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

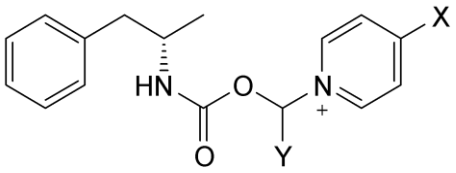
[0010] It has been shown in the conventional art that most side effects of amphetamines are caused by a large initial spike in blood concentration of the stimulant which quickly erodes to levels below therapeutic effectiveness (typically within 4-6 hours). As a consequence, the high potency of dextroamphetamine (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':

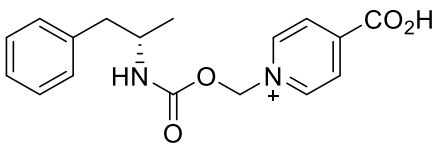


or a pharmaceutically acceptable salt of said compound,

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

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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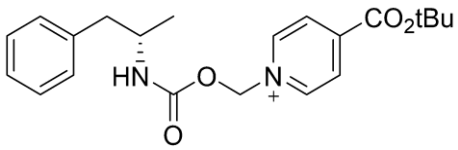
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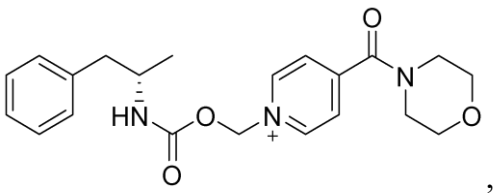
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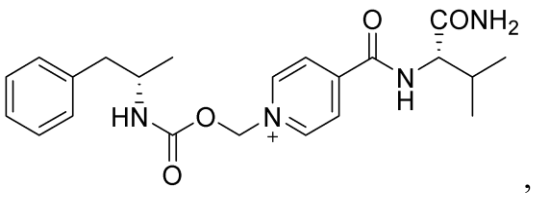
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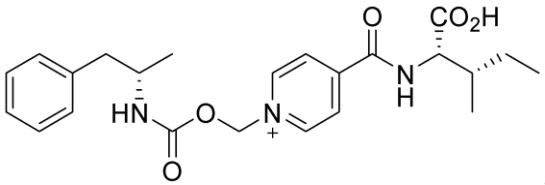
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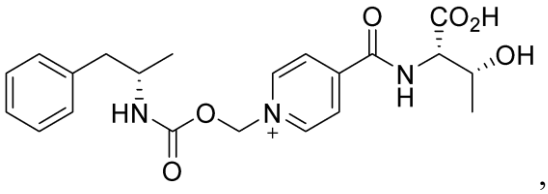
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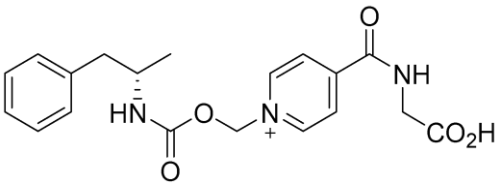
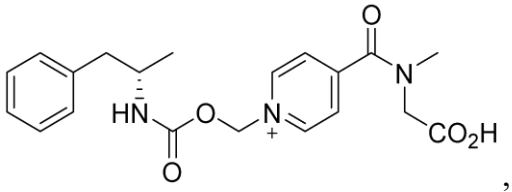
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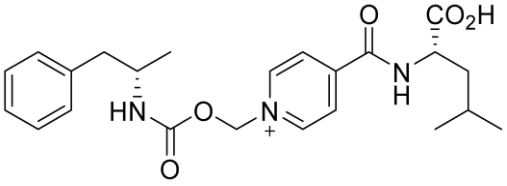
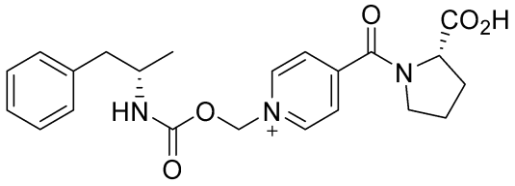
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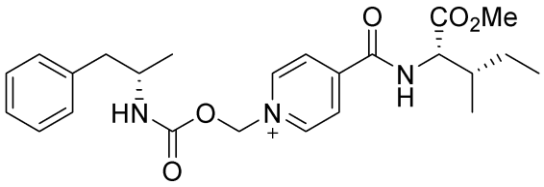
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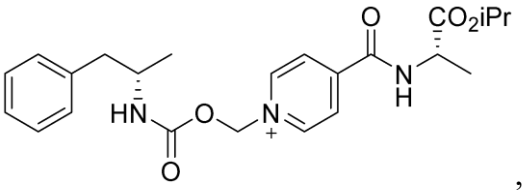
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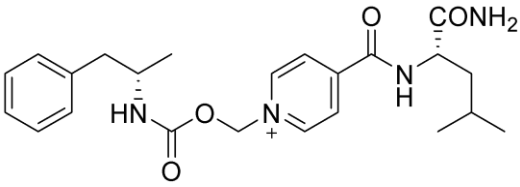
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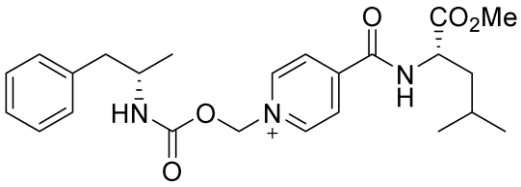
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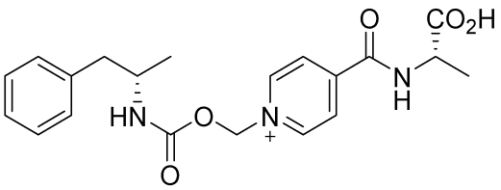
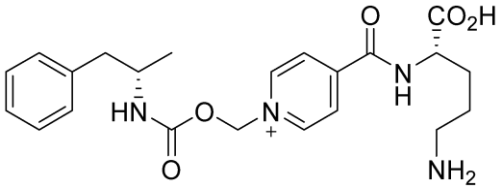
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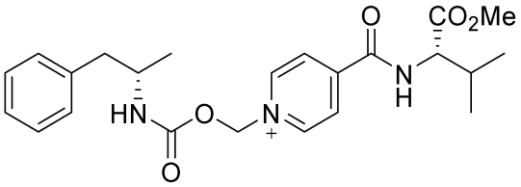
