

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
27 November 2008 (27.11.2008)

PCT

(10) International Publication Number
WO 2008/144690 A2

(51) International Patent Classification:

A61K 9/70 (2006.01) A61K 9/48 (2006.01)
A61K 9/68 (2006.01) A61K 38/16 (2006.01)

(21) International Application Number:

PCT/US2008/064233

(22) International Filing Date: 20 May 2008 (20.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

11/805,202 21 May 2007 (21.05.2007) US
61/004,099 21 November 2007 (21.11.2007) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report



WO 2008/144690 A2

(54) Title: COMPOSITIONS AND METHODS FOR ENHANCING ACTIVE AGENT ABSORPTION

(57) Abstract: Compositions and methods for enhancing the absorption of active agents across the mucosa of animal subjects are provided. Compositions having biodegradable linkages are included, conferring decreased likelihood of toxicity. Methods of use and appropriate dosage forms are also provided.

COMPOSITIONS AND METHODS FOR ENHANCING ACTIVE AGENT ABSORPTION

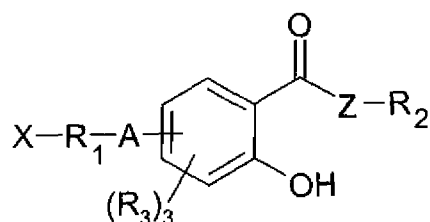
BACKGROUND

The effectiveness of a drug regimen is often highly dependent on achieving the necessary bioavailability of the drug once it is administered. Poor bioavailability of a drug makes it necessary to administer higher doses in order to achieve efficacy, but higher dosage requirements can lead to toxicity, undesirable side effects, and/or decreased patient compliance. Although the gastrointestinal tract is a common route for drug delivery, not all drugs are well absorbed through the lining of the gastrointestinal tract. In the case of some drugs, their polar nature or hydrophilic character may make them difficult to be absorbed. Delivering drugs through other routes, such as buccal, sublingual, rectal, nasal, vaginal mucosa, is one way to provide systemic access for drugs while avoiding the digestive environment of the gastrointestinal tract. However, for this to be successful, the drug administered should also overcome the resistance of these membranes to absorption. It is therefore clear that any factor that enhances the rate of absorption through such surfaces will result in improved clinical efficacy of many drug therapies.

Early efforts to enhance the absorption, and therefore bioavailability, of drugs include the use of adjuvants, such as surface active agents, including ionic and non-ionic surfactants to increase biomembrane permeability. However, use of some adjuvants is attended by the risk of damaging the biomembrane. Therefore, a need continues to exist for compositions that safely promote the absorption of poorly absorbed drugs.

SUMMARY

A composition for enhancing transmucosal absorption of an active agent can comprise a) at least one active agent; and b) an absorption enhancer having the formula:



or a pharmaceutically acceptable salt thereof. In this formula, R_1 can be null, C_1 - C_{12} alkylene, C_2 - C_{12} alkenylene, arylene, or substituted alkylene, alkenylene, or arylene. The substituted alkylene, alkenylene, or arylene can be substituted with N, O, S, or P. Further, R_2 can be hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, aryl, or cycloalkyl; and each R_3 can independently be hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, or aryl, or substituted alkyl, alkenyl, or aryl, said substituted alkyl, alkenyl, or aryl being substituted with N, O, S, or P. X can be a tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid, sulfide, sulfonic acid, sulfenic acid, sulfoxide, phosphoric acid, phosphonic acid, poly(ethylene glycol), saccharide, oligosaccharide, polyol, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, chitosan, or a combination thereof. A can be null or CONH, wherein A and R_1 are not simultaneously null; and Z can be O, S, NH, or NR wherein R is lower alkyl, or wherein Z is joined with R_2 to form a heterocyclic ring. In a more specific embodiment, R_3 , Z- R_2 and/or X- R_1 -A possess labile linkages such as ester linkages, or peptide bonds that are subjected to hydrolysis by a variety of peptidases.

The composition of the present invention may be formulated into various dosage forms configured to bring the composition into effective contact with a mucosal surface of a subject, which includes external and internal mucosal surfaces of the body. Oral or administration can be used to contact the composition with the mucosal surfaces of the intestines, whereas a buccal administration can be used to transmucosally deliver the composition through the mucosal surfaces within the oral cavity. Exemplary dosage forms for delivery include tablets, capsules, powders, suspensions, creams, and suppositories.

The present invention is also drawn to methods of enhancing transmucosal absorption of active agents in a subject, which comprises administering a composition to the subject so that the composition comes into effective contact with a mucosal surface of the subject. The composition can be the same as that described above. The present

invention also is drawn to the use of absorption enhancers in the manufacture of a medicament for enhancing transmucosal absorption of an active agent, in which the absorption enhancer comprises the composition described above.

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DETAILED DESCRIPTION

Before particular embodiments of the present invention are disclosed and described, it is to be understood that this invention is not limited to the particular process and materials disclosed herein as such may vary to some degree. It is also to be understood that the terminology used herein is used for the purpose of describing
10 particular embodiments only and is not intended to be limiting, as the scope of the present invention will be defined only by the appended claims and equivalents thereof.

It is to be noted that, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly
15 dictates otherwise.

