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(54) **Title:** OLIGOMER-CONTAINING APREMILAST MOIETY COMPOUNDS

(57) **Abstract:** The invention relates to (among other things) oligomer-containing apremilast moiety compounds. A compound of the invention, when administered by any of a number of administration routes, exhibits one or more advantages over corresponding compounds lacking the oligomer.



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OLIGOMER-CONTAINING APREMILAST MOIETY COMPOUNDS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Patent Application No. 61/527,218, filed August 25, 2011, and U.S. Provisional Patent Application No. 61/423,971, filed December 16, 2010, the disclosures of each are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] This invention comprises (among other things) chemically modified apremilast moieties that possess certain advantages over apremilast moieties lacking the chemical modification. The chemically modified apremilast moieties described herein relate to and/or have application(s) in (among others) the fields of drug discovery, pharmacotherapy, physiology, organic chemistry and polymer chemistry.

BACKGROUND OF THE INVENTION

[0003] Tumor necrosis factor alpha (TNF- α) is a cytokine that is released primarily by mononuclear phagocytes in response to immunostimulators. Excess TNF- α production has been implicated in cancers, heart disease and autoimmune diseases (such as inflammatory diseases and allergies). Thus, pharmaceutical compounds that can block the activity or inhibit the production of TNF- α may be beneficial therapeutics.

[0004] Phosphodiesterase-4 (PDE4) is one member of the eleven different phosphodiesterase families that control the localization, duration, and amplitude of cyclic nucleotide signaling within a cell. Currently available compounds that inhibit PDE4 can inhibit this signaling and have been shown to inhibit the release of TNF- α and other pro-inflammatory signals. Unfortunately, inhibition of PDE4 can also lead to deleterious cardiovascular effects, including, for example, arteritis/vasculitis. As a consequence, it is believed that the currently available PDE4 inhibitors lack selectivity in pharmacologic action, thereby limiting their use clinically.

[0005] In addition, the pharmacokinetic profiles of existing PDE4 inhibitors may not have optimum profiles.

[0006] Therefore, pharmacotherapy PDE4 inhibitors could be improved if compounds that retained some degree of the pharmacology of these drugs, yet possessed different chemical structures that could result in greater target selectivity and/or different pharmacokinetic profiles were available. As a consequence, there is an unmet need for developing novel PDE4 inhibitors.

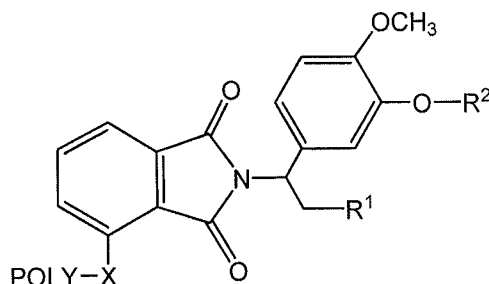
[0007] The present invention seeks to address these and other needs in the art.

SUMMARY OF THE INVENTION

[0008] In one or more embodiments of the invention, a compound is provided, the compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer.

[0009] The "apremilast moiety residue" is a compound having a structure of a therapeutically active apremilast moiety that is altered by the presence of one or more bonds, which bonds serve to attach (either directly or indirectly) one or more water-soluble, non-peptidic oligomers.

[0010] Exemplary compounds of the invention include those having the following structure:



(Formula I-Ca)

wherein:

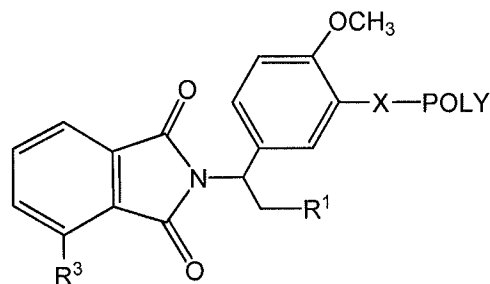
R¹ is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R² is an organic radical (e.g., ethyl, cyclopentyl, and CH₂-cyclopropyl);

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer,
and pharmaceutically acceptable salts thereof.

[0011] Further exemplary compounds of the invention include those having the following structure:



(Formula I-Cb)

wherein:

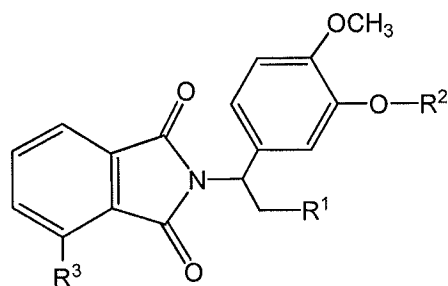
R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical (e.g., methyl);

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer, and pharmaceutically acceptable salts thereof.

[0012] In this regard, any apremilast moiety having pharmacological activity (e.g., PDE4 inhibition) can be used as the apremilast moiety from which the apremilast moiety residue is obtained. Exemplary apremilast moieties have a structure encompassed by Formula I:



(Formula I)

wherein:

R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^2 is an organic radical (e.g., ethyl, cyclopentyl, and CH₂-cyclopropyl); and

R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical (e.g., methyl).

[0013] Exemplary apremilast moieties for use in the current invention are selected from the group consisting of apremilast and 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide.

[0014] In one or more embodiments of the invention, a composition is provided, the composition comprising a compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer, and optionally, a pharmaceutically acceptable excipient.

[0015] In one or more embodiments of the invention, a dosage form is provided, the dosage form comprising a compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer, wherein the compound is present in a dosage form.

[0016] In one or more embodiments of the invention, a method is provided, the method comprising covalently attaching a water-soluble, non-peptidic oligomer to an apremilast moiety.

[0017] In one or more embodiments of the invention, a method is provided, the method comprising administering a compound to a mammal in need thereof, the compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer.

[0018] Additional embodiments of the present conjugates, compositions, methods, and the like will be apparent from the following description, examples, and claims. As can be appreciated from the foregoing and following description, each and every feature described herein, and each and every combination of two or more of such features, is included within the scope of the present disclosure provided that the features included in such a combination are not mutually inconsistent. In addition, any feature or combination of features may be specifically excluded from any embodiment of the present invention. Additional aspects and advantages of the present invention are set forth in the following description and claims.

BRIEF SUMMARY OF THE DRAWINGS

[0019] **FIG. 1** is a plot showing the *in vivo* pharmacokinetic profile of apremilast and mPEG₃₋₉-carbamate-apremilast compounds following intravenous administration, as further described in Example 5.

[0020] FIG. 2 is a plot showing the *in vitro* anti-inflammatory activities of apremilast and mPEG₃₋₉-carbamate-apremilast compounds, as further described in Example 6.

DETAILED DESCRIPTION OF THE INVENTION

[0021] As used in this specification, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0022] In describing and claiming the present invention, the following terminology will be used in accordance with the definitions described below.

[0023] "Water soluble, non-peptidic oligomer" indicates an oligomer that is at least 35% (by weight) soluble, preferably greater than 70% (by weight), and more preferably greater than 95% (by weight) soluble, in water at room temperature. Typically, an unfiltered aqueous preparation of a "water-soluble" oligomer transmits at least 75%, more preferably at least 95%, of the amount of light transmitted by the same solution after filtering. It is most preferred, however, that the water-soluble oligomer is at least 95% (by weight) soluble in water or completely soluble in water. With respect to being "non-peptidic," an oligomer is non-peptidic when it has less than 35% (by weight) of amino acid residues.

[0024] The terms "monomer," "monomeric subunit" and "monomeric unit" are used interchangeably herein and refer to one of the basic structural units of a polymer or oligomer. In the case of a homo-oligomer, a single repeating structural unit forms the oligomer. In the case of a co-oligomer, two or more structural units are repeated -- either in a pattern or randomly -- to form the oligomer. Preferred oligomers used in connection with present the invention are homo-oligomers. The water-soluble, non-peptidic oligomer comprises one or more monomers serially attached to form a chain of monomers. The oligomer can be formed from a single monomer type (i.e., is homo-oligomeric) or two or three monomer types (i.e., is co-oligomeric).

[0025] An "oligomer" is a molecule possessing from about 1 to about 30 monomers. Specific oligomers for use in the invention include those having a variety of geometries such as linear, branched, or forked, to be described in greater detail below.

[0026] "PEG" or "polyethylene glycol," as used herein, is meant to encompass any water-soluble poly(ethylene oxide). Unless otherwise indicated, a "PEG oligomer" or an oligoethylene glycol is one in which substantially all (preferably all) monomeric subunits are

ethylene oxide subunits, though, the oligomer may contain distinct end capping moieties or functional groups, e.g., for conjugation. PEG oligomers for use in the present invention will comprise one of the two following structures: $-(\text{CH}_2\text{CH}_2\text{O})_n-$ or $-(\text{CH}_2\text{CH}_2\text{O})_{n-1}\text{CH}_2\text{CH}_2-$, depending upon whether or not the terminal oxygen(s) has been displaced, e.g., during a synthetic transformation. As stated above, for the PEG oligomers, the variable (n) ranges from about 1 to 30, and the terminal groups and architecture of the overall PEG can vary. When PEG further comprises a functional group for linking to, e.g., a small molecule drug, the functional group when covalently attached to a PEG oligomer does not result in formation of (i) an oxygen-oxygen bond ($-\text{O}-\text{O}-$, a peroxide linkage), or (ii) a nitrogen-oxygen bond ($\text{N}-\text{O}$, $\text{O}-\text{N}$).

[0027] The terms "end-capped" or "terminally capped" are interchangeably used herein to refer to a terminal or endpoint of a polymer having an end-capping moiety. Typically, although not necessarily, the end-capping moiety comprises a hydroxy or C_{1-20} alkoxy group. Thus, examples of end-capping moieties include alkoxy (e.g., methoxy, ethoxy and benzyloxy), as well as aryl, heteroaryl, cyclo, heterocyclo, and the like. In addition, saturated, unsaturated, substituted and unsubstituted forms of each of the foregoing are envisioned. Moreover, the end-capping group can also be a silane. The end-capping group can also advantageously comprise a detectable label. When the polymer has an end-capping group comprising a detectable label, the amount or location of the polymer and/or the moiety (e.g., active agent) of interest to which the polymer is coupled, can be determined by using a suitable detector. Such labels include, without limitation, fluorescers, chemiluminescers, moieties used in enzyme labeling, colorimetric moieties (e.g., dyes), metal ions, radioactive moieties, and the like. Suitable detectors include photometers, films, spectrometers, and the like. In addition, the end-capping group may contain a targeting moiety.

[0028] The term "targeting moiety" is used herein to refer to a molecular structure that helps the conjugates of the invention to localize to a targeting area, e.g., help enter a cell, or bind a receptor. Preferably, the targeting moiety comprises a vitamin, antibody, antigen, receptor, DNA, RNA, sialyl Lewis X antigen, hyaluronic acid, sugars, cell-specific lectins, steroid or steroid derivative, RGD peptide, ligand for a cell surface receptor, serum component, or combinatorial molecule directed against various intra- or extracellular receptors. The targeting moiety may also comprise a lipid or a phospholipid. Exemplary phospholipids include, without limitation, phosphatidylcholines, phosphatidylserine,

phosphatidylinositol, phosphatidylglycerol, and phosphatidylethanolamine. These lipids may be in the form of micelles or liposomes and the like. The targeting moiety may further comprise a detectable label or alternately a detectable label may serve as a targeting moiety.

[0029] "Branched," in reference to the geometry or overall structure of an oligomer, refers to an oligomer having two or more polymer "arms" extending from a branch point.

[0030] "Forked," in reference to the geometry or overall structure of an oligomer, refers to an oligomer having two or more functional groups (typically through one or more atoms) extending from a branch point.

[0031] A "branch point" refers to a bifurcation point comprising one or more atoms at which an oligomer branches or forks from a linear structure into one or more additional arms.

[0032] The term "reactive" or "activated" refers to a functional group that reacts readily or at a practical rate under conventional conditions of organic synthesis. This is in contrast to those groups that either do not react or require strong catalysts or impractical reaction conditions in order to react (i.e., a "nonreactive" or "inert" group).

[0033] "Not readily reactive," with reference to a functional group present on a molecule in a reaction mixture, indicates that the group remains largely intact under conditions that are effective to produce a desired reaction in the reaction mixture.

[0034] A "protecting group" is a moiety that prevents or blocks reaction of a particular chemically reactive functional group in a molecule under certain reaction conditions. The protecting group may vary depending upon the type of chemically reactive group being protected as well as the reaction conditions to be employed and the presence of additional reactive or protecting groups in the molecule. Functional groups which may be protected include, by way of example, carboxylic acid groups, amino groups, hydroxyl groups, thiol groups, carbonyl groups and the like. Representative protecting groups for carboxylic acids include esters (such as a *p*-methoxybenzyl ester), amides and hydrazides; for amino groups, carbamates (such as *tert*-butoxycarbonyl) and amides; for hydroxyl groups, ethers and esters; for thiol groups, thioethers and thioesters; for carbonyl groups, acetals and ketals; and the like. Such protecting groups are well-known to those skilled in the art and are described, for example, in T.W. Greene and G.M. Wuts, *Protecting Groups in Organic Synthesis*, Third Edition, Wiley, New York, 1999, and references cited therein.

[0035] A functional group in "protected form" refers to a functional group bearing a protecting group. As used herein, the term "functional group" or any synonym thereof encompasses protected forms thereof.

[0036] A "physiologically cleavable" or "hydrolyzable" or "degradable" bond is a relatively labile bond that reacts with water (i.e., is hydrolyzed) under physiological conditions. The tendency of a bond to hydrolyze in water may depend not only on the general type of linkage connecting two central atoms but also on the substituents attached to these central atoms. Appropriate hydrolytically unstable or weak linkages include but are not limited to carboxylate ester, phosphate ester, anhydrides, acetals, ketals, acyloxyalkyl ether, imines, orthoesters, peptides, oligonucleotides, thioesters, and carbonates.

[0037] An "enzymatically degradable linkage" means a linkage that is subject to degradation by one or more enzymes.

[0038] A "stable" linkage or bond refers to a chemical bond that is substantially stable in water, that is to say, does not undergo hydrolysis under physiological conditions to any appreciable extent over an extended period of time. Examples of hydrolytically stable linkages include but are not limited to the following: carbon-carbon bonds (e.g., in aliphatic chains), ethers, amides, urethanes, amines, and the like. Generally, a stable linkage is one that exhibits a rate of hydrolysis of less than about 1-2% per day under physiological conditions. Hydrolysis rates of representative chemical bonds can be found in most standard chemistry textbooks.

[0039] "Substantially" or "essentially" means nearly totally or completely, for instance, 95% or greater, more preferably 97% or greater, still more preferably 98% or greater, even more preferably 99% or greater, yet still more preferably 99.9% or greater, with 99.99% or greater being most preferred of some given quantity.

[0040] "Monodisperse" refers to an oligomer composition wherein substantially all of the oligomers in the composition have a well-defined, single molecular weight and defined number of monomers, as determined by chromatography or mass spectrometry. Monodisperse oligomer compositions are in one sense pure, that is, substantially having a single and definable number (as a whole number) of monomers rather than a large distribution. A monodisperse oligomer composition possesses a MW/Mn value of 1.0005 or less, and more preferably, a MW/Mn value of 1.0000. By extension, a composition comprised of monodisperse conjugates means that substantially all oligomers of all

conjugates in the composition have a single and definable number (as a whole number) of monomers rather than a large distribution and would possess a MW/Mn value of 1.0005, and more preferably, a MW/Mn value of 1.0000 if the oligomer were not attached to the therapeutic moiety. A composition comprised of monodisperse conjugates may, however, include one or more nonconjugate substances such as solvents, reagents, excipients, and so forth.

[0041] "Bimodal," in reference to an oligomer composition, refers to an oligomer composition wherein substantially all oligomers in the composition have one of two definable and different numbers (as whole numbers) of monomers rather than a large distribution, and whose distribution of molecular weights, when plotted as a number fraction versus molecular weight, appears as two separate identifiable peaks. Preferably, for a bimodal oligomer composition as described herein, each peak is generally symmetric about its mean, although the size of the two peaks may differ. Ideally, the polydispersity index of each peak in the bimodal distribution, Mw/Mn, is 1.01 or less, more preferably 1.001 or less, and even more preferably 1.0005 or less, and most preferably a MW/Mn value of 1.0000. By extension, a composition comprised of bimodal conjugates means that substantially all oligomers of all conjugates in the composition have one of two definable and different numbers (as whole numbers) of monomers rather than a large distribution and would possess a MW/Mn value of 1.01 or less, more preferably 1.001 or less and even more preferably 1.0005 or less, and most preferably a MW/Mn value of 1.0000 if the oligomer were not attached to the therapeutic moiety. A composition comprised of bimodal conjugates may, however, include one or more nonconjugate substances such as solvents, reagents, excipients, and so forth.

[0042] An "apremilast moiety" is broadly used herein to refer to compound having a molecular weight of less than about 1000 Daltons (which is understood herein as a "small molecule drug"), some degree of pharmacological activity (e.g., PDE4 inhibition) and encompassed within (or substantially encompassed within) the generic structure of Formula I. Assays known to those of ordinary skill in the art can be used to determine whether a given apremilast moiety (as well as a compound provided herein) has pharmacological activity (e.g., PDE4 inhibition).

[0043] A "biological membrane" is any membrane made of cells or tissues that serves as a barrier to at least some foreign entities or otherwise undesirable materials. As used herein a "biological membrane" includes those membranes that are associated with

physiological protective barriers including, for example: the blood-brain barrier (BBB); the blood-cerebrospinal fluid barrier; the blood-placental barrier; the blood-milk barrier; the blood-testes barrier; and mucosal barriers including the vaginal mucosa, urethral mucosa, anal mucosa, buccal mucosa, sublingual mucosa, and rectal mucosa. Unless the context clearly dictates otherwise, the term "biological membrane" does not include those membranes associated with the middle gastro-intestinal tract (e.g., stomach and small intestines).

[0044] A "biological membrane crossing rate," provides a measure of a compound's ability to cross a biological membrane, such as the blood-brain barrier ("BBB"). A variety of methods may be used to assess transport of a molecule across any given biological membrane. Methods to assess the biological membrane crossing rate associated with any given biological barrier (e.g., the blood-cerebrospinal fluid barrier, the blood-placental barrier, the blood-milk barrier, the intestinal barrier, and so forth), are known, described herein and/or in the relevant literature, and/or may be determined by one of ordinary skill in the art.

[0045] A "reduced metabolism" refers to a measurable reduction in metabolism and/or to a measure reduction of the rate of metabolism of a water-soluble oligomer-small molecule drug conjugate as compared to the rate of metabolism of the small molecule drug not attached to the water-soluble oligomer (i.e., the small molecule drug itself) or a reference standard material. In the special case of "reduced first pass rate of metabolism," the same "reduced rate of metabolism" is required except that the small molecule drug (or reference standard material) and the corresponding conjugate are administered orally. Orally administered drugs are absorbed from the gastro-intestinal tract into the portal circulation and may pass through the liver prior to reaching the systemic circulation. Because the liver is the primary site of drug metabolism or biotransformation, a substantial amount of drug may be metabolized before it ever reaches the systemic circulation. The degree of first pass metabolism, and thus, any reduction thereof, may be measured by a number of different approaches. For instance, animal blood samples may be collected at timed intervals and the plasma or serum analyzed by liquid chromatography/mass spectrometry for metabolite levels. Other techniques for measuring a "reduced rate of metabolism" associated with the first pass metabolism and other metabolic processes are known, described herein and/or in the relevant literature, and/or may be determined by one of ordinary skill in the art. Preferably, a compound of the invention may provide a reduced rate of metabolism (relative to a compound lacking water-soluble, non-peptidic oligomers) satisfying at least one of the

following values: at least about 30%; at least about 40%; at least about 50%; at least about 60%; at least about 70%; at least about 80%; and at least about 90%. A compound (such as a small molecule drug or conjugate thereof) that is "orally bioavailable" is one that preferably possesses a bioavailability when administered orally of greater than 25%, and preferably greater than 70%, where a compound's bioavailability is the fraction of administered drug that reaches the systemic circulation in unmetabolized form.

[0046] "Alkyl" refers to a hydrocarbon chain, ranging from about 1 to 20 atoms in length. Such hydrocarbon chains are preferably but not necessarily saturated and may be branched or straight chain. Exemplary alkyl groups include methyl, ethyl, propyl, butyl, pentyl, 2-methylbutyl, 2-ethylpropyl, 3-methylpentyl, and the like. As used herein, "alkyl" includes cycloalkyl when three or more carbon atoms are referenced. An "alkenyl" group is an alkyl of 2 to 20 carbon atoms with at least one carbon-carbon double bond.

