a black box warning on the drug label to inform patients about the potential for d-amphetamine abuse and dependence.

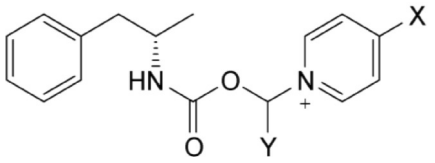
[0010] It has been shown in the conventional art that most side effects of amphetamines are caused by a large initial spike in blood concentration of the stimulant which quickly erodes to levels below therapeutic effectiveness (typically within 4-6 hours). As a consequence, the high potency of dextroamphetamine (d-amphetamine) was subsequently modulated by a series of new drugs with increasingly sustained release profiles achieved by delivering d-amphetamine more slowly into the bloodstream with the goal to create safer and less abusable treatment outcomes and regimens. The methods and technologies for generating smaller spikes in drug blood concentrations include, for example, use of mixed salts and isomer compositions (i.e., different salts of d- and less potent l-amphetamine), extended/controlled/sustained release formulations of amphetamine/dextroamphetamine salts (e.g., Adderall XR® commercially available from Shire U.S., Inc. located in Wayne, PA) and prodrugs of lisdexamfetamine salts (Vyvanse® also commercially available from Shire).

[0011] As a result, there still exists a need within the art for a safer dosage form of d-amphetamine and treatment regimen that is therapeutically effective and can provide sustained release and sustained therapeutic effect.

BRIEF SUMMARY

[0012] The presently described technology provides, in part, novel compounds, and compositions of the stimulant d-amphetamine ("d-Amp", "dextroamphetamine"), salts thereof, other derivatives thereof, and combinations thereof.

[0012a] In an aspect, there is provided a compound having the structure of Formula I:

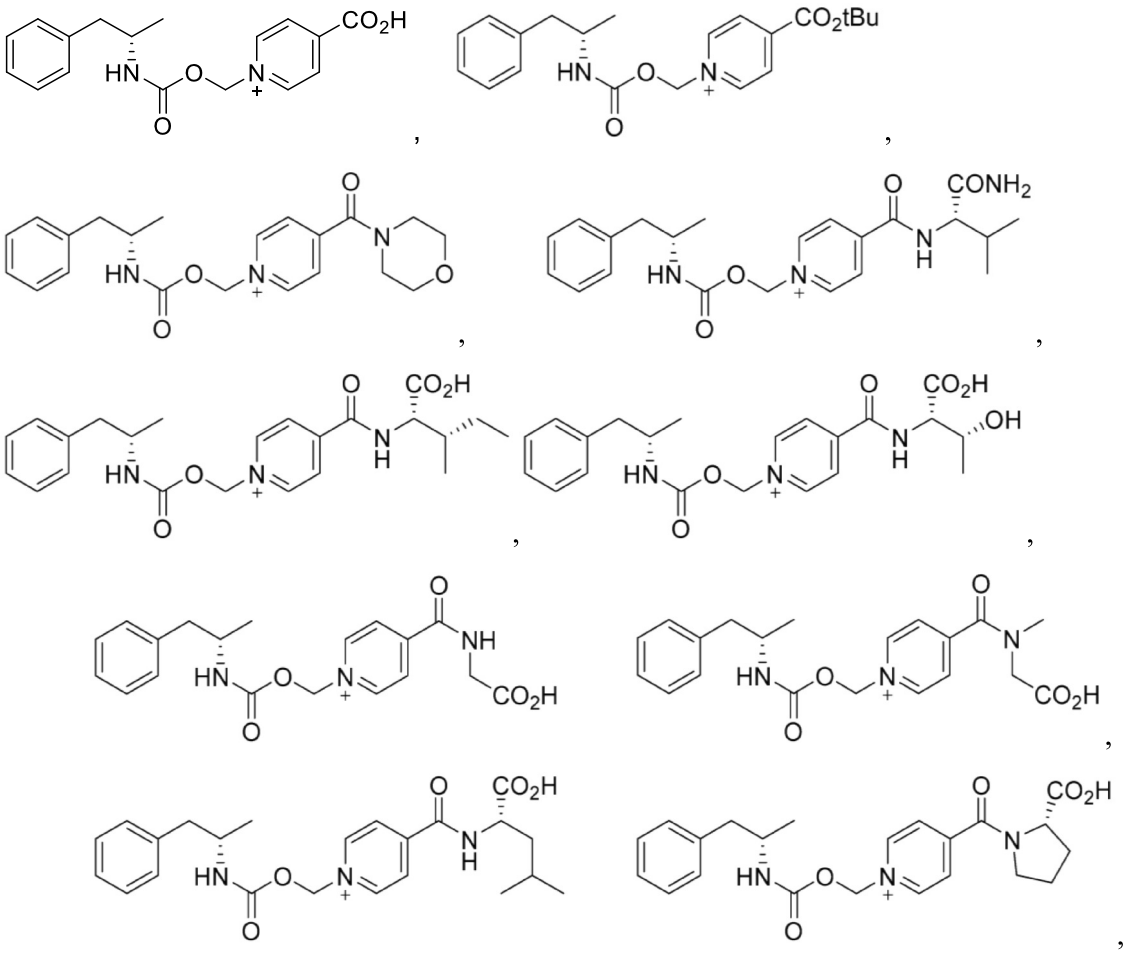


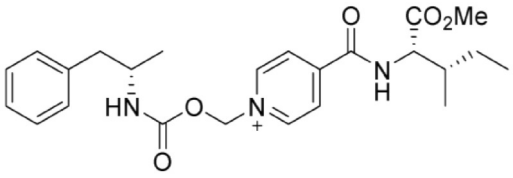
or a pharmaceutically acceptable salt of said compound,

where X is selected from the group consisting of esters, carboxylic acids, amino acids, amino acid residues, amides, and derivatives thereof,

and Y is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, substituted aryl, alkylaryl, cycloalkenyl, cycloalkyl, cycloalkynyl, heteroalkyl, heteroaryl, and heterocycle.

[0012b] In another aspect, there is provided a compound having a structure selected from the group consisting of:

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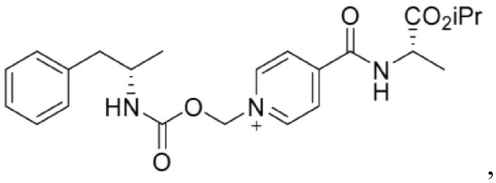
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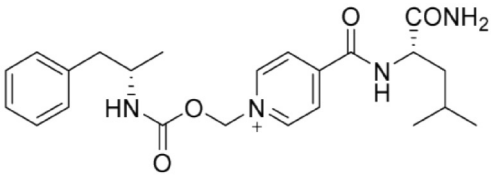
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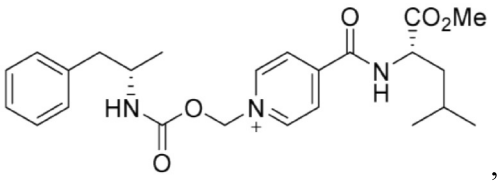
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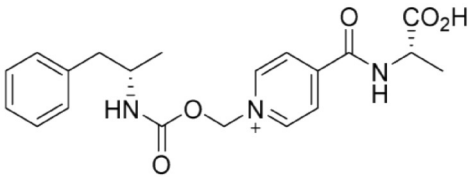
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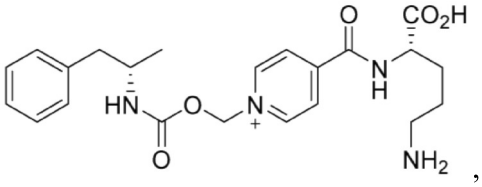
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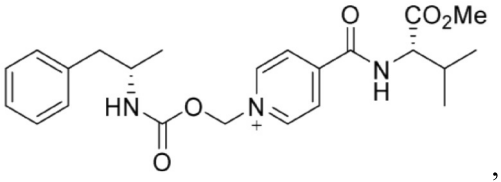
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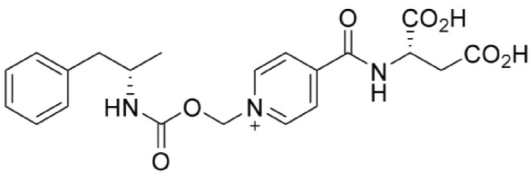
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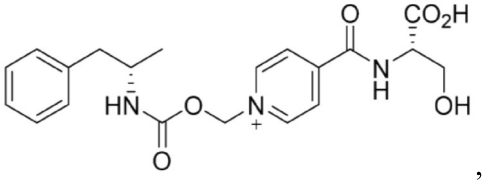
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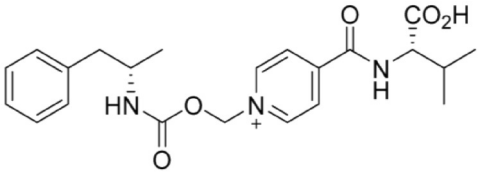
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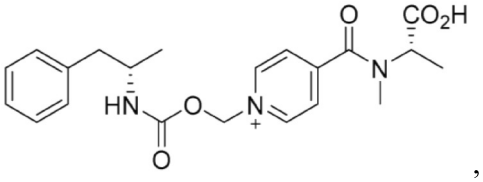
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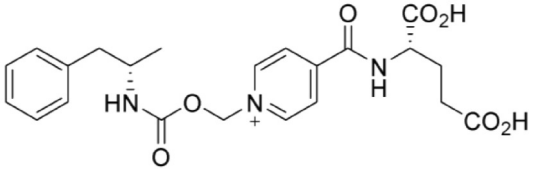
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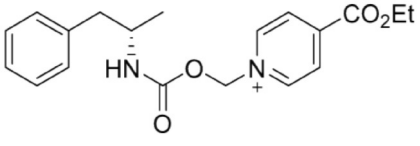
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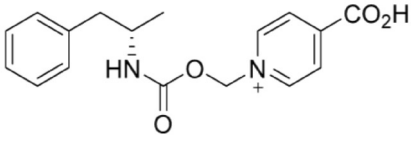
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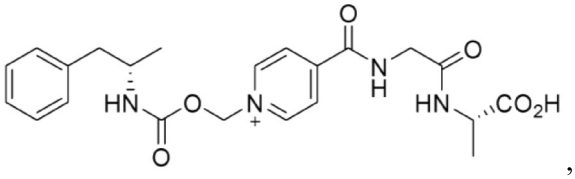
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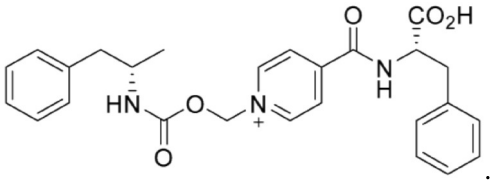
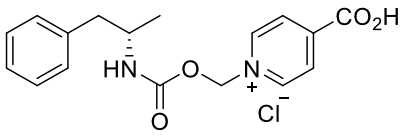


