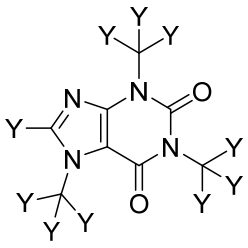
($t_{1/2}$), and rapid clearance, mainly by hepatic cytochrome P450 (CYP450) demethylation to afford paraxanthine, theobromine, and theophylline. In other words, ingestion of caffeine results in a large "spike" in caffeine plasma concentration (*i.e.*, large C_{max}) shortly after caffeine ingestion (*i.e.*, short T_{max}) followed by a "crash" in caffeine plasma concentration due to rapid metabolism and clearance. It is believed that the magnitude of this "spike" and the rapidity of this "crash" are at least partially responsible for the aforementioned adverse effects. Therefore, one approach to mitigate these adverse effects is to develop compounds and compositions that harness the positive attributes of caffeine without the negative effects, that is, with pharmacokinetic profiles exhibiting lower C_{max} values, longer half-life, and/or longer T_{max} values than caffeine.

SUMMARY ~~OF THE INVENTION~~

[0004] The present ~~invention~~ disclosure relates to compositions (*e.g.*, pharmaceutical compositions, nutraceutical compositions, foods, beverages, cosmetic compositions, diet supplements) comprising deuterated caffeine. In certain ~~embodiment~~examples, the composition is suitable for oral administration. In certain ~~embodiment~~examples, the composition is suitable for intravenous (IV) administration. In certain ~~embodiment~~examples, the composition is suitable for topical administration. In certain ~~embodiment~~examples, the composition is suitable for delivery to the lungs. In certain ~~embodiment~~examples, the composition is administered using an electronic cigarette or other vaping device, a nebulizer, a pressurized metered dose inhaler (pMDI), or a dry powder inhaler (DPI). In certain ~~embodiment~~examples, the composition is a solid dose composition (*e.g.*, tablet, capsule, granule, powder, sachet, or chewable), solution, gel, suspension, emulsion, shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste. Also provided herein are kits containing the compositions and instructions for use. Further provided herein are use of the compositions described herein for treating a disease, preventing a disease, treating a condition, and/or preventing a condition.

[0004a] In one aspect of the present disclosure, there is provided a beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):



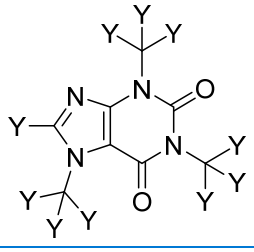
(**I**),

or a pharmaceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

[0004b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition or nutraceutical composition disclosed herein; or a compound of Formula (**I**):



(**I**),

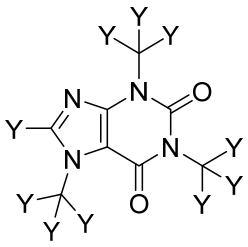
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

in the manufacture of a medicament for increasing energy levels, treating obesity, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, increasing sodium excretion, reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating aneurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

[0004c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition or nutraceutical composition disclosed herein; or a compound of Formula (**I**):



(**I**),

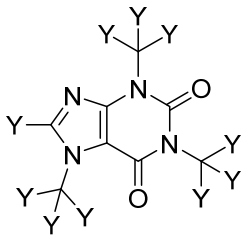
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

for use in therapy.

[0005] The compositions described herein comprise deuterated caffeine (*i.e.*, wherein at least one of the hydrogen atoms of caffeine is replaced with deuterium). In certain ~~embodiment~~examples, the composition comprises a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt, hydrate, or solvate thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

[0006] Compounds of Formula (**I**) may comprise stable isotopes of carbon, nitrogen, and oxygen in amounts greater than their natural abundance. For example, one or more carbon atoms may be enriched with ^{13}C in an amount greater than about 1.1% (e.g., 1.2-1.5%, 1.5-2%, 2-10%, or more than 10%). One or more nitrogen atoms may be enriched with ^{15}N in an amount greater than about 0.4% (e.g., 0.5-1%, 1-2%, 2-10%, or greater than 10%). Likewise, one or more oxygen atoms may be enriched with ^{16}O in an amount greater than about 0.24% (e.g., 0.25-0.5%, 0.5-1%, 1-2%, 2-10%, or greater than 10%).

[0007] In certain ~~embodiment~~examples, the composition comprises about 1 mg to about 10,000 mg of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, or solvate thereof. In certain ~~embodiment~~examples, the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, or prodrug thereof, relative to the total amount of caffeine present in the composition ranges from about 5% to about 99%. In certain ~~embodiment~~examples, the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, or prodrug thereof, relative to the total amount of caffeine present in the composition ranges from about 5% to about 100%. In another ~~aspect~~example, the composition is an oral composition. In another ~~aspect~~example, the composition is a solid dose composition (*e.g.*, tablet, capsule, granule, powder, sachet, or chewable). In another ~~aspect~~example, the composition is suitable for intravenous (IV) administration. In another ~~aspect~~example, the composition is a topical composition. In another ~~aspect~~example, the composition is a shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste. In another ~~aspect~~example, the composition is suitable for inhalation. In another ~~aspect~~example, the composition is administered using an electronic cigarette or other vaping device, a nebulizer, a pressurized metered dose inhaler (pMDI), or a dry powder inhaler (DPI). In another ~~aspect~~example, the composition is suitable for buccal admistration.

[0008] The disclosure further provides a food product comprising deuterated caffeine (*e.g.*, a compound of Formula (**I**)).

[0009] The disclosure further provides a beverage (*e.g.*, energy drink, vitamin water) comprising deuterated caffeine (*e.g.*, a compound of Formula (**I**)).

[00010] The disclosure further provides kits comprising one or more compositions described herein and instructions for using the composition(s).

[00011] The disclosure further provides methods of delivering the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, composition, or prodrug thereof, to a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate solvate, composition, or prodrug thereof.

[00012] The disclosure further provides methods of treating a disease in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain ~~embodiment~~examples, the method comprises administering a compound of Formula (**I**), wherein each Y is deuterium.