[0047] The terms "substituted alkyl" or "substituted C_{q-r} alkyl" where q and r are integers identifying the range of carbon atoms contained in the alkyl group, denotes the above alkyl groups that are substituted by one, two or three halo (e.g., F, Cl, Br, I), trifluoromethyl, hydroxy, C₁₋₇ alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, butyl, t-butyl, and so forth), C₁₋₇ alkoxy, C₁₋₇ acyloxy, C₃₋₇ heterocyclic, amino, phenoxy, nitro, carboxy, acyl, cyano. The substituted alkyl groups may be substituted once, twice or three times with the same or with different substituents.

[0048] "Lower alkyl" refers to an alkyl group containing from 1 to 6 carbon atoms, and may be straight chain or branched, as exemplified by methyl, ethyl, n-butyl, i-butyl, t-butyl. "Lower alkenyl" refers to a lower alkyl group of 2 to 6 carbon atoms having at least one carbon-carbon double bond.

[0049] "Non-interfering substituents" are those groups that, when present in a molecule, are typically non-reactive with other functional groups contained within the molecule.

[0050] "Alkoxy" refers to an -O-R group, wherein R is alkyl or substituted alkyl, preferably C₁-C₂₀ alkyl (e.g., methoxy, ethoxy, propyloxy, etc.), preferably C₁-C₇.

[0051] "Pharmaceutically acceptable excipient" or "pharmaceutically acceptable carrier" refers to a component that may be included in the compositions of the invention causes no significant adverse toxicological effects to a patient.

[0052] The term "aryl" means an aromatic group having up to 14 carbon atoms. Aryl groups include phenyl, naphthyl, biphenyl, phenanthrenyl, naphthalenyl, and the like. "Substituted phenyl" and "substituted aryl" denote a phenyl group and aryl group, respectively, substituted with one, two, three, four or five (e.g., 1-2, 1-3 or 1-4 substituents) chosen from halo (e.g., F, Cl, Br, I), hydroxy, cyano, nitro, alkyl (e.g., C₁₋₆ alkyl), alkoxy (e.g., C₁₋₆ alkoxy), benzyloxy, carboxy, aryl, and so forth.

[0053] "Pharmacologically effective amount," "physiologically effective amount," and "therapeutically effective amount" are used interchangeably herein to mean the amount of the compound of the invention present in a composition that is needed to provide a desired level of the compound (or desired metabolite thereof) in the bloodstream or in the target tissue. The precise amount may depend upon numerous factors, e.g., the particular active agent, the components and physical characteristics of the composition, intended patient population, patient considerations, and may readily be determined by one skilled in the art, based upon the information provided herein and available in the relevant literature.

[0054] A "difunctional" oligomer is an oligomer having two functional groups contained therein, typically at its termini. When the functional groups are the same, the oligomer is said to be homodifunctional. When the functional groups are different, the oligomer is said to be heterodifunctional.

[0055] A basic reactant or an acidic reactant described herein include neutral, charged, and any corresponding salt forms thereof.

[0056] The term "patient," refers to a living organism suffering from or prone to a condition that can be prevented or treated by administration of a compound of the invention as described herein, and includes both humans and animals.

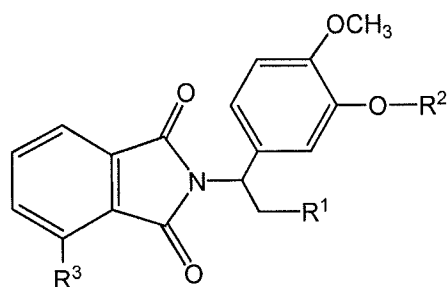
[0057] "Optional" or "optionally" means that the subsequently described circumstance may but need not necessarily occur, so that the description includes instances where the circumstance occurs and instances where it does not.

[0058] As indicated above, the present invention is directed to (among other things) a compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer.

[0059] The "apremilast moiety residue" is a compound having a structure of an apremilast moiety that is altered by the presence of one or more bonds, which bonds serve to

attach (either directly or indirectly) one or more water-soluble, non-peptidic oligomers.

Exemplary apremilast moieties have a structure encompassed by Formula I:



(Formula I)

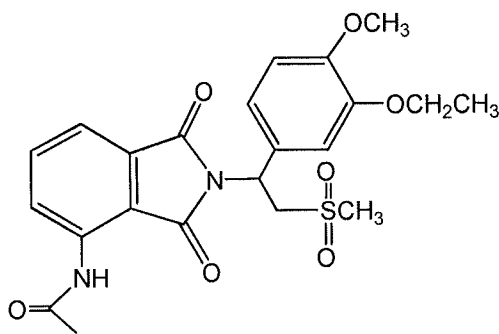
wherein:

R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

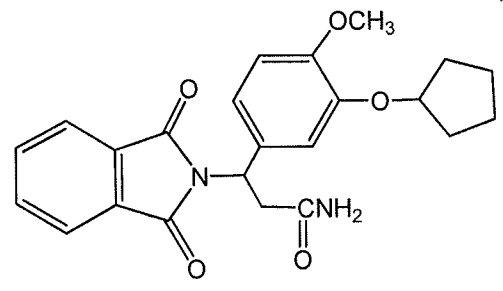
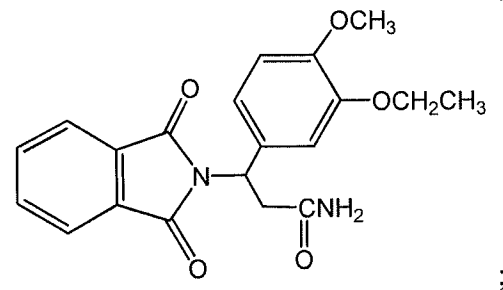
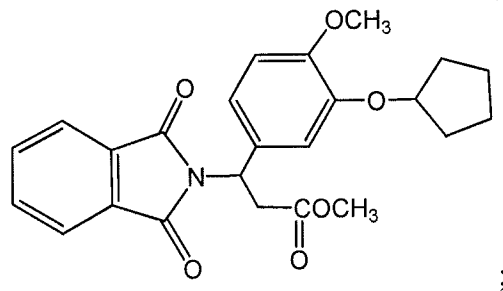
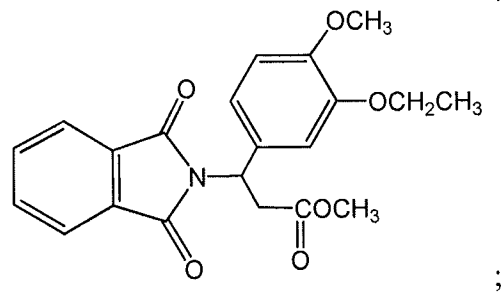
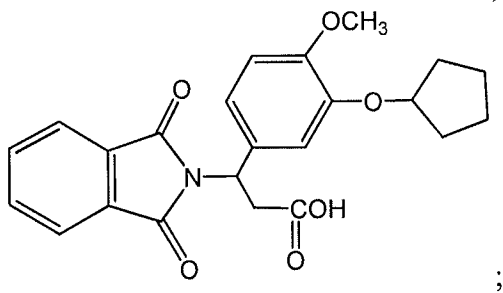
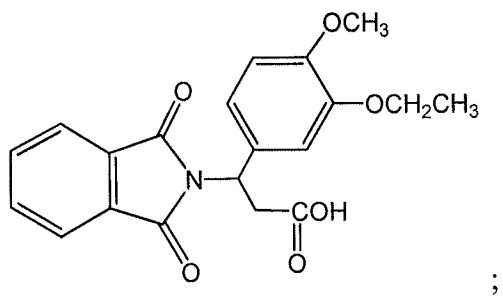
R^2 is an organic radical (e.g., ethyl, cyclopentyl, and CH₂-cyclopropyl); and

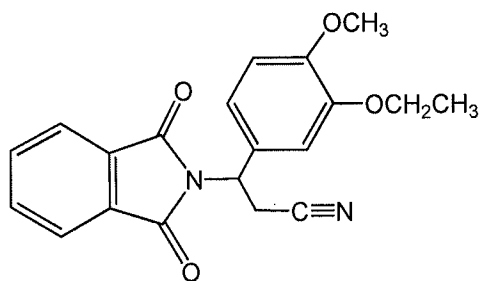
R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical (e.g., methyl).

[0060] In one or more embodiments of the invention, a compound is provided, the compound comprising an apremilast moiety residue covalently attached via a stable or degradable linkage to a water-soluble, non-peptidic oligomer, wherein the apremilast moiety residue (in a form in which the water-soluble, non-peptidic oligomer is not present) corresponds to an apremilast moiety selected from the group consisting of apremilast and 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide. The following list provides the chemical structures exemplary apremilast moieties:

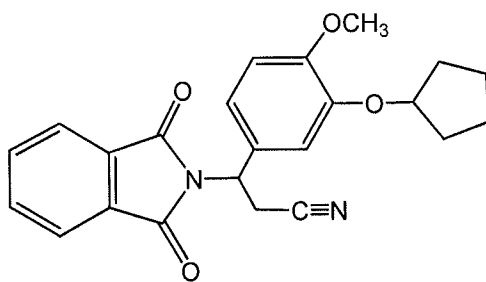


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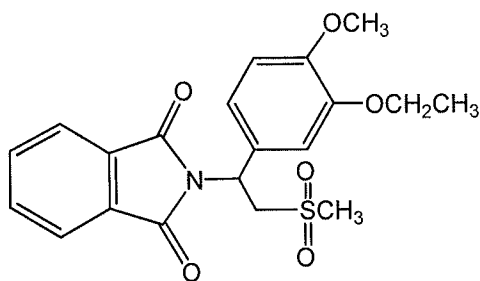




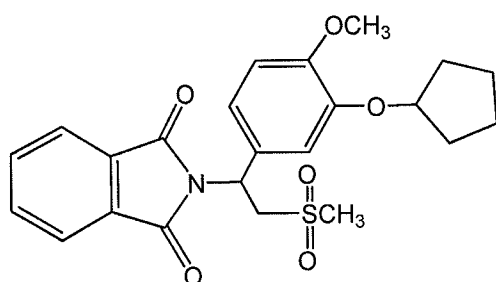
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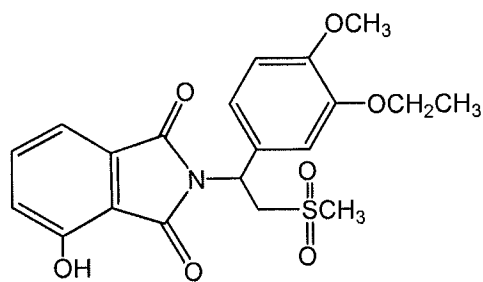
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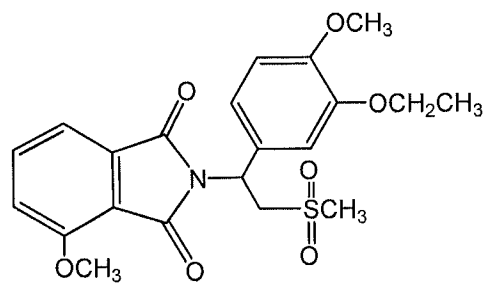
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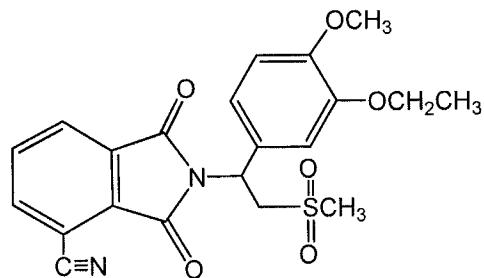
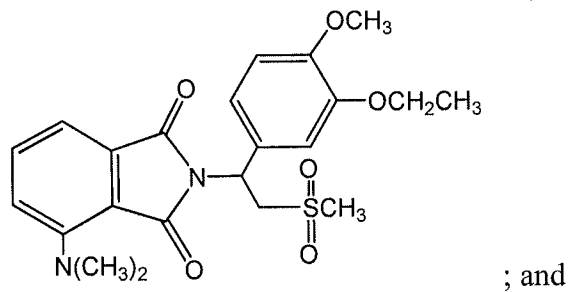
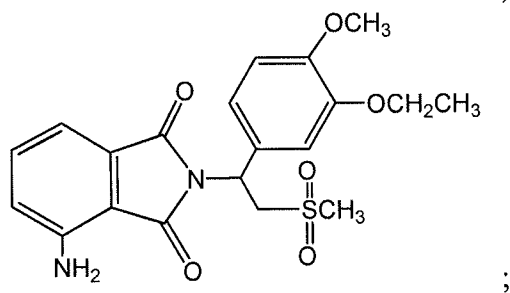
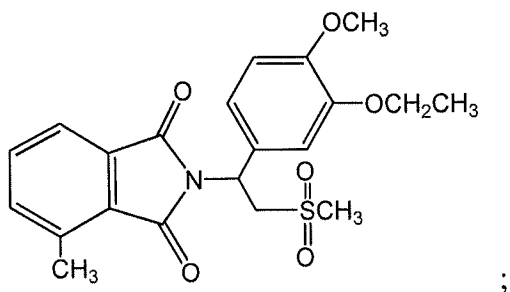
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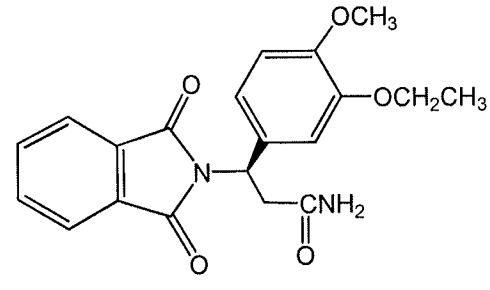
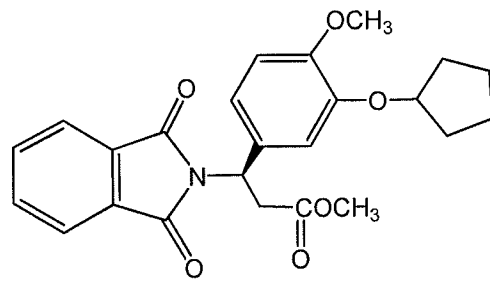
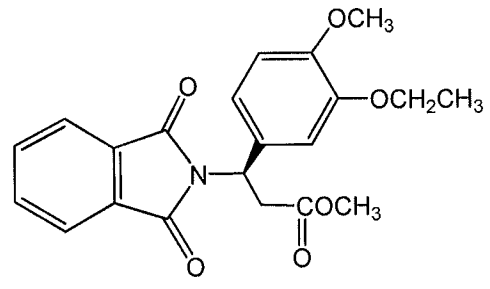
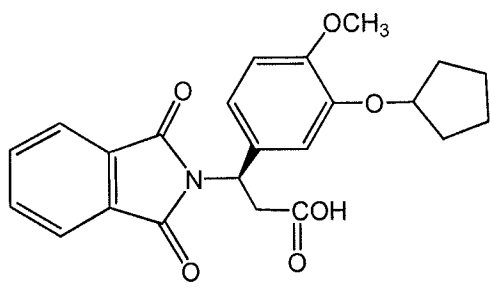
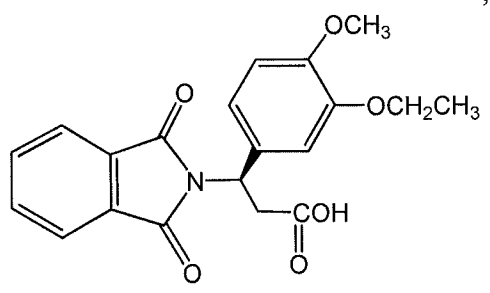
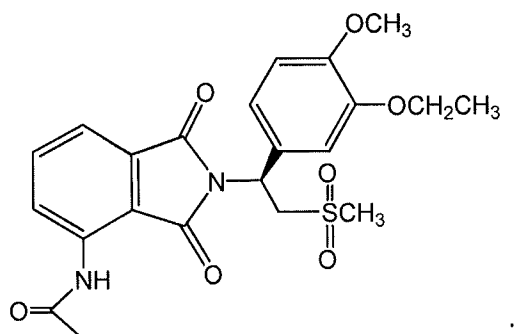
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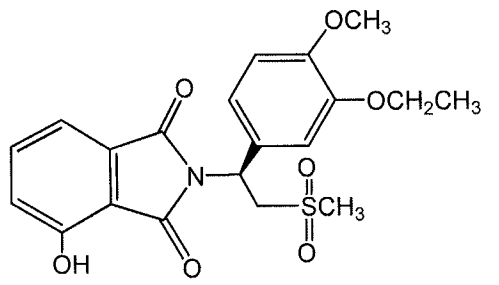
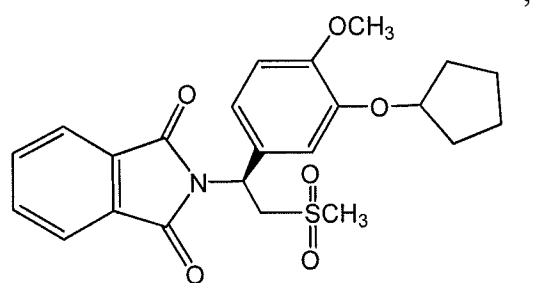
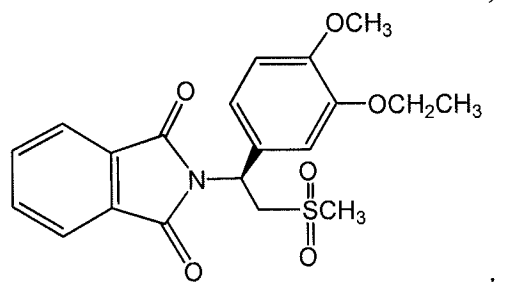
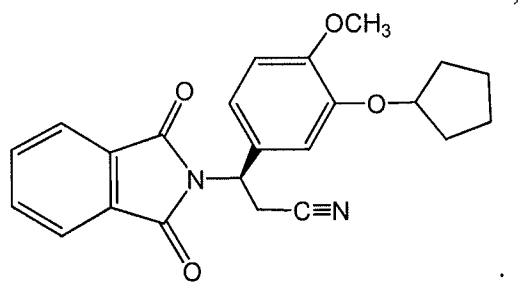
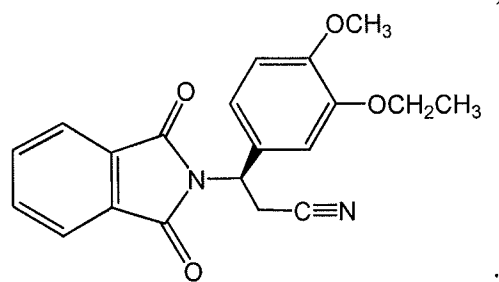
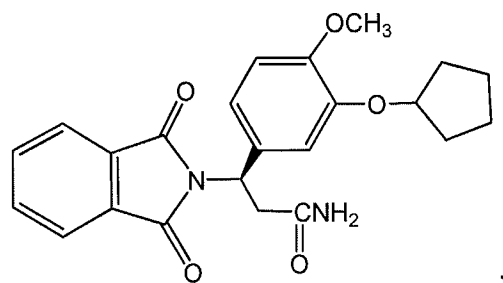


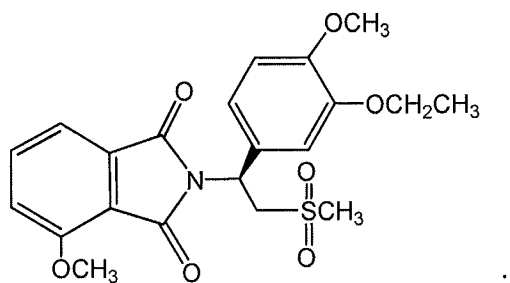
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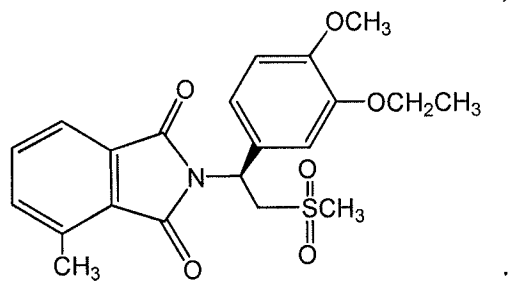
[0061] Any given apremilast moiety may have one or more chiral centers and the present disclosure contemplates all enantiomeric forms of such moieties. Exemplary apremilast moieties showing an exemplary spatial arrangement of a chiral carbon are provided below:



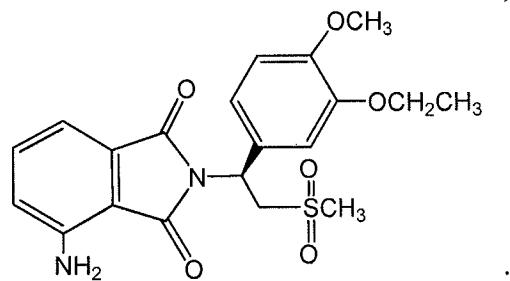




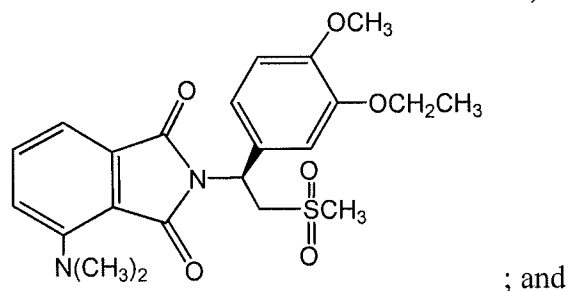
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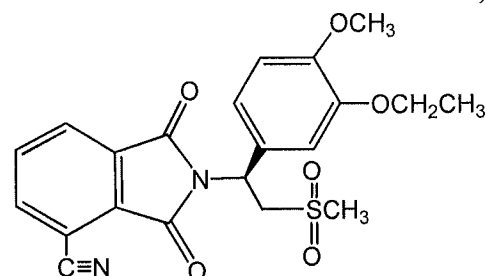
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;



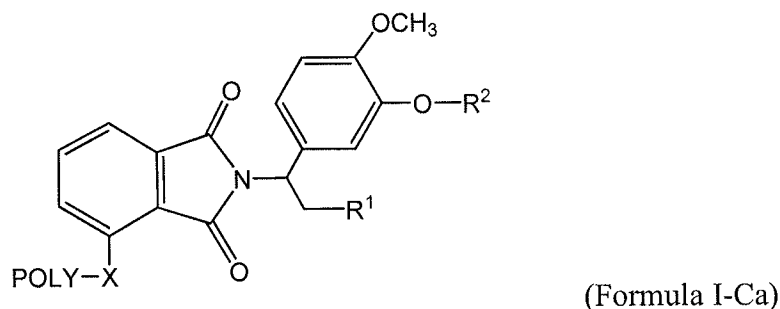
; and



[0062] In some instances, an apremilast moiety that is useful as a starting material or intermediate in synthesizing the compounds of the invention can be obtained from commercial sources. In addition, apremilast moieties can be obtained through chemical synthesis. Further examples of apremilast moieties, as well as synthetic approaches for preparing apremilast moieties, are described in the literature and in, for example, U.S. Patent Application Publication No. 2010/0129363, U.S. Patent No. 7,659,303 and Man et al. (2009)

J. Med. Chem. 52:1522-1524. Each of these (and other) apremilast moieties can be covalently attached (either directly or through one or more atoms) to a water-soluble, non-peptidic oligomer following the techniques and approaches described herein.