[0012c] In another aspect, there is provide a compound having a structure selected from the group consisting of: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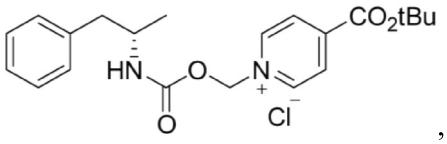
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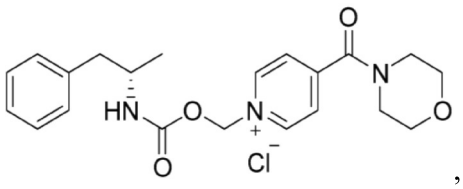
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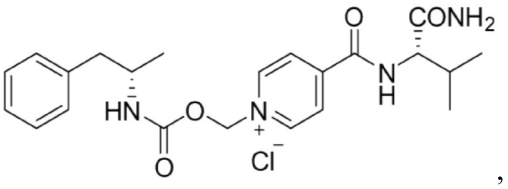
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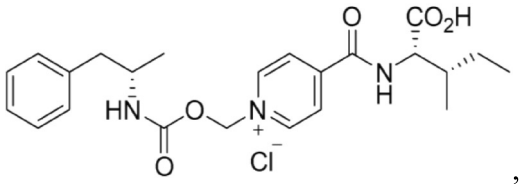
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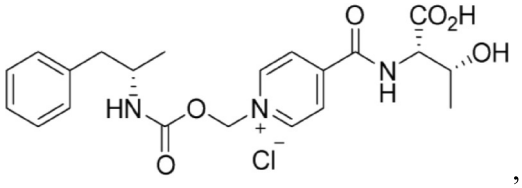
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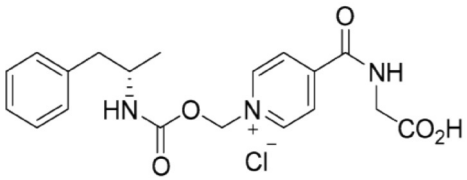
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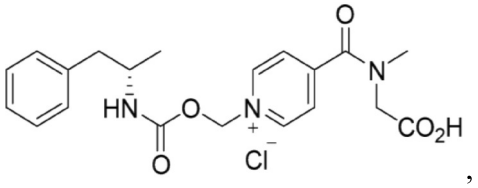
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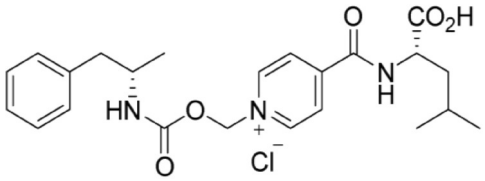
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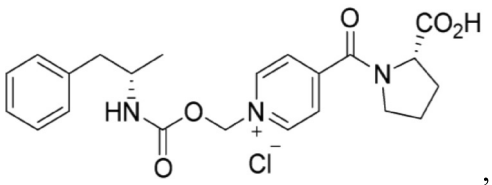
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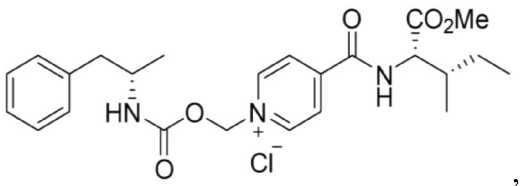
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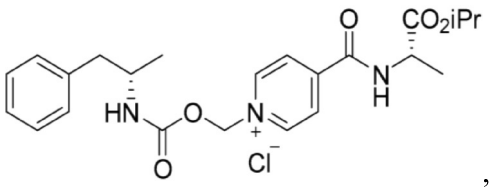
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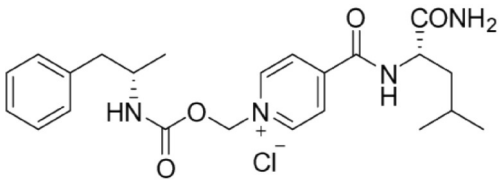
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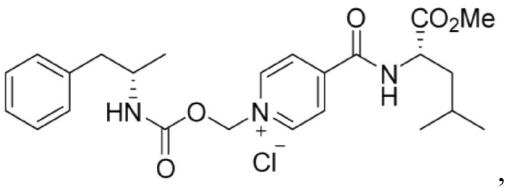