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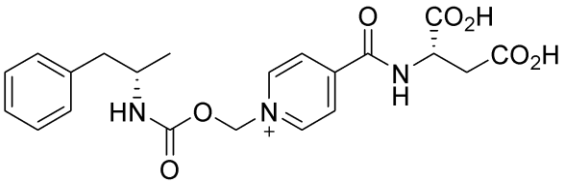
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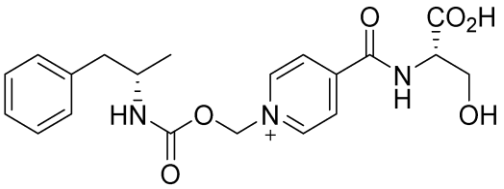
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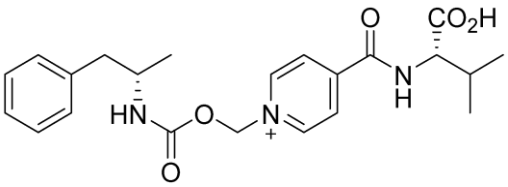
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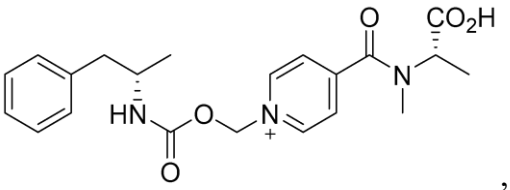
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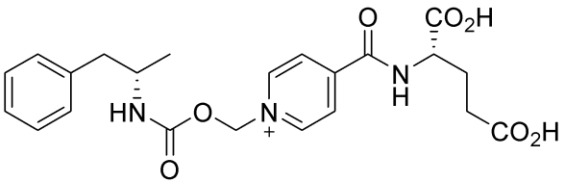
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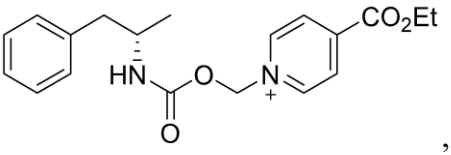
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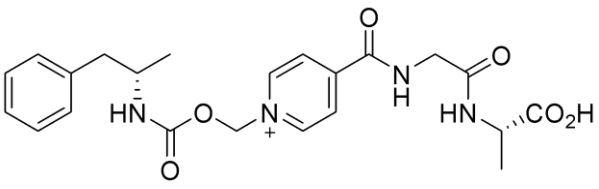
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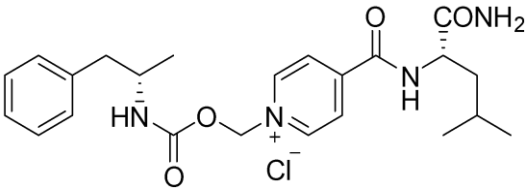
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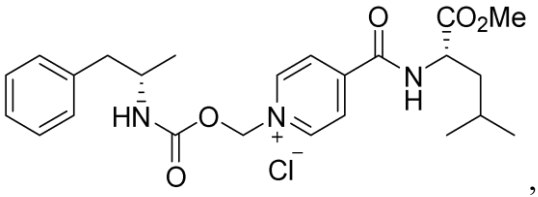
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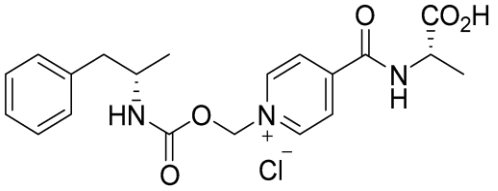
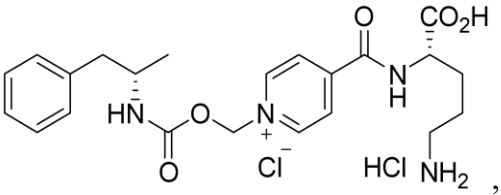
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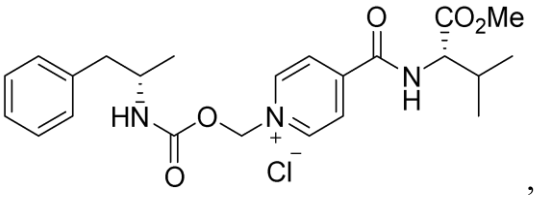
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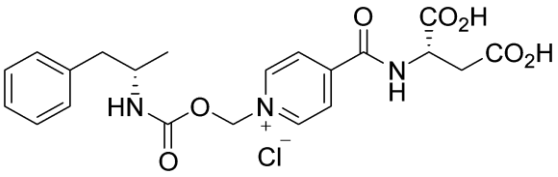
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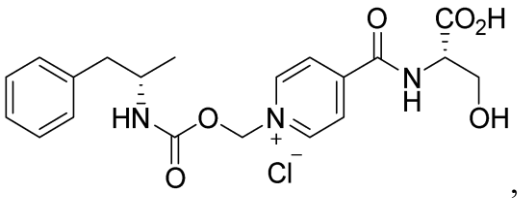
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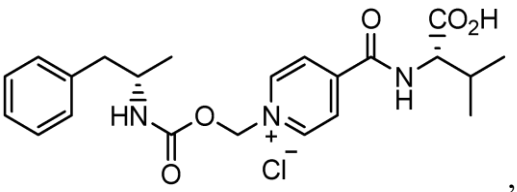
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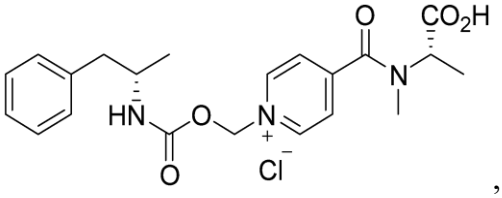
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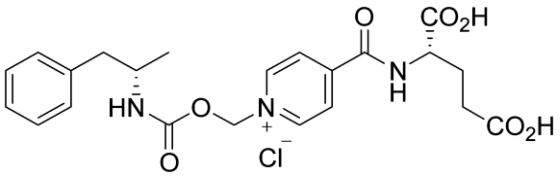
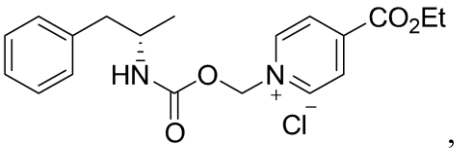
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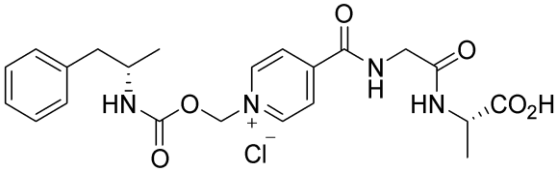
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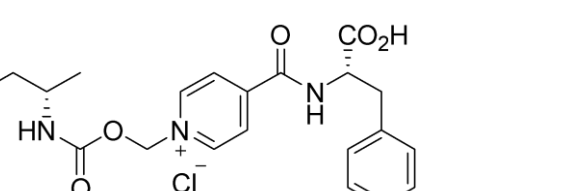
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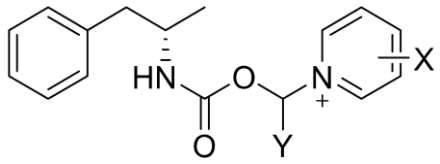
[0012d] In another aspect, there is provided a composition comprising the compound as defined above or pharmaceutically acceptable salt of the compound.

