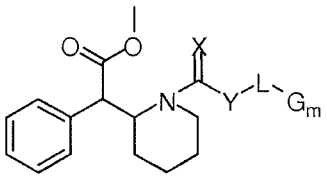
of the phosphate-CH_2OCO-methylphenidate conjugate is about 2.5 times higher than the unconjugated form.

~~[00325] In the present specification, use of the singular includes the plural except where specifically indicated.~~

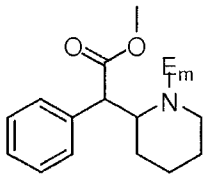
~~[00326]~~[00325] The presently described technology is now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to practice the same. It is to be understood that the foregoing describes preferred embodiments of the technology and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the appended claims.

CLAIMS

1. A prodrug composition comprising at least one conjugate of methylphenidate having a structure of formula (I) or formula (II):



(I)



(II)

wherein X is selected from the group consisting of O, S, Se and NR^1;

wherein Y is absent or selected from the group consisting of O, S, Se, NR^2 and CR^3R^4;

wherein R^1 and R^2 are selected independently from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, aminocarbonyl, 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, hydroxy, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, and polyethylene glycol;

wherein R^3 and R^4 are selected independently from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, amine, amino, aminocarbonyl, ammonium, aryl,

substituted aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylamino, arylaminocarbonyl, arylammonium, arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy, aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cyano, cycloalkenyl, cycloalkenylalkyl, carboxyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, hydroxy, nitro, oxo, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, polyethylene glycol and thiol;

wherein L is absent or $+A-Z+_n$;

wherein A is selected independently for each repeating subunit from the group consisting of CR^5R^6, aryl, substituted aryl, arylene, carbocycle, cycloalkenyl, cycloalkyl, cycloalkynyl, heterocycle and heteroaryl;

wherein R^5 and R^6 are selected independently from each other and independently for each repeating subunit from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, amine, amino, aminocarbonyl, ammonium, aryl, substituted aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylamino, arylaminocarbonyl, arylammonium, arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy, aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cyano, cycloalkenyl, cycloalkenylalkyl, carboxyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, hydroxy, nitro,

oxo, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, polyethylene glycol and thiol;

wherein Z is either absent or selected independently for each repeating subunit from the group consisting of O, S, Se and NH;

wherein n is 0-50;

wherein G is selected independently for each repeating subunit from the group consisting of alcohol, amine, amino acid, ammonium, oxoacid, peptide, poly(ethylene glycols) (PEG), thiol, derivatives thereof and combinations thereof;

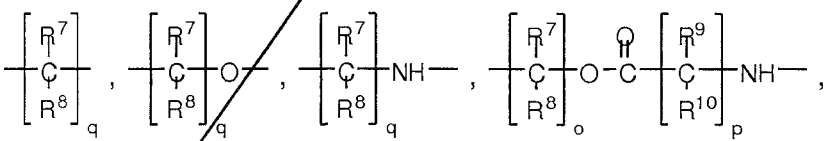
wherein E is an oxoacid; and

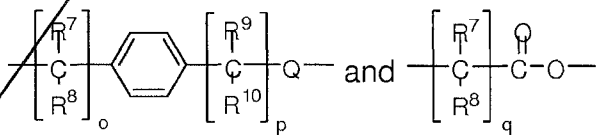
wherein m is 0-5.

2. The prodrug composition of claim 1, wherein X is O.

3. The prodrug composition of claim 1, wherein Y is absent or selected from the group consisting of O and N.

4. The prodrug composition of claim 1, wherein L is selected from the group consisting of:





wherein R^7, R^8, R^9, R^{10} are independently selected from each other and independently for each repeating subunit from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, alkynyl, aryl, substituted aryl, alkylaryl, cycloalkenyl, cycloalkyl, cycloalkynyl, heteroalkyl, heteroaryl, and heterocycle;

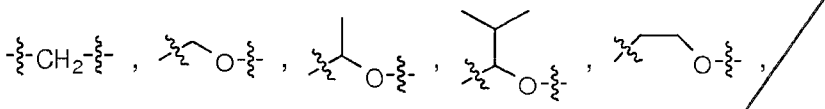
wherein q is 1-10;

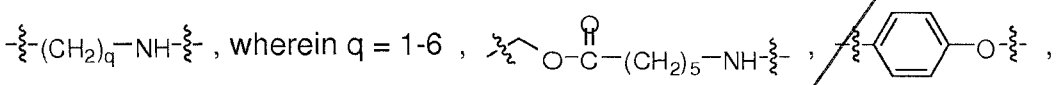
wherein o is 0-10;

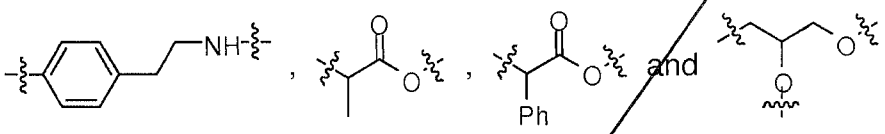
wherein p is 0-10; and

wherein Q is selected from the group consisting of NH and O.

5. The prodrug composition of claim 1, wherein L is selected from the group consisting of:







6. The prodrug composition of claim 1, wherein G is selected from the group consisting of oxoacids, tertiary amines and poly(ethylene glycol) derivatives.

