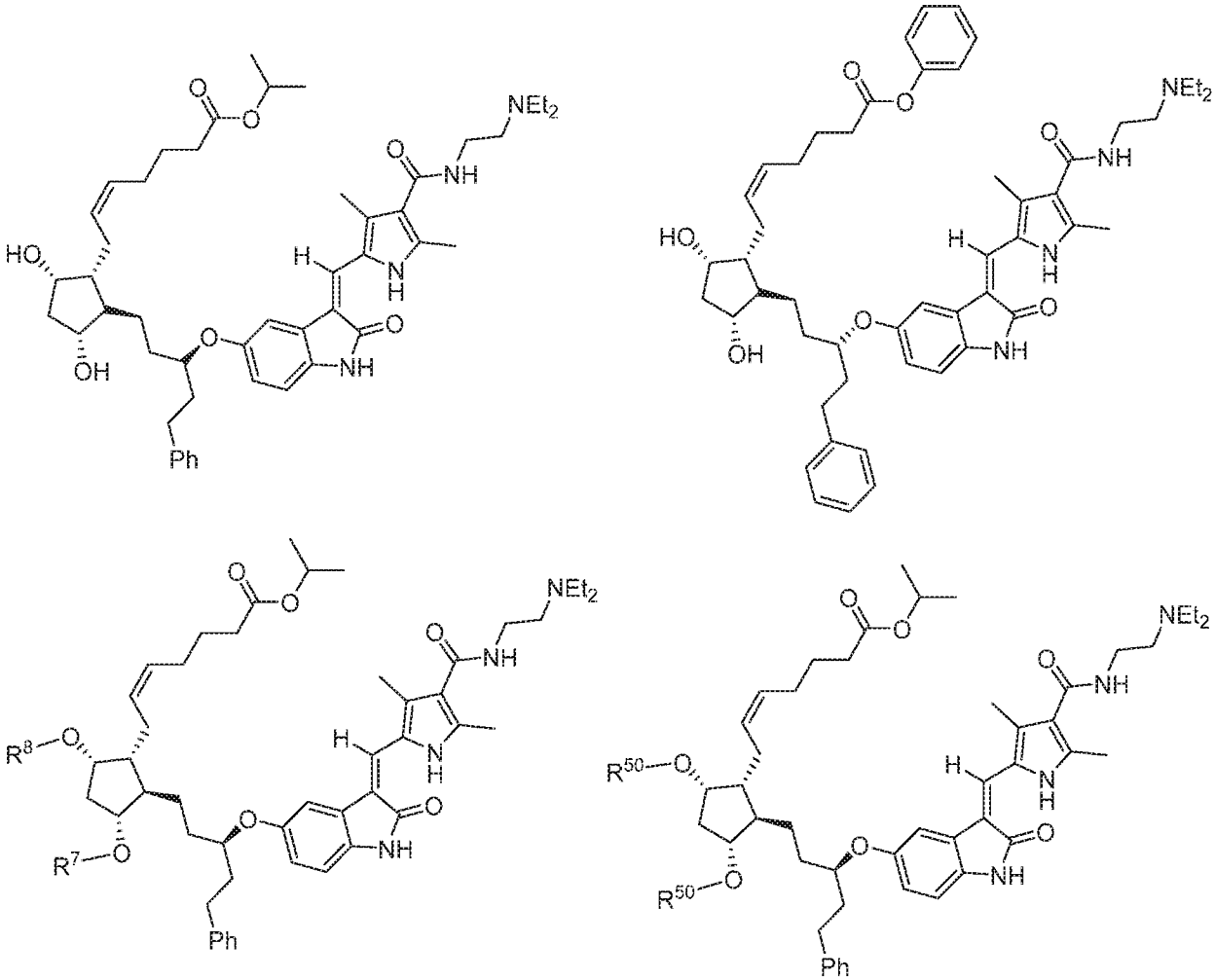


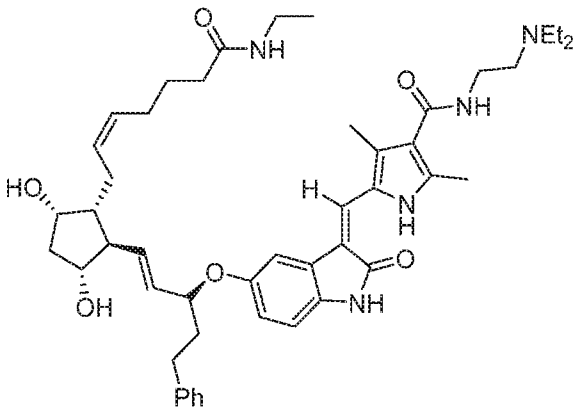


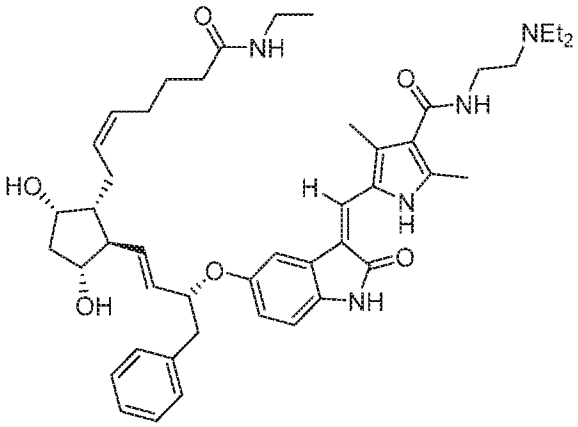


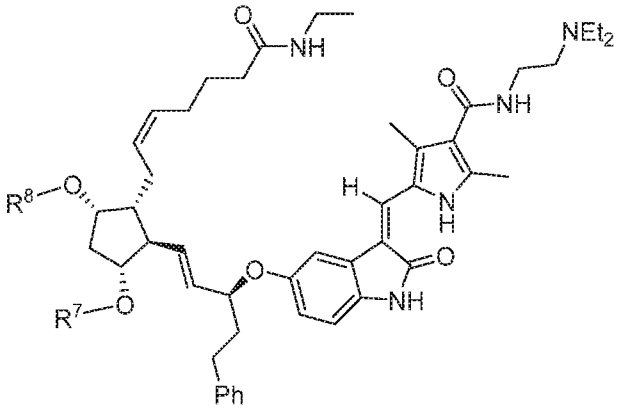


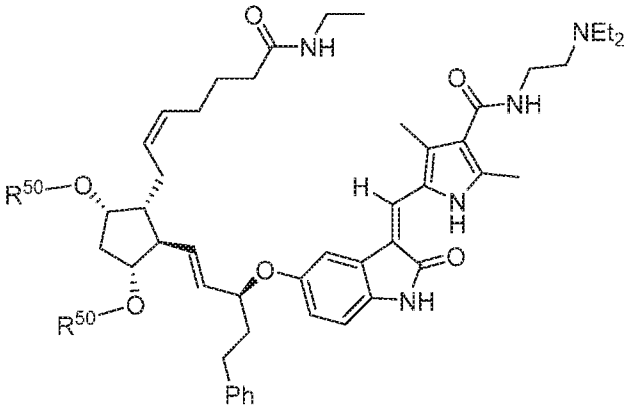
**Example 17. Non-limiting Examples of Formula X**

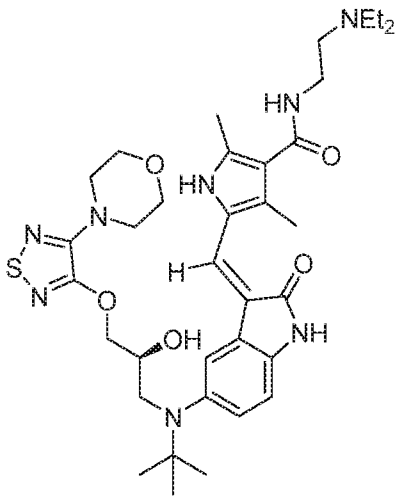


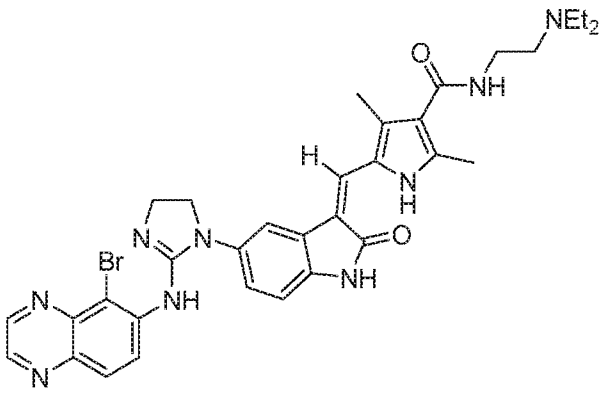




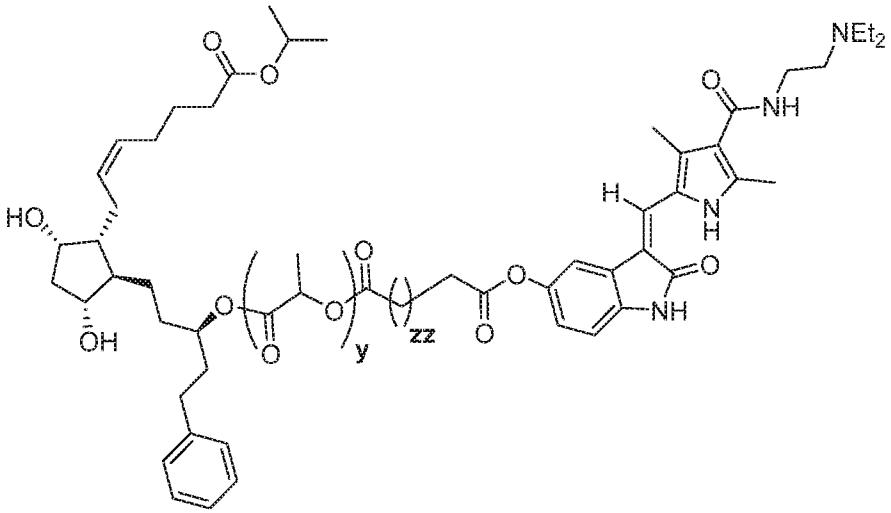


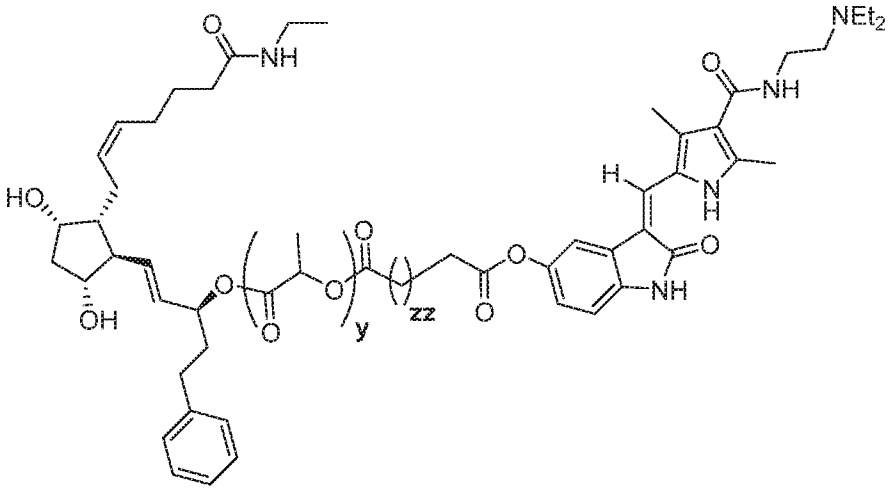


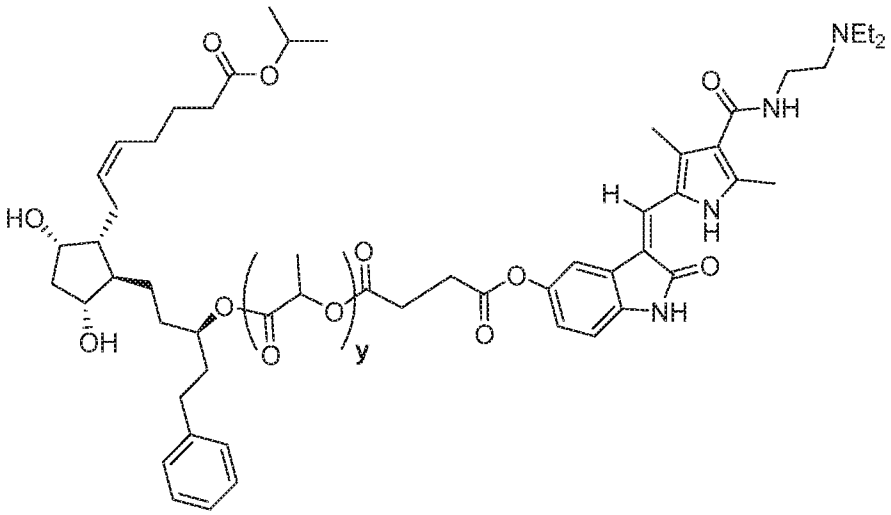


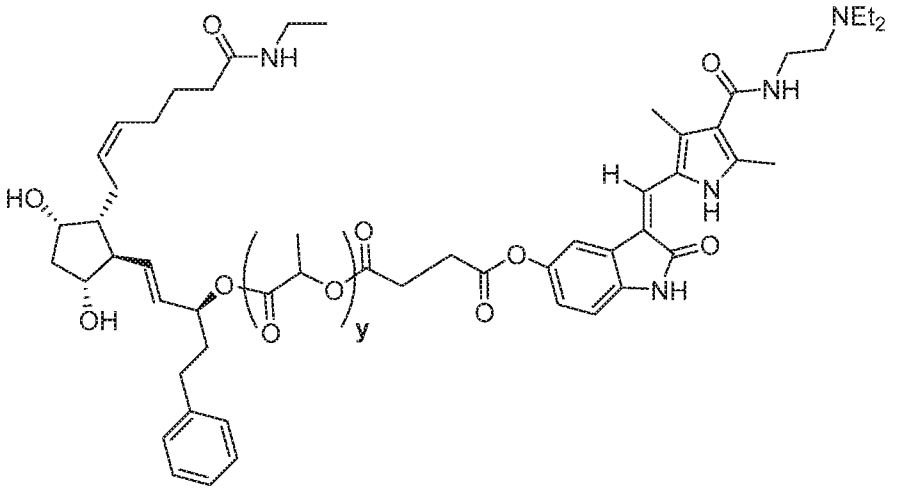


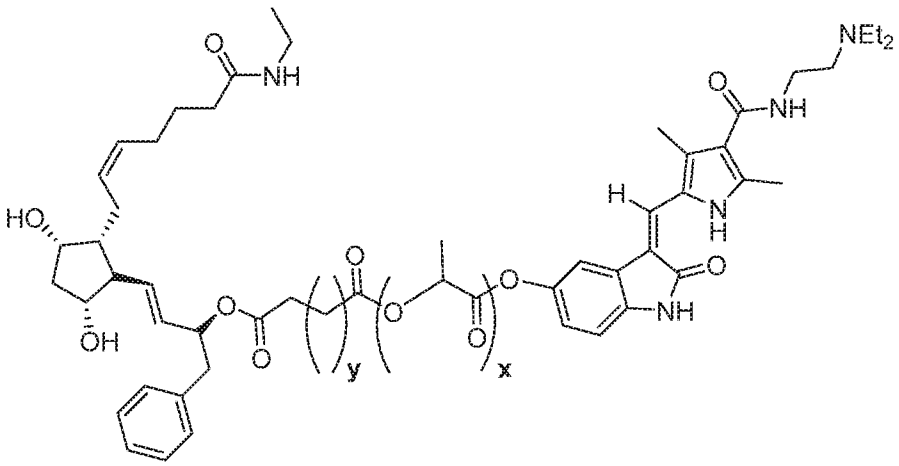
**Example 18. Non-limiting Examples of Formula XI**

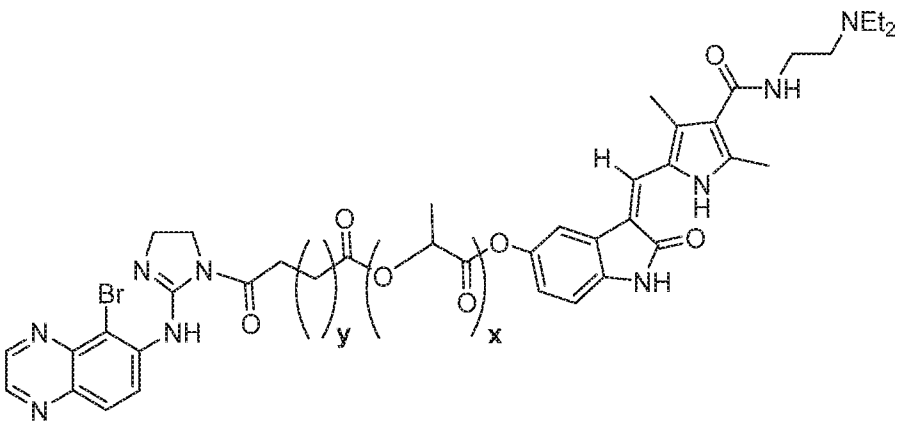


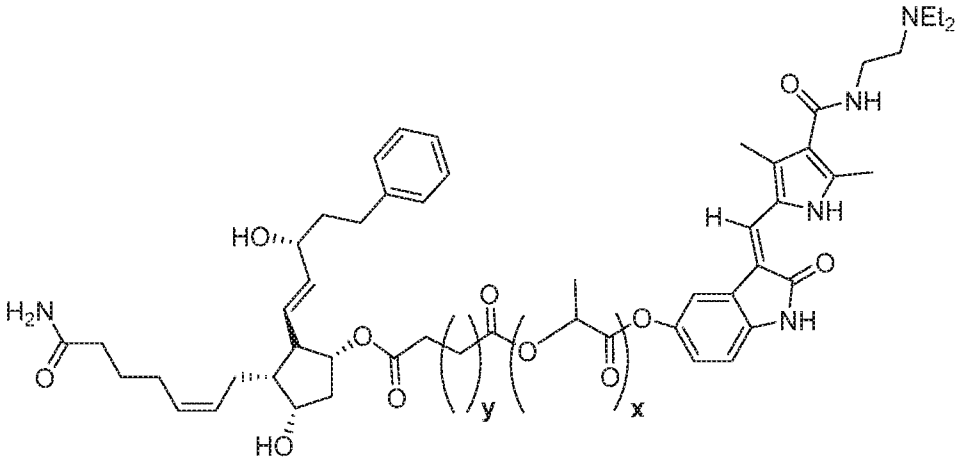




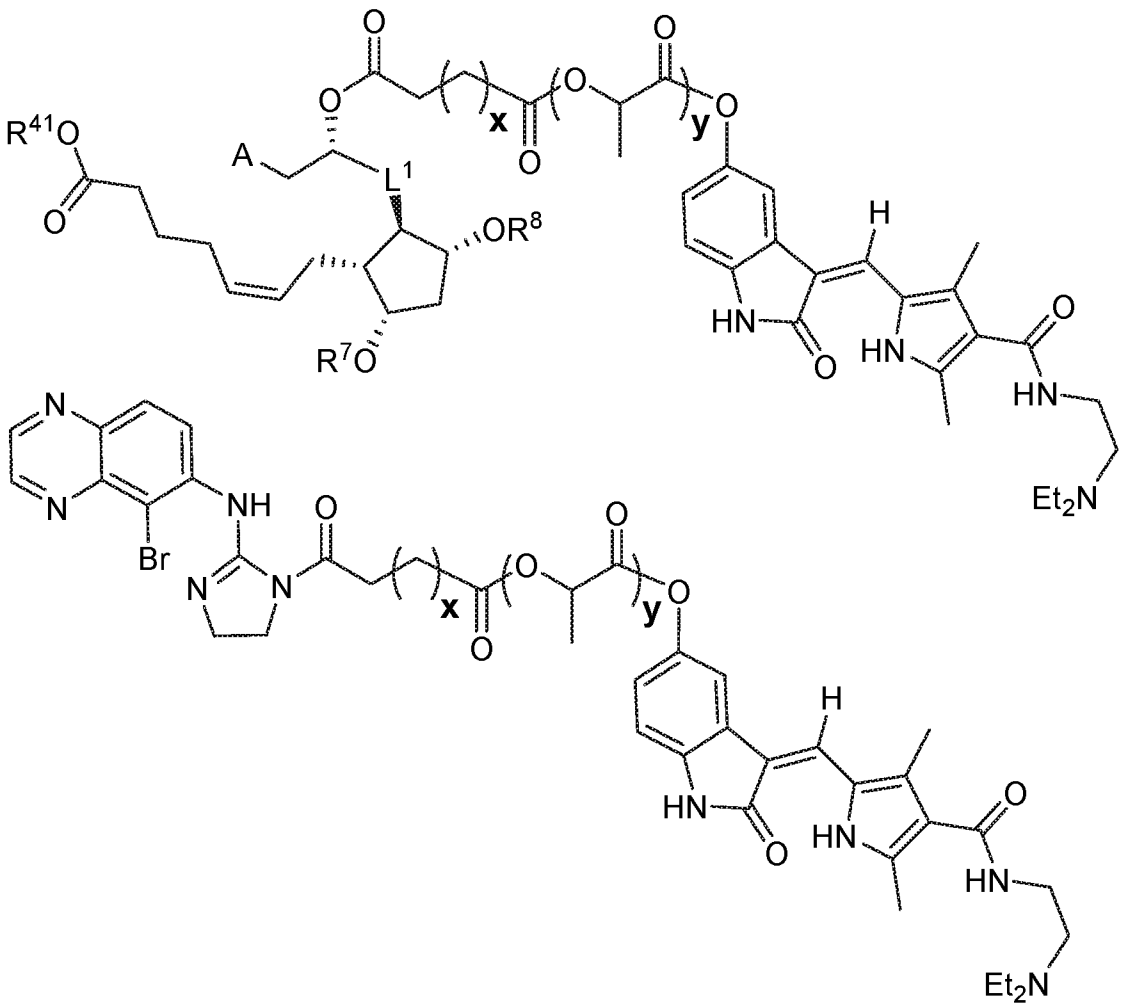


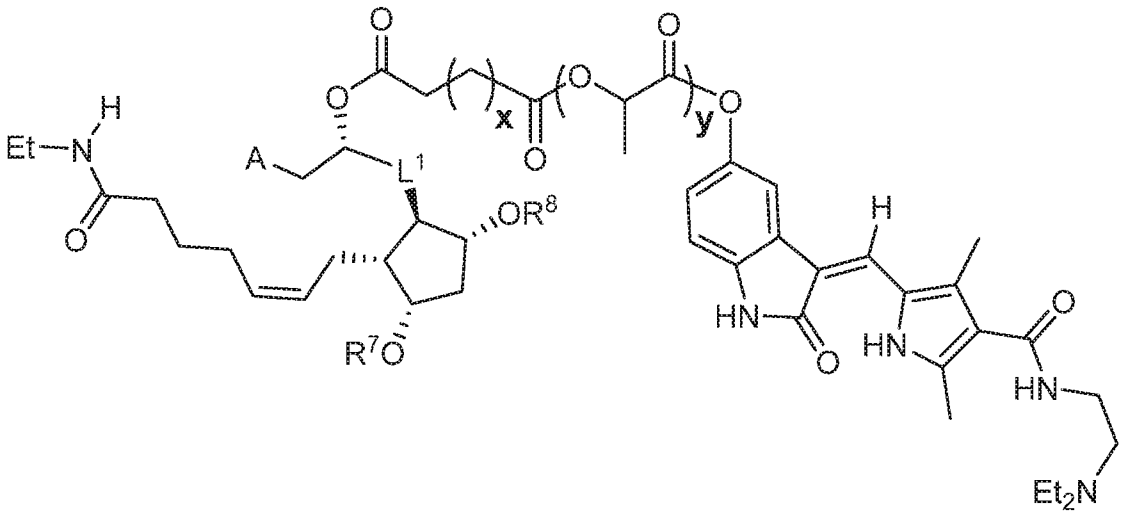




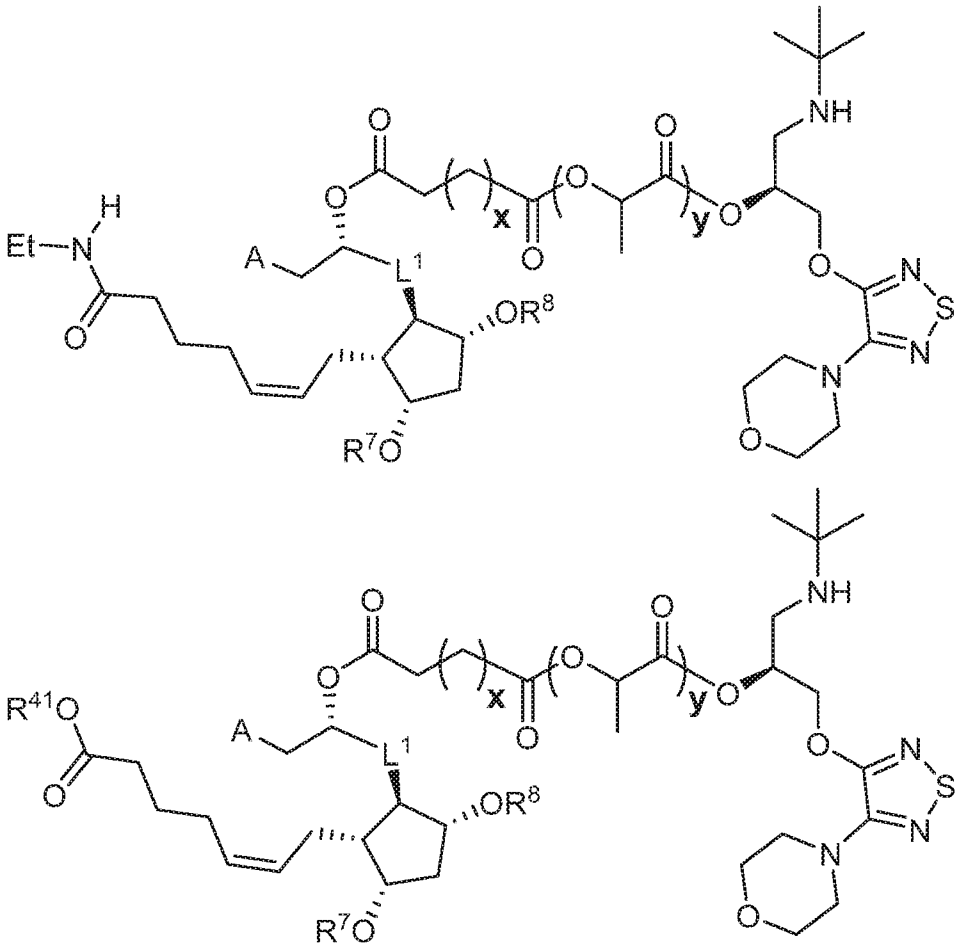


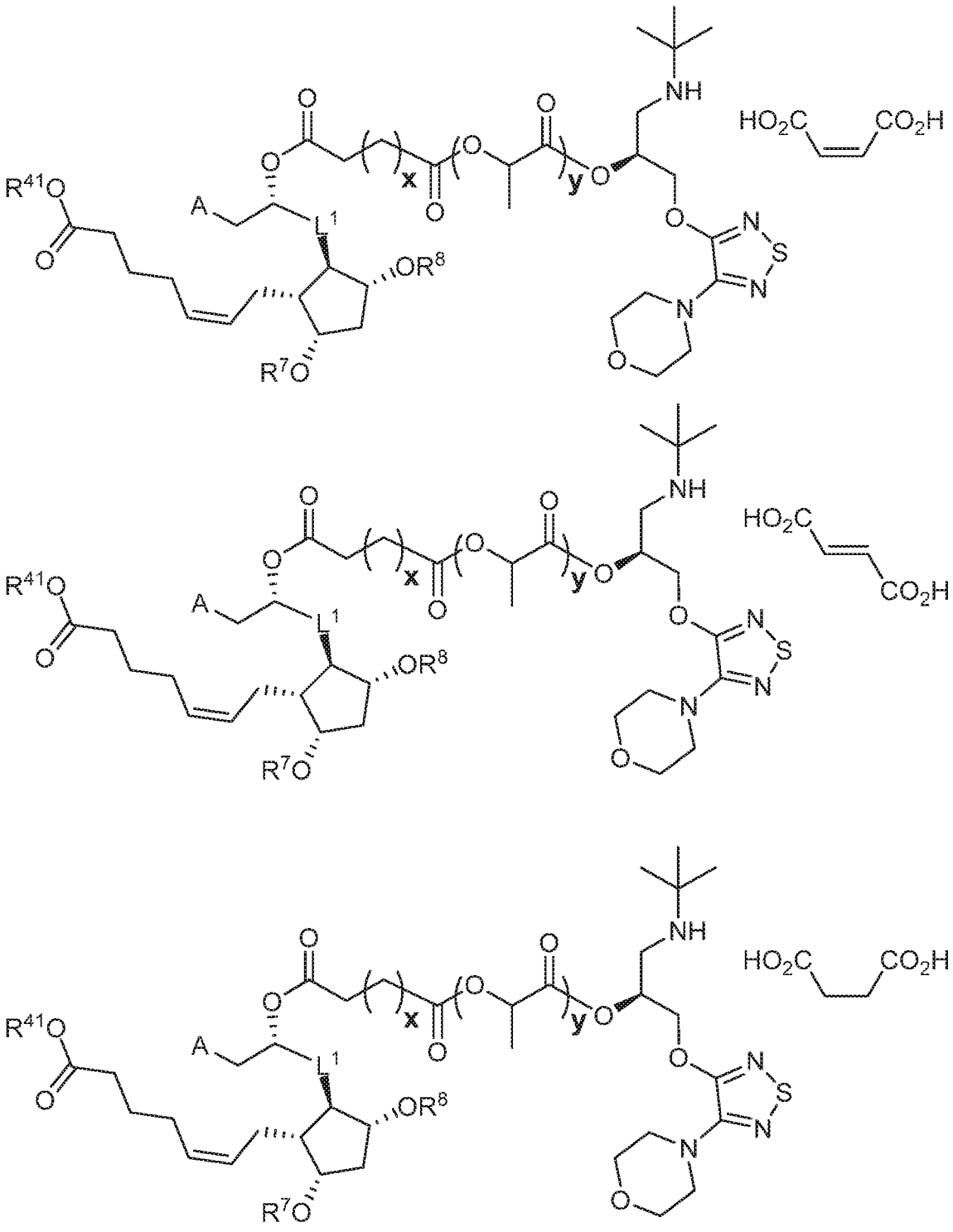
**Example 19. Non-limiting Examples of Formula XII**

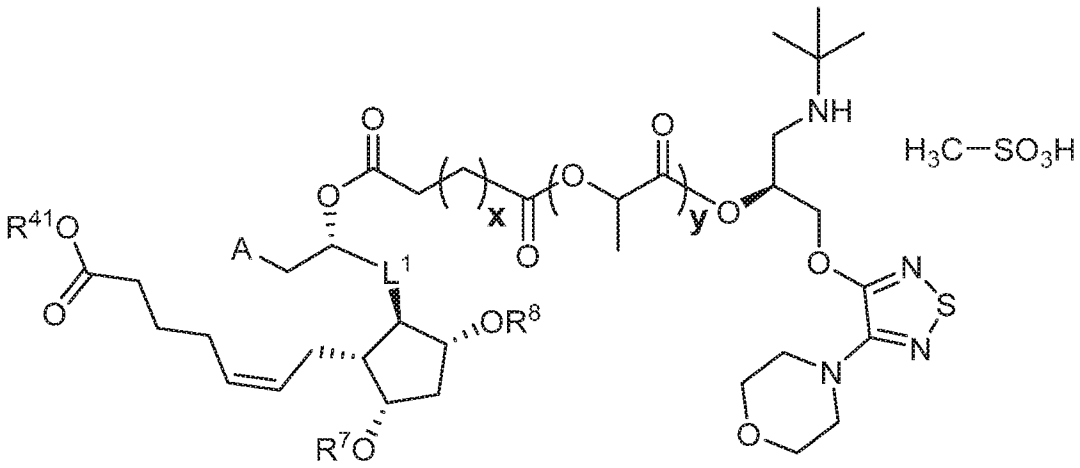


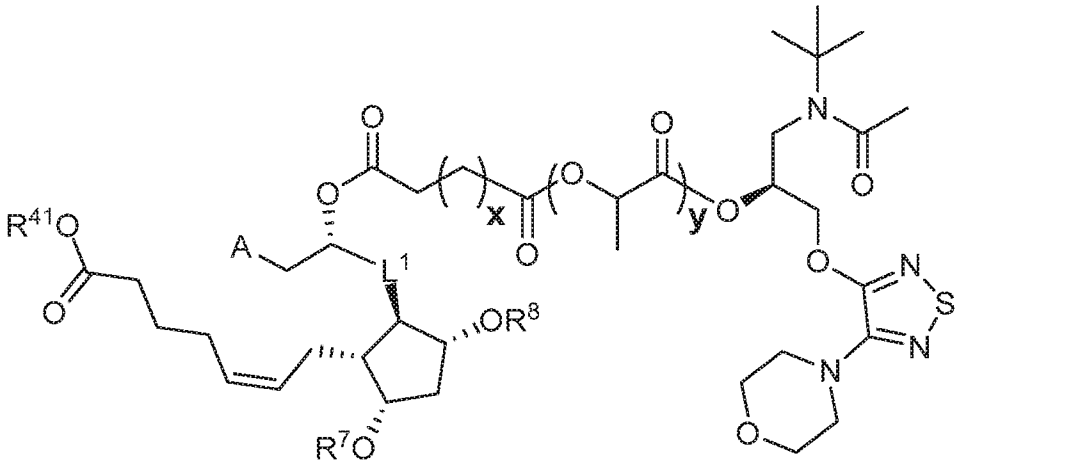


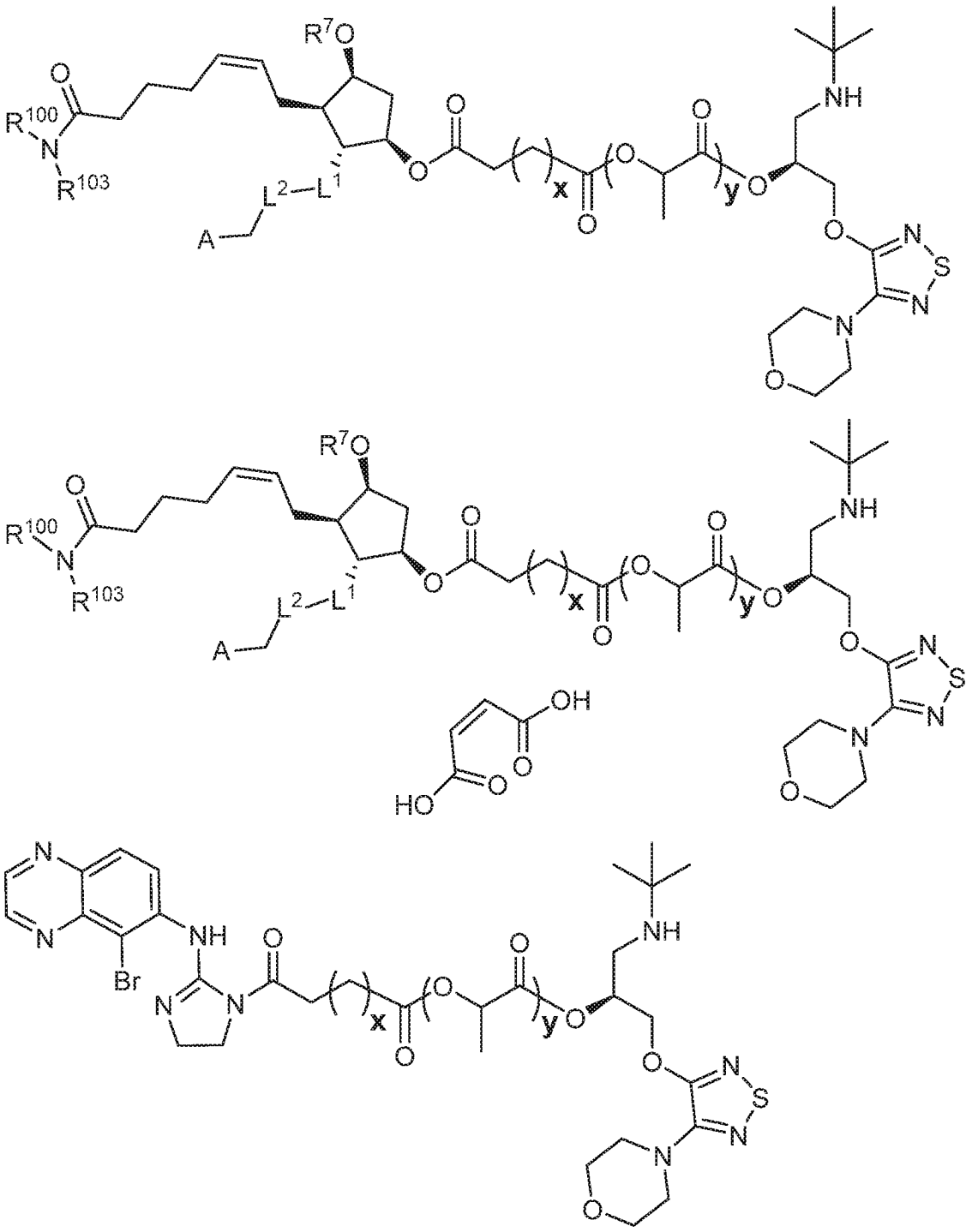
**Example 20. Non-limiting Examples of Formula XIII**

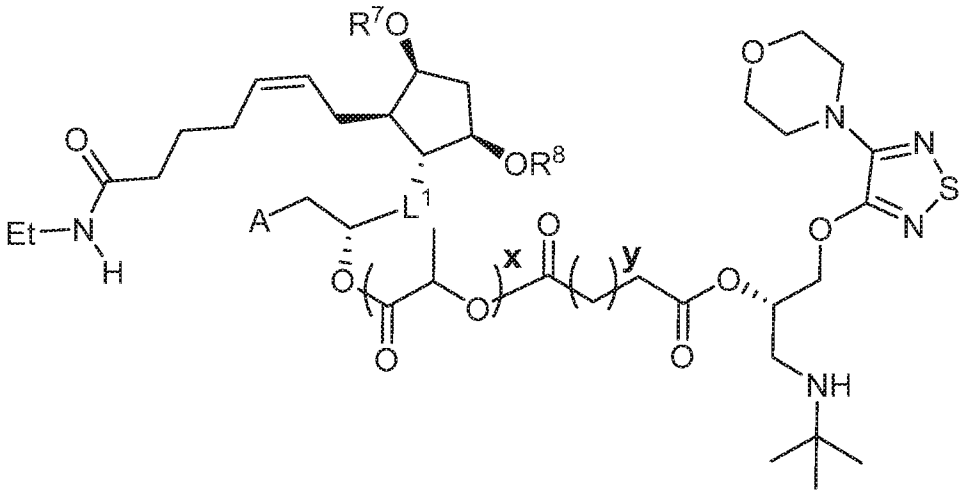




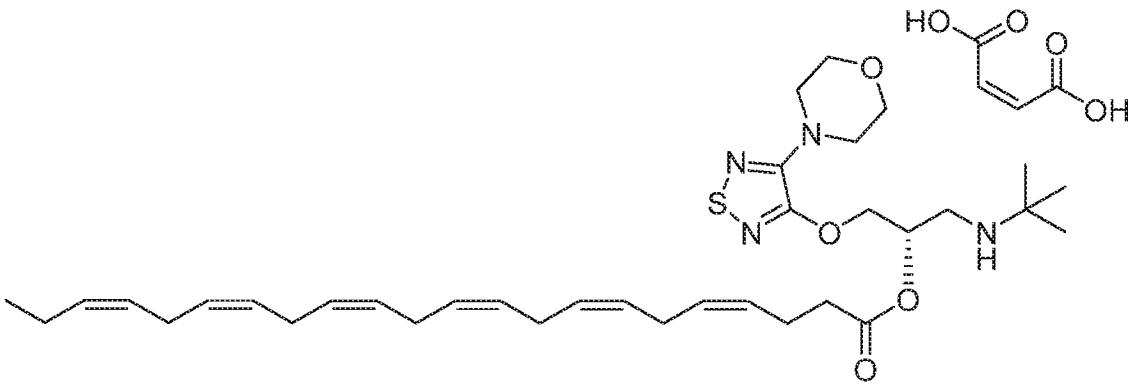


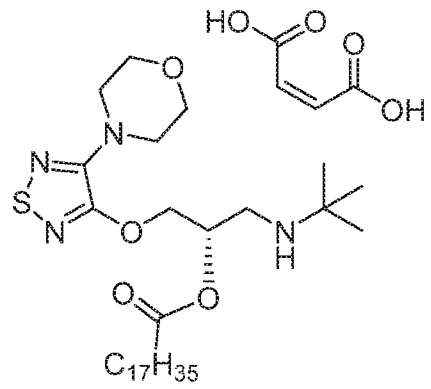




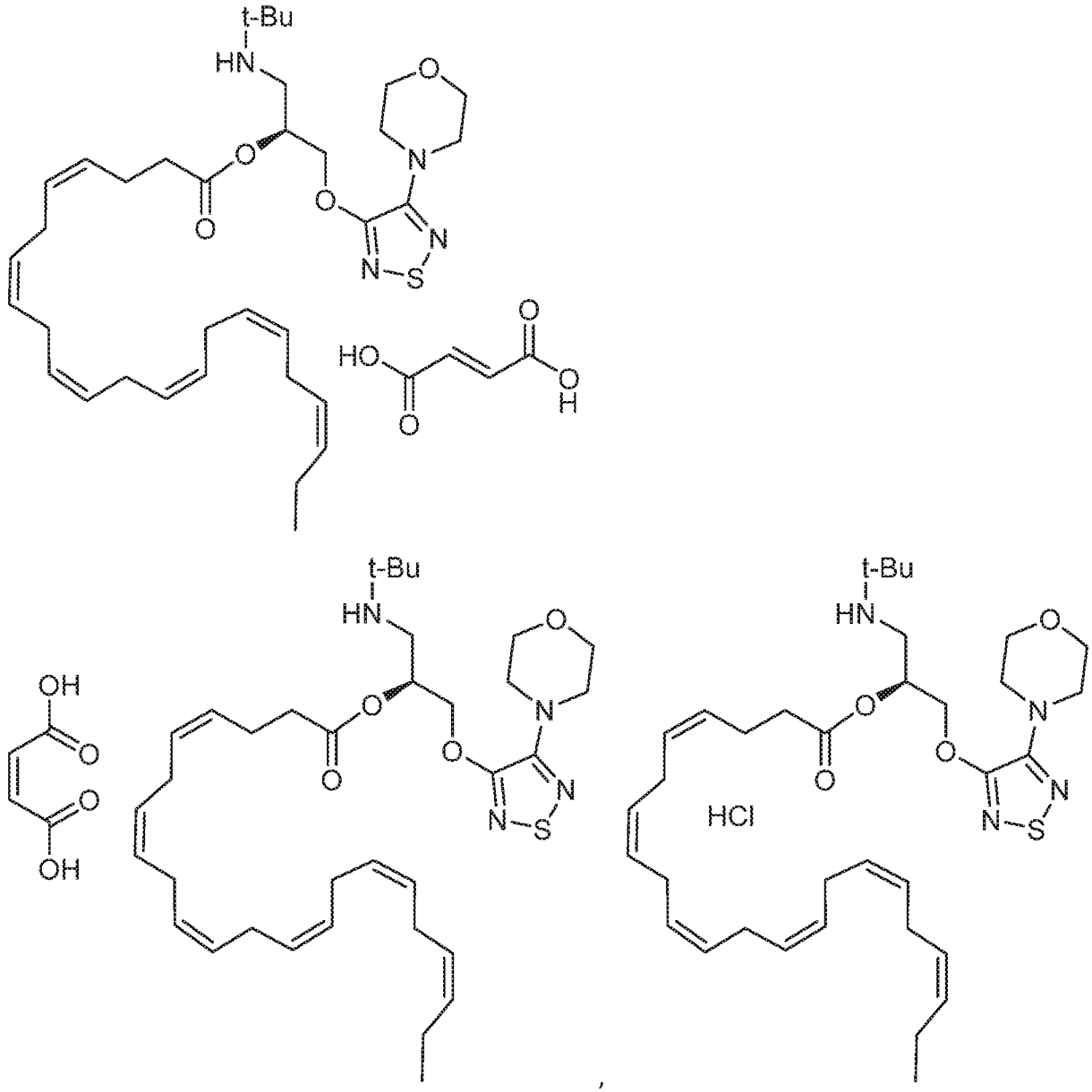


**Example 21. Non-limiting Examples of Formula XIV**

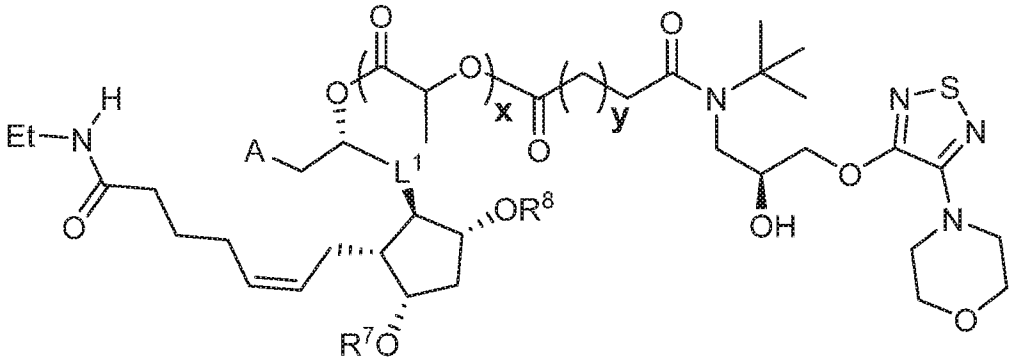


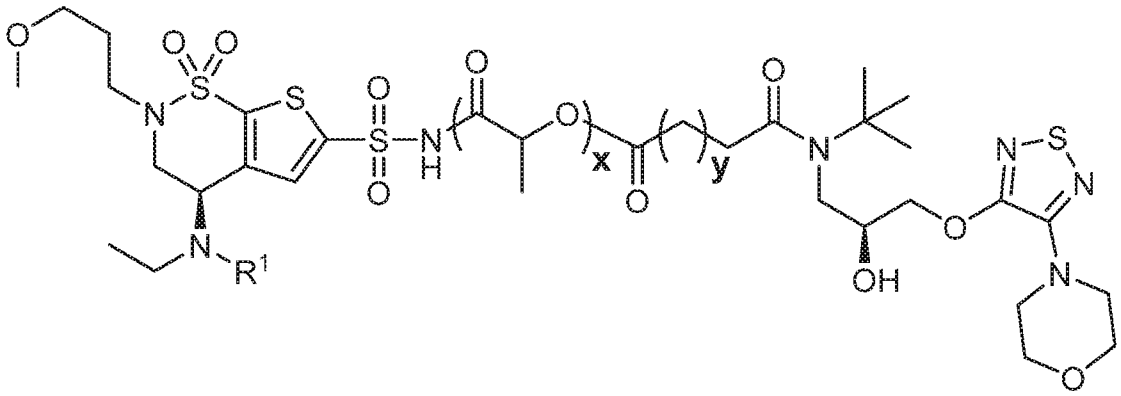


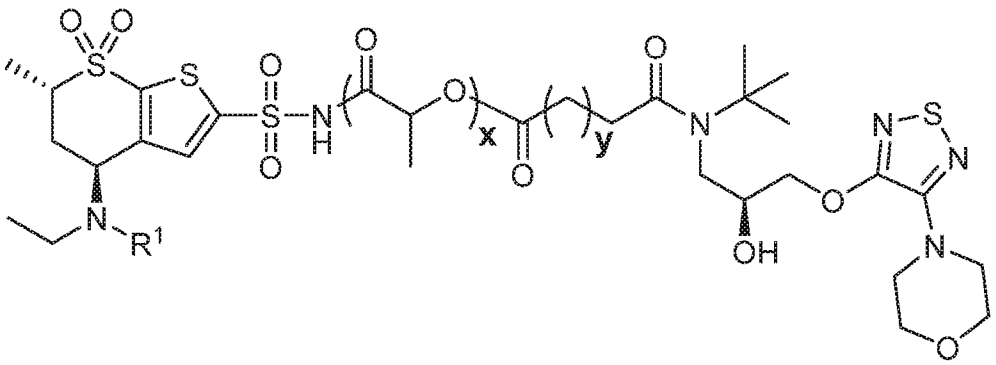
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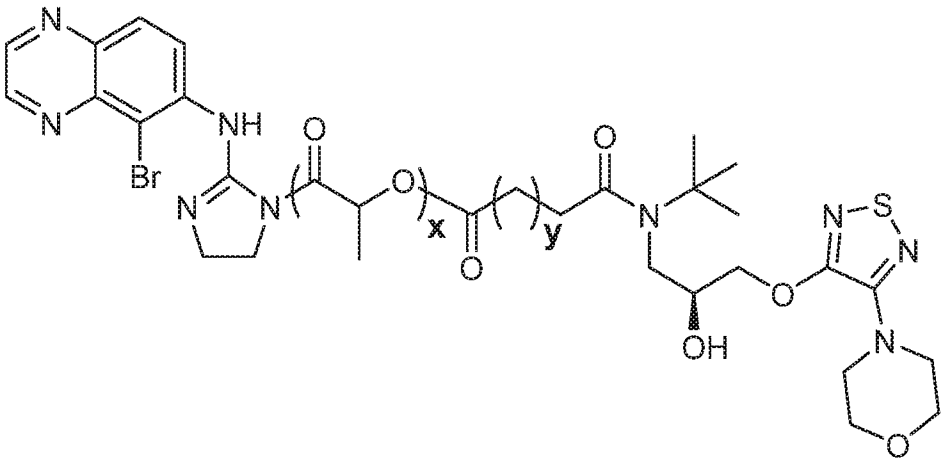


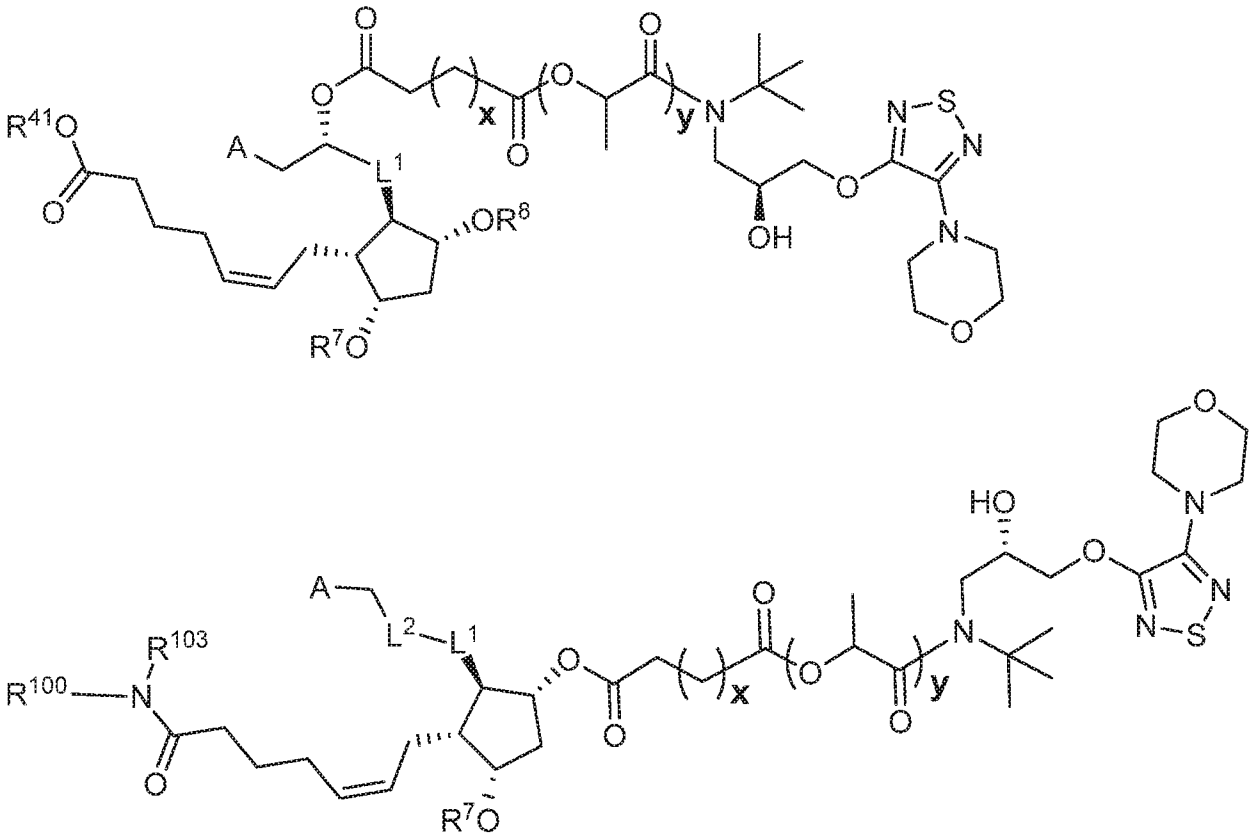

**Example 22. Non-limiting Examples of Formula XV**



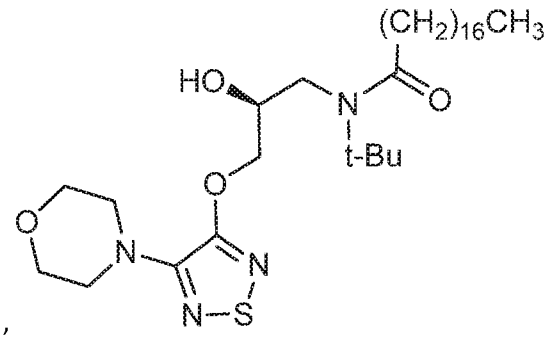




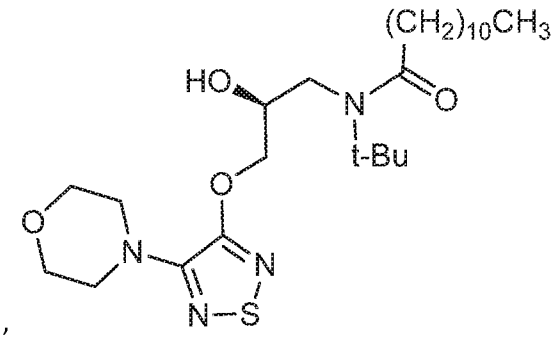




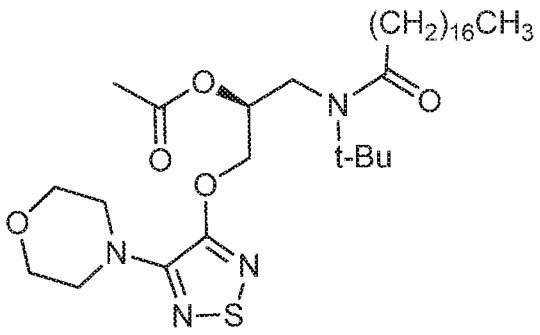
**Example 23. Non-limiting Examples of Formula XVI**



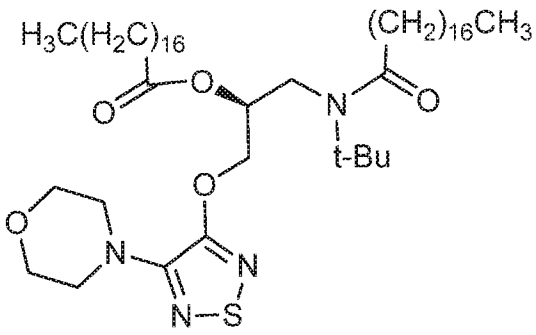
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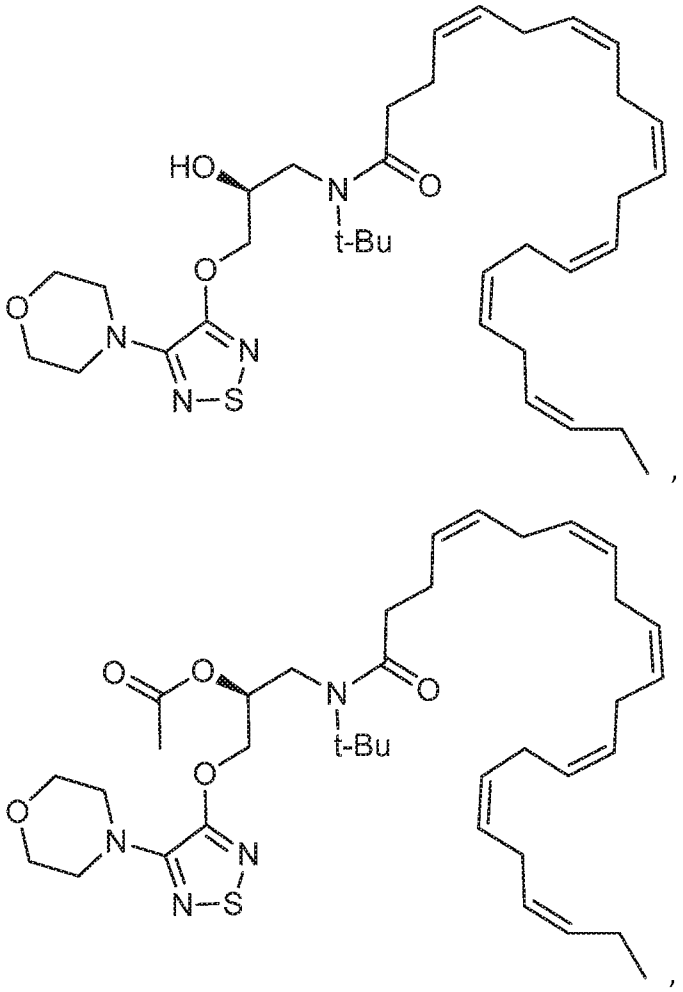
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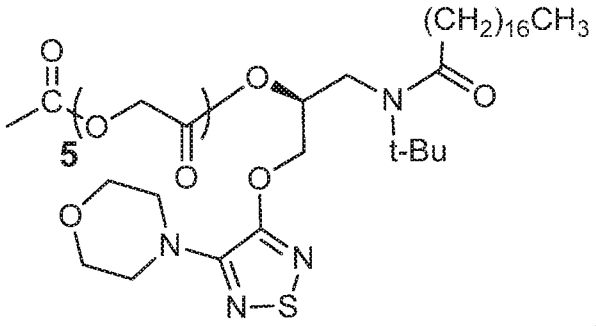
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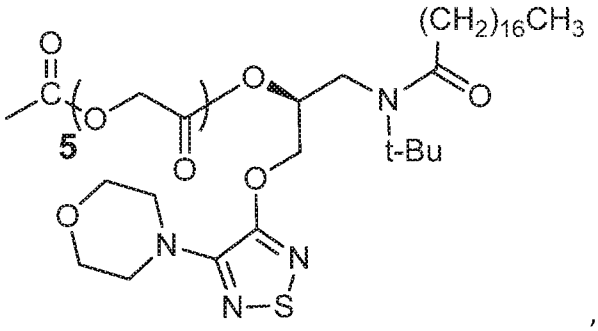
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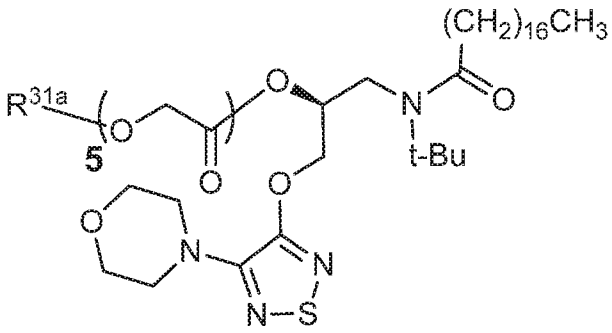
**Example 24. Non-limiting Examples of Formula XVII**



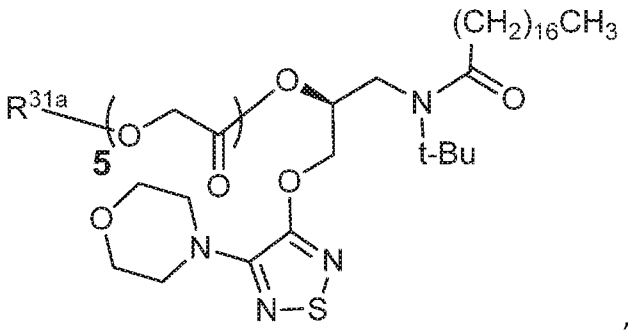
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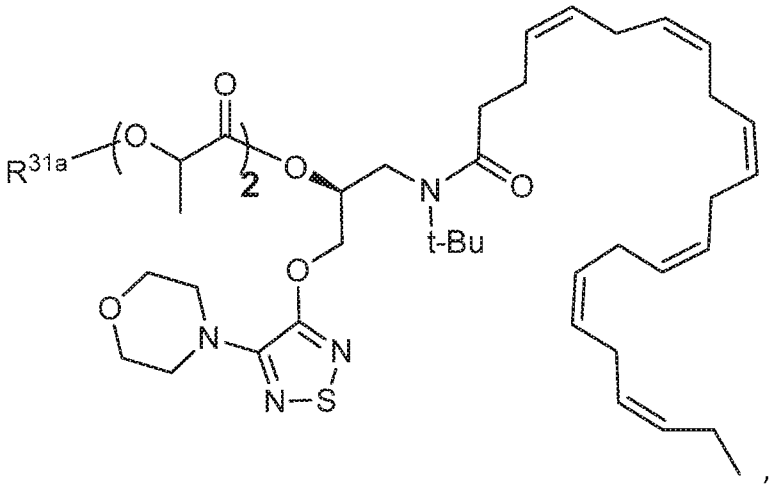
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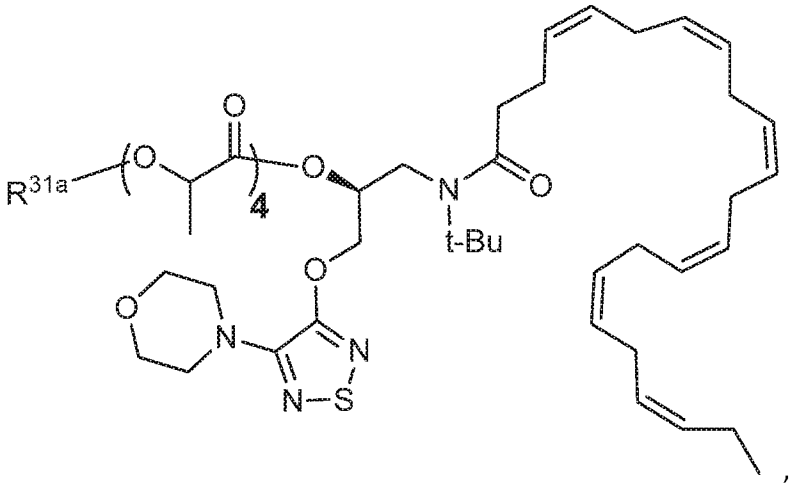
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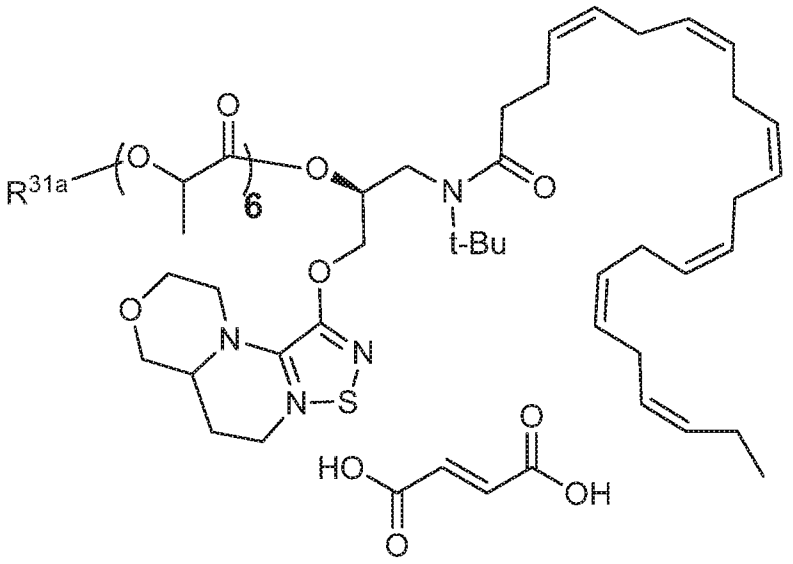


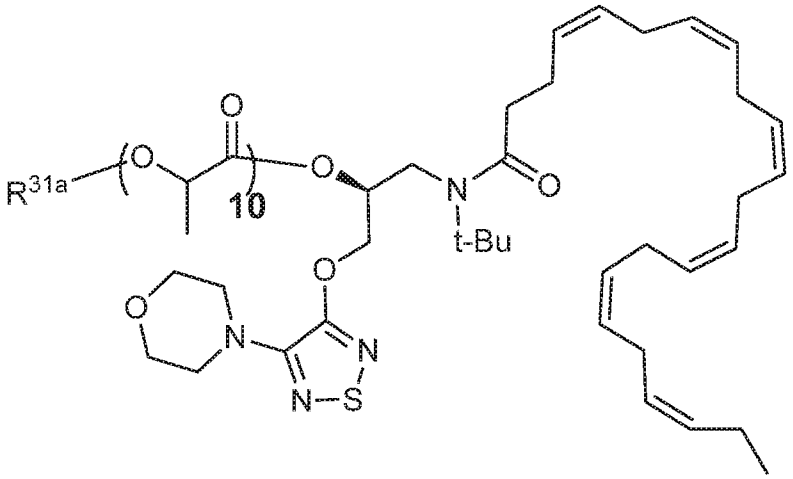
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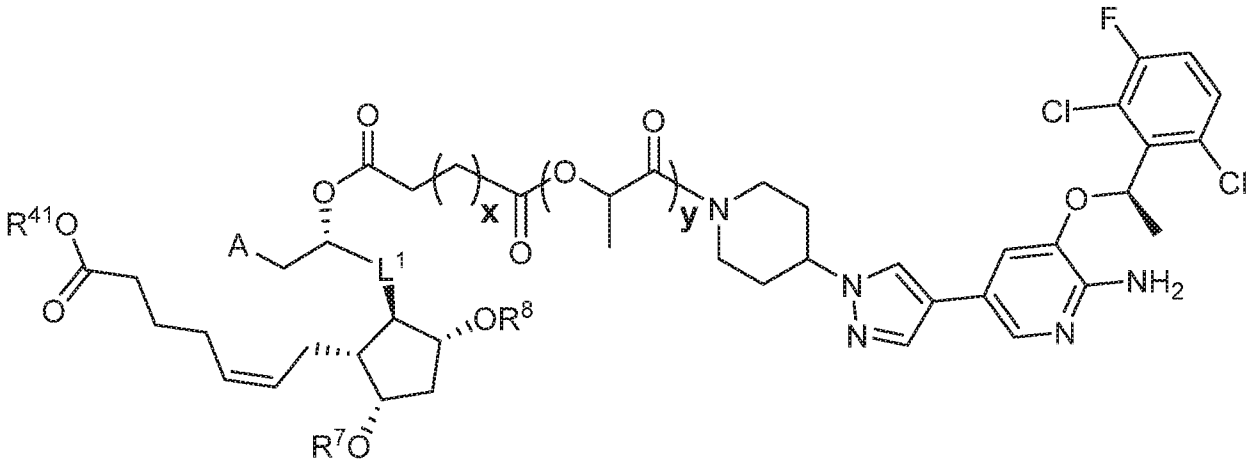
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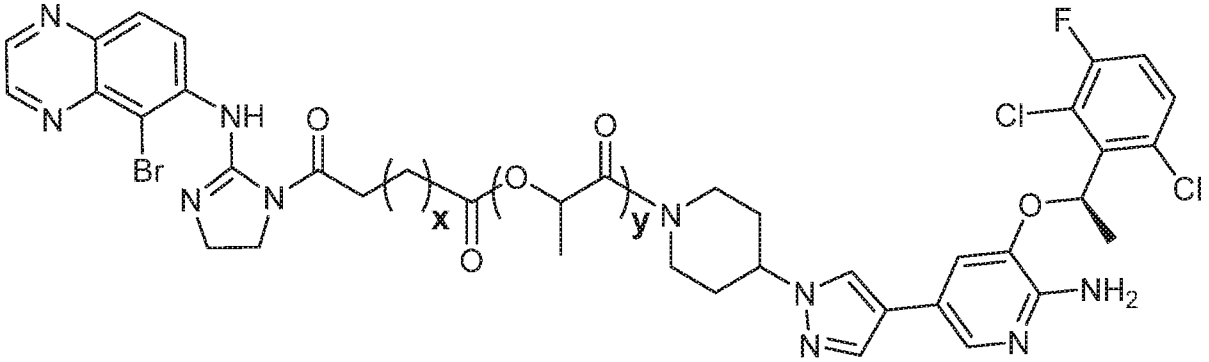


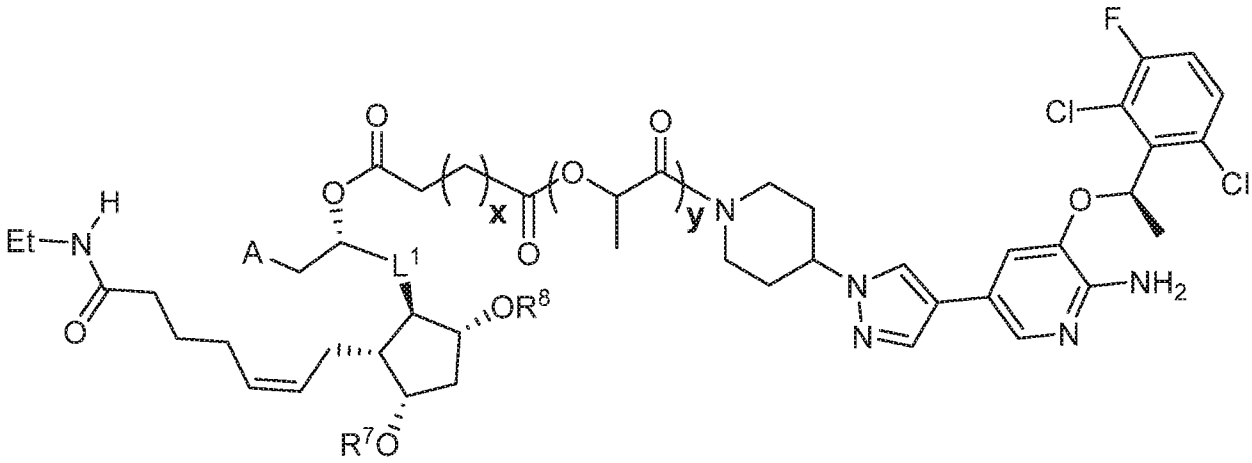


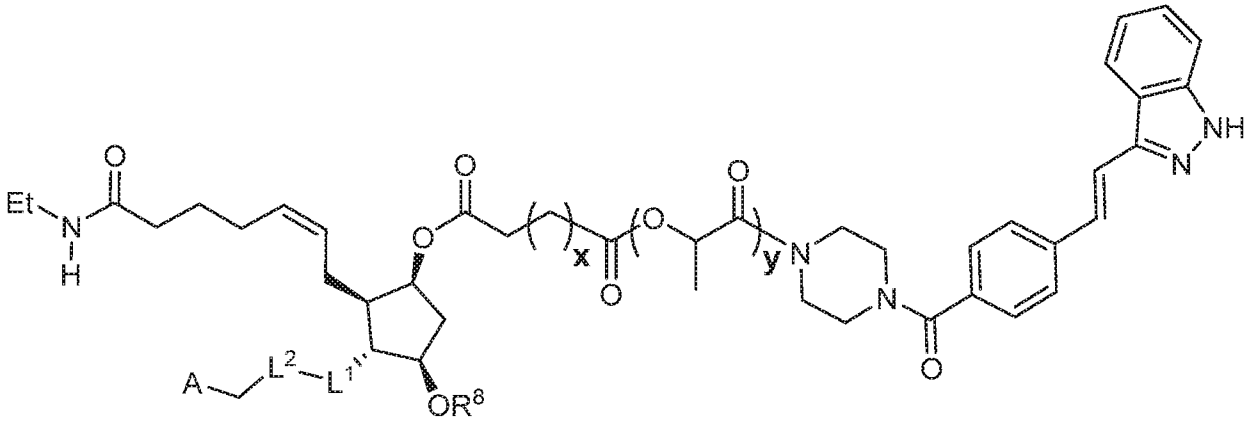


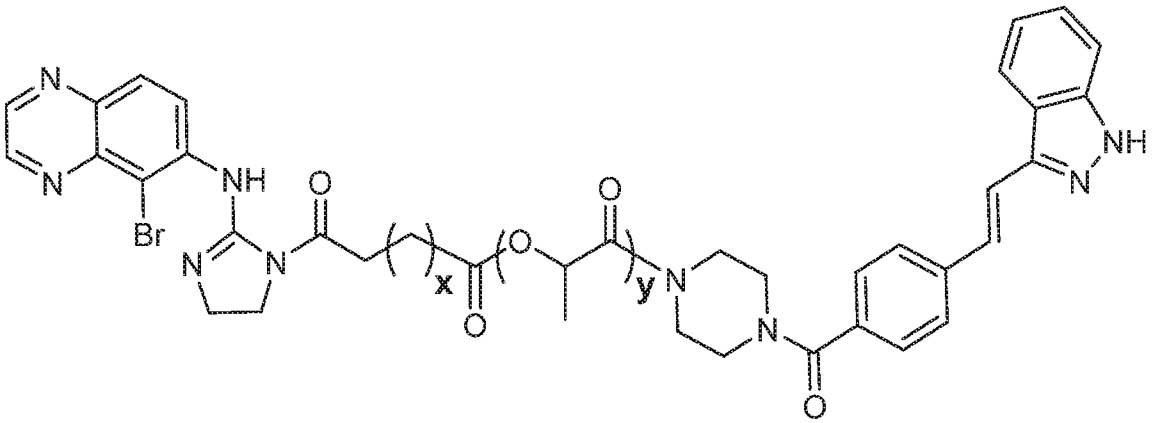
**Example 25. Non-limiting Examples of Formula XVIII, XIX, XX, XXII**

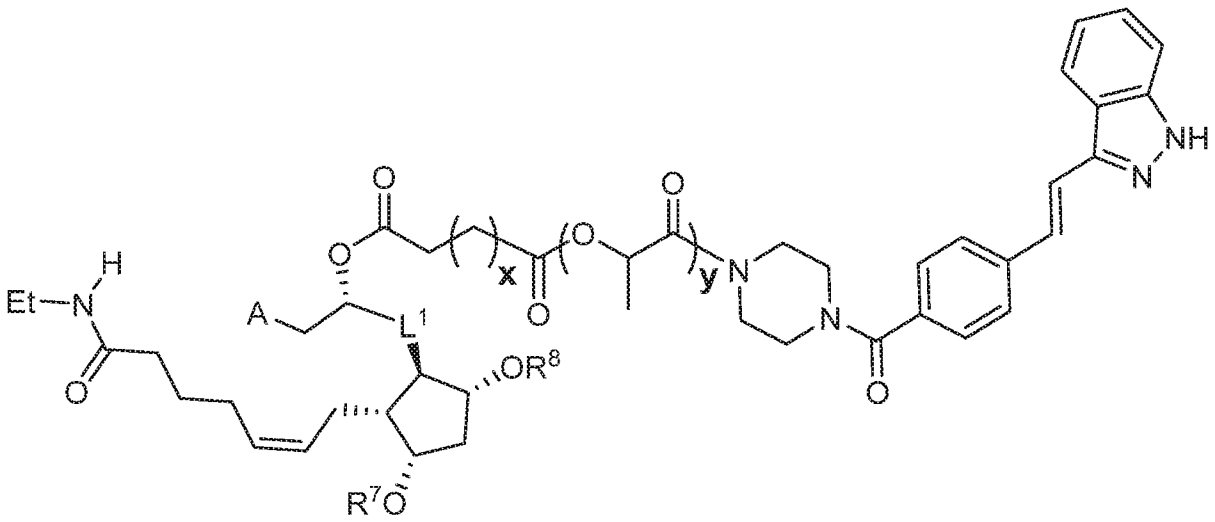


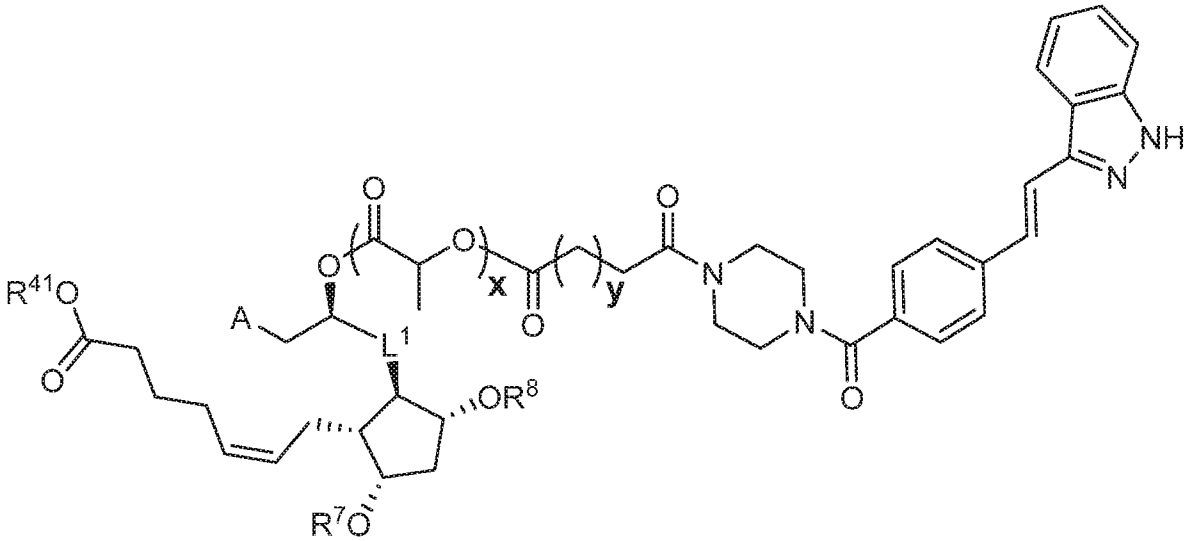


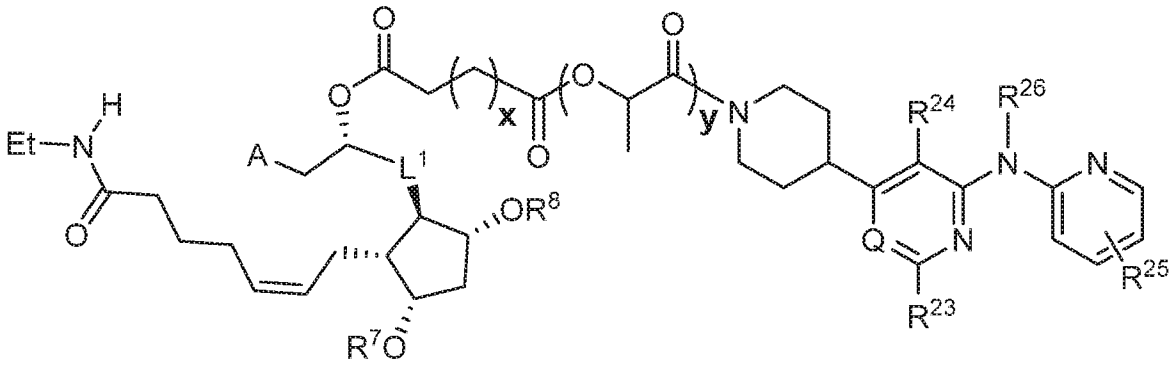


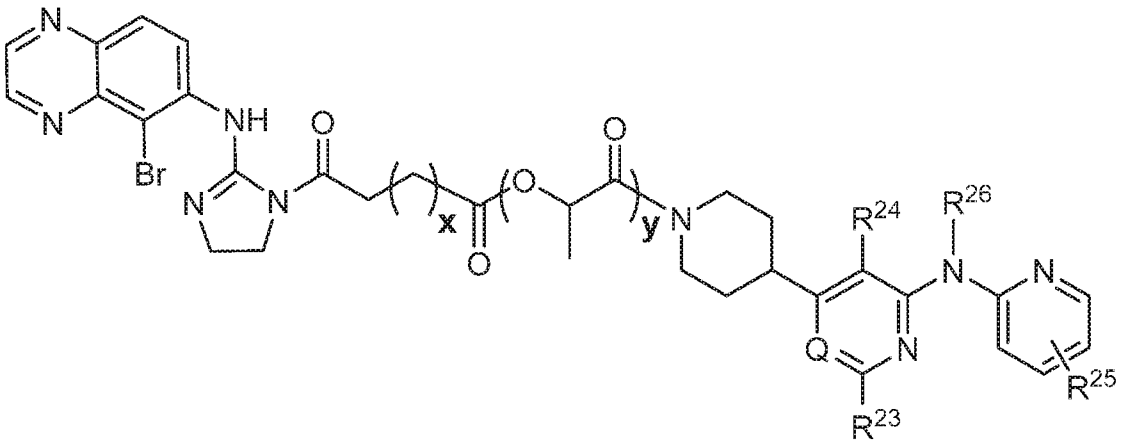


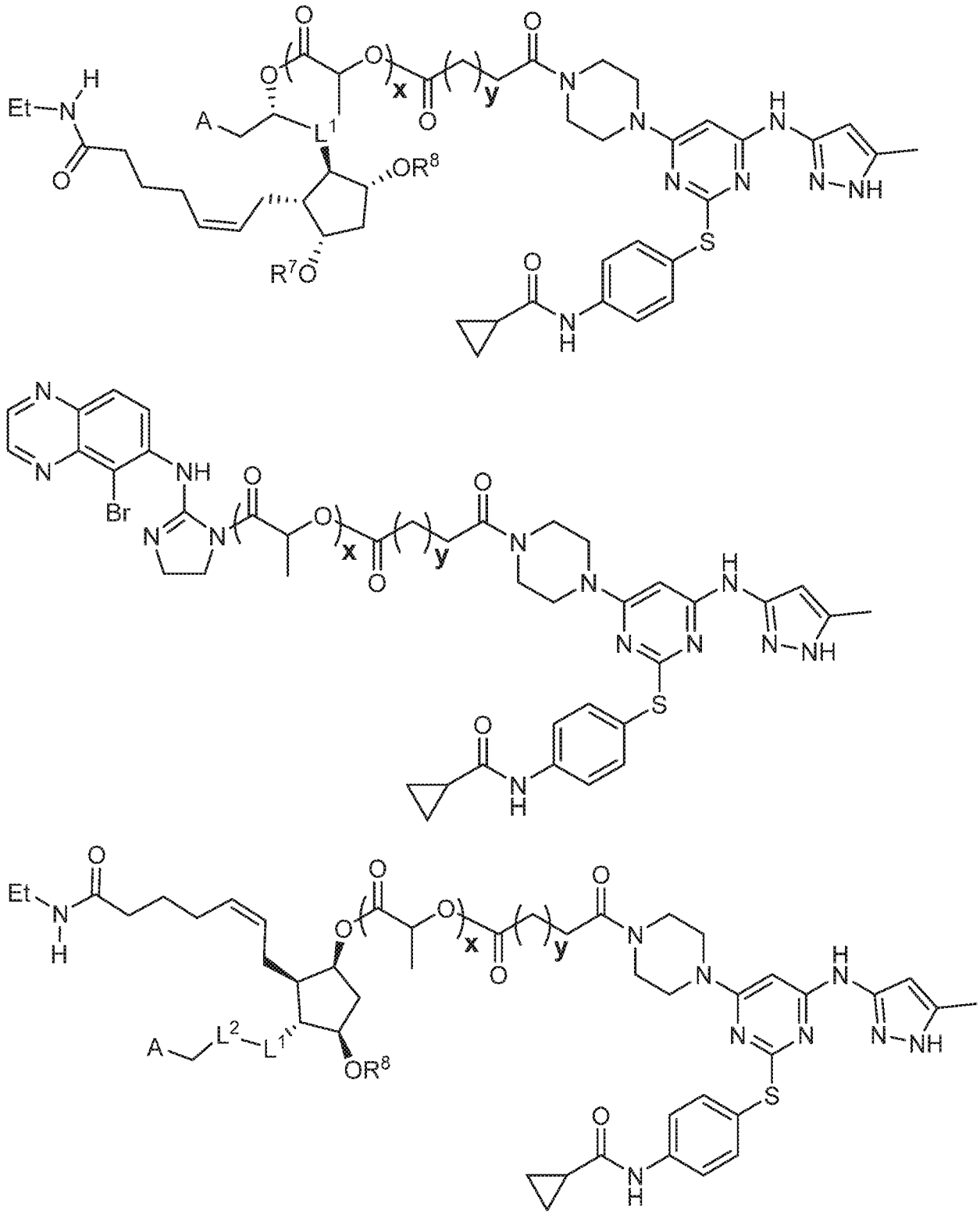




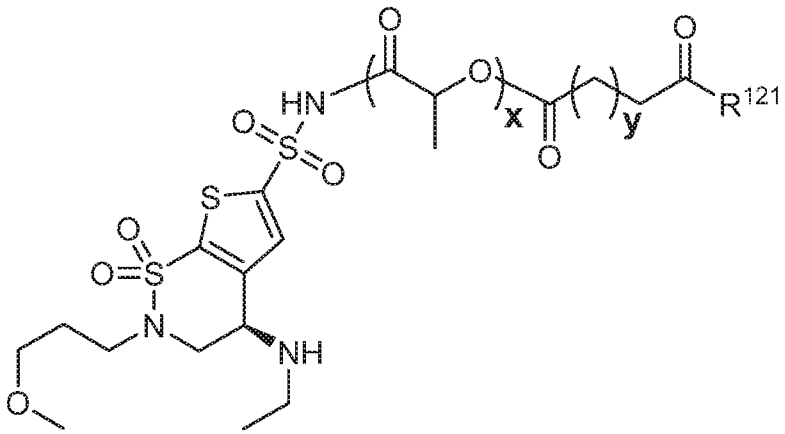


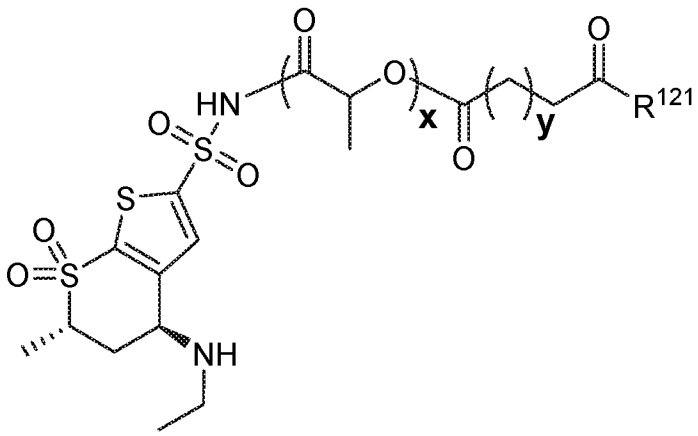


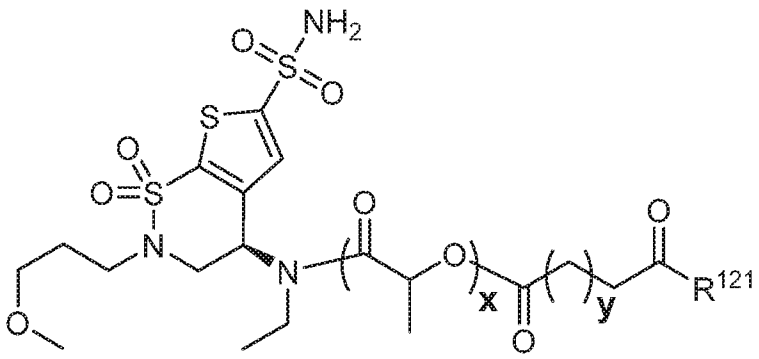


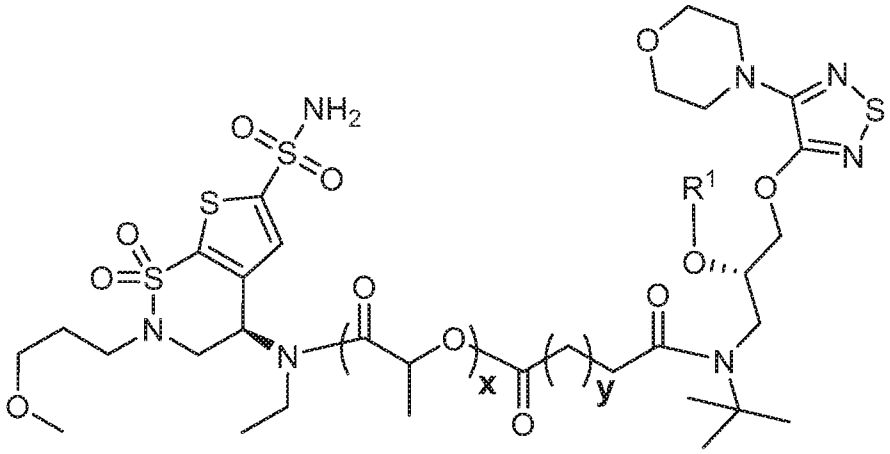


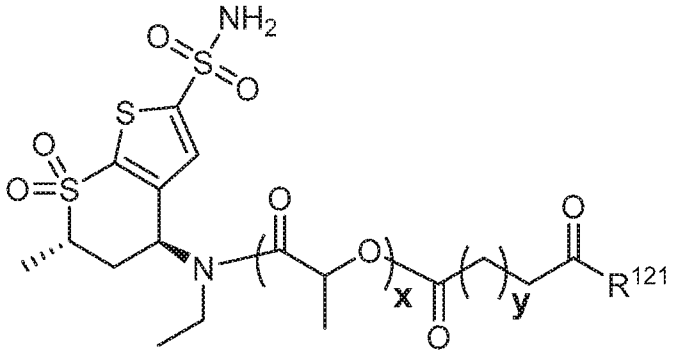
**Example 26. Non-limiting Examples of Formula XXII, XXIII, XXIV, XXV, XVI, and XXVII**

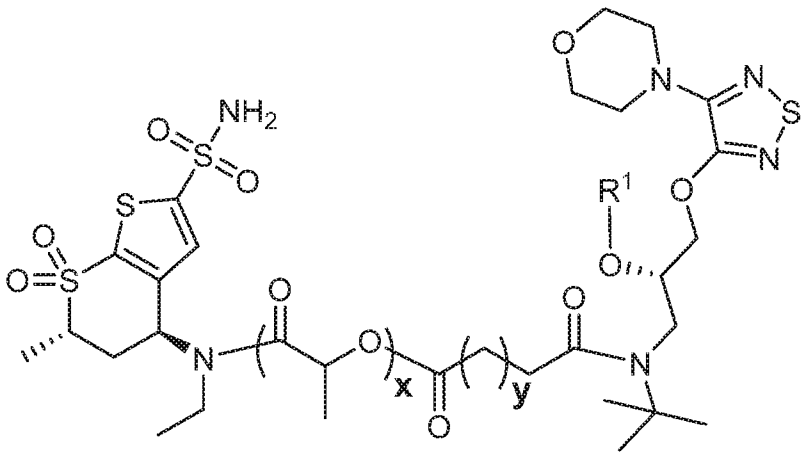


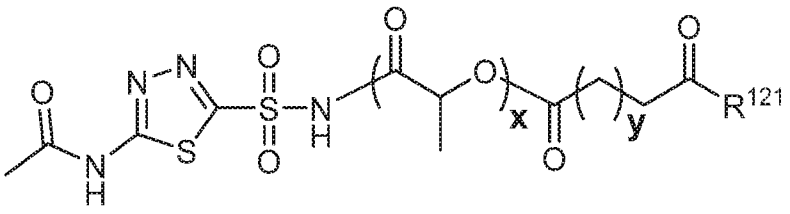


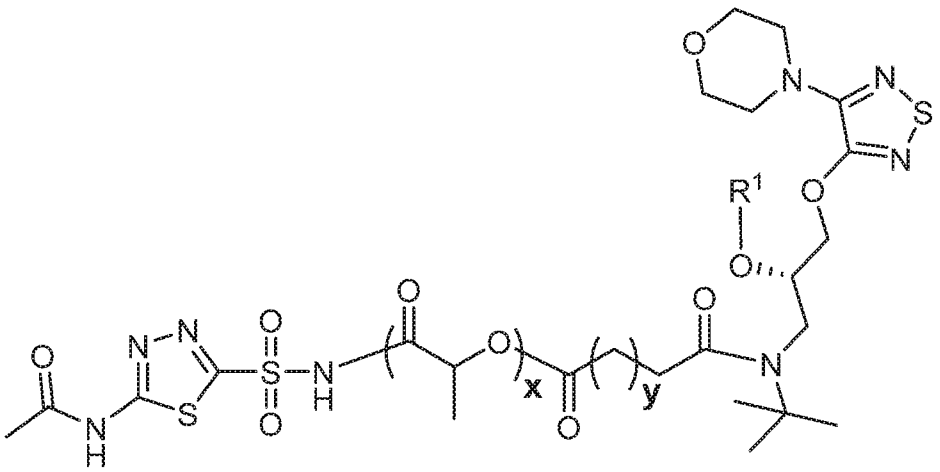


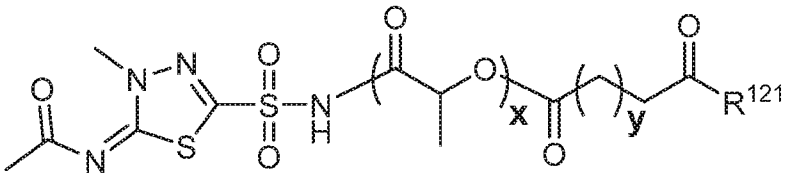


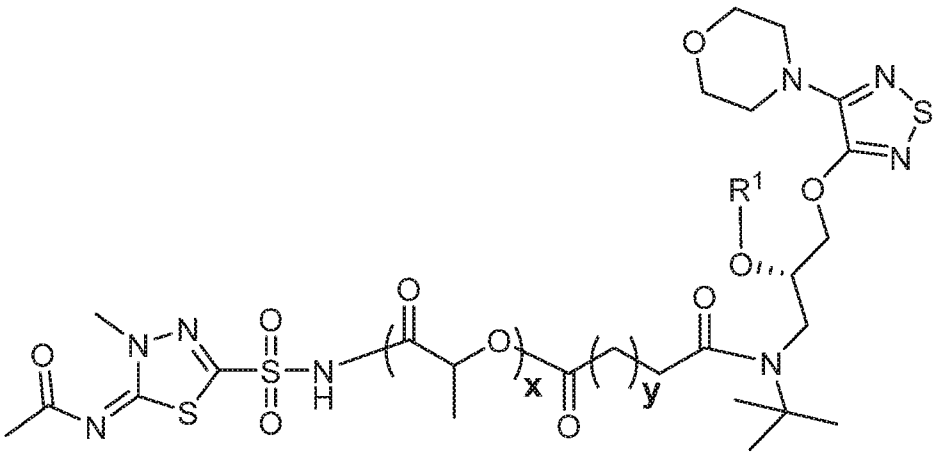


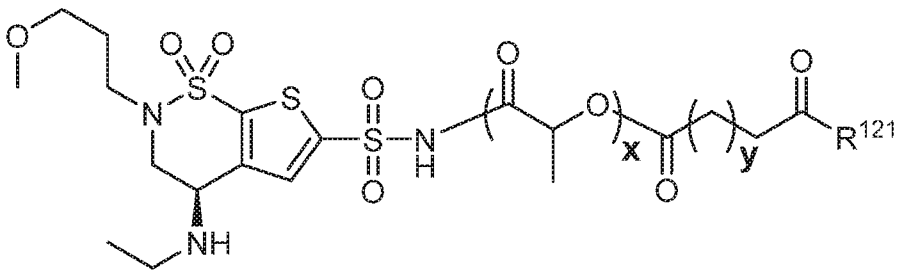


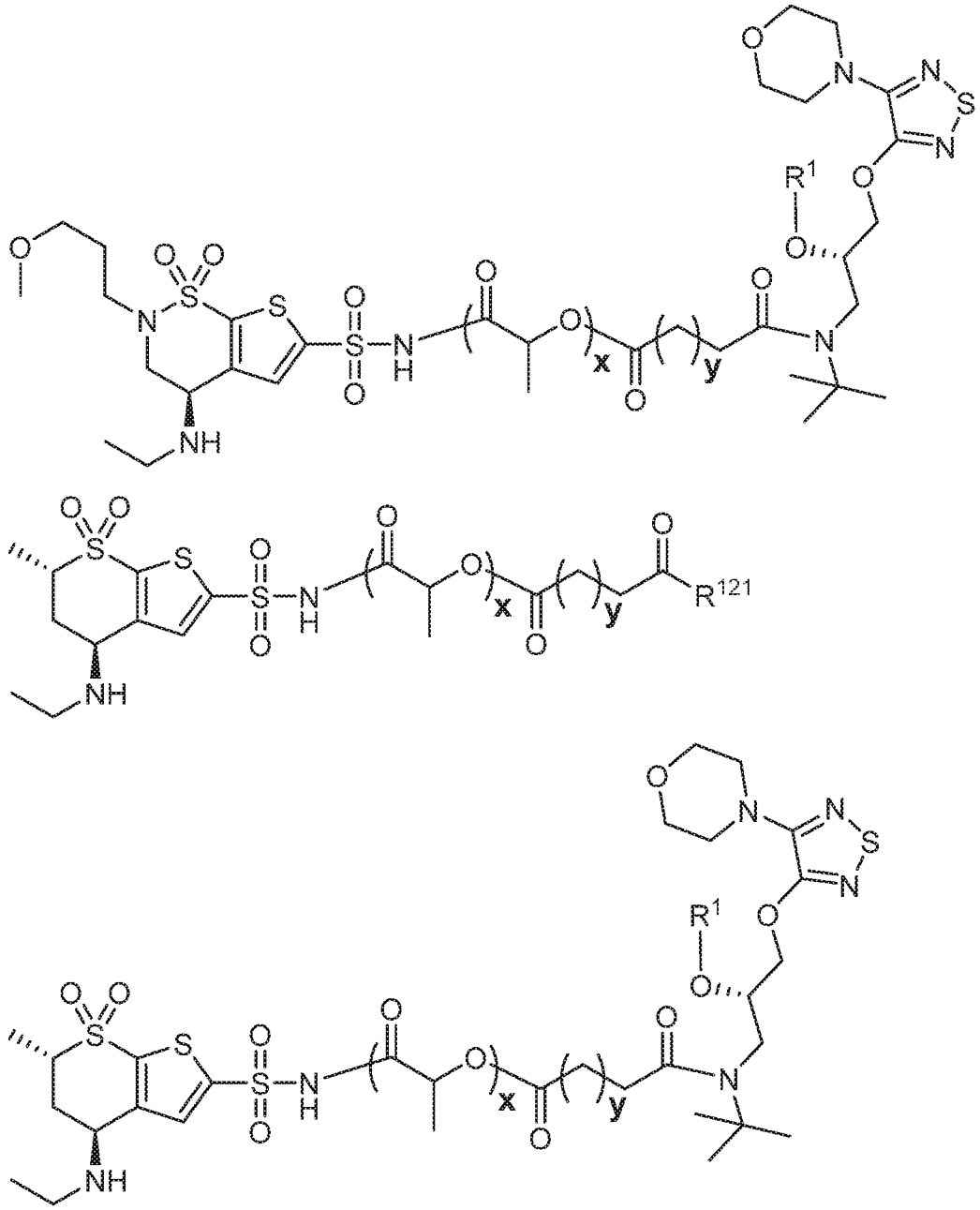




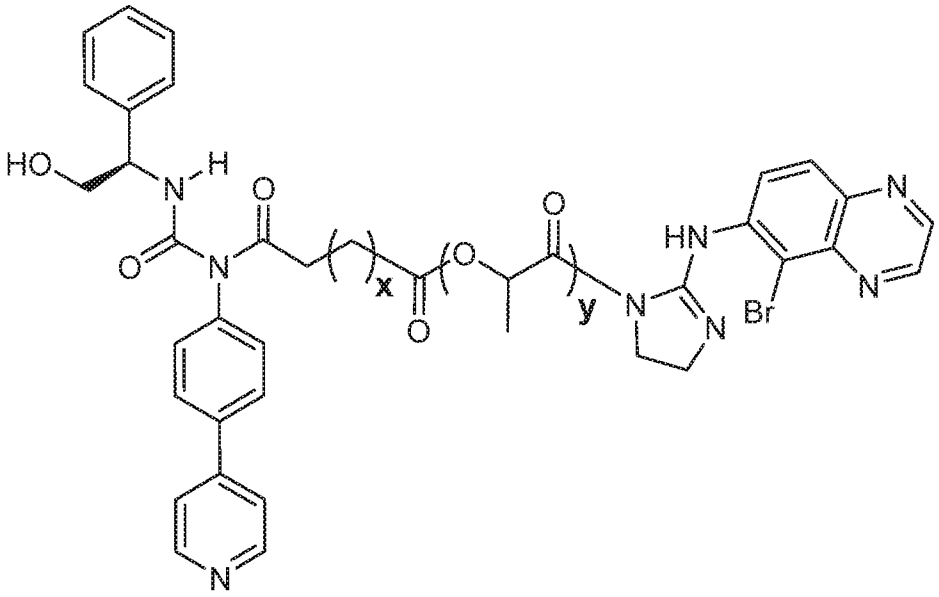


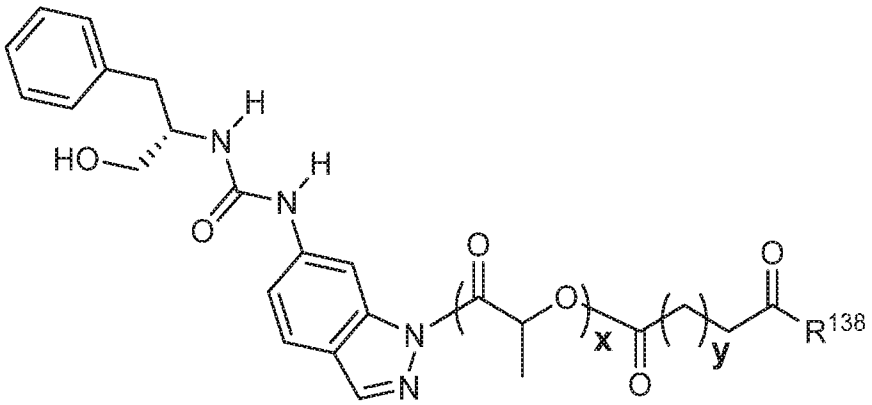


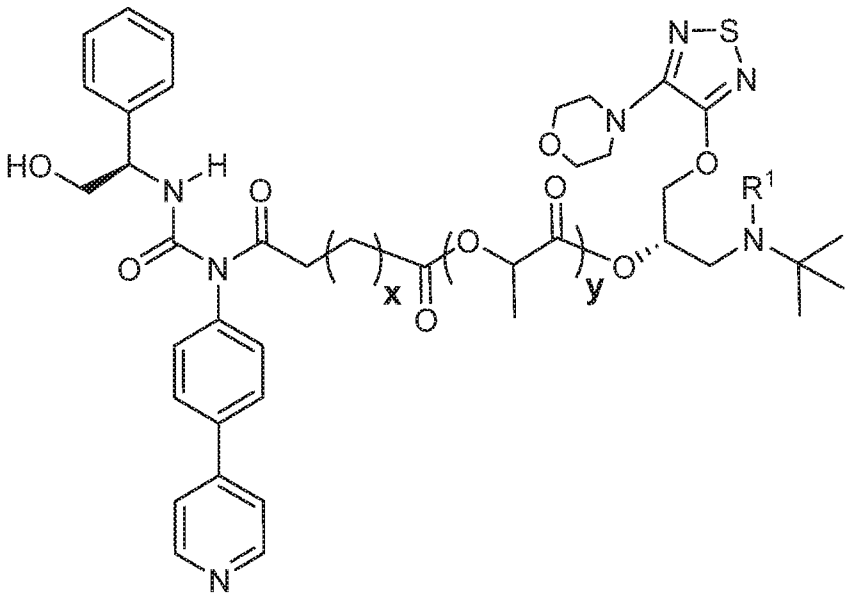


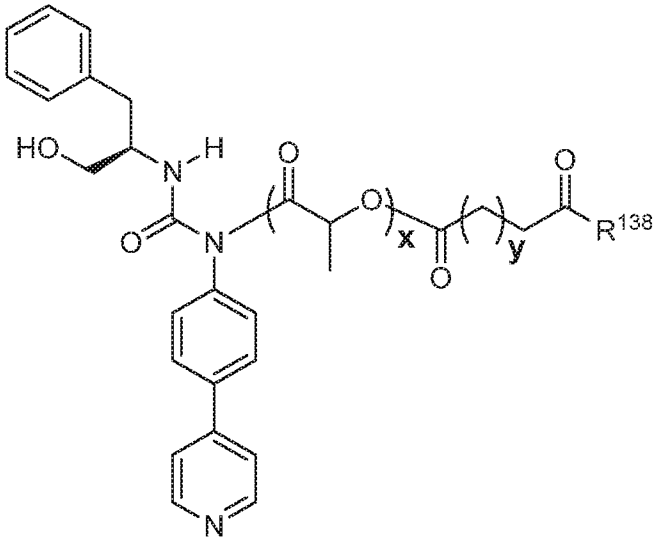


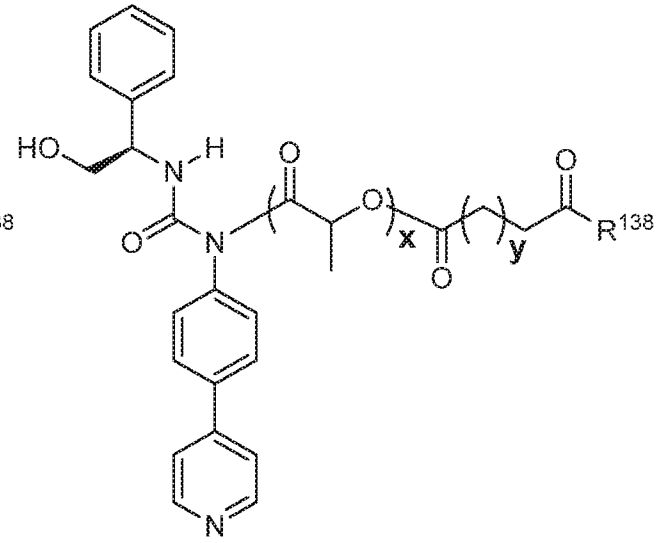
**Example 27. Non-limiting Examples of Formula XXVIII, XXIX, XXX, XXXI, XXXII, and XXXIII**

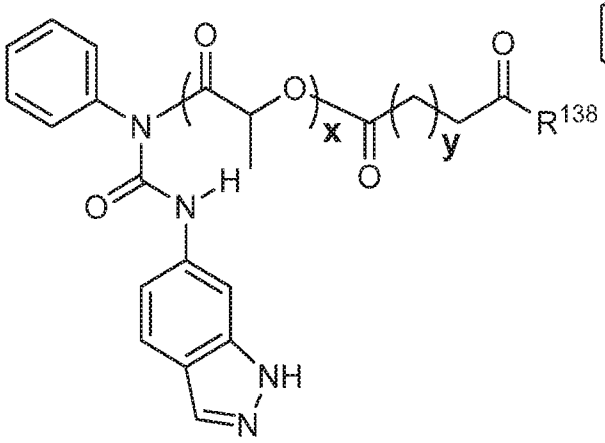


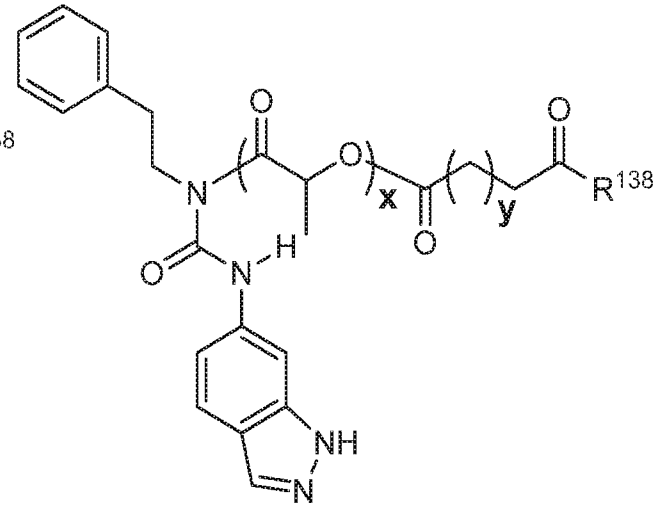


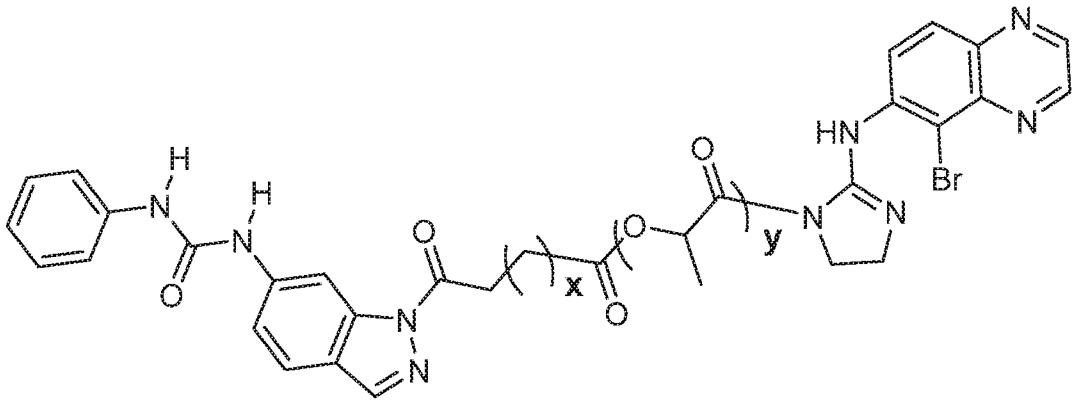


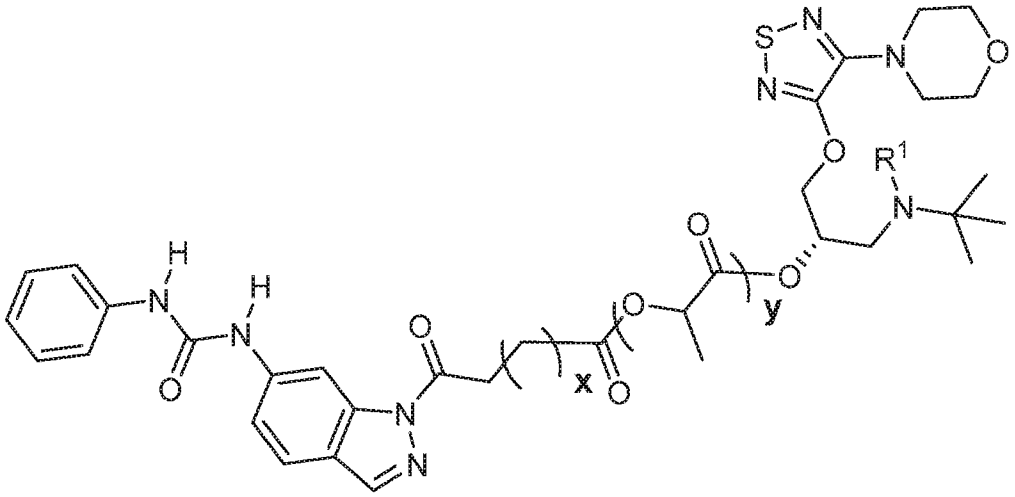


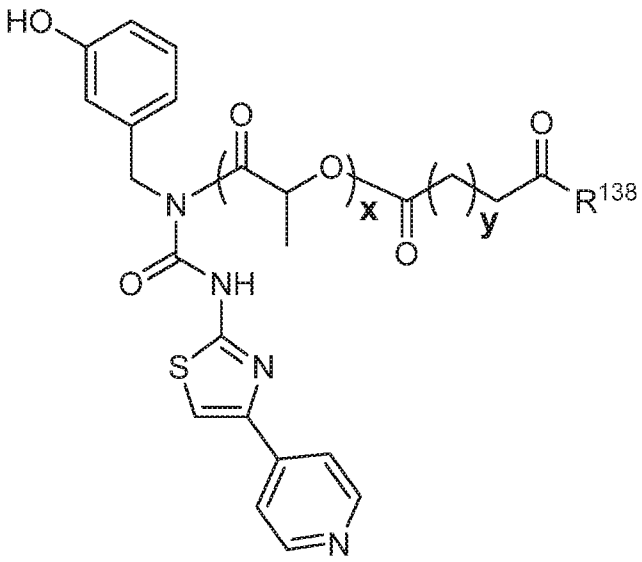


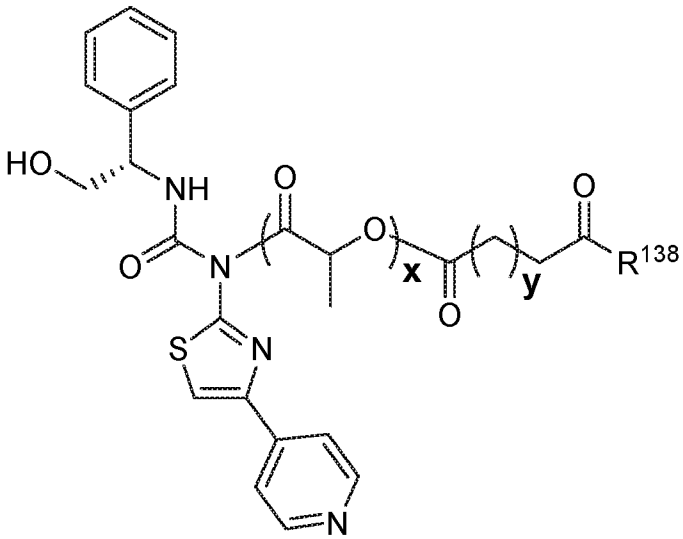


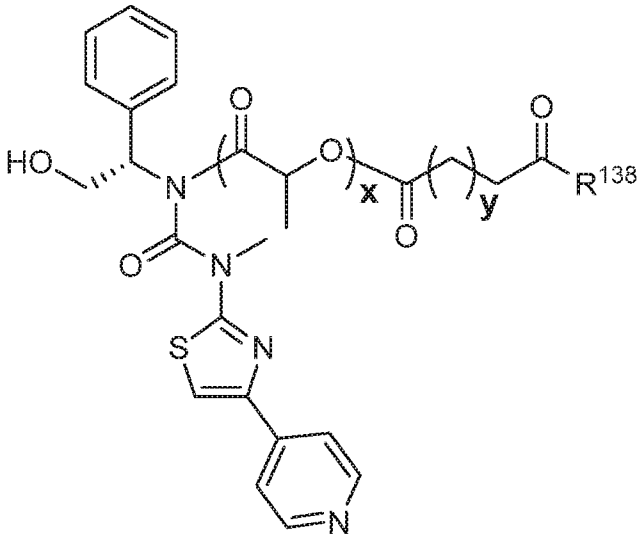


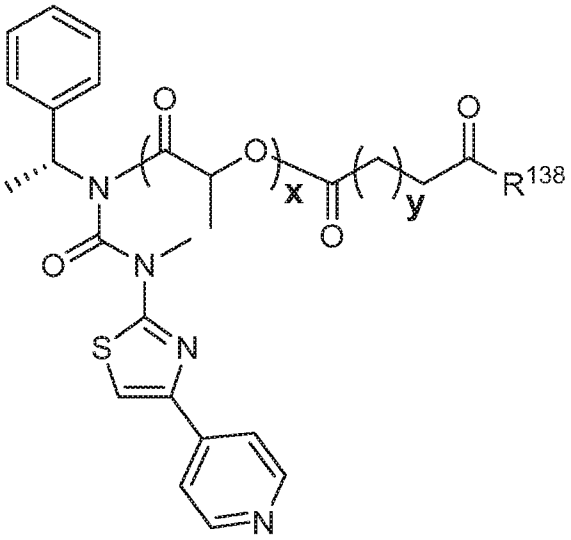


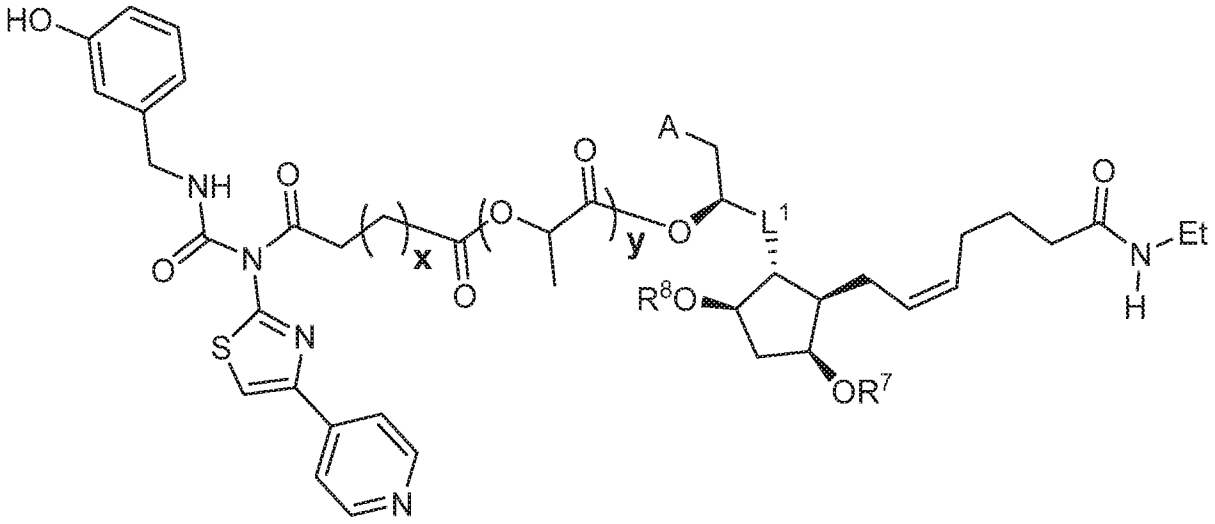


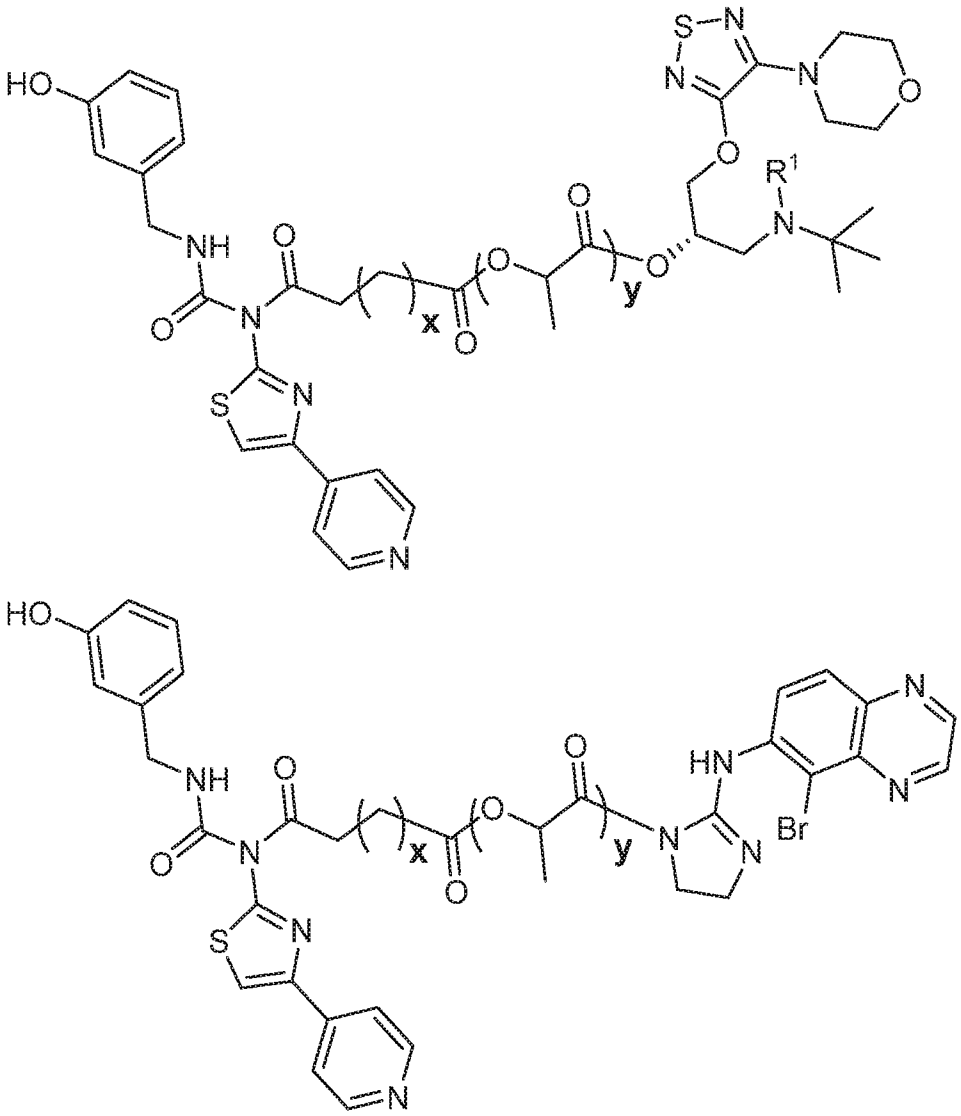




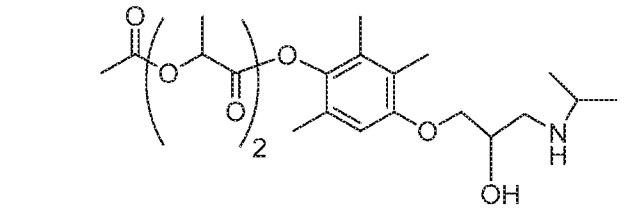


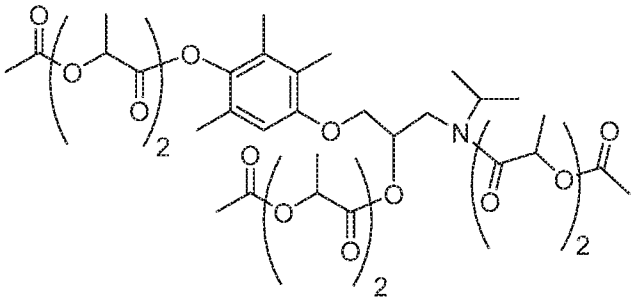


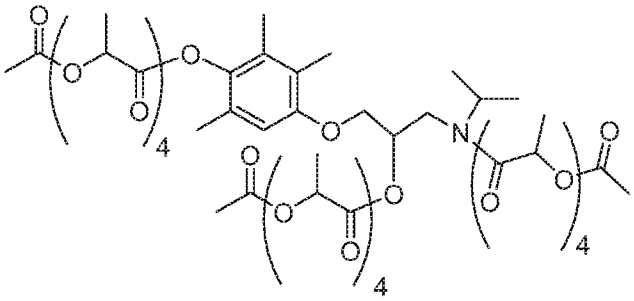


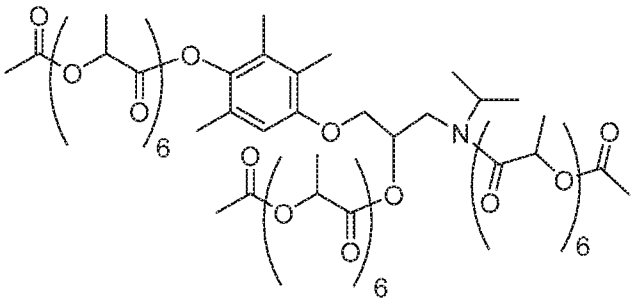


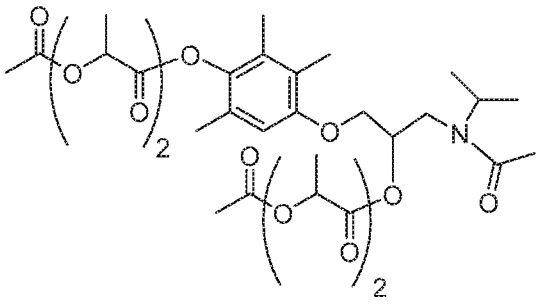
**Example 28. Non-limiting Examples of Formula XXXIV and XXXV**

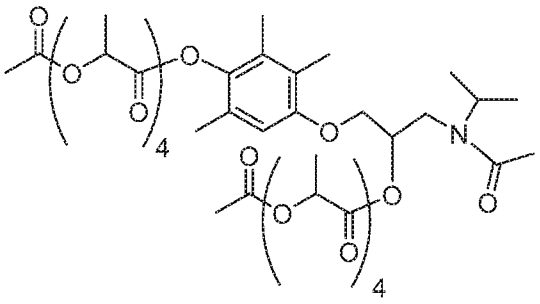


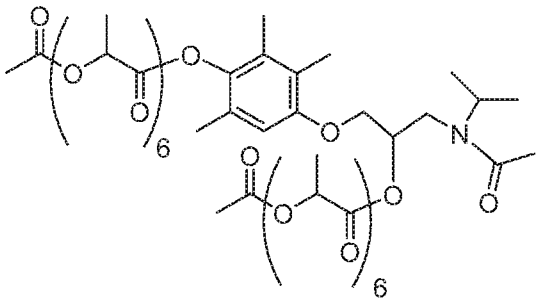




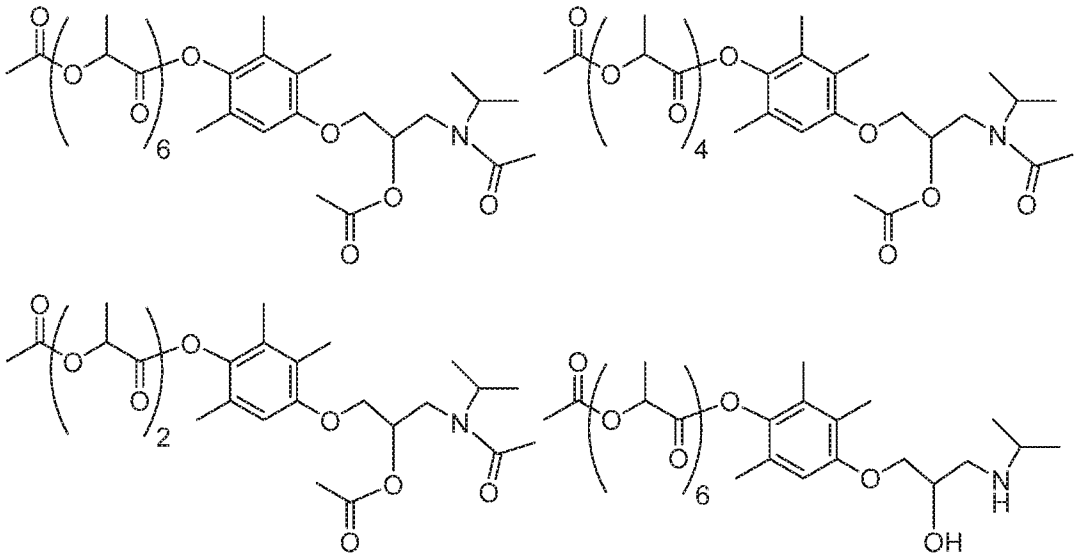




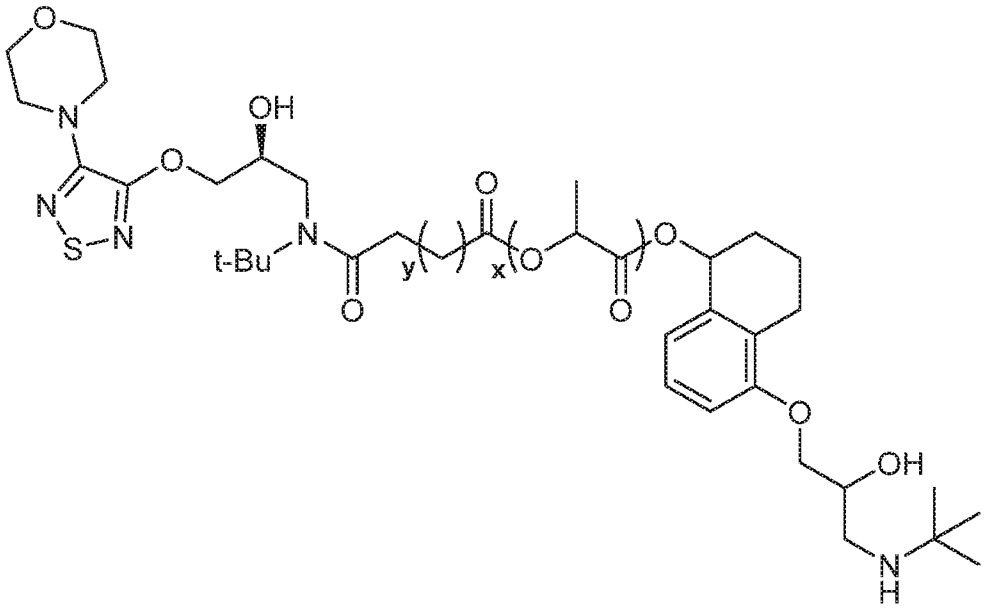


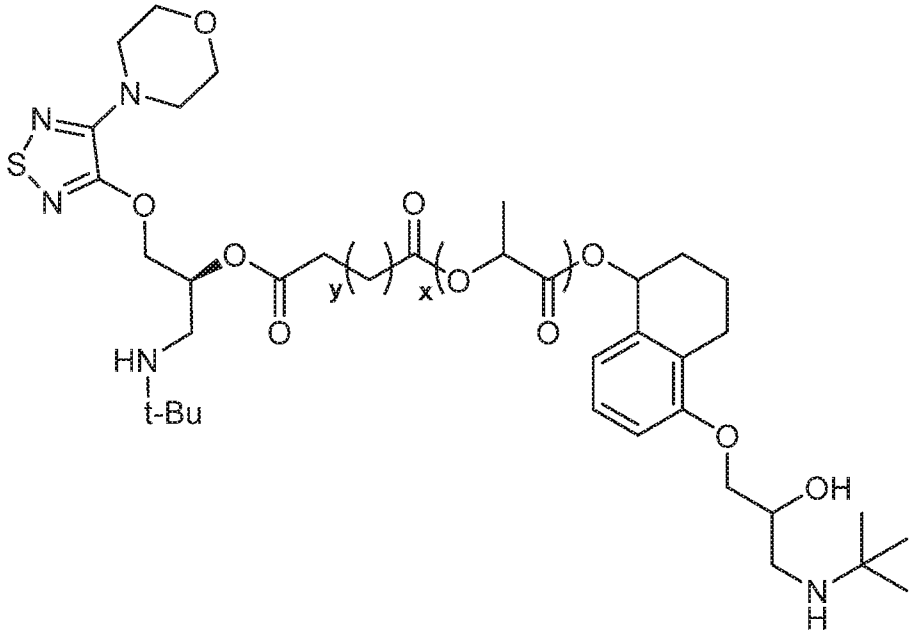


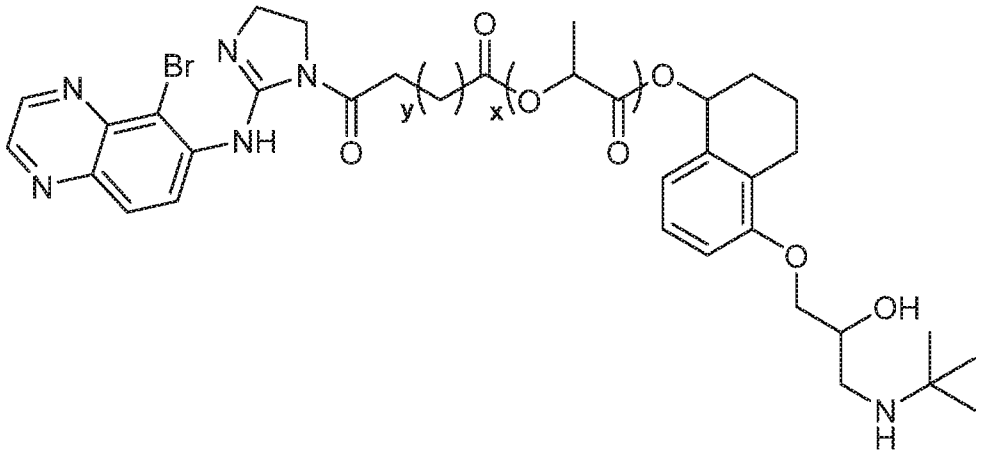
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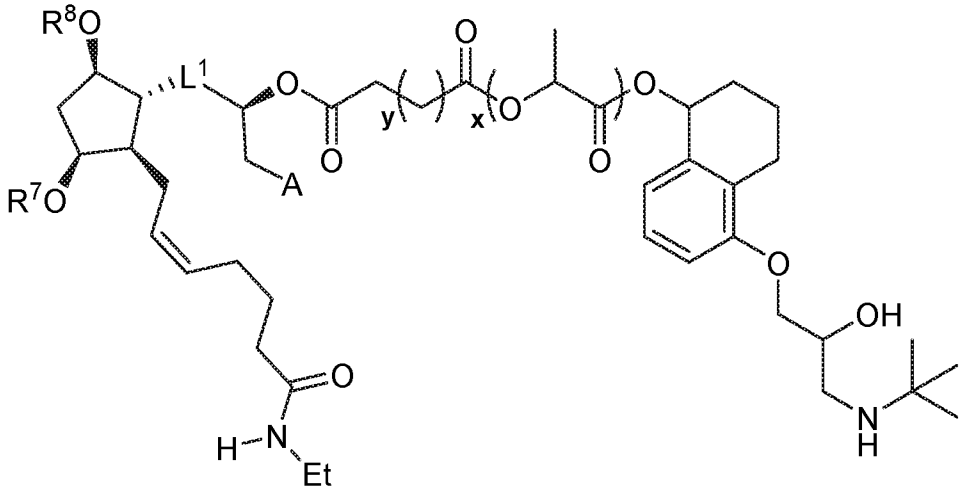


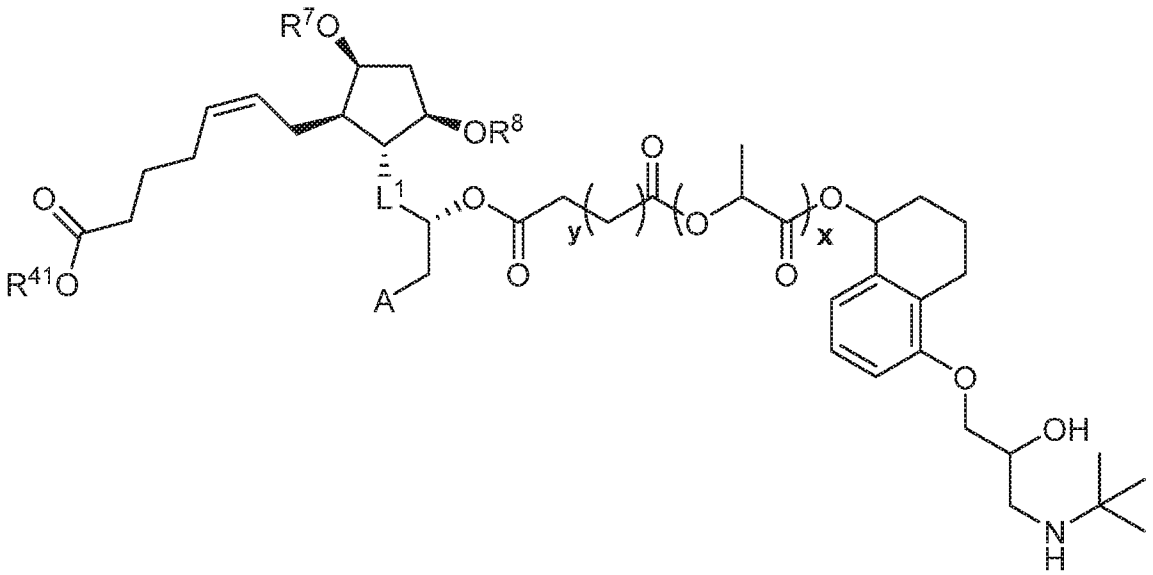
**Example 29. Non-limiting Examples of Formula XXXVI**

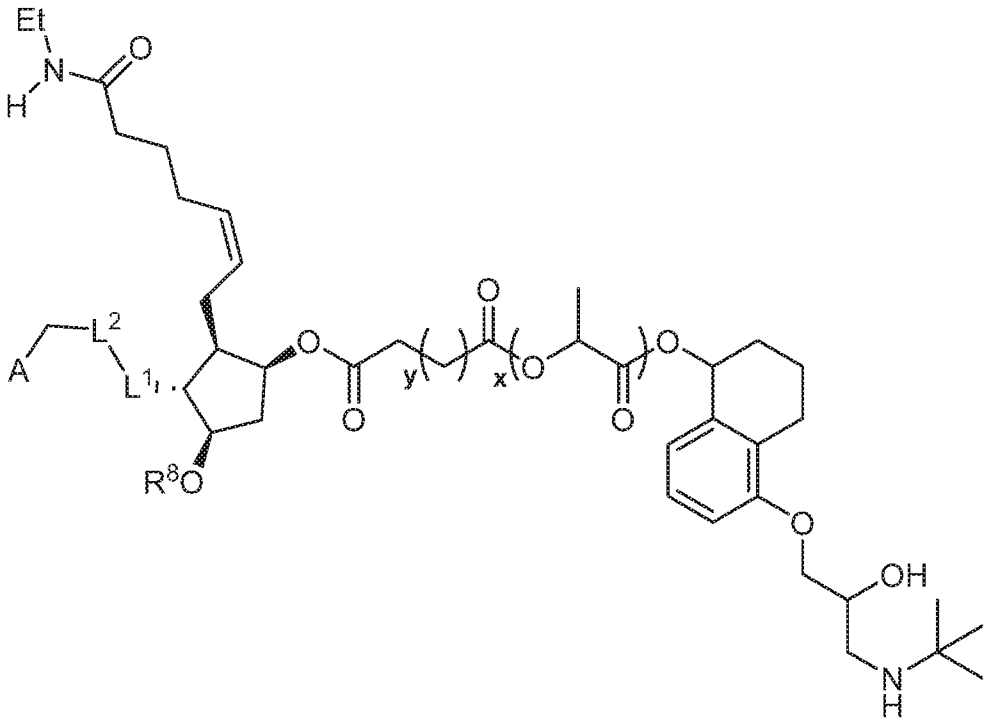




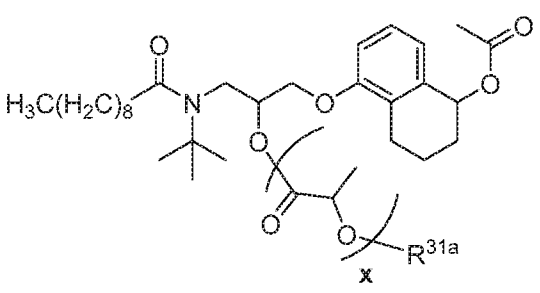


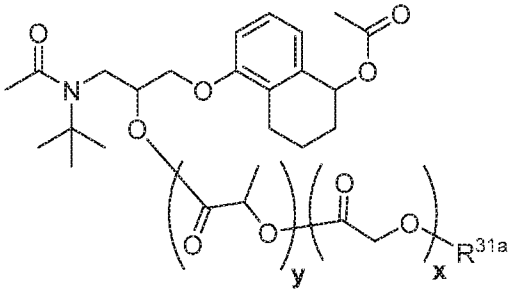


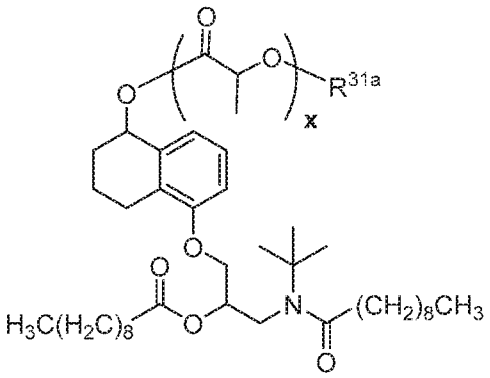


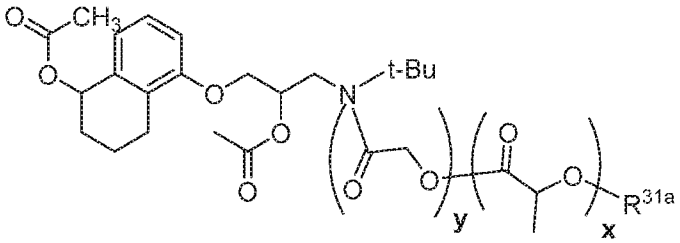


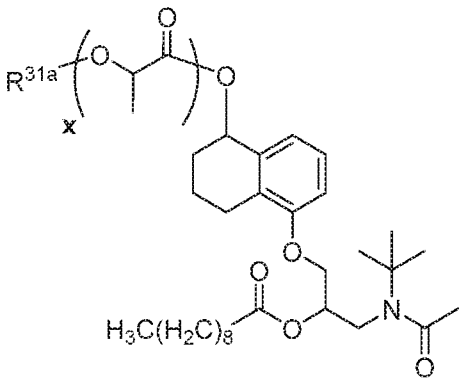
**Example 30. Non-limiting Examples of Formula XXXVII**

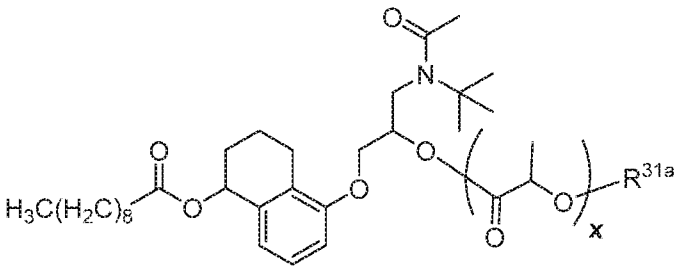




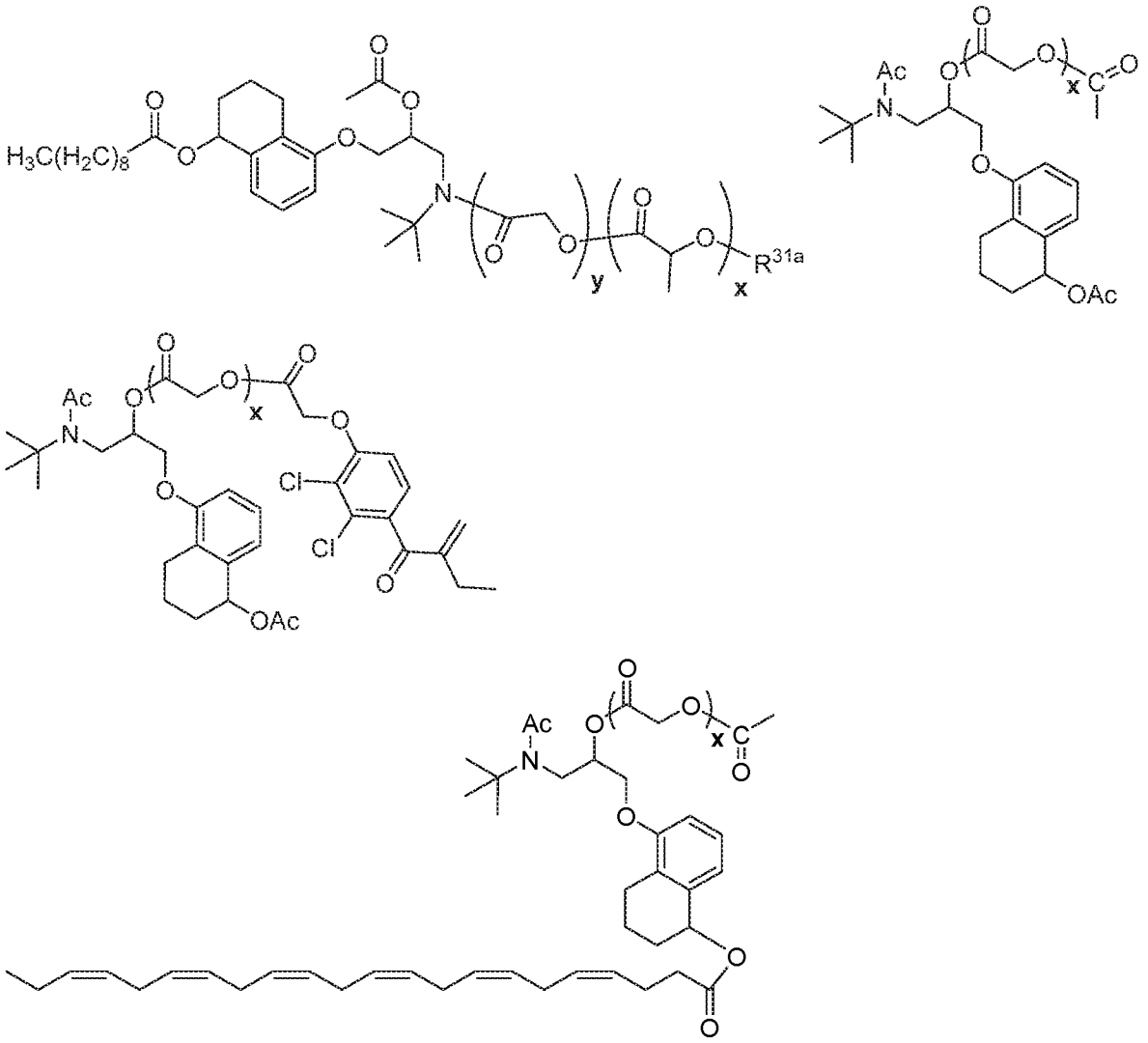




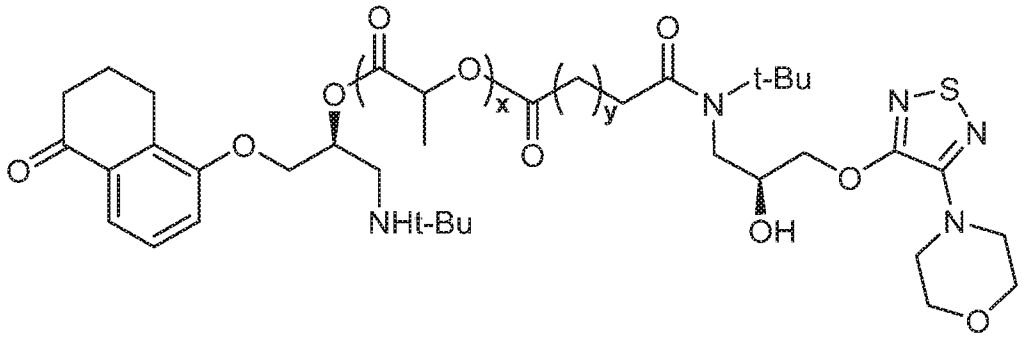


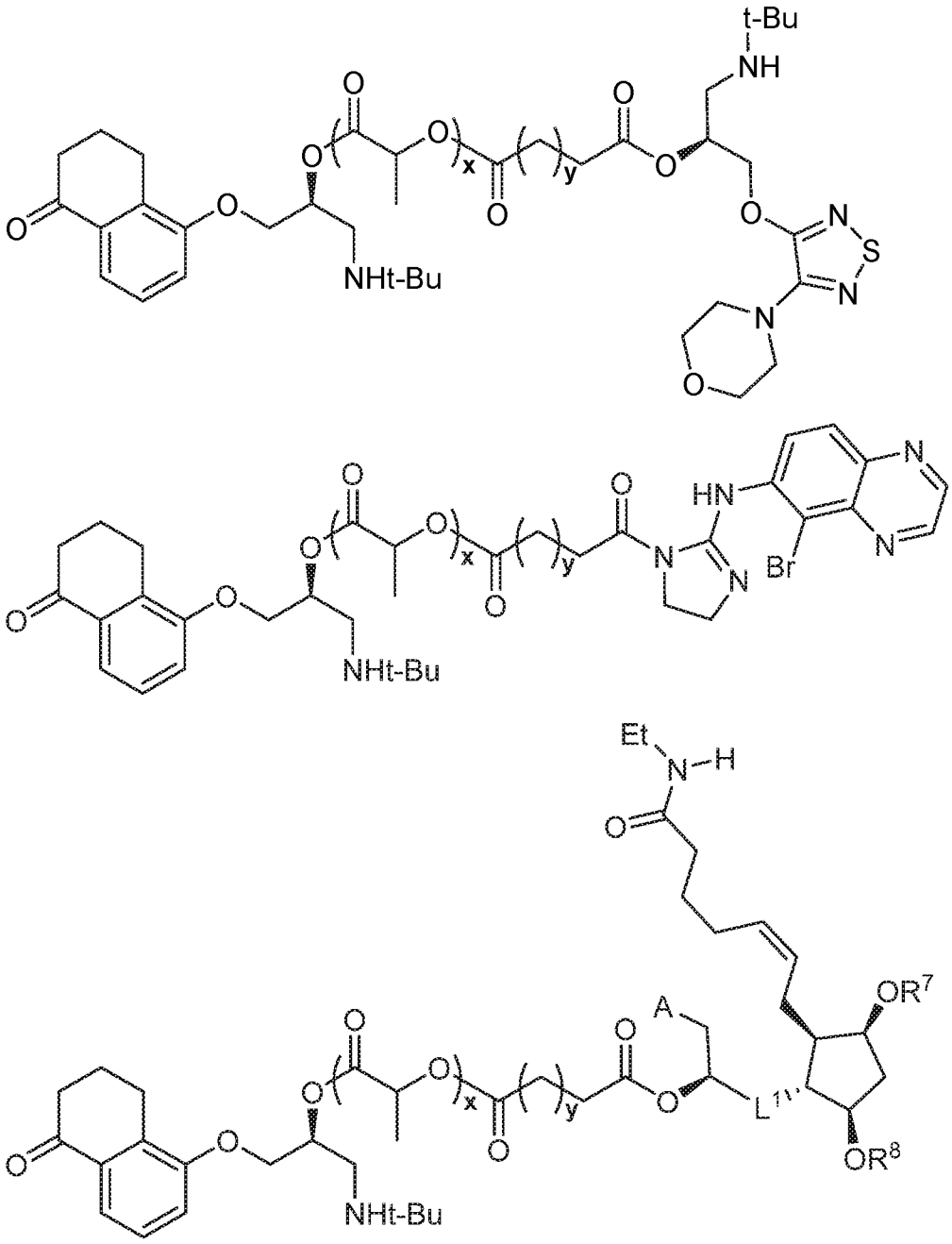


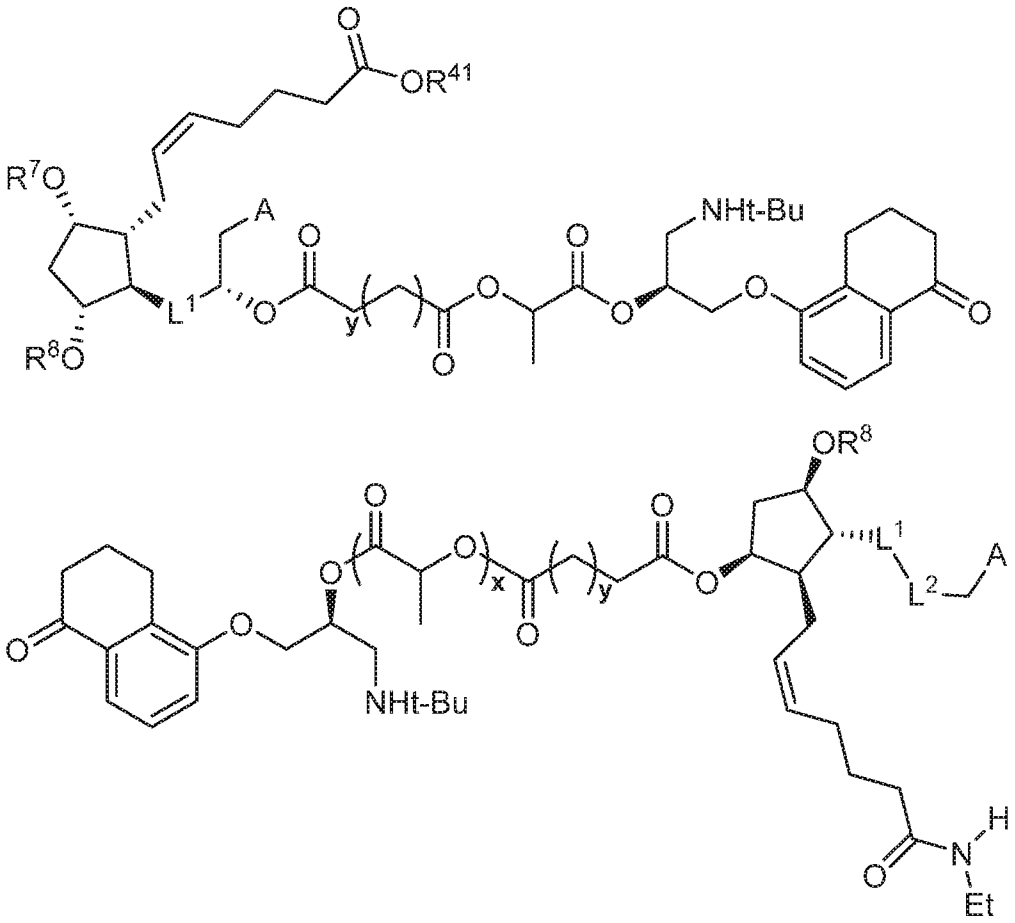
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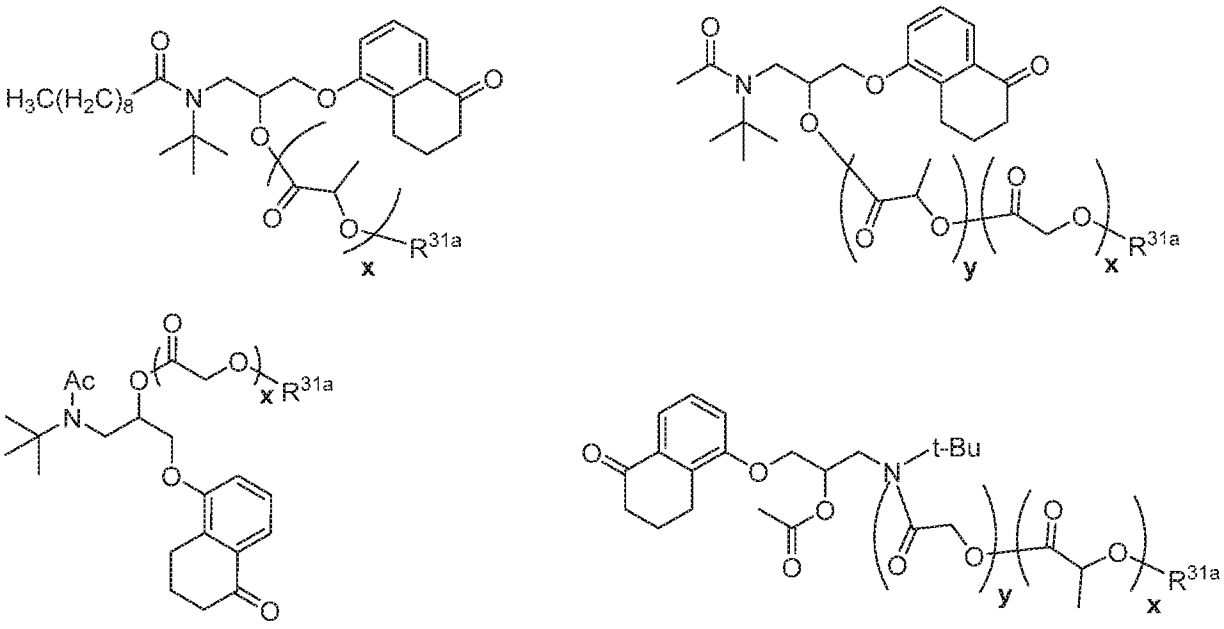
**Example 31. Non-limiting Examples of Formula XXXVIII**

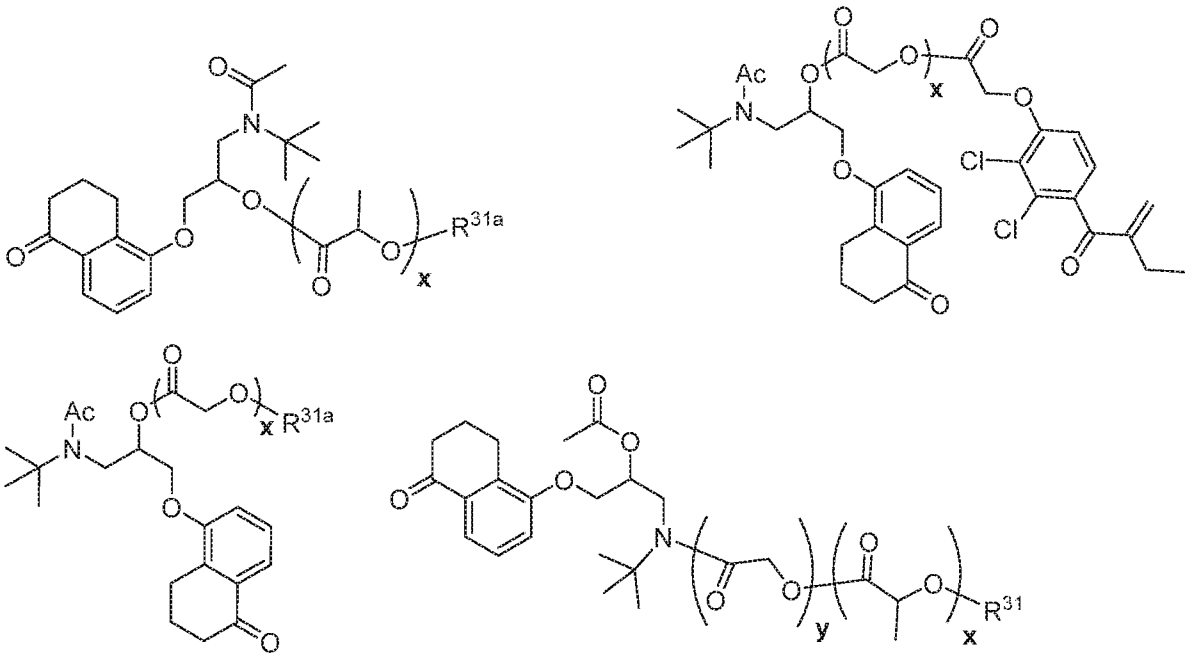



t-Bu
NH
O
O
O
O
x
y
O
O
O
O
N
S
N
N
O
NHt-Bu
HN
N
Br
N
N
Et
N–H
A
OR7
L11
OR8

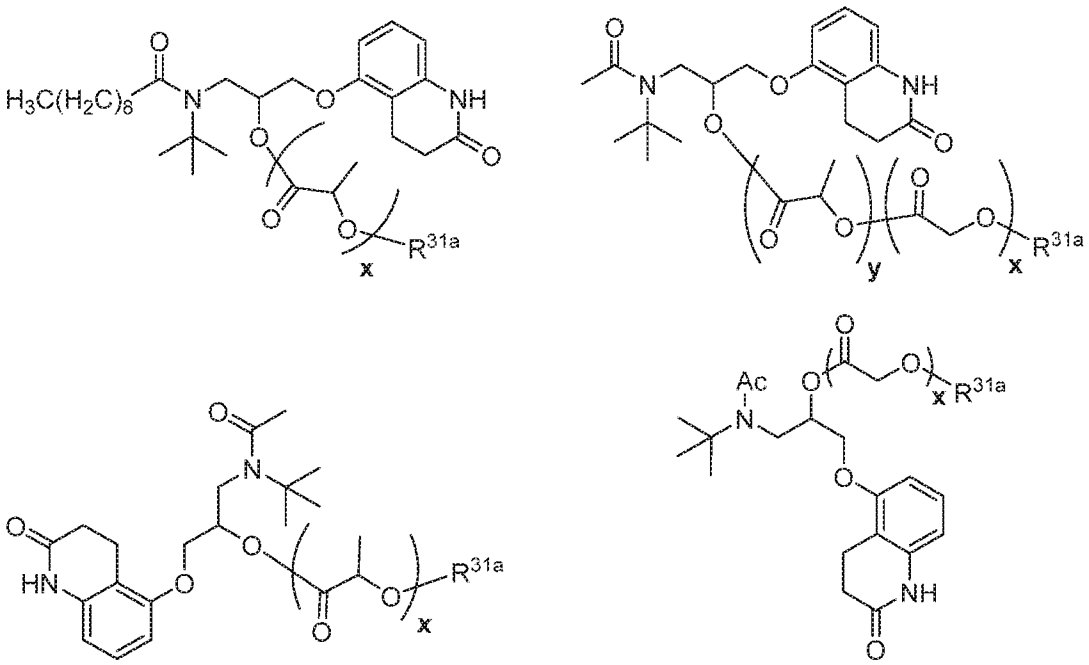


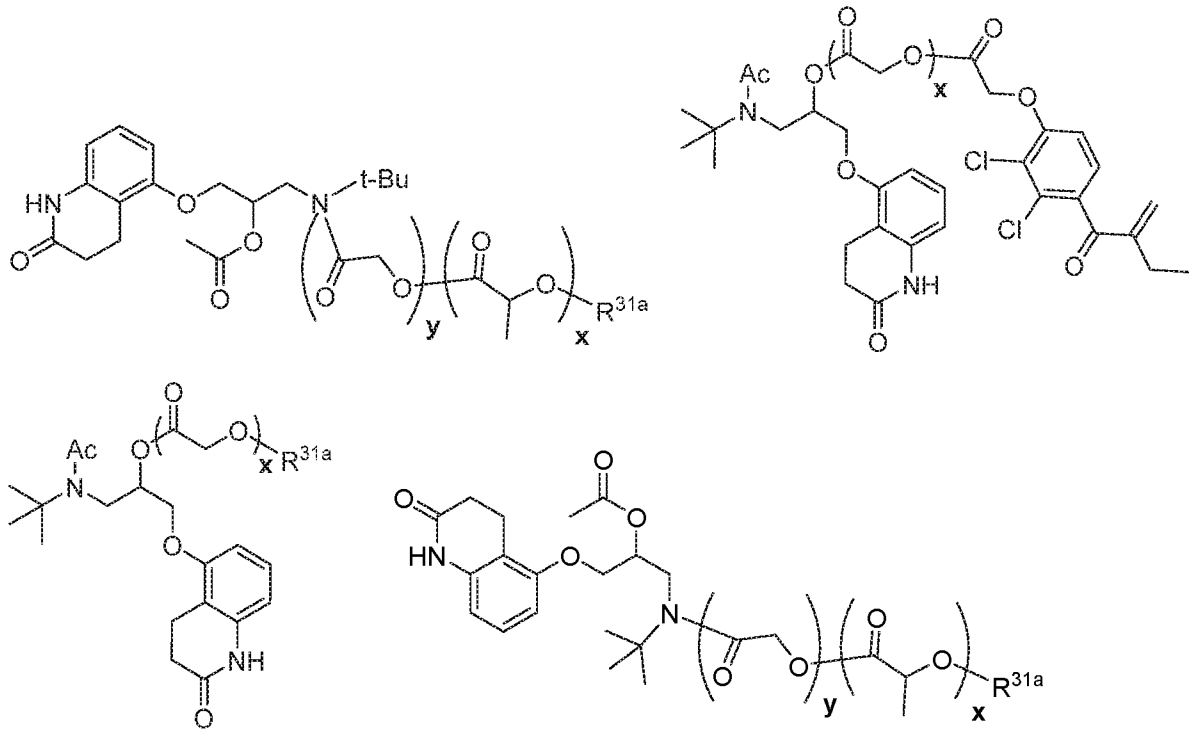
**Example 32. Non-limiting Examples of Formula XXXIX**



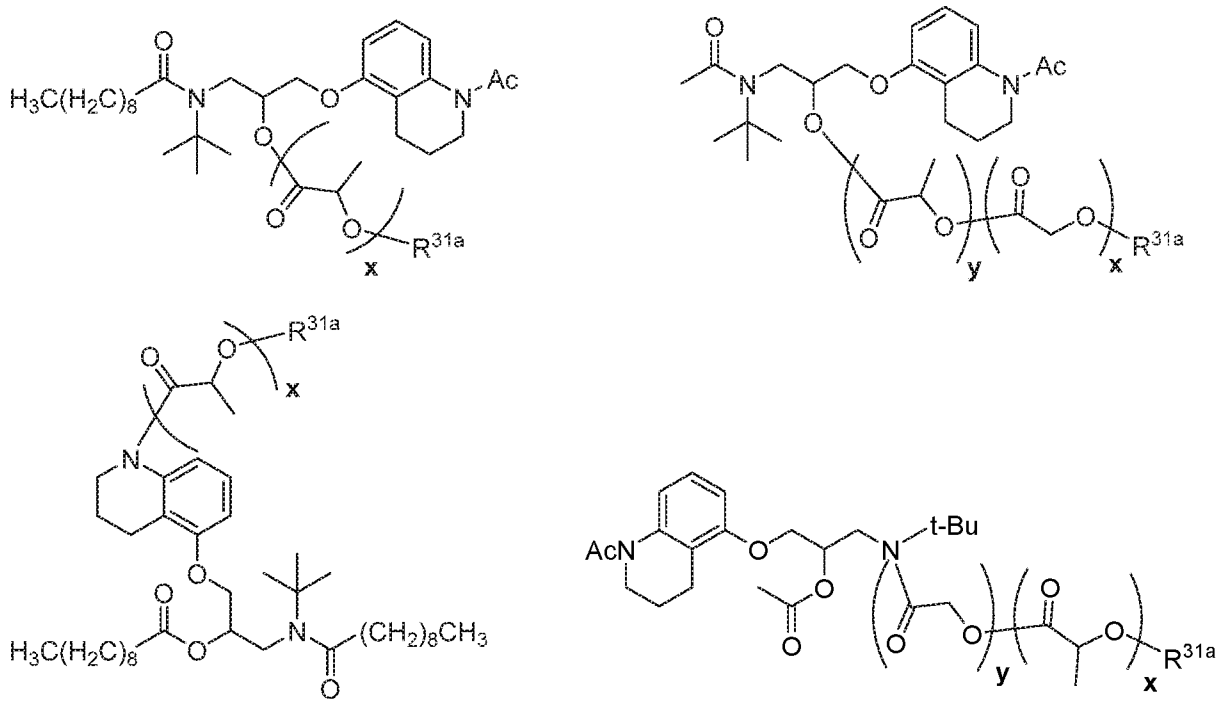


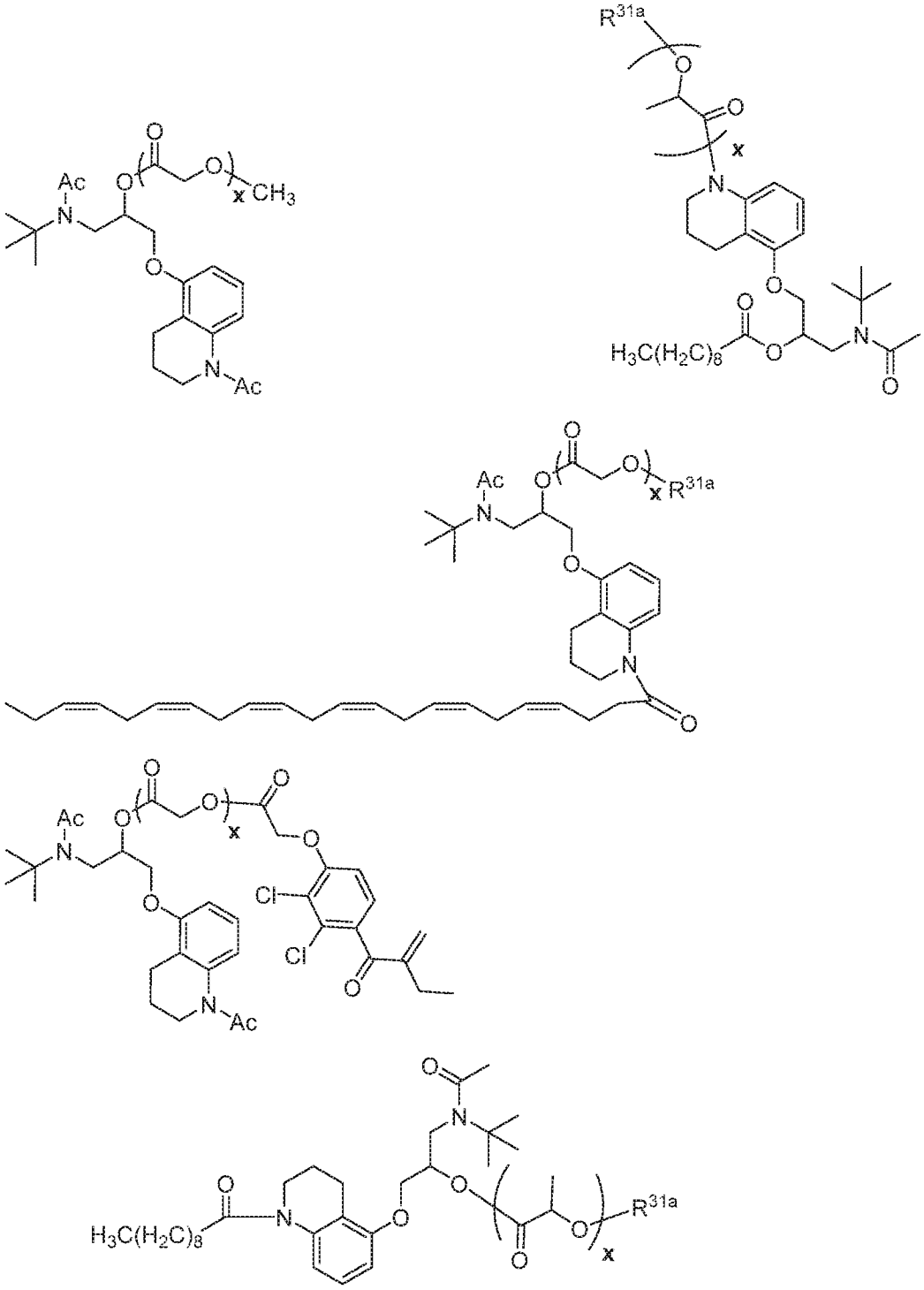
**Example 33. Non-limiting Examples of Formula XLI**

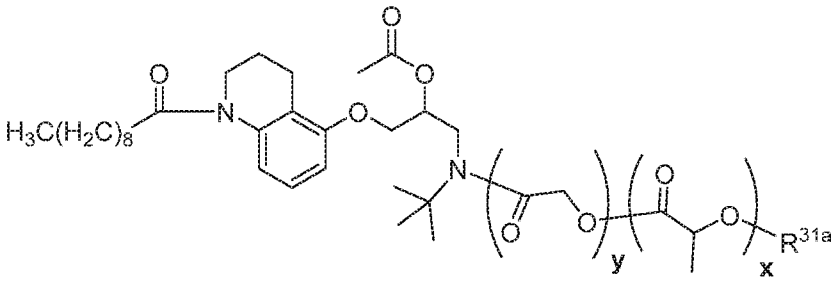




**Example 34. Non-limiting Examples of Formula XLIII**



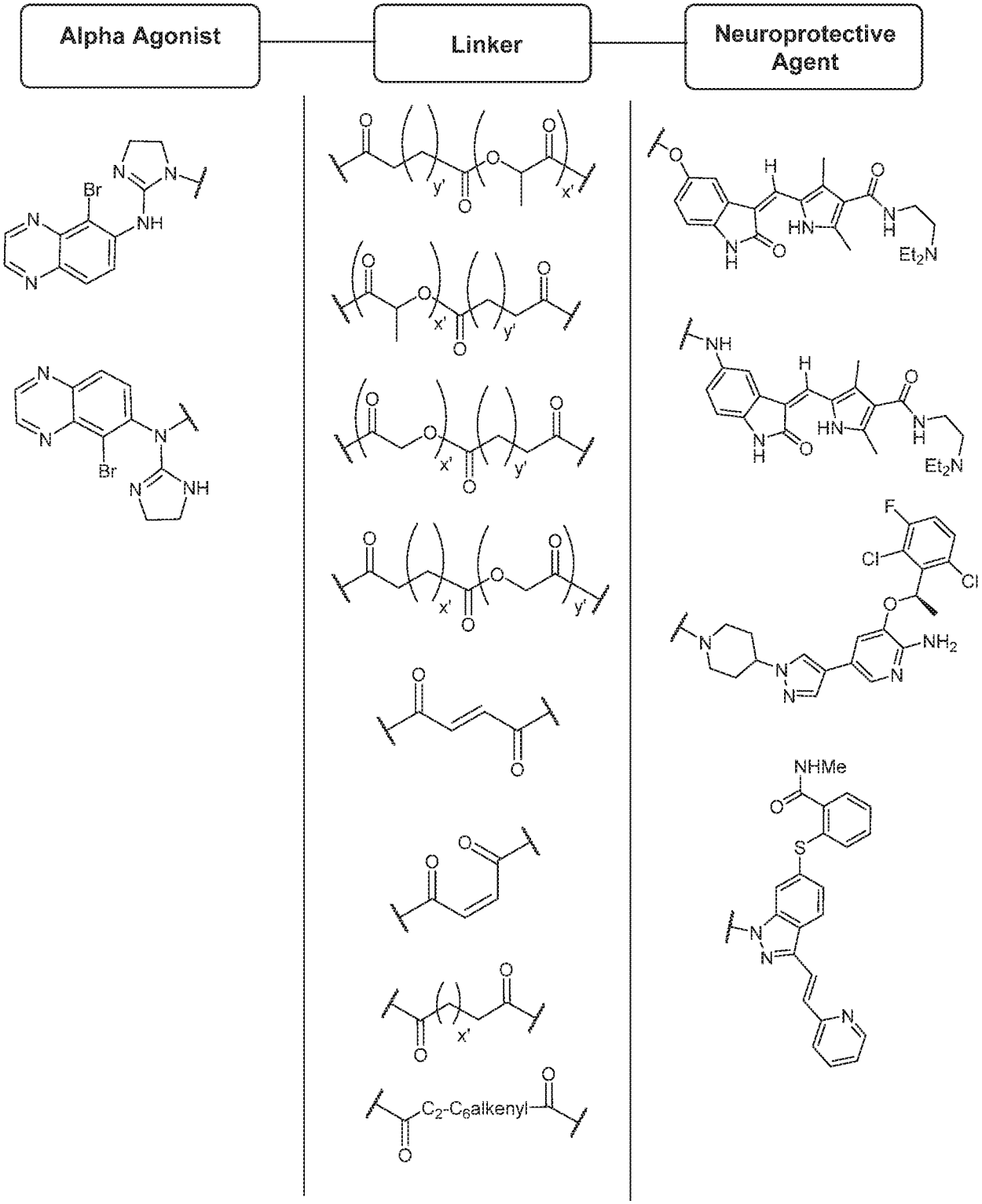


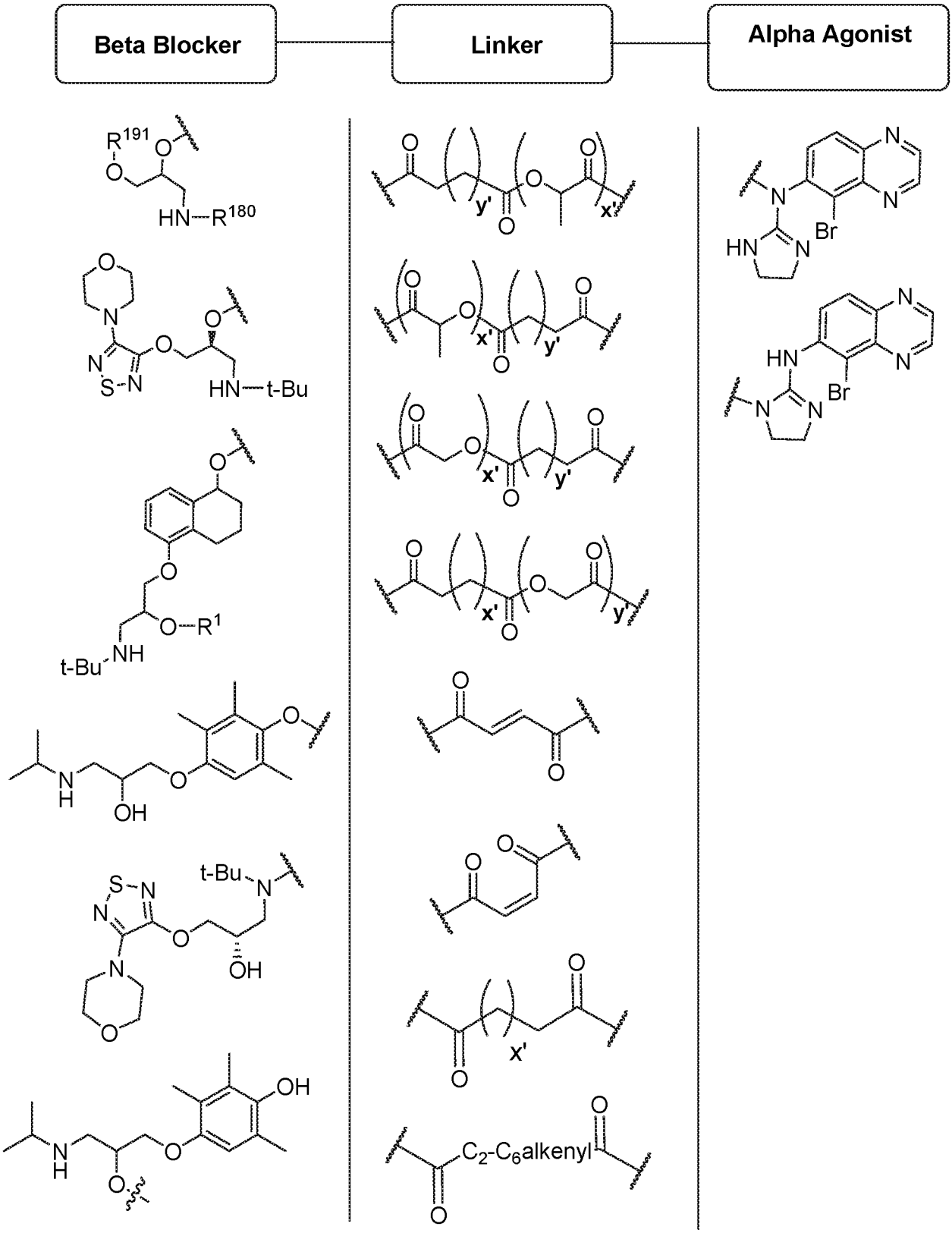


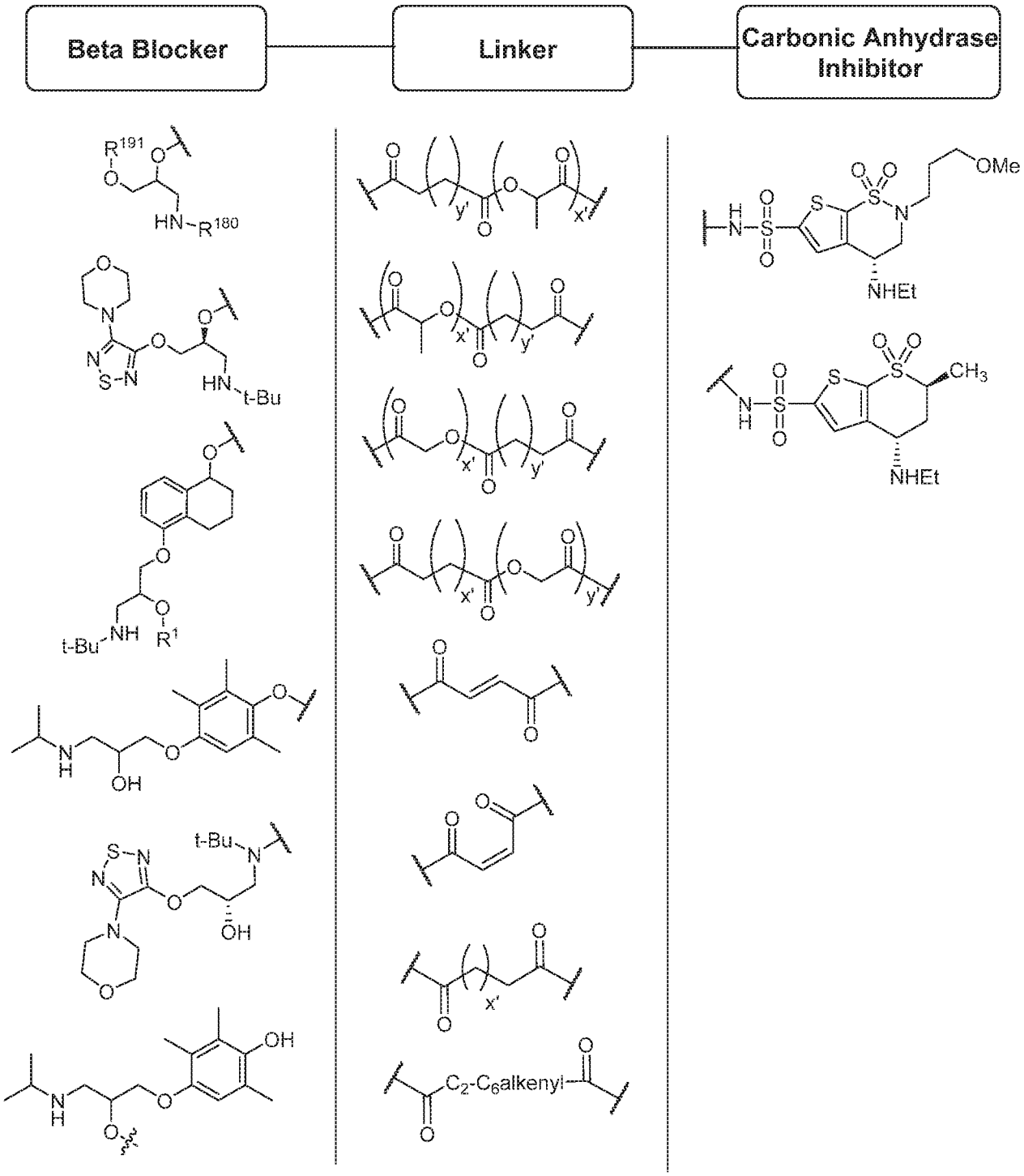
**Example 35. Examples of compounds of the present invention**

This invention is intended to include all combinations of each of the active moieties and linkers in each of the below tables as if each combination were explicitly illustrated.