[00013] The disclosure further provides methods of preventing a disease in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain ~~embodiment~~examples, the method comprises administering a compound of Formula (**I**), wherein each Y is deuterium

[00014] The disclosure further provides methods of treating a condition in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain ~~embodiment~~examples, the method comprises administering a compound of Formula (**I**) wherein each Y is deuterium

[00015] The disclosure further provides methods of preventing a condition in a subject in need thereof comprising administering to the subject in need thereof the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof. In certain ~~embodiment~~examples, the method comprises administering a compound of Formula (**I**) wherein each Y is deuterium

[00016] In certain ~~embodiment~~examples, the subject is a human. In certain ~~embodiment~~examples, the subject is an animal.

[00017] In another ~~aspect~~example, the side effects experienced after administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, are reduced relative to the administration of caffeine at an equivalent dose. In another ~~aspect~~example, the side effect is anxiety, insomnia, gastrointestinal issues (*e.g.*, loose stools, diarrhea, stomach ulcers, gastroesophageal reflux, etc.), rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.

[00018] In another ~~aspect~~example, the administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, results in an increased duration of action, reduction in frequency of administration, increase in patient compliance and/or ease of use relative to the administration of caffeine at an equivalent dose.

[00019] In another ~~aspect~~example, the administration of a compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt, hydrate, solvate, composition, or prodrug thereof, results in a similar relative magnitude of exposure in plasma and the central nervous system as compared to the administration of non-isotopically enriched caffeine at an equivalent dose.

[00020] The details of one or more ~~embodiment~~examples of the present disclosure are set forth herein. Other features, objects, and advantages of the present disclosure will be apparent from the Detailed Description, Examples, and Claims.

BRIEF DESCRIPTION OF THE DRAWINGS

[00021] The present invention is further described below with reference to the following non-limiting examples and with reference to the following figures, in which:

[00022] *Figure 1*. depicts the mean (+SD) concentrations of caffeine and D9-caffeine (Compound **14**) in plasma and brain over 14 hours following an oral (gavage) dose of caffeine or D9-caffeine (Compound **14**) to fasted male Sprague Dawley rats at a dose of 2 mg/kg.

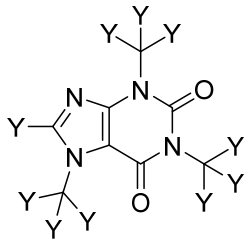
[00023] *Figure 2*. depicts the class and subclass analysis of Compound 14. Reported doses are in mg/kg.

[00024] *Figure 3.* depicts the class and subclass legend.

CLAIMS

What is claimed is:

1. A beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition comprising a compound of Formula (**I**):



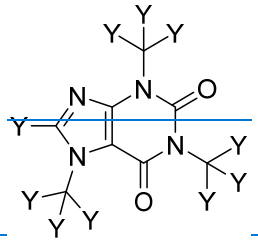
(**I**),

or a pharmaceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

2. A beverage according to claim 1 ~~nutraceutical composition comprising a compound of Formula (I):~~



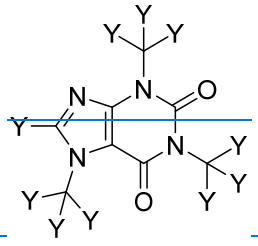
~~(I),~~

~~or a nutraceutically acceptable salt thereof;~~

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium~~.

3. A food product according to claim 1~~cosmetic composition comprising a compound of Formula (I):~~



~~(I),~~

~~or an acceptable salt thereof;~~

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium~~.

~~4. The composition of claim 1 or 2, wherein the composition is suitable for oral administration.~~

~~5. The composition of claim 1, wherein the composition is suitable for intravenous (IV) administration.~~

~~6. The composition of claim 1 or 3, wherein the composition is suitable for topical administration.~~

~~7. The composition of claim 1, wherein the composition is suitable for delivery to the lungs.~~

~~8. The composition of claim 1 or 2, wherein the composition is a solid dose composition.~~

~~9. The composition of claim 1 or 2, wherein the composition is used for weight loss.~~

~~10. The composition of claim 1 or 2, wherein the composition is used for appetite suppression.~~

~~11. The composition of claim 1 or 2, wherein the composition is used as a dietary supplement.~~

~~12. The composition of claim 1 or 2, wherein the composition is used as a diuretic composition.~~

~~13. The composition of claim 1, wherein the composition is used as an analgesic composition.~~

~~14. The composition of any one of claims 1-13, wherein at least two instances of Y are deuterium.~~

~~154~~. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~1~~3, wherein at least three instances of Y are deuterium.

~~16. The composition of any one of claims 1-13, wherein at least four instances of Y are deuterium.~~

~~17. The composition of any one of claims 1-13, wherein at least five instances of Y are deuterium.~~

~~18. The composition of any one of claims 1-13, wherein at least six instances of Y are deuterium.~~

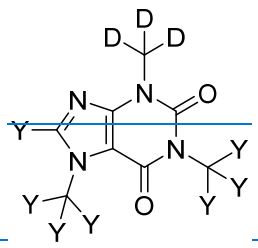
~~19. The composition of any one of claims 1-13, wherein at least seven instances of Y are deuterium.~~

~~20. The composition of any one of claims 1-12, wherein at least eight instances of Y are deuterium.~~

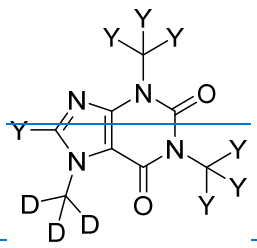
~~21. The composition of any one of claims 1-13, wherein nine instances of Y are deuterium.~~

~~22. The composition of any one of claims 1-13, wherein each Y is deuterium.~~

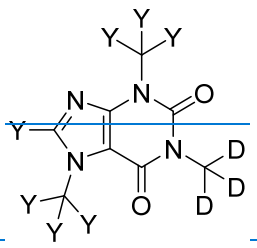
~~23. The composition of any one of claims 1-22, according to Formula (I-A), (I-B), or (I-C):~~



~~(I-A);~~

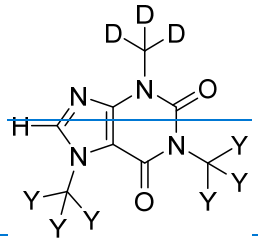
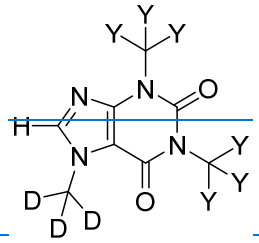
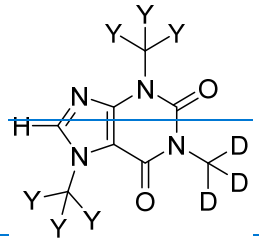


