

**PHARMACEUTICAL COMPOSITION COMPRISING (SUBSTITUTED PHENYL)-
PROPENAL COMPOUNDS AND USES THEREOF**

Field of the Invention

[0001] The present disclosure relates to pharmaceutical compositions comprising
5 (substituted phenyl)-propenal compounds and a (meth)acrylate copolymer(s), and uses of the
pharmaceutical compositions.

Background of the Invention

[0002] Compounds having (substituted phenyl)-propenal moieties were found to possess
numerous biological activities *in vitro*, such as anti-oxidant, anti-inflammatory, anti-tumor,
10 and antiangiogenesis activities, and may potentially be used in the treatment of an androgen
receptor associated medical condition, such as proliferation of abnormal cells, inflammation,
etc.

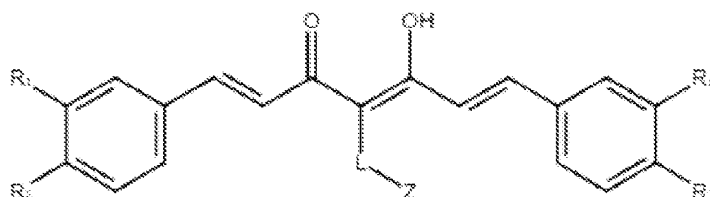
[0003] However, most of these compounds are insoluble or hardly soluble in an aqueous
medium, e.g., water, resulting in insufficient bioavailability. Existing formulations of these
15 compounds may be in a liquid form with a hydrophobic (organic) medium. Nevertheless,
manufacture (including transportation) and storage of liquid formulations may be subject to
more restrictions compared to solid formulations.

[0004] Hence, there is still a need for developing (pharmaceutical) compositions of the
compounds having (substituted phenyl)-propenal moieties for improved bioavailability,
20 manufacture and storage thereof.

Summary of the Invention

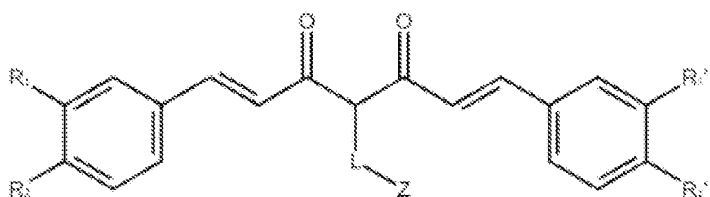
[0005] The present disclosure thus relates to a pharmaceutical composition comprising: a
compound of Formula (Ia) or of Formula (Ib), and a (meth)acrylate copolymer,

[0006]



Formula (Ia),

[0007]



Formula (Ib),

5 [0008] wherein:

[0009] R₁, R₂, R₁' and R₂' are independently selected from the group consisting of -H, -

OH, and -OCH₃;

[0010] L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

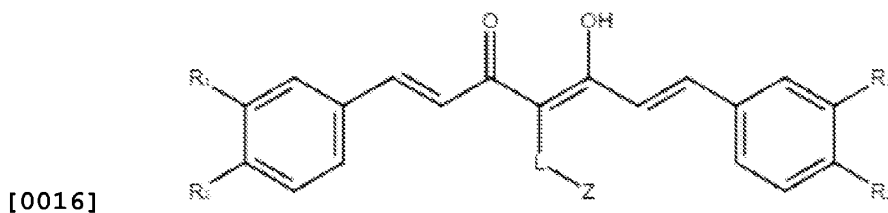
10 [0011] Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O)R_a, -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

[0012] X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and

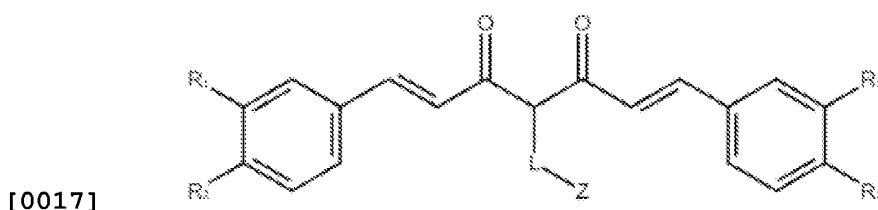
[0013] wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of diketone; and

15 [0014] the (meth)acrylate copolymer is formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates.

[0015] The present disclosure also relates to a pharmaceutical composition comprising: a compound of Formula (Ia) or of Formula (Ib);



Formula (Ia),



Formula (Ib),

5 [0018] wherein:

[0019] R_1 , R_2 , R_1' and R_2' are independently selected from the group consisting of -H, -OH, and -OCH₃;

[0020] L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

10 [0021] Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O) R_a , -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

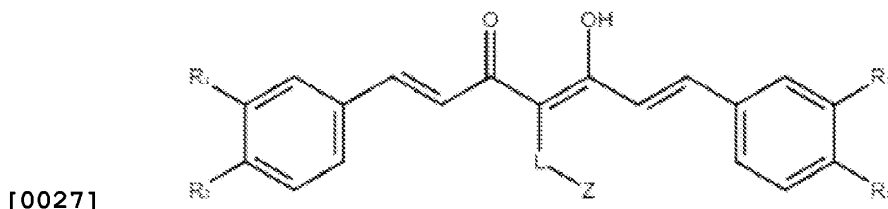
[0022] X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and

[0023] wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of diketone; and

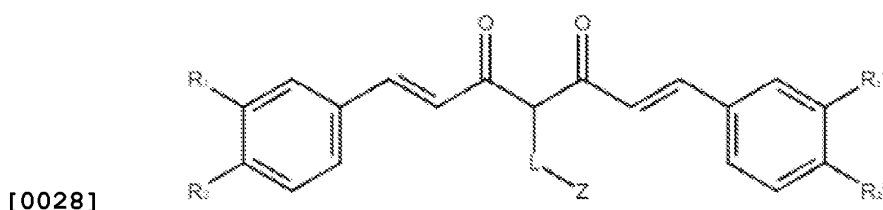
15 [0024] a (meth)acrylate copolymer used for dispersing the compound of Formula (Ia) or of Formula (Ib), wherein the (meth)acrylate copolymer is formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates.

[0025] The present disclosure also relates to a pharmaceutical composition comprising:

[0026] a compound of Formula (Ia) or of Formula (Ib);



Formula (Ia),



Formula (Ib),

[0029] wherein:

[0030] R_1 , R_2 , R_1' and R_2' are independently selected from the group consisting of -H, -OH, and -OCH₃;

[0031] L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

10 [0032] Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O) R_a , -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

[0033] X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and

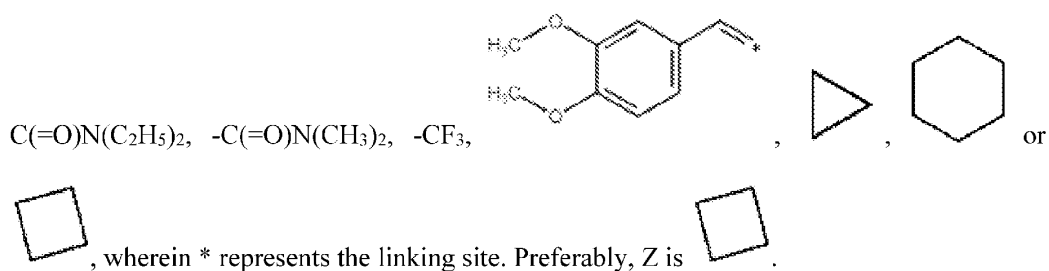
15 [0034] wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of diketone; and

[0035] a (meth)acrylate copolymer formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates; wherein the compound of Formula (Ia) or of Formula (Ib) and the (meth)acrylate copolymer are in the form of a solid dispersion.

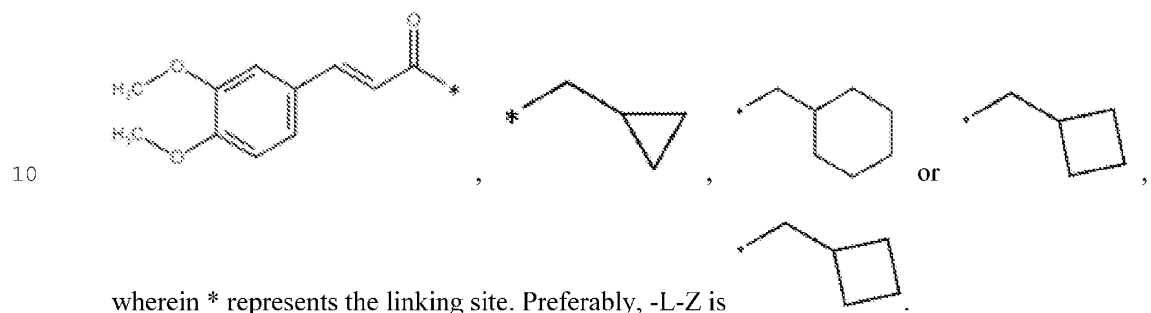
[0036] In one embodiment of any of the preceding pharmaceutical compositions, one or more of R_1 , R_2 , R_1' and R_2' is $-OCH_3$. Preferably, R_1 , R_2 , R_1' and R_2' are $-OCH_3$.