As used herein, “administration,” and “administering” refer to the manner in which a drug, formulation, or composition is introduced into the body of a subject. Administration can be accomplished by various art-known routes such as oral, parenteral, transdermal, inhalation, implantation, etc. Thus, an oral administration can be achieved
20 by swallowing, chewing, or sucking an oral dosage form comprising active agent(s). Parenteral administration can be achieved by injecting a composition intravenously, intra-arterially, intramuscularly, intrathecally, or subcutaneously, etc. Transdermal administration can be accomplished by applying, pasting, rolling, attaching, pouring, pressing, rubbing, etc., of a transdermal preparation onto a skin surface. Similarly,
25 transmucosal administration can be accomplished by applying, pasting, rolling, attaching, pouring, pressing, rubbing, etc., of a transmucosal preparation onto a mucosal surface, as well as by spraying, irrigating the surface with the preparation. These and additional methods of administration are well known in the art.

The terms “effective amount,” and “sufficient amount” may be used
30 interchangeably and refer to an amount of an ingredient which, when included in a composition, is sufficient to achieve an intended compositional or physiological effect. Thus, a “therapeutically effective amount” refers to a non-toxic, but sufficient amount of

an active agent, to achieve therapeutic results in treating a condition for which the active agent is known to be effective. Various biological factors may affect the ability of a substance to perform its intended task. Therefore, an "effective amount" or a "therapeutically effective amount" may be dependent on such biological factors. Further, while the achievement of therapeutic effects may be measured by a physician or other qualified medical personnel using evaluations known in the art, it is recognized that individual variation and response to treatments may make the achievement of therapeutic effects a subjective decision. In some instances, a "therapeutically effective amount" of an active agent can achieve a therapeutic effect that is measurable by the subject receiving the active agent. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical, medicinal, and health sciences.

The term "effective contact" as used herein refer to contact of a nature and duration sufficient to allow a desired effect to be achieved, e.g. effective contact of a preparation with a surface into which it is to be absorbed will allow a measurable amount, preferably also an effective amount, of an agent in the preparation to enter the tissues or bloodstream of a subject, depending on the application target.

As used herein, "carrier" or "inert carrier" refers to typical compounds or compositions used to carry active ingredients, such as polymeric carriers, liquid carriers, or other carrier vehicles with which a bioactive agent, such as insulin, may be combined to achieve a specific dosage form. As a general principle, carriers do not substantially react with the bioactive agent in a manner which substantially degrades or otherwise adversely affects the active agent or its therapeutic potential.

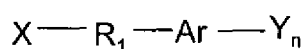
When referring to alkyl, alkylene, alkenyl, alkenylene, or the like, it is understood that these terms include either linear or branched hydrocarbon chains. These hydrocarbon chains can optionally be substituted with N, O, S, or P, for example.

The term "null" is used herein to describe variables that, though included in a compound formulation, can be removed from the formulation. For example, if a formulation is described as including a variable "B" and "B" is said to be null, $-\text{CH}_2-$, O, S, or NH, the variable "B" can be removed from the formulation, or can be substituted with $-\text{CH}_2-$, O, S, or NH.

The mechanism of adjuvants is mostly unknown. Theories including transport via paracellular routes by opening the tight junctions, or by transcellular routes via perturbing

the lipid bilayers of the epithelial cells have been proposed. However, the use of adjuvants can present particular risks. For example, the adjuvant could be toxic, e.g. it can cause damage barriers such as lipid bilayers, other membranes, and selective transport systems, both at the point of absorption or located elsewhere in the body. The instant invention addresses this problem by generally providing adjuvants into which labile linkages may be optionally introduced so that the beneficial permeation enhancing activity can be preserved and the adverse effects can be eliminated. Thus, once the adjuvant accomplishes its mission of assisting the drug molecules entering systemic circulation, it can be destroyed quickly to avoid the potential side effects. More particularly, this invention provides compounds possessing one or more biodegradable linkages that may be subjected to enzymatic or other chemical degradation, producing compounds that have no absorption enhancing effects or less enhancing effect than the parent compounds. The degradation products can then be cleared easily from the body and can therefore be safer than enhancer compounds without biodegradable linkages.

According to a general embodiment of the present invention, a composition for achieving enhanced absorption of a drug or other active agent can comprise an effective amount of the active agent itself and an absorption enhancer or a pharmaceutically acceptable salt thereof. In one embodiment, the absorption enhancer may have the general formula:



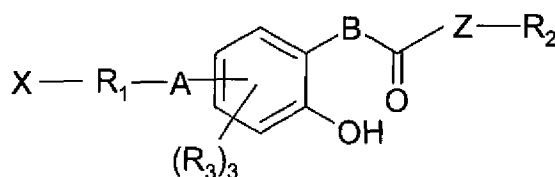
[Formula I]

where Ar can be an aromatic structure such as benzene or naphthalene; Y_n can be independently OH, H, alkyl, aryl, alkenyl, alkynyl, cycloalkyl, carbamidoyl, ester, halogen, halogen-substituted alkyl, amino, alkoxy, carbamyl, azo, thio, thioalkyl, cyano, sulfone, alkyl sulfoxide groups, or a combination thereof, where $n = 5$ when Ar is benzene, and $n = 9$ when Ar is naphthalene, and at least one Y is an OH; R_1 can be null, a saturated or unsaturated linear, branched or cyclic alkylene, or arylene, and optionally may be substituted with functional groups containing hetero-atoms such as N, O, S, or P (R_1 can be coupled to Ar through a coupling moiety); and X can include at least one hydrophilic moiety such as an ionizable functionality, e.g. tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid, sulfide, sulfonic acid, sulfenic acid, sulfoxide,

phosphoric acid, phosphonic acid, or a combination thereof, or other hydrophilic functionality such as poly(ethylene glycol), saccharides, polyvinyl alcohol, polyacrylic acid, chitosan and derivatives, or a combination of these functionalities. In a more particular aspect, either Y_n , R_1 or both can contain biodegradable linkages.

- 5 While not wishing to be bound to a particular theory, it is thought that the improvement in absorption that an enhancer provides may be increased if the enhancer has an appropriate balance of lipophilic and hydrophilic properties. As can be seen from Formula I, absorption enhancers in accordance with the present invention can comprise a functional fragment of a small molecule adjuvant, a lipophilic component, and a
- 10 hydrophilic component.

In one specific embodiment, such an enhancer can have the following formula:

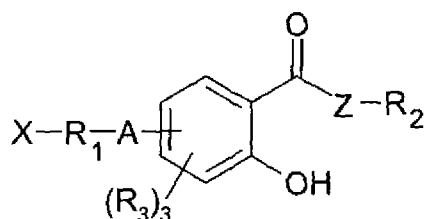


- 15 [Formula II]

- where R_1 can be null, linear, or branched C_1-C_{12} alkylene, C_2-C_{12} alkenylene, arylene, or substituted alkylene, alkenylene, or arylene, said substituted alkylene, alkenylene, or arylene being substituted with N, O, S, or P; R_2 can be hydrogen or an aliphatic chain such as C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or an aryl or cycloalkyl functional group; each R_3
- 20 can independently be hydrogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, or aryl, or substituted alkyl, alkenyl, or aryl, said substituted alkyl, alkenyl, or aryl being substituted with N, O, S, or P; X can be tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid, sulfide, sulfonic acid, sulfenic acid, sulfoxide, phosphoric acid, phosphonic acid, poly(ethylene glycol), saccharide, oligosaccharide, polyol, polyvinylpyrrolidone, polyvinyl alcohol,
- 25 polyacrylic acid, chitosan, or a combination thereof. A can be null or a coupling moiety such as amide or ester. In a more particular aspect, A is an amide such that $X-R_1-A$ is $X-R_1-CONH-$, i.e. this chain is attached to the ring via nitrogen. B can be null, $-CH_2-$, O, S, or NH; and Z can be null, O, S, NH, or NR where R is lower alkyl, or wherein Z is joined with R_2 to form a heterocyclic ring. It is noted that the aromatic ring can also be

naphthalene or another fused aromatic ring structure. In a particular aspect of this embodiment, A and R₁ are not simultaneously null, that is, if A is null, then R₁ is other than null, and if R₁ is null, then A is other than null. In another particular aspect, R₃, Z-R₂ and/or X-R₁-A may possess labile linkages such as amide or ester linkages, or peptide bonds that are subjected to hydrolysis by a variety of peptidases.

When B is null, the absorption enhancer has the formula:



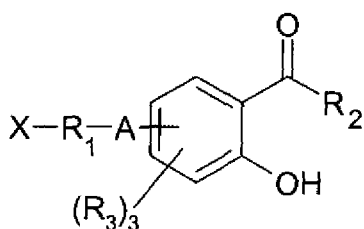
[Formula III]

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where R₁, R₂, R₃, Z, A, and X represent the same groups as with Formula II and where A and R₁ are not simultaneously null. In a particular embodiment, R₃, Z-R₂ and/or X-R₁-A possess labile linkages.

When both B and Z are null, the absorption enhancer may have the formula:

15



[Formula IV]

where R₁, R₂, R₃, A, and X represent the same groups as with Formula II and where A and R₁ are not simultaneously null. In a particular embodiment, R₃, Z-R₂ and/or X-R₁-A possess labile linkages.

In a specific aspect of any of the embodiments represented in Formulas I-IV, R₁ is attached to the aromatic ring by an amide or ester linkage. In a more particular aspect, A is an amide such that X-R₁-A is X-R₁-CONH, i.e. this chain is attached to the aromatic ring via nitrogen. In another specific aspect of these embodiments, X is COOH. In still

25

another aspect of these embodiments, any combination of R_3 , $Z-R_2$, and $X-R_1-A$ contain linkages that are labile under conditions where breakdown of the enhancer would be advantageous. In a more specific aspect, such linkages can be broken by enzymatic or other chemical action, such as hydrolysis. In particular aspects, such linkages include
5 amide linkages or ester linkages.