~~(I-B); or~~



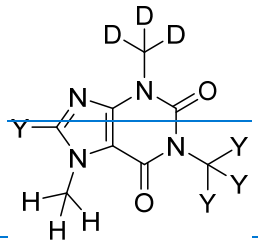
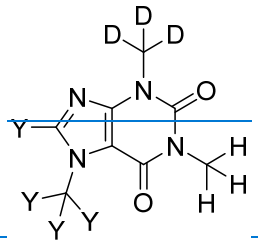
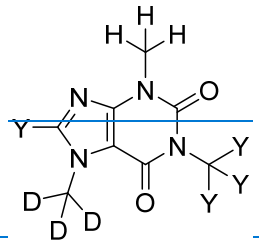
~~(I-C);~~ ~~or a pharmaceutically or nutraceutically acceptable salt thereof.~~

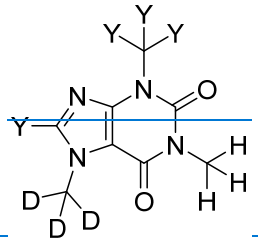
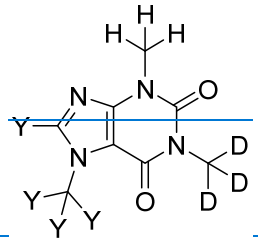
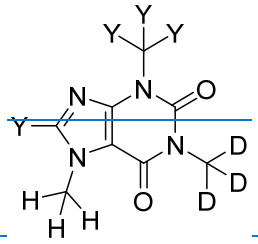
~~24. The composition of claim 23, according to Formula (I-D), (I-E), or (I-F):~~

 ~~(I-D);~~  ~~(I-E);~~  ~~(I-F);~~

~~or a pharmaceutically or nutraceutically acceptable salt thereof.~~

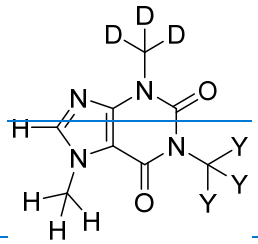
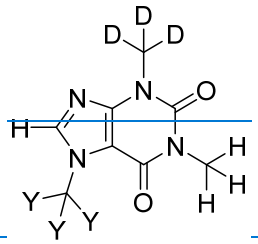
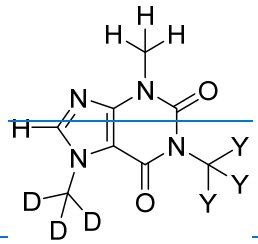
~~25. The composition of claim 23, according to Formula (I-G), (I-H), (I-I), (I-J), (I-K), or (I-L):~~

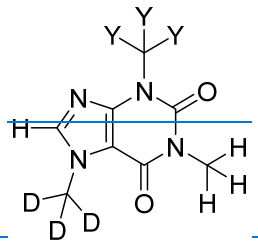
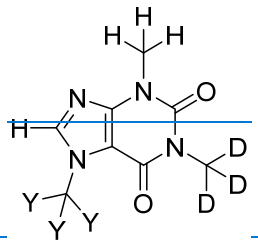
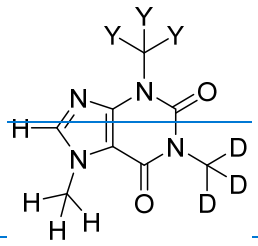
 ~~(I-G);~~  ~~(I-H);~~  ~~(I-I);~~

 ~~(I-J);~~  ~~(I-K);~~  ~~(I-L);~~

~~or a pharmaceutically or nutraceutically acceptable salt thereof.~~

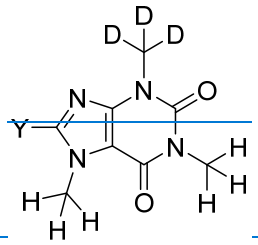
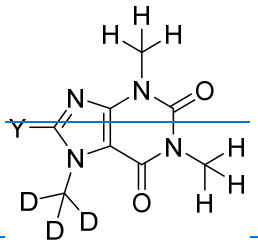
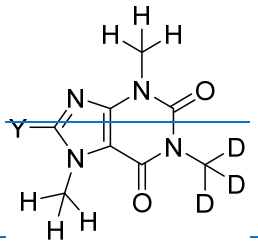
~~26. The composition of claim 23, according to Formula (I-M), (I-N), (I-O), (I-P), (I-Q), or (I-R):~~

 ~~(I-M);~~  ~~(I-N);~~  ~~(I-O);~~

 (I-P);  (I-Q);  (I-R);

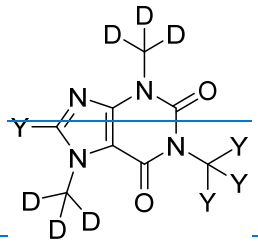
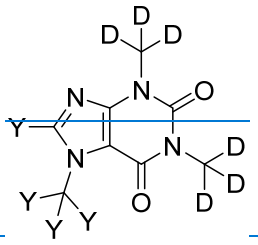
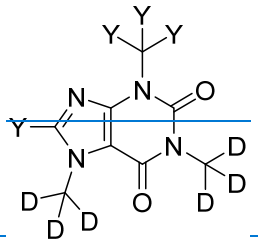
or a pharmaceutically or nutraceutically acceptable salt thereof.

27. The composition of claim 23, according to Formula (I-S), (I-T), or (I-U):

 (I-S);  (I-T);  (I-U);

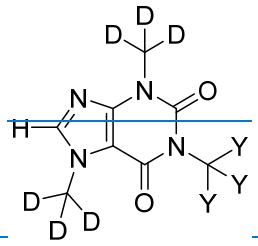
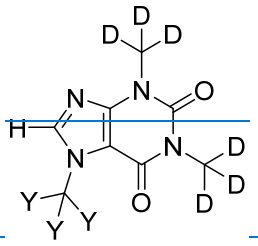
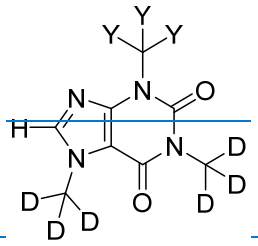
or a pharmaceutically or nutraceutically acceptable salt thereof.