[0063] Exemplary compounds of the invention include those having the following structure:



wherein:

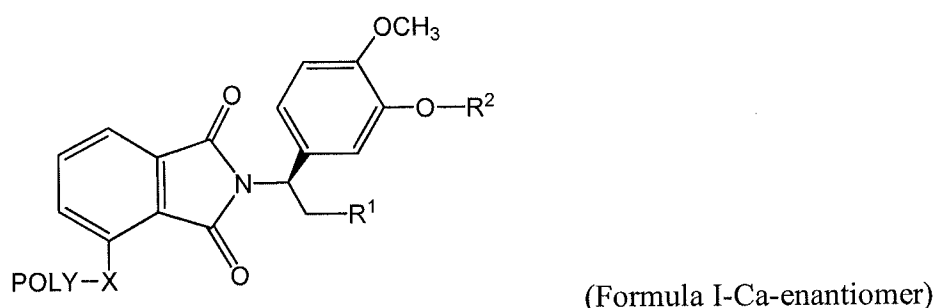
R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^2 is an organic radical (e.g., ethyl, cyclopentyl, and CH₂-cyclopropyl);

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer, and pharmaceutically acceptable salts thereof.

[0064] Still further exemplary compounds of the invention include those having the following structure:



wherein:

R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

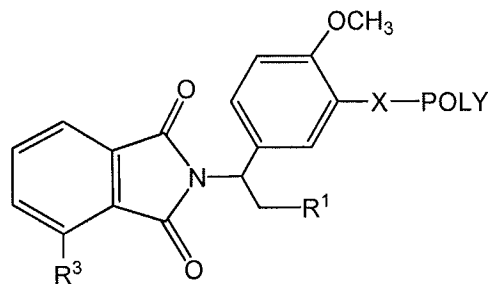
R^2 is an organic radical (e.g., ethyl, cyclopentyl, and CH₂-cyclopropyl);

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer,

and pharmaceutically acceptable salts thereof.

[0065] Still further exemplary compounds of the invention include those having the following structure:



(Formula I-Cb)

wherein:

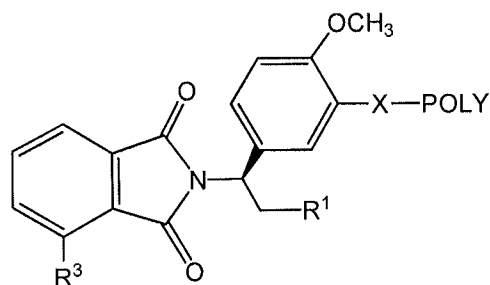
R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical (e.g., methyl);

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer, and pharmaceutically acceptable salts thereof.

[0066] Still further exemplary compounds of the invention include those having the following structure:



(Formula I-Cb-enantiomer)

wherein:

R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

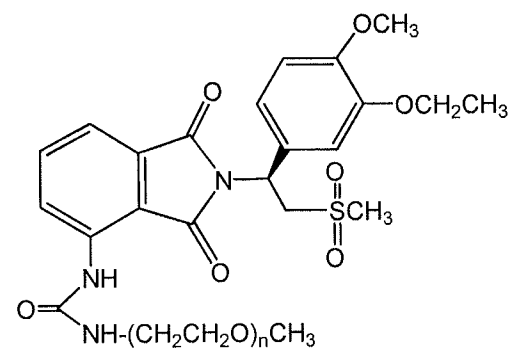
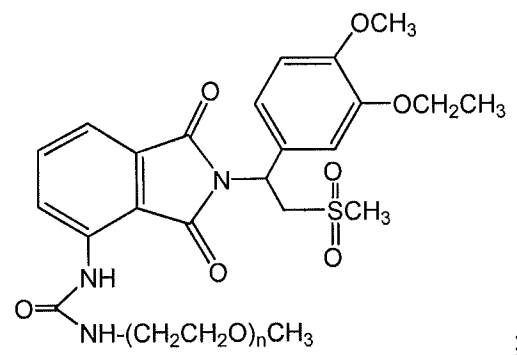
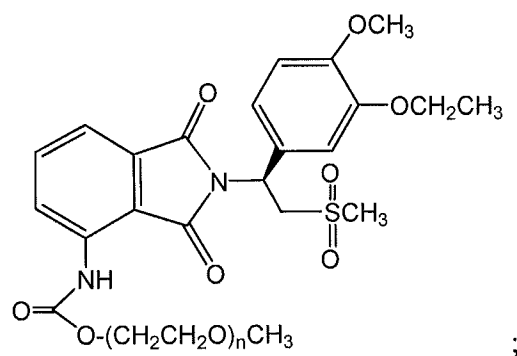
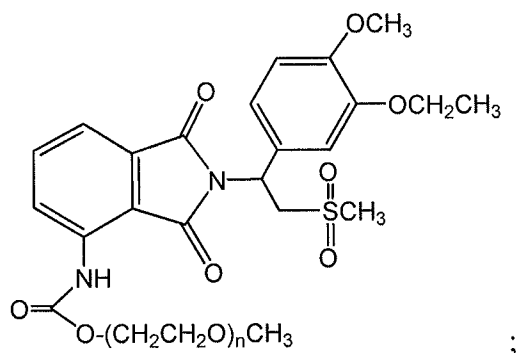
R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical (e.g., methyl);

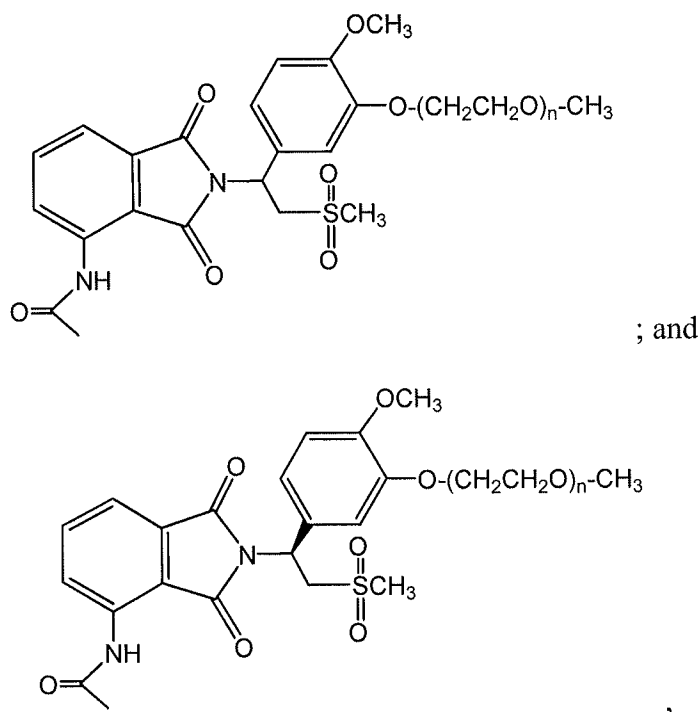
X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer,

and pharmaceutically acceptable salts thereof.

[0067] Exemplary compounds of the invention include those selected from the group consisting of





wherein (n) is an integer from 1 to 12.

[0068] Use of discrete oligomers (e.g., from a monodisperse or bimodal composition of oligomers, in contrast to relatively impure compositions) to form oligomer-containing compounds are preferred. For instance, a compound of the invention, when administered by any of a number of suitable administration routes, such as parenteral, oral, transdermal, buccal, pulmonary, or nasal, may exhibit reduced penetration across the blood-brain barrier. Moreover, the compounds of the invention maintain a degree of bioactivity as well as bioavailability in comparison to the bioactivity and bioavailability of the compound free of all oligomers.

[0069] For compounds whose degree of blood-brain barrier crossing ability is not readily known, such ability may be determined using a suitable animal model such as an *in situ* rat brain perfusion ("RBP") model as described herein. Briefly, the RBP technique involves cannulation of the carotid artery followed by perfusion with a compound solution under controlled conditions, followed by a wash out phase to remove compound remaining in the vascular space. (Such analyses may be conducted, for example, by contract research organizations such as Absorption Systems, Exton, PA). In one example of the RBP model, a cannula is placed in the left carotid artery and the side branches are tied off. A physiologic buffer containing the analyte (typically but not necessarily at a 5 micromolar concentration level) is perfused at a flow rate of about 10 mL/minute in a single pass perfusion experiment.

After 30 seconds, the perfusion is stopped and the brain vascular contents are washed out with compound-free buffer for an additional 30 seconds. The brain tissue is then removed and analyzed for compound concentrations via liquid chromatography with tandem mass spectrometry detection (LC/MS/MS). Alternatively, blood-brain barrier permeability can be estimated based upon a calculation of the compound's molecular polar surface area ("PSA"), which is defined as the sum of surface contributions of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule. The PSA has been shown to correlate with compound transport properties such as blood-brain barrier transport. Methods for determining a compound's PSA can be found, e.g., Ertl et al. (2000) *J. Med. Chem.* 43:3714-3717 and Kelder et al. (1999) *Pharm. Res.* 16:1514-1519.

[0070] With respect to the blood-brain barrier, the water-soluble, non-peptidic oligomer-containing compound of the invention may exhibit a blood-brain barrier crossing rate that is reduced as compared to the crossing rate of the small molecule drug not attached to the water-soluble, non-peptidic oligomer. Exemplary reductions in blood-brain barrier crossing rates for the compounds described herein include reductions of: at least about 5%; at least about 10%; at least about 25%; at least about 30%; at least about 40%; at least about 50%; at least about 60%; at least about 70%; at least about 80%; or at least about 90%, when compared to the blood-brain barrier crossing rate of the corresponding compound lacking water-soluble, non-peptidic oligomers. A preferred reduction in the blood-brain barrier crossing rate for a conjugate of the invention is at least about 20%.

[0071] Assays for determining whether a given compound (regardless of whether the compound includes a water-soluble, non-peptidic oligomer or not) can act as an apremilast moiety are known and/or may be prepared by one of ordinary skill in the art and are further described *infra*.

[0072] Briefly, one approach for testing whether a given apremilast moiety has PDE4 inhibition activity is a PDE4 (U937 cell-derived) enzyme assay wherein PDE4 enzyme can be purified from U937 human monocytic cells by gel filtration chromatography as described in Muller et al. (1998) *Bioorg. & Med. Chem. Lett.* 8:2669-2674. Thereafter, phosphodiesterase reactions are carried out in 50 mM Tris HCl pH 7.5, 5 mM MgCl₂, 1 μM cAMP, 10 nM [³H]-cAMP for 30 minutes at 30° C., terminated by boiling, treated with 1 mg/ml snake venom, and separated using an ion exchange resin as described in Muller et al. (1998).

[0073] Each of these (and other) apremilast moieties can be covalently attached (either directly or through one or more atoms) to a water-soluble, non-peptidic oligomer.

[0074] Exemplary molecular weights of an apremilast moiety (prior to, for example, conjugation to a water-soluble, non-peptidic oligomer) include molecular weights of: less than about 950; less than about 900; less than about 850; less than about 800; less than about 750; less than about 700; less than about 650; less than about 600; less than about 550; less than about 500; less than about 450; less than about 400; less than about 350; and less than about 300 Daltons.

[0075] The apremilast moiety used in the invention, if chiral, may be obtained from a racemic mixture, or an optically active form, for example, a single optically active enantiomer, or any combination or ratio of enantiomers (e.g., scalemic and racemic mixtures). In addition, the apremilast moiety may possess one or more geometric isomers. With respect to geometric isomers, a composition can comprise a single geometric isomer or a mixture of two or more geometric isomers. An apremilast moiety for use in the present invention can be in its customary active form, or may possess some degree of modification. For example, the apremilast moiety may have a targeting agent, tag, or transporter attached thereto, prior to or after covalent attachment of an oligomer. Alternatively, the apremilast moiety may possess a lipophilic moiety attached thereto, such as a phospholipid (e.g., distearoylphosphatidylethanolamine or "DSPE," dipalmitoylphosphatidylethanolamine or "DPPE," and so forth) or a small fatty acid. In some instances, however, it is preferred that the apremilast moiety does not include attachment to a lipophilic moiety.

[0076] The apremilast moiety for coupling to a water-soluble, non-peptidic oligomer possesses a free hydroxyl, carboxyl, thio, amino group, or the like (i.e., "handle") suitable for covalent attachment to the oligomer. In addition, the apremilast moiety may be modified by introduction of a reactive group, preferably by conversion of one of its existing functional groups to a functional group suitable for formation of a stable covalent linkage between the oligomer and the drug.

[0077] Each oligomer is composed of up to three different monomer types selected from the group consisting of: alkylene oxide, such as ethylene oxide or propylene oxide; olefinic alcohol, such as vinyl alcohol, 1-propenol or 2-propenol; vinyl pyrrolidone; hydroxyalkyl methacrylamide or hydroxyalkyl methacrylate, where alkyl is preferably methyl; α -hydroxy acid, such as lactic acid or glycolic acid; phosphazene, oxazoline, amino

acids, carbohydrates such as monosaccharides, alditol such as mannitol; and N-acryloylmorpholine. Preferred monomer types include alkylene oxide, olefinic alcohol, hydroxyalkyl methacrylamide or methacrylate, N-acryloylmorpholine, and α -hydroxy acid. Preferably, each oligomer is, independently, a co-oligomer of two monomer types selected from this group, or, more preferably, is a homo-oligomer of one monomer type selected from this group.

[0078] The two monomer types in a co-oligomer may be of the same monomer type, for example, two alkylene oxides, such as ethylene oxide and propylene oxide. Preferably, the oligomer is a homo-oligomer of ethylene oxide. Usually, although not necessarily, the terminus (or termini) of the oligomer that is not covalently attached to a small molecule is capped to render it unreactive. Alternatively, the terminus may include a reactive group. When the terminus is a reactive group, the reactive group is either selected such that it is unreactive under the conditions of formation of the final oligomer or during covalent attachment of the oligomer to a small molecule drug, or it is protected as necessary. One common end-functional group is hydroxyl or -OH, particularly for oligoethylene oxides.

[0079] The water-soluble, non-peptidic oligomer (e.g., "POLY" in various structures provided herein) can have any of a number of different geometries. For example, the water-soluble, non-peptidic oligomer can be linear, branched, or forked. Most typically, the water-soluble, non-peptidic oligomer is linear or is branched, for example, having one branch point. Although much of the discussion herein is focused upon poly(ethylene oxide) as an illustrative oligomer, the discussion and structures presented herein can be readily extended to encompass any water-soluble, non-peptidic oligomers described above.

[0080] The molecular weight of the water-soluble, non-peptidic oligomer, excluding the linker portion, is generally relatively low. Exemplary values of the molecular weight of the water-soluble polymer include: below about 1500; below about 1450; below about 1400; below about 1350; below about 1300; below about 1250; below about 1200; below about 1150; below about 1100; below about 1050; below about 1000; below about 950; below about 900; below about 850; below about 800; below about 750; below about 700; below about 650; below about 600; below about 550; below about 500; below about 450; below about 400; below about 350; below about 300; below about 250; below about 200; and below about 100 Daltons.

[0081] Exemplary ranges of molecular weights of the water-soluble, non-peptidic oligomer (excluding the linker) include: from about 100 to about 1400 Daltons; from about 100 to about 1200 Daltons; from about 100 to about 800 Daltons; from about 100 to about 500 Daltons; from about 100 to about 400 Daltons; from about 200 to about 500 Daltons; from about 200 to about 400 Daltons; from about 75 to 1000 Daltons; and from about 75 to about 750 Daltons.

[0082] Preferably, the number of monomers in the water-soluble, non-peptidic oligomer falls within one or more of the following ranges: between about 1 and about 30 (inclusive); between about 1 and about 25; between about 1 and about 20; between about 1 and about 15; between about 1 and about 12; between about 1 and about 10. In certain instances, the number of monomers in series in the oligomer (and the corresponding conjugate) is one of 1, 2, 3, 4, 5, 6, 7, or 8. In additional embodiments, the oligomer (and the corresponding conjugate) contains 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 monomers. In yet further embodiments, the oligomer (and the corresponding conjugate) possesses 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 monomers in series. Thus, for example, when the water-soluble, non-peptidic polymer includes $\text{CH}_3-(\text{OCH}_2\text{CH}_2)_n-$, "n" is an integer that 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, and can fall within one or more of the following ranges: between about 1 and about 25; between about 1 and about 20; between about 1 and about 15; between about 1 and about 12; between about 1 and about 10.

[0083] When the water-soluble, non-peptidic oligomer has 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 monomers, these values correspond to a methoxy end-capped oligo(ethylene oxide) having a molecular weights of about 75, 119, 163, 207, 251, 295, 339, 383, 427, and 471 Daltons, respectively. When the oligomer has 11, 12, 13, 14, or 15 monomers, these values correspond to methoxy end-capped oligo(ethylene oxide) having molecular weights corresponding to about 515, 559, 603, 647, and 691 Daltons, respectively.

[0084] When the water-soluble, non-peptidic oligomer is attached to the apremilast moiety (in contrast to the step-wise addition of one or more monomers to effectively "grow" the oligomer onto the apremilast moiety), it is preferred that the composition containing an activated form of the water-soluble, non-peptidic oligomer be monodisperse. In those instances, however, where a bimodal composition is employed, the composition will possess a bimodal distribution centering around any two of the above numbers of monomers. For

instance, a bimodal oligomer may have any one of the following exemplary combinations of monomer subunits: 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, and so forth; 2-3, 2-4, 2-5, 2-6, 2-7, 2-8, 2-9, 2-10, and so forth; 3-4, 3-5, 3-6, 3-7, 3-8, 3-9, 3-10, and so forth; 4-5, 4-6, 4-7, 4-8, 4-9, 4-10, and so forth; 5-6, 5-7, 5-8, 5-9, 5-10, and so forth; 6-7, 6-8, 6-9, 6-10, and so forth; 7-8, 7-9, 7-10, and so forth; and 8-9, 8-10, and so forth.

[0085] In some instances, the composition containing an activated form of the water-soluble, non-peptidic oligomer will be trimodal or even tetramodal, possessing a range of monomers units as previously described. Oligomer compositions possessing a well-defined mixture of oligomers (i.e., being bimodal, trimodal, tetramodal, and so forth) can be prepared by mixing purified monodisperse oligomers to obtain a desired profile of oligomers (a mixture of two oligomers differing only in the number of monomers is bimodal; a mixture of three oligomers differing only in the number of monomers is trimodal; a mixture of four oligomers differing only in the number of monomers is tetramodal), or alternatively, can be obtained from column chromatography of a polydisperse oligomer by recovering the "center cut", to obtain a mixture of oligomers in a desired and defined molecular weight range.