[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, and amides,

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,

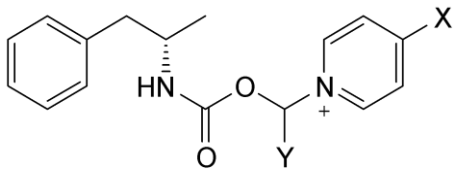
and Y is selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, substituted aryl, alkylaryl, cycloalkenyl, cycloalkyl, cycloalkynyl, heteroalkyl, heteroaryl, and heterocycle.

[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.

[0012h] In another aspect, there is provided a kit comprising individual does of a therapeutically effective amount of a composition comprising at least one compound as defined above.

CLAIMS

1. A compound having the structure of Formula I':

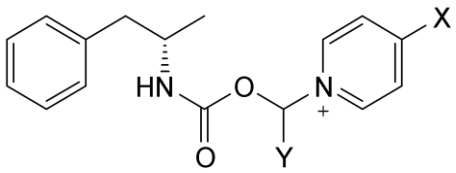


or a pharmaceutically acceptable salt of said compound,

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

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.

2. The compound of claim 1 having the structure of Formula IA or the pharmaceutically acceptable salt of said compound:



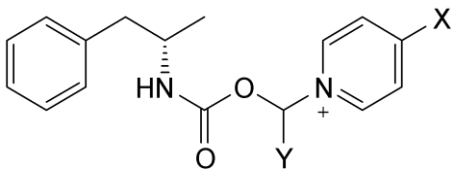
where X is A-COO-R;

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

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, and polyethylene glycol.

3. The compound of claim 1 having the structure of Formula IC or the pharmaceutically acceptable salt of said compound:



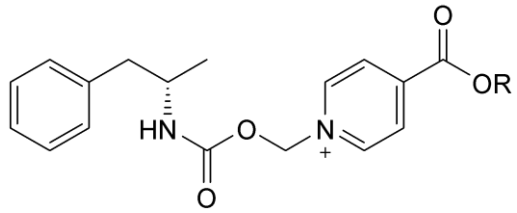
where X is A-CO-NR^1R^2;

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

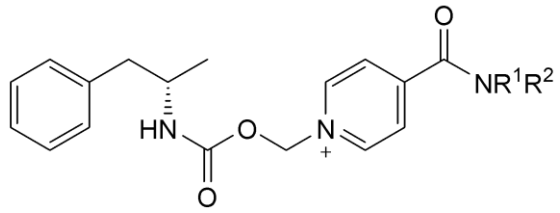
where R^1 and R^2 are independently selected from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, 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, and polyethylene glycol.

4. The compound of claim 2 or the pharmaceutically acceptable salt of said compound, wherein A is absent, Y is hydrogen, and the compound has the structure of formula IIA:



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, and polyethylene glycol.