[0037] In one embodiment of any of the preceding pharmaceutical compositions, $-L-$ is $-CH_2-$, $-C(=O)-$ or $-CH_2-CH_2-$. Preferably, $-L-$ is $-CH_2-$.

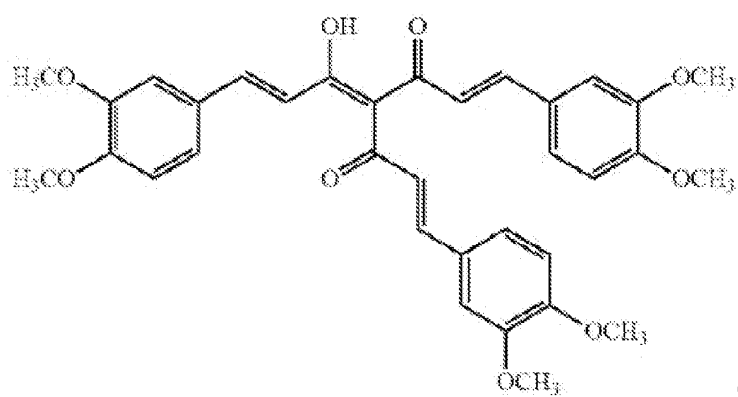
5 [0038] In one embodiment of any of the preceding pharmaceutical compositions, Z is -



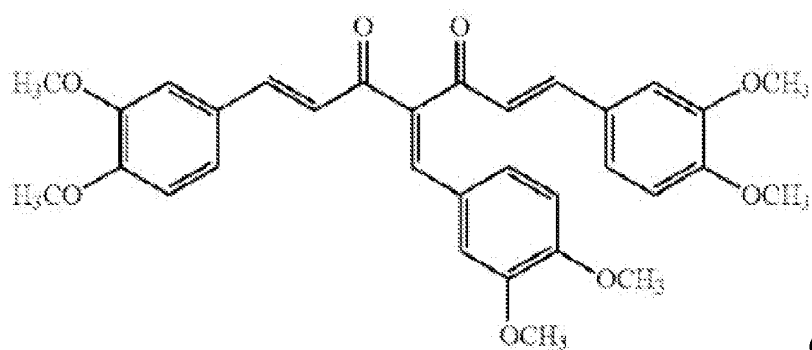
[0039] In one embodiment of any of the preceding pharmaceutical compositions, $-L-Z$ represents $-CH_2C(=O)N(C_2H_5)_2$, $-CH_2C(=O)N(CH_3)_2$, $-CH_2CH_2CF_3$,



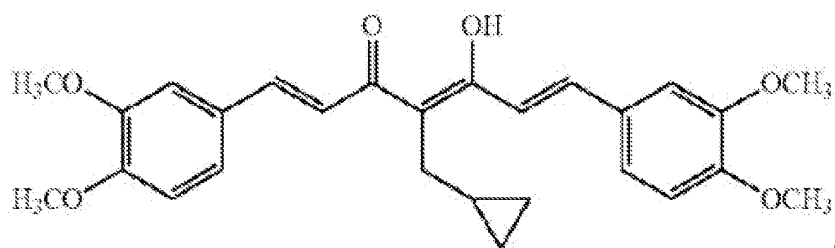
[0040] In one embodiment of any of the preceding pharmaceutical compositions, the compound is selected from the group consisting of:



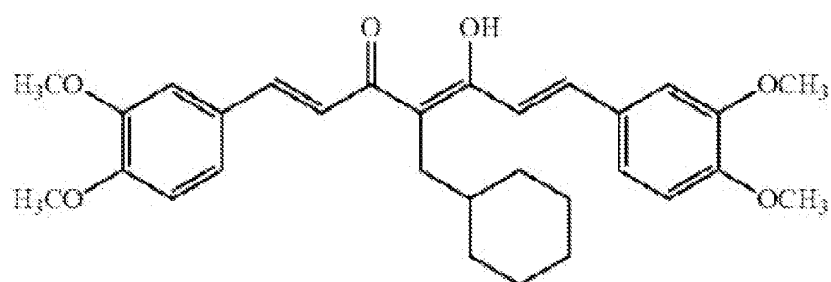
(Compound a),



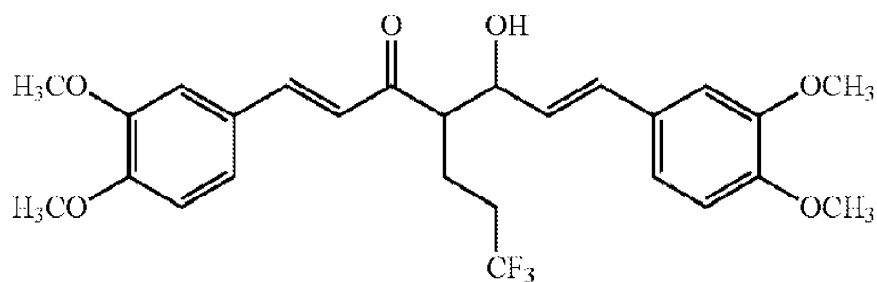
(Compound b),



(Compound c),

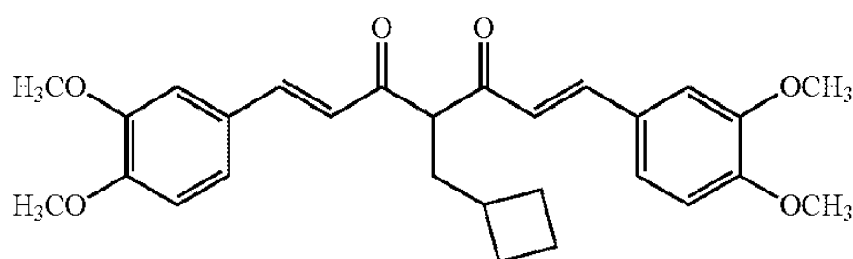


(Compound d),



(Compound e),

and



(Compound f).

[0041] In one embodiment of any of the preceding pharmaceutical compositions, the
 5 (meth)acrylic acid content is present in an amount of at least 43 wt.%, based on the total
 amounts of the (meth)acrylate copolymer.

[0042] In one embodiment of any of the preceding pharmaceutical compositions, the
 comonomers do not have an amino or ammonium group(s).

[0043] In one embodiment of any of the preceding pharmaceutical compositions, the
 10 (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and C₁₋₃
 alkyl acrylates.

[0044] In one embodiment of any of the preceding pharmaceutical compositions, the
 molecular weight of the (meth)acrylate copolymer ranges from about 24,000 to about 33,000
 g/mol.

15 [0045] In one embodiment of any of the preceding pharmaceutical compositions, the
 weight ratio of the compound to the (meth)acrylate copolymer ranges from 5:95 to 60:40.

[0046] In one embodiment of any of the preceding pharmaceutical compositions, the weight ratio of the compound to the (meth)acrylate copolymer is about 10:90.

[0047] In one embodiment of any of the preceding pharmaceutical compositions, the weight ratio of the compound to the (meth)acrylate copolymer is about 35:65.

5 [0048] In one embodiment of any of the preceding pharmaceutical compositions, the weight ratio of the compound to the (meth)acrylate copolymer is about 40:60.

[0049] In one embodiment of any of the preceding pharmaceutical compositions, the weight ratio of the compound to the (meth)acrylate copolymer is about 45:55.

10 [0050] In one embodiment of any of the preceding pharmaceutical compositions, the pharmaceutical composition is obtained by drying a liquid suspension, dispersion or solution or a wet solid comprising the compound and the (meth)acrylate copolymer. In one embodiment, the drying is spray-drying, fluidized-bed drying, oven drying or freeze-drying.

[0051] In one embodiment of any of the preceding pharmaceutical compositions, the pharmaceutical composition exhibits an undetectable concentration of the compound in
15 solubility tests in Fasted State Simulated Gastric Fluid (FaSSGF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 4 hours.

[0052] In one embodiment of any of the preceding pharmaceutical compositions, the pharmaceutical composition exhibits a concentration of the compound of at least about 60
20 µg/ml in solubility tests in Fasted State Simulated Intestinal Fluid (FaSSIF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 0.5 hours.

[0053] In one embodiment of any of the preceding pharmaceutical compositions, the compound is substantially in an amorphous form in the pharmaceutical composition.

[0054] In one embodiment of any of the preceding pharmaceutical compositions, the enol form to keto form ratio (w/w) of the compound is from 33:67 to 40:60.

5 [0055] The present disclosure also relates to use of any of the preceding pharmaceutical compositions in the manufacture of a medicament for treating an androgen receptor associated medical condition.

[0056] The present disclosure also relates to a method of treating an androgen receptor associated medical condition in a subject in need thereof, comprising administering any of the
10 preceding pharmaceutical compositions to the subject.

[0057] The present disclosure also relates to any of the preceding pharmaceutical compositions for use in treating an androgen receptor associated medical condition.

Brief Description Of The Drawings

[0058] Figures 1A to 1H show the X-ray powder diffraction (XRPD) of the
15 pharmaceutical compositions having different ratios of the compound to the polymer at the storage condition of 40°C, 75%RH for five weeks.

[0059] Figures 2A to 2F show the X-ray powder diffraction (XRPD) of the pharmaceutical compositions having different ratios of the compound to the polymer at the storage condition of 50°C, 75%RH for five weeks.