[0086] It is preferred that the water-soluble, non-peptidic oligomer is obtained from a composition that is preferably unimolecular or monodisperse. That is, the oligomers in the composition possess the same discrete molecular weight value rather than a distribution of molecular weights. Some monodisperse oligomers can be purchased from commercial sources such as those available from Sigma-Aldrich, or alternatively, can be prepared directly from commercially available starting materials such as Sigma-Aldrich. Water-soluble, non-peptidic oligomers can be prepared as described in Chen Y., Baker, G.L., *J. Org. Chem.*, 6870-6873 (1999), WO 02/098949, and U.S. Patent Application Publication No. 2005/0136031.

[0087] The spacer moiety (the linkage through which the water-soluble, non-peptidic polymer is attached to the apremilast moiety) may be a single bond, a single atom, such as an oxygen atom or a sulfur atom, two atoms, or a number of atoms. A spacer moiety is typically but is not necessarily linear in nature. The spacer moiety, "X," is preferably hydrolytically stable, and is also preferably enzymatically stable. Preferably, the spacer moiety "X" is one having a chain length of less than about 12 atoms, and preferably less than about 10 atoms, and even more preferably less than about 8 atoms and even more preferably less than about 5 atoms, whereby length is meant the number of atoms in a single chain, not counting

substituents. For instance, a urea linkage such as this, $R_{\text{oligomer}}-\text{NH}-(\text{C}=\text{O})-\text{NH}-R'_{\text{drug}}$, is considered to have a chain length of 3 atoms ($-\text{NH}-\text{C}(\text{O})-\text{NH}-$). In selected embodiments, the linkage does not comprise further spacer groups.

[0088] In some instances, the spacer moiety (e.g., "X" in various structures provided herein) comprises an ether, amide, urethane, amine, thioether, urea, or a carbon-carbon bond. Functional groups such as those discussed below, and illustrated in the examples, are typically used for forming the linkages. The spacer moiety may less preferably also comprise (or be adjacent to or flanked by) other atoms, as described further below.

[0089] More specifically, in selected embodiments, a spacer moiety (e.g., "X" in various structures provided herein) may be any of the following: "-" (i.e., a covalent bond, that may be stable or degradable, between the apremilast moiety residue and the water-soluble, non-peptidic oligomer), -O-, -NH-, -S-, -C(O)-, -C(O)O-, -OC(O)-, -CH₂-C(O)O-, -CH₂-OC(O)-, -C(O)O-CH₂-, -OC(O)-CH₂-, C(O)-NH, NH-C(O)-NH, O-C(O)-NH, -C(S)-, -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -O-CH₂-, -CH₂-O-, -O-CH₂-CH₂-, -CH₂-O-CH₂-, -CH₂-CH₂-O-, -O-CH₂-CH₂-CH₂-, -CH₂-O-CH₂-CH₂-, -CH₂-CH₂-O-CH₂-, -CH₂-CH₂-CH₂-O-, -O-CH₂-CH₂-CH₂-CH₂-, -CH₂-O-CH₂-CH₂-CH₂-, -CH₂-CH₂-O-CH₂-CH₂-, -CH₂-CH₂-CH₂-O-CH₂-, -CH₂-CH₂-CH₂-CH₂-O-, -C(O)-NH-CH₂-, -C(O)-NH-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-C(O)-NH-, -C(O)-NH-CH₂-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-, -C(O)-NH-CH₂-CH₂-CH₂-CH₂-, -CH₂-C(O)-NH-CH₂-CH₂-CH₂-, -CH₂-CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-C(O)-NH-, -NH-C(O)-CH₂-, -CH₂-NH-C(O)-CH₂-, -CH₂-CH₂-NH-C(O)-CH₂-, -NH-C(O)-CH₂-CH₂-, -CH₂-NH-C(O)-CH₂-CH₂-, -CH₂-CH₂-NH-C(O)-CH₂-CH₂-, -C(O)-NH-CH₂-, -C(O)-NH-CH₂-CH₂-, -O-C(O)-NH-CH₂-, -O-C(O)-NH-CH₂-CH₂-, -NH-CH₂-, -NH-CH₂-CH₂-, -CH₂-NH-CH₂-, -CH₂-CH₂-NH-CH₂-, -C(O)-CH₂-, -C(O)-CH₂-CH₂-, -CH₂-C(O)-CH₂-, -CH₂-CH₂-C(O)-CH₂-, -CH₂-CH₂-C(O)-CH₂-CH₂-, -CH₂-CH₂-C(O)-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-C(O)-, -CH₂-CH₂-CH₂-C(O)-NH-CH₂-CH₂-NH-C(O)-CH₂-, bivalent cycloalkyl group, -N(R⁶)-, R⁶ is H or an organic radical selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl and substituted aryl. Additional spacer moieties include, acylamino, acyl, aryloxy, alkylene bridge containing between 1 and 5 inclusive carbon atoms,

alkylamino, dialkylamino having about 2 to 4 inclusive carbon atoms, piperidino, pyrrolidino, N-(lower alkyl)-2-piperidyl, morpholino, 1-piperizinyl, 4-(lower alkyl)-1-piperizinyl, 4-(hydroxyl-lower alkyl)-1-piperizinyl, 4-(methoxy-lower alkyl)-1-piperizinyl, and guanidine. In some instances, a portion or a functional group of the drug compound may be modified or removed altogether to facilitate attachment of the oligomer. In some instances, it is preferred that X is not an amide, i.e., -CONR- and -RNCO-.

[0090] For purposes of the present invention, however, a group of atoms is not considered a linkage when it is immediately adjacent to an oligomer segment, and the group of atoms is the same as a monomer of the oligomer such that the group would represent a mere extension of the oligomer chain.

[0091] The spacer moiety between the water-soluble, non-peptidic oligomer and the small molecule is formed by reaction of a functional group on a terminus of the oligomer (or nascent oligomer when it is desired to "grow" the oligomer onto the apremilast moiety) with a corresponding functional group within the apremilast moiety. Illustrative reactions are described briefly below. For example, an amino group on an oligomer may be reacted with a carboxylic acid or an activated carboxylic acid derivative on the small molecule, or vice versa, to produce an amide linkage. Alternatively, reaction of an amine on an oligomer with an activated carbonate (e.g., succinimidyl or benzotriazolyl carbonate) on the drug, or vice versa, forms a carbamate linkage. Reaction of an amine on an oligomer with an isocyanate ($R-N=C=O$) on a drug, or vice versa, forms a urea linkage ($R-NH-(C=O)-NH-R'$). Further, reaction of an alcohol (alkoxide) group on an oligomer with an alkyl halide, or halide group within a drug, or vice versa, forms an ether linkage. In yet another coupling approach, a small molecule having an aldehyde function is coupled to an oligomer amino group by reductive amination, resulting in formation of a secondary amine linkage between the oligomer and the small molecule.

[0092] A particularly preferred water-soluble, non-peptidic oligomer is an oligomer bearing an aldehyde functional group. In this regard, the oligomer will have the following structure: $CH_3O-(CH_2-CH_2-O)_n-(CH_2)_p-C(O)H$, wherein (n) is one of 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and (p) is one of 1, 2, 3, 4, 5, 6 and 7. Preferred (n) values include 3, 5 and 7 and preferred (p) values 2, 3 and 4.

[0093] The termini of the water-soluble, non-peptidic oligomer not bearing a functional group may be capped to render it unreactive. When the oligomer includes a

further functional group at a terminus other than that intended for formation of a conjugate, that group is either selected such that it is unreactive under the conditions of formation of the spacer moiety (e.g., "X") or it is protected during the formation of the spacer moiety (e.g., "X").

[0094] As stated above, the water-soluble, non-peptidic oligomer includes at least one functional group prior to conjugation. The functional group comprises an electrophilic or nucleophilic group for covalent attachment to a small molecule, depending upon the reactive group contained within or introduced into the small molecule. Examples of nucleophilic groups that may be present in either the oligomer or the small molecule include hydroxyl, amine, hydrazine (-NHNH₂), hydrazide (-C(O)NHNH₂), and thiol. Preferred nucleophiles include amine, hydrazine, hydrazide, and thiol, particularly amine. Most small molecule drugs for covalent attachment to an oligomer will possess a free hydroxyl, amino, thio, aldehyde, ketone, or carboxyl group.

[0095] Examples of electrophilic functional groups that may be present in either the oligomer or the small molecule include carboxylic acid, carboxylic ester, particularly imide esters, orthoester, carbonate, isocyanate, isothiocyanate, aldehyde, ketone, thione, alkenyl, acrylate, methacrylate, acrylamide, sulfone, maleimide, disulfide, iodo, epoxy, sulfonate, thiosulfonate, silane, alkoxysilane, and halosilane. More specific examples of these groups include succinimidyl ester or carbonate, imidazolyl ester or carbonate, benzotriazole ester or carbonate, vinyl sulfone, chloroethylsulfone, vinylpyridine, pyridyl disulfide, iodoacetamide, glyoxal, dione, mesylate, tosylate, and tresylate (2,2,2-trifluoroethanesulfonate).

[0096] Also included are sulfur analogs of several of these groups, such as thione, thione hydrate, thioketal, 2-thiazolidine thione, etc., as well as hydrates or protected derivatives of any of the above moieties (e.g., aldehyde hydrate, hemiacetal, acetal, ketone hydrate, hemiketal, ketal, thioketal, thioacetal).

[0097] An "activated derivative" of a carboxylic acid refers to a carboxylic acid derivative that reacts readily with nucleophiles, generally much more readily than the underivatized carboxylic acid. Activated carboxylic acids include, for example, acid halides (such as acid chlorides), anhydrides, carbonates, and esters. Such esters include imide esters, of the general form -(CO)O-N[(CO)-]₂; for example, N-hydroxysuccinimidyl (NHS) esters or N-hydroxyphthalimidyl esters. Also preferred are imidazolyl esters and benzotriazole esters. Particularly preferred are activated propionic acid or butanoic acid esters, as described in

co-owned U.S. Patent No. 5,672,662. These include groups of the form $-(\text{CH}_2)_{2-3}\text{C}(=\text{O})\text{O}-\text{Q}$, where Q is preferably selected from N-succinimide, N-sulfosuccinimide, N-phthalimide, N-glutarimide, N-tetrahydrophthalimide, N-norbornene-2,3-dicarboximide, benzotriazole, 7-azabenzotriazole, and imidazole.

[0098] Other preferred electrophilic groups include succinimidyl carbonate, maleimide, benzotriazole carbonate, glycidyl ether, imidazolyl carbonate, p-nitrophenyl carbonate, acrylate, tresylate, aldehyde, and orthopyridyl disulfide.

[0099] These electrophilic groups are subject to reaction with nucleophiles, e.g., hydroxy, thio, or amino groups, to produce various bond types. Preferred for the present invention are reactions which favor formation of a hydrolytically stable linkage. For example, carboxylic acids and activated derivatives thereof, which include orthoesters, succinimidyl esters, imidazolyl esters, and benzotriazole esters, react with the above types of nucleophiles to form esters, thioesters, and amides, respectively, of which amides are the most hydrolytically stable. Carbonates, including succinimidyl, imidazolyl, and benzotriazole carbonates, react with amino groups to form carbamates. Isocyanates ($\text{R}-\text{N}=\text{C}=\text{O}$) react with hydroxyl or amino groups to form, respectively, carbamate ($\text{RNH}-\text{C}(\text{O})-\text{OR}'$) or urea ($\text{RNH}-\text{C}(\text{O})-\text{NHR}'$) linkages. Aldehydes, ketones, glyoxals, diones and their hydrates or alcohol adducts (i.e., aldehyde hydrate, hemiacetal, acetal, ketone hydrate, hemiketal, and ketal) are preferably reacted with amines, followed by reduction of the resulting imine, if desired, to provide an amine linkage (reductive amination).

[0100] Several of the electrophilic functional groups include electrophilic double bonds to which nucleophilic groups, such as thiols, can be added, to form, for example, thioether bonds. These groups include maleimides, vinyl sulfones, vinyl pyridine, acrylates, methacrylates, and acrylamides. Other groups comprise leaving groups that can be displaced by a nucleophile; these include chloroethyl sulfone, pyridyl disulfides (which include a cleavable S-S bond), iodoacetamide, mesylate, tosylate, thiosulfonate, and tresylate. Epoxides react by ring opening by a nucleophile, to form, for example, an ether or amine bond. Reactions involving complementary reactive groups such as those noted above on the oligomer and the small molecule are utilized to prepare the conjugates of the invention.

[0101] In some instances the apremilast moiety may not have a functional group suited for conjugation. In this instance, it is possible to modify (or "functionalize") the "original" apremilast moiety so that it does have a functional group suited for conjugation.

For example, if the apremilast moiety has an amide group, but an amine group is desired, it is possible to modify the amide group to an amine group by way of a Hofmann rearrangement, Curtius rearrangement (once the amide is converted to an azide) or Lossen rearrangement (once amide is converted to hydroxamide followed by treatment with tolyene-2-sulfonyl chloride/base).

[0102] It is possible to prepare a conjugate of apremilast moiety bearing a carboxyl group wherein the carboxyl group-bearing apremilast moiety is coupled to an amino-terminated oligomeric ethylene glycol, to provide a conjugate having an amide group covalently linking the apremilast moiety to the oligomer. This can be performed, for example, by combining the carboxyl group-bearing apremilast moiety with the amino-terminated oligomeric ethylene glycol in the presence of a coupling reagent, (such as dicyclohexylcarbodiimide or "DCC") in an anhydrous organic solvent.

[0103] Further, it is possible to prepare a conjugate of an apremilast moiety bearing a hydroxyl group wherein the hydroxyl group-bearing apremilast moiety is coupled to an oligomeric ethylene glycol halide to result in an ether (-O-) linked conjugate. This can be performed, for example, by using sodium hydride to deprotonate the hydroxyl group followed by reaction with a halide-terminated oligomeric ethylene glycol.

[0104] Further, it is possible to prepare a conjugate of an apremilast moiety bearing a hydroxyl group wherein the hydroxyl group-bearing apremilast moiety is coupled to an oligomeric ethylene glycol bearing an haloformate group [e.g., $\text{CH}_3(\text{OCH}_2\text{CH}_2)_n\text{OC}(\text{O})\text{-halo}$, where halo is chloro, bromo, iodo] to result in a carbonate [-O-C(O)-O-] linked small molecule conjugate. This can be performed, for example, by combining an apremilast moiety and an oligomeric ethylene glycol bearing a haloformate group in the presence of a nucleophilic catalyst (such as 4-dimethylaminopyridine or "DMAP") to thereby result in the corresponding carbonate-linked conjugate.

[0105] In another example, it is possible to prepare a conjugate of an apremilast moiety bearing a ketone group by first reducing the ketone group to form the corresponding hydroxyl group. Thereafter, the apremilast moiety now bearing a hydroxyl group can be coupled as described herein.

[0106] In still another instance, it is possible to prepare a conjugate of an apremilast moiety bearing an amine group. In one approach, the amine group-bearing apremilast moiety and an aldehyde-bearing oligomer are dissolved in a suitable buffer after which a suitable

reducing agent (e.g., NaCNBH_3) is added. Following reduction, the result is an amine linkage formed between the amine group of the amine group-containing apremilast moiety and the carbonyl carbon of the aldehyde-bearing oligomer.

[0107] In another approach for preparing a conjugate of an apremilast moiety bearing an amine group, a carboxylic acid-bearing oligomer and the amine group-bearing apremilast moiety are combined, in the presence of a coupling reagent (e.g., DCC). The result is an amide linkage formed between the amine group of the amine group-containing apremilast moiety and the carbonyl of the carboxylic acid-bearing oligomer.

[0108] While it is believed that the full scope of the compounds disclosed herein behave as described, an optimally sized oligomer can be identified as follows.

[0109] First, an oligomer is conjugated to the apremilast moiety to form a compound and administered to a subject. Next, a property of interest is measured (e.g., biological activity, extent of blood-brain crossing, and so forth) and compared to that of the unmodified parent drug. This process is repeated for a series of compounds where all variables except one (e.g., oligomer size, monomer type, spacer moiety, and so forth) remain the same. Those compounds exhibiting the desired property or properties for the particular purpose are pursued.

[0110] For example, one of ordinary skill in the art, using routine experimentation, can determine a best suited molecular size and linkage for improving oral bioavailability by first preparing a series of oligomers with different weights and functional groups and then obtaining the necessary clearance profiles by administering the conjugates to a patient and taking periodic blood and/or urine sampling. Once a series of clearance profiles have been obtained for each tested conjugate, a suitable conjugate can be identified.

[0111] Animal models (rodents and dogs) can also be used to study oral drug transport. In addition, non-*in vivo* methods include rodent everted gut excised tissue and Caco-2 cell monolayer tissue-culture models. These models are useful in predicting oral drug bioavailability.

[0112] To determine whether the apremilast moiety or a compound of the invention (e.g., a conjugate of an apremilast moiety and a water-soluble, non-peptidic oligomer) has activity as an apremilast moiety therapeutic, it is possible to test such a compound. The compound of interest may be tested using *in vitro* binding studies to receptors using various

cell lines expressing these receptors that have become routine in pharmaceutical industry and described herein.

[0113] The compounds of the invention may be administered *per se* or in the form of a pharmaceutically acceptable salt, and any reference to the compounds of the invention herein is intended to include pharmaceutically acceptable salts. If used, a salt of a compound as described herein should be both pharmacologically and pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare the free active compound or pharmaceutically acceptable salts thereof and are not excluded from the scope of this invention. Such pharmacologically and pharmaceutically acceptable salts can be prepared by reaction of the compound with an organic or inorganic acid, using standard methods detailed in the literature. Examples of useful salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluenesulfonic, tartaric, citric, methanesulfonic, formic, malonic, succinic, naphthalene-2-sulphonic and benzenesulphonic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium, or calcium salts of a carboxylic acid group.

[0114] The present invention also includes pharmaceutical preparations comprising a compound as provided herein in combination with a pharmaceutical excipient. Generally, the compound itself will be in a solid form (e.g., a precipitate), which can be combined with a suitable pharmaceutical excipient that can be in either solid or liquid form.

[0115] Exemplary excipients include, without limitation, those selected from the group consisting of carbohydrates, inorganic salts, antimicrobial agents, antioxidants, surfactants, buffers, acids, bases, and combinations thereof.

[0116] A carbohydrate such as a sugar, a derivatized sugar such as an alditol, aldonic acid, an esterified sugar, and/or a sugar polymer may be present as an excipient. Specific carbohydrate excipients include, for example: monosaccharides, such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, maltitol, lactitol, xylitol, sorbitol, myoinositol, and the like.

[0117] The excipient can also include an inorganic salt or buffer such as citric acid, sodium chloride, potassium chloride, sodium sulfate, potassium nitrate, sodium phosphate monobasic, sodium phosphate dibasic, and combinations thereof.

[0118] The preparation may also include an antimicrobial agent for preventing or deterring microbial growth. Nonlimiting examples of antimicrobial agents suitable for the present invention include benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate, thimersol, and combinations thereof.

[0119] An antioxidant can be present in the preparation as well. Antioxidants are used to prevent oxidation, thereby preventing the deterioration of the conjugate or other components of the preparation. Suitable antioxidants for use in the present invention include, for example, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, and combinations thereof.

[0120] A surfactant may be present as an excipient. Exemplary surfactants include: polysorbates, such as "Tween 20" and "Tween 80," and pluronics such as F68 and F88 (both of which are available from BASF, Mount Olive, NJ); sorbitan esters; lipids, such as phospholipids such as lecithin and other phosphatidylcholines, phosphatidylethanolamines, fatty acids and fatty esters; steroids, such as cholesterol; and chelating agents, such as EDTA, zinc and other such suitable cations.

[0121] Pharmaceutically acceptable acids or bases may be present as an excipient in the preparation. Nonlimiting examples of acids that can be used include those acids selected from the group consisting of hydrochloric acid, acetic acid, phosphoric acid, citric acid, malic acid, lactic acid, formic acid, trichloroacetic acid, nitric acid, perchloric acid, phosphoric acid, sulfuric acid, fumaric acid, and combinations thereof. Examples of suitable bases include, without limitation, bases selected from the group consisting of sodium hydroxide, sodium acetate, ammonium hydroxide, potassium hydroxide, ammonium acetate, potassium acetate, sodium phosphate, potassium phosphate, sodium citrate, sodium formate, sodium sulfate, potassium sulfate, potassium fumarate, and combinations thereof.

[0122] The amount of the compound of the invention in the composition will vary depending on a number of factors, but will optimally be a therapeutically effective dose when the composition is stored in a unit dose container. A therapeutically effective dose can be

determined experimentally by repeated administration of increasing amounts of the compound in order to determine which amount produces a clinically desired endpoint.

[0123] The amount of any individual excipient in the composition will vary depending on the activity of the excipient and particular needs of the composition. The optimal amount of any individual excipient is determined through routine experimentation, i.e., by preparing compositions containing varying amounts of the excipient (ranging from low to high), examining the stability and other parameters, and then determining the range at which optimal performance is attained with no significant adverse effects.