28. The composition of any one of claims 1-22, according to Formula (II-A), (II-B), or (II-C):

 (II-A);  (II-B);  (II-C);

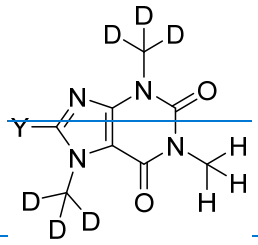
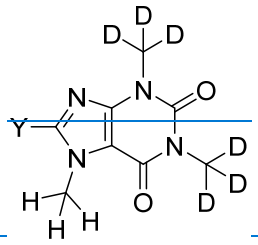
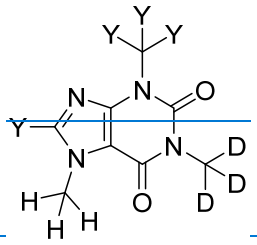
or a pharmaceutically or nutraceutically acceptable salt thereof.

29. The composition of claim 28, according to Formula (II-D), (II-E), or (II-F):

 (II-D);  (II-E);  (II-F);

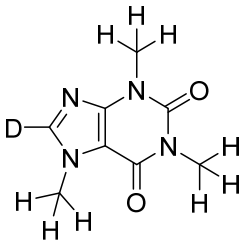
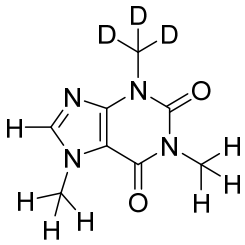
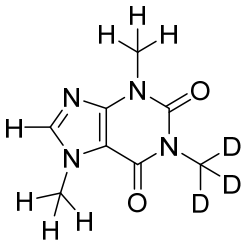
or a pharmaceutically or nutraceutically acceptable salt thereof.

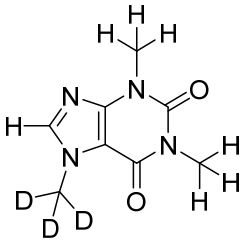
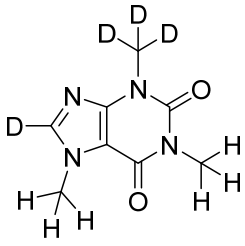
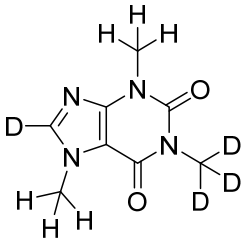
~~30. The composition of claim 28, according to Formula (II-G), (II-H), or (II-I):~~

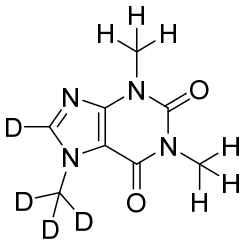
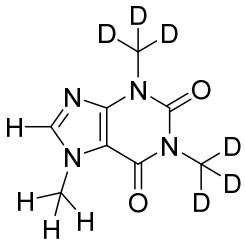
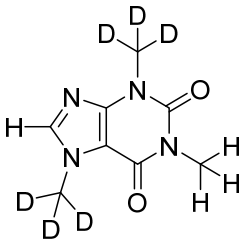

~~(II-G);~~

~~(II-H);~~

~~(II-I);~~

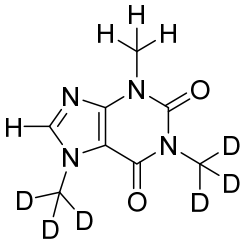
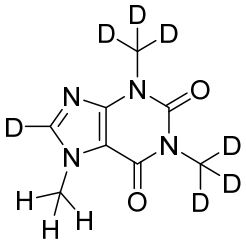
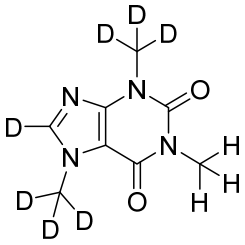
~~or a pharmaceutically or nutraceutically acceptable salt thereof.~~

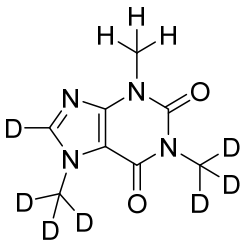
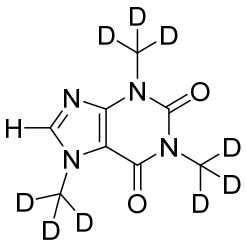
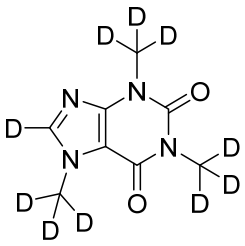
~~31~~5. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~43~~0, wherein the compound is selected from the group consisting of:


(**1**);

(**2**);

(**3**);


(**4**);

(**5**);

(**6**);

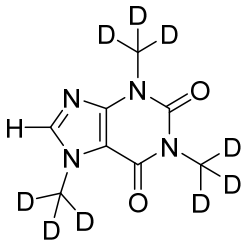

(**7**);

(**8**);

(**9**);


(**10**);

(**11**);

(**12**);

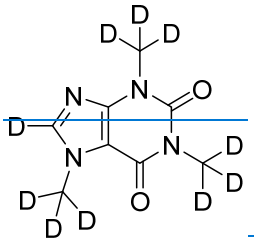
 (**13**);  (**14**);  (**15**);

or a pharmaceutically or nutraceutically acceptable salt thereof.

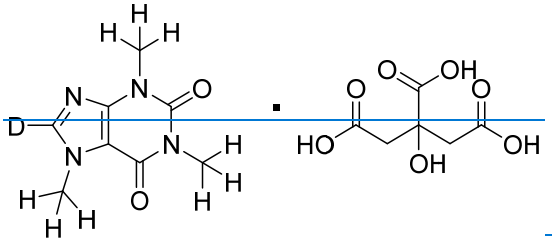
~~326~~. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~304~~, wherein the compound is

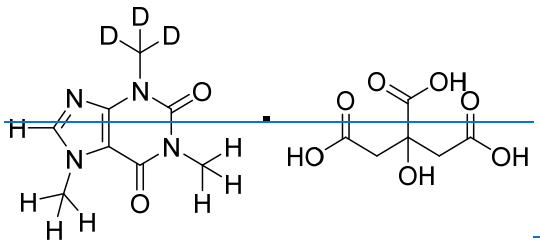
 (**14**), or a pharmaceutically or nutraceutically acceptable salt thereof.