7. The prodrug composition of claim 6, wherein G is a carboxylic acid or an inorganic oxoacid.

8. The prodrug composition of claim 1, wherein E is a carboxylic acid or an inorganic oxoacid.

9. The prodrug composition of claim 1, wherein one or more G are covalently bound to L, Y, or to another G.

10. The prodrug composition of claim 9, wherein all occurrences of G are identical.

11. The prodrug composition of claim 9, wherein all occurrences of G are different.

12. The prodrug composition of claim 9, wherein multiple occurrences of G are a combination of identical and different occurrences of G.

13. The prodrug composition of claim 1, wherein one or more E are covalently bound to the nitrogen in the piperidine ring of methylphenidate or to another E.

14. The prodrug composition of claim 13, wherein all occurrences of E are identical.

15. The prodrug composition of claim 13, wherein all occurrences of E are different.

16. The prodrug composition of claim 13, wherein multiple occurrences of E are a combination of identical and different occurrences of E.

17. The composition of claim 7 or 8, wherein the carboxylic acid is selected from the group consisting of aliphatic carboxylic acid, aryl carboxylic acid, dicarboxylic acid, and polycarboxylic acid.

18. The composition of claim 17, wherein the carboxylic acid is an aliphatic carboxylic acid selected from the group consisting of saturated carboxylic acids, monounsaturated carboxylic acids, polyunsaturated carboxylic acids, acetylenic carboxylic acids, substituted carboxylic acids, heteroatom containing carboxylic acids and ring containing carboxylic acids.

19. The prodrug composition of claim 18, wherein the saturated carboxylic acid is selected from the group consisting of methanoic, ethanoic, propanoic, butanoic, pentanoic, hexanoic, heptanoic, octanoic, 2-propylpentanoic acid, nonanoic, decanoic, dodecanoic, tetradecanoic, hexadecanoic, heptadecanoic, octadecanoic, and eicosanoic acid.

20. The prodrug composition of claim 18, wherein the monosaturated carboxylic acid is selected from the group consisting of 4-decenoic, 9-decenoic, 5-lauroleic, 4-dodecenoic, 9-tetradecenoic, 5-tetradecenoic, 4-tetradecenoic, 9-hexadecenoic, 6-hexadecenoic, 6-octadecenoic, and 9-octadecenoic acid.

21. The prodrug composition of claim 18, wherein the polyunsaturated carboxylic acid is selected from the group consisting of sorbic, octadecadienoic, octadecatrienoic, octadecatetraenoic, eicosatrienoic, eicosatetraenoic, eicosapentaenoic, docosapentaenoic, and docosahexaenoic acids.

22. The prodrug composition of claim 18, wherein the acetylenic carboxylic acid is selected from the group consisting of octadecynoic, octadecenynoic, 6,9-octadecenynoic, heptadecenynoic, tridecatetraenediynoic, tridecadienetriynoic, octadecadienediynoic, heptadecadienediynoic, octadecadienediynoic, octadecenediynoic, and octadecenetriynoic acids.

23. The prodrug composition of claim 18, wherein the substituted carboxylic acid is selected from the group consisting of methylpropanoic, isovaleric, methylhexadecanoic, 8-methyl-6-nonenoic, methyloctadecanoic, trimethyloctacosanoic, trimethyltetracosenoic, heptamethyltriacontanoic, tetramethylhexadecanoic, tetramethylpentadecanoic, lactic, glyceric, glycolic, threonic, 3-hydroxypropionic, hydroxyoctadecatrienoic, hydroxyoctadecenoic, hydroxytetracosanoic, 2-hydroxybutyric, 3-hydroxybutyric, 4-hydroxybutyric, 4-hydroxypentanoic, hydroxyoctadecadienediynoic, hydroxyoctadecadienoic, 10-hydroxydecanoic, hydroxydecenoic, hydroxyeicosenoic, hydroxyeicosadienoic, hydroxyhexadecanoic, dihydroxytetracosenoic, dihydroxydocosanoic, hydroxydocosanoic, trihydroxyoctadecanoic, trihydroxyhexadecanoic, trihydroxyicosahexaenoic, trihydroxyicosapentaenoic, 2-methoxy-5-hexadecenoic, 2-methoxy hexadecanoic, 7-methoxy-4-tetradecenoic, 9-methoxypentadecanoic, 11-methoxyheptadecanoic, 3-methoxydocosanoic, diacetoxydocosanoic, 2-acetoxydocosanoic, 2-acetoxytetracosanoic, 2-acetoxyhexacosanoic, 9-oxononanoic, oxodecanoic, oxododecenoic, hydroxyoxodecenoic, 10-oxo-8-decenoic, fluorooctadecenoic, fluorodecanoic, fluorotetradecanoic, fluorohexadecanoic, fluorooctadecadienoic, chlorohydroxyhexadecanoic, chlorohydroxyoctadecanoic, dichlorooctadecanoic, 3-bromo-2-nonaenoic, 9,10-dibromooctadecanoic, 9,10,12,13-tetrabromooctadecanoic, 10-nitro-9,12-octadecadienoic, 12-nitro-9,12-octadecadienoic, 9-nitro-9-octadecenoic, 9-oxo-2-decenoic, 9-oxo-13-octadecenoic, oxooctadecatrienoic, 15-oxo-18-tetracosenoic, 17-oxo-20-hexacosenoic, and 19-oxo-22-octacosenoic acids.