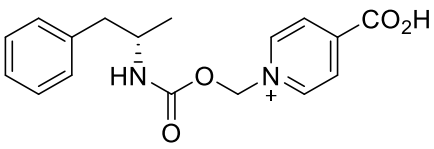
5. The compound of claim 3 or the pharmaceutically acceptable salt of said compound, wherein A is absent, Y is hydrogen, and the compound has the structure of Formula IIC:



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, and polyethylene glycol.

6. A compound having a structure selected from the group consisting of: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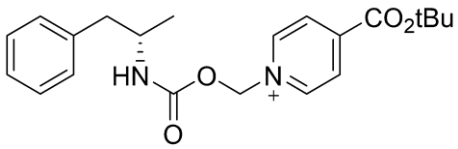
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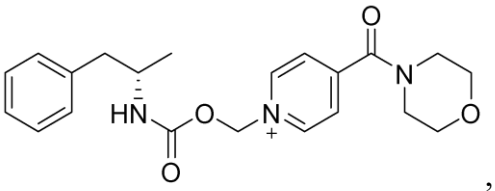
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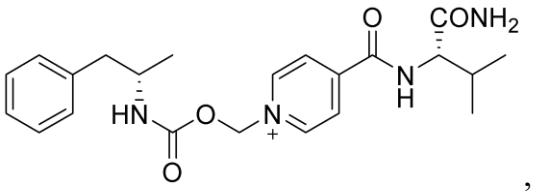
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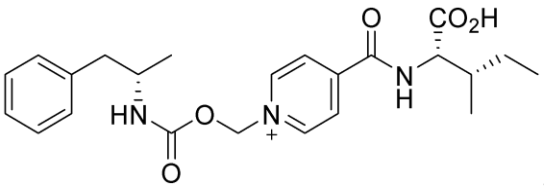
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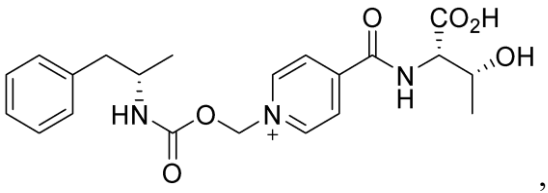
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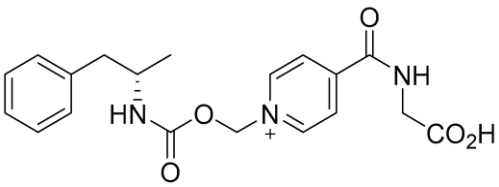
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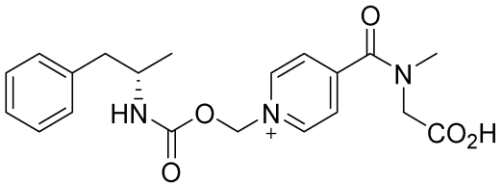
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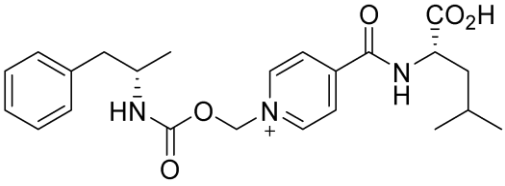
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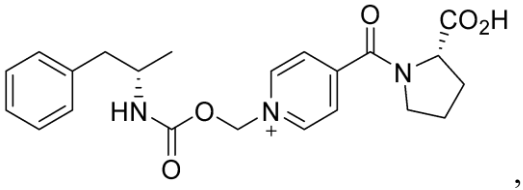
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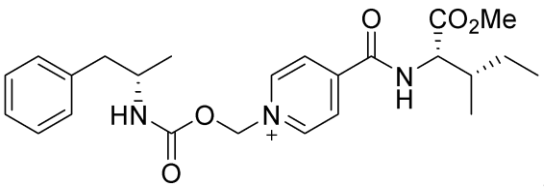
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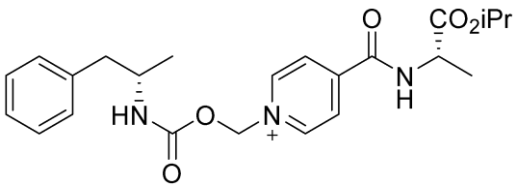
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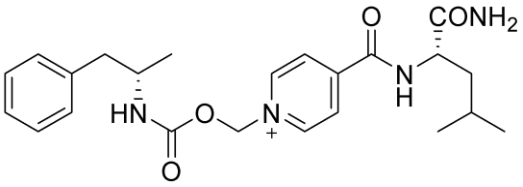
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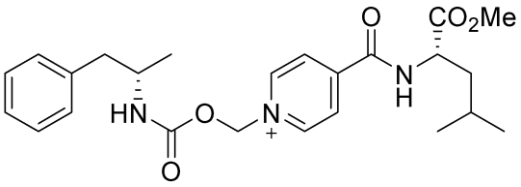
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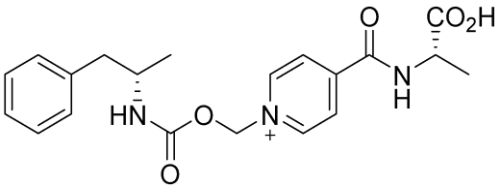
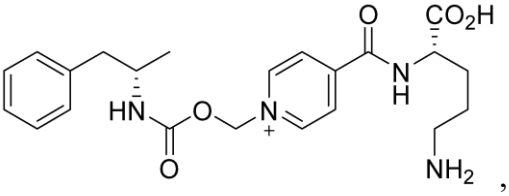
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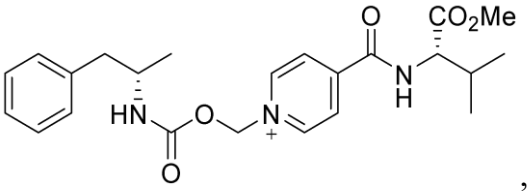
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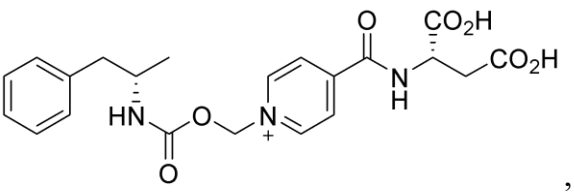
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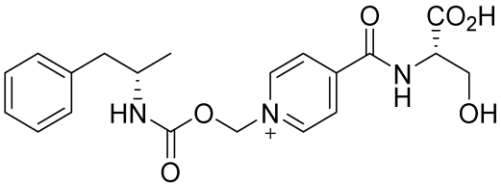
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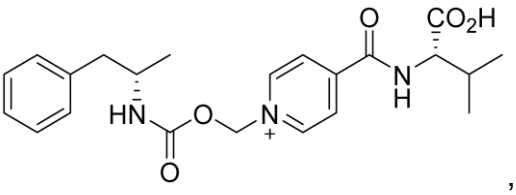
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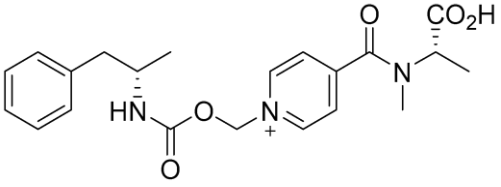
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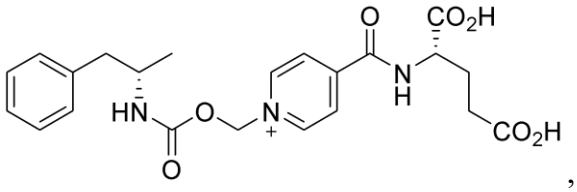
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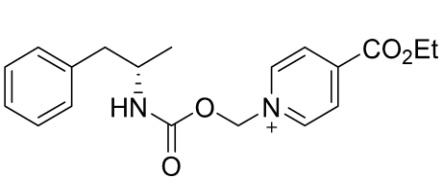
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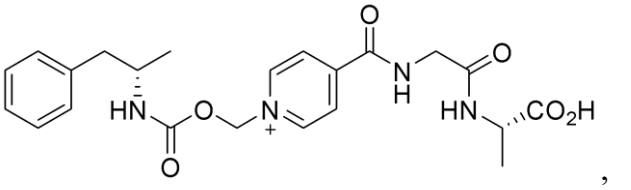
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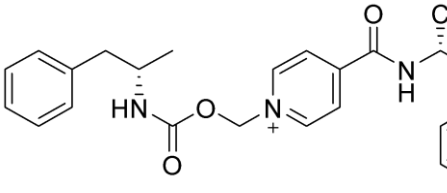
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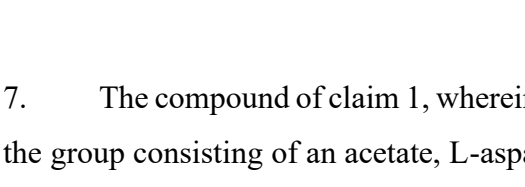
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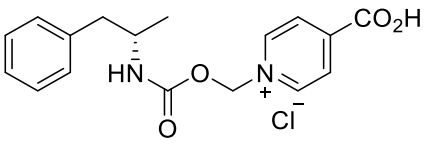
7. The compound of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of an acetate, L-aspartate, besylate, bicarbonate, carbonate, D-camsylate, L-camsylate, citrate, edisylate, formate, fumarate, gluconate, hydrobromide/bromide,

