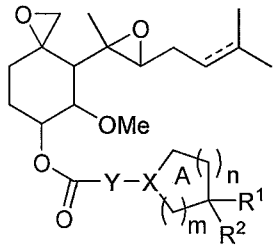
Increased expression of the MetAP2 gene has been historically associated with various forms of cancer. Molecules inhibiting the enzymatic activity of MetAP2 have been identified and have been explored for their utility in the treatment of various tumor types (Wang et al. (2003) Cancer Res. 63:7861) and infectious diseases such as microsporidiosis, leishmaniasis, and malaria (Zhang et al. (2002) J. Biomed. Sci. 9:34). Notably, inhibition of MetAP2 activity in obese and obese-diabetic animals leads to a reduction in body weight in part by increasing the oxidation of fat and in part by reducing the consumption of food (Rupnick et al. (2002) Proc. Natl. Acad. Sci. USA 99:10730).

[0005] Such MetAP2 inhibitors may be useful as well for patients with excess adiposity and conditions related to adiposity including type 2 diabetes, hepatic steatosis, and cardiovascular disease (*via* e.g. ameliorating insulin resistance, reducing hepatic lipid content, and reducing cardiac workload). Accordingly, compounds capable of modulating MetAP2 are needed to address the treatment of obesity and related diseases as well as other ailments favorably responsive to MetAP2 modulator treatment.

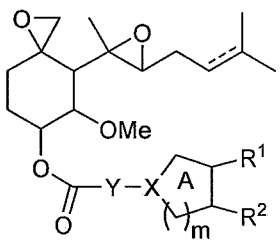
SUMMARY

[0006] The present disclosure provides, for example, compounds which may be modulators of MetAP2, and their use as medicinal agents, processes for their preparation, and pharmaceutical compositions containing them as an active ingredient both alone or in combination with other agents, as well as provides for their use as medicaments and/or in the manufacture of medicaments for the inhibition of MetAP2 activity in warm-blooded animals such as humans. In particular this disclosure relates to compounds useful for the treatment of obesity, type 2 diabetes, and other obesity-associated conditions. Also provided are pharmaceutical compositions comprising at least one disclosed compound and a pharmaceutically acceptable carrier.

[0006a] In one aspect of the present disclosure, there is provided a compound represented by Formula I or Formula Ia:



(I)



(Ia)

wherein:

 is a single or double bond;

Y is a bond or NR^a;

X is N or CR^N; wherein X is N when Y is a bond and X is CR^N when Y is NR^a;

n is 0 or 1;

m is 1 or 2;

Ring A may be optionally substituted by one or two substituents each independently selected from the group consisting of halogen, hydroxyl, C_{1-3}alkyl and C_{1-3}alkoxy, wherein C_{1-3}alkyl and C_{1-3}alkoxy may optionally be substituted by one or more fluorine atoms or a substituent selected from the group consisting of cyano, hydroxyl, and $N(R^aR^b)$;

R^1 and R^2, together with the carbon or carbons to which they are attached, form a 4-6 membered saturated heterocyclic ring B having one or two heteroatoms selected from the group consisting of O, $S(O)_w$ (wherein w is 0, 1 or 2) and NR^h or form a 3-6 membered saturated carbocyclic ring B; wherein the heterocyclic or carbocyclic ring B may optionally be substituted on a free carbon by one or two substituents each independently selected from the group consisting of halogen, hydroxyl, oxo, C_{1-3}alkyl, C_{1-3}alkoxy, -C(O)-NR^iR^j, -C(O)-$N(R^a)$-C_{1-6}alkylene-NR^iR^j, -C_{1-6}alkylene-NR^iR^j, -C_{1-6}alkylene-O-C(O)-NR^iR^j, and -O-C(O)-NR^iR^j; wherein C_{1-3}alkyl, C_{1-3}alkoxy, -C(O)-NR^iR^j, -C(O)-$N(R^a)$-C_{1-6}alkylene-NR^iR^j, -C_{1-6}alkylene-NR^iR^j, -C_{1-6}alkylene-O-C(O)-NR^iR^j, and -O-C(O)-NR^iR^j may optionally be substituted by one or more fluorine atoms or a group selected from cyano, hydroxyl, or $N(R^aR^b)$;