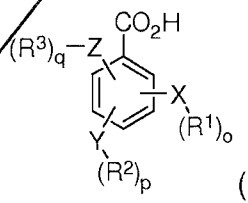
24. The prodrug composition of claim 18, wherein the heteroatom containing carboxylic acid is selected from the group consisting of 9-(1,3-nonadienoxy)-8-nonenoic, 9-(1,3,6-nonatrienoxy)-8-nonenoic, 12-(1-hexenoxy)-9,11-dodecadienoic, 12-(1,3-

hexadienoxy)-9,11-dodecadienoic, 2-dodecylsulfanylacetic, 2-tetradecylsulfanylacetic, 3-tetradecylsulfanylprop-2-enoic, and 3-tetradecylsulfanylpropanoic acid.

25. The prodrug composition of claim 18, wherein the ring containing carboxylic acid is selected from the group consisting of 10-(2-Hexylcyclopropyl)decanoic, 3-(2-[6-bromo-3,5-nondienylcyclopropyl)propanoic, 9-(2-hexadecylcyclopropylidene)non-5-enoic, 8-(2-octyl-1-cyclopropenyl)octanoic, 7-(2-octyl-1-cyclopropenyl)heptanoic, 9,10-epoxyoctadecanoic, 9,10-epoxy12-octadecenoic, 12,13-epoxy-9-octadecenoic, 14,15-epoxy-11-eicosenoic, 11-(2-cyclopenten-1-yl)undecanoic, 13-(2-cyclopenten-1-yl)tridecanoic, 13-(2-cyclopentenyl)-6-tridecenoic, 11-cyclohexylundecanoic, 13-cyclohexyltridecanoic, 7-(3,4-dimethyl-5-pentylfuran-2-yl)heptanoic, 9-(4-methyl-5-pentylfuran-2-yl)nonanoic, 4-[5]-ladderane-butanoic, 6-[5]-ladderane-hexanoic, and 6-[3]-ladderane-hexanoic acid.

26. The prodrug composition of claim 17, wherein the carboxylic acid is a benzoate or a heteroaryl carboxylic acid.

27. The prodrug composition of claim 26, wherein the benzoate has the following formula (X):



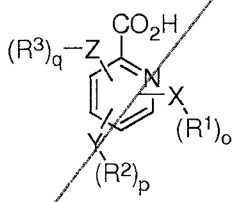
(X)

wherein X, Y and Z can be independently any combination of H, O, S or—$(CH_2)_x$-; R^1, R^2 and R^3 can be independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl , alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; and o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10.

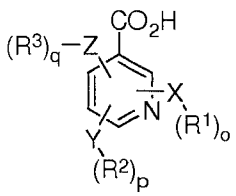
28. The prodrug composition of claim 26, wherein the benzoate is selected from the group consisting of benzoic acid, hydroxybenzoate, and combinations thereof.

29. The prodrug composition of claim 28, wherein the hydroxybenzoate is selected from the group consisting of benzoic acid, salicylic acid, acetylsalicylic acid (aspirin), 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, 6-methylsalicylic acid, *o,m,p*-cresotinic acid, anacardic acids, 4,5-dimethylsalicylic acid, *o,m,p*-thymotic acid, diflusinal, *o,m,p*-anisic acid, 2,3-dihydroxybenzoic acid (2,3-DHB), α,β,γ-resorcylic acid, protocatechuic acid, gentisic acid, piperonylic acid, 3-methoxysalicylic acid, 4-methoxysalicylic acid, 5-methoxysalicylic acid, 6-methoxysalicylic acid, 3-hydroxy-2-methoxybenzoic acid, 4-hydroxy-2-methoxybenzoic acid, 5-hydroxy-2-methoxybenzoic acid, vanillic acid, isovanillic acid, 5-hydroxy-3-methoxybenzoic acid, 2,3-dimethoxybenzoic acid, 2,4-dimethoxybenzoic acid, 2,5-dimethoxybenzoic acid, 2,6-dimethoxybenzoic acid, veratric acid (3,4-dimethoxybenzoic acid), 3,5-dimethoxybenzoic acid, gallic acid, 2,3,4-trihydroxybenzoic acid, 2,3,6-trihydroxybenzoic acid, 2,4,5-trihydroxybenzoic acid, 3-*O*-methylgallic acid (3-OMGA), 4-*O*-methylgallic acid (4-OMGA), 3,4-*O*-dimethylgallic acid, syringic acid, and 3,4,5-trimethoxybenzoic acid.

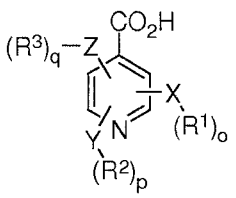
30. The prodrug composition of claim 26, wherein the heteroaryl carboxylic acid comprises at least one heteroaryl carboxylic acid, a salt thereof, a derivative thereof or a combination thereof having at least one of the the formulas (XI), (XII), (XIII) or combinations thereof:



(XI)



(XII)



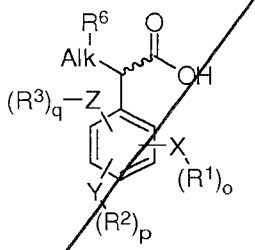
(XIII),

wherein X, Y and Z can be independently any combination of H, O, S or—$(CH_2)_x$-; R^1, R^2 and R^3 can be independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl; and o, p, q are independently selected from 0 or 1; and x is an integer between 1 and 10.