hydrochloride/chloride, D-lactate, L-lactate, D,L-lactate, D,L-malate, L-malate, mesylate, pamoate, phosphate, succinate, sulfate, bisulfate, D-tartrate, L-tartrate, D,L-tartrate, meso-tartrate, benzoate, gluceptate, D-glucuronate, hybenzate, isethionate, malonate, methylsulfate, 2-napsylate, nicotinate, nitrate, orotate, stearate, tosylate, thiocyanate, acefyllinate, aceturate, aminosalicylate, ascorbate, borate, butyrate, camphorate, camphocarbonate, decanoate, hexanoate, cholate, cypionate, dichloroacetate, edentate, ethyl sulfate, furate, fusidate, galactarate, galacturonate, gallate, gentisate, glutamate, glutarate, glycerophosphate, heptanoate, hydroxybenzoate, hippurate, phenylpropionate, iodide, xinafoate, lactobionate, laurate, maleate, mandelate, methanesulfonate, myristate, napadisilate, oleate, oxalate, palmitate, picrate, pivalate, propionate, pyrophosphate, salicylate, salicylsulfate, sulfosalicylate, tannate, terephthalate, thiosalicylate, tribrophenate, valerate, valproate, adipate, 4-acetamidobenzoate, camsylate, octanoate, estolate, esylate, glycolate, thiocyanate, undecylenate, sodium, potassium, calcium, magnesium, zinc, aluminum, lithium, cholinate, lysinium, ammonium, troethamine, and a mixture thereof.