~~33. The composition of any one of claims 1-30, wherein the compound is~~

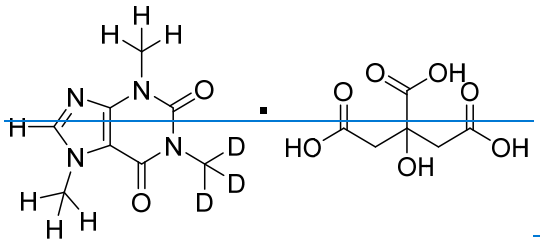
 ~~(**15**), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~34. The composition of any one of claims 1-30, wherein the compound is selected from the group consisting of:~~

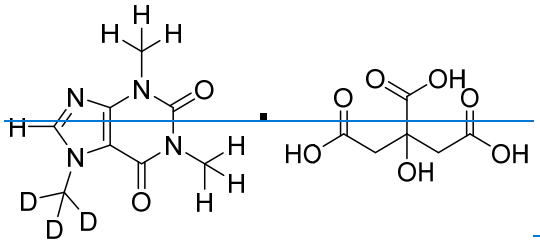
 ~~(**16**);~~



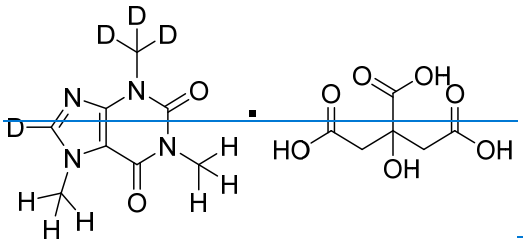
~~(17);~~



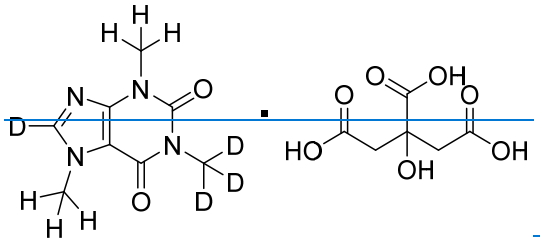
~~(18);~~



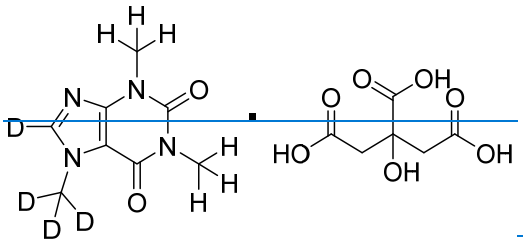
~~(19);~~



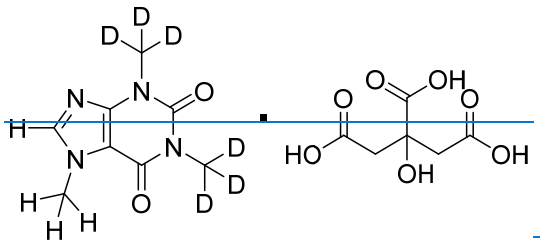
~~(20);~~



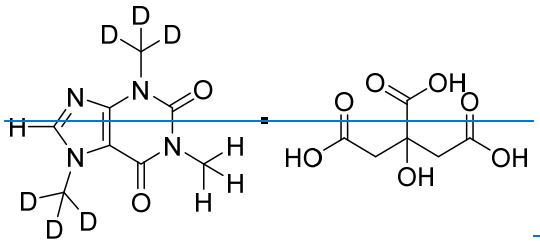
~~(21);~~



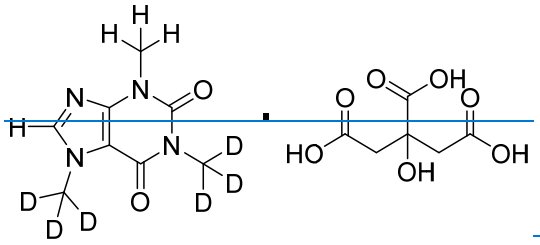
~~(22);~~



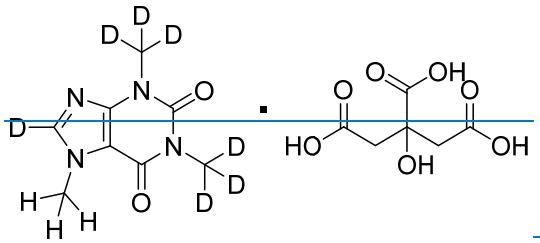
~~(23);~~



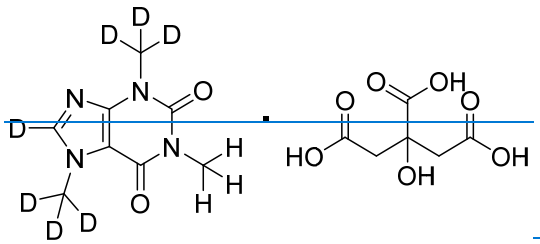
~~(24);~~



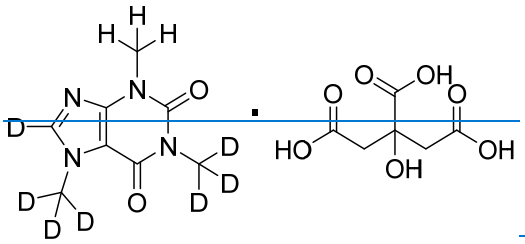
~~(25);~~



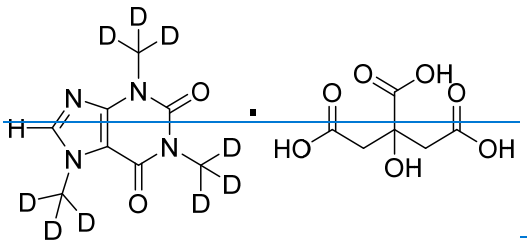
~~(26);~~



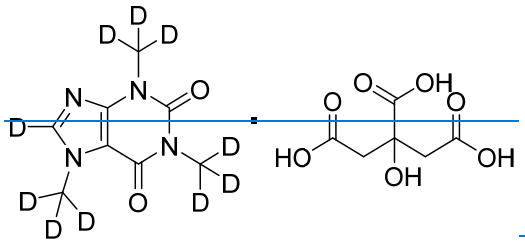
~~(27);~~



~~(28);~~

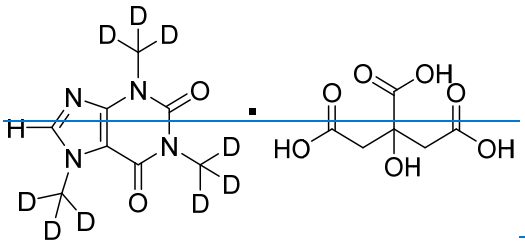


~~(29); and~~



~~(30).~~

~~35. The composition of any one of claims 1-30, wherein the compound is~~



~~(29).~~

~~36~~7. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~35~~6, further comprising a pharmaceutically or nutraceutically acceptable carrier.

