bioavailable and water soluble forms of methylphenidate that maintain the pharmacological benefit when administered, in particular via the oral route.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0012] The present technology utilizes, for example, covalent conjugation of methylphenidate, various forms and derivatives thereof with certain alcohol, amine, oxoacid, thiol, or derivatives thereof to provide, for example, improved bioavailability and increased water solubility when compared to unconjugated methylphenidate. The increased bioavailability and/or increased water solubility in some instances provides the ability of the prodrug or composition to be administered in forms that are not easily utilized with the unconjugated methylphenidate. For example, 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

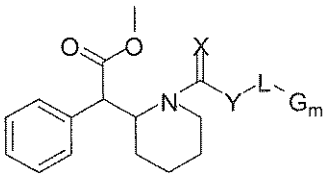
[0013] T~~In one aspect, t~~he present technology provides a prodrug composition comprising at least one conjugate, the conjugate comprising at least one methylphenidate, and at least one alcohol, amine, oxoacid, thiol, or derivatives thereof. In some aspects, the prodrug composition further comprises a linker, wherein the linker chemically bonds the at least one methylphenidate with the at least one alcohol, amine, oxoacid, thiol, or derivatives thereof. In some ~~aspects~~embodiments, the linker comprises at least one (acyloxy)alkyloxy moiety, derivatives thereof, or combinations thereof.

[0014] In further ~~aspects~~embodiments, the present technology provides one or more conjugates of methylphenidate comprising methylphenidate, a derivative thereof, or combinations thereof and at least one alcohol, amine, oxoacid, thiol, or derivatives thereof, wherein the at least one oxoacid is a carboxylic acid.

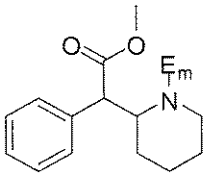
[0015] In another ~~aspect~~embodiment, the present technology provides at least one prodrug composition comprising at least one conjugate of methylphenidate, derivatives thereof or combinations thereof and at least one inorganic oxoacid, or derivatives thereof with a free –OH group, an organic derivative thereof, an inorganic derivative thereof, or a combination thereof.

[0016] In a further ~~aspect~~embodiment, the present technology provides at least one prodrug composition comprising at least one conjugate of methylphenidate, derivatives thereof or combinations thereof and an alcohol, amine, oxoacid, thiol, or derivatives thereof and a linker, wherein the linker comprises an (acyloxy)alkyloxy group, a derivative thereof or combination thereof with the general formula -C(O)O-X-O- , wherein, X is selected from a representative group including optionally substituted alkyl, optionally substituted aryl, optionally substituted alkylaryl, optionally substituted heteroalkyl, optionally substituted heteroaryl, optionally substituted heterocycle, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted cycloalkynyl, or optionally substituted alkoxy.

[0017] In another ~~aspect~~embodiment, the present technology provides a prodrug composition comprising at least one conjugate of methylphenidate having a structure of formula (I) or formula (II):



(I)



(II)

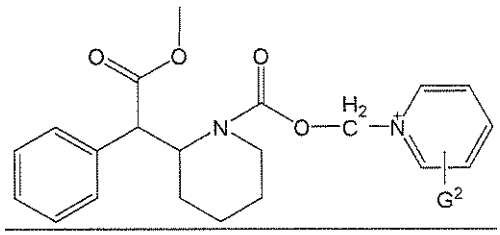
wherein X is selected from the group consisting of O, S, Se and NR^1; wherein Y is absent or selected from the group consisting of O, S, Se, NR^2 and CR^3R^4; wherein R^1 and R^2 are selected independently from the group consisting of hydrogen, alkenyl, alkenylaminocarbonyl, alkoxy, alkoxycarbonyl, alkyl, 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,

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.

[0018] In another ~~aspect~~embodiment, the present technology provides at least one prodrug composition comprising at least one conjugate, wherein the at least one conjugate can be, for example, 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-CO_2CH_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, or phosphate-(*p*-salicylate)-CH_2OCO-methylphenidate.

[0019] Moreover, the present technology provides at least one prodrug composition comprising at least one oxyalkyl carbamate.

[0019a] In an aspect, there is provided 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.

[0020] In yet another ~~aspect~~embodiment, the present technology provides a method for chemically synthesizing any of the methylphenidate conjugates of the present technology by perforing the appropriate steps to conjugate methylphenidate to at least one ligand.

[0021] In further ~~aspects~~embodiments, prodrug compositions of the present technology are believed to unexpectedly exhibit a rate of release equivalent to free or unmodified

methylphenidate. In other ~~aspects~~embodiments, the one or more prodrug composition of the present technology are believed to surprisingly exhibit a slower rate of release over time as compared to unmodified methylphenidate.

[0022] In yet other ~~aspects~~embodiments, conjugates or prodrugs of the present technology are believed to unexpectedly exhibit an increased absorption when administered orally as compared to unmodified methylphenidate. Additionally, conjugates or prodrugs of the present technology are believed to surprisingly have increased bioavailability as compared to unmodified methylphenidate.

[0023] In yet a further ~~aspect~~embodiment, the conjugates or prodrugs of the present technology are believed to surprisingly exhibit less interpatient variability in the oral pharmacokinetic (PK) profile when compared to unconjugated methylphenidate.

[0024] In yet another ~~aspect~~embodiment, the conjugates or prodrugs of the present technology are provided in an amount sufficient to provide an increased AUC when compared to unconjugated methylphenidate when administered orally at equimolar doses. In still other ~~aspects~~embodiments, the conjugates or prodrugs are provided in an amount sufficient to provide an unexpected increased C_{max} as compared to unconjugated methylphenidate when administered orally at equimolar doses.

[0025] In yet further ~~aspects~~embodiments, the conjugates or prodrugs of the present technology are provided in an amount sufficient to provide a surprisingly increased C_{max} and an increased AUC as compared to unconjugated methylphenidate when administered orally at equimolar doses.

[0026] In yet an alternative ~~aspect~~embodiment, the conjugates or prodrugs of the present technology provide reduced side effects as compared to unconjugated methylphenidate when administered at equimolar doses, and are also contemplated in some alternative ~~aspects~~embodiments to provide reduced abuse potential as compared to unconjugated methylphenidate.

[0027] In addition, the conjugates or prodrugs of the present technology are also believed to unexpectedly provide an amount sufficient to provide an extended T_{max} when compared to unconjugated methylphenidate when administered at equimolar

doses, and/or provide an equivalent T_{max} when compared to unconjugated methylphenidate when administered at equimolar doses.

[0028] Moreover, the present technology provides at least one method of treating one or more patients (human or animal) having at least one disease, disorder or condition mediated by controlling, preventing, limiting, or inhibiting neurotransmitter uptake/re-uptake or hormone uptake/re-uptake comprising orally administering to one or more patients a pharmaceutically effective amount of at least one of the prodrug compositions of the present technology.

[0029] In still yet a further ~~aspect~~embodiment, the present technology provides at least one method of treating a patient (human or animal) having at least one disorder or condition requiring stimulation of the central nervous system of the patient, comprising orally administering a pharmaceutically effective amount of one or more prodrug compositions of the present technology.

[0030] In yet another ~~aspect~~embodiment, the present technology provides one or more methods of administering at least one [methylphenidate] composition or prodrug of the present technology wherein the administration decreases the number and/or amount of metabolites produced when compared with unconjugated methylphenidate. In other ~~aspects~~embodiments, the one or more methods of administering the one or more [methylphenidate] compositions or prodrugs of the present technology is believed to decrease the exposure of the patient to ritalinic acid when compared with unconjugated methylphenidate.

[0031] In yet a further embodiment, the one or more compositions or prodrugs of the present technology are believed to provide an increased water solubility of the methylphenidate-based conjugate or prodrug compared to unconjugated methylphenidate. In another embodiment, the increased water solubility is believed to allow for the prodrug to be formed into certain dosage forms at higher concentrations, dosage strengths, or higher dose loading capacities than unconjugated methylphenidate. In some embodiments, such dosage forms include, for example, oral thin films or strips with.

[0037] In another ~~aspect~~embodiment, the present technology provides 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] Figure 1. Chemical structures of some hydroxybenzoates for use in the making of the conjugates of the present technology.

[0039] Figure 2. Chemical structures of some heteroaryl carboxylic acids for use in the making of the conjugates of the present technology.

[0040] Figure 3. Chemical structures of some phenylacetates for use in the making of the conjugates of the present technology.

[0041] Figure 4. Chemical structures of some benzylacetates for use in the making of the conjugates of the present technology.

[0042] Figure 5. Chemical structures of some cinnamates for use in the making of the conjugates of the present technology.

[0043] Figure 6. Chemical structures of some dicarboxylic acids for use in the making of the conjugates of the present technology.

[0044] Figure 7. Chemical structures of some tricarboxylic acids for use in the making of the conjugates of the present technology.

[0045] Figure 8. Chemical structures of some inorganic oxoacids for use in the making of the conjugates of the present technology.

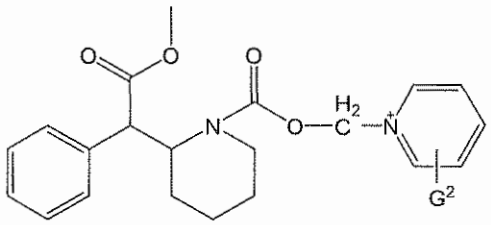
[0046] Figure 9. Chemical structures of some inorganic oxoacid derivatives for use in the making of the conjugates of the present technology.

[0047] Figure 10. Chemical structures of some standard amino acids for use in the making of the conjugates of the present technology.

[0048] Figure 11. Chemical structures of some non-standard amino acids for use in the making of the conjugates of the present technology.

CLAIMS

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



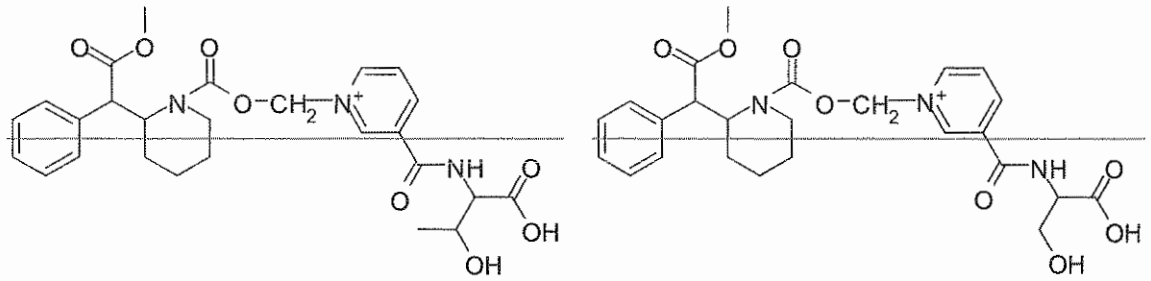
wherein G^2 is selected from the group consisting of standard amino acids, nonstandard amino acids and synthetic amino acids~~; and~~

~~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:~~



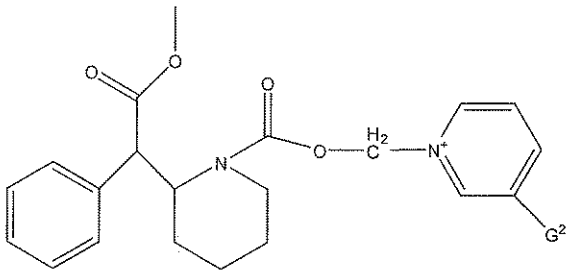
~~5.~~4. The prodrug composition of claim 1, wherein the conjugate is a pharmaceutically acceptable anionic, amphoteric, zwitterionic or cationic salt form or salt mixtures thereof.

~~6.~~5. The prodrug composition of claim ~~5~~4, 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, 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.~~6. The prodrug composition of claim ~~5~~4, wherein the cationic salt form is selected from the group consisting of sodium, potassium, calcium, magnesium, zinc, aluminium, lithium, cholinate, lysinium, ammonium and tromethamine.

~~8.~~7. 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.

98. 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~~.