Detailed Description of the Present Disclosure

20 [0060] As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising," "comprises" and "comprised" are not intended to exclude other additives, components, integers or steps.

[0061] As used herein, except where the context requires otherwise, the term "consist (essentially) of" and variations of the term, such as "consisting (essentially) of," "consists (essentially) of" and "consisted (essentially) of," mean that specific further component(s) can be present, namely, those not materially affecting the essential characteristics of the compound or composition.

[0062] As used herein, except where the context requires otherwise, the method steps disclosed are not intended to be limiting, nor are they intended to indicate that each step is essential to the method or that each step must occur in the order disclosed.

[0063] As used herein, the use of "or" means "and/or" unless stated otherwise. In the context of a multiple dependent claim, the use of "or" refers back to more than one preceding independent or dependent claim in the alternative only.

[0064] As used herein, all numbers may refer to the exact value or may be approximate, and may be varied to account for measurement error and the rounding of significant digits. The use of "about" before certain measured quantities includes variations due to sample impurities, measurement error, human error, and statistical variation, as well as the rounding of significant digits.

[0065] As used herein, the term "about" refers to an acceptable deviation of a given value measured by a person of ordinary skill in the art, depending, in part, on how to measure or determine the value.

[0066] As used herein, the term "aliphatic" or "aliphatic group" may include saturated or unsaturated, linear, branched or cyclic groups, e.g., alkyls, alkenyls, alkynyls, (cyclo)alkanes, (cyclo)alkenes, (cyclo)alkynes, etc. In certain cases, the aliphatic groups may contain heteroatom(s) interrupted in the chain or acting as a ring member atom.

[0067] As used herein, the term "alkyl" refers to a substituent derived from a saturated, straight or branched alkane, which comprises preferably 1-20 carbon atoms, more preferably 1-12 carbon atoms and most preferably 1-6 carbon atoms, or the number of carbon atoms is specified. Examples of alkyl include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, 2-ethylbutyl, n-pentyl, isopentyl, 1-methylpentyl, 1,3-dimethylbutyl, n-hexyl, 1-methylhexyl, n-heptyl, isoheptyl, 1,1,3,3-tetramethylbutyl, 1-methylheptyl, 3-methylheptyl, n-octyl, 2-ethylhexyl, 1,1,3-trimethylhexyl, 1,1,3,3-tetramethylpentyl, nonyl, decyl, undecyl, 1-methylundecyl, dodecyl, 1,1,3,3,5,5-hexamethylhexyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, or the like.

[0068] As used herein, the term "alkenyl" refers to a substituent derived from a straight or branched hydrocarbon alkene, which contains at least one carbon-to-carbon double bond, preferably 2-10 carbon atoms, more preferably 2-6 carbon atoms and most preferably 2-4 carbon atoms wherein hydrogen may be replaced by a monovalent substituent. Examples of alkenyl include, but are not limited to, ethenyl, prop-1-enyl, or the like.

[0069] As used herein, the term "alkynyl" refers to a substituent derived from a straight or branched hydrocarbon alkene, which contains at least one carbon-to-carbon triple bond, preferably 2-10 carbon atoms, more preferably 2-6 carbon atoms and most preferably 2-4 carbon atoms wherein hydrogen may be replaced by a monovalent substituent. Examples of alkynyl include, but are not limited to, ethynyl, prop-1-ynyl, or the like.

[0070] As used herein, the suffix "-ene" following "alkyl" or "alkenyl" refers to a divalent group derived from "alkyl" or "alkenyl." Examples of alkylene include, but are not limited to, methylene (-CH₂-), propylenes (-CH₂CH₂CH₂-, -CH₂(CH-)CH₃), etc.), butylenes, petanylenes,

etc. Examples of alkenylene include, but are not limited to, ethenylene ($-\text{CH}=\text{CH}-$), propenylenes ($-\text{CH}=\text{CH}-\text{CH}_2-$ or $-\text{CH}=\text{C}-\text{CH}_3$), butenylenes, pentenylenes, etc.

[0071] As used herein, the term "alkoxyl" or "alkoxy" means a group having a formula "-O-alkyl," wherein the definition of the "alkyl" in said formula has the meaning of "alkyl" as stated above.

[0072] As used herein, the term "cycloalkyl" means a saturated or partially unsaturated cyclic carbon radical containing 3 to 10 ring carbon atoms, preferably 3 to 8 ring carbon atoms and more preferably 3 to 6 ring carbon atoms, and optionally an alkyl or alkoxy substituent(s) on the ring. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclopropenyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-cyclohexen-1-yl, and the like.

[0073] As used herein, the term "aromatic," "aromatic group" or "aryl" refers to those having aromaticity, which may have 6 to 12 ring members, preferably 6 to 9 ring members, and may have a monocyclic ring or a polycyclic (fused) ring, and optionally these groups may have a substituent(s). Examples of the aromatic groups include, but are not limited to, phenyl, benzyl, biphenyl, naphthalene, fluorene, etc.

[0074] As used herein, the term "halogen" or "halo" denotes fluorine, chlorine, bromine or iodine.

[0075] As used herein, the term "carbonyl" means the moiety " $-\text{C}(=\text{O})-$." In certain embodiments, the term "carbonyl" may also refer to said moiety in other functional groups, e.g., in carboxy, amide, urethane, urea, etc.

[0076] As used herein, the term "amino" means a functional group of the formula $-\text{NR}'\text{R}''$, wherein R' and R'' each independently represent hydrogen, an aliphatic group or an aromatic group as defined above.

[0077] As used herein, the term "ammonium" means a functional group of the formula - $N^+R'R''R'''$, with or without a counter-anionic group, e.g., halogen, wherein R' , R'' and R''' each independently represent hydrogen, an aliphatic group or an aromatic group as defined above.

5 [0078] As used herein, the expression "(meth)acrylic" refers to an acrylic and/or methacrylic moiety. Similarly, the expression "(meth)acrylate" as used herein refers to an acrylate and/or methacrylate moiety.

[0079] As used herein, the term "polymer" and "(co)polymer" may be construed as a generic concept to include homopolymers and copolymers, unless otherwise specified. As
10 used herein, copolymers may be in various configurations, such as alternating copolymers, random copolymers, block copolymers, terpolymers, etc.

[0080] As used herein, the molecular weight of a (co)polymer, if not otherwise specified, refers to weight average molecular weight (i.e., M_w).

[0081] The term "prodrug" refers to compounds, including derivatives of the compounds
15 described herein, which have cleavable groups and become by solvolysis or under physiological conditions the compounds described herein, which are pharmaceutically active in vivo. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like. Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form, they
20 often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism. Prodrugs include acid derivatives well known to practitioners of the art, such as esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by

reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides.

[0082] The term "administer," "administering," or "administration," as used herein, refers to implanting, absorbing, ingesting, injecting, inhaling, or otherwise introducing an inventive compound, or a pharmaceutical composition thereof, in or on a subject.

[0083] As used herein, the terms "condition," "disease," and "disorder" are used interchangeably.

[0084] An "effective amount" of a compound described herein refers to an amount sufficient to elicit the desired biological response, i.e., treating the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0085] A "therapeutically effective amount" of a compound described herein is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term "therapeutically effective amount" can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, and/or enhances the therapeutic efficacy of another therapeutic agent.

[0086] As used herein, the term "pharmaceutically acceptable carrier" refers to a solid, semisolid, or liquid filler, diluent, encapsulating material, formulation auxiliary, or carrier conventional in the art for use with a therapeutic agent for administration to a subject. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentration
5 employed, and is compatible with other ingredients of the formulation. Pharmaceutically acceptable carriers are determined in part by the particular composition being administered, as well as by the particular method used to administer the composition.

[0087] As used herein, the term "subject" is defined to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats,
10 rabbits, rats, mice and the like. In specific embodiments, the subject is a human. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human.

[0088] As used herein, the terms "treat," "treating" and "treatment" refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the
15 disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more prophylactic or therapeutic agents to a subject with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound or dosage form provided herein, with or without one or more additional active agents, after the diagnosis or onset of
20 symptoms of the particular disease.

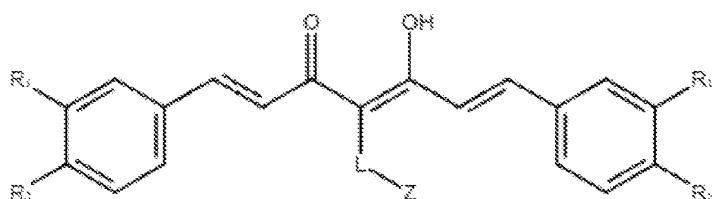
[0089] As used herein, the terms "prevent," "preventing" and "prevention" refer to the prevention of the onset, recurrence or spread of a disease or disorder, or of one or more symptoms thereof. In certain embodiments, the terms refer to the treatment with or

administration of a compound or an antibody or dosage form provided herein, with or without one or more other additional active agents, prior to the onset of symptoms, particularly to patients at risk of disease or disorders provided herein. The terms encompass the inhibition or reduction of a symptom of the particular disease.

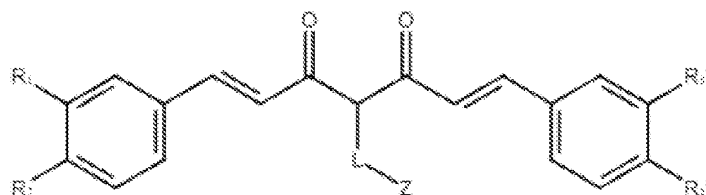
5 **[0090]** As used herein, the terms "co-administration" and "in combination with" include the administration of two or more therapeutic agents simultaneously, concurrently, separately or sequentially within no specific time limits unless otherwise indicated. In one embodiment, the therapeutic agents are in the same composition or unit dosage form. In other embodiments, the therapeutic agents are in separate compositions or unit dosage forms.

10 **[0091] Compounds in the pharmaceutical composition**

[0092] The compounds with (substituted phenyl)-propenal moieties in the present disclosure have Formula (Ia) or Formula (Ib):



Formula (Ia),



Formula (Ib),

[0093] wherein the definitions of R₁, R₂, R₁', R₂', L, Z, X are as those described above.

[0094] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$.

[0095] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is $-C(=O)NR_aR_b$, wherein both R_a and R_b are methyl. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is $-C(=O)NR_aR_b$, wherein both R_a and R_b are methyl.

[0096] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is $-C(=O)NR_aR_b$, wherein both R_a and R_b are ethyl. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is $-C(=O)NR_aR_b$, wherein both R_a and R_b are ethyl.

[0097] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methine (methylylidene) ($=CH-$) and Z is dimethoxyphenyl. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methine (methylylidene) ($=CH-$) and Z is dimethoxyphenyl.

[0098] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is carbonyl-vinyl ($-C(=O)-CH=CH-$) and Z is dimethoxyphenyl. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is carbonyl-vinyl ($-C(=O)-CH=CH-$) and Z is dimethoxyphenyl.

[0099] In one embodiment, in Formula (Ia), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is 1,1,1-trifluoroethyl, cyclopropyl, cyclopentyl or cyclohexyl. In one embodiment, in Formula (Ib), R_1 , R_2 , R_1' and R_2' all are $-OCH_3$, $-L-$ is methylene and Z is 1,1,1-trifluoroethyl, cyclopropyl, cyclopentyl or cyclohexyl.

[00100] In one embodiment, in Formula (Ia), R₁, R₂, R₁' and R₂' all are -OCH₃, -L- is methylene and Z is cyclohexyl. In one embodiment, in Formula (Ib), R₁, R₂, R₁' and R₂' all are -OCH₃, -L- is methylene and Z is cyclohexyl.

[00101] Without being bound to the theory, keto-enol tautomerization between the compounds of Formula (Ia) and Formula (Ib) may occur and thus the compounds are the equilibrate tautomers as a common phenomenon of diketone.

[00102] In one embodiment, the compound of Formula (Ia) or Formula (Ib) comprise a pharmaceutically acceptable salts, solvates, hydrates, isomers, and/or stereoisomers of the compound.

[00103] The water solubility of the compound of Formula (Ia) or Formula (Ib) may be less than 0.25 µg/mL in neutral water at 37°C.

[00104] (Meth)acrylate copolymers in the pharmaceutical composition

[00105] In order to enhance the bioavailability of hydrophilic components, hydrophilic components may be used in combination therewith. However, the compatibility between these components may not be easily inferred, and thus there may be certain hindrances when designing drug formulations. Here, the inventors surprisingly found that specific (meth)acrylate copolymers would be suitable to the compounds as described herein for enhancing bioavailability by achieving particular goals.

[00106] In particular, one of the goals is to increase the solubility of the compound, which is representative for the amount of the compound released, in the intestinal environment, which would be beneficial to (efficient) absorption by a subject; one of the goals is to achieve rapid release (e.g., within 30 minutes) of the compound in the intestinal environment, which may be beneficial to more efficiently absorbed by a subject; one of the goals is to achieve

prolonged or sustained release (e.g., for 240 minutes) of the compound in the intestinal environment, which may be beneficial to optimizing the pharmacokinetic behavior; and one of the goals is to prevent release of the compound in the gastric environment, which would be beneficial to preventing degradation of the compound. Without being bound to theory, absorption of the compound in the former part of the intestine, e.g., duodenum, is more efficient than in other part of the intestine. If the release of the compound occurs in a shorter period, e.g., 0.5 hrs, then better absorption of the compound would be expected since the release occurs in the former part of the intestine, e.g., duodenum. On the other hand, if release of the compound does not occur in 0.5 hrs but needs more time, the compound may move forward and begin to be released in the latter part of the intestine, which may result in lower absorption efficiency.

[00107] The specific (meth)acrylate copolymers used herein may be those formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates. In one embodiment, the comonomers comprise methacrylic acid and methyl methacrylate. In one embodiment, the comonomers comprise methacrylic acid and ethyl methacrylate. In one embodiment, the comonomers comprise methacrylic acid and propyl methacrylate. In one embodiment, the comonomers comprise methacrylic acid and one or more of methyl methacrylate, ethyl methacrylate and propyl methacrylate. In one embodiment, the comonomers comprise acrylic acid and methyl methacrylate. In one embodiment, the comonomers comprise acrylic acid and ethyl methacrylate. In one embodiment, the comonomers comprise acrylic acid and propyl methacrylate. In one embodiment, the comonomers comprise acrylic acid and one or more of methyl methacrylate, ethyl methacrylate and propyl methacrylate. In one embodiment, the comonomers comprise

methacrylic acid and methyl (meth)acrylate. In one embodiment, the comonomers comprise methacrylic acid and ethyl (meth)acrylate. In one embodiment, the comonomers comprise methacrylic acid and propyl (meth)acrylate. In one embodiment, the comonomers comprise methacrylic acid and one or more of methyl (meth)acrylate, ethyl (meth)acrylate and propyl (meth)acrylate.

[00108] In one embodiment, the (meth)acrylate copolymer consists of two types of monomers. In one embodiment, the (meth)acrylate copolymer consists of three types of monomers, i.e., a terpolymer.

[00109] In one embodiment, the (meth)acrylic acid content is present in an amount of at least 43 wt.%, preferably ranging from 43 wt.% to 51 wt.%, e.g., from 43 wt.% to 48 wt.%, from 46 wt.% to 51 wt.%, or any reasonable numeric ranges constituted by the terminal point values, based on the total amounts of the (meth)acrylate copolymer. In one embodiment, the comonomers do not have an amino or ammonium group(s). In one embodiment, the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and C₁₋₃ alkyl acrylates, preferably methacrylic acid and ethyl acrylate. In one embodiment, the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and C₁₋₃ alkyl acrylate, wherein the molar ratio of methacrylic acid content to C₁₋₃ alkyl acrylates content ranges from 1:0.95 to 1:1.35, preferably from 1:0.97 to 1.18, from 1:1.1 to 1:1.31, or any reasonable numeric ranges constituted by the terminal point values. In one embodiment, the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and ethyl acrylate, wherein the molar ratio of methacrylic acid content to ethyl acrylate content ranges from 1:0.95 to 1:1.35, preferably from 1:0.97 to 1.18, from 1:1.1 to 1:1.31, or any reasonable numeric ranges constituted by the terminal point values. In one embodiment, the

molecular weight of the (meth)acrylate copolymer ranges from 24,000 to 33,000 g/mol, e.g., from 25,000 to 32,000 g/mol, from 26,500 to 30,000 g/mol, from 24,500 to 31,000 g/mol, or any reasonable numeric ranges constituted by the terminal point values.

5 **[00110] Pharmaceutical compositions comprising the compound and the (meth)acrylate copolymer**

[00111] Without being bound to the theory, the proportions of the compound and the (meth)acrylate copolymer may be suitably adjusted to achieve the desired result, such as good stability (upon storage), specific solubility and releasing behaviors in different (simulated human) conditions, etc. In one embodiment, the (meth)acrylate copolymer is used for dispersing the compound. In one embodiment, the compound and the (meth)acrylate copolymer are in the form of a solid dispersion.

[00112] The weight ratio of the compound and the (meth)acrylate copolymer can be adjusted to range from 5:95 to 60:40, e.g., about or at least 10:90, about or at least 20:80, about or at least 35:65, about, at least or at most 40:60, about, at least or at most 45:55, about, at least or at most 50:50, or any reasonable numeric ranges constituted by the terminal point or single point values.

[00113] The compound used for or after the preparation of the pharmaceutical composition may be present in various configurations. In one embodiment, the enol form to keto form ratio (w/w) of the compound ranges from 33:67 to 40:60, preferably from 36:64 to 39:61, or any reasonable numeric ranges constituted by the terminal point values. In one embodiment, the compound used for the preparation or after storage (e.g., at 40°C or 50°C, 75%RH for 2 to 5 weeks) of the pharmaceutical composition is substantially in an amorphous form in the pharmaceutical composition, as evidenced by X-ray powder diffraction (XRPD). In one

embodiment, the impurity content in the pharmaceutical composition upon storage (e.g., at 40°C or 50°C, 75%RH for 2 to 5 weeks) is less than 2.5 wt.% based on the total weight of the composition. In one embodiment, the impurity content in the pharmaceutical composition upon storage (e.g., at 40°C or 50°C, 75%RH for 2 to 5 weeks) is less than 500%, preferably less than 350% of the initial impurity content in the pharmaceutical composition (before storage).

[00114] In one embodiment, the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and ethyl acrylate, wherein the (meth)acrylic acid content is present in an amount of at least 43 wt.%, based on the total amounts of the (meth)acrylate copolymer; the molecular weight of the (meth)acrylate copolymer ranges from 24,000 to 33,000 g/mol; and the weight ratio of the compound and the (meth)acrylate copolymer ranges from 10:90 to 45:55, preferably 35:65 or 40:60. In one embodiment, the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and ethyl acrylate, wherein the molar ratio of methacrylic acid content to ethyl acrylate content ranges from 1:0.95 to 1:1.35; the molecular weight of the (meth)acrylate copolymer ranges from 24,000 to 33,000 g/mol; and the weight ratio of the compound and the (meth)acrylate copolymer ranges from 10:90 to 45:55, preferably 35:65 or 40:60.

[00115] The above-mentioned pharmaceutical compositions may exhibit a concentration of the compound of at least about 60 µg/ml, preferably at least 100 µg/ml, more preferably at least 300 µg/ml, in solubility tests in Fasted State Simulated Intestinal Fluid (FaSSIF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 0.5 hours. In one embodiment, when solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring

speed for 4 hours, the pharmaceutical compositions exhibit at least about 50%, preferably at least about 60%, more preferably at least about 70% of the concentration of the compound in the solubility tests for 0.5 hours.

[00116] The above-mentioned pharmaceutical compositions may also exhibit an undetectable concentration of the compound in solubility tests in Fasted State Simulated Gastric Fluid (FaSSGF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 4 hours.

[00117] In one embodiment, the pharmaceutical composition exhibits a concentration of the compound of at least about 60 µg/ml in solubility tests in Fasted State Simulated Intestinal Fluid (FaSSIF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 0.5 hours; and exhibits an undetectable concentration of the compound in solubility tests in Fasted State Simulated Gastric Fluid (FaSSGF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 4 hours. In one embodiment, the pharmaceutical composition exhibits a concentration of the compound of at least about 60 µg/ml in solubility tests in Fasted State Simulated Intestinal Fluid (FaSSIF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 0.5 hours, at least about 50% of the concentration of the compound in the solubility tests for 0.5 hours in the tests for 4 hours; and exhibits an undetectable concentration of the compound in solubility tests in Fasted State Simulated Gastric Fluid (FaSSGF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 4 hours.

[00118] Preparation of the pharmaceutical composition may be achieved from liquid-
(dissolved/dispersed) solid separation of the solution or homogenous dispersion of the
compound and the (meth)acrylate copolymer. In one embodiment, the pharmaceutical
composition is obtained by spray drying a liquid suspension, dispersion or solution or a wet
5 solid comprising the compound and the (meth)acrylate copolymer. The liquid suspension,
dispersion or solution may comprise a suitable solvent/dispersant or solvent/dispersant
mixture to dissolve or homogeneously disperse the compound and the (meth)acrylate
copolymer therein. Examples of the solvent/dispersant include, but are not limited to, C₁-
aliphatic alcohols such as methanol, ethanol, n-propanol, iso-propanol; lower alkyl ketones
10 such as acetone, methyl-ethyl ketone; sulfoxides such as dimethyl sulfoxide; ... etc., or any
mixtures of the aforementioned solvent/dispersant. Any suitable drying techniques may be
applied to obtain the pharmaceutical composition. Examples of the drying techniques include,
but are not limited to, spray-drying, fluidized-bed drying, oven drying and freeze-drying.

[00119] Additional processing, such as protective coating, milling, granulating, adding
15 excipient(s), etc., on the pharmaceutical composition may be conducted to form various solid
forms for a direct use or further applications.

[00120] Therapeutic applications of the pharmaceutical compositions

[00121] The pharmaceutical compositions may be used in a method of treating an androgen
receptor associated medical condition in a subject in need thereof, the method comprising
20 administering the pharmaceutical composition to the subject. The pharmaceutical
compositions may also be used in the manufacture of a medicament for treating an androgen
receptor associated medical condition in a subject.

[00122] Examples of the androgen receptor associated medical conditions include, but are not limited to, inflammation, acne, alopecia, hirsutism, wounds, Spinal and Bulbar Muscular Atrophy (SBMA, Kennedy's Disease), cancers or carcinomas (e.g., prostate cancer, bladder cancer, liver cancer, breast cancer), an unwanted immune response, or an immune disorder.

5 [00123] The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

EXAMPLE

10 [00124] **Example 1 - Preparation of pharmaceutical compositions**

[00125] The compounds described herein (i.e., Formula (Ia) or Formula (Ib)) and polymers were blended based on the contents noted in Table 1 below.

Table 1

Group/Sample No.		Compound	Polymer	Weight Ratio (cmpd.:polymer)
I	I-a1	a	methacrylic acid-methyl methacrylate copolymer (1:1)	10:90
	I-a2			35:65
	I-a3			40:60
	I-a4			45:55
	I-a5			50:50
	I-a6			55:45
	I-a7			65:35
	I-a8			90:10
I'	I'-f1	f	methacrylic acid-methyl methacrylate copolymer (1:1)	10:90
	I'-f2			35:65
	I'-f3			40:60
	I'-f4			45:55
	I'-f5			50:50
	I'-f6			55:45
	I'-f7			65:35
	I'-f8			90:10
II	II-e1	e	methacrylic acid-ethyl acrylate copolymer (1:1)	10:90
	II-e2			35:65

Group/Sample No.		Compound	Polymer	Weight Ratio (cmpd.:polymer)
	II-e3			40:60
	II-e4			45:55
	II-e5			50:50
	II-e6			55:45
	II-e7			65:35
	II-e8			90:10
II'	II'-f1	f	methacrylic acid-ethyl acrylate copolymer (1:1)	10:90
	II'-f2			35:65
	II'-f3			40:60
	II'-f4			45:55
	II'-f5			50:50
	II'-f6			55:45
	II'-f7			65:35
	II'-f8			90:10
III	III-d1	d	methacrylic acid-ethyl acrylate copolymer (1:2)	10:90
	III-d2			35:65
	III-d3			40:60
	III-d4			45:55
	III-d5			50:50
	III-d6			55:45
	III-d7			65:35
	III-d8			90:10
III'	III'-f1	f	methacrylic acid-ethyl acrylate copolymer (1:2)	10:90
	III'-f2			35:65
	III'-f3			40:60
	III'-f4			45:55
	III'-f5			50:50
	III'-f6			55:45
	III'-f7			65:35
	III'-f8			90:10
IV	IV-c1	c	butyl methacrylate-dimethylaminoethyl methacrylate-methyl methacrylate copolymer (1:1:1)	10:90
	IV-c2			35:65
	IV-c3			40:60
	IV-c4			45:55
	IV-c5			50:50
	IV-c6			55:45
	IV-c7			65:35
	IV-c8			90:10
IV'	IV'-f1	f	butyl methacrylate-dimethylaminoethyl methacrylate-methyl methacrylate copolymer (1:1:1)	10:90
	IV'-f2			35:65
	IV'-f3			40:60
	IV'-f4			45:55
	IV'-f5			50:50

Group/Sample No.		Compound	Polymer	Weight Ratio (cmpd.:polymer)
	IV'-f6			55:45
	IV'-f7			65:35
	IV'-f8			90:10
V	V-b1	b	methyl acrylate-methyl methacrylate-methacrylic acid copolymer (7:3:1)	10:90
	V-b2			35:65
	V-b3			40:60
	V-b4			45:55
	V-b5			50:50
	V-b6			55:45
	V-b7			65:35
	V-b8			90:10
V'	V'-f1	f	methyl acrylate-methyl methacrylate-methacrylic acid copolymer (7:3:1)	10:90
	V'-f2			35:65
	V'-f3			40:60
	V'-f4			45:55
	V'-f5			50:50
	V'-f6			55:45
	V'-f7			65:35
	V'-f8			90:10
VI	VI-f1	f	HPMCP HP55 (hypromellose phthalate)	10:90
	VI-f2			35:65
	VI-f3			40:60
	VI-f4			45:55
	VI-f5			50:50
	VI-f6			55:45
	VI-f7			65:35
	VI-f8			90:10
VII	VII-f1	f	HPMCAS MP (hypromellose acetate succinate)	10:90
	VII-f2			35:65
	VII-f3			40:60
	VII-f4			45:55
	VII-f5			50:50
	VII-f6			55:45
	VII-f7			65:35
	VII-f8			90:10

[00126] After blending, a proper solvent (e.g., acetone and ethanol) was added to the blend and stirred for dissolving or dispersing it. The concentration of the blend in the solution/dispersion ranges from 3% (w/v) to 5% (w/v), and in one particular case, 4% (w/v).

[00127] The solution/dispersion was spray dried under proper conditions (e.g., gas flow rate, pump rate and temperature) and the dried powder was collected for subsequent experiments.

[00128] **Example 2**

5 [00129] In order to evaluate the dissolution and release profile in both gastric and intestinal environments for pharmaceutical compositions comprising different polymers, Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF) were prepared for use as media. The media are commercially available.

