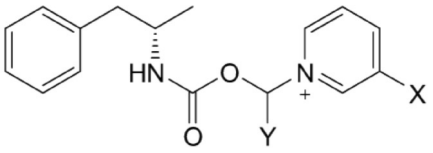
BRIEF SUMMARY

[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:



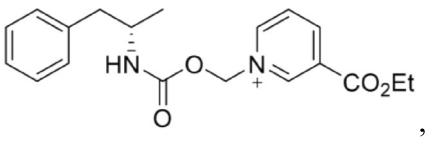
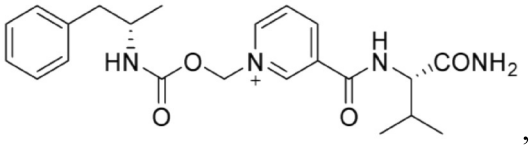
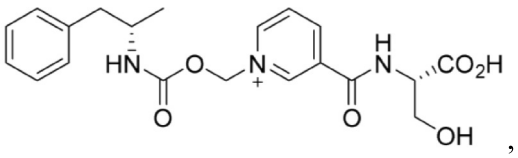
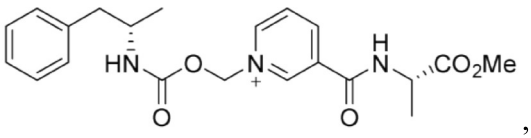
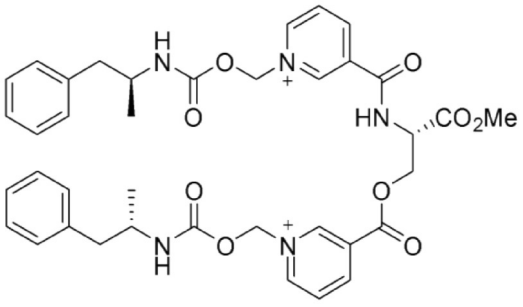
or a pharmaceutically acceptable salt thereof,

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

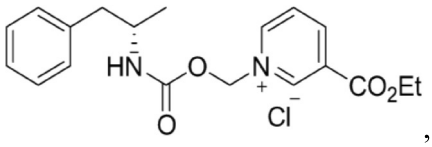
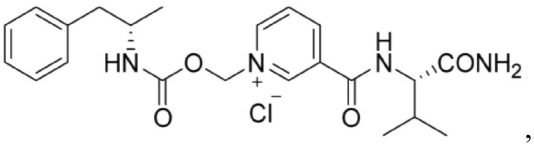
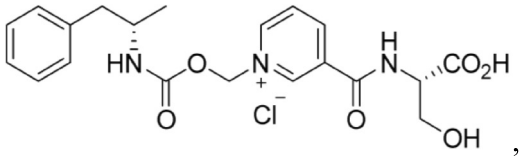
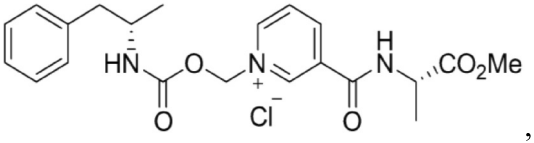
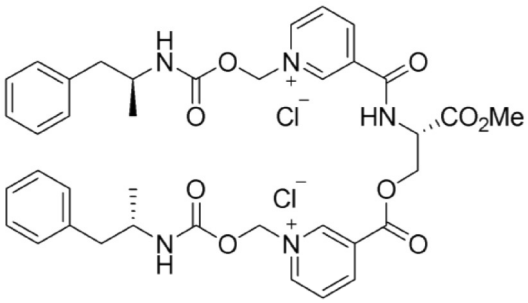
wherein when X is an amide, at least one amide substituent is hydrogen, or at least one amide substituent comprises at least two carbons,

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


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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.

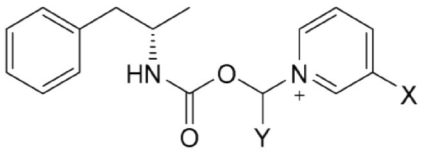
[0012f] In another aspect, there is provided a kit comprising individual doses of a therapeutically effective amount of a composition comprising at least one compound as defined above, a pharmaceutical salt thereof, or a combination thereof.

[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, unusual, 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, 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 IB:



Formula IB

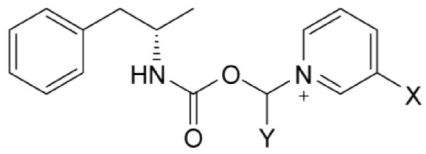
[0016] where X is A-COO-R;

[0017] 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

[0018] 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.

[0019] In some examples, the compound has the structure of Formula ID



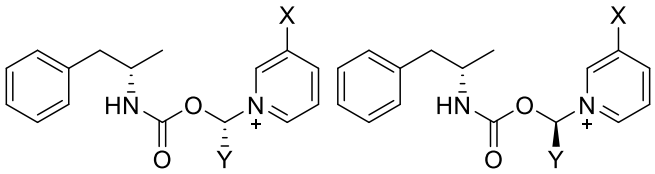
[0020] Formula ID

[0021] where X is A-CO-NR^1R^2;

[0022] 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

[0023] where R^1 and R^2 are independently 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.

[0024] It should be appreciated that the carbon atom attached to Y is a chiral center if Y is not hydrogen.

[0025] 

[0026] 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.

[0027] 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 safe

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.

[0028] 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.

[0029] 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 be administered using dosing regimens that are not easily utilized with the unconjugated d-amphetamine.

[0030] At least some compositions comprising the d-amphetamine compounds of the present technology are resistant to abuse by parenteral routes of administration, such as intravenous "shooting," intranasal "snorting," or inhalation "smoking," that are often employed during illicit use. The present technology thus provides a stimulant based treatment modality and dosage form for certain disorders requiring the stimulation of the CNS such as ADHD, ADD, obesity, narcolepsy, appetite suppressant, depression, anxiety, sleep disorders, excessive daytime sleepiness, insomnia, binge eating, and wakefulness with reduced or prevented abuse potential. Although not wanting to be bound by any particular theory, it is believed that compositions of the present technology result in

substantially decreased abuse potential or abuse liability as compared to existing stimulant treatment modalities and dosage forms.“

[0031] At least some compositions comprising the d-amphetamine compound of the present technology can also be used for treating stimulant (cocaine, methamphetamine) abuse and addiction, substance use disorder, improving battlefield alertness, and/or for combating fatigue.

[0032] The compositions of the present technology preferably have no or a substantially decreased pharmacological activity when administered through injection or intranasal routes of administration. However, they remain orally bioavailable with respect to d-amphetamine. The bioavailability can be a result of the hydrolysis of the covalent linkage between d-amphetamine and the remaining portion of the conjugate following oral administration. Hydrolysis is time-dependent, thereby allowing d-amphetamine and other metabolites such as *p*-hydroxyamphetamine and *p*-hydroxyephedrine to become available in its active form over 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.

[0033] 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.

[0034] 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

[0035] FIG. 1. Oral PK curves comparing d-amphetamine sulfate and d-amphetamine-CO_2CH_2-nicotinate ethyl ester (AMP-CO_2CH_2-nicotinate(Et)).