[0124] Generally, however, excipients will be present in the composition in an amount of about 1% to about 99% by weight, preferably from about 5%-98% by weight, more preferably from about 15-95% by weight of the excipient, with concentrations less than 30% by weight most preferred.

[0125] These foregoing pharmaceutical excipients along with other excipients and general teachings regarding pharmaceutical compositions are described in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), and Kibbe, A.H., Handbook of Pharmaceutical Excipients, 3rd Edition, American Pharmaceutical Association, Washington, D.C., 2000.

[0126] The pharmaceutical compositions can take any number of forms and the invention is not limited in this regard. Exemplary preparations are most preferably in a form suitable for oral administration such as a tablet, caplet, capsule, gel cap, troche, dispersion, suspension, solution, elixir, syrup, lozenge, transdermal patch, spray, suppository, and powder.

[0127] Oral dosage forms are preferred for those conjugates that are orally active, and include tablets, caplets, capsules, gel caps, suspensions, solutions, elixirs, and syrups, and can also comprise a plurality of granules, beads, powders or pellets that are optionally encapsulated. Such dosage forms are prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts.

[0128] Tablets and caplets, for example, can be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred when preparing tablets or caplets containing the conjugates described herein. In addition to the conjugate, the tablets and caplets will generally contain inactive,

pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, flow agents, and the like. Binders are used to impart cohesive qualities to a tablet, and thus ensure that the tablet remains intact. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, microcrystalline cellulose, ethyl cellulose, hydroxyethylcellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture, promoting powder flow and preventing particle capping (i.e., particle breakage) when pressure is relieved. Useful lubricants are magnesium stearate, calcium stearate, and stearic acid. Disintegrants are used to facilitate disintegration of the tablet, and are generally starches, clays, celluloses, algin, gums, or crosslinked polymers. Fillers include, for example, materials such as silicon dioxide, titanium dioxide, alumina, talc, kaolin, powdered cellulose, and microcrystalline cellulose, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, and sorbitol. Stabilizers, as well known in the art, are used to inhibit or retard drug decomposition reactions that include, by way of example, oxidative reactions.

[0129] Capsules are also preferred oral dosage forms, in which case the conjugate-containing composition can be encapsulated in the form of a liquid or gel (e.g., in the case of a gel cap) or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules include hard and soft capsules, and are generally made of gelatin, starch, or a cellulosic material. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like.

[0130] Included are parenteral formulations in the substantially dry form (as a lyophilizate or precipitate, which can be in the form of a powder or cake), as well as formulations prepared for injection, which are liquid and require the step of reconstituting the dry form of parenteral formulation. Examples of suitable diluents for reconstituting solid compositions prior to injection include bacteriostatic water for injection, dextrose 5% in water, phosphate-buffered saline, Ringer's solution, saline, sterile water, deionized water, and combinations thereof.

[0131] In some cases, compositions intended for parenteral administration can take the form of nonaqueous solutions, suspensions, or emulsions, normally being sterile. Examples of nonaqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and corn oil, gelatin, and injectable organic esters such as ethyl oleate.

[0132] The parenteral formulations described herein can also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. The formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat.

[0133] The compounds of the invention can also be administered through the skin using conventional transdermal patch or other transdermal delivery system, wherein the conjugate is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the compound is contained in a layer, or "reservoir," underlying an upper backing layer. The laminated structure can contain a single reservoir, or it can contain multiple reservoirs.

[0134] The compounds of the invention can also be formulated into a suppository for rectal administration. With respect to suppositories, the compound is mixed with a suppository base material which is (e.g., an excipient that remains solid at room temperature but softens, melts or dissolves at body temperature) such as cocoa butter (theobroma oil), polyethylene glycols, glycerinated gelatin, fatty acids, and combinations thereof. Suppositories can be prepared by, for example, performing the following steps (not necessarily in the order presented): melting the suppository base material to form a melt; incorporating the compound (either before or after melting of the suppository base material); pouring the melt into a mold; cooling the melt (e.g., placing the melt-containing mold in a room temperature environment) to thereby form suppositories; and removing the suppositories from the mold.

[0135] In some embodiments of the invention, the compositions comprising the compounds of the invention may further be incorporated into a suitable delivery vehicle. Such delivery vehicles may provide controlled and/or continuous release of the compounds and may also serve as a targeting moiety. Non-limiting examples of delivery vehicles include, adjuvants, synthetic adjuvants, microcapsules, microparticles, liposomes, and yeast cell wall particles. Yeast cells walls may be variously processed to selectively remove

protein component, glucan, or mannan layers, and are referred to as whole glucan particles (WGP), yeast beta-glucan mannan particles (YGMP), yeast glucan particles (YGP), Rhodotorula yeast cell particles (YCP). Yeast cells such as *S. cerevisiae* and *Rhodotorula* species are preferred; however, any yeast cell may be used. These yeast cells exhibit different properties in terms of hydrodynamic volume and also differ in the target organ where they may release their contents. The methods of manufacture and characterization of these particles are described in U.S. Patent Nos. 5,741,495, 4,810,646, 4,992,540, 5,028,703 and 5,607,677, and U.S. Patent Application Publication Nos. 2005/0281781 and 2008/0044438.

[0136] The invention also provides a method for administering a compound of the invention as provided herein to a patient suffering from a condition that is responsive to treatment with the compound. The method comprises administering, generally orally, a therapeutically effective amount of the compound (preferably provided as part of a pharmaceutical preparation). Other modes of administration are also contemplated, such as pulmonary, nasal, buccal, rectal, sublingual, transdermal, and parenteral. As used herein, the term "parenteral" includes subcutaneous, intravenous, intra-arterial, intraperitoneal, intracardiac, intrathecal, and intramuscular injection, as well as infusion injections.

[0137] In instances where parenteral administration is utilized, it may be necessary to employ somewhat bigger oligomers than those described previously, with molecular weights ranging from about 500 to 30K Daltons (e.g., having molecular weights of about 500, 1000, 2000, 2500, 3000, 5000, 7500, 10000, 15000, 20000, 25000, 30000 or even more).

[0138] The method of administering may be used to treat any condition that can be remedied or prevented by administration of a particular compound of the invention. Those of ordinary skill in the art appreciate which conditions a specific compound can effectively treat. Exemplary conditions include inflammation, psoriasis, allergies, asthma, chronic obstructive pulmonary disease, acute obstructive pulmonary disease, Crohn's disease, colitis, Bechet's disease, myelodysplastic syndrome and myeloproliferative disease. The actual dose to be administered will vary depend upon the age, weight, and general condition of the subject as well as the severity of the condition being treated, the judgment of the health care professional, and conjugate being administered. Therapeutically effective amounts are known to those skilled in the art and/or are described in the pertinent reference texts and literature. Generally, a therapeutically effective amount will range from about 0.001 mg to

1000 mg, preferably in doses from 0.01 mg/day to 750 mg/day, and more preferably in doses from 0.10 mg/day to 500 mg/day.

[0139] The unit dosage of any given compound of the invention (again, preferably provided as part of a pharmaceutical preparation) can be administered in a variety of dosing schedules depending on the judgment of the clinician, needs of the patient, and so forth. The specific dosing schedule will be known by those of ordinary skill in the art or can be determined experimentally using routine methods. Exemplary dosing schedules include, without limitation, administration five times a day, four times a day, three times a day, twice daily, once daily, three times weekly, twice weekly, once weekly, twice monthly, once monthly, and any combination thereof. Once the clinical endpoint has been achieved, dosing of the composition is halted.

[0140] All articles, books, patents, patent publications and other publications referenced herein are incorporated by reference in their entireties. In the event of an inconsistency between the teachings of this specification and the art incorporated by reference, the meaning of the teachings and definitions in this specification shall prevail (particularly with respect to terms used in the claims appended herein). For example, where the present application and a publication incorporated by reference defines the same term differently, the definition of the term shall be preserved within the teachings of the document from which the definition is located.

EXPERIMENTAL

[0141] It is to be understood that while the invention has been described in conjunction with certain preferred and specific embodiments, the foregoing description as well as the examples that follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

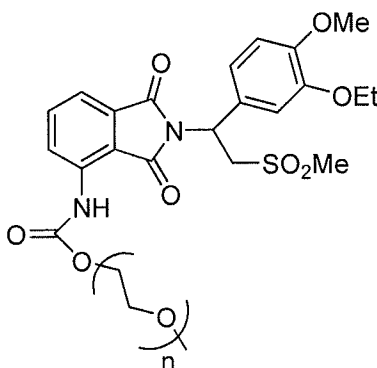
[0142] All non-PEG chemical reagents referred to in the appended examples are commercially available unless otherwise indicated. The preparation of PEG-mers is described in, for example, U.S. Patent Application Publication No. 2005/0136031.

[0143] ¹H NMR (nuclear magnetic resonance) data was generated by an NMR spectrometer. All reactions were conducted in a well-ventilated fume hood under N₂ using a Teflon-coated magnetic stir bar at the temperature indicated. Reactions heated by microwave

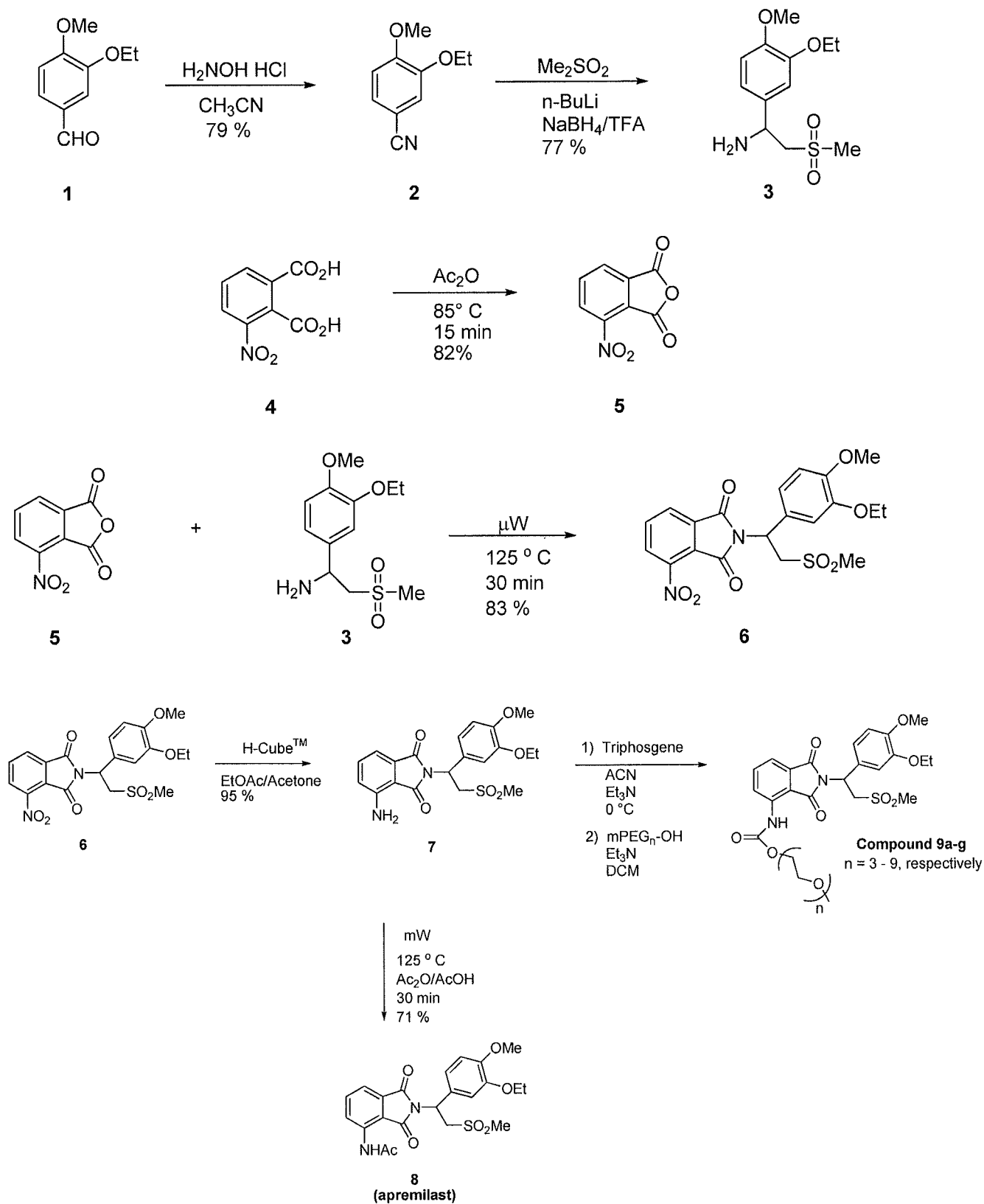
utilized a Biotage® Initiator 2.5 microwave utilizing 100 W of energy (indicated by a "μW" in the schematic), with the solvents indicated. Unless otherwise indicated, removal of solvents was conducted by using a rotary evaporator, and residual solvent was removed from nonvolatile compounds using a vacuum manifold maintained at approximately 1 torr. Purification of compounds was conducted on a Biotage Isolera using prepackaged silica gel cartridges, under gradient elution. All yields reported are isolated yields. Nitro functional group reductions were conducted on a ThalesNano H-cube™ hydrogen reactor (Budapest Hungary), using pre-packaged catalyst cartridges (10 % Pd/C; 30 mm L) and ethyl acetate:acetone (1:1) as the solvent. ¹H-NMR spectra were obtained on a Bruker 500 MHz magnetic resonance spectrometer (Bruker Inc., Billerica MA). ¹H-NMR spectra are reported as chemical shifts in parts-per-million (ppm) relative to an internal solvent reference. Peak multiplicity abbreviations are as follows: s (singlet), br s (broad singlet), d (doublet), dd (doublets of doublets), t (triplet), q (quartet), quin (quintet), and m (multiplet). Analytical HPLC and mass spectrometry were conducted using a reverse-phase Agilent1100 Series. Purities for final compounds were measured using UV detection at 254 nm.

EXAMPLE 1

Synthesis of Compounds Comprising a Carbamate Linkage



[0144] An exemplary approach for preparing compounds of the invention comprising a carbamate linkage is provided schematically below. Using this approach, racemic mixtures were prepared; individual isomers and compositions of the same can be also be prepared and are contemplated.



[0145] Preparation of 3-Ethoxy-4-methoxybenzonitrile (Compound 2). 3-Ethoxy-4-methoxybenzaldehyde (Compound 1, 10.0 gm, 54.9 mmol, Aldrich) and hydroxylamine hydrochloride (4.67 gm, 65.9 mmol, Aldrich) were charged to a 250 mL three-necked flask at room temperature, followed by the addition of anhydrous acetonitrile (50 mL). The reaction mixture was stirred at room temperature for thirty minutes and then heated to reflux (oil bath at 85 °C). After two hours of reflux, the reaction mixture was cooled to room temperature, and added 50 mL of deionized water. The mixture was concentrated under reduced pressure to remove acetonitrile and then transferred to a separatory funnel with an additional 80 mL of deionized water and 80 mL dichloromethane. The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed successively with water (80 mL) and saturated sodium chloride (80 mL). The organic layer was dried over anhydrous sodium sulfate (approximately 20 gm). The organic layer was filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 1 % MeOH/DCM) afforded 3-Ethoxy-4-methoxybenzonitrile (Compound 2) as a white solid (7.69 gm, 79 % yield). MS (ESI positive ion) m/z 178.1 ($M + 1$). HPLC indicated >99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 1.32 (t, 3H), 3.83 (s, 3H), 4.05 (q, 2H), 7.10 (d, $J = 8.0$ Hz, 1H), 7.35 (d, $J = 2.0$ Hz, 1H), 7.40 (dd, $J = 2.0$ Hz, 1H).

[0146] Preparation of 1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethanamine (Compound 3). Dimethylsulfone (2.60 gm, 27.1 mmol, Aldrich) and tetrahydrofuran (10 mL, Aldrich) were charged to a 250 mL three-necked flask at room temperature. The mixture was cooled to 0 - 5 °C, and the solution gradually turned white. *n*-Butyllithium (10.8 mL, 27.1 mmol, 2.5 M solution in hexanes, Aldrich) was added to the flask at a rate such that the reaction mixture was maintained at 5 - 10 °C. The mixture was stirred at 0 - 5 °C for one hour, turning light-yellow. 3-Ethoxy-4-methoxybenzonitrile (Compound 2, 4.01 gm, 22.5 mmol) in tetrahydrofuran (8 mL) was then charged to the flask at a rate such that the reaction mixture was maintained at 0 - 5 °C. The mixture was stirred at 0 - 5 °C for another 15 minutes. After warming to room temperature, the reaction mixture was stirred for another 1.5 hours and then transferred to a second 250 mL three-necked flask containing a suspension of sodium borohydride (1.13 gm, 29.3 mmol, Aldrich) in tetrahydrofuran (11 mL), maintained at - 5 - 0 °C for 30 minutes. Trifluoroacetic acid ("TFA," 5.26 mL, 68.3 mmol, Aldrich) was charged to the flask at a rate such that the reaction mixture was maintained at 0 - 5 °C. The mixture was stirred at 0 - 5 °C for 40

minutes and an additional 17 hours at room temperature. The reaction mixture was then charged with 2.7 mL of deionized water over five minutes at room temperature. The mixture was stirred at room temperature for 15 hours. Aqueous NaOH (10 N, 4.9 mL) was charged to the flask over 15 minutes at 45 °C. The mixture was stirred at 45 °C for two hours, at 60 °C for 1.5 hours, and at room temperature overnight. After approximately 17 hours at room temperature the mixture was cooled to 0 °C for thirty minutes and then concentrated under reduced pressure. The residual material was charged with deionized water (3 mL) and absolute ethanol (3 mL) and stirred at 0 - 5 °C for 2 hours. The mixture was filtered under vacuum, and the filtered solid was washed with cold absolute ethanol (3 x 5 mL), followed by deionized water until the pH of the wash was about 8. The solid was air dried overnight, and then in a vacuum oven at 60 °C for 17 hours to afford Compound **3** as a white solid (4.75 gm, 77 %). MS (ESI positive ion) m/z 274.1 ($M + 1$). $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 1.32 (t, $J = 7.0$ Hz, 3H), 2.08 (bs, 2H), 2.95 (s, 3H), 3.23 (dd, $J = 4.0$ Hz, 1H), 3.40 (dd, $J = 9.5$ Hz, 1H), 3.72 (s, 3H), 4.01 (q, $J = 7.0$ Hz, 2H), 4.25 (dd, $J = 3.5$ Hz, 1H), 6.88 (s, 2H), 7.02 (s, 1H).

[0147] Preparation of 4-Nitroisobenzofuran-1,3-dione (Compound 5). Into a 250 mL round bottom flask, fitted with a reflux condenser, was placed 3-nitrophthalic acid (21.0 gm, 99 mmol, Aldrich) and acetic anhydride (18.8 mL, 199 mmol, Aldrich). The solid mixture was heated to 85 °C, under nitrogen, with gradual melting of the solids. The yellow mixture was heated at 85 °C for 15 minutes, and there was noticeable thickening of the mixture. After 15 minutes at 85 °C, the hot mixture was poured into a weighing dish, and allowed to cool. The yellow solid was grinded to a powder and then placed on a cindered funnel, under vacuum. The solid was washed with diethyl ether (3 x 15 mL), under vacuum and allowed to air dry overnight, to afford 4-nitroisobenzofuran-1,3-dione, Compound **5**, as a light-yellow solid (15.8 gm, 82 %). MS (ESI positive ion) m/z 194.0 ($M + 1$). TLC: $R_f = 0.37$ (10% MeOH/DCM with 2 drops Acetic acid) $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 8.21 (dd, $J = 7.5$ Hz, 1H), 8.39 (dd, $J = 7.5$ Hz, 1H), 8.50 (dd, $J = 7.5$ Hz, 1H).

[0148] Preparation of 2-(1-(3-Ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-4-nitroisindoline-1,3-dione (Compound 6). Into a 2 - 5 mL microwave vial was added 4-nitroisobenzofuran-1,3-dione (Compound **5**, 0.35 gm, 1.82 mmol), the amino-sulfone intermediate (Compound **3**, 0.50 gm, 1.82 mmol) and 4.0 mL of glacial acetic acid. The mixture was placed in a microwave at 125 °C for 30 minutes. After 30 minutes the acetic acid was removed under reduced pressure. The yellow oil was taken up

in ethyl acetate and applied to a 10 gm snap Biotage samplet. Purification by silica gel chromatography (0 to 20 % Ethyl Acetate/Hexanes) afforded Compound **6** as a light-yellow solid (0.67 gm, 82 %). MS (ESI positive ion) m/z 449.0 ($M + 1$). TLC: R_f = 0.19

(EtOAc:Hexanes, 1:1). HPLC indicated 99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 1.32 (t, 3H), 2.99 (s, 3H), 3.73 (s, 3H), 4.02 (m, 2H), 4.21 (dd, J = 5.0 Hz, 1H), 4.29 (dd, J = 10.0 Hz, 1H), 5.81 (dd, J = 5.0 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 7.00 (dd, J = 2.0 Hz, 1H), 7.10 (d, J = 2.5 Hz, 1H), 8.07 (t, J = 15.5 Hz, 1H), 8.19 (dd, J = 8.5 Hz, 1H), 8.30 (dd, J = 9.0 Hz, 1H).