[00130] The dried powders described in Example 1 were tested by the following procedure:
10 10 mg of powders were weighed into the 10 mL amber screw thread vial; 5 mL of FaSSGF or FaSSIF was introduced; the stirring rod was set at a speed of 300 rpm and the tested sample was collected at 30 and 240 minutes (0.5 hrs to 4 hrs); the supernatant of the tested sample was diluted with a solvent mixture ACN:MeOH (1:1, v/v) at a sample:solvent mixture ratio of 1:9 (v/v); the diluted sample was centrifuged at 12,000 rpm for 10 minutes; finally, the
15 supernatant was analyzed to obtain the concentration of the compound.

[00131] Results of certain samples are shown in Table 2 below; the values listed in this table were average of the tested results in each group:

Table 2

Group No.	FaSSGF (conc. of compound: µg/ml)		FaSSIF (conc. of compound: µg/ml)	
	0.5 hrs	4 hrs	0.5 hrs	4 hrs
Compound f	n.d.	n.d.	n.d.	n.d.
I'	n.d.	n.d.	72.0	66.6
II'	n.d.	n.d.	365.5	277.9
III'	n.d.	n.d.	20.5	3.5
IV'	570.0	265.3	269.4	105.2
V'	n.d.	n.d.	18.8	18.3
VI	6.9	9.3	91.6	51.9

Group No.	FaSSGF (conc. of compound: µg/ml)		FaSSIF (conc. of compound: µg/ml)	
	0.5 hrs	4 hrs	0.5 hrs	4 hrs
VII	6.9	3.0	73.3	55.8

*The weight ratio between Compound f and the polymer of the samples in each group ranges from 10:90 to 45:55.

**The symbol “n.d.” means “not detected.”

[00132] Results showed that pharmaceutical compositions comprising the compounds and (meth)acrylate copolymers as required herein may exhibit advantageous effects of fast and prolonged release of the compound in the intestinal environment (thereby benefiting from efficient absorption of the active compound in the intestines) and no substantial release of the compound in the gastric environment (thereby preventing the potential degradation of the active compound in the stomach).

[00133] The results in the same tests may also be examined group by group to evaluate the dissolution and release profile in the intestinal environment for pharmaceutical compositions with different weight ratios between the compound and the polymer in Group II'. Exemplary results are shown in Table 3 below:

Table 3

Weight ratio between Compound and polymer	FaSSGF (conc. of compound: µg/ml)		FaSSIF (conc. of compound: µg/ml)		
	0.5 hrs	4 hrs	0.5 hrs	4 hrs	0.5 hrs/ 4 hrs (ratio)
10:90	n.d.	n.d.	>>>> 60	>> 60	> 1.2 fold
35:65	n.d.	n.d.	>>>> 60	>>>> 60	> 1.2 fold
40:60	n.d.	n.d.	>>>> 60	>>>> 60	> 1.2 fold
45:55	n.d.	n.d.	>>>> 60	>>> 60	> 1.1 fold
50:50	n.d.	n.d.	> 60	>> 60	< 0.75 fold
55:45	n.d.	n.d.	> 60	> 60	< 0.75 fold
65:35	n.d.	n.d.	<< 60	< 60	< 0.75 fold
90:10	n.d.	n.d.	<< 60	<<<< 60	****

* The symbol “n.d.” means “not detected.”

**The symbol “>>” means at least 1.5 times the indicated value. The symbol “>>>” means at least 3 times the indicated value. The symbol “>>>>” means at least 4 times the indicated value.

***The symbol "<<" means no more than 75% of the indicated value. The symbol "<<<<" means no more than 25% of the indicated value.

****This data may not be representative for the 90:10 group; the amount of the polymer is too small to disperse the compound and the compound precipitated quickly, thereby leading to a lower concentration detected at 4hrs.

[00134] These exemplary results show that adjusting the weight ratios of the compound to the polymer may provide different release profiles in the intestinal environment such as a rapid increase of compound concentration (see also, ratios of compound concentrations between different time frames), sustained release of compound (e.g., at least up to 4 hours), etc.), and there may be an upper limit of the proportion of the polymer.

[00135] **Example 3**

[00136] Long-term stability tests were conducted on the samples by, e.g., examining whether the amount of impurities increases or "precipitation" of the compounds from the pharmaceutical compositions occurs.

[00137] The inventors surprisingly found that the initial ratio of the enol form to the keto form of the compound (e.g., the ratio of the compound of Formula (Ia) to the compound Formula (Ib)) for use in preparing the pharmaceutical composition may affect the stability of the composition upon storage. Compounds in different enol:keto form ratios were chosen for exemplary experiments to demonstrate this fact. In particular, samples with the compounds in different enol:keto ratios were prepared based on the process described in Example 1. The samples (e.g., Group II' f2) were divided into control groups and experimental groups. Samples in the control groups were refrigerated at 2-8°C, and samples in the experimental groups were stored at 50°C in a 75% RH stability chamber for 2 weeks. Upon completion of the tests, the enol form content and impurities were determined via HPLC. Results are shown in Table 4 below:

Table 4

Initial Enol Form Content	End Enol Form Content	Final Impurity Content (Relative Increase)
26.39%	36.74%	4.01% (about 57 fold)
31.80%	37.53%	2.44% (about 13.5 fold)
38.52%	37.48%	2.01% (about 3.9 fold)

[00138] The results may indicate that the enol form to keto form ratio of the compound may be optimized to prevent the increase of impurity amounts upon storage. In particular, it is observed that when the samples were stored, e.g., at 50°C in a 75% RH stability chamber for 2 weeks, the final (end) enol form to keto form ratio (w/w) of the compound would reach an equilibrium ratio, e.g., ranging from 33:67 to 40:60, preferably from 36:64 to 39:61, regardless of the initial enol form content. For example, if the initial enol form deviates from (e.g., is lower than) the equilibrium ratio, there may be a risk of increasing the impurity amount.

[00139] Tests for observing whether the precipitation of the compound from the pharmaceutical composition upon storage were also conducted. Compounds with the polymers in different weight ratios were used in the tests. In particular, samples with the compound/polymer in different weight ratios were prepared based on the process described in Example 1. The samples in Group II' were stored at 40°C, 75% RH or 50°C, in a 75% RH stability chamber for 5 weeks. Upon completion of the tests, the samples were analyzed by X-ray powder diffraction (XRPD): Bruker, D2 PHASER X-ray Powder Diffractometer, scanning range from 5° to 45° at an interval of 0.05°, hold time (per interval) at 0.5s with Cu (K-α). For the tests conducted at 40°C, 75% RH, the XRPD patterns of the samples with compound/polymer ratios ranging from 10:90 to 55:45 show a broad peak, as shown in Figures 1A to 1F, which represents that no precipitation of the compound from the pharmaceutical composition occurs, and the compound is substantially in an amorphous form in the pharmaceutical composition. On the other hand, sharp peaks can be observed in the

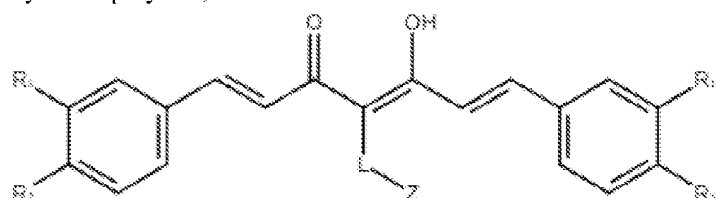
XRPD patterns of the samples with compound/polymer ratios ranging from 65:35 to 90:10, as shown in Figures 1G and 1H, which may reflect the precipitation of the compound from the pharmaceutical composition. Similar tendencies in the results were also observed in the tests conducted at 50°C, 75% RH, as shown in Figures 2A to 2F.

- 5 [00140] It is understood that the foregoing examples are merely illustrative of the present invention. Certain modifications of the articles and/or methods employed may be made and still achieve the objectives of the invention. Such modifications are contemplated as being within the scope of the claimed invention.

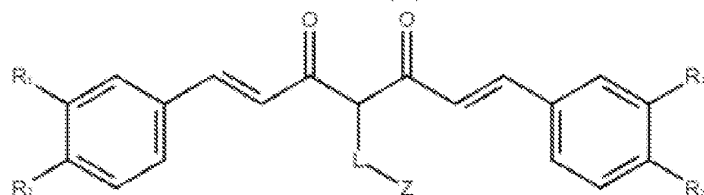
Claims

What is claimed is:

1. A pharmaceutical composition comprising: a compound of Formula (Ia) or of Formula (Ib),
and a (meth)acrylate copolymer,



Formula (Ia),



Formula (Ib),

wherein:

R₁, R₂, R₁' and R₂' are independently selected from the group consisting of -H, -OH, and -OCH₃;

L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

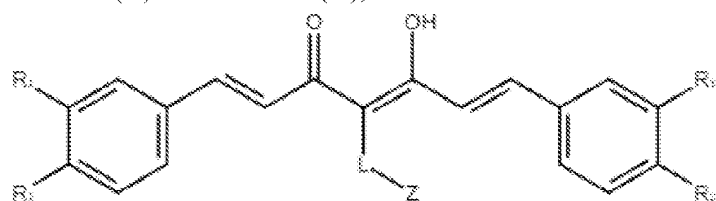
Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O)R_a, -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and

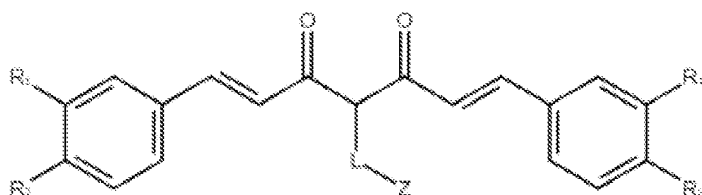
wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of diketone; and

the (meth)acrylate copolymer is formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates.