~~37. The composition of claim 8, wherein the solid dose composition is a tablet, capsule, granule, powder, sachet, or chewable.~~

~~38. The composition of claim 6, wherein the topical composition is a shampoo, conditioner, cream, foam, gel, lotion, ointment, transdermal patch, tincture, or paste.~~

~~39. The composition of claim 7, wherein the composition is administered using a nebulizer, pressurized metered dose inhaler (pMDI), or dry powder inhaler (DPI).~~

~~40~~8. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~739~~ further comprising an additional agent.

~~41. The composition of claim 40, wherein the additional agent is ergotamine, an anti-inflammatory agent, a steroid, a barbiturate, an opioid analgesic, or a combination thereof.~~

~~42. The composition of claim 41, wherein the anti-inflammatory agent is a cyclooxygenase-3 (COX-3) inhibitor, a non-steroidal anti-inflammatory drug (NSAID), or a cyclooxygenase-2 (COX-2) inhibitor.~~

~~43. The composition of claim 41, wherein any of the hydrogen atoms in ergotamine, the anti-inflammatory agent, the steroid, the barbiturate, or the opioid analgesic is replaced with deuterium.~~

~~44. The composition of claim 43, wherein the percentage of deuterium in ergotamine, the anti-inflammatory agent, the steroid, the barbiturate, or the opioid analgesic is at least 5%.~~

~~45. The composition of claim 43, wherein the NSAID is ibuprofen, naproxen, sulindac, ketoprofen, tolmetin, etodolac, fenoprofen, diclofenac, flurbiprofen, piroxicam, ketorolac, indomethacin, nabumetone, oxaprozin, mefanamic acid, or diflunisal.~~

~~46. The composition of claim 43, wherein the opioid analgesic is codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, or oxycodone.~~

~~47. The composition of claim 43, wherein the barbiturate is secobarbital, mephobarbital, pentobarbital, butabarbital, phenobarbital, or amobarbital.~~

~~48. The composition of claim 43, wherein the COX-2 inhibitor is celecoxib, valdecoxib, rofecoxib, or etoricoxib.~~

~~49. The composition of claim 43, wherein the COX-3 inhibitor is acetaminophen, phenacetin, antipyrine, or dipyrone.~~

~~50~~9. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~8~~49, comprising ~~wherein the composition comprises~~ about 1 mg to about 200 mg of the compound of Formula (**I**), or a salt thereof.

~~51. The composition of claim 50, wherein the composition comprises about 1 mg to about 125 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~52. The composition of claim 50, wherein the composition comprises about 5 mg to about 75 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~53~~10. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-8 ~~or 5~~, comprising ~~wherein the composition comprises~~ about 1 mg/ml to about 25 mg/ml of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof.

~~54. The composition of claim 53, wherein the composition comprises about 2 mg/ml to about 15 mg/ml of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~55. The composition of claim 53, wherein the composition comprises about 5 mg/ml to about 15 mg/ml of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~56~~11. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-10~~55~~, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the amount of caffeine ~~present in the composition~~ ranges from about 10% to about 99%.

~~57. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 10% to about 25%.~~

~~58. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 25% to about 100%.~~

~~59. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 25% to about 75%.~~

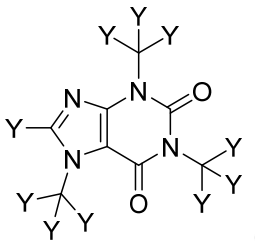
~~60. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 30% to about 70%.~~

~~61. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 25% to about 50%.~~

~~62. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 40% to about 60%.~~

~~63. The composition of claim 56, wherein the percentage of the amount of the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the composition ranges from about 50% to about 100%.~~

~~64~~12. Use of a pharmaceutical composition or nutraceutical composition of any one of claims 1-11~~A method for increasing energy levels of a subject, for reducing fatigue or drowsiness in a subject, or for increasing alertness in a subject, the method comprising administering to the subject a composition of any one of claims 1-63~~; or a compound of Formula (**I**):

 (**I**),

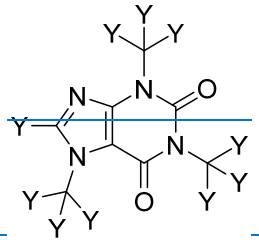
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

in the manufacture of a medicament for increasing energy levels, treating obesity, causing weight loss, increasing metabolic rate, reducing appetite, increasing energy expenditure, increasing urine output, increasing sodium excretion, reducing edema, treating a pain disorder, treating apnea, treating hypotension, treating an encephalopathy, treating aneurological or psychiatric disorder, or treating an inflammatory disorder in a subject.

~~65. A method for treating obesity in a subject, for causing weight loss in a subject, for increasing metabolic rate in a subject, for reducing appetite in a subject, or for increasing energy expenditure in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):~~

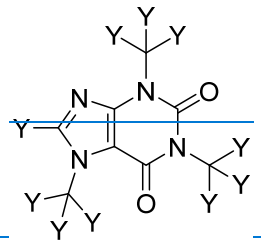
 ~~(I),~~

~~or a pharmaceutically or nutraceutically acceptable salt thereof;~~

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium.~~

~~66. A method for increasing urine output in a subject, for increasing sodium excretion in a subject, or for reducing edema in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):~~



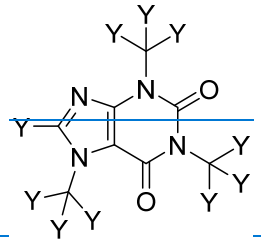
(I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

67. A method for treating a pain disorder in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):



(I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

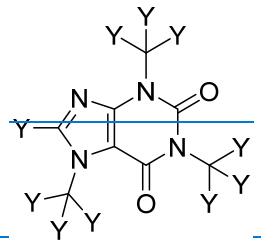
wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

68. The method of claim 67, wherein the pain disorder is migraine, arthritis, headache, back pain, bursitis, chronic pain, acute pain, musculoskeletal pain, osteoarthritis, psoriatic arthritis, rheumatoid arthritis, or sciatica.