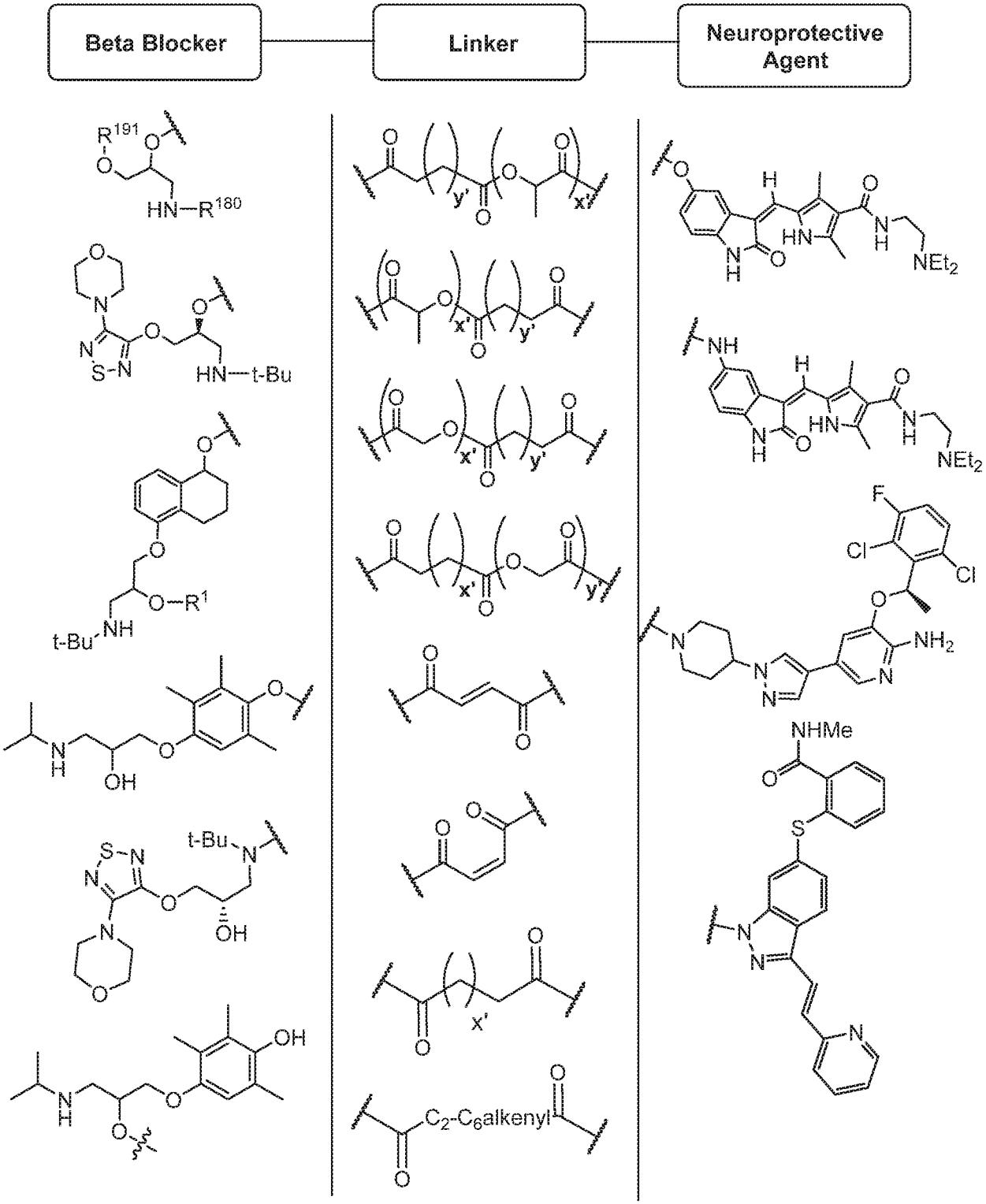
x', and y' are each independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and wherein if x' and y' are within the linker then x' and y' cannot both be 0.

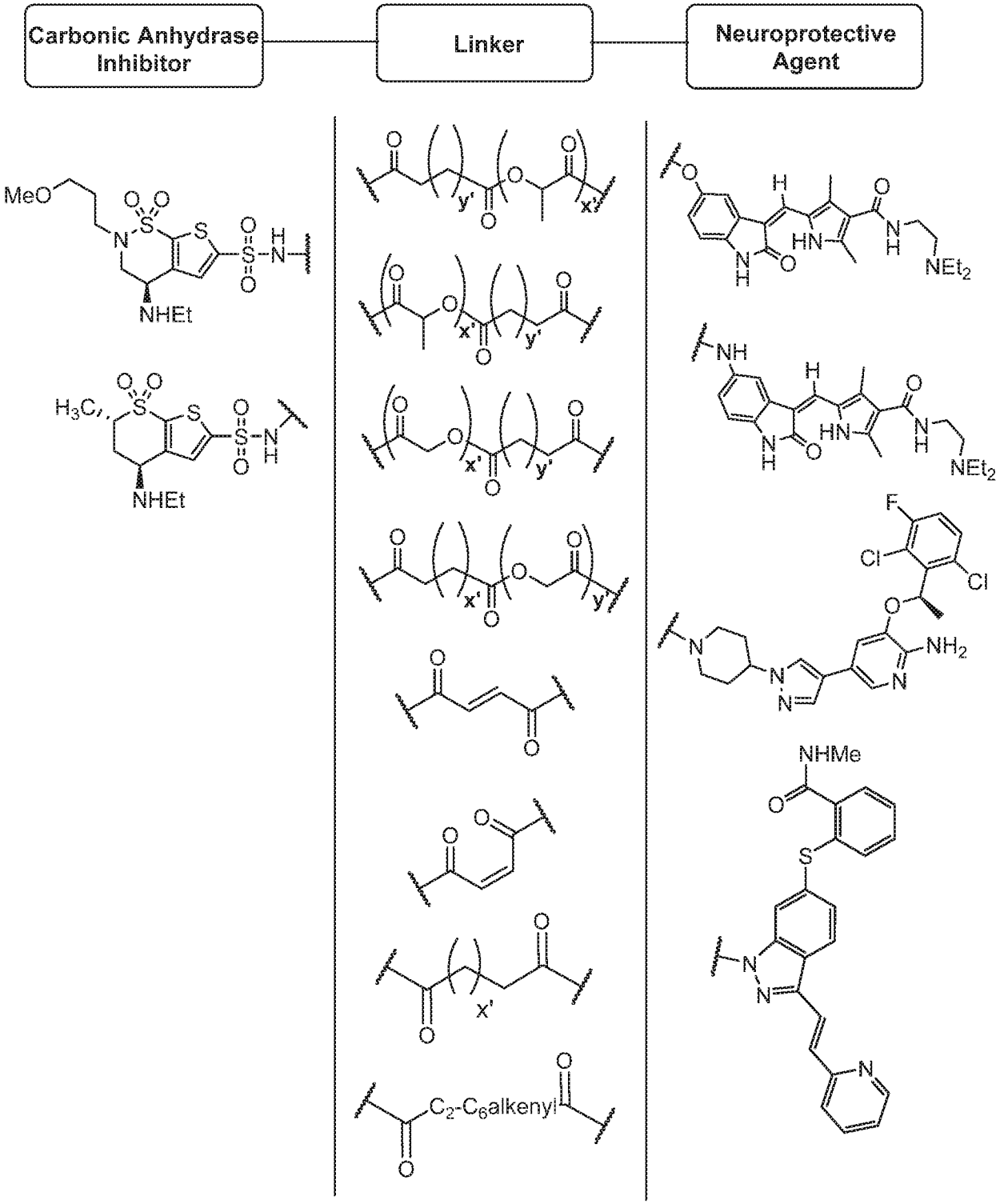

Alpha Agonist
Linker
Neuroprotective Agent
Br
NH
N
Br
NH
N
y'
x'
x'
y'
x'
y'
x'
y'
x'
C2-C6alkenyl
O
H
HN
N
H
Et2N
NH
F
Cl
Cl
NH2
NHMe
S

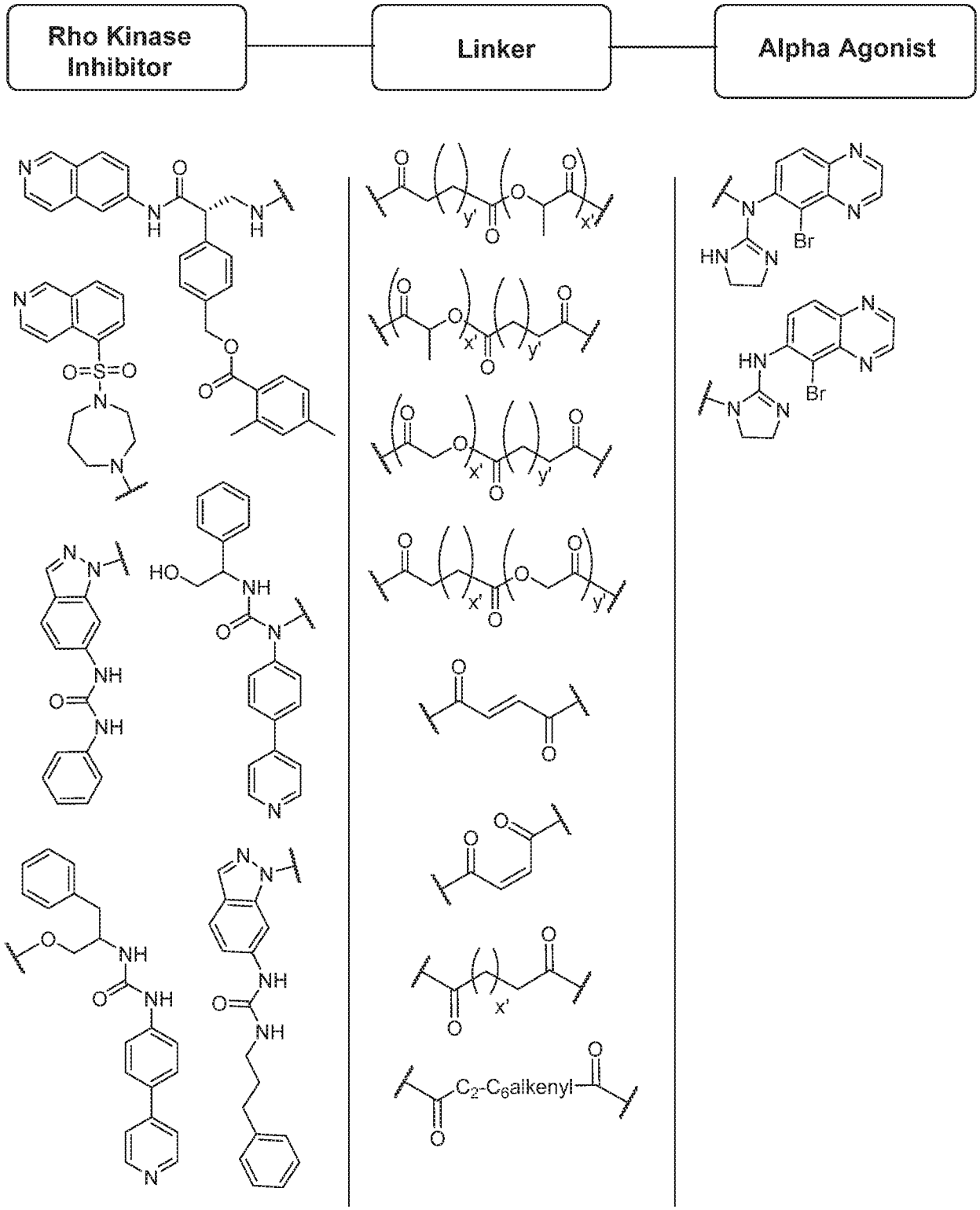

Beta Blocker
Linker
Alpha Agonist
R191
HN—R180
HN—t-Bu
t-Bu
NH
R1
OH
t-Bu
C2-C6alkenyl
Br
HN
x'
y'

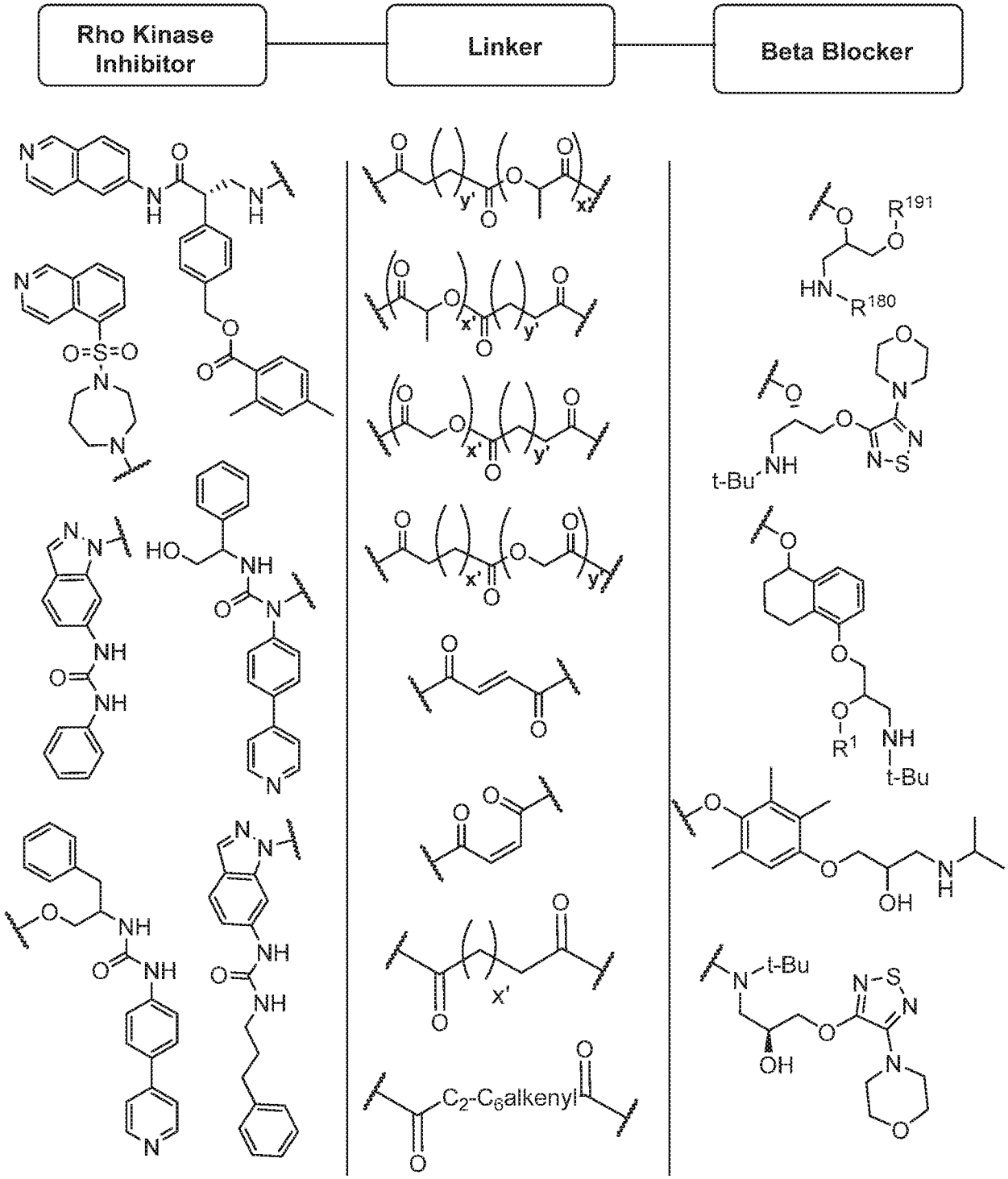

Beta Blocker
Linker
Carbonic Anhydrase Inhibitor
R191
HN
R180
t-Bu
NH
R1
OH
OMe
NHEt
CH3
C2-C6alkenyl
x'
y'

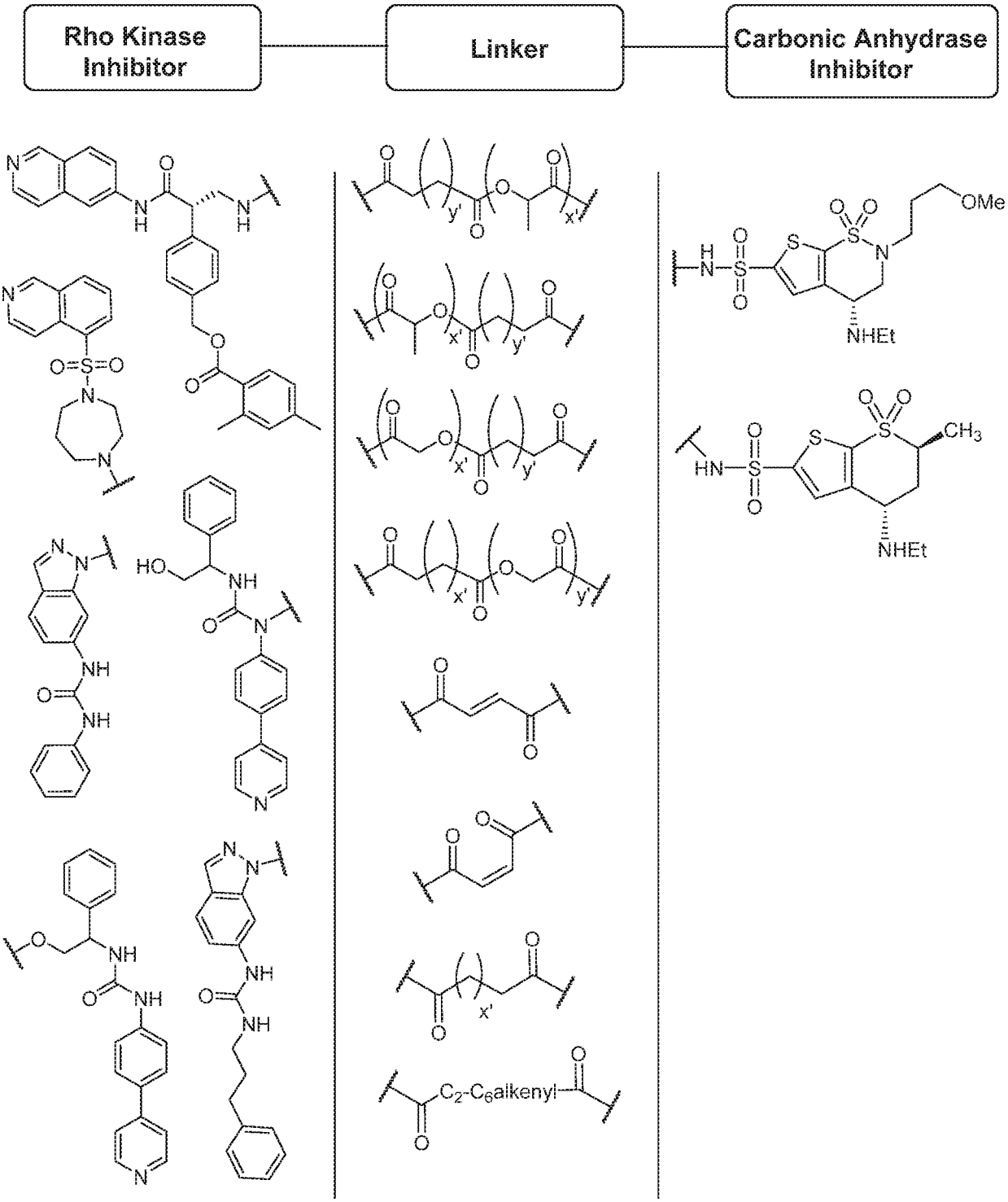
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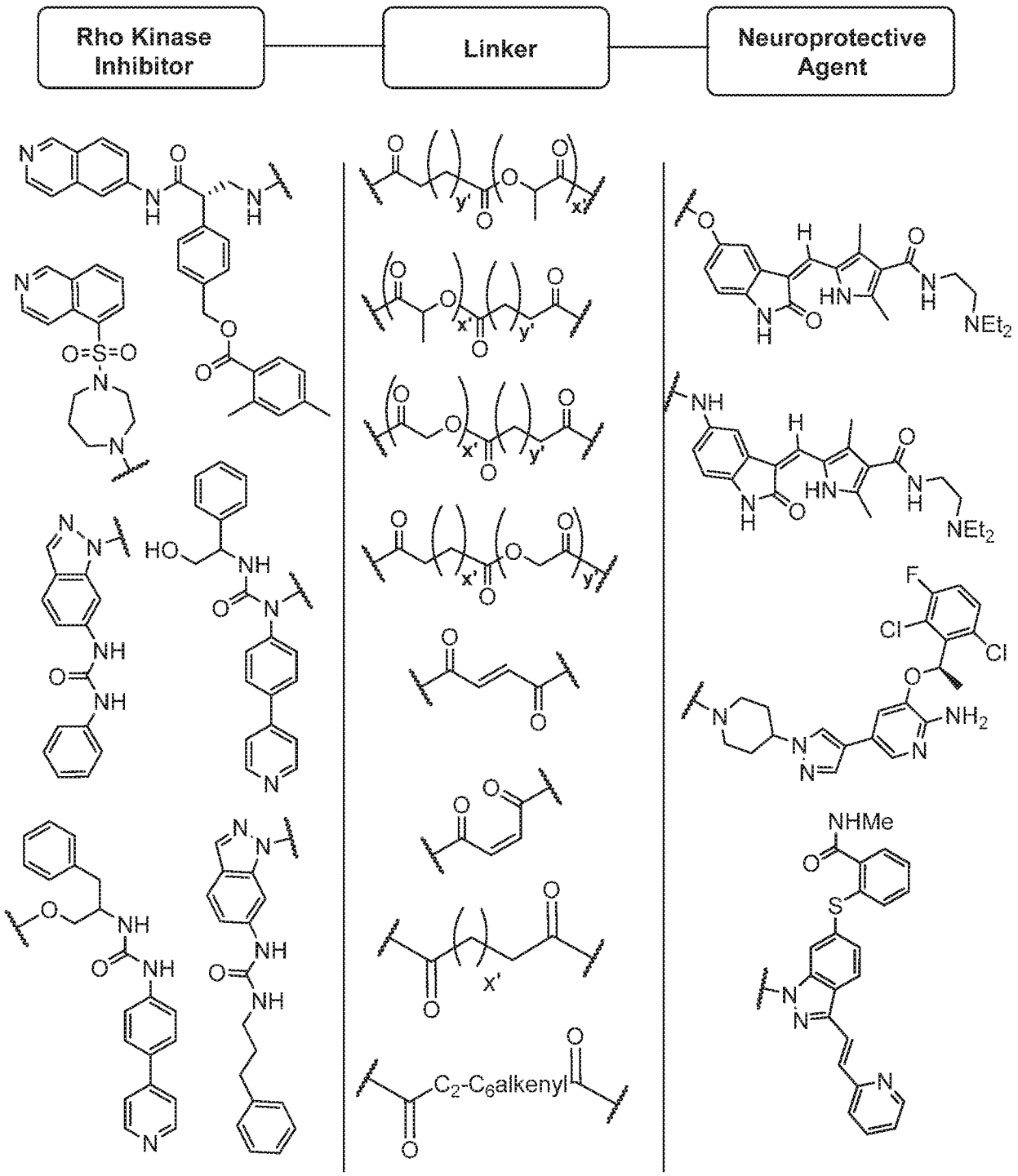

Beta Blocker
Linker
Neuroprotective Agent
R191
HN—R180
HN—t-Bu
t-Bu
NH
R1
OH
S-N
N
O
x'
y'
C2-C6alkenyl
NEt2
NH2
F
Cl
NHMe
S


Carbonic Anhydrase Inhibitor
Linker
Neuroprotective Agent
MeO
NHEt
H3C
NHEt
C2-C6alkenyl
NHMe
NEt2
NH2
Cl
F


Rho Kinase Inhibitor
Linker
Alpha Agonist
C2-C6alkenyl


Rho Kinase Inhibitor
Linker
Beta Blocker
C2-C6alkenyl

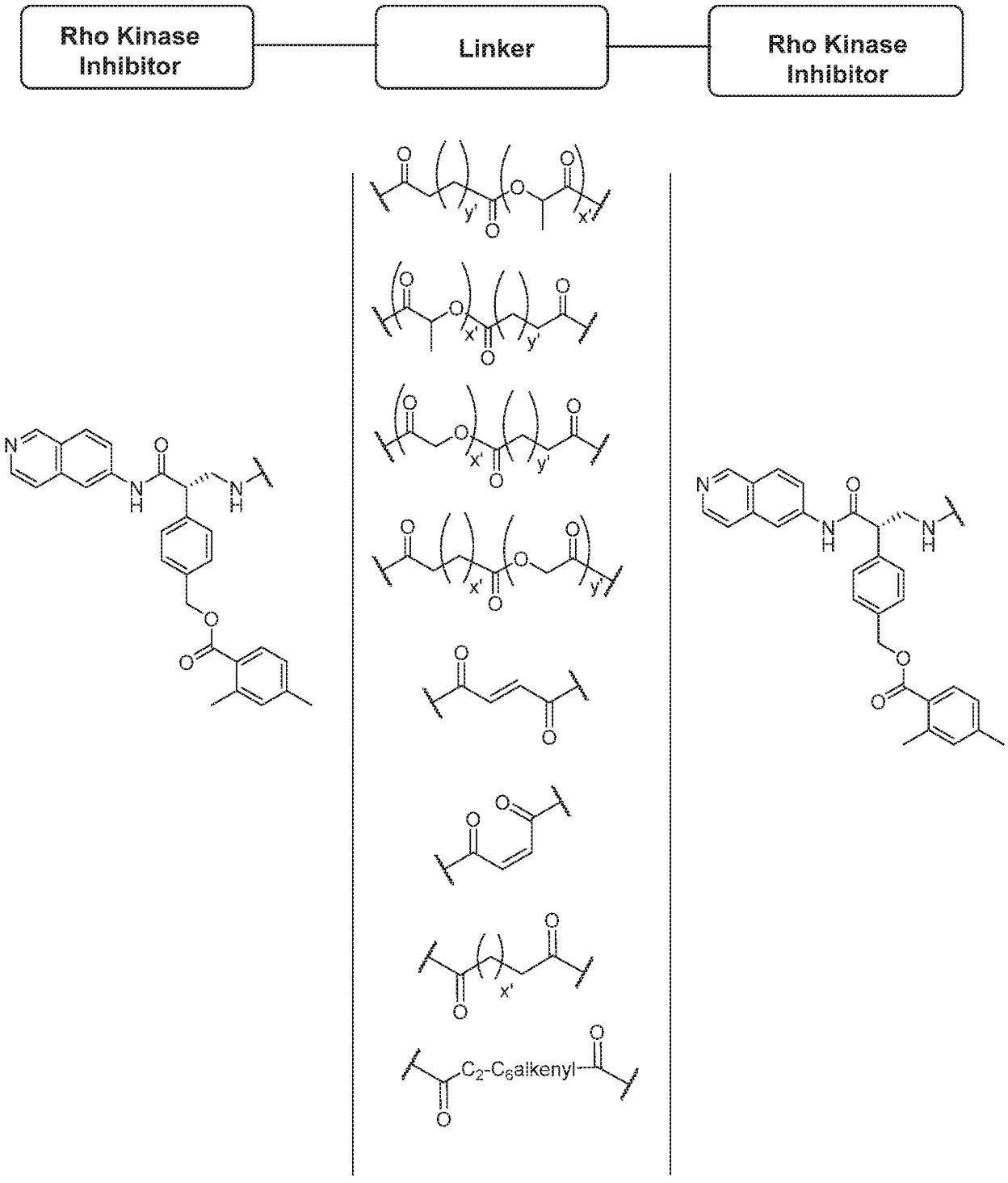

Rho Kinase Inhibitor
Linker
Carbonic Anhydrase Inhibitor
C2-C6alkenyl
OMe
NHEt
CH3
NHEt

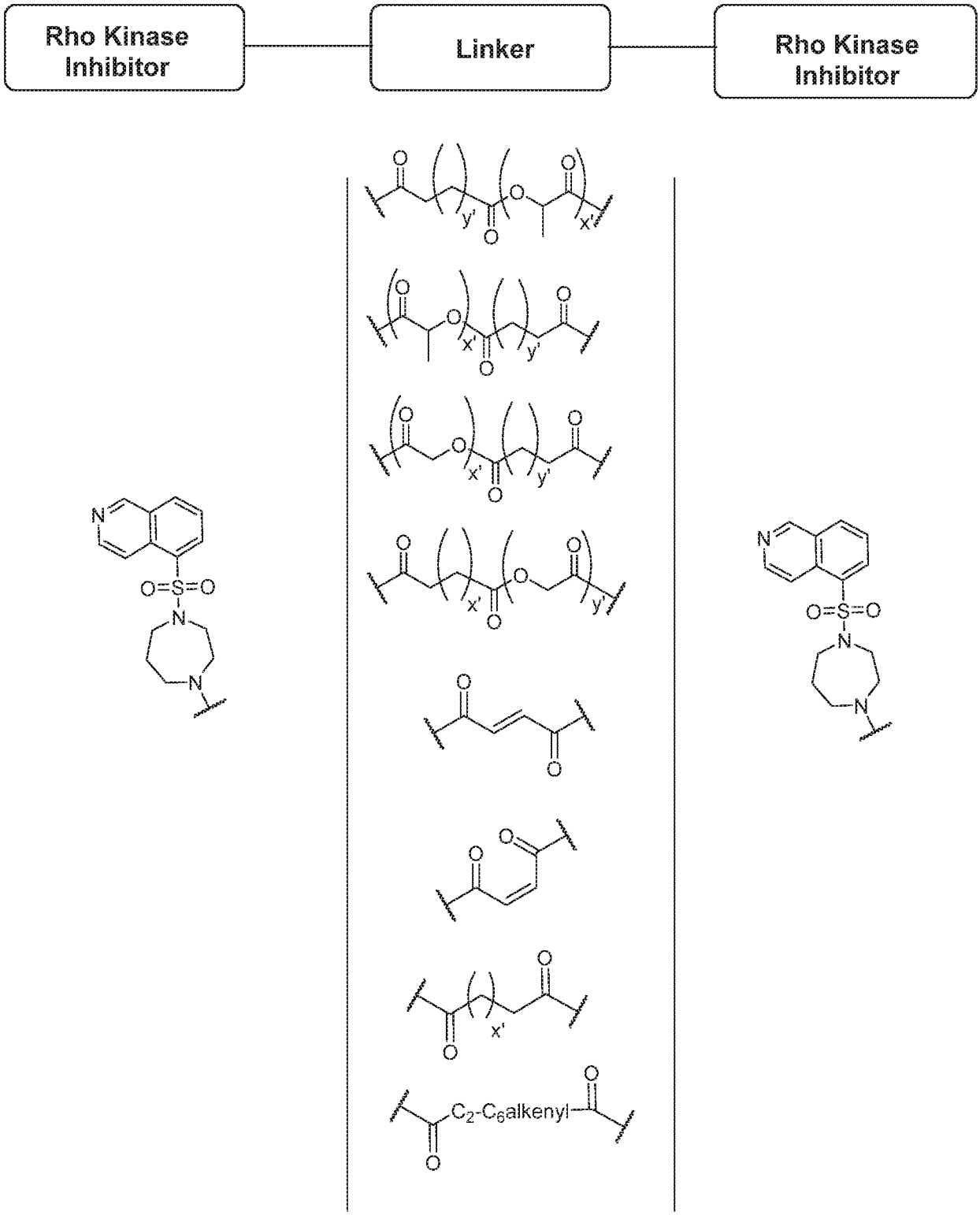


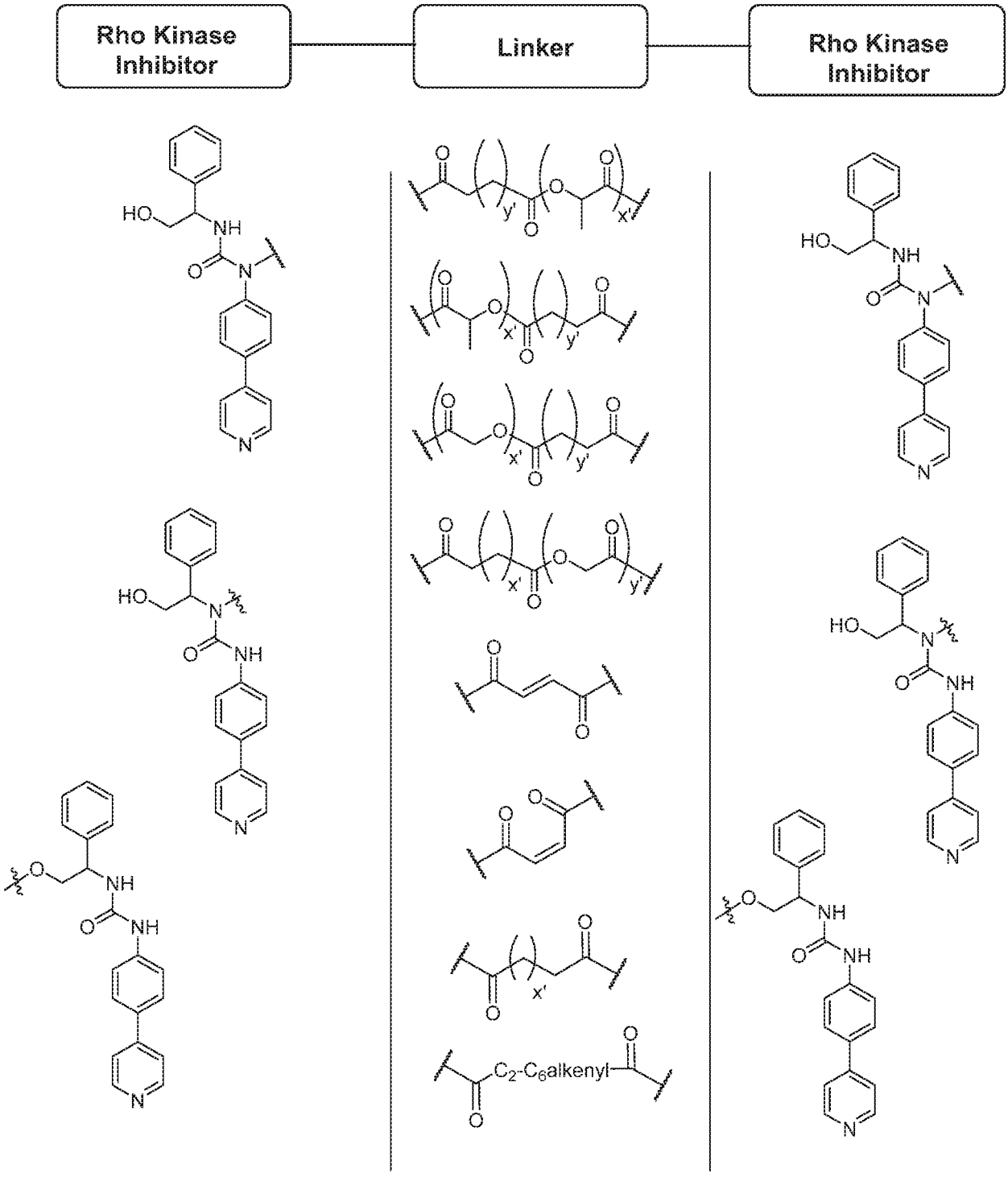

**Example 36. Examples of compounds of the present invention**

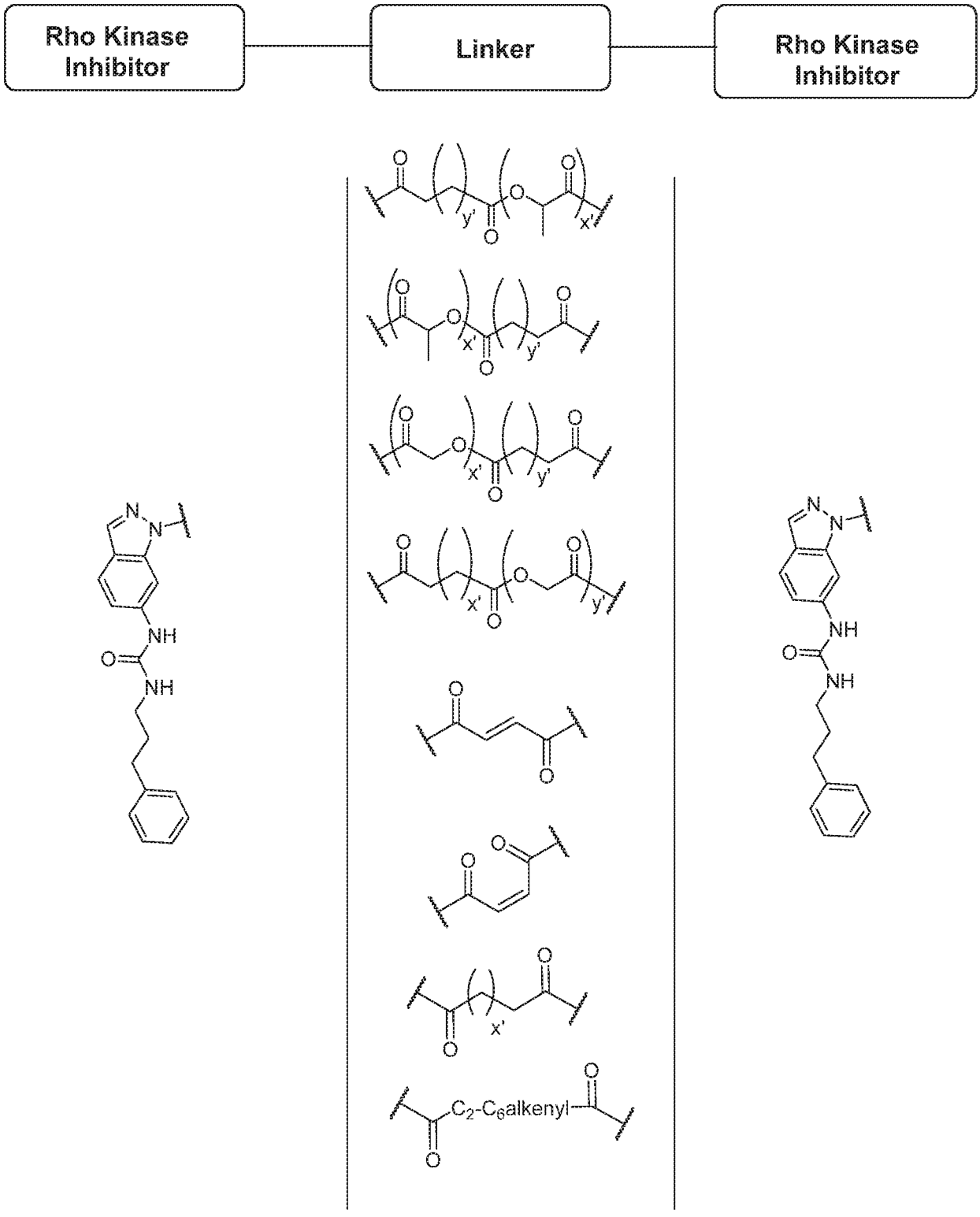
This invention includes the specific combinations of each species and each linker in each of the below tables with each other as if each compound were explicitly described.

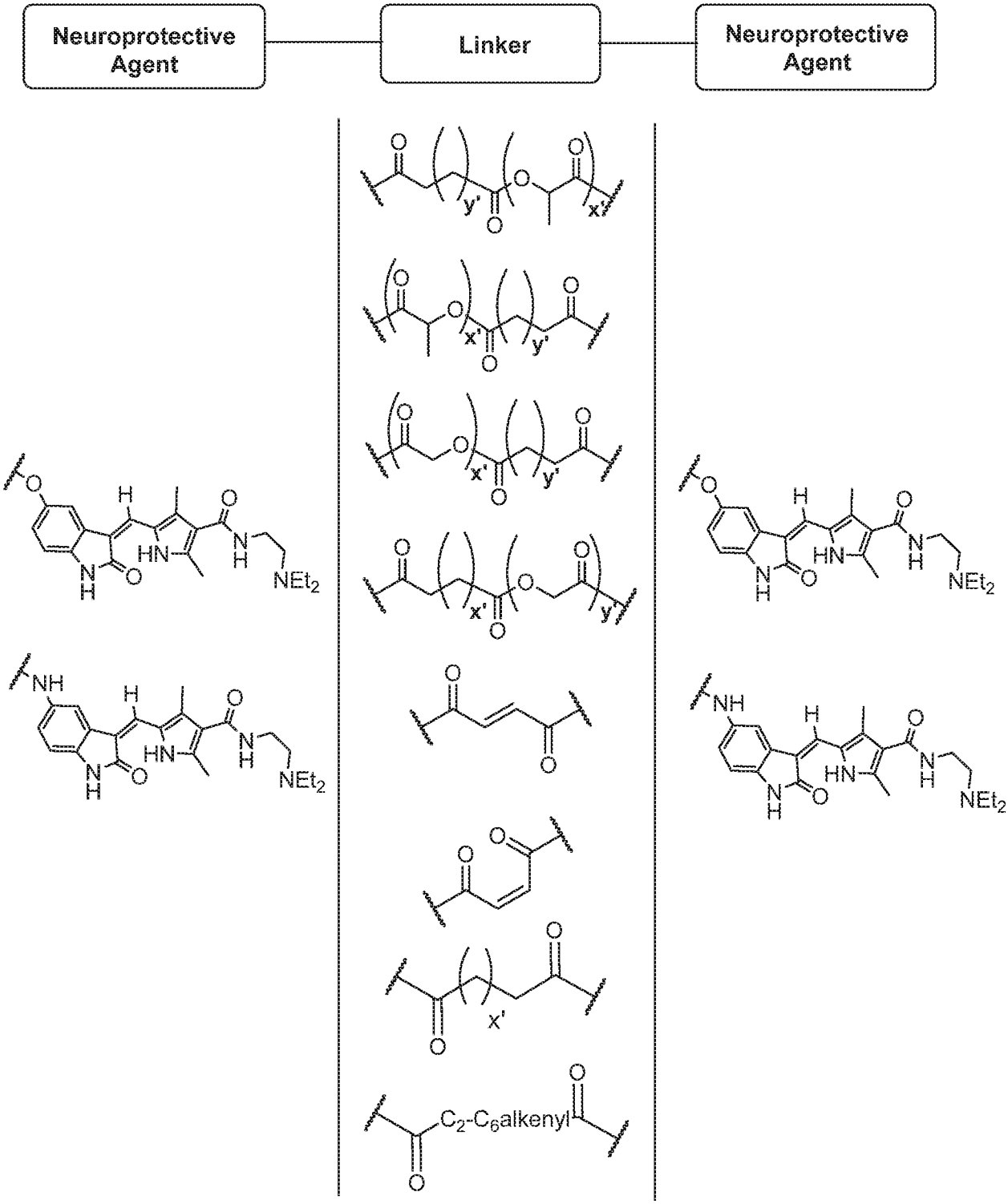
x', y', and z' are each independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

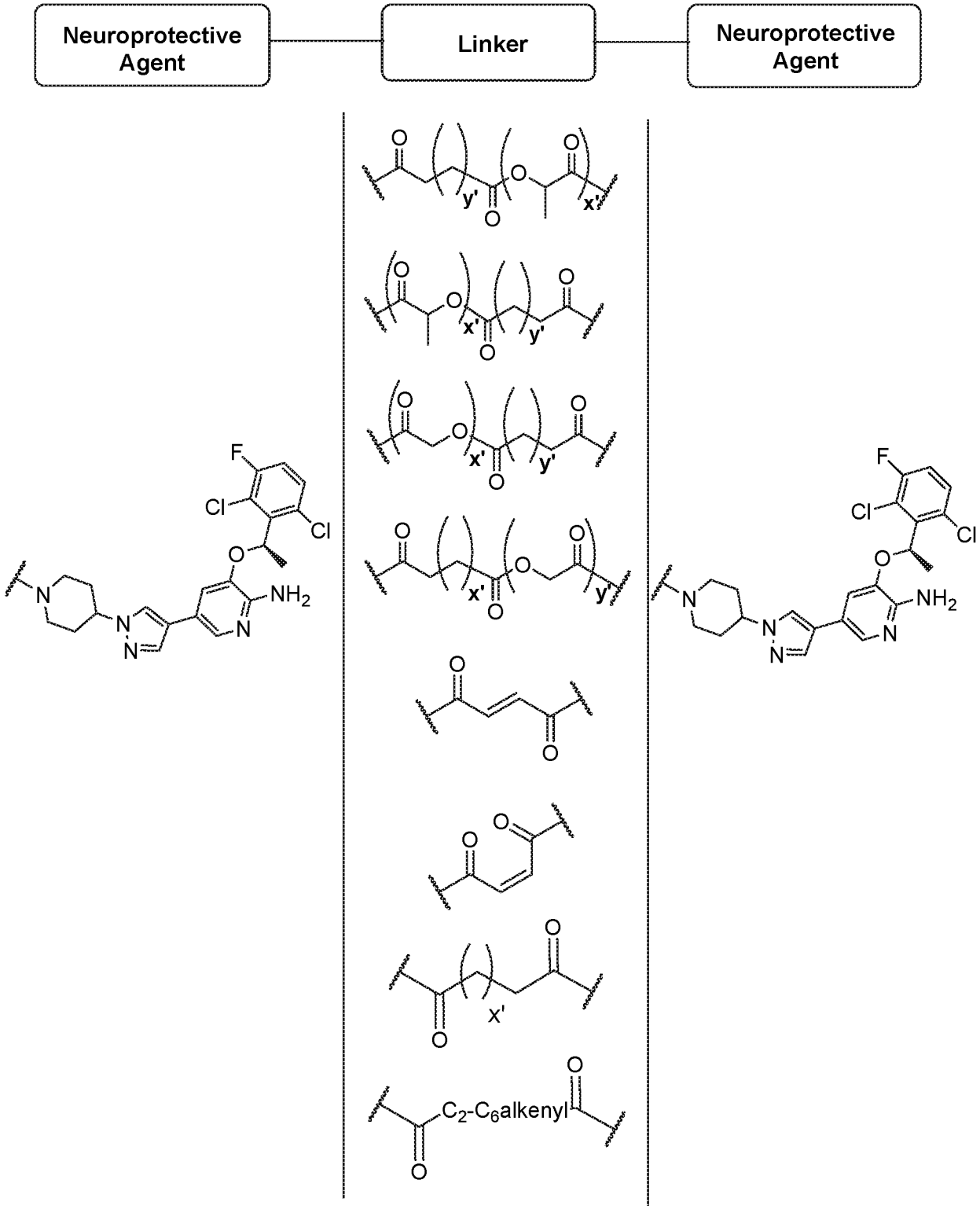


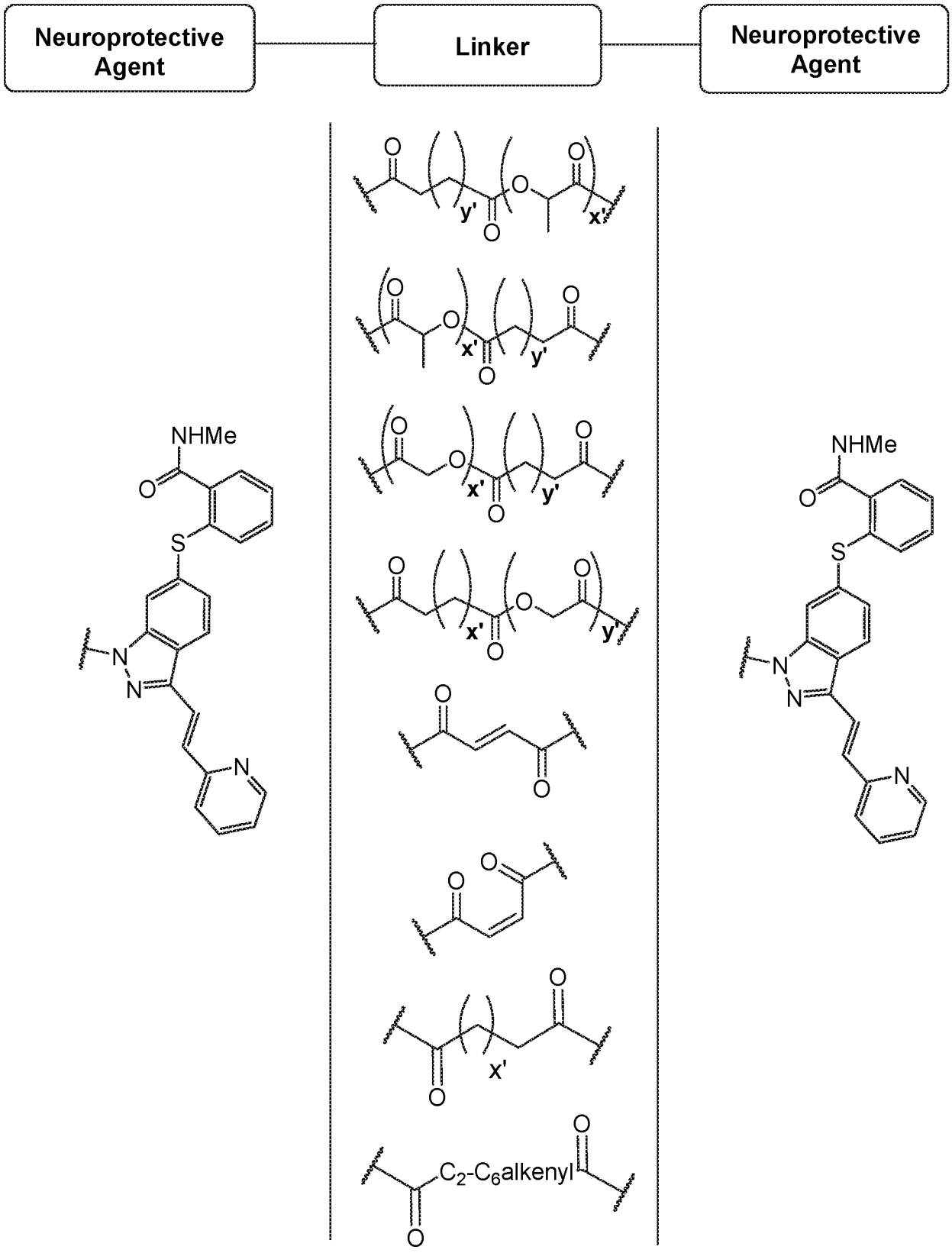

Rho Kinase Inhibitor
Linker
Rho Kinase Inhibitor
C2-C6alkenyl

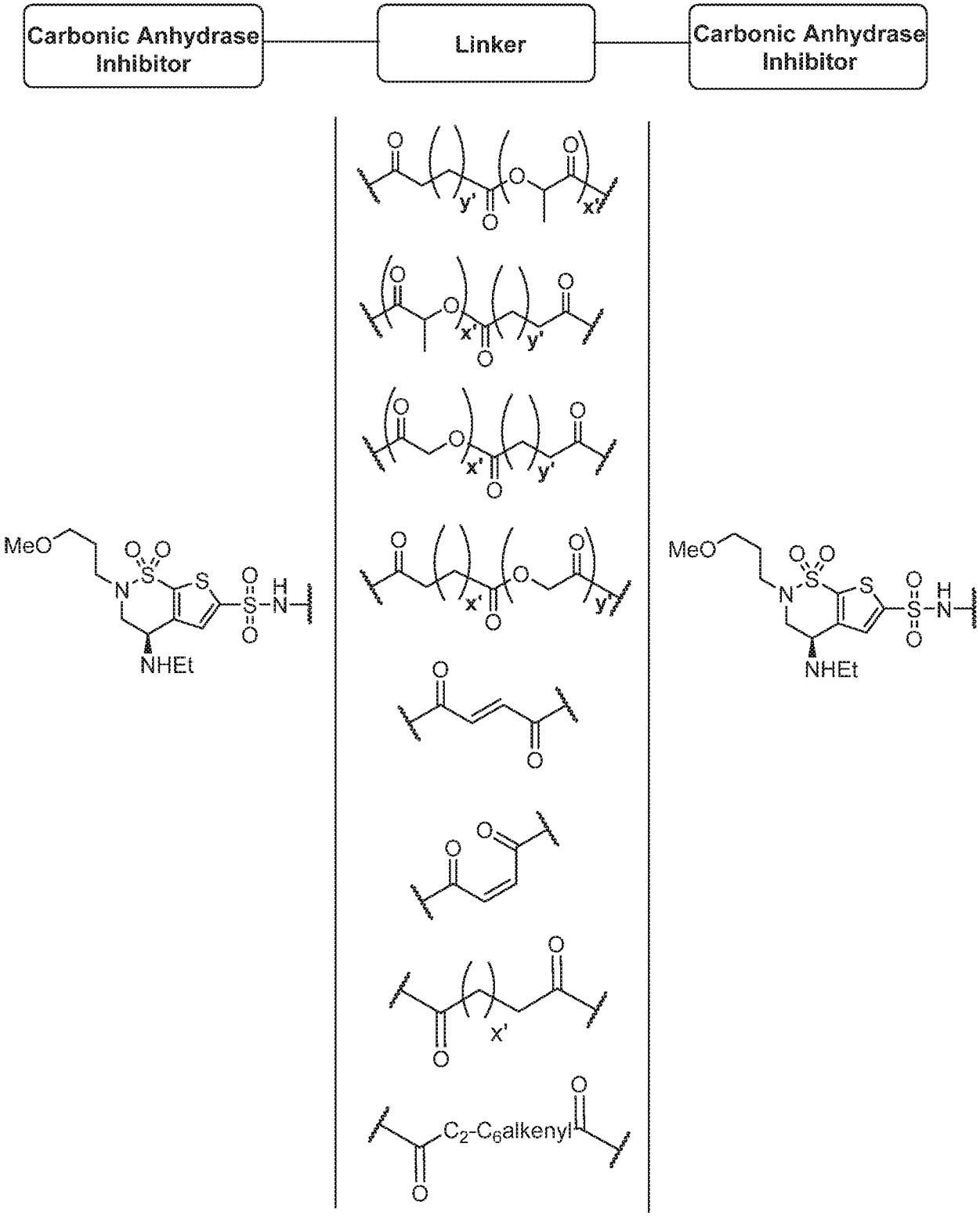

Rho Kinase Inhibitor
Linker
Rho Kinase Inhibitor
HO
NH
O
N
x'
y'
C2-C6alkenyl

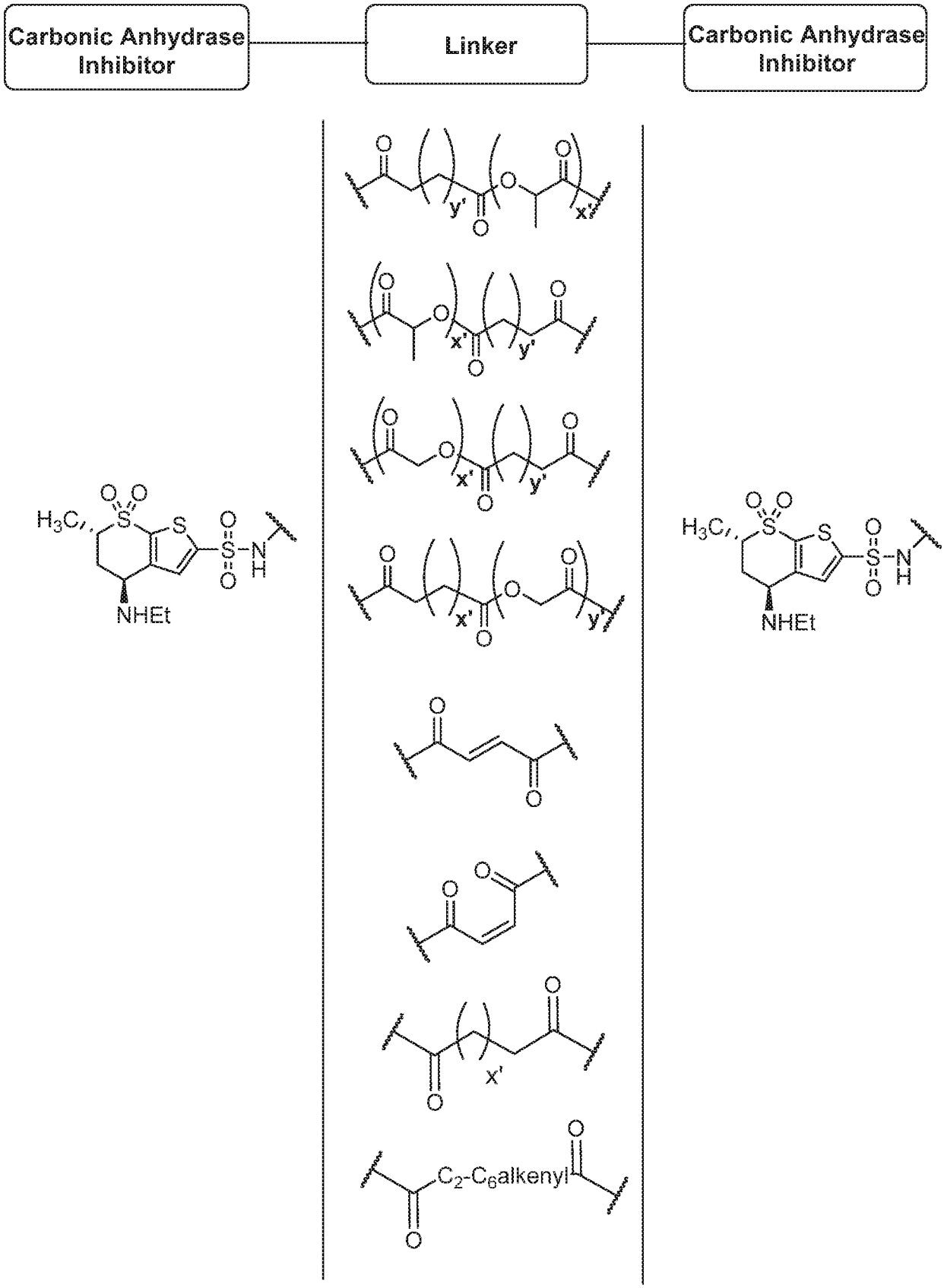

Rho Kinase Inhibitor
Linker
Rho Kinase Inhibitor
C2-C6alkenyl

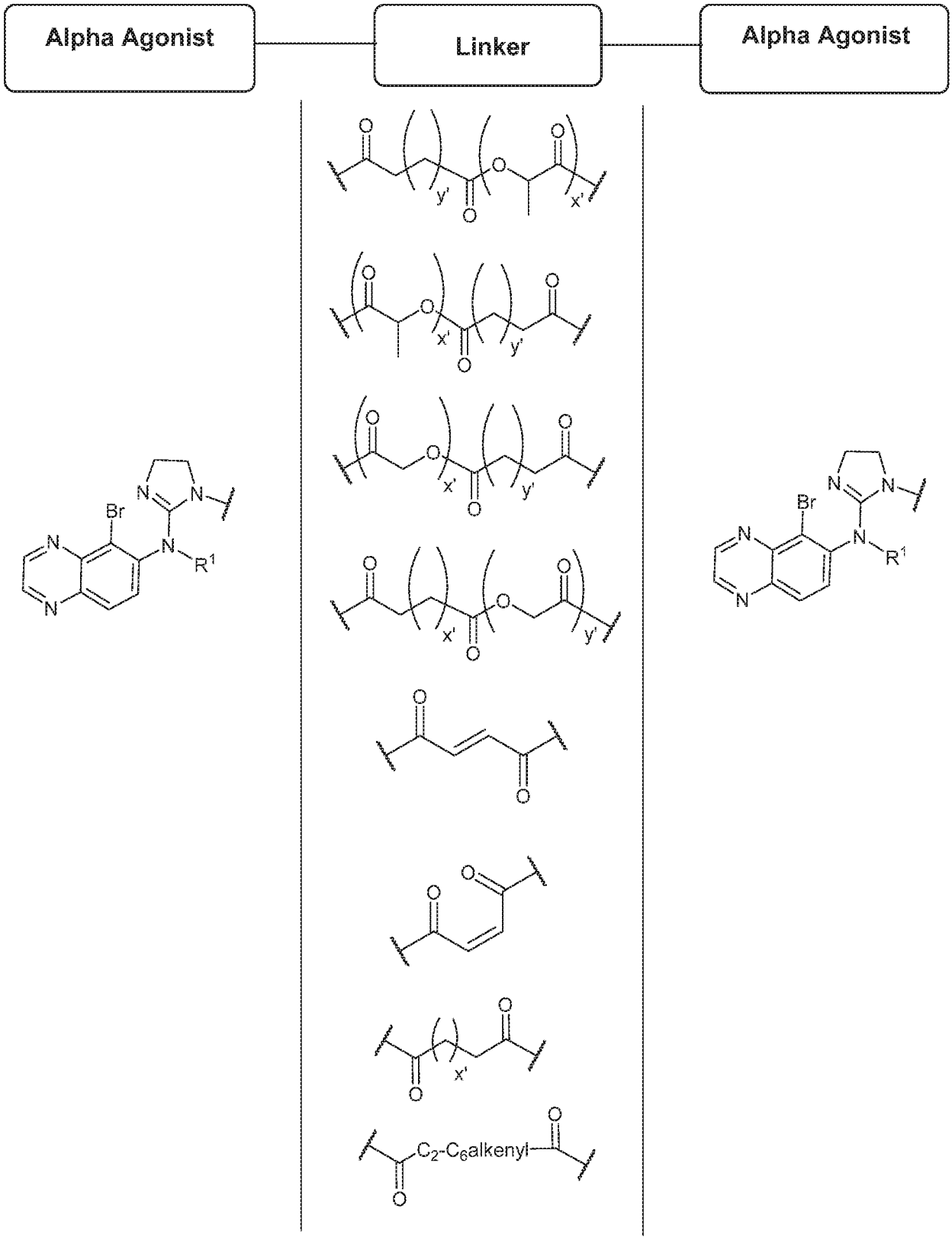

Neuroprotective Agent
Linker
Neuroprotective Agent
C2-C6alkenyl

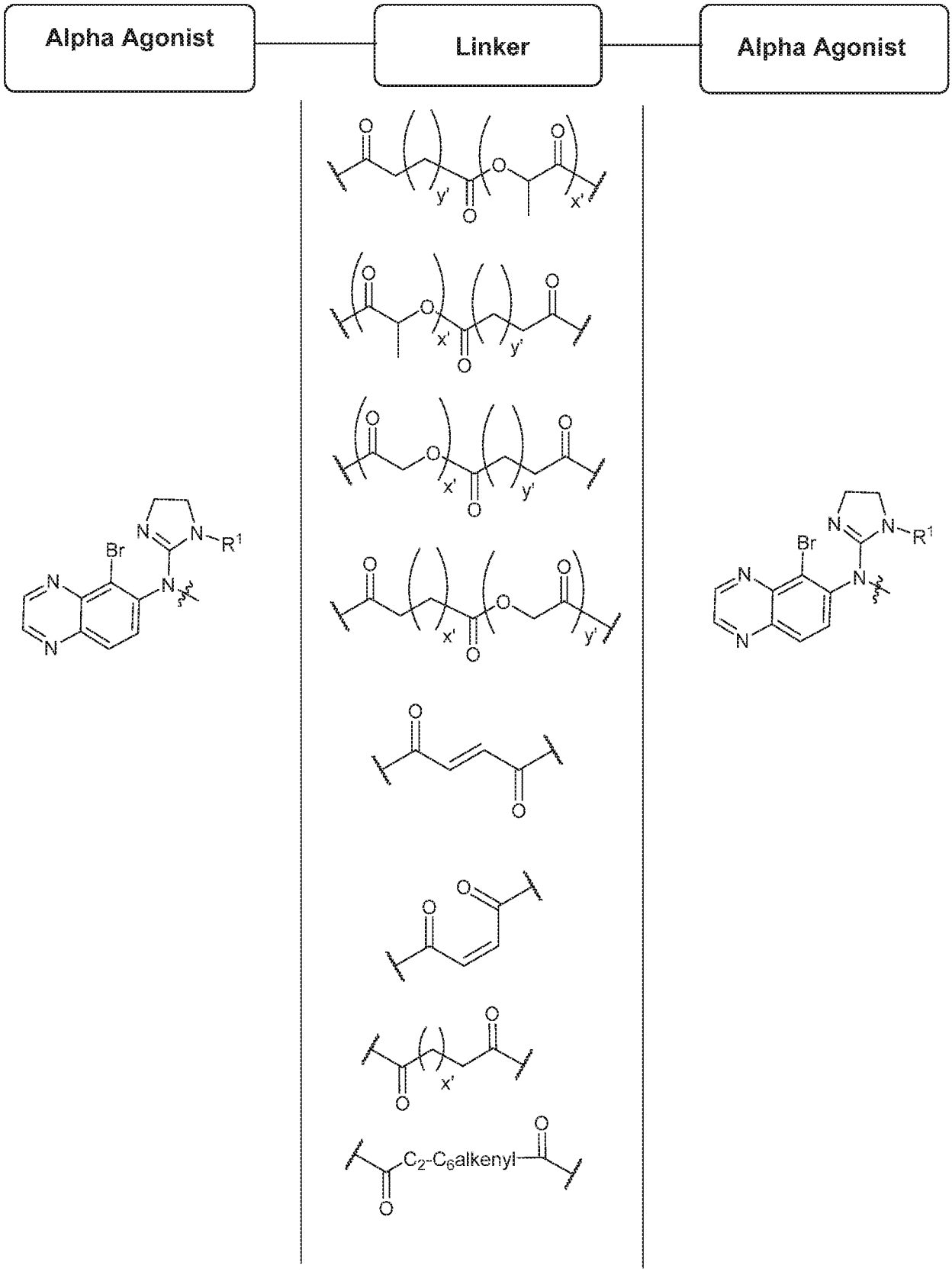

Neuroprotective Agent
Linker
Neuroprotective Agent
F
Cl
Cl
O
NH2
N
N
N
y'
x'
C2-C6alkenyl

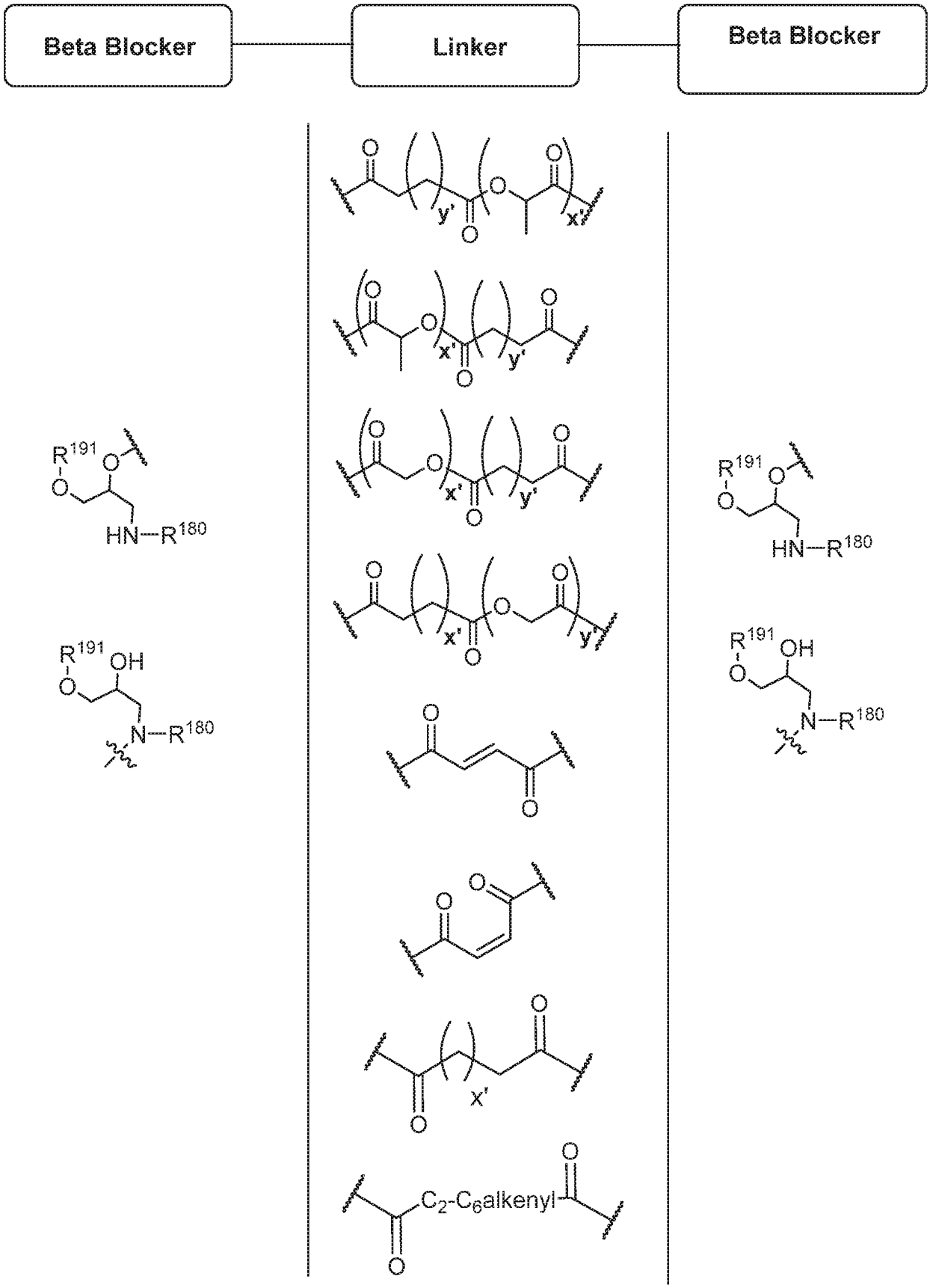

Neuroprotective Agent
Linker
Neuroprotective Agent
NHMe
O
S
N
N
N
y'
x'
x'
y'
x'
y'
x'
y'
x'
C2-C6alkenyl
NHMe
O
S
N
N
N

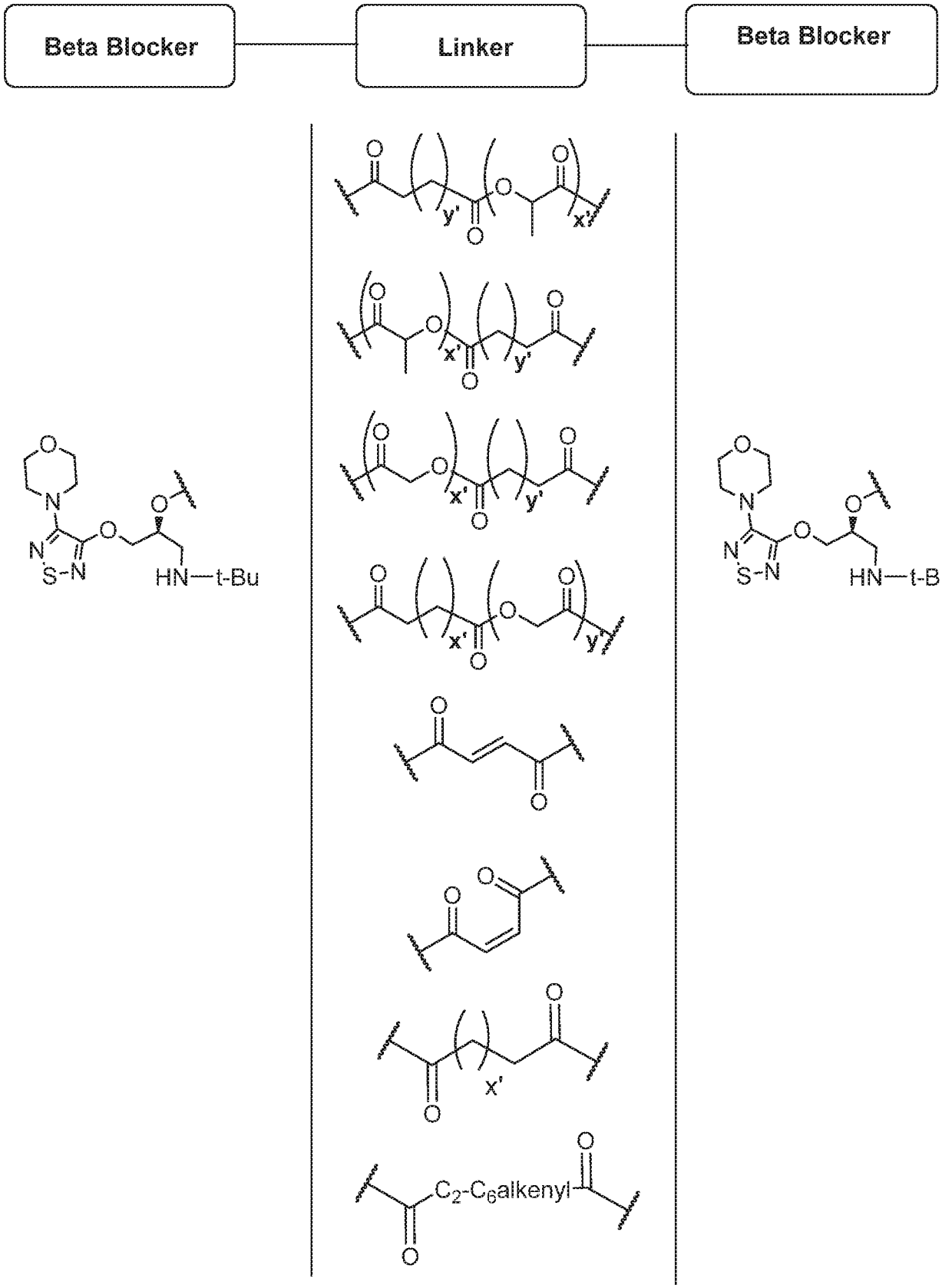

Carbonic Anhydrase Inhibitor
Linker
Carbonic Anhydrase Inhibitor
MeO
NHEt
x'
y'
C2-C6alkenyl

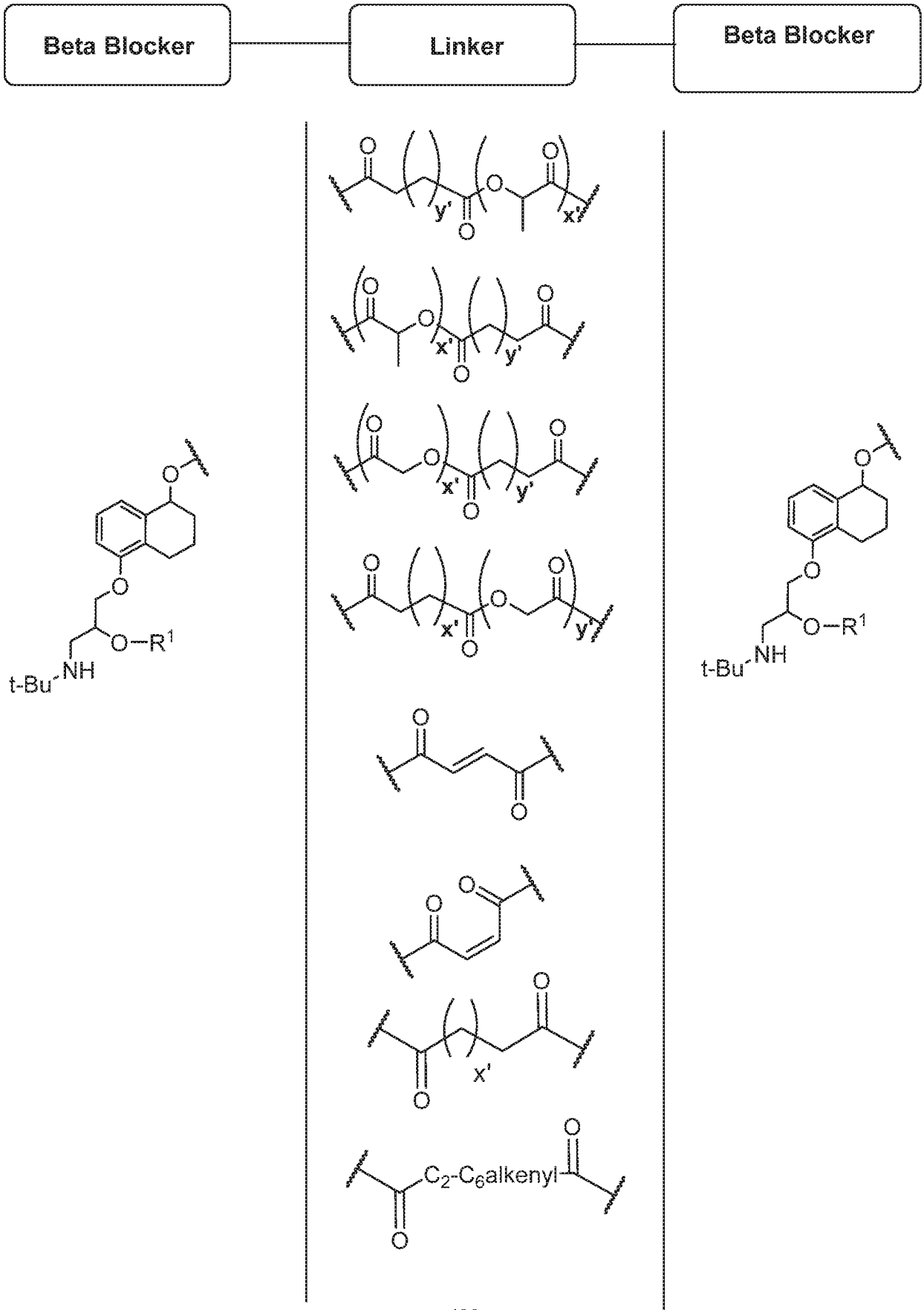

Carbonic Anhydrase Inhibitor
Linker
Carbonic Anhydrase Inhibitor
NHEt
NHEt
C2-C6alkenyl

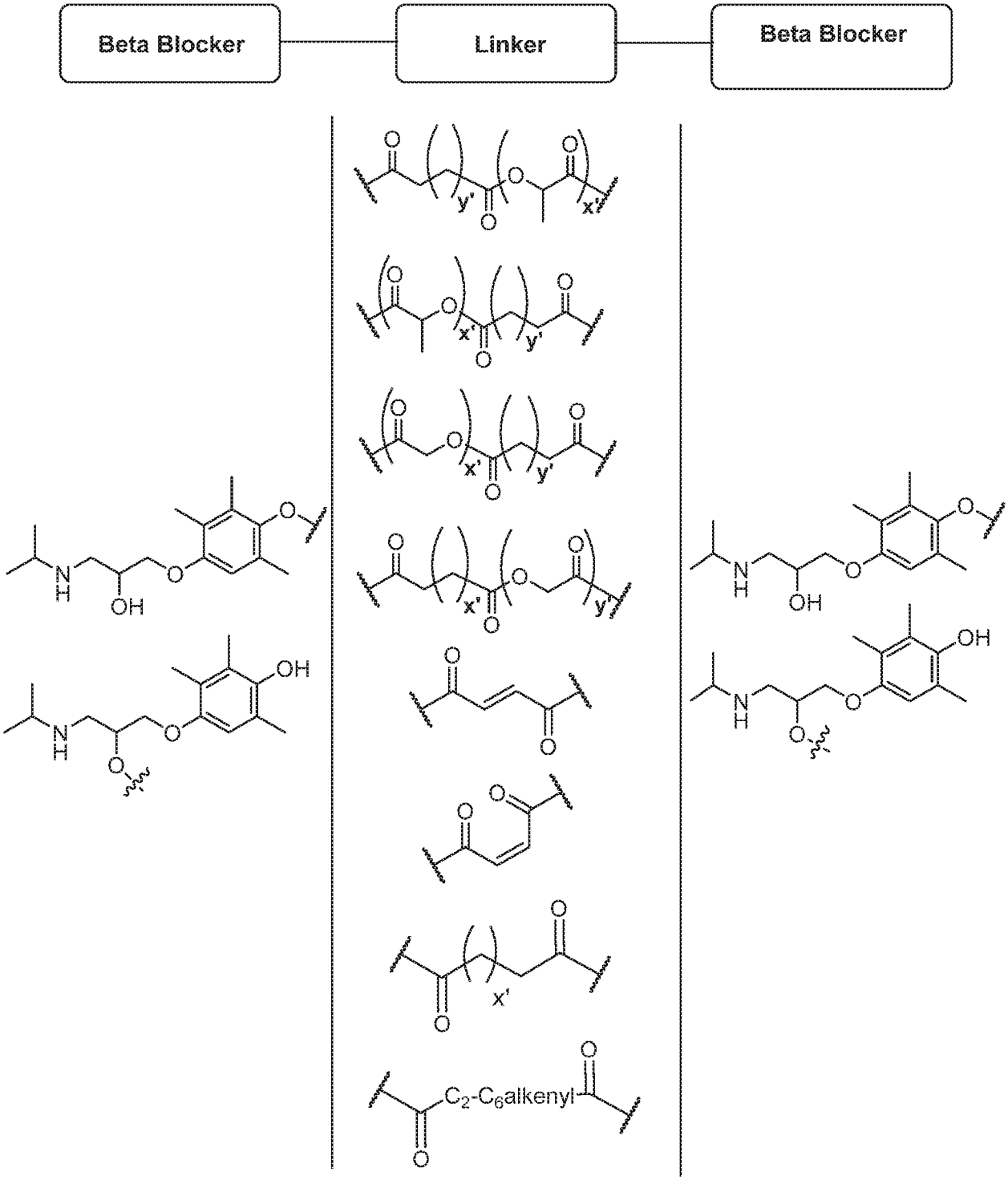

Alpha Agonist
Linker
Alpha Agonist
Br
N
N
N
R1
C2-C6alkenyl

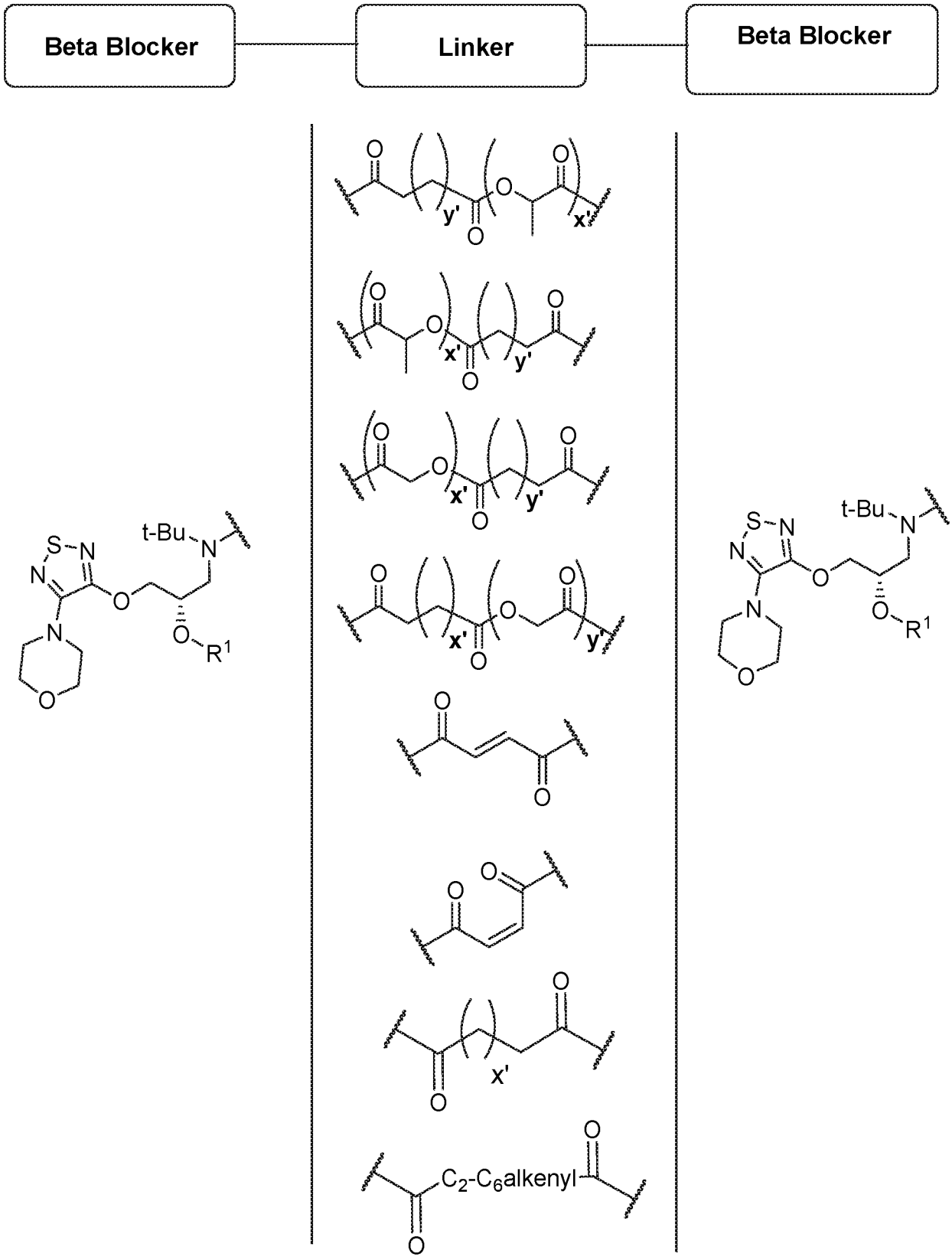

Alpha Agonist
Linker
Alpha Agonist
C2-C6alkenyl


Beta Blocker
Linker
Beta Blocker
R191
O
HN—R180
R191
OH
N—R180
y'
x'
C2-C6alkenyl


Beta Blocker
Linker
Beta Blocker
HN—t-Bu
HN—t-Bu
C2-C6alkenyl

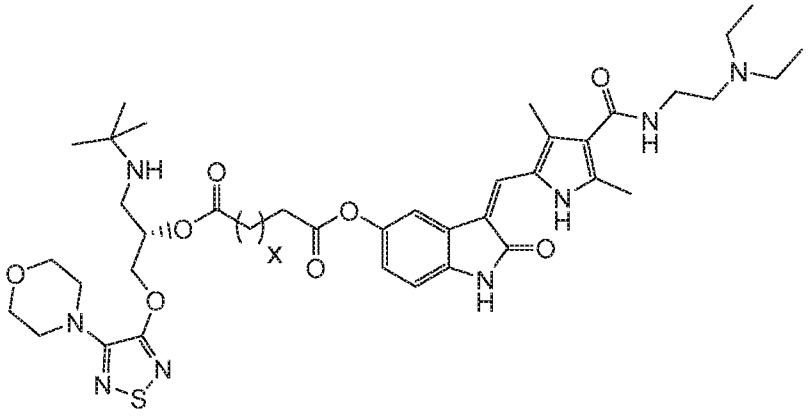

Beta Blocker
Linker
Beta Blocker
t-Bu
NH
O—R1
x'
y'
C2-C6alkenyl


Beta Blocker
Linker
Beta Blocker
y'
x'
x'
y'
x'
y'
x'
y'
x'
y'
x'
C2-C6alkenyl
N
H
OH
O

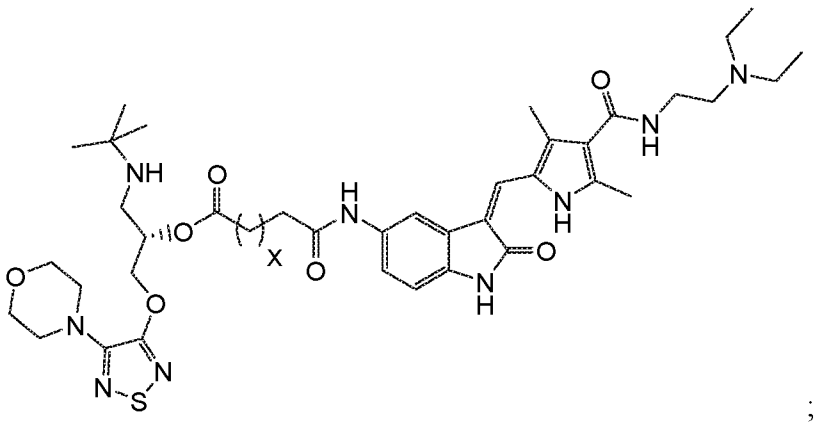

Beta Blocker
Linker
Beta Blocker
t-Bu
S
N
O
R1
y'
x'
C2-C6alkenyl

**Example 37. Compounds of the Present Invention**

In one embodiment the compound of the present invention is selected from:



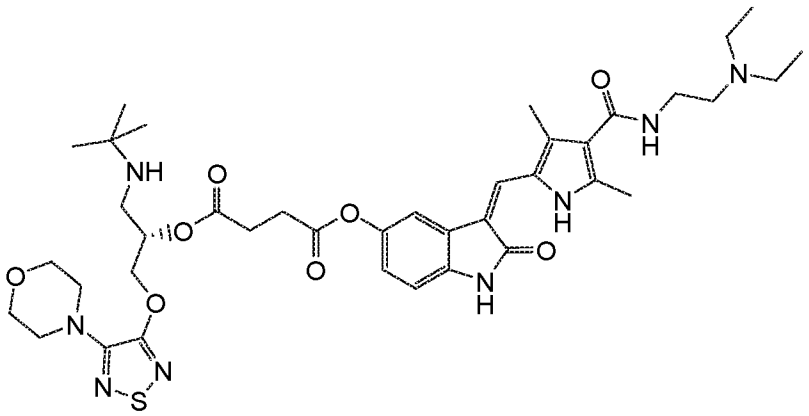
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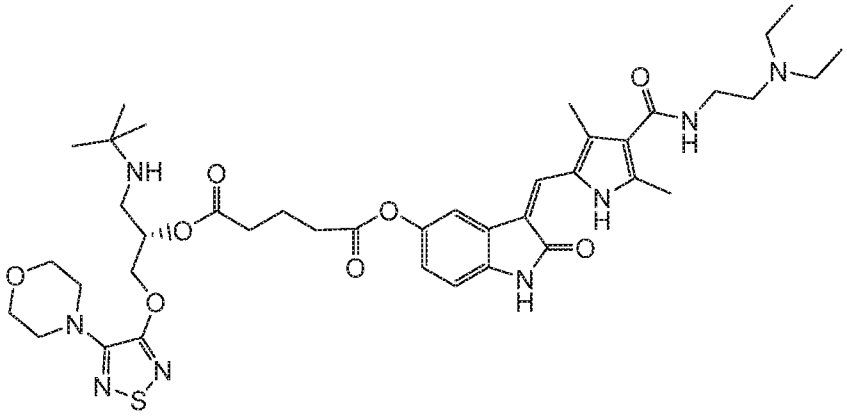


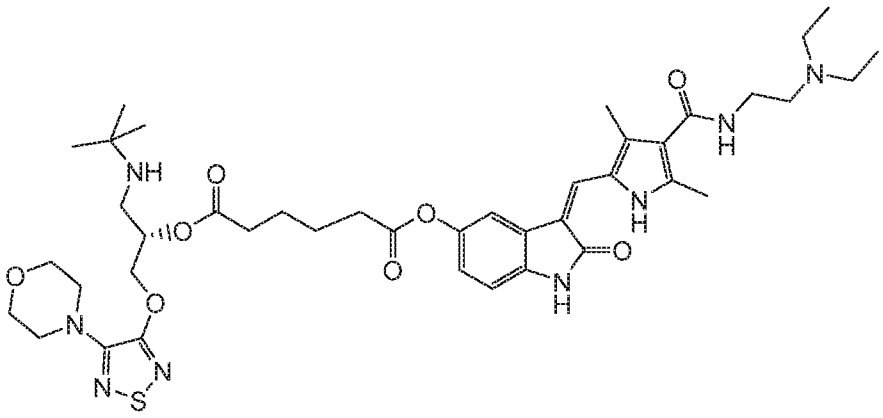
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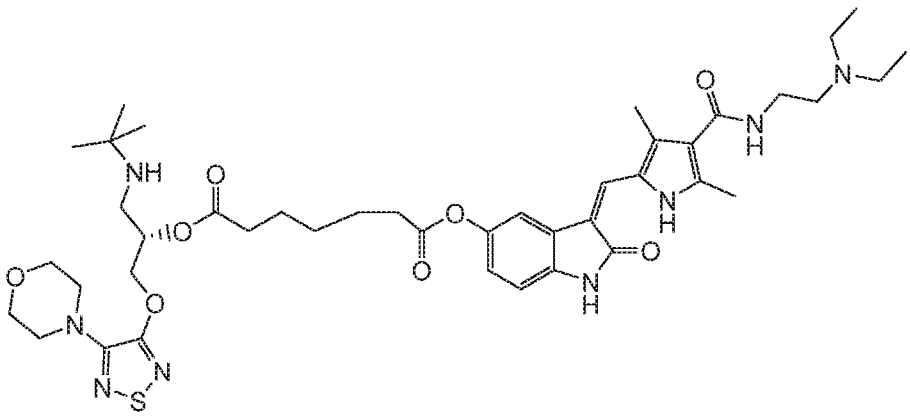
wherein x is 1, 2, 3, 4, 5, 6, 7, 8, or 9.

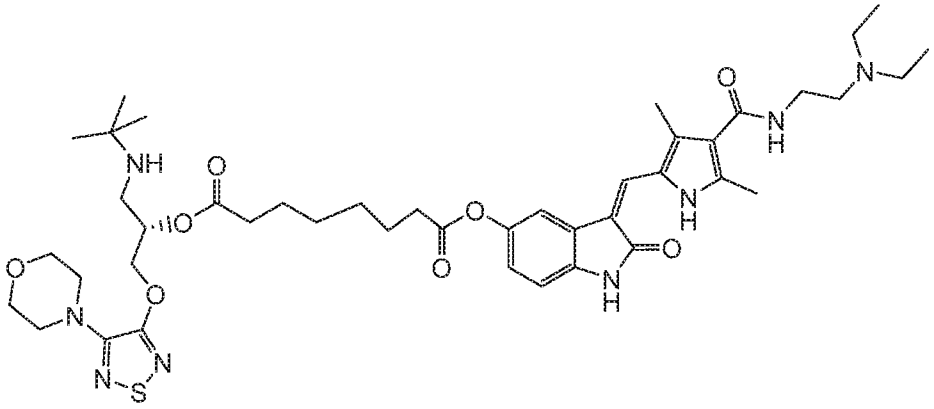
In one embodiment the compound of the present invention is selected from:

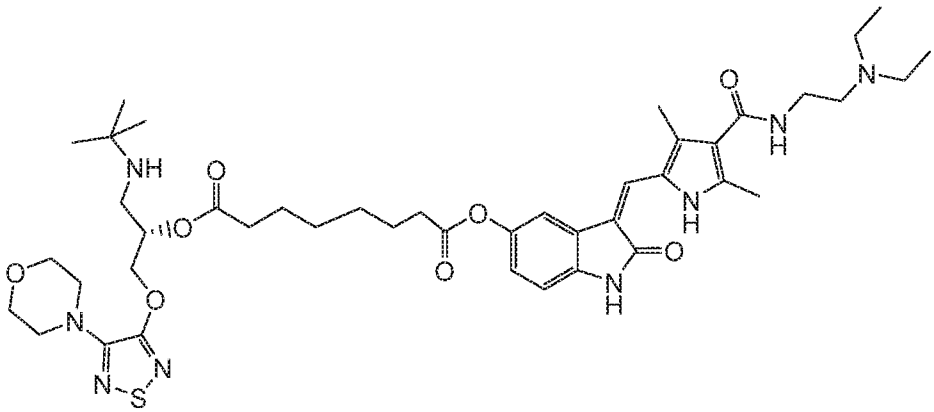


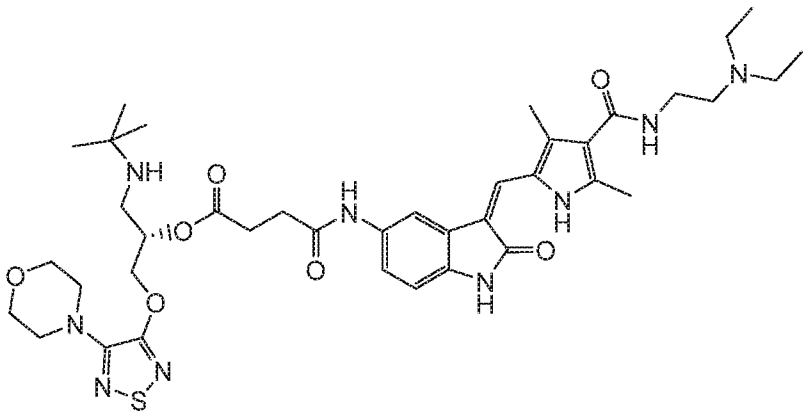


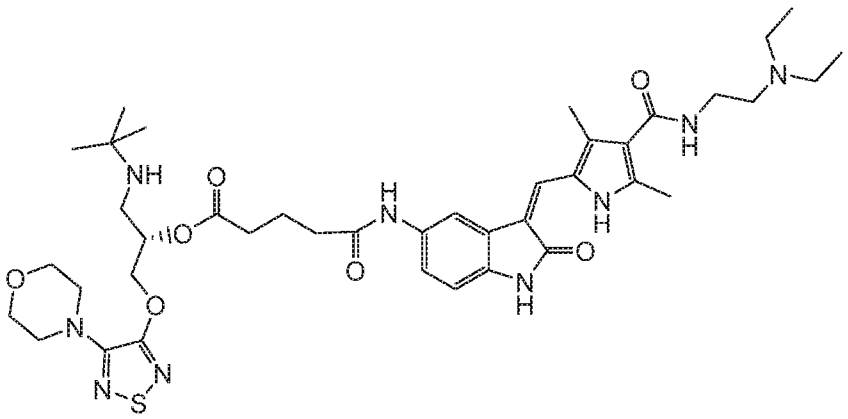


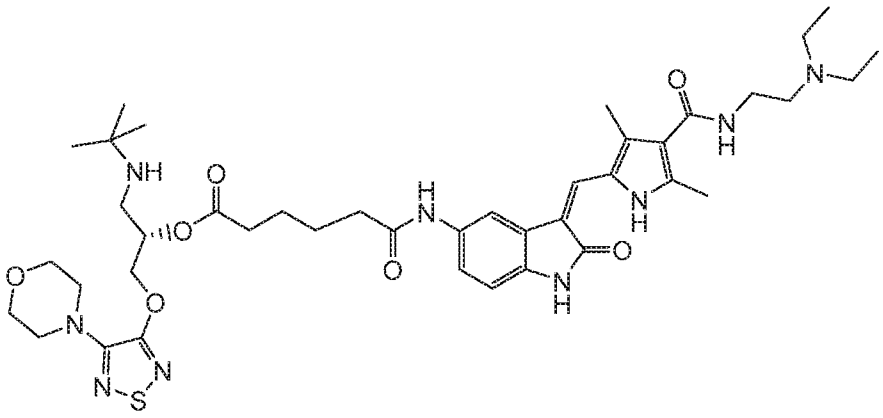




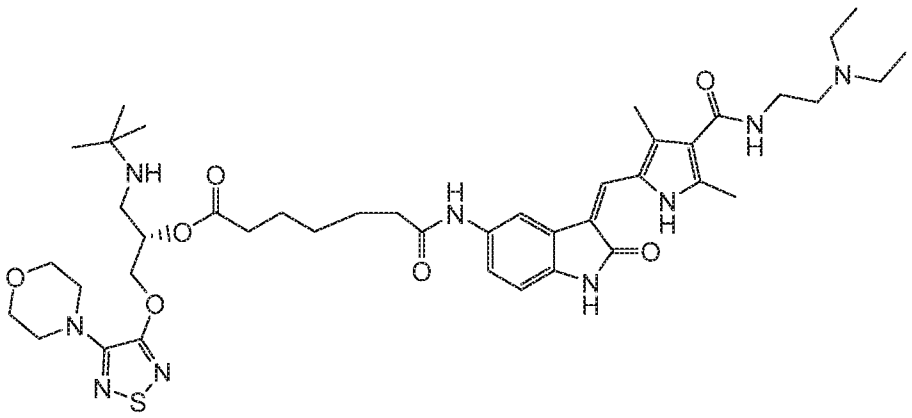






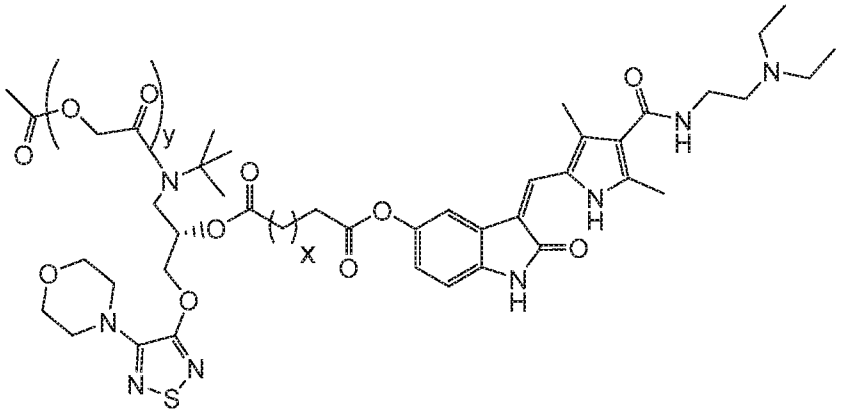


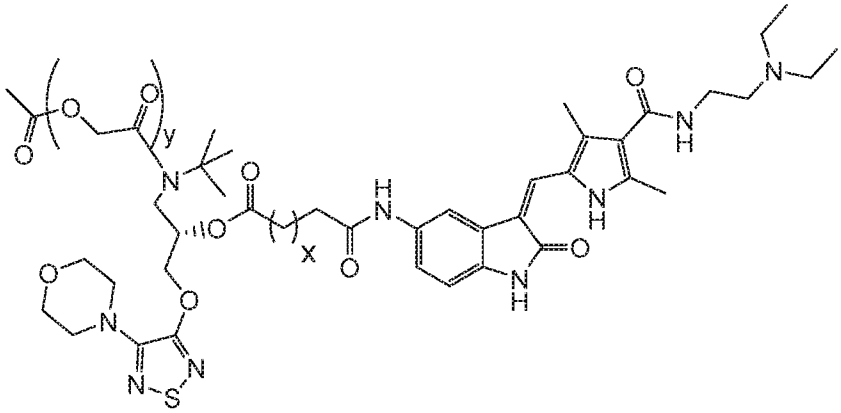
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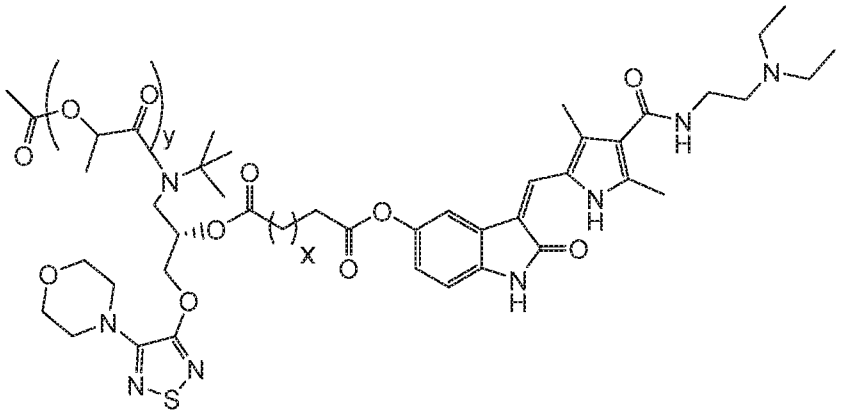


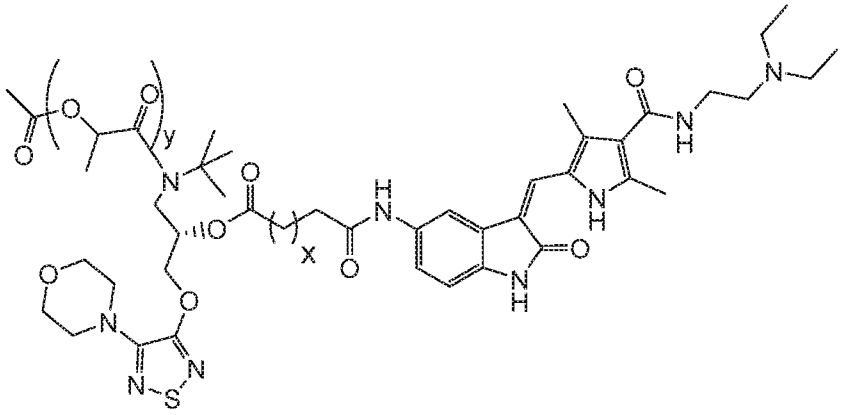
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In one embodiment the compound of the present invention is selected from:





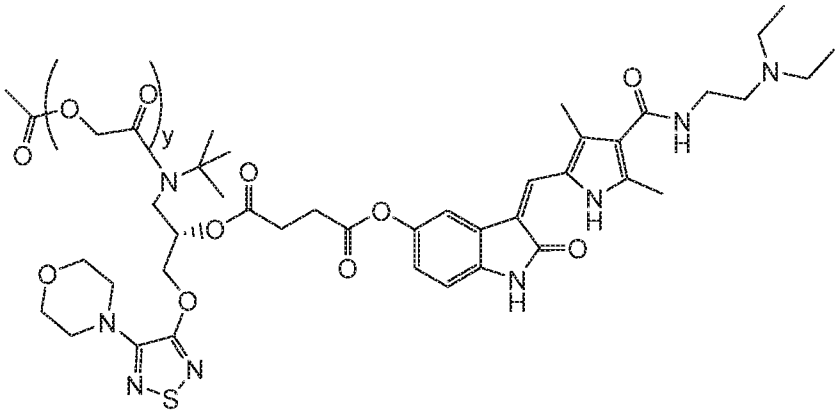


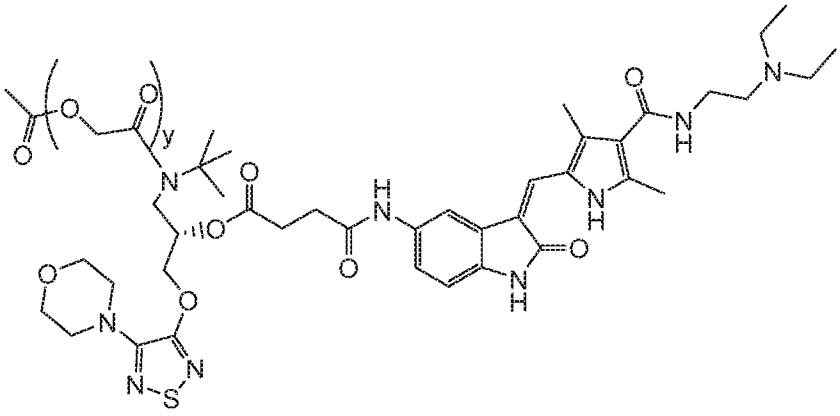


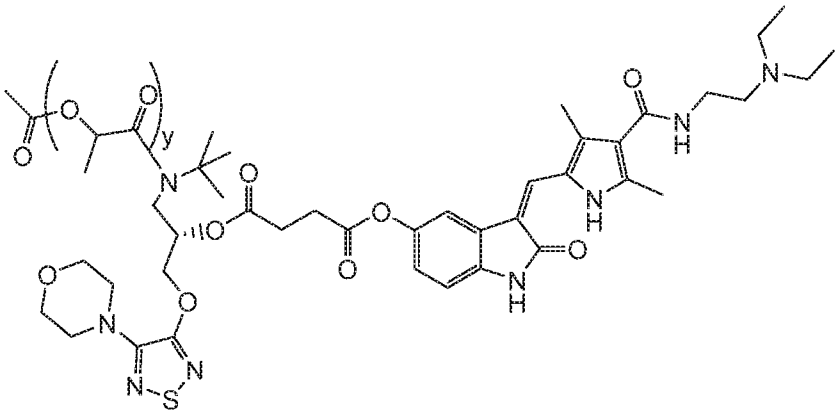
;

wherein x and y are independently 1, 2, 3, 4, 5, 6, 7, 8, or 9.

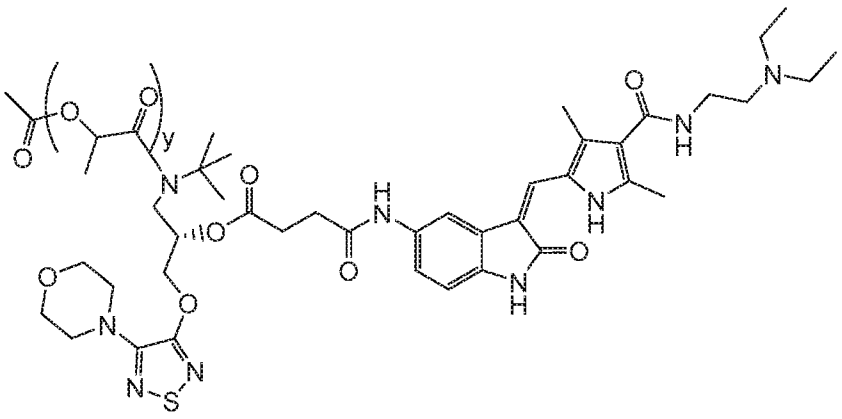
In one embodiment the compound of the present invention is selected from:

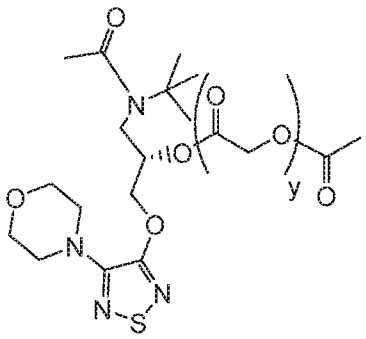




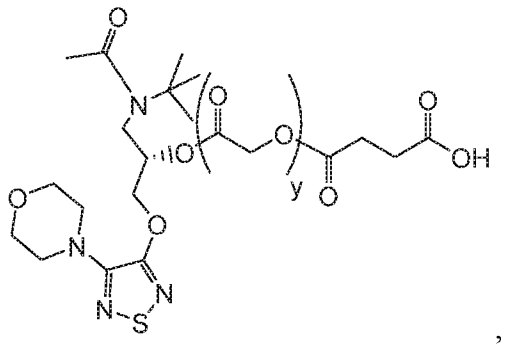


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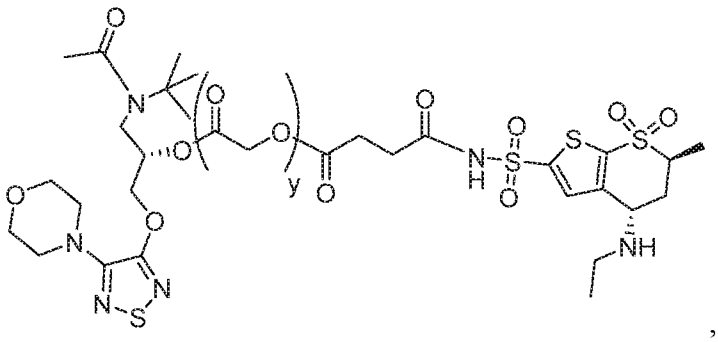




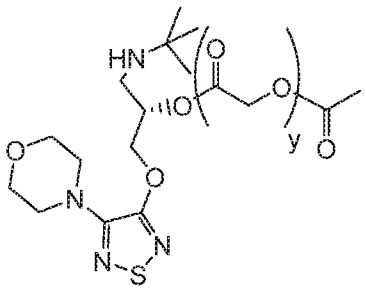
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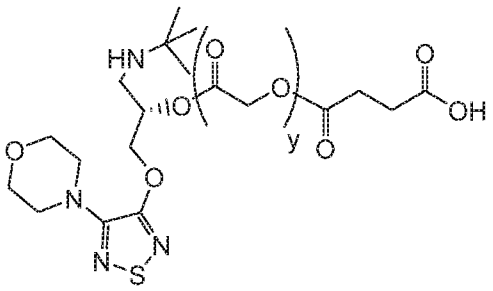
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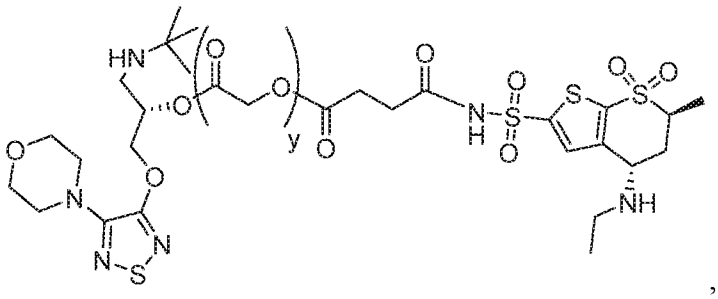
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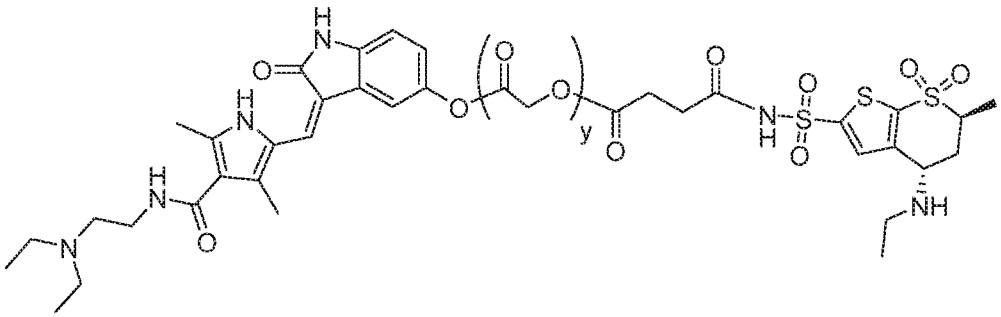
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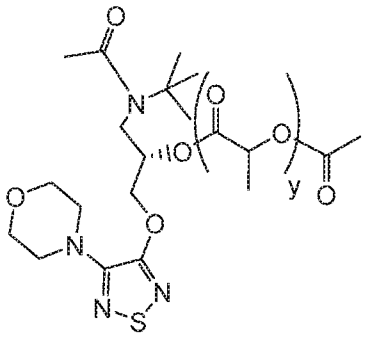


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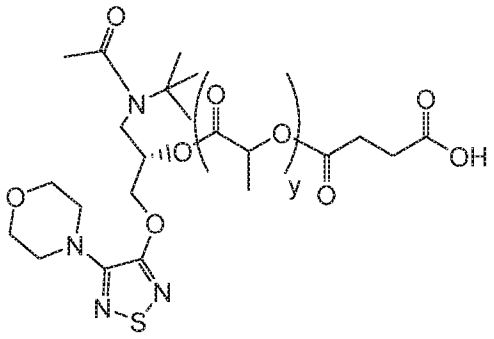


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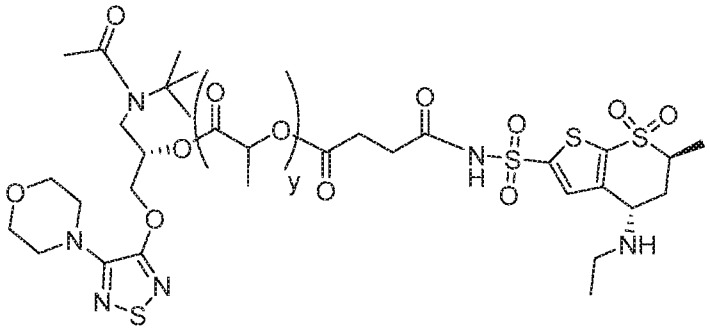




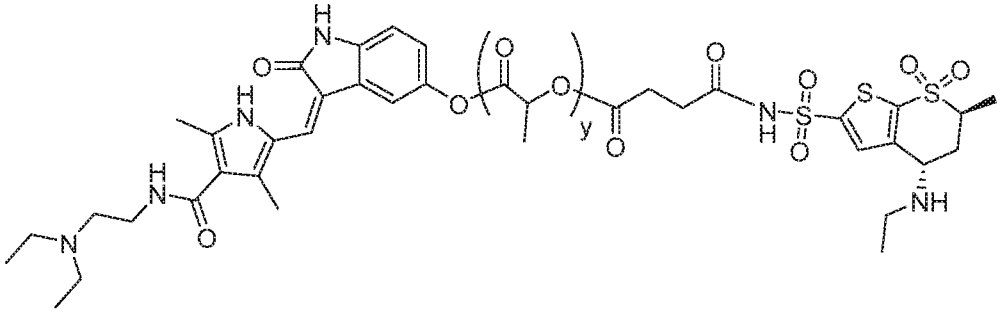
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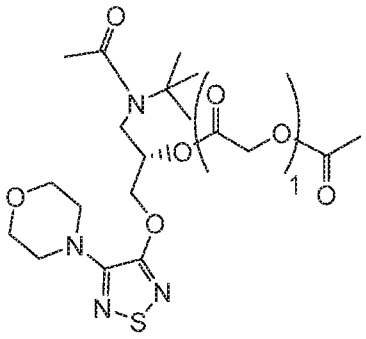
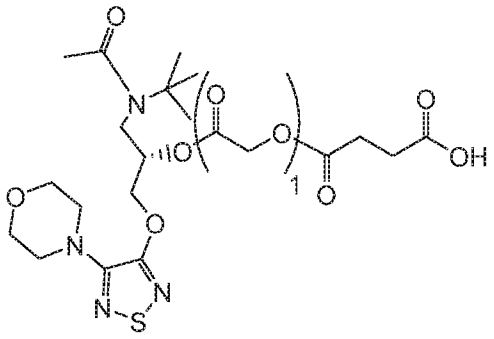
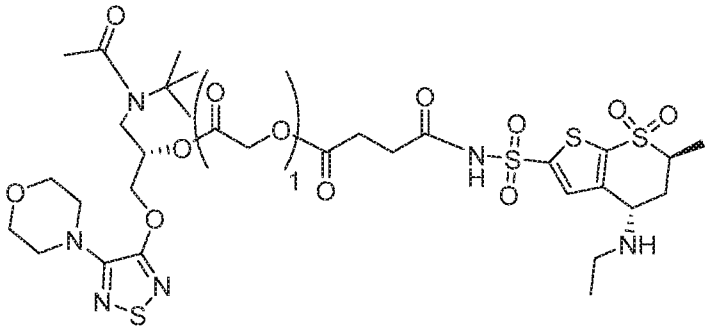
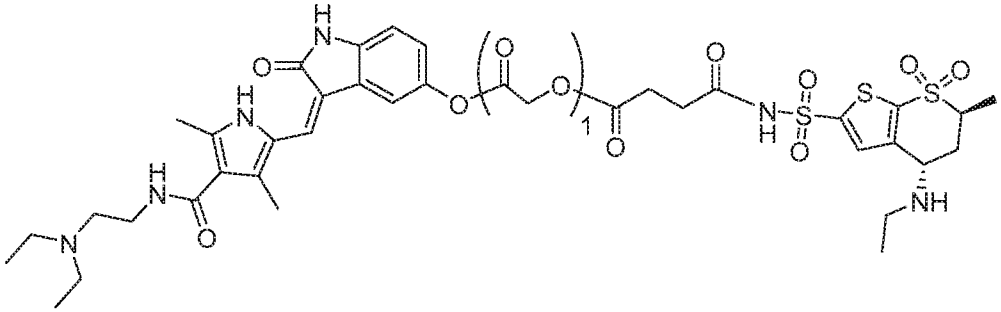
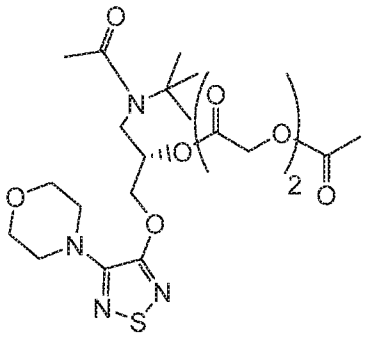
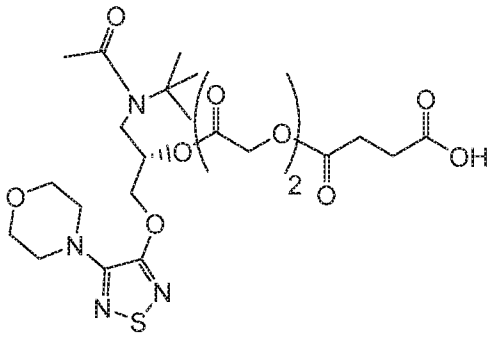


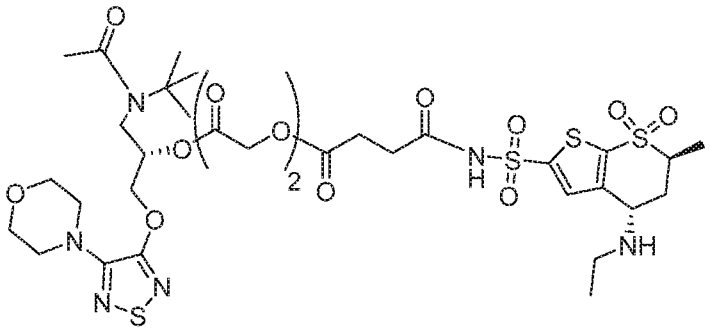
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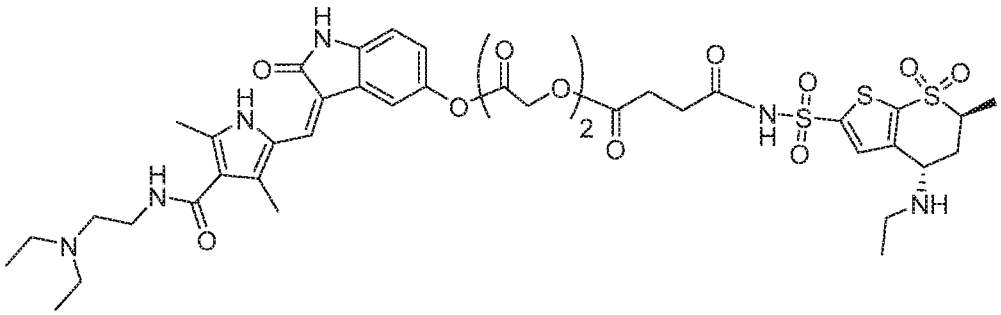
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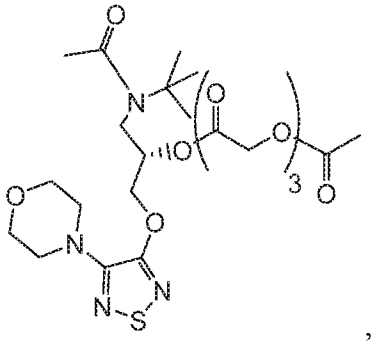



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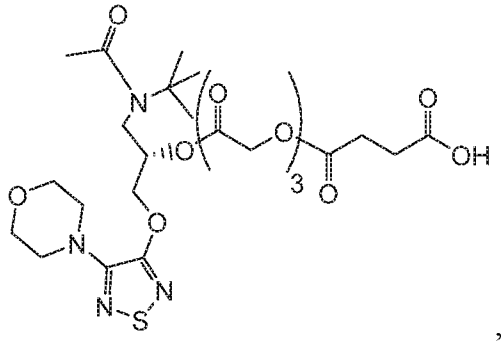


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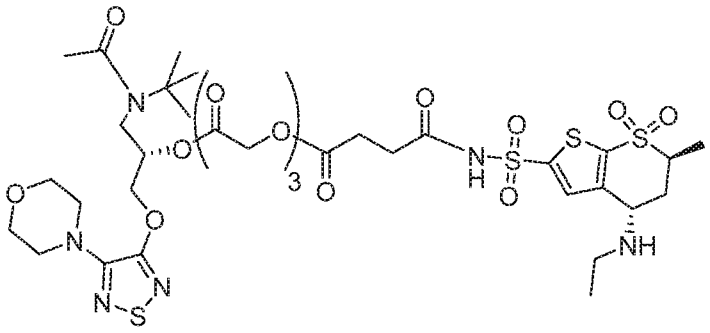




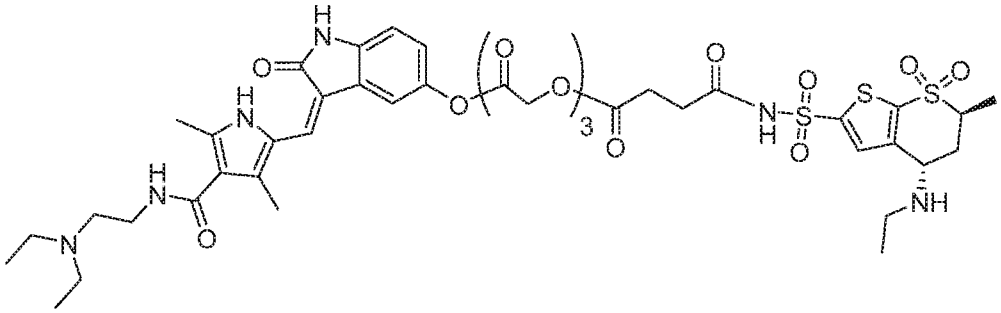
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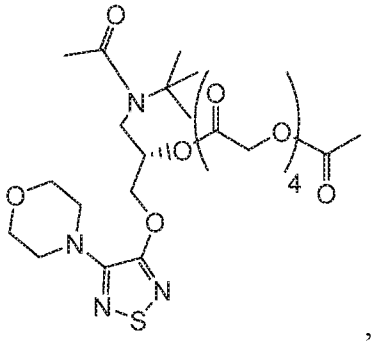


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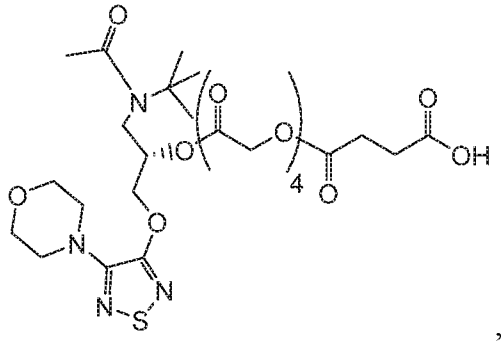


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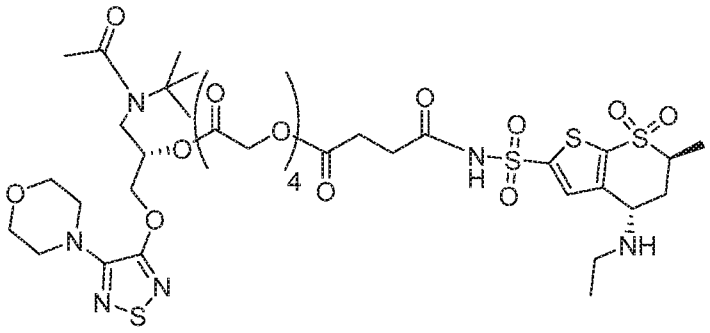




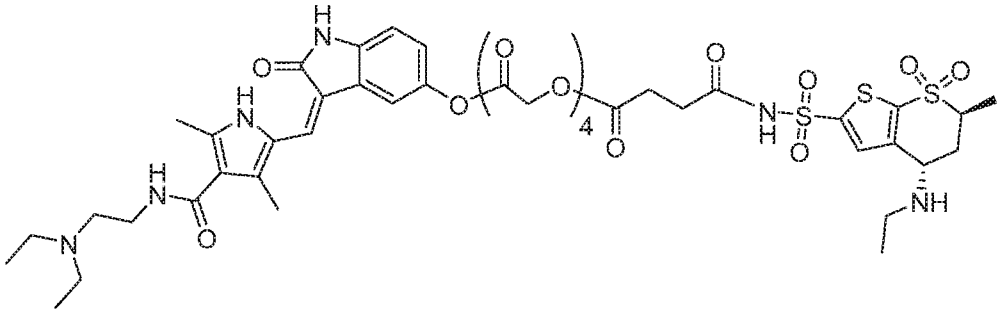
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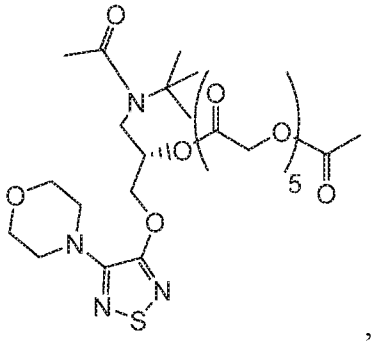


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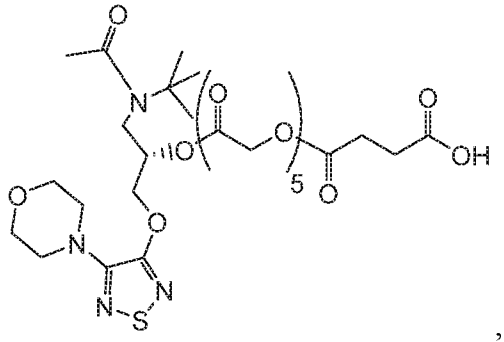


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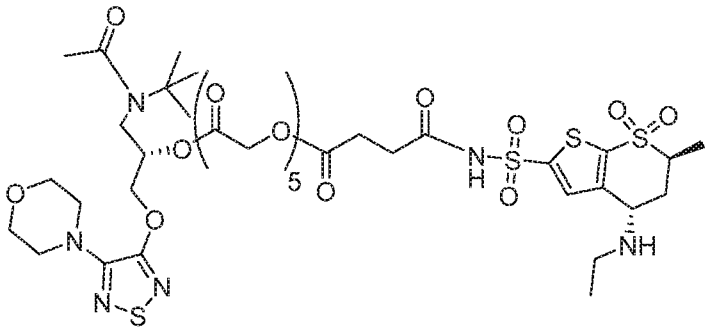




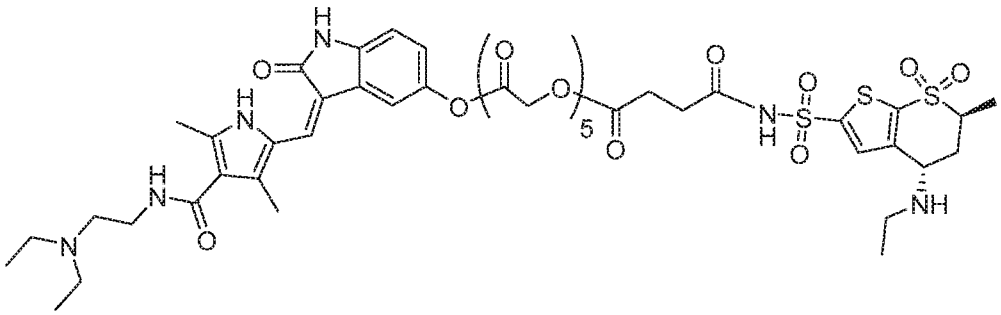
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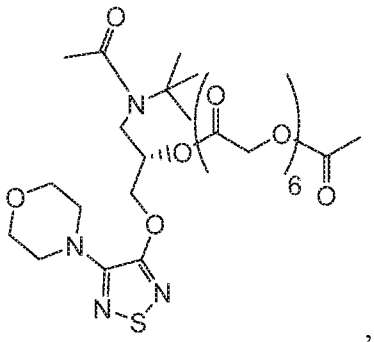


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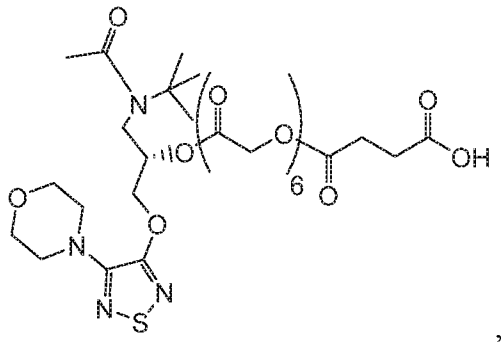


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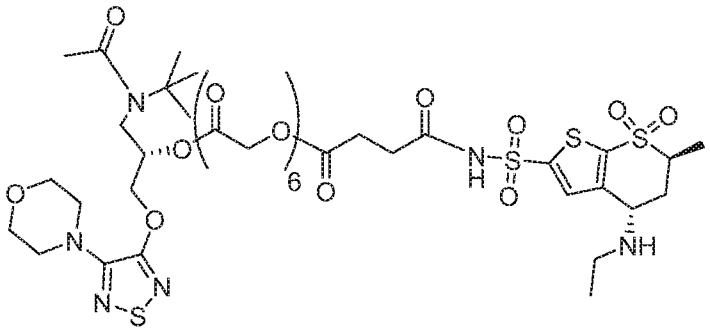




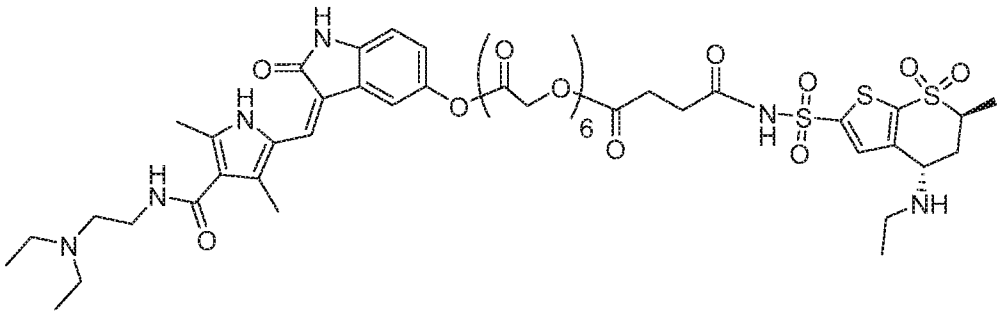
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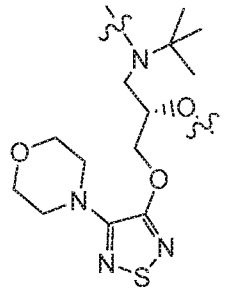
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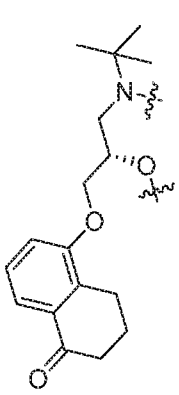
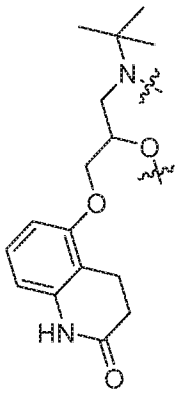
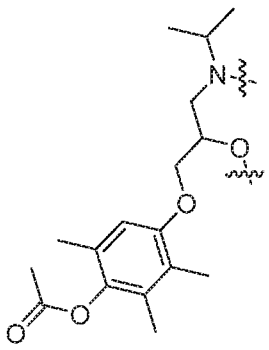
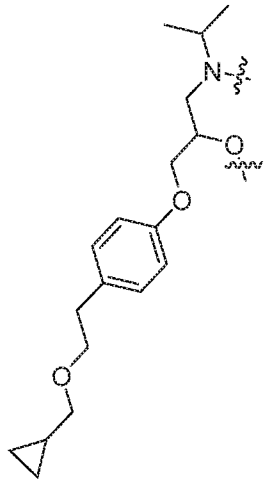


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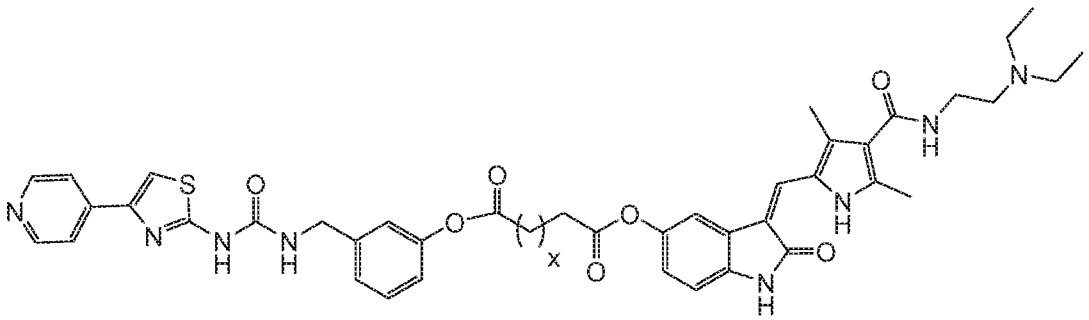


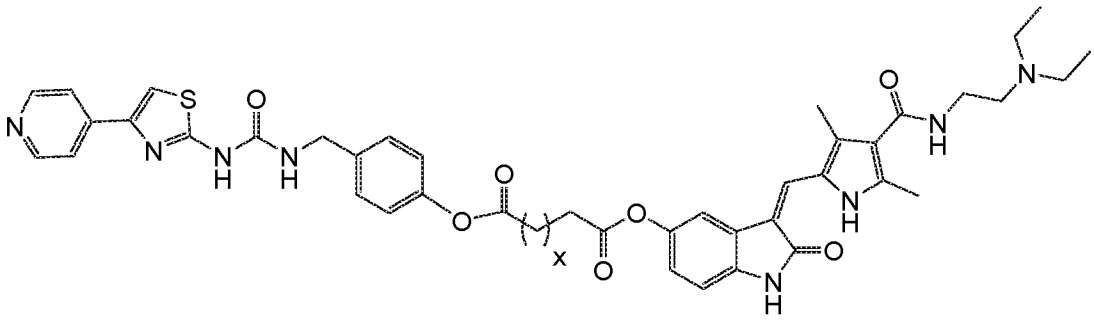
In one embodiment of the above structures,  is replaced with  wherein A is defined above.