31. The composition of claim 30, wherein the heteroaryl carboxylic acid is selected from the group consisting of nicotinic acid, isonicotinic acid, picolinic acid, 3-hydroxypicolinic acid, 6-hydroxynicotinic acid, citrazinic acid, 2,6-dihydroxynicotinic acid, kynurenic acid, xanthurenic acid, 6-hydroxykynurenic acid, 8-methoxykynurenic acid, 7,8-dihydroxykynurenic acid, and 7,8-dihydro-7,8-dihydroxykynurenic acid.

32. The composition of claim 17, wherein the carboxylic acid is selected from the grouop consisting of a phenylacetate, a branched phenylpropionate, an unbranched phenylpropionate (benzylacetate), a phenylpropenoate (cinnamate), salts thereof, derivatives thereof, and combinations thereof.

33. The composition of claim 32, wherein the carboxylic acid comprises derivatives of phenylacetate having the formula (XIV):



(XIV)

wherein X, Y and Z can be independently any combination of H, O, S or—$(CH_2)_x$-; R^1, R^2 and R^3 can be independently selected from the group consisting of H, alkyl, alkoxy, aryl, substituted aryl, alkenyl, alkynyl, halo, haloalkyl, alkylaryl, arylalkyl, heterocycle, arylalkoxy, cycloalkyl, cycloalkenyl and cycloalkynyl;

wherein o, p, q are independently selected from 0 or 1; x is an integer between 1 and 10; Alk comprises an alkyl chain $-(CH_2)_n$-, wherein n is selected from 0 or 1; and

wherein R^6 can be H, OH, or carbonyl.

34. The prodrug composition of claim 32, wherein the phenylacetate is selected from the group consisting of phenylacetic acid (hydratropic acid), 2-hydroxyphenylacetic acid, 3-hydroxyphenylacetic acid, 4-hydroxyphenylacetic acid, homoprotocatechuic acid, homogentisic acid, 2,6-dihydroxyphenylacetic acid, homovanillic acid, homoisovanillic acid, homoveratric acid, atropic acid, *d,l*-tropic acid,

diclofenac, *d,l*-mandelic acid, 3,4-dihydroxy-*d,l*-mandelic acid, vanillyl-*d,l*-mandelic acid, isovanillyl-*d,l*-mandelic acid, ibuprofen, fenoprofen, carprofen, flurbiprofen, ketoprofen, and naproxen.

35. The prodrug composition of claim 32, wherein the carboxylic acid is a benzylacetate selected from the group consisting of benzylacetic acid, melilotic acid, 3-hydroxyphenylpropanoic acid, 4-hydroxyphenylpropanoic acid, 2,3-dihydroxyphenylpropanoic acid, *d,l*-phenyllactic acid, *o,m,p*-hydroxy-*d,l*-phenyllactic acid, and phenylpyruvic acid.

36. The prodrug composition of claim 32, wherein the carboxylic acid is a cinnamate, derivatives thereof and combinations thereof.

37. The prodrug composition of claim 36, wherein the cinnamate is selected from the group consisting of cinnamic acid, *o,m,p*-coumaric acid, 2,3-dihydroxycinnamic acid, 2,6-dihydroxycinnamic acid, caffeic acid, ferulic acid, isoferulic acid, 5-hydroxyferulic acid, sinapic acid, and 2-hydroxy-3-phenylpropenoic acid.

38. The prodrug composition of claim 17, wherein the dicarboxylic acid is of the general formula HOOC-R-COOH, where R is selected from the group consisting of an alkyl, alkenyl, alkynyl, aryl, or substituted aryl group, and derivatives thereof.

39. The prodrug composition of claim 38, wherein the dicarboxylic acid is selected from the group consisting of oxalic, malonic, succinic, glutaic, adipic, pimelic, suberic, azelaic, sebacic, brassylic, thapsic, malic, tartaric, dihydroxymesoxalic, α-hyroxyglutaric, methylmalonic, meglutol, diaminopimelic, carbamoyl aspartic, fumaric, maleic, mesaconic, 3-methylglutaconic, traumatic, phthalic acid, isophthalic, terephthalic, and dipicolinic.

40. The prodrug composition of claim 17, wherein the polycarboxylic acid is selected from the group consisting of citric acid, isocitric, carballylic, and trimesic acid.

41. The prodrug composition of claim 7 or 8, wherein the at least one inorganic oxoacid contains an -OH group.

42. The prodrug composition of claim 41, wherein the at least one inorganic oxoacids, organic derivative thereof or inorganic derivative thereof is selected from the group consisting of phosphates, phosphonates, phosphinates, phosphoramidates, phosphoramidites, diphosphates, triphosphates, biphosphonates, phosphorothioates, phosphorodithioates, phosphites, sulfates, sulfonates, sulfamates, sulfites, thiosulfates, thiosulfites, sulfinates, nitrate, nitrite, borates, boronates, hypochlorite, carbonates, and carbamates.