69. The method of claim 67 or 68, wherein the pain disorder is migraine or headache.

70. A method for treating apnea in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):

 (I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

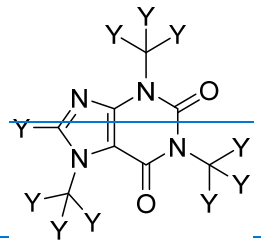
71. The method of claim 70, wherein the apnea is sleep apnea.

72. The method of claim 71, wherein the sleep apnea is obstructive sleep apnea, central sleep apnea, apnea of prematurity, or complex sleep apnea syndrome.

73. The method of any one of claim 71-72, wherein the subject is a neonate, preterm infant, premature infant, or low birthweight infant.

74. The method of any one of claim 71-73, wherein the subject is an adult.

75. A method for treating hypotension in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):

 (I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

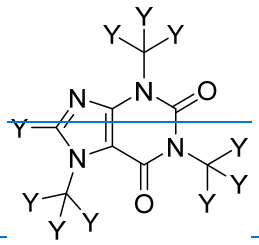
wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

76. The method of claim 75, wherein the hypotension is orthostatic hypotension, postprandial hypotension, or multiple system atrophy with orthostatic hypotension.

77. The method of claim 75, wherein the hypotension is postprandial hypotension.

78. A method for treating an encephalopathy in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):



(I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

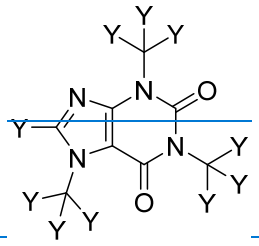
wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

79. The method of claim 78, wherein the encephalopathy is chronic traumatic encephalopathy, glycine encephalopathy, Hashimoto's encephalopathy, hepatic encephalopathy, hypertensive encephalopathy, hypoxic ischemic encephalopathy, toxic metabolic encephalopathy, infectious encephalopathy, uremic encephalopathy, or Wernicke encephalopathy.

80. The method of claim 78, wherein the encephalopathy is hypoxic ischemic encephalopathy.

81. A method for treating a neurological or psychiatric disorder in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (I):



(I),

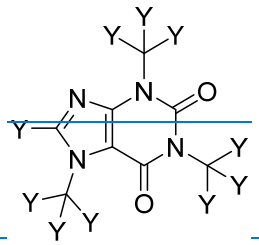
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

82. The method of claim 81, wherein the neurological or psychiatric disorder is narcolepsy, Alzheimer's disease, attention deficit hyperactivity disorder (ADHD), schizophrenia, Parkinson's disease, or depression.

83. A method for treating an inflammatory disorder in a subject, the method comprising administering to the subject a composition of any one of claims 1-63; or a compound of Formula (**I**):



(**I**),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

84. The method of claim 83, wherein the inflammatory disorder is a pulmonary inflammatory disorder.

85. The method of claim 84, wherein the inflammatory disorder is asthma, chronic obstructive pulmonary disorder (COPD), pulmonary fibrosis, or interstitial lung disease.

86. The method of any one of claims 64-85, such that the maximum plasma concentration (C_{max}) of the compound of Formula (**I**) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.

87. The method of any one of claims 64-85, such that the maximum plasma concentration (C_{max}) of the compound of Formula (**I**) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically

~~acceptable salt thereof, is lower than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~88. The method of any one of claims 64-85, such that the time of maximum plasma concentration (T_{max}) of the compound of Formula (**I**) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~89. The method of any one of claims 64-85, such that the time of maximum plasma concentration (T_{max}) of the compound of Formula (**I**) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~90. The method of any one of claims 64-85, such that the plasma half-life ($t_{1/2}$) of the compound of Formula (I) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~91. The method of any one of claims 64-85, such that the plasma half-life ($t_{1/2}$) of the compound of Formula (I) after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~92. The method of any one of claims 64-85, such that the maximum concentration (C_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration of the composition of any one of claims 1-63; or the compound of Formula (**I**), or a pharmaceutically or nutraceutically acceptable salt thereof, is at least 5%, 10%, 25%, or 50% lower than of non-isotopically enriched caffeine at an equivalent dose.~~

~~93. The method of any one of claims 64-85, such that the maximum concentration (C_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after~~

~~administration of the composition of any one of claims 1-63; or the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, is lower than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~94. The method of any one of claims 64-85, such that the time of maximum concentration (T_{max}) of the compound of Formula (I) in the central nervous system (CNS) of the subject after administration of the composition of any one of claims 1-63; or the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~95. The method of any one of claims 64-85, such that the time of maximum concentration (T_{max}) of the compound of Formula (I) in the central nervous system (CNS) of the subject after administration of the composition of any one of claims 1-63; or the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, is longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~96~~13. The ~~method~~ use of claim 12~~any one of claims 64-85~~, ~~such that~~ wherein side effects are reduced relative to the administration of caffeine at an equivalent dose.

~~97~~14. The ~~method~~ use of claim ~~96~~13, wherein the side effect is anxiety, insomnia, gastrointestinal issues, rhabdomyolysis, addiction, hypertension, rapid heart rate, atrial fibrillation, fatigue, irritability, nervousness, restlessness, nausea, or muscle tremors.

~~98. The composition of any one of claims 1-63, such that the maximum plasma concentration (C_{max}) of the compound of Formula (I) after administration of the composition is at least 5%, 10%, 25%, or 50% lower than of non-isotopically enriched caffeine at an equivalent dose.~~

~~99~~15. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~63~~11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein ~~such that~~ the maximum plasma concentration (C_{max}) of the

compound of Formula (I) after administration ~~of the composition~~ is lower than that of non-isotopically enriched caffeine at an equivalent dose.