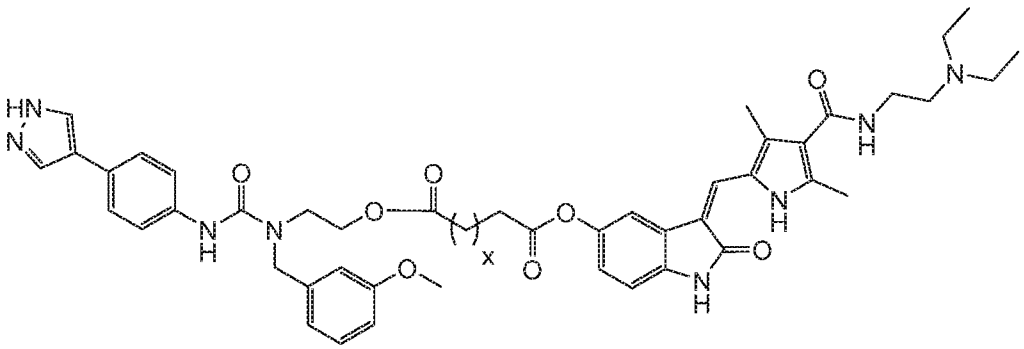
In another embodiment of the above structures,  is replaced with

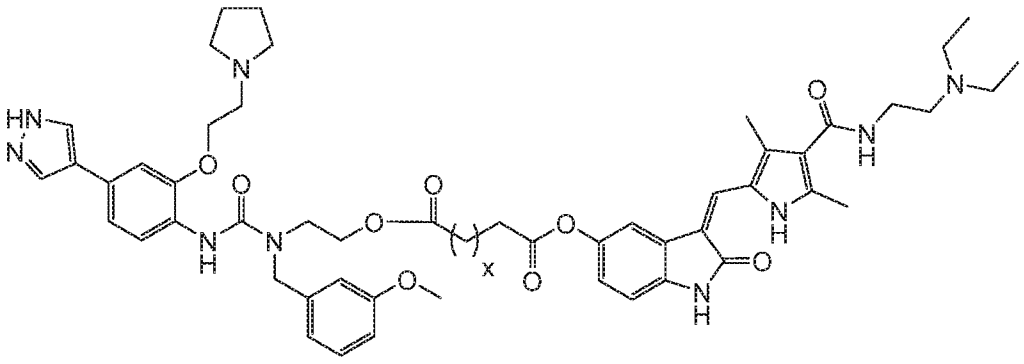
, , , or .

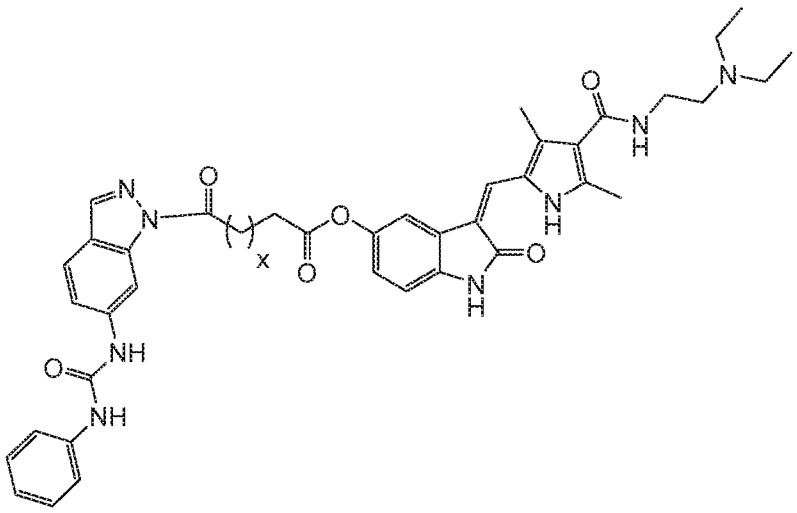
In another embodiment the compound of the present invention is selected from:



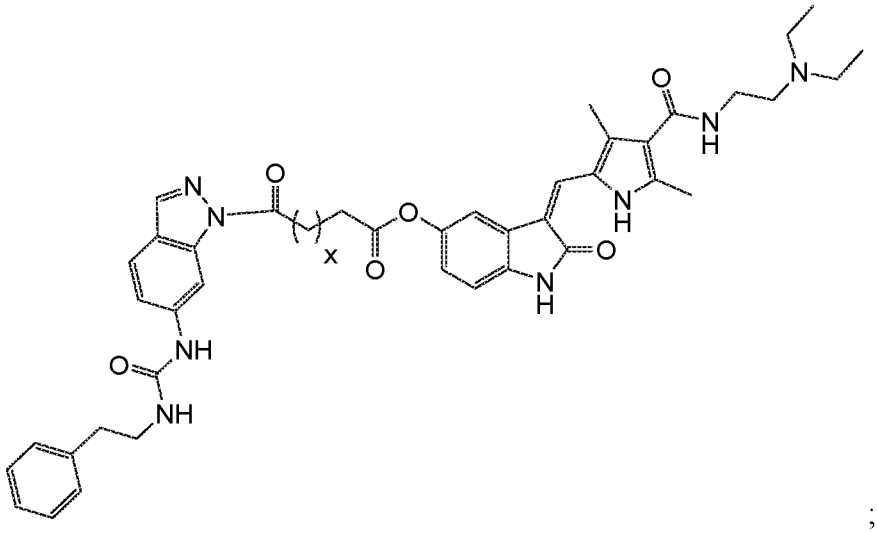








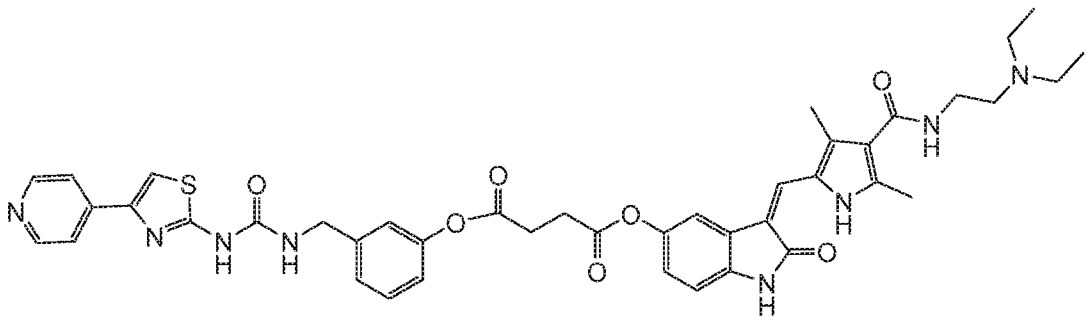
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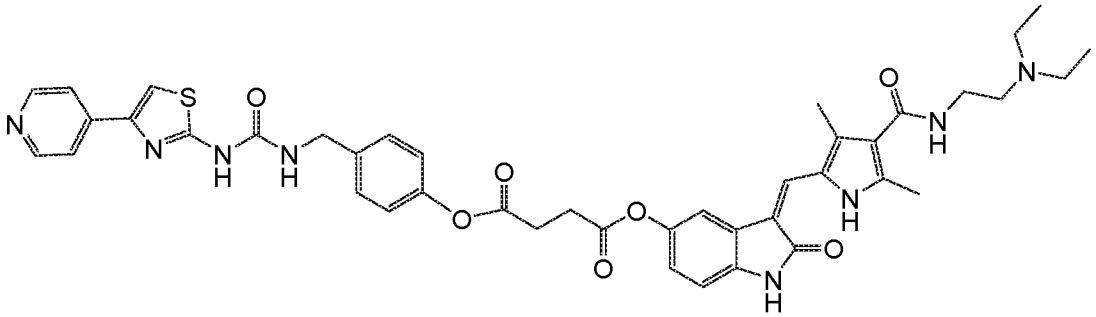


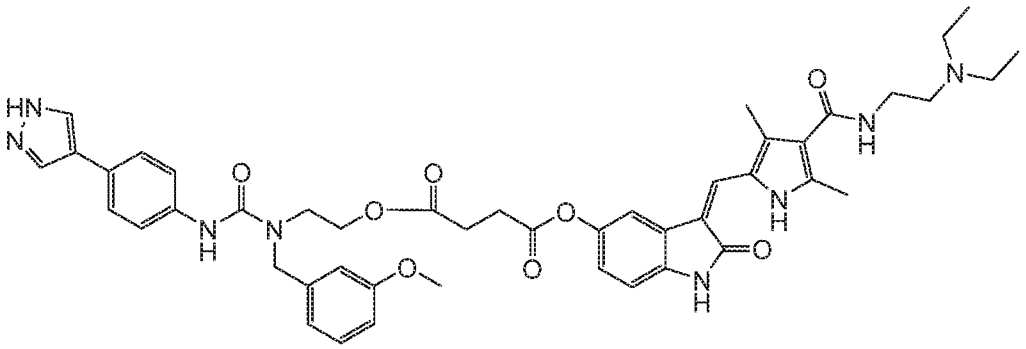
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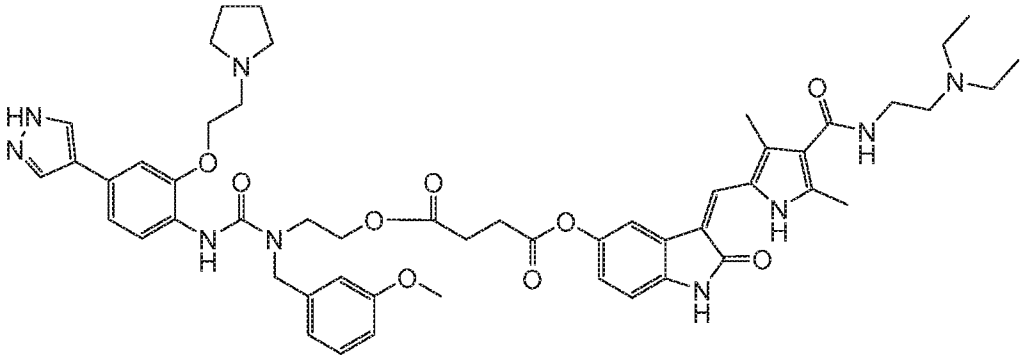
wherein x is 1, 2, 3, 4, 5, 6, 7, 8, or 9.

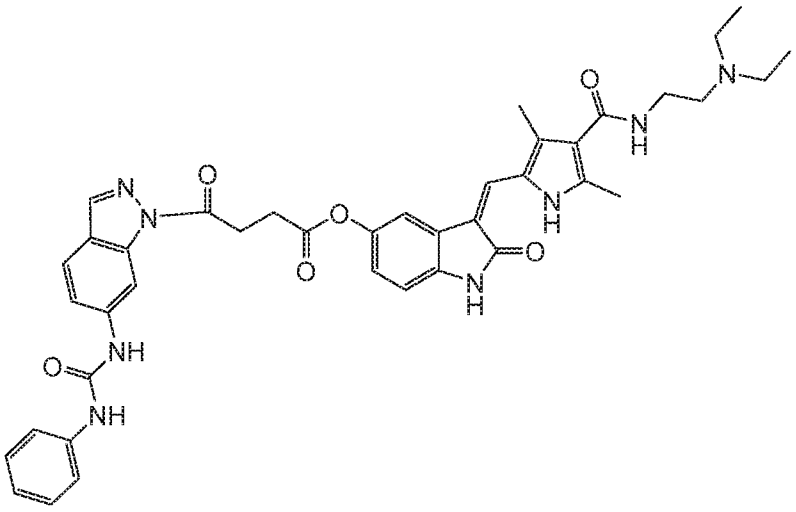
In one embodiment the compound of the present invention is selected from:

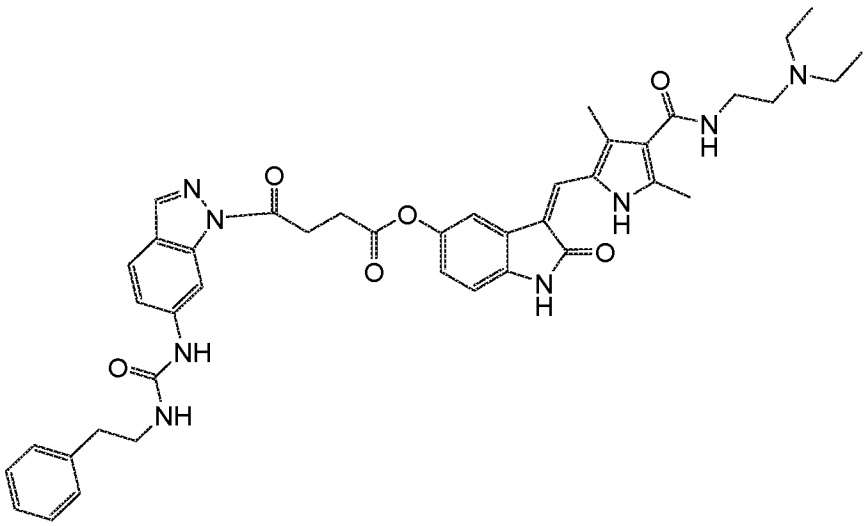


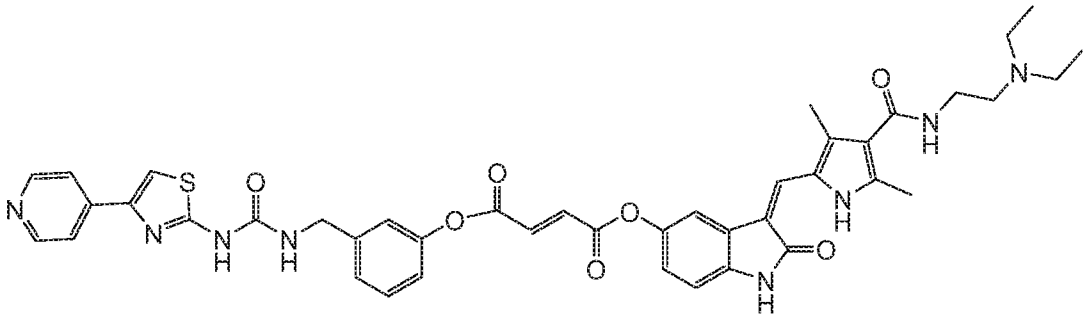


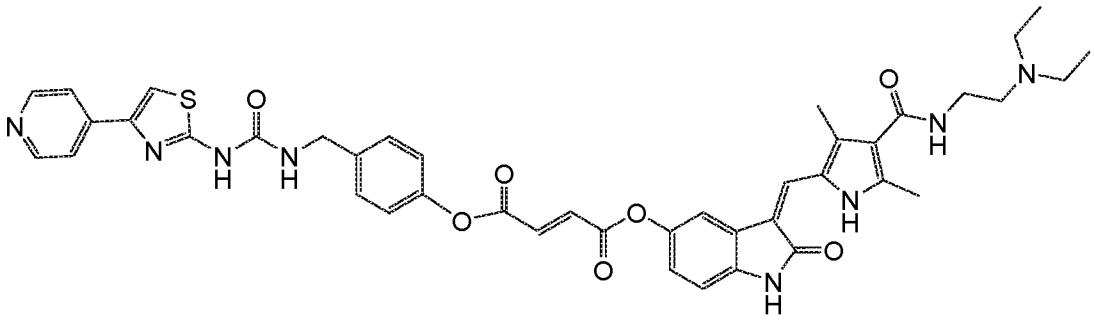


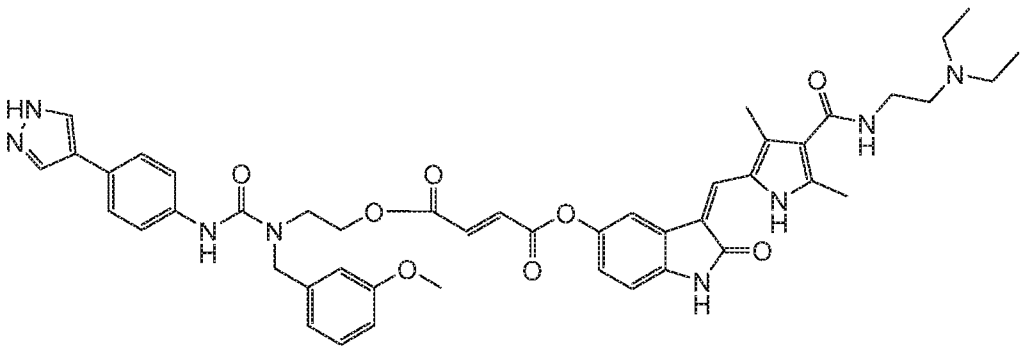


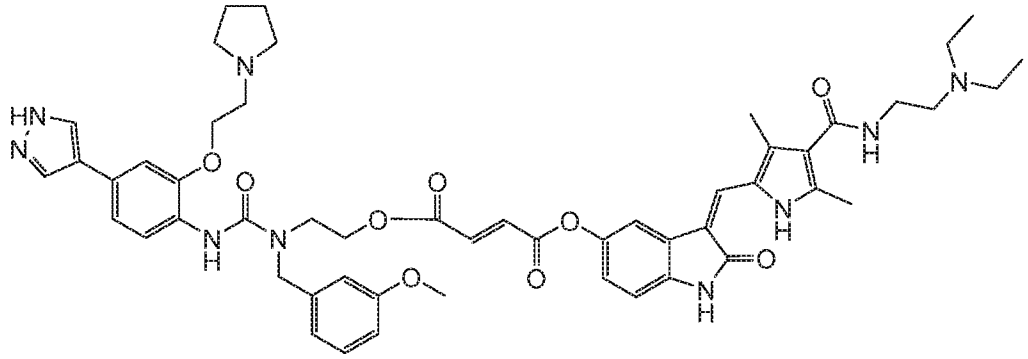


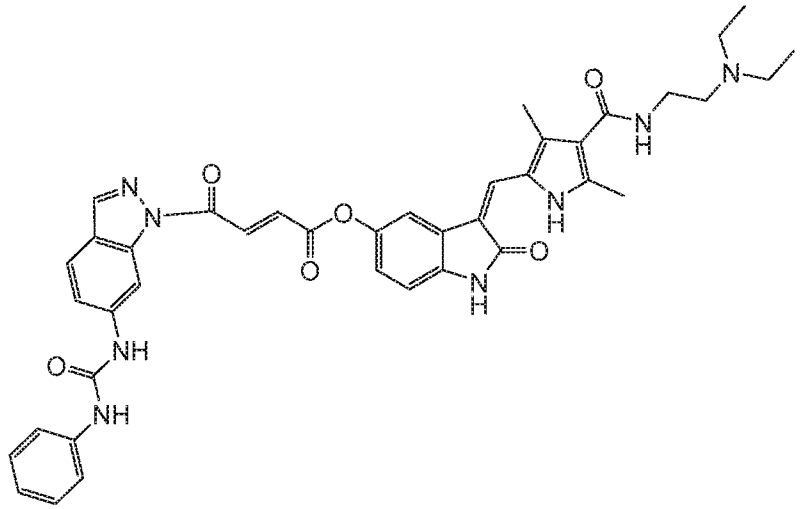


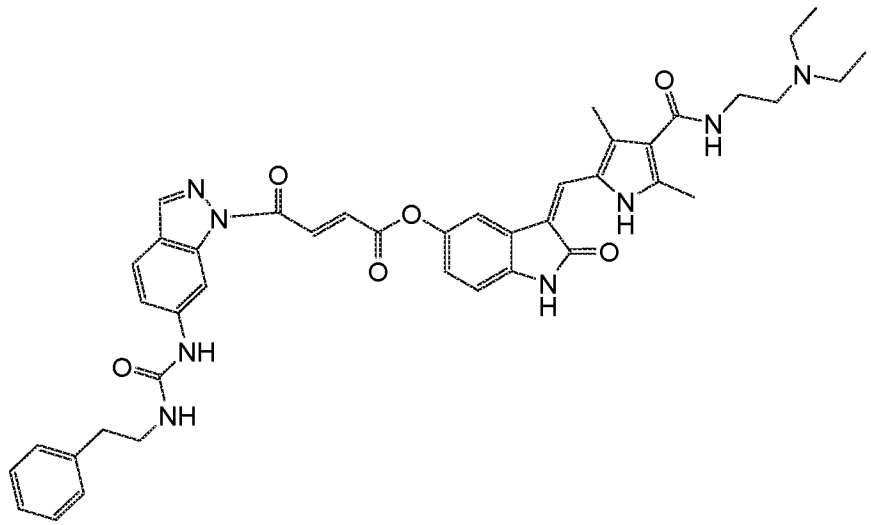


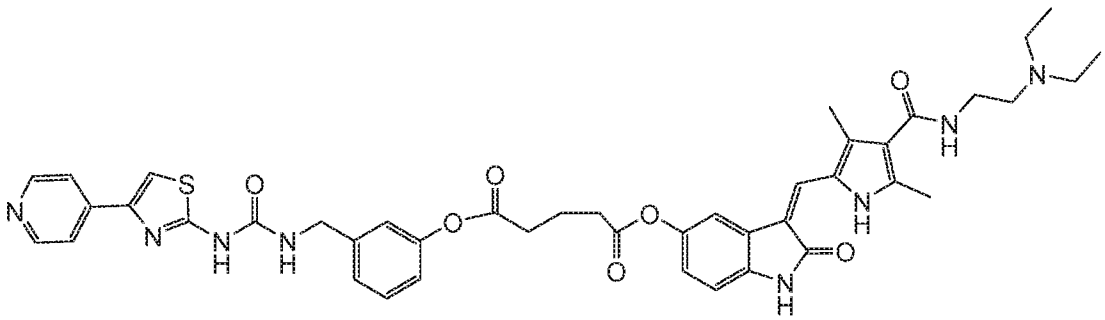


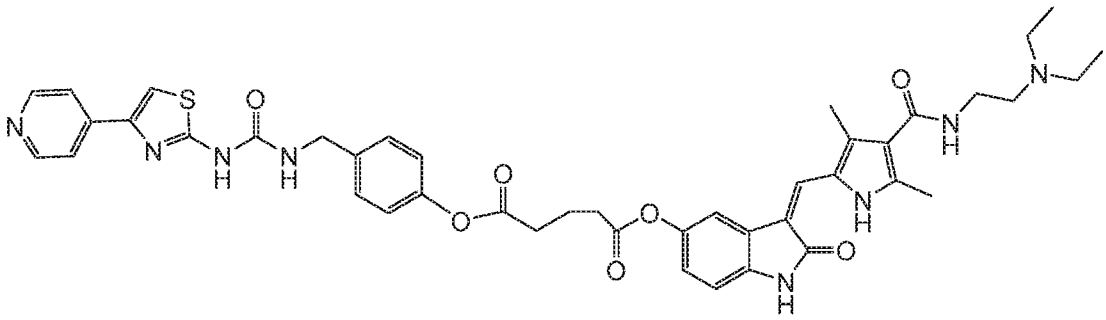


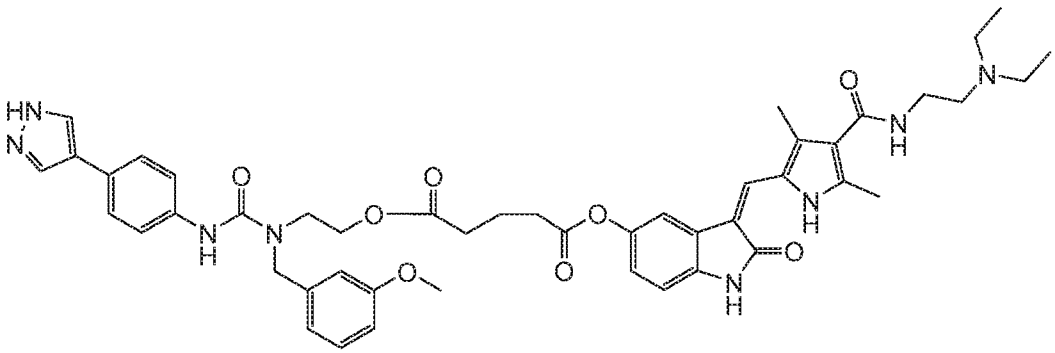


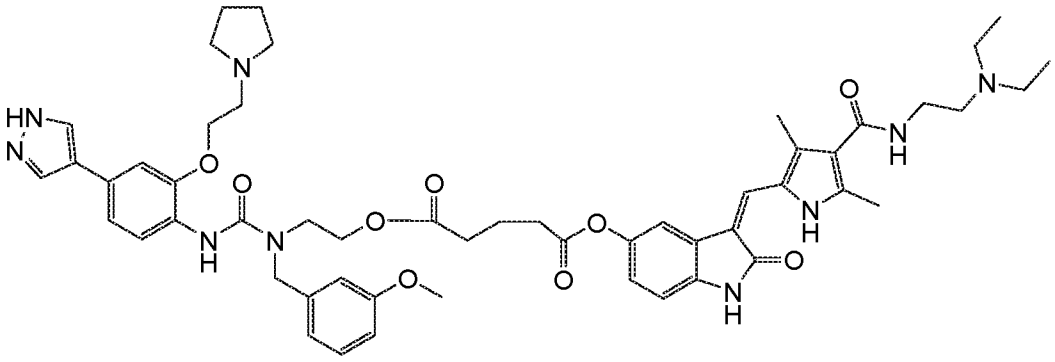


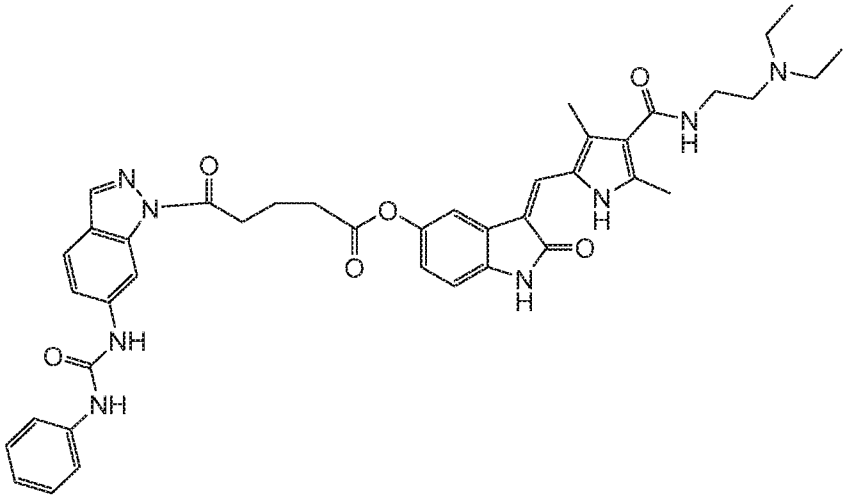


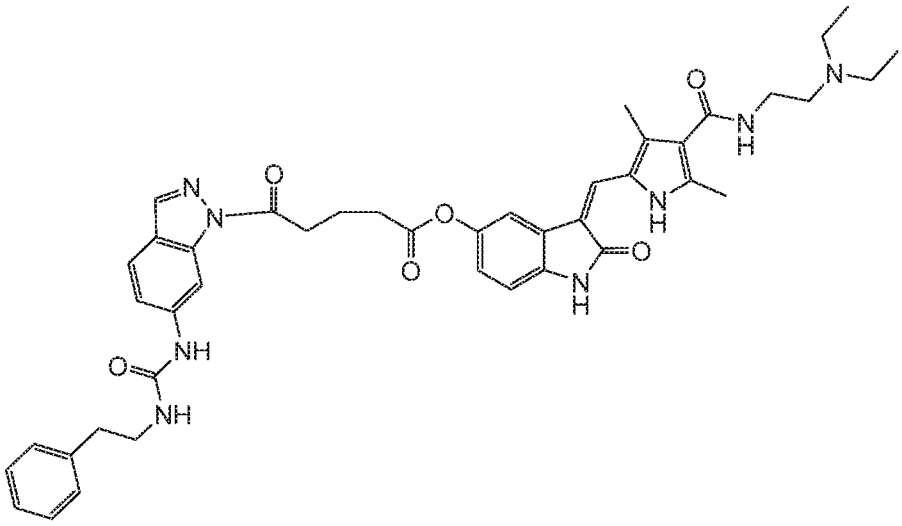


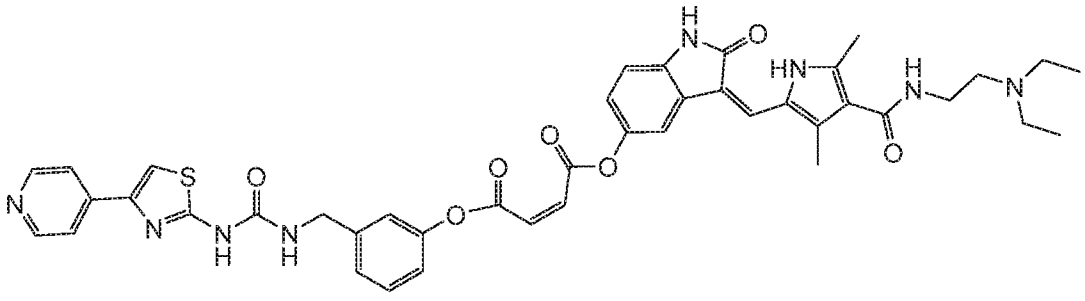


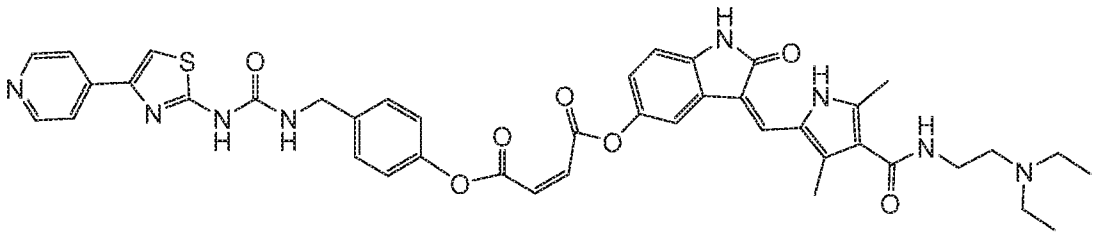


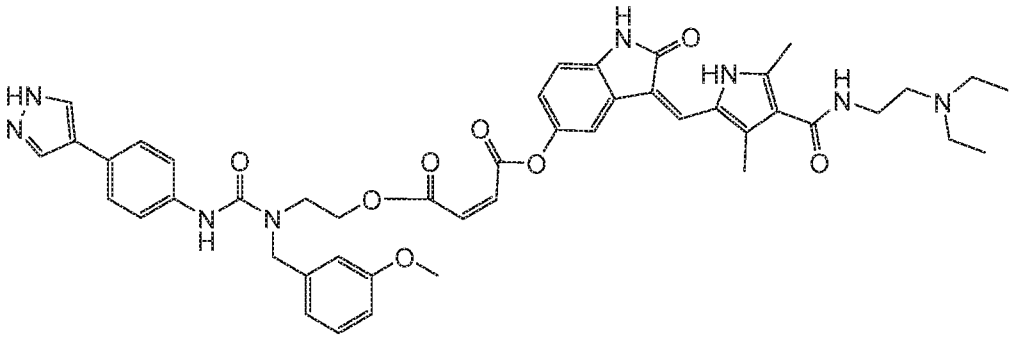


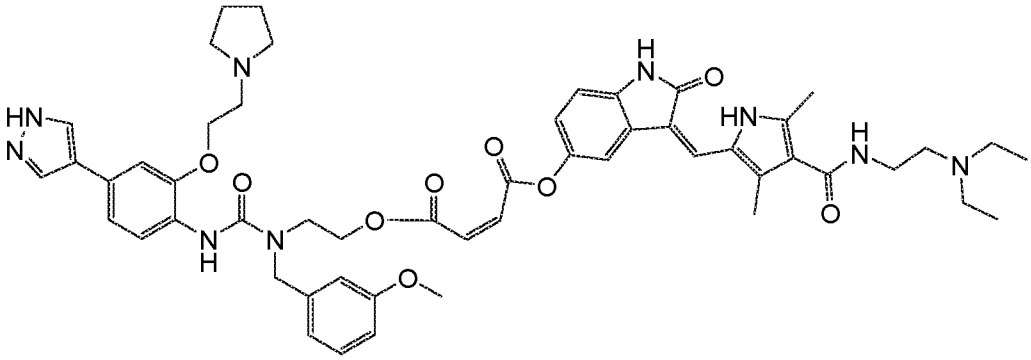


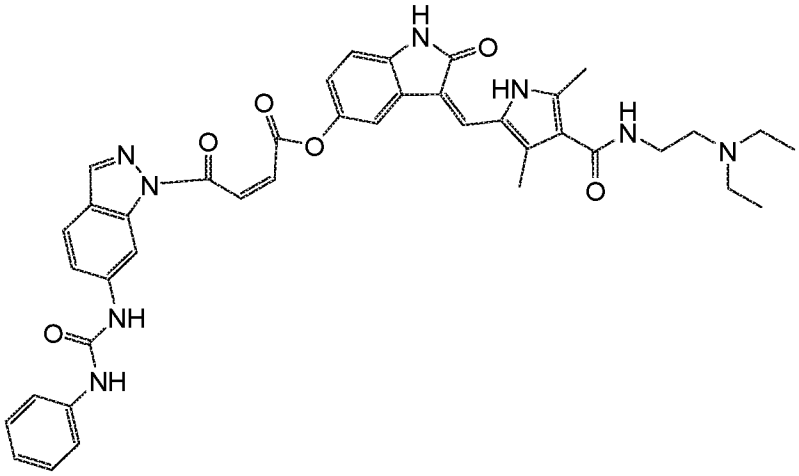


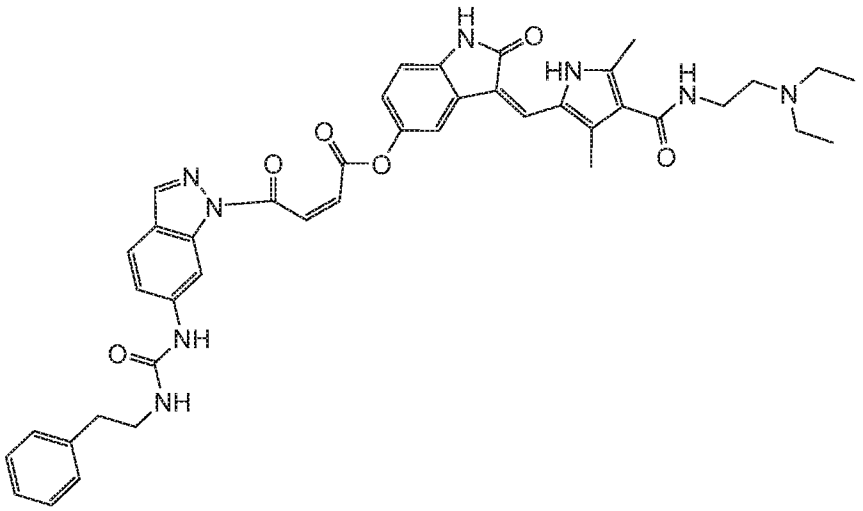


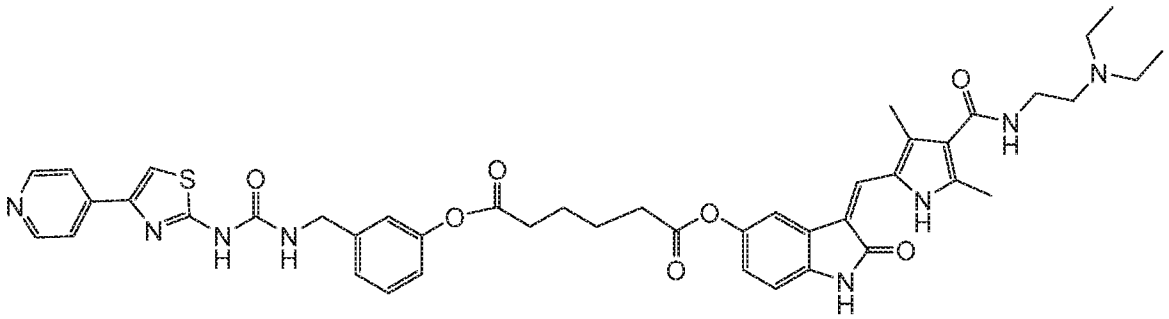


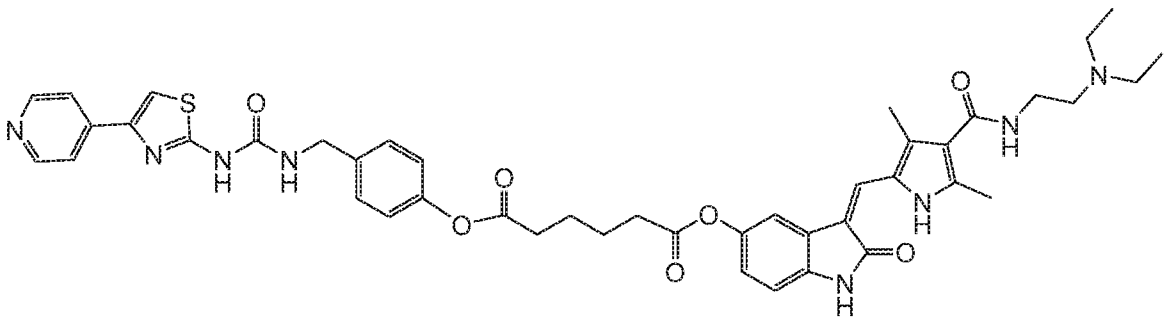


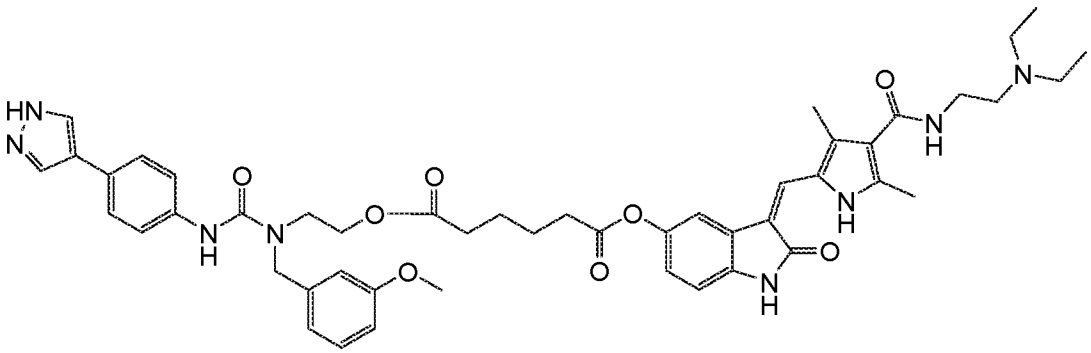


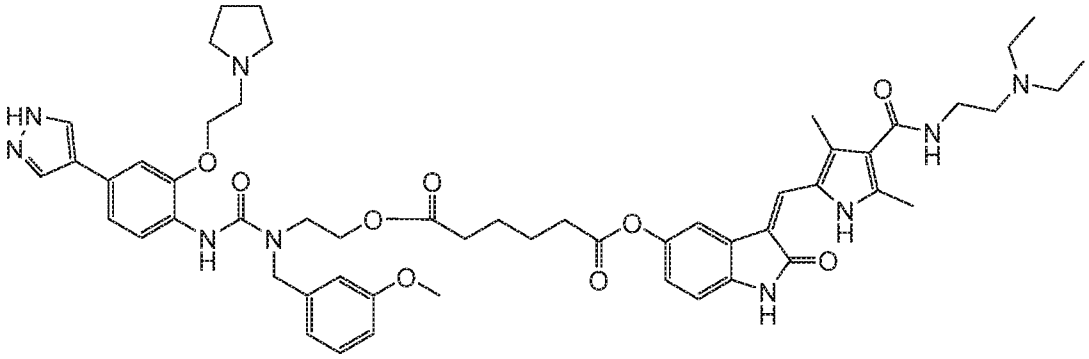


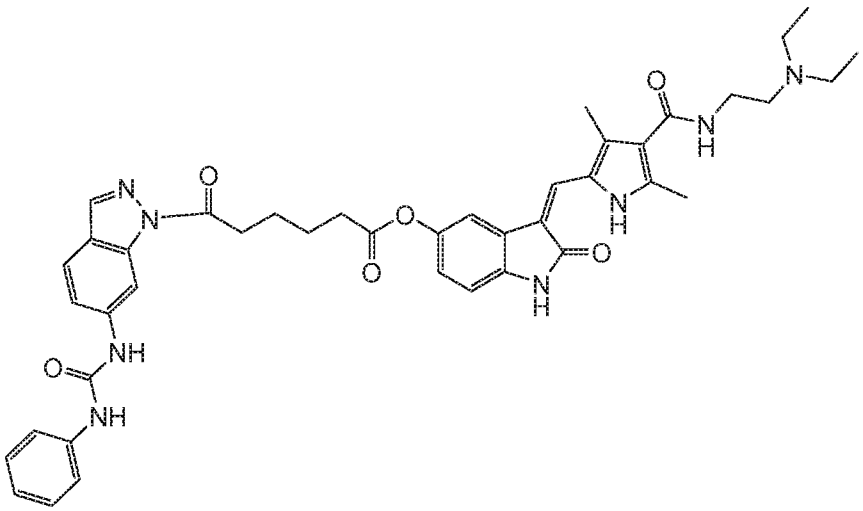




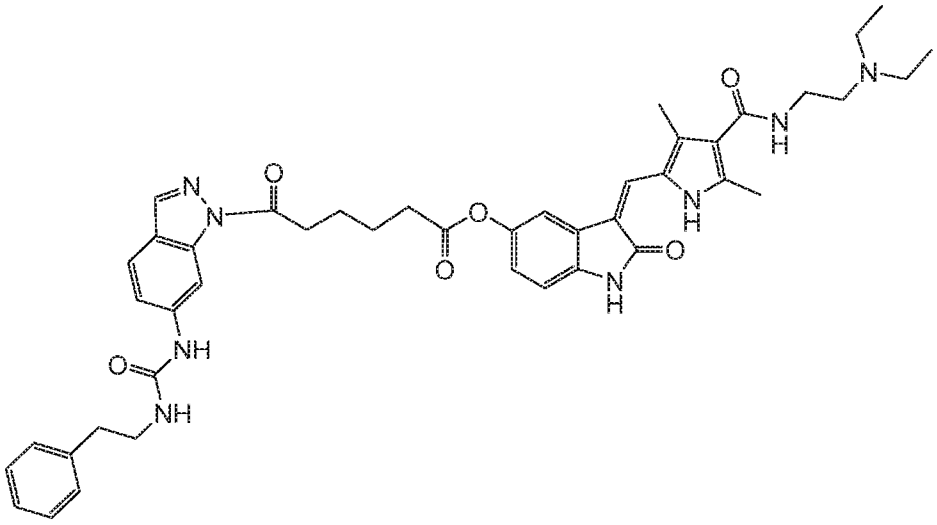






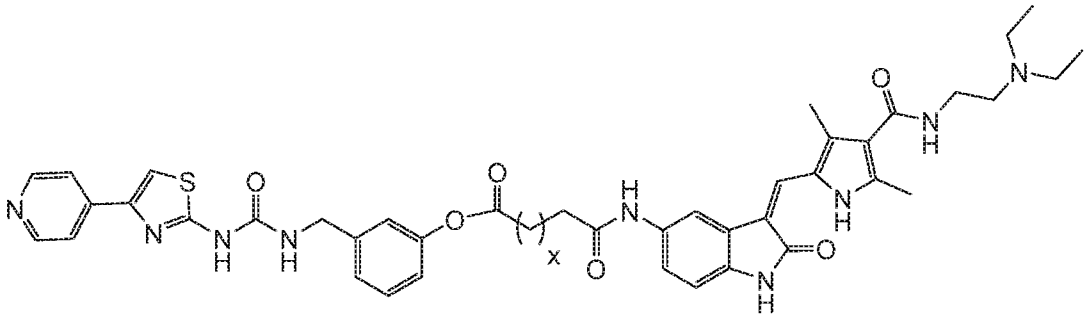


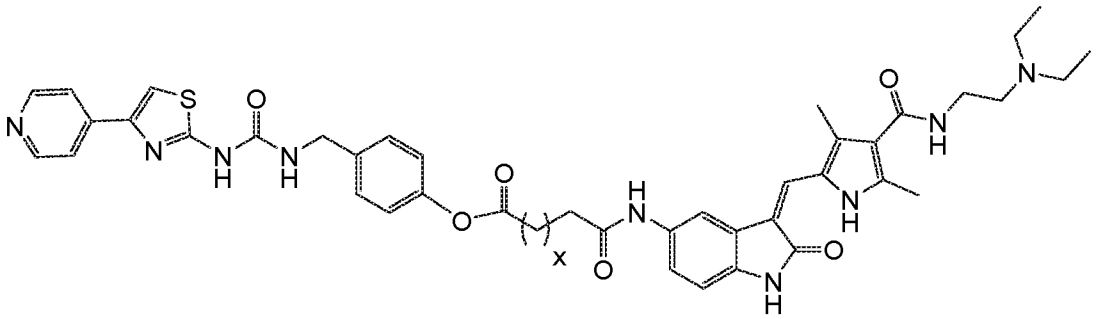
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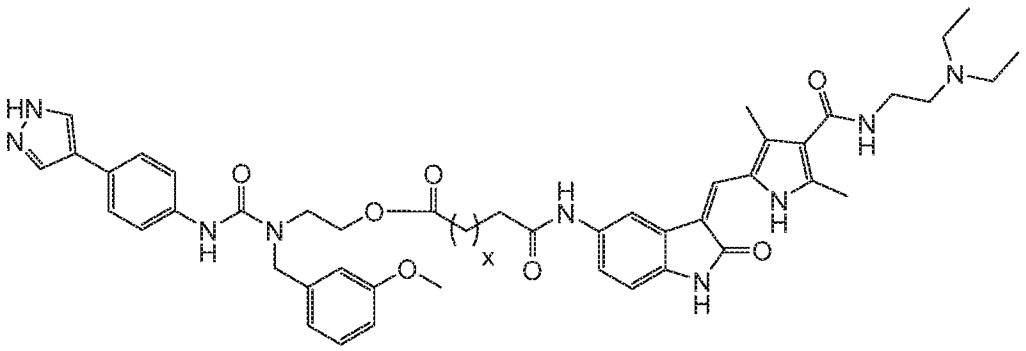


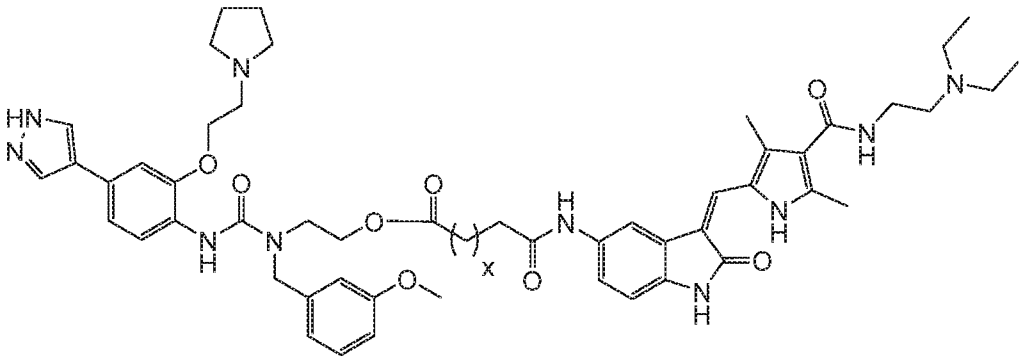
5

In another embodiment the compound of the present invention is selected from:

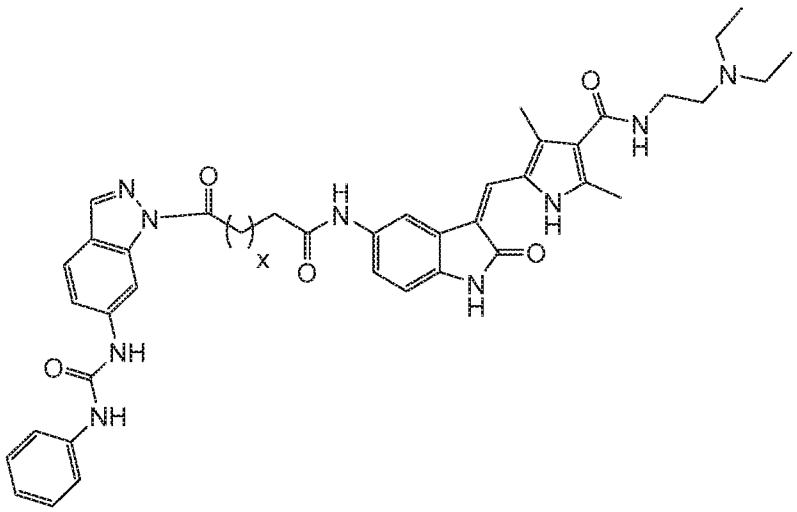




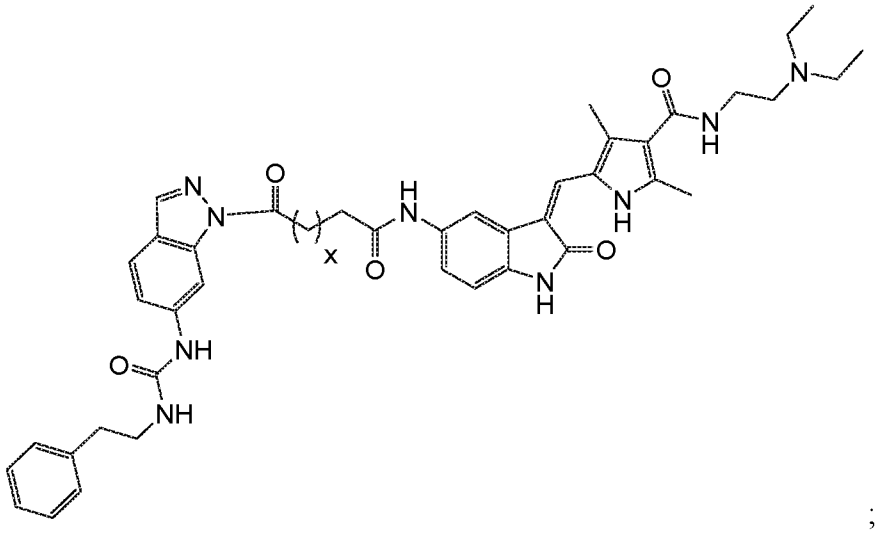




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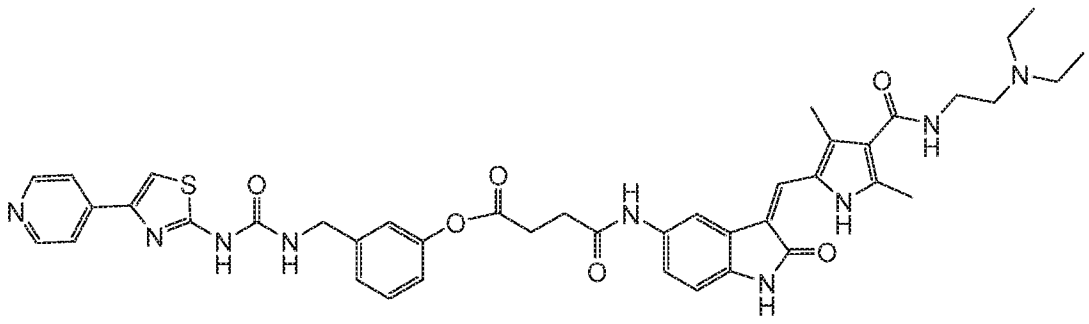
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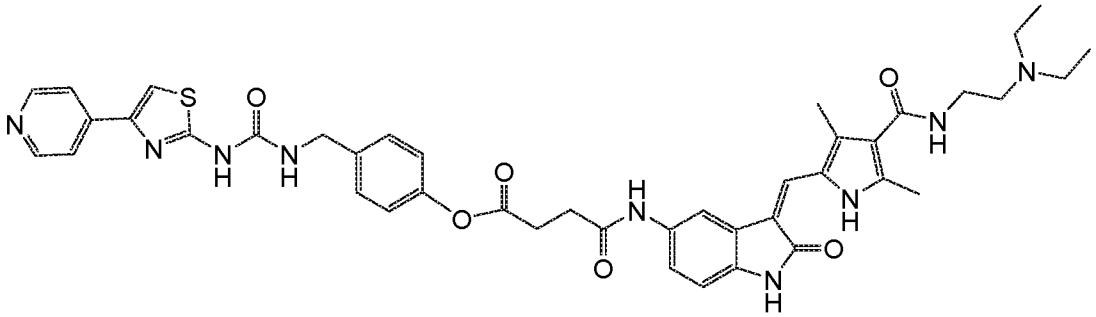


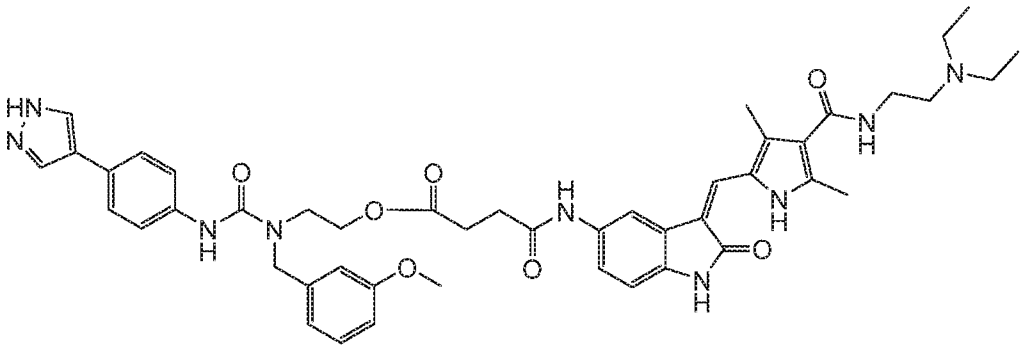
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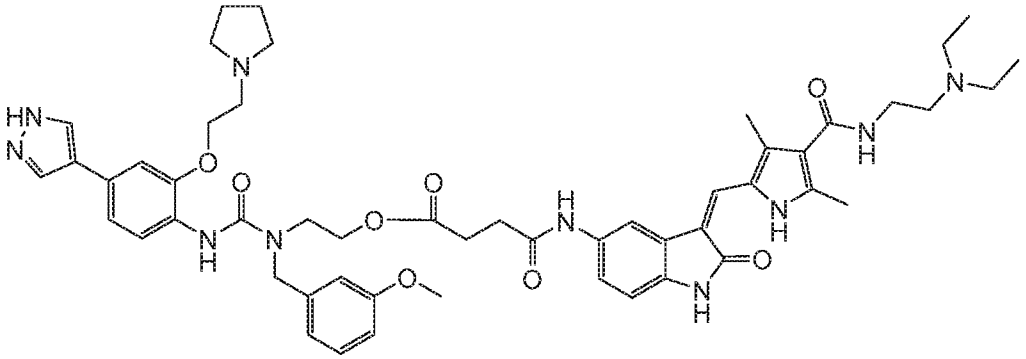
wherein x is 1, 2, 3, 4, 5, 6, 7, 8, or 9.

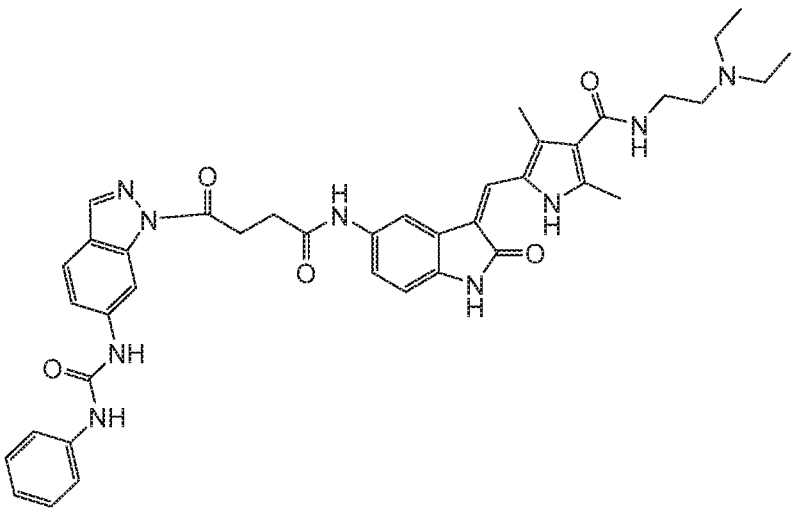
In one embodiment the compound of the present invention is selected from:

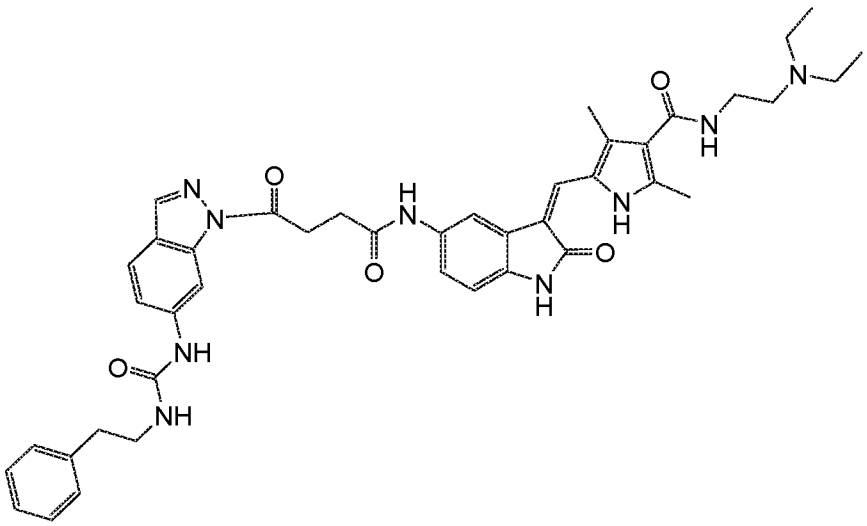


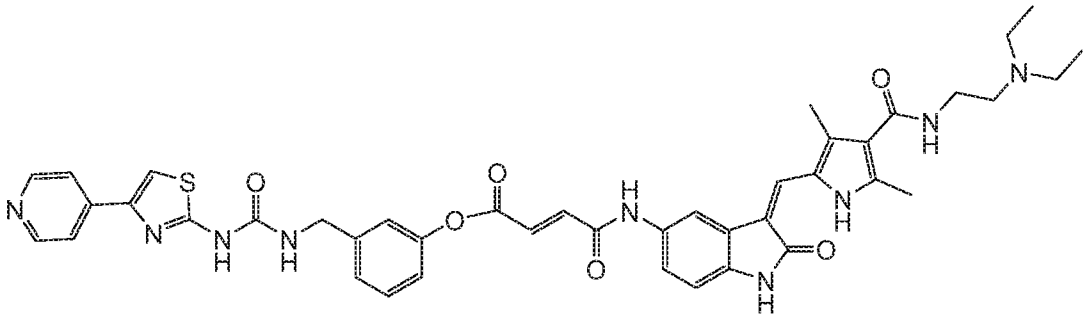


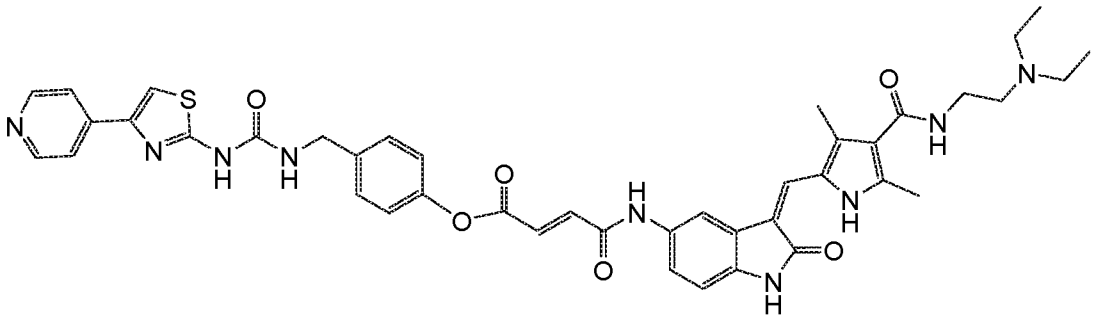


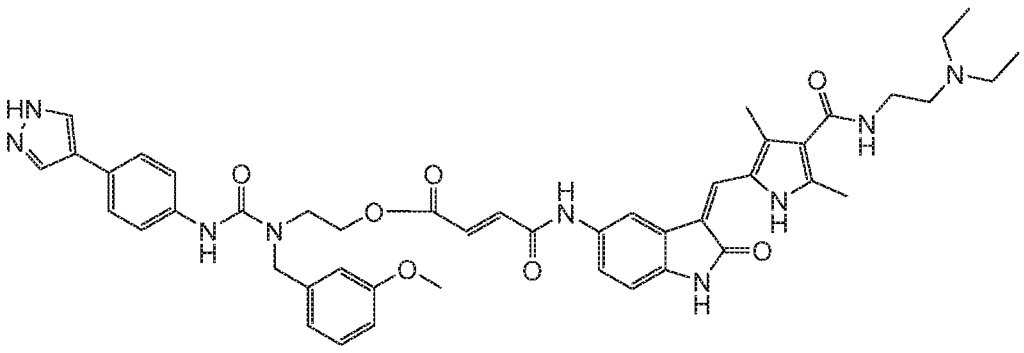


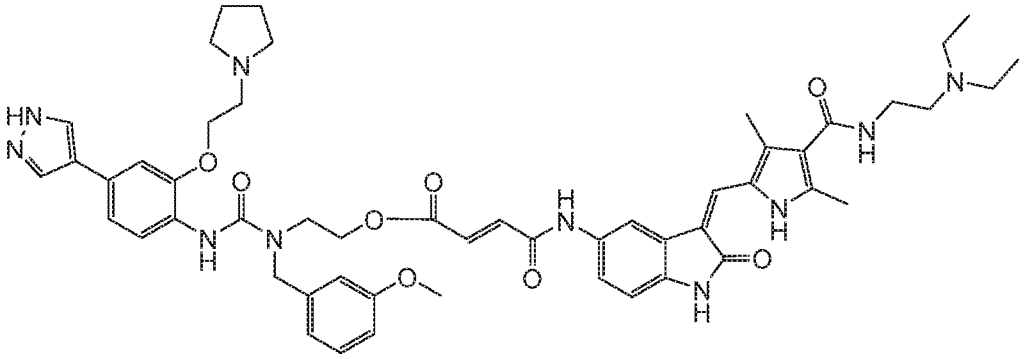


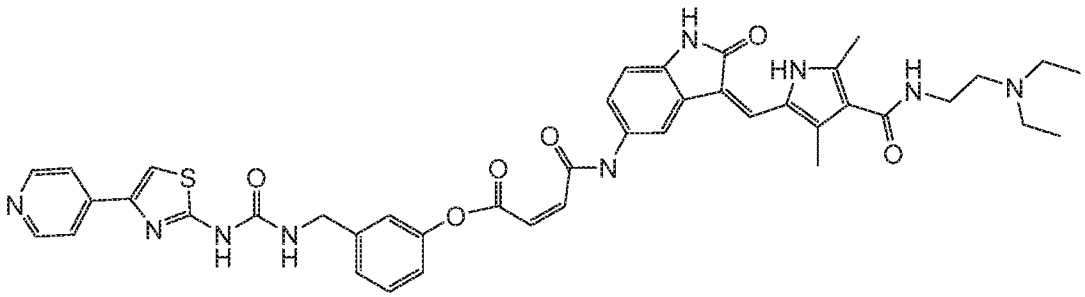


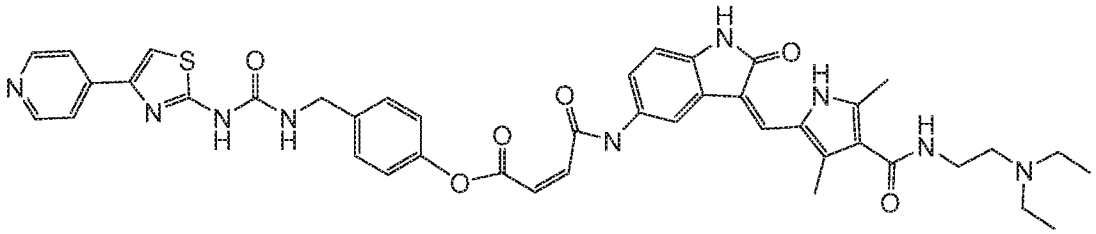


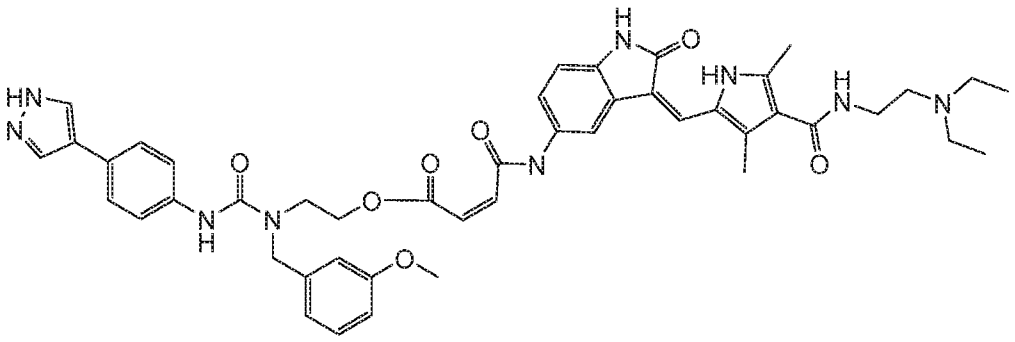


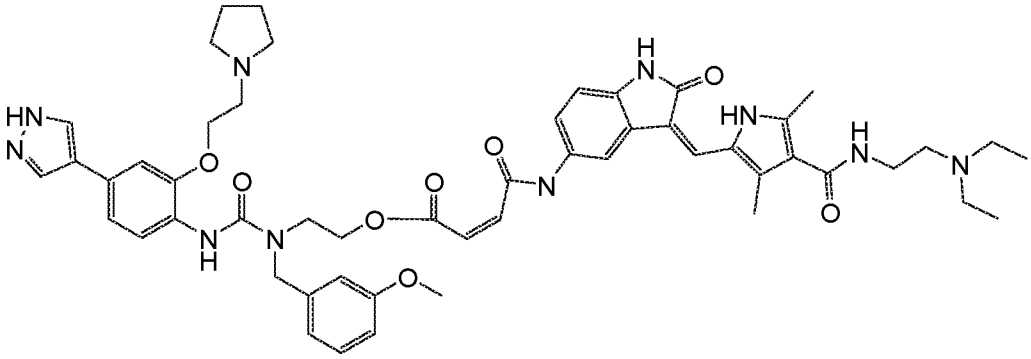


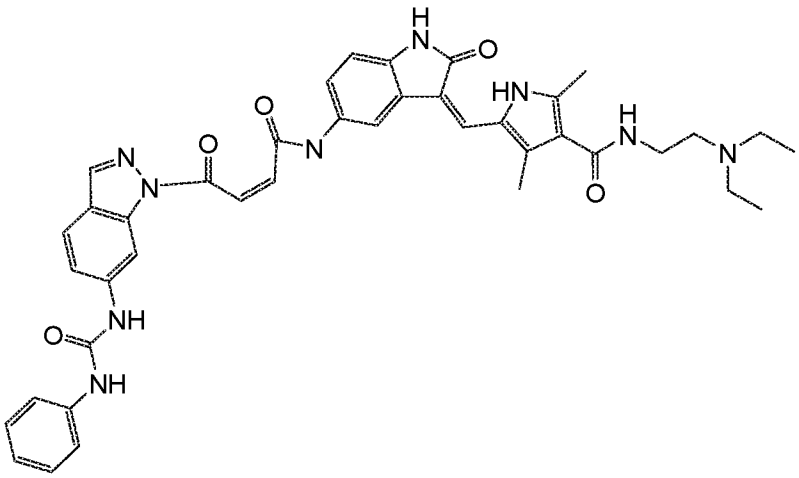


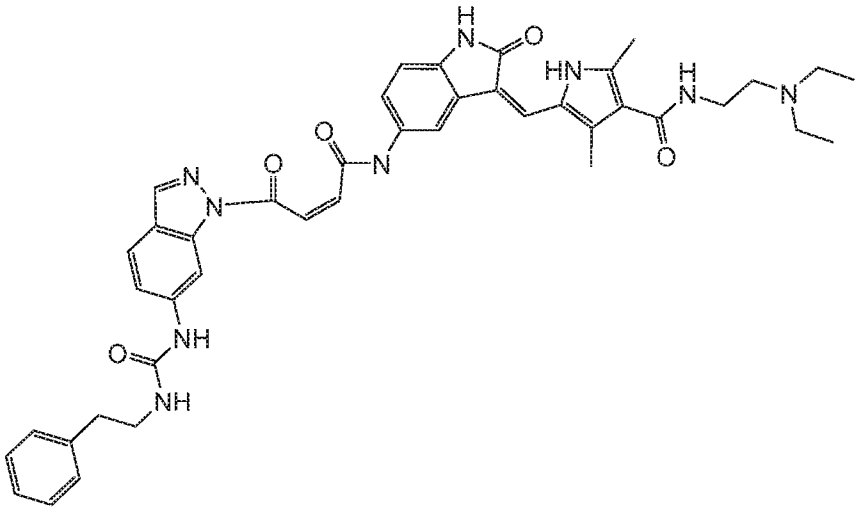


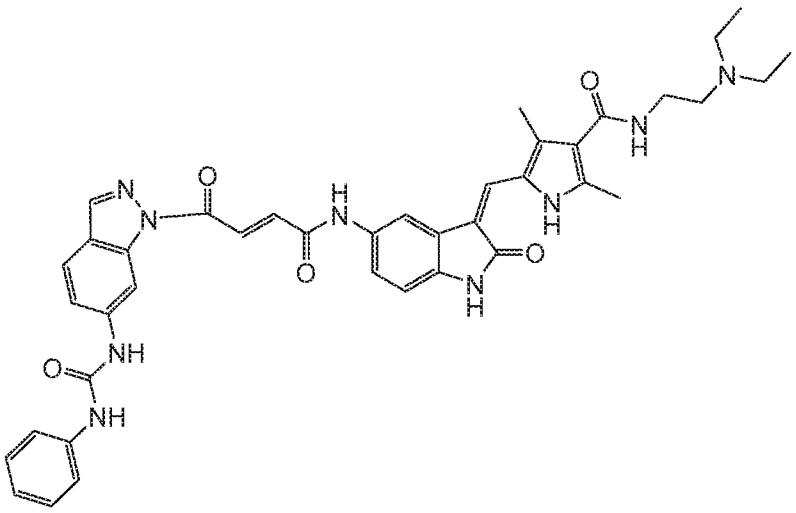


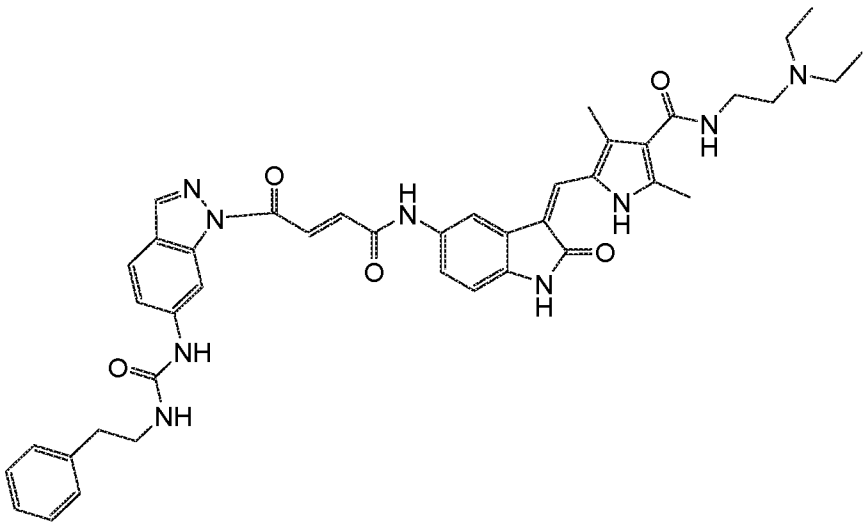


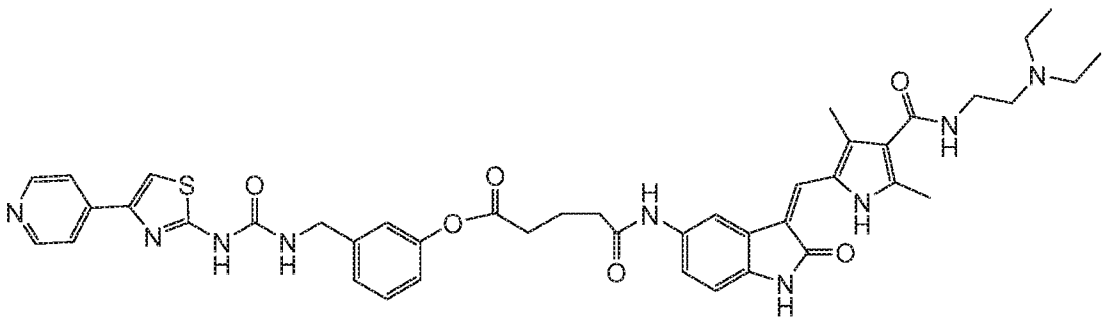


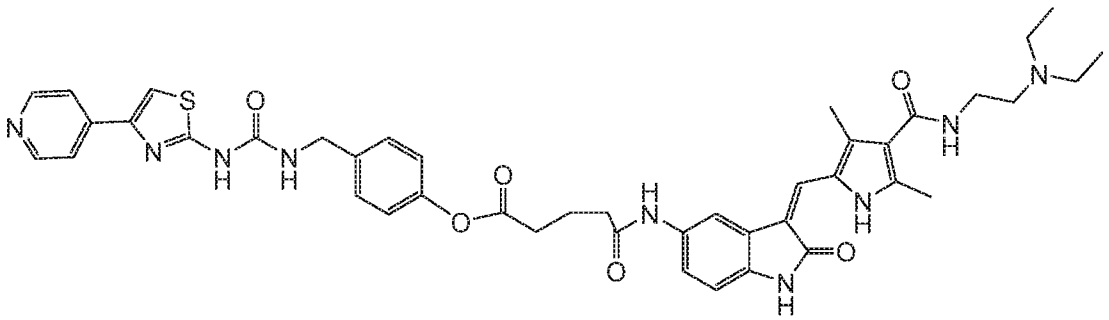


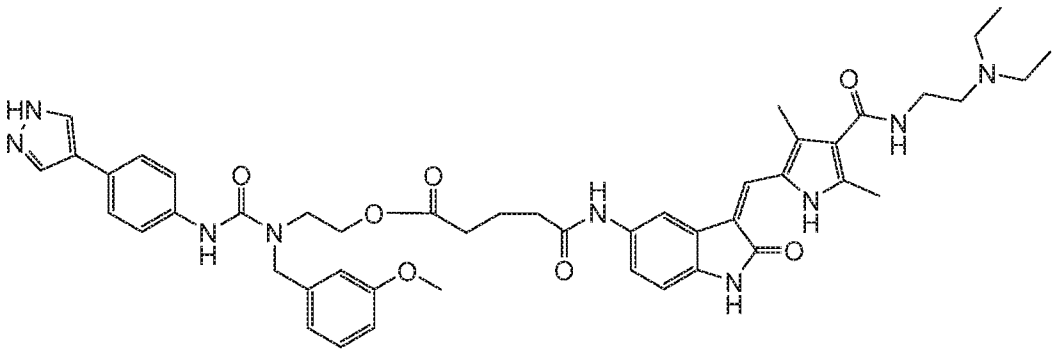


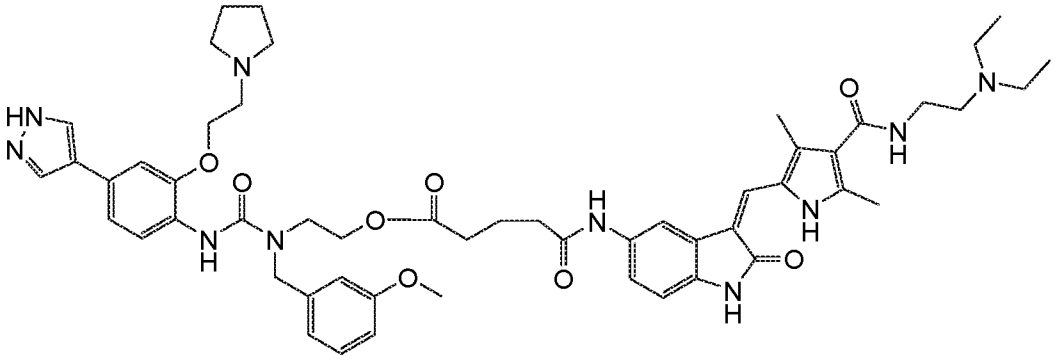


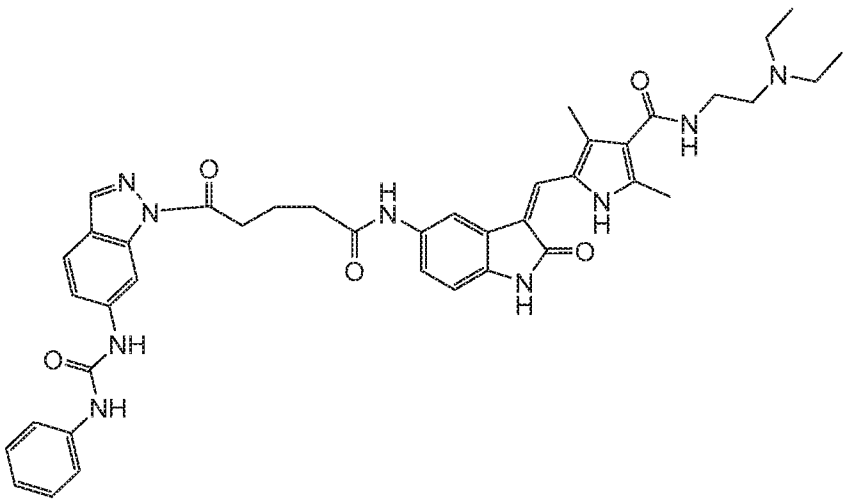


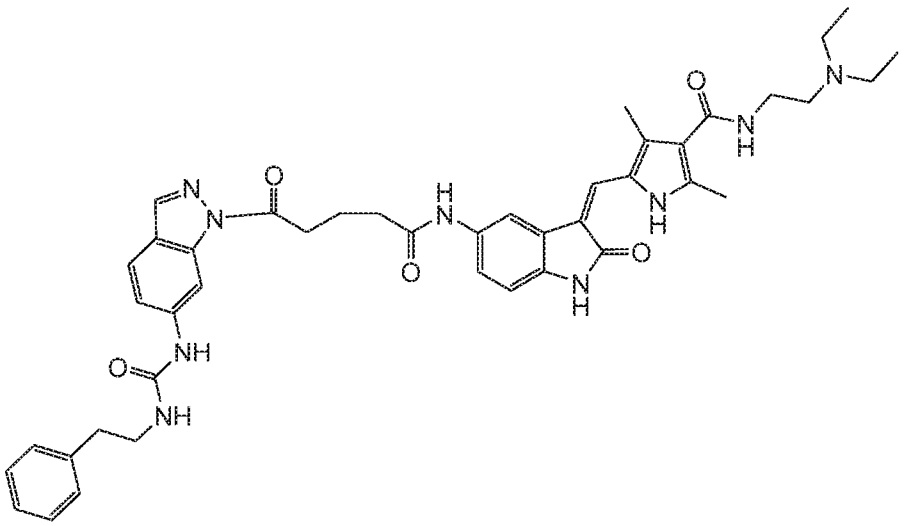


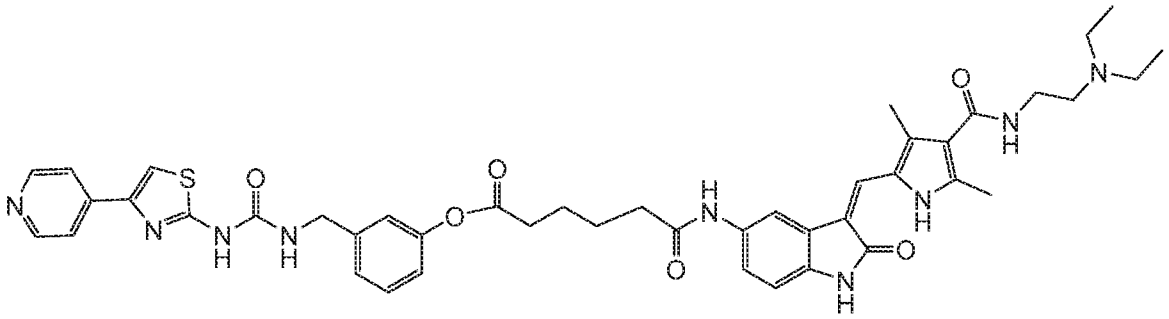


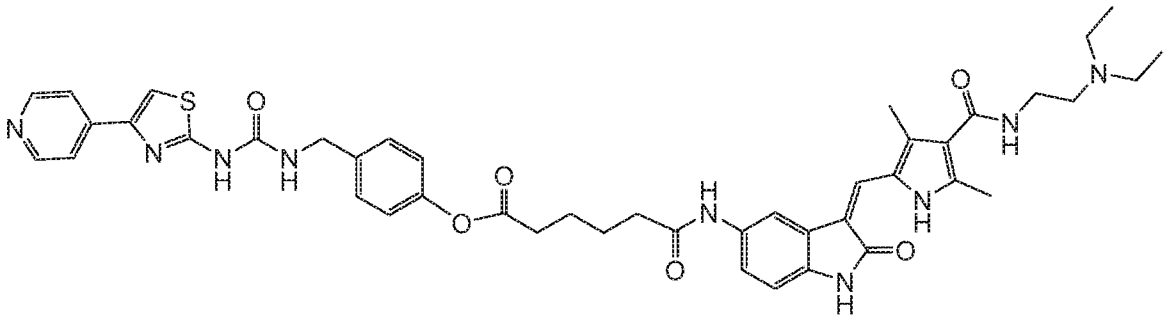


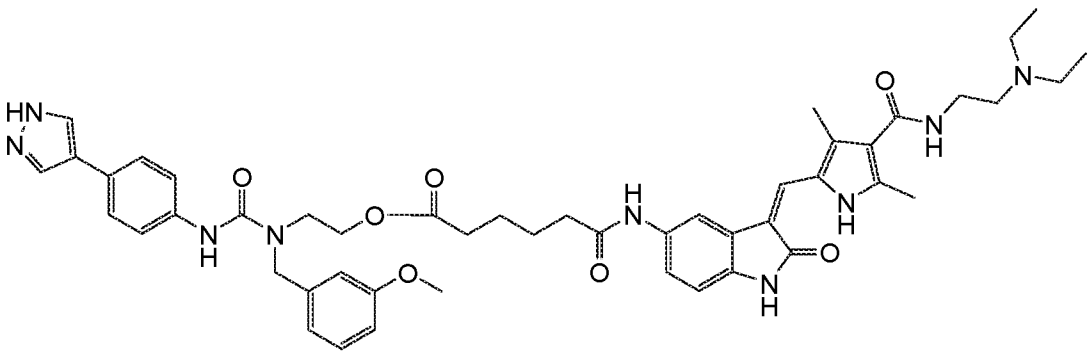


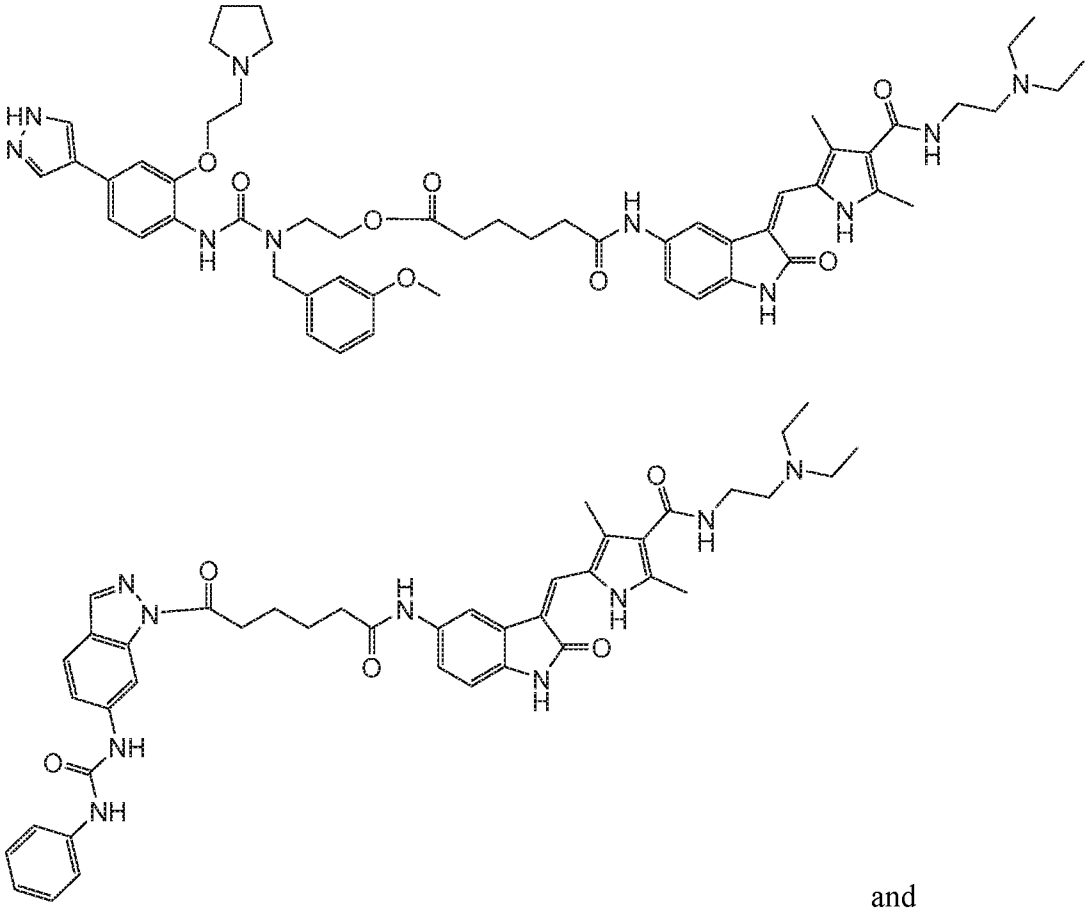




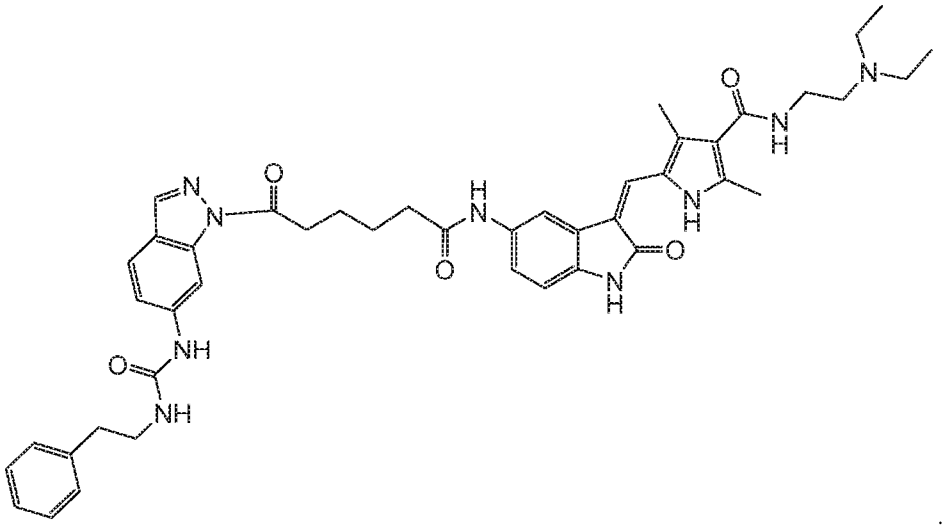




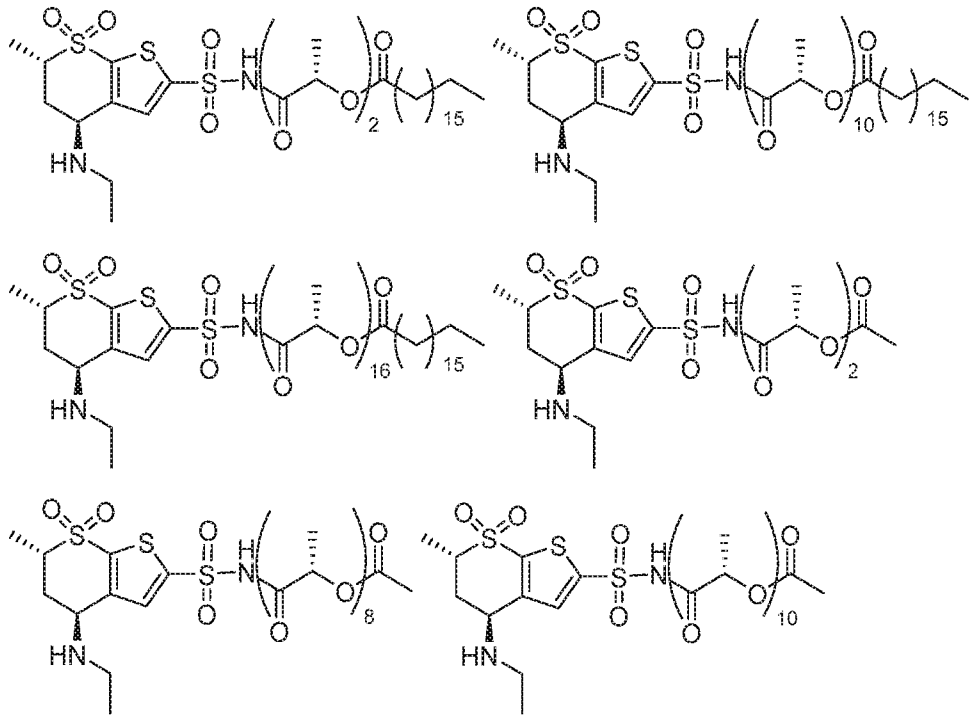




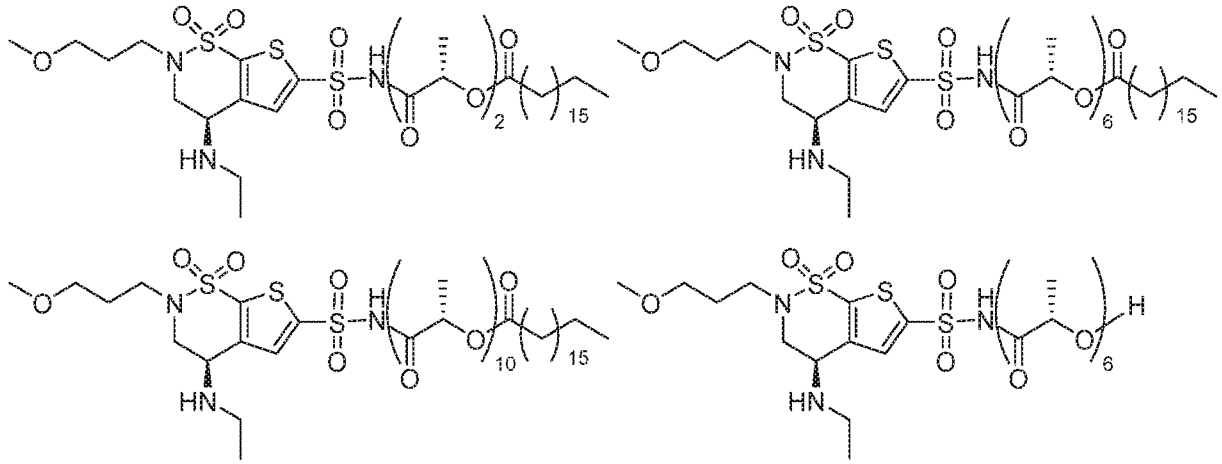
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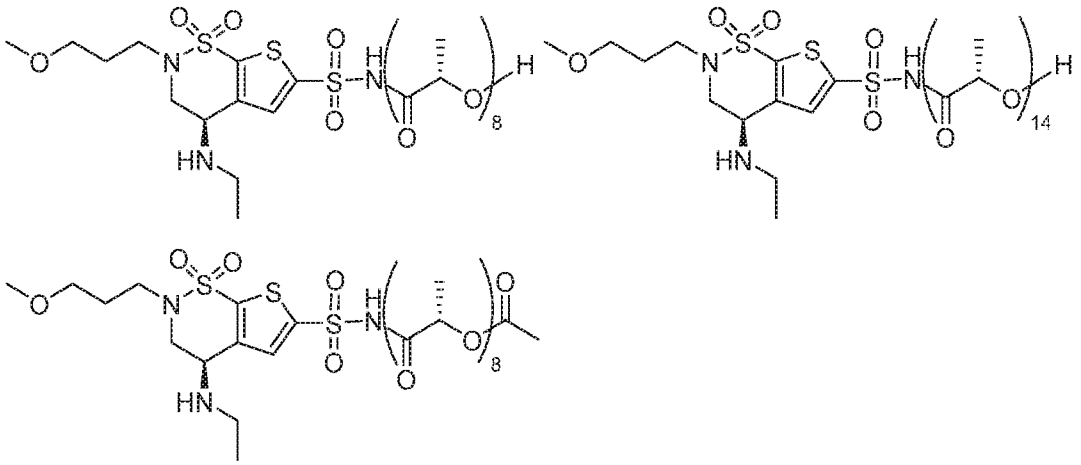


**Example 38. Non-limiting Examples of Dorzolamide Mono-Prodrugs**

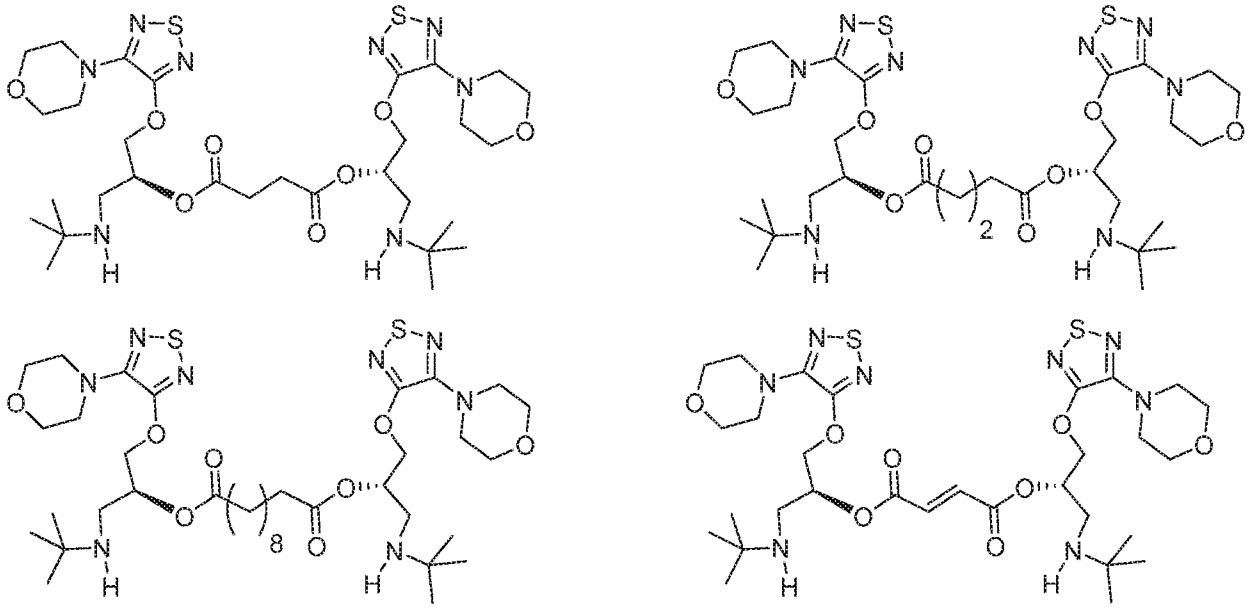


**Example 39. Non-limiting Examples of Brinzolamide Mono-Prodrugs**

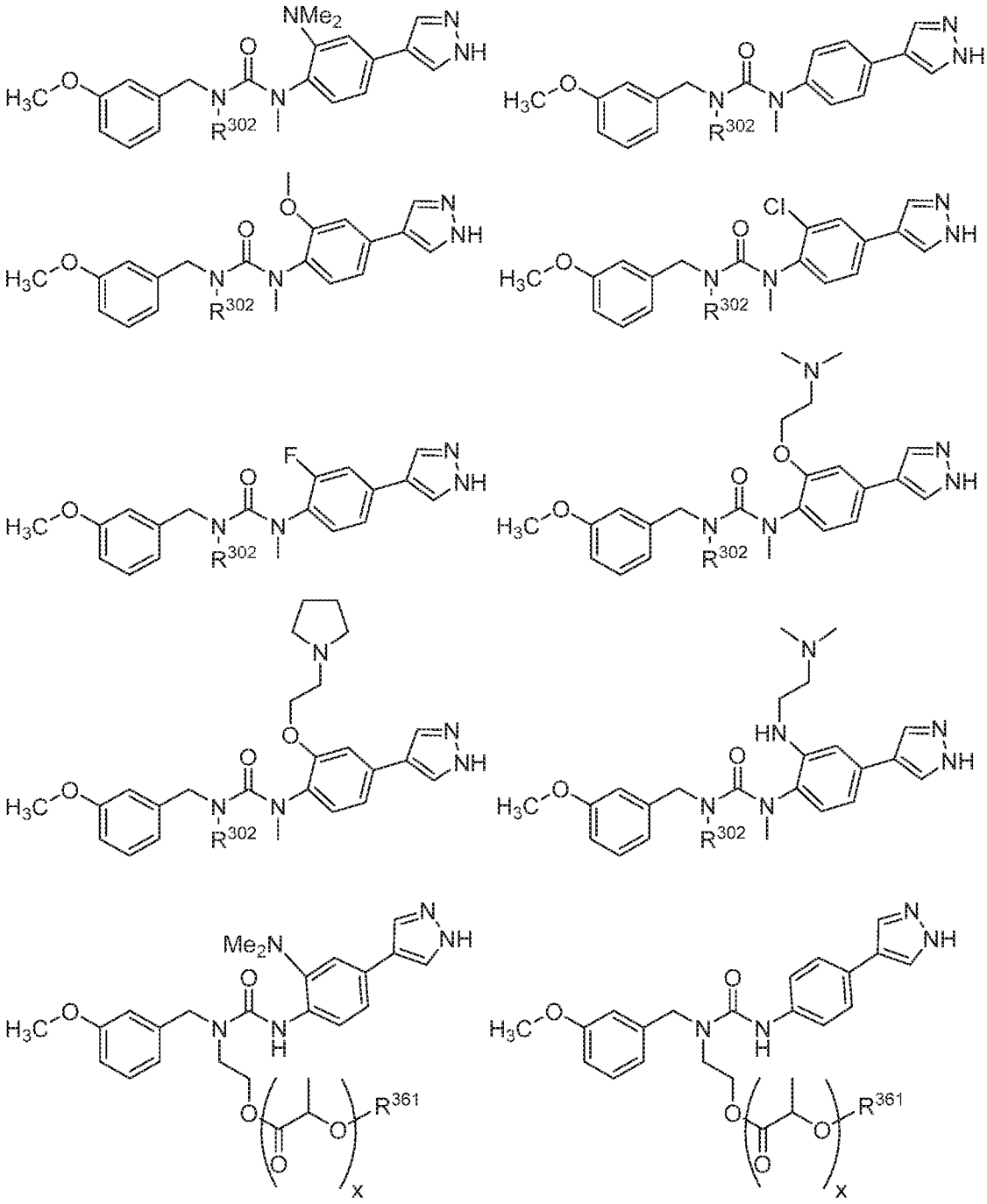


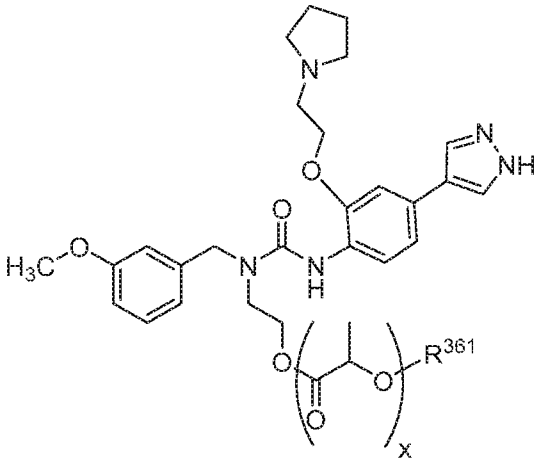


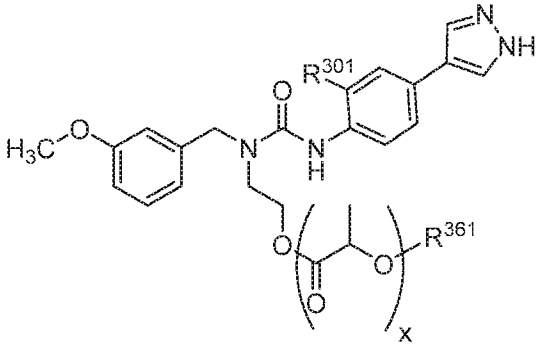
**Example 40. Non-limiting Examples of Compounds of the Present Invention**

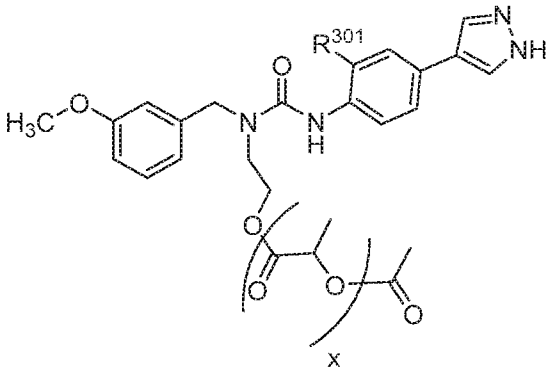


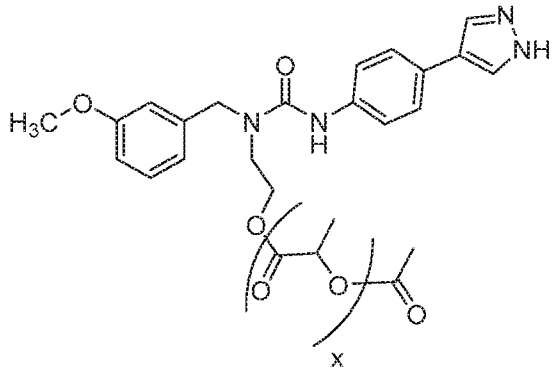
**Example 41. Non-limiting Examples of Compounds of Formula L**

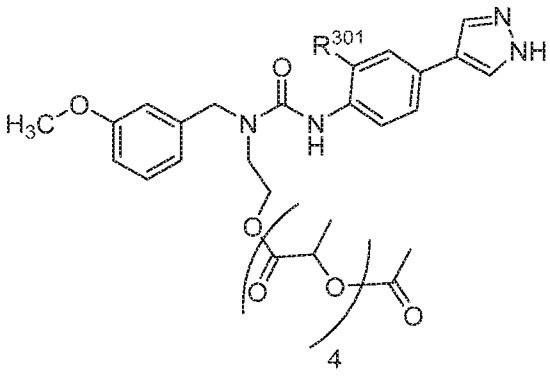


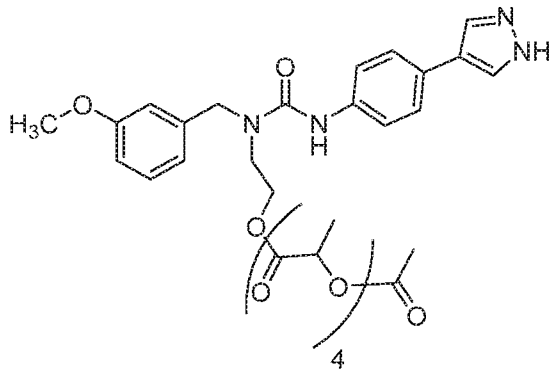


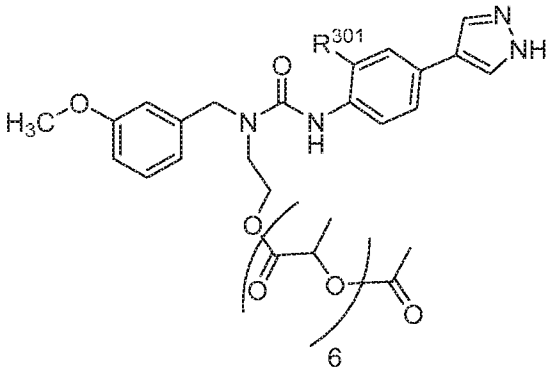


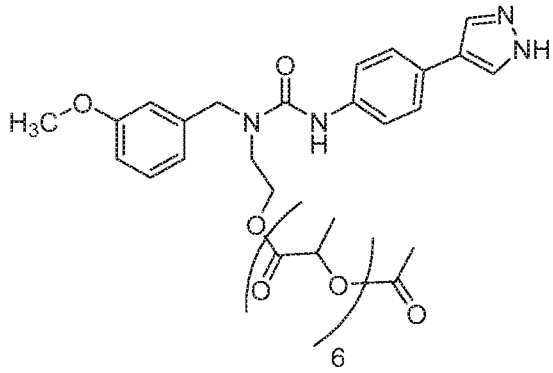


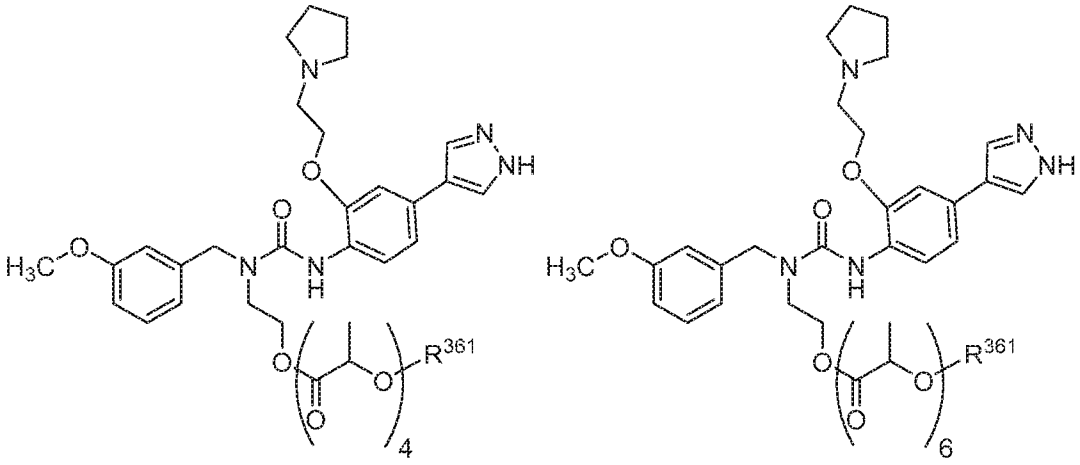




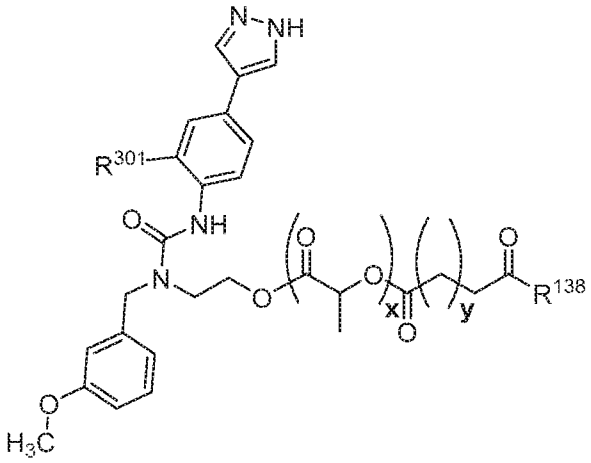


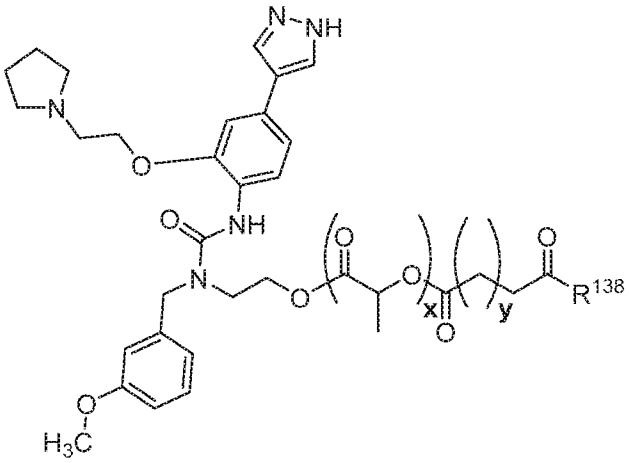


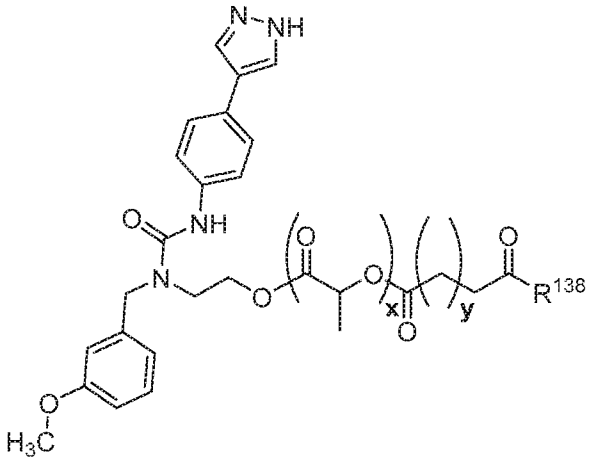


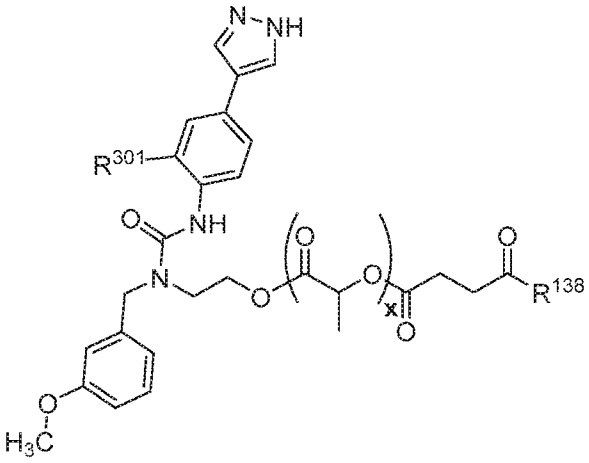


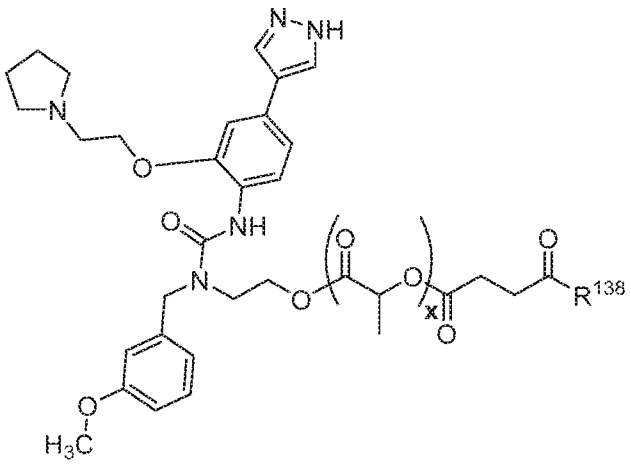
**Example 42. Non-limiting Examples of Compounds of Formula LII**

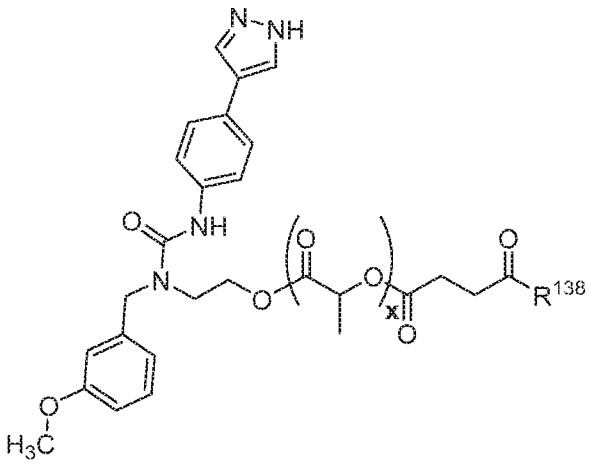


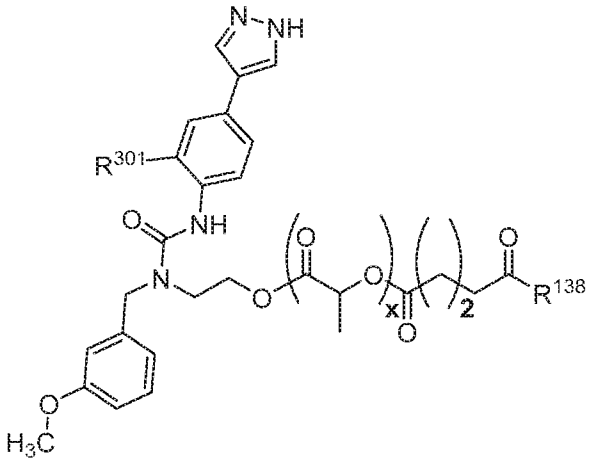


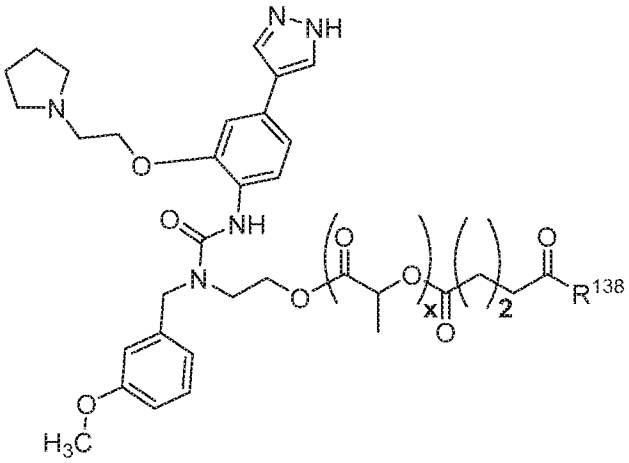


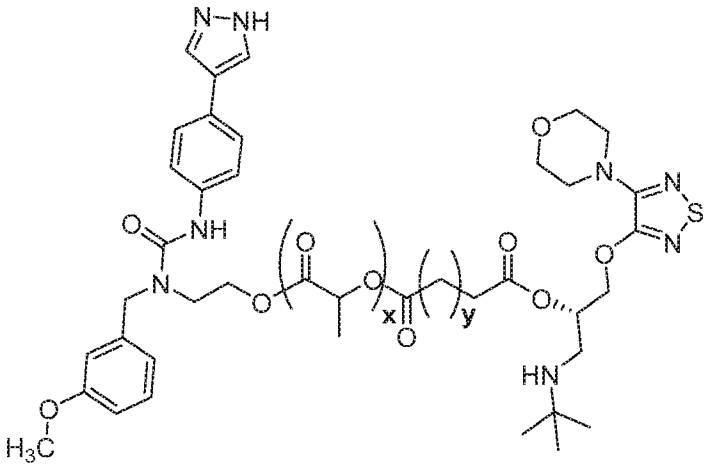


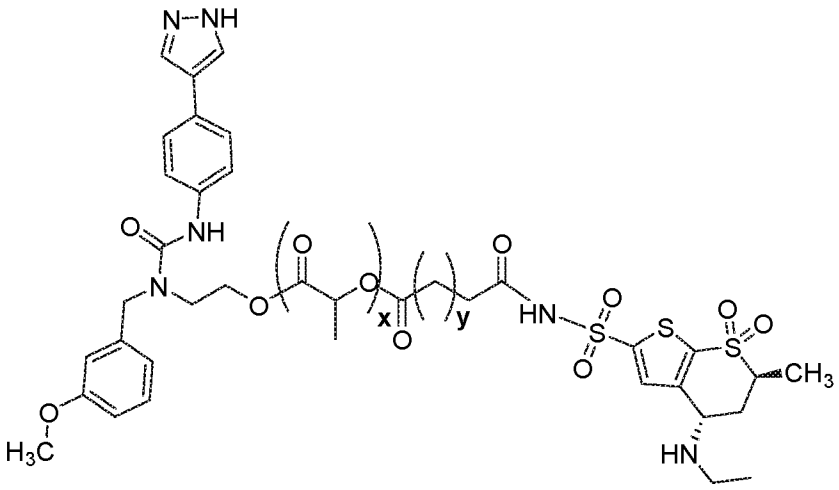


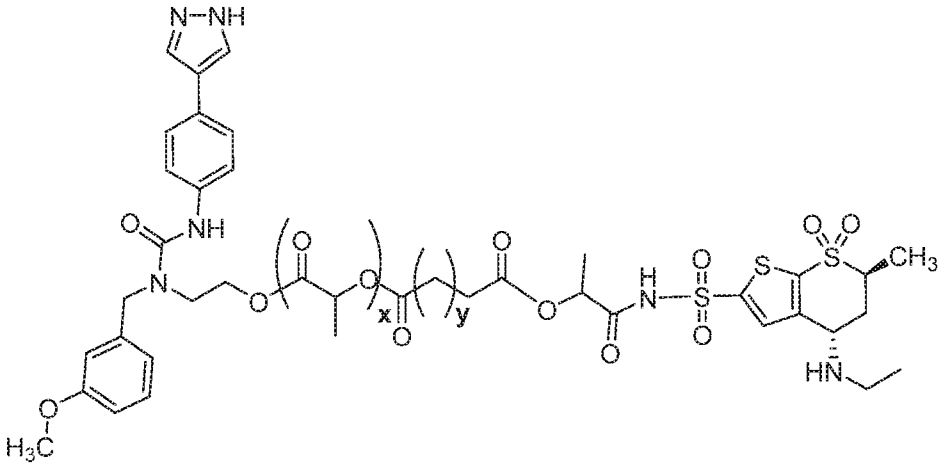


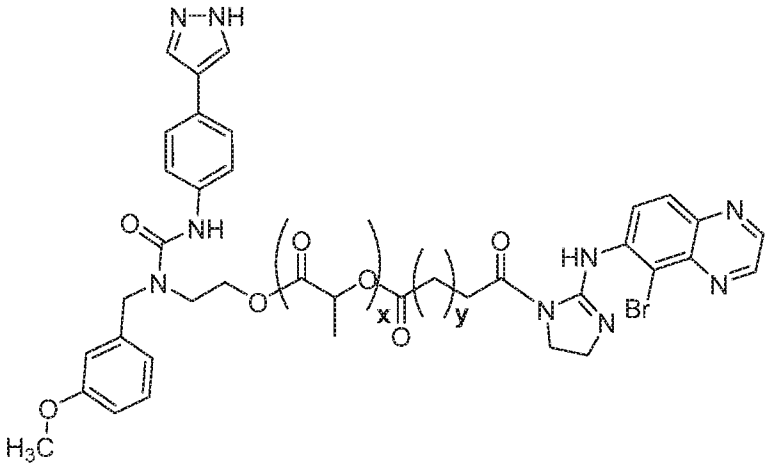


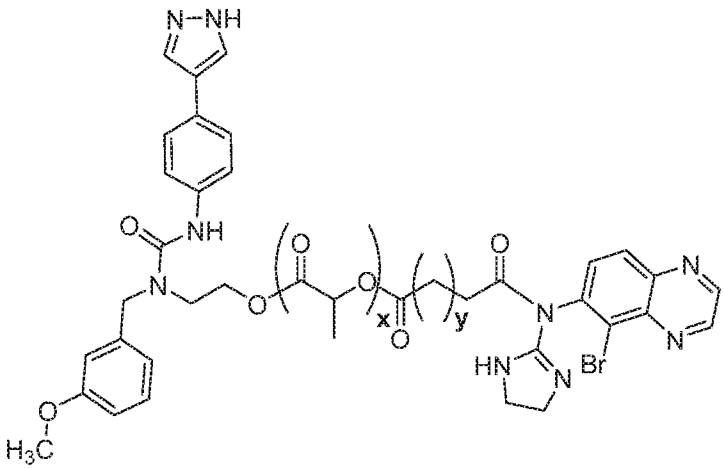


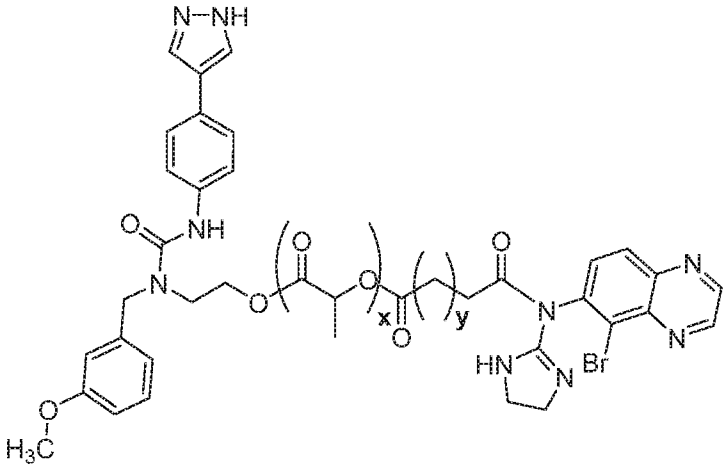


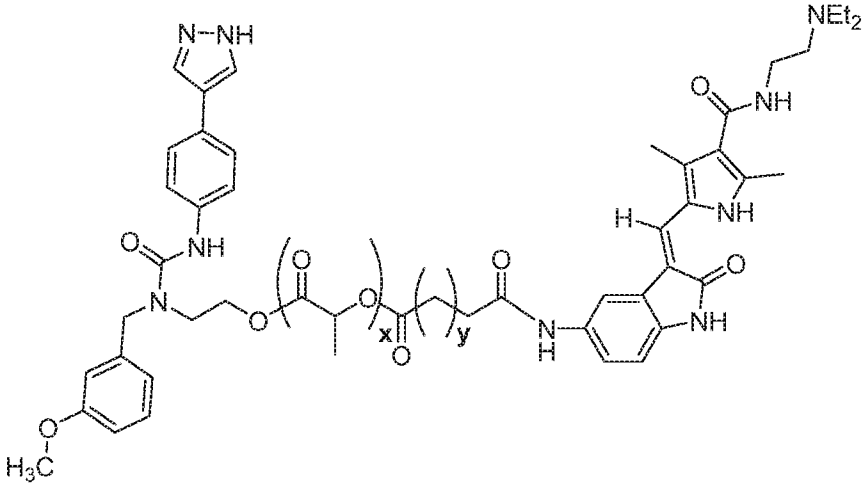


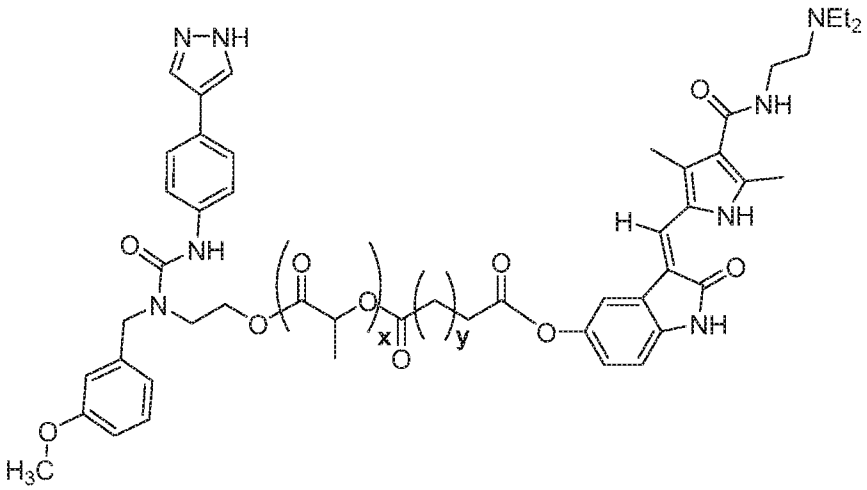


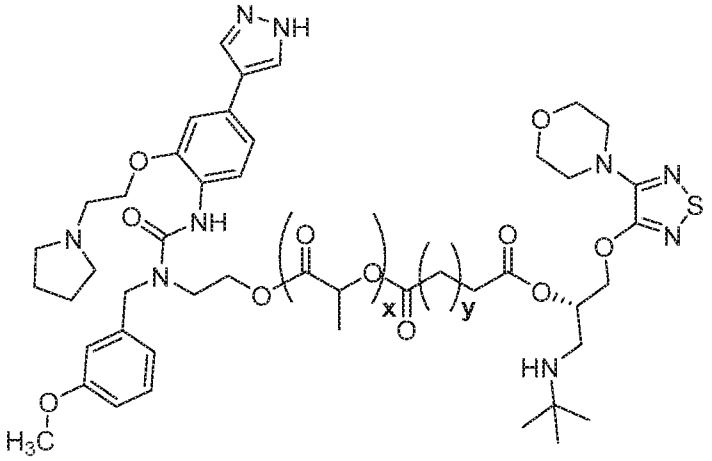


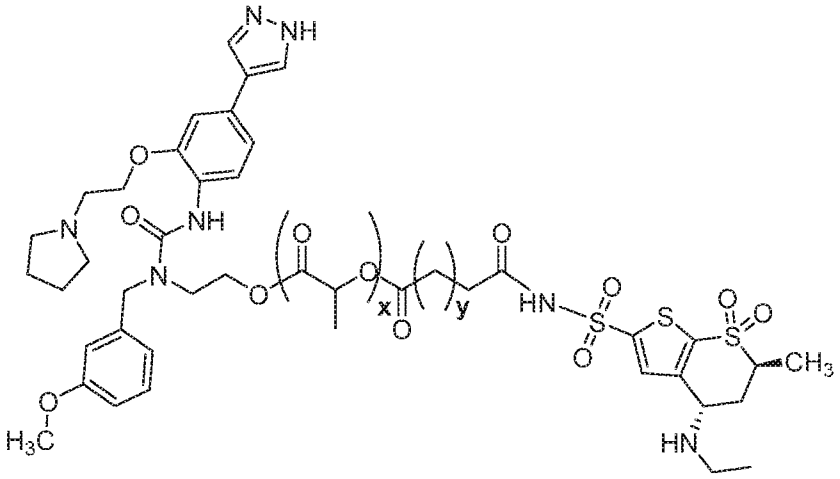


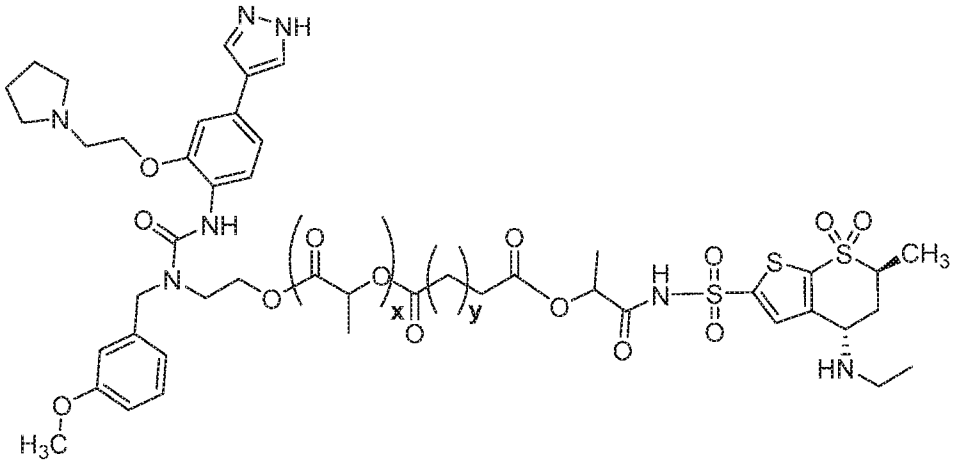


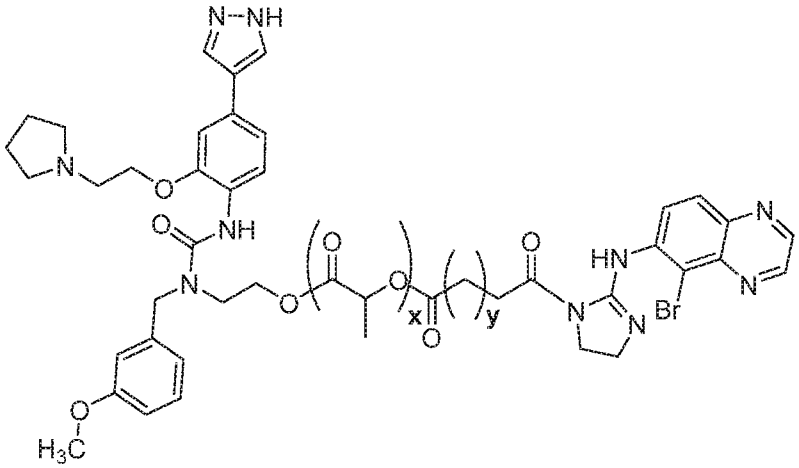


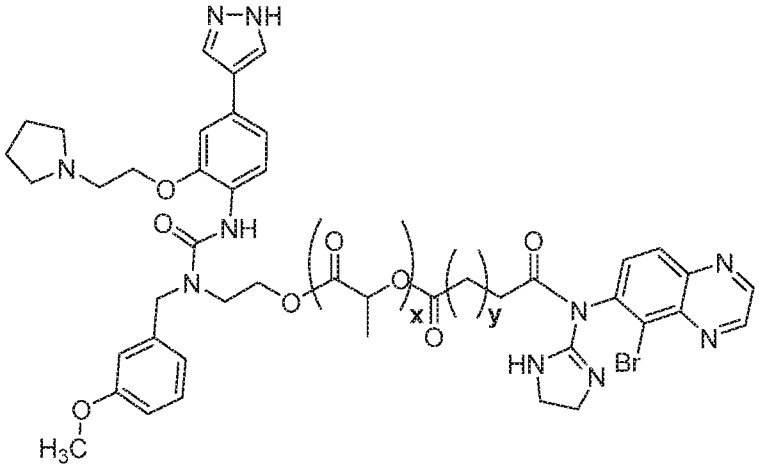


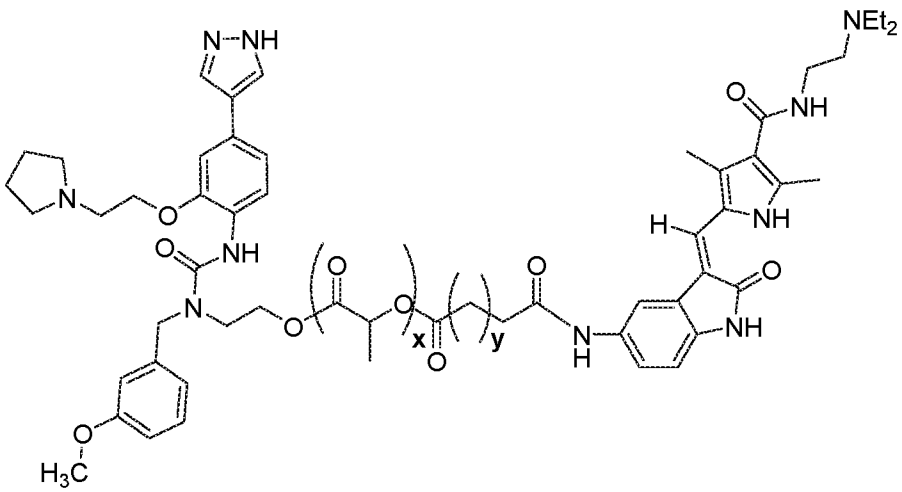


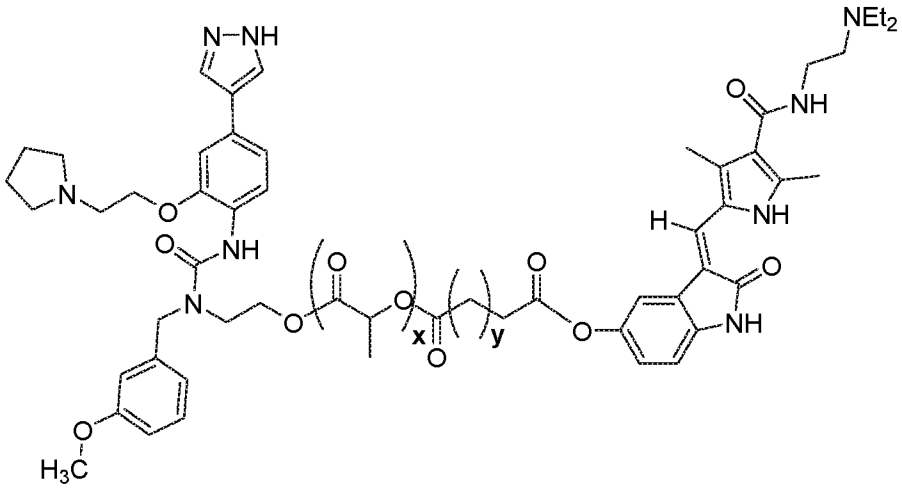




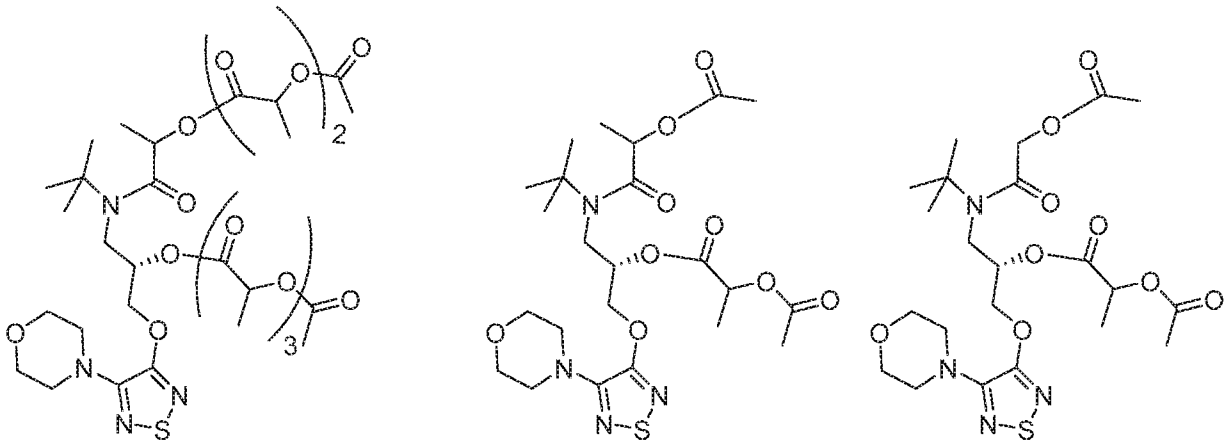


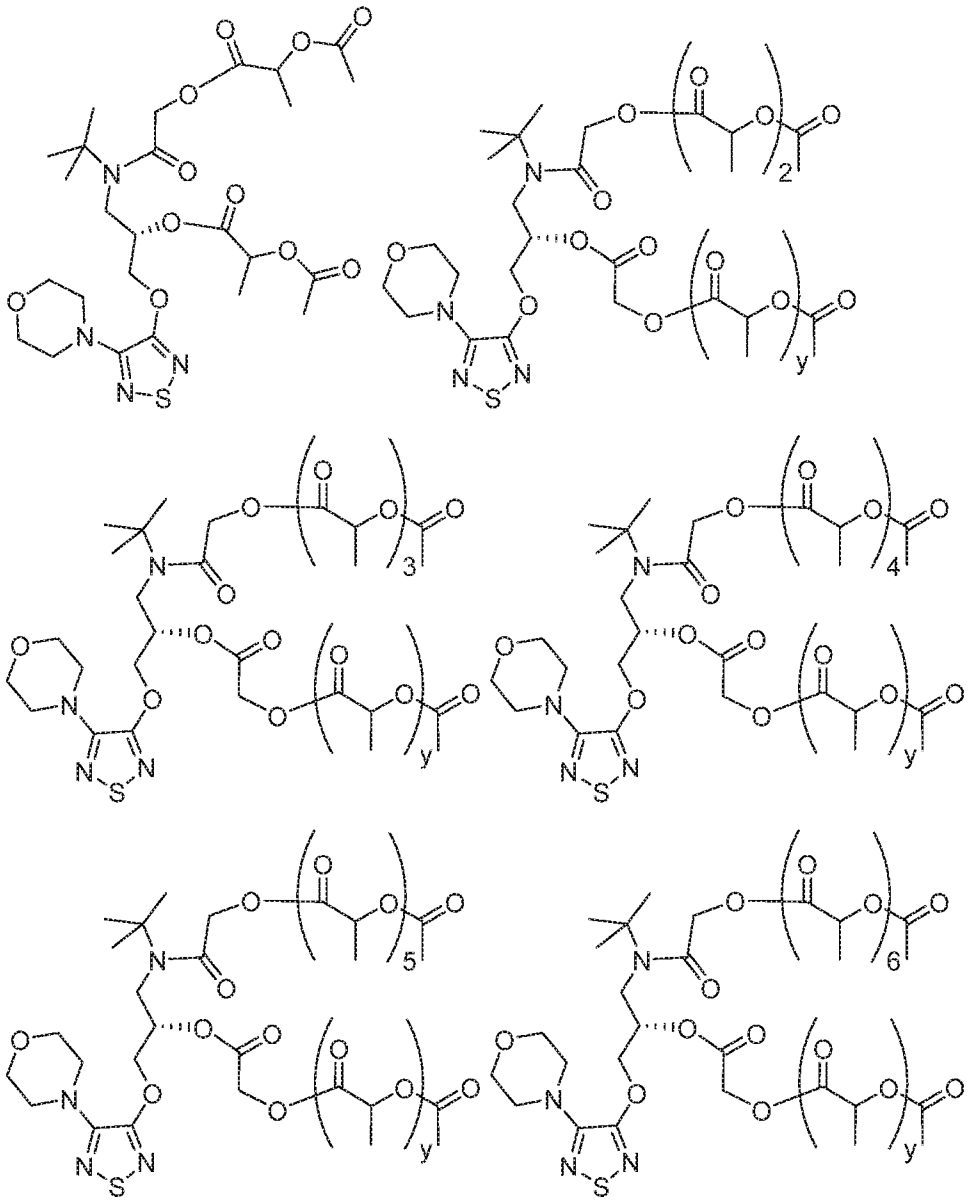




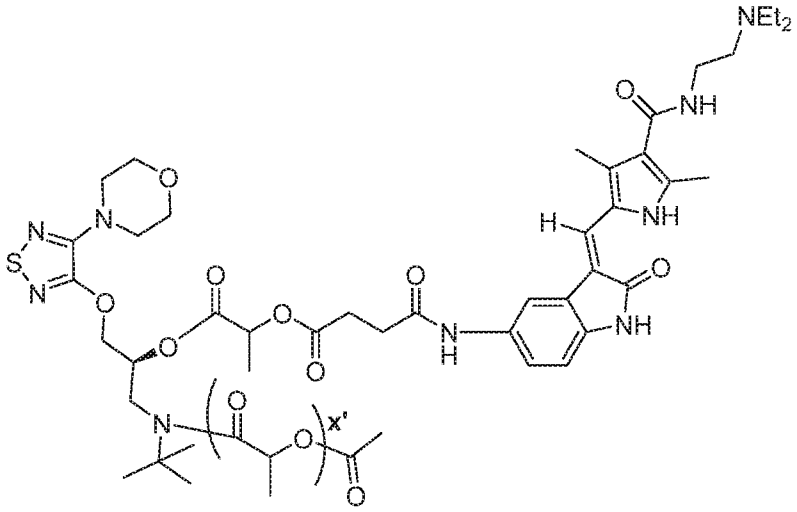


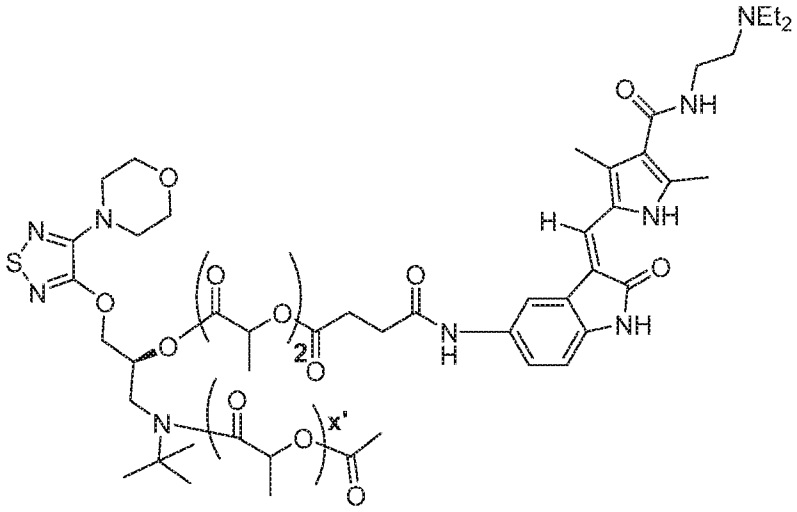
**Example 43. Non-limiting Examples of Compouds of Formula XVII**

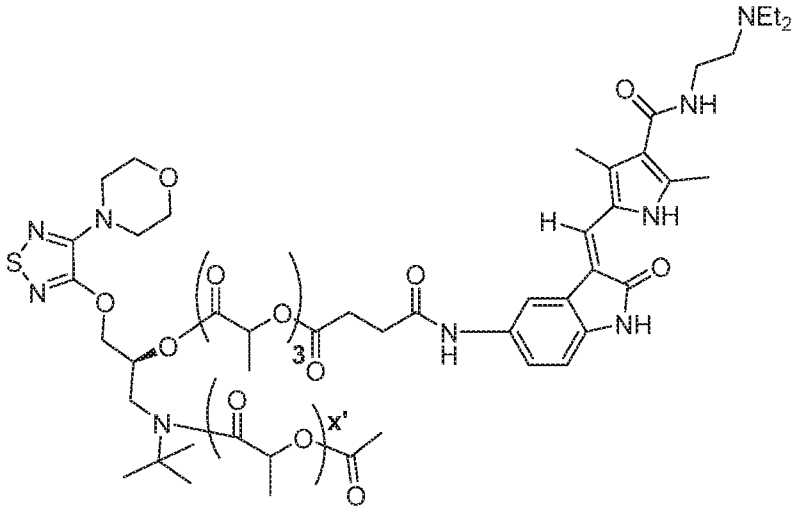


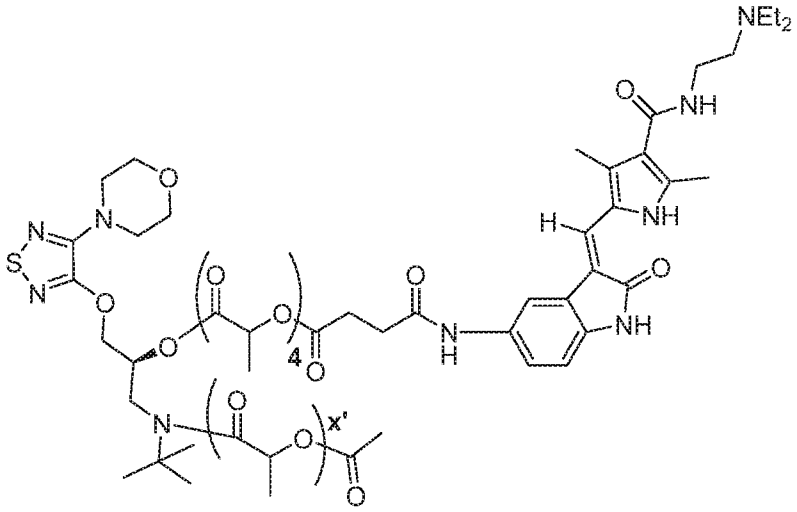


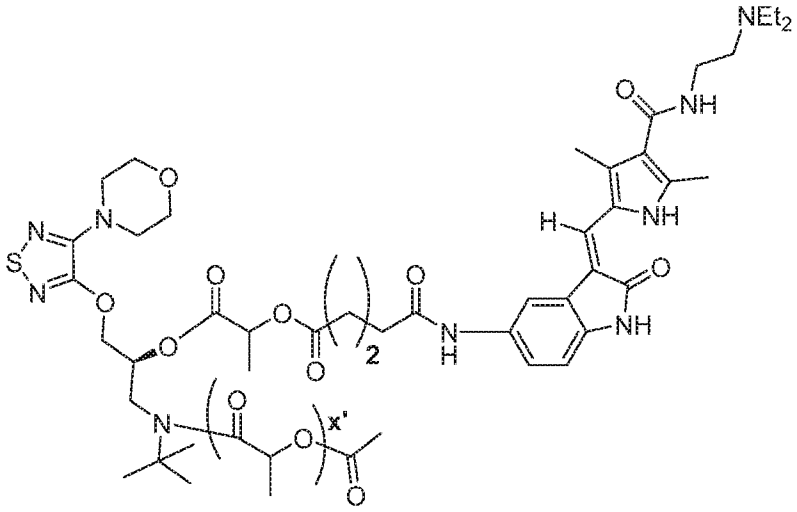
**Example 44. Non-limiting Examples of Compouds of Formula XV'**

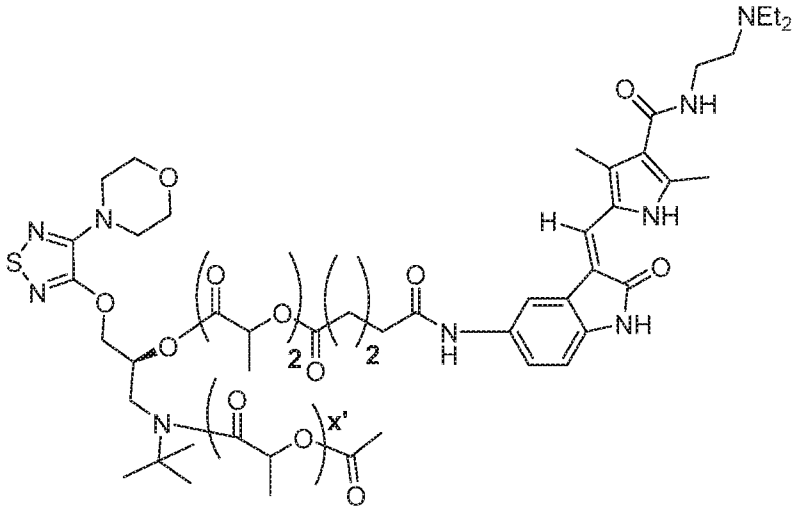


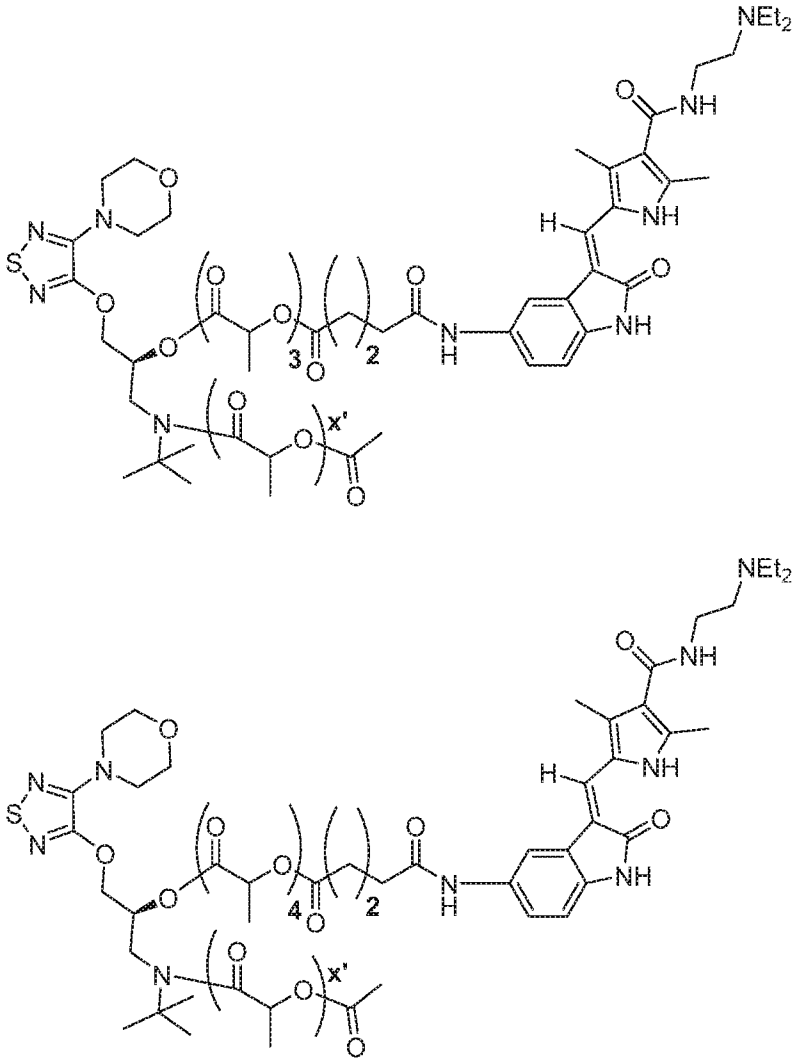




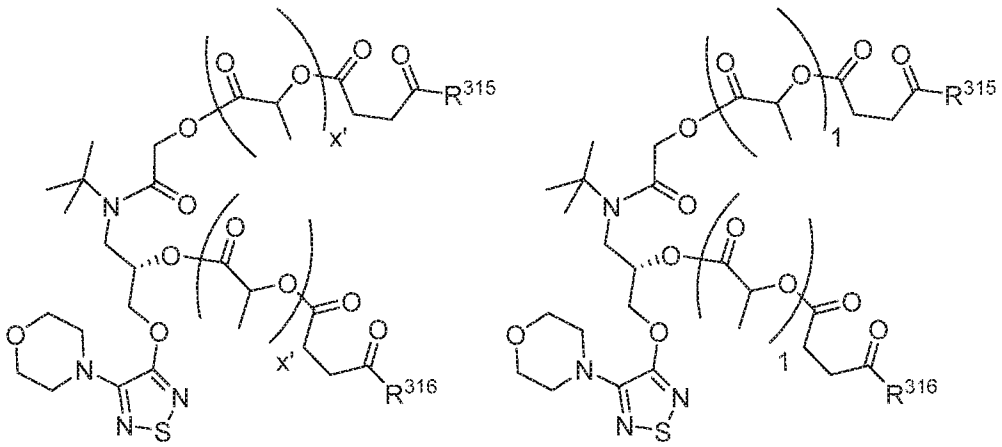


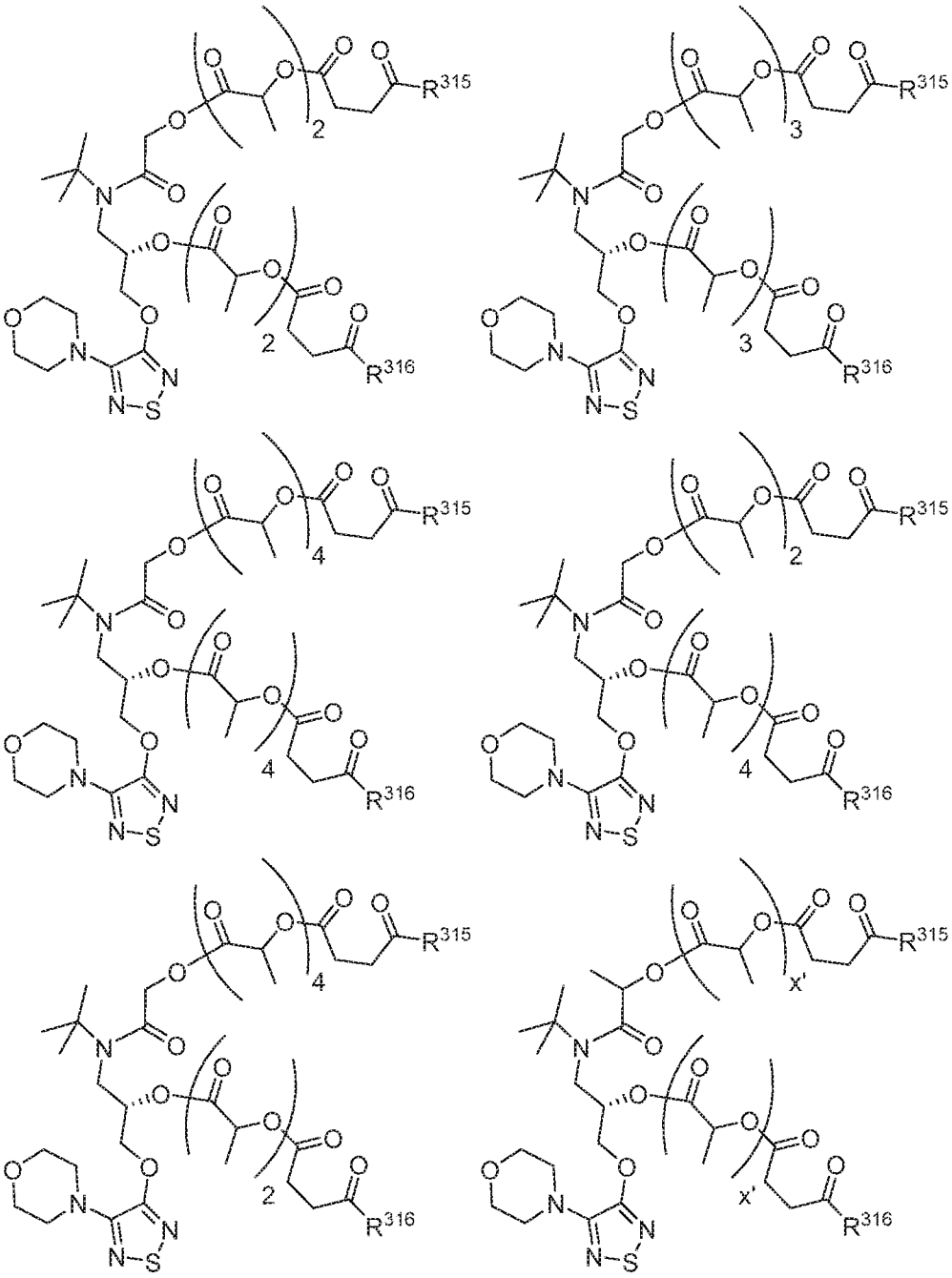


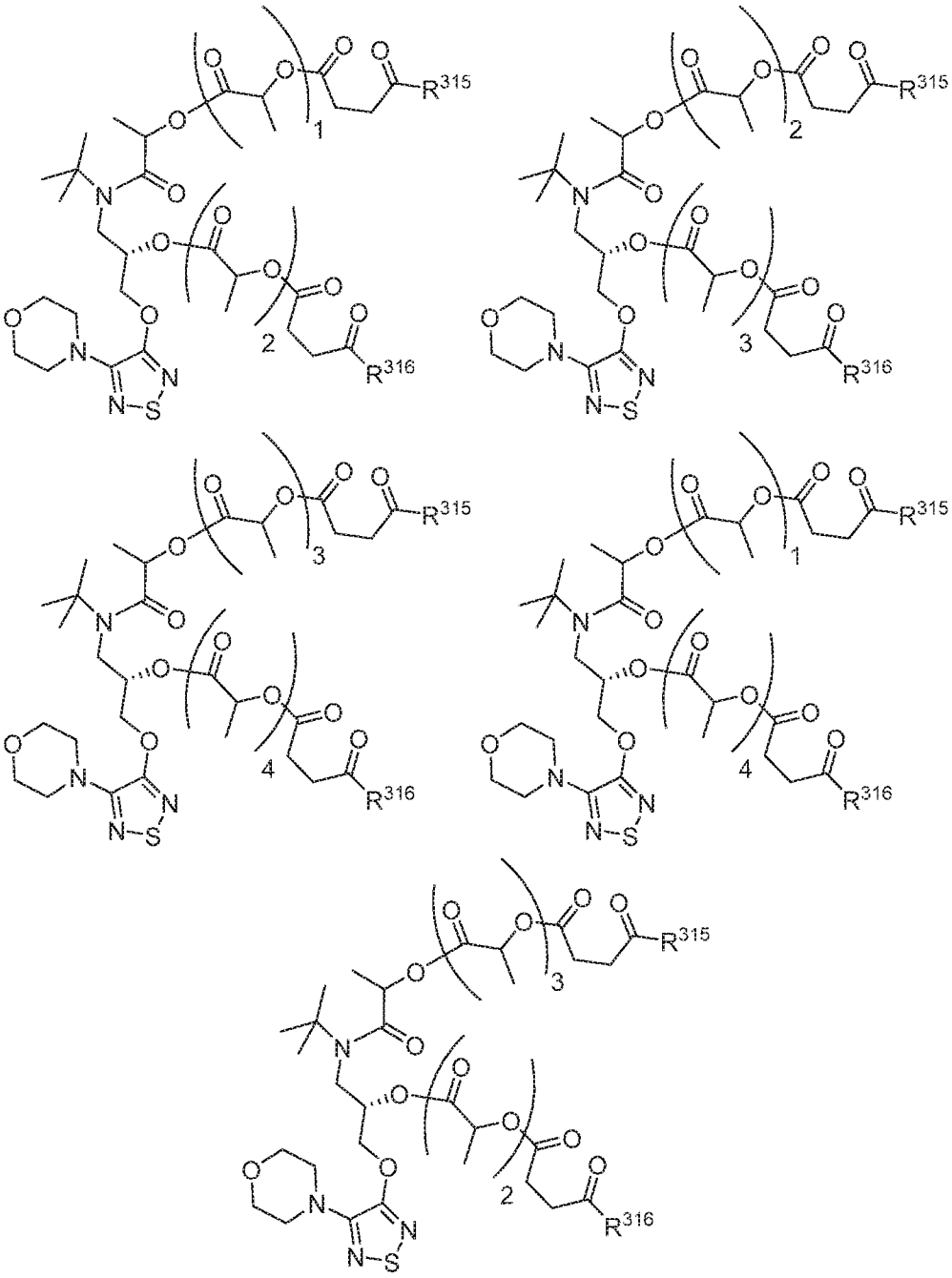


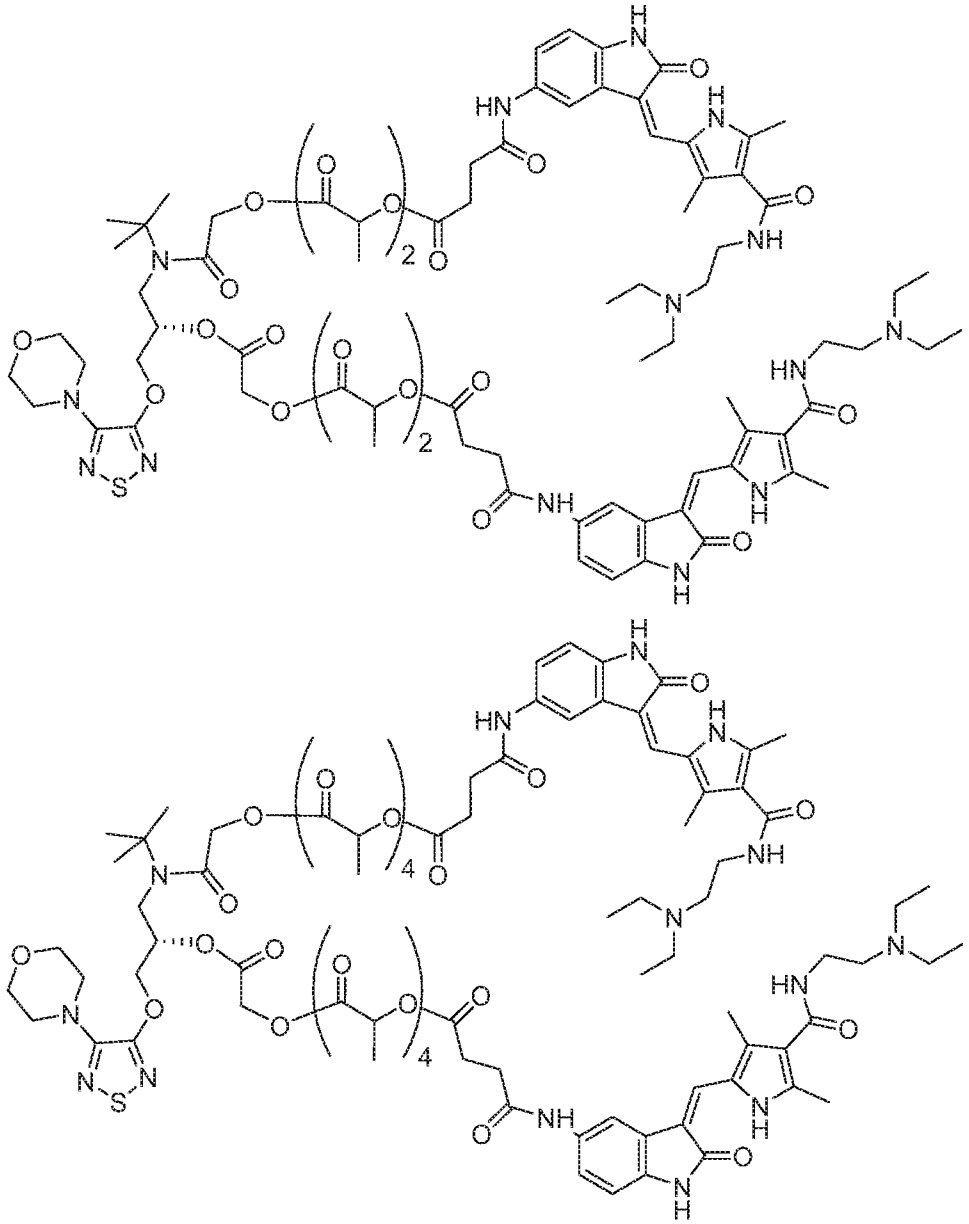


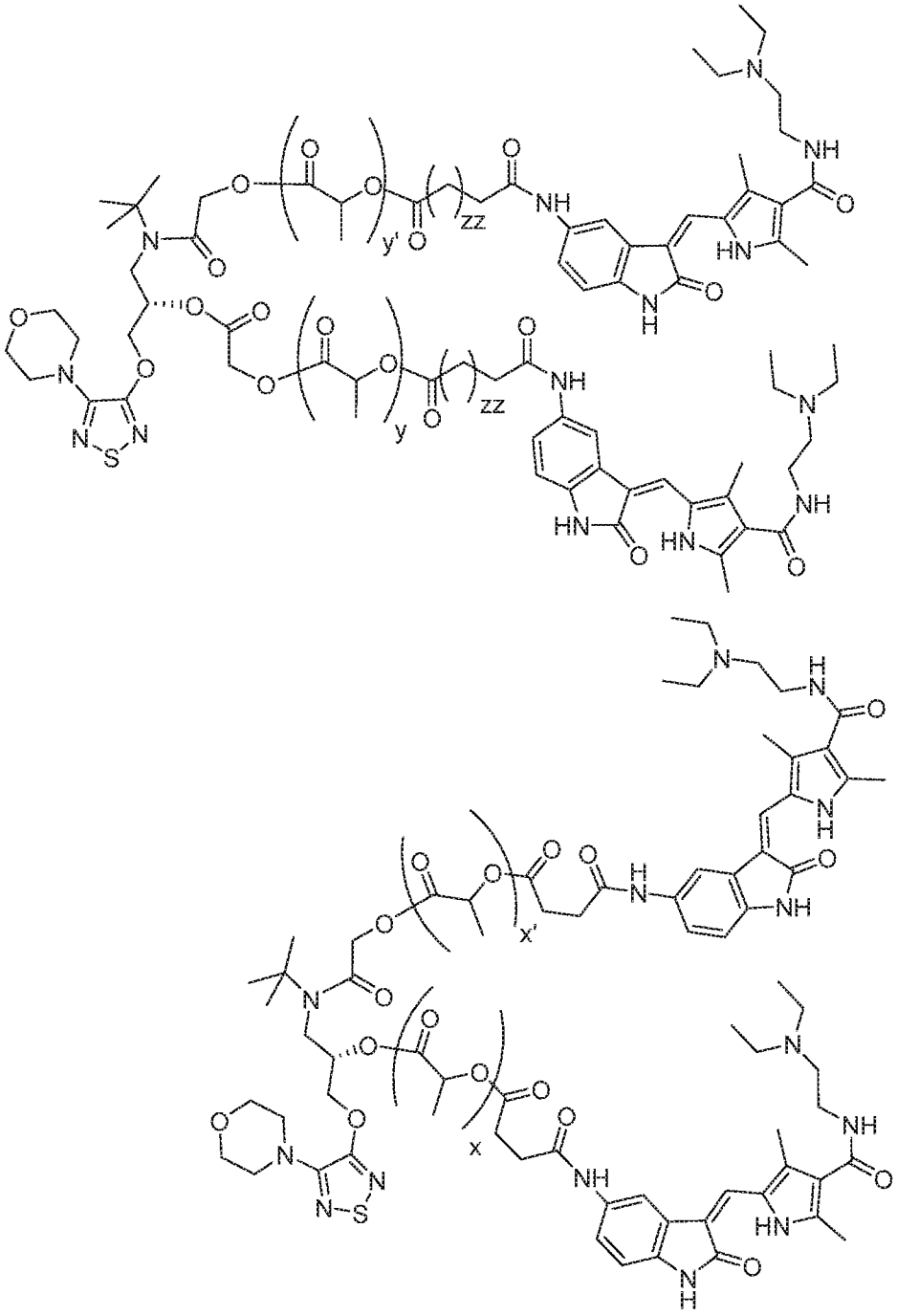
**Example 45. Non-limiting Examples of Compounds of Formula LIV**