2. A pharmaceutical composition comprising:
a compound of Formula (Ia) or of Formula (Ib);



Formula (Ia),



Formula (Ib),

wherein:

R_1 , R_2 , R_1' and R_2' are independently selected from the group consisting of -H, -OH, and -OCH₃;

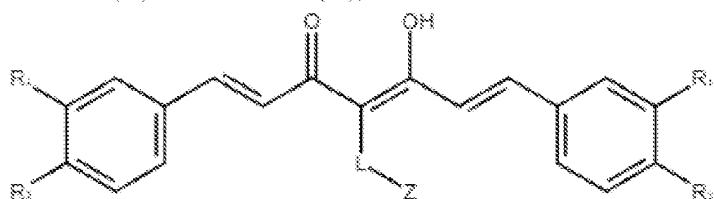
L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O) R_a , -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

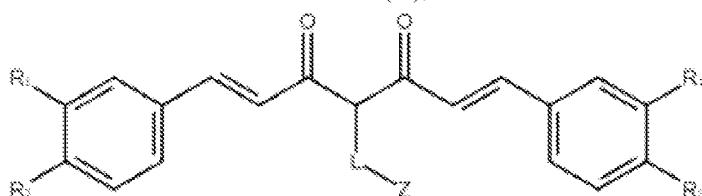
X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of diketone; and

a (meth)acrylate copolymer used for dispersing the compound of Formula (Ia) or of Formula (Ib), wherein the (meth)acrylate copolymer is formed from comonomers comprising (meth)acrylic acid and C₁₋₃alkyl (meth)acrylates.

3. A pharmaceutical composition comprising:
a compound of Formula (Ia) or of Formula (Ib);



Formula (Ia),



Formula (Ib),

wherein:

R_1 , R_2 , R_1' and R_2' are independently selected from the group consisting of -H, -OH, and -OCH₃;

L is a carbonyl, an alkylene or an alkenylene, or L is alkynyl when Z is not present;

Z is selected from the group consisting of -H, -OH, a substituted styrenyl, an aromatic ring, a cycloalkyl, -C(=O) R_a , -C(=O)NR_aR_b and -CX₃, wherein R_a and R_b are independently selected from the group consisting of -H, -CH₃ and -C₂H₅, or Z is not present;

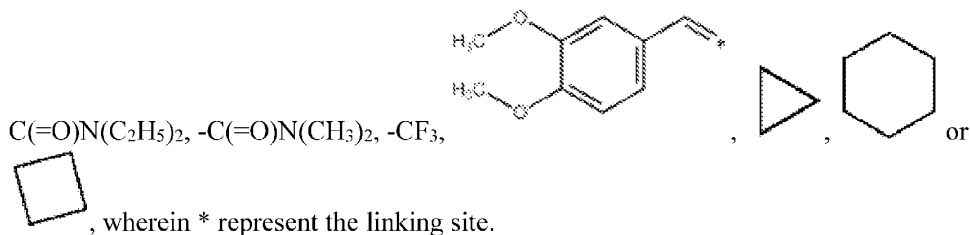
X is a halogen atom selected from the group consisting of -F, -Cl and -Br; and wherein the formula Ia and Ib are the equilibrate tautomers as a common phenomenon of

diketone; and

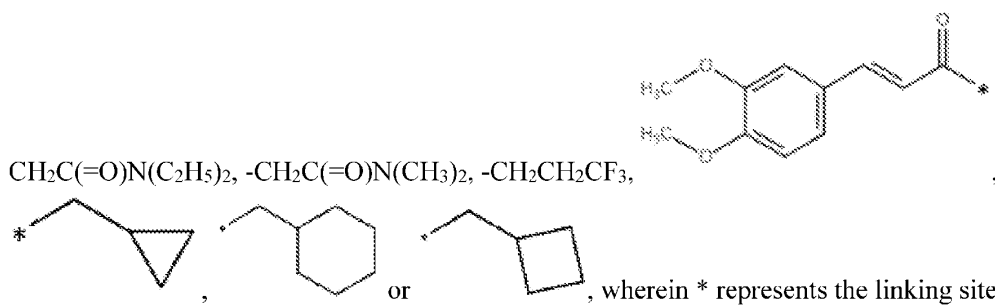
a (meth)acrylate copolymer formed from comonomers comprising (meth)acrylic acid and C_{1-3} alkyl (meth)acrylates;

wherein the compound of Formula (Ia) or of Formula (Ib) and the (meth)acrylate copolymer are in the form of a solid dispersion.

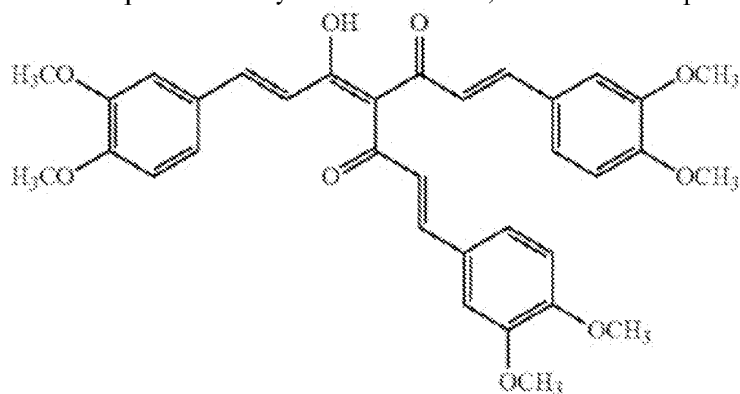
- 5 4. The pharmaceutical composition of any one of the preceding claims, wherein one or more of R_1 , R_2 , R_1' and R_2' is $-OCH_3$.
5. The pharmaceutical composition of any one of the preceding claims, wherein $-L-$ is $-CH_2-$, $-C(=O)-$ or $-CH_2-CH_2-$.
- 10 6. The pharmaceutical composition of any one of the preceding claims, wherein Z is -



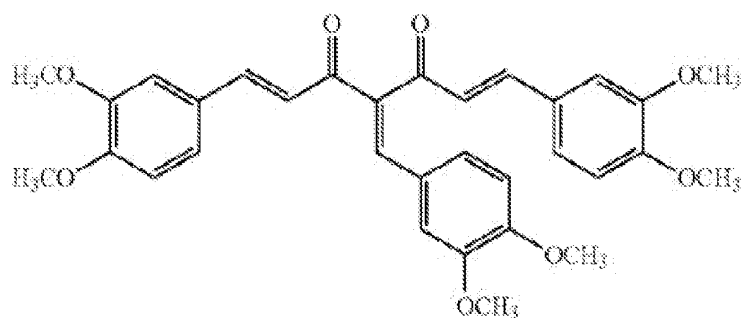
7. The pharmaceutical composition of any one of claims 1-3, wherein $-L-Z$ represents -



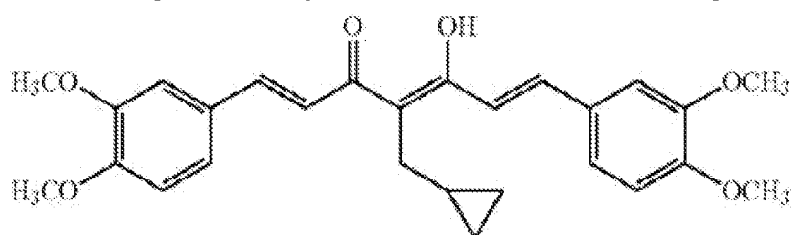
- 15 8. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:



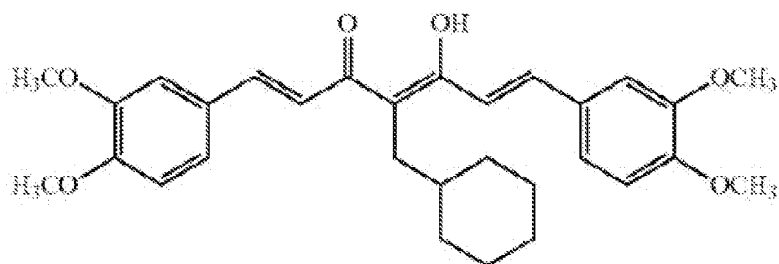
9. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:



10. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:

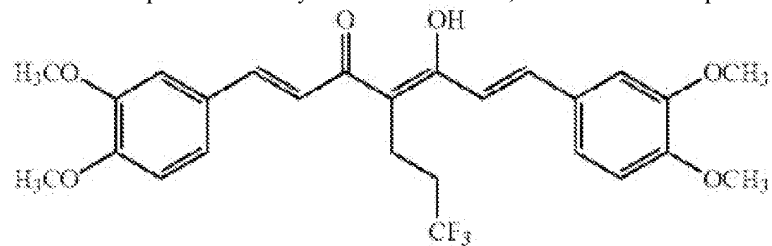


11. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:

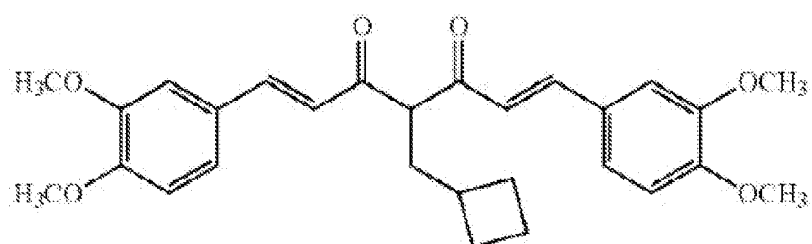


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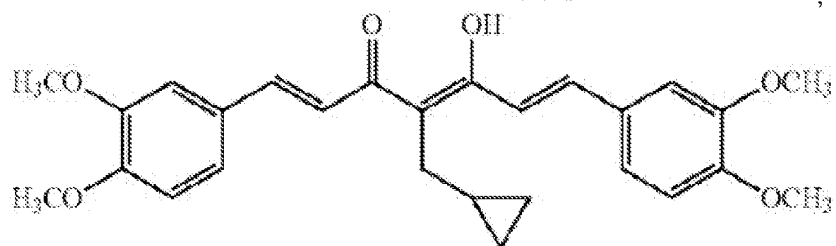
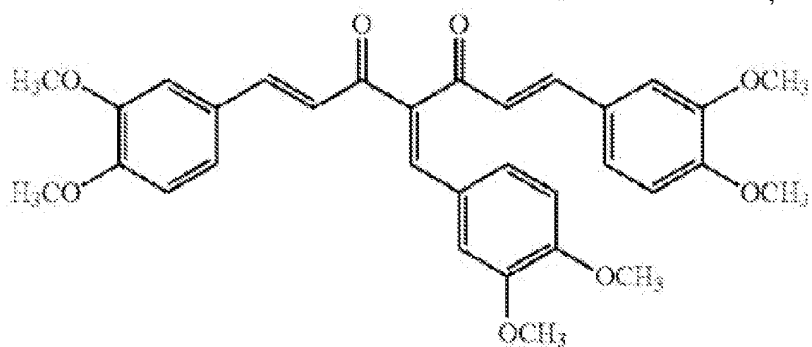
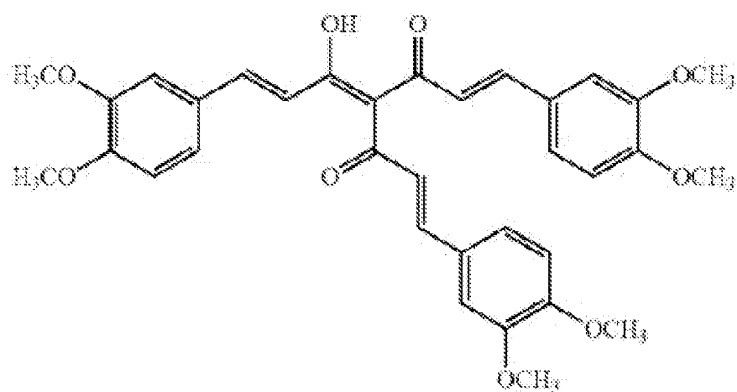
12. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:

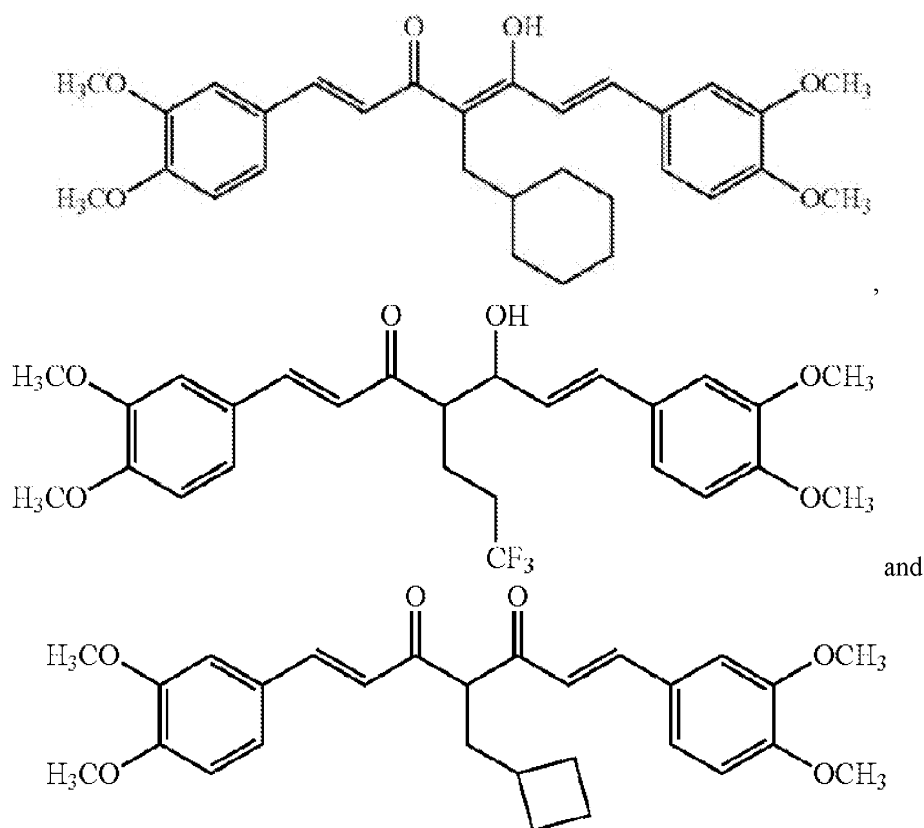


13. The pharmaceutical composition of any one of claims 1-3, wherein the compound is:



14. The pharmaceutical composition of any one of claims 1-3, wherein the compound is selected from the group consisting of:





15. The pharmaceutical composition of any one of the preceding claims, wherein the (meth)acrylic acid content is present in an amount of at least 43 wt.%, based on the total amounts of the (meth)acrylate copolymer.
16. The pharmaceutical composition of any one of the preceding claims, wherein the comonomers do not have an amino or ammonium group(s).
17. The pharmaceutical composition of any one of the preceding claims, wherein the (meth)acrylate copolymer is formed from comonomers consisting of methacrylic acid and C₁₋₃ alkyl acrylates.
18. The pharmaceutical composition of claim 17, wherein the molar ratio of methacrylic acid content to C₁₋₃ alkyl acrylates content ranges from 1:0.95 to 1:1.35.
19. The pharmaceutical composition of any one of the preceding claims, wherein the molecular weight of the (meth)acrylate copolymer ranges from 24,000 to 33,000 g/mol.
20. The pharmaceutical composition of any one of the preceding claims, wherein the weight ratio of the compound to the (meth)acrylate copolymer ranges from 5:95 to 60:40.
21. The pharmaceutical composition of any one of the preceding claims, wherein the weight ratio of the compound to the (meth)acrylate copolymer is about 10:90.
22. The pharmaceutical composition of any one of claims 1-20, wherein the weight ratio of the compound to the (meth)acrylate copolymer is about 35:65.
23. The pharmaceutical composition of any one of claims 1-20, wherein the weight ratio of the compound to the (meth)acrylate copolymer is about 40:60.

24. The pharmaceutical composition of any one of claims 1-20, wherein the weight ratio of the compound to the (meth)acrylate copolymer is about 45:55.
25. The pharmaceutical composition of any one of the preceding claims, which is obtained by drying a liquid suspension, dispersion or solution or a wet solid comprising the compound and the (meth)acrylate copolymer.
26. The pharmaceutical composition of claim 25, wherein the drying is spray-drying, fluidized-bed drying, oven drying or freeze-drying.
27. The pharmaceutical composition of any one of the preceding claims, which exhibits undetectable concentration of the compound in solubility tests in Fasted State Simulated Gastric Fluid (FaSSGF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm stirring speed for 4 hours.
28. The pharmaceutical composition of any one of the preceding claims, which exhibits a concentration of the compound of at least about 60 µg/ml in solubility tests in Fasted State Simulated Intestinal Fluid (FaSSIF), wherein the solubility tests are conducted at a concentration of 10 mg solid dispersion/5mL FaSSGF at 300 rpm for 0.5 hours.
29. The pharmaceutical composition of any one of the preceding claims, wherein the compound is substantially in an amorphous form in the pharmaceutical composition.
30. Use of the pharmaceutical composition of any one of claims 1-29 in the manufacture of a medicament for treating an androgen receptor associated medical condition.
31. A method of treating an androgen receptor associated medical condition in a subject in need thereof, comprising administering the pharmaceutical composition of any one of claims 1-29.
32. A pharmaceutical composition of any one of claims 1-29 for use in treating an androgen receptor associated medical condition.
33. The pharmaceutical composition of any one of claims 1-29, wherein the enol form to keto form ratio (w/w) of the compound is from 33:67 to 40:60.