~~100. The composition of any one of claims 1-63, such that the time of maximum plasma concentration (T_{max}) of the compound of Formula (**I**) after administration of the composition is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~101~~16. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11~~63~~, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein ~~such that~~ the time of maximum plasma concentration (T_{max}) of the compound of Formula (**I**) after administration ~~of the composition~~ is longer than that of non-isotopically enriched caffeine at an equivalent dose.

~~102. The composition of any one of claims 1-63, such that the plasma half-life ($t_{1/2}$) of the compound of Formula (**I**) after administration of the composition is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~103~~17. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims~~1~~ 1-11~~63~~, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein ~~such that~~ the plasma half-life ($t_{1/2}$) of the compound of Formula (**I**) after administration ~~of the composition~~ is longer than that of non-isotopically enriched caffeine at an equivalent dose.

~~104. The composition of any one of claims 1-63, such that the maximum concentration (C_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration of the composition is at least 5%, 10%, 25%, or 50% lower than of non-isotopically enriched caffeine at an equivalent dose.~~

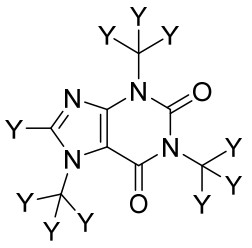
~~105~~18. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-11~~63~~, wherein the beverage, food product,

pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein ~~such that~~ the maximum concentration (C_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration ~~of the composition~~ is lower than that of non-isotopically enriched caffeine at an equivalent dose.

~~106. The composition of any one of claims 1-63, such that the time of maximum concentration (T_{max}) of the compound of Formula (I) in the central nervous system (CNS) of the subject after administration of the composition is at least 5%, 10%, 25%, 50%, 100%, 200%, 300%, or 400% longer than that of non-isotopically enriched caffeine at an equivalent dose.~~

~~107~~19. The beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition of any one of claims 1-~~63~~11, wherein the beverage, food product, pharmaceutical composition, nutraceutical composition, or cosmetic composition is to be administered, and wherein ~~such that~~ the time of maximum concentration (T_{max}) of the compound of Formula (**I**) in the central nervous system (CNS) of the subject after administration ~~of the composition~~ is longer than that of non-isotopically enriched caffeine at an equivalent dose.

20. A pharmaceutical composition or nutraceutical composition of any one of claims 1-11; or a compound of Formula (**I**):



(**I**),

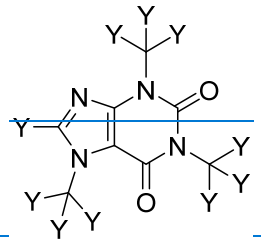
or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium;

for use in therapy.

108. A beverage comprising water and a compound of Formula (I):



(I),

or a pharmaceutically or nutraceutically acceptable salt thereof;

wherein each Y is independently hydrogen or deuterium; and

at least one Y is deuterium.

109. A beverage comprising water and a composition of any one of claims 1-63.

110. The beverage of claim 108 or 109, wherein the beverage further comprises one or more of a flavoring and a sweetener.

111. The beverage of any one of claims 108-110, wherein the beverage further comprises one or more of vitamins, minerals, co-factors, proteins, lipids, peptides, and amino acids.

112. The beverage of claim 111, wherein the beverage is an energy beverage.

113. The beverage of claim 111, wherein the beverage is a vitamin water.

114. The beverage of claim 112, wherein the energy beverage further comprises one or more of water, taurine, citicoline, vitamin B6, vitamin B12, folic acid, niacinamide, glucuronolactone, N-acetyl-L-tyrosine, L-phenylalanine, and malic acid.

115. The beverage of claim 113, wherein the vitamin water further comprises one or more of water, vitamin C, vitamin B5, vitamin B6, vitamin B12, magnesium, and pantothenic acid.

116. The beverage of any one of claims 108-115, wherein the beverage comprises about 1 mg to about 200 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.

~~117. The beverage of any one of claims 108-115, wherein the beverage comprises about 1 mg to about 125 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~118. The beverage of any one of claims 108-115, wherein the beverage comprises about 5 mg to about 75 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~119. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 10% to about 99%.~~

~~120. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 10% to about 25%.~~

~~121. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 25% to about 99%.~~

~~122. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 25% to about 75%.~~

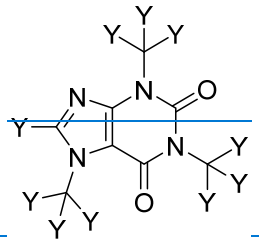
~~123. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 30% to about 70%.~~

~~124. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 25% to about 50%.~~

~~125. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 40% to about 60%.~~

~~126. The beverage of any one of claims 108-118, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the beverage ranges from about 50% to about 99%.~~

~~127. A food product comprising a compound of Formula (I):~~



~~(I),~~

~~or a pharmaceutically or nutraceutically acceptable salt thereof;~~

~~wherein each Y is independently hydrogen or deuterium; and~~

~~at least one Y is deuterium.~~

~~128. The food product of claim 127, wherein the food product is an energy bar, energy gel, pre-work out supplement, or other performance enhancing supplements.~~

~~129. The food product of claim 128, wherein the energy bar further comprises one or more of sugar, cocoa butter, chocolate liquor, whole milk powder, soy lecithin, vanilla extract, caramel, peanuts, peanut butter, almonds, oats, molasses, cinnamon, salt, and soybean oil.~~

~~130. The food product of any one of claims 127-129, wherein the food product comprises about 1 mg to about 200 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~131. The food product of any one of claims 127-129, wherein the food product comprises about 1 mg to about 125 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~132. The food product of any one of claims 127-129, wherein the food product comprises about 5 mg to about 75 mg of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof.~~

~~133. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 10% to about 99%.~~

~~134. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 10% to about 25%.~~

~~135. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 25% to about 99%.~~

~~136. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 25% to about 75%.~~

~~137. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt~~

~~thereof, relative to the total amount of caffeine present in the food product ranges from about 30% to about 70%.~~

~~138. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 25% to about 50%.~~

~~139. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 40% to about 60%.~~

~~140. The food product of any one of claims 127-129, wherein the percentage of the amount of the compound of Formula (I), or a pharmaceutically or nutraceutically acceptable salt thereof, relative to the total amount of caffeine present in the food product ranges from about 50% to about 100%.~~