The activity of the enhancers can also be affected by the overall lipophilicity of the molecule contributed by R_1 and R_2 as well as substitution(s) on the aromatic ring. For example, where $X-R_1-A$ in Formula III is a $\text{HOOCCH}_2\text{CH}_2\text{CONH}$ (and $Z = \text{NH}$), a more optimal length of R_2 can provide the maximal enhancement, while a shorter or
10 longer chain length may provide a lesser benefit in some circumstances. In addition, enhancement may be affected by the position of the moiety containing R_1 and the amide group of the moiety containing R_2 .

In the salicylate-based enhancers described in Formulas II-IV, the basic structure of salicylic acid is preserved to the extent that an OH group is present at carbon 2 of the
15 ring (and therefore is *ortho* to the carbonyl carbon at position 1). Furthermore, the lipophilic functionality R_2 extends from the carbonyl, ester, or amide group at position 1, while R_1 is linked to the ring at any one of carbons 3-6. However, other structural arrangements that will provide both lipophilic and hydrophilic properties are considered within the scope of this invention. For example, R_3 may be attached, directly or through
20 an ether, ester, or amide linkage, at any of carbons 3-6 instead of R_1 , with an alkyl or alkenyl group providing lipophilicity and a polar group (such as carbonyl, nitro, cyano, tri-chloro- or tri-fluoro- substituted groups) providing polarity. Note, however, that in these arrangements, the relative orientation of the hydroxyl and carbonyl remains the same (i.e. *ortho*), as in Formulas II-IV. Also, as with those previously described
25 embodiments, the length of the carbon chain in R_2 may be adjusted to provide the maximal enhancement.

Biologically and chemically active agents that can be made more useful by enhancing their absorption are exemplified, without limitation, by the following: growth hormones, including human growth hormones (hGH), bovine growth hormones, and
30 porcine growth hormones; growth hormone releasing hormones; interferons; cytokines; naturally occurring or recombinant insulins, including porcine, bovine, and human, optionally having counter ions including sodium, zinc, calcium, and ammonium; insulin-

like growth factors, including IGF-1; heparin, including unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin, and ultra-low molecular weight heparin; calcitonin, including salmon, eel, and human; erythropoietin; granulocyte-colony stimulating factor; atrial natriuretic factor; 5 antigens; monoclonal antibodies; somatostatin; protease inhibitors; adrenocorticotropin; gonadotropin releasing hormone; oxytocin; leutinizing hormone releasing hormone; follicle stimulating hormone; glucocerebrosidase; thrombopoietin; human granulocyte colony stimulating factor; prostaglandins; cyclosporin; vasopressin; cromolyn sodium; cephalosporins; vancomycin; desferrioxamine; parathyroid hormone, including its 10 fragments; vitamins; polyethylene glycol derivatives of these compounds, or any combination of these, as well as other proteins, polypeptides, hormones, polysaccharides, carbohydrates, and other organic compounds exhibiting poor bioavailability when administered to a subject. Other agents include vaccines, nucleotides, and antiviral agents. The compositions of the present invention are particularly useful for Type III 15 agents, that is, highly water soluble but poorly gastrointestinal membrane permeable agents, as classified by Biopharmaceutics Classification System set forth by the United States Food and Drug Administration.

The compositions of the present invention are useful for administering biologically or chemically active agents to animals, including but not limited to birds such 20 as chickens, and mammals such as cows, pigs, dogs, cats, primates, and particularly humans. The present invention may also be utilized to deliver agents such as pesticides and hormone disruptors to insects.

The compositions of the present invention can be particularly useful in enhancing the absorption of active agents across mucosal surfaces outside of the small and large 25 intestines, so as to provide a viable alternate delivery route to a subject's system other than by oral routes. Besides avoiding the likely degradation an active agent would encounter in the gastrointestinal environment, transmucosal administration can be a less invasive alternative to oral administration, due to the relatively easy access to a number of mucosal surfaces, such as in the buccal cavity, nose, vagina, and rectum. Other possible 30 transmucosal routes include the sublingual, ocular, intraduodenal, intracolonic, pulmonary mucosa, jejunum mucosa, and ileum mucosa. The compositions of the present invention also encompass both traditional oral delivery routes as well as through oral

mucosa. As such, the present invention also provides methods of enhancing absorption of active agents in a subject by administering a composition comprising an active agent and an enhancer so that it comes into effective contact with a mucosal surface of the subject, such as any of the surfaces listed above. The dosage form utilized in such a method will depend on the mucosal surface involved, and the manner of access provided to the surface.

Accordingly, dosage forms for providing enhanced absorption of active agents by any of these routes can comprise the active agent(s) and any absorption enhancer in accordance with the present invention. For oral administration, dosage forms include liquid suspensions or elixirs, capsules, coated and uncoated tablets, quick dissolving formulations, lozenges, gels, pastes, etc. Buccal administration can include buccal patches, tablets, lozenges, gels, pastes, etc. Rectal and vaginal dosage forms include liquids, gels, pastes, creams, and suppositories. Nasal administration may be accomplished with liquids, gels, pastes, or dry powders.