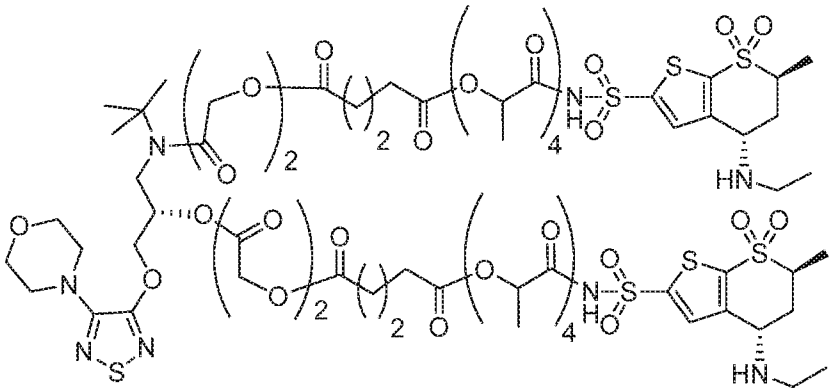


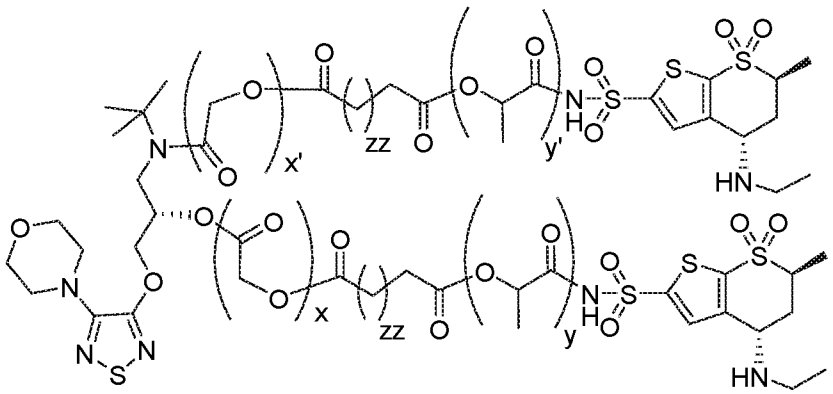


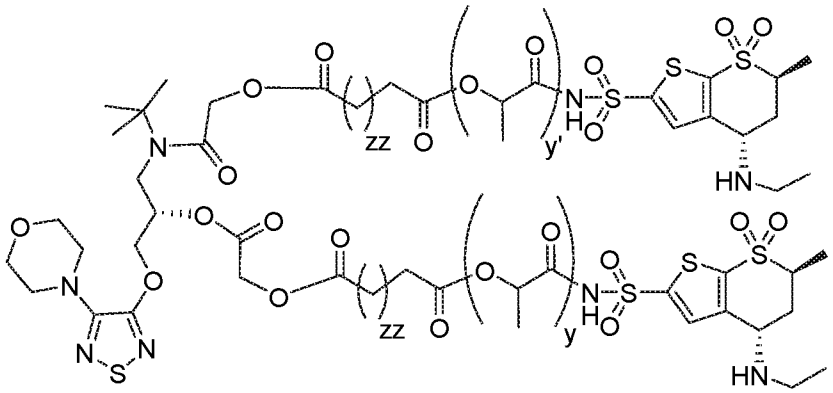






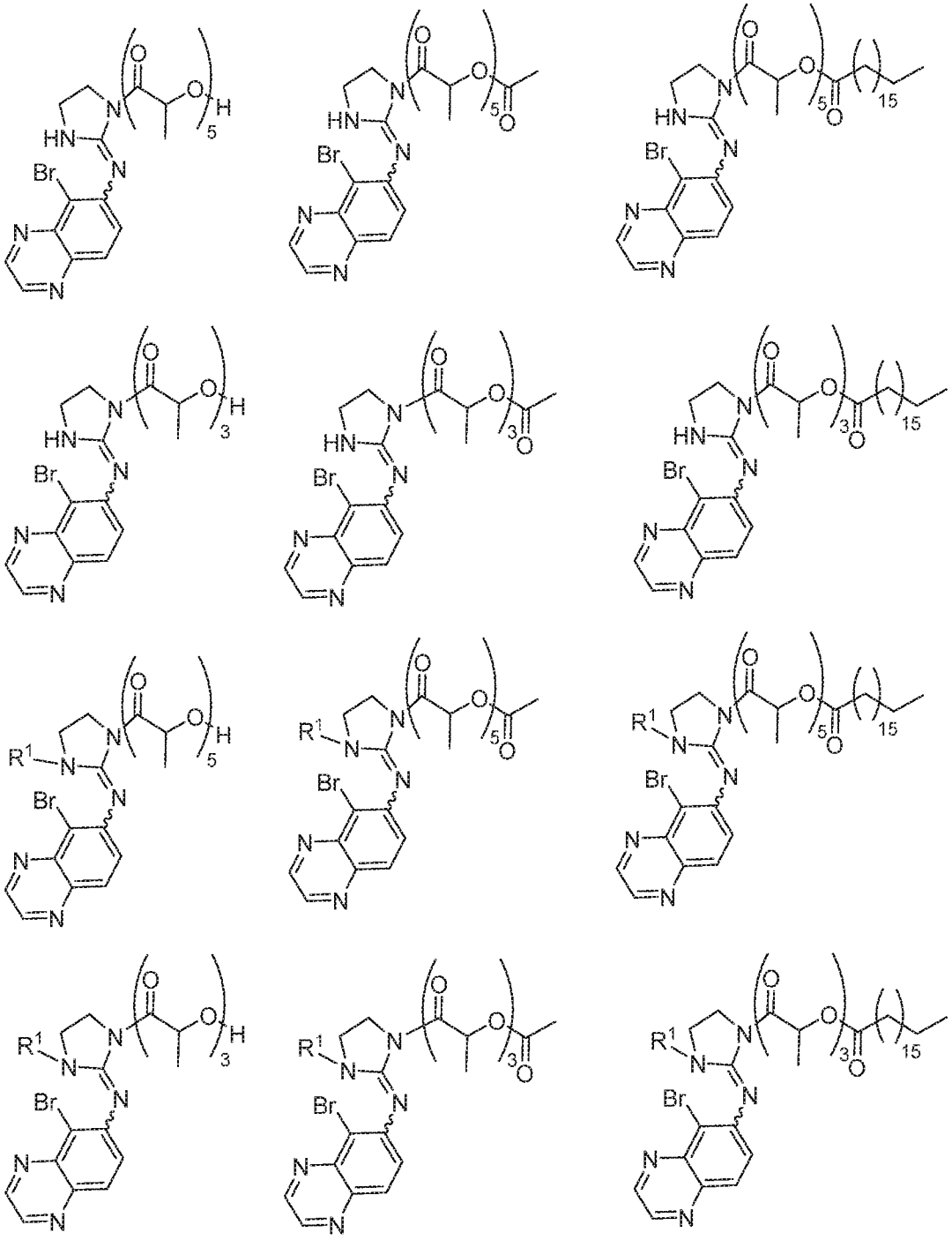


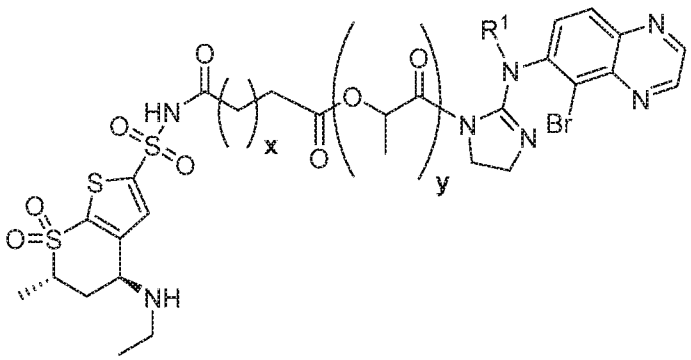


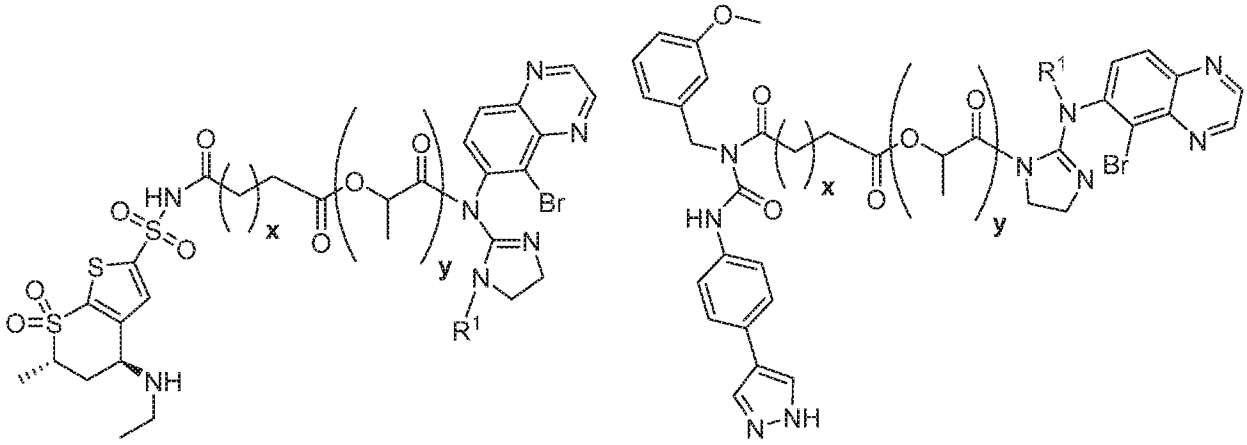


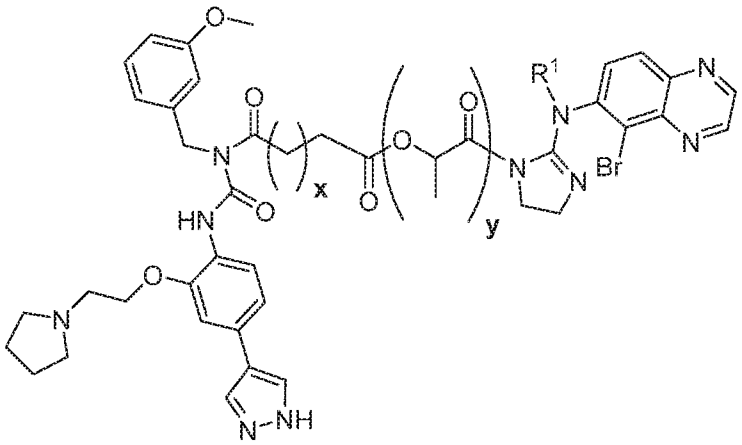
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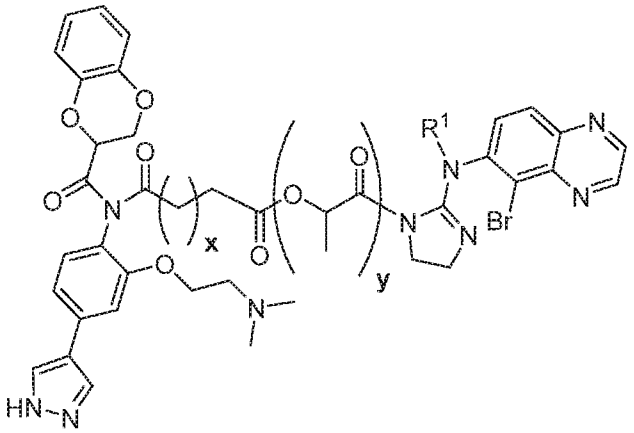
**Example 46. Non-limiting Examples of Compounds of Formula VIII', IX, IX' amd IX''**



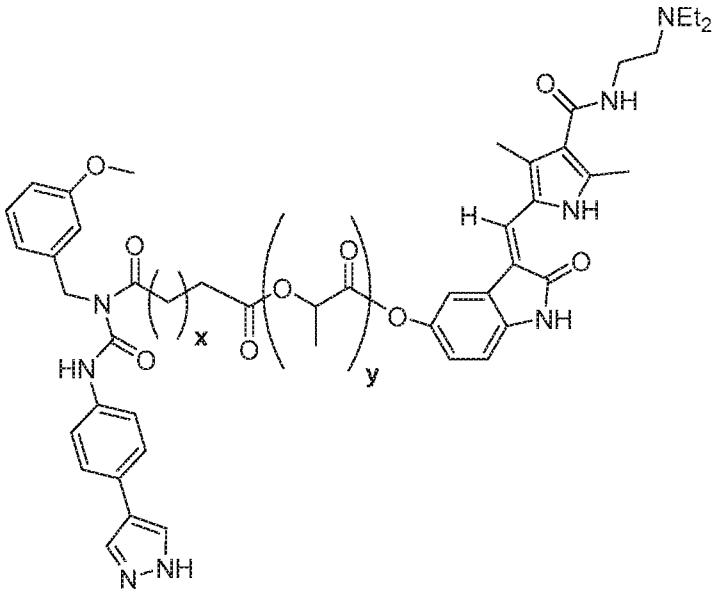


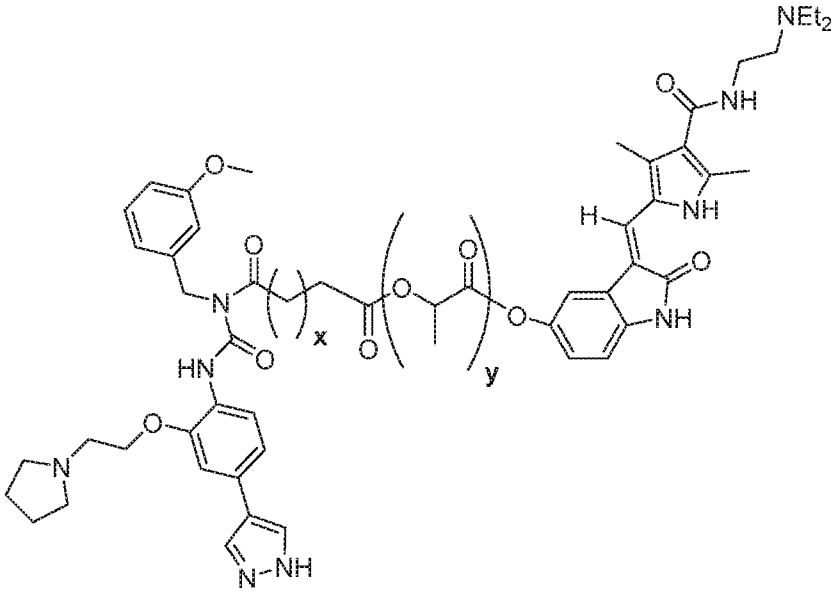


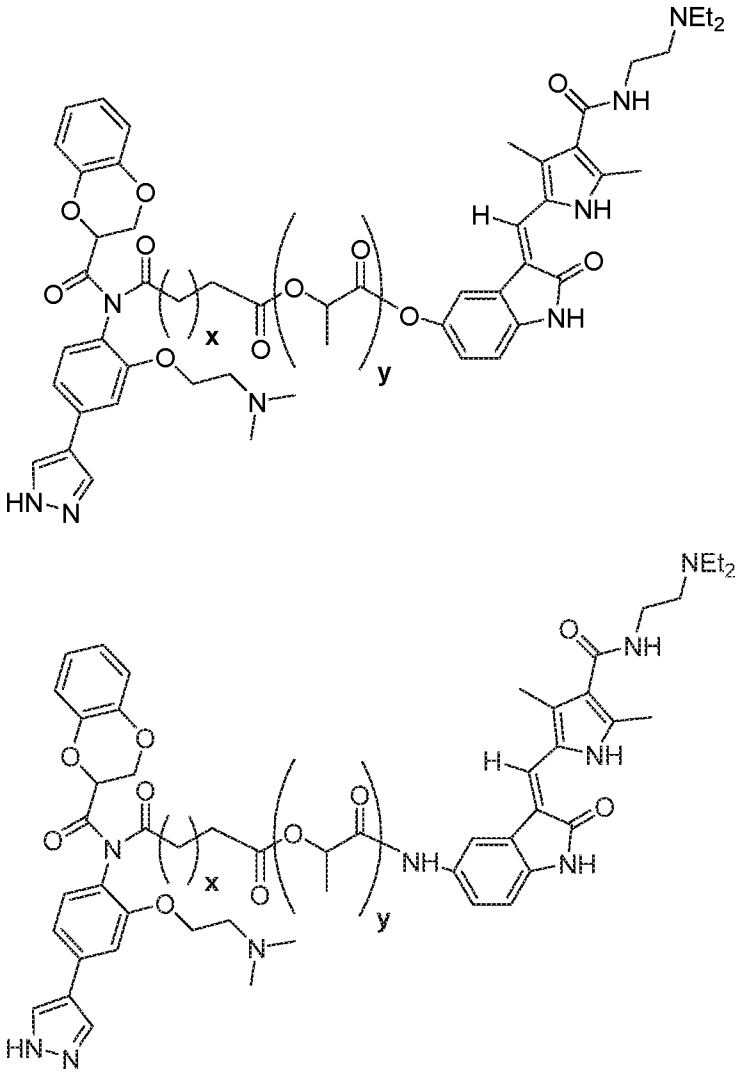




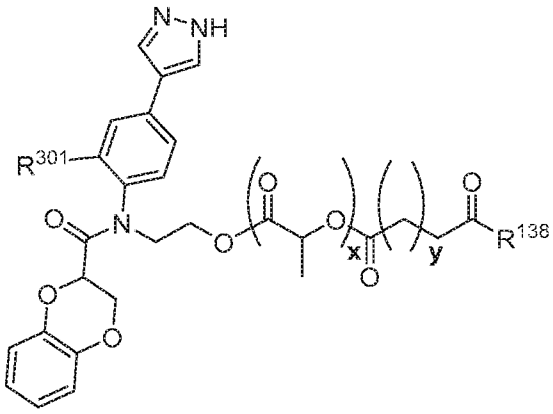
**Example 47. Non-limiting Examples of Compounds of Formula XI**

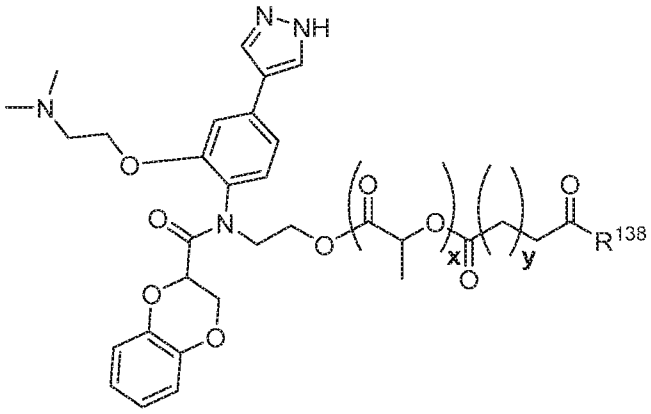


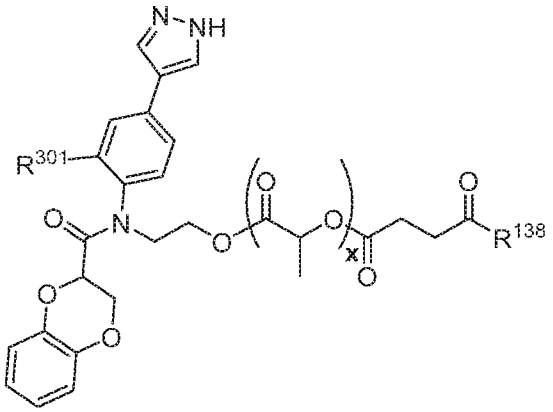


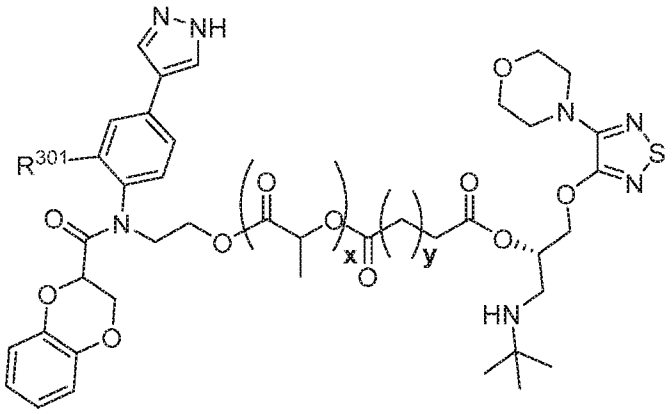


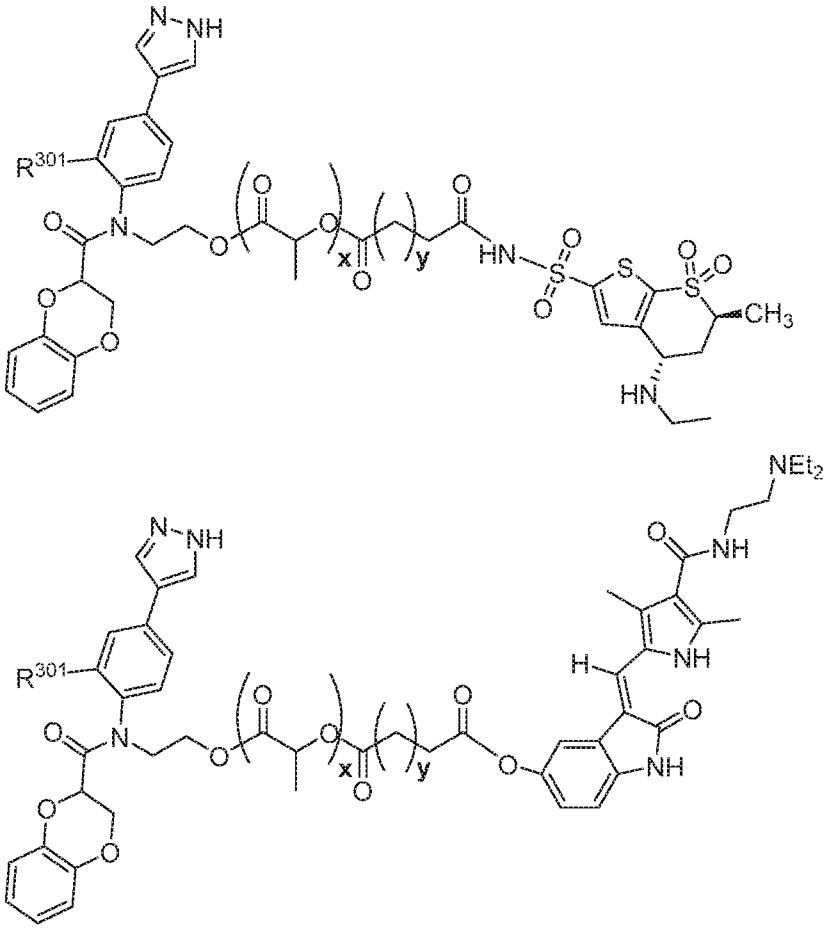
**Example 48. Non-limiting Examples of Compounds of Formula LIII**







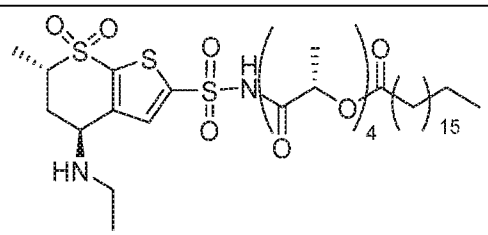


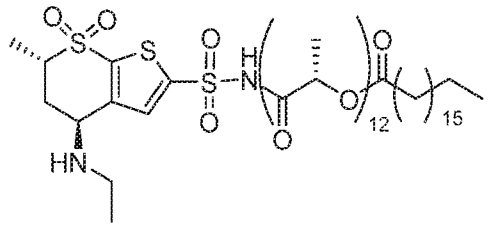
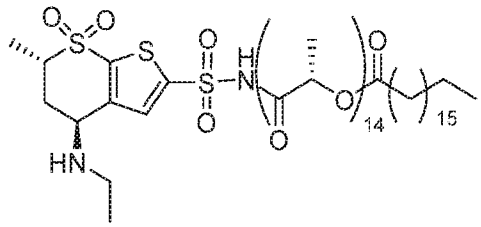
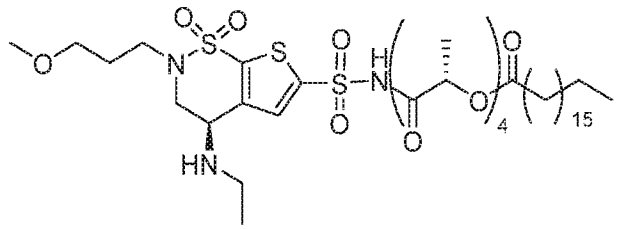
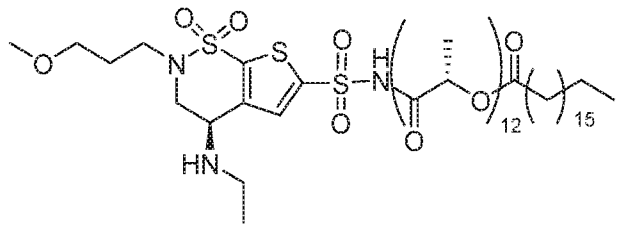
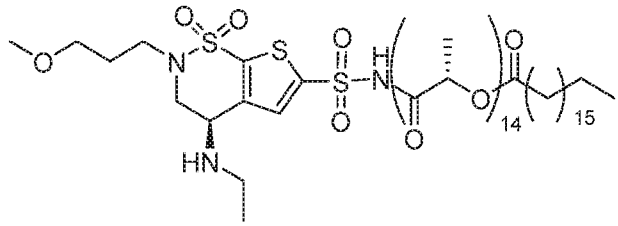
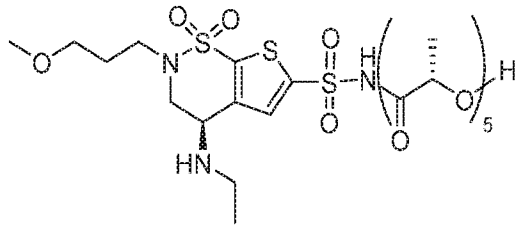


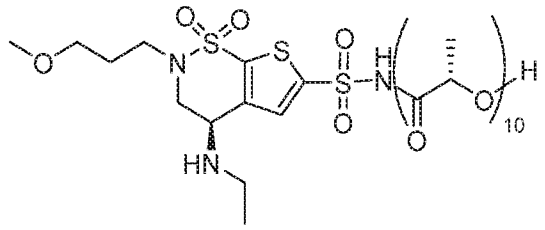
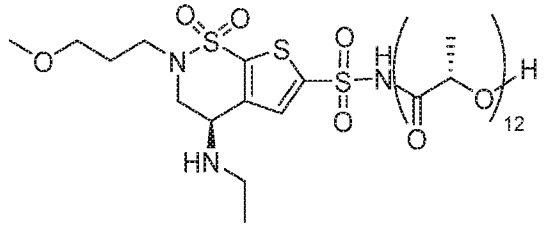
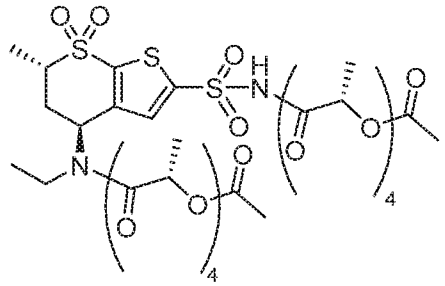
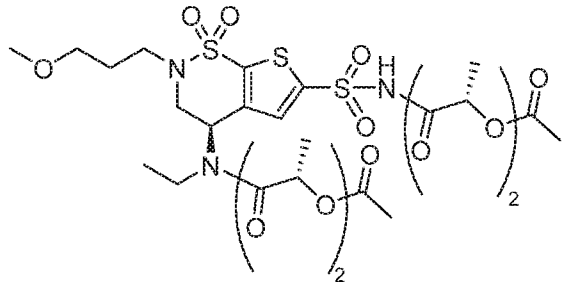
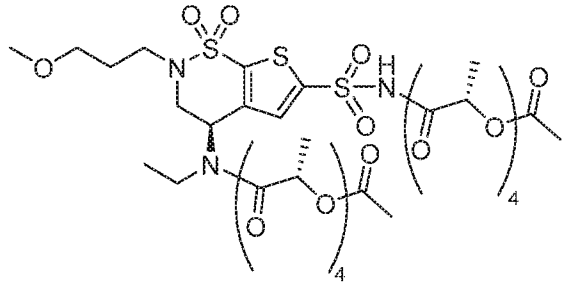
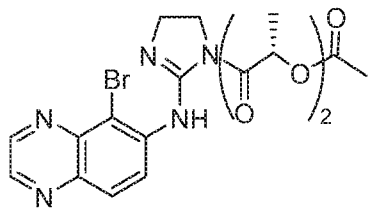
**Example 49. Non-limiting Examples of Compounds of the Present Invention**

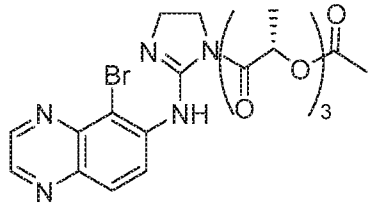
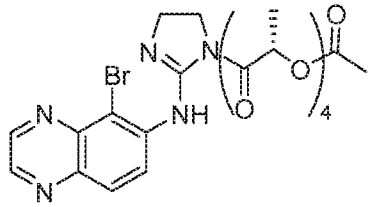
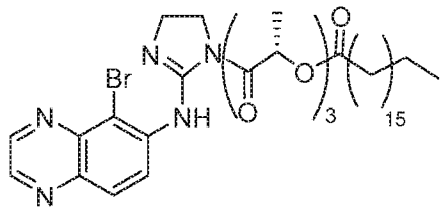
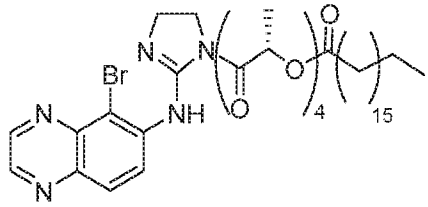
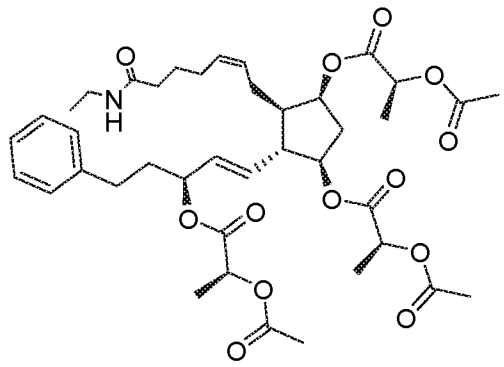
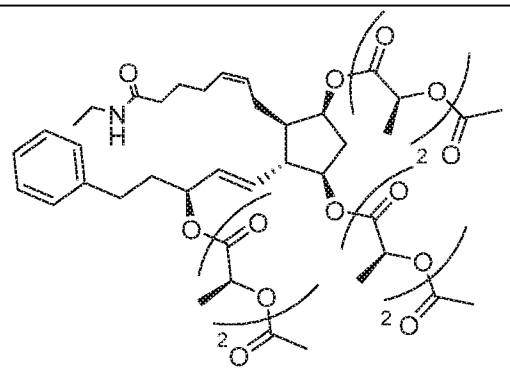
**Table 8A, Table 8B, Table 8C, Table 8D, Table 8E** present illustrative compounds of the present invention. **Table 8F** presents characterization data for select compounds of the present invention.

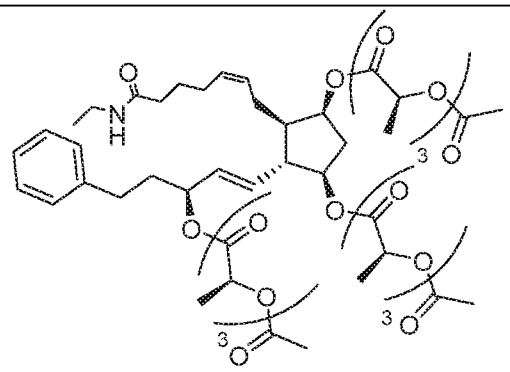
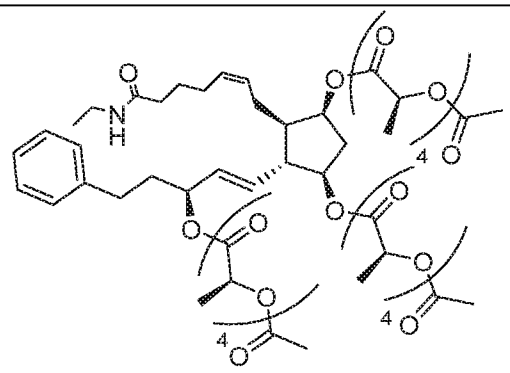
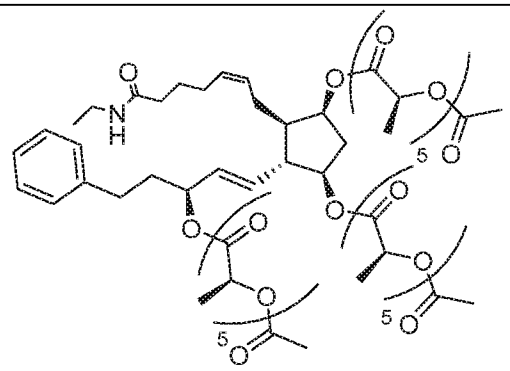
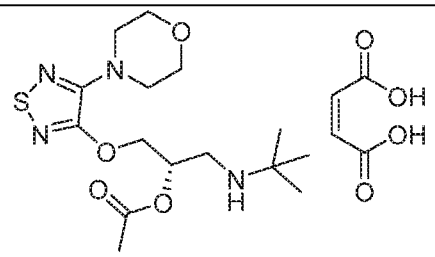
**Table 8A.** Non-limiting Examples of compounds of Formula II, VII, IX, XI, XIV, XV, and XVII

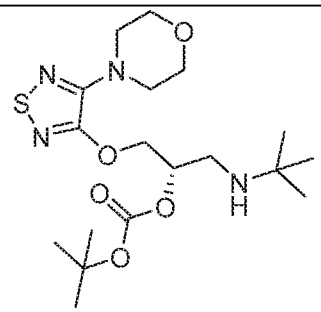
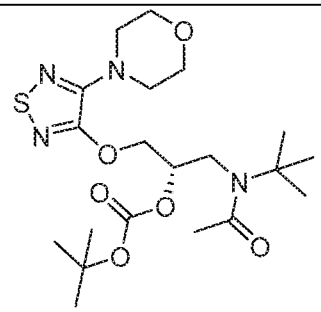
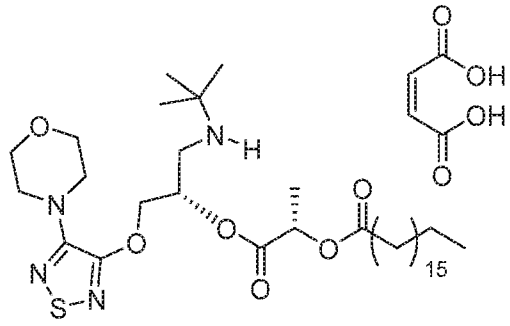
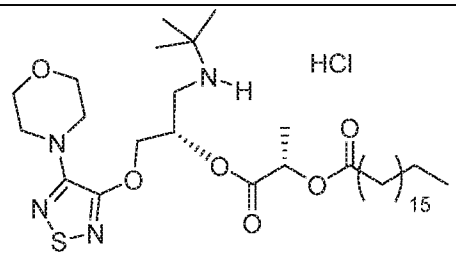
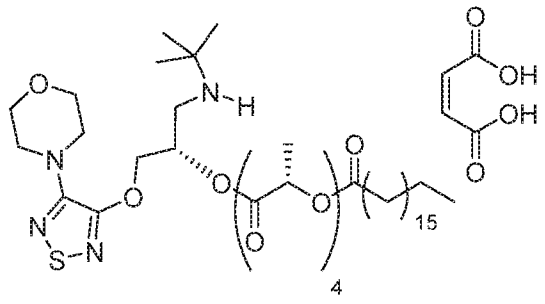
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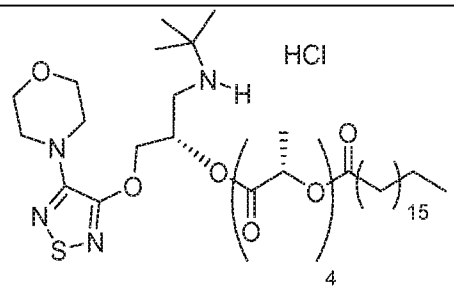
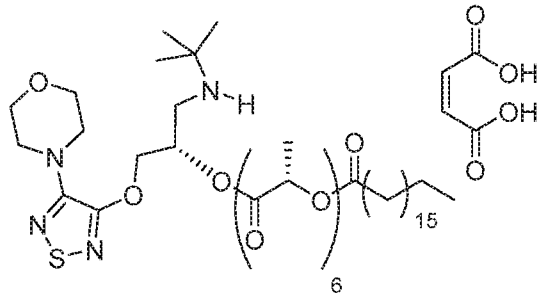
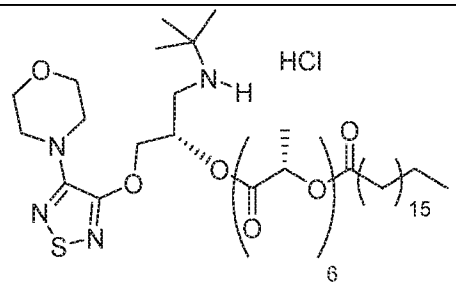
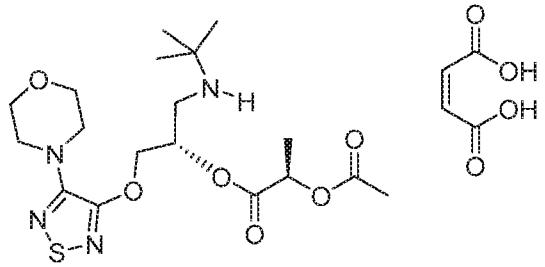
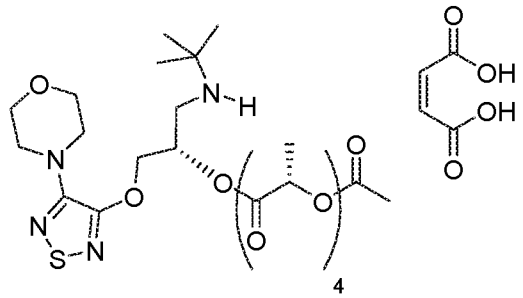
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| **15-2** |  |
| **16-1** |  |
| **17-1** |  |
| **18-3** |  |

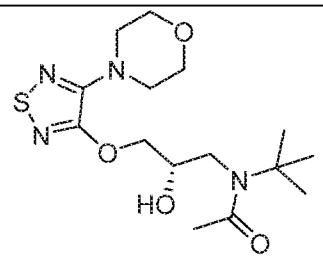
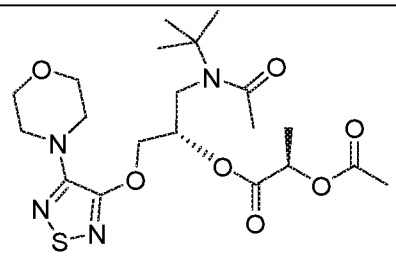
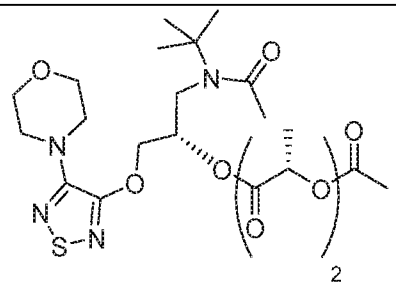
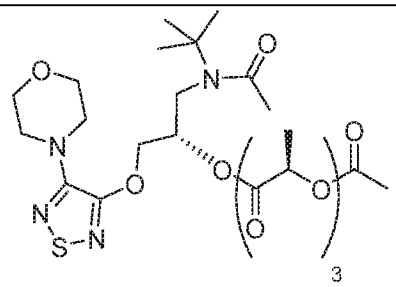
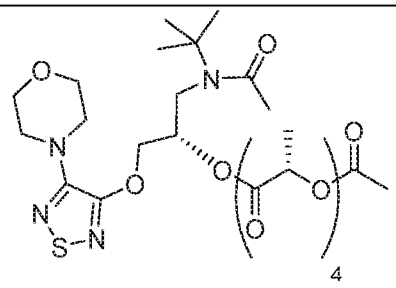
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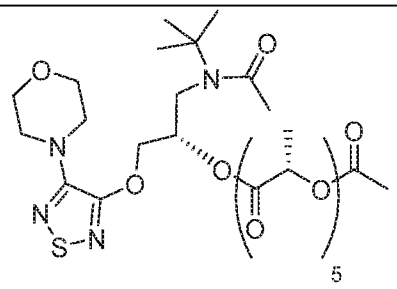
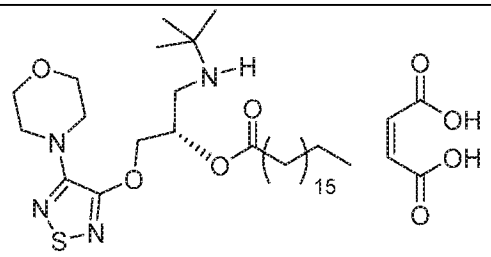
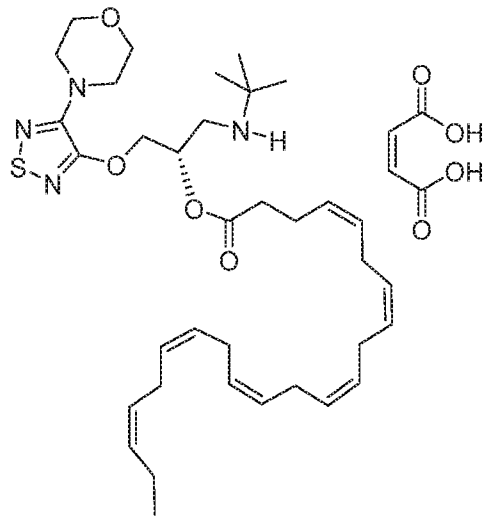
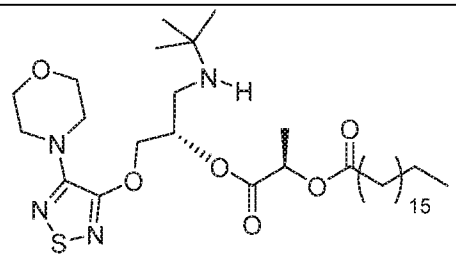
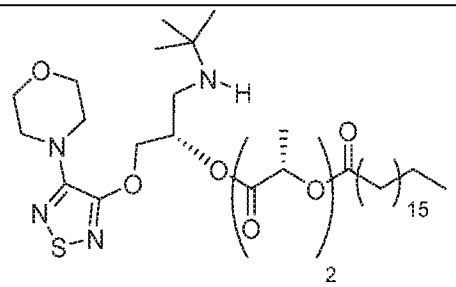
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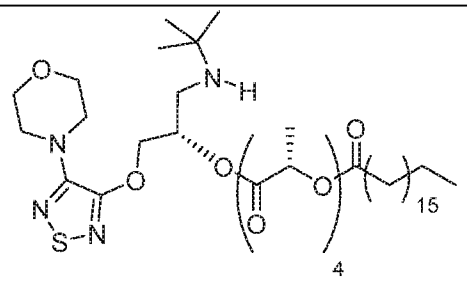
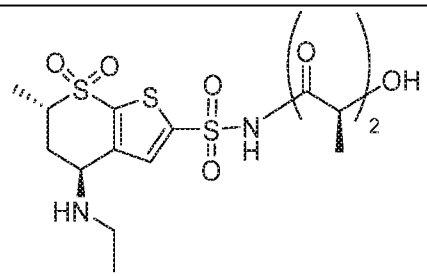
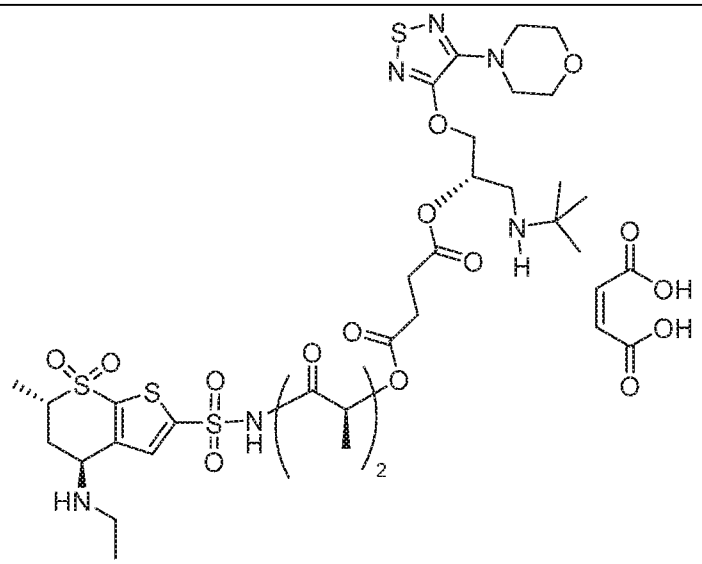
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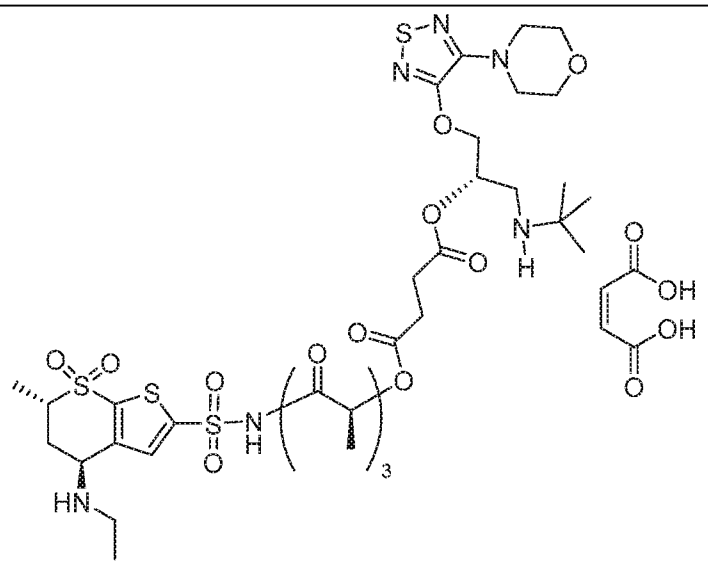
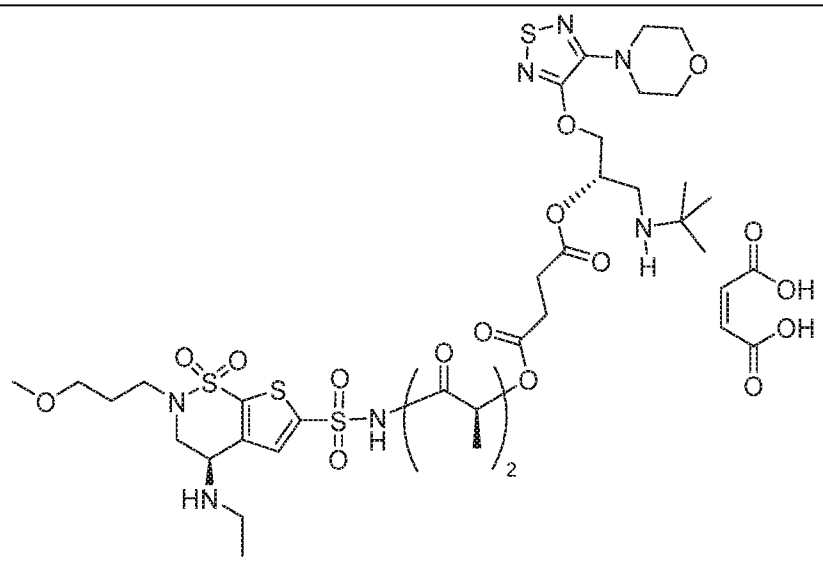
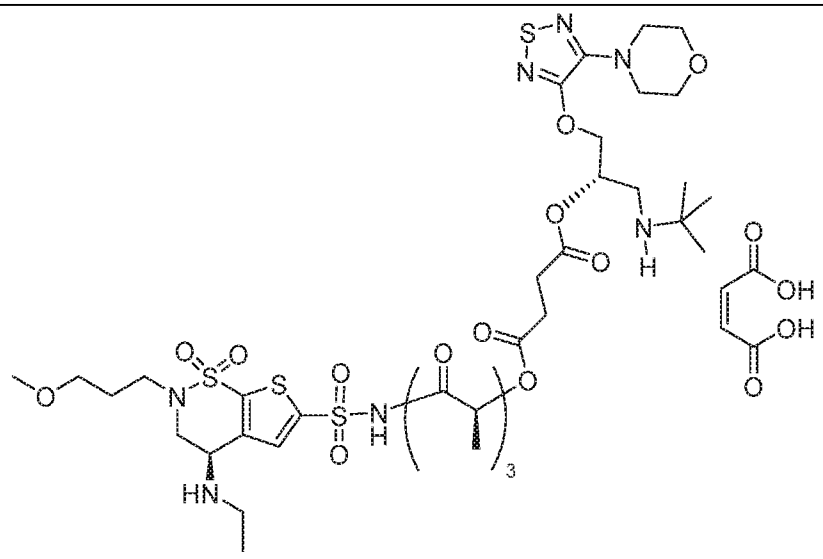
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| **40-2** |  |

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| **41-2** |  |
| **42-2** |  |
| **43-1** |  |
| **44-2** |  |
| **45-2** |  |

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|---|---|
| **46-4** |  |
| **47-1** |  |
| **48-1** |  |
| **49-1** |  |
| **50-1** |  |

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| **51-1** |  |
| **52-2** |  |
| **53-3** |  |
| **54-1** |  |
| **55-2** |  |

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|---|---|
| **56-1** |  |
| **56-2** |  |
| **57-4** |  |

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| **58-3** |  |
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| **60-3** |  |

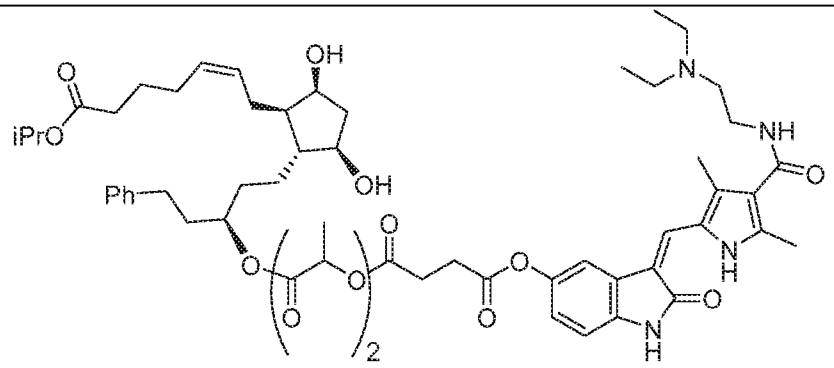
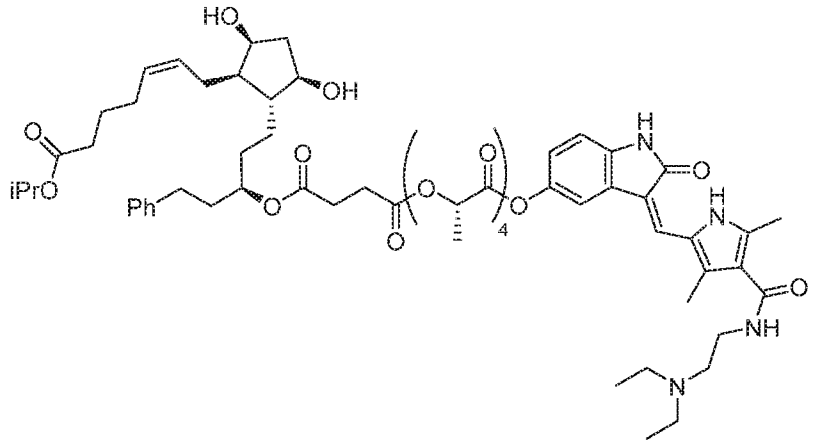
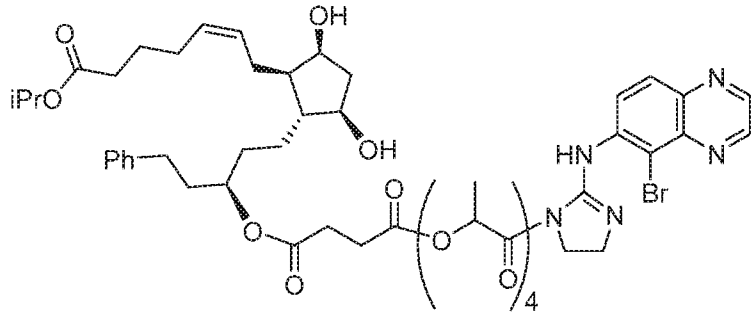
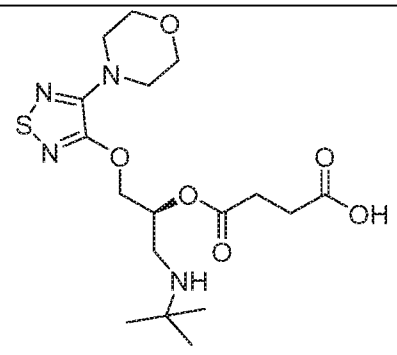
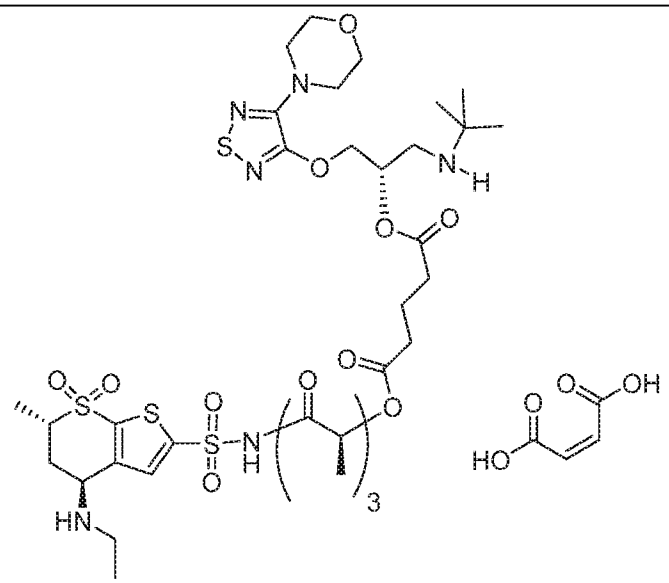
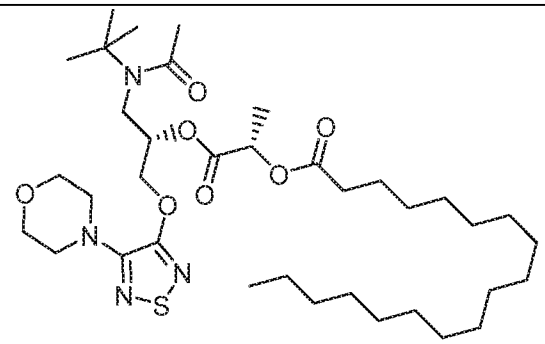
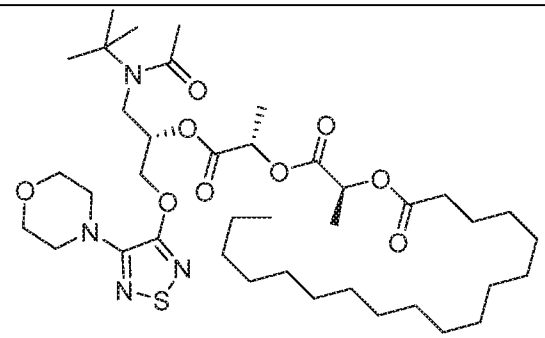
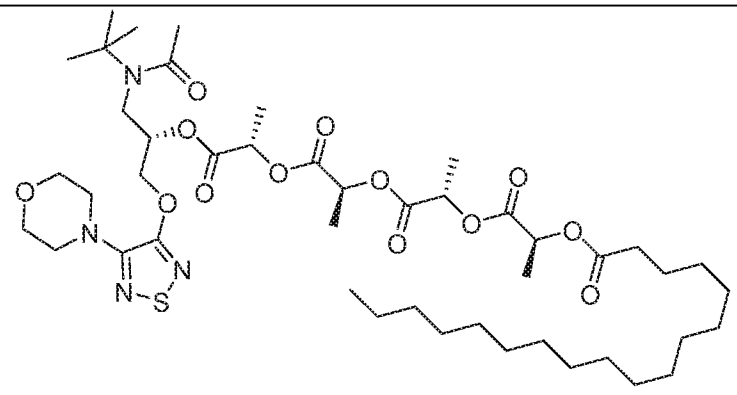
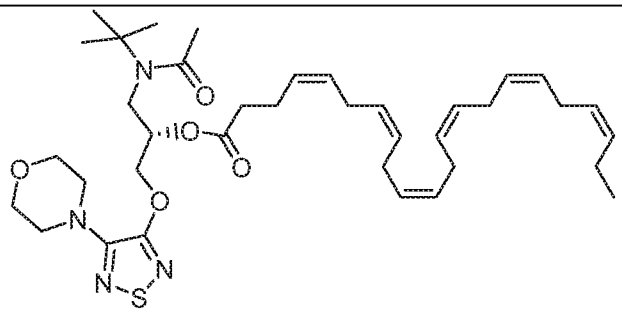
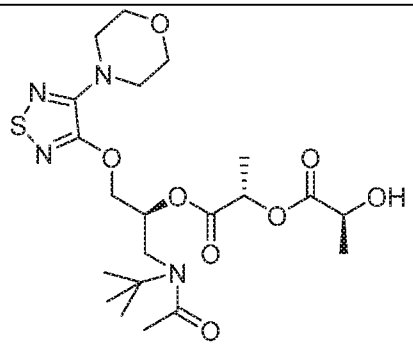
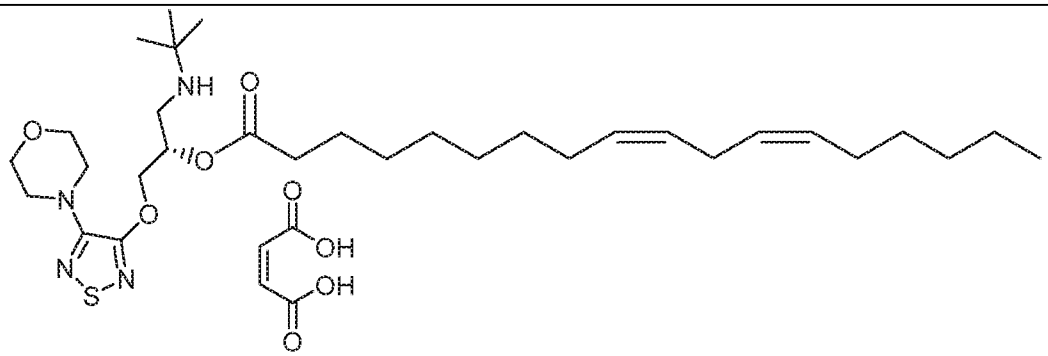
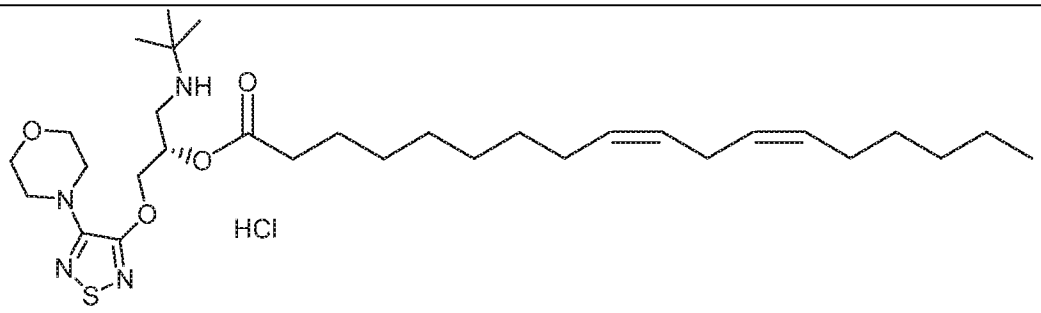
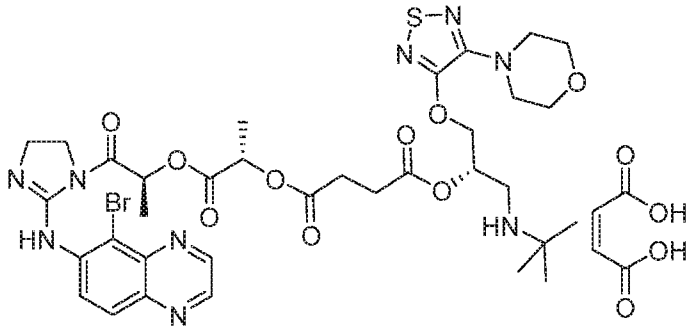
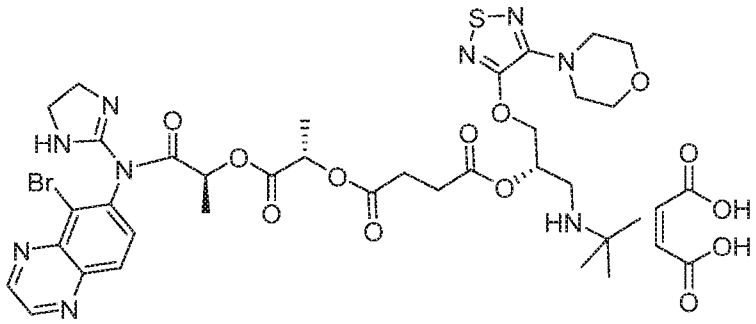
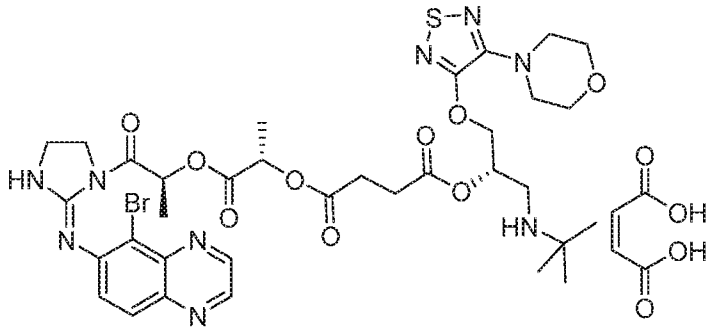
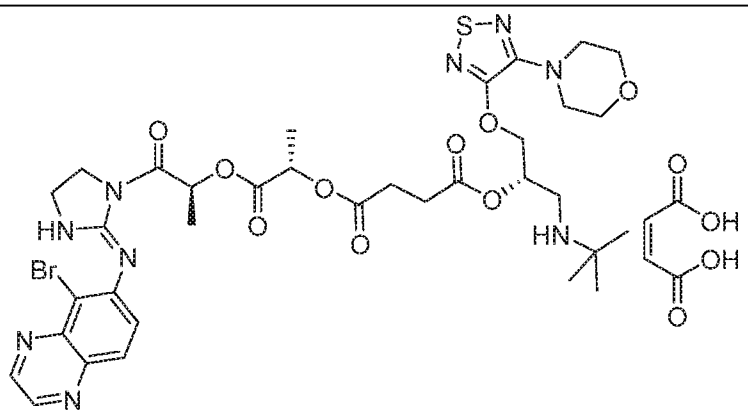
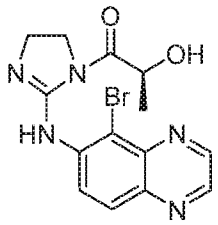
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| **63-1** |  |

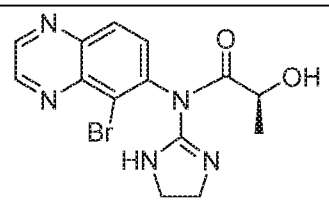
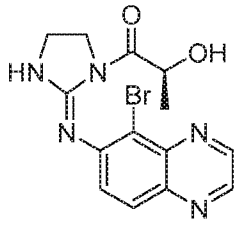
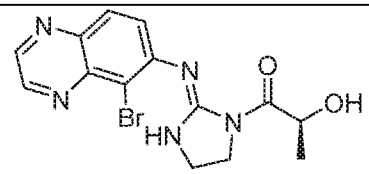
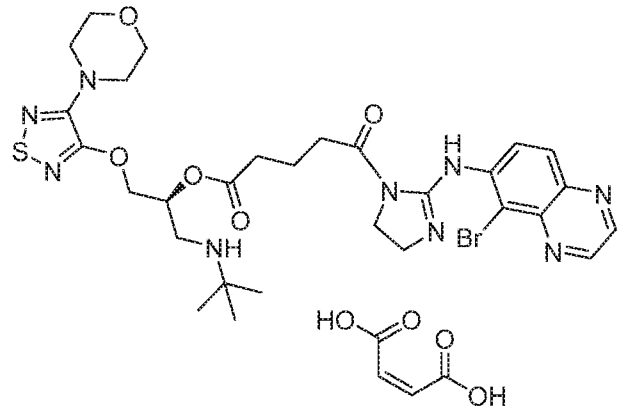
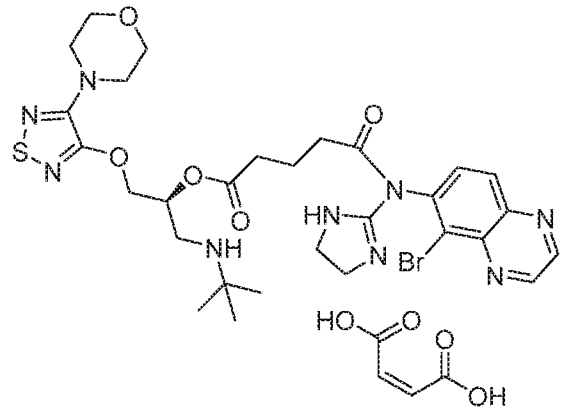
**Table 8B.** Additional Non-limiting Examples of compounds of the Present Invention

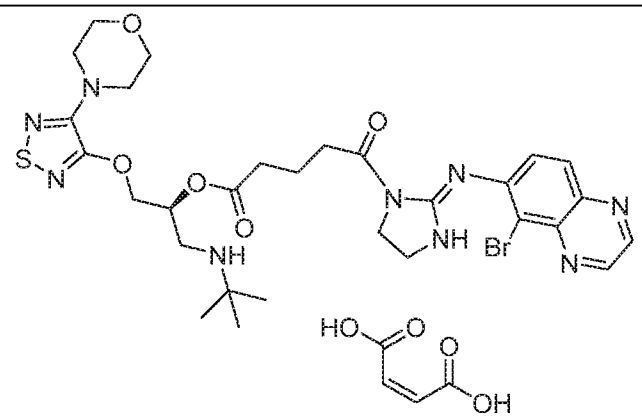
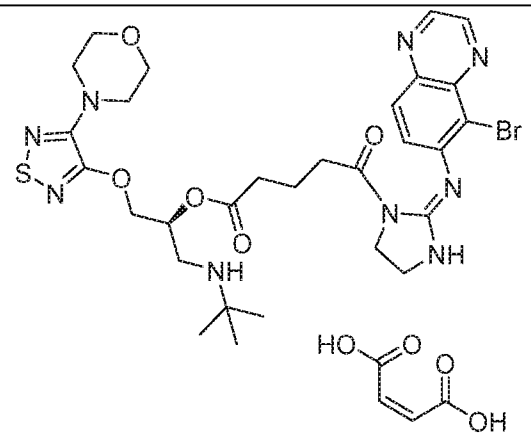
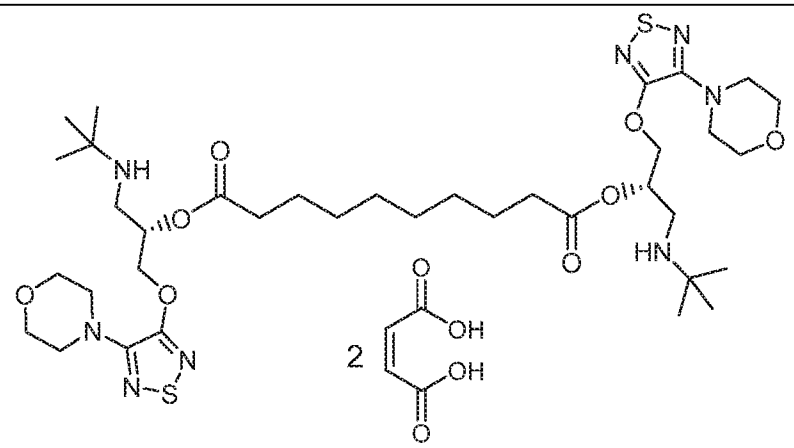
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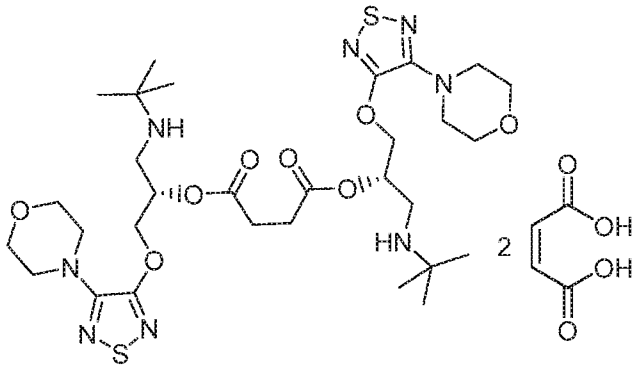
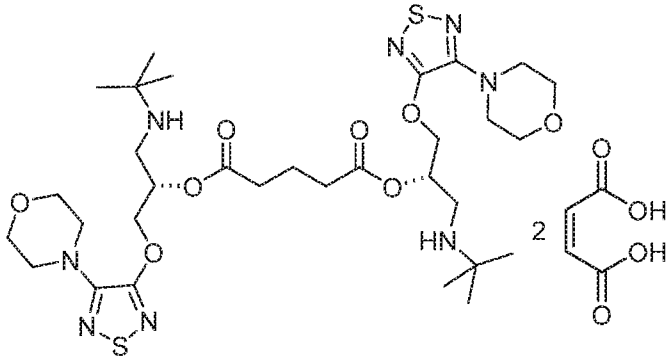
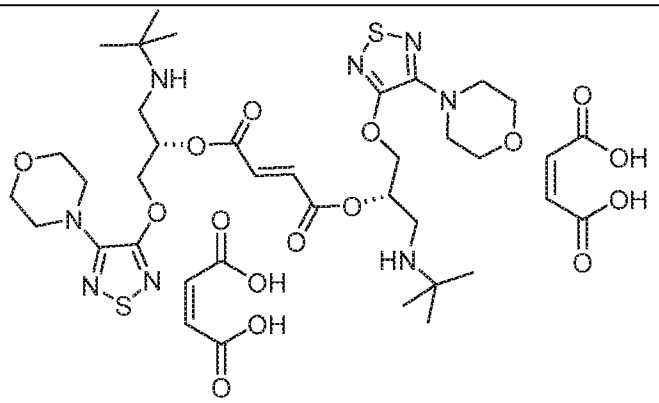
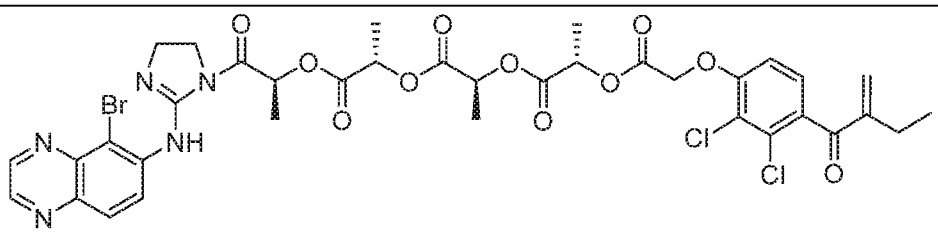
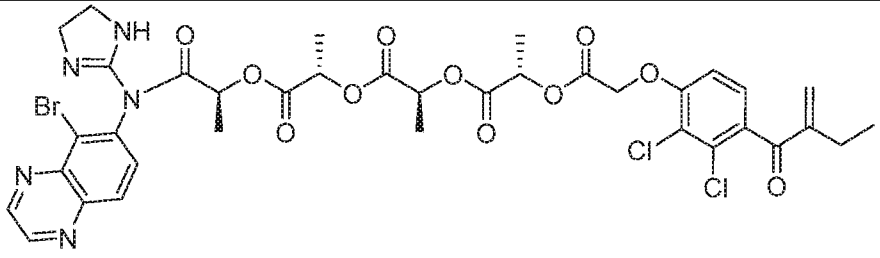
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| **64-4** |  |
| **65-1** |  |
| **66-1** |  |
| **67-1** |  |

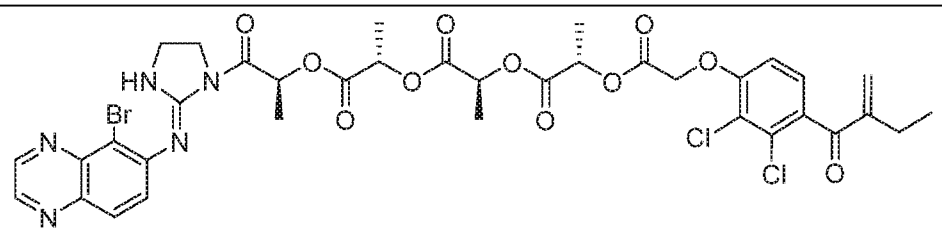
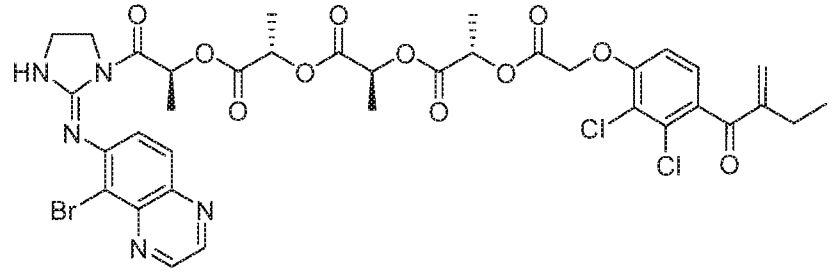
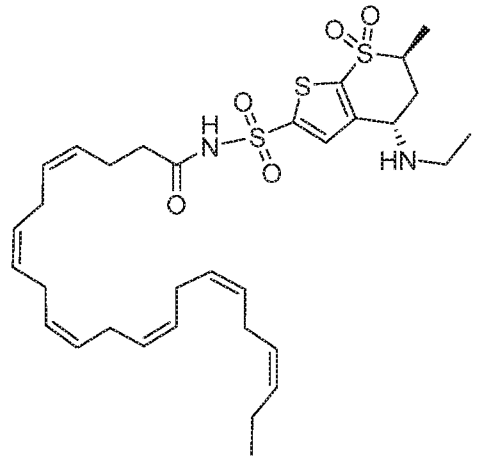
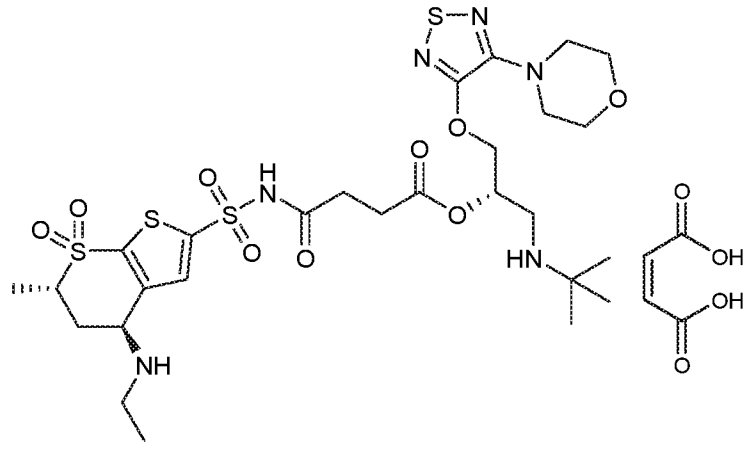
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| **68-1** |  |
| **69-1** |  |
| **70-1** |  |
| **71-1** |  |

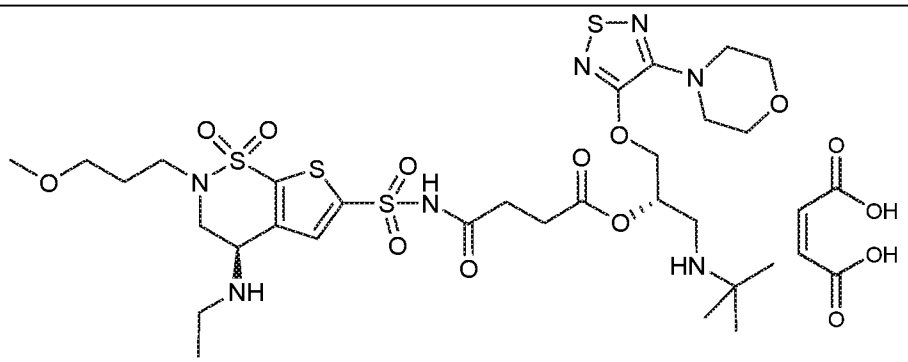
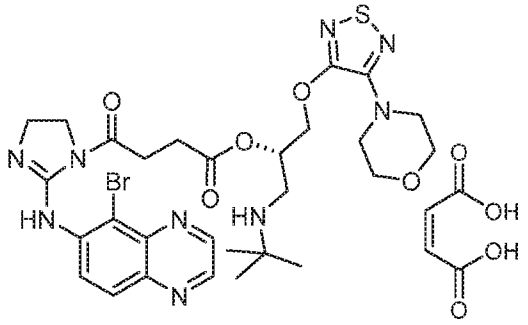
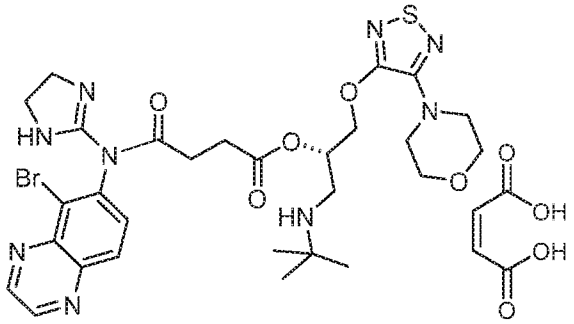
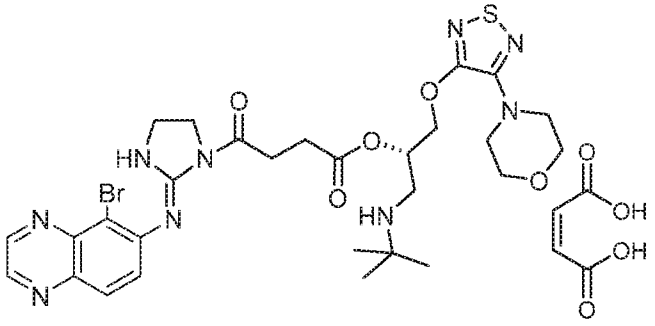
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| **72-4a** |  |
| **72-4b** |  |
| **72-4c** |  |
| **73-1** |  |

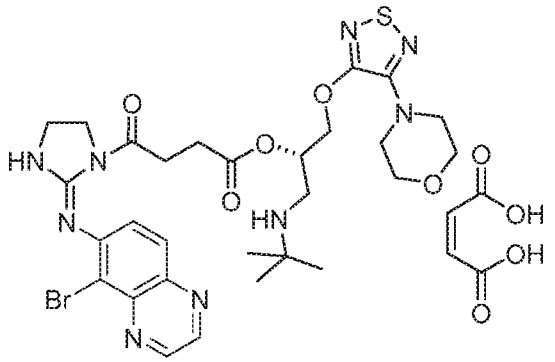
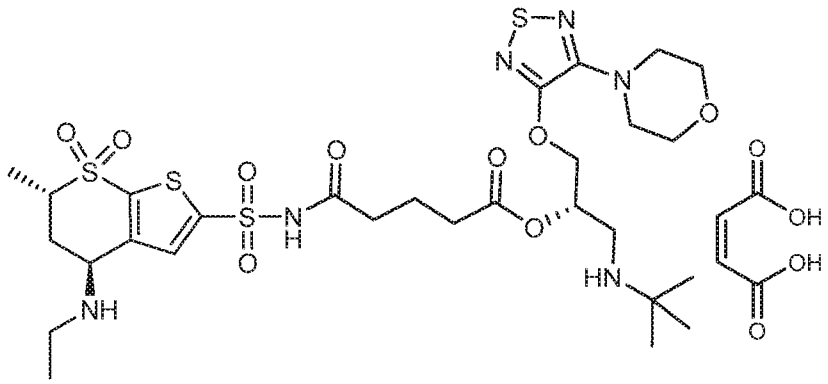
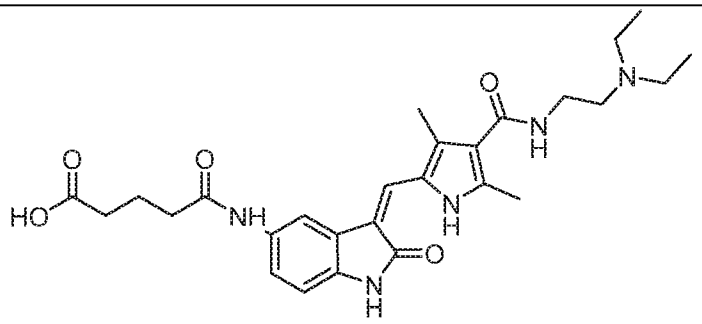
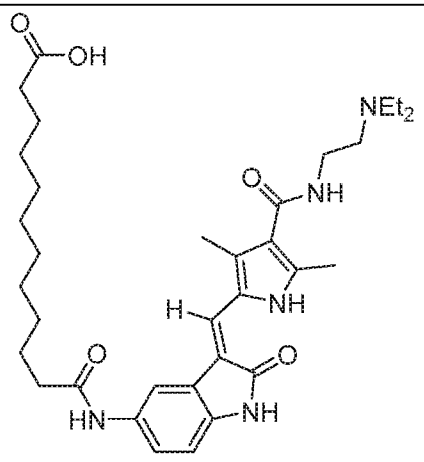
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| **73-1a** |  |
| **73-1b** |  |
| **73-1c** |  |
| **74-1** |  |
| **74-1a** |  |

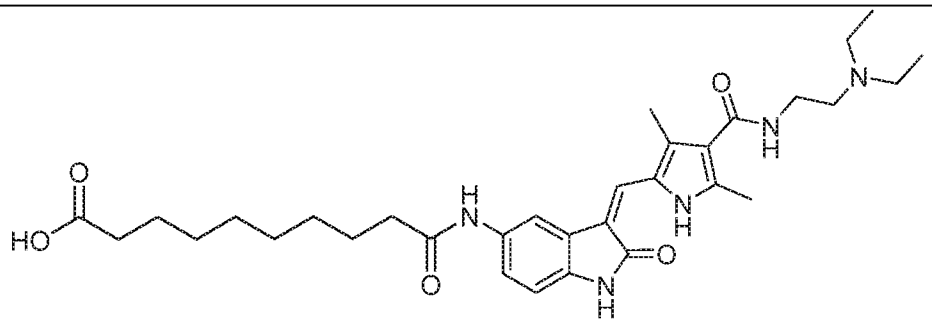
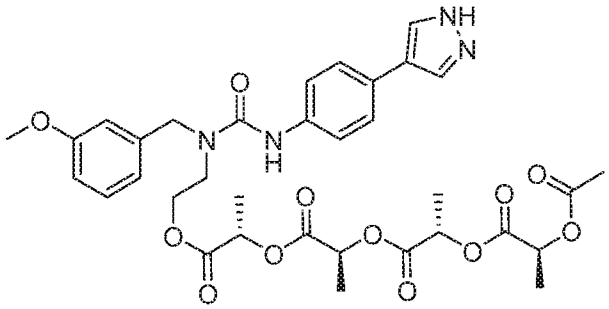
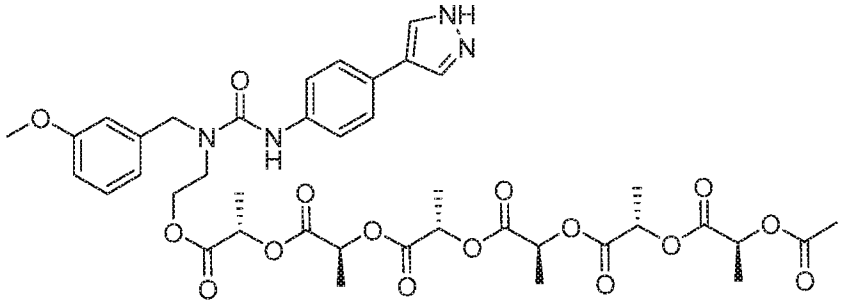
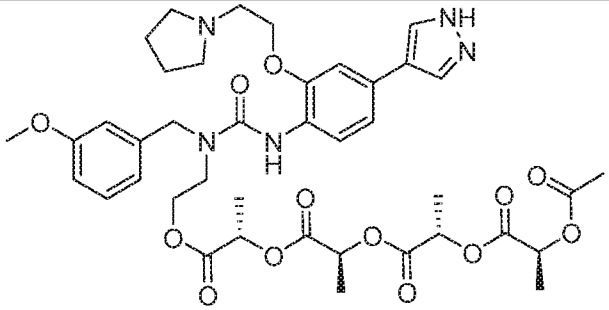
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| **74-1c** |  |
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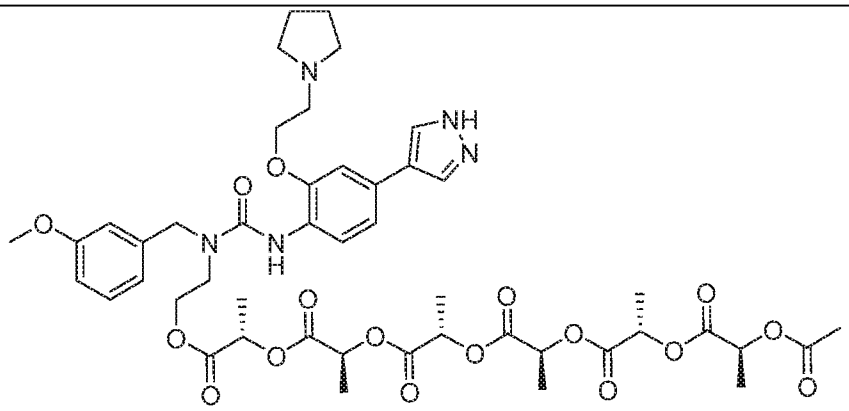
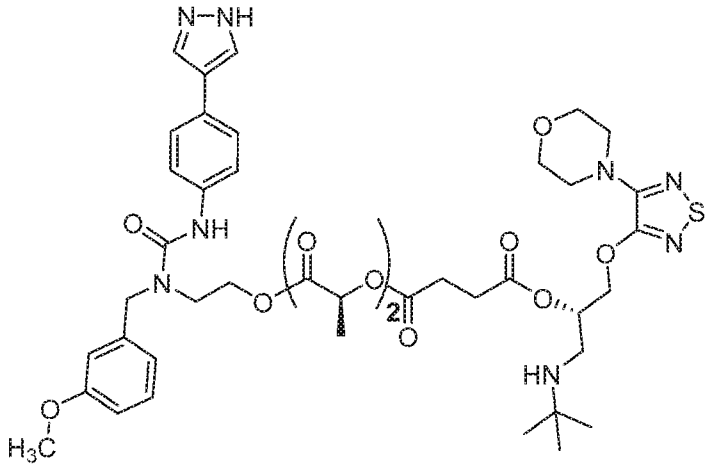
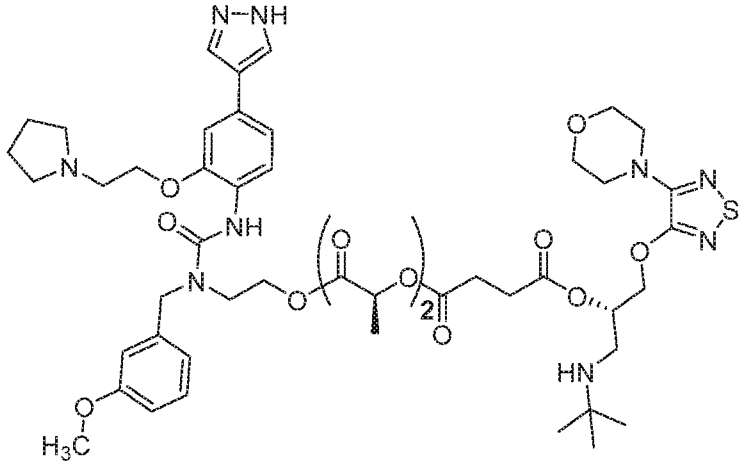
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| **77-1** |  |
| **78-1** |  |
| **79-3** |  |
| **79-3a** |  |

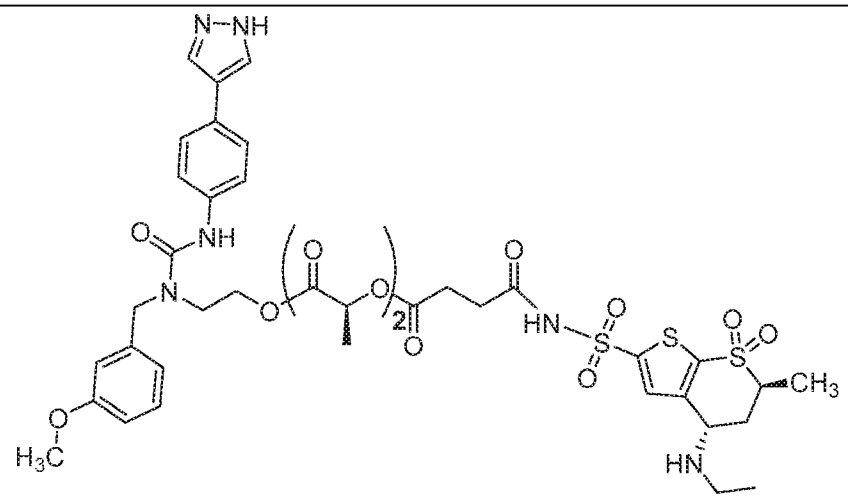
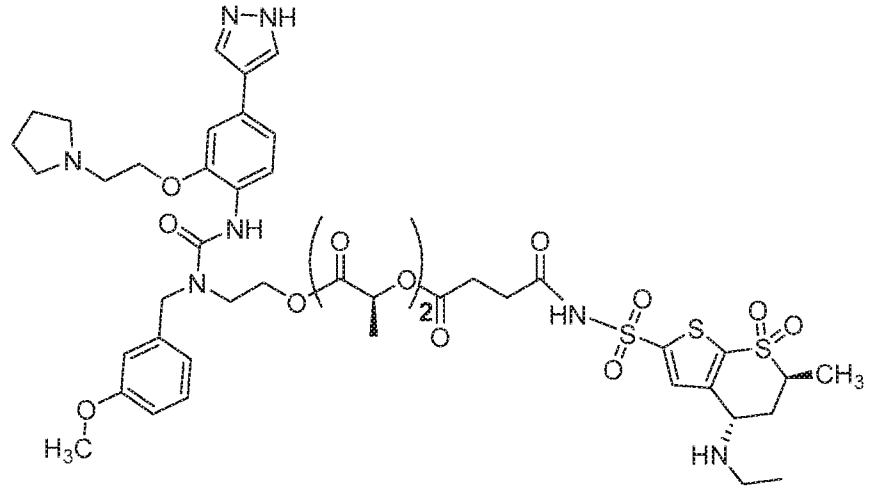
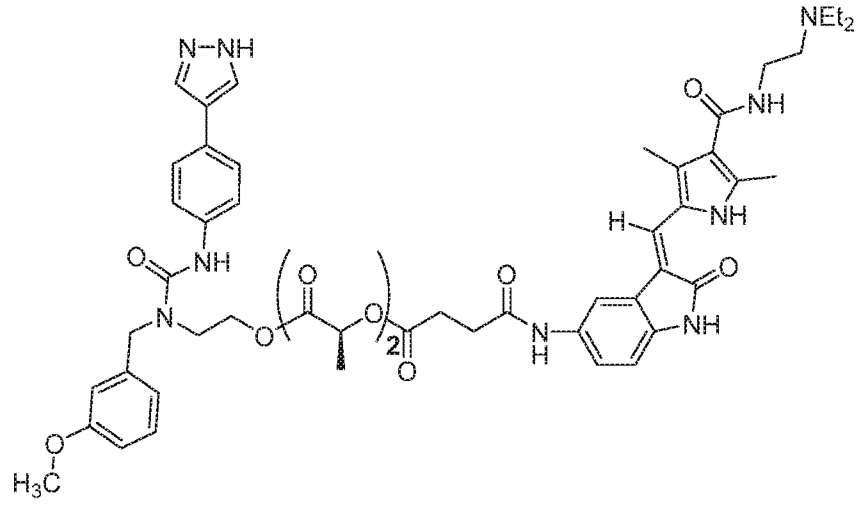
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| **79-3c** |  |
| **80-3** |  |
| **81-1** |  |

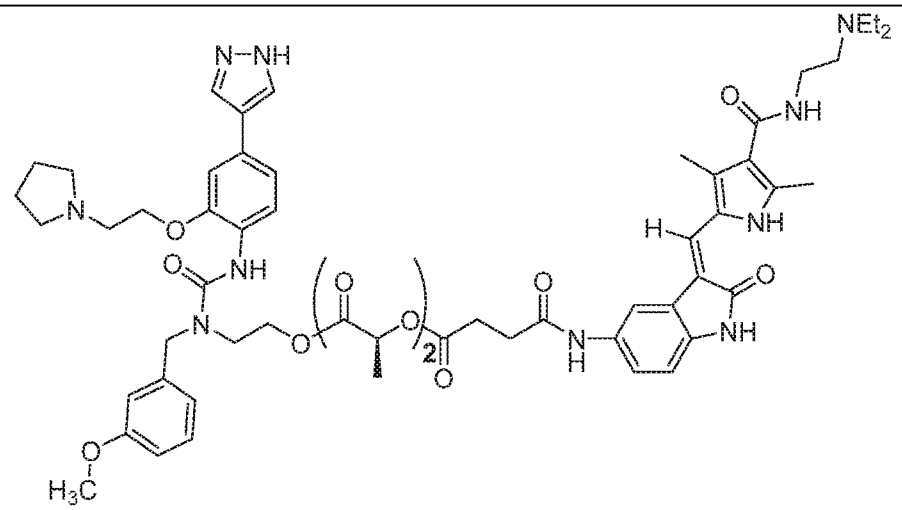
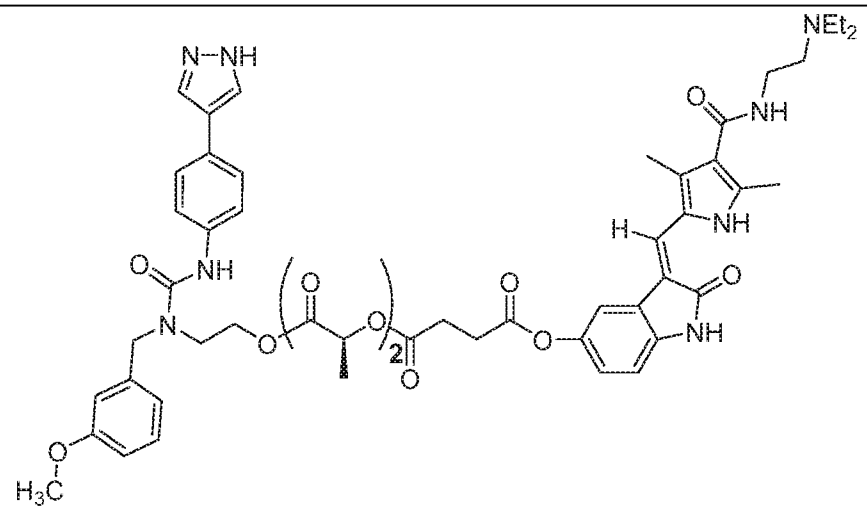
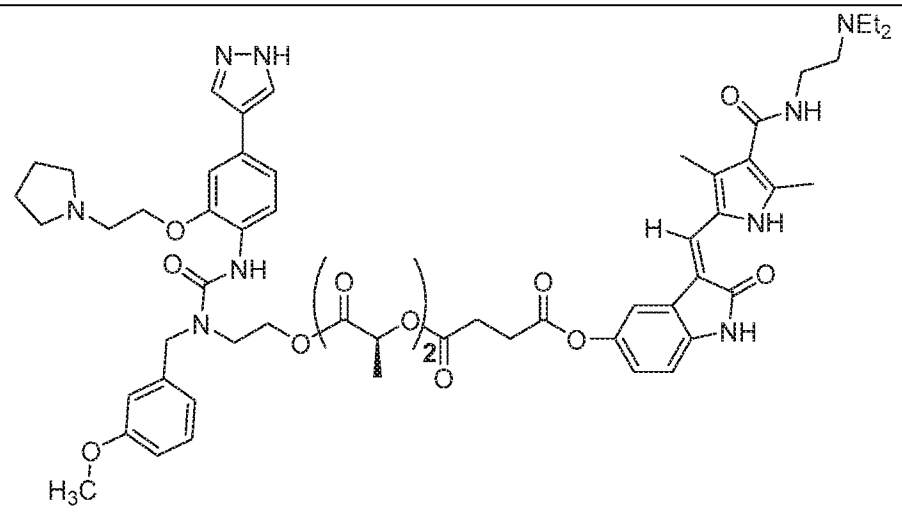
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| **83-4** |  |
| **83-4a** |  |
| **83-4b** |  |

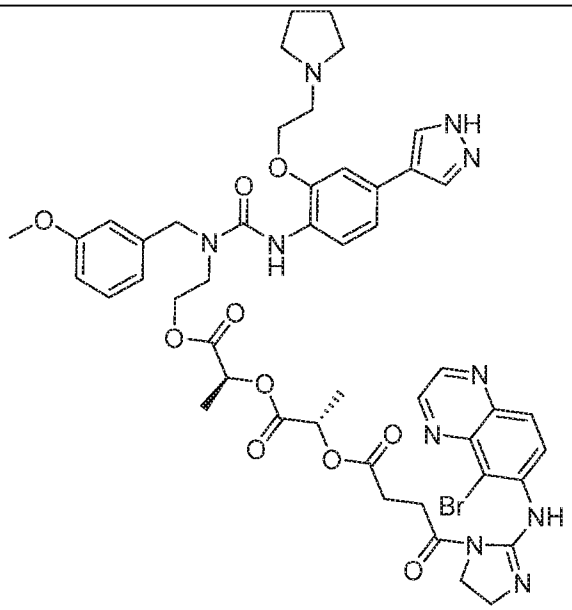
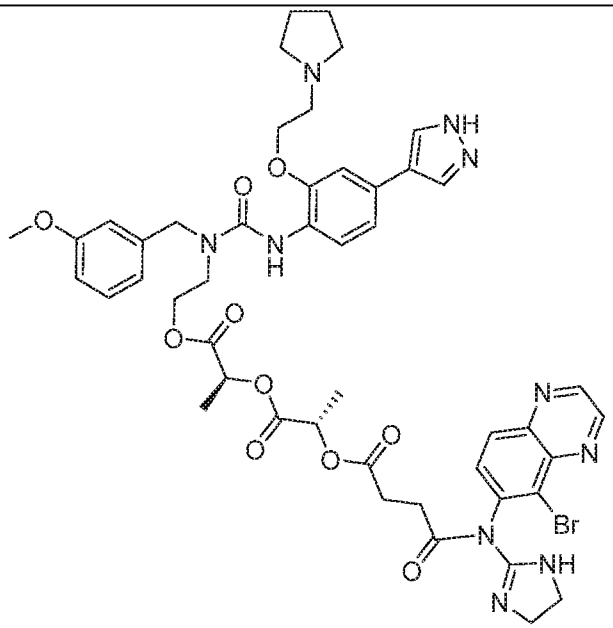
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| **84-1** |  |
| **85-1** |  |
| **86-1** |  |

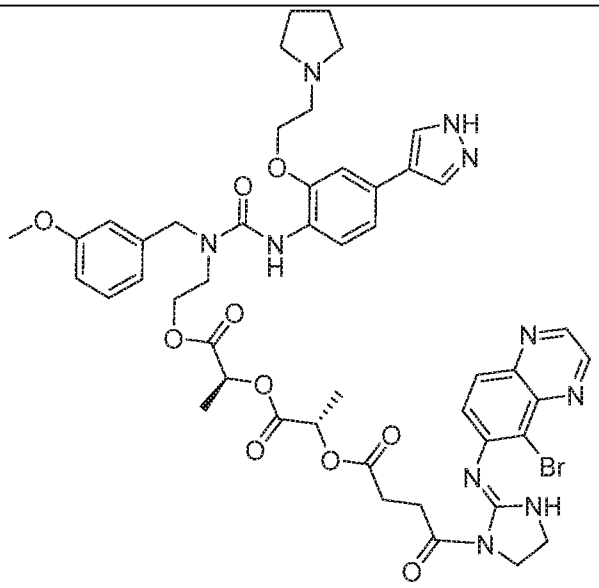
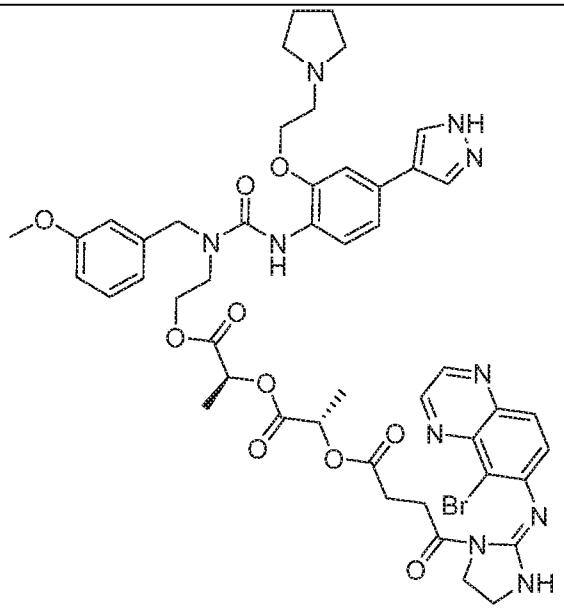
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| **88-3** |  |
| **89-3** |  |
| **90-1** |  |

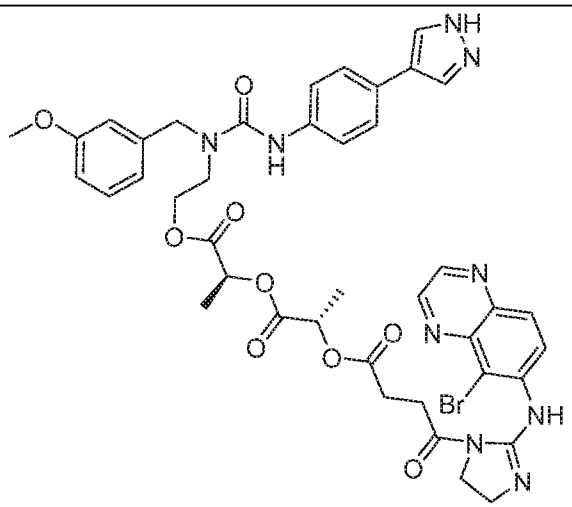
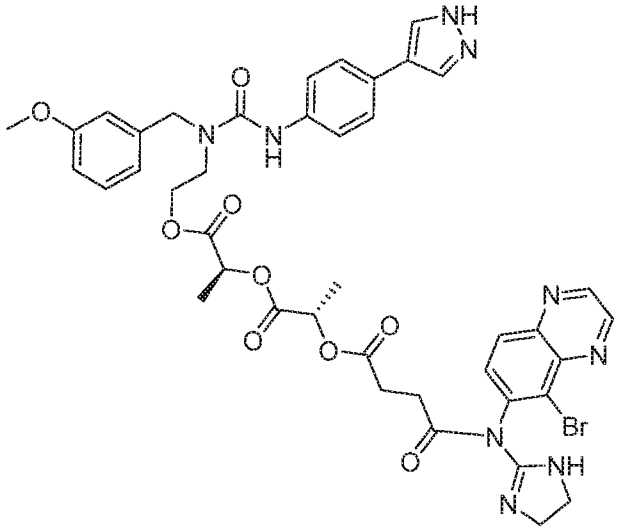
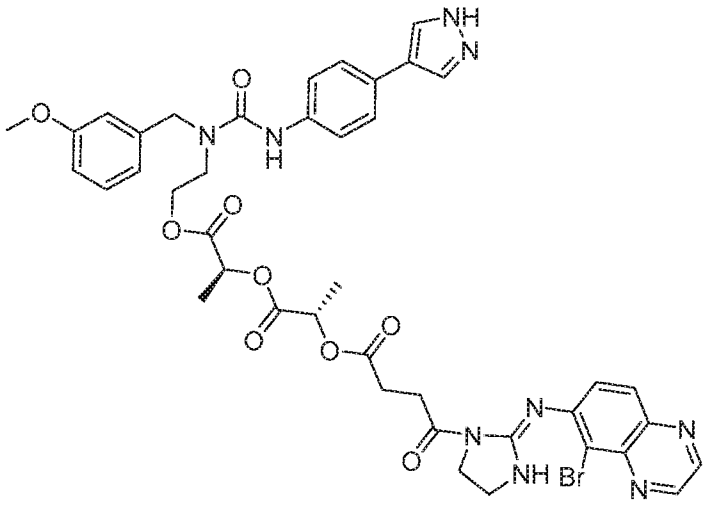
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| **91-2** |  |
| **92-1** |  |
| **93-1** |  |

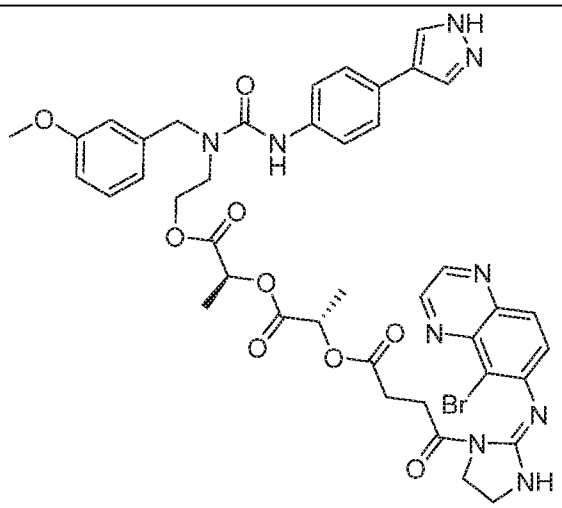
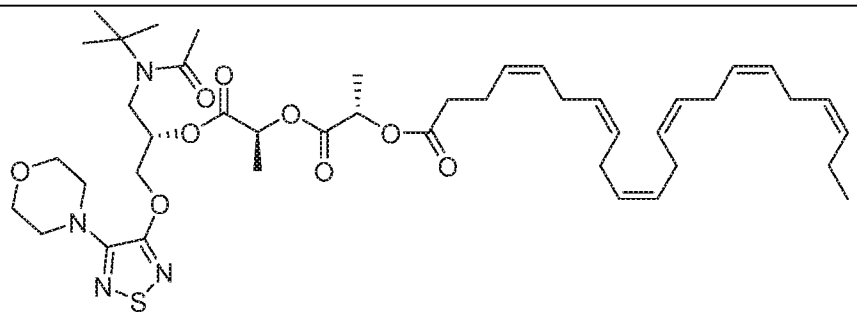
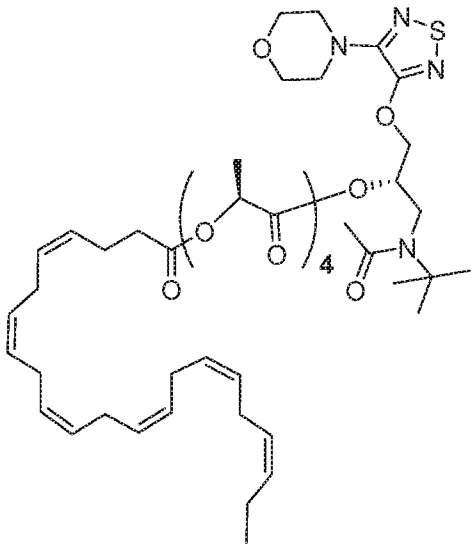
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| **96-1** |  |

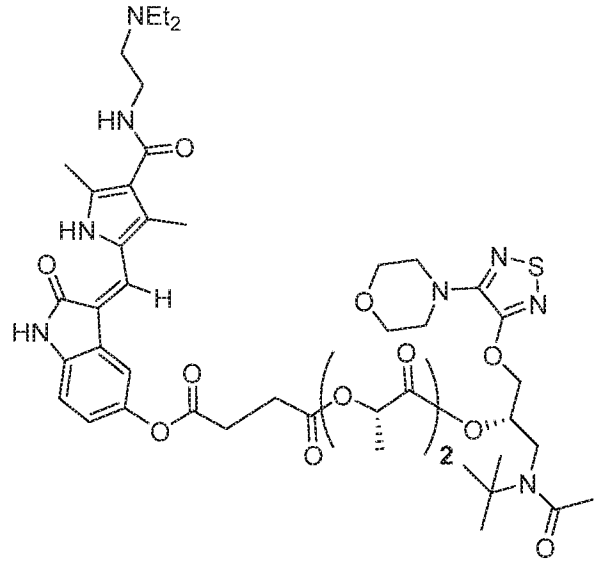
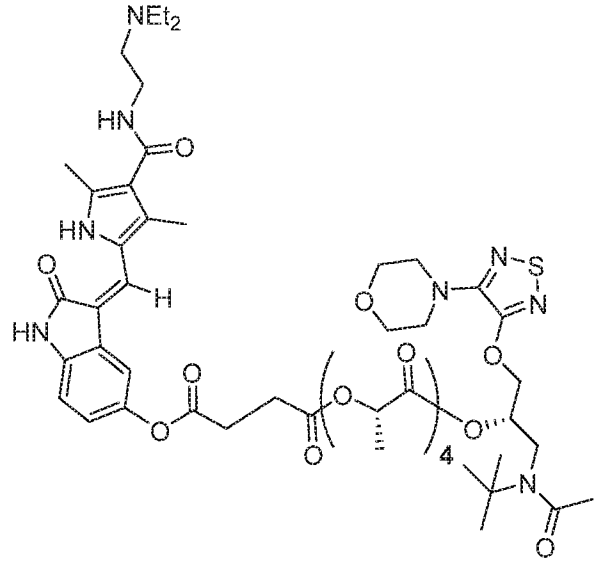
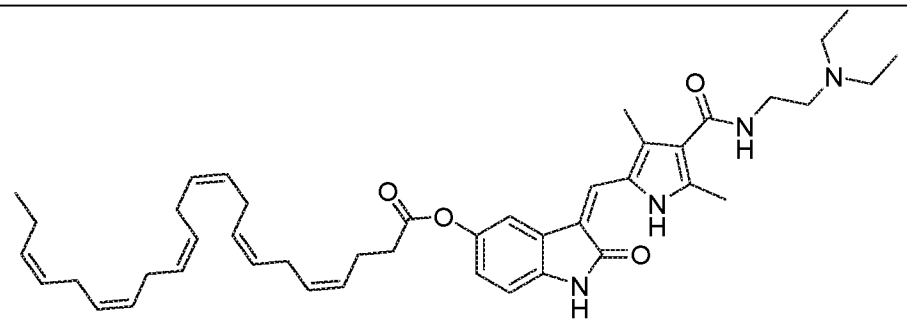
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| **98-1** |  |
| **99-1** |  |

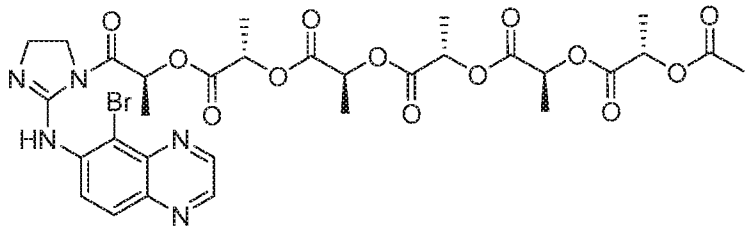
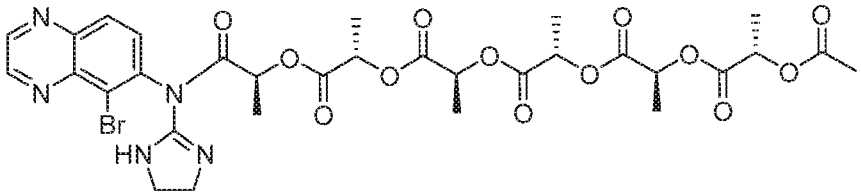
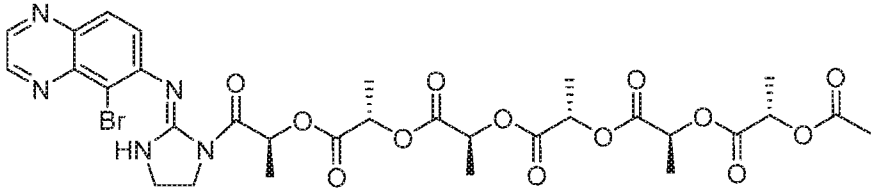
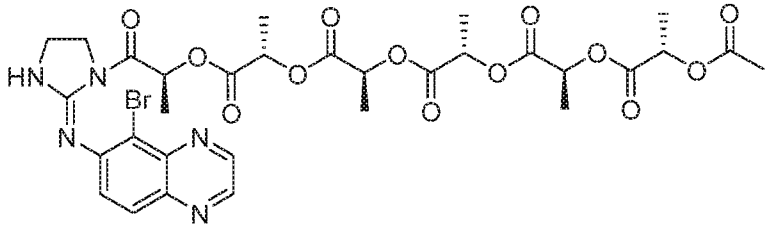
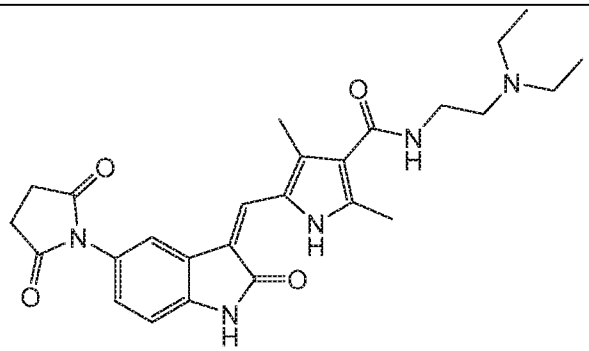
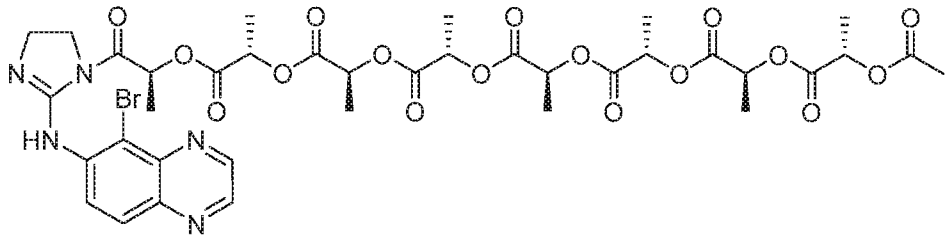
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| **100-1** |  |
| **100-1a** |  |

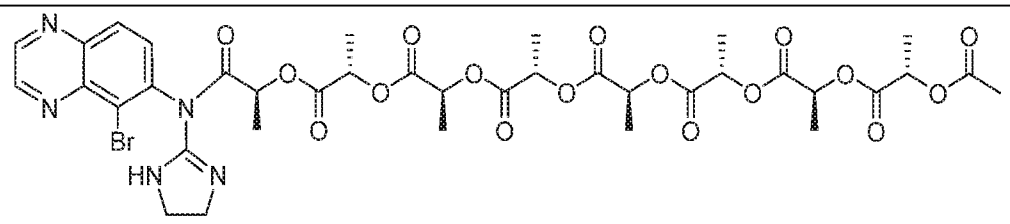
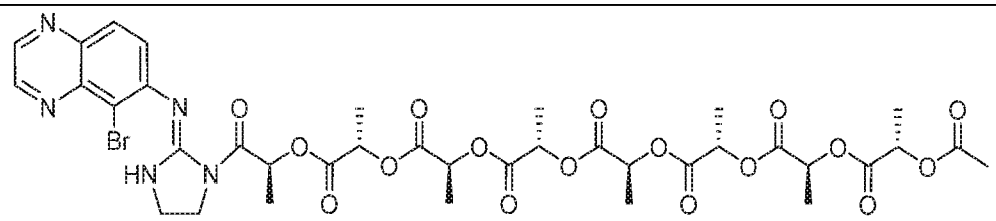
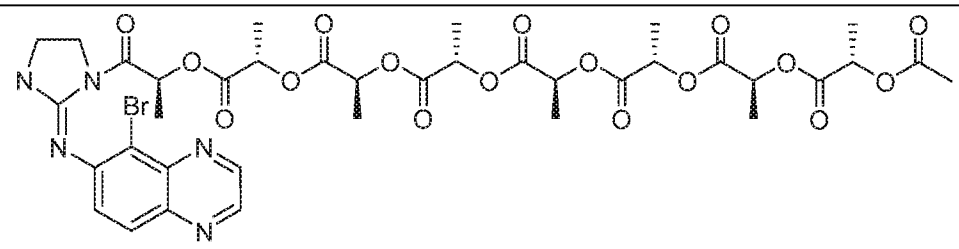
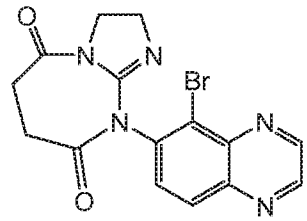
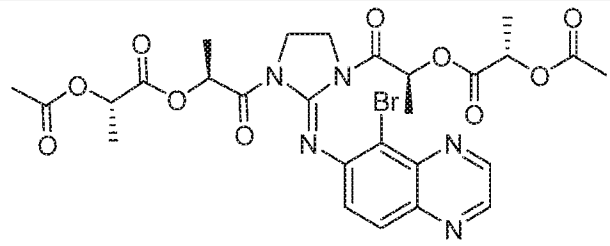
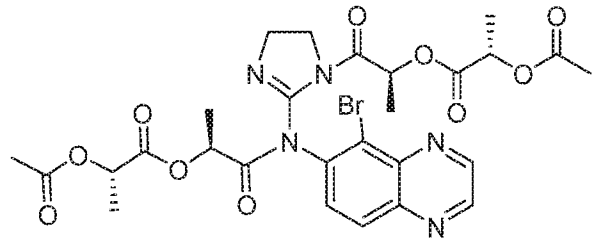
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| **100-1b** |  |
| **100-1c** |  |

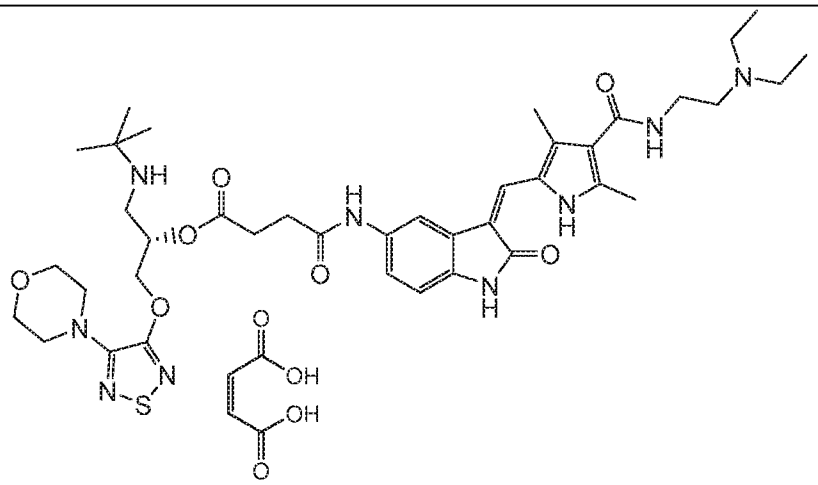
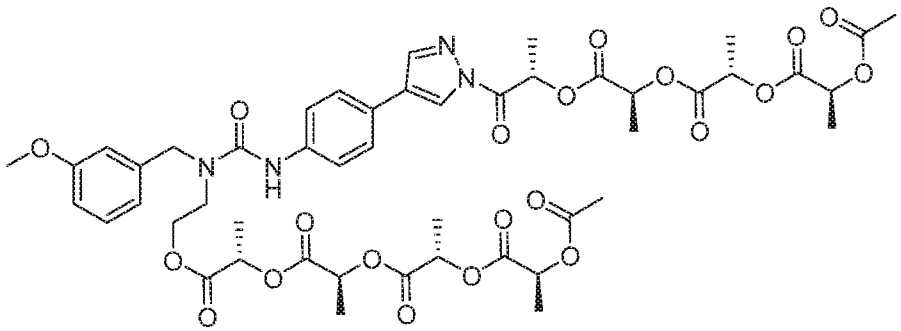
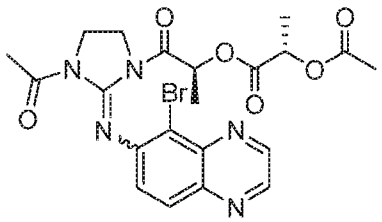
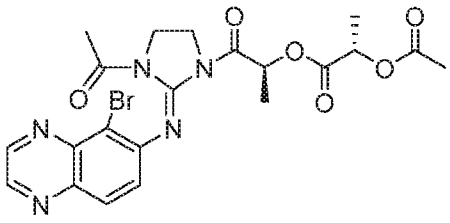
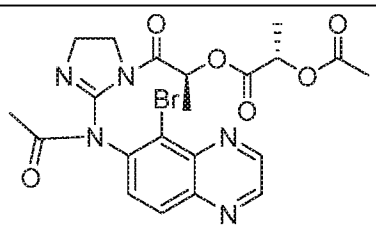
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| **101-3a** |  |
| **101-3b** |  |

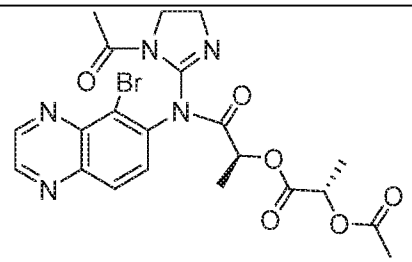
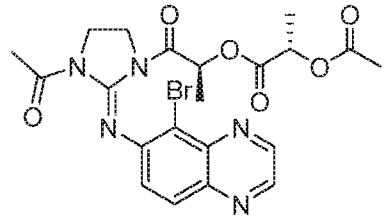
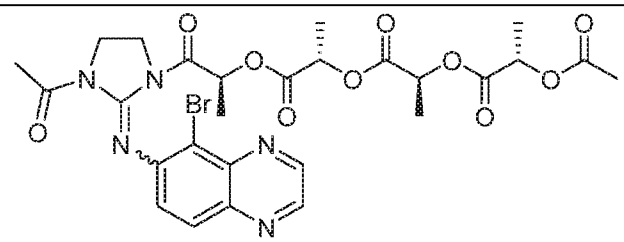
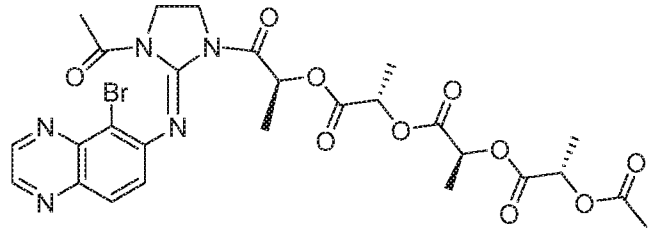
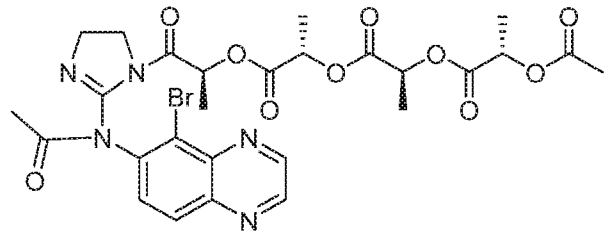
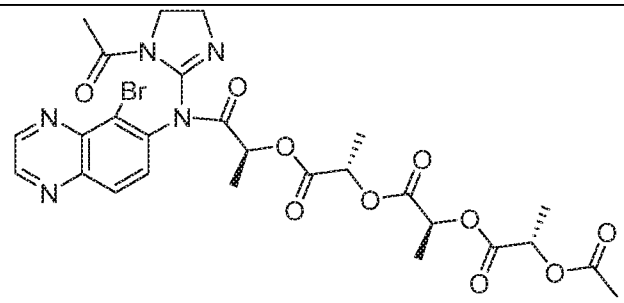
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| **101-3c** |  |
| **102-1** |  |
| **103-1** |  |

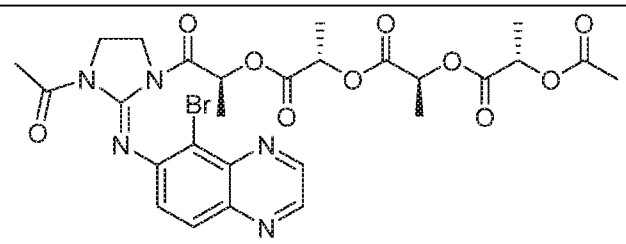
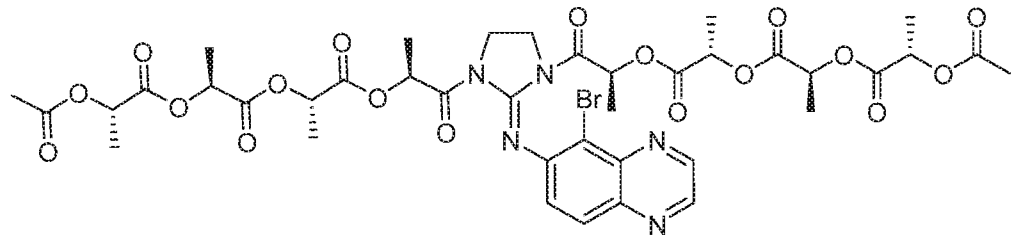
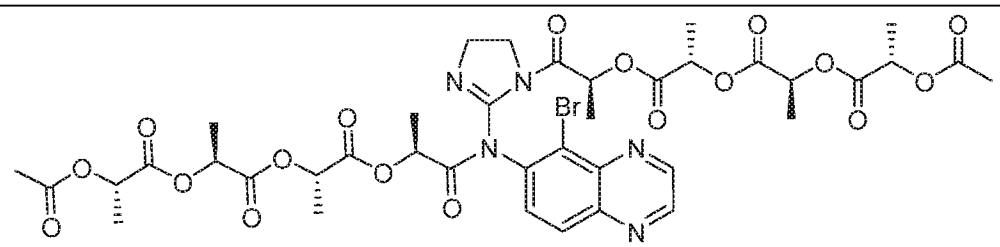
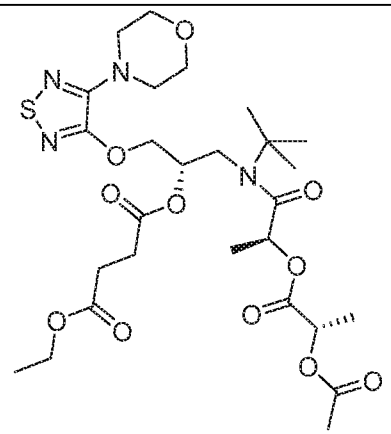
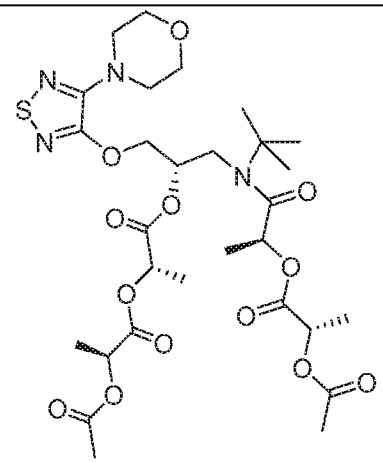
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| **104-1** |  |
| **105-1** |  |
| **106-1** |  |

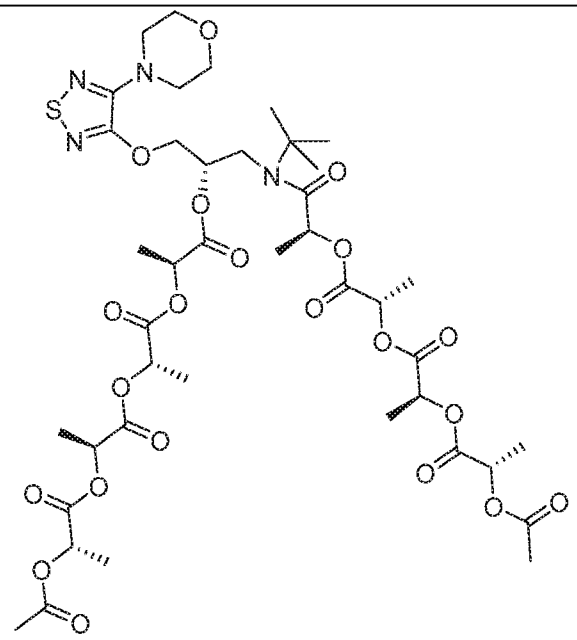
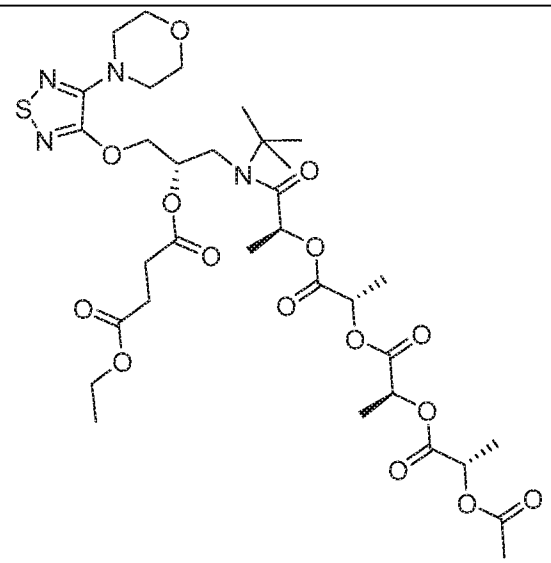
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| **108-3** |  |
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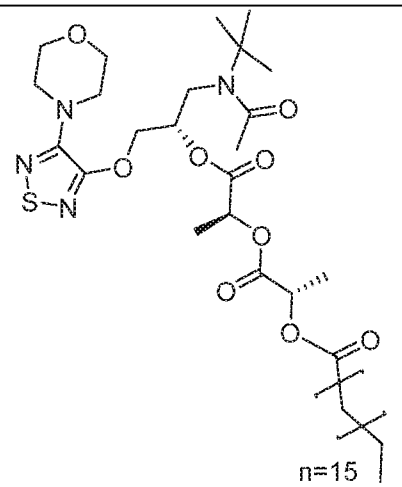
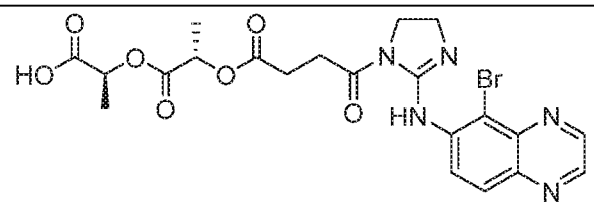
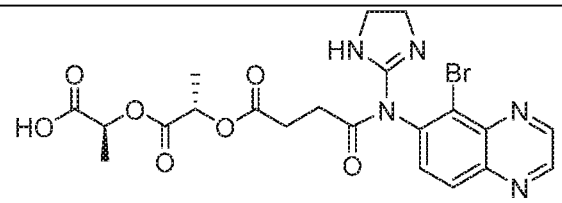
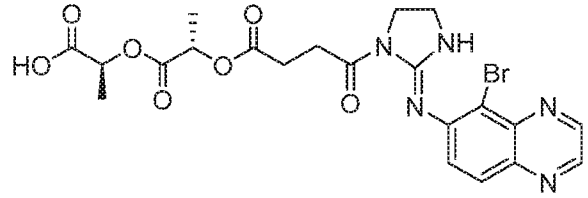
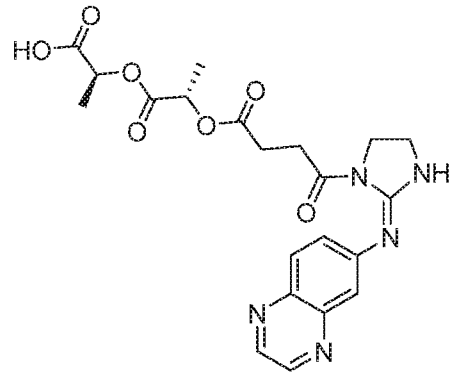
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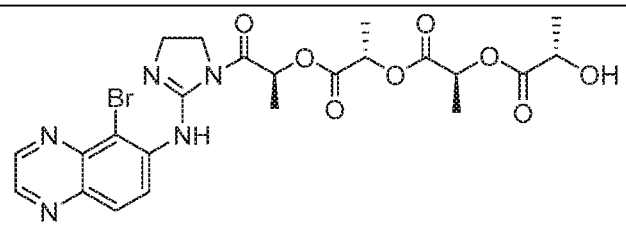
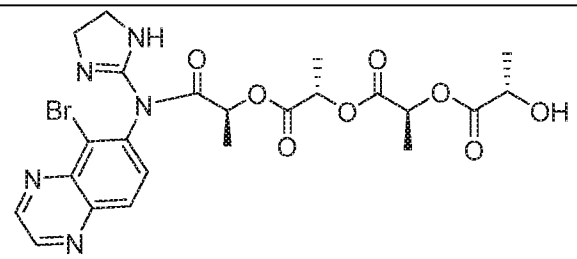
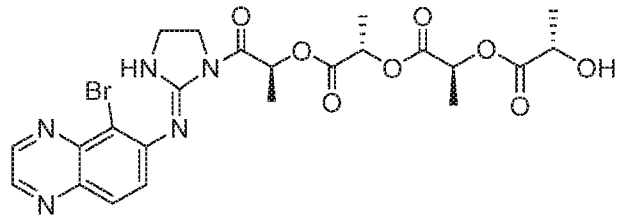
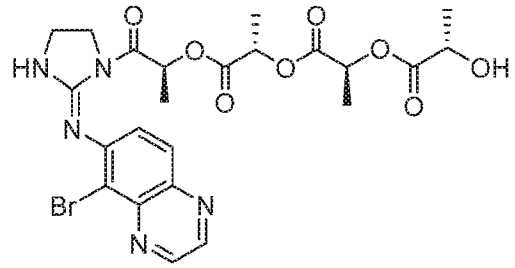
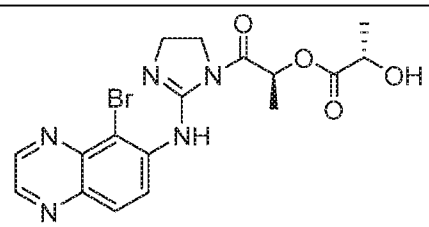
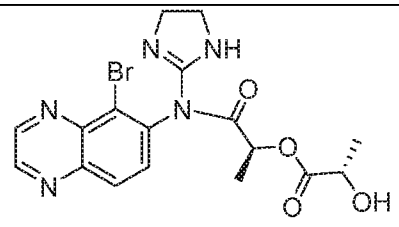
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| **114-4** |  |
| **114-4a** |  |
| **114-4b** |  |

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| **114-4c** |  |
| **114-4d** |  |
| **115-1** |  |
| **115-1a** |  |
| **115-1b** |  |
| **115-1c** |  |

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| **115-1d** |  |
| **116-1** |  |
| **116-1a** |  |
| **117-6** |  |
| **118-1** |  |

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| **119-6** |  |
| **120-1** |  |

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| **121-3** |  |
| **122-4** |  |
| **122-4a** |  |
| **122-4b** |  |
| **122-4c** |  |

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| **124-4** |  |
| **124-4a** |  |

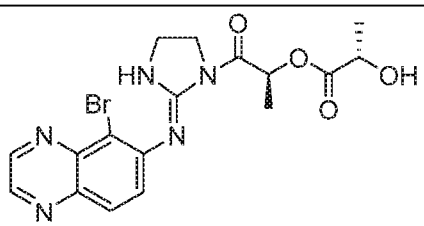
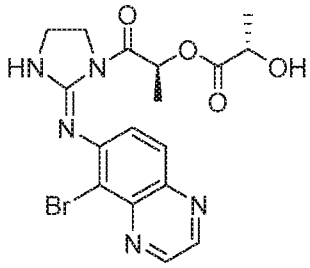
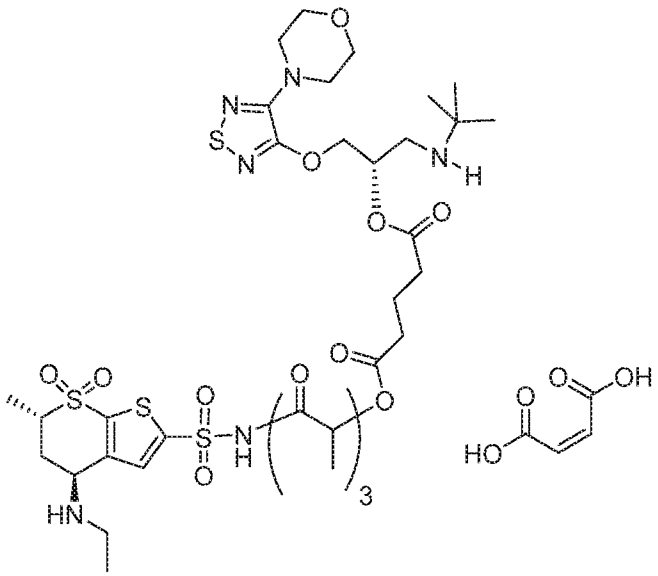
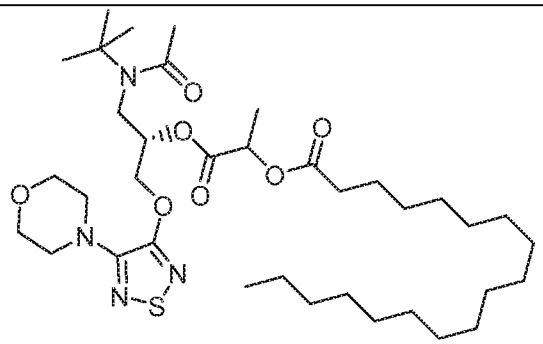
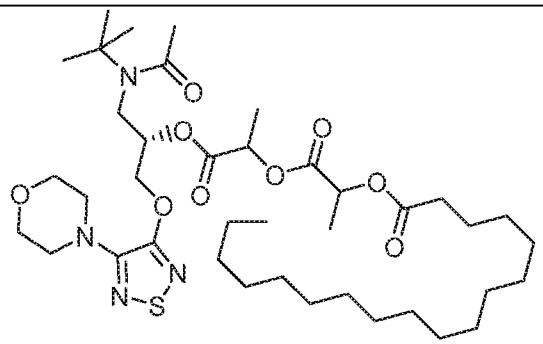
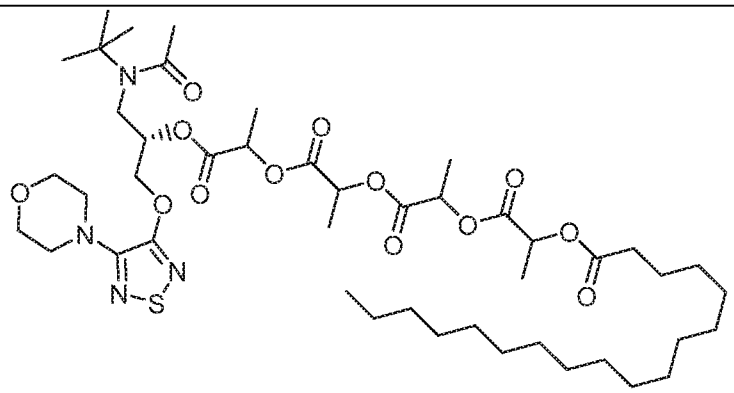
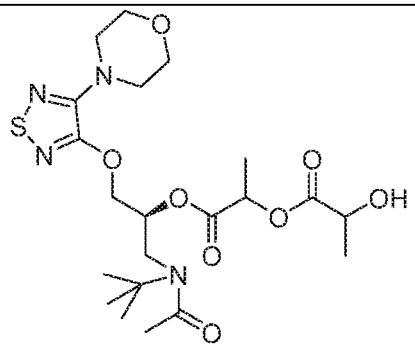
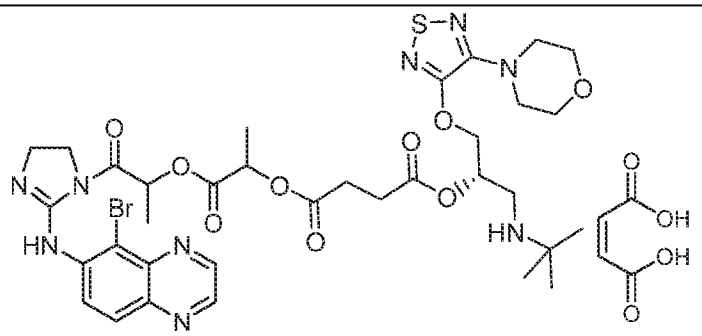
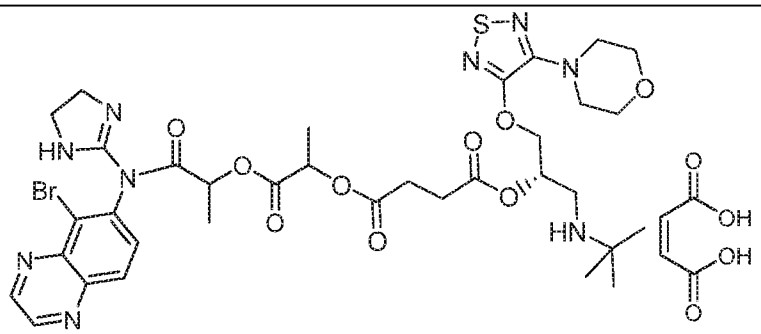
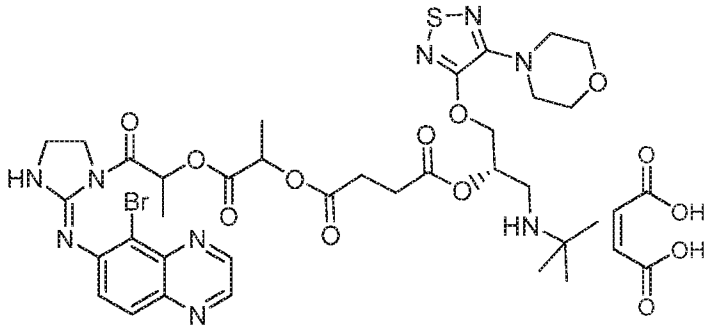
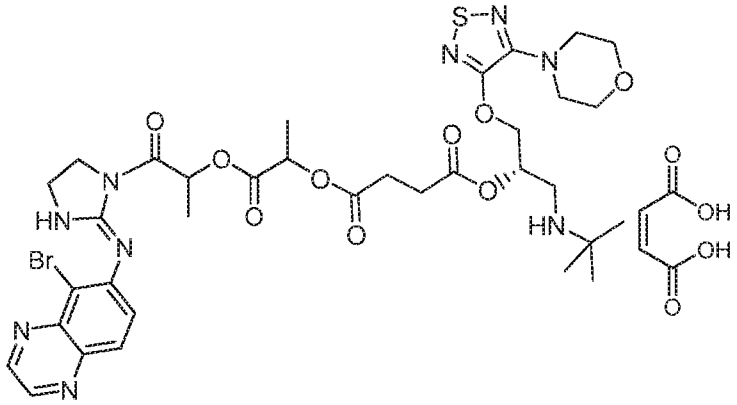
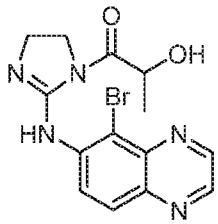
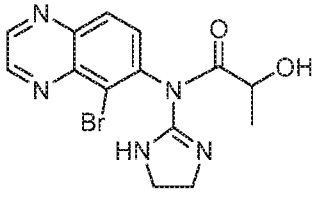
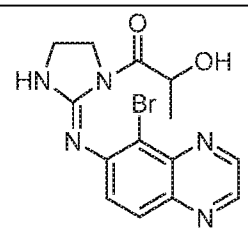
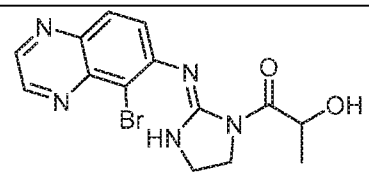
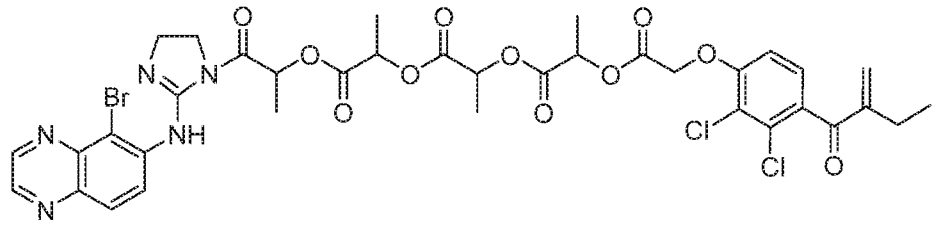
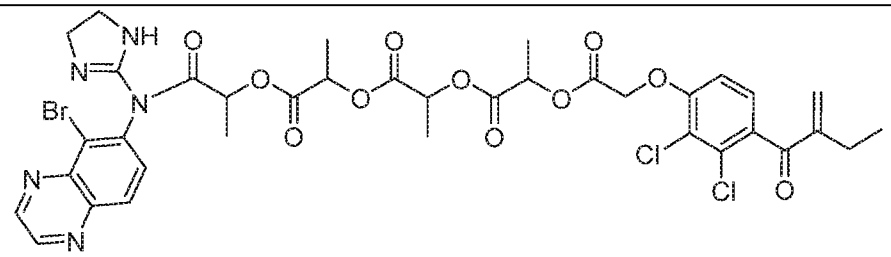
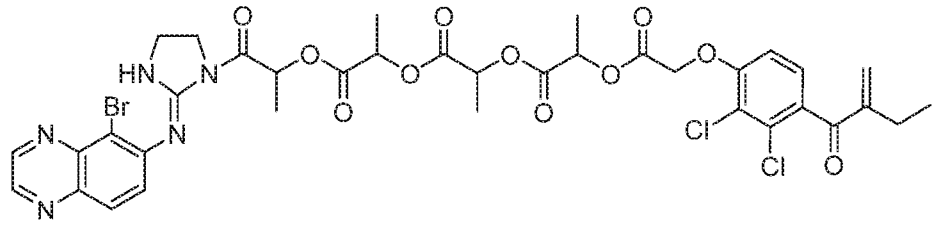
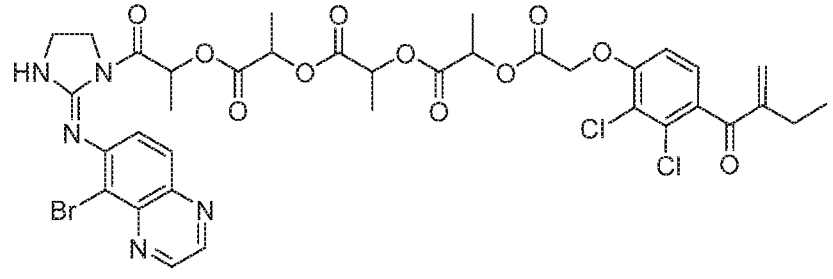
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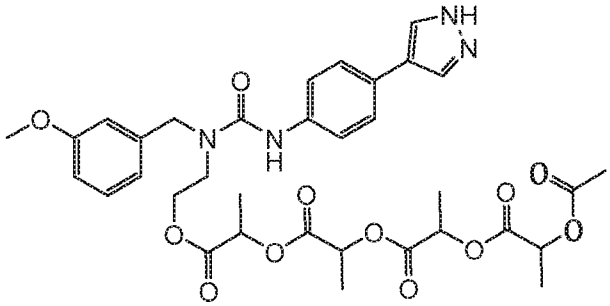
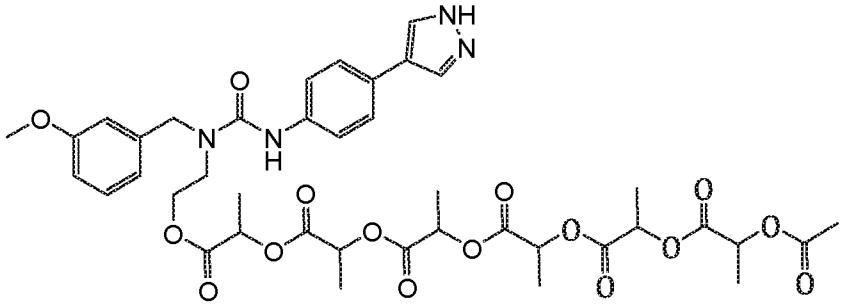
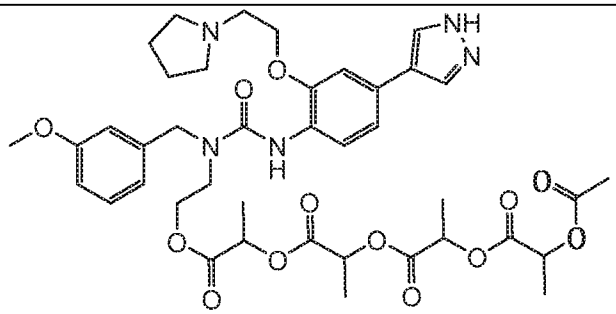
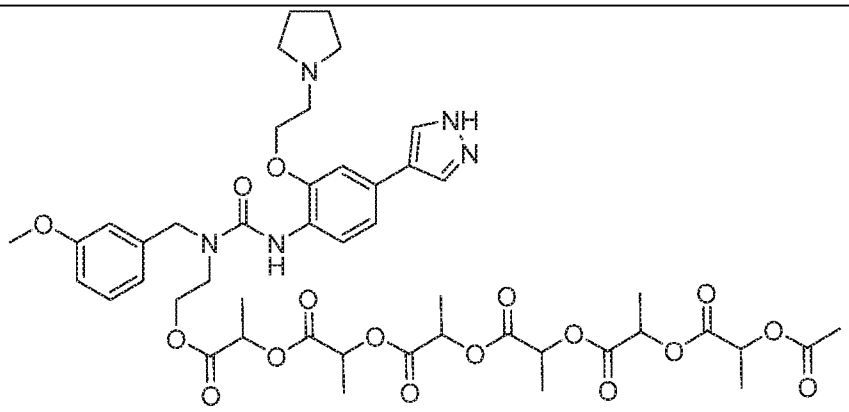
**Table 8C: Select Compounds of the Present Invention**