43. The composition of claim 7 or 8, wherein the carboxylic acid is an amino acid.

44. The prodrug composition of claim 43, wherein the amino acid is selected from the group consisting of standard amino acids, non-standard amino acids, and synthetic amino acids.

45. The prodrug composition of claim 44, wherein the standard amino acid is selected from the group consisting of alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, pyrrolysine, selenocysteine, serine, threonine, tryptophan, tyrosine and valine.

46. The prodrug composition of claim 44, wherein the non-standard amino acid is an amino acid that occurs in nature but is not encoded by the genetic code.

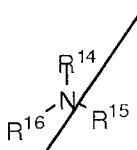
47. The prodrug composition of claim 46, wherein the non-standard amino acid is selected from the group consisting of ornithine, homoarginine, citrulline, homocitrulline, homoserine, theanine, γ-aminobutyric acid, 6-aminohexanoic acid, sarcosine, carnitine, 2-aminoadipic acid, pantothenic acid, taurine, hypotaurine, lanthionine, thiocysteine, cystathionine, homocysteine, β-amino acids such as 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), α,α-disubstituted amino acids such as 2-aminoisobutyric acid, isovaline, di-n-ethylglycine, ~~*N*-methyl acids such as *N* methyl alanine, L abrine, 4 hydroxyproline, 5 hydroxylysine,~~

3-hydroxyleucine, 4-hydroxyisoleucine, 5-hydroxy-L-tryptophan, cyclic amino acids such as 1-aminocyclopropyl-1-carboxylic acid, azetidine-2-carboxylic acid and pipecolic acid.

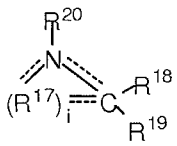
48. The prodrug composition of claim 44, wherein the synthetic amino acid is an amino acid that does not occur in nature.

49. The prodrug composition of claim 48, wherein the synthetic amino acid is selected from the group consisting of 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, and 4-(dimethylamino)cinnamic acid.

50. The prodrug composition claim 6, wherein the tertiary amine comprises at least one tertiary amine having the structure of formula (III) or (IV):



(III)



(IV)

wherein R^{17} is independently for each repeating subunit selected from O, S, Se, NR^{21} or $CR^{22}R^{23}$;

wherein R^{14}, R^{15}, R^{16}, R^{20}, R^{21} are selected independently from alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, aminocarbonyl, 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, hydroxy, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, or polyethylene glycol;

wherein R^{20} may be absent;

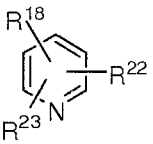
wherein R^{18}, R^{19}, R^{22}, R^{23} are selected independently from each other and independently for each repeating subunit (of R^{17}) from hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, amine, amino, aminocarbonyl, ammonium, aryl, substituted aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylamino, arylaminocarbonyl, arylammonium, arylazo, arylcarbonyl, arylcarbonylamino, arylcarbonyloxy, arylcycloalkyl, aryloxy, aryloxyalkyl, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, arylsulfonylamino, arylthio, arylthioalkyl, cyano, cycloalkenyl, cycloalkenylalkyl, carboxyl, cycloalkyl, cycloalkylalkyl, cycloalkylamino, cycloalkyloxy, cycloalkynyl, cycloheteroalkyl, cycloheteroalkylalkyl, halo, haloalkoxy, haloalkyl, heteroaryl, heteroarylalkenyl, heteroarylalkyl, heteroarylamino, heteroarylcarbonyl, heteroarylcarbonylamino, heteroaryloxo, heteroaryloxy, heteroarylsulfinyl, heteroarylsulfonyl, heteroarylthio, hydroxy, nitro, oxo, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, polyethylene glycol or thiol; and

wherein i = 0-10.

51. The prodrug composition of claim 50 wherein the tertiary amine is a heterocycle with a ring size of 3-10 atoms, of which at least one is a nitrogen atom and at least one is a carbon atom, and the ring may be aliphatic containing any number and combination of single, double or triple bonds or the ring may be aromatic.

52. The prodrug composition of claim 50 wherein the tertiary amine is covalently bound to L via its tertiary nitrogen or via an amino, hydroxyl or carboxyl functional group of one of its substituents.

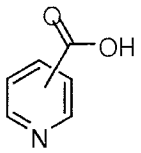
53. The prodrug composition of claim 50, wherein the tertiary amine comprises at least one tertiary amine having the structure of formula (V):



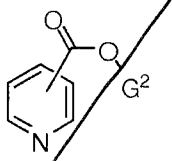
(V)

wherein R^{18}, R^{22}, R^{23} as defined for structure (IV).

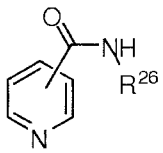
54. The prodrug composition of claim 50, wherein the tertiary amine comprises at least one carboxypyridine derivative having the structure of formula (VI), (VII) or (VIII):



(VI)



(VII)



(VIII)

wherein R^{26} is selected from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, alkylamino, alkylaminocarbonyl, alkylammonium, alkylcarbonyl, alkylcarbonylamino, alkylcarbonyloxy, alkylsulfinyl, alkylsulfonyl, alkylthio, alkynyl, alkynylaminocarbonyl, aminocarbonyl, 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,

hydroxy, polycycloalkenyl, polycycloalkenylalkyl, polycycloalkyl, polycycloalkylalkyl, and polyethylene glycol; and

wherein G^2 is optionally bound via an ester or amide bond to the carboxypyridine derivative.