8. A compound having a structure selected from the group consisting of: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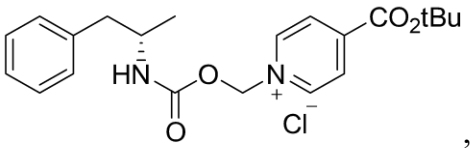
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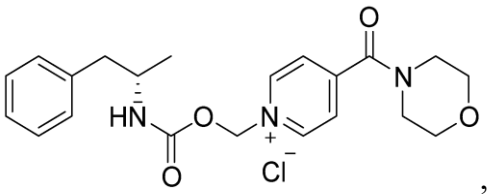
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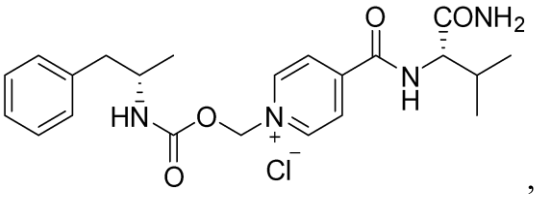
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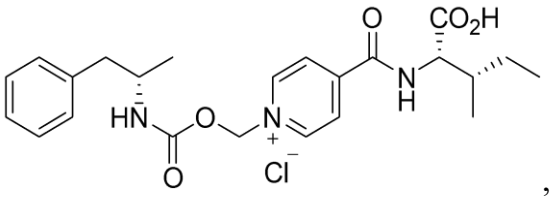
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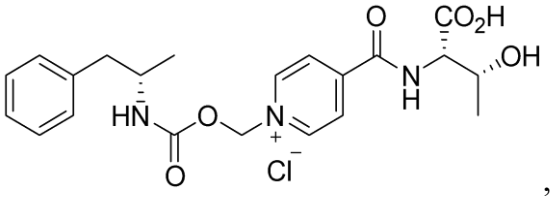
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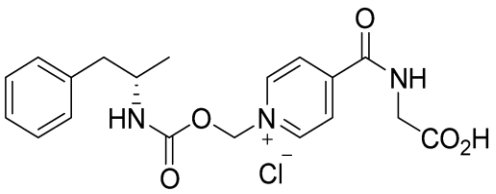
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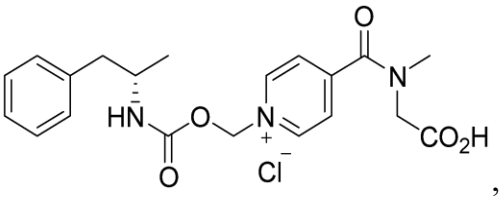
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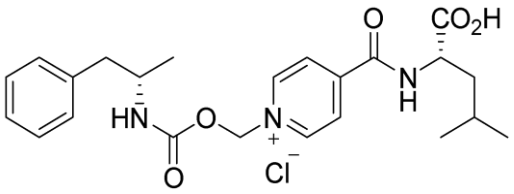
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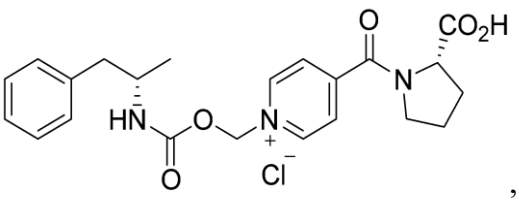
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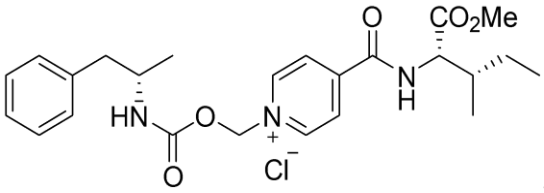
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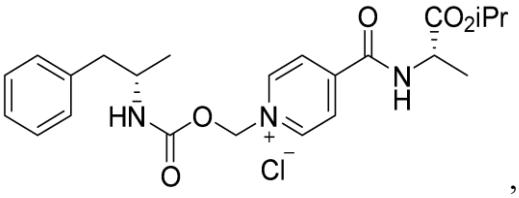
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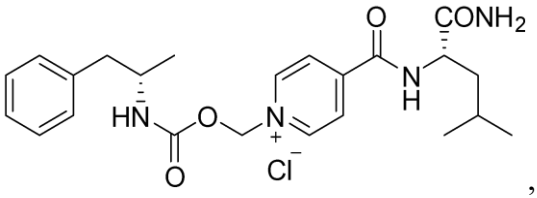
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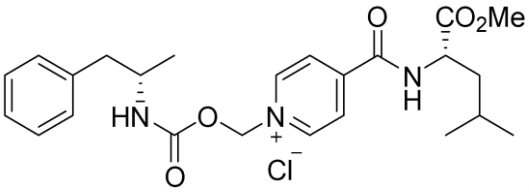
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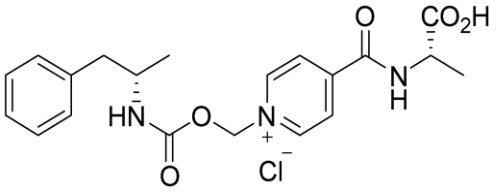
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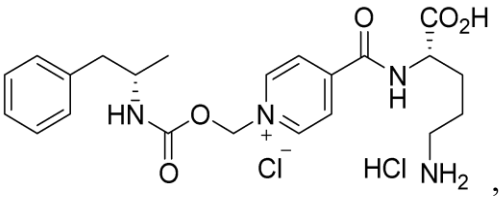
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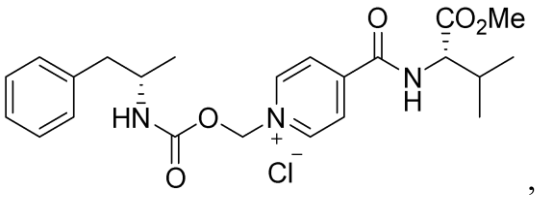
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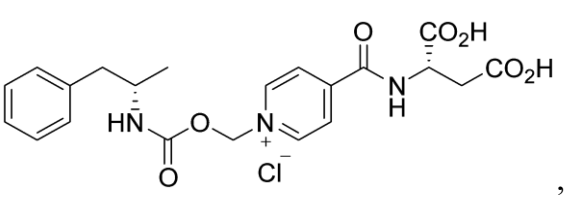
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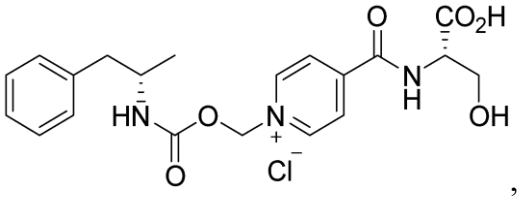
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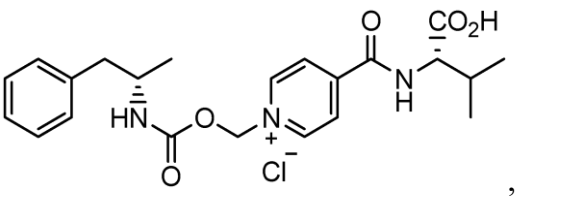
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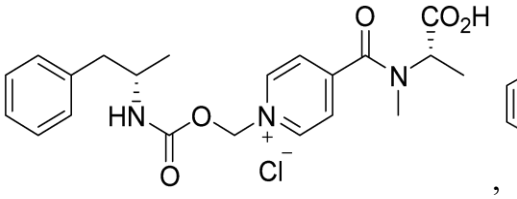
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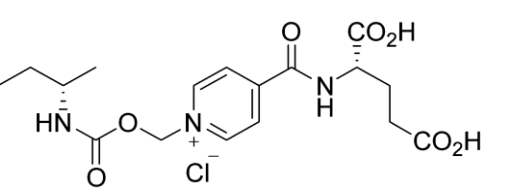
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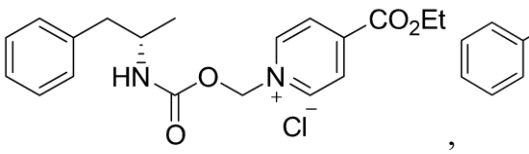