R^i and R^j are selected independently for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{3-6}cycloalkyl, heterocyclyl and heterocyclylcarbonyl; wherein C_{1-6}alkyl, C_{2-6}alkenyl and C_{3-6}cycloalkyl may be optionally substituted by one or more substituents independently selected from the group consisting of fluorine, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl- and C_{1-3}alkoxy; and wherein heterocyclyl and heterocyclylcarbonyl may be optionally substituted by one or more substituents independently selected from the group consisting of C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, halo-C_{1-6}-alkyl, hydroxyl-C_{1-6}-alkyl, R^aR^bN-C_{1-6}alkyl- and C_{1-6}-alkoxy-C_{1-6}-alkyl; and wherein if said heterocyclyl or heterocyclylcarbonyl contains a -NH moiety that nitrogen may optionally be substituted by one or more groups independently

selected from the group consisting of C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$- and C_{1-6}-alkylcarbonyl;

or R^i and R^j taken together with the nitrogen to which they are attached form a 4-9 membered heterocyclic ring, which may have an additional heteroatom selected from the group consisting of N, O, and $S(O)_w$ (wherein w is 0, 1 or 2); wherein the heterocyclic ring may be optionally substituted on carbon by one, two, or more substituents selected from the group consisting of halogen, hydroxyl, oxo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, R^aR^bN-, R^aR^bN-SO_2- and R^aR^bN-carbonyl-; wherein said C_{1-6}alkyl and C_{1-6}alkoxy may optionally be substituted the group consisting of fluorine, hydroxyl, and cyano; and wherein if said heterocyclic ring contains a -NH moiety that nitrogen may be optionally substituted by a substituent selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl-, and C_{1-6}alkoxycarbonyl- may optionally be substituted by one or more substituents selected from the group consisting of fluorine, hydroxyl, and cyano;

R^h is independently selected for each occurrence from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl-, C_{1-6}alkoxycarbonyl-, R^iR^jN-carbonyl- and R^iR^jN-SO_2-; wherein C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkyl-$S(O)_2$-, C_{1-6}alkylcarbonyl-, and C_{1-6}alkoxycarbonyl- may optionally be substituted by one or more substituents selected from R^P;

R^P is independently selected, for each occurrence, from the group consisting of halogen, hydroxyl, cyano, C_{1-6}alkoxy, R^iR^jN-, R^iR^jN-carbonyl-, R^iR^jN-SO_2-, and R^iR^jN-carbonyl-$N(R^a)$-;

R^N is selected from the group consisting of hydrogen, halogen, hydroxyl, and C_{1-6}alkyl; and

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-4}alkyl; wherein C_{1-4}alkyl may optionally be substituted by one or more substituents selected from the group consisting of halogen, cyano, oxo, and hydroxyl;

and pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof.

[0006b] In another aspect of the present disclosure, there is provided a compound selected from the group consisting of: (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-

methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 3-oxa-9-azaspiro[5.5]undecane-9-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-6-azaspiro[3.3]heptane-6-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 7-oxa-2-azaspiro[3.5]nonane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-7-azaspiro[3.5]nonane-7-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-oxa-2-azaspiro[3.4]octane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (7-methyl-7-azaspiro[3.5]nonan-2-yl)carbamate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 7-methyl-2,7-diazaspiro[3.5]nonane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 7-(2,2-difluoroethyl)-2,7-diazaspiro[3.5]nonane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (2-methyl-2-azaspiro[3.3]heptan-6-yl)carbamate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (6-methyl-6-azaspiro[3.4]octan-2-yl)carbamate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-methyl-2,6-diazaspiro[3.3]heptane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-tetrahydro-1H-furo[3,4-c]pyrrole-5(3H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 9-(2,2-difluoroethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-(2,2-difluoroethyl)-2,6-diazaspiro[3.4]octane-6-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 8-(2,2-difluoroethyl)-2,8-diazaspiro[4.5]decane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-(2,2-difluoroethyl)-2,6-diazaspiro[3.4]octane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-(2,2-difluoroethyl)-2,6-

diazaspiro[3.3]heptane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(2,2-difluoroethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 5-methylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6,6-difluoro-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-thia-6-azaspiro[3.3]heptane-6-carboxylate 2,2-dioxide; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 7-oxo-2,6-diazaspiro[3.4]octane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 8-methyl-2,8-diazaspiro[4.5]decane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 8-oxa-2-azaspiro[4.5]decane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 9-methyl-3,9-diazaspiro[5.5]undecane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 3-oxo-2,8-diazaspiro[4.5]decane-8-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 8-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 9-methyl-8-oxo-3,9-diazaspiro[5.5]undecane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(methylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(dimethylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-carbamoyl-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-

oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(3,3-difluoroazetidine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(diethylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-((2-morpholinoethyl)carbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(methyl(2-morpholinoethyl)carbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6S)-6-((3,3-difluoroazetidin-1-yl)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6S)-6-(morpholinomethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6S)-6-((diethylamino)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; 2-((3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl) 5-methyl (3aR,6aS)-tetrahydropyrrolo[3,4-c]pyrrole-2,5(1H,3H)-dicarboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(dimethylcarbamoyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(ethylcarbamoyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(methylcarbamoyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-isobutyrylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-propionylhexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(2-(diethylamino)-2-oxoethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(2-morpholino-2-

oxoethyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(((methylcarbamoyl)oxy)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(((dimethylcarbamoyl)oxy)methyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-(morpholinomethyl)-2-azaspiro[3.3]heptane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(2,2-difluoropropyl)hexahydropyrrolo[3,4-c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-((4-(2,2-difluoroethyl)piperazin-1-yl)methyl)-2-azaspiro[3.3]heptane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(morpholinomethyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(ethylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(pyrrolidine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,5S,6aS)-5-((dimethylcarbamoyl)oxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(azetidine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-((diethylamino)methyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5 (((methylcarbamoyl)oxy)methyl)hexahydrocyclopenta[c] pyrrole-2(1H)-carboxylate; and a pharmaceutically acceptable salt or stereoisomer thereof.

[0006c] In yet another aspect of the present disclosure, there is provided a pharmaceutically acceptable composition comprising a compound as defined herein and a pharmaceutically acceptable excipient.

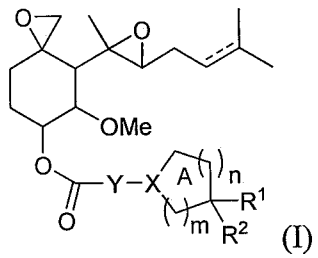
[0006d] In a further aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for treating and/or controlling obesity in a patient in need thereof.

[0006e] In another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for inducing weight loss in a patient in need thereof.

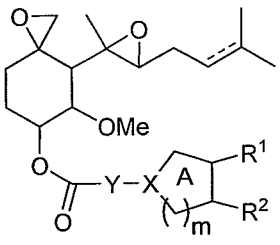
[0006f] In yet another aspect of the present disclosure, there is provided a use of a compound as defined herein in the manufacture of a medicament for substantially preventing weight gain in a patient in need thereof.

[0006g] In a further aspect of the present disclosure, there is provided a compound as defined herein for use in treating and/or controlling obesity; inducing weight loss; and substantially preventing weight gain.

[0007] For example, provided herein are compounds represented by Formula I or Formula Ia and pharmaceutically acceptable salts, stereoisomers, esters, and prodrugs thereof:



(I)

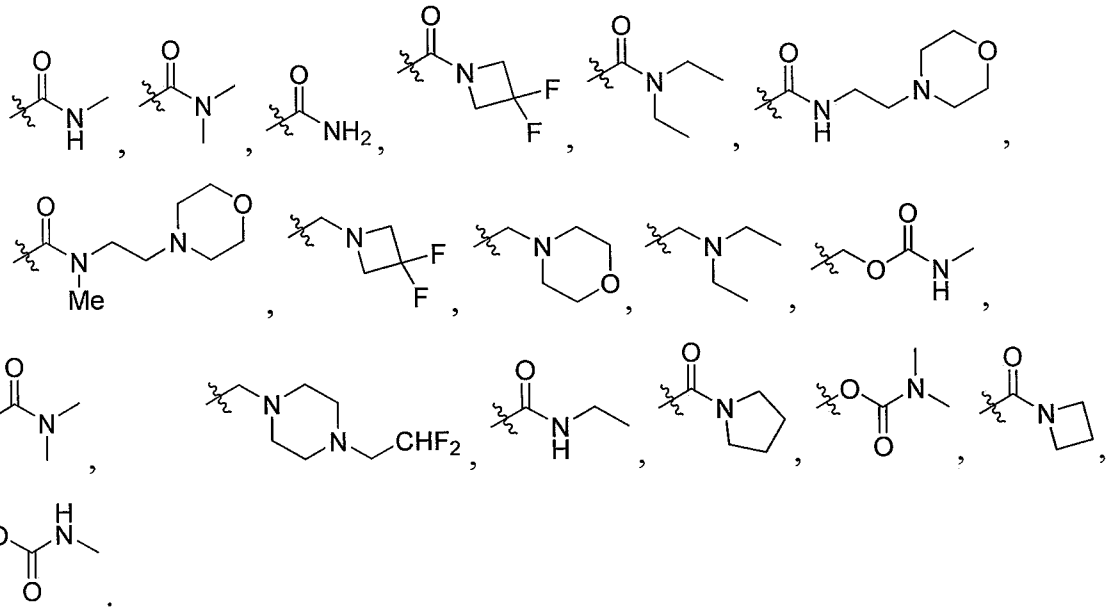


(Ia)