As appropriate to the form utilized, these dosage forms may each also comprise excipients in addition to the active agent and enhancer. For example, liquid oral dosage forms may include diluents, solubilizers, flavorants, taste masking agents, surfactants, buffering agents, preservatives, antioxidants, colorants, ethanol, propylene glycol, saccharides, and polyethylene glycol, as well as other appropriate additives known to those skilled in the art, and any combination thereof. Solid oral dosage forms such as tablets, coated tablets, capsules, and powders may be prepared by conventional skills in the art, and include excipients such as fillers, diluents, disintegrants, lubricants, glidants, plasticizers, colorants, flavorants, taste masking agents, saccharides, surfactants, binders, buffering agents, preservatives, antioxidants, colorants, polymer coatings, pore formers, and any combination thereof. Formulations for nasal administration may require a propellant. Suppositories may also contain suppository bases to provide proper consistency, such as coconut butter, polyethylene glycol, etc. Any of these dosage forms may optionally include any of a number of enzyme inhibitors known in the art such as actinonin or epiactinonin, and derivatives thereof; aprotinin; and Bowman-Birk inhibitor.

30

EXAMPLES

Example 1 - *Synthesis of methyl 4-aminosalicylate bisulfate*

4-Aminosalicylic acid (12.3 g) is placed in a round bottom flask. The flask is charged with 150 mL of methanol and 20 mL of concentrated sulfuric acid. The reaction mixture is brought to gentle reflux for 1 day, and then allowed to cool to room
5 temperature. The mixture is further chilled in a freezer and methyl 4-aminosalicylate bisulfate is crystallized. The crystals are collected and washed with cold methanol to afford 15.8 g of the product as off-white needles.

Example 2 - *Synthesis of methyl 4-(3-carboxy-propionylamino)-2-hydroxybenzoate*

10 Methyl 4-aminosalicylate bisulfate from Example 1 (5 g) is placed in a 50-mL round bottom flask. The flask is charged with 20 mL of methylene chloride and 15 mL of triethylamine. Finally, succinic anhydride (2.75 g) is added. The reaction mixture is then allowed to stir at ambient conditions overnight. Solvents are removed under reduced pressure, yielding a viscous residue, to which 1 N HCl is added. Methyl (3-carboxy-
15 propionylamino)-2-hydroxybenzoate is yielded as tan powder. The powders are collected by filtration, washed with water, and dried.

Example 3 - *Synthesis of N-n-hexyl 4-(3-carboxy-propionylamino)-2-hydroxybenzamide*

20 Methyl 4-(3-carboxy-propionylamino)-2-hydroxybenzoate from Example 2 (1 g) is dissolved in 15 mL of methanol. n-Hexylamine (5 mL) is added to this solution, and the reaction mixture is brought to mild reflux for 2 days. Solvents are removed under vacuum and residue acidified using 1 N HCl. N-n-hexyl 4-(3-carboxy-propionylamino)-
2-hydroxybenzamide precipitate is collected, washed with water, and dried.

25

Example 4 - *Synthesis of 4-(3-carboxy-propionylamino)-2-hydroxybenzamide*

Methyl 4-(3-carboxy-propionylamino)-2-hydroxybenzoate (1 g) from Example 2 is dissolved in 5 mL of 28% ammonium hydroxide solution. The reaction mixture is stirred at ambient conditions for 16 hours. In an ice-water bath, the solution is carefully
30 acidified using concentrated hydrochloric acid. The precipitate is collected by filtration, washed with water and dried.

Example 5 - *Synthesis of 4-aminosalicylamide*

Methyl 4-aminosalicylate bisulfate from Example 1 (5 g) is suspended in 20 mL of methanol. To the solution, 20 mL of 28% ammonium hydroxide is added slowly until all solid is dissolved. The reaction mixture is stirred at ambient conditions overnight.

5 Solvent is removed under reduced pressure and water is lyophilized. The residue is collected, washed with minimum amount of ice water and dried to yield 2.5 g of the product as off-white powders.

Example 6 - *Synthesis of 4-(9-carboxy-nonanoylamino)-2-hydroxybenzamide*

10 4-aminosalicylamide (2 g) from Example 5 is charged with 20 mL of methylene chloride. To the solution, 3.3 g of methyl 10-chloro-10-oxodecanoate is added. The reaction is initiated by addition of 2.6 mL of triethylamine. The reaction mixture is allowed to stir at ambient conditions for 2 days. Solvent is removed and the residue is acidified using 1 N HCl. The precipitate is extracted into ethyl acetate. The organic layer
15 is further extracted with 1 N NaOH and saturated NaCl solutions. After drying over anhydrous sodium sulfate, solvent is removed. The residue is reconstituted in tetrahydrofuran (10 mL) and 10 mL of 2 N NaOH is added. The solution is brought to gentle reflux for 2 hours. The disappearance of the methyl ester is followed by HPLC. When all ester is hydrolyzed, the solution is cooled and acidified and the product is
20 extracted into ethyl acetate. The organic layer is washed with saturated NaCl and dried over anhydrous sodium sulfate. Solvent is removed under reduced pressure and the product is obtained as off-white powder.

Example 7 - *Synthesis of n-butyl 4-aminosalicylate*

25 4-Aminosalicylic acid (12.3 g) is placed in a round bottom flask. The flask is charged with 150 mL of n-butanol and 20 mL of concentrated sulfuric acid. The reaction mixture is brought to gentle reflux for 1 day, and then allowed to cool to room temperature. The mixture is further chilled in a freezer and n-butyl 4-aminosalicylate bisulfate is crystallized. The crystals are collected and washed with cold methanol to
30 afford 15.8 g of the product as off-white needles.