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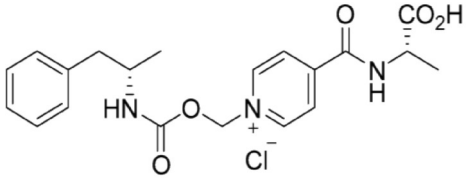
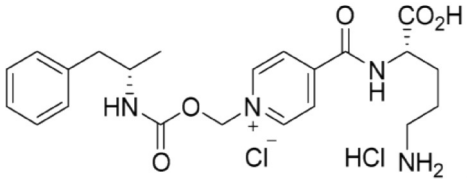
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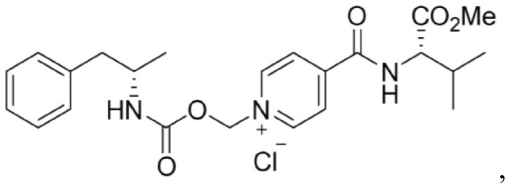
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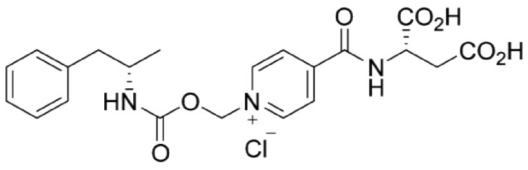
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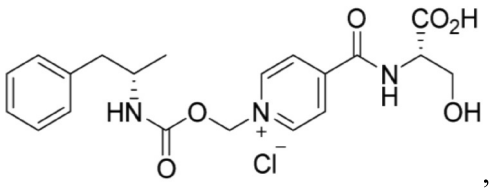
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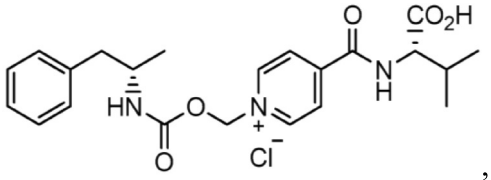
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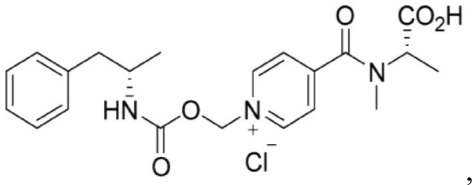
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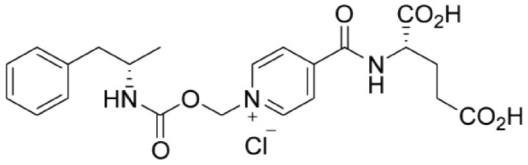
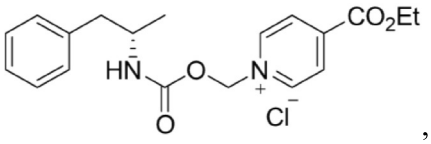
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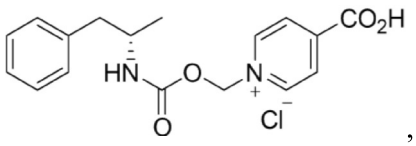
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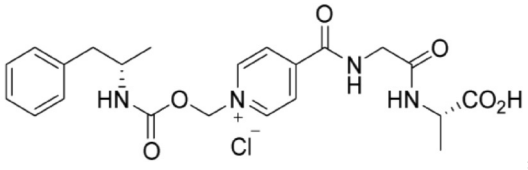
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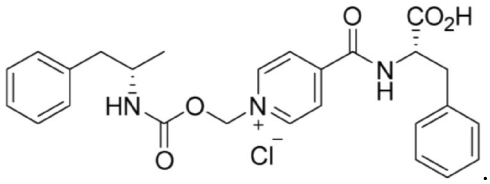
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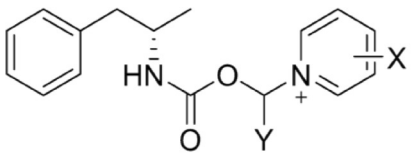
[0012d] In another aspect, there is provided a composition comprising the compound as defined above or pharmaceutically acceptable salt of the compound.