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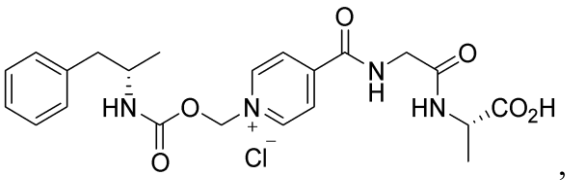

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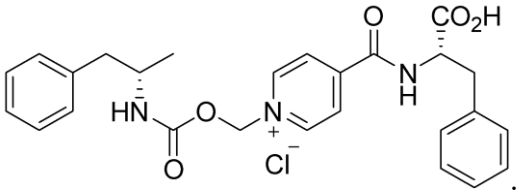

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9. A composition comprising the compound of claim 1 or pharmaceutically acceptable salt of the compound.

10. The composition of claim 9, wherein the composition is formulated for oral administration or suppository administration.

11. The composition of claim 10, wherein the composition formulated for oral administration is in a dosage form selected from the group consisting of solid form, a tablet, a capsule, a caplet, a soft gel, a suppository, a troche, a lozenge, an oral powder, a solution, a syrup, an oral film, a thin strip, a slurry, an emulsion, an elixir, and a suspension.

12. The composition of claim 10, wherein the composition further comprises one or more excipients, wherein the excipients are selected from the group consisting of anti-adherents, binders, coatings, disintegrants, fillers, flavors, dyes, colors, glidants, lubricants, preservatives, sorbents, sweeteners, and combinations thereof.

13. The composition of claim 12 wherein the binder is selected from the group consisting of hydroxypropylmethyl cellulose, ethyl cellulose, povidone, acrylic and methacrylic acid co-polymers, pharmaceutical glaze, gums, whey and starches, and combinations thereof.

14. The composition of claim 9, wherein the compound present in an amount per unit dose of between 0.1 mg and 2000 mg per unit dose.

15. The composition of claim 13, wherein the compound is present in an amount per unit dose of between 0.5 mg and 500 mg per unit dose.

16. The composition of claim 15, wherein the compound is present in an amount per unit dose of between 1 mg and 250 mg per unit dose.

17. The composition of claim 16, wherein the compound is present in an amount per unit dose of between 1.5 mg and 100 mg per unit dose.

18. The composition of claim 9, wherein the composition further comprises one or more additional pharmacological substance selected from the group consisting of stimulants, anti-depressants, combinations thereof, and prodrugs thereof.

19. The composition of claim 9, wherein the composition further comprises one or more of methylphenidate, aripiprazole, atomoxetine, baclofen, clonidine, desipramine, dihydrotetrabenazine, guanfacine, haloperidol, levetiracetam, mecamylamine, etoclopramide, olanzapine, ondansetron, pergolide, pimozide, pramipexole, risperidone, selegiline, sulpiride, tetrabenazine, topiramate, ziprasidone, or one or more of additional amphetamine, or any combination thereof.

20. The composition of claim 19, wherein the one or more additional amphetamine is unconjugated amphetamine, a conjugate of amphetamine, a prodrug of amphetamine, any isomer thereof, or any combination thereof.

21. The composition of claim 20, wherein the isomer of unconjugated amphetamine is unconjugated d-amphetamine.

22. The composition of claim 19, wherein the methylphenidate is unconjugated methylphenidate, a conjugate of methylphenidate, a prodrug of methylphenidate, any isomer thereof, or any combination thereof.

23. The composition of claim 22, wherein the isomer of unconjugated methylphenidate is unconjugated d-methylphenidate.

24. The composition of claim 22, wherein the conjugate of methylphenidate is serdexmethylphenidate.

25. The composition of claim 9, wherein the compound is provided in an amount sufficient to provide a decreased AUC when compared to unconjugated d-amphetamine when orally administered at equimolar doses.

26. The composition of claim 9, wherein the compound is provided in an amount sufficient to provide a decreased C_{max} as compared to unconjugated d-amphetamine when administered orally at equimolar doses.

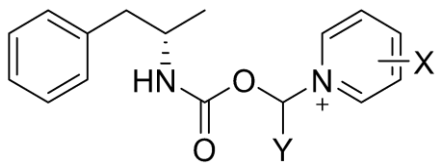
27. The composition of claim 9, wherein the compound is provided in an amount sufficient to provide a decreased C_{max} and a decreased AUC as compared to unconjugated d-amphetamine when administered orally at equimolar doses.

28. The composition of claim 9, wherein intranasal or intravenous administration of the compound provides a decreased AUC and/or C_{max} when compared to an equivalent molar amount of unconjugated d-amphetamine.

29. The composition of claim 9, wherein the compound provides reduced abuse potential as compared to unconjugated d-amphetamine.

30. A kit comprising individual doses of a therapeutically effective amount of a composition comprising the compound of claim 1, a pharmaceutical salt thereof, or a combination thereof.

31. A compound having the structure of Formula I:



or a pharmaceutically acceptable salt of the compound,

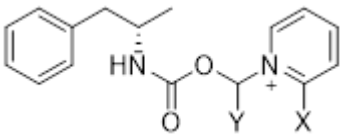
where X is selected from the group consisting of esters, carboxylic acids, amino acids, amino acid residues, and amides,

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.

32. The compound of claim 31, wherein the pharmaceutically acceptable salt is selected from the group consisting of an acetate, L-aspartate, besylate, bicarbonate, carbonate, D-camsylate, L-camsylate, citrate, edisylate, formate, fumarate, gluconate, hydrobromide/bromide, hydrochloride/chloride, D-lactate, L-lactate, D,L-lactate, D,L-malate, L-malate, mesylate, pamoate, phosphate, succinate, sulfate, bisulfate, D-tartrate, L-tartrate, D,L-tartrate, meso-tartrate, benzoate, gluceptate, D-glucuronate, hybenzate, isethionate,

malonate, methylsulfate, 2-napsylate, nicotinate, nitrate, orotate, stearate, tosylate, thiocyanate, acefyllinate, aceturate, aminosalicylate, ascorbate, borate, butyrate, camphorate, camphocarbonate, decanoate, hexanoate, cholate, cypionate, dichloroacetate, edentate, ethyl sulfate, furate, fusidate, galactarate, galacturonate, gallate, gentisate, glutamate, glutarate, glycerophosphate, heptanoate, hydroxybenzoate, hippurate, phenylpropionate, iodide, xinafoate, lactobionate, laurate, maleate, mandelate, methanesulfonate, myristate, napadisilate, oleate, oxalate, palmitate, picrate, pivalate, propionate, pyrophosphate, salicylate, salicylsulfate, sulfosalicylate, tannate, terephthalate, thiosalicylate, tribrophenate, valerate, valproate, adipate, 4-acetamidobenzoate, camsylate, octanoate, estolate, esylate, glycolate, thiocyanate, undecylenate, sodium, potassium, calcium, magnesium, zinc, aluminum, lithium, cholinate, lysinium, ammonium, troethamine, and a mixture thereof.

33. The compound of 31, wherein the compound has the structure of 

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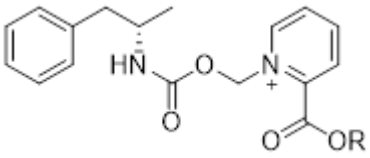
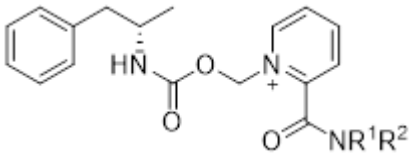
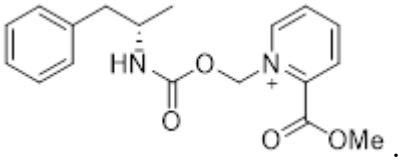
34. The compound of claim 33, wherein the compound has the structure of 

or 

wherein where R, R^1, or R^2 is 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, and polyethylene glycol.

35. The compound of claim 34, wherein the compound has a structure of 

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36. A kit comprising individual doses of a therapeutically effective amount of a composition comprising at least one compound of claim 6, a pharmaceutical salt thereof, or a combination thereof.

37. A kit comprising individual doses of a therapeutically effective amount of a composition comprising at least one compound of claim 8.

38. A kit comprising individual doses of a therapeutically effective amount of a composition comprising the compound of claim 31, a pharmaceutical salt thereof, or a combination thereof.