Example 8 - *Synthesis of n-butyl 4-(3-carboxy-propionylamino)-2-hydroxybenzoate*

n-Butyl 4-aminosalicylate bisulfate (5 g) is placed in a 50-mL round bottom flask. The flask is charged with 20 mL of methylene chloride and 15 mL of triethylamine. Finally, succinic anhydride (2.75 g) is added. The reaction mixture is then allowed to stir at ambient conditions overnight. Solvents are removed under reduced pressure, yielding a viscous residue, to which 1 N HCl is added. n-Butyl (3-carboxy-propionylamino)-2-hydroxybenzoate is yielded as tan powder. The powders are collected by filtration, washed with water, and dried.

10 Example 9 - *Enhancement of bioavailability of insulin using absorption enhancer*

In a vial, 0.5 g of N-n-hexyl 4-(3-carboxy-propionylamino)-2-hydroxybenzamide from Example 3 is suspended in 2 mL of water. It is neutralized by 1 equivalent of sodium hydroxide. The pH is adjusted to 7-8 by 1N HCl and saturated sodium bicarbonate. Bovine pancreatic insulin (1.75 mL; Sigma, 10 mg/mL; in pH 8.2 HEPES buffer) is added and mixed by gentle swirling. The solution density is determined so that the required dose may be calculated.

The solution is then given to Sprague-Dawley rats (2-day fasting, female, 250-300 g, n=3), intracolonicly. Blood samples are taken from the tail vein and glucose levels measured using an OneTouch® UltraSmart® blood glucose meter. The analysis yields a blood glucose profile in which increasing the dose of absorption enhancer results in greater decreases in blood glucose, as shown in Table 1.

25 *Table 1 - Blood glucose depression (in % of basal level) induced by intracolonicly administrated bovine pancreatic insulin using N-n-hexyl 4-(3-carboxy-propionylamino)-2-hydroxybenzamide as the absorption enhancer*

Time (min)	Dose of enhancer				
	% Glucose Depression From Basal Level				
	0 mg/kg	5 mg/kg	25 mg/kg	100 mg/kg	200 mg/kg
0	100	100	100	100	100
30	94 ± 4	78 ± 9	52 ± 7	50 ± 8	46 ± 4
60	102 ± 7	83 ± 3	28 ± 3	29 ± 3	28 ± 3

90	105 ± 3	77 ± 5	29 ± 3	20 ± 2	33 ± 3
120	107 ± 7	99 ± 4	31 ± 8	19 ± 3	25 ± 3
150	94 ± 7	105 ± 6	29 ± 6	29 ± 6	26 ± 4
180	111 ± 7	96 ± 7	47 ± 8	22 ± 2	33 ± 2
210	113 ± 4	113 ± 8	67 ± 5	30 ± 6	29 ± 4
240	100 ± 7	105 ± 6	77 ± 5	49 ± 5	54 ± 7

Examples 10 – 21

The general procedure followed in Example 12 above is followed in Examples 13-26 (using different compounds and different dosages as set forth below, given intracolonicly or by oral gavage), with the following results.

*Table 2 - Blood glucose depression from basal level
as a function of absorption enhancer structure and dose*

Example No.	Enhancer				Route	Dose mg/Kg	Insulin mg/Kg	50% depression at 60 min.
	Formula	R ₃	(X-)R ₁ -A	Z-R ₂				
10	III	H	4-HOOC(CH ₂) ₂ CONH	NH ₂	C	200	7	negative
11	III	H	4-HOOC(CH ₂) ₂ CONH	NHC ₂ H ₅	C	200	7	negative
12	III	H	4-HOOC(CH ₂) ₂ CONH	NHC ₄ H ₉	C/O	100	7	positive
13	III	H	4-HOOC(CH ₂) ₂ CONH	NHC ₆ H ₁₃	C	25	7	positive
14	III	H	4-HOOC(CH ₂) ₂ CONH	NHC ₈ H ₁₇	C	25	7	positive
15	III	H	4-HOOC(CH ₂) ₂ CONH	NHC ₁₀ H ₂₁	C	50	7	positive
16	III	H	4-HOOCCH ₂ CH(CH ₃) CH ₂ CONH	NHC ₆ H ₁₃	C/O	200	7	positive
17	III	H	4-HOOC(CH ₂) ₂ CONH	OCH ₃	C	200	7	negative
18	III	H	4-HOOC(CH ₂) ₂ CONH	OC ₂ H ₅	C	200	7	negative
19	III	H	4-HOOC(CH ₂) ₂ CONH	OC ₄ H ₉	C	50	7	Positive
20	III	H	4-HOOC(CH ₂) ₂ CONH	OC ₆ H ₁₃	C	50	7	Positive
21	III	H	5-HOOC(CH ₂) ₂ CONH	OC ₈ H ₁₇	C	100	7	Positive

C: Colonicly

10 O: By oral gavage.

It is noted that though Examples 10, 11, 17, and 18 are shown as “negative,” that does not mean that no enhancement occurred. It only means that a 50% reduction in glucose levels was not reached in 60 minutes. As insulin reduces glucose levels in the blood, a depression in glucose levels indicates insulin reaching the blood efficaciously.