55. The prodrug composition of claim 54, wherein G^2 is a hydrogen atom or an alkyl group.

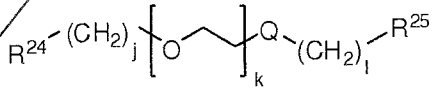
56. The prodrug composition of claim 54, wherein the carboxypyridine derivative is nicotinic acid or an isomer thereof.

57. The prodrug composition of claim 54, wherein G^2 is an alcohol or an oxoacid.

58. The prodrug composition of claim 57, wherein the oxoacid is any one of the oxoacids of claims 17-49.

59. The prodrug composition of claim 58, wherein the oxoacid is an amino acid.

60. The prodrug composition claim 6, wherein the poly(ethylene glycol) derivative comprises at least one poly(ethylene glycol) derivative having the structure of formula (IX):



(IX)

wherein R^{24} is selected from the group consisting of H and NH_2;

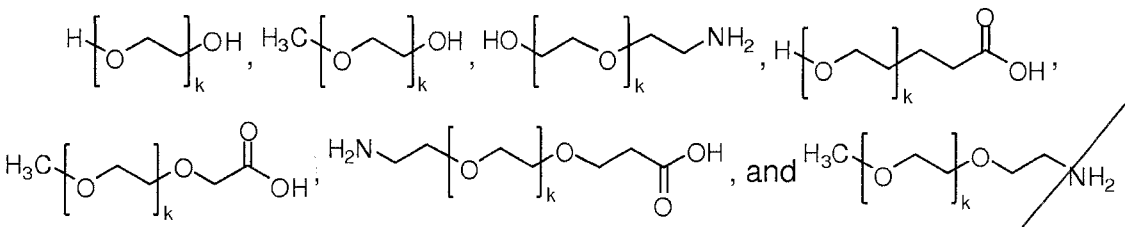
wherein R^{25} is selected from the group consisting of H, NH_2 and CO_2H;

wherein Q is absent or O;

wherein J and I = 0-5; and

wherein k = 1-100.

61. The prodrug composition of claim 60 wherein the poly(ethylene glycol) derivative is selected from the group consisting of:



wherein k = 1-100.

62. The prodrug composition of claim 61, wherein k is 1-50.

63. The prodrug composition of claim 61, wherein k is 1-10.

64. The prodrug composition of claim 1, wherein the at least one methylphenidate is at least one or more stereoisomers.

65. The prodrug composition of any of the previous claims, wherein the at least one methylphenidate is selected from the group consisting of: *d-erythro*-methylphenidate, *l-erythro*-methylphenidate, *d*-threo-methylphenidate, *l-threo*-methylphenidate, salts thereof, and mixtures thereof.

66. The prodrug composition of any of the previous claims, wherein the at least one methylphenidate is a mixture of racemates, wherein the racemates comprises *threo*-methylphenidate.

67. The prodrug composition of any of the previous claims, wherein methylphenidate is *d-threo*-methylphenidate isomer.

68. The prodrug composition of any of the previous claims, wherein the conjugate is a neutral prodrug composition.

69. The prodrug composition of any of the previous claims, wherein the conjugate is a free acid.

70. The prodrug composition of any of the previous claims, wherein the conjugate is a free base.

71. The prodrug composition of any of the previous claims, wherein the conjugate is a pharmaceutically acceptable anionic, amphoteric, zwitterionic or cationic salt form or salt mixtures thereof.

72. The prodrug composition of claim 71, wherein the anionic salt form is selected from the group consisting of 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, methylsufate, 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 (mucate), galacturonate, gallate, gentisate, glutamate, glutamate, glutarate, glycerophosphate, heptanoate (enanthate), hydroxybenzoate, hippurate, phenylpropionate, iodide, xinafoate, lactobionate, laurate, maleate, mandelate, methanesufonate, 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, and undecylenate.

73. The prodrug composition of claim 71, wherein the anionic salt form is selected from the group consisting of sodium, potassium, calcium, magnesium, zinc, aluminium, lithium, cholinate, lysinium, ammonium and tromethamine.

74. The prodrug composition of claim 1, wherein the at least one conjugate is selected from the group consisting of nicotinate-CH_2OCO-methylphenidate, phosphate-CH_2OCO-methylphenidate, phosphate-CH_2OCO-methylphenidate, gallate-CH_2OCO-methylphenidate, gallate-CH_2OCO-methylphenidate, lactate-CH_2OCO-methylphenidate, methylphenidate-CO_2CH_2-nicotinoyl-Asp, methylphenidate-$CO2CH_2$-nicotinoyl-Val, methylphenidate-CO_2CH_2-nicotinoyl-Gly-Ala, Val-6-aminohexanoate-CH_2OCO-

methylphenidate, methylphenidate-CO_2CH_2-nicotinamide, 6-Aminohexanoate-CH_2OCO-methylphenidate, methylphenidate-CO_2CH_2-nicotinoyl-O^{t}Bu, methylphenidate-CO_2CH_2-nicotinate, methylphenidate-CO_2CH_2-nicotinoyl-OEt, methylphenidate-CO_2CH_2-pyridine, isonicotinate-CH_2OCO-methylphenidate and phosphate-(*p*-salicylate)-CH_2OCO-methylphenidate.

75. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate exhibits a rate of release equivalent to free or unmodified methylphenidate.

76. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate exhibits a slower rate of release over time as compared to unmodified methylphenidate.

77. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate exhibits increased absorption when administered orally as compared to unmodified methylphenidate.

78. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate has increased bioavailability as compared to unmodified methylphenidate.

79. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate exhibits less interpatient variability in the oral PK profile when compared to unconjugated methylphenidate.

80. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate is provided in an amount sufficient to provide an increased AUC when compared to unconjugated methylphenidate when administered orally at equimolar doses.

81. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate is provided in an amount sufficient to provide an increased C_{max} as

compared to unconjugated methylphenidate when administered orally at equimolar doses.

82. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate is provided in an amount sufficient to provide an increased C_{max} and an increased AUC as compared to unconjugated methylphenidate when administered orally at equimolar doses.

83. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate provides reduced side effects as compared to unconjugated methylphenidate when administered at equimolar doses.

84. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate provides reduced abuse potential as compared to unconjugated methylphenidate.

85. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate is provided in an amount sufficient to provide an extended T_{max} when compared to unconjugated methylphenidate when administered at equimolar doses.

86. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate is provided in an amount sufficient to provide an equivalent T_{max} when compared to unconjugated methylphenidate when administered at equimolar doses.

87. The prodrug composition of any one of claims 1-74, wherein the at least one conjugate has increased water solubility when compared to unconjugated methylphenidate.

88. Use of a pharmaceutically effective amount of the prodrug composition of any one of claims 1-87 in the manufacture of a medicament for treating a patient having a disease, disorder or condition mediated by controlling, preventing, limiting, or inhibiting neurotransmitter uptake/re-uptake or hormone uptake/re-uptake, wherein the medicament is to be administered orally.

89. Use of a pharmaceutically and/or therapeutically effective amount of the composition of any one of claims 1-87 in the manufacture of a medicament for treating a patient having a disorder or condition requiring stimulation of the central nervous system of the patient, wherein the medicament is administered orally to the patient.

90. The use of claim 88 or 89, wherein the disease or condition is selected from the group consisting of attention-deficit hyperactivity disorder, attention deficit disorder, autistic spectrum disorder, autism, Asperger's disorder, pervasive developmental disorder, sleep disorder, obesity, depression, bipolar disorder, eating disorder, chronic fatigue syndrome, schizophrenia, major depressive disorder, narcolepsy, postural orthostatic tachycardia syndrome, lethargy, depression, neural insult and obesity.

91. The use of claim 88, wherein the hormone is a catecholamine.

92. The use of claim 88, wherein the neurotransmitter is selected from the group consisting of serotonin, dopamine and norepinephrine.

93. The use of any one of claims 88-92, wherein the composition or prodrug to be administered decreases the number and/or amount of metabolites produced when compared with unconjugated methylphenidate.

94. The use of claim 93, wherein the composition or prodrug to be adminstered decreases the exposure to ritalinic acid when compared with unconjugated methylphenidate.

95. The use of any one of claims 88-92, wherein the increased water solubility of the conjugate compared to unconjugated methylphenidate provides the ability of the conjugate or prodrug to be administered in an oral thin film or strip with higher dose loading capacity as compared to unconjugated methylphenidate.

96. The use of any one of claims 88-92, wherein the composition or prodrug to be adminstered provides a reduced interpatient variability of methylphenidate plasma concentrations.

97. The use of any one of claims 1-87, wherein the composition has an improved safety profile when compared to unconjugated methylphenidate.

98. Use of a pharmaceutically effective amount of the prodrug composition of any one of claims 1-87 in the manufacture of a medicament for treating attention-deficit hyperactivity disorder.

99. A prodrug composition of any one of claims 1-87 for treating a patient having a disorder or condition requiring stimulation of the central nervous system of the patient, wherein the prodrug composition has reduced abuse potential when administered compared to unconjugated methylphenidate.

100. The prodrug composition of any one of claims 1-87, wherein the prodrug has a reduced or prevented pharmacological activity when administered by parenteral routes.

101. The prodrug composition of any one of claims 1-87, wherein the prodrug has a reduced plasma or blood concentration of released methylphenidate when administered intranasally or intravenously as compared to free unconjugated methylphenidate when administered in equimolar amounts.

102. The prodrug composition of any one of claims 1-87, wherein the composition is in the form comprising a tablet, a capsule, a caplet, a troche, a lozenge, an oral powder, a solution, a thin strip, an oral thin film (OTF), an oral strip, a rectal film, a transdermal patch, a syrup, a suspension, an inhalation compound or a suppository.

103. A pharmaceutical kit comprising a specified amount of individual doses in a package containing a pharmaceutically effective amount of at least one conjugate of methylphenidate of any one of claims 1-87, a salt thereof, or a combination thereof.

104. The pharmaceutical kid of claim 103, wherein the kit further comprises instructions for use of the kit in a method of treating or preventing attention deficit hyperactivity disorder symptoms in a human or animal patient.