[0149] Preparation of 4-Amino-2-(1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 7). Compound **6** (0.54 gm, 1.20 mmol) was taken up in ethyl acetate / acetone (1:1, 24 mL) and flowed through the H-cubeTM hydrogen reactor using a 10 % Pd/C CatCartTM catalyst cartridge system (ThalesNano, Budapest Hungary). After eluting, the yellow solvent was concentrated under reduced pressure to give Compound **7** as a yellow foam solid (0.48 gm, 95 %). MS (ESI positive ion) m/z 419.1 ($M + 1$). $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 1.31 (t, J = 7.0 Hz, 3H), 2.99 (s, 3H), 3.72 (s, 3H), 4.04 (q, J = 7.0 Hz, 2H), 4.09 (m, 1H), 4.34 (m, 1H), 5.71 (dd, J = 5.5 Hz, 1H), 6.52 (bs, 2H), 6.92-6.98 (m, 3H), 7.06 (bs, 1H), 7.42 (dd, J = 7.0 Hz, 1H).

[0150] Preparation of N-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-yl)acetamide (Apremilast, Compound 8).

Into a 2-5 mL microwave vial was placed Compound **7** (0.18 gm, 0.43 mmol), acetic anhydride (0.052 mL, 0.53 mmol) and acetic acid (4 mL). The microwave vial was placed into a Biotage microwave and heated to 125 °C for 30 minutes. The solvents were removed under reduced pressure and the residue was purified by silica gel chromatography (0 to 5% MeOH/DCM) to afford apremilast (Compound **8**) as a yellow oil (0.14 gm, 71%). HPLC indicated 94.6% purity by peak area. $^1\text{H-NMR}$ (500 MHz, $\text{DMSO-}d_6$): δ ppm 1.31 (t, 3H), 2.18 (s, 3H), 3.01 (s, 3H), 3.73 (s, 3H), 4.01 (t, J = 7.0 Hz, 2H), 4.14 (dd, J = 4.0 Hz, 1H), 4.33 (m, 1H), 5.76 (dd, J = 3.0 Hz, 1H), 6.95 (m, 2H), 7.06 (d, J = 1.5 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.79 (t, J = 7.7 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 9.72 (bs, 1H).

[0151] Preparation of 2-(2-(2-methoxyethoxy)ethoxy)ethyl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate

(Compound 9a wherein $n=3$, "mPEG₃-carbamate apremilast"). To a solution of triphosgene (0.31 gm, 1.07 mmol) in anhydrous acetonitrile (30 mL) at - 5 °C were added an

acetonitrile (20 mL) solution of Compound 7 (0.75 gm, 1.79 mmol) and triethylamine (0.33 mL, 2.33 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-3-OH (0.30 gm, 1.88 mmol) and triethylamine (0.33 mL, 2.33 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (20 mL) and transferred to a separatory funnel with deionized water (25 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with deionized water (2 x 20 mL) and saturated sodium chloride (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **9a** as a yellow oil. (0.39 gm, 36 % yield). TLC product: R_f = 0.48 (5% MeOH/DCM). MS (ESI positive ion) m/z 609.2 ($M + 1$). $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.47 (t, J = 8.4 Hz, 3H), 2.87 (s, 3H), 3.37 (s, 3H), 3.56 (m, 2H), 3.70 (m, 6H), 3.76 (m, 3H), 3.84 (s, 3H), 4.10 (q, J = 8.3 Hz, 2H), 4.36 (m, 2H), 4.56 (dd, J = 5.0 Hz, 1H), 5.86 (dd, J = 5.0 Hz, 1H), 6.84 (d, J = 10.0 Hz, 1H), 7.09 (m, 2H), 7.43 (d, J = 10.0 Hz, 1H), 7.63 (t, J = 10.0 Hz, 1H), 8.48 (d, J = 10.0 Hz), 8.94 (bs, 1H).

[0152] Preparation of 2,5,8,11-tetraoxatridecan-13-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate (Compound 9b wherein n=4, "mPEG₄-carbamate apremilast"). To a solution of triphosgene (0.22 gm, 0.75 mmol) in anhydrous acetonitrile (15 mL) at - 5 °C were added an acetonitrile (20 mL) solution of Compound 7 (0.63 gm, 1.50 mmol) and triethylamine (0.26 mL, 1.88 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-4-OH (0.40 gm, 1.88 mmol) and triethylamine (0.26 mL, 1.88 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **9b** as a yellow oil. (0.67 gm, 68 % yield). TLC product: R_f = 0.72 (10% MeOH/DCM). MS (ESI positive ion) m/z

653.3 (M + 1). ¹H-NMR (500 MHz, CDCl₃): δ ppm 1.46 (t, J = 7.0 Hz, 3H), 2.88 (s, 3H), 3.36 (s, 3H), 3.54 (m, 2H), 3.63 – 3.72 (m, 10H), 3.76 – 3.82 (m, 4H), 3.85 (s, 3H), 4.10 (q, 2H), 4.36 (m, 2H), 4.54 (dd, J = 10.5 Hz, 1H), 5.86 (dd, J = 4.5 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 7.09 (m, 2H), 7.42 (d, J = 7.0 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.94 (bs, 1H)

[0153] Preparation of 2,5,8,11,14-pentaoxaheptadecan-16-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate

(Compound 9c wherein n=5, "mPEG₅-carbamate apremilast"). To a solution of triphosgene (0.28 gm, 0.94 mmol) in anhydrous acetonitrile (15 mL) at - 5 °C were added an acetonitrile (20 mL) solution of Compound 7 (0.66 gm, 1.57 mmol) and triethylamine (0.29 mL, 2.05 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-5-OH (0.50 gm, 1.97 mmol) and triethylamine (0.29 mL, 2.05 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound 9c as a yellow oil. (0.29 gm, 26 % yield). TLC product: R_f = 0.66 (10% MeOH/DCM). MS (ESI positive ion) m/z 697.3 (M + 1). ¹H-NMR (500 MHz, CDCl₃): δ ppm 1.47 (t, J = 8.4 Hz, 3H), 2.87 (s, 3H), 3.37 (s, 3H), 3.56 (m, 2H), 3.69 (m, 15H), 3.76 (m, 3H), 3.85 (s, 3H), 4.10 (q, J = 8.3 Hz, 2H), 4.36 (m, 2H), 4.54 (dd, J = 5.0 Hz, 1H), 5.86 (dd, J = 5.0 Hz, 1H), 6.84 (d, J = 10.0 Hz, 1H), 7.09 (m, 2H), 7.43 (d, J = 10.0 Hz, 1H), 7.63 (t, J = 10.0 Hz, 1H), 8.48 (d, J = 10.0 Hz), 8.94 (bs, 1H).

[0154] Preparation of 2,5,8,11,14,17-hexaoxanonadecan-19-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate

(Compound 9d wherein n=6, "mPEG₆-carbamate apremilast"). To a solution of triphosgene (0.17 gm, 0.57 mmol) in anhydrous acetonitrile (15 mL) at - 5 °C were added an acetonitrile (15 mL) solution of Compound 7 (0.48 gm, 1.14 mmol) and triethylamine (0.20 mL, 1.43 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-6-OH (0.42 gm, 1.43

mmol) and triethylamine (0.20 mL, 1.43 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a crude orange oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **9d** as a yellow oil. (0.43 gm, 50 % yield). TLC product: R_f = 0.57 (10% MeOH/DCM). MS (ESI positive ion) m/z 741.3 ($M + 1$). HPLC indicated 99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.47 (t, J = 7.0 Hz, 3H), 3.37 (s, 3H), 3.54 (m, 2H), 3.62 – 3.69 (m, 20H), 3.78 (m, 3H), 3.84 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 4.36 (m, 2H), 4.54 (dd, J = 10.2 Hz, 1H), 5.86 (dd, J = 4.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 7.10 (m, 2H), 7.43 (d, J = 7.0 Hz, 1H), 7.64 (t, J = 8.5 Hz, 1H), 8.48 (d, J = 8.5 Hz, 1H), 8.94 (bs, 1H).

[0155] Preparation of 2,5,8,11,14,17,20-heptaoadocosan-22-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate

(Compound 9e wherein $n=7$, "mPEG₇-carbamate apremilast"). To a solution of triphosgene (0.26 gm, 0.90 mmol) in anhydrous acetonitrile (12 mL) at - 5 °C were added an acetonitrile (15 mL) solution of Compound **7** (0.63 gm, 1.50 mmol) and triethylamine (0.27 mL, 1.95 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (15 mL) solution of mPEG-7-OH (0.64 gm, 1.88 mmol) and triethylamine (0.27 mL, 1.95 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **9e** as a yellow oil. (0.66 gm, 55 % yield). MS (ESI positive ion) m/z 785.3 ($M + 1$). HPLC indicated 99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.47 (t, J = 7.0 Hz, 3H), 3.37 (s, 3H), 3.54 (m, 2H), 3.62 – 3.69 (m, 20H), 3.78 (m, 3H), 3.84 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 4.36 (m,

2H), 4.54 (dd, $J = 10.2$ Hz, 1H), 5.85 (dd, $J = 4.5$ Hz, 1H), 6.84 (d, $J = 8.5$ Hz, 1H), 7.09 (m, 2H), 7.46 (d, $J = 7.0$ Hz, 1H), 7.64 (t, $J = 8.5$ Hz, 1H), 8.49 (d, $J = 8.5$ Hz, 1H), 8.94 (bs, 1H).

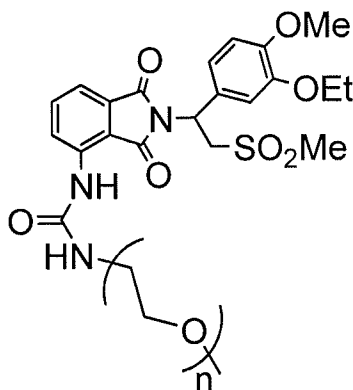
[0156] Preparation of 2,5,8,11,14,17,20,23-octaoxapentacosan-25-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate (Compound 9f wherein $n=8$, "mPEG₈-carbamate apremilast"). To a solution of triphosgene (0.13 gm, 0.44 mmol) in anhydrous acetonitrile (8 mL) at -5 °C were added an acetonitrile (8 mL) solution of Compound 7 (0.34 gm, 0.81 mmol) and triethylamine (0.14 mL, 1.01 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-8-OH (0.39 gm, 1.01 mmol) and triethylamine (0.14 mL, 1.01 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound 9f as a yellow oil. (0.55 gm, 81 % yield). MS (ESI positive ion) m/z 829.4 ($M + 1$). TLC product: $R_f = 0.58$ (10% MeOH/DCM). HPLC indicated 99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.44 (t, $J = 7.0$ Hz, 3H), 2.86 (s, 3H), 3.34 (s, 3H), 3.51 (m, 3H), 3.62 – 3.69 (m, 42H), 3.78 (m, 4H), 3.84 (s, 3H), 4.07 (q, $J = 7.0$ Hz, 2H), 4.33 (m, 2H), 4.51 (dd, $J = 10.5$ Hz, 1H), 5.83 (dd, $J = 4.5$ Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 7.06 (m, 2H), 7.40 (d, $J = 6.5$ Hz, 1H), 7.61 (t, $J = 7.5$ Hz, 1H), 8.45 (d, $J = 8.5$ Hz, 1H), 8.91 (bs, 1H).

[0157] Preparation of 2,5,8,11,14,17,20,23,26-nonaooctacosan-28-yl 2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-ylcarbamate (Compound 9g wherein $n=9$, "mPEG₉-carbamate apremilast"). To a solution of triphosgene (0.10 gm, 0.35 mmol) in anhydrous acetonitrile (8 mL) at -5 °C were added an acetonitrile (8 mL) solution of Compound 7 (0.27 gm, 0.641 mmol) and triethylamine (0.11 mL, 0.80 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloromethane (20 mL) solution of mPEG-9-OH (0.35 gm, 0.80 mmol) and triethylamine (0.11 mL, 0.80 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water

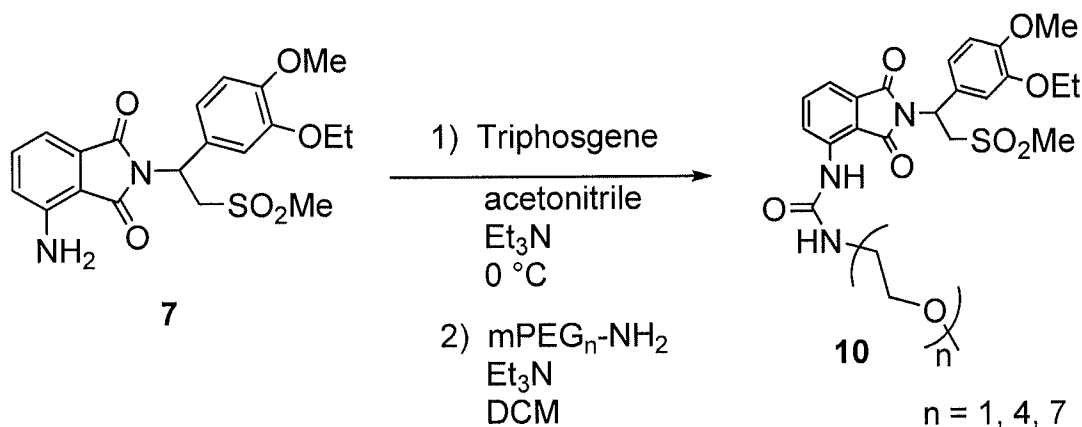
(40 mL). The aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic layers were washed with deionized water (2 x 35 mL) and saturated sodium chloride (35 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **9g** as a yellow oil. (0.47 gm, 83 % yield). MS (ESI positive ion) m/z 873.4 ($M + 1$). TLC product: R_f = 0.53 (10% MeOH/DCM). HPLC indicated 99% purity by peak area. $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.47 (t, J = 7.0 Hz, 3H), 2.89 (s, 3H), 3.37 (s, 3H), 3.55 (m, 2H), 3.62 – 3.69 (m, 36H), 3.78 (m, 3H), 3.84 (s, 3H), 4.10 (q, J = 7.0 Hz, 2H), 4.36 (m, 2H), 4.54 (dd, J = 10.5 Hz, 1H), 5.86 (dd, J = 4.2 Hz, 1H), 6.84 (d, J = 9.0 Hz, 1H), 7.09 (m, 2H), 7.43 (d, J = 7.5 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 8.47 (d, J = 8.5 Hz, 1H), 8.94 (bs, 1H).

EXAMPLE 2

Synthesis of Compounds Comprising a Urea Linkage



[0158] An exemplary approach for preparing compounds of the invention comprising a urea linkage is provided schematically below. Using this approach, racemic mixtures were prepared; individual isomers and compositions of the same can be also be prepared and are contemplated.



[0159] Preparation of 1-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-yl)-3-(2-methoxyethyl)urea (Compound

10a wherein n=1, "mPEG₁-urea apremilast"). To a solution of triphosgene (0.26 gm, 0.87 mmol) in anhydrous acetonitrile (5 mL) at -5°C were added an acetonitrile (5 mL) solution of 4-amino-2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 7, prepared in accordance with the procedure set forth in Example 1) (0.61 gm, 1.45 mmol) and triethylamine (0.27 mL, 1.89 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0°C , and then a dichloroethane (5 mL) solution of mPEG₁-NH₂ ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{-NH}_2$) (0.11 gm, 1.45 mmol) and triethylamine (0.27 mL, 1.89 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (20 mL) and transferred to a separatory funnel with deionized water (25 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with deionized water (2 x 20 mL) and saturated sodium chloride (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **10a** as a yellow oil. (0.26 gm, 30 % yield). TLC product: $R_f = 0.55$ (10 % MeOH/DCM). MS (ESI positive ion) m/z 520.2 ($M + 1$). ¹H-NMR (500 MHz, CDCl_3): δ ppm 1.46 (t, 3H), 2.85 (s, 3H), 3.39 (s, 3H), 3.45 (m, 2H), 3.52 (m, 2H), 3.75 (dd, 1H), 3.84 (s, 3H), 4.08 (q, 2H), 4.52 (dd, $J = 10.5$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 7.06 (m, 2H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.56 (dd, $J = 7.0$ Hz, 1H), 8.61 (d, $J = 8.5$ Hz), 8.66 (bs, 1H).

[0160] Preparation of 1-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-

(methylsulfonyl)ethyl)-1,3-dioxoisindolin-4-yl)-3-(2,5,8,11-tetraoxatridecan-13-yl)urea (Compound 10b wherein n=4, "mPEG₄-urea apremilast"). To a solution of triphosgene

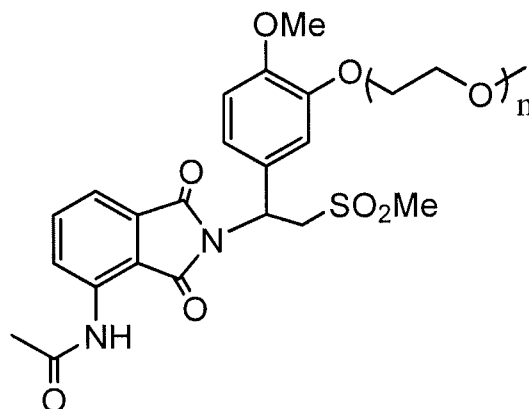
(0.085 gm, 0.28 mmol) in anhydrous acetonitrile (2.5 mL) at - 5 °C were added an acetonitrile (5 mL) solution of 4-amino-2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 7, prepared in accordance with the procedure set forth in Example 1) (0.20 gm, 0.47 mmol) and triethylamine (0.088 mL, 0.62 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloroethane (5 mL) solution of mPEG₄-NH₂ (0.099 gm, 0.47 mmol) and triethylamine (0.088 mL, 0.62 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (20 mL) and transferred to a separatory funnel with deionized water (25 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with deionized water (2 x 20 mL) and saturated sodium chloride (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **10b** as a yellow oil. (0.08 gm, 26 % yield). TLC product: R_f = 0.25 (3 % MeOH/DCM). MS (ESI positive ion) *m/z* 652.0 (*M* + 1). ¹H-NMR (500 MHz, CDCl₃): δ ppm 1.45 (t, 3H), 2.82 (s, 3H), 3.32 (s, 3H), 3.45 (m, 2H), 3.52 (m, 2H), 3.62 – 3.69 (m, 9H), 3.71 (s, 3H), 3.80 (dd, 1H), 4.08 (q, 2H), 4.49 (dd, *J* = 10.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 7.06 (m, 2H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.56 (dd, *J* = 7.0 Hz, 1H), 8.65 (d, *J* = 8.5 Hz), 8.69 (bs, 1H).

[0161] Preparation of 1-(2,5,8,11,14,17,20-heptaodocosan-22-yl)-3-(2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-1,3-dioxoisoindolin-4-yl)urea (Compound 10c wherein n=7, "mPEG₇-urea apremilast"). To a solution of triphosgene (0.16 gm, 0.54 mmol) in anhydrous acetonitrile (8 mL) at - 5 °C were added an acetonitrile (20 mL) solution of 4-amino-2-(1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 7, prepared in accordance with the procedure set forth in Example 1) (0.38 gm, 0.90 mmol) and triethylamine (0.16 mL, 1.18 mmol) over a period of ten minutes. The mixture was stirred for an additional 30 minutes at 0 °C, and then a dichloroethane (15 mL) solution of mPEG₇-NH₂ (0.38 gm, 1.13 mmol) and triethylamine (0.16 mL, 1.18 mmol) was slowly added. The reaction mixture was allowed to equilibrate to room temperature overnight. After 18 hours the mixture was diluted with dichloromethane (40 mL) and transferred to a separatory funnel with deionized water (45 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with deionized water (2 x 40 mL) and saturated sodium chloride

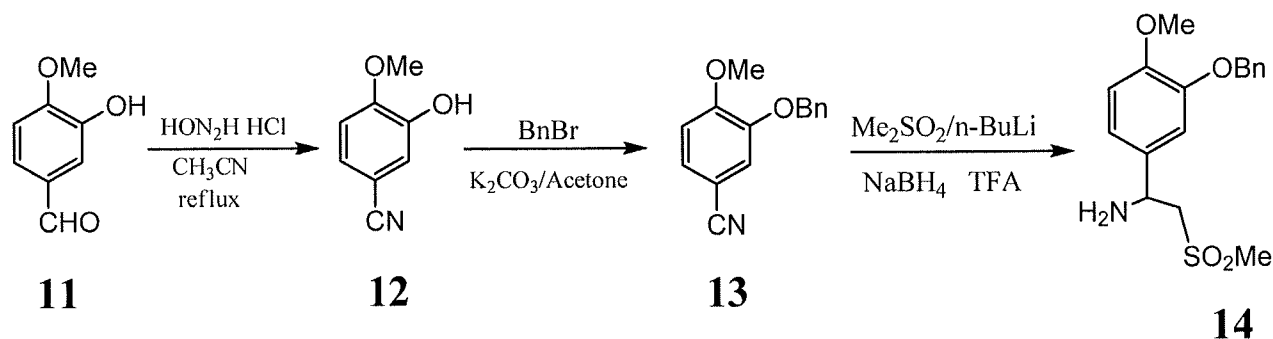
(40 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a yellow oil. Purification by silica gel chromatography (0 to 5 % MeOH/DCM) afforded Compound **10c** as a yellow oil. (0.24 gm, 33 % yield). TLC product: R_f = 0.29 (5 % MeOH/DCM). MS (ESI positive ion) m/z 784.2 ($M + 1$). $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ ppm 1.47 (t, 3H), 2.83 (s, 3H), 3.37 (s, 3H), 3.48 (m, 2H), 3.55 (m, 2H), 3.62 – 3.73 (m, 23H), 3.76 (dd, 1H), 3.85 (s, 3H), 3.80 (dd, 1H), 3.85 (s, 3H), 4.10 (q, 2H), 4.50 (dd, J = 10.5 Hz, 1H), 5.84 (dd, 1H), 6.83 (d, J = 8.5 Hz, 1H), 7.08 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.59 (dd, J = 7.0 Hz, 1H), 8.66 (d, J = 8.5 Hz), 8.70 (bs, 1H).