[0012e] In another aspect, there is provided a kit comprising individual doses of a therapeutically effective amount of a composition comprising the compound as defined above, a pharmaceutical salt thereof, or a combination thereof.

[0012f] In another aspect, there is provided a compound having the structure of Formula I:



or a pharmaceutically acceptable salt of the compound,

where X is selected from the group consisting of esters, carboxylic acids, amino acids, amino acid residues, amides, and derivatives thereof,

wherein X is located at the C-2 or C-4 position of the pyridine ring or X is located at two or more of the C-2, C-3, C-4, C-5 or C-6 positions of the pyridine ring,

and Y is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, substituted aryl, alkylaryl, cycloalkenyl, cycloalkyl, cycloalkynyl, heteroalkyl, heteroaryl, and heterocycle.

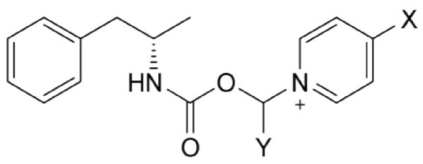
[0012g] In another aspect, there is provided a kit comprising individual doses of a therapeutically effective amount of a composition comprising at least one compound as defined above, a pharmaceutical salt thereof, or a combination thereof.

[0013] In some examples, the present technology provides compounds and/or compositions comprising d-amphetamine and one or more organic compounds. In some examples of the present technology, the organic compound comprises a heterocyclic nitrogen compound. Heterocyclic nitrogen compounds are commonly found in nature and are involved in several biological functions in plants and animals. Examples of heterocyclic nitrogen compounds for use in the practice of the present technology include, but are not limited to, for example, pyridine derivatives, some of which play an important role in the nicotinate and tryptophan metabolism. In these compounds, one carbon of the phenyl ring is commonly replaced by a nitrogen atom.

[0014] In some examples of the present technology, the organic compound comprises an amino acid. Amino acids are organic compounds containing both a carboxyl (—COOH) and amino (—NH_2) group, and a variable side chain group. Amino acids that may be used in the present technology can be natural, standard, non-standard, synthetic, and/or essential amino acids, and can be an L-amino acid or a D-amino acid, or a combination thereof. Examples of amino acids for use in the practice of the present technology include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, norleucine, 3-nitrotyrosine, pyroglutamic acid, nitroarginine, ornithine, homoarginine, citrulline, homocitrulline, homoserine, theanine, γ-aminobutyric acid, 6-aminohexanoic acid, sarcosine, carnitine, 2-aminoadipic acid, pantothenic acid, taurine, hypotaurine, lanthionine, thiocysteine, cystathionine, homocysteine, β-alanine, β -aminoisobutyric acid, β-leucine, β-lysine, β-arginine, β-tyrosine, β-phenylalanine, isoserine, β-glutamic acid, β-tyrosine, β-dopa (3,4-dihydroxy-L-phenylalanine), 2-aminoisobutyric acid, isovaline, di-N-ethylglycine, N-methyl-alanine, L-abrine, 4-hydroxyproline, 5-hydroxylysine, 3-hydroxyleucine, 4-

hydroxyisoleucine, 5-hydroxy-L-tryptophan, 1-aminocyclopropyl-1-carboxylic acid, azetidine-2-carboxylic acid, pipecolic acid, allylglycine, cyclohexylglycine, N-(4-hydroxyphenyl)glycine, N-(chloroacetyl)glycline ester, 2-(trifluoromethyl)-phenylalanine, 4-(hydroxymethyl)-phenylalanine, 4-amino-phenylalanine, 2-chlorophenylglycine, 3-guanidino-propionic acid, 3,4-dehydro-proline, 2,3-diaminobenzoic acid, 2-amino-3-chlorobenzoic acid, 2-amino-5-fluorobenzoic acid, allo-isoleucine, tert-leucine, 3-phenylserine, isoserine, 3-aminopentanoic acid, 2-amino-octanedioic acid, 4-chloro-β-phenylalanine, β-homoproline, β-homoalanine, 3-amino-3-(3-methoxyphenyl)propionic acid, N-isobutyryl-cysteine, 3-amino-tyrosine, 5-methyl-tryptophan, 2,3-diaminopropionic acid, 5-aminovaleric acid, 4-(dimethylamino)cinnamic acid, 2-pyridylalanine (2-Pal), and 3-pyridylalanine (3-Pal).

[0015] In some examples, the compound has the structure of Formula IA



[0016] Formula IA

[0017] where X is A-COO-R;

[0018] where A is either absent or, when present, is selected from the group consisting of alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, aryl, substituted aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylamino, arylaminocarbonyl, arylammonium, arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy,

aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, and polyethylene glycol; and

[0019] where R is selected from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, aryl, substituted aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylamino, arylaminocarbonyl, arylammonium, arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy, aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, polyethylene glycol, amino acid, and amino acid residue.