105. The pharmaceutical kit of claim 103, wherein the kit further comprises instructions for use of the kit in a method of treating or preventing attention deficit disorder symptoms in a human or animal patient.

106. The pharmaceutical kit of claim 103, wherein the kit further comprises instructions for use of the kit in a method for treating or preventing drug withdrawal symptoms in a human or animal patient.

107. The pharmaceutical kit of any one of claims 103-106, wherein the patient is a pediatric patient.

108. The pharmaceutical kit of any one of claims 103-106, wherein the patient is an elderly patient.

109. The pharmaceutical kit of any one of claims 103-106, wherein the patient is a normative patient.

110. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 0.5 mg or higher of at least one methylphenidate conjugate.

111. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 2.5 mg or higher of at least one methylphenidate conjugate.

112. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 5.0 mg or higher of at least one methylphenidate conjugate.

113. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 10 mg or higher of at least one methylphenidate conjugate.

114. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 20 mg or higher of at least one methylphenidate conjugate.

115. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 50 mg or higher of at least one methylphenidate conjugate.

116. The pharmaceutical kit of any one of claims 103-106, wherein the individual dosages comprise at least about 100 mg or higher of at least one methylphenidate conjugate.

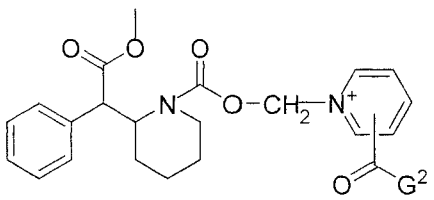
117. The pharmaceutical kit of any one of claims 103-106, wherein the kit comprises from about 1 to about 60 individual doses.

118. The pharmaceutical kit of any one of claims 103-106, wherein the kit comprises from about 10 to about 30 individual doses.

119. A method for chemically synthesizing any of the conjugates of claims 1 – 87 comprising the step of conjugating methylphenidate to at least one ligand.

CLAIMS

1. A prodrug composition comprising at least one conjugate of methylphenidate wherein the conjugate is of the following structure:



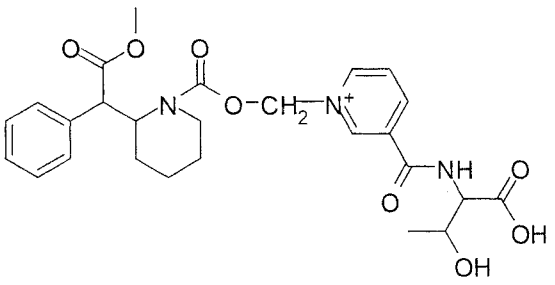
wherein G^2 is selected from the group consisting of standard amino acids, nonstandard amino acids and synthetic amino acids; and

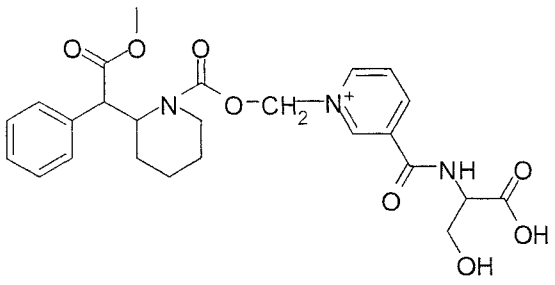
wherein the amino acid is attached to the rest of the molecule by an amide linkage.

2. The prodrug composition of claim 1, wherein the amino acid is threonine.

3. The prodrug composition of claim 1, wherein the amino acid is serine.

4. The prodrug composition of claim 1, wherein the prodrug of methylphenidate has one of the following structures:





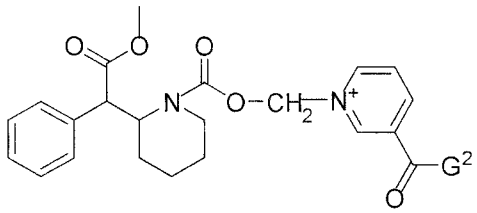
5. The prodrug composition of claim 1, wherein the conjugate is a pharmaceutically acceptable anionic, amphoteric, zwitterionic or cationic salt form or salt mixtures thereof.

6. The prodrug composition of claim 5, wherein the anionic salt form is selected from the group consisting of 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, methylsufate, 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 (mucate), galacturonate, gallate, gentisate, glutamate, glutamate, glutarate, glycerophosphate, heptanoate (enanthate), hydroxybenzoate, hippurate, phenylpropionate, iodide, xinafoate, lactobionate, laurate, maleate, mandelate, methanesufonate, 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, and undecylenate.

7. The prodrug composition of claim 5, wherein the anionic salt form is selected from the group consisting of sodium, potassium, calcium, magnesium, zinc, aluminium, lithium, cholinate, lysinium, ammonium and tromethamine.

8. The prodrug composition of claim 1, wherein the composition is in the form comprising a tablet, a capsule, a caplet, a troche, a lozenge, an oral powder, a solution, a thin strip, an oral thin film (OTF), an oral strip, a rectal film, a transdermal patch, a syrup, a suspension, an inhalation compound or a suppository.

9. The prodrug composition of claim 1, wherein the conjugate is of the following structure:



wherein G^2 is selected from the group consisting of standard amino acids, nonstandard amino acids and synthetic amino acids; and

wherein the amino acid is attached to the rest of the molecule by an amide linkage.