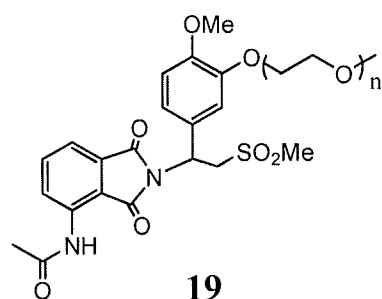
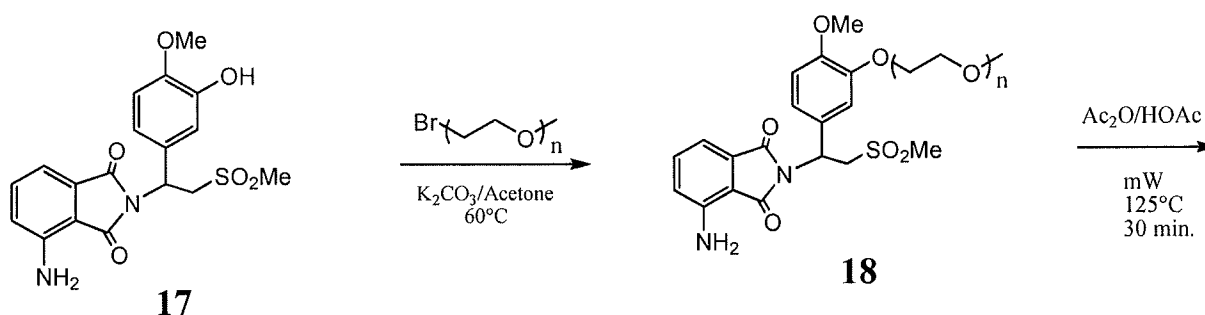
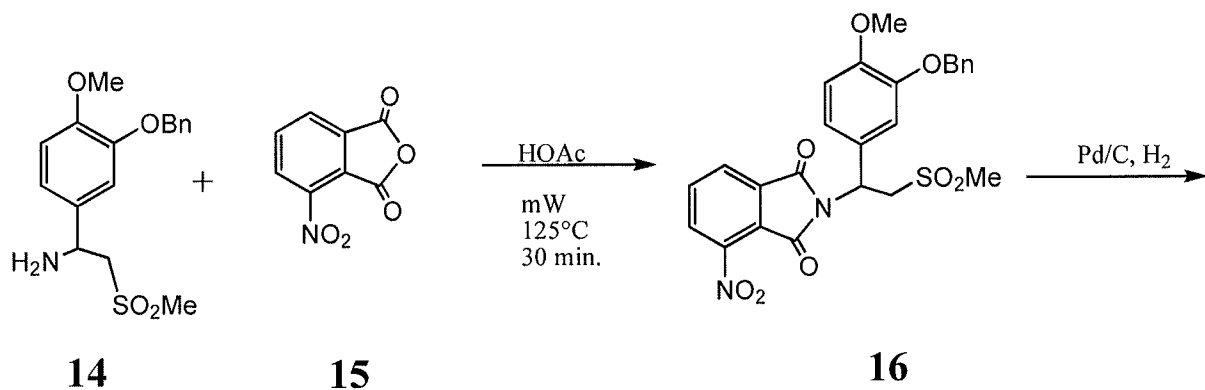
EXAMPLE 3

Synthesis of Compounds Comprising an Ether Linkage



[0162] An exemplary approach for preparing compounds of the invention comprising an ether linkage is provided schematically below.





[0163] **General procedure for the synthesis of 3-Hydroxy-4-methoxybenzonitrile (Compound 12).** 3-Hydroxy-4-methoxybenzaldehyde (Compound **11**, 10.0 g, 65.7mmol) and hydroxylamine hydrochloride (4.57g, 65.7 mmol) were charged to a 250 mL three neck flask at room temperature, followed by the addition of anhydrous acetonitrile (150 mL). The reaction mixture was stirred at room temperature for thirty minutes and then heated to 85° C for reflux overnight. The reaction mixture was then cooled to room temperature and deionized water (100 mL) was added to the flask. The mixture was concentrated under reduced pressure to remove acetonitrile. An additional 400 mL of deionized water was added

to the concentrated residue and allowed to stir for two hours. The mixture was then filtered at room temperature. The filtered solid was washed with 300 mL of deionized water. The desired product (Compound **12**) was a white powder obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 18CV, 40S column). (Yield~ 62%) ¹H-NMR (500 MHz, CDCl₃)- δ ppm 7.16 (m, 1H), 7.11 (s, 1H), 6.90 (d, 1H), 5.68 (s, 1H), 3.90 (s, 3H) LC-MS: Calc. 149.05; Found, 150.1 (MH⁺).

[0164] General procedure for the synthesis of 3-(benzyloxy)-4-methoxybenzonitrile (Compound 13). 3-Hydroxy-4-methoxybenzonitrile (Compound **12**, 6.41 g, 43.0 mmol) was charged to a 250 mL round bottom flask at room temperature, followed by the addition of acetone (150 mL). Benzyl bromide (5.11 mL, 43.0 mmol) was slowly added to the flask and allowed to stir overnight. HPLC was used to monitor the reaction. Upon reaction completion 150 mL of DCM was added. The organic phase was washed with 150 mL of deionized water and dried over sodium sulfate. The solvent was removed under reduced pressure. The desired product (Compound **13**) was a white powder obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 18 CV, 40S column). (Yield~ 71.4%) ¹H-NMR (500 MHz, CDCl₃)- δ ppm 7.37 (m, 5H) 7.16 (m, 1H), 7.11 (s, 1H), 6.90 (d, 1H), 5.68 (s, 1H), 3.90 (s, 3H) LC-MS: Calc. 239.1; Found, 240.1 (MH⁺).

[0165] General procedure for the synthesis of 1-(3-(benzyloxy)-4-methoxyphenyl)-2-(methylsulfonyl)ethanamine (Compound 14). Dimethylsulfone (1.9g, 20.18 mmol) and tetrahydrofuran (100mL) were charged to a 250 mL three-necked flask at room temperature. The reaction mixture was cooled to 0 °C, and the solution gradually turned white. n-Butyl lithium (8.07 mL, 20.18 mmol, 2.5 M solution in hexanes) was added to the flask at a rate such that the reaction mixture temperature was maintained at 5-10 °C. The mixture was stirred at 0-5 °C for one hour, turning light-yellow. 3-Benzyloxy-4-methoxybenzonitrile (Compound **13**, 3.5 g, 14.63 mmol) (3) in THF (7.5 mL) was charged to the flask at a rate such that the reaction mixture temperature was maintained at 0-5° C. The mixture was stirred for fifteen minutes at 0-5°C. After warming to room temperature the reaction was stirred for an additional 1.5 hours and then sodium borohydride (0.827 g, 21.87 mmol) was added and maintained at 0-5° C for thirty minutes. Acetic acid (4.5 mL, 79 mmol) was added while maintaining a reaction temperature of 0-5° C. The mixture was then stirred for two hours at 0-5°C.

[0166] Then 2.5N NaOH solution (22 mL) was charged to the flask and stirred at 0-5 °C for another thirty minutes. After warming to room temperature, the reaction mixture was heated to reflux at 60° C overnight. Then the mixture was cooled to 40°C and 30 mL of deionized water was added. The mixture was further cooled to 0-5° C for a period of two hours. The resulting mixture was filtered under vacuum, and the filtered solid was washed with absolute ethanol. The desired product (Compound 14) was obtained as a white powder. (Yield~77.0%) ¹H-NMR (500 MHz, DMSO-d₆) δ ppm 7.51 (m, 5H) 7.17 (s, 1H), 6.95 (s, 2H), 5.14 (s, 2H), 4.28 (m, 1H), 3.89 (s, 3H), 3.60 (m, 1H), 3.25 (m, 1H), 2.94 (s, 3H), 2.10 (br, 2H) LC-MS: Calc. 335.1; Found, 336.1 (MH⁺).

[0167] **General procedure for the synthesis of 2-(1-(3-(benzyloxy)-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-4-nitroisindoline-1,3-dione (Compound 16).** Into a 2-5 mL microwave vial was added 4-nitroisobenzofuran-1,3-dione (Compound 15, 0.345 g, 1.789 mmol) from Aldrich, the amino-sulfone intermediate (Compound 14, 0.600g, 1.789 mmol) and 4.0 mL of acetic acid. The mixture was placed in a microwave vial at 125°C for thirty minutes. After thirty minutes 10 mL DCM was added and the organic phase was washed with 10 mL deionized water and dried over sodium sulfate. The solvent was removed under reduced pressure. The desired product (Compound 16) was obtained as a yellow solid by Biotage Flash Chromatography on silica gel (2-10%)MeOH in DCM in 27 CV, 40S column) (Yield~65.7%) ¹H-NMR (500 MHz, DMSO-d₆) δ ppm 8.25 (m, 1H), 8.14 (m, 1H), 8.03 (t, 1H), 7.33 (m, 5H) 7.19 (s, 1H), 7.17 (m, 1H), 6.97 (d, 1H), 5.72 (s, 2H), 4.99 (s, 2H), 4.18 (m, 2H), 3.94 (m, 1H), 3.71 (s, 3H), 2.94 (s, 3H), 1.10 (t, 1H) LC-MS: Calc. 510.1; Found, 511.1 (MH⁺).

[0168] **General procedure for the synthesis of 4-amino-2-(1-(3-hydroxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isindoline-1,3-dione (Compound 17).** 2-(1-(3-(Benzyloxy)-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)-4-nitroisindoline-1,3-dione (Compound 16, 0.265g, 0.519 mmol) was dissolved in 10 mL tetrahydrofuran and placed in a hydrogenation vessel. Then Pd/C catalyst was added (0.092g) to the vessel. The reaction mixture was hydrogenated for five hours at 40 psi. After filtration to remove the catalyst the solvent was removed under reduced pressure. The desired product a yellow solid was obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 23 CV, 25M column). (Yield~74.0%) ¹H-NMR (500 MHz, DMSO-d₆) δ ppm 7.18 (m, 5H), 7.07 (s, 1H), 6.97 (m, 1H), 6.88 (d, 1H), 5.72 (m, 1H), 4.99 (s, 2H), 4.21 (m, 2H), 3.67 (s, 3H), 3.24 (s, 3H), 1.15 (t, 1H) LC-MS: Calc. 390.1; Found, 391.1 (MH⁺).

[0169] General procedure for the synthesis of 4-amino-2-(1-(4-methoxy-3-(2-methoxyethoxy)phenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 18 where n = 3). 4-Amino-2-(1-(3-hydroxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 17, 0.100g, 0.266 mmol) was dissolved in 10 mL acetone and charged to a 100 mL round bottom flask. The reaction mixture was heated to 60°C and then potassium carbonate (0.074g, 0.533 mmol) was added to the solution and finally mPEG₃-Br was added (0.121 g, 0.533 mmol) and stirred overnight. HPLC was used to monitor the reaction. The desired product (Compound 18 where n=3) as a yellow oil was obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 23 CV, 25M column). N=3: (Yield~70.0%) ¹H-NMR (500 MHz, CDCl₃)-δ ppm 7.23 (m, 2H), 7.18 (m, 2H), 6.87 (m, 1H), 5.91 (m, 1H), 5.32 (s, 1H), 4.55 (t, 1H), 4.20 (s, 2H), 3.9 (m, 2H), 3.76 (s, 3H), 3.73-3.57 (m, 13H), 2.91 (s, 3H), 1.27 (s, 3H) LC-MS: Calc. 536.1; Found, 537.2 (MH⁺).

[0170] General procedure for the synthesis of N-(2-(1-(4-methoxy-3-(2-methoxyethoxy) phenyl)-2-(methylsulfonyl) ethyl)-1, 3-dioxoisindolin-4-yl) acetamide (Compound 19, mPEG₃-ether apremilast). A 2-5 mL microwave vial was charged with 4-amino-2-(1-(4-methoxy-3-(2-methoxyethoxy) phenyl)-2-(methylsulfonyl) ethyl) isoindoline-1, 3-dione (Compound 18 where n=3, 0.070 g, 0.130 mmol), acetic anhydride (0.017 g, 0.163 mmol) and 4.0 mL of acetic acid. The mixture was placed in a microwave vial at 125°C for thirty minutes. After thirty minutes, 10 mL DCM added and the organic phase was washed with 10 mL dionized water and dried over sodium sulfate. The solvent was removed under reduced pressure. The desired product (Compound 19 where n=3) as a yellow oil was obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 23 CV, 25M column). N=3: (Yield~68.9 %) ¹H-NMR (500 MHz, CDCl₃)- δ ppm 9.51 (s, 1H), 8.78 (s, 1H), 7.69 (3, 1H), 7.66 (s, 1H), 7.12 (m, 2H), 6.87 (d, 1H), 5.91 (m, 1H), 4.55 (t, 1H), 4.20 (m, 2H), 3.9 (m, 2H), 3.76 (s, 3H), 3.73-3.57 (m, 13H), 2.91 (s, 3H), 2.34 (s, 3H), 1.27 (s, 3H) LC-MS: Calc. 578.2; Found, 579.2 (MH⁺).

[0171] General procedure for the synthesis of 2-(1-(3-(2, 5, 8, 11, 14-pentaoxahexadecan-16-yloxy)-4-methoxyphenyl)-2-(methylsulfonyl) ethyl)-4-aminoisoindoline-1, 3-dione (Compound 18 where n = 5). 4-Amino-2-(1-(3-hydroxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl)isoindoline-1,3-dione (Compound 17 0.250 g, 0.640 mmol) was dissolved in 10 mL acetone and charged to a 100 mL round bottom flask. The reaction mixture was heated to 60°C and then potassium carbonate (0.354 g, 2.56 mmol)

was added to the solution and finally mPEG₅-Br was added (0.807 g, 2.56 mmol) and stirred overnight. HPLC was used to monitor the reaction. The desired product (Compound **18** where n=5) as a yellow oil was obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 23 CV, 25M column). N=5: (Yield~77.0%) ¹H-NMR (500 MHz, CDCl₃)- δ ppm 7.51 (m, 2H), 7.17 (m, 2H), 6.85 (m, 1H), 5.90 (m, 1H), 5.43 (s, 1H), 4.55 (t, 1H), 4.22 (s, 2H), 3.92 (m, 2H), 3.76 (s, 3H), 3.73-3.57 (m, 20H), 2.90 (s, 3H), 1.59 (s, 3H) LC-MS: Calc. 624.1; Found, 625.2 (MH⁺).

[0172] General Procedure for the synthesis of N-(2-(1-(3-(2, 5, 8, 11, 14-pentaoxahexadecan-16-yloxy)-4-methoxyphenyl)-2-(methylsulfonyl) ethyl)-1, 3-dioxoisindolin-4-yl) acetamide (Compound 19, mPEG₅-ether apremilast). A 2-5 mL microwave vial was charged with 2-(1-(3-(2, 5, 8, 11, 14-pentaoxahexadecan-16-yloxy)-4-methoxyphenyl)-2-(methylsulfonyl) ethyl)-4-aminoisindoline-1, 3-dione (Compound **18** where n=5, 0.300 g, 0.480 mmol), acetic anhydride (0.061 g, 0.600 mmol) and 4.0 mL of acetic acid. The mixture was placed in a microwave vial at 125°C for 30 minutes. After 30 minutes, 10 mL DCM added and the organic phase was washed with 10 mL deionized water and dried over sodium sulfate. The solvent was removed under reduced pressure. The desired product as a yellow oil was obtained by Biotage Flash Chromatography on silica gel (2-8% MeOH in DCM in 23 CV, 25M column). N=5: (Yield~62.2 %) ¹H-NMR (500 MHz, CDCl₃)- δ ppm 9.52 (s, 1H), 8.79 (s, 1H), 7.69 (s, 1H), 7.66 (s, 1H), 7.12 (m, 2H), 6.87 (d, 1H), 5.91 (m, 1H), 4.54 (t, 1H), 4.22 (m, 2H), 3.92 (m, 2H), 3.76 (s, 3H), 3.72-3.55 (m, 20H), 2.91 (s, 3H), 2.34 (s, 3H), 1.27 (s, 3H) LC-MS: Calc. 666.2; Found, 667.2 (MH⁺).

[0173] Although the preparation of mPEG₃-ether apremilast and mPEG₅-ether apremilast are provided herein with respect to Example 3, other compounds can be prepared following this same approach wherein mPEG₃-Br or mPEG₅-Br is substituted with mPEG_n-Br where n = 1, 2, 4 and 6-9.

EXAMPLE 4

PDE4 *In Vitro* Activity Assays

[0174] Compounds of interest were assayed for *in vitro* PDE4A, PDE4B, PDE4C, and PDE4D inhibitory activity. Briefly, IC₅₀s were determined by cAMP hydrolysis assay. The principle of the assay is based on hydrolysis of cAMP by recombinant PDE4 enzymes; the cAMP levels in the reaction mixture are then measured by competitive immunoassay,

where the signal is inversely proportional to the concentration of cAMP in the standard or sample. With respect to sourcing of the PDE4A enzyme, full length human PDE4A1A with N-terminal GST tag, expressed in a baculovirus infected Sf9 cell expression system was used. With respect to sourcing of the PDE4B enzyme, full length human PDE4B2 with N-terminal GST tag, expressed in a baculovirus infected Sf9 cell expression system was used. With respect to sourcing of the PDE4C enzyme, full length human PDE4C1 with N-terminal GST tag, expressed in a baculovirus infected Sf9 cell expression system was used. With respect to sourcing of the PDE4D enzyme, full length human PDE4D2 with N-terminal GST tag, expressed in a baculovirus infected Sf9 cell expression system was used.

[0175] Compounds of interest were 3-fold serially diluted at least 6 times in 1% DMSO in assay buffer (50 mM Tris + 6 mM MgCl₂, pH 7.4). Each dilution (10 µl) was transferred into triplicate wells of a black polystyrene 96-well assay plate (Corning #3993). In addition to the compound dilutions, each assay plate contained control wells with 1% DMSO in assay buffer (to define 0% enzyme inhibition). Using a pipette, 20 µl of cAMP (Sigma A9501) at 10 nM in assay buffer was transferred to each assay well. Next, 20 µl of PDE4 enzyme in assay buffer was added and the plates were shaken for 60 seconds at 200 rpm to start the cAMP hydrolysis reaction. The final amounts of enzyme used per well were: PDE4A, 10 U; PDE4B, 10 U; PDE4C, 10 U; and PDE4D, 10 U (where one unit is defined as the amount of enzyme that hydrolyzes 1 pmol cAMP per min at 37°C). Assay plates were covered and incubated for 60 minutes at 37° C. The amounts of cAMP remaining in all wells were then measured using a cAMP homogeneous time-resolved fluorescence competitive immunoassay kit (CisBio #62AM4PEB). IC₅₀s were calculated using fluorescence ratios corrected for background with non-linear regression curve fitting.