[0020] In some examples, the compound has the structure of Formula IC

arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy, aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, polyethylene glycol, amino acid, and amino acid residue.

[0025] It should be appreciated that the carbon atom attached to Y is a chiral center if Y is not hydrogen. It should further be appreciated that in certain examples, X is attached to at least one of C-2, C-3, C-4, C-5 and/or C-6.

[0026] 

[0027] In some examples, the present technology comprises conjugates where this chiral carbon has an R configuration. In other examples, the present technology comprises conjugates where this chiral carbon has an S configuration. In further examples, the present technology comprises a mixture of stereoisomers where some conjugates contain a chiral carbon having an R configuration and some conjugates contain a chiral carbon having an S configuration.

[0028] The presently described technology further provides methods of controlled therapeutic delivery of d-amphetamine compositions by oral administration. In at least one example, the presently described technology is focused on a slow/sustained controlled release composition

of d-amphetamine, in compound form, that allows slow/sustained/controlled delivery of the stimulant into the blood system of a human or animal within a therapeutic window upon oral administration. At least some compositions/formulations of the current technology can lessen the rebound effect, cardiovascular stress, addiction/abuse potential and/or other common stimulant side effects associated with d-amphetamine and similar compounds. Such compositions may also increase the duration of therapeutic efficacy, ease of application, patient compliance and/or any combination of these characteristics when administered, in particular, orally.

[0029] The release of d-amphetamine following oral administration of the compounds of the present technology can occur gradually over an extended period of time thereby eliminating unintended excessive rapid elevations (e.g., large blood level concentration spikes) of drug levels in the bloodstream of a human or animal patient. Not wanting to be bound by any particular theory, it is also believed that such spikes in blood levels can lead to a euphoric drug "high" and cardiovascular effects like increased blood pressure and heart rate. Additionally, sustained blood levels are achieved within an effective therapeutic range for a longer duration than other conventional therapies, thereby preventing a rebound effect.

[0030] In some examples, the present technology provides particular d-amphetamine ("d-Amp", "dexamphetamine") compounds, compositions, or pharmaceutically acceptable salts thereof, to provide, for example, at least one single daily dose form of a d-amphetamine compound in a composition with unconjugated d-amphetamine that can provide both immediate and extended release PK profiles when compared to unconjugated d-amphetamine. The release profile in some instances provides the ability of the compound or composition to

an extended period of time. In at least one further example, release of d-amphetamine is diminished when compared to unconjugated d-amphetamine or eliminated when the composition of the present technology is delivered by parenteral routes.

[0034] For example, in one example, the composition of the present technology maintains its effectiveness and abuse resistance following the crushing of the tablet, capsule or other oral dosage form utilized to deliver the therapeutic component (i.e., active ingredient/drug) due to the controlled release components being a designed property of the composition, not the formulation. In contrast, conventional extended release formulations used to control the release of d-amphetamine are subject to release of up to the entire d-amphetamine content immediately following crushing. When the content of the crushed tablet is injected or snorted, the large dose of d-amphetamine produces the "rush" effect sought by addicts.

[0035] Other objects, advantages, and examples of the disclosure are described below and will be obvious from this description and practice of the disclosure.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

[0036] FIG. 1. Oral PK curves comparing lisdexamfetamine (LDX), d-amphetamine-CO_2CH_2-isonicotinoyl-valinamide (AMP-CO_2CH_2-isonicotinoyl-Val-NH_2), and d-amphetamine-CO_2CH_2-isonicotinoyl-ethyl alanine ethyl ester (AMP-CO_2CH_2-isonicotinoyl-Ala-OEt).

[0037] FIG. 2. Oral PK curves comparing lisdexamfetamine (LDX), d-amphetamine-CO_2CH_2-isonicotinoyl-isoleucine (AMP-CO_2CH_2-isonicotinoyl-Ile), and d-amphetamine-CO_2CH_2-isonicotinoyl-glutamate (AMP-CO_2CH_2-isonicotinoyl-Glu).