23. The compound of claim 17, wherein one of R^{11} or R^{22} is hydrogen and the other is selected from the group consisting of -C(O)-NR^iR^j, -C(O)-NH-CH_2-CH_2-NR^iR^j, -C(O)-NMe-CH_2-CH_2-NR^iR^j, -CH_2-NR^iR^j, -CH_2-O-C(O)-NR^iR^j, and -O-C(O)-NR^iR^j.

24. The compound of claim 23, wherein R^i and R^j are independently selected from the group consisting of hydrogen and C_{1-3}alkyl, or R^i and R^j taken together with the nitrogen to which they are attached form a 4-6 membered heterocyclic ring, which may have an additional heteroatom selected from the group consisting of N and O; wherein the heterocyclic ring may be optionally substituted on carbon by one, two, or more fluorine atoms; and wherein if said heterocyclic ring contains a -NH moiety that nitrogen may be optionally substituted by C_{1-3}alkyl; wherein C_{1-3}alkyl may optionally be substituted by one or more fluorine atoms.

25. The compound of claim 23 or 24, wherein one of R^{11} or R^{22} is hydrogen and the other is selected from the group consisting of:



and .

26. A compound selected from the group consisting of: (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 3-oxa-9-azaspiro[5.5]undecane-9-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-6-azaspiro[3.3]heptane-6-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 7-oxa-2-azaspiro[3.5]nonane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 2-oxa-6-azaspiro[3.4]octane-6-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-

methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl 6-((4-(2,2-difluoroethyl)piperazin-1-yl)methyl)-2-azaspiro[3.3]heptane-2-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-(morpholinomethyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(ethylcarbamoyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(pyrrolidine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,5S,6aS)-5-((dimethylcarbamoyl)oxy)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (1R,5S,6R)-6-(azetidine-1-carbonyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5-((diethylamino)methyl)hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate; (3R,4S,5S,6R)-5-methoxy-4-((2R,3R)-2-methyl-3-(3-methylbut-2-en-1-yl)oxiran-2-yl)-1-oxaspiro[2.5]octan-6-yl (3aR,6aS)-5 (((methylcarbamoyl)oxy)methyl)hexahydrocyclopenta[c] pyrrole-2(1H)-carboxylate; and a pharmaceutically acceptable salt or stereoisomer thereof.

27. A pharmaceutically acceptable composition comprising a compound of any one of claims 1-26 and a pharmaceutically acceptable excipient.

28. The composition of claim 27, wherein the composition is formulated as a unit dose.

29. The composition of claim 27, wherein the composition is formulated for subcutaneous administration.

30. The composition of claim 27, wherein the composition is formulated for intravenous administration.

31. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for treating and/or controlling obesity in a patient in need thereof.

32. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for inducing weight loss in a patient in need thereof.

33. Use of a compound of any one of claims 1-26 in the manufacture of a medicament for substantially preventing weight gain in a patient in need thereof.

34. The use of any one of claims 31-33, wherein the patient is a human.

35. The use of any one of claims 31-33, wherein the patient is a cat or dog.

36. The use of any one of claims 31-33, wherein the patient has a body mass index greater than or equal to about 30 kg/m^2 before the medicament is to be administered.

37. The use of any one of claims 31-36, wherein the medicament is to be administered subcutaneously.

38. The use of any one of claims 31-36, wherein the medicament is to be administered intravenously.

39. The use of any one of claims 31-36, wherein the medicament is to be administered once, twice, or thrice weekly.

40. The use of any one of claims 31-39, wherein the medicament is to be administered in an amount sufficient to establish inhibition of intracellular MetAP2 effective to increase thioredoxin production in the patient and to induce multi organ stimulation of anti-obesity processes in the subject.

41. The use of claim 40, wherein the medicament is to be administered in an amount insufficient to reduce angiogenesis in the patient.

42. A compound of any one of claims 1-26 for use in treating and/or controlling obesity; inducing weight loss; and substantially preventing weight gain.