5

While the forgoing examples are illustrative of the principles of the present invention in one or more particular applications, it will be apparent to those of ordinary skill in the art that numerous modifications in form, usage and details of implementation can be made without the exercise of inventive faculty, and without departing from the principles and concepts of the invention. Accordingly, it is not intended that the invention be limited, except as by the claims set forth below.

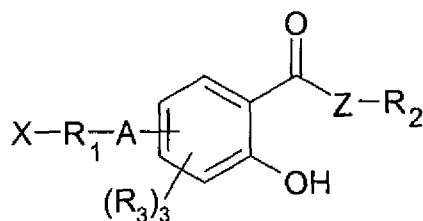
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CLAIMS

What Is Claimed Is:

1. A composition, comprising:

- 5 a) at least one active agent; and
b) an absorption enhancer having the formula:



or a pharmaceutically acceptable salt thereof, wherein

10 R_1 is null, C_1 - C_{12} alkylene, C_2 - C_{12} alkenylene, arylene, or substituted alkylene, alkenylene, or arylene, said substituted alkylene, alkenylene, or arylene being substituted with N, O, S, or P;

R_2 is hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, aryl, or cycloalkyl;

15 each R_3 is independently hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, or aryl, or substituted alkyl, alkenyl, or aryl, said substituted alkyl, alkenyl, or aryl being substituted with N, O, S, or P;

20 X is tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid, sulfide, sulfonic acid, sulfenic acid, sulfoxide, phosphoric acid, phosphonic acid, poly(ethylene glycol), saccharide, oligosaccharide, polyol, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, chitosan, or a combination thereof;

Z is null, O, S, NH, or NR where R is C_1 to C_6 lower alkyl, or wherein Z is joined with R_2 to form a heterocyclic ring; and

A is null or CONH, wherein A and R_1 are not simultaneously null.

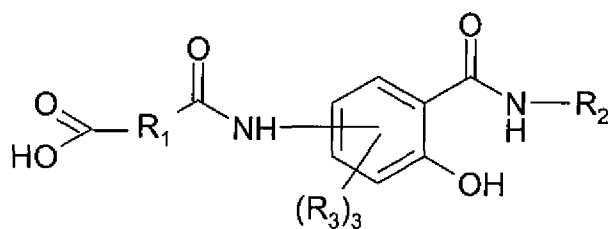
25 2. The composition of claim 1, wherein X- R_1 -A, R_3 , and (C=O)-Z- R_2 collectively contain at least one chemically or enzymatically labile linkage.

3. The composition of claim 1, wherein the at least one active agent is selected from the group consisting of growth hormones, growth hormone releasing hormones, interferons, cytokines, insulins, insulin-like growth factors, heparins, calcitonins, erythropoietin, granulocyte-colony stimulating factor, atrial naturetic factor, antigens, monoclonal antibodies, somatostatin; protease inhibitors, adrenocorticotropin, 5 gonadotropin releasing hormone, oxytocin, leutinizing hormone releasing hormone, follicle stimulating hormone, glucocerebrosidase, thrombopoietin, human granulocyte colony stimulating factor, prostaglandins, cyclosporin, vasopressin, cromolyn sodium, cephalosporins, vancomycin, desferrioxamine, parathyroid hormone, polyethylene glycol 10 derivatives of these compounds, and combination thereof.

4. The composition of claim 1, further comprising an enzyme inhibitor.

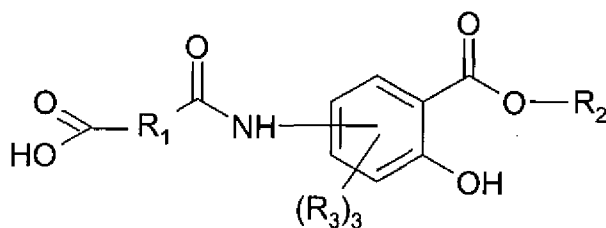
5. The composition of claim 1, formulated into a dosage form selected from the 15 group consisting of tablet, capsule, lozenge, liquid solution, liquid suspension, paste, gel, cream, powder, patch, or suppository.

6. The composition of claim 1, wherein the absorption enhancer has the formula:



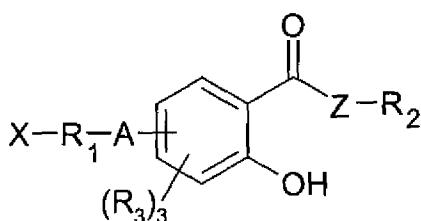
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7. The composition of claim 1, wherein the absorption enhancer has the formula:



8. A method of enhancing transmucosal absorption of active agents in a subject,
 5 comprising administering a composition to the subject so that the composition comes into
 effective contact with a mucosal surface of the subject, said composition comprising:

- a) at least one active agent; and
 b) an absorption enhancer having the formula:



10

or a pharmaceutically acceptable salt thereof, wherein

R₁ is null, C₁-C₁₂ alkylene, C₂-C₁₂ alkenylene, arylene, or substituted
 alkylene, alkenylene, or arylene, said substituted alkylene, alkenylene, or arylene
 being substituted with N, O, S, or P;