[0176] The evaluated compounds were mPEG₃₋₉-carbamate apremilast compounds prepared in accordance with Example 1, mPEG_{1,4,7}-urea apremilast compounds of Example 2, and mPEG₃-ether apremilast of Example 3. The results of the assay for the mPEG₃₋₉-carbamate apremilast compounds and mPEG_{1,4,7}-urea apremilast compounds are provided in Table 1 below. Inhibition of PDE4B is believed to be indicative of the anti-inflammatory effects of PDE4 inhibitors, whereas inhibition of PDE4D is believed to be indicative of the emetic adverse effects of PDE4 inhibitors. The mPEG₃₋₉-carbamate apremilast compounds and mPEG_{1,4,7}-urea apremilast compounds retained activity within 10x of parent for all PDE4 isoforms tested, while the mPEG₃-ether apremilast conjugate showed a biologically significant loss in activity against all PDE4 isoforms tested.

Table 1
***In Vitro* PDE4 Inhibitory Activities of Tested Compounds**

Compound Tested	PDE4A IC ₅₀	PDE4B IC ₅₀	PDE4C IC ₅₀	PDE4D IC ₅₀
apremilast	7.0	7.9	1.0	1.3
mPEG ₃ -carbamate apremilast (Compound 9a)	3.6	6.4	0.9	0.9
mPEG ₄ -carbamate apremilast (Compound 9b)	5.4	2.5	1.1	0.8
mPEG ₅ -carbamate apremilast (Compound 9c)	2.7	4.9	3.1	0.8
mPEG ₆ -carbamate apremilast (Compound 9d)	3.2	2.5	2.2	0.9
mPEG ₇ -carbamate apremilast (Compound 9e)	5.6	3.0	2.4	1.6
mPEG ₈ -carbamate apremilast (Compound 9f)	9.6	3.9	1.2	2.0
mPEG ₉ -carbamate apremilast (Compound 9g)	6.8	2.8	0.6	1.3
mPEG ₁ -urea apremilast (Compound 10a)	n.d.	11.5	n.d.	1.0
mPEG ₄ -urea apremilast (Compound 10b)	n.d.	7.5	n.d.	0.5
mPEG ₇ -urea apremilast (Compound 10c)	n.d.	35.6	n.d.	2.7

n.d. = not done

EXAMPLE 5

Pharmacokinetics of mPEG₃₋₉-Carbamate Apremilast Compounds

[0177] The pharmacokinetics of the mPEG₃₋₉-carbamate apremilast compounds (Compounds 9a through 9g, respectively) prepared in accordance with Example 1 were examined in male Sprague-Dawley mice (3 per test compound) following oral (PO) or intravenous (IV) administration. The animals were fasted for a minimum of four hours prior to dosing and food was withheld through the first two hours of blood sample collection. The compounds of interest were suspended or dissolved in appropriate buffer for *in vivo* administration and administered via a single IV dose by tail vein injection at 5 mg/kg in a dose volume of 5 ml/kg and via a single PO oral gavage dose at 10 mg/kg in a dose volume of 10 ml/kg. Blood samples (approximately 0.5 ml) were collected from the jugular vein cannula at specified time intervals from two minutes to 48 hours and placed into tubes containing Na₂EDTA. The samples were centrifuged under refrigerated conditions and the resulting plasma was separated and stored frozen until analyzed. Plasma concentrations of the compounds of interest were determined by LC-MS/MS and pharmacokinetic parameters,

including oral bioavailability and elimination half-life ($t_{1/2}$), were determined by modeling using WinNonlin PK/PD software (Pharsight; Sunnyvale, CA).

[0178] The results of the assay are provided in the FIG. 1, Table 2 and Table 3 below. As evidenced therein, the mPEG₃₋₉-carbamate apremilast compounds had lower bioavailability and more rapid clearance than apremilast.

Table 2
Intravenous Pharmacokinetic Parameters of Tested Compounds

	apremilast	mPEG ₃ - carbamate apremilast	mPEG ₄ - carbamate apremilast	mPEG ₅ - carbamate apremilast	mPEG ₆ - carbamate apremilast	mPEG ₇ - carbamate apremilast	mPEG ₈ - carbamate apremilast	mPEG ₉ - carbamate apremilast
AUC _{all} (ng•hr/ml)	2610 ± 1040	877 ± 261	1480 ± 113	1150 ± 86	1560 ± 257	1250 ± 66	1220 ± 303	1530 ± 352
C ₀ (ng/ml)	5580 ± 5730	9850 ± 1330	5530 ± 3090	1910 ± 2410	8330 ± 4450	7980 ± 3430	6370 ± 3720	5090 ± 469
C _{max} (ng/ml)	4010 ± 3320	4580 ± 1410	4410 ± 2240	1810 ± 2000	5710 ± 1590	4980 ± 1190	4790 ± 1890	4380 ± 552
CL (ml•hr/kg)	1860 ± 785	6030 ± 1550	3420 ± 254	4380 ± 329	3270 ± 59	4040 ± 210	4310 ± 1150	3130 ± 751
V _{ss} (ml/kg)	5250 ± 4450	3230 ± 1420	2160 ± 1400	4790 ± 2700	1330 ± 353	1810 ± 289	1720 ± 674	2220 ± 474
t _{1/2} (hr)	6.85 ± 1.35	1.23 ± 0.24	1.42 ± 0.19	1.56 ± 0.15	1.35 ± 0.16	1.40 ± 0.25	1.28 ± 0.44	3.08 ± 0.13
MRT _{last} (hr)	2.95 ± 1.67	0.48 ± 0.11	0.59 ± 0.37	1.07 ± 0.65	0.38 ± 0.07	0.40 ± 0.05	0.36 ± 0.03	0.59 ± 0.07

Table 3
Oral bioavailability of Tested Compounds

	apremilast	mPEG ₃ - carbamate apremilast	mPEG ₄ - carbamate apremilast	mPEG ₅ - carbamate apremilast	mPEG ₆ - carbamate apremilast	mPEG ₇ - carbamate apremilast	mPEG ₈ - carbamate apremilast	mPEG ₉ - carbamate apremilast
F%	32	0.32	1.0	0.5	0.8	3.0	2.0	0.2
T _{max} (hr)	1.0	0.25	0.25	0.25	0.25	0.5	0.25	0.25

EXAMPLE 6

In Vitro Anti-Inflammatory Activity Assays

[0179] Compounds of interest were assayed for *in vitro* anti-inflammatory activity. Briefly, IC₅₀s were determined by TNFα ELISA. The principle of the assay is based on production of TNFα by the mouse-derived RAW264.7 macrophage cell line in response to *E. coli* lipopolysaccharide (LPS); the TNFα levels in supernatants from cell cultures exposed to vehicle or the compounds of interest prior to stimulation with LPS are measured by sandwich enzyme-linked immunosorbance assay (ELISA). With respect to sourcing of the LPS, lipopolysaccharide from *Escherichia coli* 0111:B4 was used.

[0180] Compounds of interest were 3-fold serially diluted at least 11 times in cell culture media. Each dilution (100 μ l) was transferred into duplicate wells of a tissue-cultured treated 96-well assay plate containing adherent RAW264.7 cells at 2.5E6/ml, 100 μ l per well. Cells were incubated for one hour, and then LPS in saline was added to each well to a final concentration of 100 ng/ml. In addition to the compound dilutions, each assay plate contained control wells where cells were treated with LPS but no test compound (to define 0% inhibition). After 16-24 hours of incubation at 37° C, cell supernatants were collected by centrifugation, and the amounts of TNF α in all wells were then measured using a commercially available kit (Pierce #EMTNFA). IC₅₀ values were calculated using TNF α concentrations in all wells corrected for background with non-linear regression curve fitting.

[0181] The results of the assay are provided in Table 4 and **FIG. 2**. As evidenced therein, all mPEG₃₋₉-carbamate apremilast conjugates retained activity within 10x of apremilast.

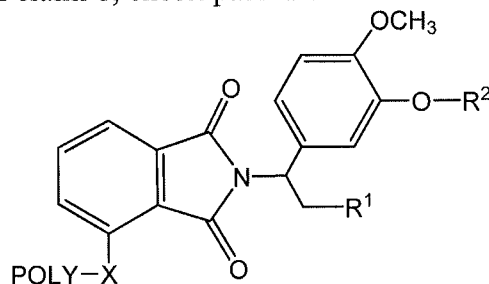
Table 4
***In Vitro* Anti-Inflammatory Activity of Tested Compounds**

Compound Tested	IC₅₀ (nM)
apremilast	549
mPEG ₃ -carbamate apremilast	57
mPEG ₄ -carbamate apremilast	279
mPEG ₅ -carbamate apremilast	191
mPEG ₆ -carbamate apremilast	351
mPEG ₇ -carbamate apremilast	966
mPEG ₈ -carbamate apremilast	1630
mPEG ₉ -carbamate apremilast	3406

WHAT IS CLAIMED IS:

1. A compound comprising an apremilast moiety residue covalently attached via a linkage to a water-soluble, non-peptidic oligomer.

2. The compound of claim 1, encompassed within the formula:



(Formula I-Ca)

wherein:

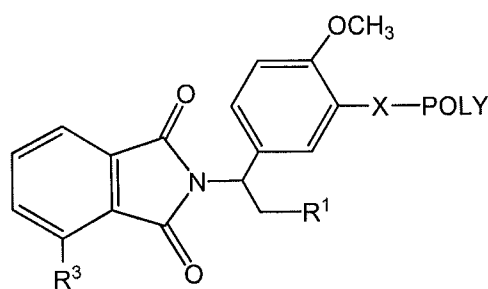
R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^2 is an organic radical;

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer,
and pharmaceutically acceptable salts thereof

3. The compound of claim 1, encompassed within the formula:



(Formula I-Cb)

wherein:

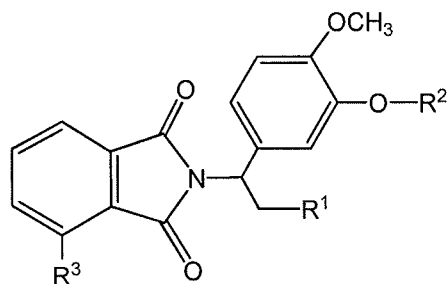
R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical;

X is a spacer moiety; and

POLY is a water-soluble, non-peptidic oligomer,
and pharmaceutically acceptable salts thereof.

4. The compound of claim 1, wherein the apremilast moiety residue is a residue of an apremilast moiety encompassed within the formula:



(Formula I)

wherein:

R^1 is selected from the group consisting of COOH, COOCH₃, CONH₂, CN and SO₂CH₃;

R^2 is an organic radical; and

R^3 is selected from the group consisting of H, OH, OCH₃, NH₂, N(CH₃)₂, NHCOCH₃ and an organic radical.

5. The compound of claim 1, wherein the apremilast moiety residue is a residue of an apremilast moiety selected from the group consisting of apremilast and 3-(3-acetoamidophthalimido)-3-(3-ethoxy-4-methoxyphenyl)-N-hydroxypropionamide.

6. The compound of claim 5, wherein the apremilast moiety residue is a residue of apremilast.

7. The compound of any one of claims 1 to 6, wherein the water-soluble, non-peptidic oligomer is a poly(alkylene oxide).

8. The compound of claim 7, wherein the poly(alkylene oxide) is a poly(ethylene oxide).

9. The compound of any one of claims 1 to 8, wherein water-soluble, non-peptidic oligomer has from about 1 to about 30 monomers.

10. The compound of claim 9, wherein the water-soluble, non-peptidic oligomer has from about 1 to about 10 monomers.

11. The compound of claim 7, wherein the poly(alkylene oxide) includes an alkoxy or hydroxy end-capping moiety.

12. The compound of any one of claims 1 to 11, wherein a single water-soluble, non-peptidic oligomer is attached to the apremilast moiety residue.

13. The compound of any one of claims 1 to 11, wherein more than one water-soluble, non-peptidic oligomer is attached to the apremilast moiety residue.

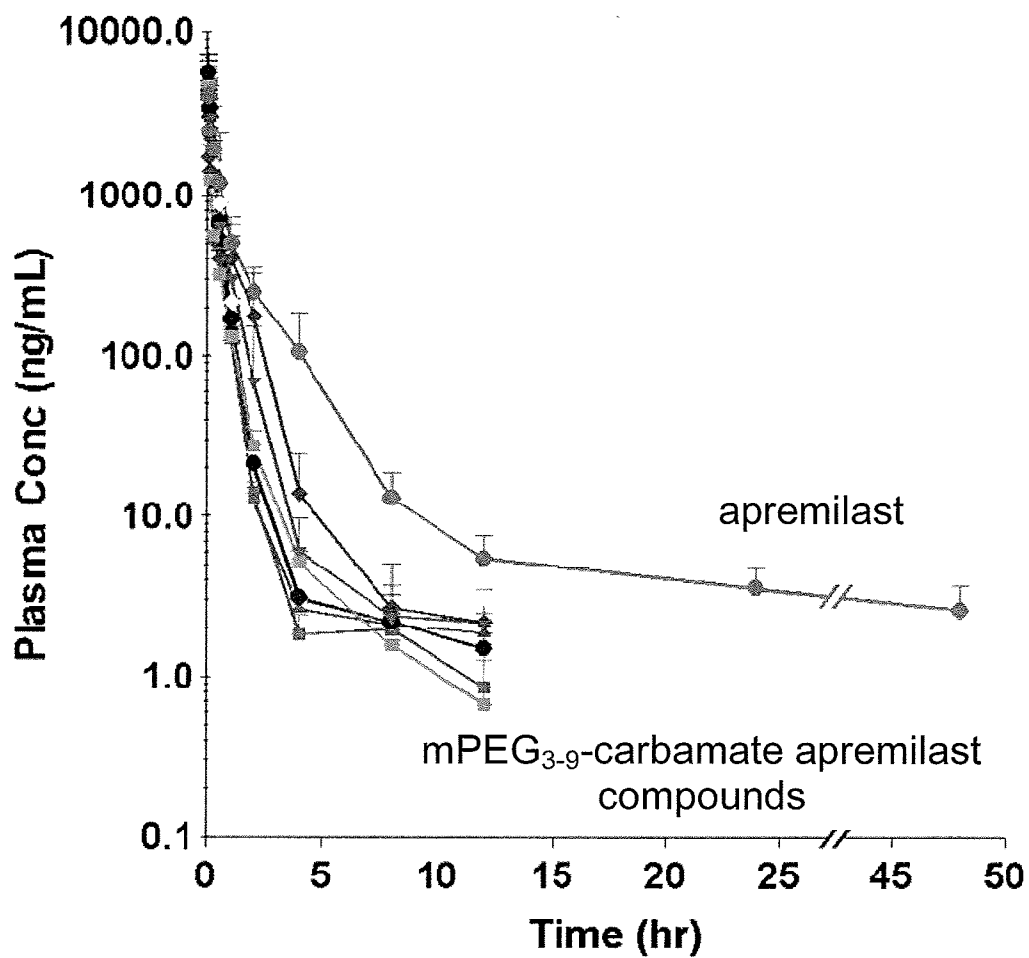
14. The compound of any one of claims 1 to 13, wherein the linkage is a stable linkage.

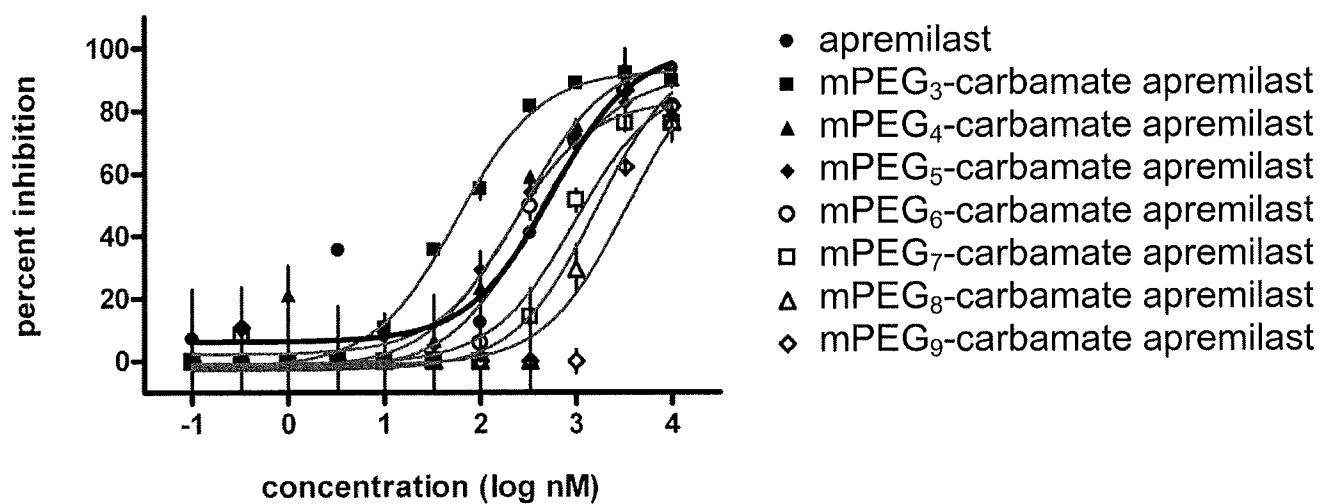
15. The compound of any one of claims 1 to 13, wherein the linkage is a releasable linkage.

16. A composition comprising a compound comprising an apremilast moiety residue covalently attached via a linkage to a water-soluble, non-peptidic oligomer, and optionally, a pharmaceutically acceptable excipient.

17. A composition of matter comprising a compound comprising an apremilast moiety residue covalently attached via a linkage to a water-soluble, non-peptidic oligomer, wherein the compound is present in a dosage form.

18. A method of treatment comprising administering a compound comprising an apremilast moiety residue covalently attached via a linkage to a water-soluble, non-peptidic oligomer, to a subject in need thereof.

**FIG. 1**

**FIG. 2**

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/065458

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K47/48 A61P35/00
ADD.

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)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/187052 A1 (MULLER GEORGE W [US] ET AL) 2 October 2003 (2003-10-02) cited in the application paragraph [0025] - paragraph [0026]; claim 1	1-18
X	----- US 2005/136031 A1 (BENTLEY MICHAEL D [US] ET AL) 23 June 2005 (2005-06-23) cited in the application paragraph [0105]; examples 1-6 ----- -/--	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

13 April 2012

Date of mailing of the international search report

23/04/2012

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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2011/065458

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MULLER G W ET AL: "STRUCTURAL MODIFICATIONS OF THALIDOMIDE PRODUCE ANALOGS WITH ENHANCED TUMOR NECROSIS FACTOR INHIBITORY ACTIVITY", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 39, no. 17, 1 January 1996 (1996-01-01), pages 3238-3240, XP002938446, ISSN: 0022-2623, DOI: 10.1021/JM9603328 the whole document	1-18
Y	HON-WAH MAN ET AL: "Discovery of (S)-N-{2-[1-(3-ethoxy-4-methoxy-phenyl)-2-methanesulfonylethyl]-1,3-dioxo-2,3-dihydro-1 H-isoindol-4-yl}acetamide (Apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-.alpha. inhibitor", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, [Online] vol. 52, no. 6, 3 March 2009 (2009-03-03), pages 1522-1524, XP002670076, ISSN: 0022-2623, DOI: 10.1021/JM900210D Retrieved from the Internet: URL:http://pubs.acs.org/doi/abs/10.1021/jm900210d> [retrieved on 2009-03-03] cited in the application the whole document	1-18
Y	WO 00/25777 A1 (CELGENE CORP [US]) 11 May 2000 (2000-05-11) claims 1-18	1-18

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2011/065458

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2003187052	A1	02-10-2003	US 2003187052 A1 02-10-2003
			US 2005192336 A1 01-09-2005
			US 2005267196 A1 01-12-2005
			US 2008207730 A1 28-08-2008
			US 2008242719 A1 02-10-2008
			US 2010160405 A1 24-06-2010

US 2005136031	A1	23-06-2005	US 2005136031 A1 23-06-2005
			US 2006182692 A1 17-08-2006
			US 2010210676 A1 19-08-2010
			US 2010305147 A1 02-12-2010
			US 2012088745 A1 12-04-2012

WO 0025777	A1	11-05-2000	AT 350033 T 15-01-2007
			AT 471718 T 15-07-2010
			AU 756308 B2 09-01-2003
			BR 9915201 A 30-10-2001
			CA 2348993 A1 11-05-2000
			DE 69934708 T2 18-10-2007
			DK 1126839 T3 14-05-2007
			DK 1752148 T3 27-09-2010
			EP 1126839 A1 29-08-2001
			EP 1752148 A2 14-02-2007
			EP 2305248 A1 06-04-2011
			ES 2278467 T3 01-08-2007
			ES 2343744 T3 09-08-2010
			HK 1038696 A1 03-08-2007
			HK 1103224 A1 03-12-2010
			JP 4530543 B2 25-08-2010
			JP 2002528496 A 03-09-2002
			NO 20012021 A 26-06-2001
			NZ 511253 A 28-02-2003
			PT 1126839 E 30-03-2007
			PT 1752148 E 28-09-2010
			US 6011050 A 04-01-2000
			US 6020358 A 01-02-2000
			WO 0025777 A1 11-05-2000