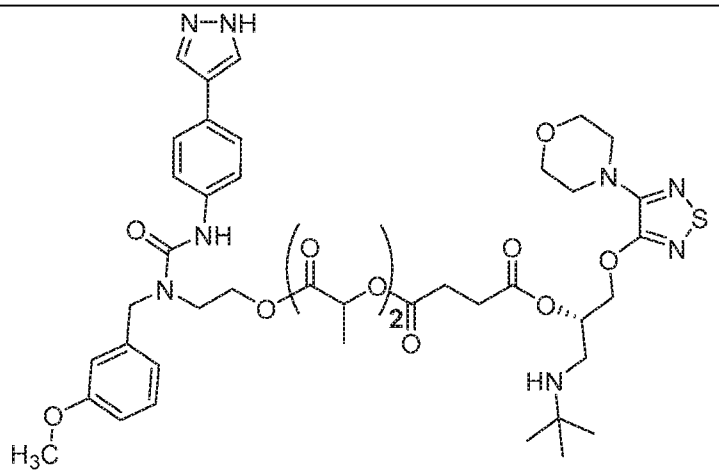
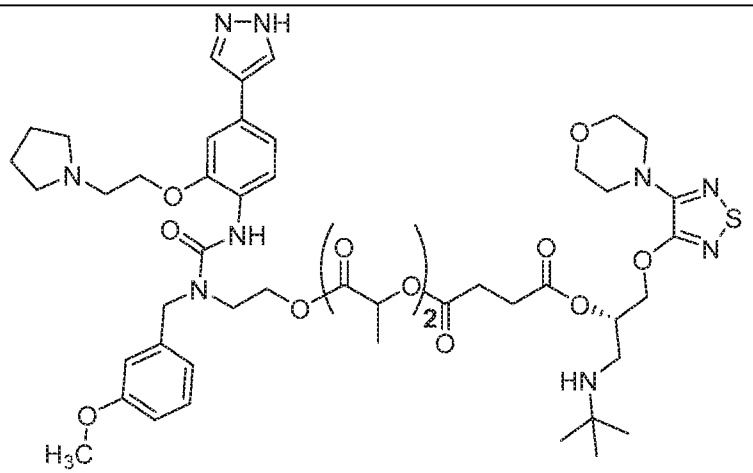
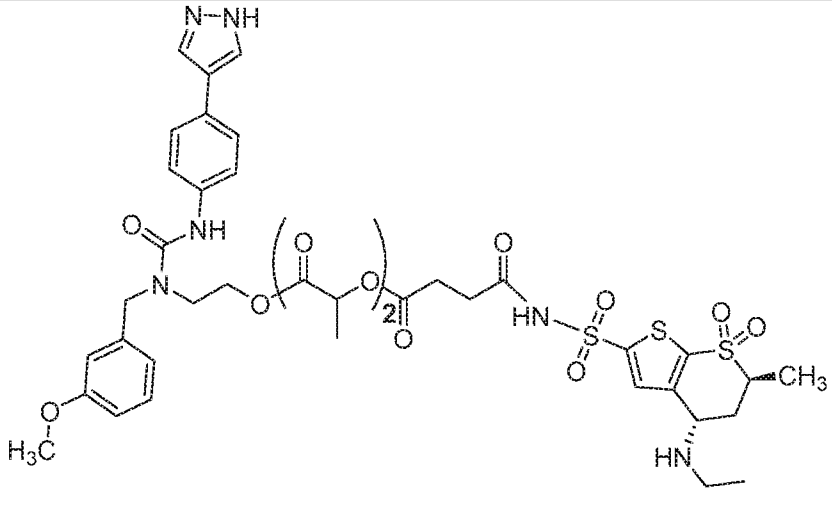
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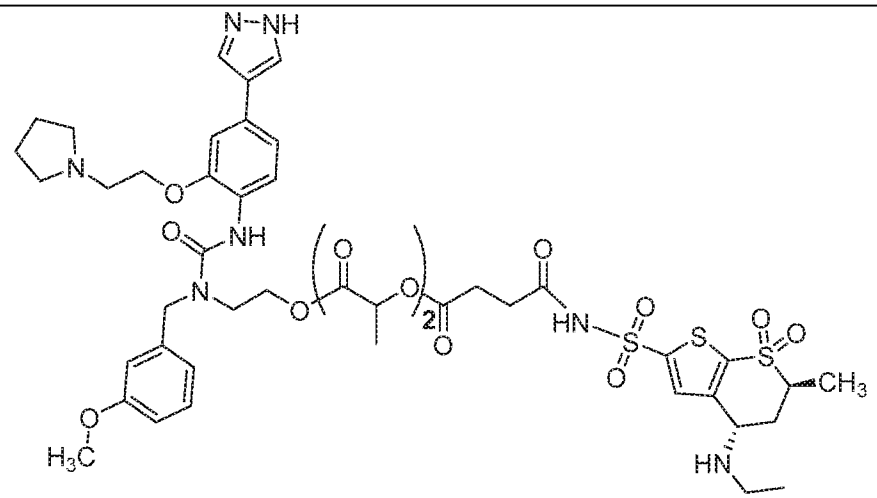
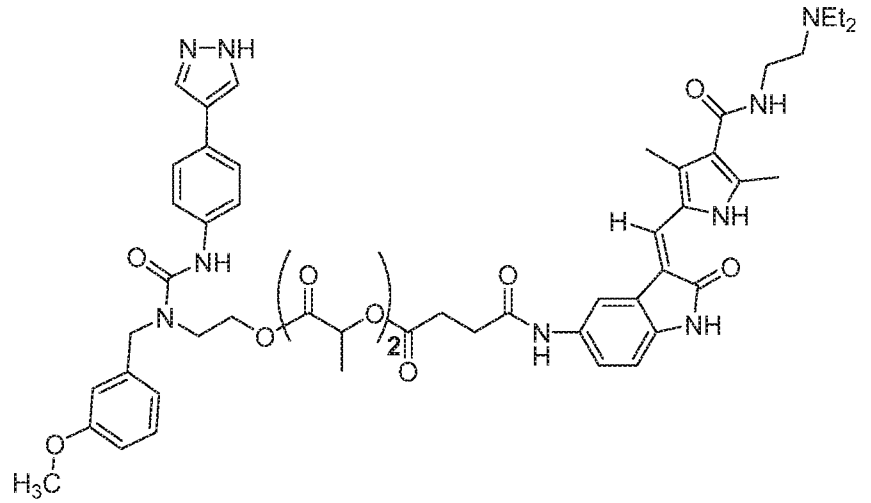
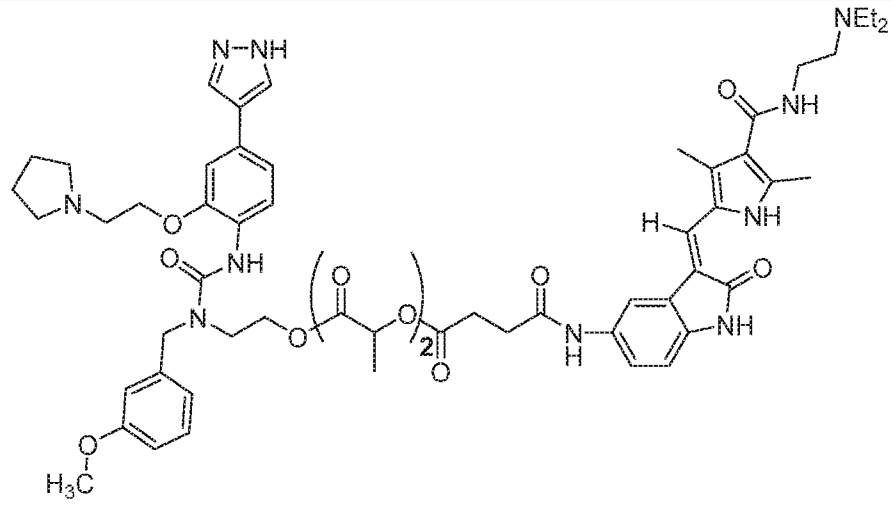
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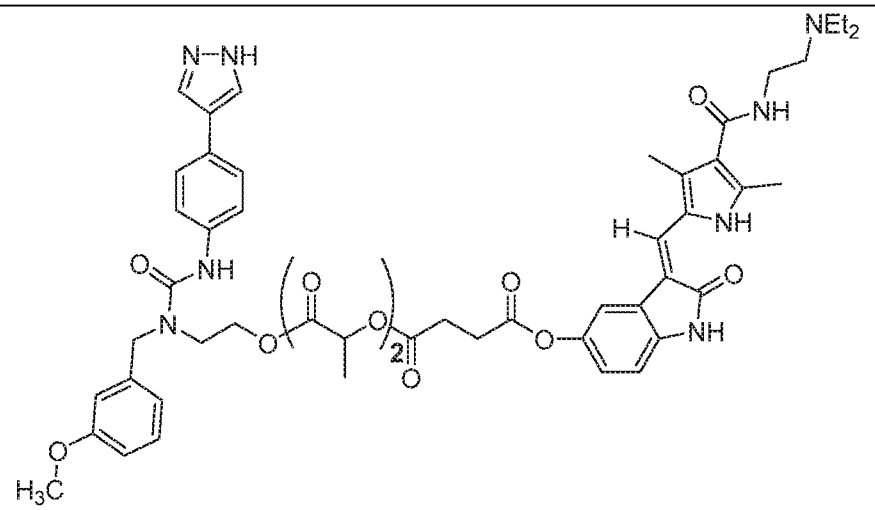
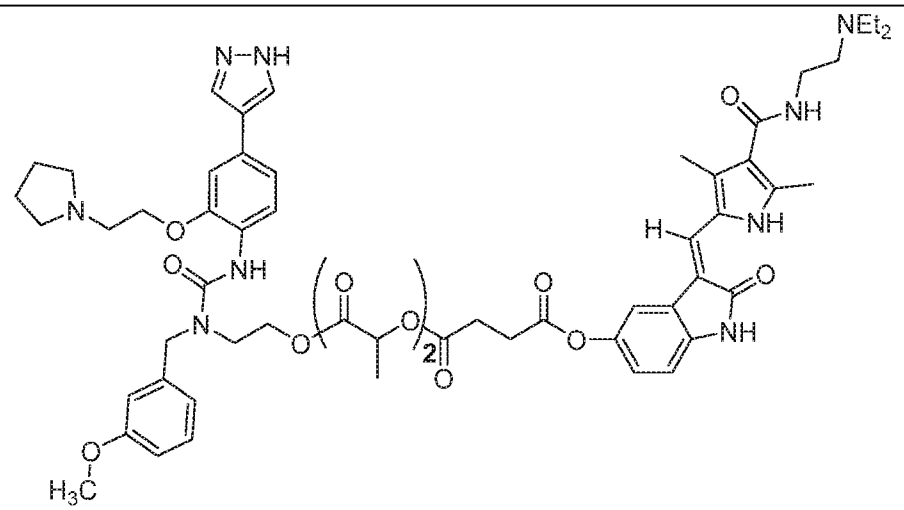
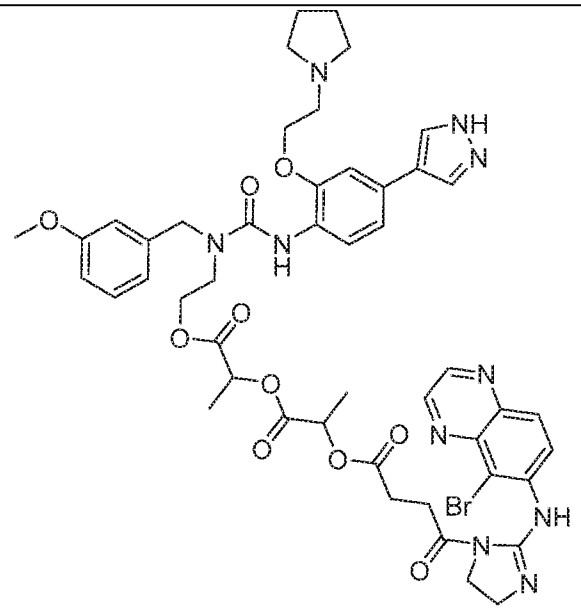
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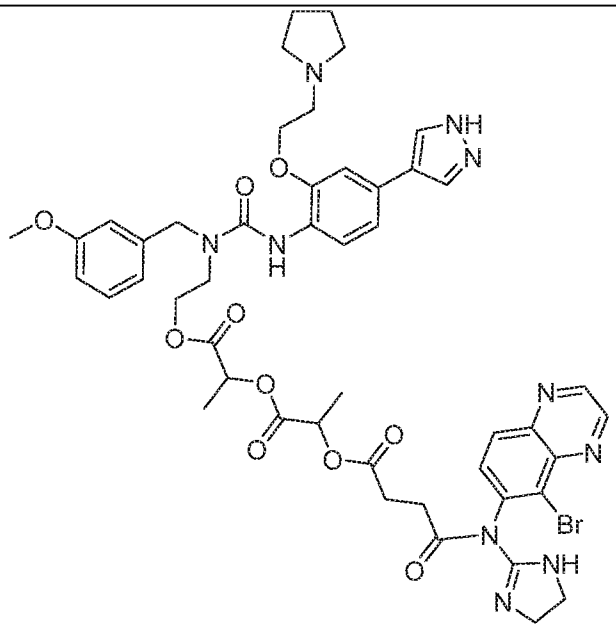
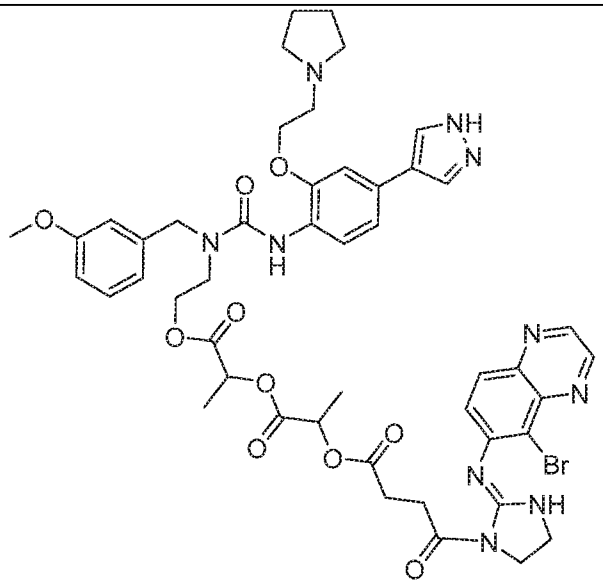
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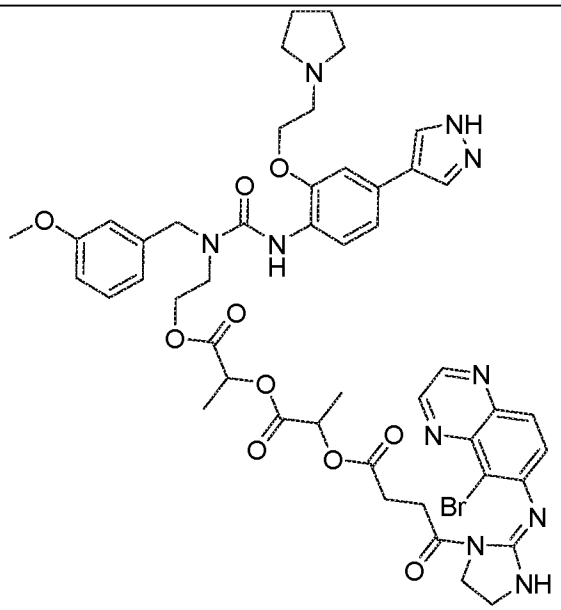
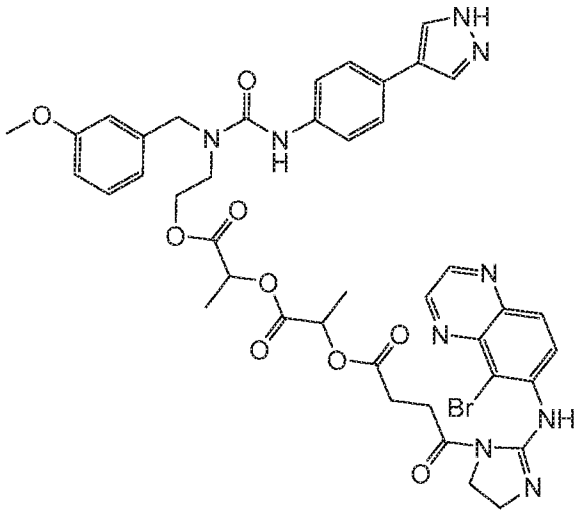
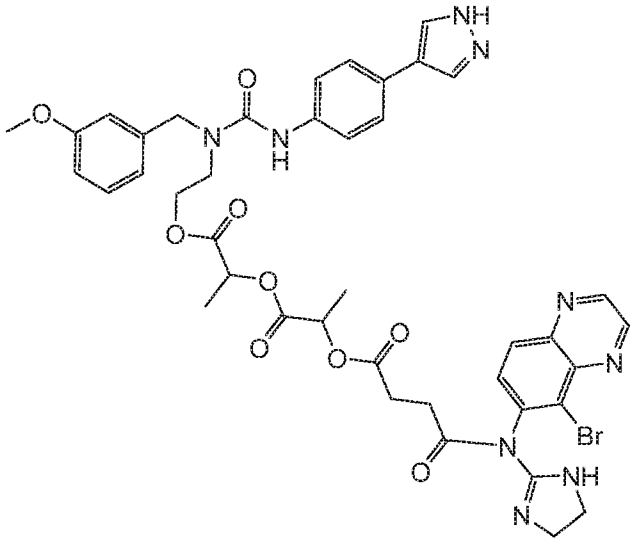
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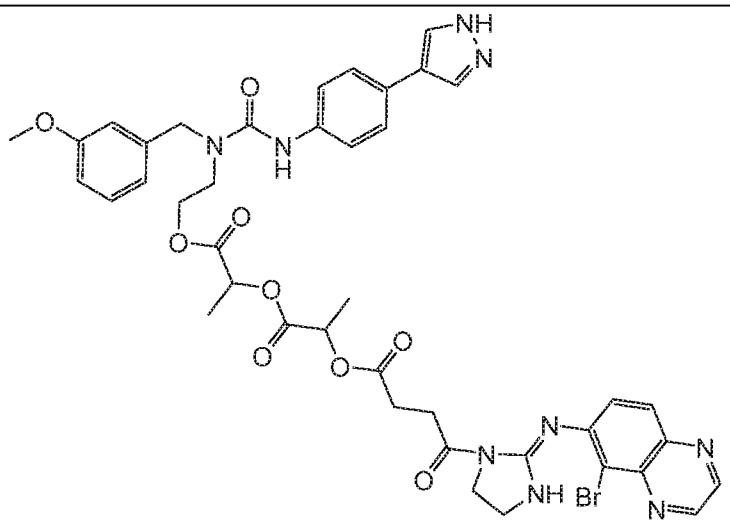
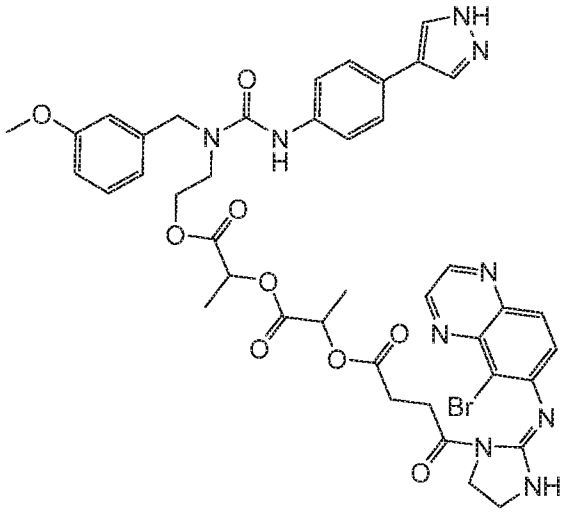
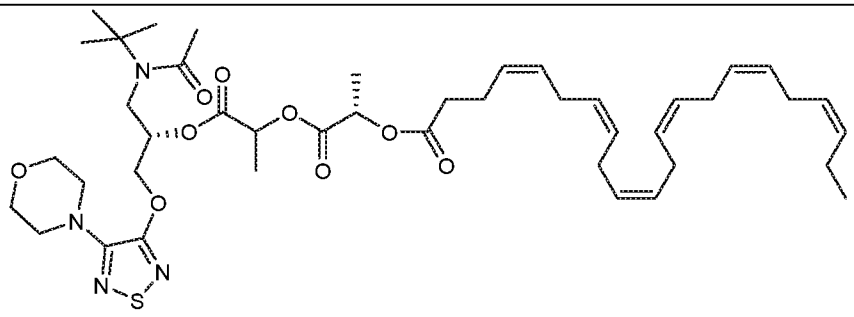
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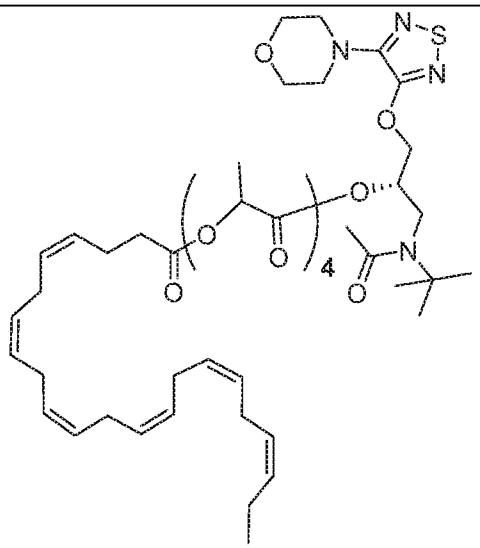
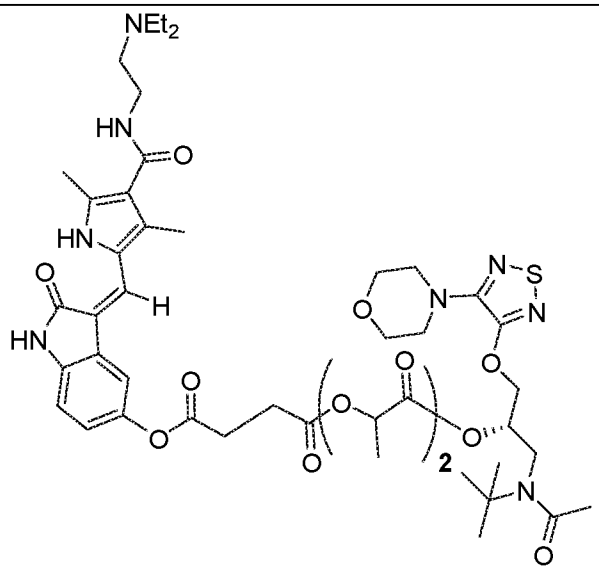
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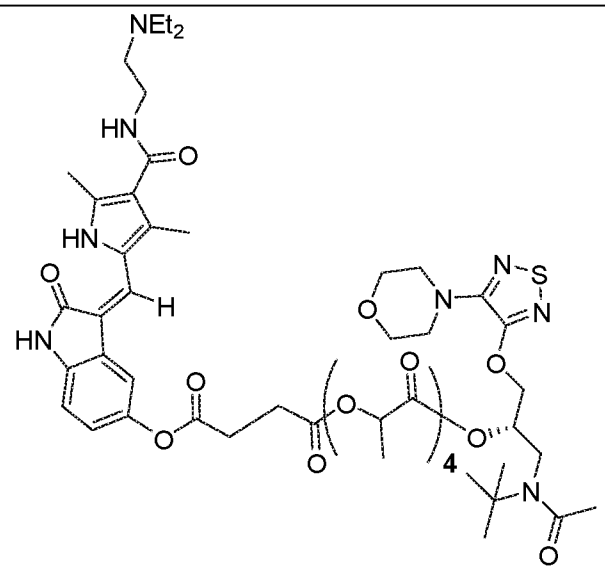
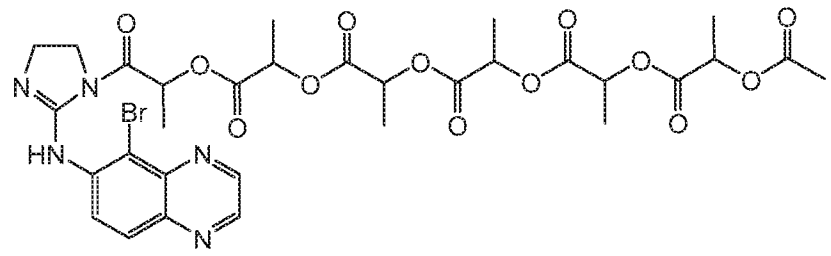
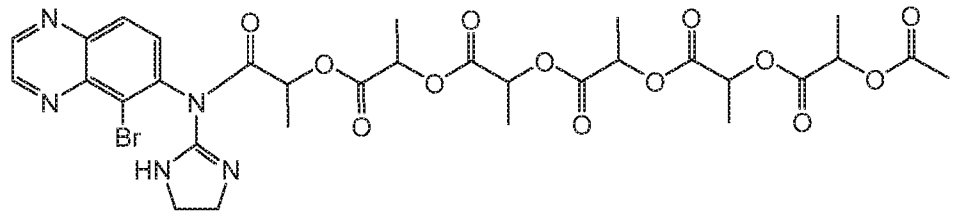
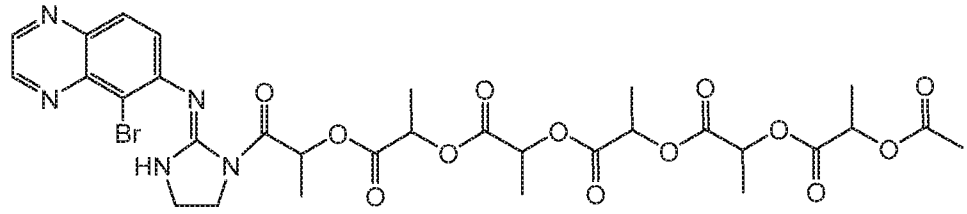
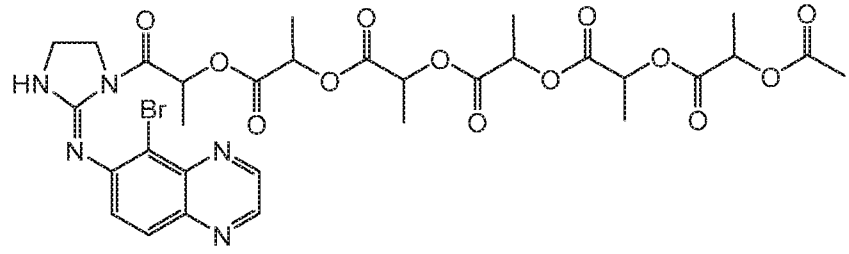
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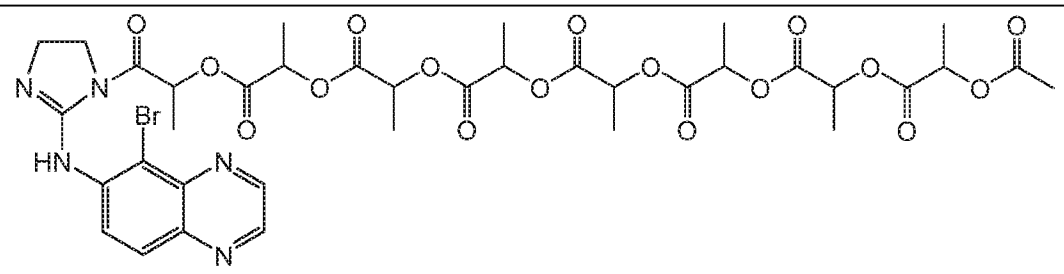
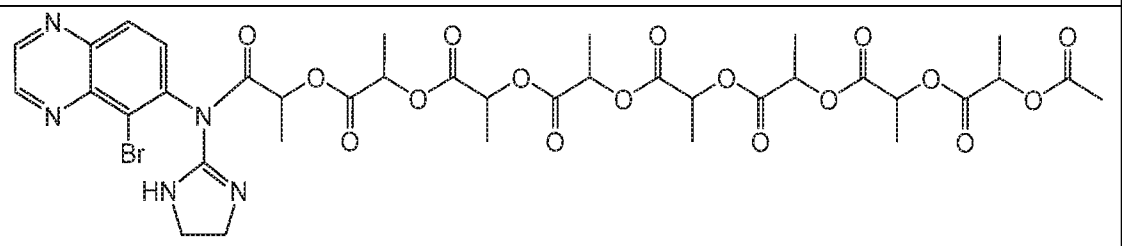
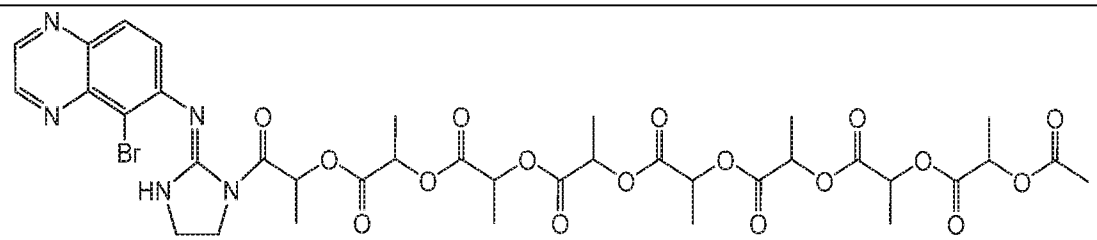
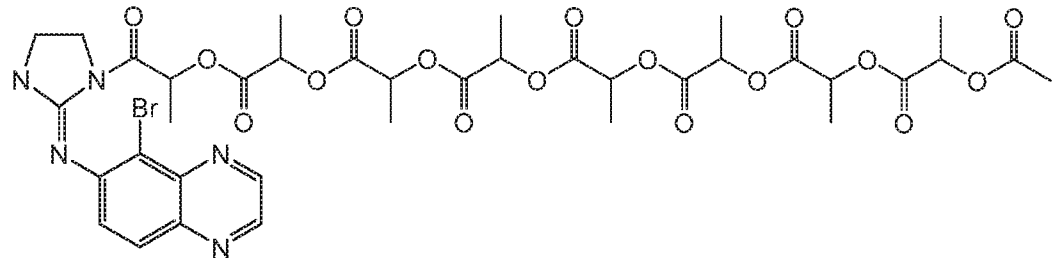
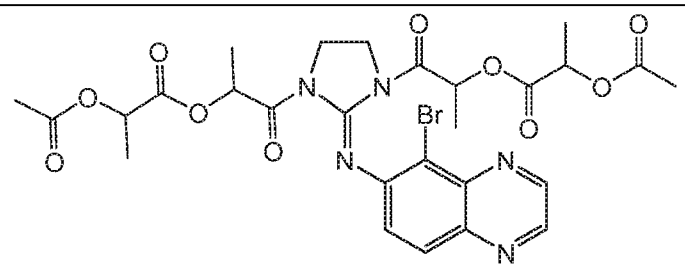
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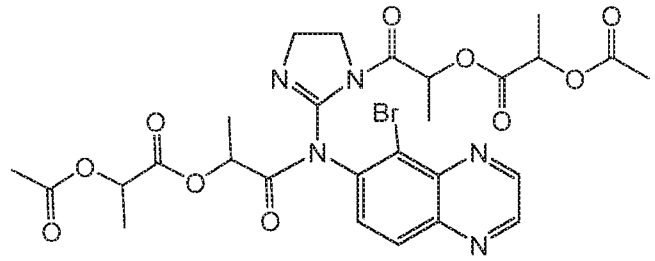
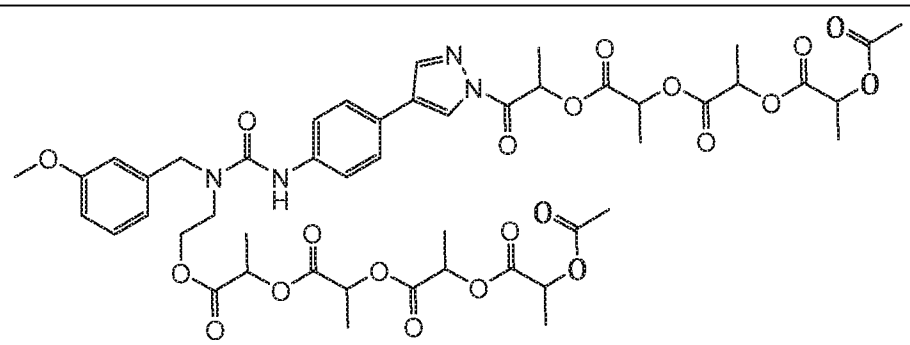
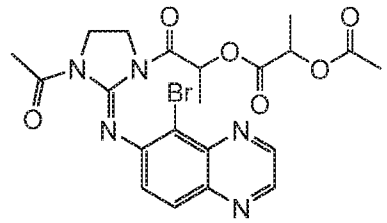
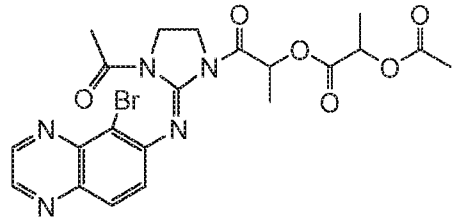
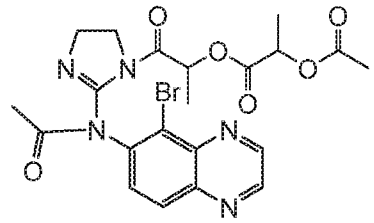
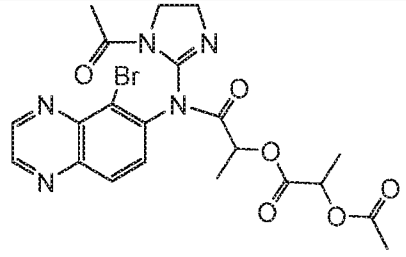
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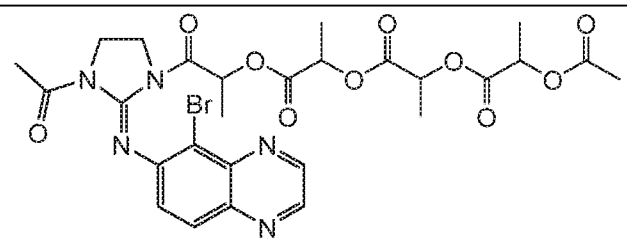
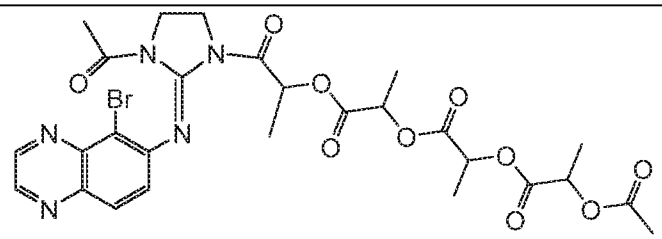
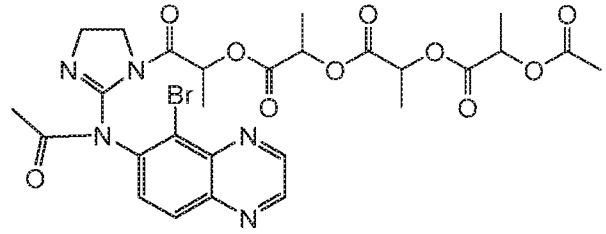
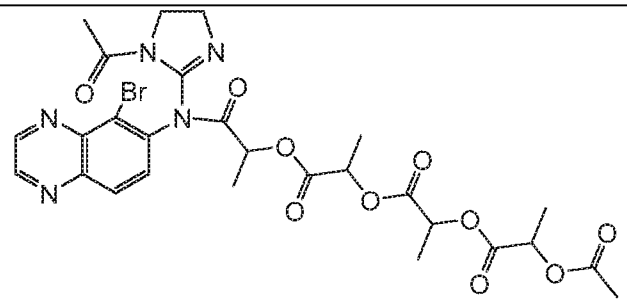
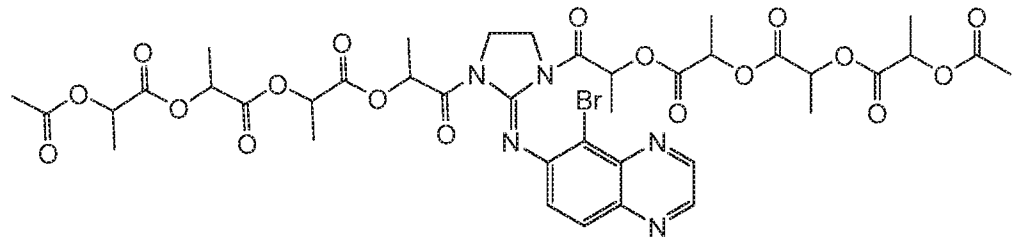
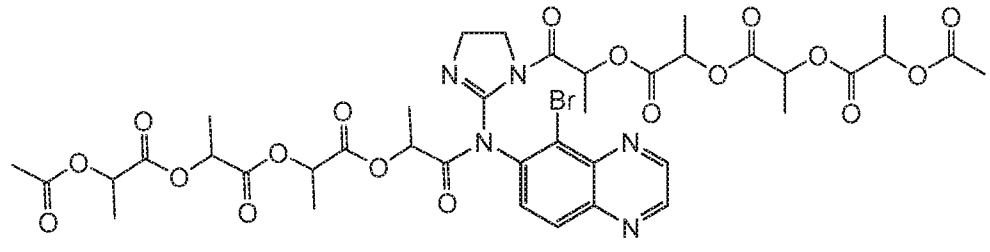
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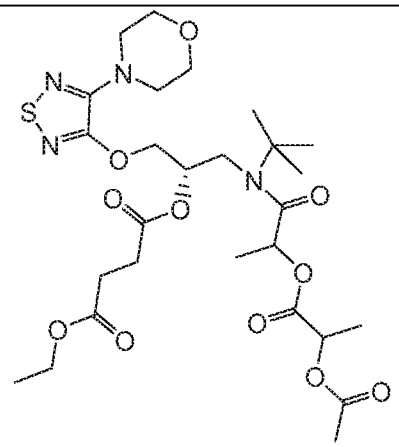
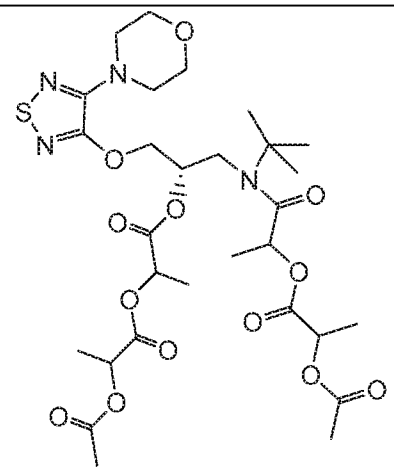
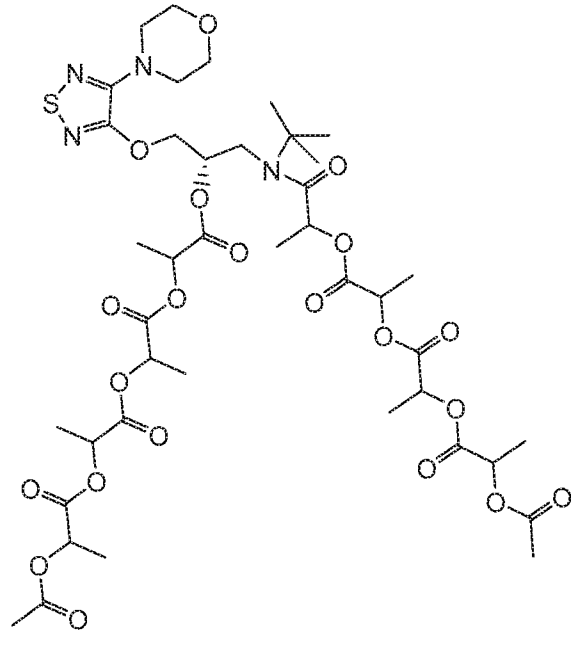
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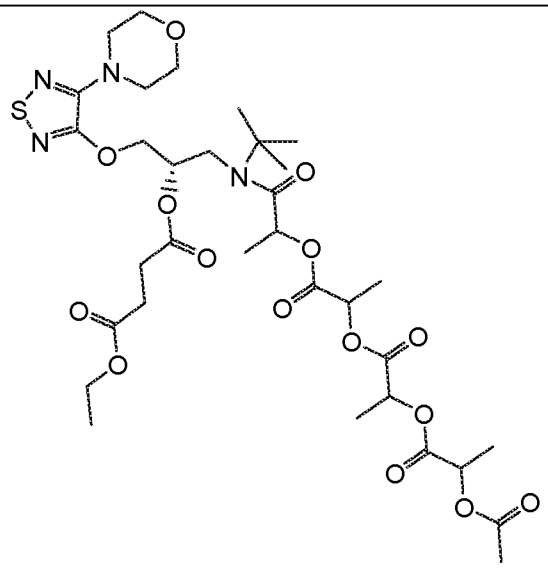
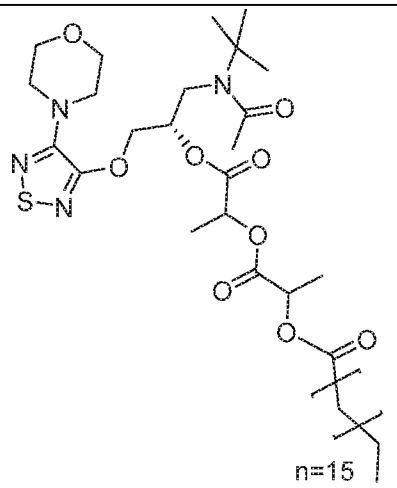
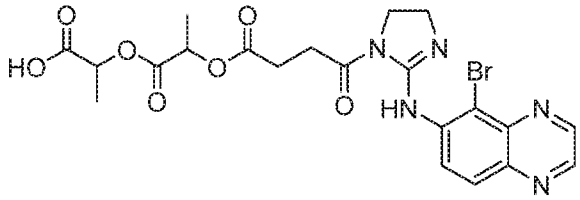
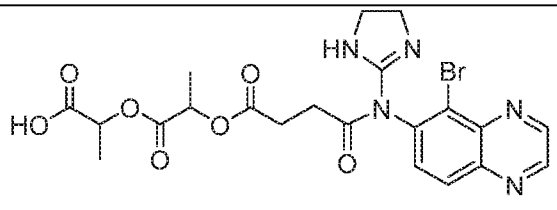
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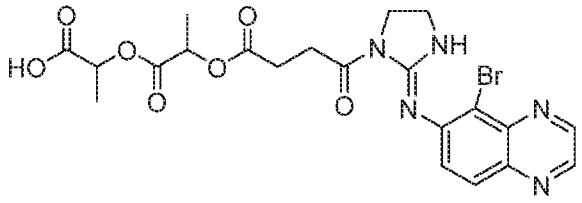
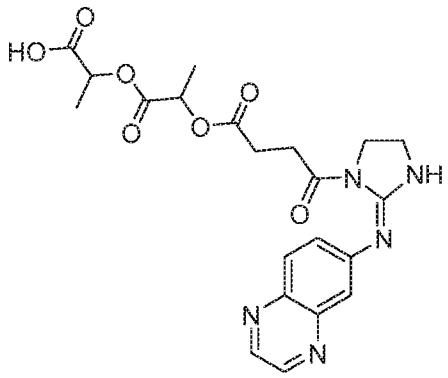
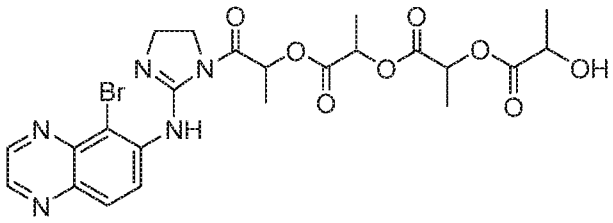
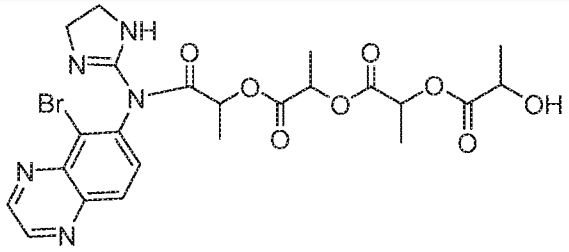
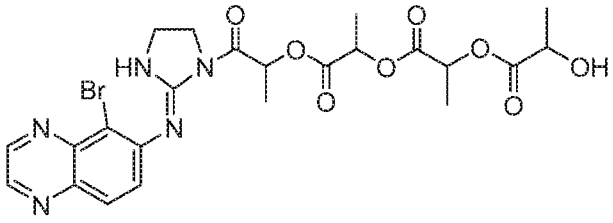
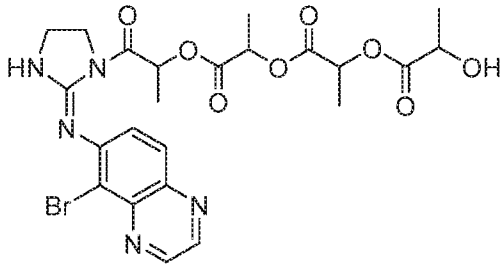
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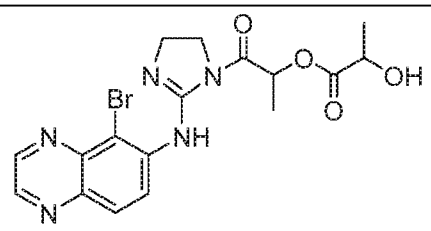
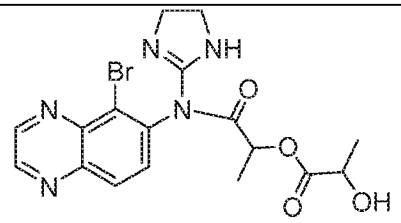
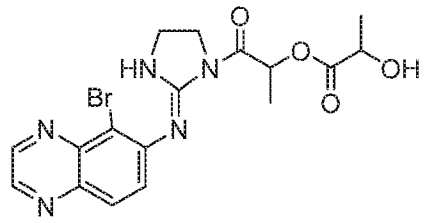
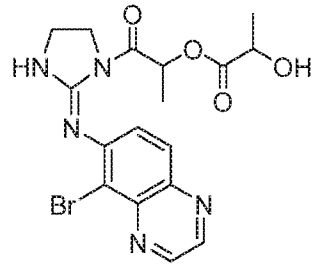
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**Table 8D. l Non-limiting Examples of Compounds of the Present Invention**

| Active Moiety | General Name | Mw | Mw w/ Salt | Molecular Formula |
|---|---|---|---|---|
| Timolol | N-acyl-Timolol-DHA | 668.95 | NA | $C_{37}H_{56}N_4O_5S$ |
| Timolol | N-acyl-Timolol-PLA (n=2)-DHA | 813.07 | NA | $C_{43}H_{64}N_4O_9S$ |
| Timolol | N-acyl-Timolol-PLA (n=4)-DHA | 957.2 | NA | $C_{49}H_{72}N_4O_{13}S$ |
| Timolol | N-acyl-Timolol-PLA (n=2) | 502.59 | NA | $C_{21}H_{34}N_4O_8S$ |
| Timolol, Sunitinib | N-acyl-Timolol-PLA (n=2)-succinate-Sunitinib | 981.14 | NA | $C_{47}H_{64}N_8O_{13}S$ |
| Timolol, Sunitinib | N-acyl-Timolol-PLA (n=4)-succinate-Sunitinib | 1125.27 | NA | $C_{53}H_{72}N_8O_{17}S$ |
| Ethacrynic acid | Ethacrynic acid-PLA (n=4)-Ethyl ester | 619.45 | NA | $C_{27}H_{32}C_{l2}O_{12}$ |

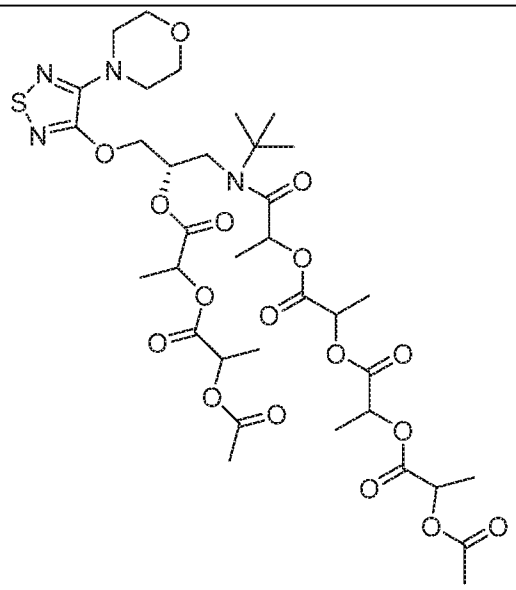
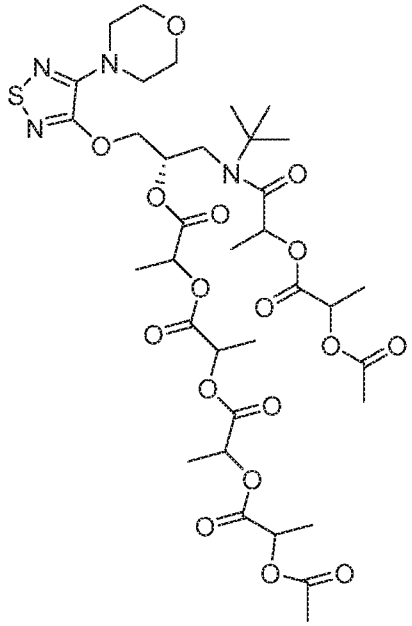
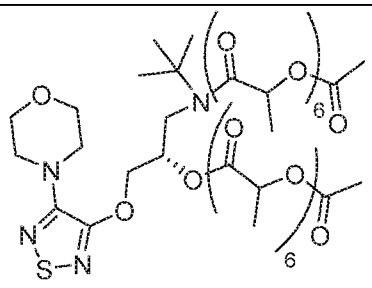
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| Ethacrynic acid | Ethacrynic acid-PLA (n=2)-Ethyl ester | 475.33 | NA | $C_{21}H_{24}C_{l2}O8$ |
| Timolol | Timolol-O-Succinate | 416.5 | NA | $C_{17}H_{28}N_4O_6S$ |
| Timolol | Timolol-O-Ethylsuccinate-Maleate | 444.55 | 560.62 (Maleate salt) | $C_{19}H_{32}N_4O_6S$ . $C_4H_4O_4$ |
| Timolol | Timolol-O-Ethylsuccinate-HCl salt | 444.55 | 481.01 (HCl salt) | $C_{19}H_{32}N_4O_6S$ . HCl |
| Timolol | Timolol-O-Maleate | 414.48 | NA | $C_{17}H_{26}N_4O_6S$ |
| Timolol | Timolol-O-Ethylmaleate-Maleic acid salt | 442.54 | 558.61 (Maleate salt) | $C_{19}H_{30}N_4O_6S$ . $C_4H_4O_4$ |
| Timolol | Timolol-O-Ethylmaleate-HCl salt | 442.54 | 479.0 (HCl salt) | $C_{19}H_{30}N_4O_6S$ . HCl |
| Timolol | Timolol-O-Linoleic acid-Maleate | 578.86 | 694.93 (Maleate salt) | $C_{31}H_{54}N_4O_4S$ . C4H4O4 |
| Timolol | Timolol-O-Linoleic acid-HCl salt | 578.86 | 615.32 (HCl salt) | $C_{31}H_{54}N_4O_4S$ . HCl |
| DHA | DHA | 328.5 | NA | $C_{22}H_{32}O_2$ |
| Brinzolamide | N-Methyl-Brinzolamide | 397.54 | NA | $C_{13}H_{23}N_3O_5S_3$ |
| Brinzolamide | N-Methyl-Dorzolamide | 338.47 | NA | $C_{11}H_{18}N_2O_4S_3$ |
| Dorzolamide | Dorzolamide-DHA conjugate | 634.93 | NA | $C_{32}H_{46}N_2O_5S_3$ |
| Timolol, Dorzolamide | Timolol-succinate-Dorzolamide-maleate | 722.93 | 839.00 (Maleate salt) | $C_{27}H_{42}N_6O_9S_4$ . $C_4H_4O_4$ |
| Timolol, Brinzolamide | Timolol-succinate-Brinzolamide-maleate | 781.99 | 898.06 (Maleate salt) | $C_{29}H_{47}N_7O_{10}S_4$ . $C_4H_4O_4$ |
| Timolol, Brimonidine | Brimonidine-Succinate-Timolol-maleate | 690.62 | 806.69 (Maleate salt) | $C_{28}H_{36}BrN_9O_5S$ ·$C_4H_4O_4$ |
| Sunitinib | 5-Hydroxy Sunitinib-DHA | 706.98 | NA | $C_{44}H_{58}N_4O_4$ |
| Timolol | Timolol-Succinate-Ethyl-PLA (n=4)-Maleate | 732.81 | 848.81 (Maleate salt) | $C_{31}H_{48}N_4O_{14}S$ . $C_4H_4O_4$ |

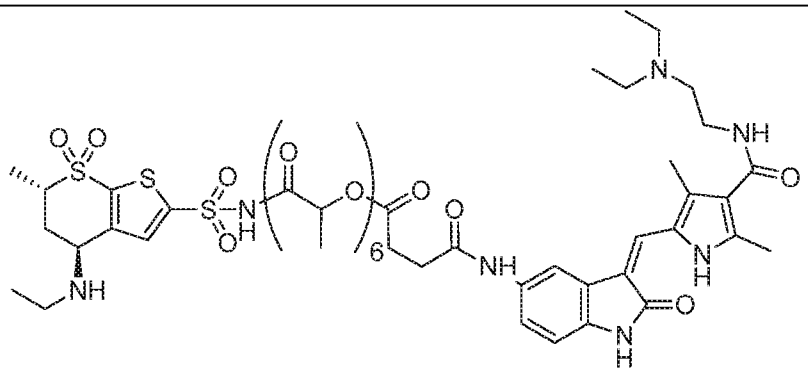
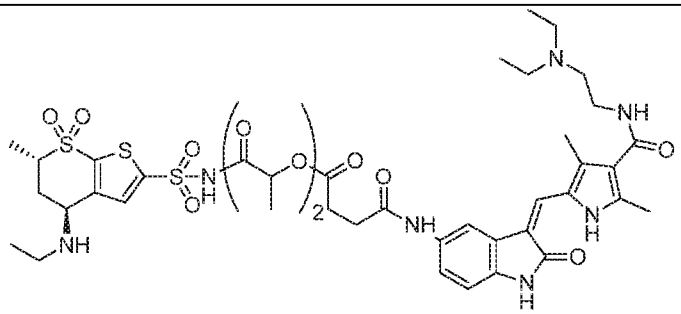
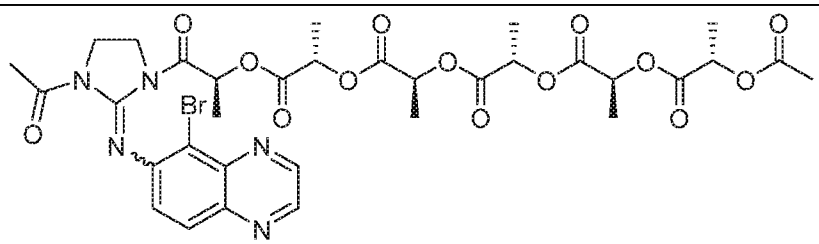
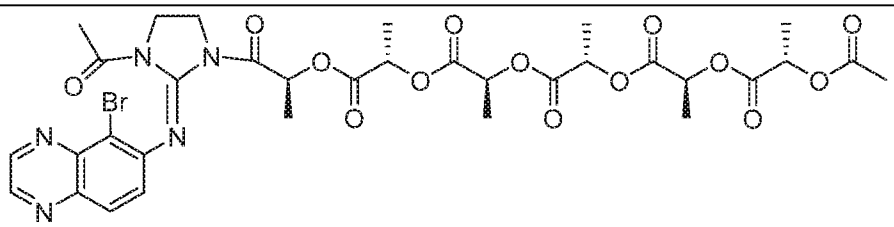
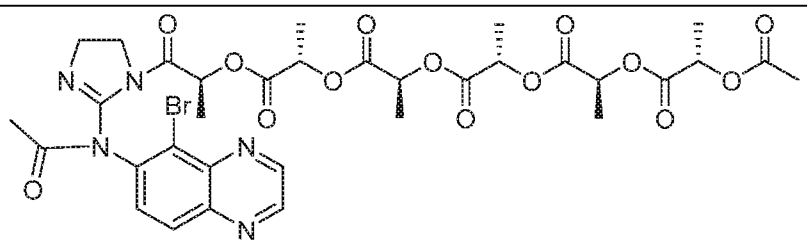
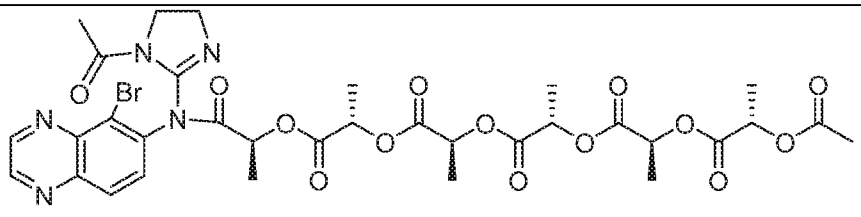
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| Timolol, Brimonidine | Timolol-succinate-PLA (n=2)-Brimonidine | 834.75 | 950.82 (Maleate salt) | $C_{34}H_{44}BrN_9O_9S$ . $C_4H_4O_4$ |
| Brimonidine | Brimonidine-PLA (n=1) | 364.2 | NA | $C_{14}H_{14}BrN_5O_2$ |
| Timolol, Dorzolamide | Timolol-Glutarate-Dorzolamide-maleate | 736.95 | 853.02 (Maleate salt) | $C_{28}H_{44}N_6O_9S_4$ . $C_4H_4O_4$ |
| SA12590 | SA12590 | 307.35 | NA | $C_{19}H_{17}NO_3$ |
| Timolol, Dorzolamide | Timolol-O-Glutarate-PLA (n=3)-Dorzolamide-maleate | 953.15 | 1069.22 (Maleate salt) | $C_{37}H_{56}N_6O_{15}S_4$ . $C_4H_4O_4$ |
| Sorafenib | Sorafenib acid | 451.79 | NA | $C_{20}H_{13}ClF_3N_3O_4$ |
| Timolol, Brimonidine | Timolol-O-Glutarate-Brimonidine-Maleate | 704.65 | 820.72 (Maleate salt) | $C_{29}H_{38}BrN_9O_5S$ . $C_4H_4O_4$ |
| Timolol | Timolol-Sebacic acid-Timolol-Maleate | 799.07 | 1031.21 (Maleate salt) | $C_{36}H_{62}N_8O_8S_2$ . 2 $C_4H_4O_4$ |
| Sunitinib | 5-Amino-Sunitinib-Glutarate | 509.61 | NA | $C_{27}H_{35}N_5O_5$ |
| Sunitinib | 5-Amino-Sunitinib-Dodecanedioic acid | 607.8 | 838.1 (Dodecanedioic acid salt) | $C_{34}H_{49}N_5O_5$. $C_{12}H_{22}O_4$ |
| Timolol | Timolol-O-Ethylmaleate-HCl salt | 442.54 | 479.0 (HCl salt) | $C_{19}H_{30}N_4O_6S$ . HCl |
| Dorzolamide | Dorzolamaide-Ethylfumarate | 450.55 | NA | $C_{16}H_{22}N_2O_7S_3$ |
| Sunitinib | 5-Amino-Sunitinib-Sebacic acid | 579.75 | 693.77 (TFA salt) | $C_{32}H_{45}N_5O_5$ . $C_2HF_3O_2$ |
| Timolol | Timolol-Succinic acid-Timolol-Maleate | 714.91 | 947.05 (Maleate salt) | $C_{30}H_{50}N_8O_8S_2$ . 2 $C_4H_4O_4$ |
| Timolol | Timolol-Glutaric acid-Timolol-Maleate | 728.94 | 961.08 (Maleate salt) | $C_{31}H_{52}N_8O_8S_2$ . 2 $C_4H_4O_4$ |
| Dorzolamide | Dorzolamide-Stearylfumarate | 674.99 | NA | $C_{32}H_{54}N_2O_7S_3$ |
| Dorzolamide | Dorzolamide-Laurylmaleate | 590.83 | NA | $C_{26}H_{42}N_2O_7S_3$ |

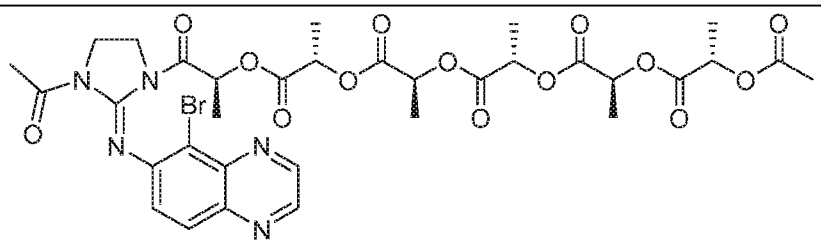
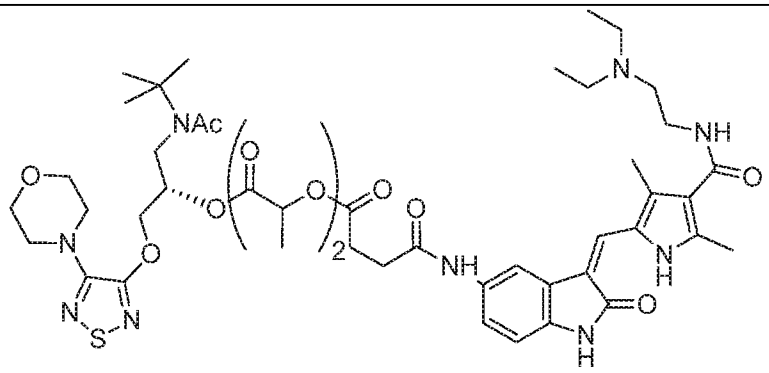
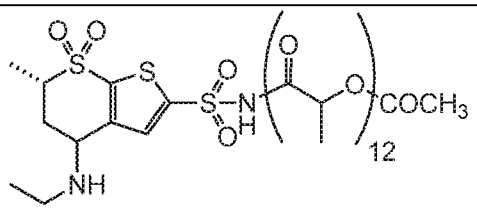
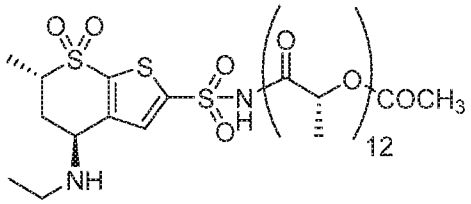
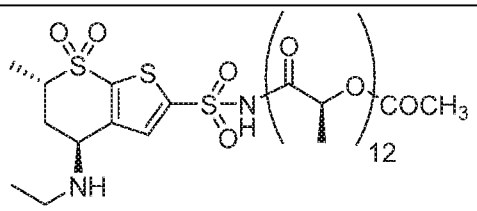
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|---|---|---|---|---|
| Timolol | Timolol-O-Laurylfumarate-maleate | 582.81 | 698.88 (Maleate salt) | $C_{29}H_{50}N_4O_6S$ . $C_4H_4O_4$ |
| Timolol | Timolol-O-Stearylfumarate-maleate | 666.97 | 783.04 (Maleate salt) | $C_{35}H_{62}N_4O_6S$ . $C_4H_4O_4$ |
| Timolol | Timolol-Fumarate-Timolol-Maleate | 712.89 | 945.03 (Maleate salt) | $C_{30}H_{48}N_8O_8S2$ . 2 $C_4H_4O_4$ |
| Ethacrynic acid, Brimonidine | Brimonidine-PLA (n=4)-Etacrynic acid | 865.53 | NA | $C_{36}H_{36}BrCl_2N_5O_{11}$ |
| RKI 1y | ROCK inhibitor-1y | 463.58 | NA | $C_{26}H_{33}N_5O_3$ |
| RKI Hydroxy 1y | 1-(2-hydroxyethyl)-1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)-2-[2-(pyrrolidin-1-yl)ethoxy]phenyl]urea (RKI-Hydroxy-1y) | 479.58 | NA | $C_{26}H_{33}N_5O_4$ |
| SR5834 | 1-(2-hydroxyethyl)-1-[(3-methoxyphenyl)methyl]-3-[4-(1H-pyrazol-4-yl)phenyl]urea (RKI SR5834) | 366.42 | NA | $C_{20}H_{22}N_4O_3$ |
| Ethacrynic acid, Dorzolamide | Dorzolamide-PLA (n=4)-Etacrynic acid | 897.83 | NA | $C_{35}H_{42}Cl_2N_2O_{15}S_3$ |
| Brimonidine | Brimonidine-Acetyl PLA(n=6) | 766.56 | NA | $C_{31}H_{36}BrN_5O_{13}$ |
| Sunitinib | 5-Amino-Sunitinib-Succinamide | 477.57 | NA | $C_{26}H_{31}N_5O_4$ |
| Brimonidine | Brimonidine-Acetyl PLA(n=8) | 910.69 | NA | $C_{37}H_{44}BrN_5O_{17}$ |
| Brimonidine | Brimonidine-Succinamide | 374.2 | NA | $C_{15}H_{12}BrN_5O_2$ |
| Brimonidine | Brimonidine-Bis-Acetyl PLA(n=2) | 664.47 | NA | $C_{27}H_{30}BrN_5O_{10}$ |
| Ethacrynic acid | Ethyl PLA (n=6)- Etacrynic acid | 763.58 | NA | $C_{33}H_{40}C_{l2}O_{16}$ |
| Ethacrynic acid | Ethyl PLA (n=8)- Etacrynic acid | 907.71 | NA | $C_{39}H_{48}C_{l2}O_{20}$ |
| Ethacrynic acid, Sunitinib | 5-Amino Sunitinib-Etacrynic acid | 680.64 | NA | $C_{35}H_{39}Cl_2N_5O_5$ |
| Timolol, Sunitinib | Timolol-Succinate-5-Amino Sunitinib-maleate | 793.99 | 910.06 (Maleate salt) | $C_{26}H_{31}N_5O_4$ |
| SR5834 | SR5834-Acetyl PLA(n=4) | 696.72 | NA | $C_{34}H_{40}N_4O_{12}$ |

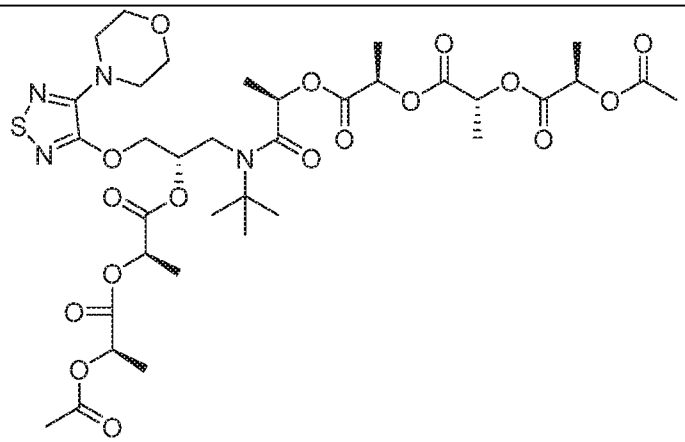
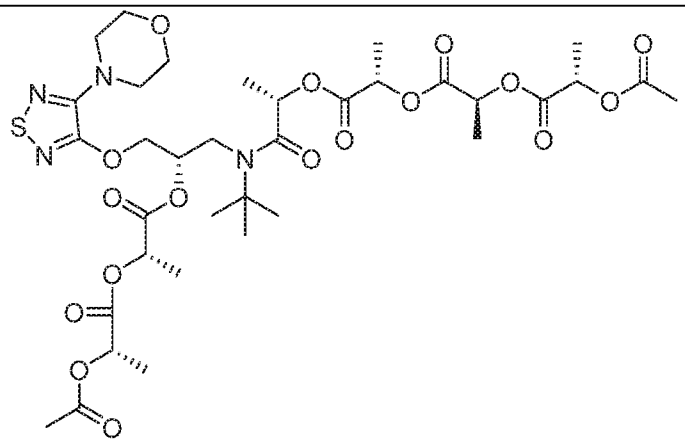
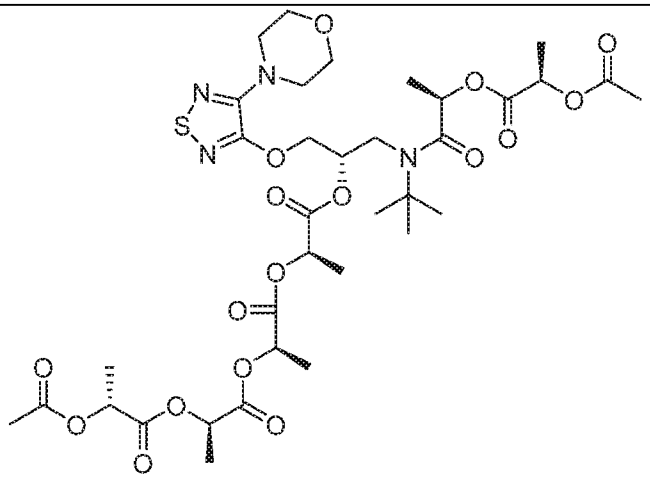
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|---|---|---|---|---|
| SR5834 | SR5834-Bis-Acetyl PLA(n=4) | 1027.01 | NA | $C_{48}H_{58}N_4O_{21}$ |
| RKI Hydroxy ly | RKI-Hydroxy-ly-Acetyl PLA (n=4) | 809.88 | NA | $C_{40}H_{51}N_5O_{13}$ |
| SR5834 | 1-(2-{[(3-methoxyphenyl)methyl]({[4-(1H-pyrazol-4-yl)phenyl]carbamoyl})amino}ethoxy)-1-oxopropan-2-yl 2-{[2-({2-[(2-{[2-(acetyloxy)propanoyl]oxy}propanoyl)oxy]propanoyl}oxy)propanoyl]oxy}propanoate | 840.85 | NA | $C_{40}H_{48}N_4O_{16}$ |
| Brimonidine | Brimonidine-Acetyl PLA(n=2)-N-acetate | 520.34 | NA | $C_{21}H_{22}BrN_5O_6$ |
| Brimonidine | Brimonidine-Acetyl PLA(n=4)-N-acetate | 664.47 | NA | $C_{27}H_{30}BrN_5O_{10}$ |
| Brimonidine | Brimonidine-Bis-Acetyl PLA (n=4) | 952.73 | NA | $C_{39}H_{46}BrN_5O_{18}$ |
| Timolol, Ethacrynic acid | Timolol-Etacrynic acid-maleate | 601.55 | 717.62 (Maleate salt) | $C_{26}H_{34}Cl_2N_4O_6S \cdot C_4H_4O_4$ |
| Timolol | Timolol-Bis-N-Acetyl-PLA (n=2)-O-Ethyl-succinate | 630.72 | NA | $C_{27}H_{42}N_4O_{11}S$ |
| Timolol | Timolol-Bis-Acetyl-PLA (n=2) | 688.76 | NA | $C_{29}H_{44}N_4O_{13}S$ |
| SR5834, Brimonidine | SR5834-PLA(n=2)-succinate-Brimonidine | 884.75 | NA | $C_{41}H_{42}BrN_9O_9$ |
| Ethacrynic acid, Sunitinib | 5-Amino Sunitinib-1,2-propyleneglycol-Etacrynic acid | 838.79 | NA | $C_{42}H_{49}Cl_2N_5O_9$ |
| Timolol | Timolol-Bis-Acetyl-PLA (n=4) | 977.01 | NA | $C_{41}H_{60}N_4O_{21}S$ |
| Timolol | Timolol-Bis-N-Acetyl-PLA (n=4)-O-Ethyl-succinate | 774.85 | NA | $C_{33}H_{50}N_4O_{15}S$ |

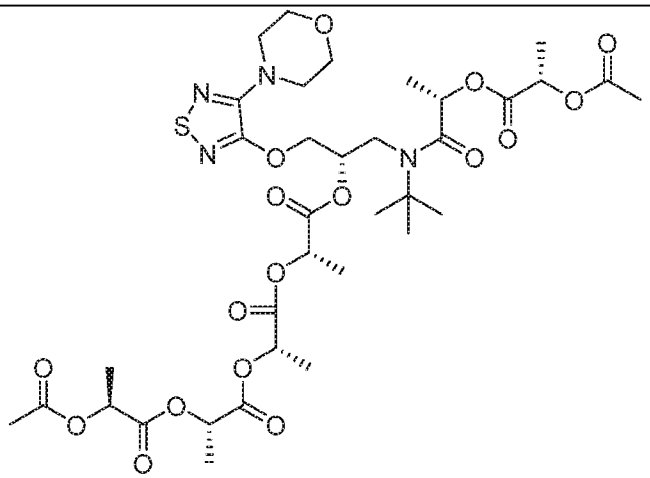
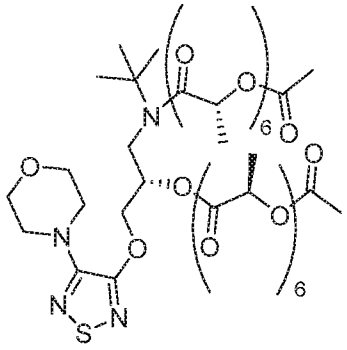
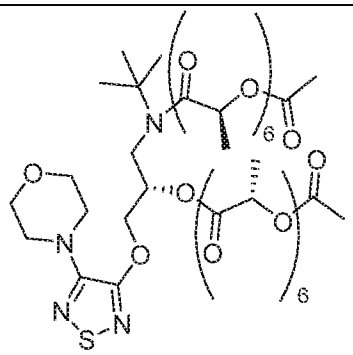
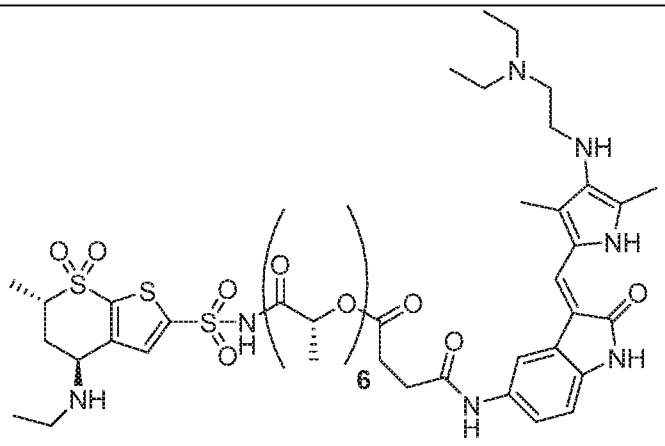
**Table 8E. Select Compounds of the Present Invention**

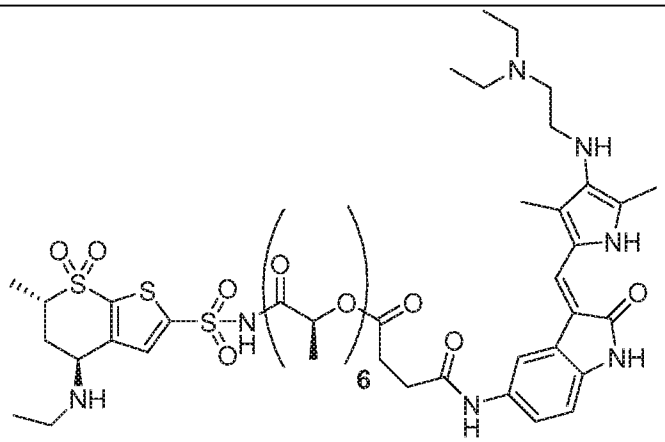
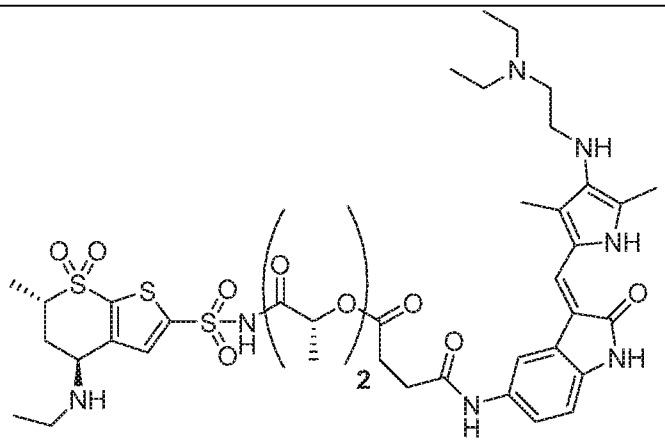
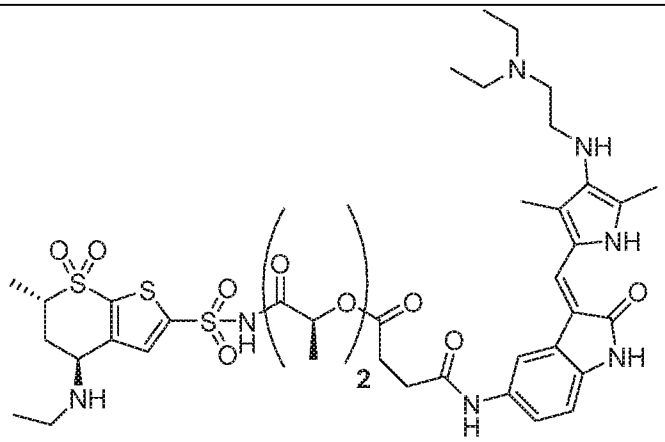
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| **230** |  |
| **231** |  |

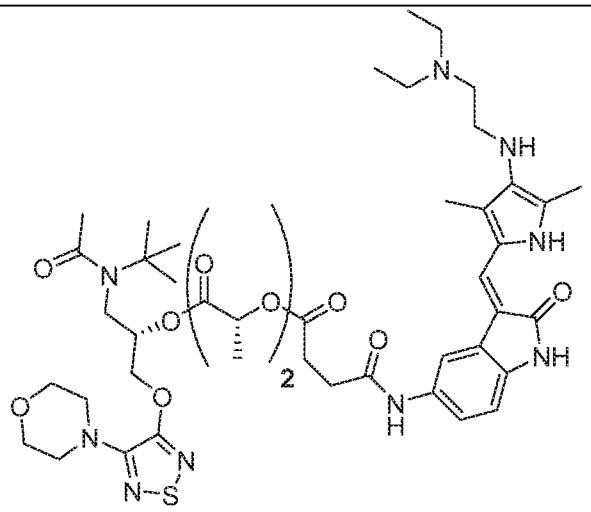
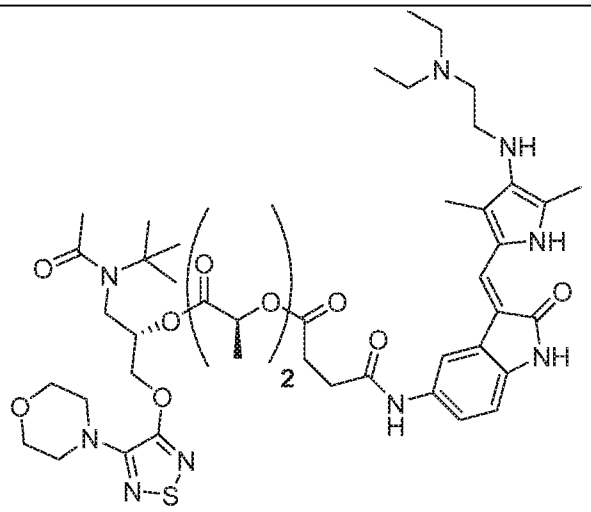
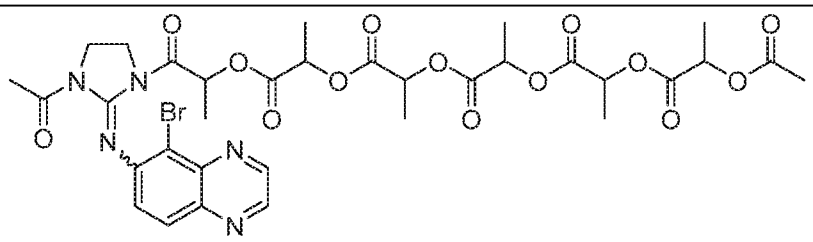
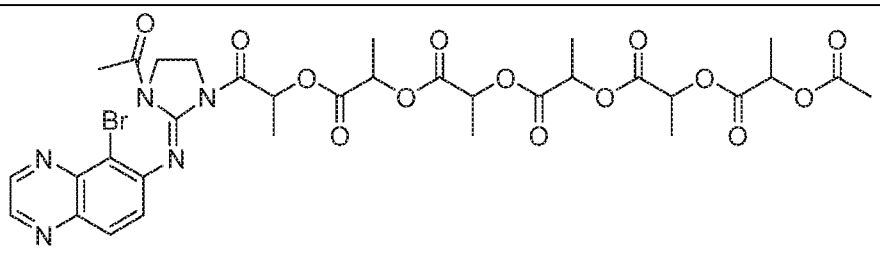
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| **232** |  |
| **233** |  |
| **234-3** |  |
| **234-3a** |  |
| **234-3b** |  |
| **234-3c** |  |

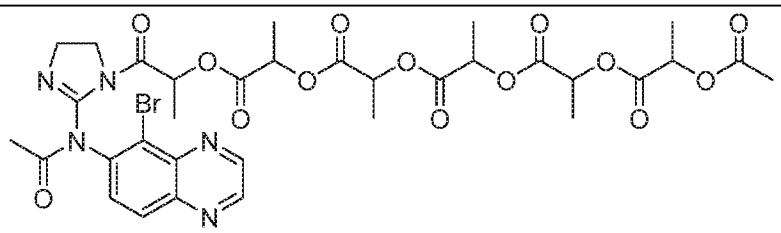
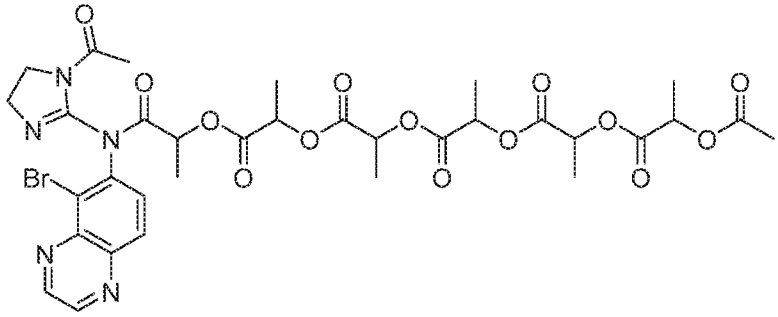
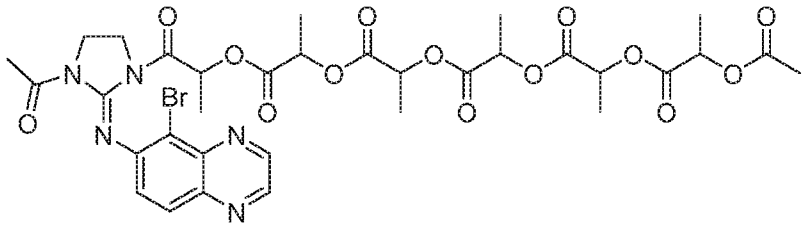
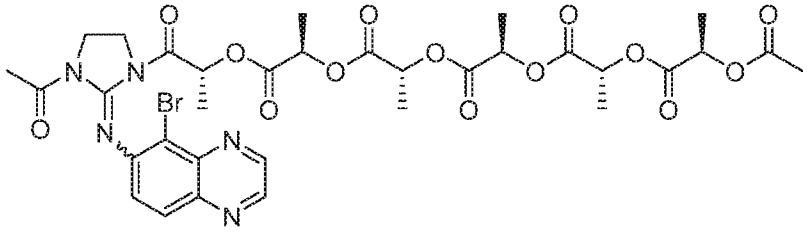
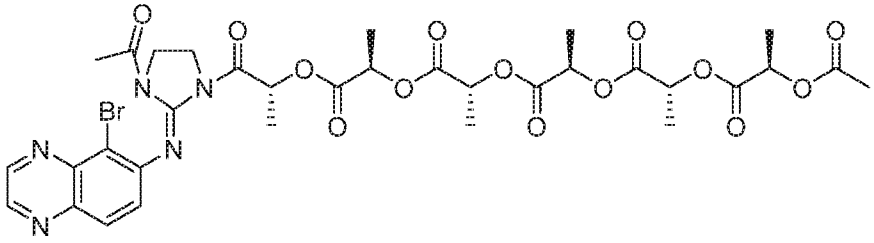
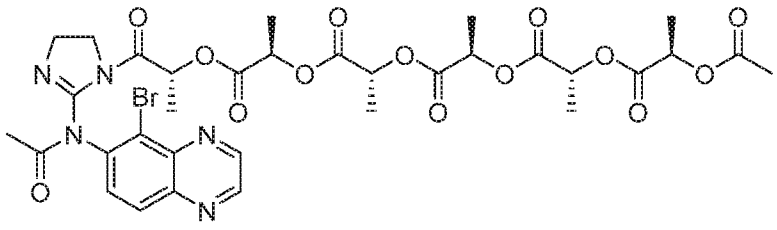
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| **234-3d** |  |
| **235** |  |
| **236** |  |
| **237** |  |
| **238-5** |  |

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| **239** |  |
| **240-6** |  |
| **241** |  |

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| **242-3** |  |
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| **244** |  |
| **245** |  |

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| **246-4** |  |
| **247** |  |
| **248-7** |  |

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| **249-3** |  |
| **250** |  |
| **251** |  |
| **251a** |  |

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| **251b** |  |
| **251c** |  |
| **251d** |  |
| **252** |  |
| **252a** |  |
| **252b** |  |

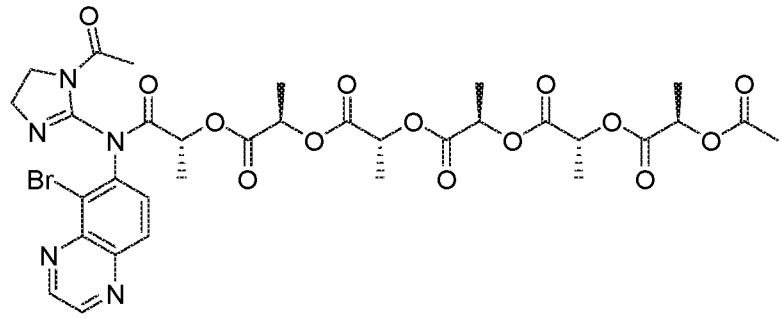
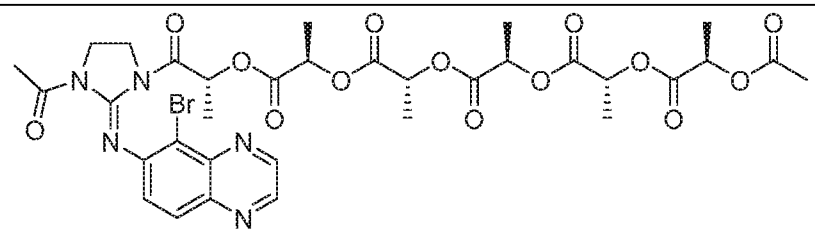
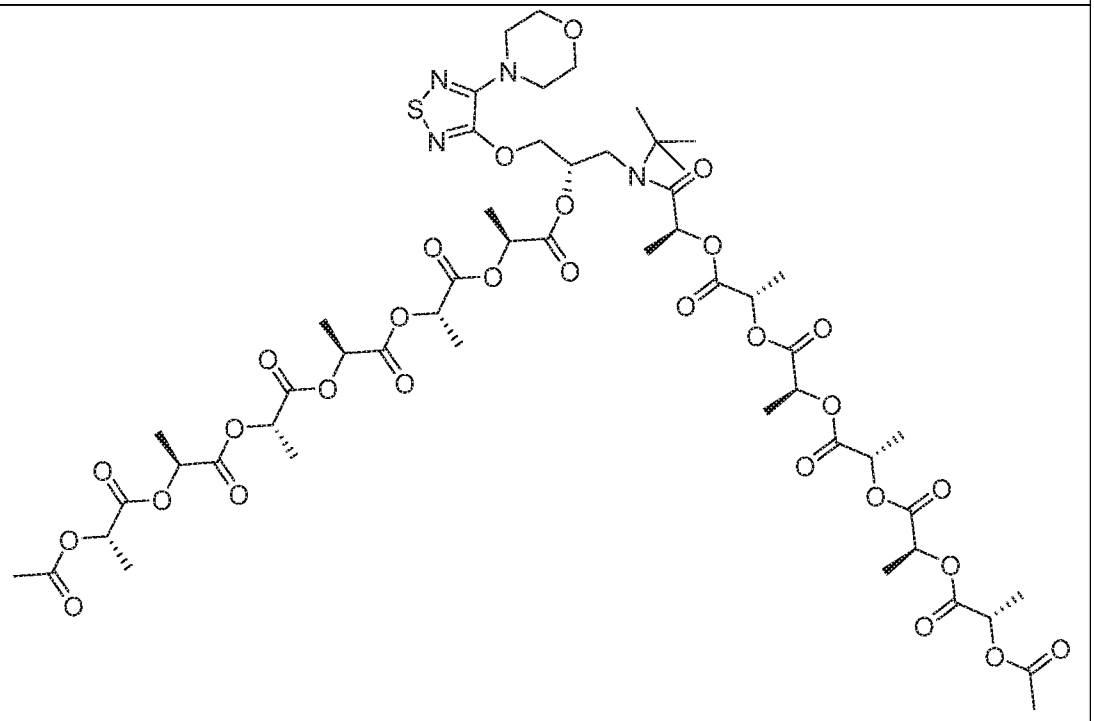
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| **252c** |  |
| **252d** |  |
| **253-3** |  |

**Table 8F. Characterization Data of Select Compounds of the Present Invention**

| | |
|---|---|
| **57-2** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.19 (quintet, 1H), 4.59 (dd, 1H), 4.47 (dd, 1H), 3.72-3.65 (m, 4H), 3.45-3.28 (m, 4H), 2.82-2.72 (m, 2H), 2.5-2.35 (m, 4H), 1.04 (s, 9H). MS *m/z* $[M+H]^+$ 417.7. |

| | |
|---|---|
| **64-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.9-8.2 (bm, 4H), 7.71 (s, 1H), 6.10 (s, 2H), 5.5-5.4 (m, 1H), 5.12-5.0 (m, 2H), 4.80 (q, 1H), 4.7-4.5 (m, 2H), 4.47 (dd, 1H), 4.0-3.9 (m, 1H), 3.74-3.66 (m, 4H), 3.5-2.9 (m, 8H), 2.65-2.2 (m, 6H), 1.84-1.72 (m, 2H), 1.49 (d, 3H), 1.42 (d, 3H), 1.37 (d, 3H), 1.35-1.25 (m, 12H), 1.21 (t, 3H), MS *m/z* $[M-H]^-$ 952.3. |
| **65-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.44-5.36 (m, 1H), 4.97 (q, 1H), 4.53 (dd, 1H), 4.41 (dd, 1H), 3.78-3.61 (m, 6H), 3.45-3.36 (m, 4H), 2.30 (t, 2H), 2.08 (s, 3H), 1.5-1.15 (m, 42H) 0.84 (t, 3H). MS *m/z* $[M+H]^+$ 697.8. |
| **66-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.47-5.37 (m, 1H), 5.09-5.01 (m, 2H), 4.55 (dd, 1H), 4.41 (dd, 1H), 3.78-3.62 (m, 6H), 3.42-3.35 (m, 4H), 2.30 (t, 2H), 2.08 (s, 3H), 1.55-1.15 (m, 45H) 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 770.1. |
| **67-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.46-5.39 (m, 1H), 5.22 (q, 1H), 5.13 (q, 1H), 5.08-5.01 (m, 2H), 4.55 (dd, 1H), 4.41 (dd, 1H), 3.80-3.64 (m, 6H), 3.41-3.36 (m, 4H), 2.33 (t, 2H), 2.08 (s, 3H), 1.55-1.18 (m, 51H) 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 914.3. |
| **68-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.4-5.2 (m, 13H), 4.56 (dd, 1H), 4.43 (dd, 1H), 3.76-3.60 (m, 6H), 3.47-3.32 (m, 4H), 2.85-2.7 (m, 10H), 2.4-2.2 (m, 4H), 2.07 (s, 3H), 2.03 (quintet, 2H), 1.34 (s, 9H), 0.91 (t, 3H). MS *m/z* $[M+H]^+$ 669.9. |
| **69-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.58-5.47 (m, 2H), 5.00 (q, 1H), 4.54 (dd, 1H), 4.41 (dd, 1H), 4.18 (quintet, 1H), 3.8-3.6 (m, 6H), 3.45-3.35 (m, 4H), 2.09 (s, 3H), 1.4-1.2 (m, 15H). MS *m/z* $[M+H]^+$ 502.7. |
| **70-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.57 (bs, 1H), 8.33 (bs, 1H), 6.07 (s, 2H), 5.48-5.39 (m, 1H), 5.37-5.24 (m, 4H), 4.65 (dd, 1H), 4.48 (dd, 1H), 3.72-3.65 (m, 4H), 3.5-3.15 (m, 6H), 2.73 (t, 2H), 2.33 (t, 2H), 2.06-1.94 (m, 4H), 1.57-1.44 (m, 2H), 1.35-1.17 (m, 23H), 0.86 (t, 3H). MS *m/z* $[M+H]^+$ 579.9. |

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| **71-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (bs, 1H), 8.53 (bs, 1H), 5.49-5.42 (m, 1H), 5.37-5.23 (m, 4H), 4.65 (dd, 1H), 4.48 (dd, 1H), 3.72-3.65 (m, 4H), 3.44-3.30 (m, 5H), 3.23-3.13 (m, 1H), 2.72 (t, 2H), 2.33 (t, 2H), 2.06-1.94 (m, 4H), 1.56-1.43 (m, 2H), 1.35-1.17 (m, 23H), 0.85 (t, 3H). MS *m/z* $[M+H]^+$ 579.9. |
| **72-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 8.53 (bs, 1H), 8.25 (bs, 1H), 7.99 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 7.30 (s, 1H), 6.53 (q, 1H), 6.03 (s, 2H), 5.46-5.36 (m, 1H), 5.05 (q, 1H), 4.63 (dd, 1H), 4.47 (dd, 1H), 3.89 (t, 2H), 3.72-3.63 (m, 5H), 3.45-3.3.1 (m, 7H), 2.72-2.56 (m, 4H), 1.64 (d, 3H), 1.50 (d, 3H), 1.27 (s, 9H). MS *m/z* $[M+H]^+$ 835.7. |
| **73-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 8.00 (d, J = 9 Hz, 1H), 7.63 (d, J = 9 Hz, 1H), 7.32 (s, 1H), 5.75 (d, 1H), 5.26 (quintet, 1H) ,3.97-3.85 (m, 2H), 3.43-3.30 (m, 2H), 1.35 (d, 3H). MS *m/z* $[M+H]^+$ 366.4. |
| **74-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.93 (d, J = 2 Hz, 1H), 8.83 (d, J = 2 Hz, 1H), 8.54 (bs, 1H), 8.26 (bs, 1H), 7.97 (d, J = 9 Hz, 1H), 7.54 (d, J = 9 Hz, 1H), 7.09 (s, 1H), 6.02 (s, 2H), 5.46-5.36 (m, 1H), 4.64 (dd, 1H), 4.45 (dd, 1H), 3.88 (t, 2H), 3.72-3.62 (m, 5H), 3.55-3.3.1 (m, 7H), 2.6-2.4 (m, 4H), 1.92 (quintet, 2H), 1.27 (s, 9H). MS *m/z* $[M+H]^+$ 705.5. |
| **75-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.6 (bs, 2H), 8.3 (bs, 2H), 6.03 (s, 4H), 5.46-5.36 (m, 2H), 4.64 (dd, 2H), 4.46 (dd, 2H), 3.72-3.63 (m, 8H), 3.45-3.1 (m, 12H), 2.4-2.2 (m, 4H), 1.48 (quintet, 4H), 1.33 (s, 18H), 1.3-1.1 (m, 8H). MS *m/z* $[M+H]^+$ 799.8. |
| **76-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.6 (bs, 2H), 8.3 (bs, 2H), 6.03 (s, 4H), 5.46-5.34 (m, 2H), 4.64 (dd, 2H), 4.49 (dd, 2H), 3.73-3.634 (m, 8H), 3.48-3.13 (m, 12H), 2.74-2.54 (m, 4H), 1.29 (s, 18H). MS *m/z* $[M+H]^+$ 715.7. |
| **77-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.6 (bs, 2H), 8.4 (bs, 2H), 6.03 (s, 4H), 5.48-5.36 (m, 2H), 4.65 (dd, 2H), 4.46 (dd, 2H), 3.75-3.65 (m, 8H), 3.5-3.1 (m, 12H), 2.5-2.3 (m, 4H), 1.77 (quintet, 2H), 1.29 (s, 18H). MS *m/z* $[M+H]^+$ 730.1. |
| **78-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.66 (bs, 2H), 8.33 (bs, 2H), 6.88 (s, 2H), 6.12 (s, 2H), 5.65-5.53 (m, 2H), 4.74 (dd, 2H), 4.52 (dd, 2H), 3.7-3.55 (m, 10H), 3.55-3.1 (m, 10H), 1.30 (s, 18H). MS *m/z* $[M+H]^+$ 713.9, $[M+2H]^{2+}$ 358.0. |
| **79-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 7.34-7.29 (m, 2H), 7.15 (d, J = 9 |

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| | Hz, 1H,), 6.52 (q, 1H), 6.06 (s, 1H), 5.55 (s, 1H), 5.27-5.11 (m, 5H), 3.96-3.83 (m, 2H), 3.43-3.33 (m, 2H), 2.36 (q, 2H), 1.64 (d, 3H), 1.52-1.42 (m, 9H), 1.07 (t, 3H),. MS *m/z* $[M+H]^+$ 886.8. |
| **80-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.8 (bs, 2H), 7.71 (s, 1H), 5.4-5.2 (m, 12H), 4.59 (bs, 1H), 4.0-3.9 (m, 1H), 3.25-3.1 (m, 1H), 3.1-2.9 (m, 1H), 2.9-2.7 (m, 10H), 2.65-2.4 (m, 2H), 2.18 (q, 2H), 2.1-1.96 (m, 4H), 1.36 (d, 3H), 1.3-1.1 (m, 3H), 0.91 (t, 3H). MS *m/z* $[M+H]^+$ 635.7. |
| **81-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 9.0-7.9 (bm, 4H), 7.69 (s, 1H), 6.05 (s, 2H), 5.5-5.4 (m, 1H), 4.68-4.55 (m, 2H), 4.49 (dd, 1H), 4.0-3.9 (m, 1H), 3.71-3.63 (m, 4H), 3.5-3.1 (m, 7H), 3.05-2.95 (m, 1H), 2.7-2.3 (m, 6H), 1.1-1.4 (m, 15H), MS *m/z* $[M+H]^+$ 723.6. |
| **82-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 9.0 (bs, 2H), 8.6 (bs, 1H), 8.0 (bs, 1H), 7.77 (s, 1H), 6.07 (s, 2H), 5.5-5.4 (m, 1H), 4.87-4.6 (m, 1H), 4.65 (dd, 1H), 4.49 (dd, 1H), 4.08-3.96 (m, 2H), 3.71-3.65 (m, 4H), 3.5-2.9 (m, 15H), 2.6-2.3 (m, 4H), 1.81 (quintet, 2H), 1.35-1.1 (m, 12H), MS *m/z* $[M+H]^+$ 780.9. |
| **83-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 2 Hz, 1H), 8.82 (d, J = 2 Hz, 1H), 7.97 (d, J = 9 Hz, 1H), 7.55 (d, J = 9 Hz, 1H), 7.09 (s, 1H), 5.20-5.10 (m, 1H), 4.59 (dd, 1H), 4.45 (dd, 1H), 3.82 (t, 2H), 3.69-3.61 (m, 4H), 3.45-3.30 (m, 8H), 2.77-2.59 (m, 4H), 0.98 (s, 9H). MS *m/z* $[M+H]^+$ 692.1. |
| **83-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 2 Hz, 1H), 8.83 (d, J = 2 Hz, 1H), 8.6 (bs, 1H), 8.3 (bs, 1H), 7.98 (d, J = 9 Hz, 1H), 7.55 (d, J = 9 Hz, 1H), 7.12 (s, 1H), 6.04 (s, 2H), 5.48-5.39 (m, 1H), 4.62 (dd, 1H), 4.48 (dd, 1H), 3.9-3.7 (m, 2H), 3.70-3.60 (m, 4H), 3.56-3.15 (m, 8H), 2.72 (t, 2H), 1.29 (s, 9H). MS *m/z* $[M+H]^+$ 692.3. |

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| **84-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 9.1-8.3 (bm, 4H), 7.69 (s, 1H), 6.04 (s, 2H), 5.5-5.4 (m, 1H), 4.7-4.5 (m, 2H), 4.48 (dd, 1H), 4.0-3.9 (m, 1H), 3.74-3.62 (m, 4H), 3.5-2.9 (m, 8H), 2.65-2.2 (m, 4H), 2.15-1.95 (m, 2H), 1.8-1.6 (m, 2H), 1.36 (d, 3H), 1.28 (s, 9H), 1.20 (t, 3H), MS *m/z* $[M-H]^-$ 735.9. |
| **85-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.73 (s, 1H), 12.12 (bs, 1H), 10.88 (s, 1H), 9.79 (s, 1H), 9.29 (bs, 1H), 7.95 (s, 1H), 7.80 (t, 1H), 7.47 (s, 1H), 7.20 (d, *J* = 8 Hz, 1H), 6.82 (d, *J* = 8 Hz, 1H), 3.6-3.5 (m, 2H), 3.3-3.1 (m, 6H), 2.46, (s, 3H), 2.40 (s, 3H), 2.36-2.22 (m, 4H), 1.85-1.75 (m, 2H), 1.21 (t, 6H). MS *m/z* $[M+H]^+$ 510.7. |
| **86-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.72 (s, 1H), 12.03 (bs, 2H), 10.86 (s, 1H), 9.73 (s, 1H), 7.93 (s, 1H), 7.73 (t, 1H), 7.46 (s, 1H), 7.21 (d, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 3.6-3.5 (m, 2H), 3.3-3.0 (m, 6H), 2.46, (s, 3H), 2.42 (s, 3H), 2.3-2.1 (m, 4H), 1.6-1.4 (m, 4H), 1.3-1.1 (m, 18H). MS *m/z* $[M+H]^+$ 608.9. |
| **87-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.73 (s, 1H), 12.0 (bs, 1H), 10.88 (s, 1H), 9.76 (s, 1H), 9.34 (bs, 1H), 7.96 (s, 1H), 7.81 (t, 1H), 7.47 (s, 1H), 7.22 (d, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 3.65-3.5 (m, 2H), 3.3-3.1 (m, 6H), 2.47, (s, 3H), 2.42 (s, 3H), 2.3-2.1 (m, 4H), 1.65-1.4 (m, 4H), 1.35-1.15 (m, 14H). MS *m/z* $[M+H]^+$ 580.9. |
| **88-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 12.81 (s, 1H), 8.46 (s, 1H), 8.2-7.7 (m, 2H), 7.7-7.4 (m, 4H), 7.29-7.20 (m, 1H), 6.86-6.70 (m, 3H), 5.24-4.98 (m, 4H), 4.68-4.54 (m, 2H), 4.32-4.13 (m, 2H), 3.73 (s, 3H), 3.58 (t, 2H), 2.06 (s, 3H), 1.50-1.34 (m, 12H). MS *m/z* $[M+H]^+$ 697.9. |
| **89-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 12.82 (s, 1H), 8.46 (s, 1H), 8.07 (bs, 1H), 7.82 (bs, 1H), 7.50-7.40 (m, 4H), 7.29-7.20 (m, 1H), 6.86-6.77 (m, 3H), 5.24-4.98 (m, 6H), 4.68-4.54 (m, 2H), 4.32-4.13 (m, 2H), 3.73 (s, 3H), 3.58 (t, 2H), 2.06 (s, 3H), 1.51-1.34 (m, 18H). MS *m/z* $[M+H]^+$ 842.1. |

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| **90-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.1-7.9 (m, 2H), 7.75-7.6 (m, 2H), 7.34-7.26 (m, 1H), 7.25 (s, 1H), 7.15 (d, 1H), 6.90-6.83 (m, 3H), 5.25-4.98 (m, 4H), 4.68-4.54 (m, 2H), 4.35-4.12 (m, 2H), 3.74 (s, 3H), 3.63 (t, 2H), 3.4-3.3 (m, 2H), 3.9-3.4 (m, 6H), 2.06 (s, 3H), 1.75-1.66 (m, 4H), 1.50-1.36 (m, 12H). MS *m/z* $[M+H]^+$ 811.1. |
| **91-2** | $^1$H-NMR (400 MHz, DMSO-d6) δ 12.9 (bs, 1H), 8.1-7.9 (m, 2H), 7.9-7.5 (m, 2H), 7.36-7.2 (m, 2H), 7.17 (d, 1H), 6.90-6.83 (m, 3H), 5.24-4.95 (m, 6H), 4.72-4.54 (m, 2H), 4.4-4.2 (m, 4H), 3.75 (s, 3H), 3.63 (t, 2H), 3.3-2.6 (m, 6H), 2.06 (s, 3H), 1.9-1.7 (m, 4H), 1.50-1.36 (m, 18H). MS *m/z* $[M+H]^+$ 955.1. |
| **101-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 12.8 (bs, 1H), 8.94 (d, J = 2 Hz, 1H), 8.83 (d, J = 2 Hz, 1H), 8.46 (s, 1H), 8.15-7.8 (m, 3H), 7.56 (d, 1H), 7.50-7.40 (m, 4H), 7.29-7.21 (m, 1H), 7.10 (s, 1H), 6.86-6.77 (m, 3H), 5.14-5.02 (m, 2H), 4.67-4.54 (m, 2H), 4.32-4.12 (m, 2H), 4.9-4.8 (m, 2H), 3.72 (s, 3H), 3.58 (t, 2H), 3.45-3.25 (m, 2H), 2.8-2.4 (m, 4H), 1.43 (d, 3H), 1.38 (d, 3H). MS *m/z* $[M+H]^+$ 883.7. |
| **102-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.5-5.4 (m, 1H), 5.4-5.2 (m, 12H), 5.1-5.0 (m, 2H), 4.56 (dd, 1H), 4.44 (dd, 1H), 3.8-3.63 (m, 6H), 3.42-3.34 (m, 4H), 2.85-2.73 (m, 10H), 2.4-2.2 (m, 4H), 2.09 (s, 3H), 2.02 (quintet, 2H), 1.45-1.32 (m, 15H), 0.91 (t, 3H). MS *m/z* $[M+H]^+$ 814.3. |
| **103-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.5-5.4 (m, 1H), 5.4-5.0 (m, 16H), 4.55 (dd, 1H), 4.42 (dd, 1H), 3.8-3.63 (m, 6H), 3.42-3.34 (m, 4H), 2.85-2.74 (m, 10H), 2.42-2.37 (m, 2H), 2.36-2.24 (m, 2H), 2.08 (s, 3H), 2.02 (quintet, 2H), 1.45-1.32 (m, 21H), 0.91 (t, 3H). MS *m/z* $[M+H]^+$ 957.7. |
| **104-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.74 (s, 1H), 10.98 (s, 1H), 9.1 (bs, 1H), 7.77 (t, 1H), 7.68 (s, 1H), 7.61 (d, 1H), 6.9-6.8 (m, 2H), 5.5-5.4 (m, 1H), 5.2-5.0 (m, 2H), 4.56 (dd, 1H), 4.44 (dd, 1H), 3.8-3.6 (m, 6H), 3.6-3.5 (m, 2H), 3.5-3.1 (m, 10H), 2.85-2.65 (m, 4H), 2.47 (s, 3H), 2.44 (s, 3H), 2.07 (s, 3H), 1.44-1.32 (m, 15H), 1.20 (t, 6H); MS *m/z* $[M+H]^+$ 982.3 |

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| **105-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.74 (s, 1H), 10.99 (s, 1H), 9.1 (bs, 1H), 7.77 (t, 1H), 7.69 (s, 1H), 7.61 (d, 1H), 6.9-6.8 (m, 2H), 5.5-5.4 (m, 1H), 5.26-4.98 (m, 4H), 4.56 (dd, 1H), 4.43 (dd, 1H), 3.8-3.6 (m, 6H), 3.6-3.5 (m, 2H), 3.5-3.18 (m, 10H), 2.9-2.7 (m, 4H), 2.47 (s, 3H), 2.44 (s, 3H), 2.08 (s, 3H), 1.5-1.3 (m, 21H), 1.23 (t, 6H); MS *m/z* $[M+H]^+$ 1126.7. |
| **106-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.74 (s, 1H), 10.97 (s, 1H), 7.75 (t, 1H), 7.65 (s, 1H), 7.61 (d, 1H), 6.9-6.8 (m, 2H), 5.5-5.2 (m, 12H), 3.6-3.5 (m, 2H), 3.3-3.15 (m, 6H), 2.9-2.7 (m, 12H), 2.7-2.6 (m, 2H), 2.47 (s, 3H), 2.42 (s, 3H), 2.02 (quintet, 2H), 1.23 (t, 6H), 0.90 (t, 3H); MS *m/z* $[M+H]^+$ 708.2. |
| **107-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 7.30 (s, 1H), 6.52 (q, 1H), 5.26-5.16 (m, 4H), 5.03 (q, 1H), 3.95-3.84 (m, 2H), 3.44-3.34 (m, 2H), 2.06 (s, 3H), 1.64 (d, 3H), 1.52-1.39 (m, 15H). MS *m/z* $[M+H]^+$ 767.1. |
| **108-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.68 (s, 1H), 11.10 (s, 1H), 7.71 (t, 1H), 7.65 (s, 2H), 6.97 (s, 2H), 3.55-3.45 (m, 2H), 3.3-3.0 (m, 6H), 2.81 (s, 4H), 2.47 (s, 3H), 2.42 (s, 3H), 1.18 (t, 6H); MS *m/z* $[M+H]^+$ 478.7. |
| **109-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 7.29 (s, 1H), 6.52 (q, 1H), 5.25-5.14 (m, 6H), 5.04 (q, 1H), 3.97-3.85 (m, 2H), 3.44-3.34 (m, 2H), 2.06 (s, 3H), 1.63 (d, 3H), 1.54-1.36 (m, 21H). MS *m/z* $[M+H]^+$ 911.6. |
| **110-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 9.08 (d, J = 2H, 1H), 9.07 (d, J = 2Hz, 1H), 8.19 (d, J = 9 Hz, 1H), 7.97 (d, J = 9 Hz, 1H), 4.14-3.91 (m, 2H), 3.63-3.46 (m, 2H), 3.21-3.12 (m, 1H), 3.04-2.85 (m, 3H). MS *m/z* $[M+H]^+$ 376.1. |
| **111-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.86 (d, J = 2 Hz, 1H), 7.93-7.87 (m, 1H), 7.63-7.54 (m, 1H), 6.2-5.6 (m, 2H), 5.05-4.93 (m, 2H), 4.2-3.9 (m, 4H), 2.05 (s, 3H), 2.03 (s, 3H), 1.5-1.2 (m, 12H). MS *m/z* $[M+H]^+$ 738.6. |

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| **112-1** | $^1$H-NMR (400 MHz, DMSO-d6, TFA) δ 13.74 (s, 1H), 10.87 (s, 1H), 9.99 (s, 1H), 9.25 (bs, 1H), 8.74 (bt, 1H), 8.25 (bt, 1H), 7.86 (d, 1H), 7.80 (t, 1H), 7.43 (s, 1H), 7.17 (dd, 1H), 6.80 (d, 1H), 6.25 (s, 2H), 5.51-5.43 (m, 1H), 4.64 (dd, 1H), 4.46 (dd, 1H), 3.7-3.5 (m, 6H), 3.5-3.3 (m, 6H), 3.3-3.1 (m, 6H), 2.75-2.55 (m, 4H), 2.46 (s, 3H), 2.40 (s, 3H) 1.27 (s, 9H), 1.22, (t, 6H); MS *m/z* $[M+H]^+$ 795.0. |
| **113-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.82 (s, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 7.68 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 7.29-7.22 (m, 1H), 6.86-6.77 (m, 3H), 6.09 (q, 1H), 5.31-4.99 (m, 7H), 4.68-4.54 (m, 2H), 4.32-4.15 (m, 2H), 3.73 (s, 3H), 3.58 (t, 2H), 2.06 (s, 6H), 1.60 (d, 3H), 1.52 (d, 3H), 1.50-1.34 (m, 18H). MS *m/z* $[M+H]^+$ 1028.5. |
| **114-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 6.3-6.1 (m, 1H), 5.02 (q, 1H), 4.14-3.85 (m, 4H), 2.09 (bs, 3H), 1.99 (s, 3H), 1.55-1.37 (m, 6H). MS *m/z* $[M+H]^+$ 521.2. |
| **115-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.95 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.59 (d, J = 9 Hz, 1H), 6.3-6.1 (m, 1H), 5.23-5.13 (m, 2H), 5.01 (q, 1H), 4.15-3.85 (m, 4H), 2.06 (s, 6H), 1.55-1.37 (m, 12H). MS *m/z* $[M+H]^+$ 665.8. |
| **116-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.96 (d, J = 2 Hz, 1H), 8.85 (d, J = 2 Hz, 1H), 7.93-7.86 (m, 1H), 7.62-7.54 (m, 1H), 6.1-5.7 (m, 2H), 5.24-4.96 (m, 6H), 4.2-3.9 (m, 4H), 2.06 (s, 6H), 1.5-1.2 (m, 24H). MS *m/z* $[M+H]^+$ 954.1. |
| **117-6** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.5-5.3 (m, 2H), 4.98 (q, 1H), 4.65-4.4 (m, 2H), 4.06-3.9 (m, 2H), 3.85-3.55 (m, 6H), 3.46-3.33 (m, 4H), 2.6-2.4 (m, 4H), 2.06 (s, 3H), 1.45-1.28 (m, 15H), 1.2-1.05 (m, 3H). MS *m/z* $[M+H]^+$ 632.2. |
| **118-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.5-5.3 (m, 2H), 5.15-4.94 (m, 3H), 4.7-4.5 (m, 1H), 4.5-4.35 (m, 1H), 3.8-3.6 (m, 6H), 3.46-3.3 (m, 4H), 2.06 (s, 3H), 2.05 (s, 3H), 1.45-1.28 (m, 21H). MS *m/z* $[M+H]^+$ 691.7, $[M+Na]^+$ 712.1. |

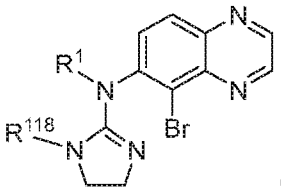
| | |
|---|---|
| **119-6** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.4-5.0 (m, 7H), 4.7-4.5 (m, 1H), 4.5-4.35 (m, 1H), 3.8-3.6 (m, 6H), 3.46-3.3 (m, 4H), 2.06 (s, 6H), 1.45-1.28 (m, 33H). MS *m/z* $[M+H]^+$ 998.0, $[M+Na]^+$ 1000.5. |
| **120-1** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.23-5.01 (m, 3H), 4.65-4.4 (m, 2H), 4.1-3.95 (m, 3H), 3.85-3.55 (m, 5H), 3.5-3.3 (m, 4H), 2.6-2.4 (m, 4H), 2.07 (s, 3H), 1.4-1.2 (m, 21H), 1.2-1.05 (m, 3H). MS *m/z* $[M+H]^+$ 776.7. |
| **234-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 8.94 (d, J = 2 Hz, 1H), 8.84 (d, J = 2 Hz, 1H), 7.90 (d, J = 9 Hz, 1H), 7.58 (d, J = 9 Hz, 1H), 6.3-6.1 (m, 1H), 5.24-5.14 (m, 4H), 5.02 (q, 1H), 4.15-3.85 (m, 4H), 2.06 (s, 6H), 1.55-1.37 (m, 18H). MS *m/z* $[M+H]^+$ 808.6. |
| **238-5** | $^1$H-NMR (400 MHz, DMSO-d6) δ 7.37 (s, 1H), 5.26-5.13 (m, 9H), 5.13-5.00 (m, 2H), 4.79 (q, 1H), 3.94-3.75 (m, 2H), 2.7-2.5 (m, 2H), 2.32-2.2 (m, 2H), 2.07 (s, 3H), 1.51-1.38 (m, 33H), 1.35-1.25 (m, 6H), 1.02 (t, 3H); MS *m/z* $(M+H)^+$ 1232.4. |
| **240-6** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.25-4.92 (m, 5H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.45-3.3 (m, 4H), 2.06 (s, 3H), 2.05 (s, 3H), 1.5-1.35 (m, 18H), 1.35 (s, 9H). MS *m/z* $[M+Na]^+$ 856.3. |
| **242-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.23-5.01 (m, 5H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.47-3.3 (m, 4H), 2.05 (s, 3H), 2.03 (s, 3H), 1.5-1.35 (m, 18H), 1.34 (s, 9H). MS *m/z* $[M+Na]^+$ 856.5. |
| **244** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.3-5.0 (m, 11H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.45-3.3 (m, 4H), 2.07 (s, 6H), 1.5-1.35 (m, 36H), 1.33 (s, 9H). MS *m/z* $[M+NH_4]^+$ 1284.3. |
| **246-4** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.71 (s, 1H), 10.86 (s, 1H), 9.88 (s, 1H), 8.14 (s, 1H), 7.94 (d, *J* = 2 Hz, 1H), 7.68 (t, 1H), 7.5-7.4 (m, 2H), 7.17 (dd, *J* = 2 Hz, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 5.25-5.0 (m, 5H), 4.79 (q, 1H), 4.1-3.8 (m, 2H), 3.55-3.4 (m, 2H), 3.15-2.9 (m, 6H), 2.8-2.5 (m, 6H), 2.46 (s, 3H), 2.41 (s, |

| | |
|---|---|
| | 3H), 2.4-2.2 (m, 2H), 1.55-1.4 (m, 15H), 1.36-1.24 (m, 6H), 1.16 (t, 6H), 1.06 (t, 3H); MS *m/z* $[M+H]^+$ 1235.6, $[M+2H]^{2+}$ 619.8. (As mono-formate salt) |
| **248-7** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.71 (s, 1H), 10.87 (s, 1H), 9.88 (s, 1H), 8.14 (s, 1H), 7.94 (d, *J* = 2 Hz, 1H), 7.69 (t, 1H), 7.5-7.4 (m, 2H), 7.17 (dd, *J* = 2 Hz, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 4.99 (q, 1H), 4.80 (q, 1H), 4.1-3.8 (m, 2H), 3.5-3.4 (m, 2H), 3.1-2.95 (m, 6H), 2.8-2.5 (m, 6H), 2.46 (s, 3H), 2.42 (s, 3H), 2.4-2.2 (m, 2H), 1.46 (d, 3H), 1.4-1.3 (m, 6H), 1.16 (t, 6H), 1.06 (t, 3H); MS *m/z* $[M+H]^+$ 947.4 (As mono-formate salt) |
| **249-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 13.64 (s, 1H), 10.84 (s, 1H), 9.87 (s, 1H), 7.89 (d, *J* = 2 Hz, 1H), 7.47 (t, 1H), 7.43 (s, 1H), 7.21 (dd, *J* = 2 Hz, *J* = 8 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 5.48-5.36 (m, 1H), 5.12-4.97 (m, 2H), 4.54 (dd, 1H), 4.41 (dd, 1H), 3.8-3.6 (m, 6H), 3.5-3.3 (m, 6H), 2.7-2.5 (m, 8H), 2.44 (s, 3H), 2.39 (s, 3H), 2.09 (s, 3H), 1.5-1.3 (m, 15H), 0.99 (t, 6H); MS *m/z* $[M+H]^+$ 981.4. |
| **253-3** | $^1$H-NMR (400 MHz, DMSO-d6) δ 5.55-5.3 (m, 2H), 5.3-5.0 (m, 11H), 4.7-4.3 (m, 2H), 3.8-3.6 (m, 6H), 3.45-3.3 (m, 4H), 2.07 (s, 6H), 1.5-1.35 (m, 36H), 1.33 (s, 9H). MS *m/z* $[M+NH_4]^+$ 1284.3. |

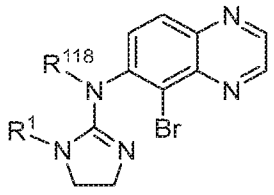
This specification has been described with reference to embodiments of the invention. However, one of ordinary skill in the art appreciates that various modifications and changes can be made without departing from the scope of the invention as set forth herein. Accordingly, the specification is to be regarded in an illustrative rather than a restrictive sense, and all such modifications are intended to be included within the scope of invention.

WHAT IS CLAIMED IS:

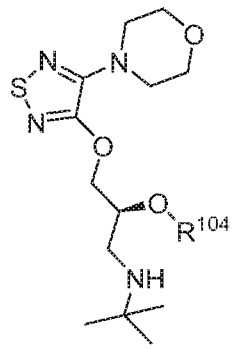
1. A compound of Formula VII, Formula VIII, Formula XIV, Formula XVI, Formula XVII, Formula XXXI, Formula XXXIII, Formula XXXV, Formula XXXVII, Formula XXXIX, Formula XLI, Formula XLIII, Formula XLV, Formula XLVII, or Formula XLIX:



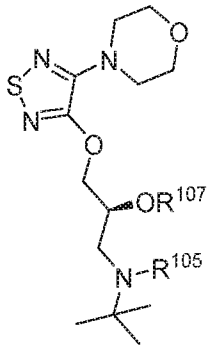
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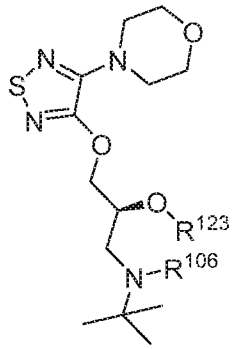
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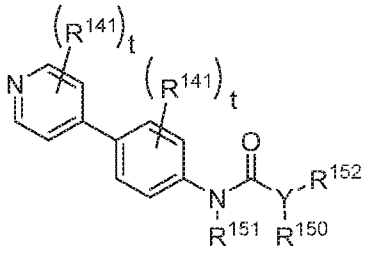
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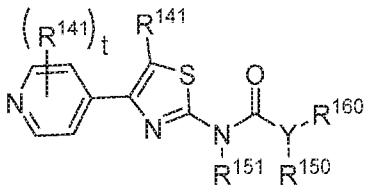
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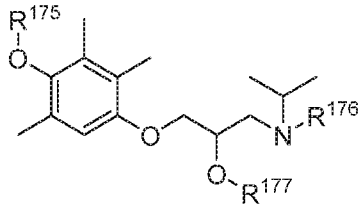
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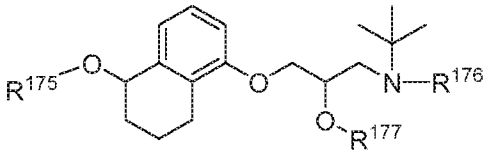
(XXXI)



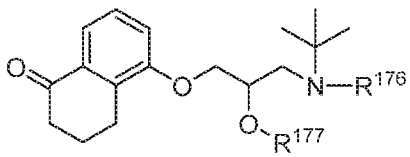
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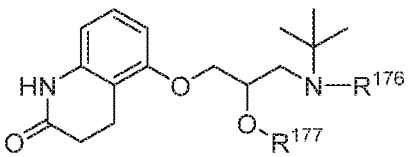
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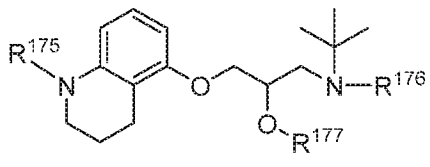
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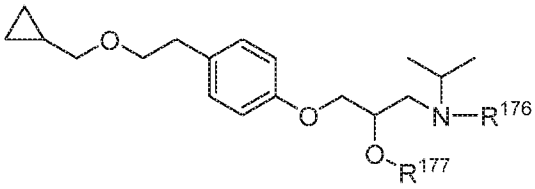
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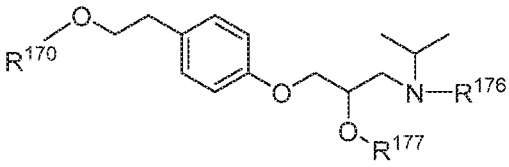
(XLI)



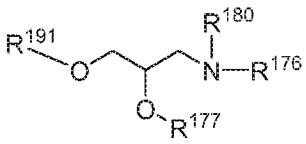
(XLIII)



(XLV)



(XLVII)



(XLIX)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof;

wherein:

$R^1$ and $R^2$ are independently selected from -C(O)$R^4$, C(O)A, or hydrogen;

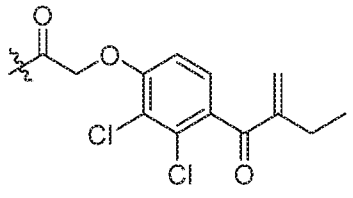
$R^4$ is selected from:

(i) –$C_{20}$-$C_{30}$alkyl$R^5$, –$C_{20}$-$C_{30}$alkenyl$R^5$, -$C_{20}$-$C_{30}$alkynyl$R^5$, -$C_{20}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{20}$-$C_{30}$alkyl, –$C_{20}$-$C_{30}$alkenyl, -$C_{20}$-$C_{30}$alkynyl, and -$C_{20}$-$C_{30}$alkenylalkynyl; and

(ii) an unsaturated fatty acid residue selected from –$(CH_2)_3(CHCHCH_2)_6CH_3$), –$(CH_2)_4(CHCHCH_2)_5CH_3$), docosatetraenoic acid, and nervonic acid;

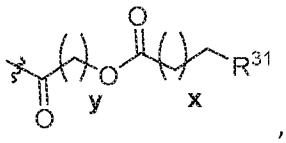
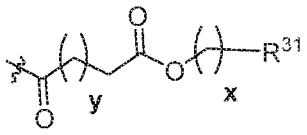
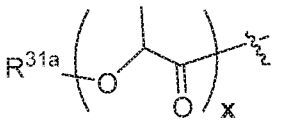
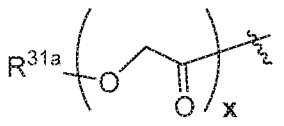
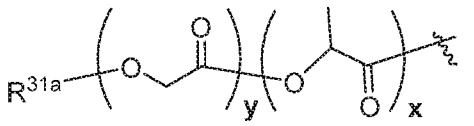
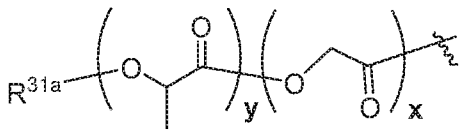
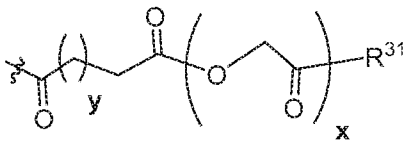
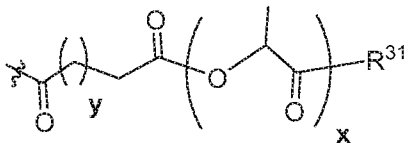
$R^5$ is selected from halogen, hydroxyl, cyano, mercapto, amino, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si$(CH_3)_3$, -COOH, -COOalkyl, and -$CONH_2$;

$R^{31}$ is hydrogen, hydroxy, amino, A, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, or polyethylene glycol;

$R^{31a}$ is hydrogen, A, -C(O)alkyl, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polyglycolic acid, polyethylene glycol, stearoyl, or ;

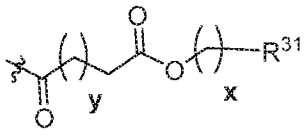
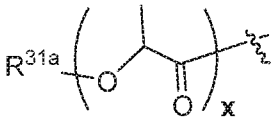
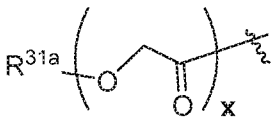
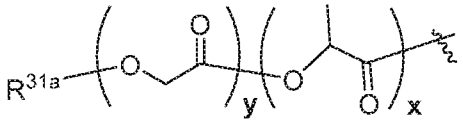
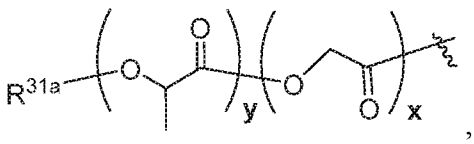
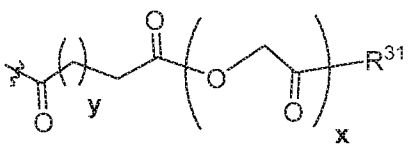
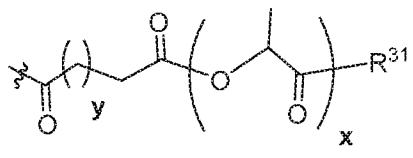
$R^{104}$ is selected from -C(O)$C_{17-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain, -C(O)($C_{10-30}$alkenyl with at least one $R^5$ substituent on the alkenyl chain, and -C(O)($C_{10-30}$alkynyl with at least one $R^5$ substituent on the alkynyl chain;

$R^{105}$ is selected from:

(i) , , , , , , , and ; and

(ii) -C(O)$C_{10-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain, -C(O)($C_{10-30}$alkenyl with at least one $R^5$ substituent on the alkenyl chain, -C(O)($C_{10-30}$alkynyl with at least one $R^5$ substituent on the alkynyl chain, -(lactic acid)$_{1-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)$_{C4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH,

-(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, and -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl;

R$^{106}$ is selected from , , , , , , , acyl, aryl, alkyl, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

R$^{107}$ is selected from hydrogen, -C(O)A, aryl, alkyl, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl;

R$^{118}$ is selected from:

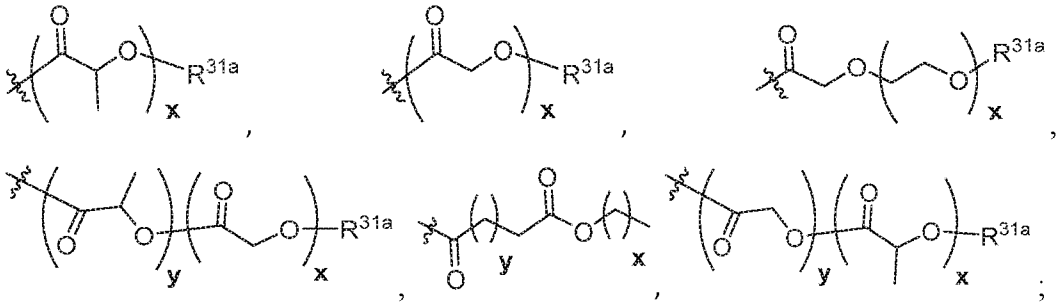
(i) –C(O)C$_5$-C$_{30}$alkylR$^5$, -C(O)C$_2$-C$_{30}$alkenylR$^5$, -C(O)C$_2$-C$_{30}$alkynylR$^5$, -C(O)C$_4$-C$_{30}$alkenylalkynylR$^5$, –C(O)C$_5$-C$_{30}$alkyl, -C(O)C$_2$-C$_{30}$alkenyl, -C(O)C$_2$-C$_{30}$alkynyl, and -C(O)C$_4$-C$_{30}$alkenylalkynyl;

(ii) -C(O)(C$_{1-30}$alkyl with at least one R$^5$ substituent on the alkyl chain, -C(O)(C$_{1-30}$alkenyl with at least one R$^5$ substituent on the alkenyl chain, -C(O)(C$_{1-30}$alkynyl with at least one R$^5$ substituent on the alkynyl chain, -(lactic acid)$_{1-20}$C(O)C$_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)C$_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)C$_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-30}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)C$_{1-30}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-12}$alkyl, -(lactide-

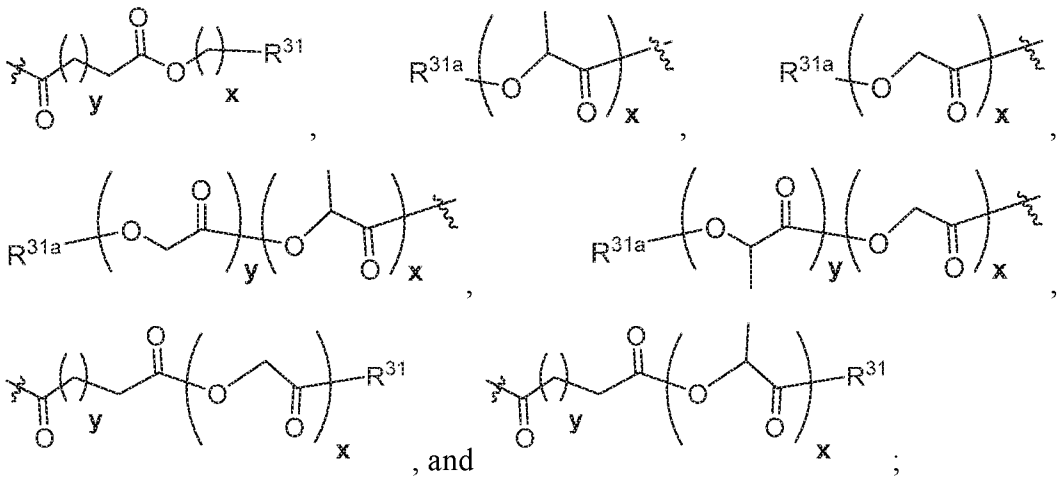
co-glycolide)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, and -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl;

(iii) a carbonyl fragment of an unsaturated fatty acid residue selected from -(CH$_2$)$_8$(CH)$_2$CH$_2$(CH)$_2$(CH$_2$)$_4$CH$_3$), –(CH$_2$)$_3$(CHCHCH$_2$)$_6$CH$_3$), –(CH$_2$)$_4$(CHCHCH$_2$)$_5$CH$_3$), –(CH$_2$)$_8$(CHCHCH$_2$)$_3$CH$_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iv) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, and polyester; and

(v) ;

R$^{123}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , and ;

(ii) -C(O)$C_{17-30}$alkyl, -C(O)$C_{10-30}$alkenyl, -C(O)$C_{10-30}$alkynyl, -C(O)($C_{10-30}$alkyl with at least one $R^5$ substituent on the alkyl chain, -C(O)($C_{10-30}$alkenyl with at least one $R^5$ substituent on the alkenyl chain, -C(O)($C_{10-30}$alkynyl with at least one $R^5$ substituent on the alkynyl chain, -(lactic acid)$_{1-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-22}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)$C_{1-22}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, and -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl;

$R^{134}$ and $R^{135}$ are independently selected from H, alkyl, -$SO_2CH_3$, -C(O)$CH_3$, and -C(O)$NH_2$;

$R^{141}$ is selected from hydrogen, -C(O)$NR^1R^2$, -C(O)$R^1$, -C(O)$OR^1$, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, and halogen;

$R^{150}$ and $R^{151}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{156}$;

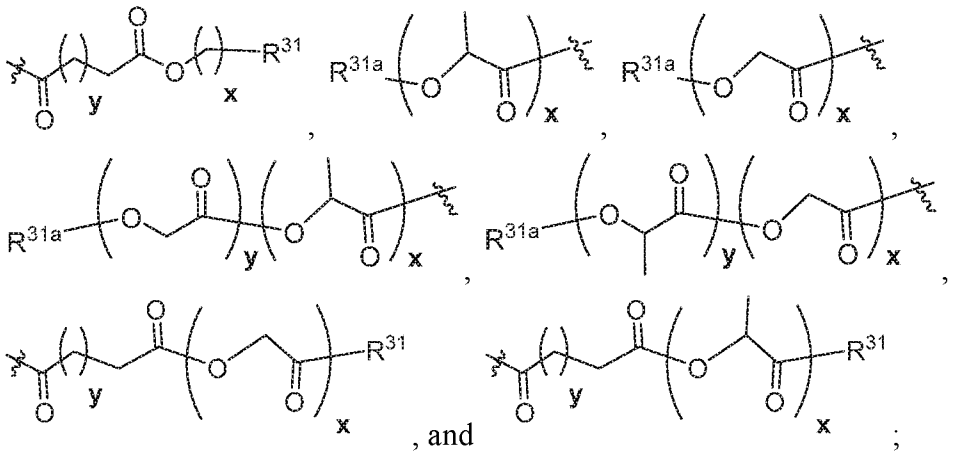
wherein at least one of $R^{150}$ and $R^{151}$ is $R^{156}$;

$R^{152}$ is selected from $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and alkylaryl;

or $R^{151}$ and $R^{152}$ can together form a cycloalkyl or heterocycloalkyl;

$R^{156}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid) polyglycolic acid, polyester, polyamide; and

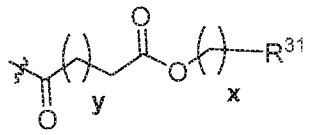
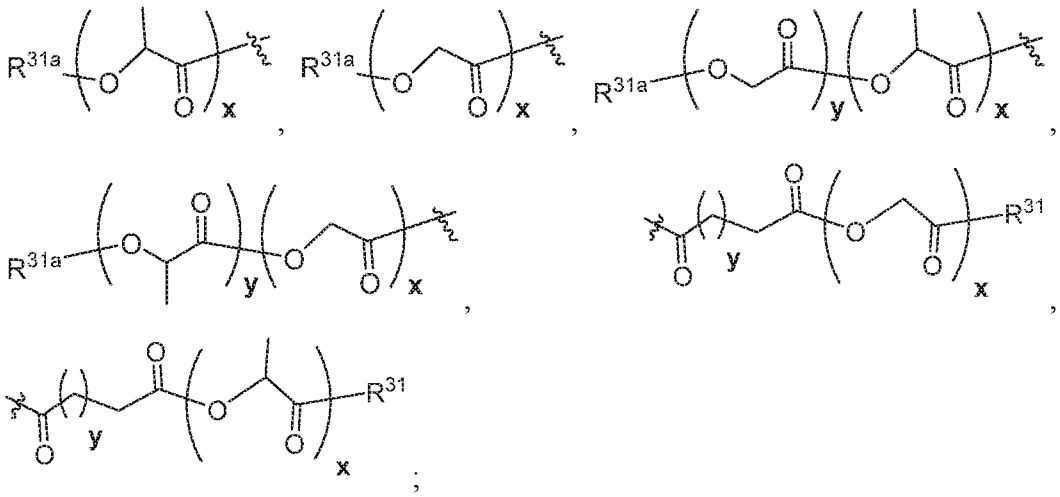
(ii) , and ;

$R^{160}$ is selected from H, $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, and aryl;

$R^{175}$, $R^{176}$, and $R^{177}$ are independently selected from C(O)A, C(O)$R^4$, and $R^{178}$;

wherein at least one of $R^{175}$, $R^{176}$, and $R^{177}$ is $R^{178}$;

$R^{178}$ is selected from:

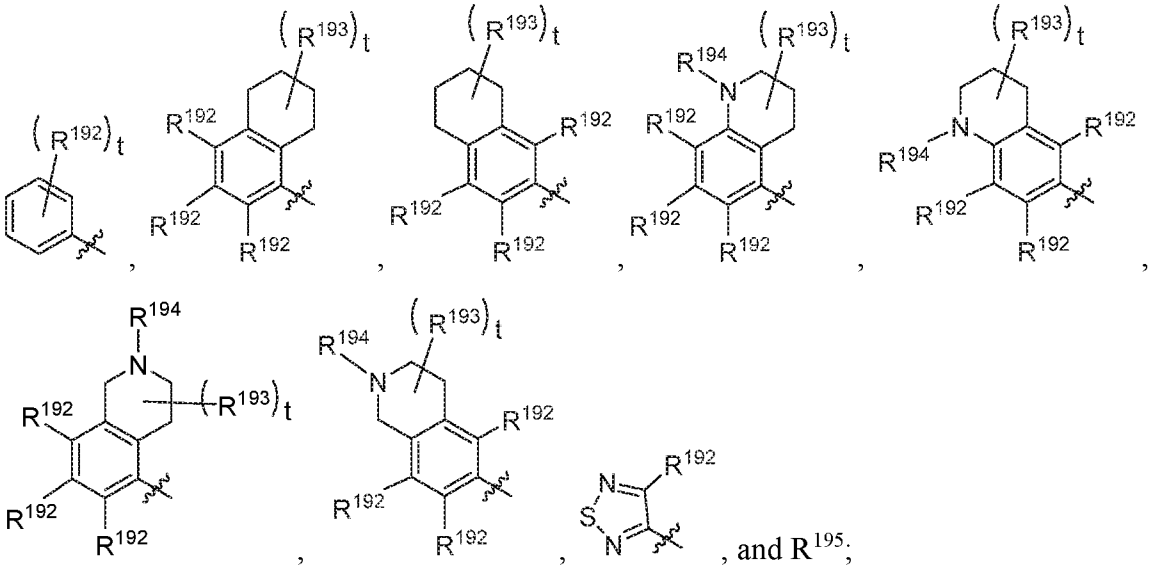
(i) carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , ;

(ii) -(lactic acid)$_{1\text{-}20}$C(O)$C_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)$C_{1\text{-}22}$alkyl, -(lactic acid)$_{4\text{-}20}$C(O)$C_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)$C_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)$C_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}10}$C(O)OH, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)$C_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{4\text{-}10}$C(O)$C_{1\text{-}22}$alkyl, -(lactide-co-

glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, and -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl;

$R^{180}$ is $C_1$-$C_6$ alkyl, acyl, or hydrogen;

$R^{191}$ is selected from:



, and $R^{195}$;

$R^{192}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{192}$ is optionally substituted with a $R^{175}$ group;

$R^{193}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

$R^{194}$ is selected from alkyl, cycloalkyl, $R^{175}$, and acyl; and

$R^{195}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{195}$ is optionally substituted with 1, 2, 3, or 4 $R^{192}$ groups;

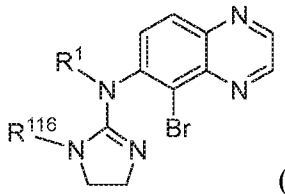
A is selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy;

Y is $CR^{150}$ or N;

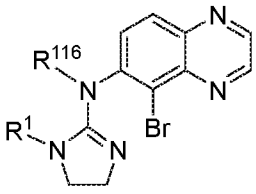
t is independently selected from 0, 1, 2, 3, and 4; and

x and y are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30.

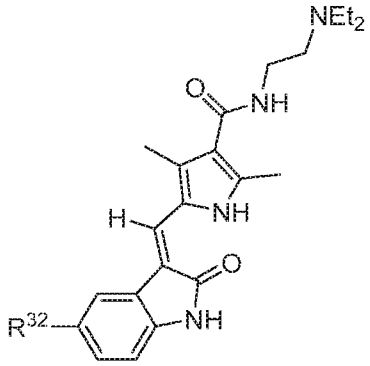
2. A compound of Formula IX, Formula IX', Formula XI, Formula XV, Formula XXVI, Formula XXVII, Formula XXVIII, Formula XXIX, Formula XXX, Formula XXX', Formula XXX'', Formula XXXII, Formula XXXIV, Formula XXXVI, Formula XXXVIII, Formula XL, Formula XLII, Formula XLIV, Formula XLVI, or Formula XLVIII:



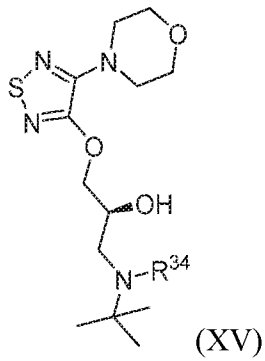
(IX)



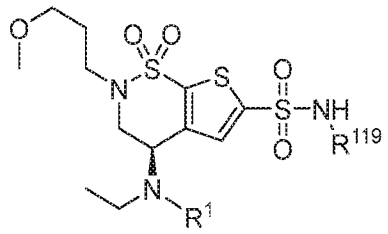
(IX')



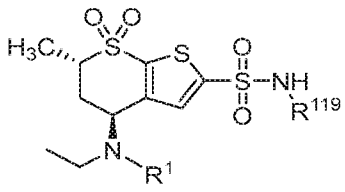
(XI)



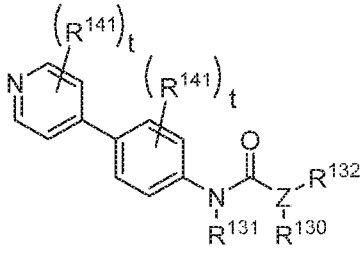
(XV)



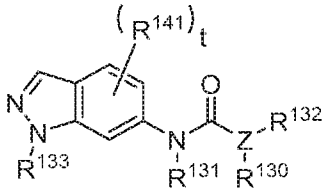
(XXVI)



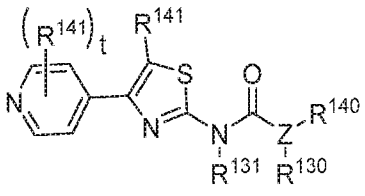
(XXVII)

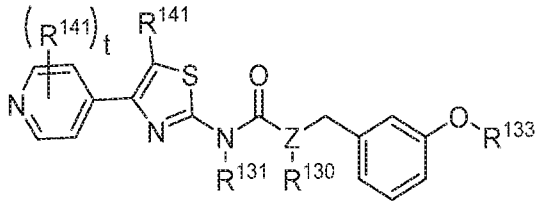


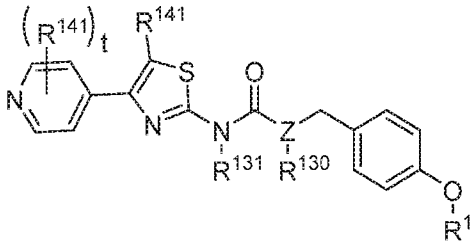
(XXVIII)

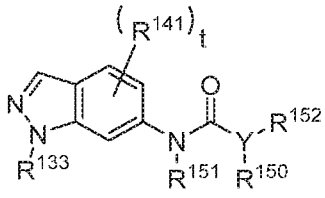


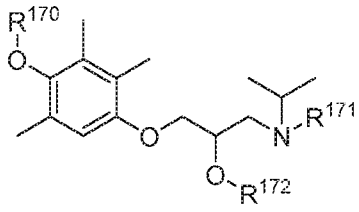
(XXIX)

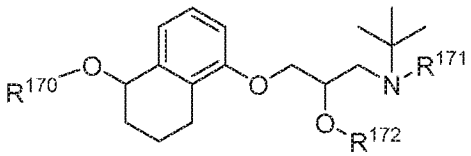

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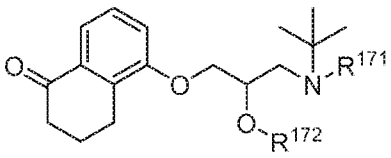

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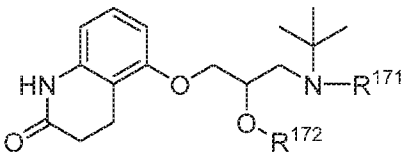

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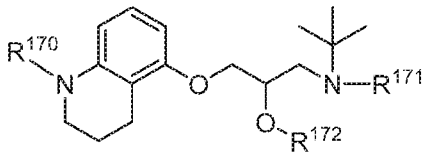

(XXXII)

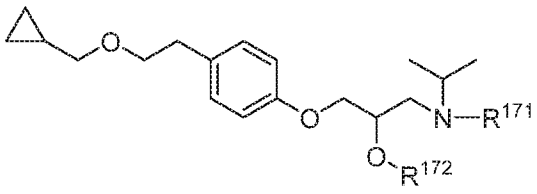

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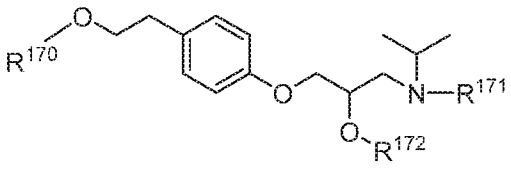

(XXXVI)

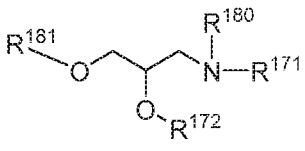

(XXXVIII)


(XL)


(XLII)

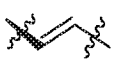
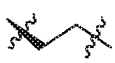

(XLIV)

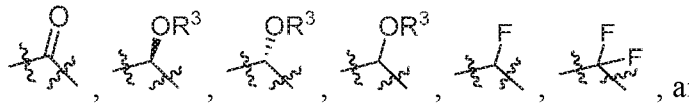
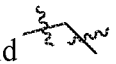

(XLVI)


(XLVIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof;

wherein:

$L^1$ is selected from , , , and ;

$L^2$ is selected from , and ;

$L^4$ is selected from bond, alkyl, alkenyl, alkynyl, -C(O)-, -C(S)-, -NH-, -N(alkyl)-, -O-, and alkyl-C(O)-;

$L^8$ is -C(O)-alkyl-C(O)-;

$R^1$, $R^2$, and $R^3$ are independently selected from -C(O)$R^4$, C(O)A, and hydrogen;

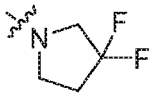
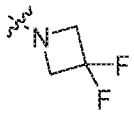
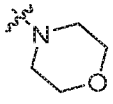
$R^4$ is selected from:

(i) –$C_{20}$-$C_{30}$alkyl$R^5$, –$C_{20}$-$C_{30}$alkenyl$R^5$, -$C_{20}$-$C_{30}$alkynyl$R^5$, -$C_{20}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{20}$-$C_{30}$alkyl, –$C_{20}$-$C_{30}$alkenyl, -$C_{20}$-$C_{30}$alkynyl, and -$C_{20}$-$C_{30}$alkenylalkynyl; and

(ii) an unsaturated fatty acid residue selected from –$(CH_2)_3(CHCHCH_2)_6CH_3$), –$(CH_2)_4(CHCHCH_2)_5CH_3$), docosatetraenoic acid, and nervonic acid;

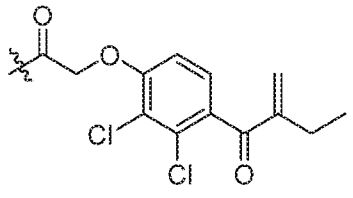
$R^5$ is selected from halogen, hydroxyl, cyano, mercapto, amino, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si$(CH_3)_3$, -COOH, -COOalkyl, and -$CONH_2$;

$R^7$ and $R^8$ are independently selected from -C(O)$R^4$, -C(O)A, hydrogen, and $R^{50}$;

$R^{23}$, $R^{24}$, and $R^{25}$ are independently selected from hydrogen, halogen, hydroxyl, cyano, mercapto, nitro, amino, aryl, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si$(CH_3)_3$, -COOH, -COOalkyl, -$CONH_2$, , , , and ;

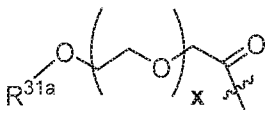
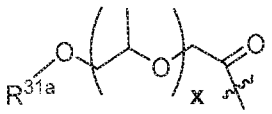
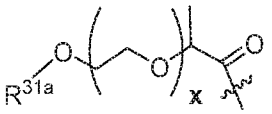
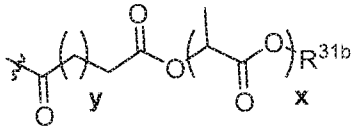
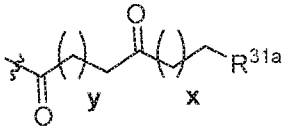
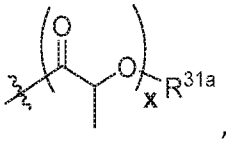
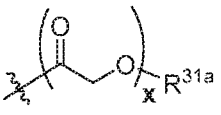
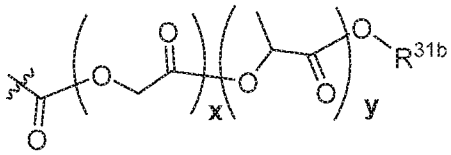
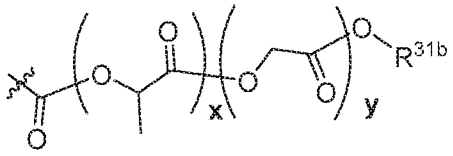
$R^{26}$ is selected from H, C(O)A, -$C_0$-$C_{10}$alkyl$R^5$, -$C_2$-$C_{10}$alkenyl$R^5$, –$C_2$-$C_{10}$alkynyl$R^5$, -$C_2$-$C_{10}$alkenyl, and –$C_2$-$C_{10}$alkynyl;

$R^{31}$ is hydrogen, hydroxy, amino, A, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, or polyethylene glycol;

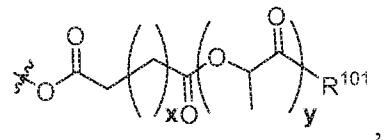
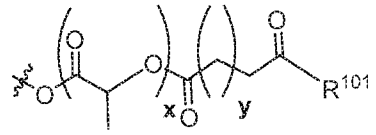
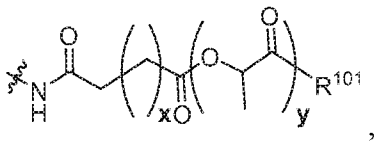
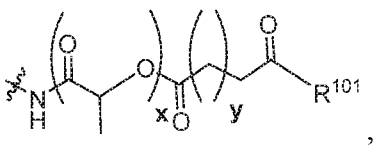
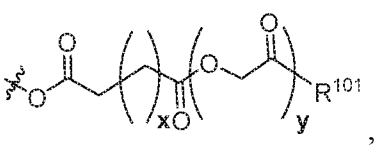
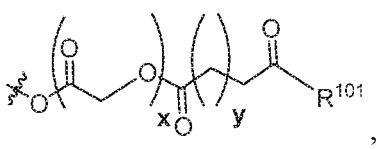
$R^{31a}$ is hydrogen, A, -C(O)alkyl, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, stearoyl, or ;

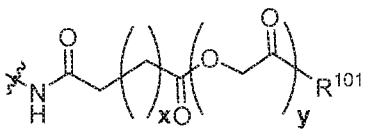
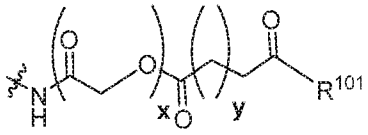
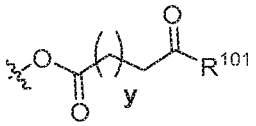
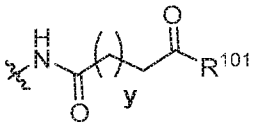
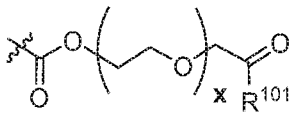
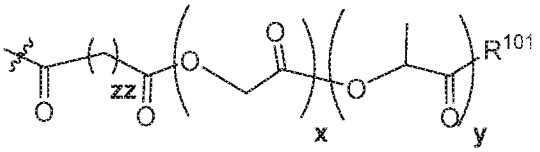
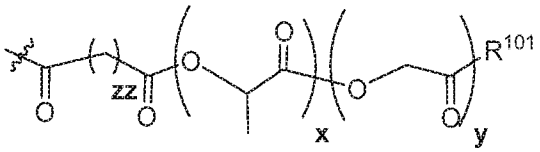
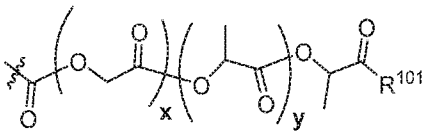
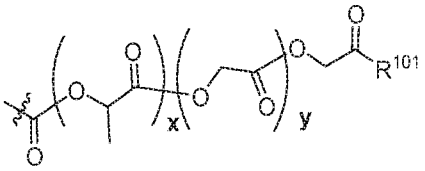
$R^{31b}$ is hydrogen, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polyethylene glycol, polylactic acid, polygylcolic acid, or stearoyl;

$R^{32}$ is $R^{35}$;

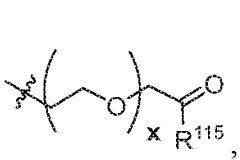
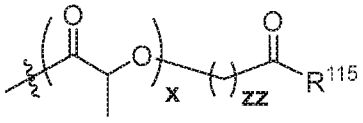
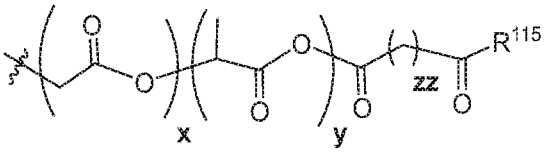
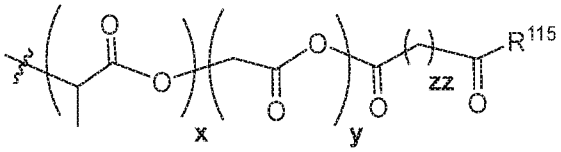
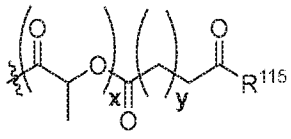
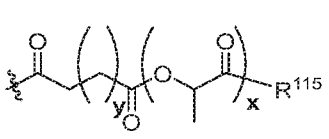
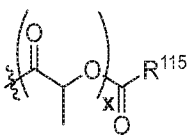
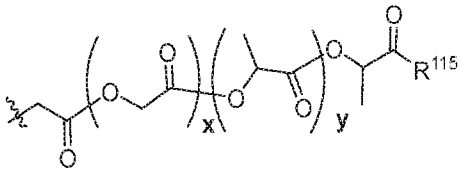
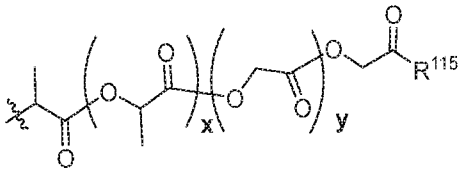
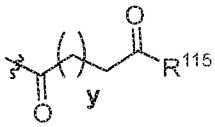
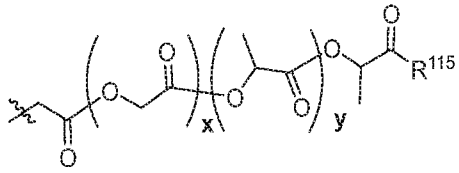
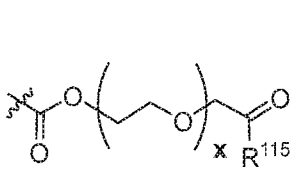
$R^{34}$ is selected from acyl, $R^{36}$, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, a polyamide, , , , , , , , , and ;

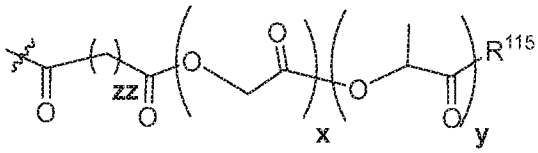
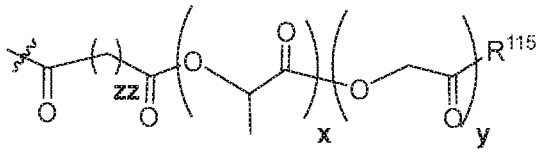
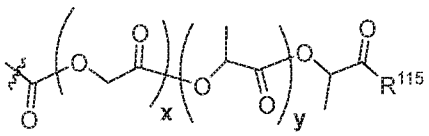
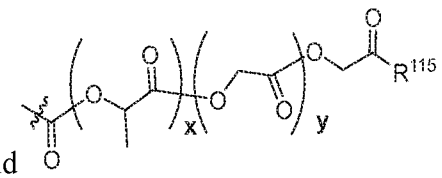
$R^{35}$ is selected from:

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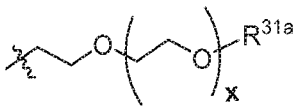
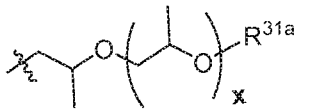
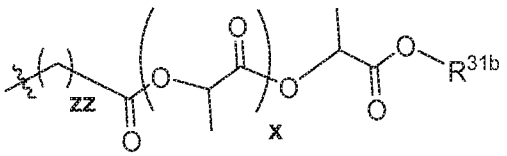
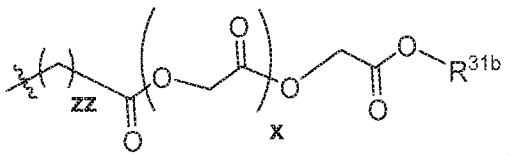
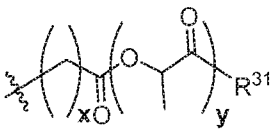
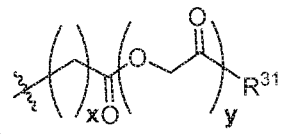
$R^{36}$ is selected from:


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$R^{41}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, a polyamide,


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; and

(ii) –$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl; and

(iii) an unsaturated fatty acid residue; and

(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl;

$R^{50}$ is selected from carbonyl derivatives of polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, and polyamide;

$R^{53}$ and $R^{54}$ are independently selected from –C(O)$R^4$, -C(O)A, and hydrogen;

$R^{55}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, and a polyamide;

(ii) –$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$,

–$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl;

(iii) an unsaturated fatty acid residue selected from -$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), –$(CH_2)_3(CHCHCH_2)_6CH_3$), -$(CH_2)_4(CHCHCH_2)_5CH_3$), –$(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl;

$R^{100}$ is selected from:

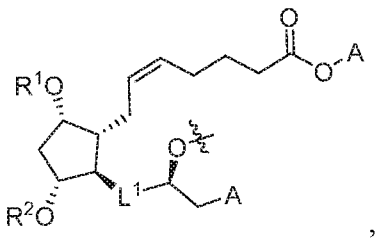
(i) $C_1$-$C_{10}$alkyl, -$C_0$-$C_{10}$alkyl($C_3$-$C_7$cycloalkyl), heterocycle, –$C_0$-$C_{10}$alkyl($C_3$-$C_7$heterocycloalkyl), –aryl$C_0$-$C_{10}$alkyl, –heteroarylalkyl, -$C_0$-$C_{10}$alkyl$C_2$-$C_{10}$alkenyl, and $C_2$-$C_{10}$alkynyl;

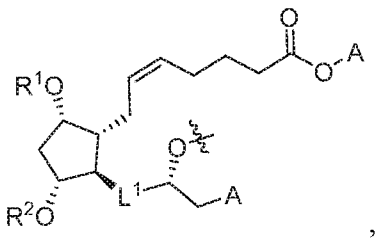
(ii) an unsaturated fatty acid residue selected from -$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), –$(CH_2)_3(CHCHCH_2)_6CH_3$), -$(CH_2)_4(CHCHCH_2)_5CH_3$), –$(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

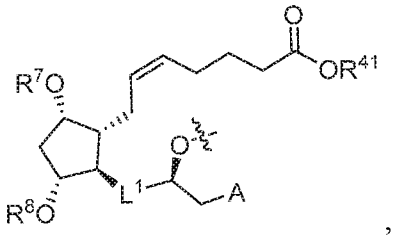
(iii)–$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl; and

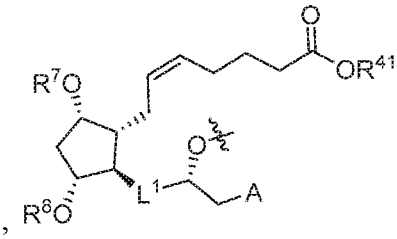
(iv) $R^{50}$;

$R^{101}$ is selected from

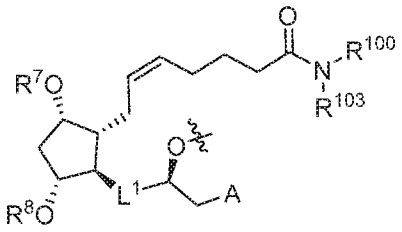
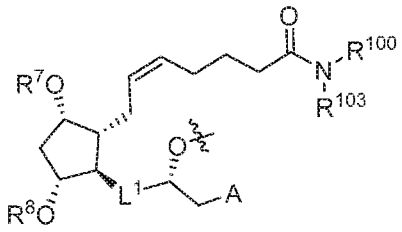
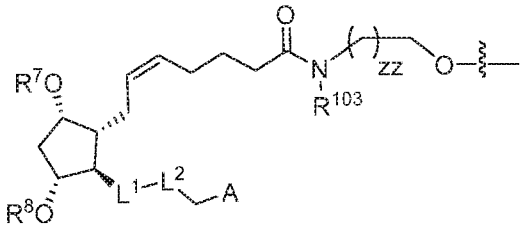
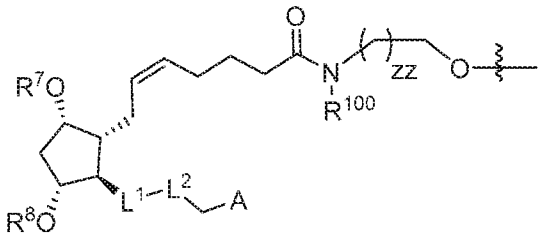
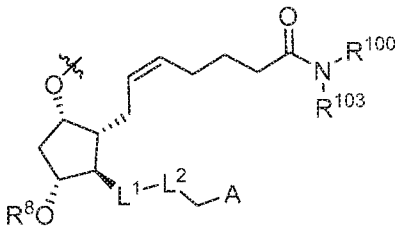
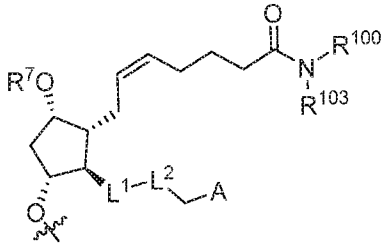
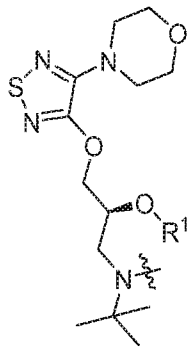
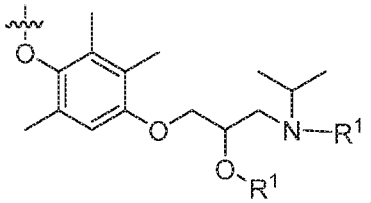
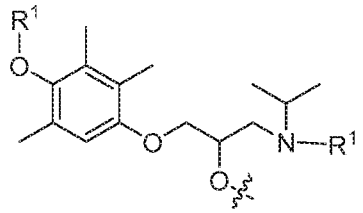
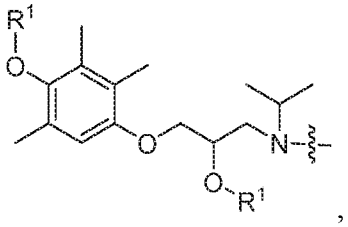
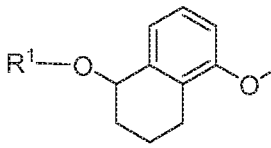
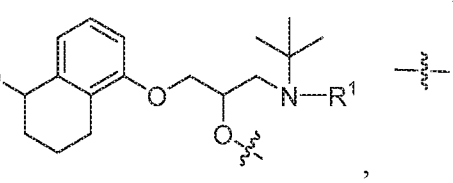


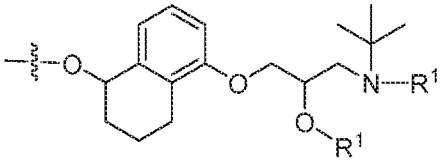
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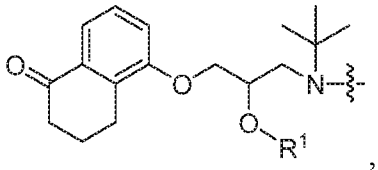
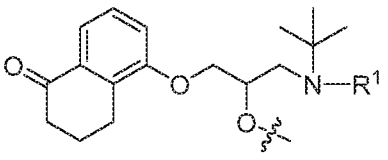
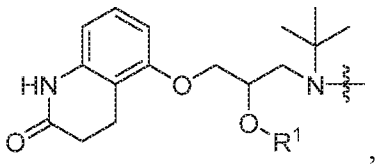
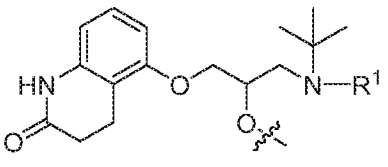
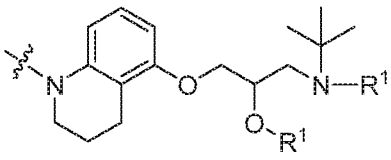
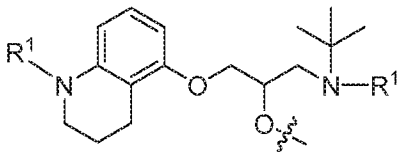
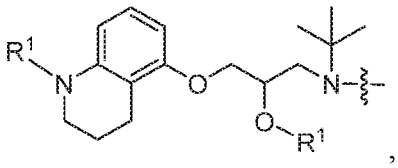
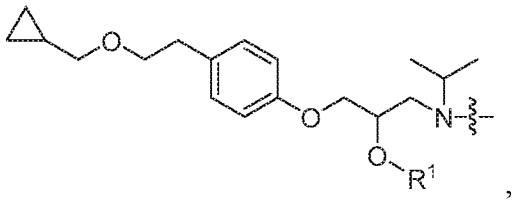
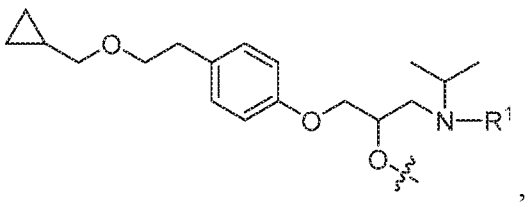
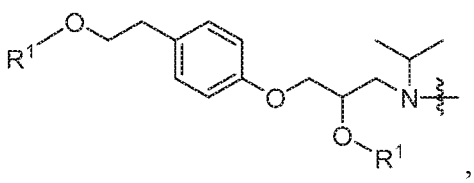
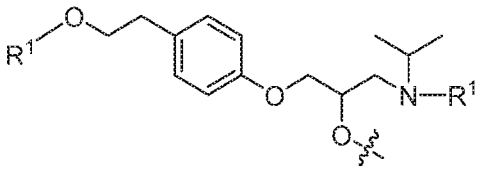
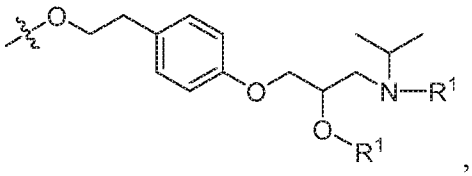
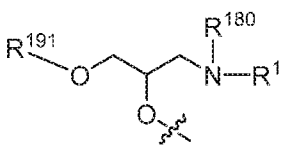
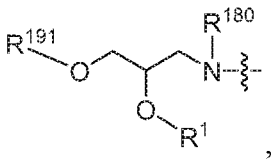
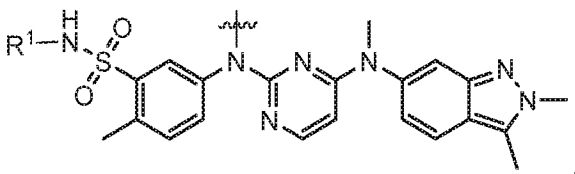
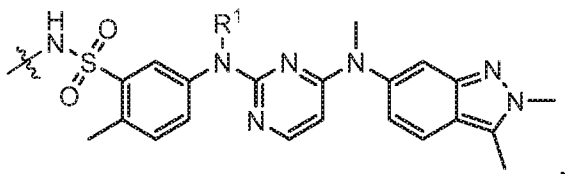
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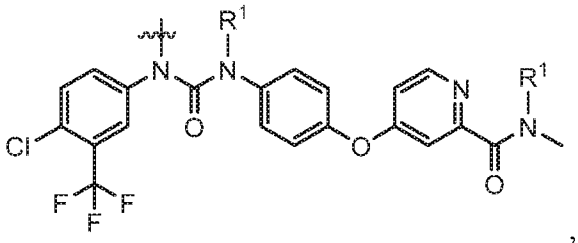
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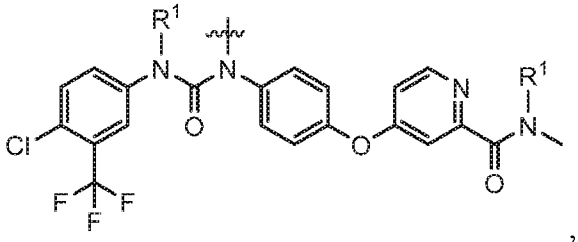

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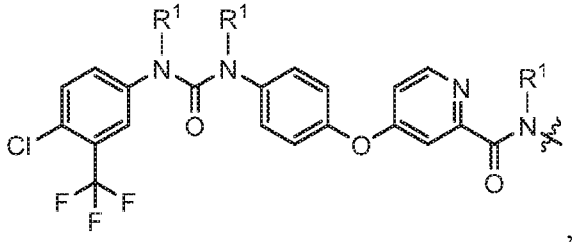

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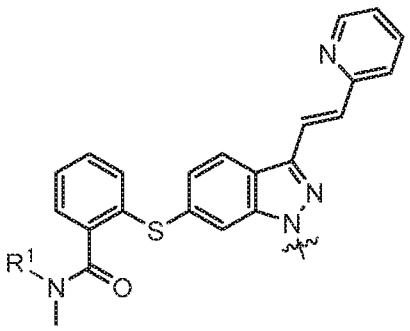
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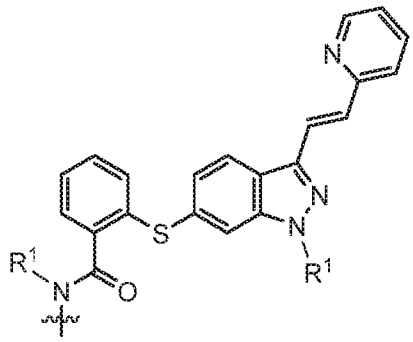
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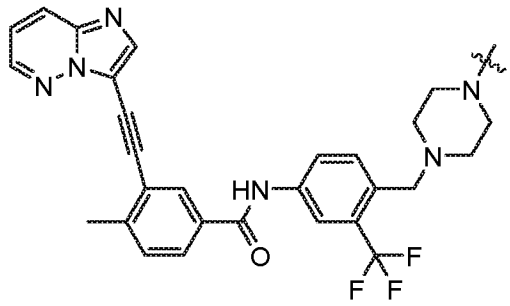
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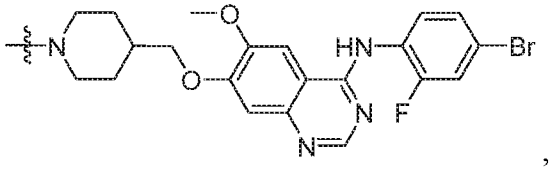
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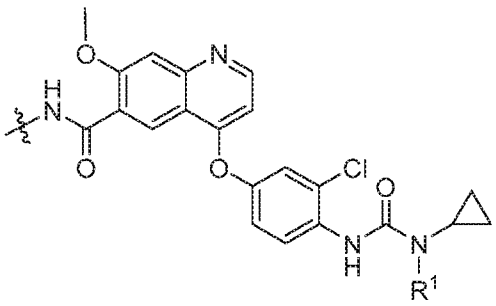
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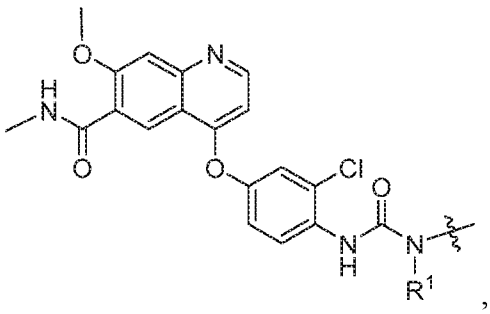
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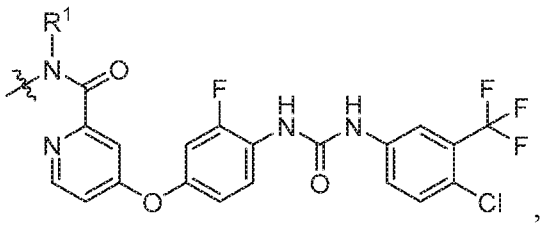
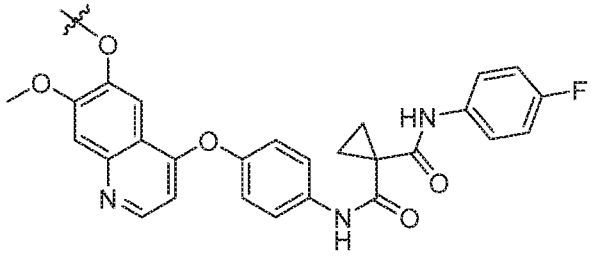
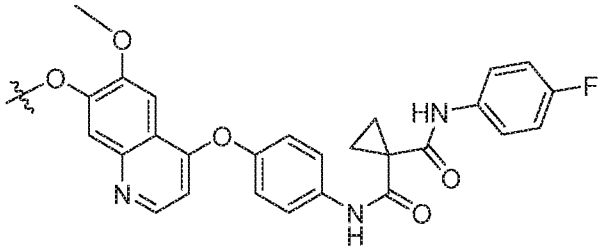
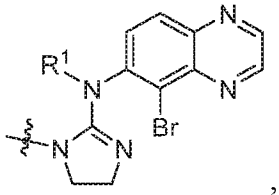
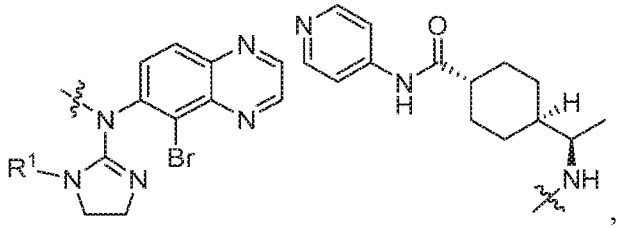
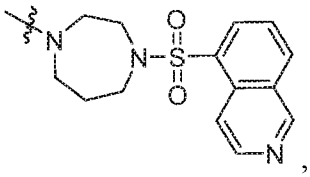
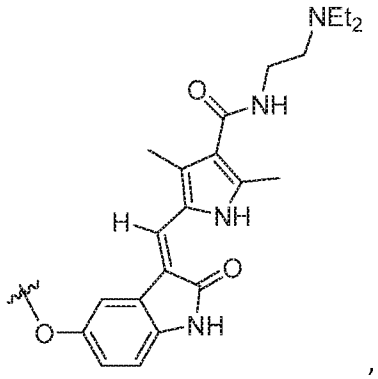
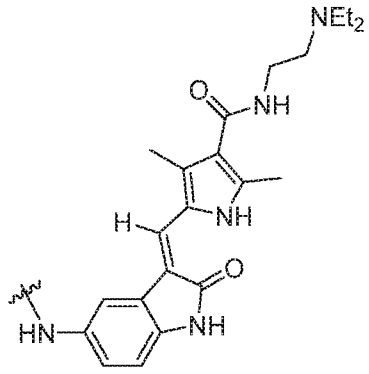
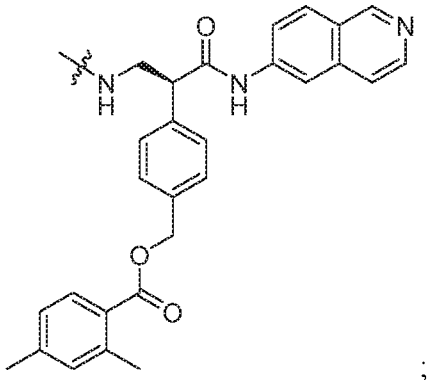
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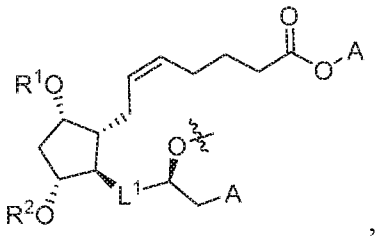
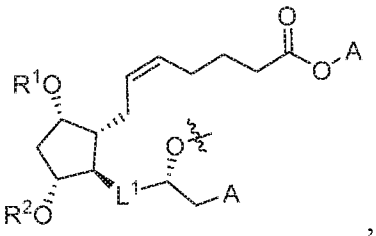
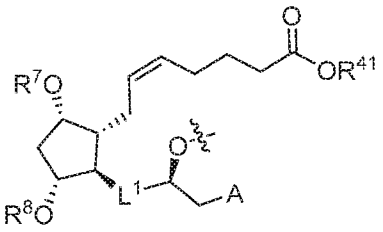
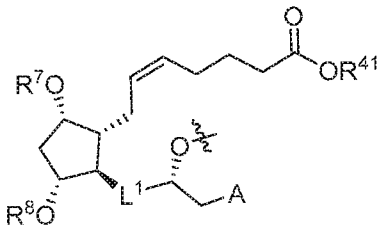
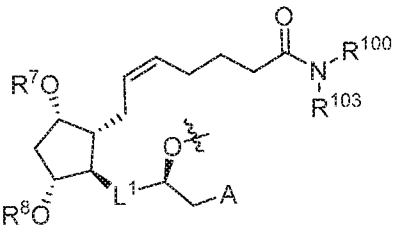
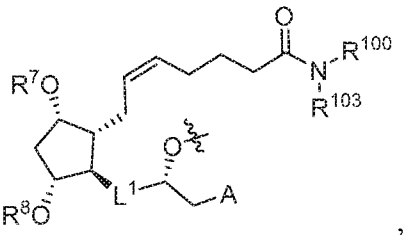
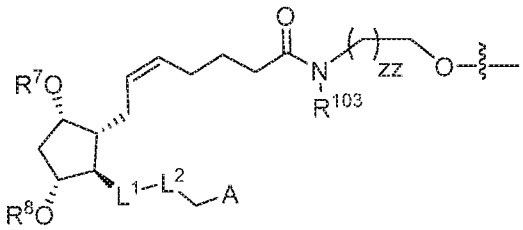
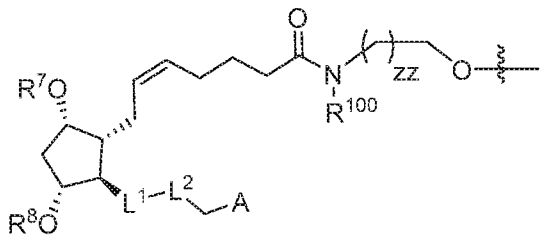
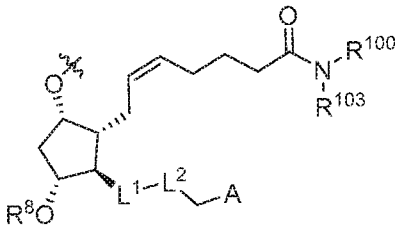
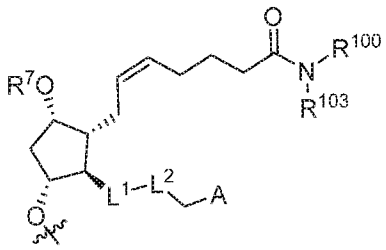
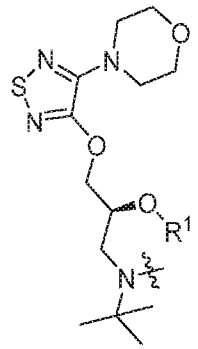
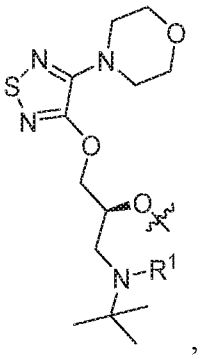
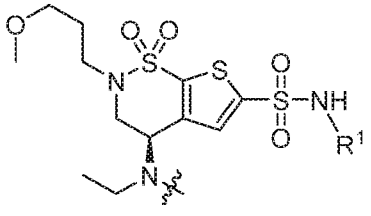
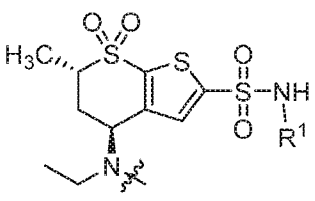
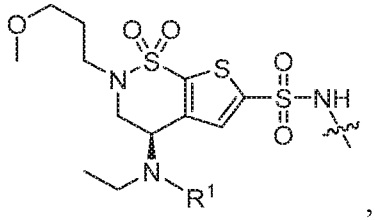


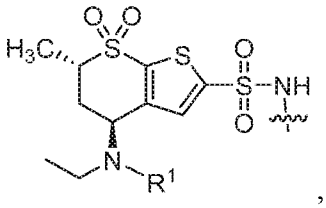
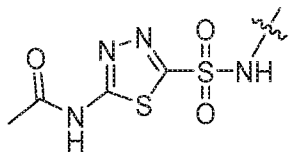
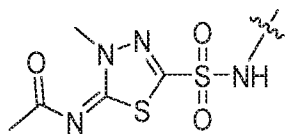
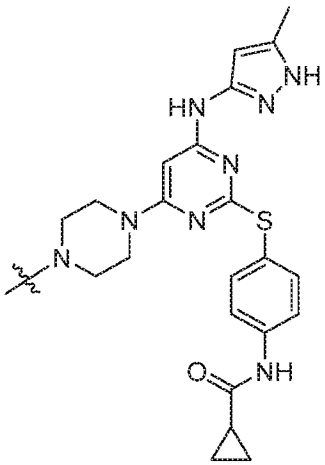
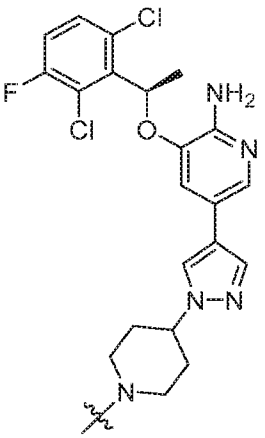
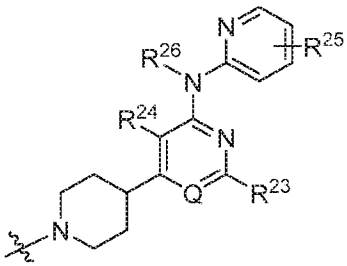
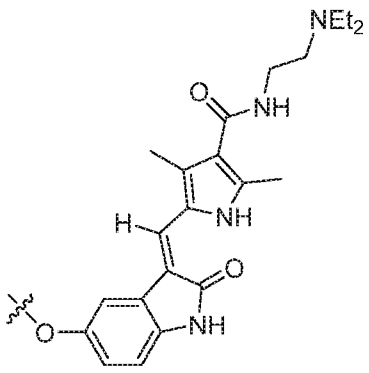
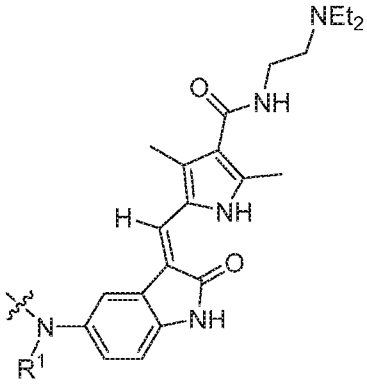
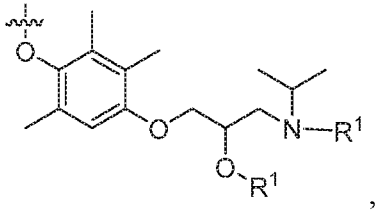
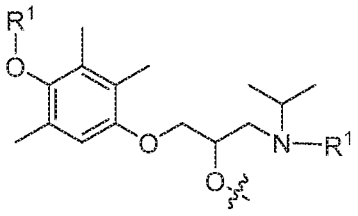
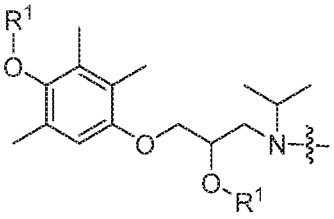
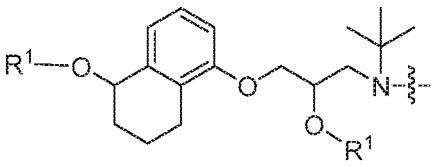
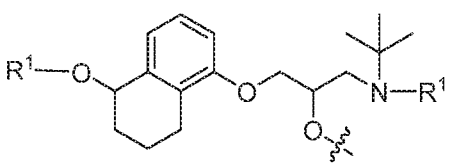
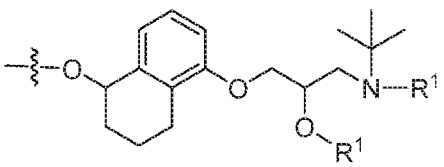
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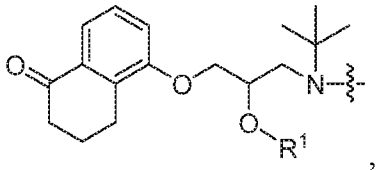
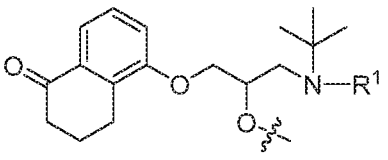
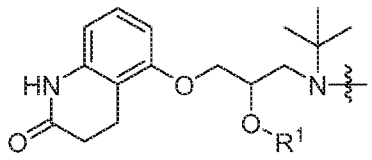
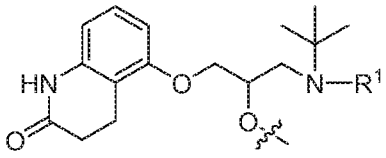
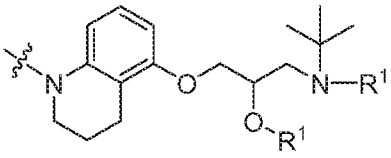
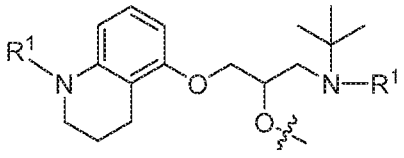
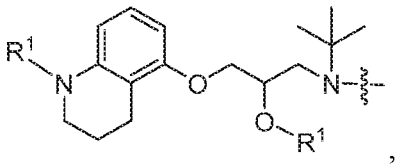
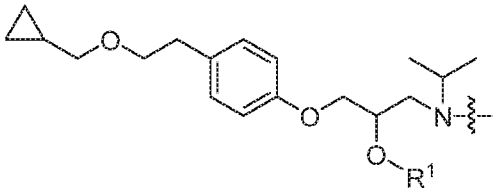
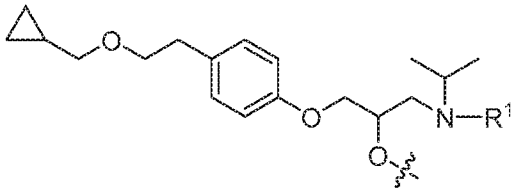
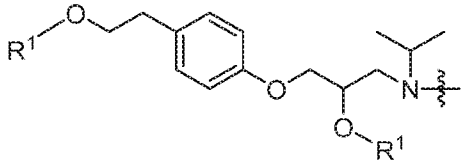
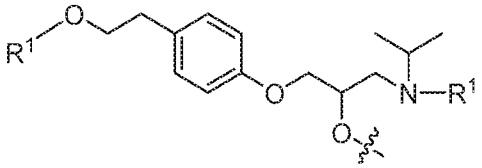
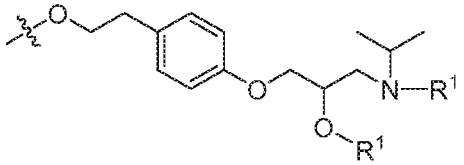

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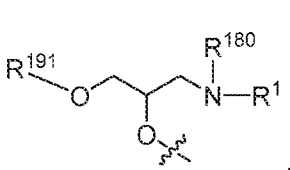
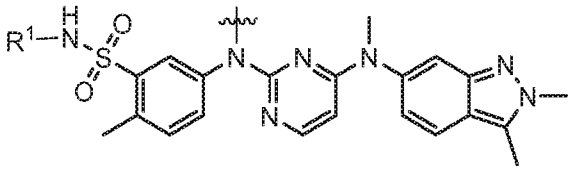
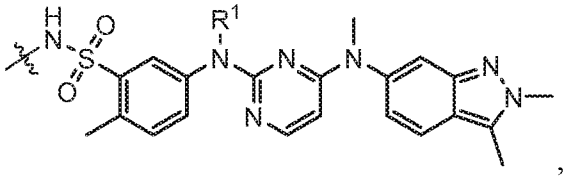
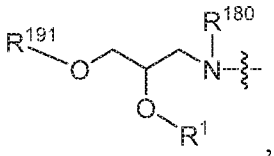
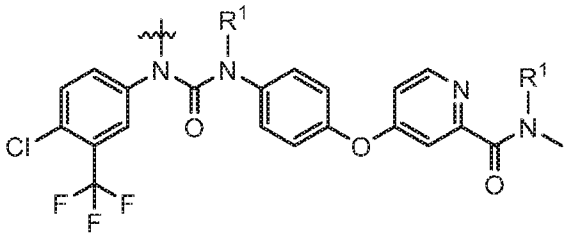
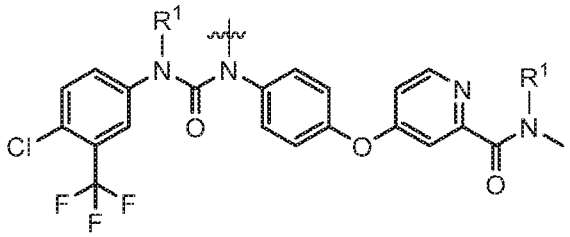
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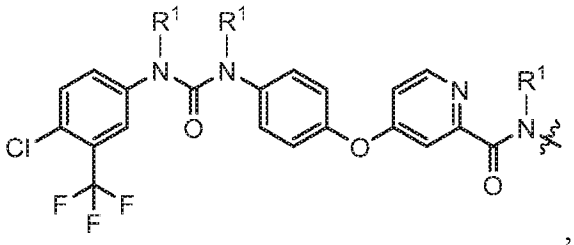
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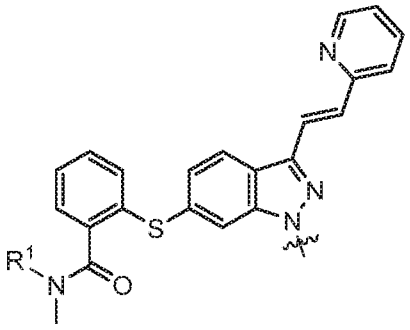

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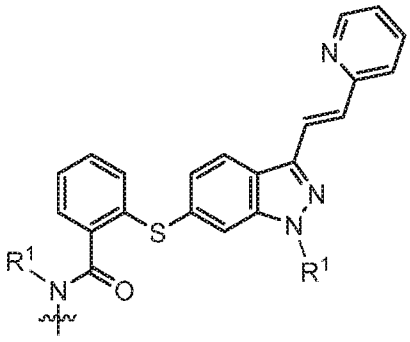

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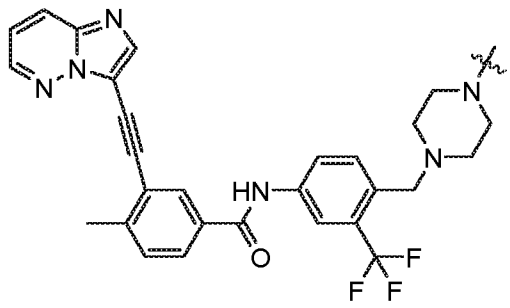

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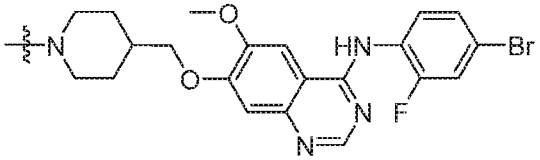

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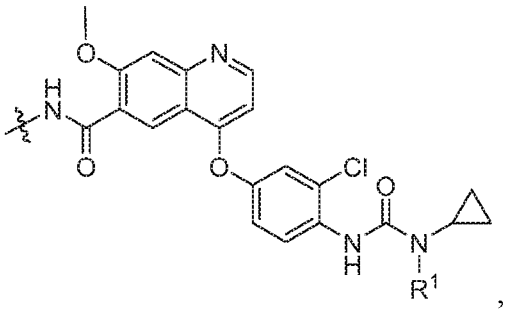


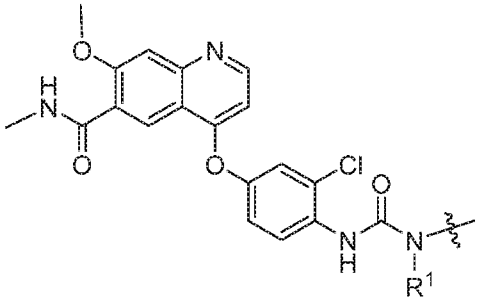


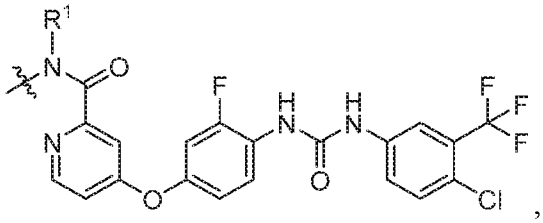


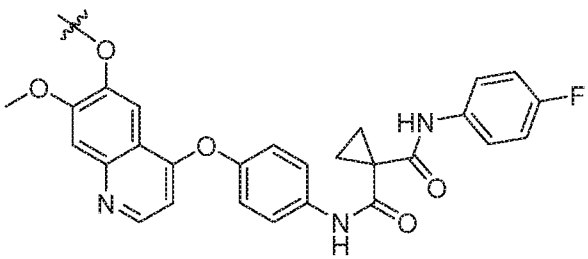


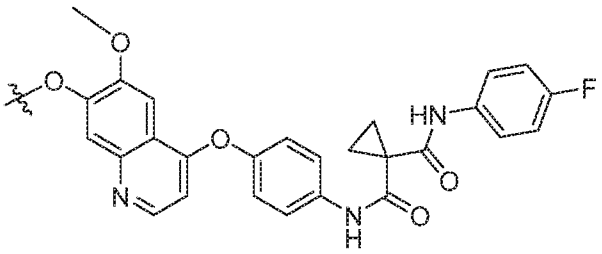


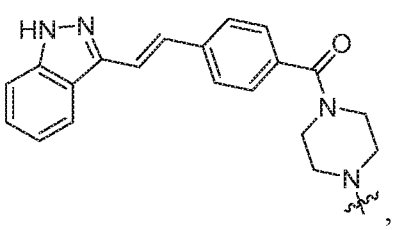
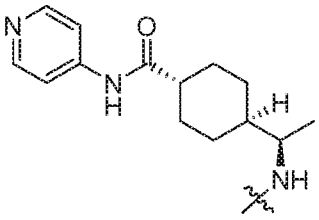
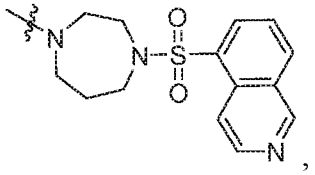
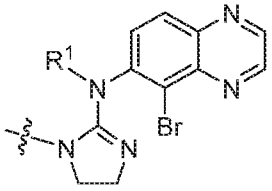
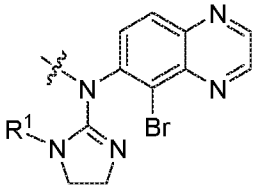
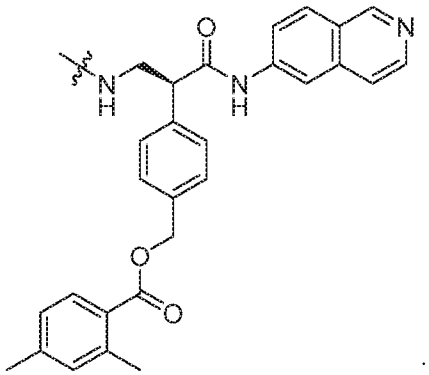




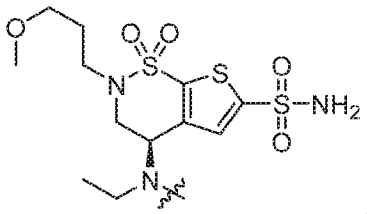
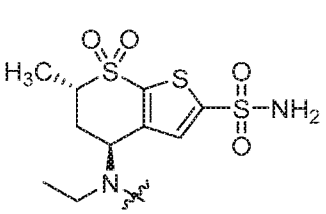
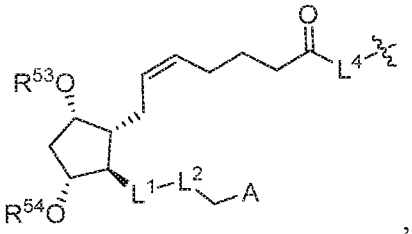
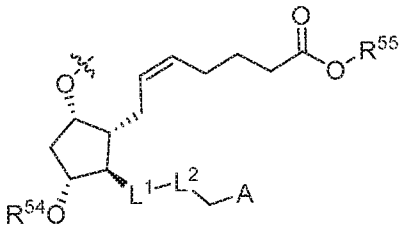
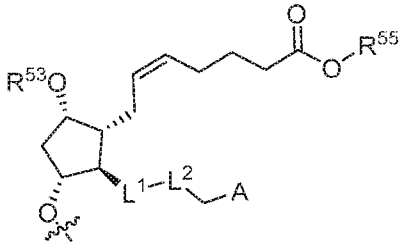
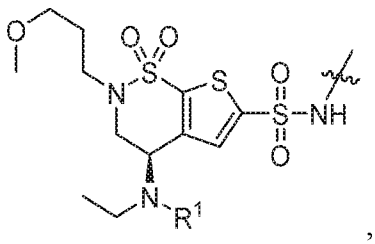
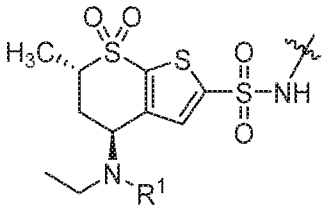
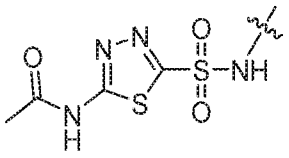
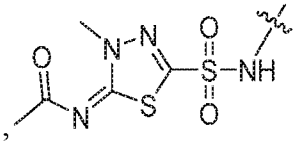
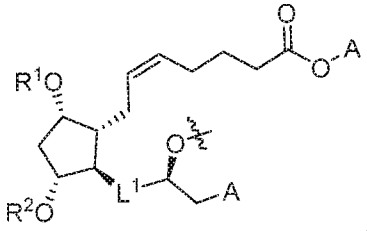
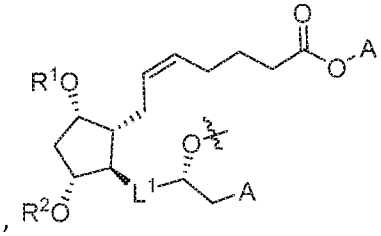
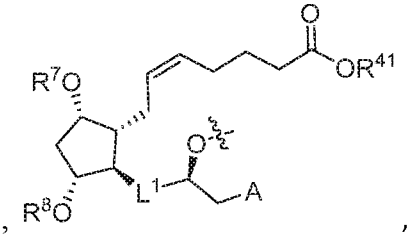


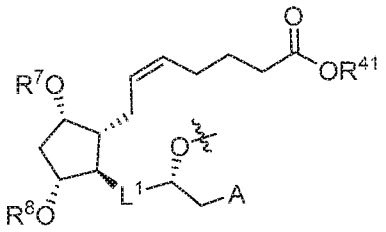
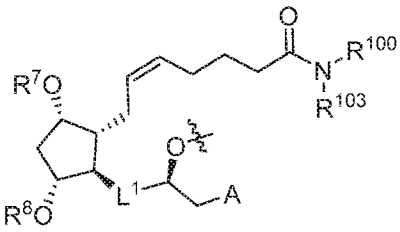
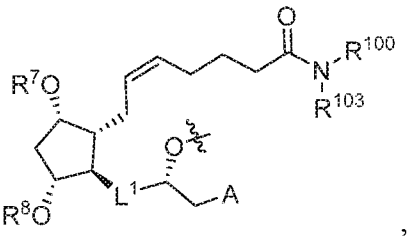
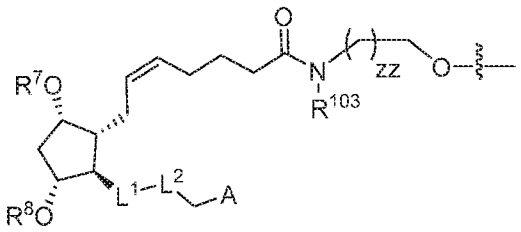
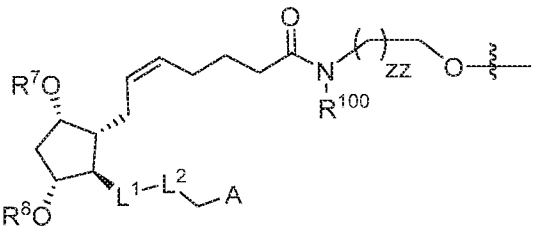
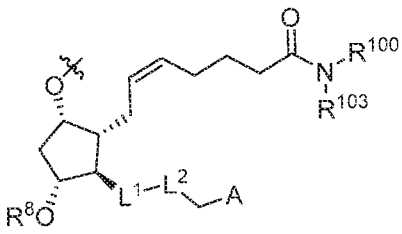
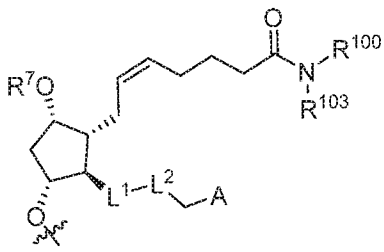
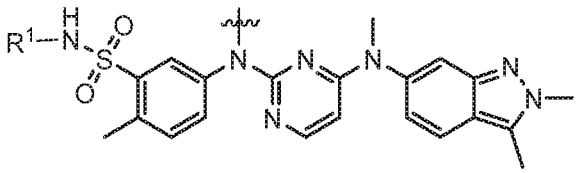
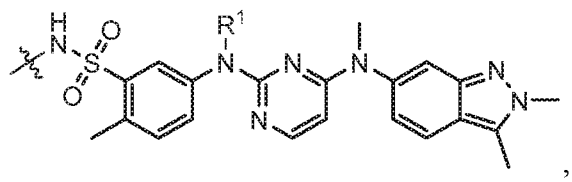
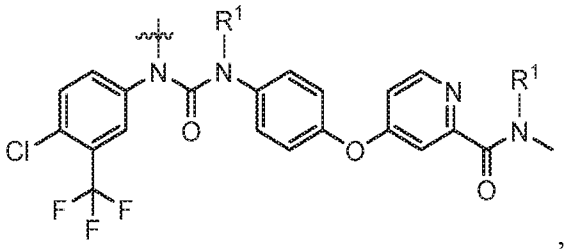
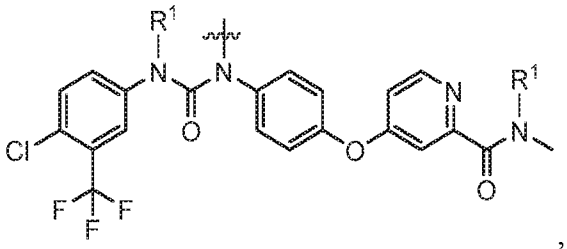
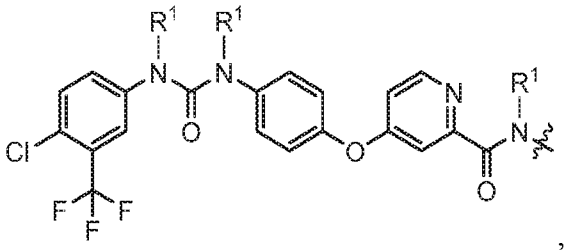
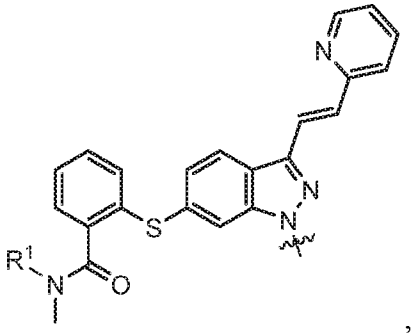


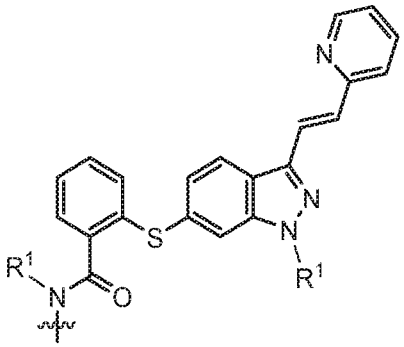
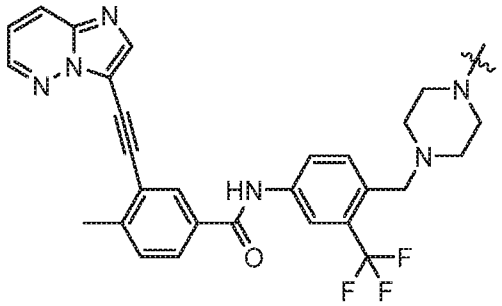
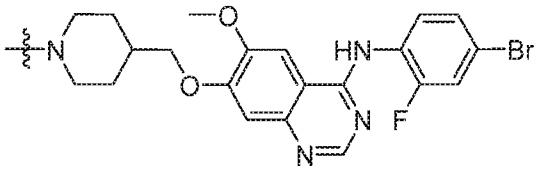
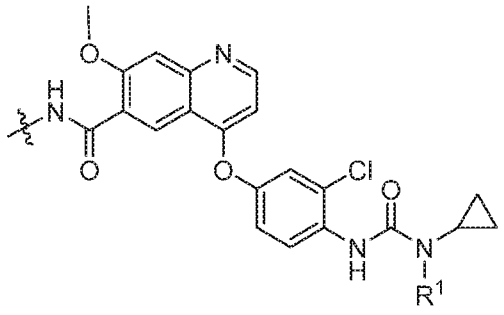
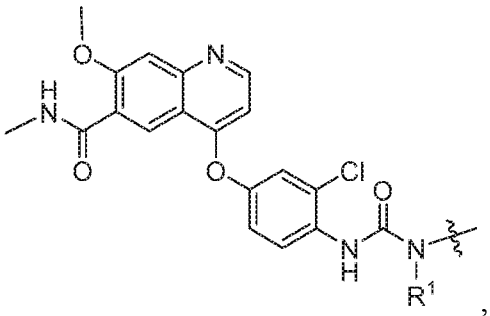
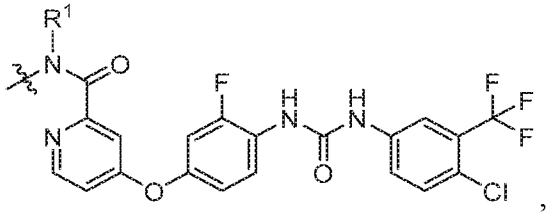
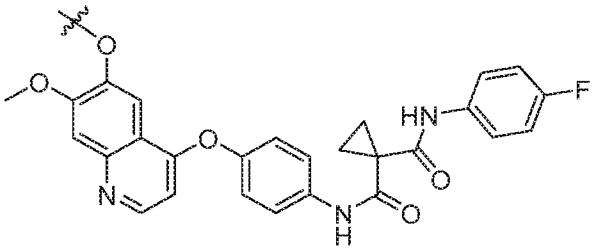
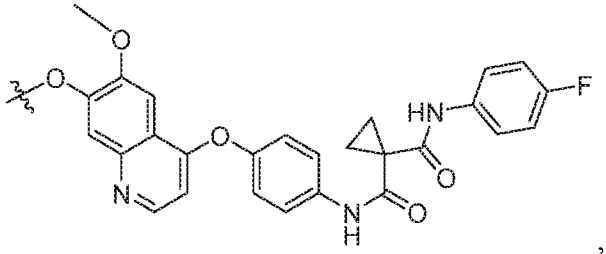
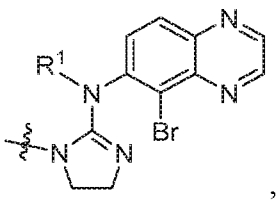
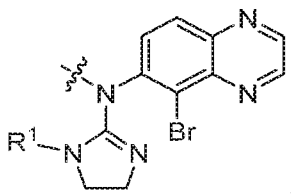
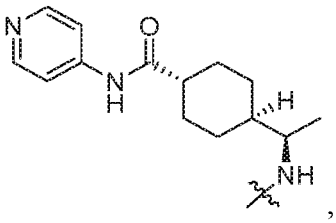
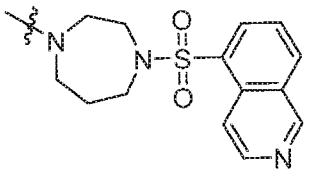
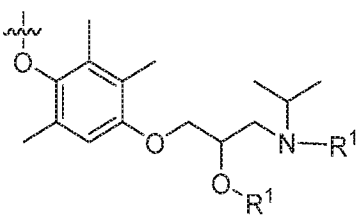
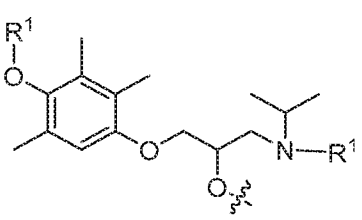
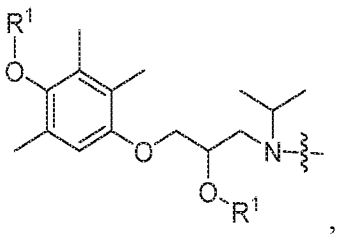


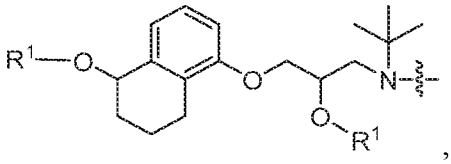
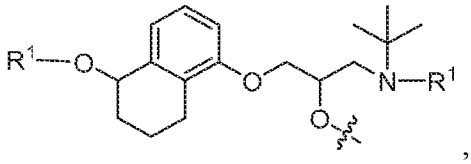

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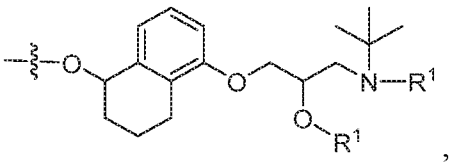
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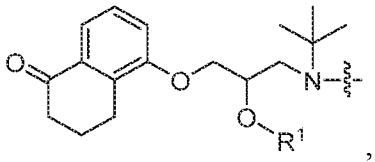
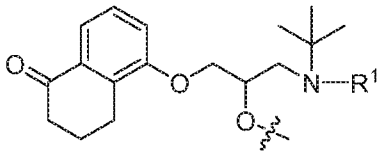
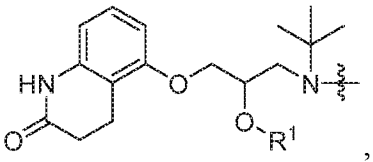

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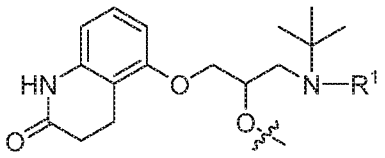
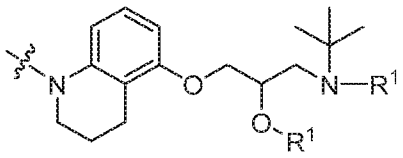
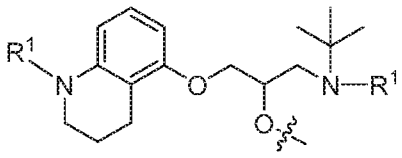

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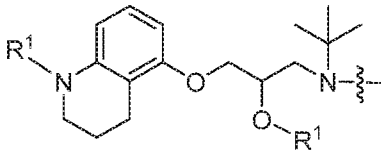
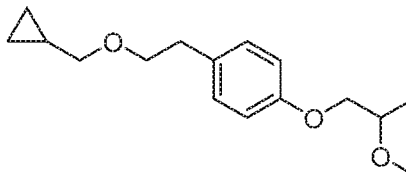

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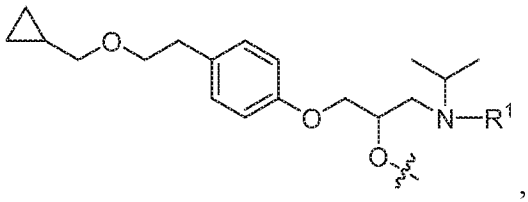
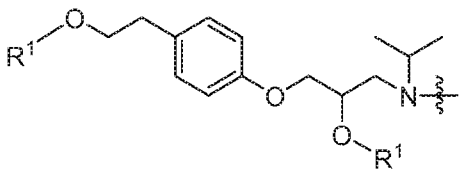

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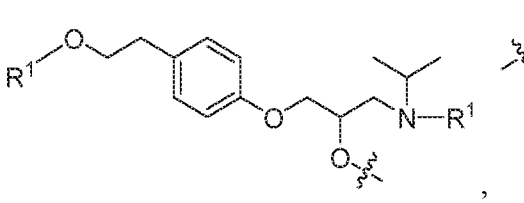
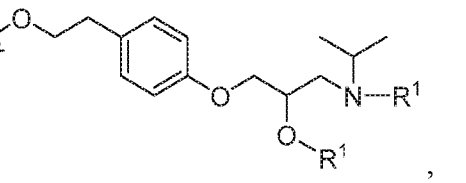

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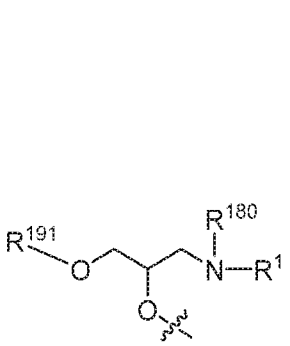
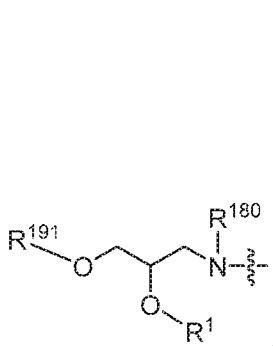
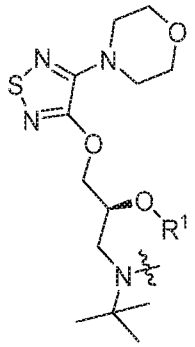
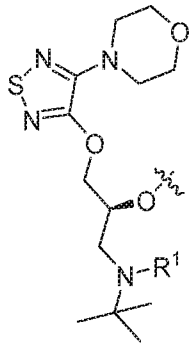
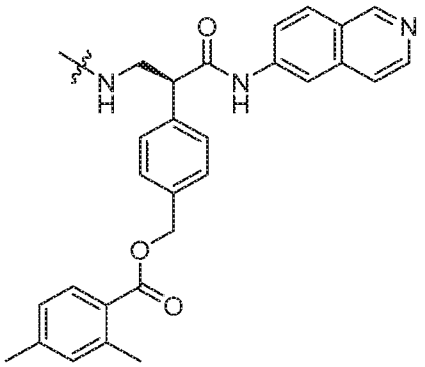

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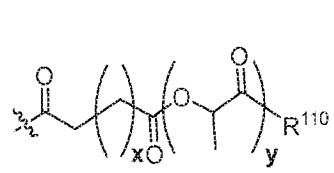
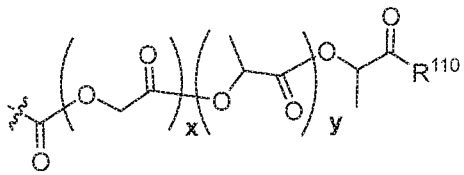
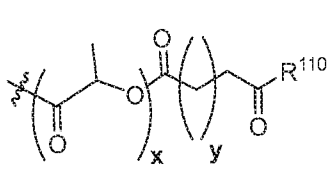
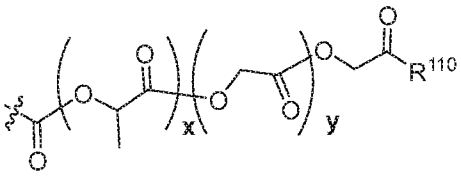
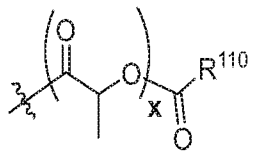
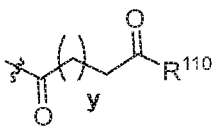
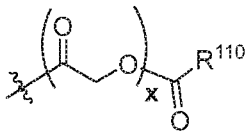
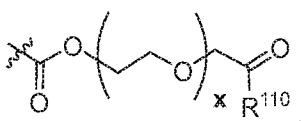
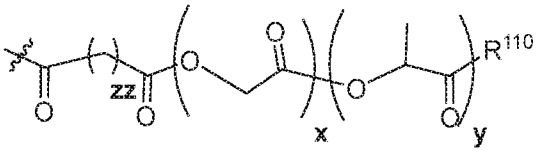

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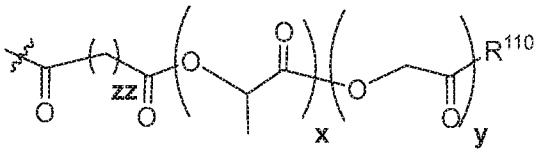
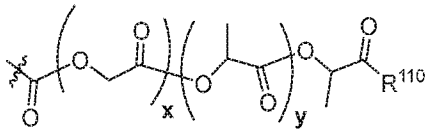
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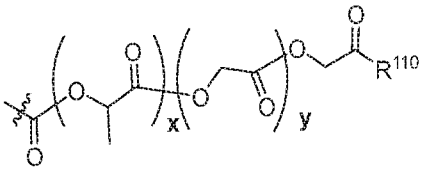

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and

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$R^{116}$ is $R^{117}$;

$R^{117}$ is selected from:

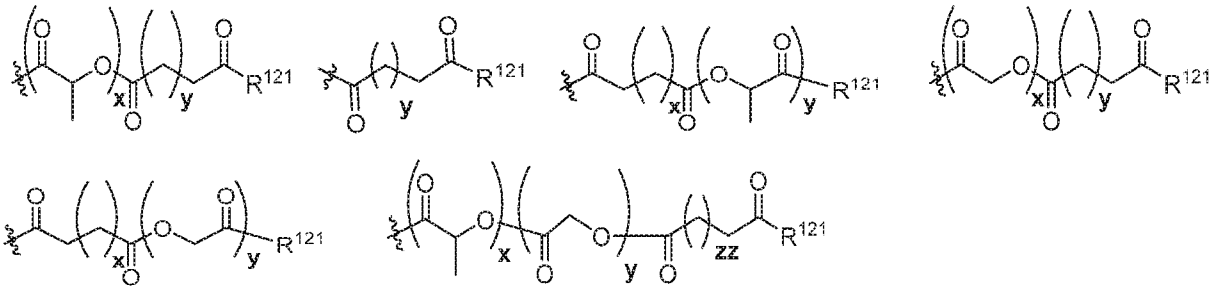

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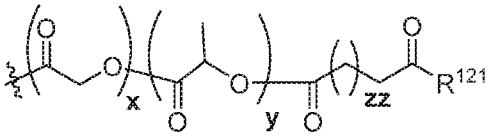


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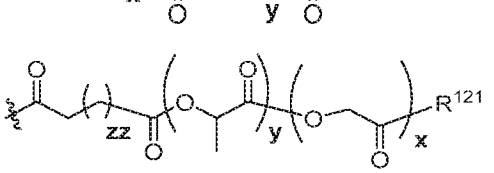
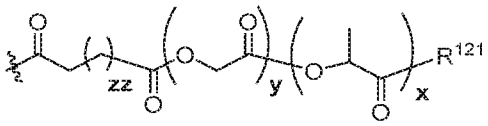

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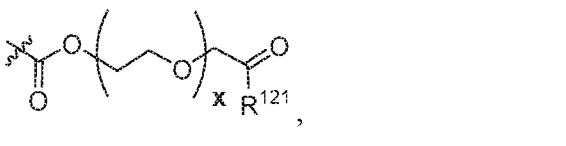
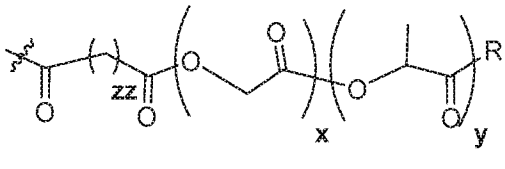
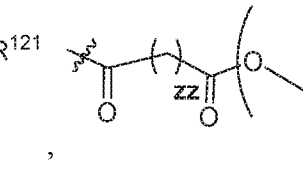
$R^{119}$ is $R^{120}$;

$R^{120}$ is selected from:



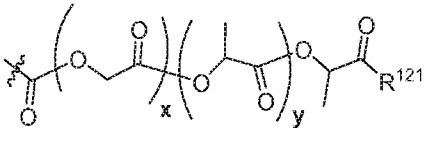
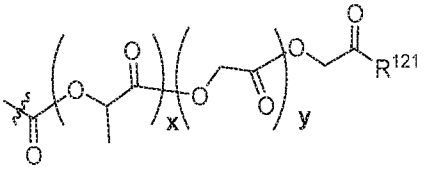


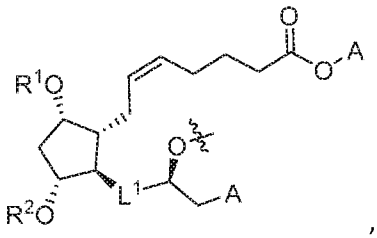
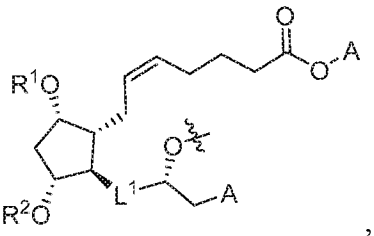
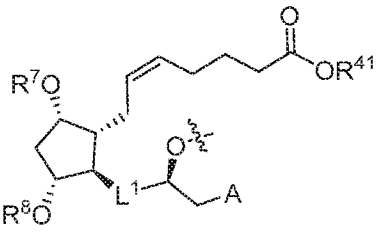
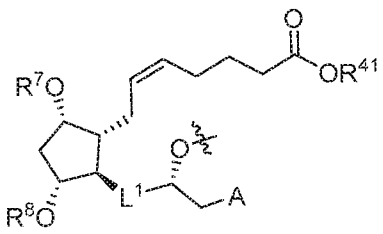
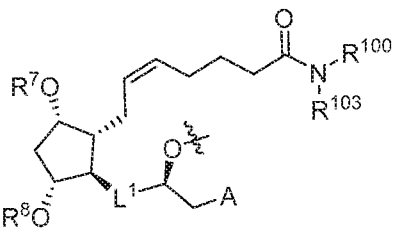
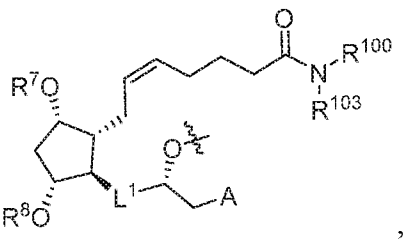
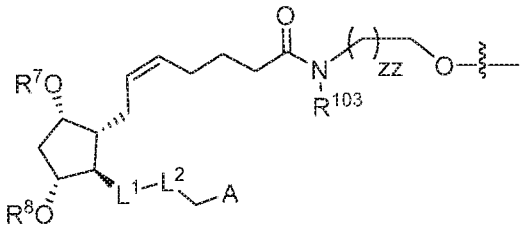
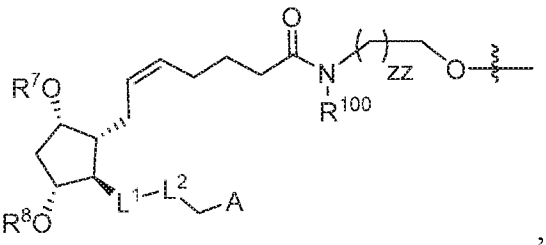
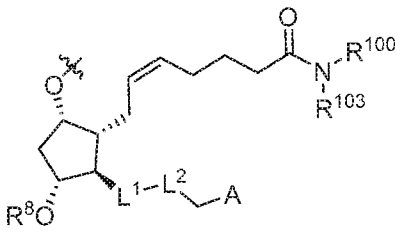
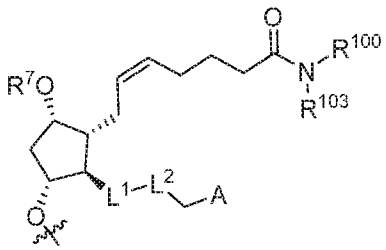
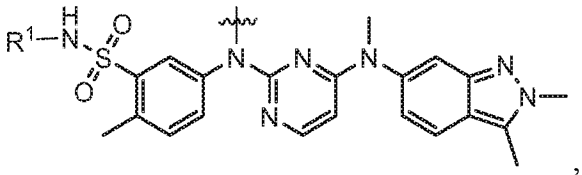
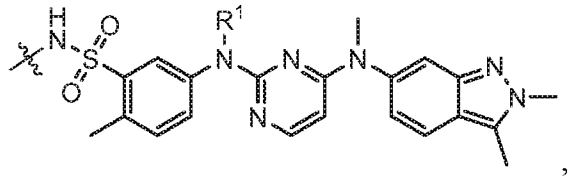
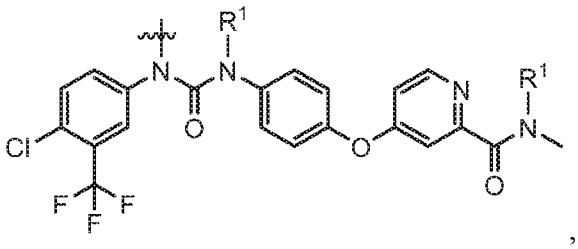
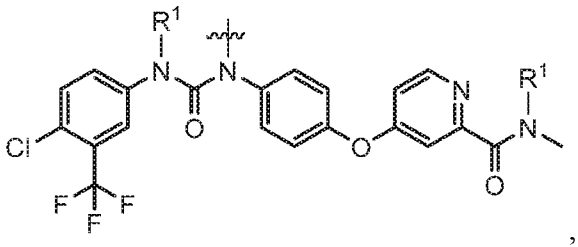



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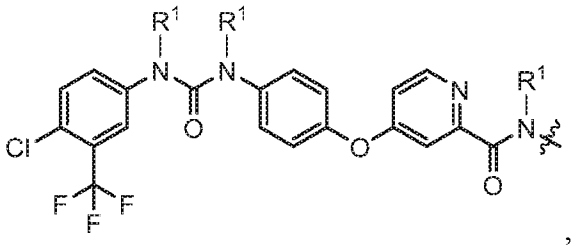
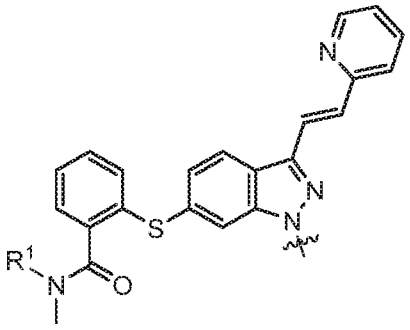
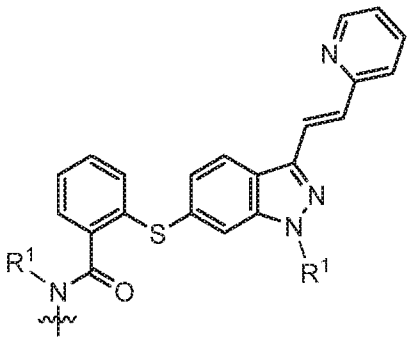
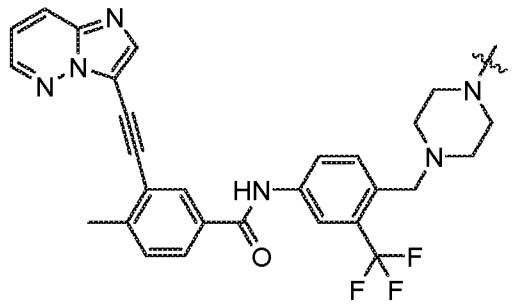
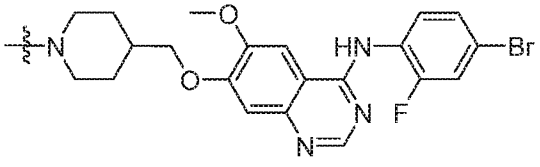
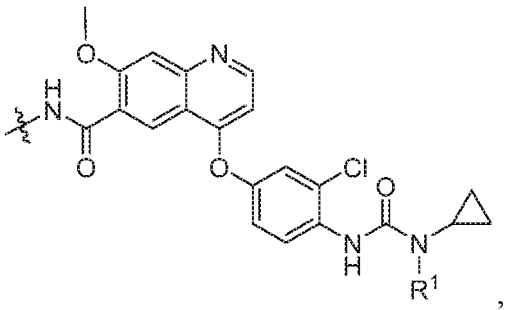
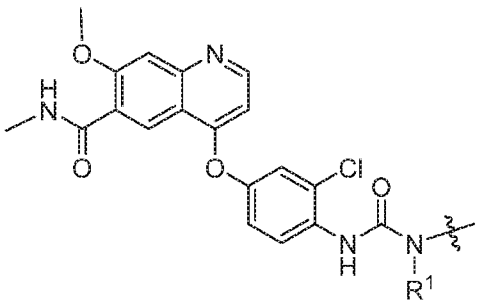
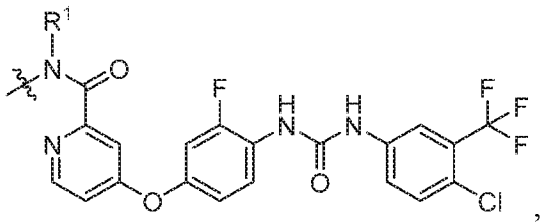
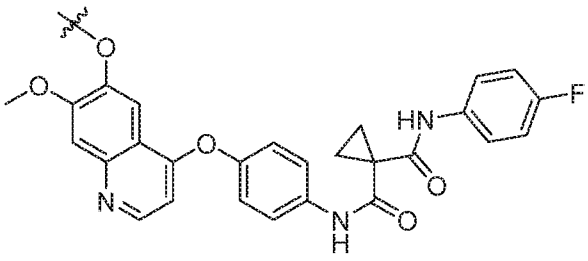
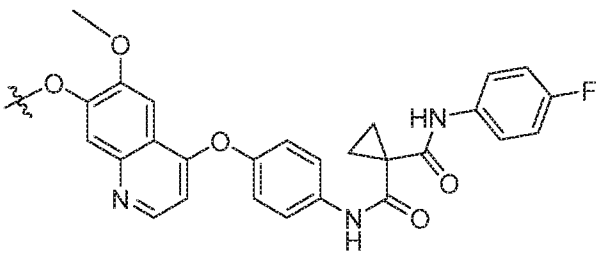

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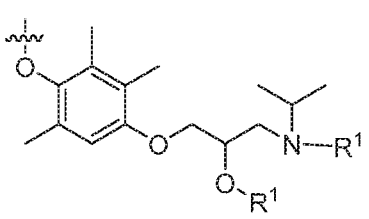
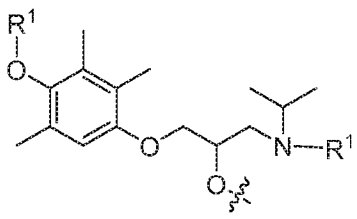
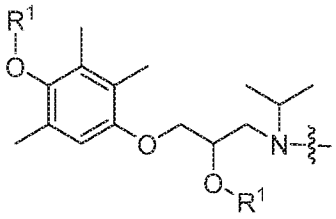
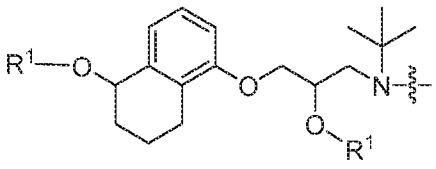
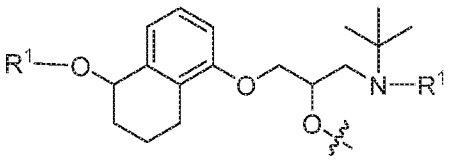
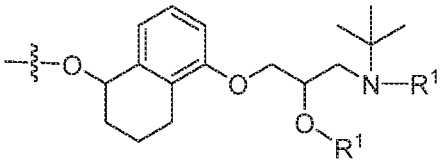
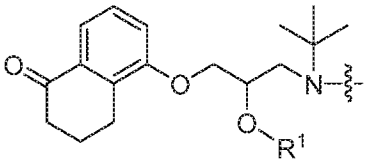
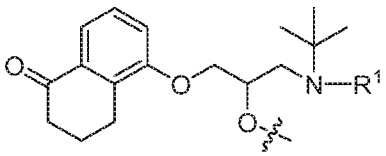
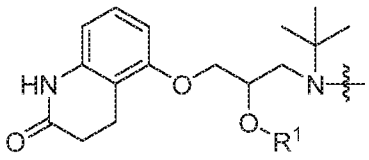
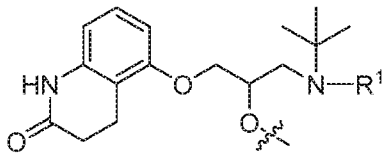
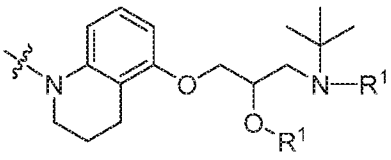
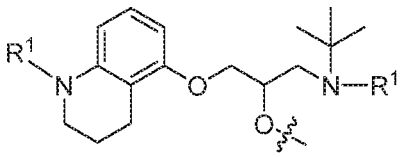
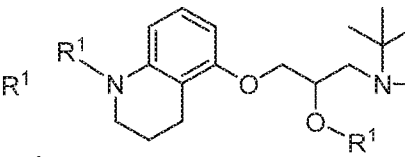
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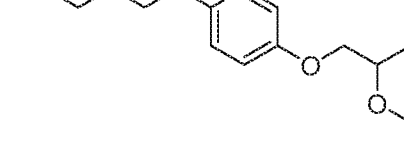
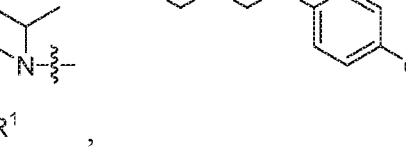

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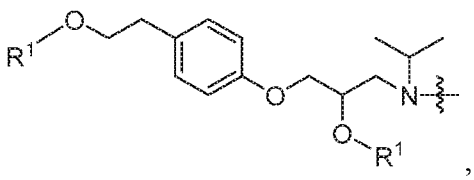
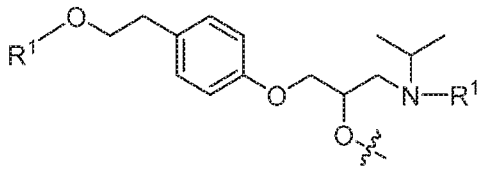
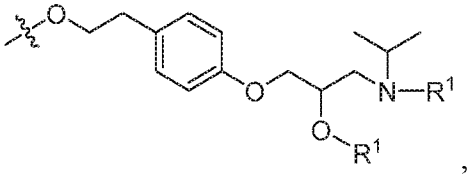
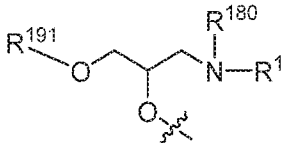
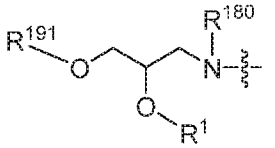
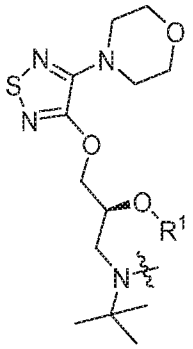
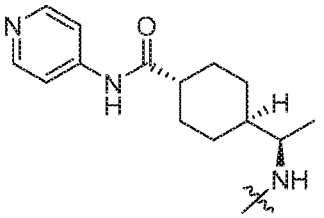
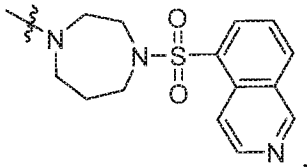
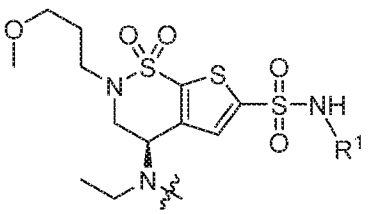
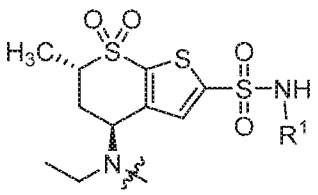
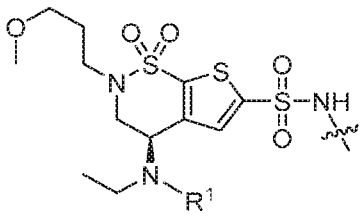
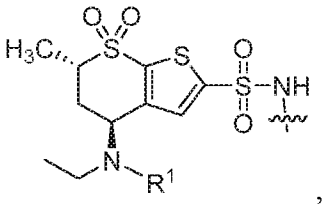
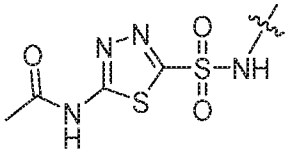
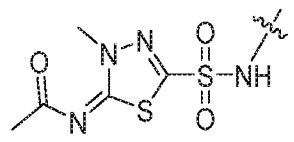
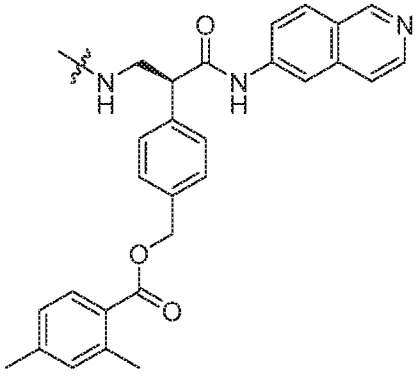

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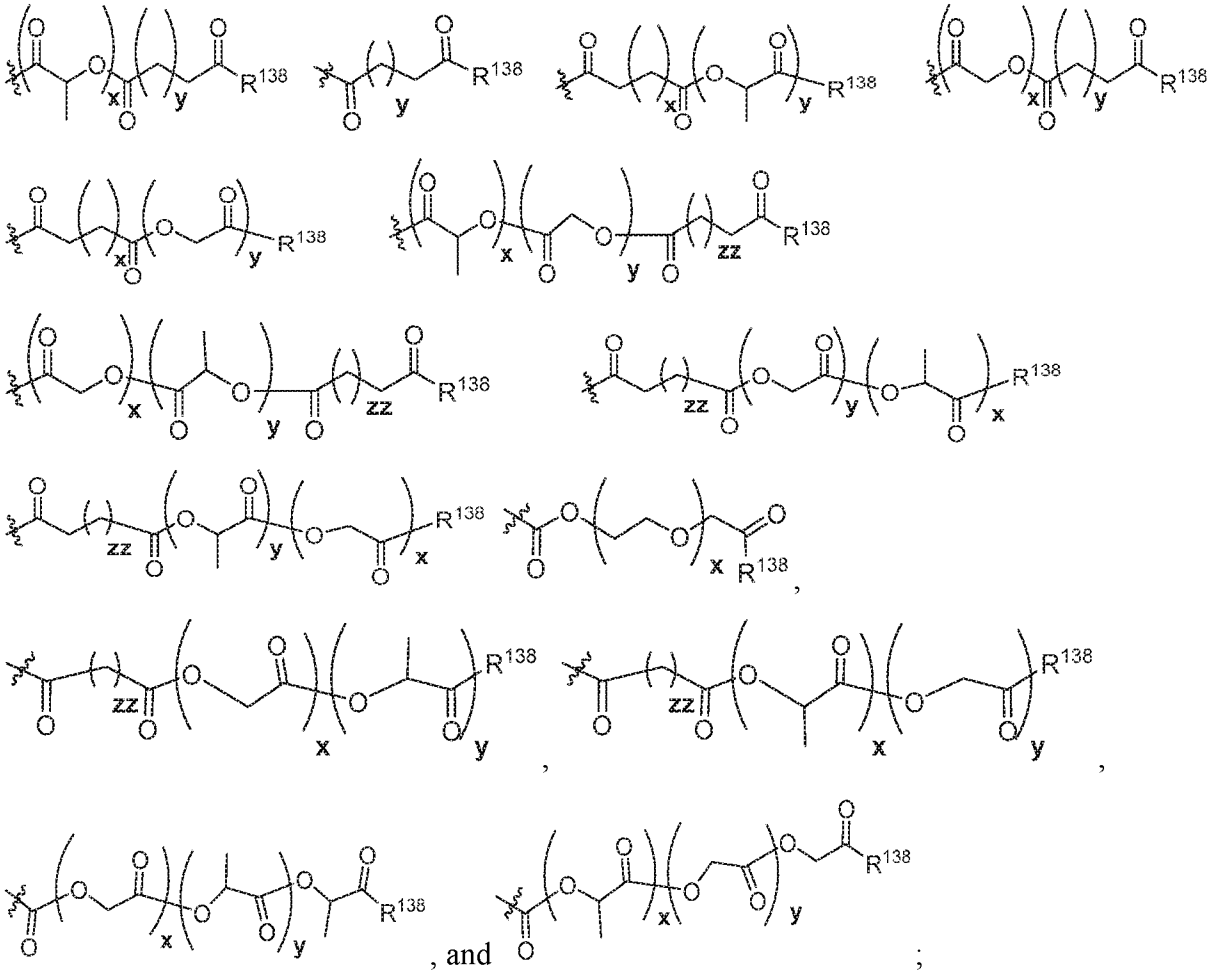
$R^{130}$, $R^{131}$, and $R^{133}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{136}$;

$R^{132}$ is selected from $R^{136}$, $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and alkylaryl;

$R^{134}$ and $R^{135}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

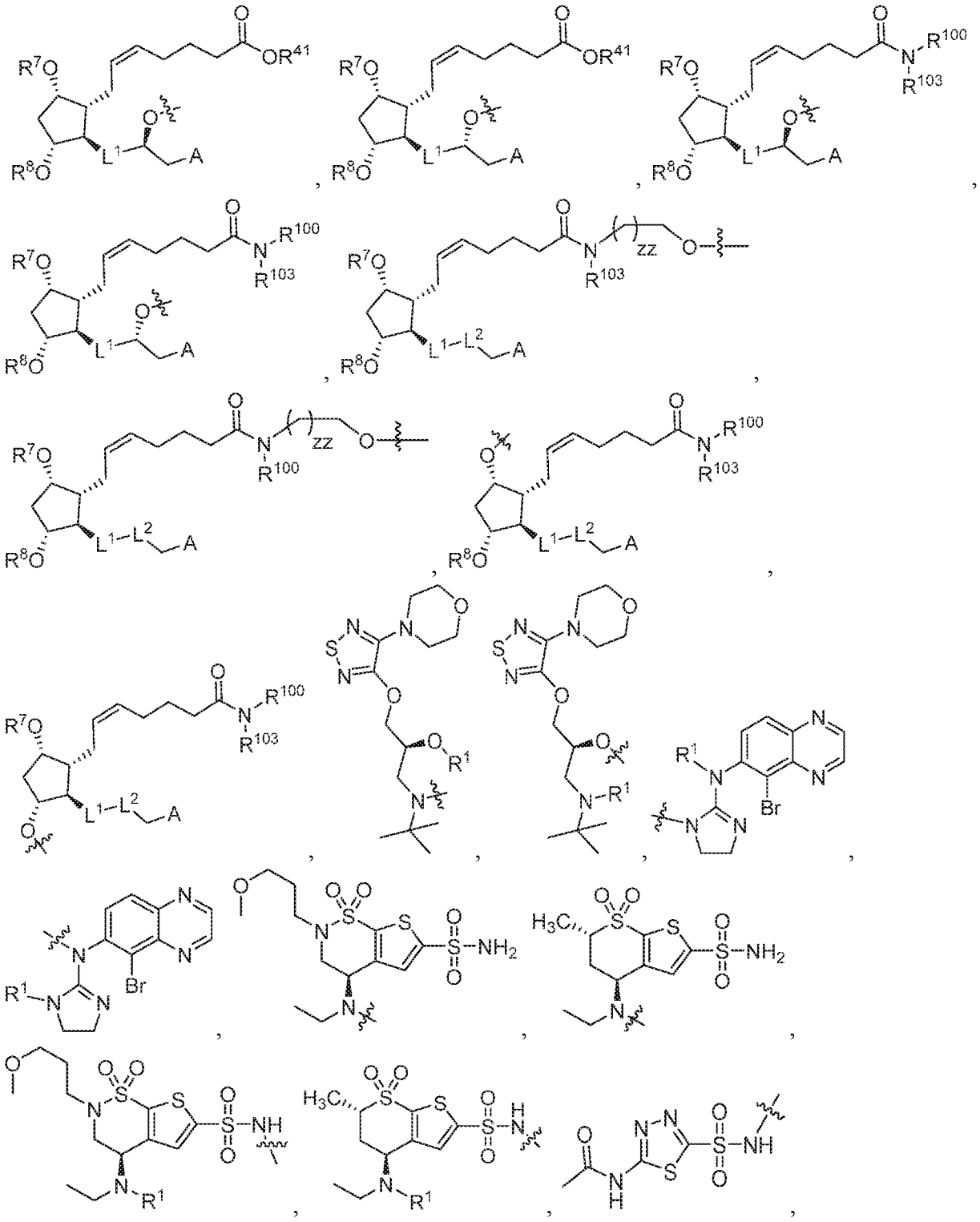
$R^{136}$ is selected from $R^{137}$ wherein at least one of $R^{130}$, $R^{131}$, and $R^{133}$ is $R^{136}$;

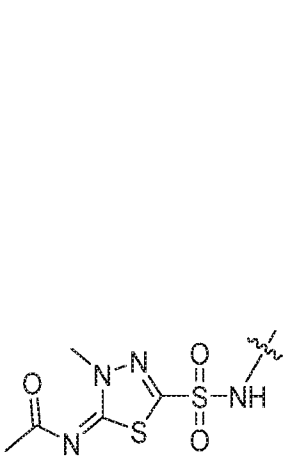
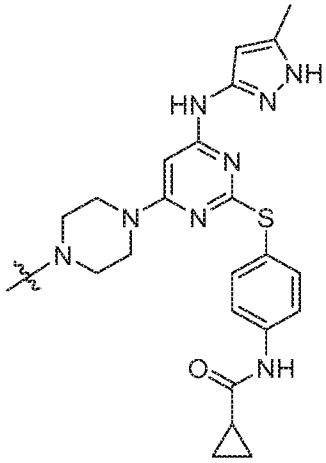
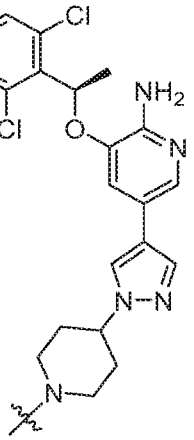
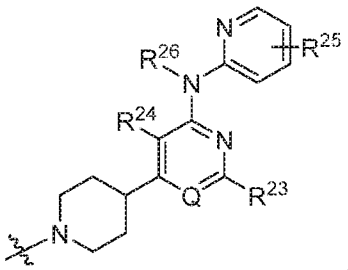
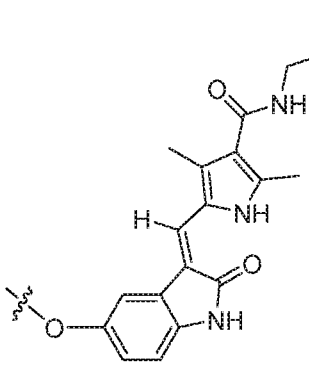
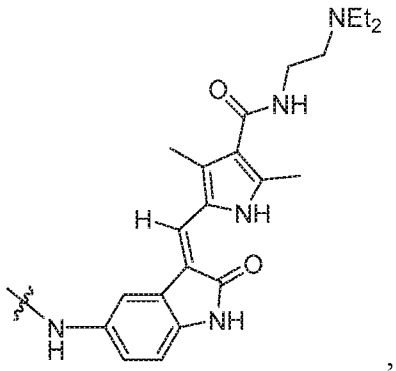
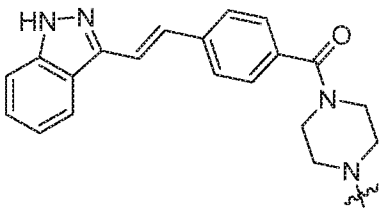
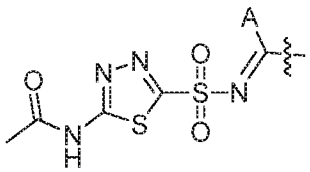
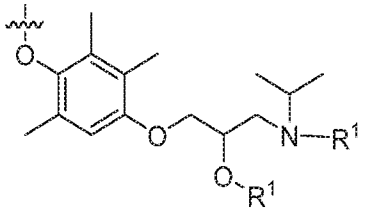
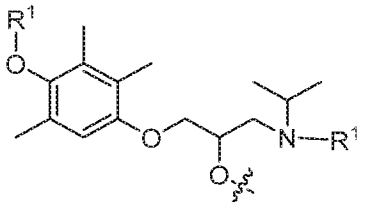
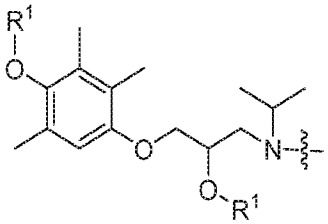
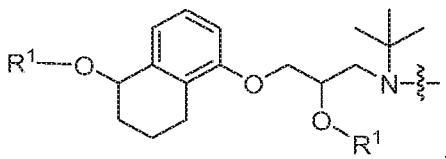
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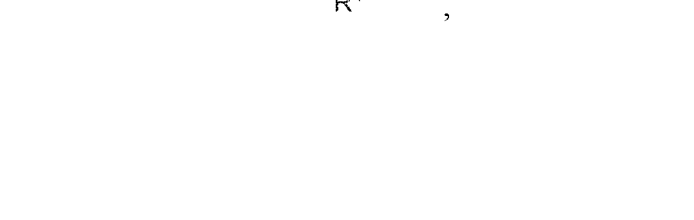


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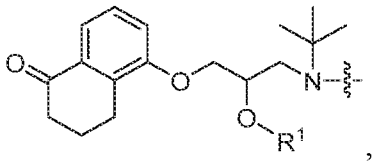
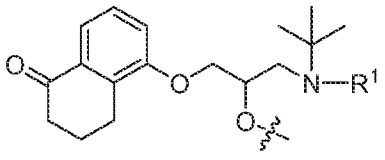
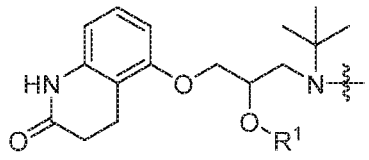
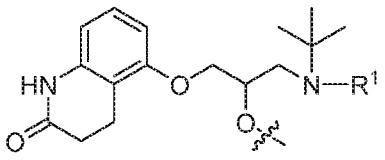
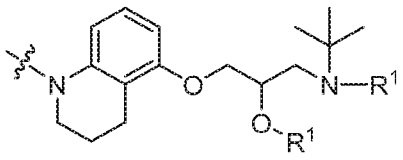
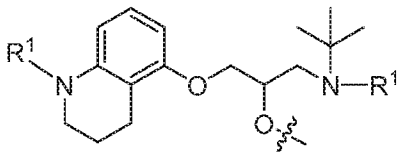
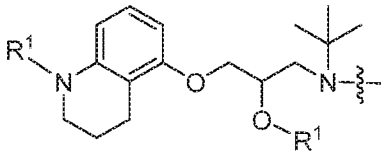
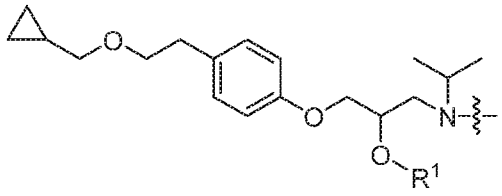
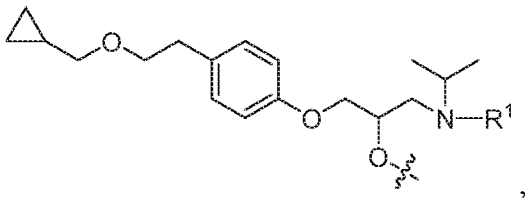
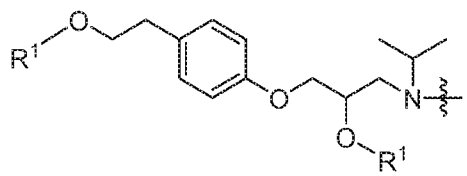
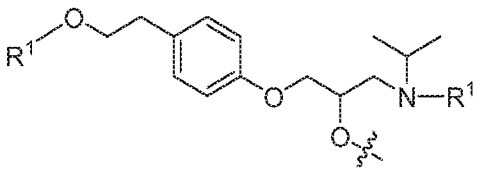
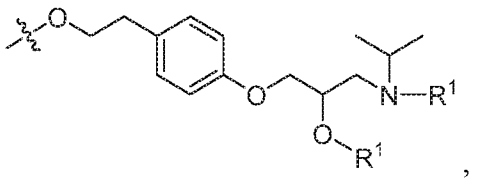
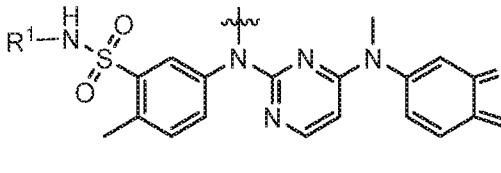
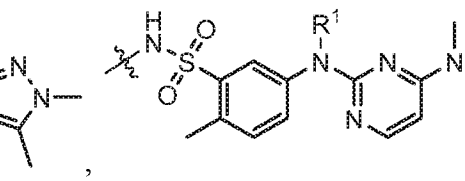
$R^{138}$ is selected from:




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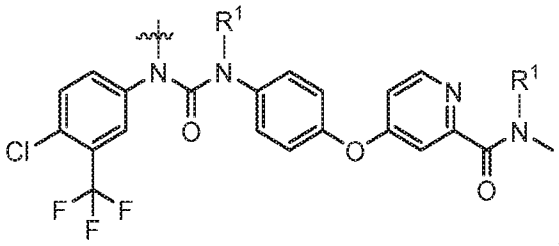
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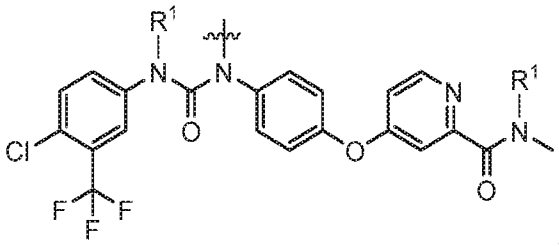

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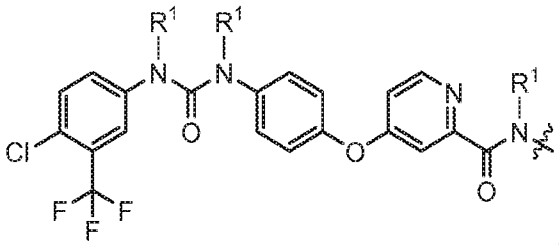
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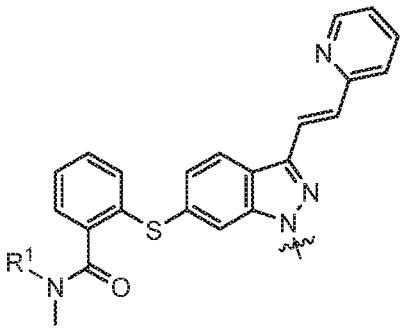
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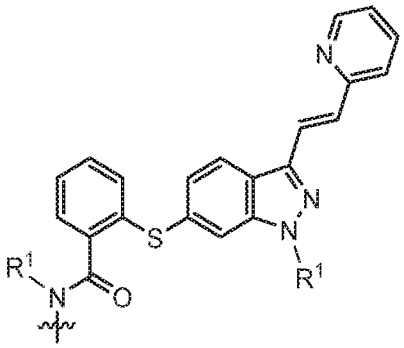
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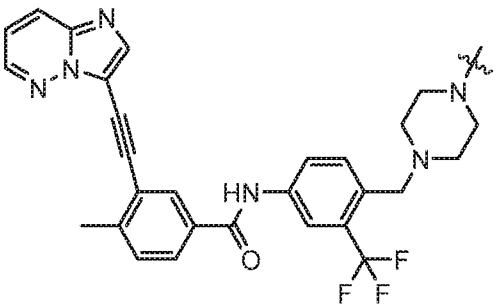
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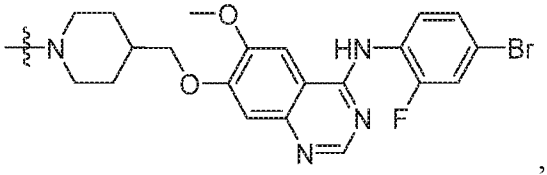
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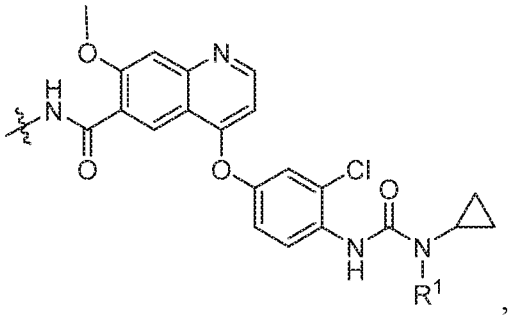
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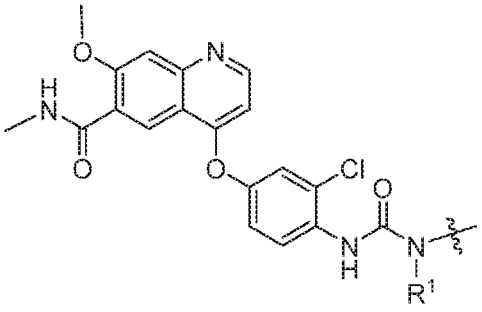
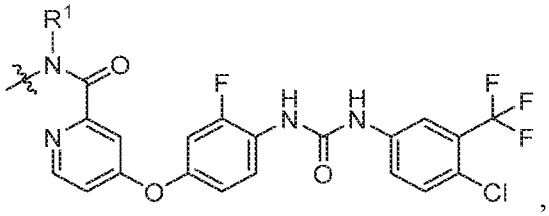
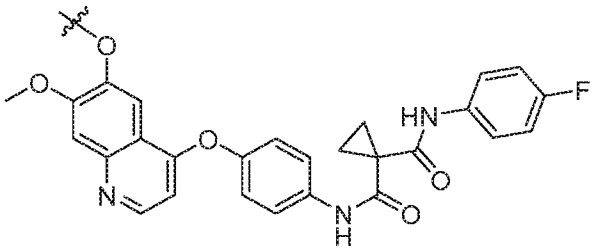
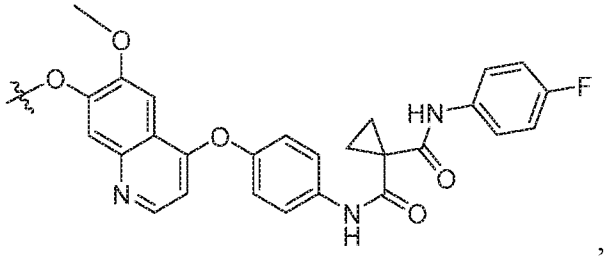
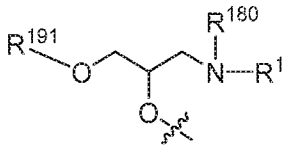
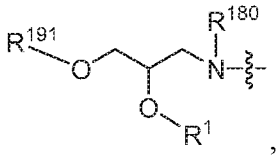
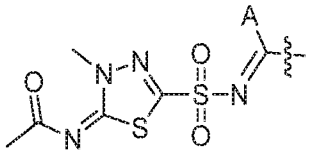
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$R^{140}$ is selected from $R^{136}$, hydrogen, alkyl, cycloalkyl, heterocycloalkyl, and aryl;

$R^{141}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, and halogen;

$R^{150}$ and $R^{151}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, $-C(O)C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, and $R^{156}$;

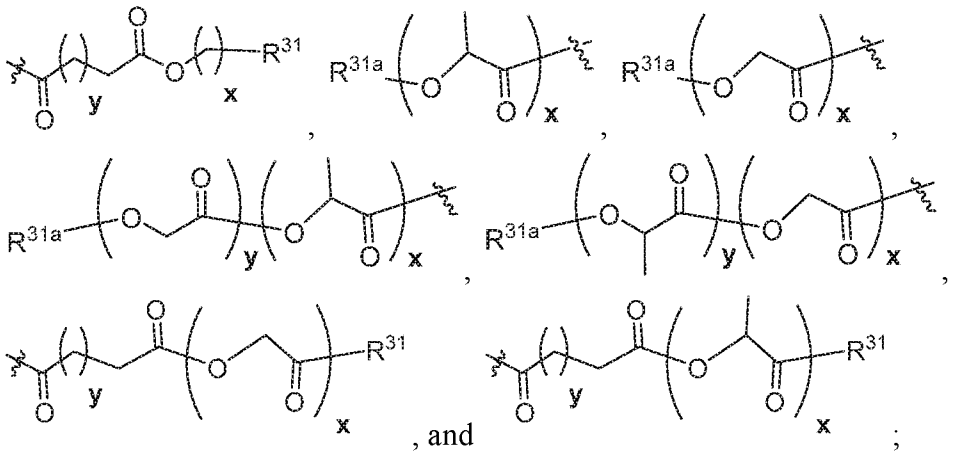
wherein at least one of $R^{150}$ and $R^{151}$ is $R^{156}$;

$R^{152}$ is selected from $C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and alkylaryl;

or $R^{151}$ and $R^{152}$ can together form a cycloalkyl or heterocycloalkyl;

$R^{156}$ is selected from:

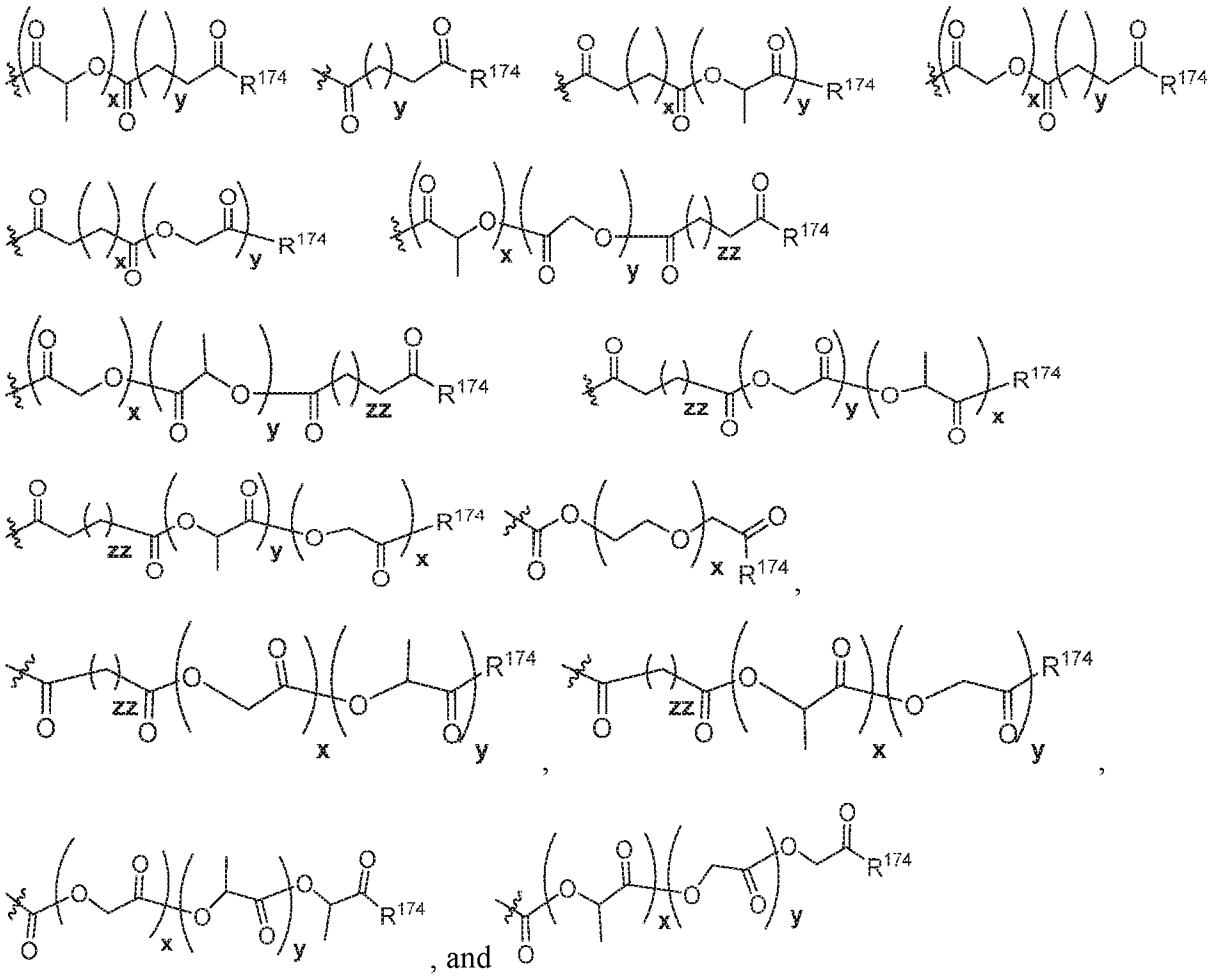
(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid) polyglycolic acid, polyester, polyamide; and

(ii) 

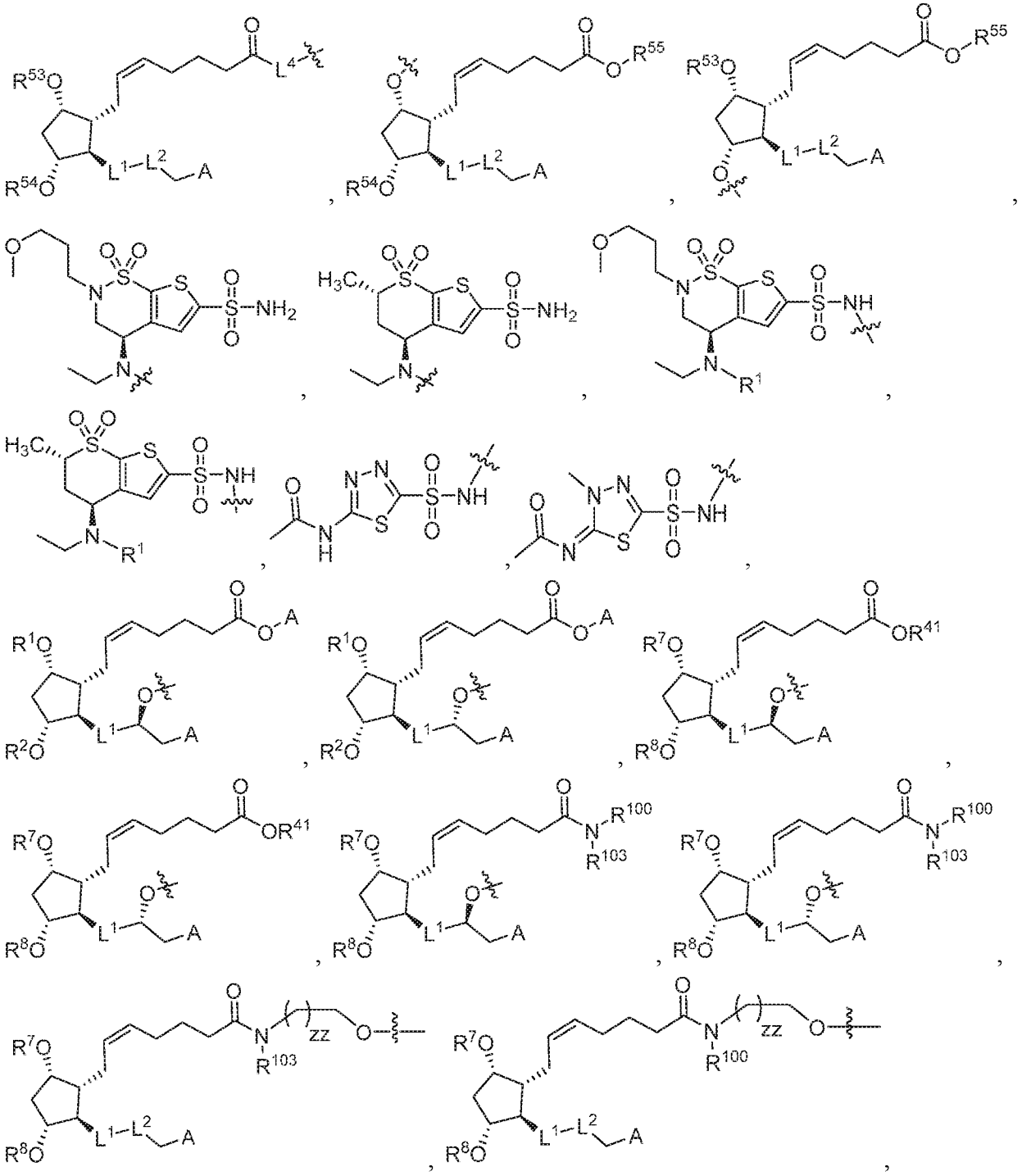
, and ;

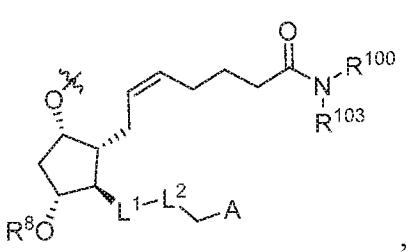
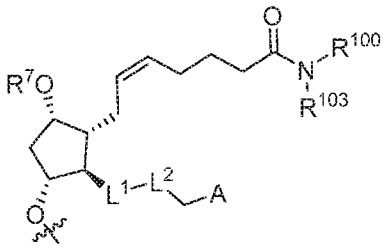
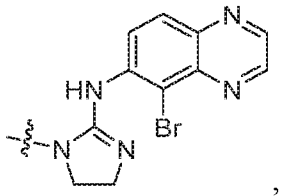
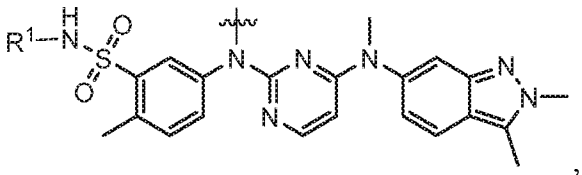
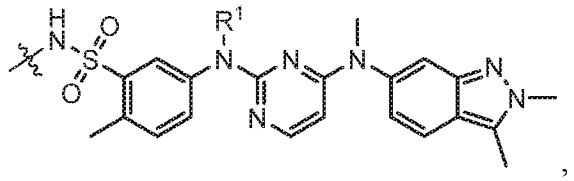
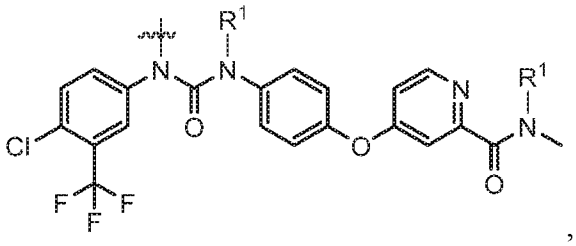
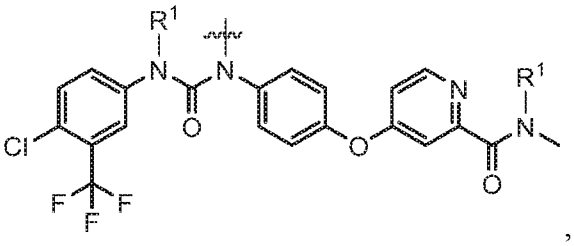
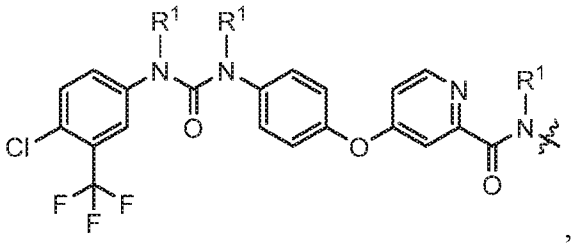
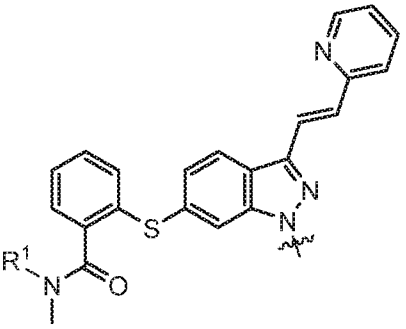
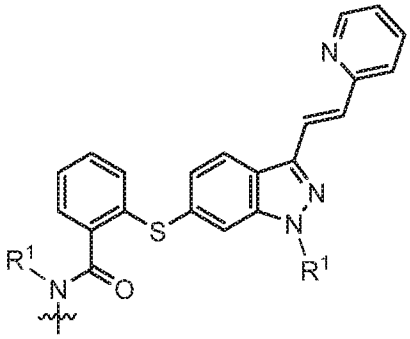
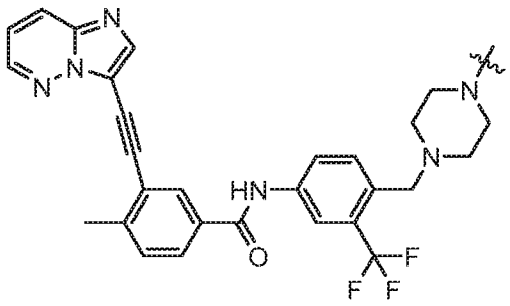
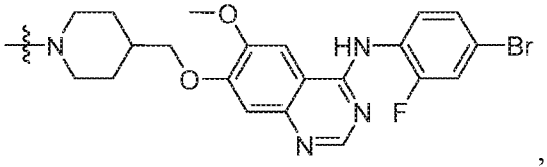
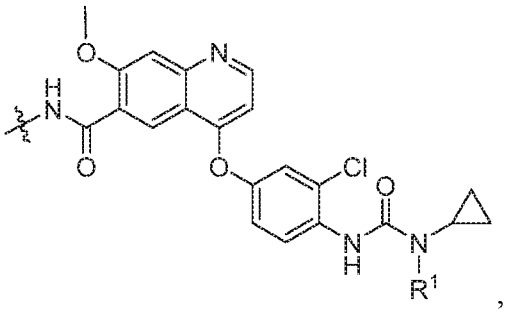
$R^{170}$, $R^{171}$, and $R^{172}$ are independently selected from $R^1$, $R^{173}$, acyl, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, and polyamide; wherein at least one of $R^{170}$, $R^{171}$, and $R^{172}$ is $R^{173}$ or substituted with $L^8$-$R^{174}$

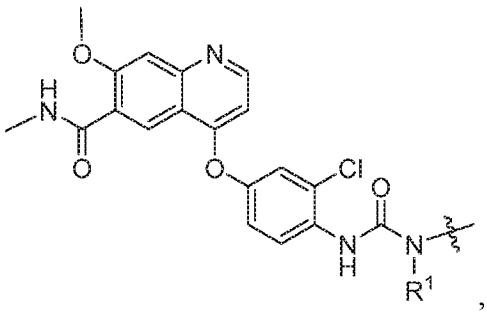
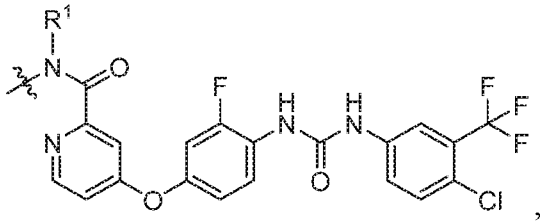
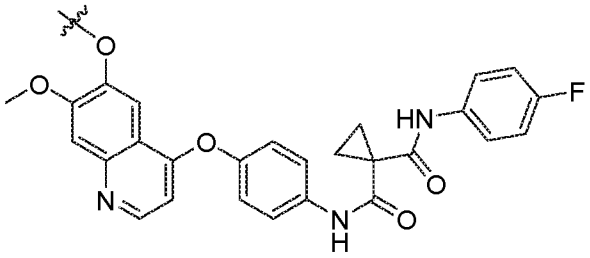
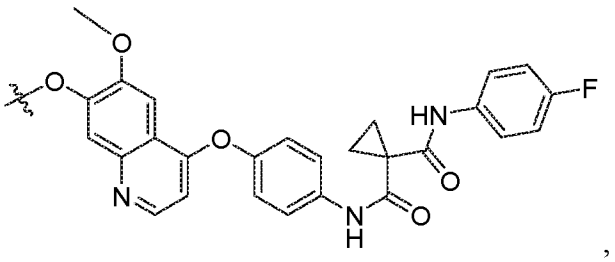
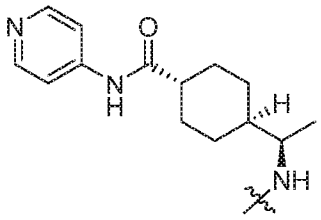
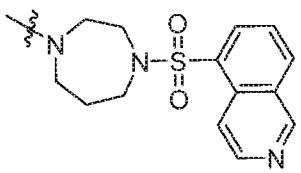
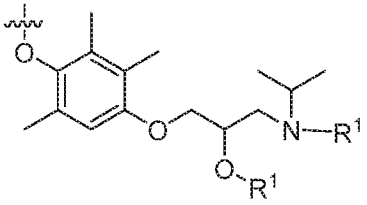
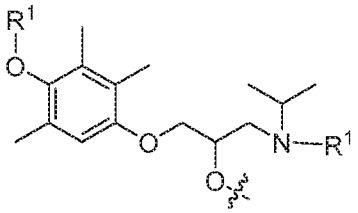
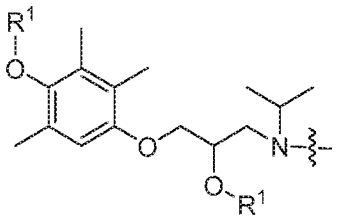
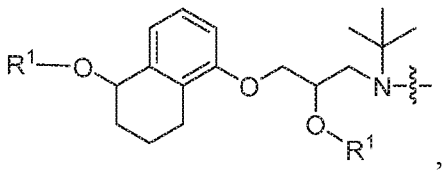
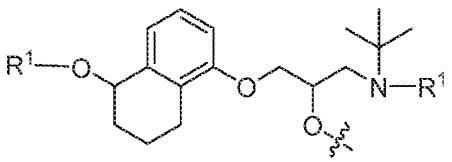
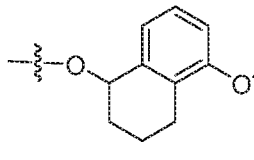
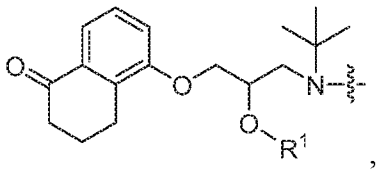
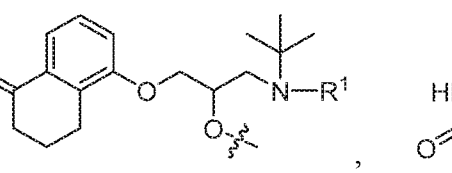
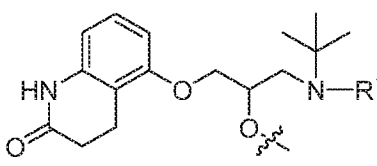
$R^{173}$ is selected from:

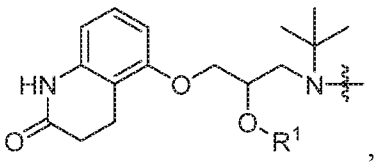


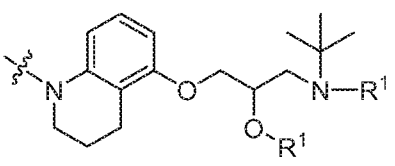
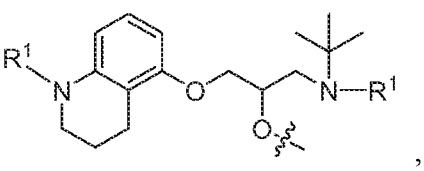
$R^{174}$ is selected from:

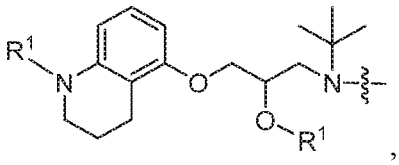
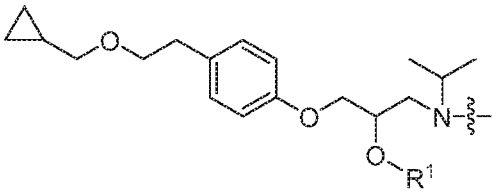
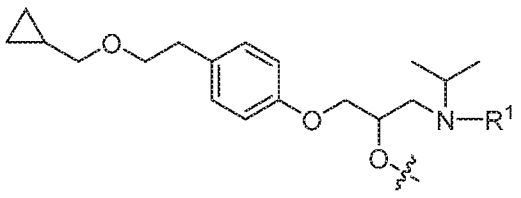
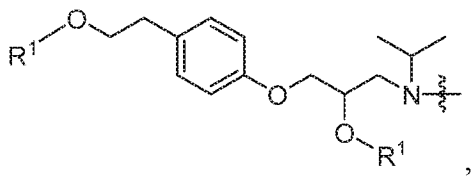
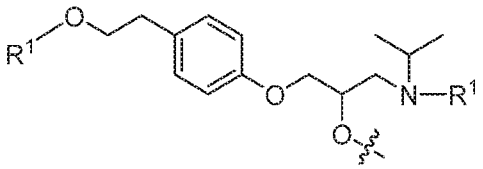
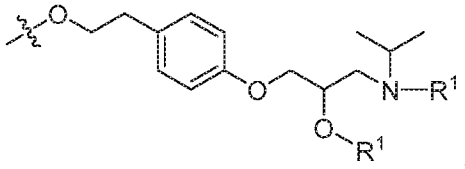
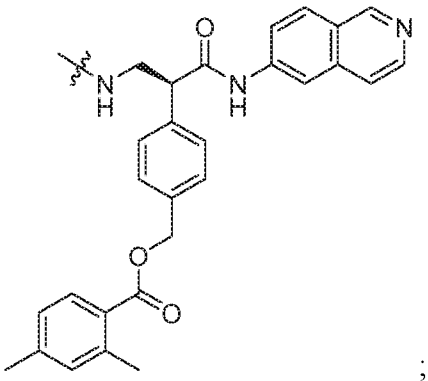



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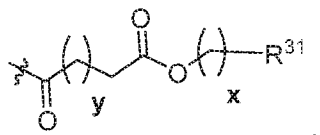
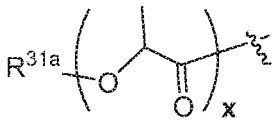
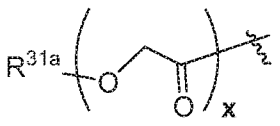
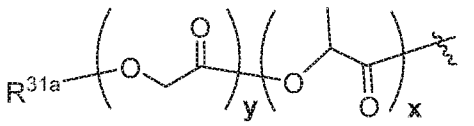
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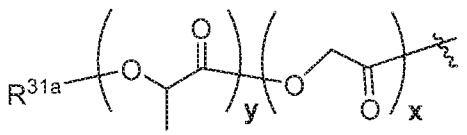
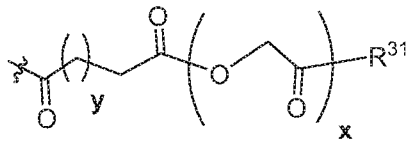
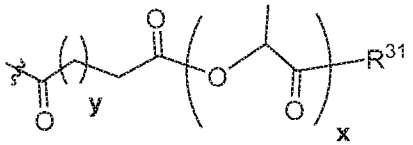
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$R^{175}$ is selected from C(O)A, C(O)$R^4$, and $R^{178}$;

$R^{178}$ is selected from:

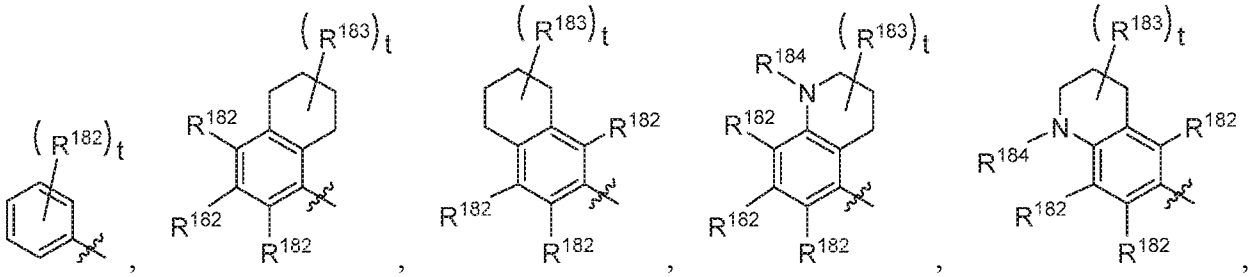
(i) carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide,

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; and

(ii) -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{4\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}10}$C(O)OH, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{4\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, and -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl;

$R^{180}$ is $C_1$-$C_6$ alkyl, acyl, or hydrogen;

$R^{181}$ is selected from:


, and $R^{185}$;

$R^{182}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{182}$ is optionally substituted with a $R^{170}$ group;

$R^{183}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

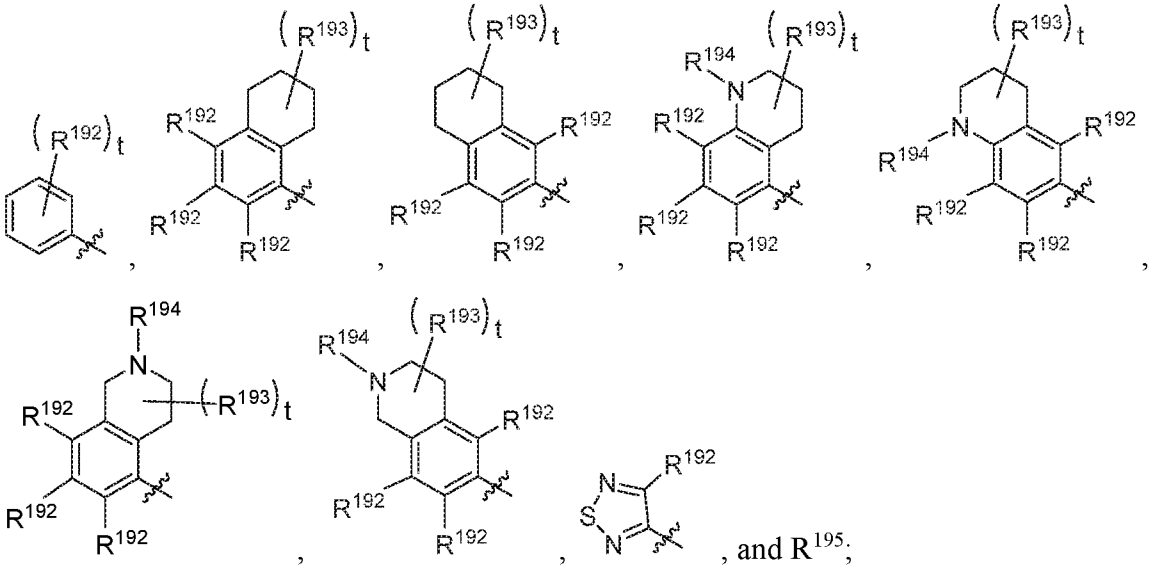
or two $R^{183}$ groups with the carbon to which they are linked form a carbonyl group;

or two $R^{183}$ groups with the carbon(s) to which they are linked form a fused or spirocyclic ring;

$R^{184}$ is selected from alkyl, cycloalkyl, $R^{170}$, and acyl;

$R^{185}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{185}$ is optionally substituted with 1, 2, 3, or 4 $R^{182}$ groups;

$R^{191}$ is selected from:



, and $R^{195}$;

$R^{192}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{192}$ is optionally substituted with a $R^{175}$ group;

$R^{193}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

$R^{194}$ is selected from alkyl, cycloalkyl, $R^{175}$, and acyl; and

$R^{195}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{195}$ is optionally substituted with 1, 2, 3, or 4 $R^{192}$ groups;

A is selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy;

Q is selected from: N, CH, and $CR^{23}$;

Y is $CR^{150}$ or N;

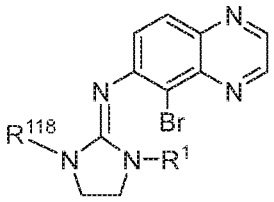
Z is $CR^{130}$ or N;

t is independently selected from 0, 1, 2, 3, and 4;

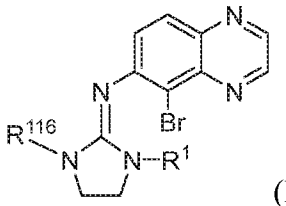
x, y, and z are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30; and

zz is selected from 1, 2, 3, 4, 5, or 6.

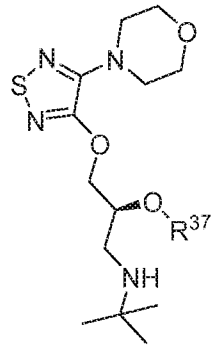
3. A compound of Formula VIII', Formula IX'', Formula XIII, Formula XV', Formula XVII', Formula XVII'', Formula XVII''', Formula L, Formula L', Formula LI, Formula LII, Formula LII', or Formula LIII



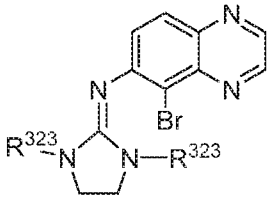
(VIII')



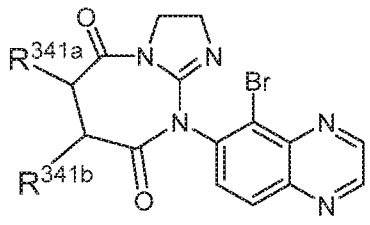
(IX'')



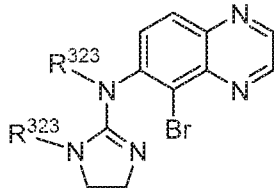
(XIII)



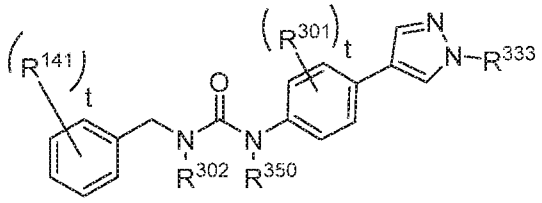
(XVII')



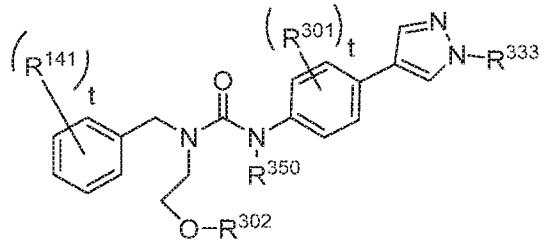
(XVII'')



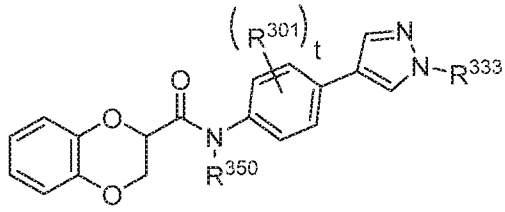
(XVII''')



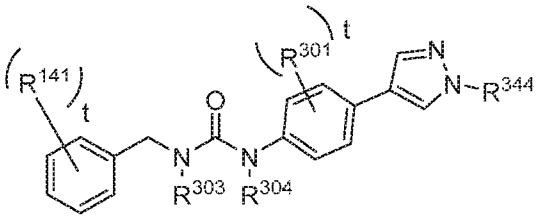
(L)



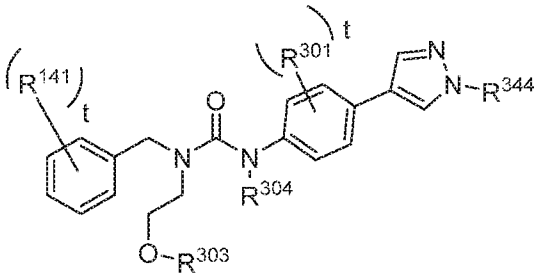
(L')



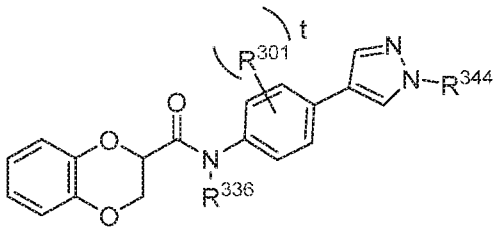
(LI)



(LII)



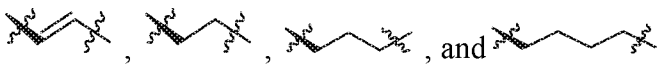
(LII')

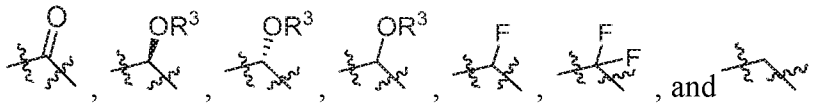


(LIII)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof;

wherein:

$L^1$ is selected from ;

$L^2$ is selected from .

$R^1$, $R^2$, and $R^3$ are independently selected from -C(O)$R^4$, C(O)A, and hydrogen;

$R^4$ is selected from:

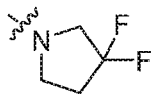
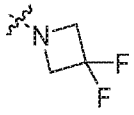
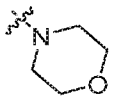
(i) –$C_{20}$-$C_{30}$alkyl$R^5$, –$C_{20}$-$C_{30}$alkenyl$R^5$, -$C_{20}$-$C_{30}$alkynyl$R^5$, -$C_{20}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{20}$-$C_{30}$alkyl, –$C_{20}$-$C_{30}$alkenyl, -$C_{20}$-$C_{30}$alkynyl, and -$C_{20}$-$C_{30}$alkenylalkynyl; and

(ii) an unsaturated fatty acid residue selected from –$(CH_2)_3(CHCHCH_2)_6CH_3$), –$(CH_2)_4(CHCHCH_2)_5CH_3$), docosatetraenoic acid, and nervonic acid;

$R^5$ is selected from halogen, hydroxyl, cyano, mercapto, amino, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si$(CH_3)_3$, -COOH, -COOalkyl, and -$CONH_2$;

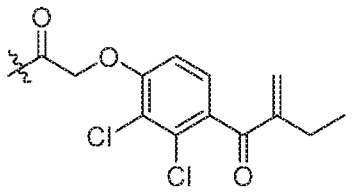
$R^7$ and $R^8$ are independently selected from -C(O)$R^4$, -C(O)A, hydrogen, and $R^{50}$;

$R^{23}$, $R^{24}$, and $R^{25}$ are independently selected from hydrogen, halogen, hydroxyl, cyano, mercapto, nitro, amino, aryl, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl,

-S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -COOalkyl, -CONH$_2$, , , , and ;

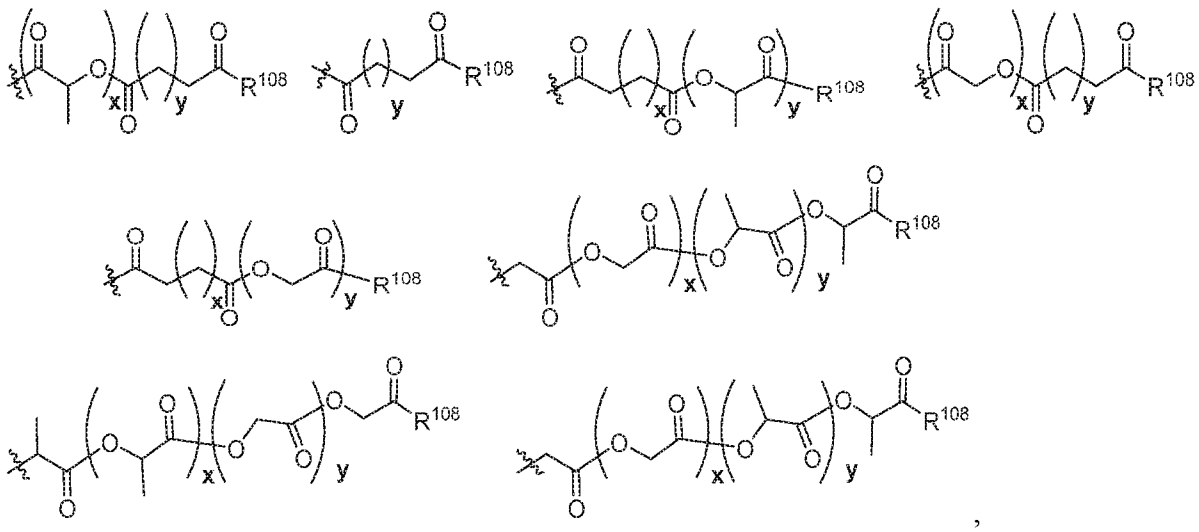
$R^{26}$ is selected from H, C(O)A, -C$_0$-C$_{10}$alkyl$R^5$, -C$_2$-C$_{10}$alkenyl$R^5$, –C$_2$-C$_{10}$alkynyl$R^5$, -C$_2$-C$_{10}$alkenyl, and –C$_2$-C$_{10}$alkynyl;

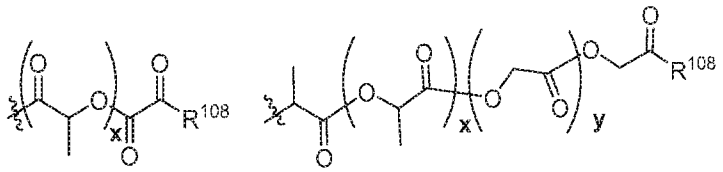
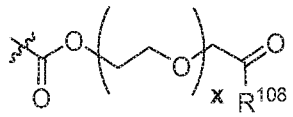
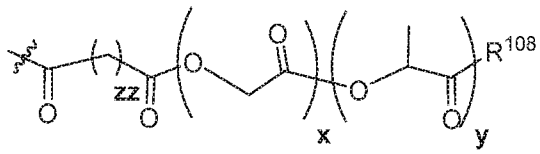
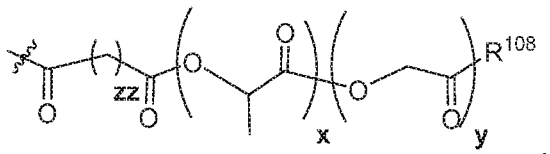
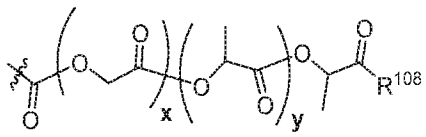
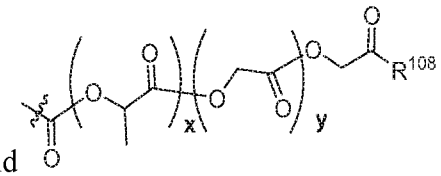
$R^{31}$ is hydrogen, hydroxy, amino, A, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, or polyethylene glycol;

$R^{31a}$ is hydrogen, A, -C(O)alkyl, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, stearoyl, or ;

$R^{37}$ is $R^{38}$;

$R^{38}$ is selected from:

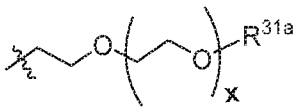
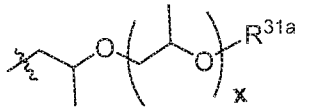
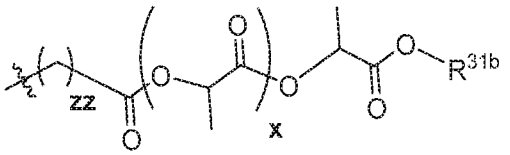
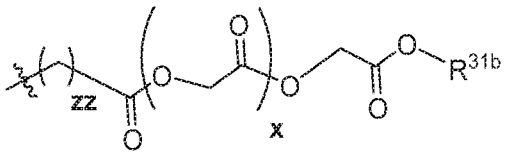
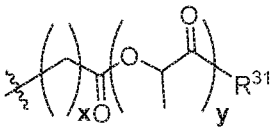
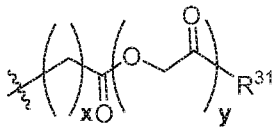
,

, and ;

$R^{41}$ is selected from:

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, a polyamide,

, and ; and

(ii) –$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl; and

(iii) an unsaturated fatty acid residue; and

(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl;

$R^{50}$ is selected from carbonyl derivatives of polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, and polyamide;

$R^{53}$ and $R^{54}$ are independently selected from –C(O)$R^4$, -C(O)A, and hydrogen;

$R^{55}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, and a polyamide;

(ii) –$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl; and

(iii) an unsaturated fatty acid residue selected from -$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), –$(CH_2)_3(CHCHCH_2)_6CH_3$), -$(CH_2)_4(CHCHCH_2)_5CH_3$), –$(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid; and

(iv) alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl;

$R^{100}$ is selected from:

(i) $C_1$-$C_{10}$alkyl, -$C_0$-$C_{10}$alkyl($C_3$-$C_7$cycloalkyl), heterocycle, –$C_0$-$C_{10}$alkyl($C_3$-$C_7$heterocycloalkyl), –aryl$C_0$-$C_{10}$alkyl, –heteroarylalkyl, -$C_0$-$C_{10}$alkyl$C_2$-$C_{10}$alkenyl, and $C_2$-$C_{10}$alkynyl;

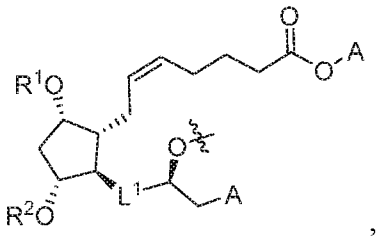
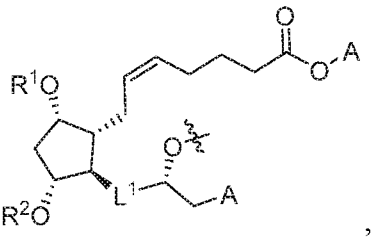
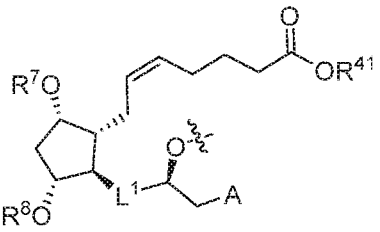
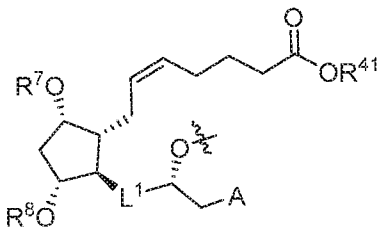
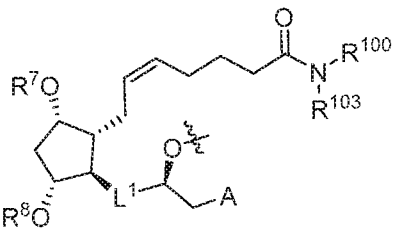
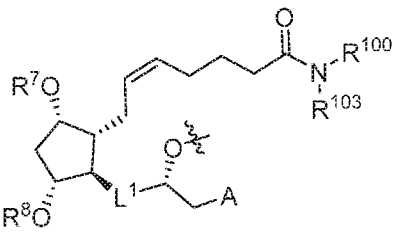
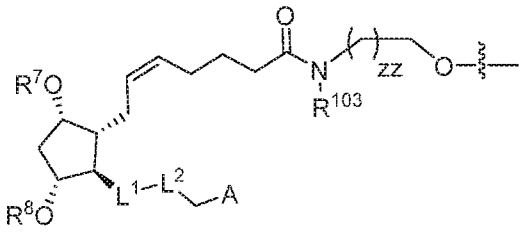
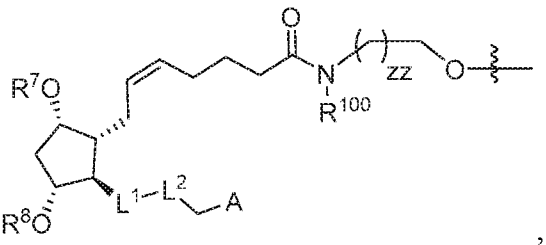
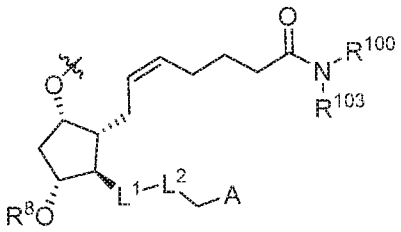
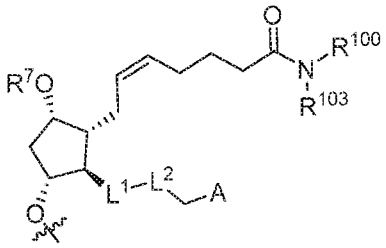
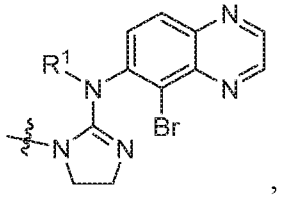
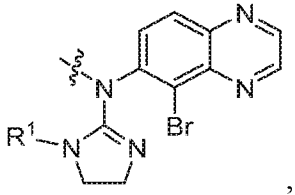
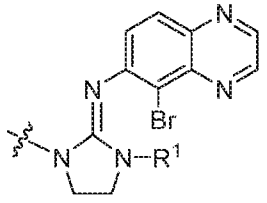
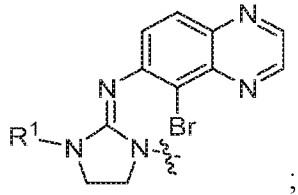
(ii) an unsaturated fatty acid selected from -$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), –$(CH_2)_3(CHCHCH_2)_6CH_3$), -$(CH_2)_4(CHCHCH_2)_5CH_3$), –$(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iii)–$C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, –$C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl; and

(iv) $R^{50}$;

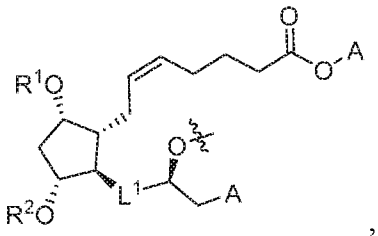
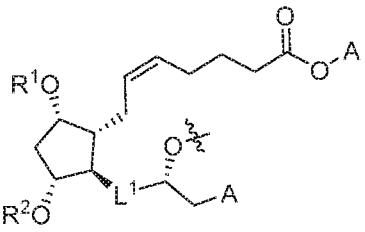
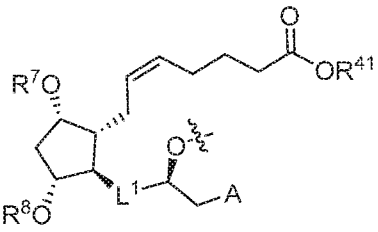
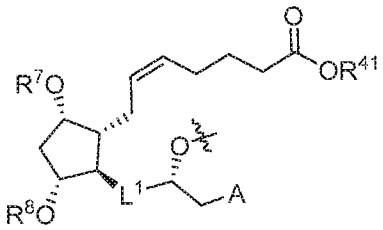
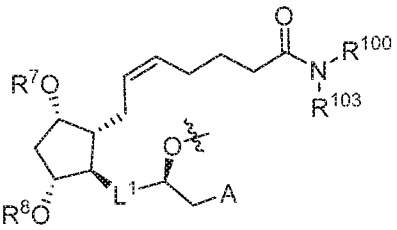
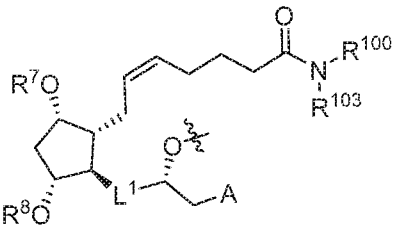
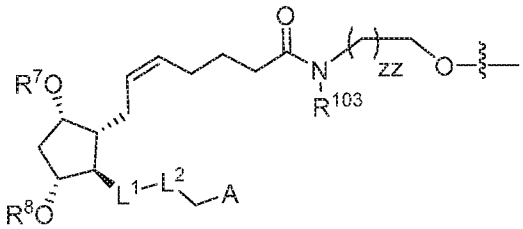
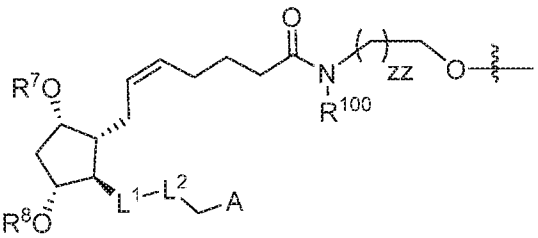
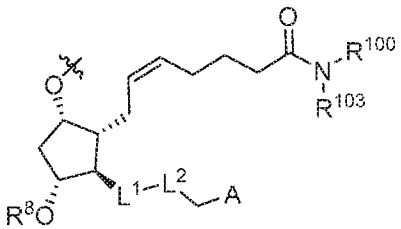
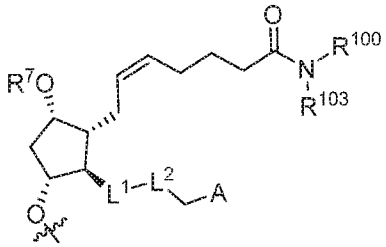
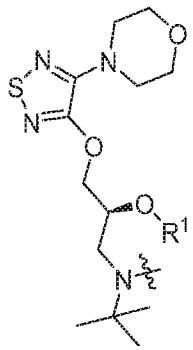
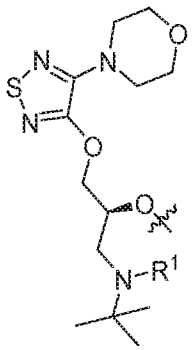
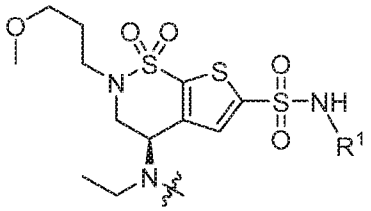
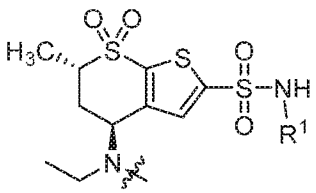
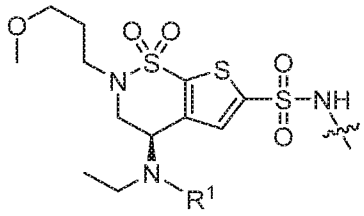
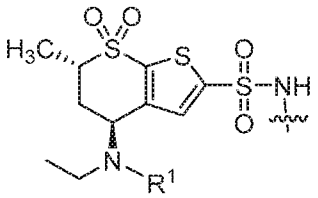
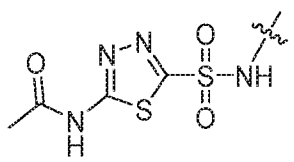
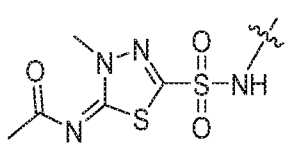
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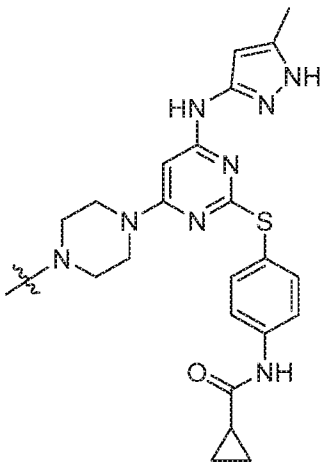
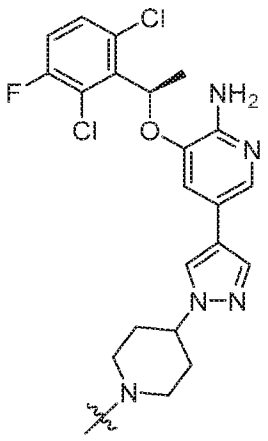
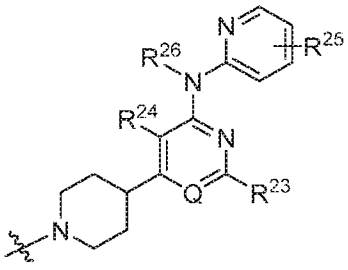
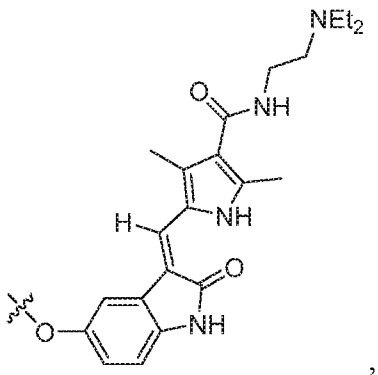
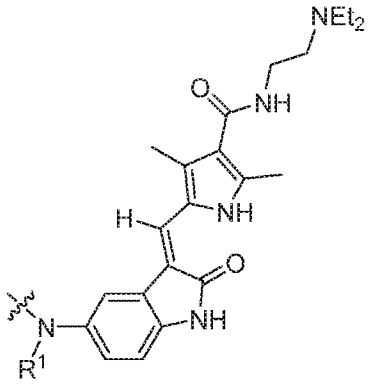
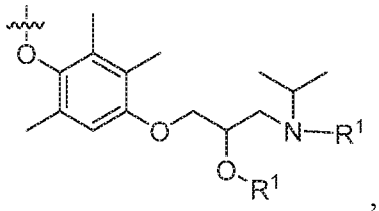
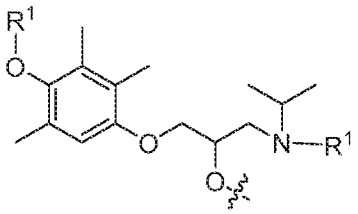
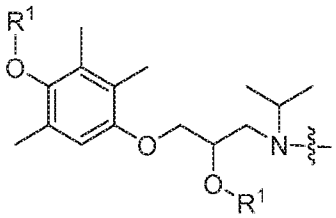
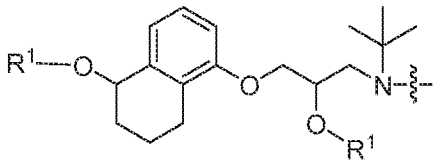
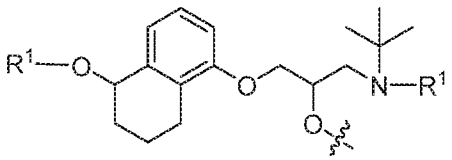
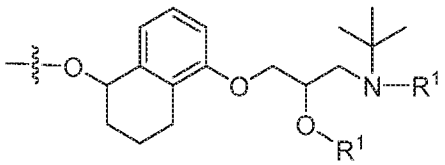
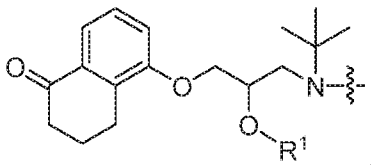
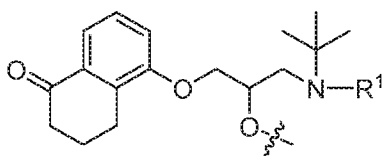
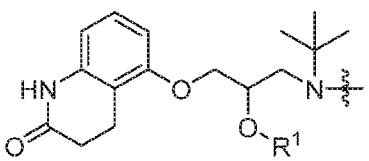
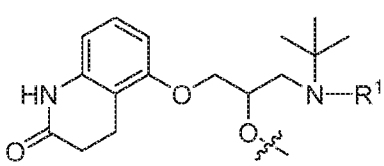
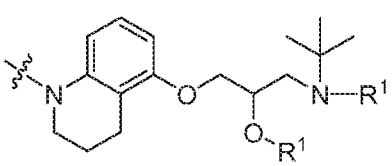
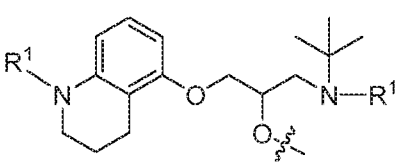
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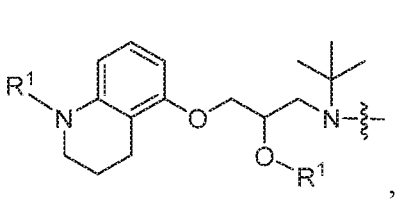
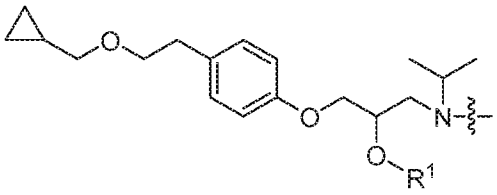
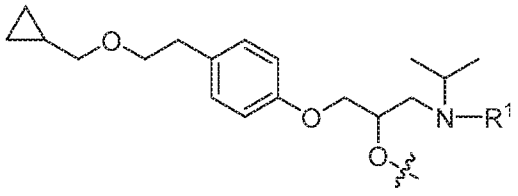
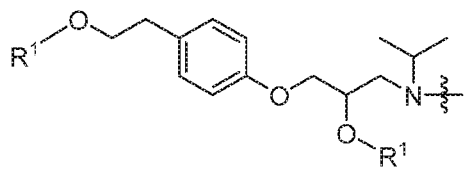
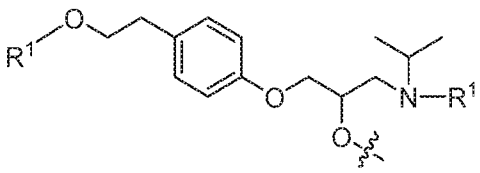
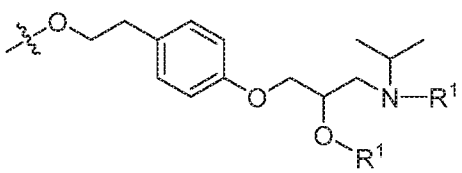
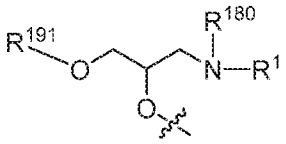
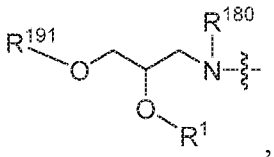
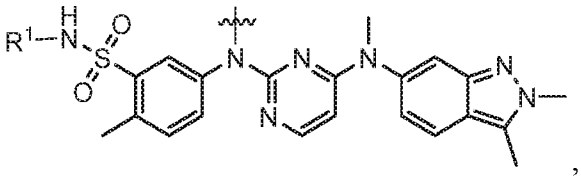
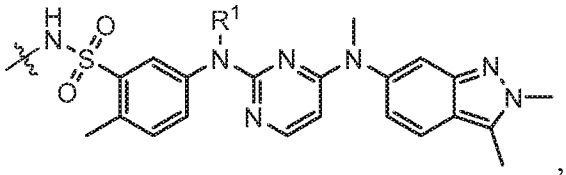
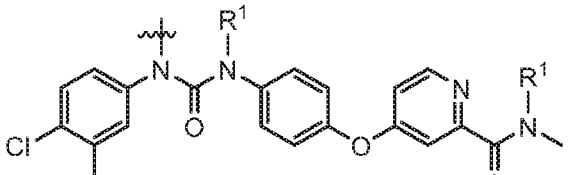















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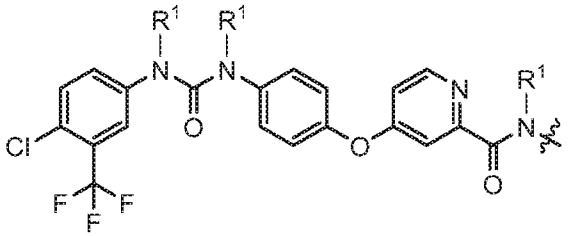
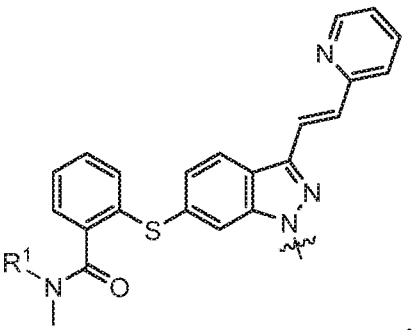
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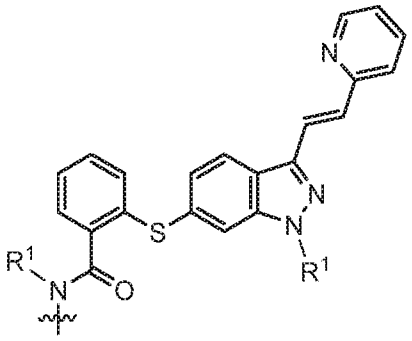
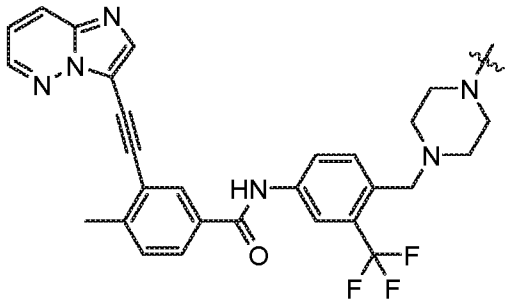
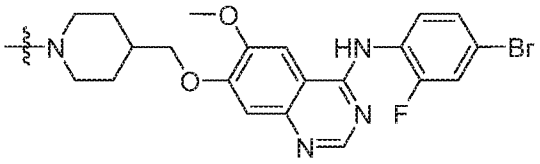
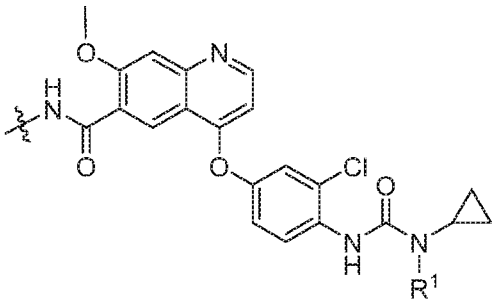
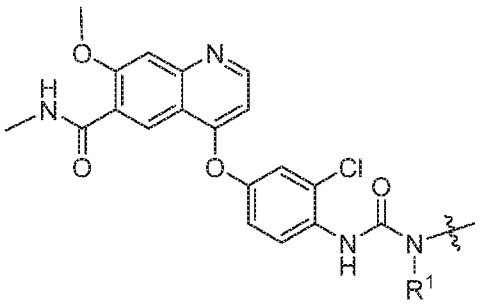
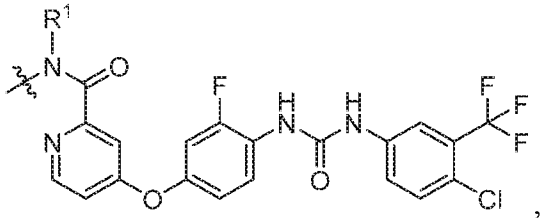
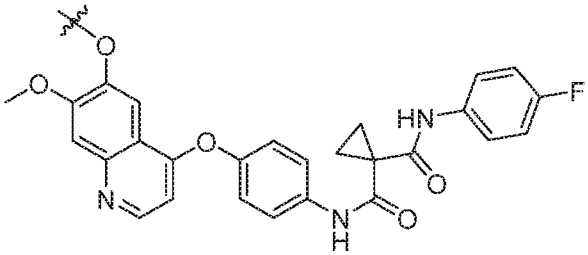
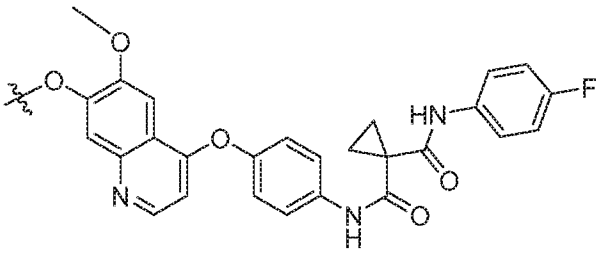

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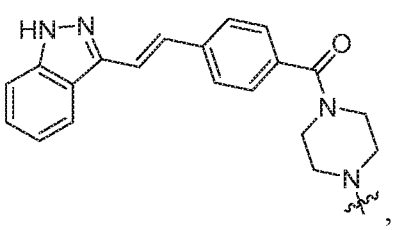
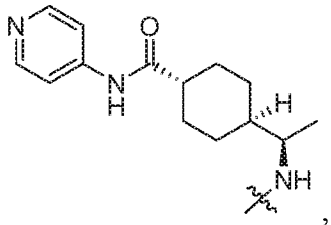
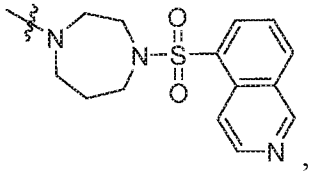
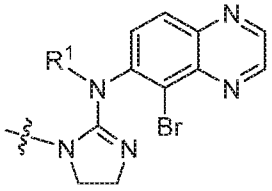
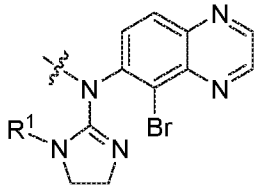
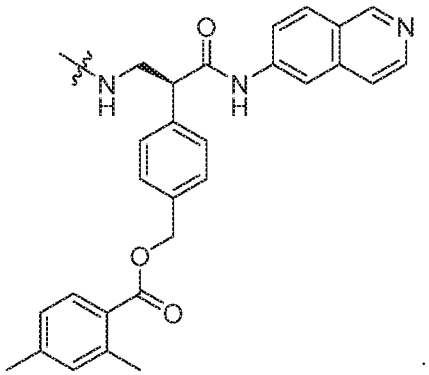



















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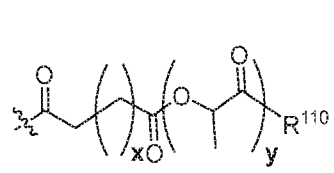
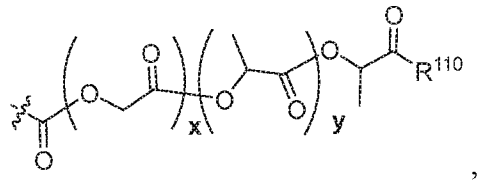
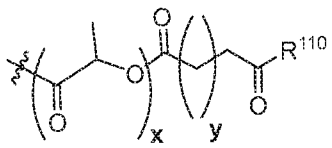
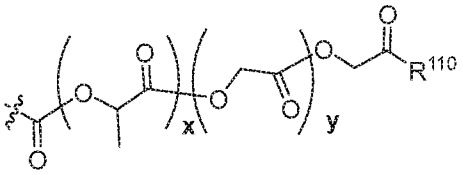
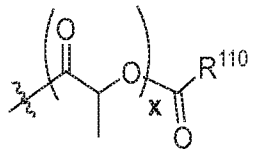
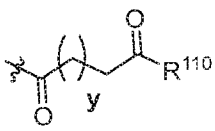
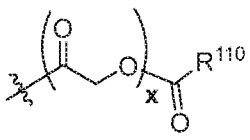
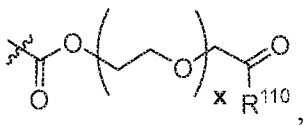
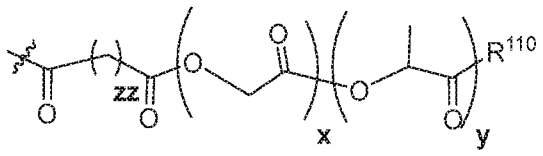
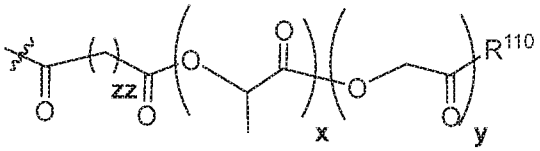
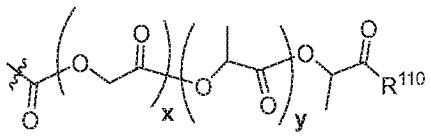
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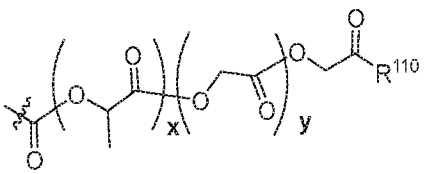

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$R^{116}$ is $R^{117}$;

$R^{117}$ is selected from:












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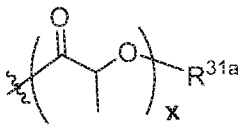
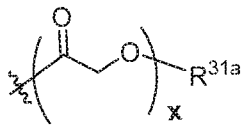
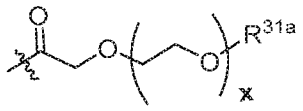
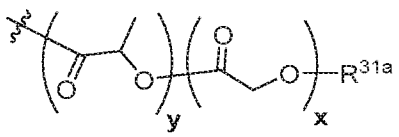
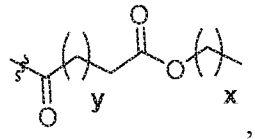
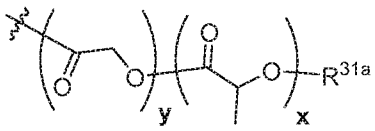
$R^{118}$ is selected from:

(i) –C(O)$C_5$-$C_{30}$alkyl$R^5$, -C(O)$C_2$-$C_{30}$alkenyl$R^5$, -C(O)$C_2$-$C_{30}$alkynyl$R^5$, -C(O)$C_4$-$C_{30}$alkenylalkynyl$R^5$, –C(O)$C_5$-$C_{30}$alkyl, -C(O)$C_2$-$C_{30}$alkenyl, -C(O)$C_2$-$C_{30}$alkynyl, and -C(O)$C_4$-$C_{30}$alkenylalkynyl;

(ii) -C(O)($C_{1-30}$alkyl with at least one $R^5$ substituent on the alkyl chain, -C(O)($C_{1-30}$alkenyl with at least one $R^5$ substituent on the alkenyl chain, -C(O)($C_{1-30}$alkynyl with at least one $R^5$ substituent on the alkynyl chain, -(lactic acid)$_{1-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{4-20}$C(O)$C_{1-30}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-30}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)$C_{1-30}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)$C_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl, and -(lactic acid)$_{1-10}$C(O)$C_{4-10}$alkyl;

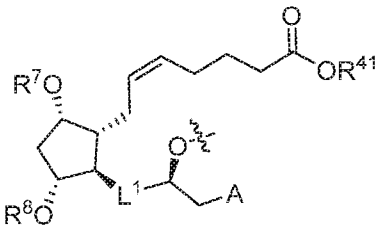
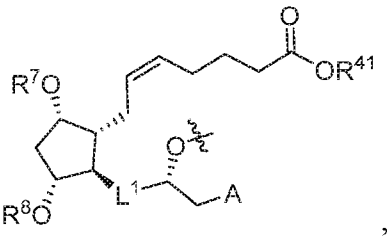
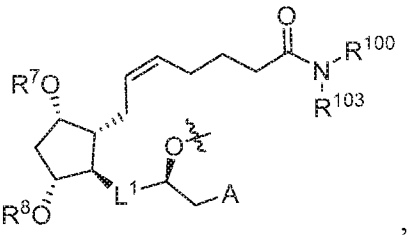
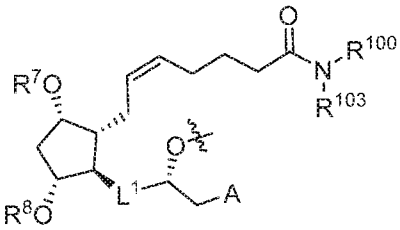
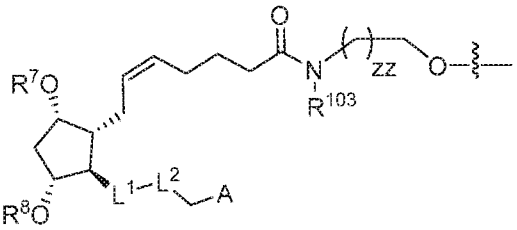
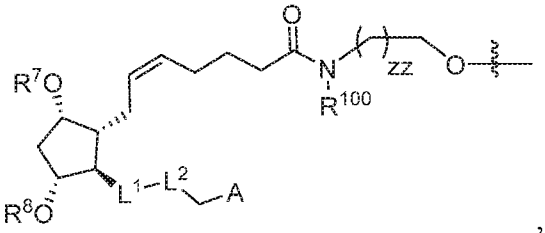
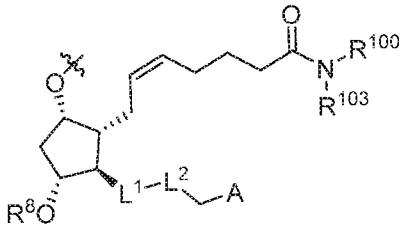
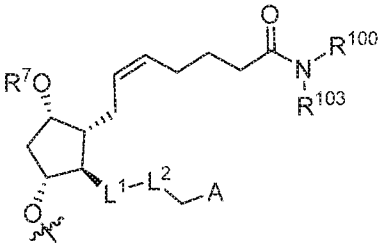
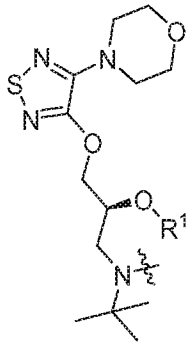
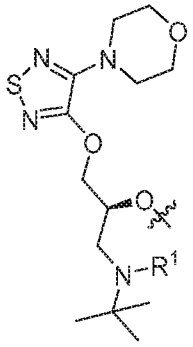
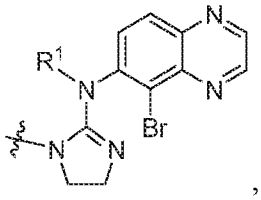
(iii) an unsaturated fatty acid residue selected from -$(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), –$(CH_2)_3(CHCHCH_2)_6CH_3$), –$(CH_2)_4(CHCHCH_2)_5CH_3$), –$(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

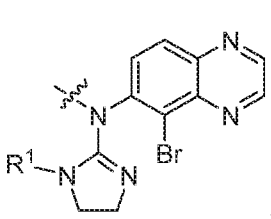
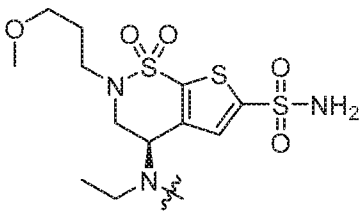
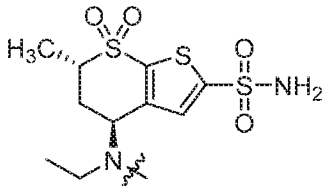
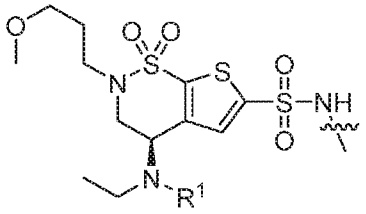
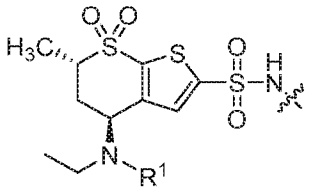
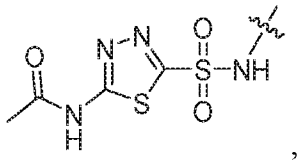
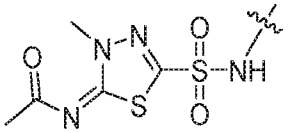
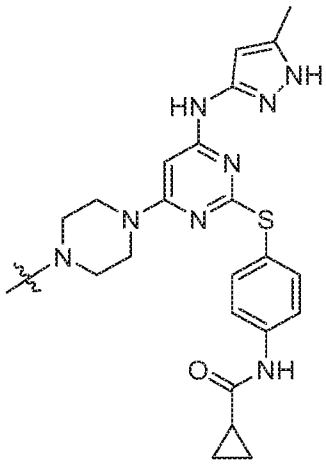
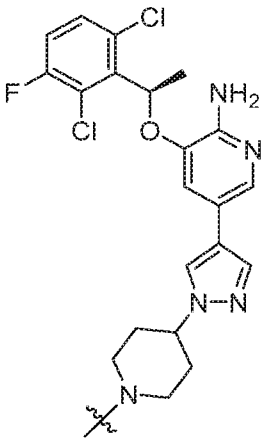
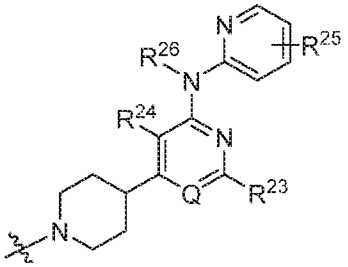
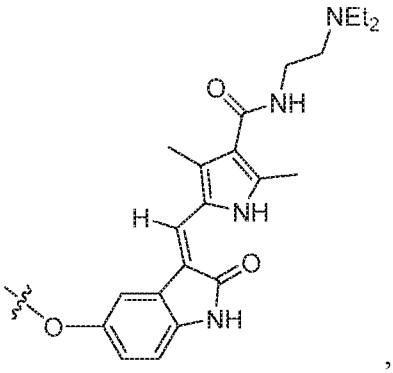
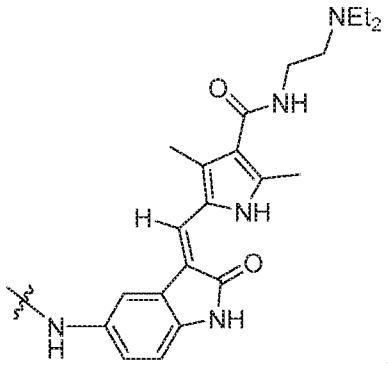
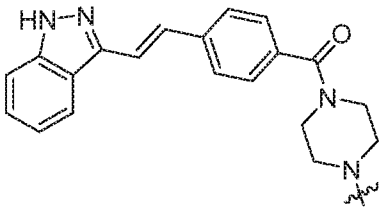
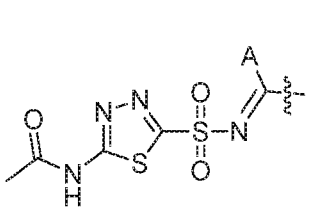
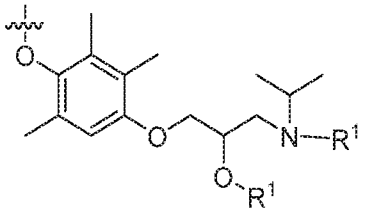
(iv) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, a polyester, and a polyamide; and

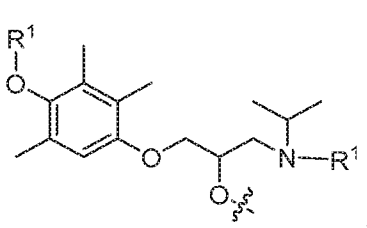
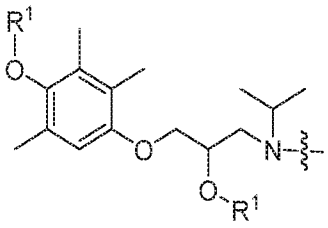
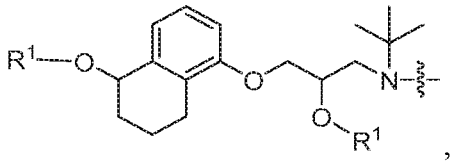
(v) , , , , , and ;

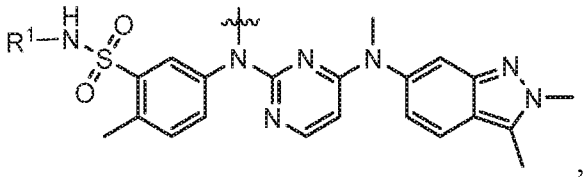
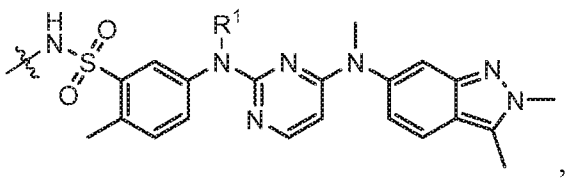
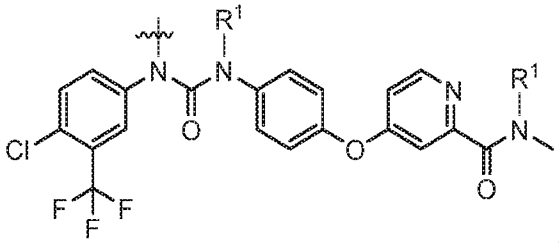
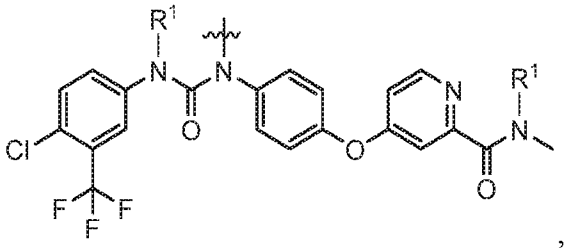
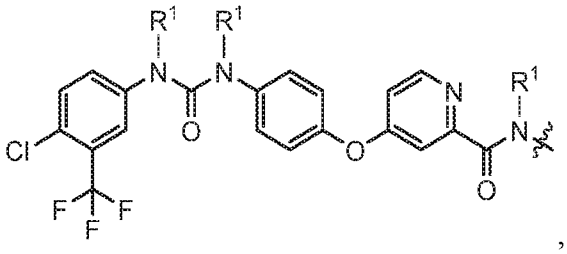
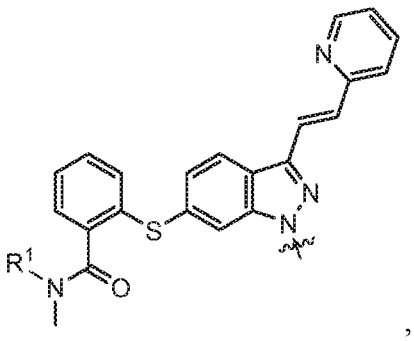
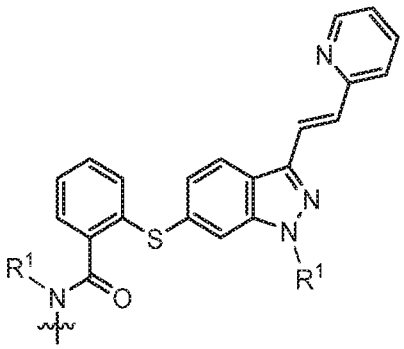
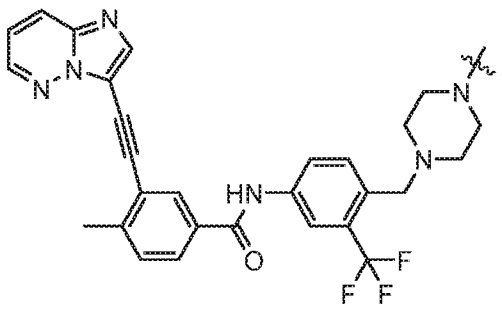
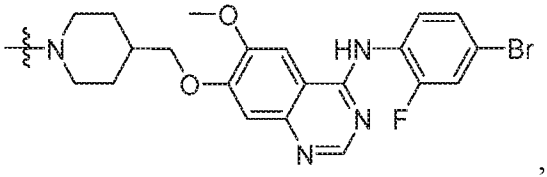
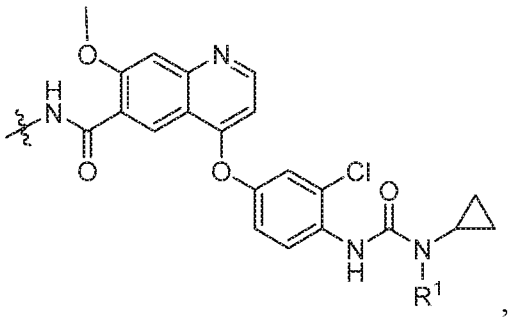
$R^{134}$ and $R^{135}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

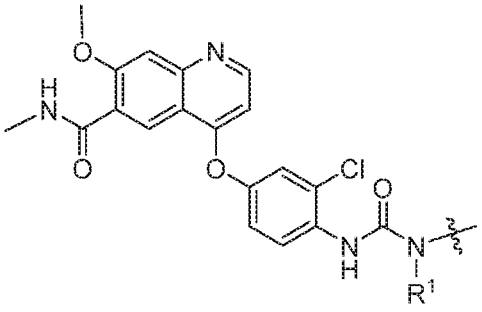
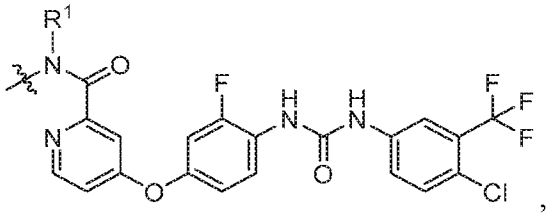
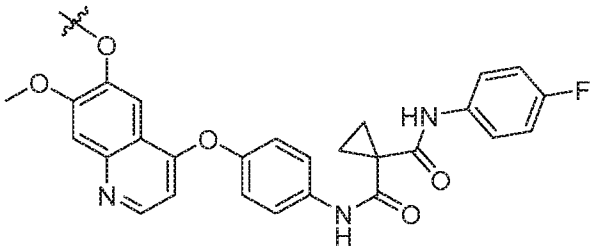
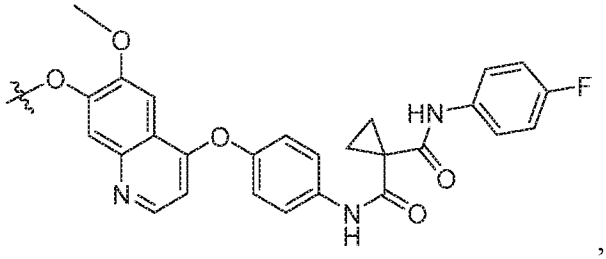
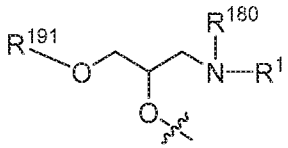
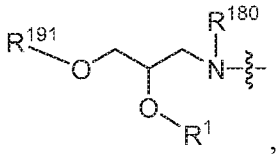
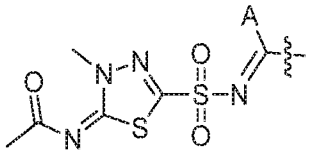
$R^{138}$ is selected from:

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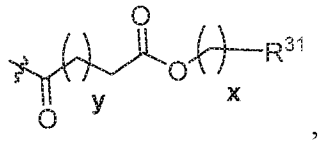
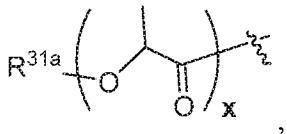
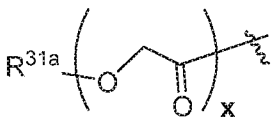
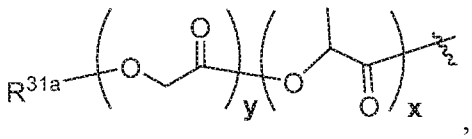

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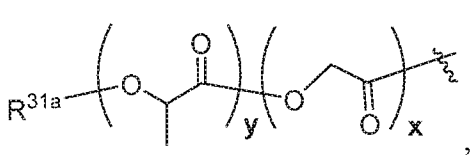
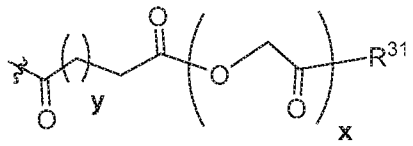
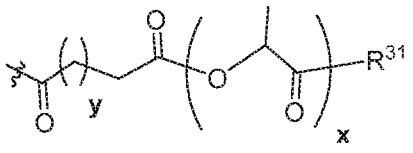

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$R^{141}$ is selected from hydrogen, -C(O)$NR^1R^2$, -C(O)$R^1$, -C(O)$OR^1$, nitro, amino, -$NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, and halogen;

$R^{175}$ is C(O)A, C(O)$R^4$, or $R^{178}$;

$R^{178}$ is selected from:

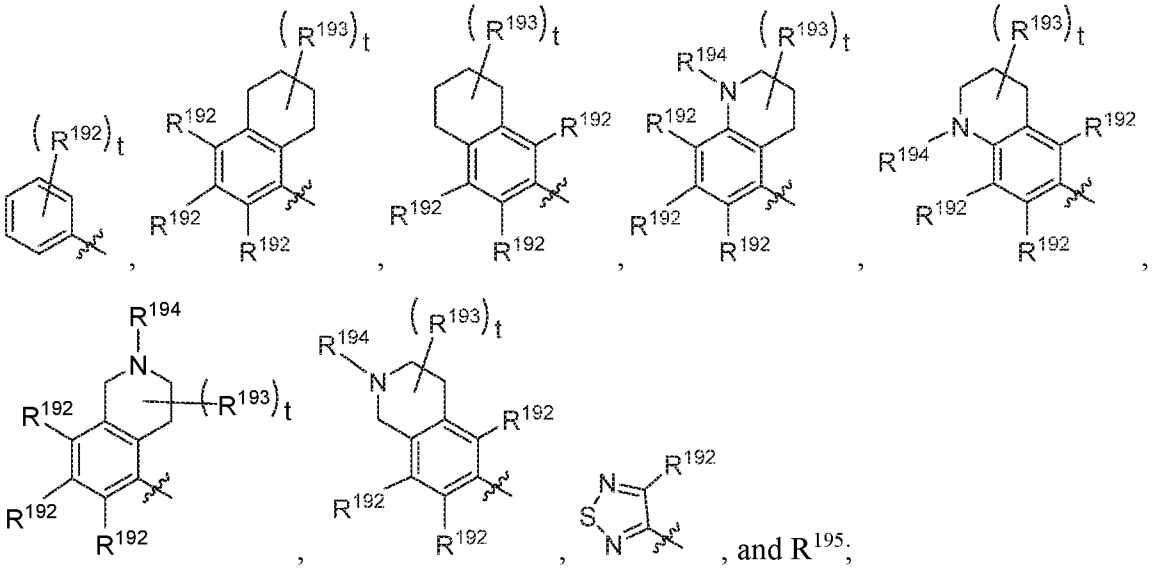
(i) carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide,

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(ii) -(lactic acid)$_{1-20}$C(O)C$_{1-22}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{1-22}$alkyl, -(lactic acid)$_{4-20}$C(O)C$_{1-22}$alkyl, -(lactic acid)$_{1-20}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-20}$C(O)C$_{4-10}$alkyl, -(lactic acid)$_{1-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-20}$C(O)OH, -(lactic acid)$_{1-10}$C(O)OH, -(lactic acid)$_{4-10}$C(O)OH, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{4-10}$C(O)C$_{1-22}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{1-12}$alkyl, -(lactide-co-glycolide)$_{1-10}$C(O)C$_{4-22}$alkyl, -(glycolic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(glycolic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{4-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{1-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl, and -(lactic acid)$_{1-10}$C(O)C$_{4-10}$alkyl;

$R^{180}$ is C$_1$-C$_6$ alkyl, acyl, or hydrogen;

$R^{191}$ is selected from:


, and $R^{195}$;

$R^{192}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{192}$ is optionally substituted with a $R^{175}$ group;

$R^{193}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

$R^{194}$ is selected from alkyl, cycloalkyl, $R^{175}$, and acyl;

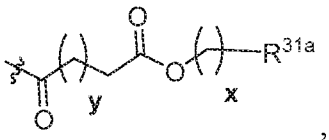
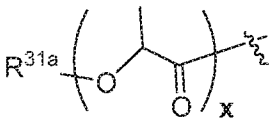
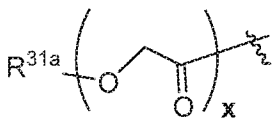
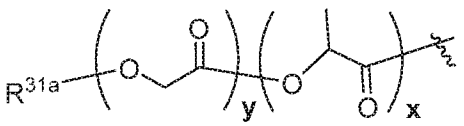
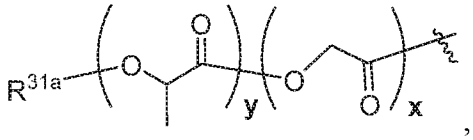
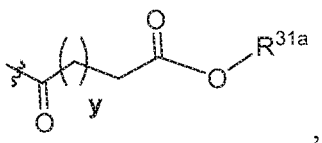
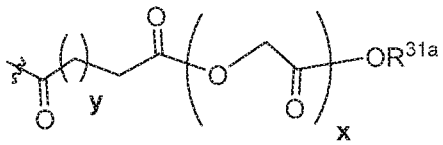
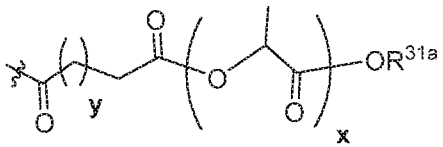
$R^{195}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{195}$ is optionally substituted with 1, 2, 3, or 4 $R^{192}$ groups;

$R^{301}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, halogen, $-O(CH_2)_2NR^{334}R^{335}$, and $-N(CH_3)(CH_2)_2NR^{334}R^{335}$;

$R^{302}$ and $R^{333}$ are independently selected from H, $C_1$-$C_{30}$alkyl, $-C(O)C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, $C_2$-$C_{30}$alkenyl, and $R^{356}$;

$R^{303}$, $R^{304}$, and $R^{344}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, $-C(O)C_1$-$C_{30}$alkyl, $C_2$-$C_{30}$alkenyl, $C_1$-$C_{30}$heteroalkyl, and $R^{336}$;

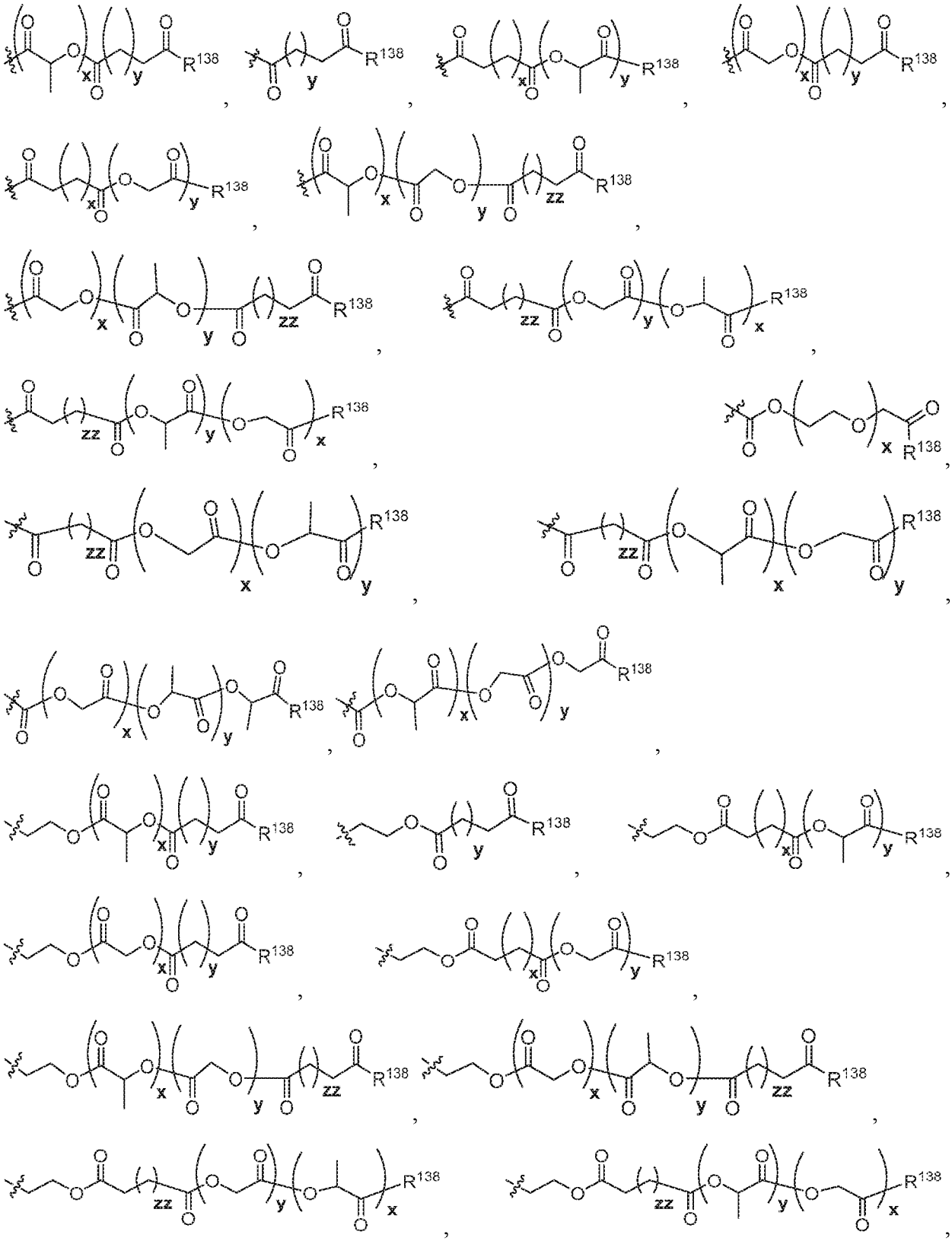
wherein at least one of $R^{303}$, $R^{304}$, and $R^{344}$ is $R^{336}$;

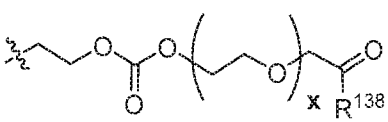
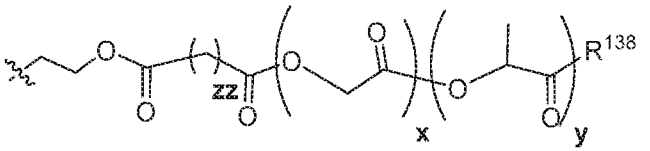
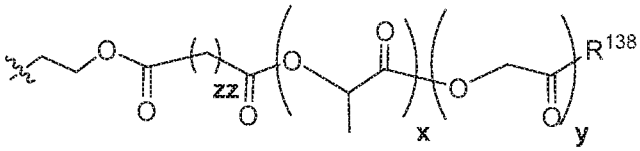
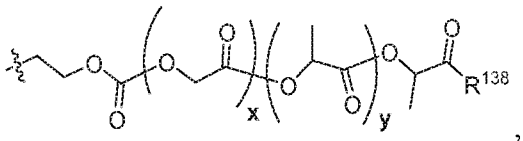
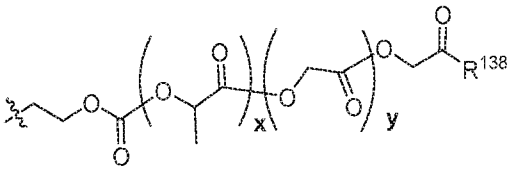
$R^{323}$ is independently selected from polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , , , , , , , and ;

$R^{334}$ and $R^{335}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

or $R^{334}$ and $R^{335}$ can together form a heterocycloalkyl;

$R^{336}$ is selected from:



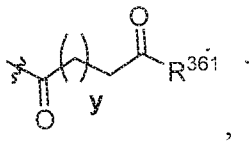
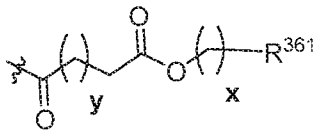
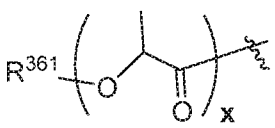
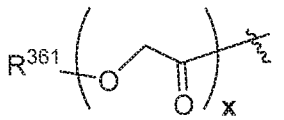
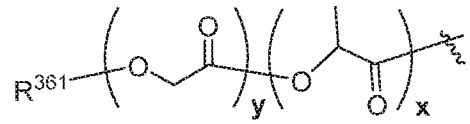
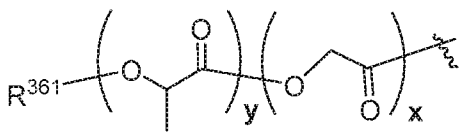
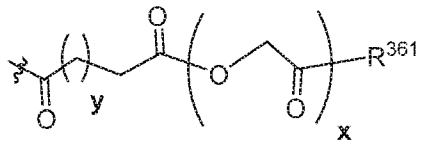
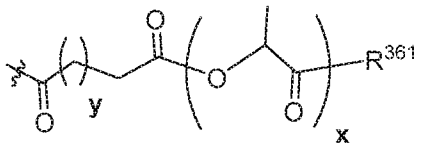
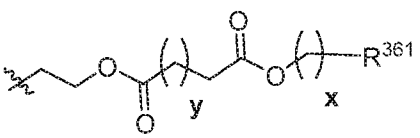
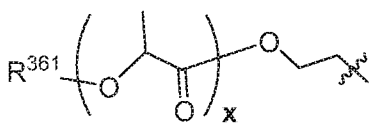
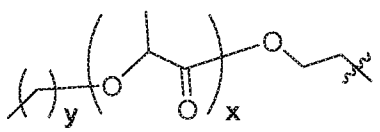

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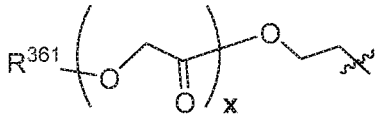
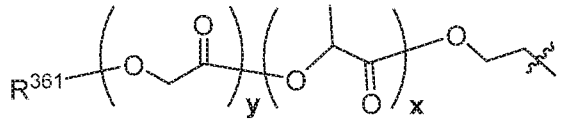
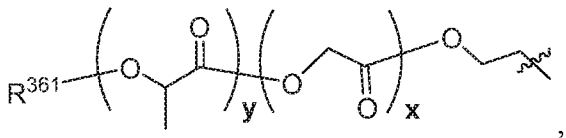
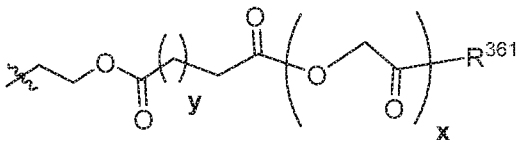
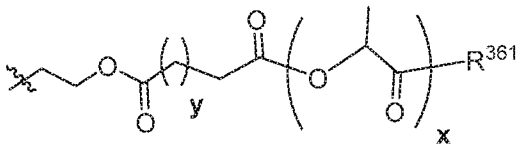
$R^{341a}$ and $R^{341b}$ are independently selected from hydrogen and alkyl;

$R^{350}$ is selected from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, $C_2$-$C_{30}$alkenyl, and $R^{356}$;

$R^{356}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid) polyglycolic acid, a polyester, and a polyamide; and

(ii)

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$R^{361}$ is selected from hydrogen, A, -C(O)alkyl, -C(O)A, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, and stearoyl;

A is selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy;

Q is selected from N, CH, and $CR^{23}$;

Y is $CR^{150}$ or N;

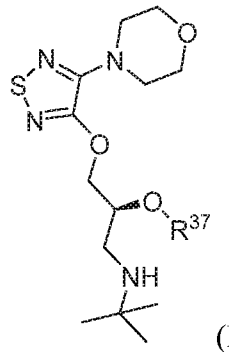
t is independently selected from 0, 1, 2, 3, and 4;

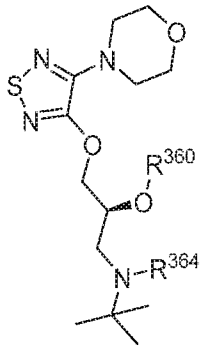
x' and y' are independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and wherein if x' and y' are within the linker then x' and y' cannot both be 0;

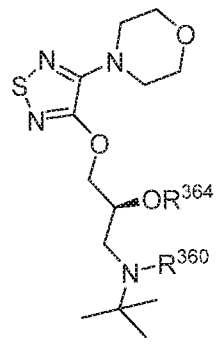
x and y are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30; and

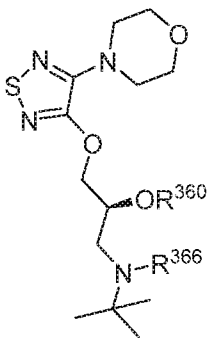
zz is selected from 1, 2, 3, 4, 5, or 6;

4. A compound of Formula XIII, Formula XV', Formula XV'', or Formula LIV:


(XIII)


(XV')

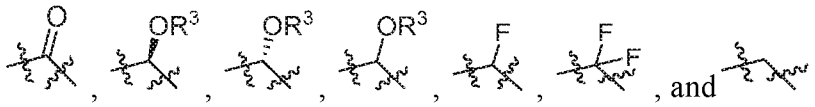

(XV'')


(LIV)

or a pharmaceutically acceptable composition, salt, or isotopic derivative thereof;

wherein:

$L^1$ is selected from: ;

$L^2$ is selected from ;

$L^4$ is selected from: bond, alkyl, alkenyl, alkynyl, -C(O)-, -C(S)-, -NH-, -N(alkyl)-, -O-, and alkyl-C(O)-;

$R^1$, $R^2$, and $R^3$ are independently selected from -C(O)$R^4$, C(O)A, and hydrogen;

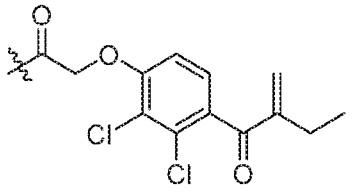
$R^4$ is selected from:

(i) $-C_{20}$-$C_{30}$alkyl$R^5$, $-C_{20}$-$C_{30}$alkenyl$R^5$, -$C_{20}$-$C_{30}$alkynyl$R^5$, -$C_{20}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{20}$-$C_{30}$alkyl, $-C_{20}$-$C_{30}$alkenyl, -$C_{20}$-$C_{30}$alkynyl, and -$C_{20}$-$C_{30}$alkenylalkynyl; and

(ii) an unsaturated fatty acid residue selected from $-(CH_2)_3(CHCHCH_2)_6CH_3$), $-(CH_2)_4(CHCHCH_2)_5CH_3$), docosatetraenoic acid, and nervonic acid;

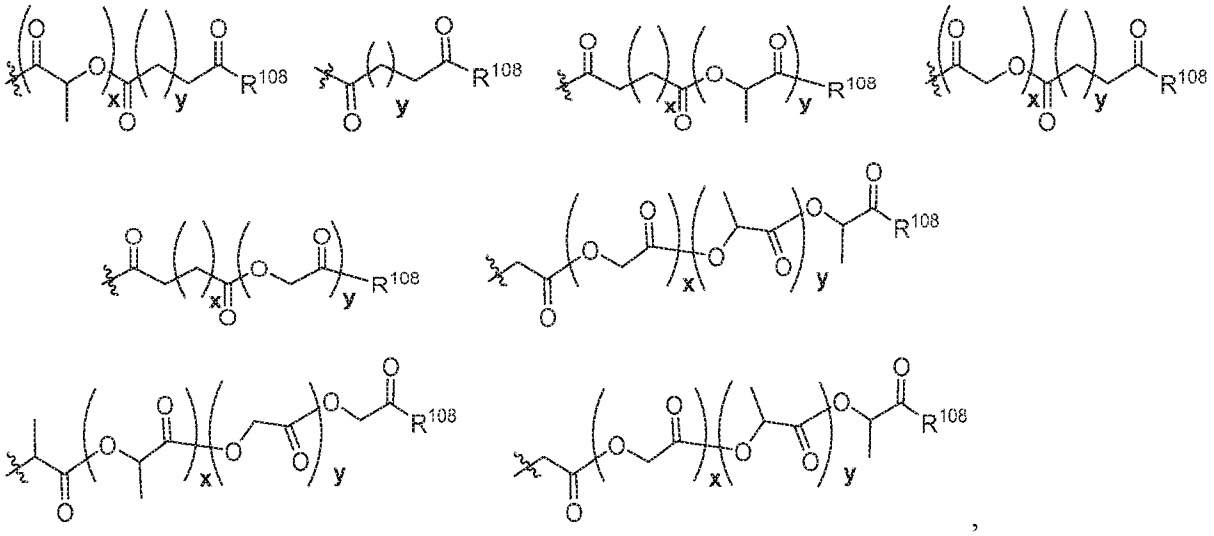
$R^5$ is selected from halogen, hydroxyl, cyano, mercapto, amino, alkoxy, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, -S(O)$_2$alkyl, -S(O)alkyl, -P(O)(Oalkyl)$_2$, B(OH)$_2$, -Si(CH$_3$)$_3$, -COOH, -COOalkyl, and -CONH$_2$;

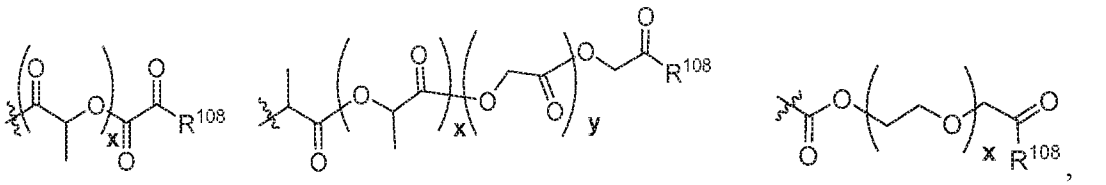
$R^{31}$ is hydrogen, hydroxy, amino, A, alkyl, alkoxy, alkenyl, alkynyl cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, or polyethylene glycol;

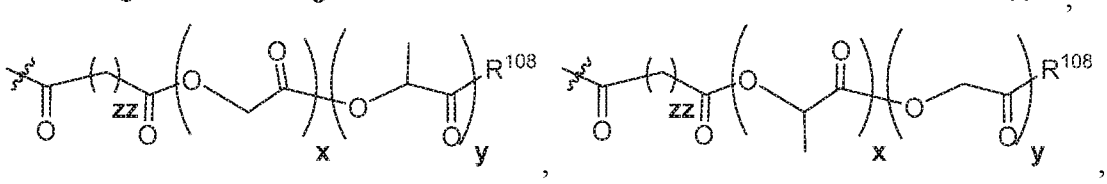
$R^{31a}$ is hydrogen, A, -C(O)alkyl, aryl, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroaryl, heteroarylalkyl, polylactic acid, polygylcolic acid, polyethylene glycol, stearoyl, or ;

$R^{37}$ is $R^{38}$;

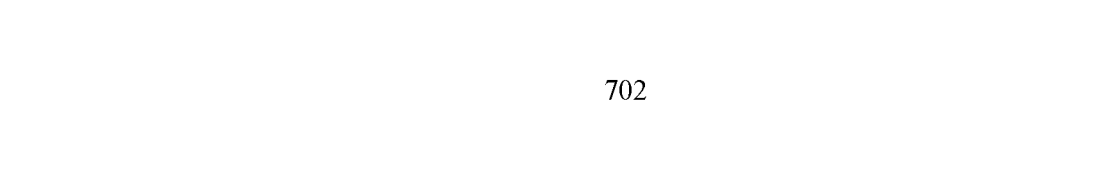
$R^{38}$ is selected from:

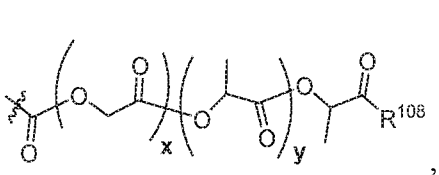
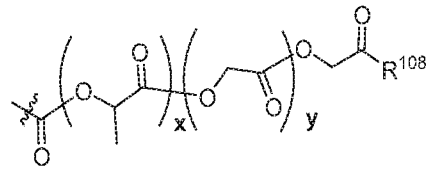
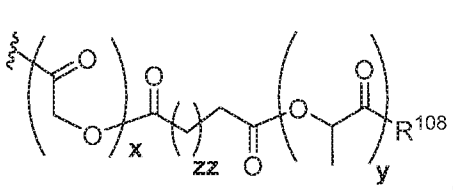
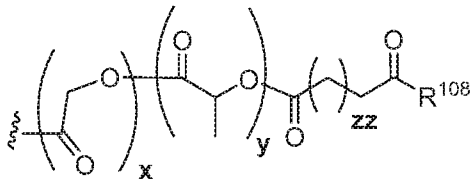











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and

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$R^{53}$ and $R^{54}$ are independently selected from $-C(O)R^4$, -C(O)A, and hydrogen;

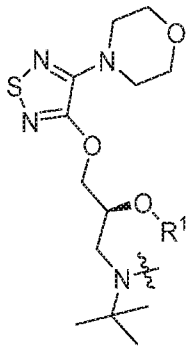
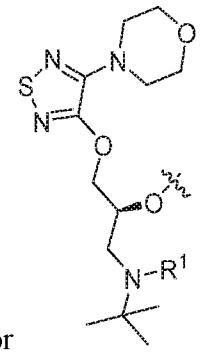
$R^{55}$ is selected from

(i) polyethylene glycol, polypropylene glycol, polypropylene oxide, polylactic acid, and poly(lactic-co-glycolic acid), polyglycolic acid, or a polyester, and a polyamide;

(ii) $-C_{10}$-$C_{30}$alkyl$R^5$, -$C_{10}$-$C_{30}$alkenyl$R^5$, -$C_{10}$-$C_{30}$alkynyl$R^5$, -$C_{10}$-$C_{30}$alkenylalkynyl$R^5$, $-C_{10}$-$C_{30}$alkyl, -$C_{10}$-$C_{30}$alkenyl, -$C_{10}$-$C_{30}$alkynyl, and -$C_{10}$-$C_{30}$alkenylalkynyl;

(iii) an unsaturated fatty acid residue selected from $-(CH_2)_8(CH)_2CH_2(CH)_2(CH_2)_4CH_3$), $-(CH_2)_3(CHCHCH_2)_6CH_3$), $-(CH_2)_4(CHCHCH_2)_5CH_3$), $-(CH_2)_8(CHCHCH_2)_3CH_3$), stearidonic acid, y-linolenic acid, arachidonic acid, docosatetraenoic acid, palmitoleic acid, vaccenic acid, paullinic acid, oleic acid, elaidic acid, gondoic acid, euric acid, nervonic acid and mead acid;

(iv)alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, arylalkyl, and heteroarylalkyl;

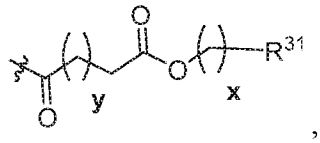
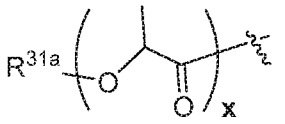
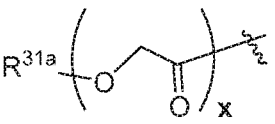
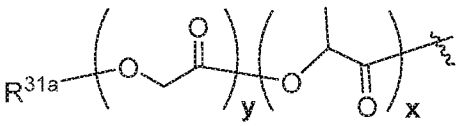
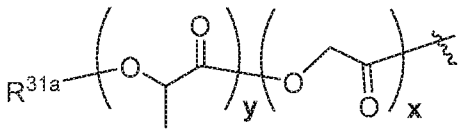
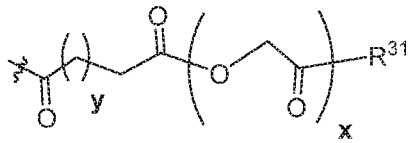
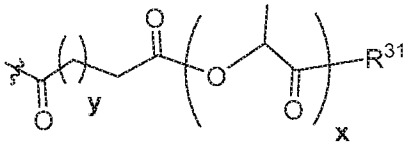
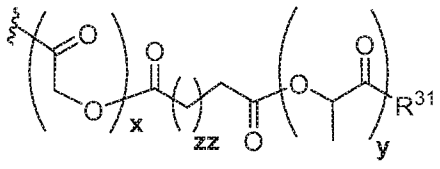
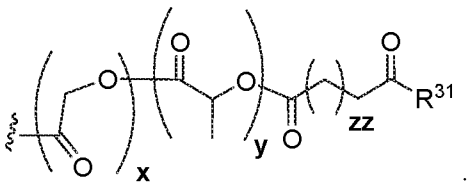
$R^{108}$ is  or  ;

$R^{134}$ and $R^{135}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

$R^{141}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, and halogen;

$R^{175}$ is selected from C(O)A, C(O)$R^4$, and $R^{178}$;

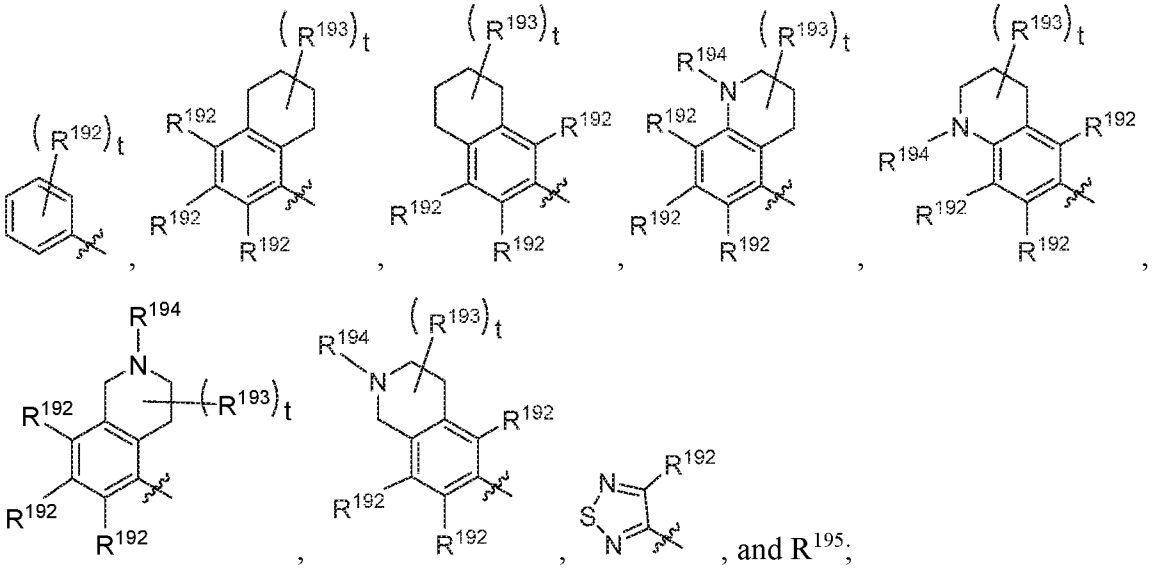
$R^{178}$ is selected from:

(i) carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide, , , , , , , ,  and ; and

(ii) -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{4\text{-}20}$C(O)C$_{1\text{-}22}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}20}$C(O)OH, -(lactic acid)$_{1\text{-}10}$C(O)OH, -(lactic acid)$_{4\text{-}10}$C(O)OH, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{4\text{-}10}$C(O)C$_{1\text{-}22}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{1\text{-}12}$alkyl, -(lactide-co-glycolide)$_{1\text{-}10}$C(O)C$_{4\text{-}22}$alkyl, -(glycolic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(glycolic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{4\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{1\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl, and -(lactic acid)$_{1\text{-}10}$C(O)C$_{4\text{-}10}$alkyl;

$R^{180}$ is C$_1$-C$_6$ alkyl, acyl, or hydrogen;

$R^{191}$ is selected from:



, and $R^{195}$;

$R^{192}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, cyano, amino, hydroxyl, and acyl, each of which $R^{192}$ is optionally substituted with a $R^{175}$ group;

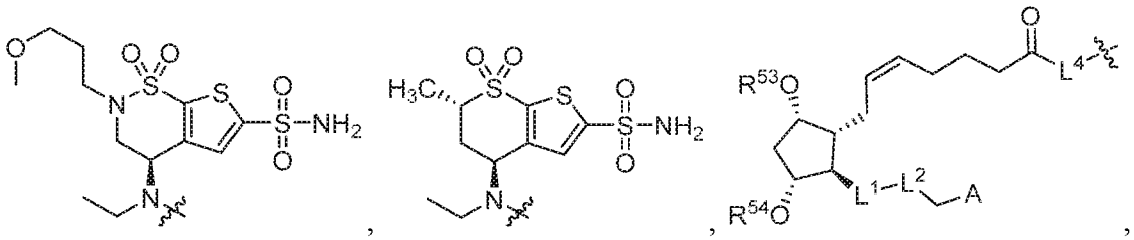
$R^{193}$ is independently selected from alkyl, cycloalkyl, aryl, heteroaryl, heterocycle, amino, hydroxyl, and acyl;

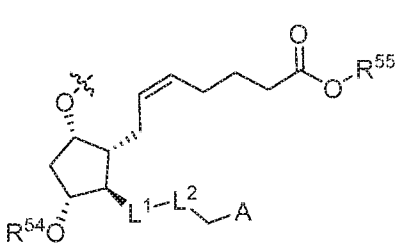
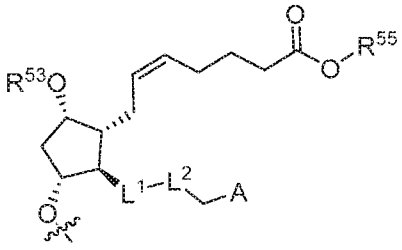
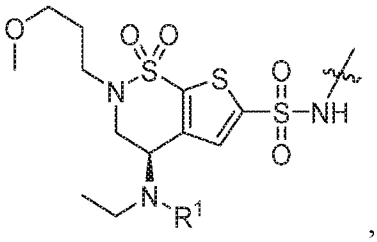
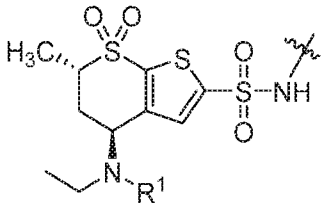
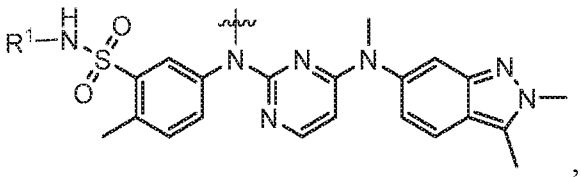
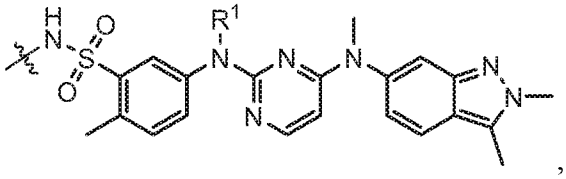
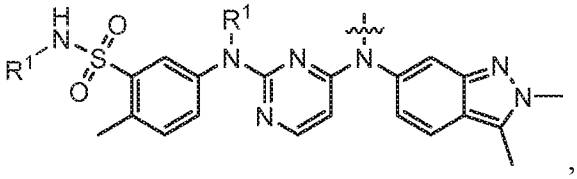
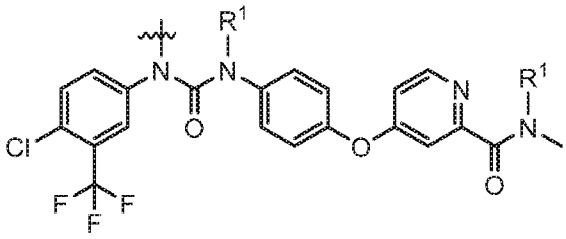
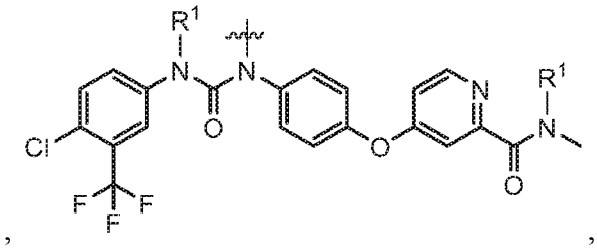
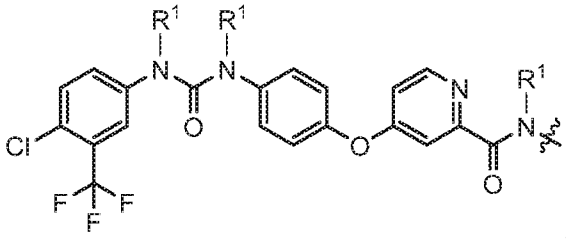
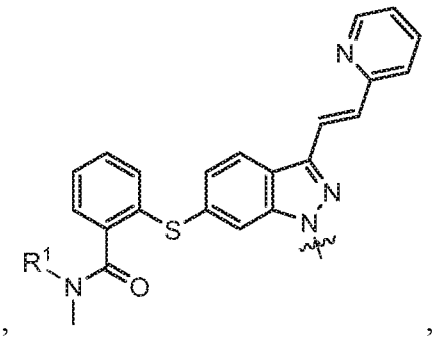
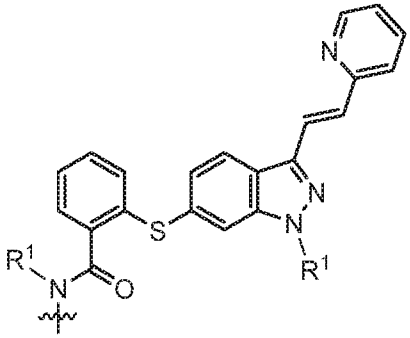
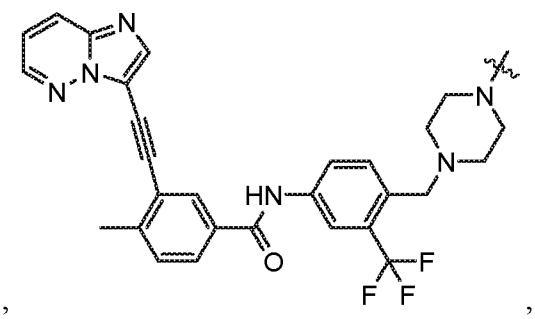
$R^{194}$ is selected from alkyl, cycloalkyl, $R^{175}$, and acyl;

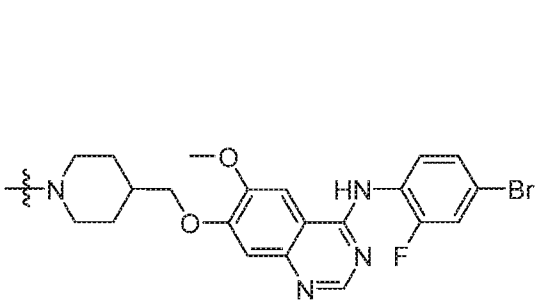
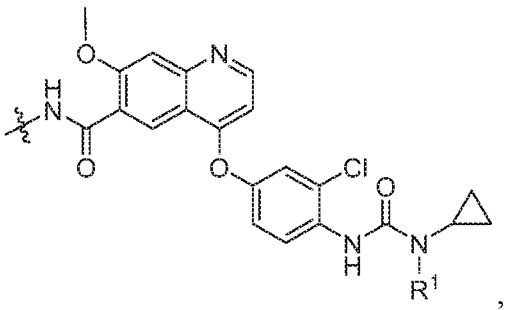
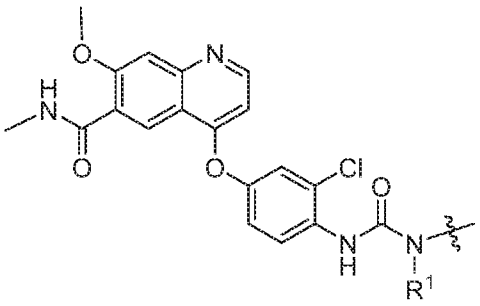
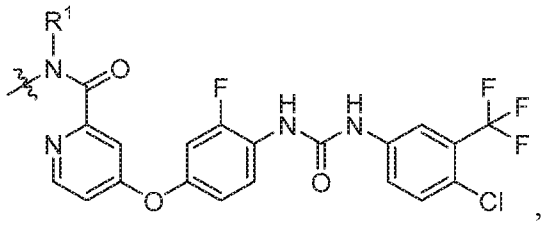
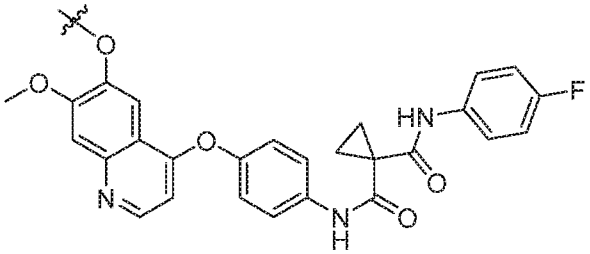
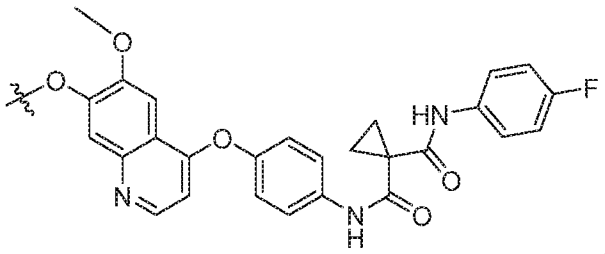
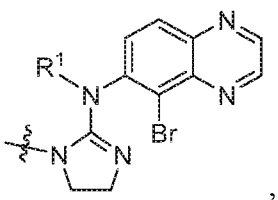
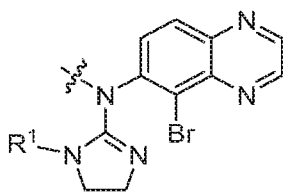
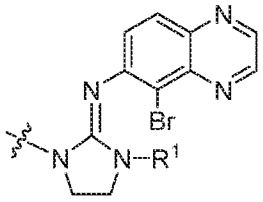
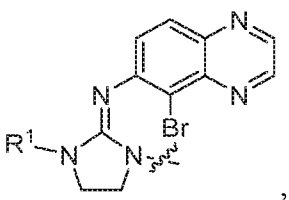
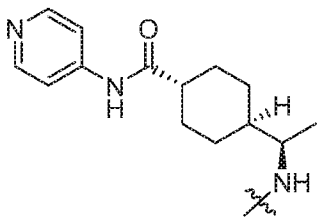
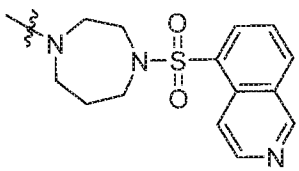
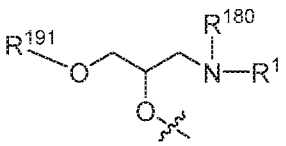
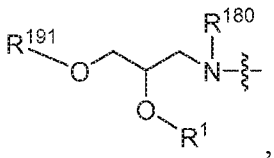
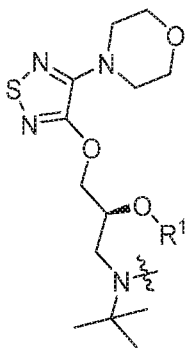
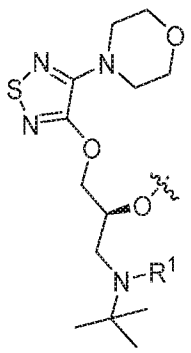
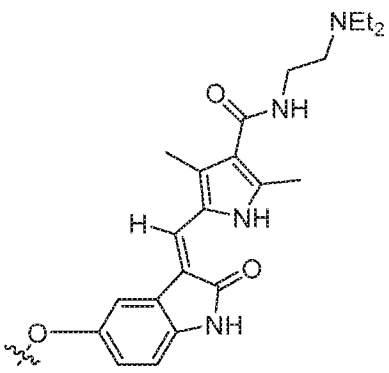
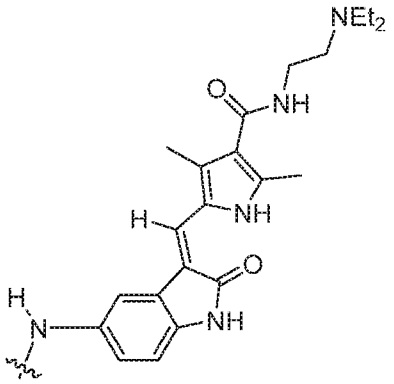
$R^{195}$ is selected from aryl, heteroaryl, cycloalkyl, and heterocycle, wherein each $R^{195}$ is optionally substituted with 1, 2, 3, or 4 $R^{192}$ groups;

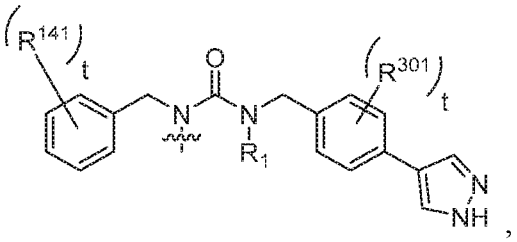
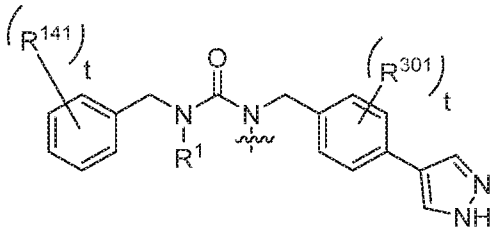
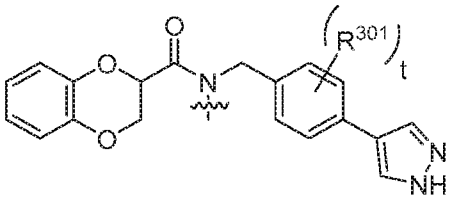
$R^{301}$ is selected from hydrogen, $-C(O)NR^1R^2$, $-C(O)R^1$, $-C(O)OR^1$, nitro, amino, $-NR^{134}R^{135}$, alkyl, alkoxy, alkylalkoxy, alkoxyalkoxy, haloalkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl, halogen, $-O(CH_2)_2NR^{334}R^{335}$, and $-N(CH_3)(CH_2)_2NR^{334}R^{335}$;

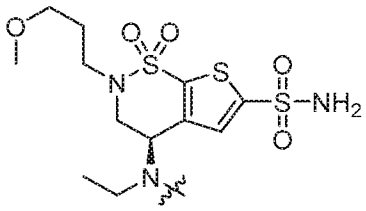
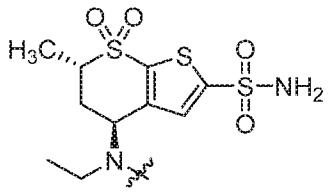
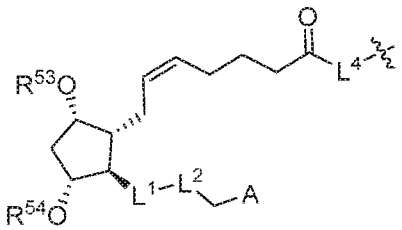
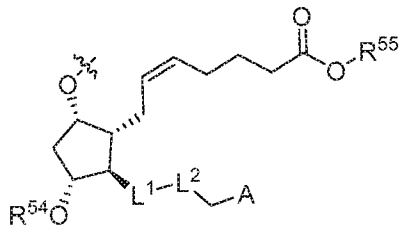
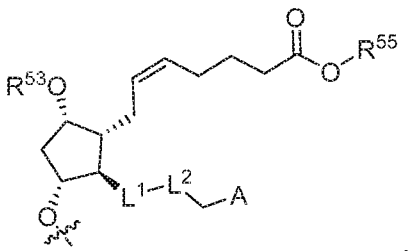
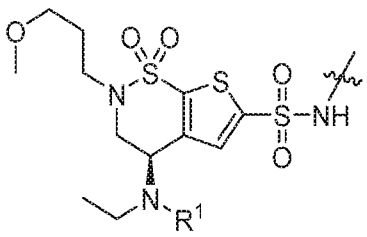
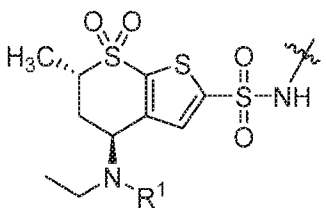
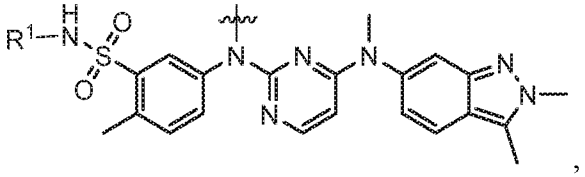
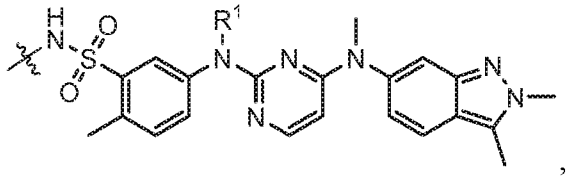
$R^{315}$ is selected from

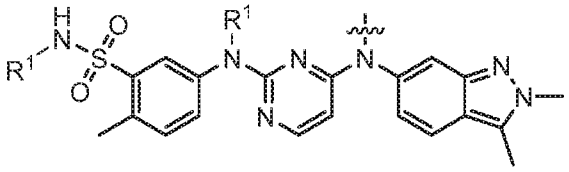
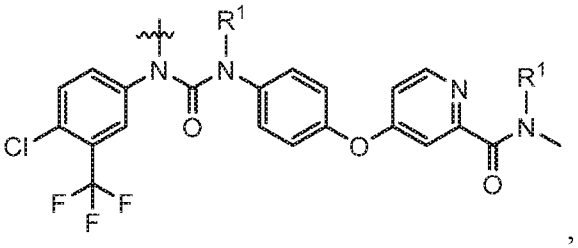
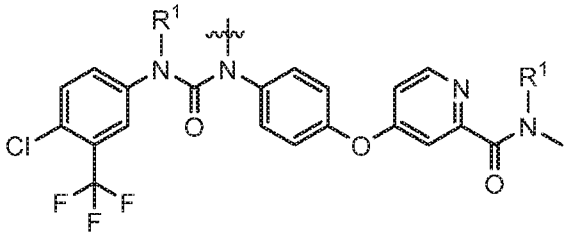
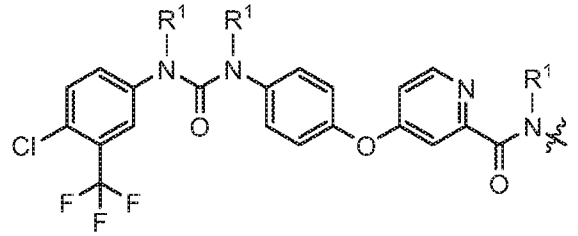
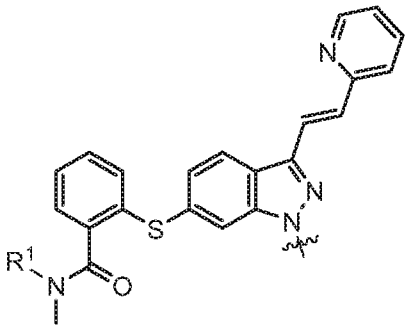
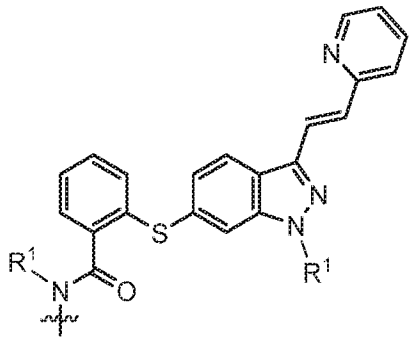
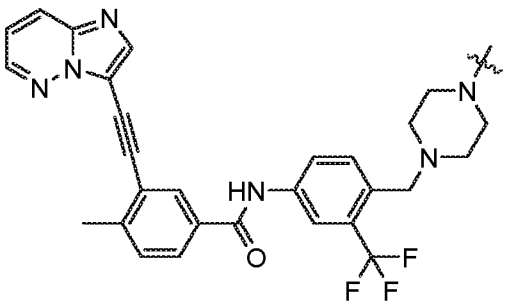
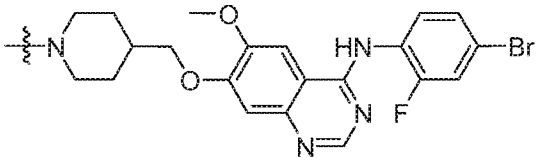
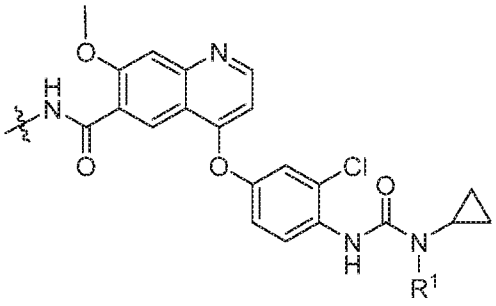
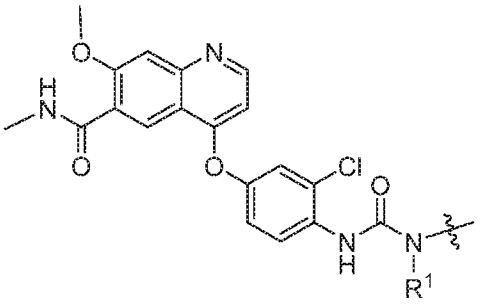


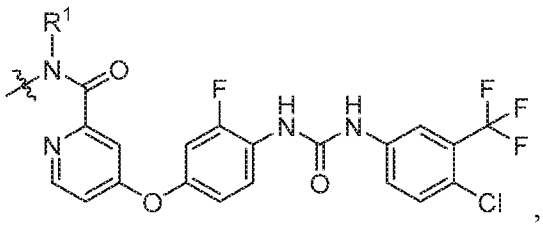
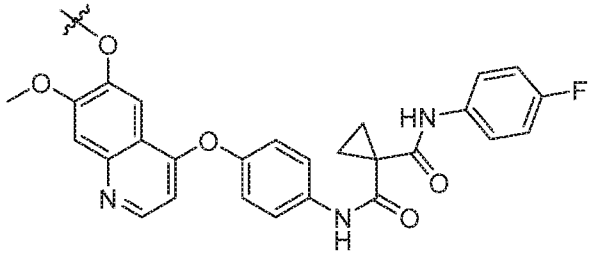
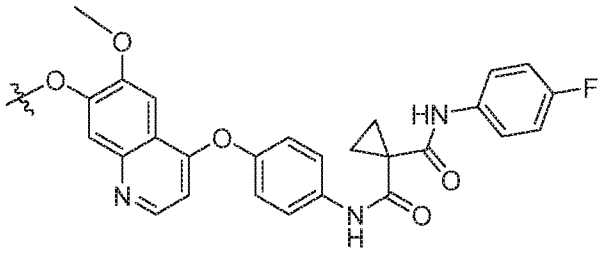
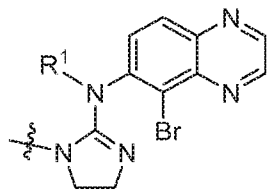
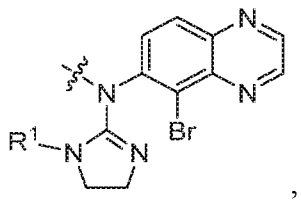
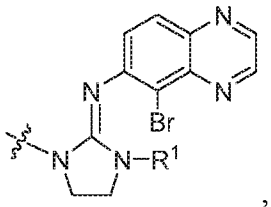
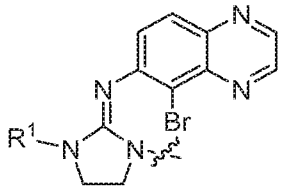
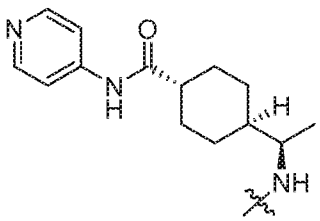
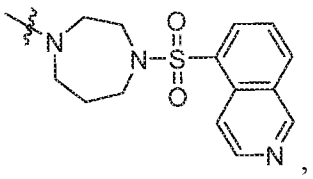
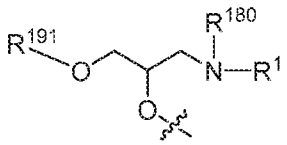
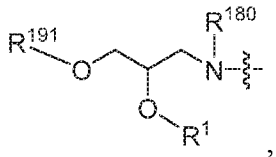
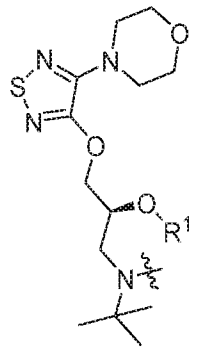
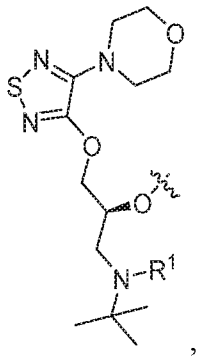
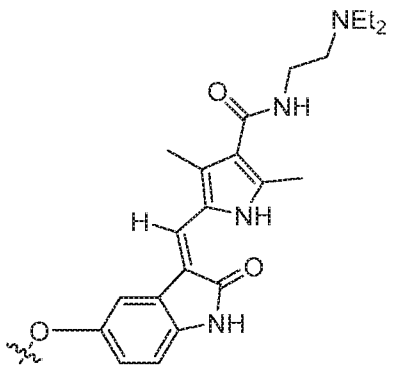
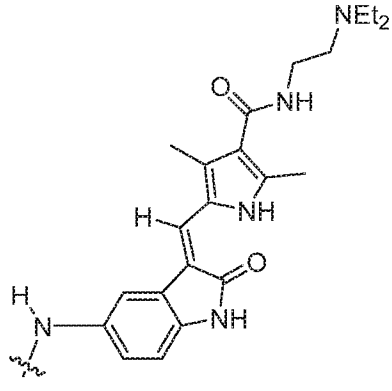

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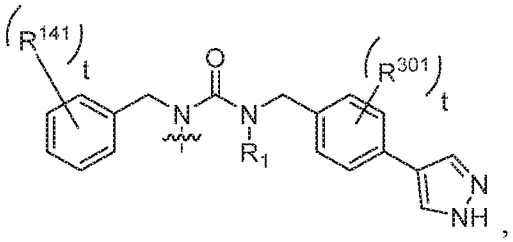
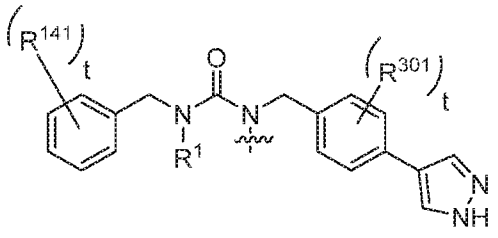

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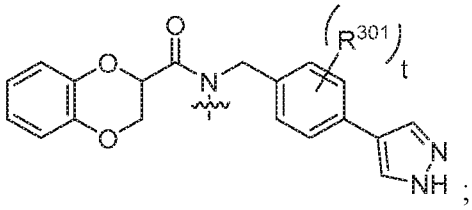

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$R^{316}$ is selected from

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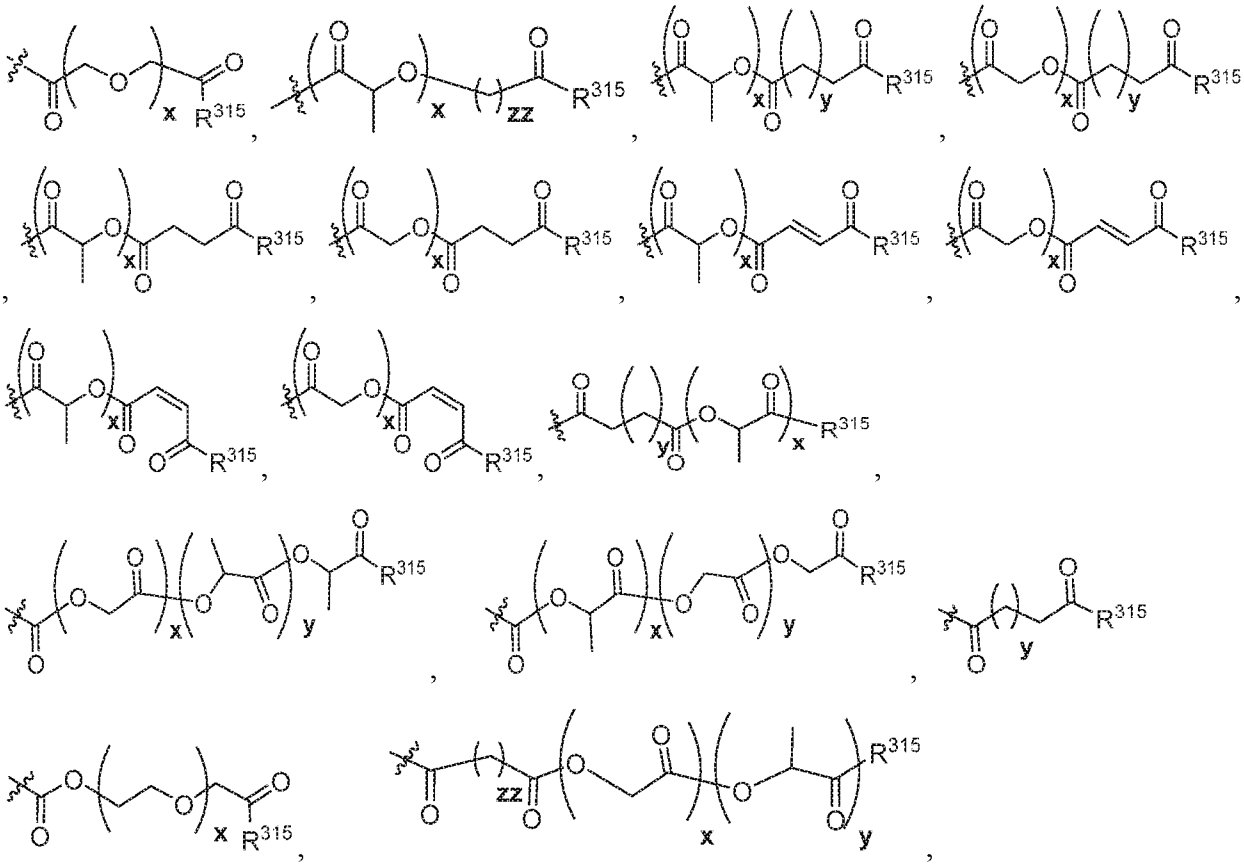


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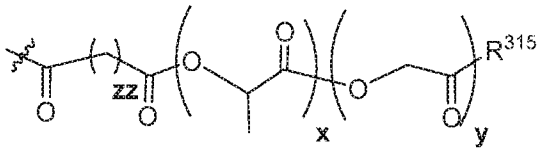
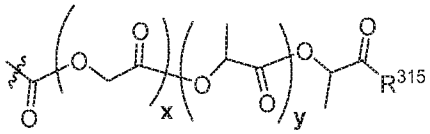
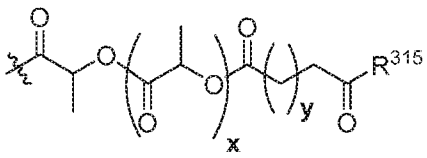
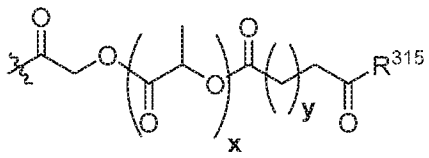
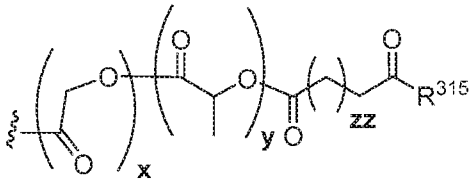
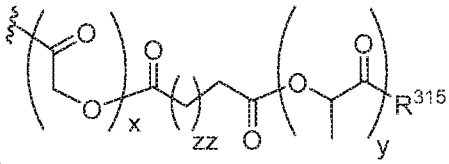

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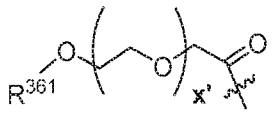
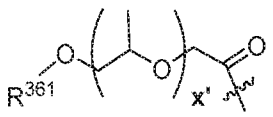
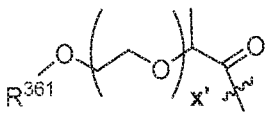
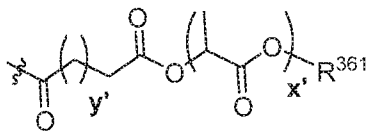
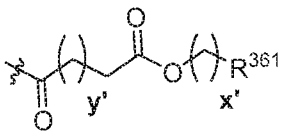
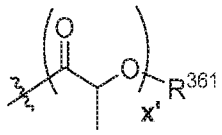
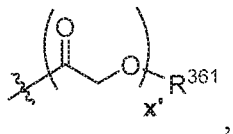
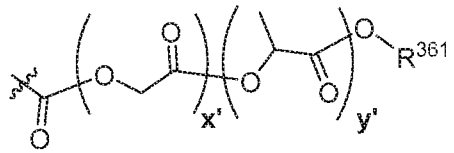
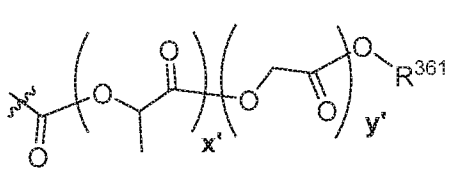
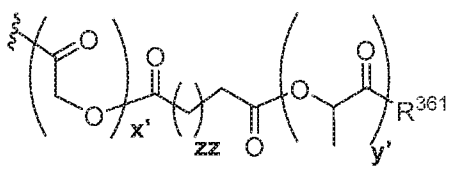
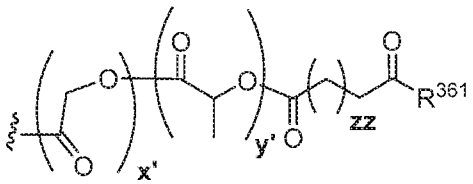
$R^{334}$ and $R^{335}$ are independently selected from H, alkyl, $-SO_2CH_3$, $-C(O)CH_3$, and $-C(O)NH_2$;

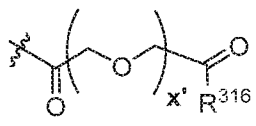
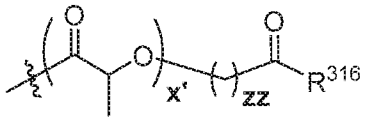
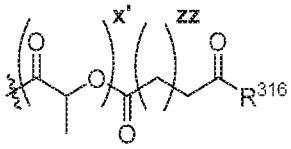
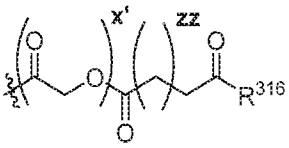
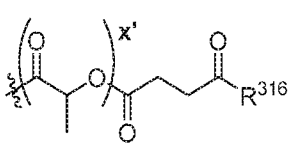
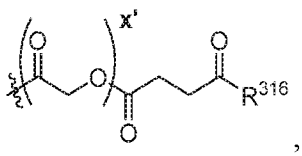
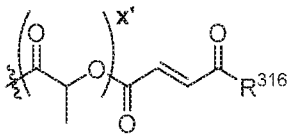
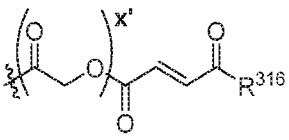
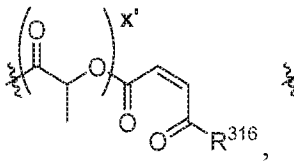
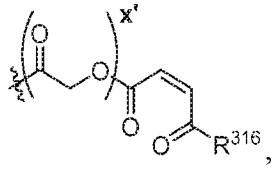
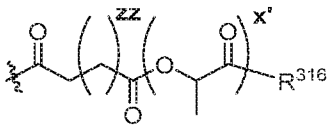
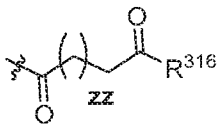
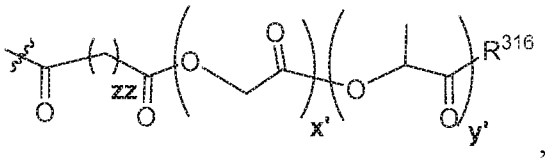
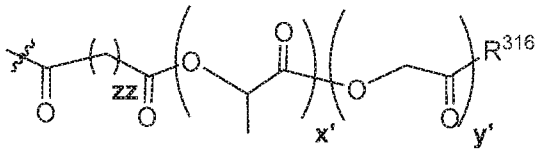
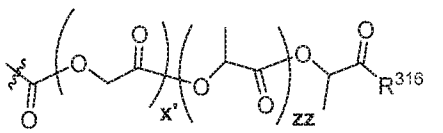
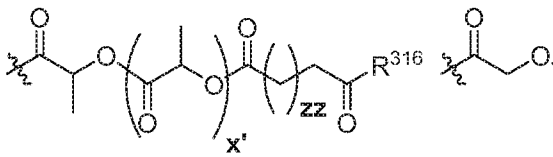
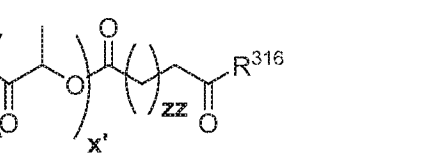
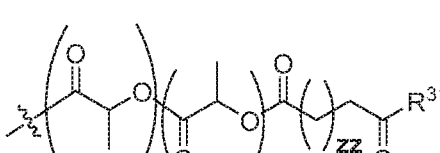
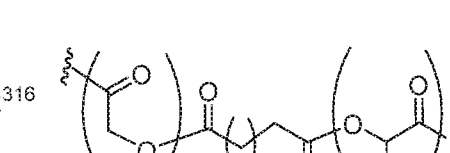
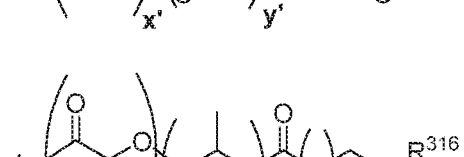
or $R^{334}$ and $R^{335}$ can together form a heterocycloalkyl;

$R^{360}$ is selected from




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and;

$R^{364}$ is selected from acyl, carbonyl linked polyethylene glycol, carbonyl linked polypropylene glycol, carbonyl linked polypropylene oxide, polylactic acid, poly(lactic-co-glycolic acid), polyglycolic acid, polyester, polyamide,

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$R^{366}$ is selected from , , , , , , , , , , , , , , , , , , , ,  and ;

A is selected from H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycle, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, and alkyloxy;

t is independently selected from 0, 1, 2, 3, and 4;

x' and y' are independently selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10, and wherein if x' and y' are within the linker then x' and y' cannot both be 0;

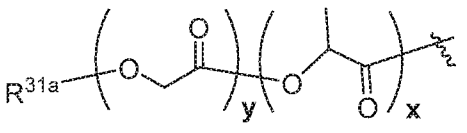
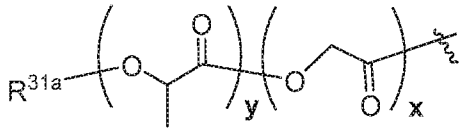
x and y are independently selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 and 30; and

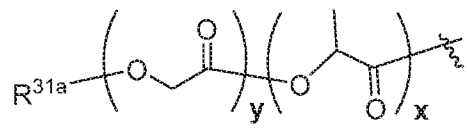
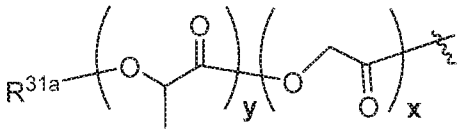
zz is selected from 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

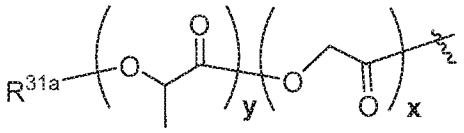
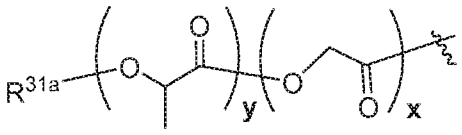
5. The compound of claim 1 or 3, wherein $R^{118}$ is selected from

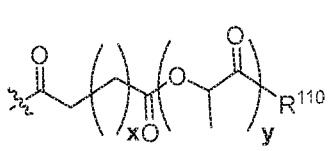
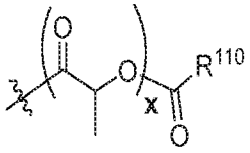
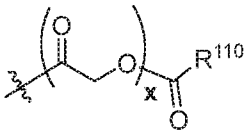
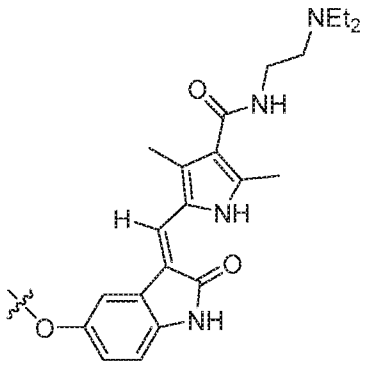
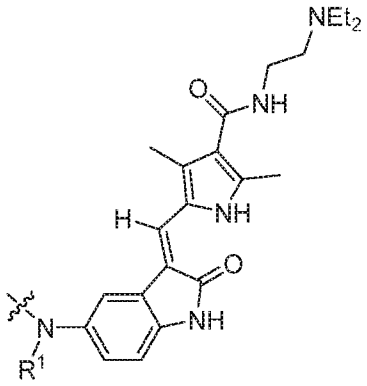
$-(C(O)CH(CH_3)O)_{1-20}C(O)C_{1-30}$alkyl, $-(C(O)CH(CH_3)O)_{1-10}C(O)C_{1-30}$alkyl,
$-(C(O)CH(CH_3)O)_{4-20}C(O)C_{1-30}$alkyl, $-(C(O)CH(CH_3)O)_{1-20}C(O)C_{1-10}$alkyl,
$-(C(O)CH(CH_3)O)_{1-20}C(O)C_{4-10}$alkyl, $-(C(O)CH(CH_3)O)_{1-10}C(O)C_{4-10}$alkyl,
$-(C(O)CH(CH_3)O)_{1-10}C(O)C_{4-10}$alkyl, $-(C(O)CH(CH_3)O)_{1-10}C(O)C_{4-10}$alkyl,
$-(C(O)CH_2O)_{1-10}(C(O)CH(CH_3)O)_{1-10}C(O)C_{1-30}$alkyl,
$-(C(O)CH_2O)_{2-10}(C(O)CH(CH_3)O)_{2-10}C(O)C_{1-30}$alkyl,
$-(C(O)CH_2O)_{1-10}(C(O)CH(CH_3)O)_{1-10}C(O)C_{1-12}$alkyl,
$-(C(O)CH_2O)_{1-10}(C(O)CH(CH_3)O)_{1-10}C(O)C_{4-22}$alkyl,
$-(C(O)CH(CH_3)O)_{1-10}(C(O)CH_2O)_{1-10}C(O)C_{1-30}$alkyl,
$-(C(O)CH(CH_3)O)_{2-10}(C(O)CH_2O)_{2-10}C(O)C_{1-30}$alkyl,
$-(C(O)CH(CH_3)O)_{1-10}(C(O)CH_2O)_{1-10}C(O)C_{1-12}$alkyl, and
$-(C(O)CH(CH_3)O)_{1-10}(C(O)CH_2O)_{1-10}C(O)C_{4-22}$alkyl.

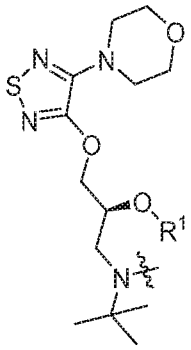
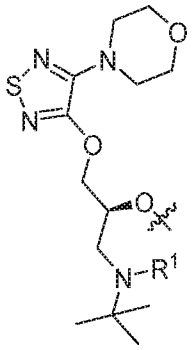
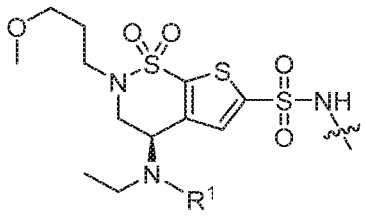
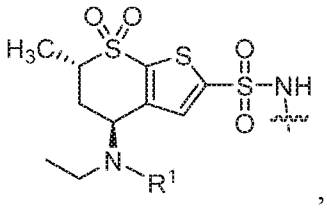
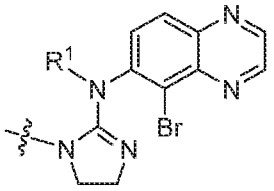
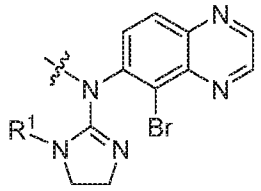
6. The compound of claim 1, wherein

$R^{106}$ is  or ; and

$R^{123}$ is  or .

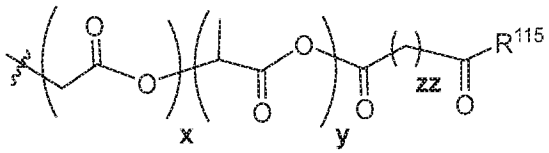
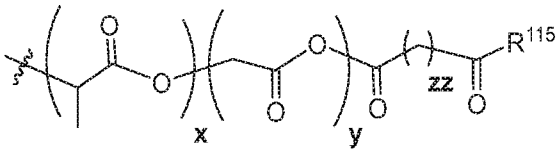
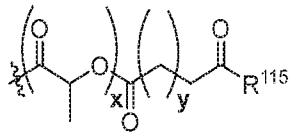
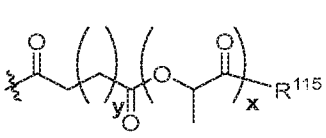
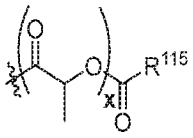
7. The compound of claim 1, wherein $R^{106}$ is  and $R^{123}$ is .

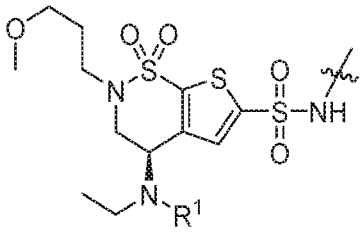
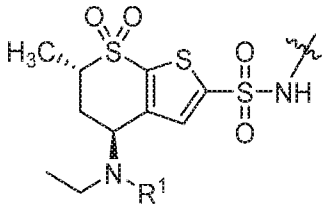
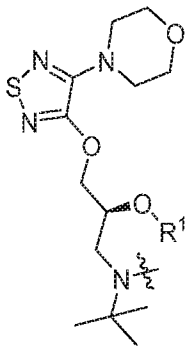
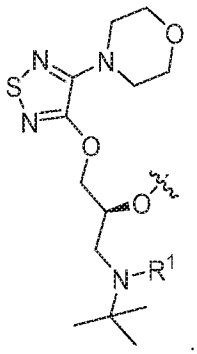
8. The compound of claim 2 or 3,
wherein
$R^{117}$ is selected from ,  and ; and
$R^{110}$ is selected from , ,


,

,

,

,

and

.

9. The compound of claim 2,

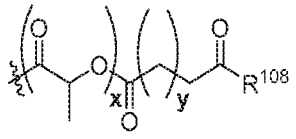
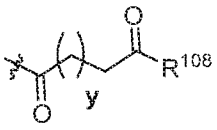
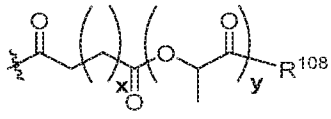
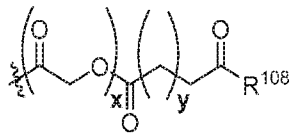
wherein $R^{34}$ is $R^{36}$;

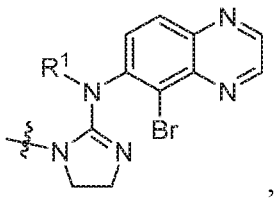
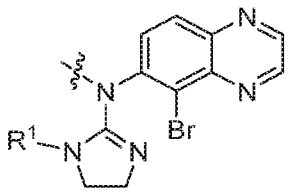
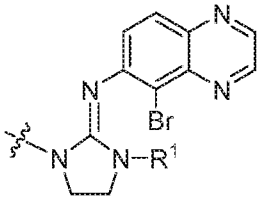
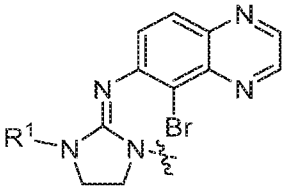
$R^{36}$ is selected from

,

,

, and

,

; and

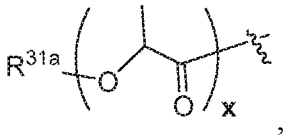
$R^{115}$ is selected from , , , and .

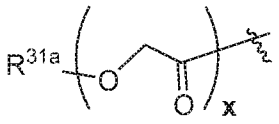
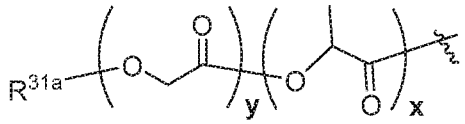
10. The compound of claim 3,

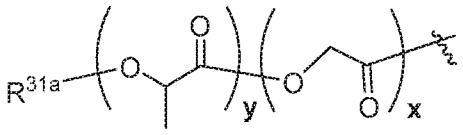
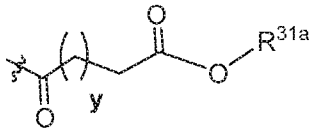
wherein

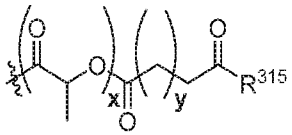
$R^{38}$ is selected from , , , , and ; and

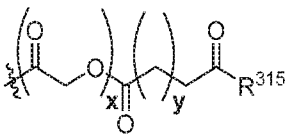
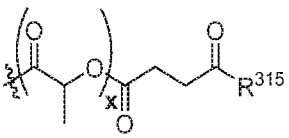
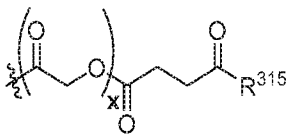
$R^{108}$ is selected from , , , , and .

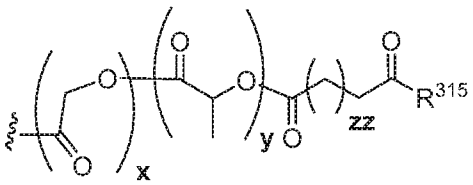
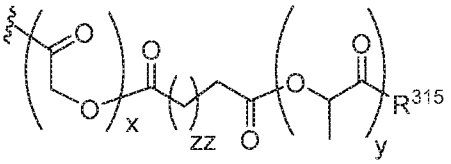
11. The compound of claim 3, wherein $R^{323}$ is selected from ,

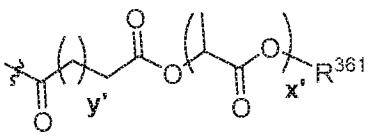
, ,

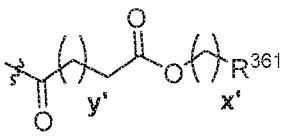
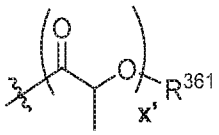
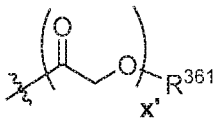
, and .

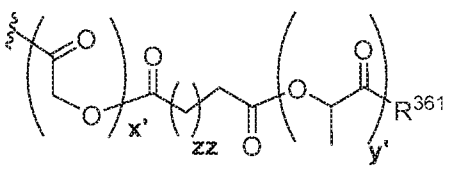
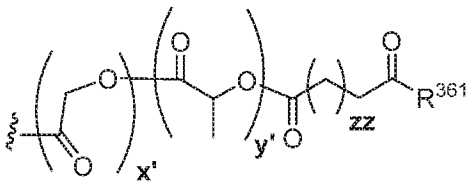
12. The compound of claim 4, wherein $R^{360}$ is selected from ,

, , ,

, and .

13. The compound of claim 4, wherein $R^{364}$ is selected from ,

, , ,

, and ; and

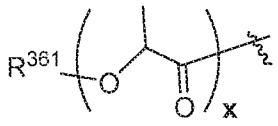
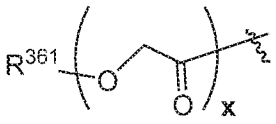
$R^{361}$ is selected from A, -C(O)alkyl, -C(O)A.

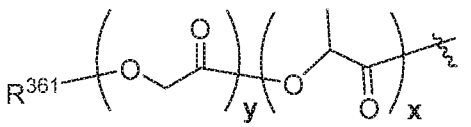
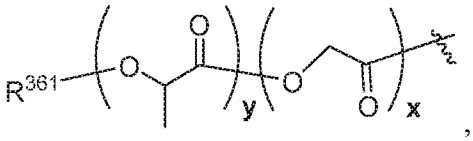
14. The compound of claim 3,

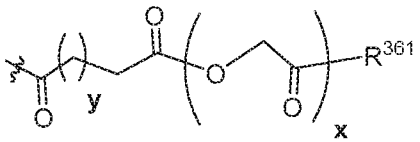
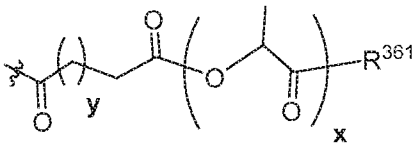
wherein

$R^{302}$ and $R^{333}$ are independently selected from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_1$-$C_{30}$heteroalkyl, $C_2$-$C_{30}$alkenyl;

$R^{350}$ is $R^{356}$;

$R^{356}$ is selected from , ,

, ,

, and , and

$R^{361}$ is A, -C(O)alkyl, or –C(O)A.

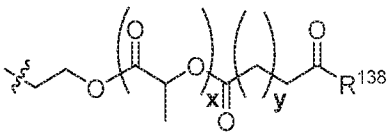
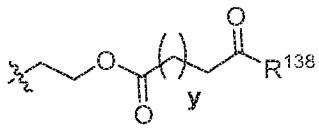
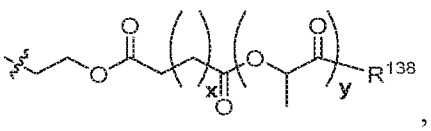
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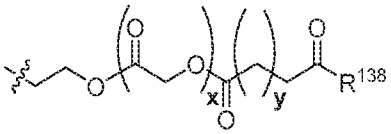
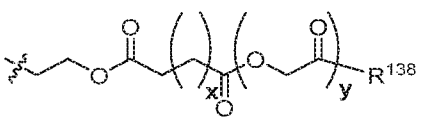
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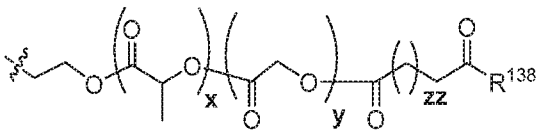
$R^{303}$ and $R^{344}$ are independently selected at each occurrence from H, $C_1$-$C_{30}$alkyl, -C(O)$C_1$-$C_{30}$alkyl, $C_2$-$C_{30}$alkenyl, and $C_1$-$C_{30}$heteroalkyl;

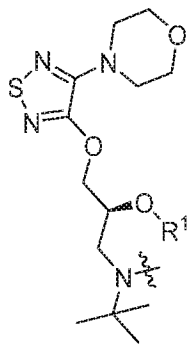
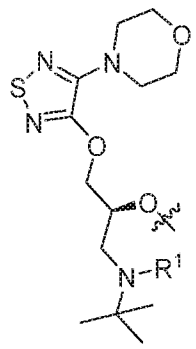
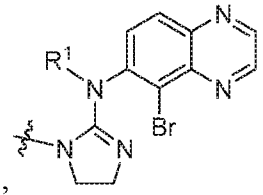
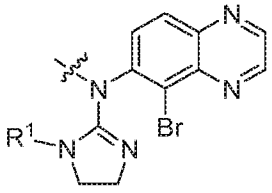
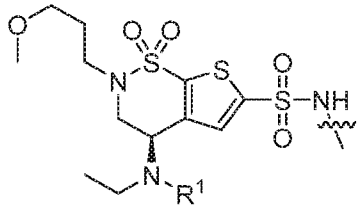
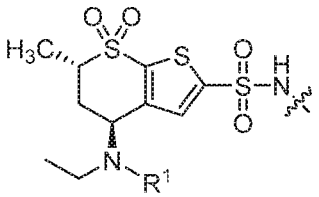
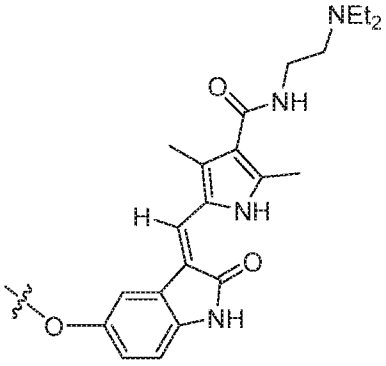
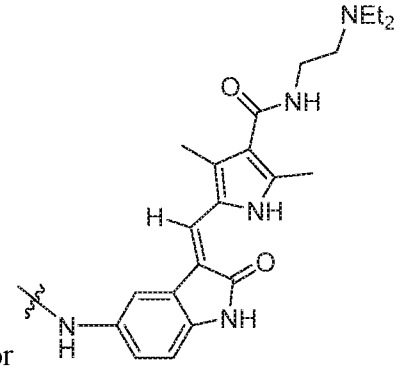
$R^{304}$ is $R^{336}$;

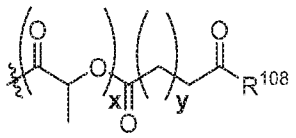
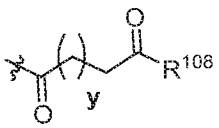
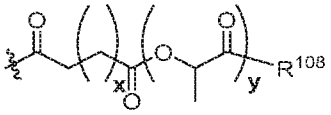
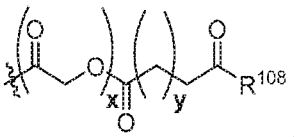
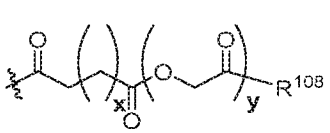
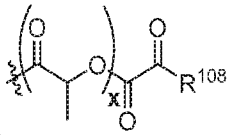
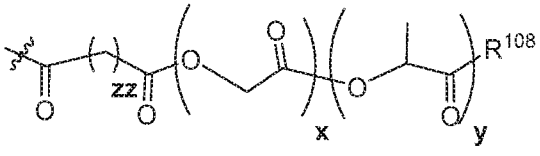
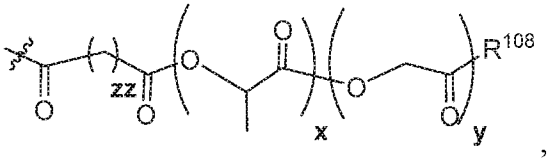
$R^{336}$ is selected from:

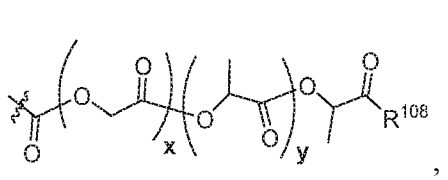
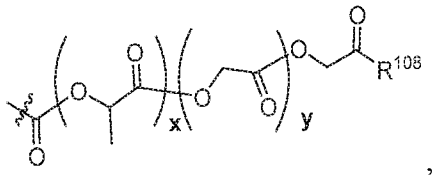
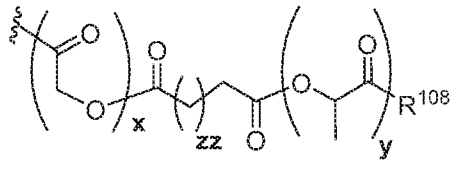
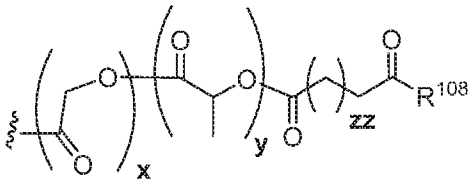
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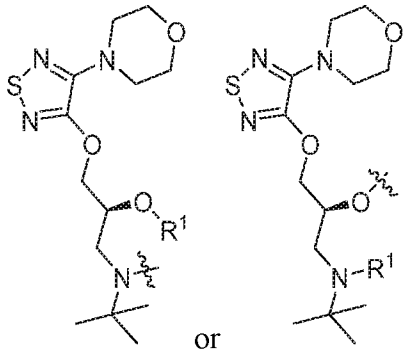
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; and

$R^{138}$ is selected from , , , , , , , or .

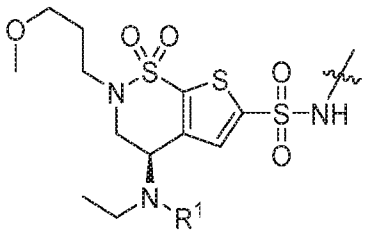
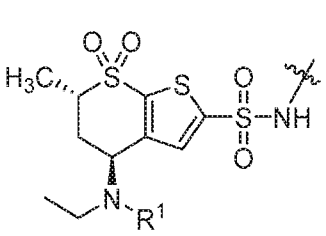
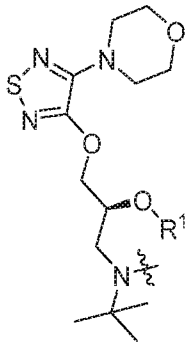
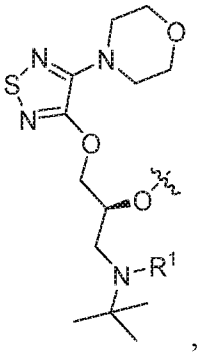
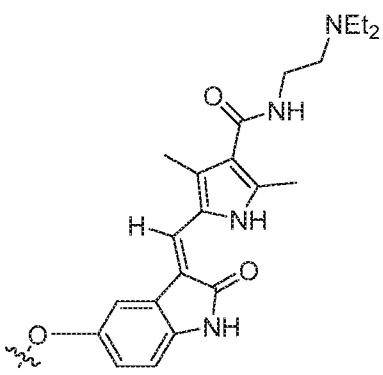
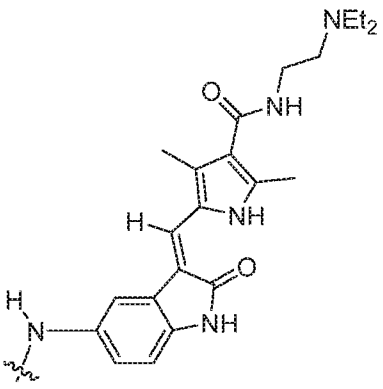
16. The compound of claim 4, wherein $R^{38}$ is selected from , , , , , , , ,

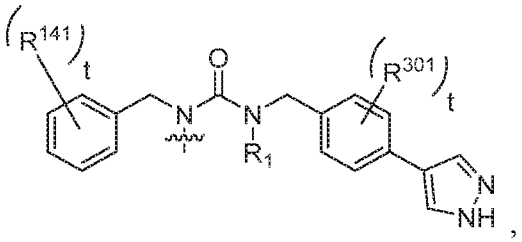
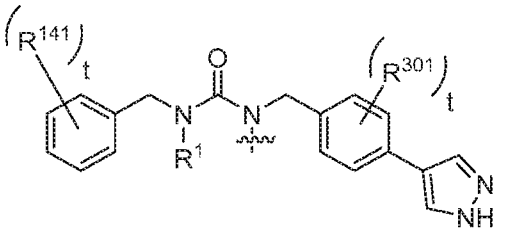
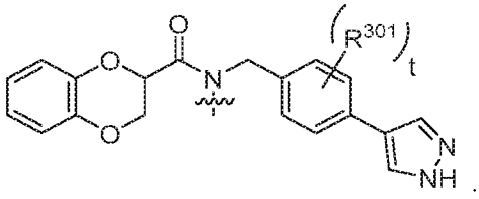

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and

; and

$R^{108}$ is

or

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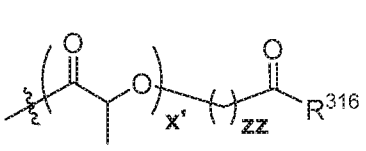
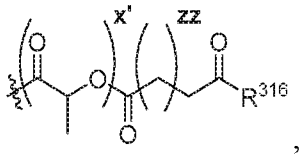
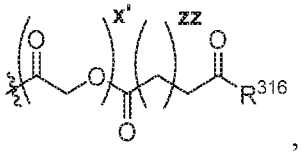
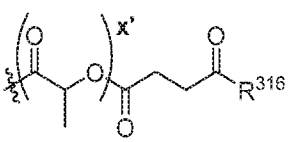
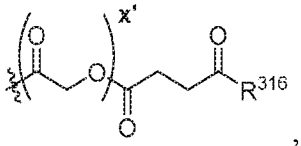
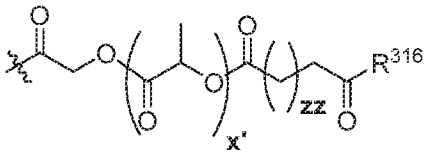
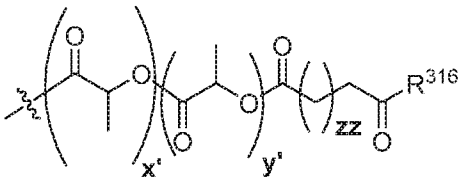
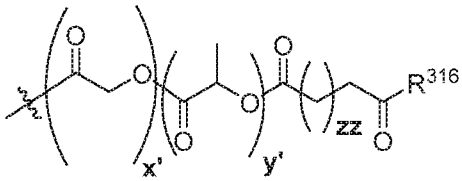
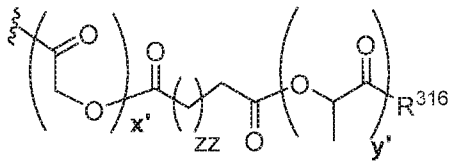
17. The compound of claim 12 wherein $R^{315}$ is selected from

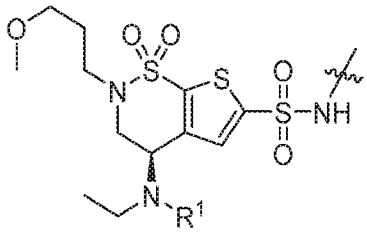
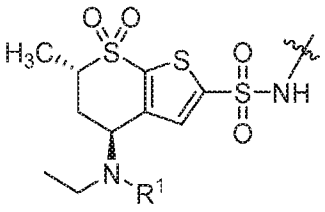
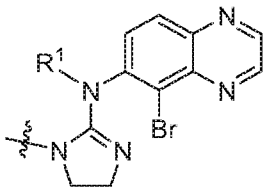
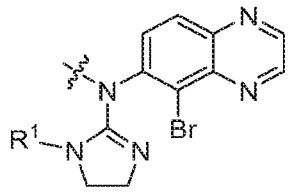
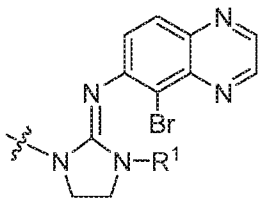
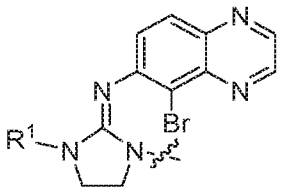
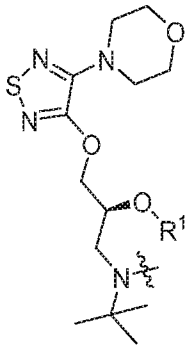
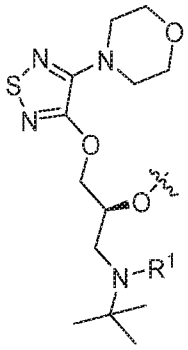
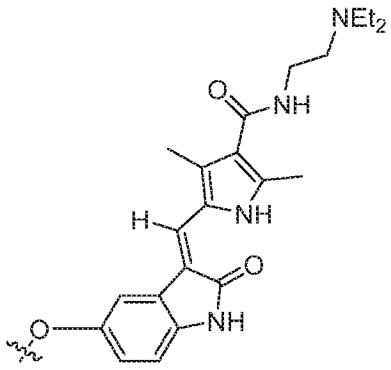
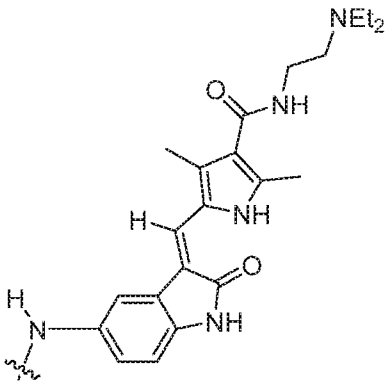
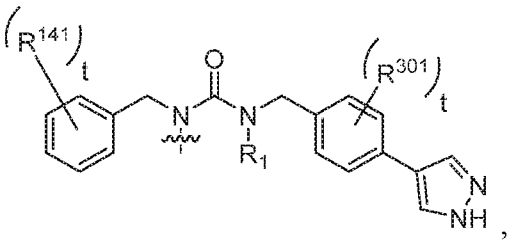
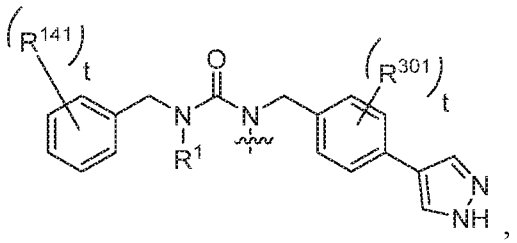
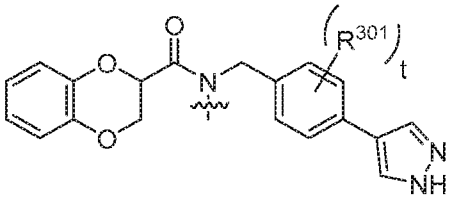

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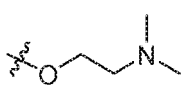
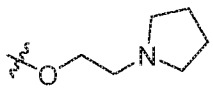
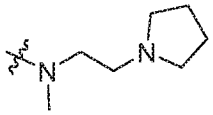
18. The compound of claim 4,

wherein

$R^{366}$ is selected from

,

,

,

,

,

,

,

, and

;

$R^{316}$ is selected from , , , , , , , , , , , , and .

19. The compound of any one of claims 3, 4, or 14-18, wherein $R^{301}$ is selected from

$-N(CH_3)_2$, , , and .

20. The compound of any one of claim 3, 4, or 10-19, wherein x' and y' are selected from 1, 2, 3, 4, 5, or 6.

21. The compound of any one of claim 3, 4, or 10-19, wherein zz is 1, 2, or 3.

22. The compound of claim 20, wherein x' and y' are 1, 2, or 3.

23. The compound of claims 1-22, wherein $R^{31}$ or $R^{31a}$ are selected from A or –C(O)alkyl wherein alkyl is methyl.

24. The compound of any one of claims 1-4 and 6-23, wherein x and y are selected from 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12.

25. The compound of claim 24, wherein x is 1, 2, 3, 4, 5, or 6 and y is 1, 2, or 3.

26. The compound of claim 24, wherein x is 1, 2, or 3 and y is 1, 2, 3, 4, 5, or 6.

27. A method for the treatment of an ocular disorder in a host in need thereof comprising administering an effective amount of a compound of any one of claims 1-26 optionally in a pharmaceutically acceptable carrier.

28. The method of claim 27, wherein the disorder is selected from glaucoma, age-related macular degeneration, a disorder related to an increase in intraocular pressure (IOP), a disorder requiring neuroprotection, and diabetic retinopathy

29. The method of claim 28, wherein the host is a human.

30. A compound of any one of claims 1-26 optionally in a pharmaceutically acceptable carrier for use to treat an ocular disorder in a host in need thereof.

31. The compound of claim 30, wherein the disorder is selected from glaucoma, age-related macular degeneration, a disorder related to an increase in intraocular pressure (IOP), a disorder requiring neuroprotection, and diabetic retinopathy.

32. The compound of claim 31, where in the host is a human.

33. The use of a compound of any one of claims 1-26 optionally in a pharmaceutically acceptable carrier in the manufacture of a medicament for the treatment of an ocular disorder.

34. The use of claim 33, wherein the disorder is selected from glaucoma, age-related macular degeneration, a disorder related to an increase in intraocular pressure (IOP), a disorder requiring neuroprotection, and diabetic retinopathy.

35. The use of claim 34, wherein the host is a human.

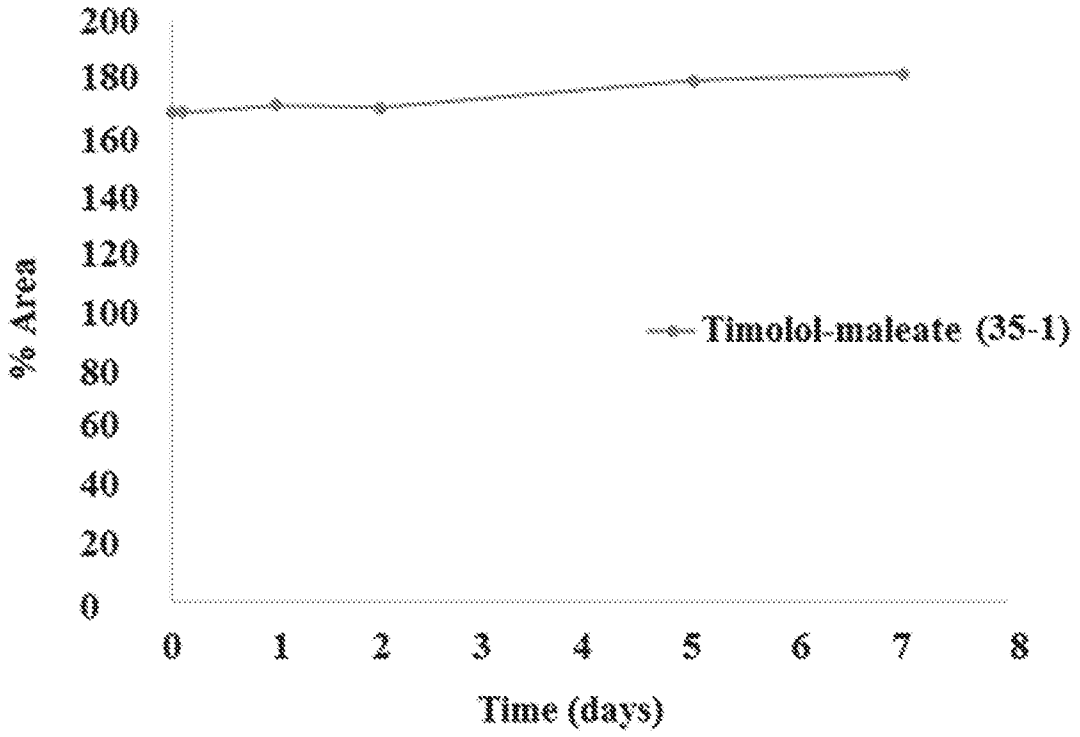

200
180
160
140
120
100
80
60
40
20
0
% Area
Timolol-maleate (35-1)
0
1
2
3
4
5
6
7
8
Time (days)

FIG. 1

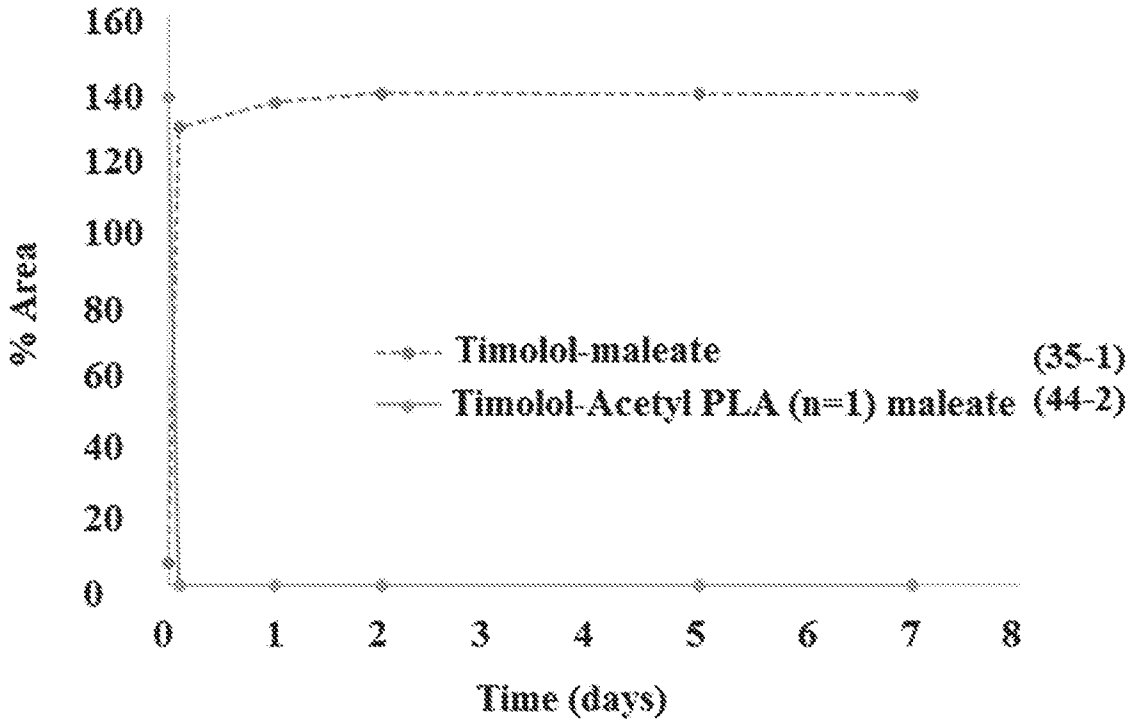

160
140
120
100
80
60
40
20
0
% Area
Timolol-maleate (35-1)
Timolol-Acetyl PLA (n=1) maleate (44-2)
0
1
2
3
4
5
6
7
8
Time (days)

FIG. 2

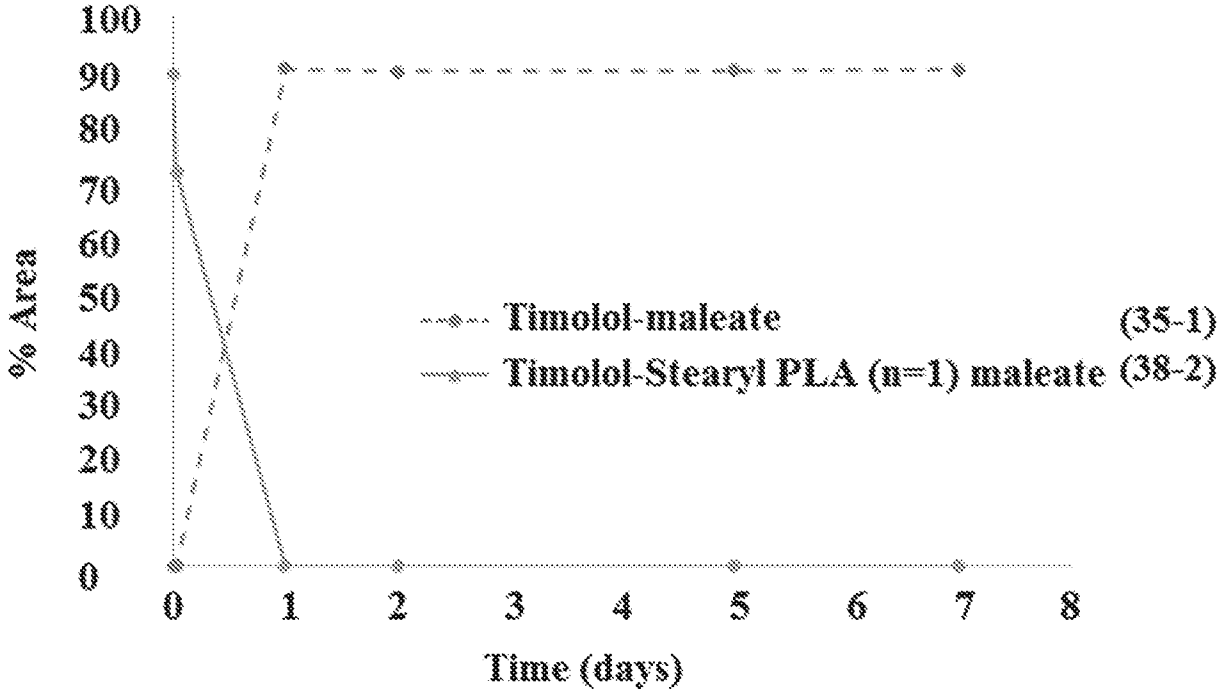

100
90
80
70
60
50
40
30
20
10
0
% Area
0
1
2
3
4
5
6
7
8
Time (days)
Timolol-maleate (35-1)
Timolol-Stearyl PLA (n=1) maleate (38-2)

FIG. 3

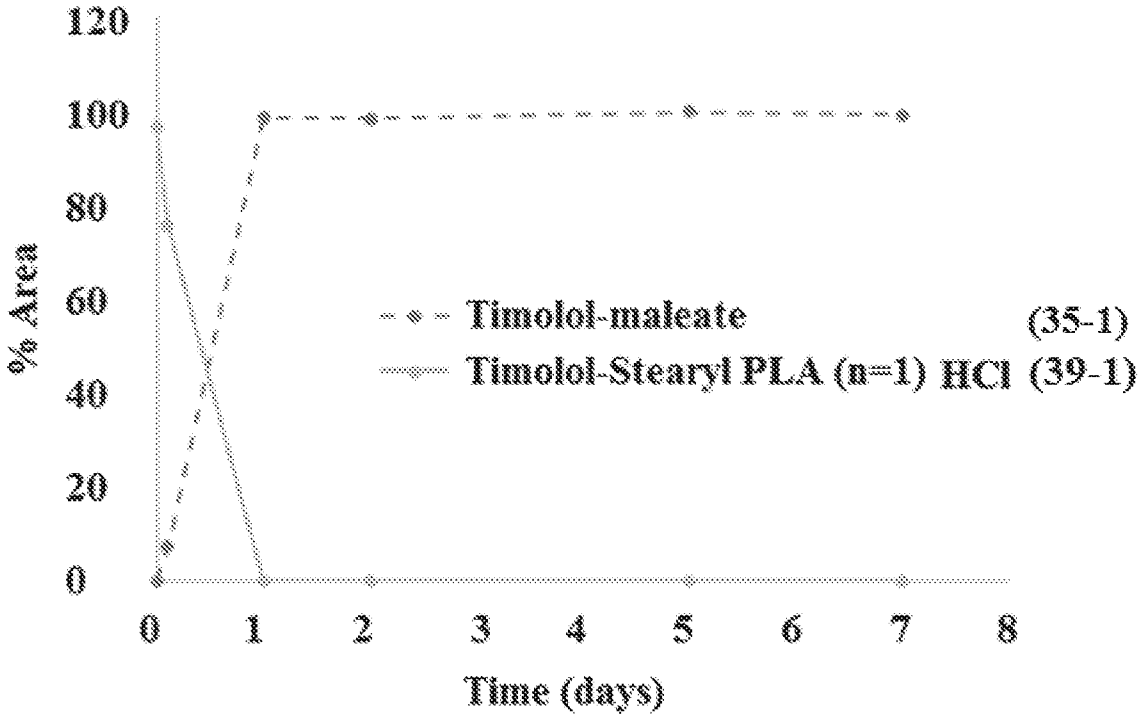

120
100
80
60
40
20
0
% Area
0
1
2
3
4
5
6
7
8
Time (days)
Timolol-maleate (35-1)
Timolol-Stearyl PLA (n=1) HCl (39-1)

FIG. 4

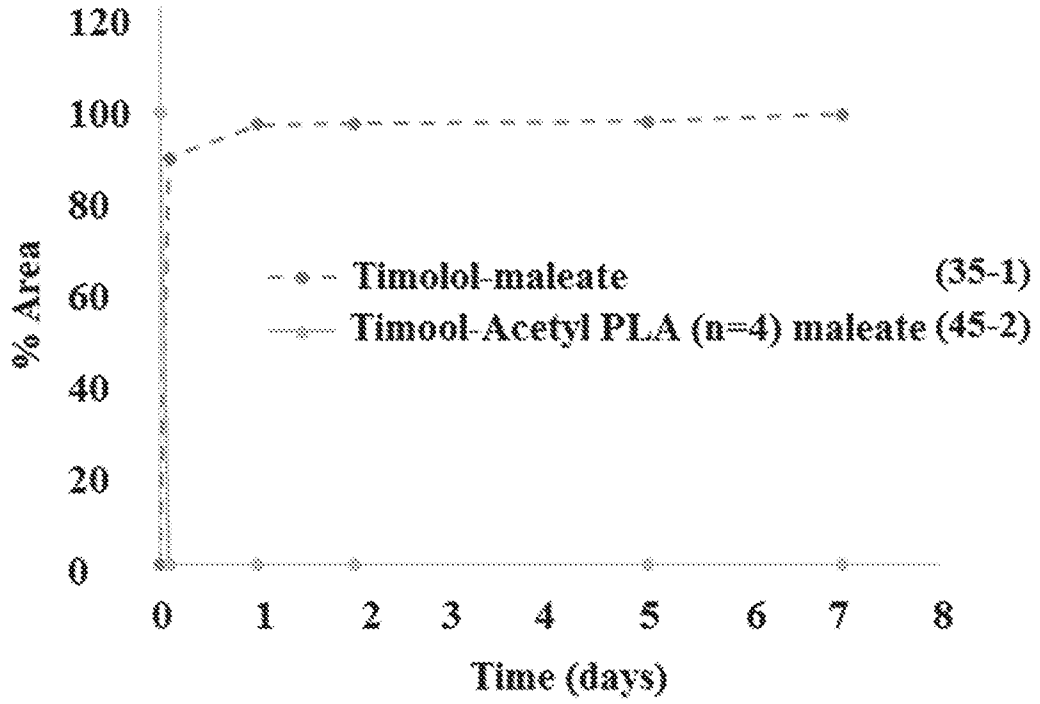

120
100
80
60
40
20
0
% Area
Timolol-maleate (35-1)
Timool-Acetyl PLA (n=4) maleate (45-2)
0 1 2 3 4 5 6 7 8
Time (days)

FIG. 5

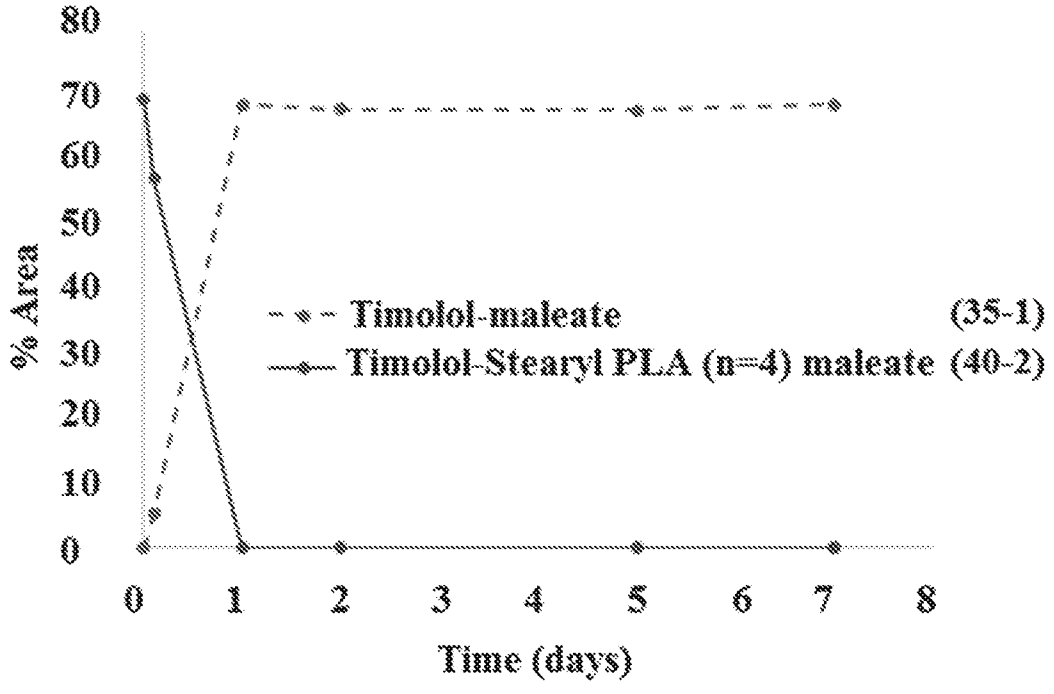

80
70
60
50
40
30
20
10
0
% Area
Timolol-maleate (35-1)
Timolol-Stearyl PLA (n=4) maleate (40-2)
0 1 2 3 4 5 6 7 8
Time (days)

FIG. 6

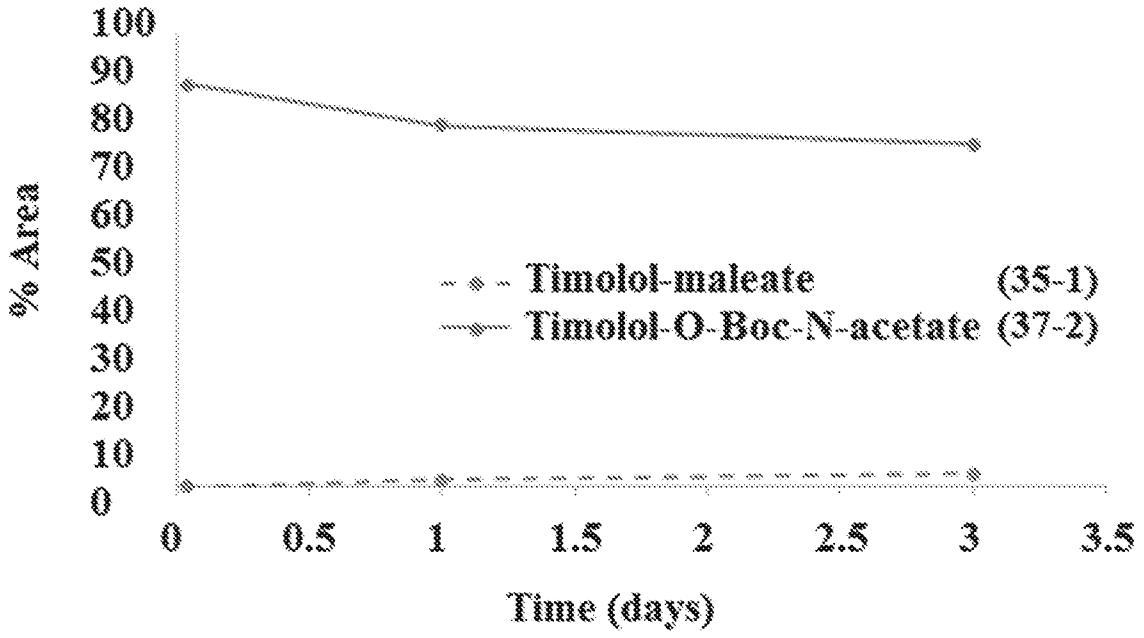

100
90
80
70
60
50
40
30
20
10
0
% Area
Timolol-maleate (35-1)
Timolol-O-Boc-N-acetate (37-2)
0
0.5
1
1.5
2
2.5
3
3.5
Time (days)

FIG. 7

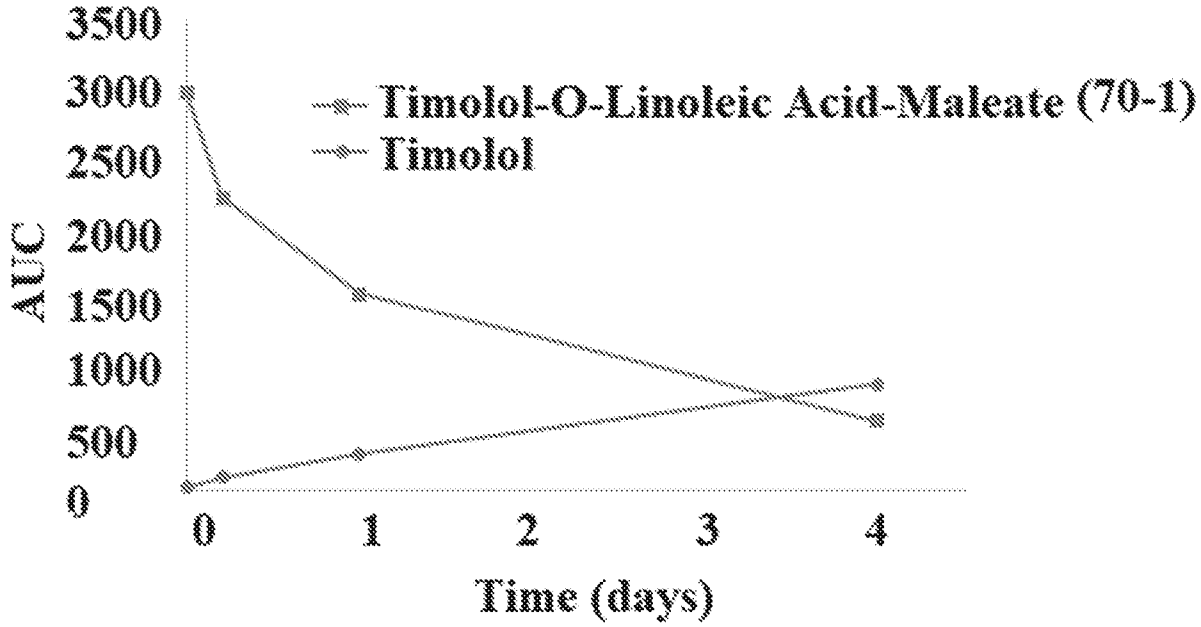

3500
3000
2500
2000
1500
1000
500
0
AUC
Timolol-O-Linoleic Acid-Maleate (70-1)
Timolol
0
1
2
3
4
Time (days)

FIG. 8

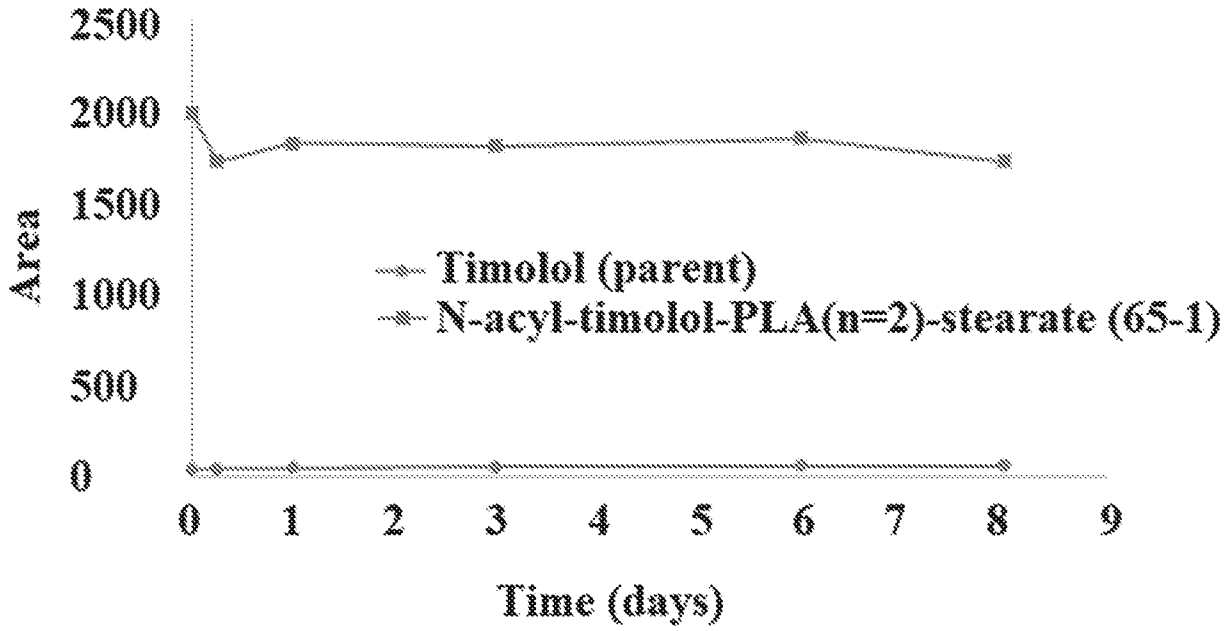

2500
2000
1500
1000
500
0
Area
Timolol (parent)
N-acyl-timolol-PLA(n=2)-stearate (65-1)
0 1 2 3 4 5 6 7 8 9
Time (days)

FIG. 9

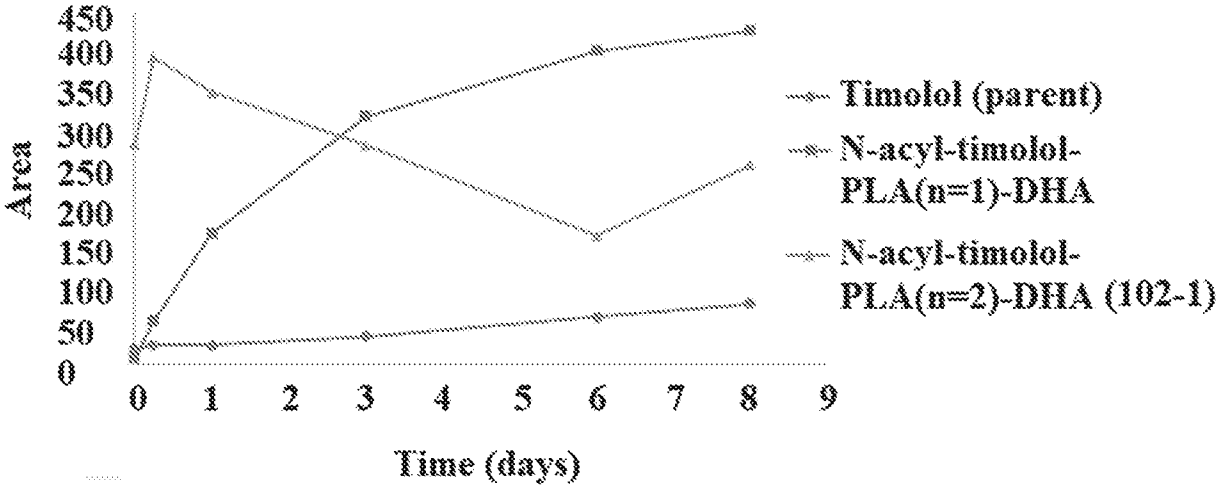

450
400
350
300
250
200
150
100
50
0
Area
Timolol (parent)
N-acyl-timolol-PLA(n=1)-DHA
N-acyl-timolol-PLA(n=2)-DHA (102-1)
0 1 2 3 4 5 6 7 8 9
Time (days)

FIG. 10

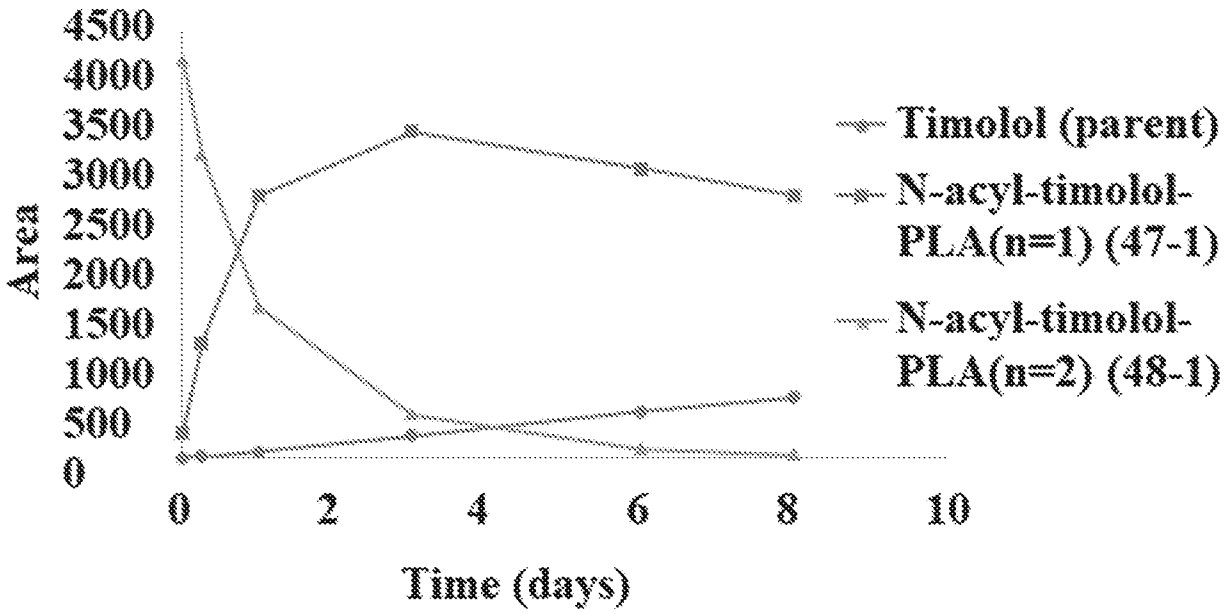

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
2
4
6
8
10
Time (days)
Timolol (parent)
N-acyl-timolol-PLA(n=1) (47-1)
N-acyl-timolol-PLA(n=2) (48-1)

FIG. 11

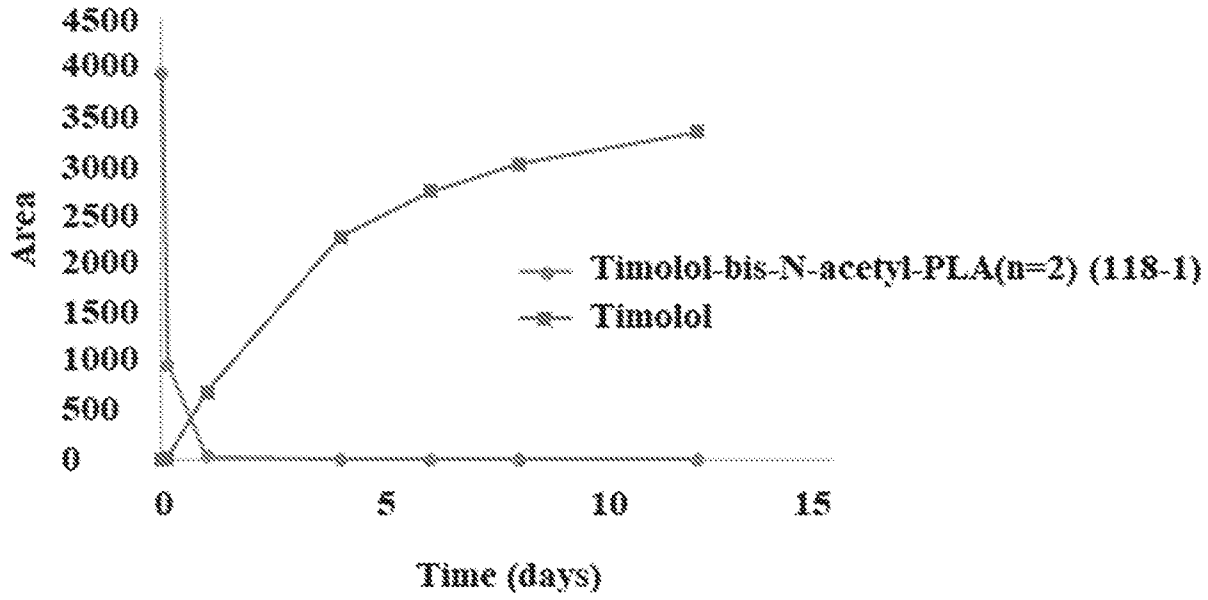

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
5
10
15
Time (days)
Timolol-bis-N-acetyl-PLA(n=2) (118-1)
Timolol

FIG. 12

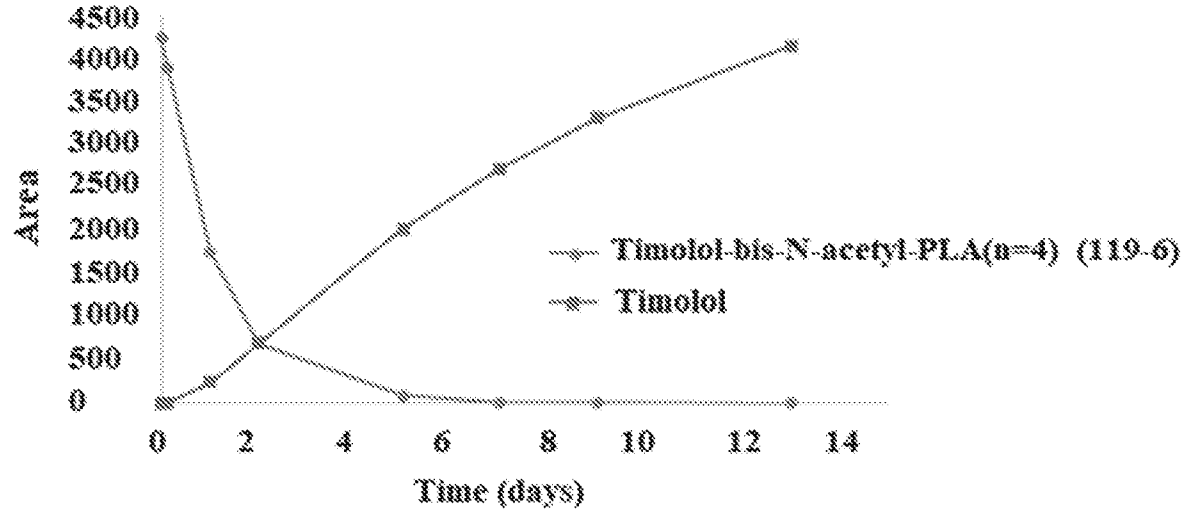

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
2
4
6
8
10
12
14
Time (days)
Timolol-bis-N-acetyl-PLA(n=4) (119-6)
Timolol

FIG. 13

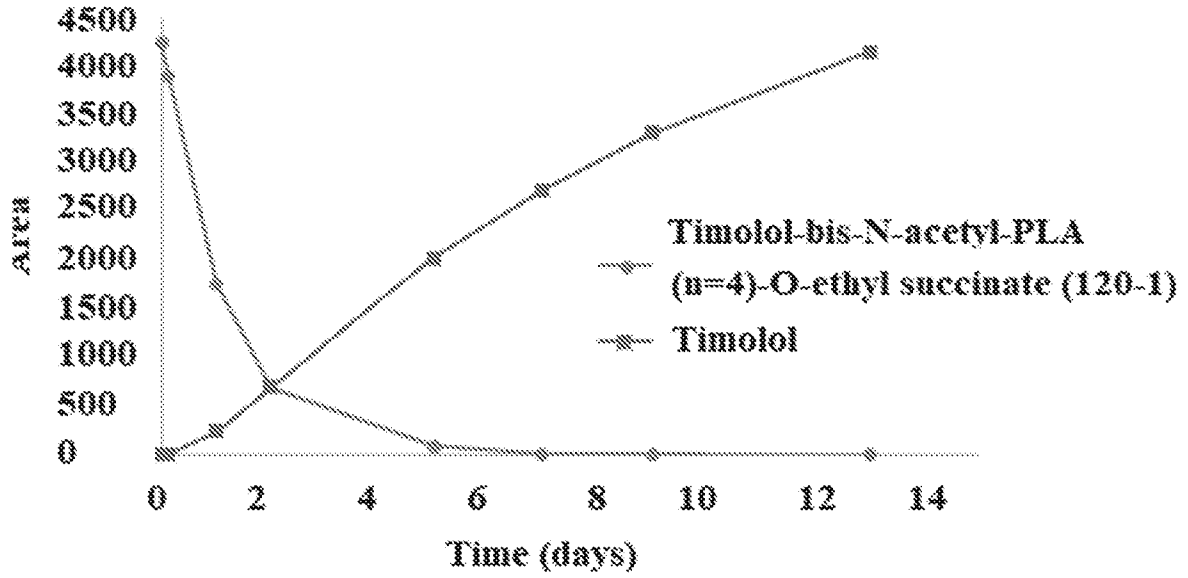

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
2
4
6
8
10
12
14
Time (days)
Timolol-bis-N-acetyl-PLA
(n=4)-O-ethyl succinate (120-1)
Timolol

FIG. 14

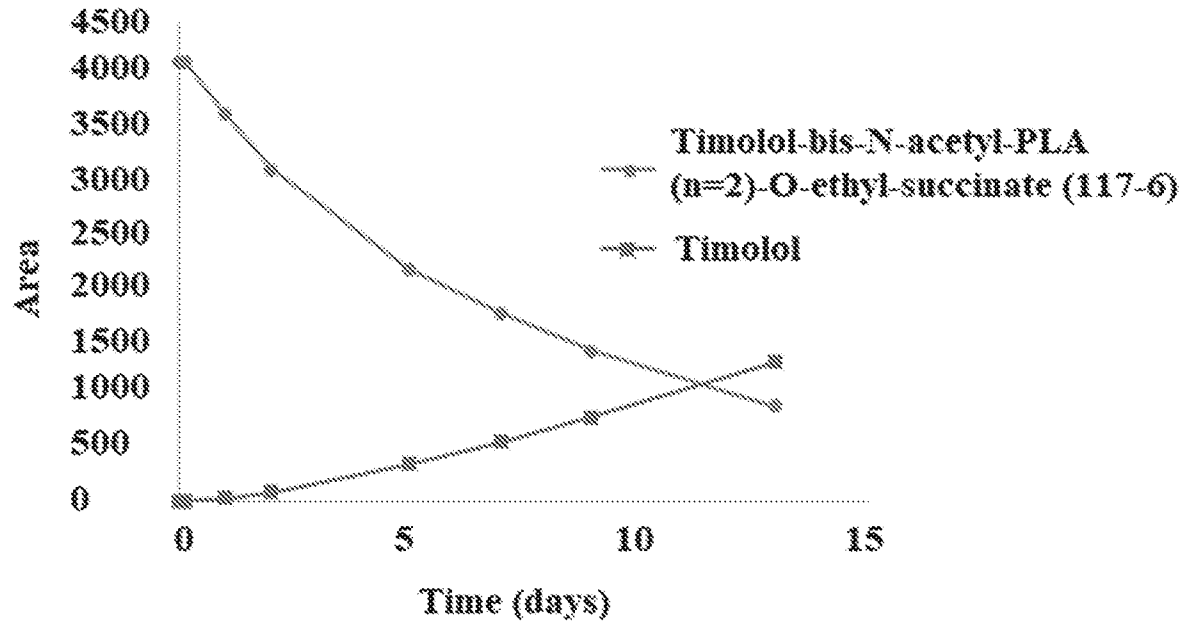

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
5
10
15
Time (days)
Timolol-bis-N-acetyl-PLA (n=2)-O-ethyl-succinate (117-6)
Timolol

FIG. 15

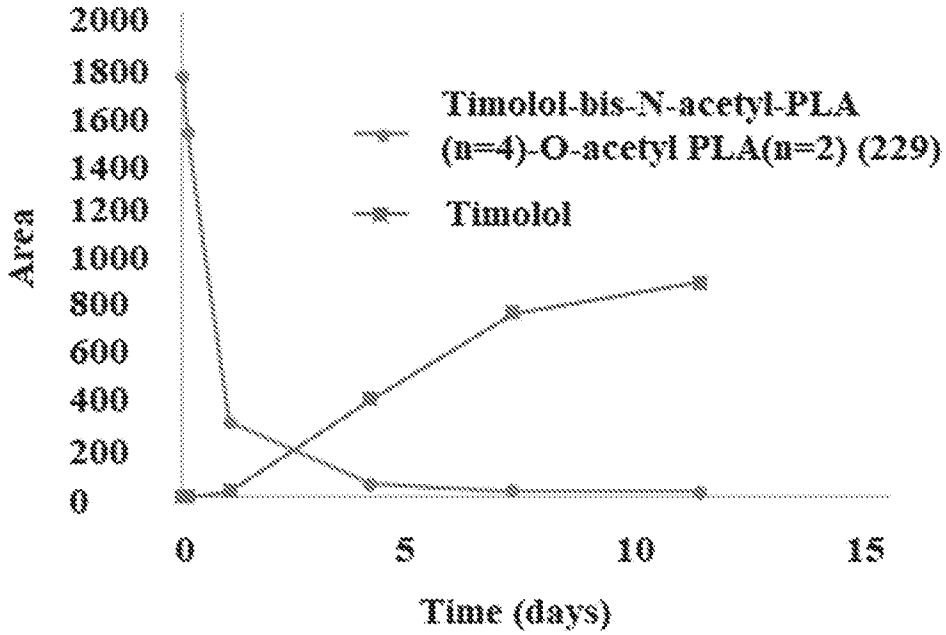

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Area
0
5
10
15
Time (days)
Timolol-bis-N-acetyl-PLA (n=4)-O-acetyl PLA(n=2) (229)
Timolol

FIG. 16

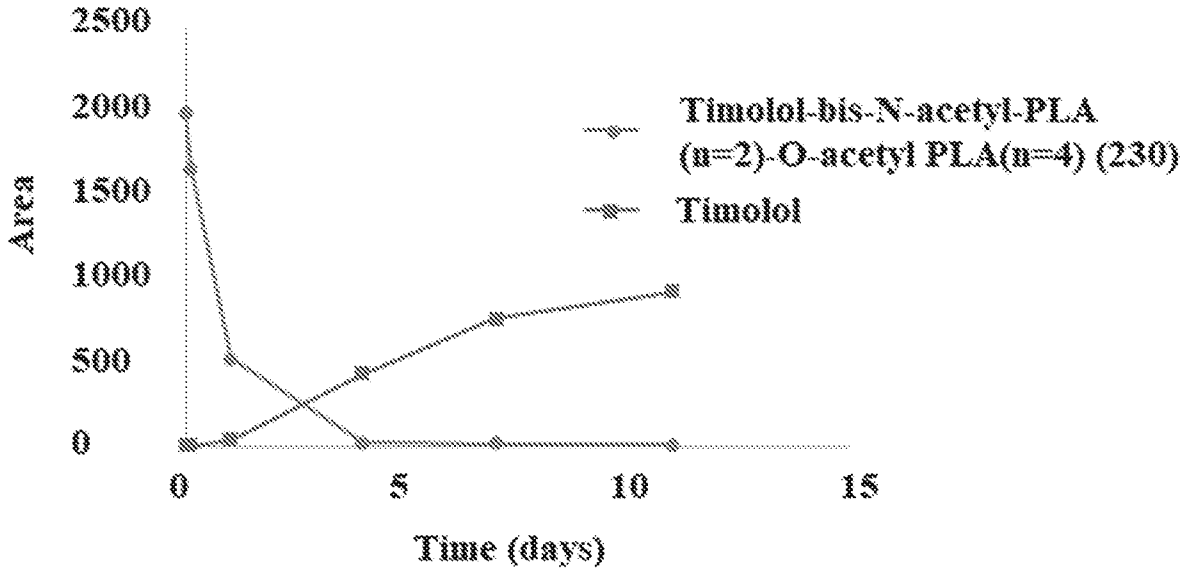



FIG. 17

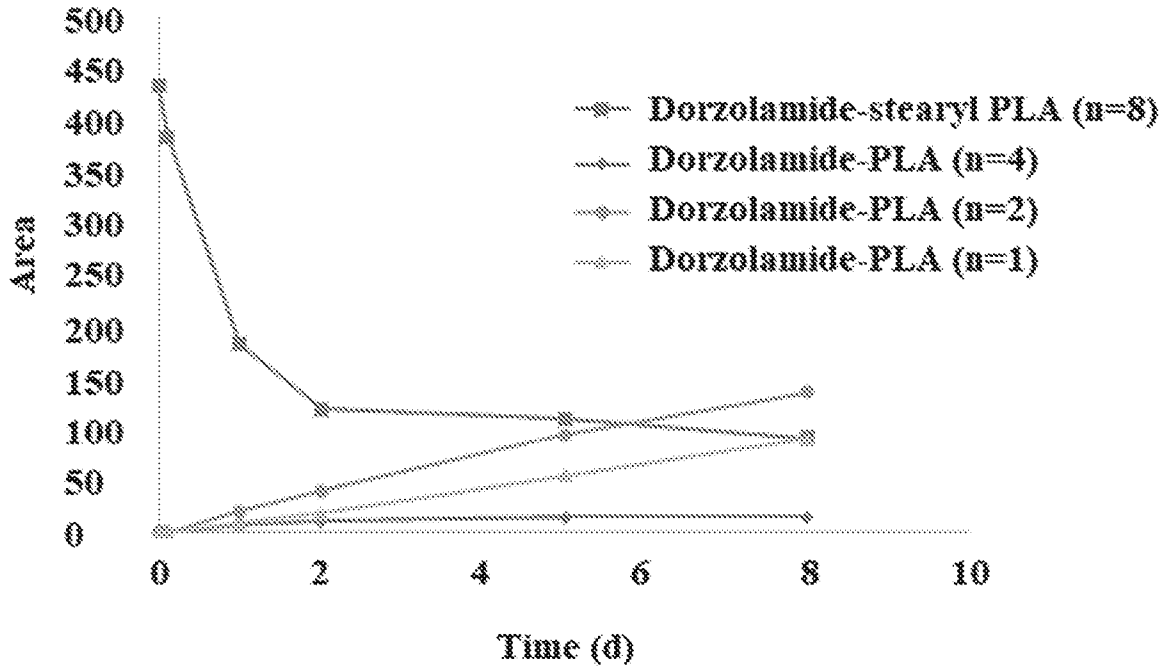



FIG. 18A

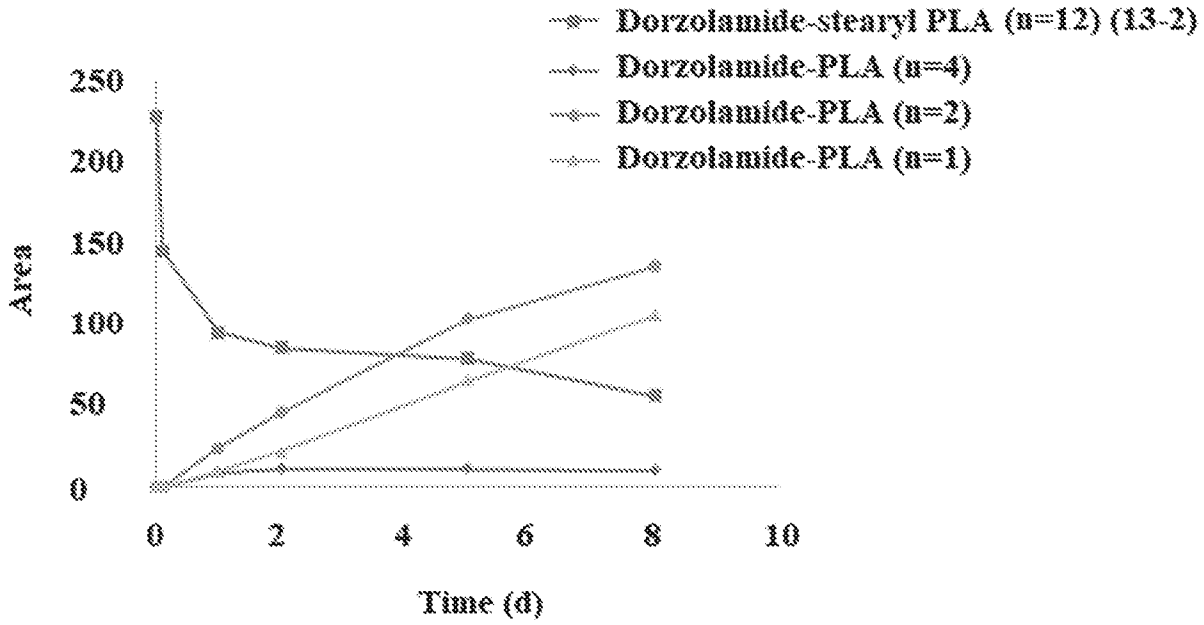



FIG. 18B

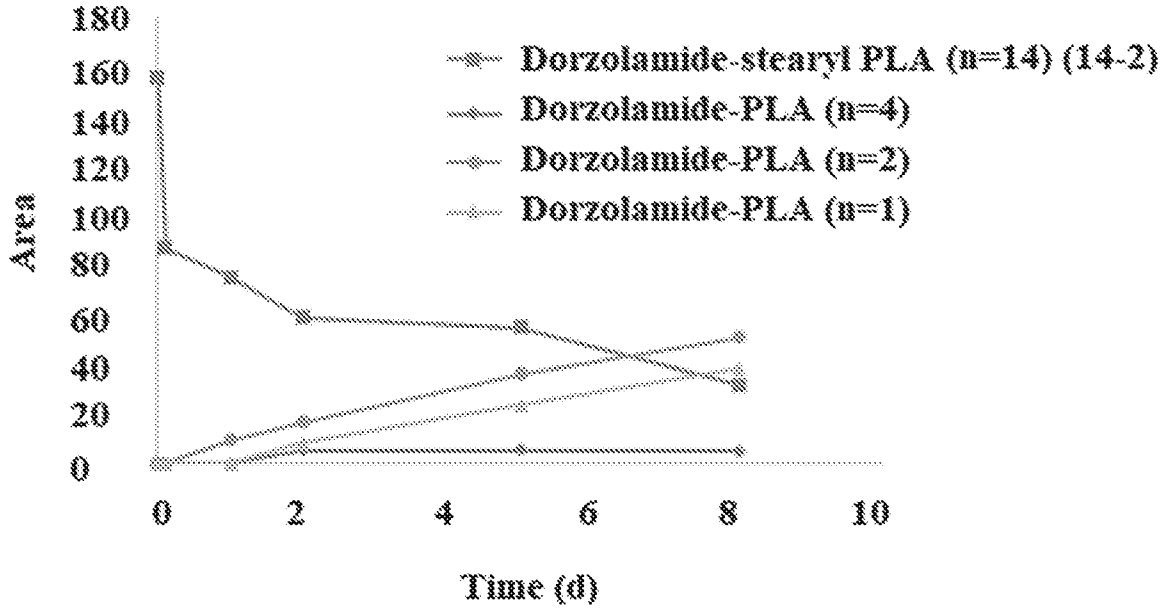



FIG. 18C

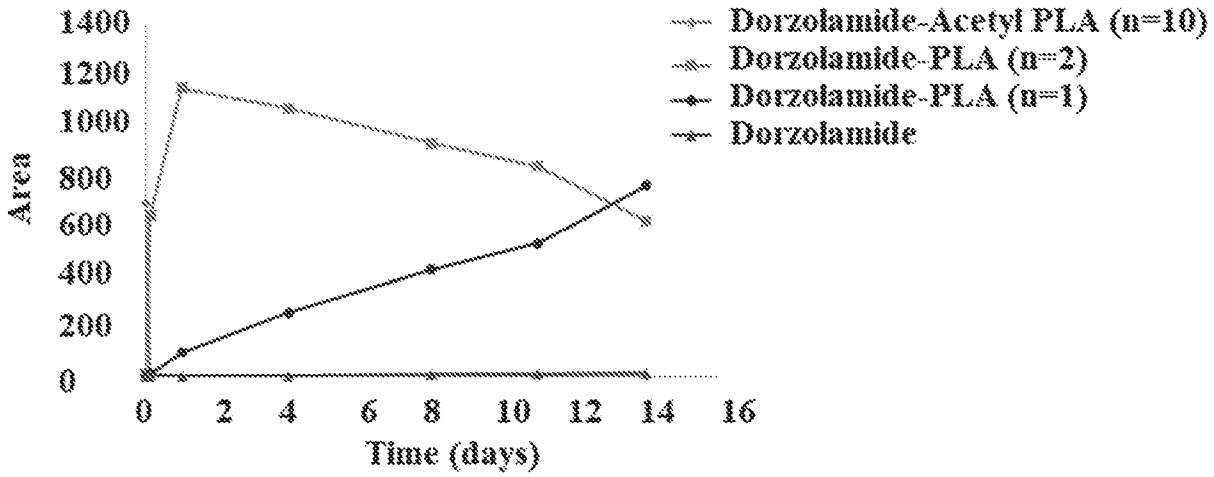



FIG. 19A

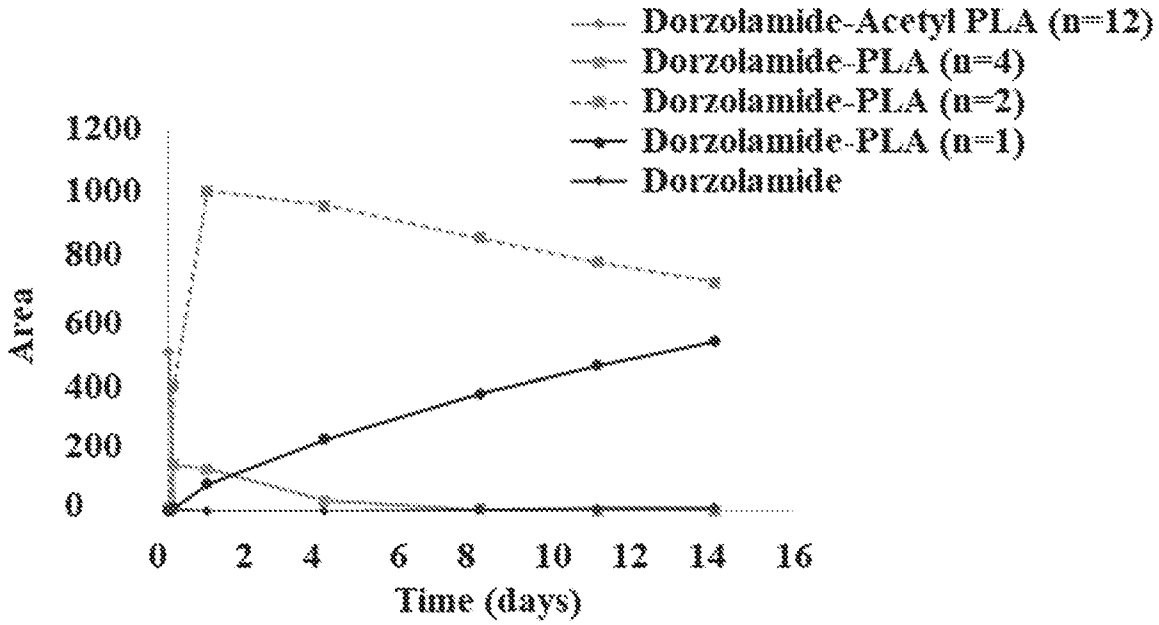



FIG. 19B

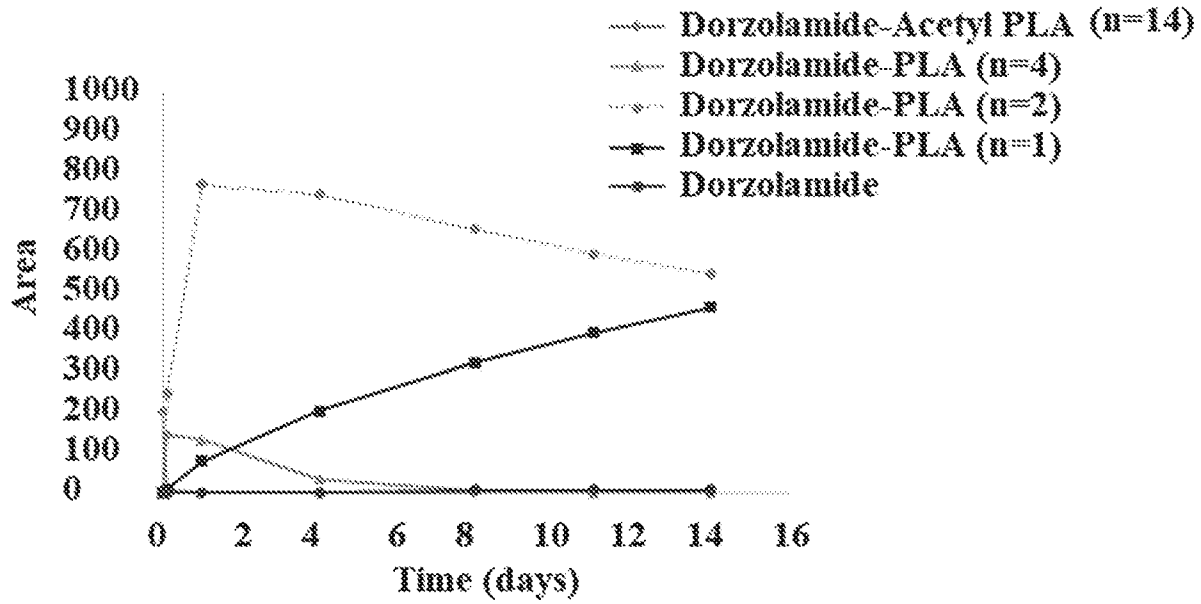

Dorzolamide-Acetyl PLA (n=14)
Dorzolamide-PLA (n=4)
Dorzolamide-PLA (n=2)
Dorzolamide-PLA (n=1)
Dorzolamide
Area
1000
900
800
700
600
500
400
300
200
100
0
0 2 4 6 8 10 12 14 16
Time (days)

FIG. 20

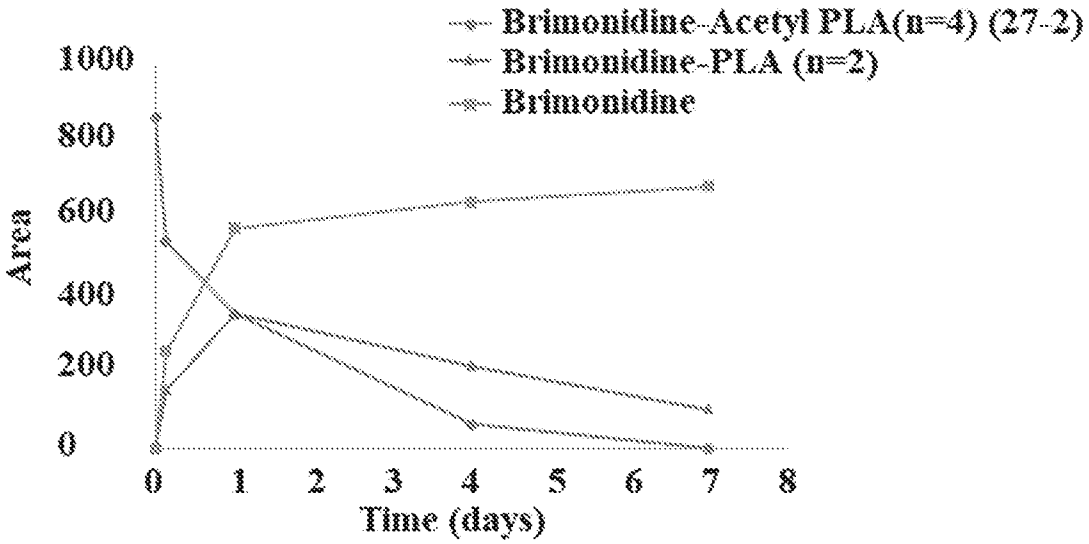

Brimonidine-Acetyl PLA(n=4) (27-2)
Brimonidine-PLA (n=2)
Brimonidine
Area
1000
800
600
400
200
0
0 1 2 3 4 5 6 7 8
Time (days)

FIG. 21

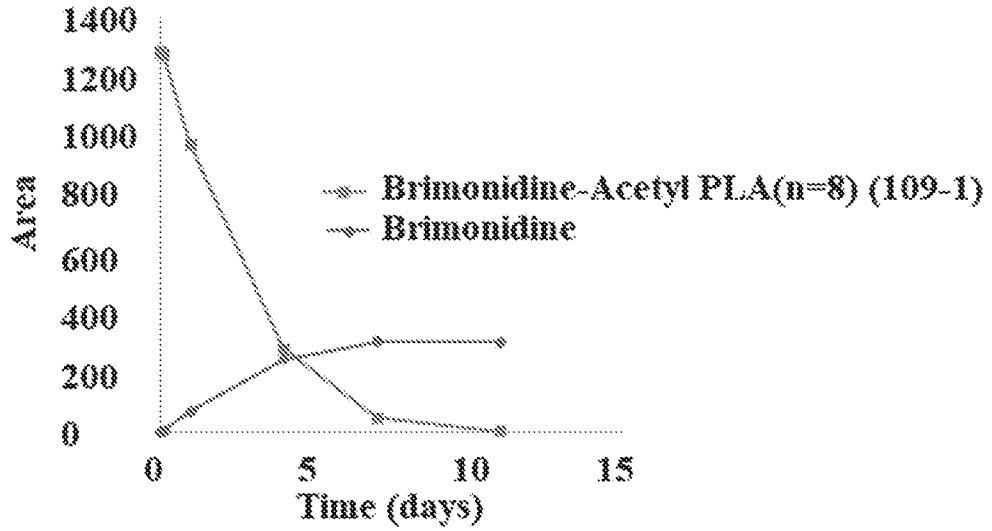

1400
1200
1000
800
600
400
200
0
Area
0
5
10
15
Time (days)
Brimonidine-Acetyl PLA(n=8) (109-1)
Brimonidine

FIG. 22

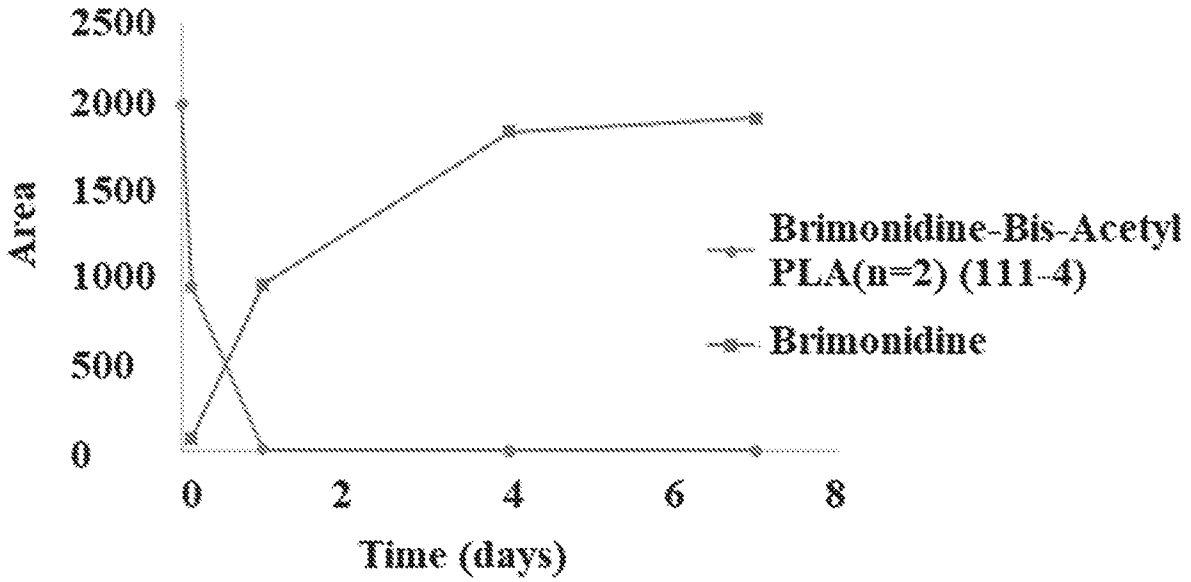

2500
2000
1500
1000
500
0
Area
0
2
4
6
8
Time (days)
Brimonidine-Bis-Acetyl PLA(n=2) (111-4)
Brimonidine

FIG. 23

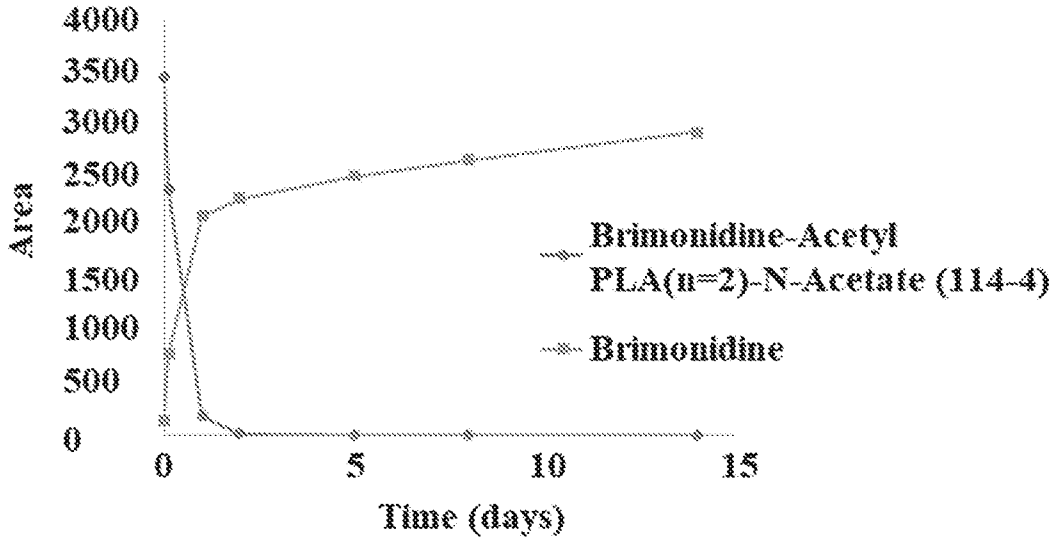

4000
3500
3000
2500
2000
1500
1000
500
0
Area
0
5
10
15
Time (days)
Brimonidine-Acetyl PLA(n=2)-N-Acetate (114-4)
Brimonidine

FIG. 24

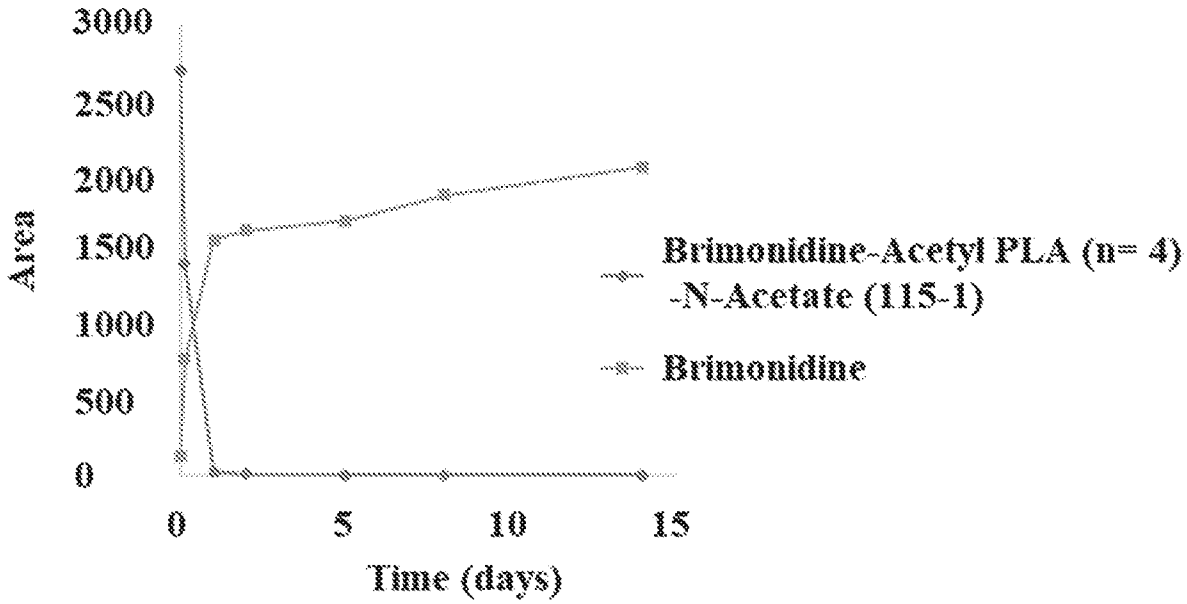

3000
2500
2000
1500
1000
500
0
Area
0
5
10
15
Time (days)
Brimonidine-Acetyl PLA (n= 4) -N-Acetate (115-1)
Brimonidine

FIG. 25

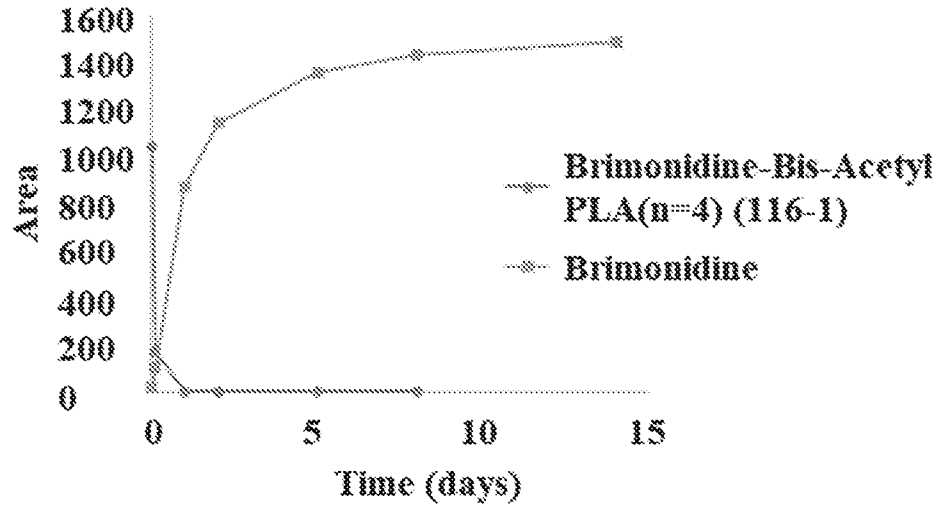

1600
1400
1200
1000
800
600
400
200
0
Area
0
5
10
15
Time (days)
Brimonidine-Bis-Acetyl PLA(n=4) (116-1)
Brimonidine

FIG. 26

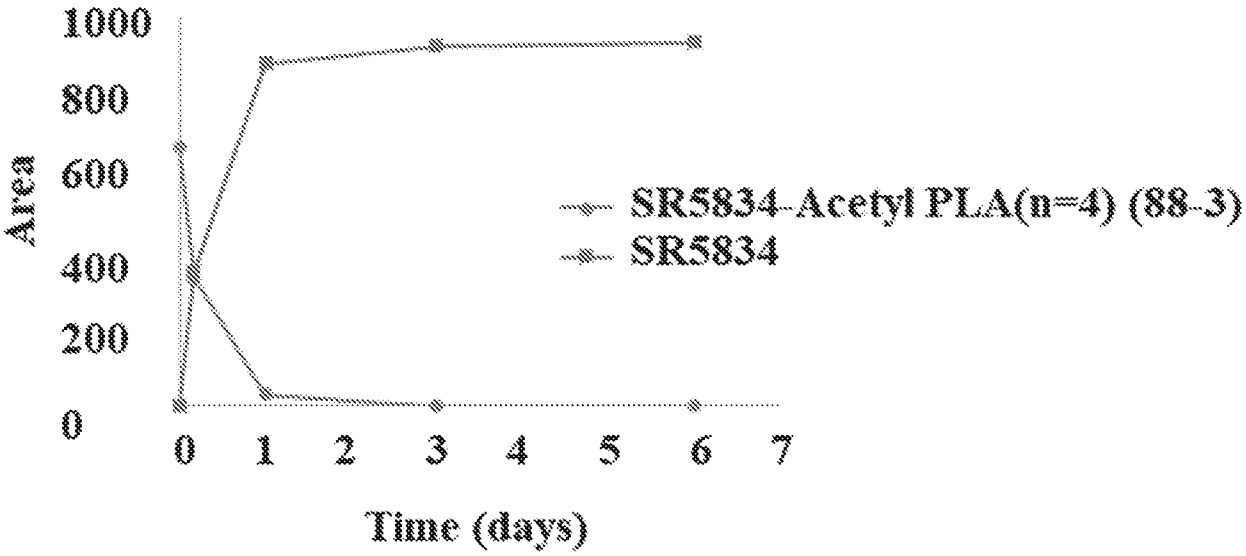

1000
800
600
400
200
0
Area
0
1
2
3
4
5
6
7
Time (days)
SR5834-Acetyl PLA(n=4) (88-3)
SR5834

FIG. 27

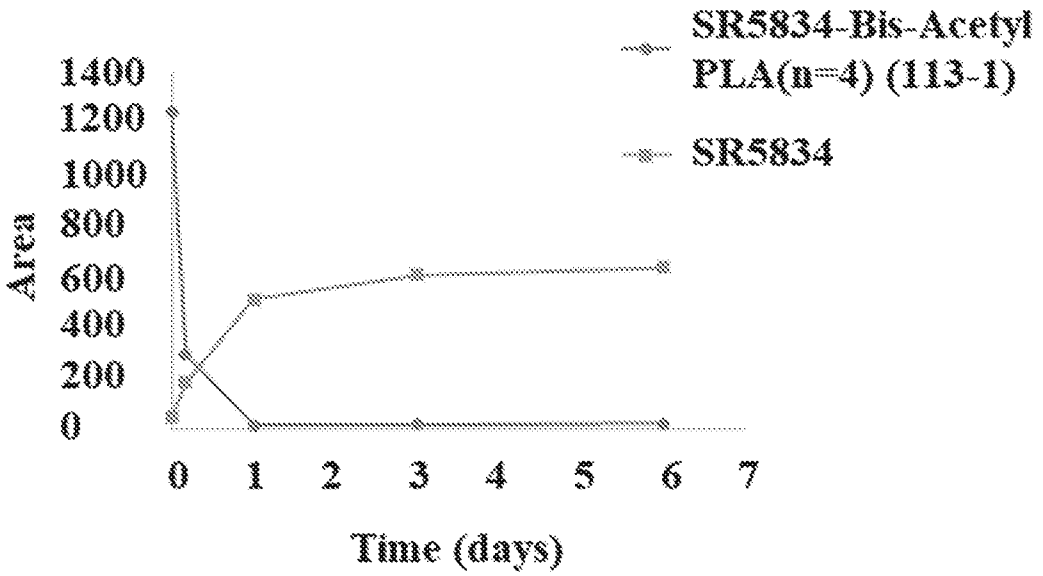

SR5834-Bis-Acetyl PLA(n=4) (113-1)
SR5834
1400
1200
1000
800
600
400
200
0
Area
0 1 2 3 4 5 6 7
Time (days)

FIG. 28

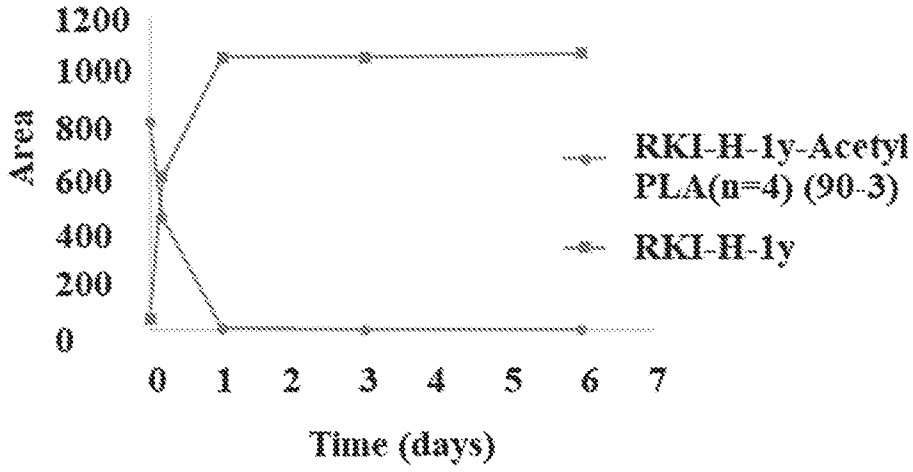

1200
1000
800
600
400
200
0
Area
RKI-H-1y-Acetyl PLA(n=4) (90-3)
RKI-H-1y
0 1 2 3 4 5 6 7
Time (days)

FIG. 29

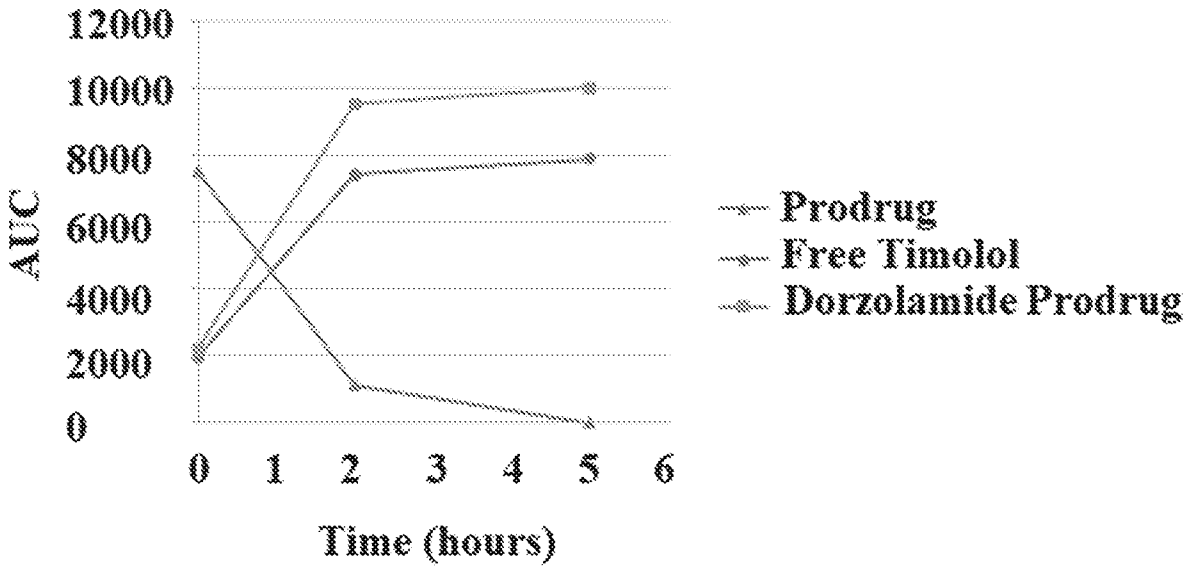



FIG. 30A

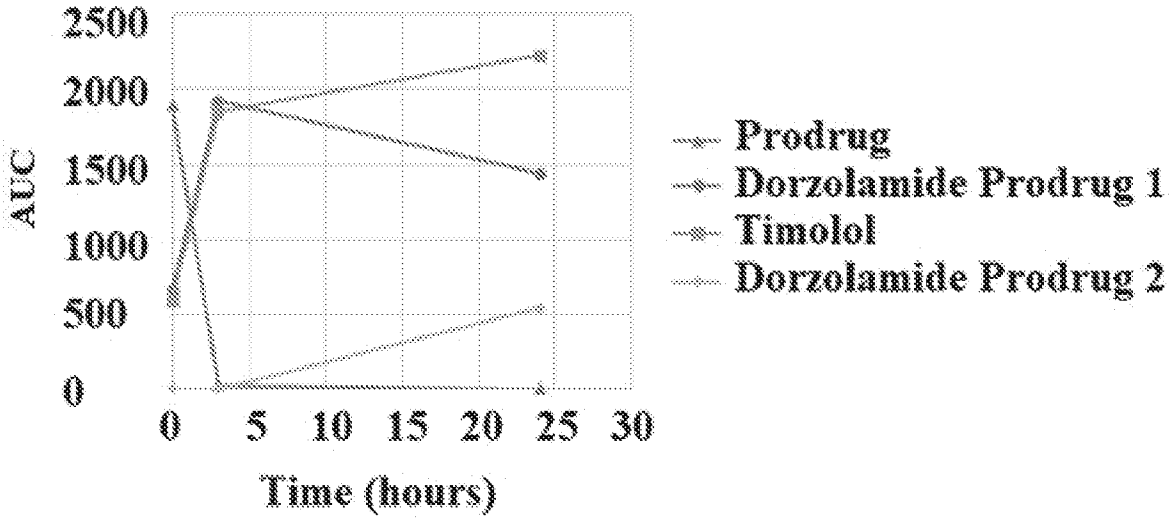



FIG. 30B

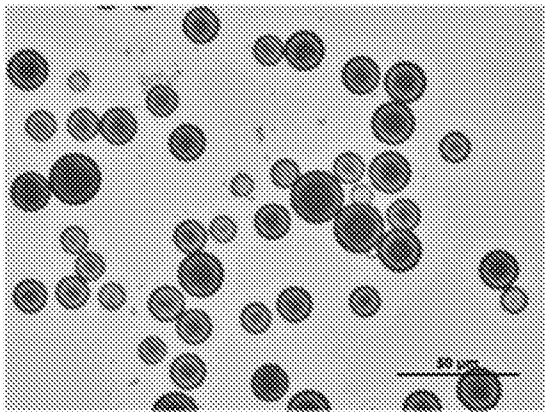


FIG. 31A

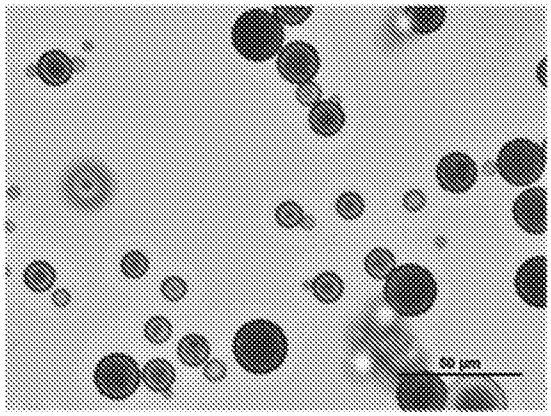


FIG. 31B

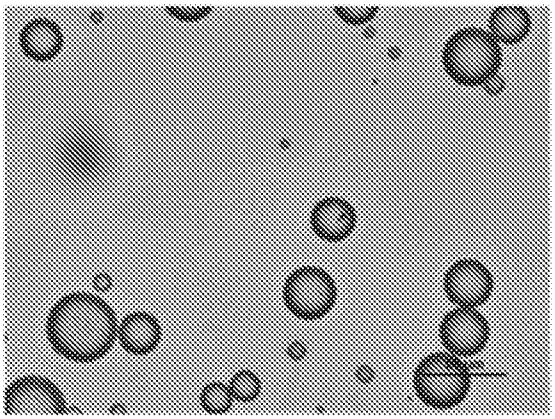


FIG. 31C

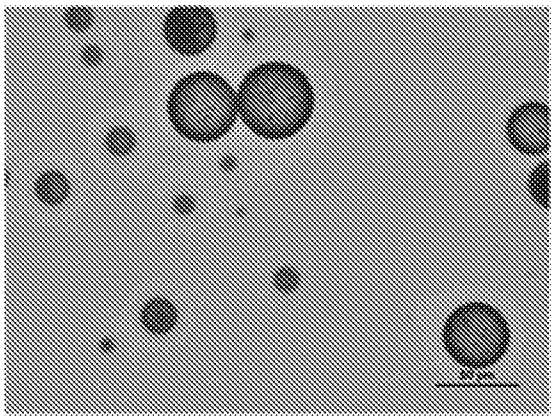


FIG. 31D

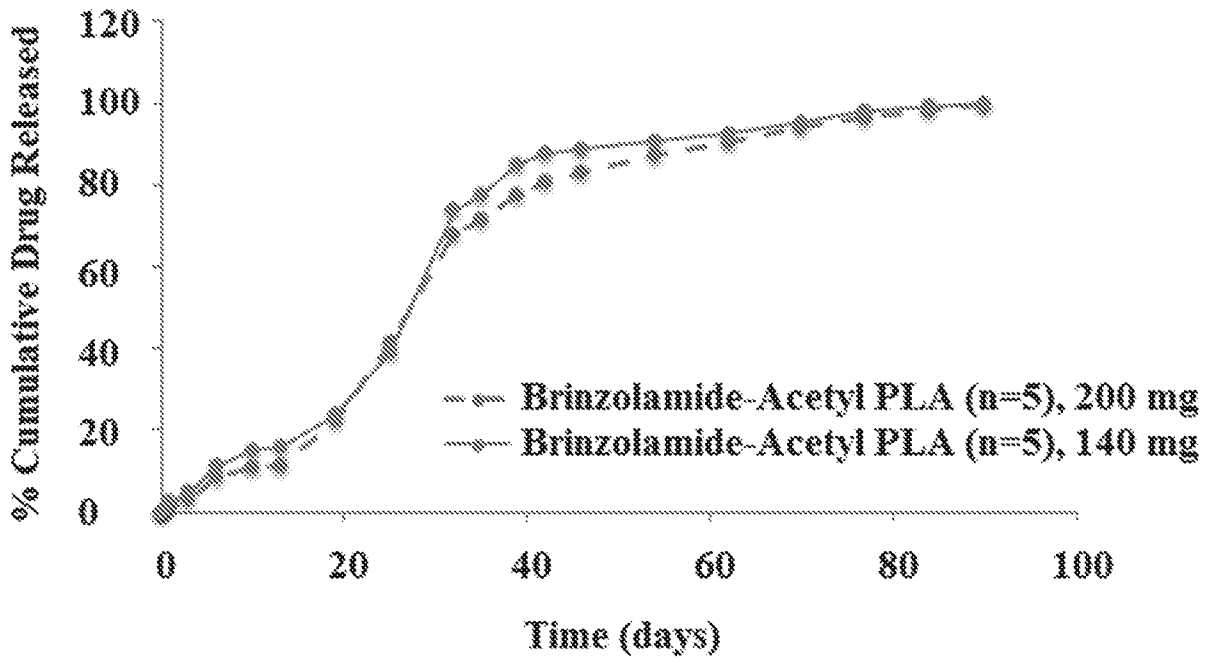

% Cumulative Drug Released
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (days)
Brinzolamide-Acetyl PLA (n=5), 200 mg
Brinzolamide-Acetyl PLA (n=5), 140 mg

FIG. 32

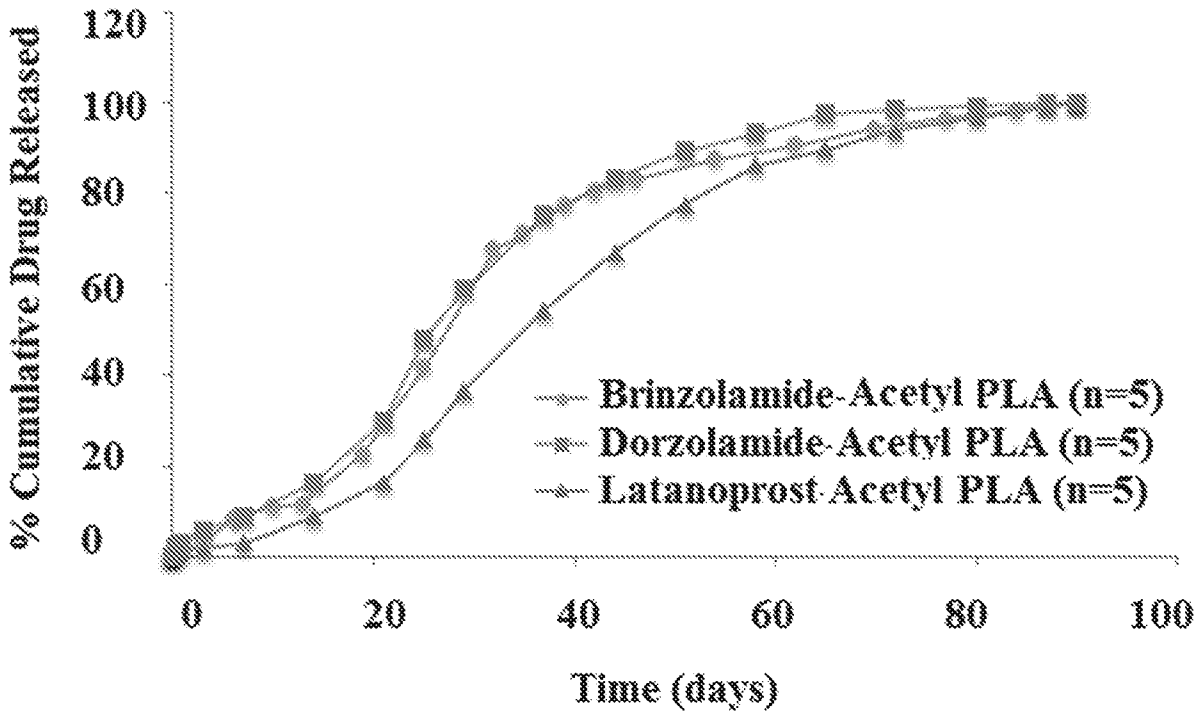

% Cumulative Drug Released
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (days)
Brinzolamide-Acetyl PLA (n=5)
Dorzolamide-Acetyl PLA (n=5)
Latanoprost-Acetyl PLA (n=5)

FIG. 33

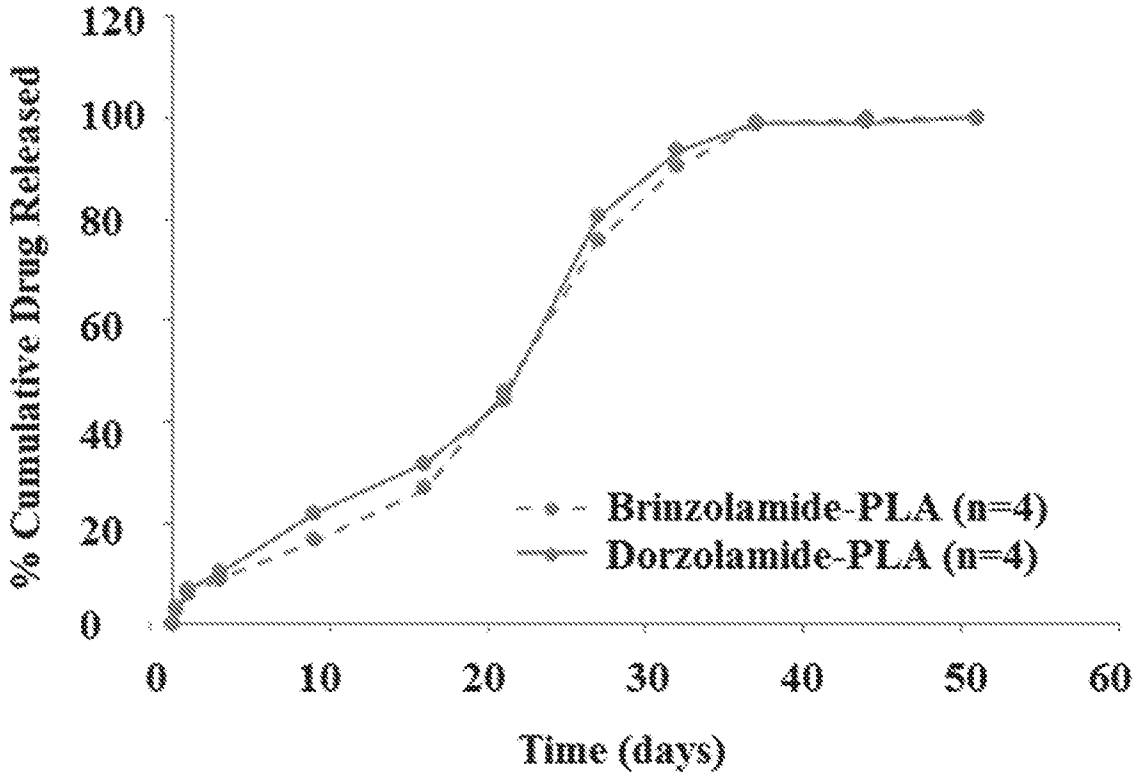

% Cumulative Drug Released
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (days)
Brinzolamide-PLA (n=4)
Dorzolamide-PLA (n=4)

FIG. 34

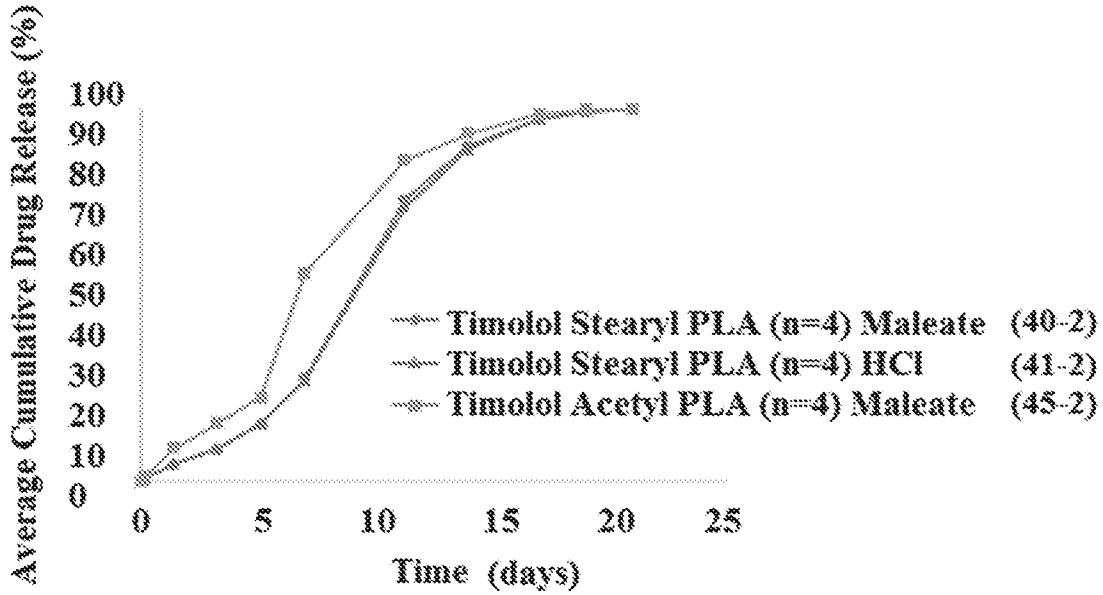

Average Cumulative Drug Release (%)
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (days)
Timolol Stearyl PLA (n=4) Maleate (40-2)
Timolol Stearyl PLA (n=4) HCl (41-2)
Timolol Acetyl PLA (n=4) Maleate (45-2)

FIG. 35

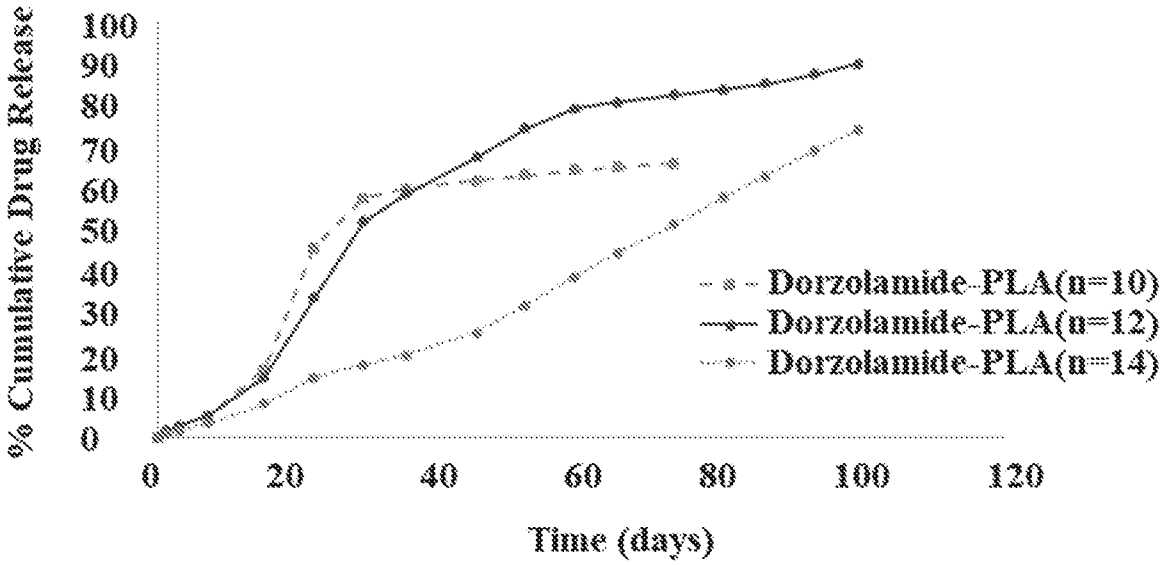

% Cumulative Drug Release
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Time (days)
Dorzolamide-PLA(n=10)
Dorzolamide-PLA(n=12)
Dorzolamide-PLA(n=14)

FIG. 36

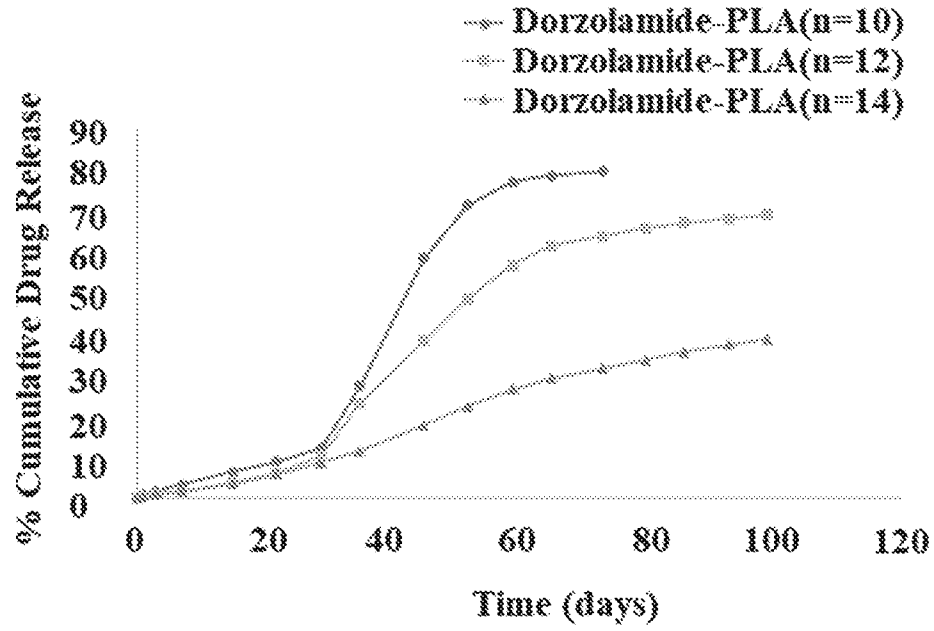

Dorzolamide-PLA(n=10)
Dorzolamide-PLA(n=12)
Dorzolamide-PLA(n=14)
% Cumulative Drug Release
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Time (days)

FIG. 37

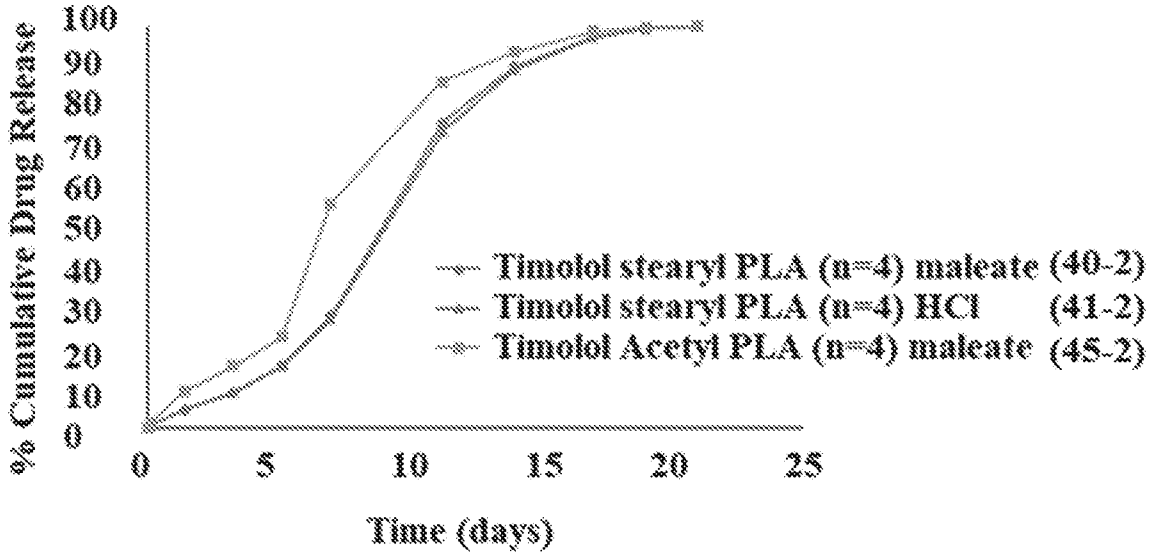

% Cumulative Drug Release
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time (days)
Timolol stearyl PLA (n=4) maleate (40-2)
Timolol stearyl PLA (n=4) HCl (41-2)
Timolol Acetyl PLA (n=4) maleate (45-2)

FIG. 38

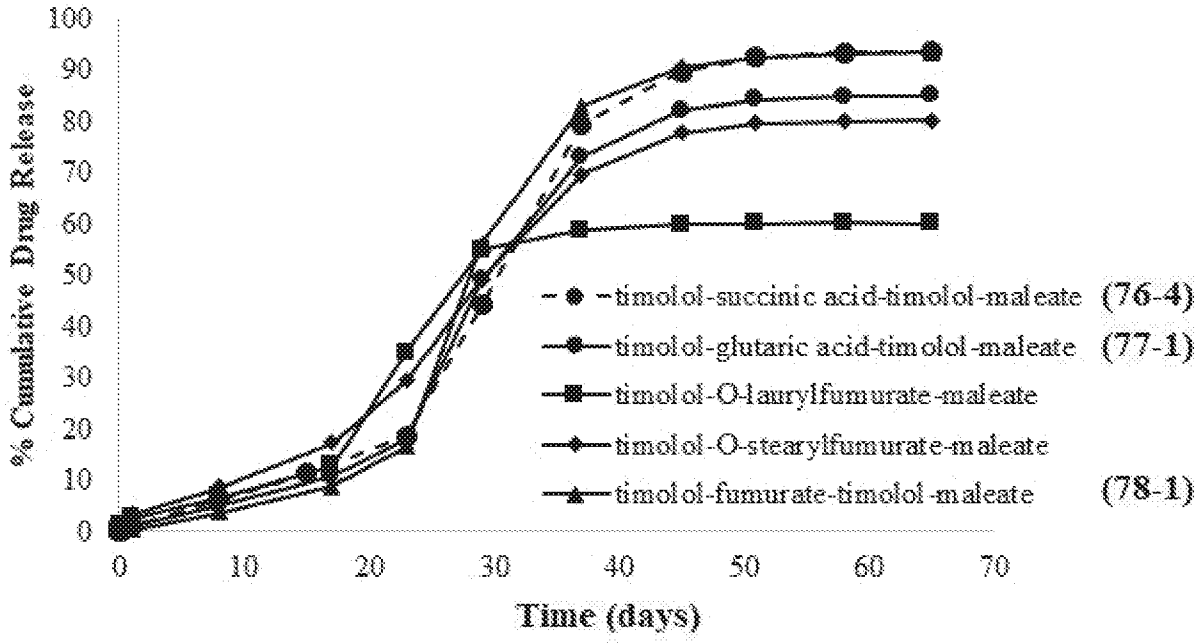

% Cumulative Drug Release
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
Time (days)
timolol-succinic acid-timolol-maleate (76-4)
timolol-glutaric acid-timolol-maleate (77-1)
timolol-O-laurylfumurate-maleate
timolol-O-stearylfumurate-maleate
timolol-fumurate-timolol-maleate (78-1)

FIG. 39

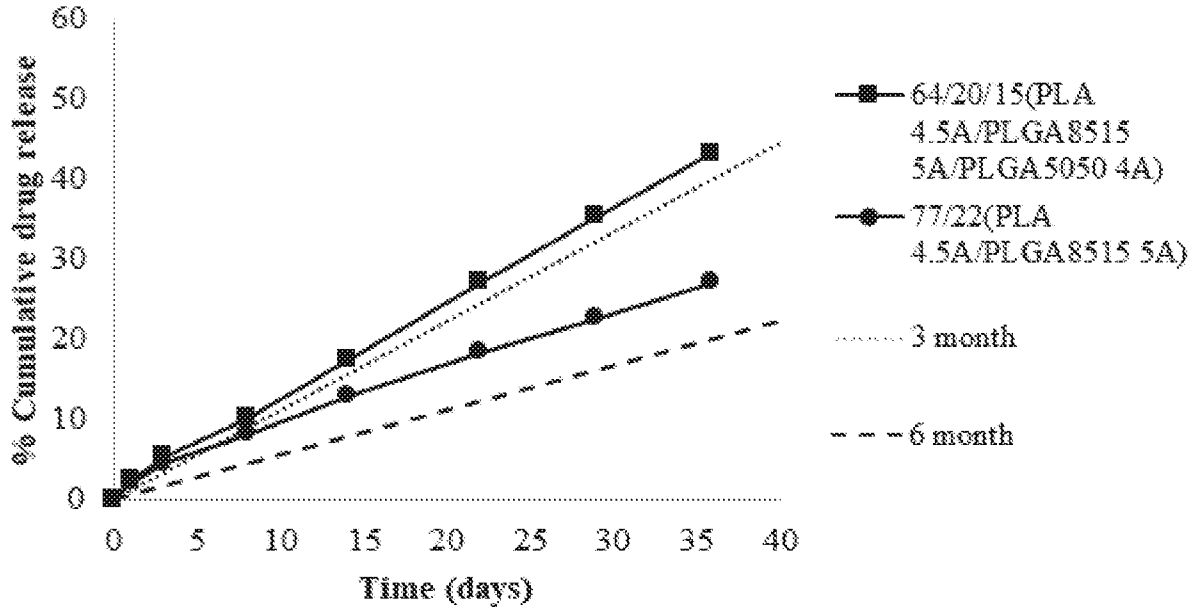

% Cumulative drug release
60
50
40
30
20
10
0
0
5
10
15
20
25
30
35
40
Time (days)
64/20/15(PLA 4.5A/PLGA8515 5A/PLGA5050 4A)
77/22(PLA 4.5A/PLGA8515 5A)
3 month
6 month

FIG. 40

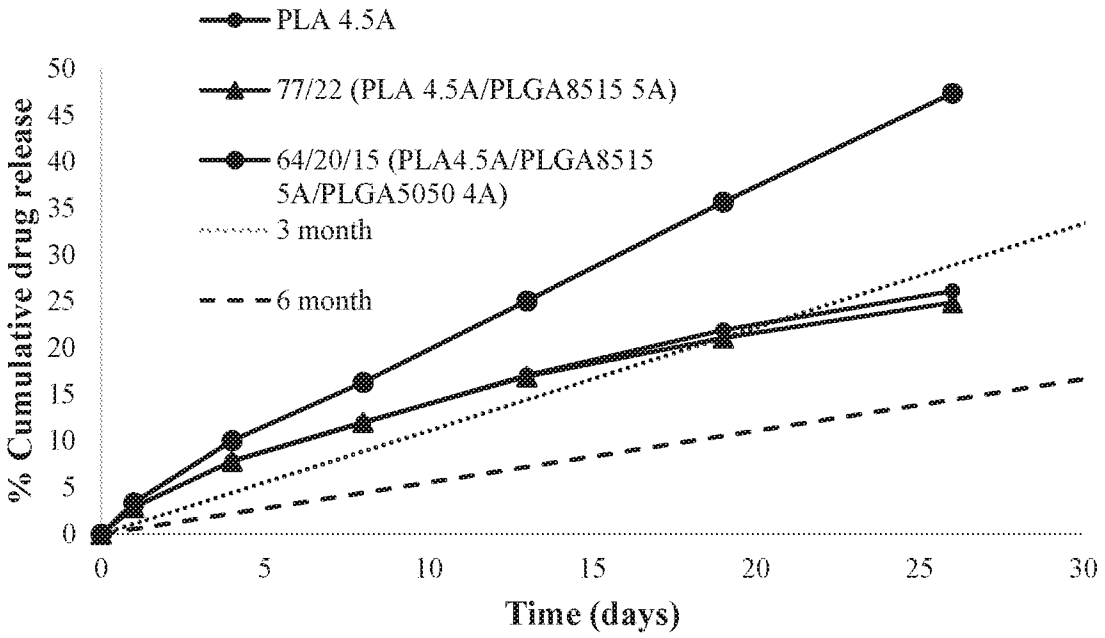

% Cumulative drug release
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time (days)
PLA 4.5A
77/22 (PLA 4.5A/PLGA8515 5A)
64/20/15 (PLA4.5A/PLGA8515 5A/PLGA5050 4A)
3 month
6 month

FIG. 41

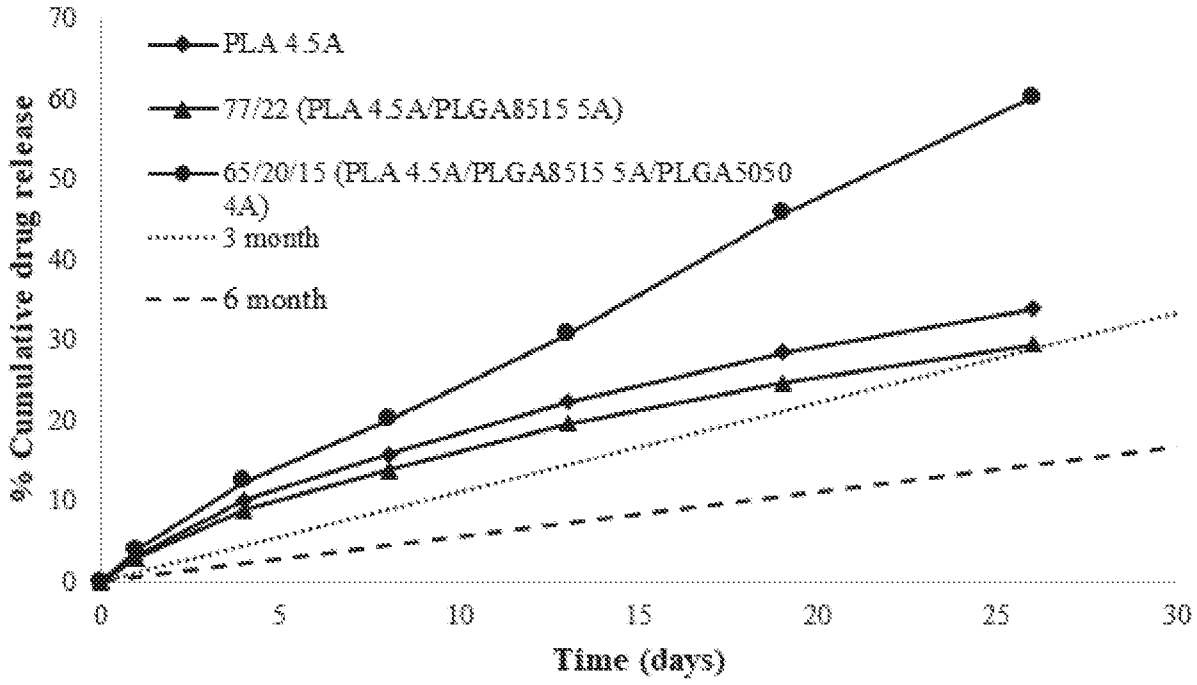

% Cumulative drug release
Time (days)
PLA 4.5A
77/22 (PLA 4.5A/PLGA8515 5A)
65/20/15 (PLA 4.5A/PLGA8515 5A/PLGA5050 4A)
3 month
6 month
0
10
20
30
40
50
60
70
0
5
10
15
20
25
30

FIG. 42

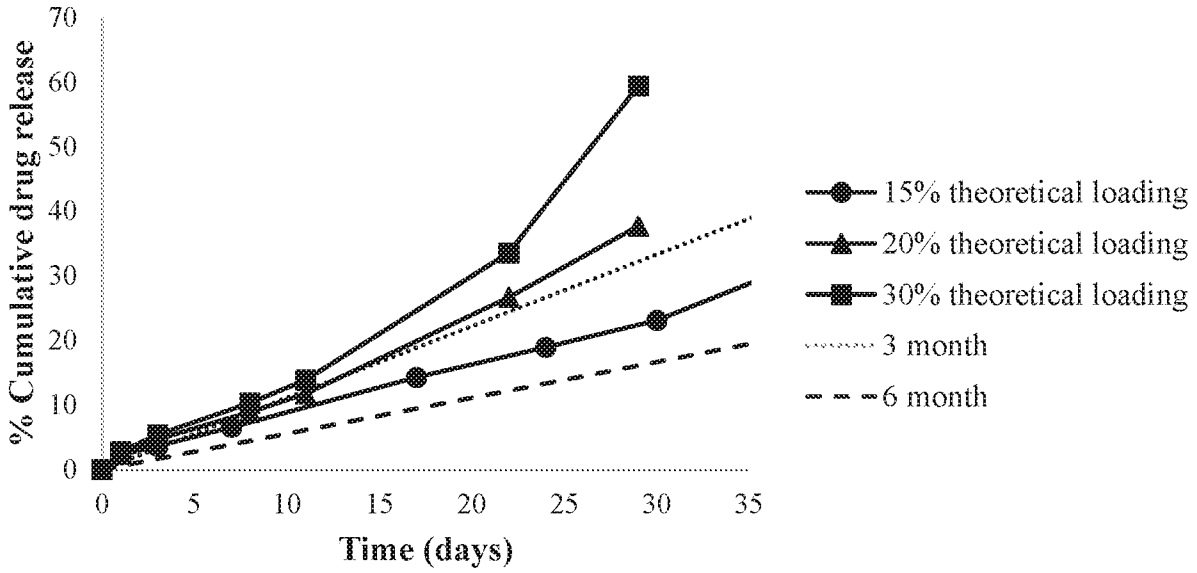

% Cumulative drug release
Time (days)
15% theoretical loading
20% theoretical loading
30% theoretical loading
3 month
6 month
0
10
20
30
40
50
60
70
0
5
10
15
20
25
30
35

FIG. 43

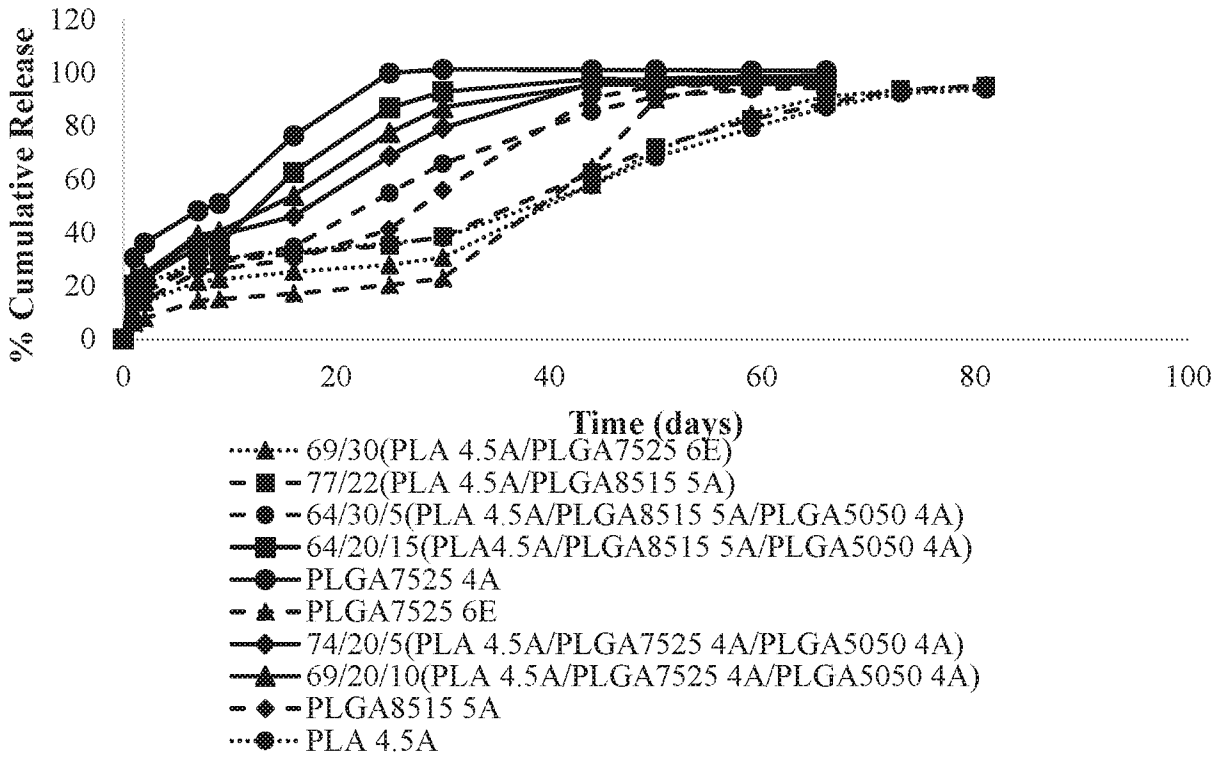

% Cumulative Release
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (days)
69/30(PLA 4.5A/PLGA7525 6E)
77/22(PLA 4.5A/PLGA8515 5A)
64/30/5(PLA 4.5A/PLGA8515 5A/PLGA5050 4A)
64/20/15(PLA4.5A/PLGA8515 5A/PLGA5050 4A)
PLGA7525 4A
PLGA7525 6E
74/20/5(PLA 4.5A/PLGA7525 4A/PLGA5050 4A)
69/20/10(PLA 4.5A/PLGA7525 4A/PLGA5050 4A)
PLGA8515 5A
PLA 4.5A

FIG. 44

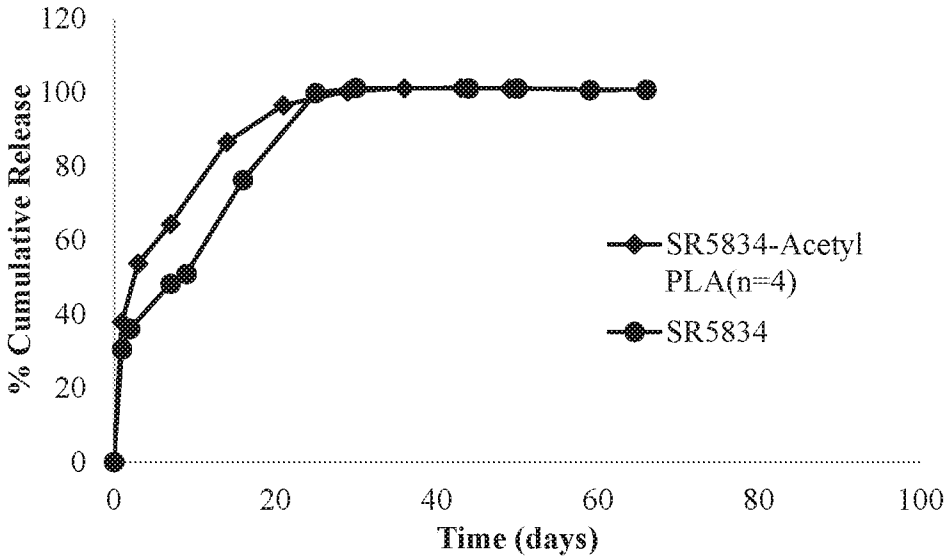

% Cumulative Release
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (days)
SR5834-Acetyl PLA(n=4)
SR5834

FIG. 45

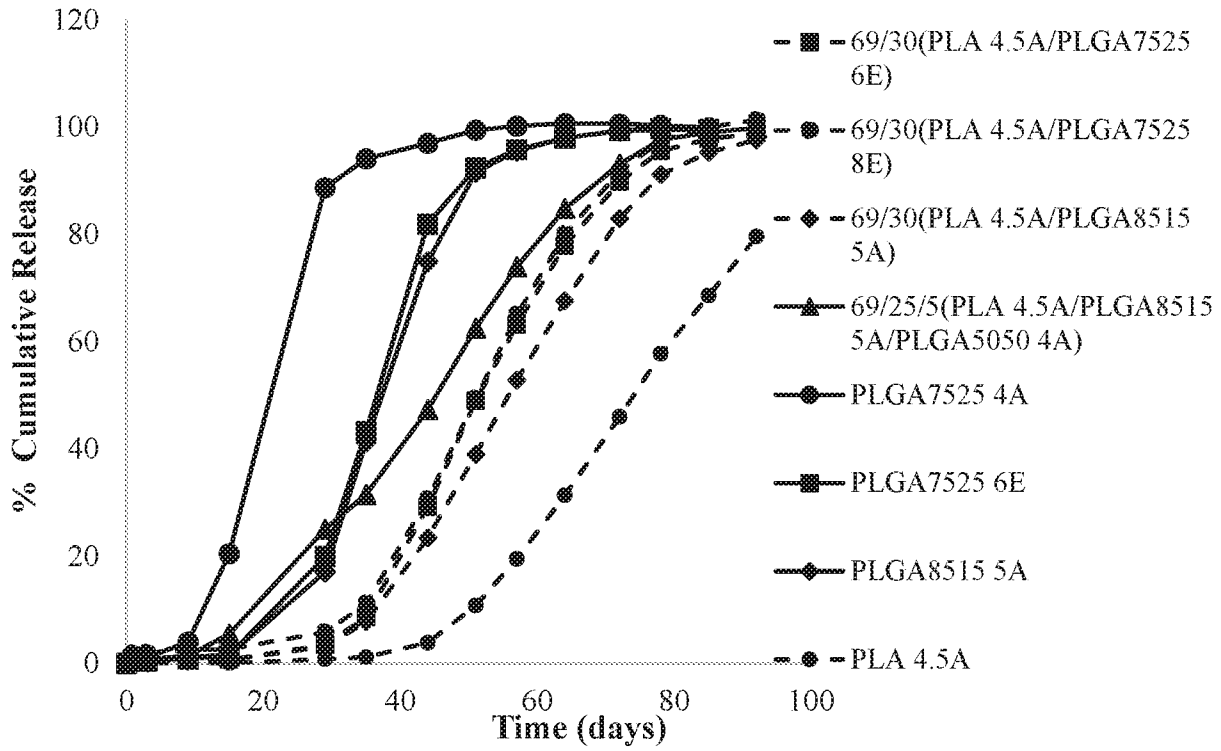

120
100
80
60
40
20
0
% Cumulative Release
0
20
40
60
80
100
Time (days)
69/30(PLA 4.5A/PLGA7525 6E)
69/30(PLA 4.5A/PLGA7525 8E)
69/30(PLA 4.5A/PLGA8515 5A)
69/25/5(PLA 4.5A/PLGA8515 5A/PLGA5050 4A)
PLGA7525 4A
PLGA7525 6E
PLGA8515 5A
PLA 4.5A

FIG. 46

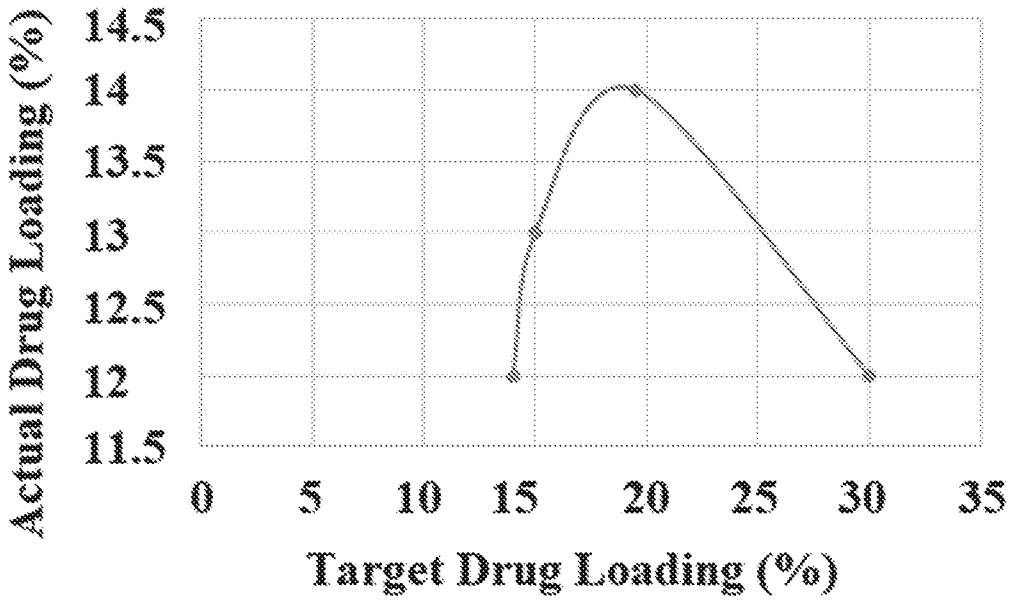

Actual Drug Loading (%)
14.5
14
13.5
13
12.5
12
11.5
0
5
10
15
20
25
30
35
Target Drug Loading (%)

FIG. 47

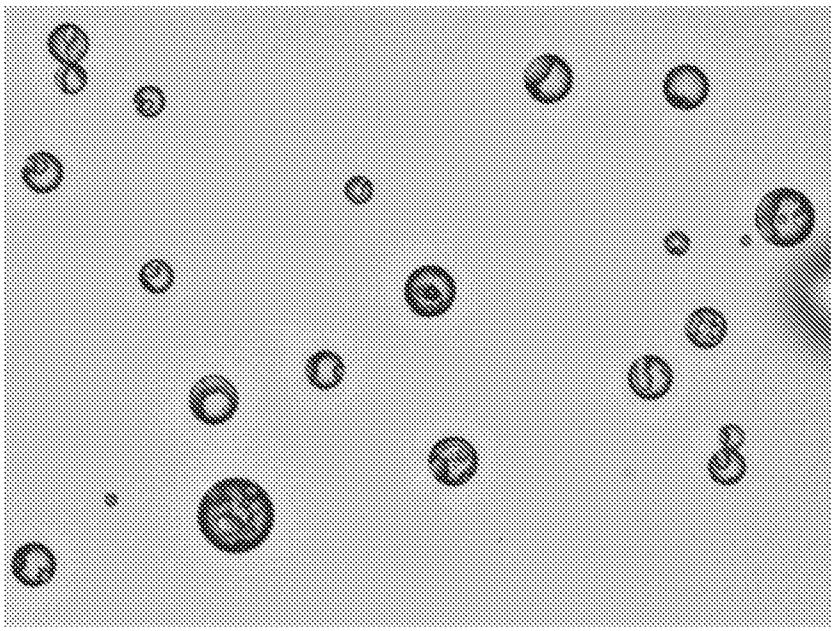


FIG. 48

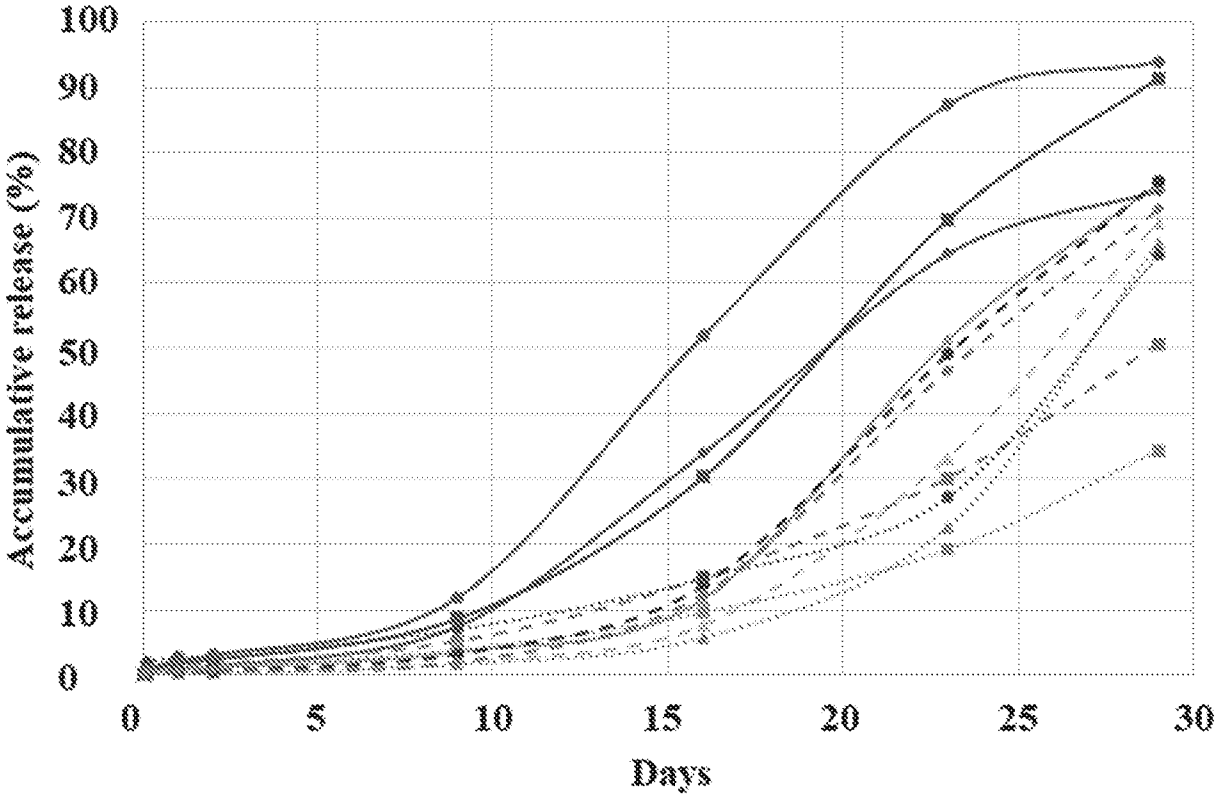
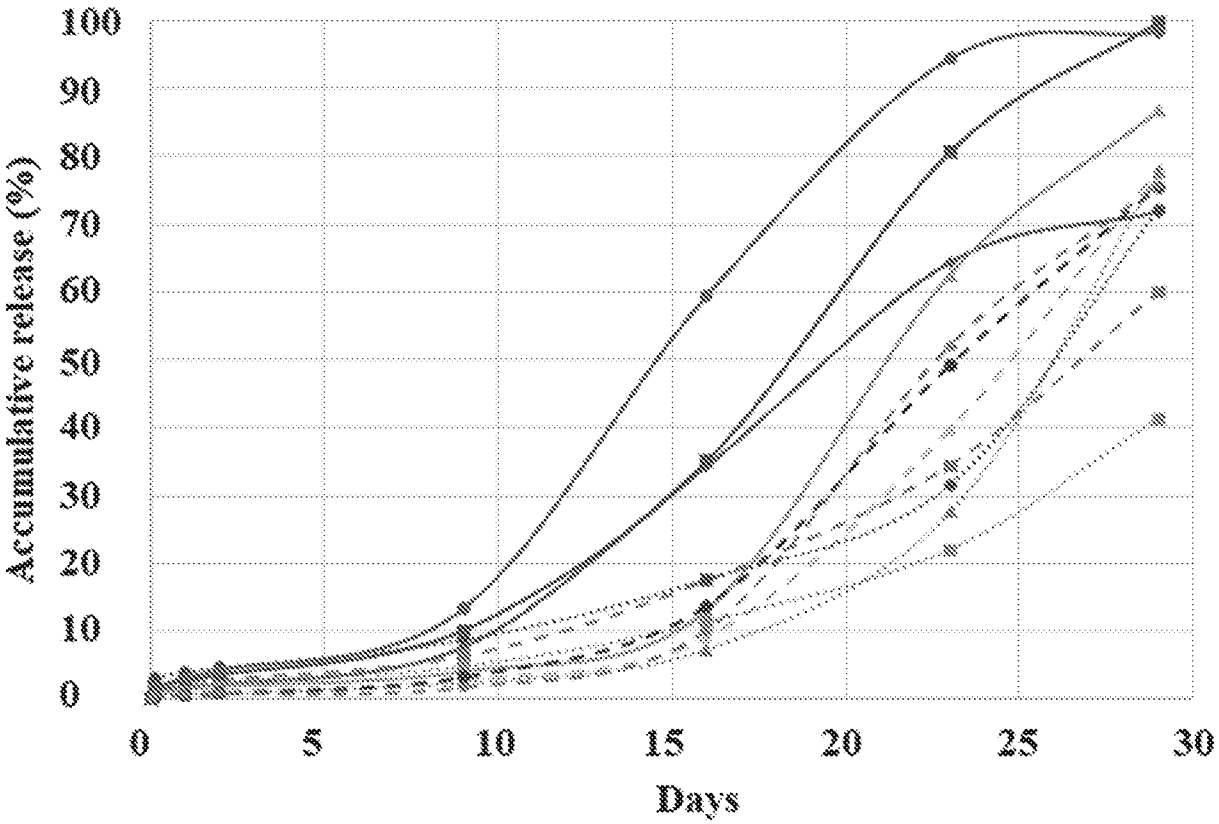

100
90
80
70
60
50
40
30
20
10
0
Accumulative release (%)
0
5
10
15
20
25
30
Days
PLA 4A/PLGA 7525 4A 70:30, 5% PLGA 5050
PLA 4A/PLGA 7525 85:15
PLA 4A/PLGA 7525 4A 85:15, 5% PLGA 5050
PLA 4A/PLGA 7525 6E 70:30, 5% PLGA 5050
PLA 4A/PLGA 7525 8E 70:30, 5% PLGA 5050
PLA 4A/PLGA 8515 5A 70:30
PLA 4A/PLGA 8515 5A 70:30, 5% PLGA 5050
PLA 4A/PLGA 8515 5A 85:15
PLA 4A/PLGA 8515 5A 85:15, 5% PLGA 5050
PLA 4A/PLGA 8515 5A 85:15, 10% PLGA 5050
PLA 4A/PLGA 7525 70:30

FIG. 49A




PLA 4A/PLGA 7525 4A 70:30, 5% PLGA 5050

PLA 4A/PLGA 7525 85:15

PLA 4A/PLGA 7525 4A 85:15, 5% PLGA 5050

PLA 4A/PLGA 7525 6E 70:30, 5% PLGA 5050

PLA 4A/PLGA 7525 8E 70:30, 5% PLGA 5050

PLA 4A/PLGA 8515 5A 70:30

PLA 4A/PLGA 8515 5A 70:30, 5% PLGA 5050

PLA 4A/PLGA 8515 5A 85:15

PLA 4A/PLGA 8515 5A 85:15, 5% PLGA 5050

PLA 4A/PLGA 8515 5A 85:15, 10% PLGA 5050

PLA 4A/PLGA 7525 70:30

FIG. 49B

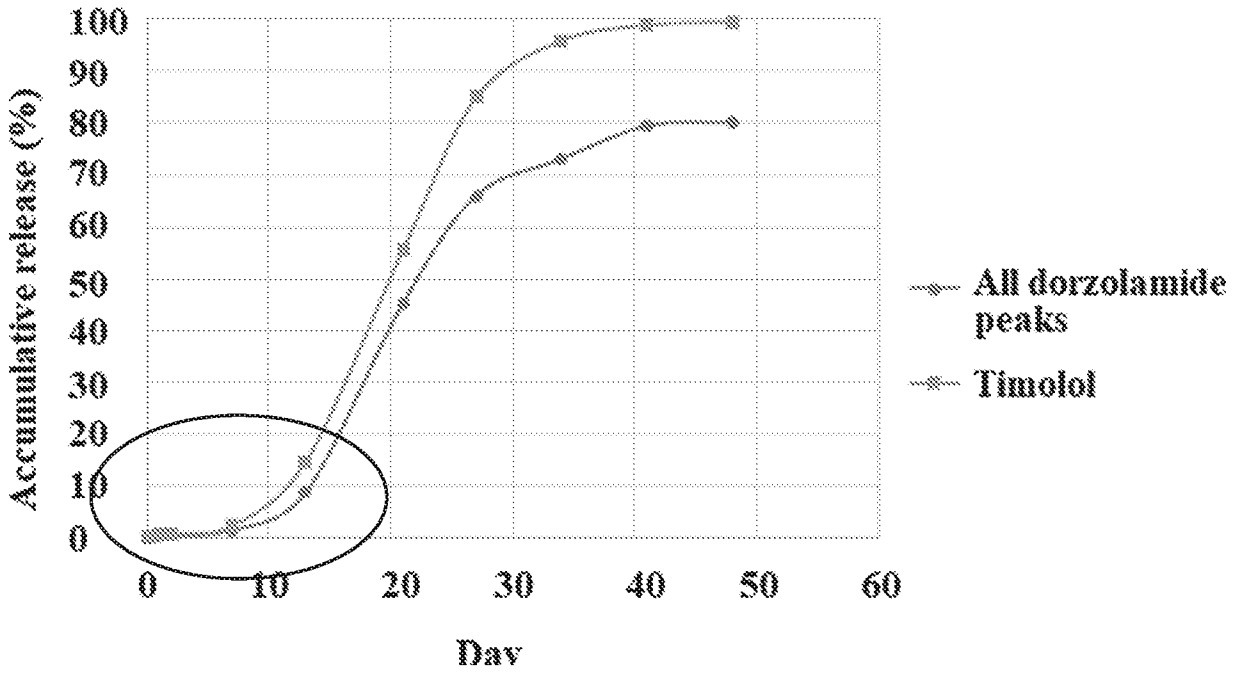

Accumulative release (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
Dav
All dorzolamide peaks
Timolol

FIG. 50

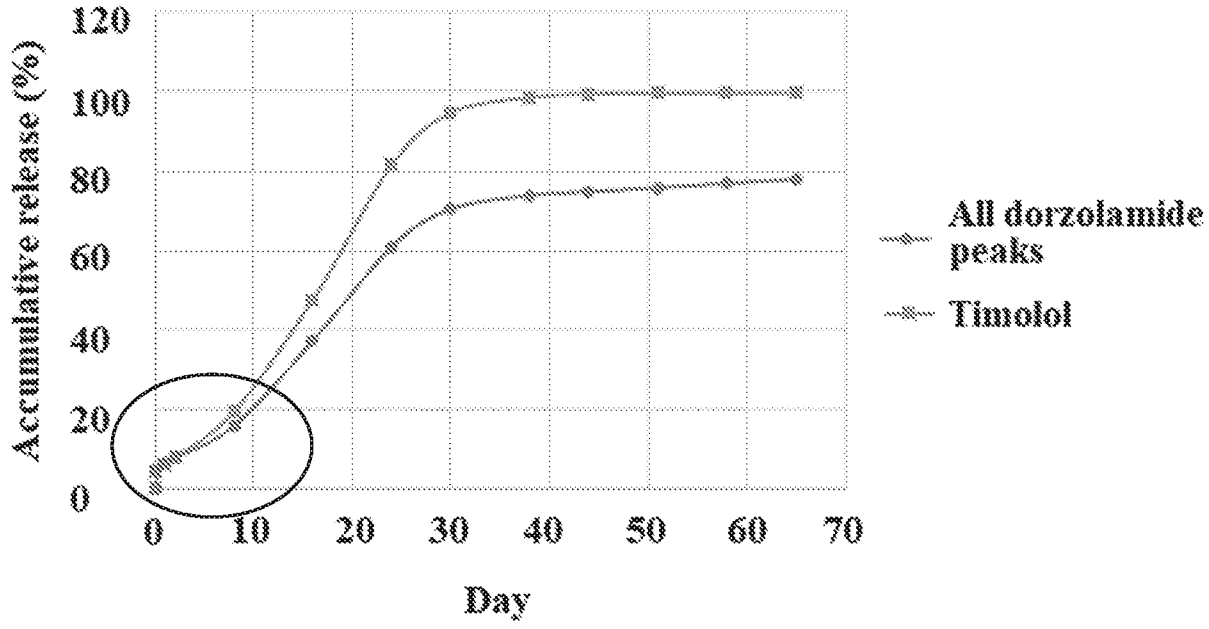

Accumulative release (%)
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
Day
All dorzolamide peaks
Timolol

FIG. 51

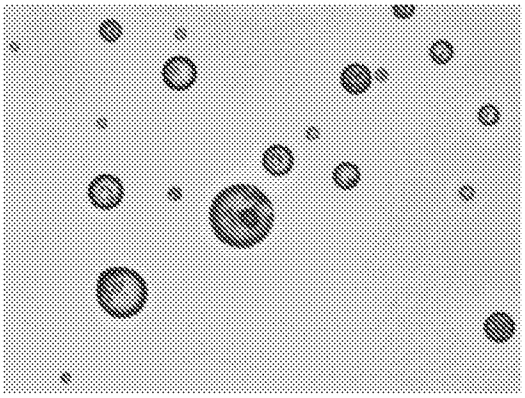


FIG. 52A

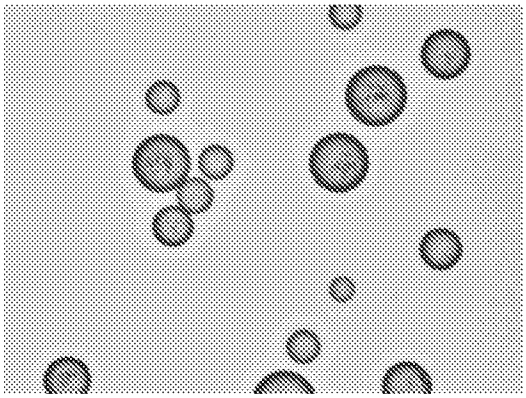


FIG. 52B

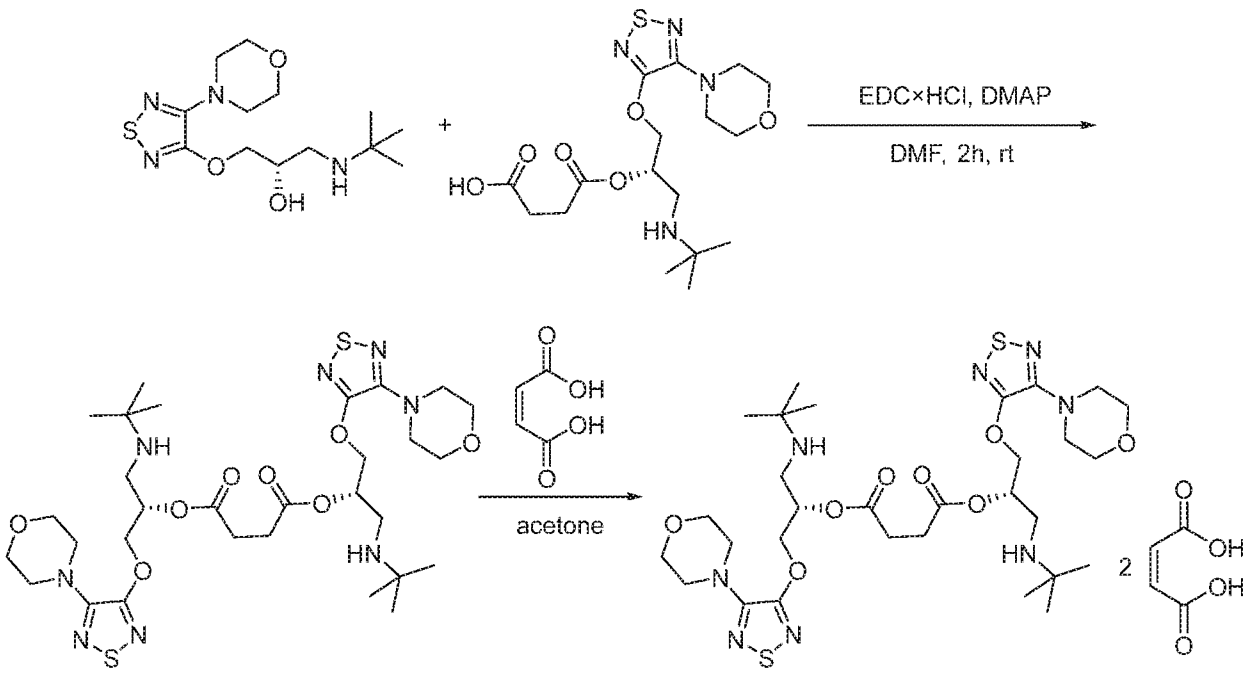



FIG. 53

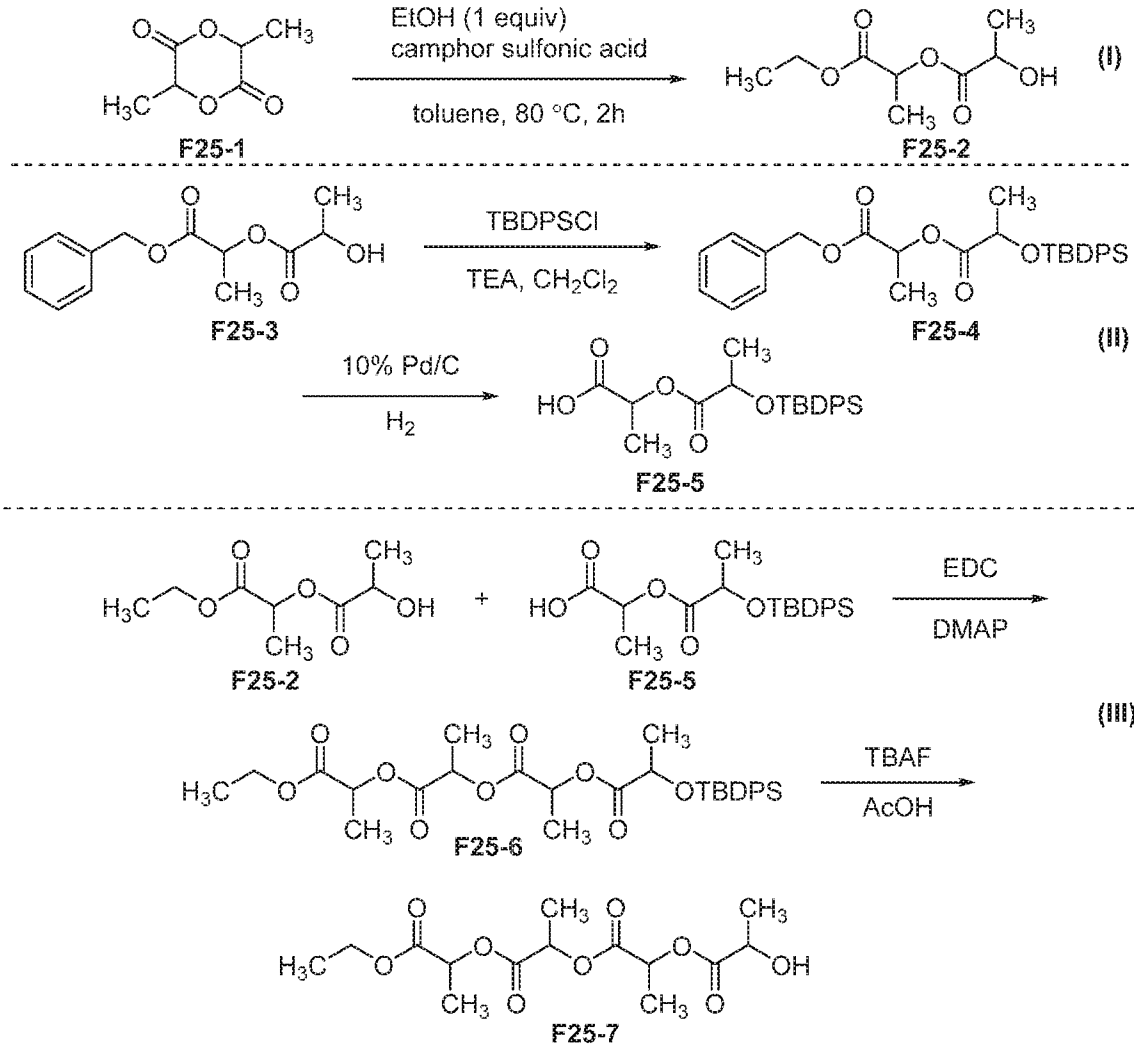

EtOH (1 equiv)
camphor sulfonic acid
toluene, 80 °C, 2h
F25-1
F25-2
(I)
TBDPSCl
TEA, CH2Cl2
F25-3
F25-4
10% Pd/C
H2
F25-5
(II)
EDC
DMAP
F25-2
F25-5
TBAF
AcOH
F25-6
F25-7
(III)

FIG.54

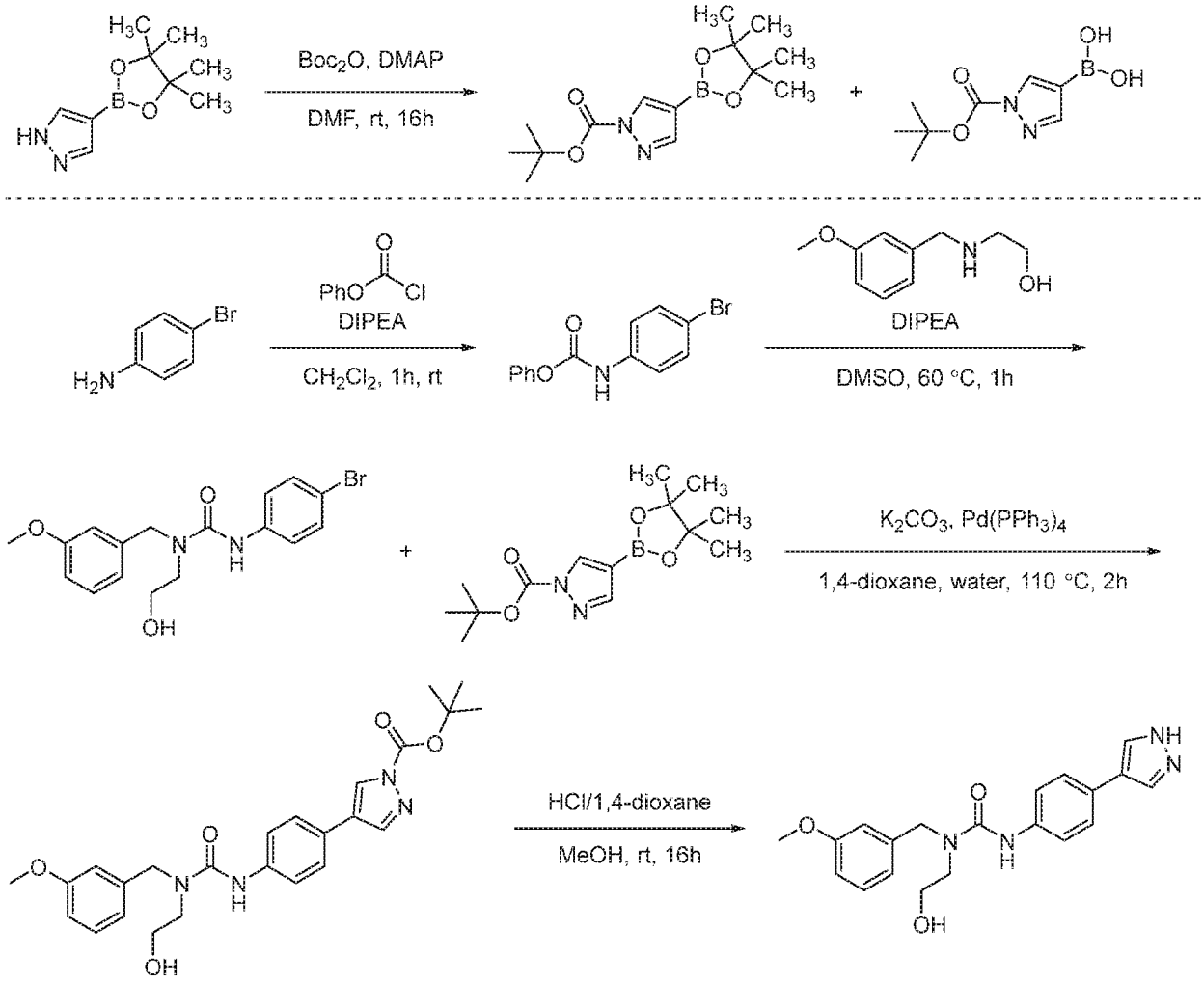

Boc2O, DMAP
DMF, rt, 16h
PhO Cl
DIPEA
CH2Cl2, 1h, rt
DIPEA
DMSO, 60 °C, 1h
K2CO3, Pd(PPh3)4
1,4-dioxane, water, 110 °C, 2h
HCl/1,4-dioxane
MeOH, rt, 16h

FIG. 55

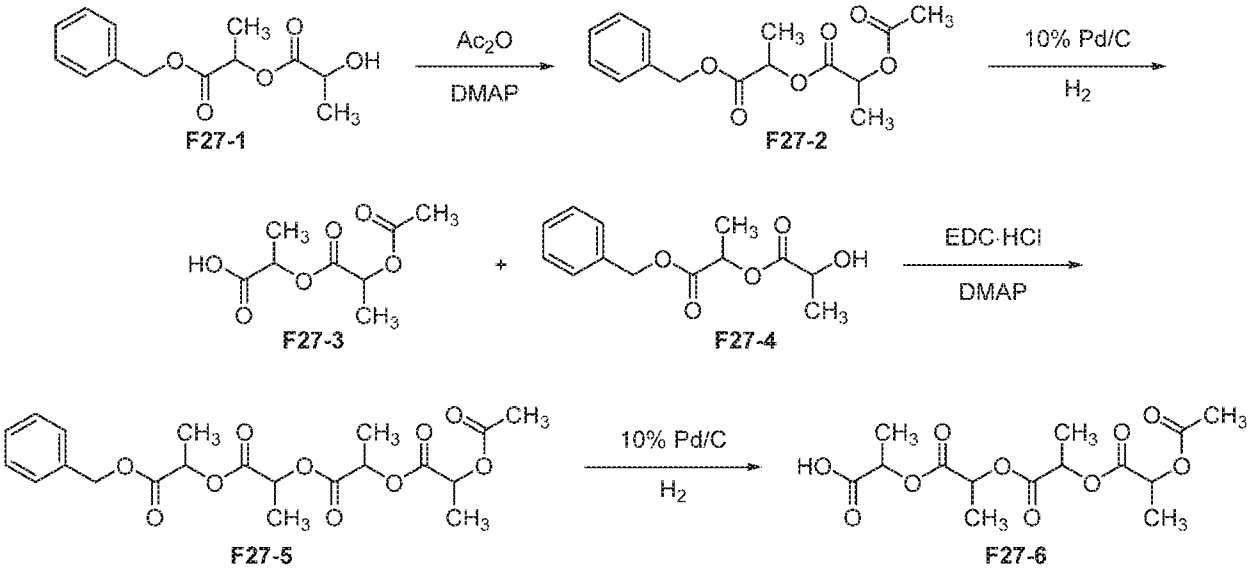

Ac2O
DMAP
10% Pd/C
H2
EDC·HCl
DMAP
10% Pd/C
H2
F27-1
F27-2
F27-3
F27-4
F27-5
F27-6

FIG. 56

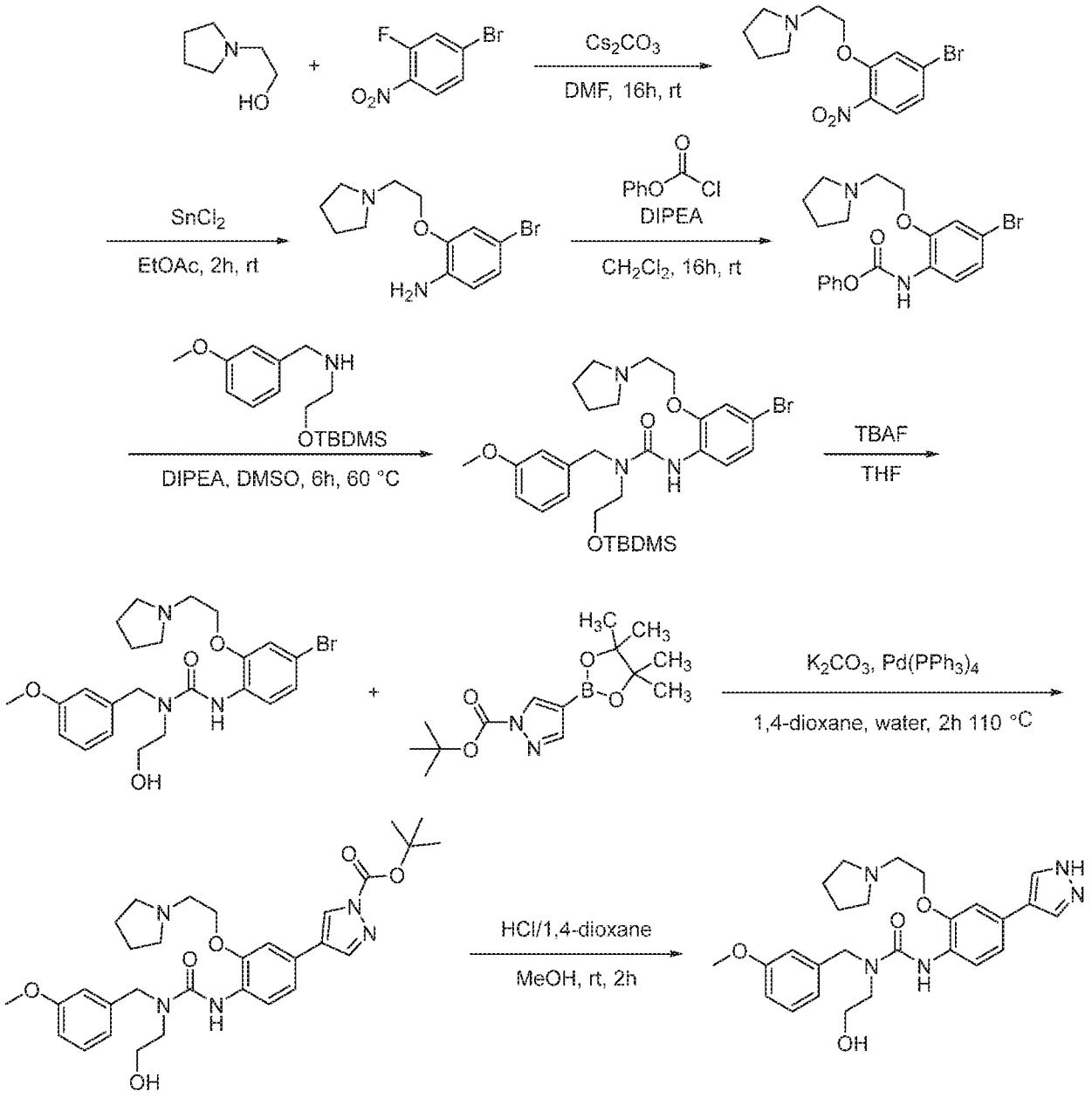

Cs2CO3
DMF, 16h, rt
SnCl2
EtOAc, 2h, rt
DIPEA
CH2Cl2, 16h, rt
OTBDMS
DIPEA, DMSO, 6h, 60 °C
TBAF
THF
K2CO3, Pd(PPh3)4
1,4-dioxane, water, 2h 110 °C
HCl/1,4-dioxane
MeOH, rt, 2h

FIG. 57

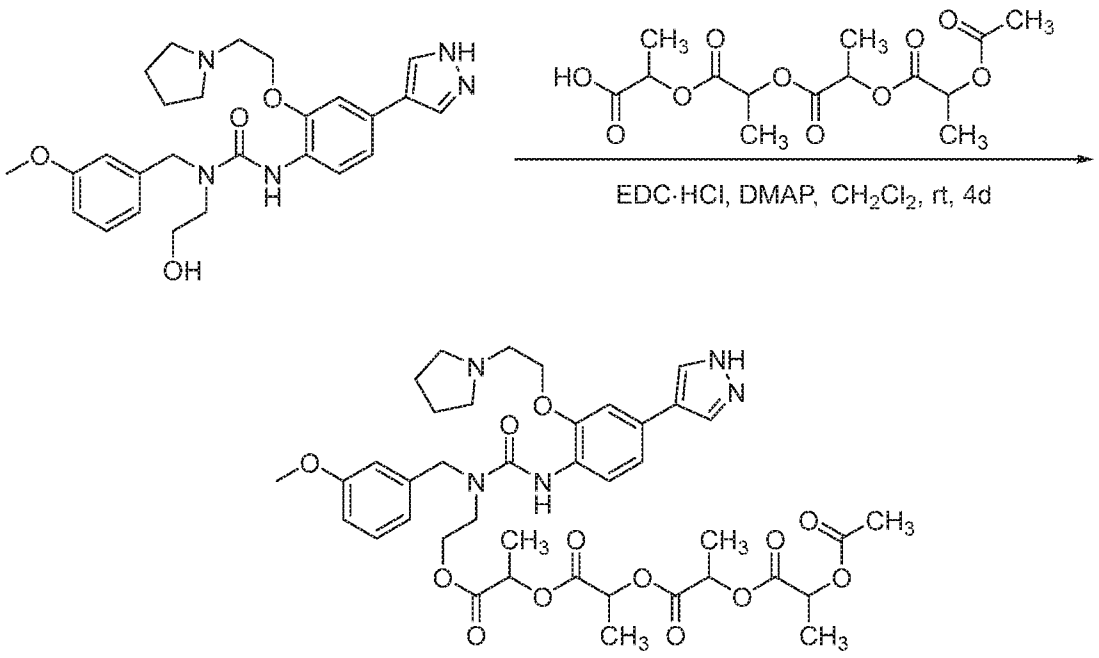



FIG. 58

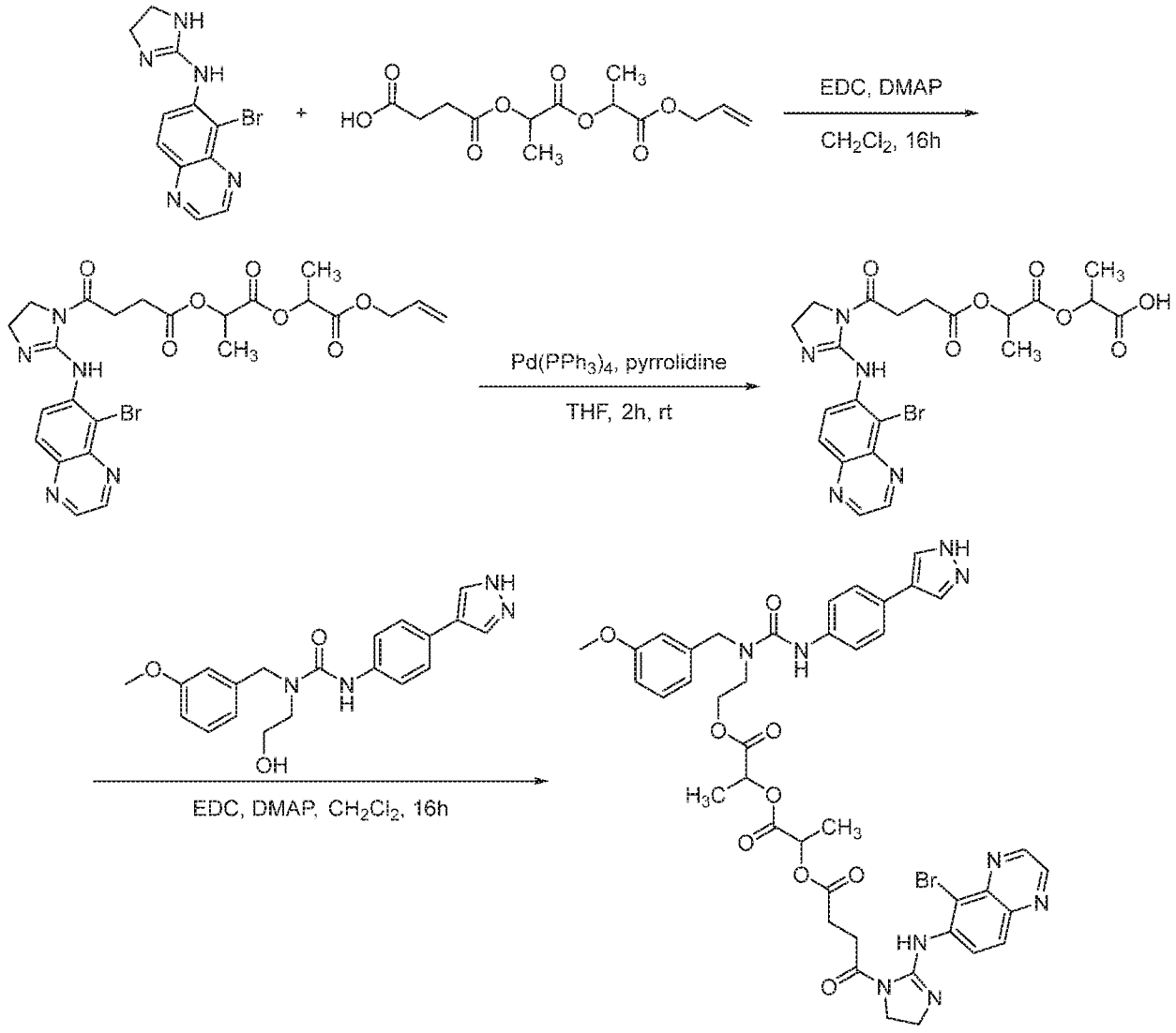

EDC, DMAP
CH2Cl2, 16h
Pd(PPh3)4, pyrrolidine
THF, 2h, rt
EDC, DMAP, CH2Cl2, 16h

FIG. 59

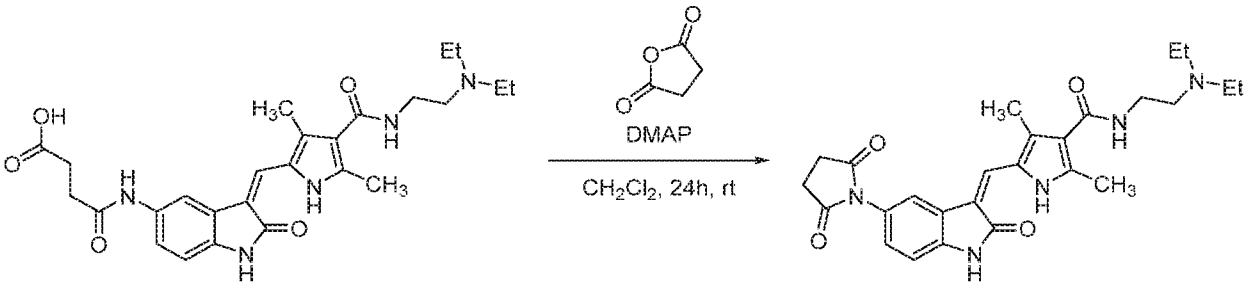

DMAP
$CH_2Cl_2$, 24h, rt

FIG. 60

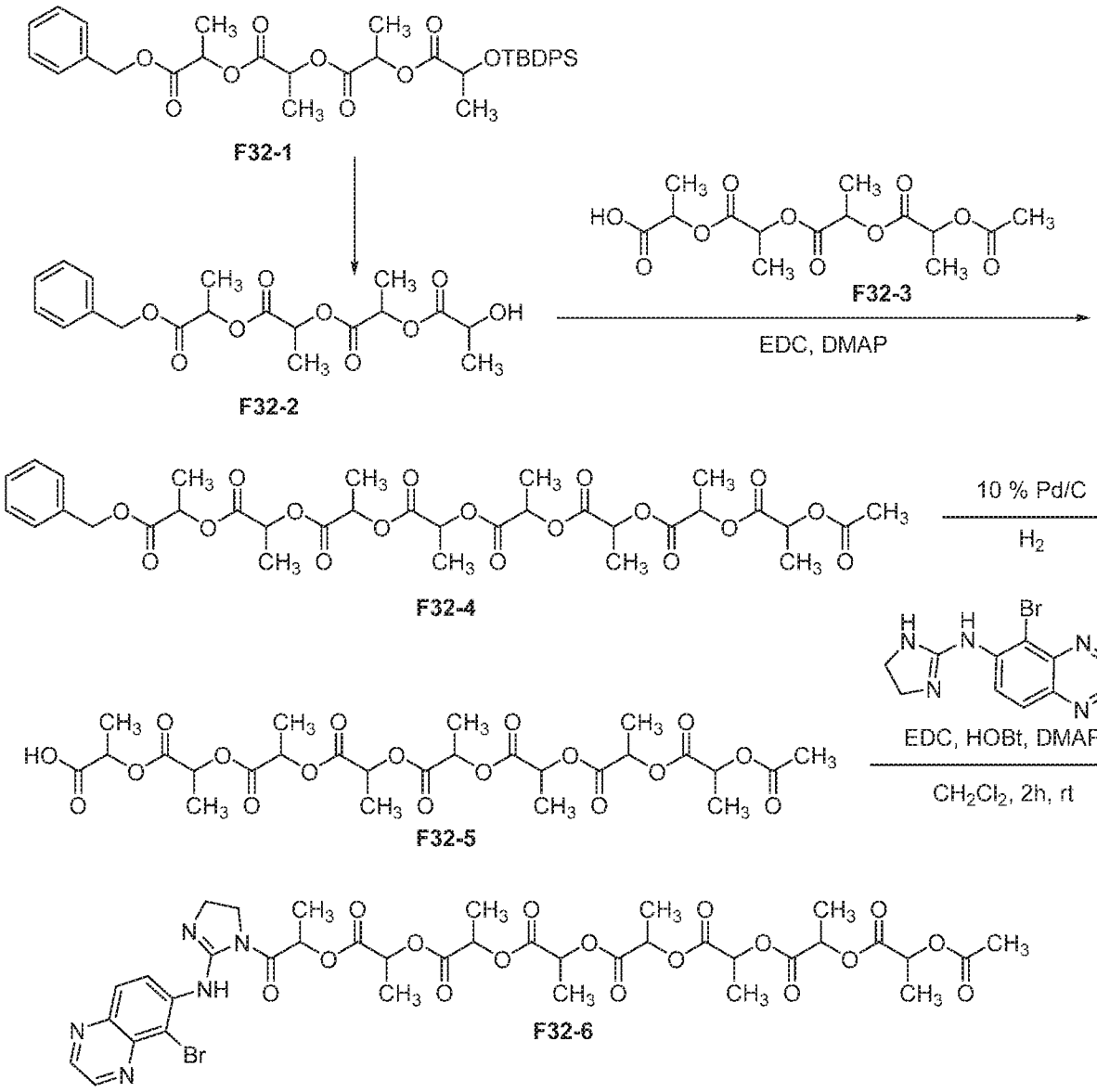

OTBDPS
F32-1
F32-3
EDC, DMAP
F32-2
10 % Pd/C
$H_2$
F32-4
EDC, HOBt, DMAP
$CH_2Cl_2$, 2h, rt
F32-5
F32-6

FIG. 61

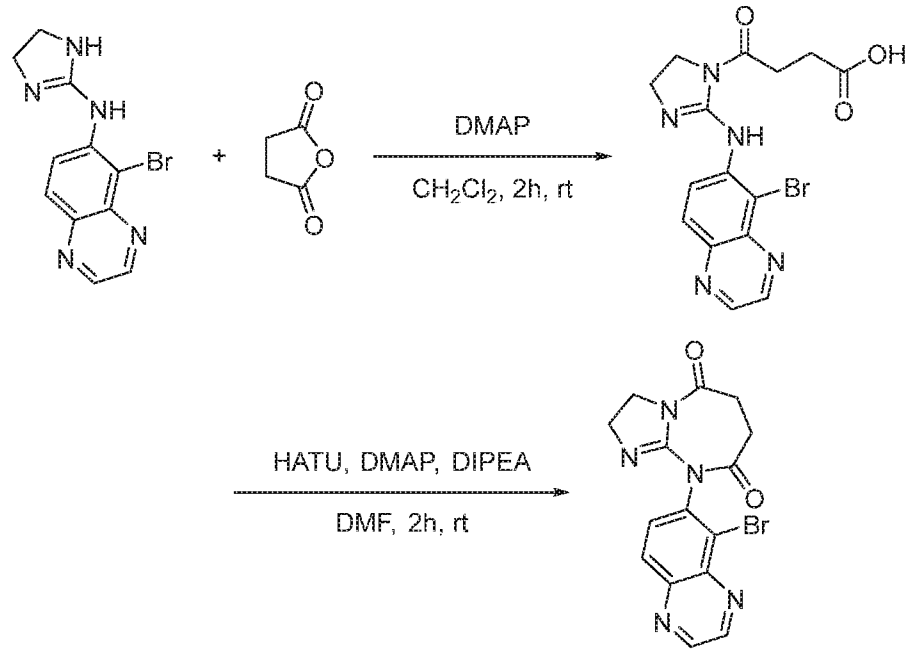

NH
N
NH
Br
N
N
+
O
O
O
DMAP
$CH_2Cl_2$, 2h, rt
O
OH
O
N
N
NH
Br
N
N
HATU, DMAP, DIPEA
DMF, 2h, rt
O
N
N
N
O
Br
N
N

FIG. 62

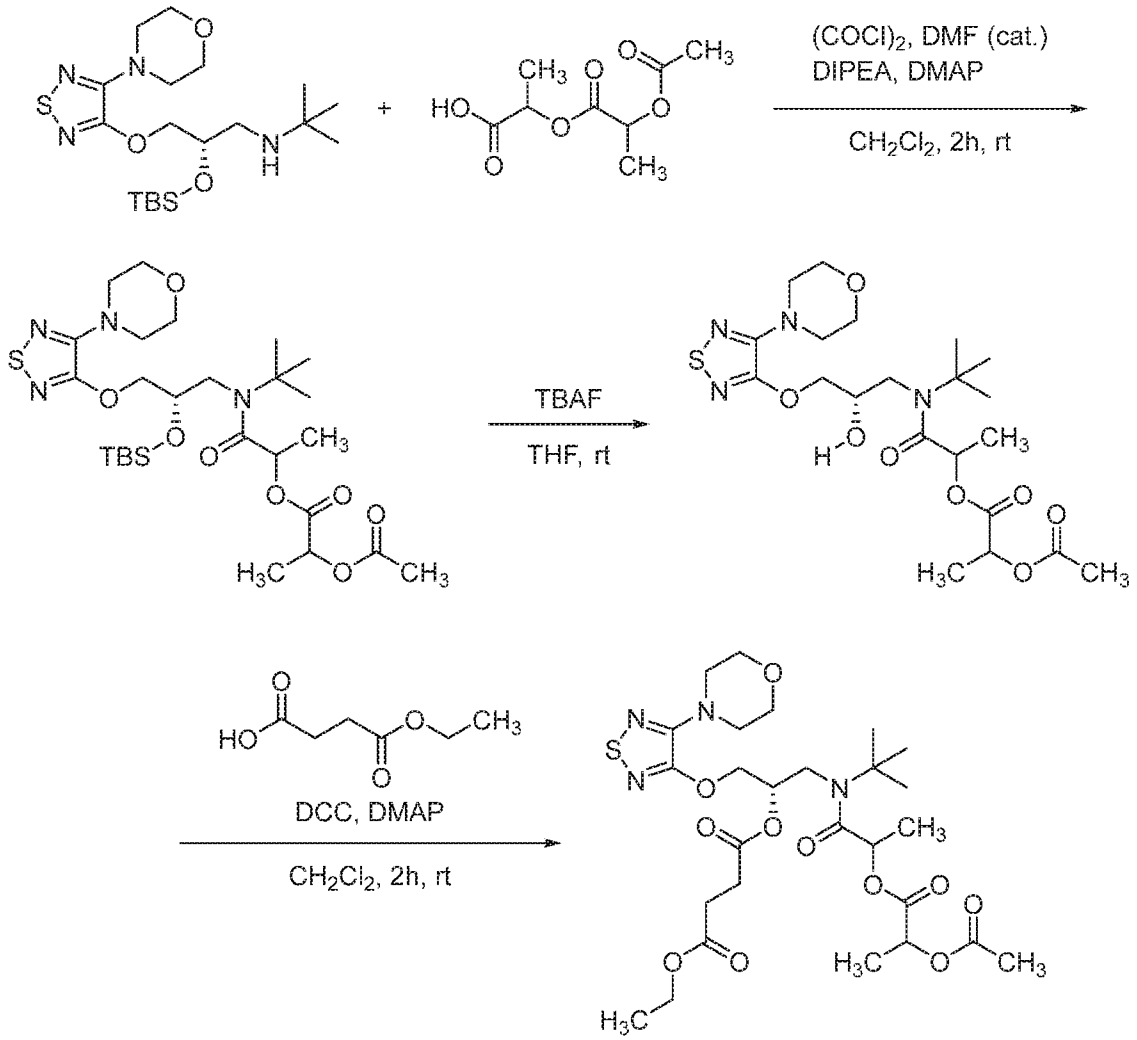

(COCl)2, DMF (cat.)
DIPEA, DMAP
CH2Cl2, 2h, rt
TBAF
THF, rt
DCC, DMAP
CH2Cl2, 2h, rt

FIG. 63

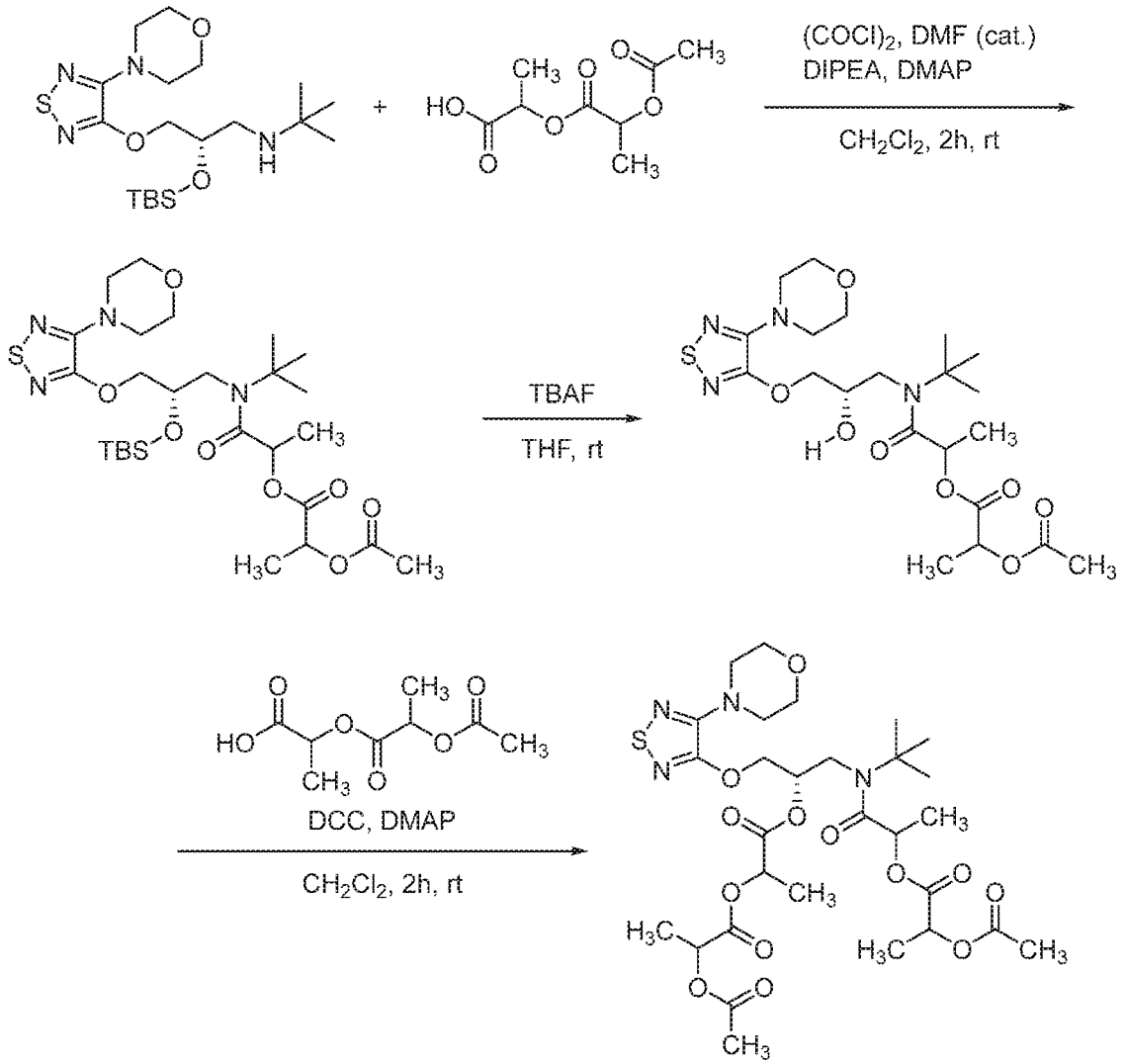

(COCl)2, DMF (cat.)
DIPEA, DMAP
CH2Cl2, 2h, rt
TBAF
THF, rt
DCC, DMAP
CH2Cl2, 2h, rt

FIG. 64

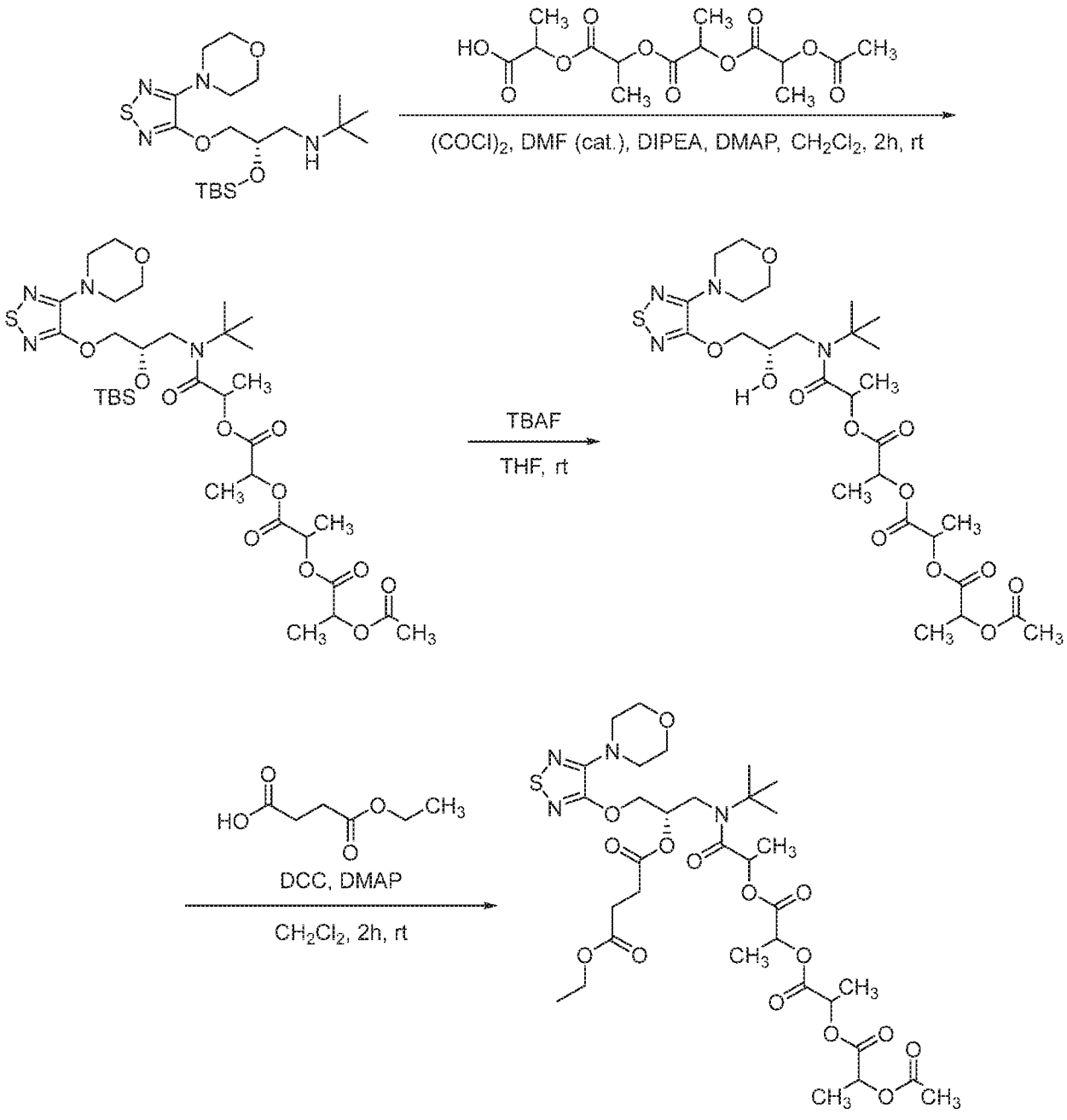

TBS
(COCl)2, DMF (cat.), DIPEA, DMAP, CH2Cl2, 2h, rt
TBAF
THF, rt
DCC, DMAP
CH2Cl2, 2h, rt

FIG. 65

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/24080

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/498; C07D 241/44; A61P 27/02 (2018.01)
CPC - C07D 241/44; A61K 31/498

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X<br>--<br>A | WO 2007/090793 A1 (NICOX S.A.) 16 August 2007 (16.08.2007); pg. 9, pg. 29, ln 20-30 | 1<br>---<br>5/1 |
| A | US 9,161,938 B2 (Huang et al.) 20 October 2015 (20.10.2015); col 7, ln 55-65 | 1, 5/1 |
| A | WO 2009/109501 A2 (CTG Pharma S.r.l.) 11 September 2009 (11.09.2009); pg. 16, ln 1-3 | 1, 5/1 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 16 July 2018 | 30 JUL 2018 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer:<br>Lee W. Young<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

Form PCT/ISA/210 (second sheet) (January 2015)

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/24080

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 20-35
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:
(see supplemental page)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 5/1

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/24080

--continued from Box No. III--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: Claims 1-19 directed to a compound selected from compounds of Formula VII, Formula VIII, Formula XIV, Formula XVI, Formula XVII, Formula XXXI, Formula XXXIII, Formula XXXV, Formula XXXVII, Formula XXXIX, Formula XLI, Formula XLIII, Formula XLV, Formula XLVII, Formula XLIX, IX, Formula IX', Formula XI, Formula XV, Formula XXVI, Formula XXVII, Formula XXVIII, Formula XXIX, Formula XXX, Formula XXX', Formula XXX", Formula XXXII, Formula XXXIV, Formula XXXVI, Formula XXXVIII, Formula XL, Formula XLII, Formula XLIV, Formula XLVI, Formula XLVIII, Formula VIII', Formula IX", Formula XIII, Formula XV', Formula XVII', Formula XVII", Formula XVII"', Formula L, Formula L', Formula LI, Formula LII, Formula LII', Formula LIII. Formula XV", and Formula LIV. The compound will be searched to the extent that it encompasses Formula VII (the first formula of claim 1). It is believed that claims 1 and 5 read on this first named invention, and thus these claims will be searched without fee to the extent that they encompass a compound of Formula VII. Applicant is invited to elect additional compound(s), wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be a compound of Formula (XIV) (i.e., claims 1 and 6-7).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound, which is not required by any other invention of Group I+.

Common technical features:

The compounds of Group I+ contain various heterocyclic compounds having different core structures.

Formulae VII, VIII, VIII', IX, IX', IX", XVII', XVII" and XVII"' share the core structure of a quinoxaline compound. This shared technical feature, however, is not a contribution over the prior art, as being anticipated by Pubchem CID 2435 (Create Date: 25 March 2005) which discloses the quinoxaline compound, brimonidine (pg 3, Fig).

Formulae XIII, XIV, XV', XV", XVI, XVII, XV and LIV share the core structure of timolol. This shared technical feature, however, is not a contribution over the prior art, as being anticipated by Pubchem CID 33624 (Create Date: 24 June 2005), which discloses Timolol (pg 4, Fig).

Formulae XLI, XLIII, XL and XLII share a tetrahydroquinoline core structure. This shared technical feature, however, is not a contribution over the prior art, as being anticipated by Pubchem CID 2583 (Create Date: 25 March 2005), which discloses the tetrahydroquinoline compound, carteolol (pg 3, Fig).

Formulae XXXVII, XXXIX, XXXVI and XXXVIII, share the core structure of a tetrahydronaphthalene compound. This shared technical feature, however, is not a contribution over the prior art, as being anticipated by Pubchem CID 162349 (Create Date: 08 August 2005), which discloses the tetrahydronaphthalene compound dihydrobunolol (pg 3, Fig).

Formulae XXVIII, XXXI, XXXIII, XXX, XXX', XXX", L, L', LII and LII' share the core structure of a aryl-heteroaryl-urea compound. This shared technical feature, however, is not a contribution over the prior art, as being anticipated by Pubchem CID 12805966 (Create Date: 08 February 2007), which discloses an aryl-heteroaryl urea compound (pg 4, Fig).

As said compounds were known in the art at the time of the invention, these cannot be considered special technical features which would, otherwise unify the inventions of Group I+.

Note reg. item 4: Claims 20-35 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are, therefore, not included in the above analysis.