15

R₂ is hydrogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, aryl, or cycloalkyl;

each R₃ is independently hydrogen, C₁-C₁₂ alkyl, C₂-C₁₂ alkenyl, or aryl,
 or substituted alkyl, alkenyl, or aryl, said substituted alkyl, alkenyl, or aryl being
 substituted with N, O, S, or P;

20

X is tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid,
 sulfide, sulfonic acid, sulfenic acid sulfoxide, phosphoric acid, phosphonic acid,
 poly(ethylene glycol), saccharide, oligosaccharide, polyol, polyvinylpyrrolidone,
 polyvinyl alcohol, polyacrylic acid, chitosan, or a combination thereof;

Z is null, O, S, NH, or NR where R is lower alkyl, or wherein Z is joined
 with R₂ to form a heterocyclic ring; and

25

A is null or CONH, wherein A and R₁ are not simultaneously null.

9. The method of claim 8, wherein X-R₁-A, R₃, and (C=O)-Z-R₂ collectively
 contain at least one chemically or enzymatically labile linkage.

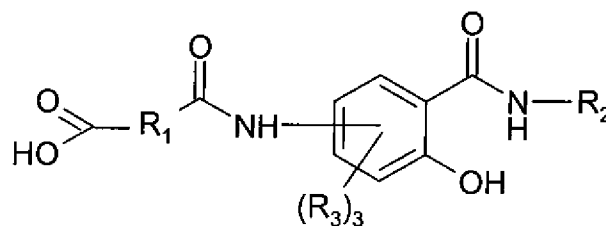
10. The method of claim 8, wherein the mucosal surface is selected from the group consisting of buccal, sublingual, nasal, rectal, pulmonary, ocular, or vaginal.

5 11. The method of claim 8, wherein the composition is administered orally.

12. The method of claim 11, wherein the active agent is absorbed through the duodenum, ileum, jejunum, or colon.

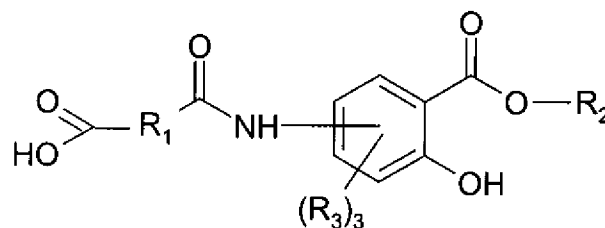
10 13. The method of claim 11, wherein the composition is administered in a dosage form selected from the group consisting of tablet, capsule, powder, elixir, and suspension.

14. The method of claim 8, wherein the absorption enhancer has the formula:



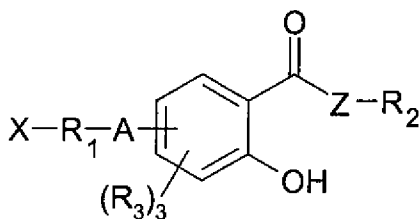
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15. The method of claim 8, wherein the absorption enhancer has the formula:



20

16. The use of an absorption enhancer in the manufacture of a medicament for enhancing transmucosal absorption of an active agent, wherein the absorption enhancer has the formula:



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or a pharmaceutically acceptable salt thereof, wherein

R_1 is null, C_1 - C_{12} alkylene, C_2 - C_{12} alkenylene, arylene, or substituted alkylene, alkenylene, or arylene, said substituted alkylene, alkenylene, or arylene being substituted with N, O, S, or P;

10

R_2 is hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, aryl, or cycloalkyl;

each R_3 is independently hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, or aryl, or substituted alkyl, alkenyl, or aryl, said substituted alkyl, alkenyl, or aryl being substituted with N, O, S, or P;

15

X is tertiary amine, quaternary amine, tertiary sulfur, carboxylic acid, sulfide, sulfonic acid, sulfenic acid, sulfoxide, phosphoric acid, phosphonic acid, poly(ethylene glycol), saccharide, oligosaccharide, polyol, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, chitosan, or a combination thereof;

Z is null, O, S, NH, or NR where R is C_1 to C_6 lower alkyl, or wherein Z is joined with R_2 to form a heterocyclic ring; and

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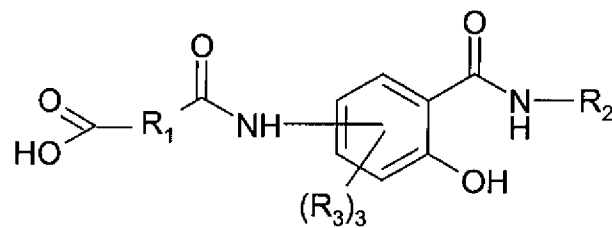
A is null or CONH, wherein A and R_1 are not simultaneously null.

17. The use of claim 16, wherein X- R_1 -A, R_3 , and (C=O)-Z- R_2 collectively contain at least one chemically or enzymatically labile linkage selected from the group consisting of amide, ester, and peptide.

25

18. The use of claim 16, wherein the absorption enhancer further comprises an enzyme inhibitor.

19. The use of claim 16, wherein the absorption enhancer has the formula:



5 20. The use of claim 16, wherein the absorption enhancer has the formula:

