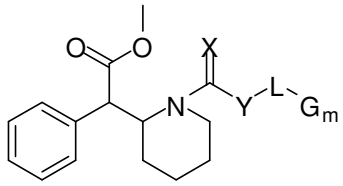
bioavailable and water soluble forms of methylphenidate that maintain the pharmacological benefit when administered, in particular via the oral route.

BRIEF SUMMARY

[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

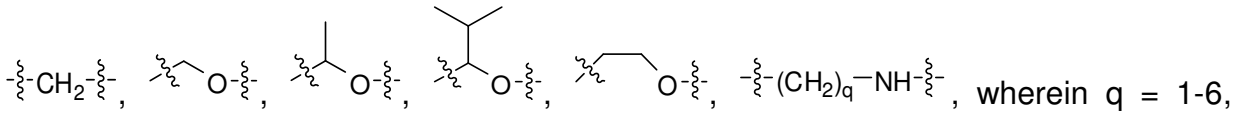
[0012a] In an aspect, there is provided a compound having a structure represented by formula (I)



or pharmaceutically acceptable salt of said compound, wherein X is O;

Y is selected from the group consisting of O and N;

L is selected from the group consisting of:

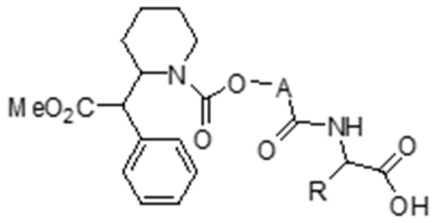


;

wherein m is 0-5;

wherein G is a carboxypyridine derivative bound via an ester or amide bond to a second moiety (G^2), wherein G is covalently bound to L via its tertiary nitrogen and wherein G^2 is an amino acid.

[0012b] In another aspect, there is provided a compound comprising at least one conjugate of methylphenidate wherein the conjugate is of the following structure:



wherein A is selected from the group consisting of $–CH_2$-, $–CH_2(CH_3)$-, and –CH(Ph)-, and R is a side chain of an amino acid.

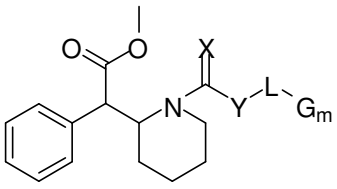
[0013] The present technology provides a prodrug composition comprising at least one conjugate, the conjugate comprising at least one methylphenidate, and at least one alcohol, amine, oxoacid, thiol, or derivatives thereof. In some examples, the prodrug composition further comprises a linker, wherein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

[0014] In further examples, 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.

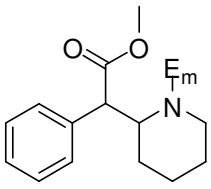
[0015] In another example, the present technology provides at least one prodrug composition comprising at least one conjugate of methylphenidate, derivatives thereof or combinations thereof and at least one inorganic oxoacid, or derivatives thereof with a free –OH group, an organic derivative thereof,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

[0016] In a further example, 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 example, the present technology provides a prodrug 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 example, 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**.**

[0020] In yet another example, 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 example, prodrug compositions of the present technology are believed to unexpectedly exhibit a rate of release equivalent to free or unmodified

methylphenidate. In other examples, 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 examples, 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 example, 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 example, 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 examples, 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 examples, 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 example, 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 examples 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 example, 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 example, 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 examples, 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 example, 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 example, 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 examples, such dosage forms include, for example, oral thin films or strips with.

[0032] In still yet a further example, the administration of one or more methylphenidate-based compositions or prodrugs are believed to provide a reduced interpatient variability of methylphenidate plasma concentrations, and are believed to have an improved safety profile when compared to unconjugated methylphenidate.

[0033] In yet another alternative example, the present technology provides at least one method of treating attention-deficit hyperactivity disorder comprising administering a pharmaceutically effective amount of one or more conjugates or prodrug compositions of the present technology.

[0034] In another further example, the present technology provides at least one prodrug composition for treating at least one patient having a disorder or condition requiring stimulation of the central nervous system of the patient, wherein the at least one prodrug or composition has a reduced abuse potential when administered compared to unconjugated methylphenidate.

[0035] In a further example, the one or more methylphenidate-based prodrug or conjugate compositions of the present technology are contemplated to exhibit reduced or prevented pharmacological activity when administered by parenteral routes, or reduced plasma or blood concentration of released methylphenidate when administered intranasally, intravenously, intramuscularly, subcutaneously or rectally as compared to free unconjugated methylphenidate when administered at equimolar amounts.

[0036] In yet another example, the present technology provides at least one methylphenidate-based conjugate prodrug composition having an extended or controlled release profile as measured by plasma concentrations of released methylphenidate when compared to unconjugated methylphenidate when administered orally at equimolar doses. In some examples, the plasma concentration of methylphenidate released from the prodrug would increase more slowly and over a longer period of time after oral administration, resulting in a delay in peak plasma concentration of released methylphenidate and in a longer duration of action when compared to unconjugated methylphenidate.

[0037] In another example, 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.

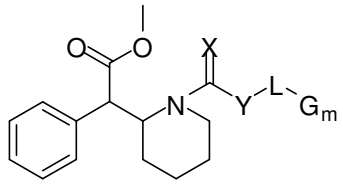
[0046] Figure 9. Chemical structures of some inorganic oxoacid derivatives for use in the making of the conjugates of the present technology.

[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

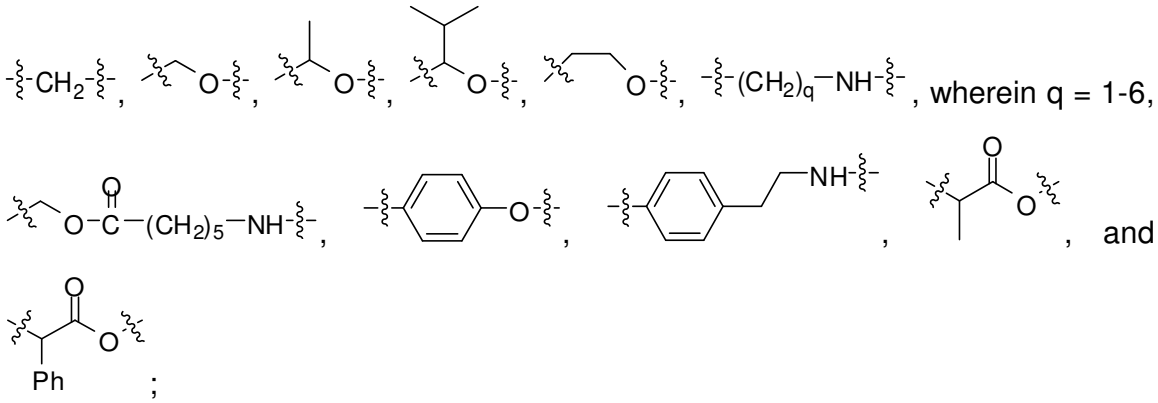
1. A compound having a structure represented by formula (I)



or pharmaceutically acceptable salt of said compound, wherein X is O;

Y is selected from the group consisting of O and N;

L is selected from the group consisting of:



wherein m is 0-5;

wherein G is a carboxypyridine derivative bound via an ester or amide bond to a second moiety (G^2), wherein G is covalently bound to L via its tertiary nitrogen and wherein G^2 is an amino acid.

2. The compound of claim 1, wherein the pharmaceutically acceptable salt is selected from the group consisting of anionic salt, amphoteric salt, zwitterionic salt, and salt mixtures thereof.

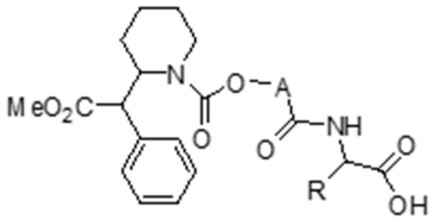
3. The compound of claim 2, wherein the anionic salt is selected from the group consisting of acetate, *l*-aspartate, besylate, bicarbonate, carbonate, *d*-camsylate, *l*-

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, 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, 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, undecylenate, and mixtures thereof.

4. The compound of claim 3, wherein the anionic salt is hydrochloride/chloride.

5. The compound of any one of claims 1-4, wherein the 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.

6. A compound comprising at least one conjugate of methylphenidate wherein the conjugate is of the following structure:



wherein A is selected from the group consisting of $–CH_2-$, $–CH(CH_3)-$, and –CH(Ph)-, and R is a side chain of an amino acid.

7. The compound of claim 6, wherein the 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.