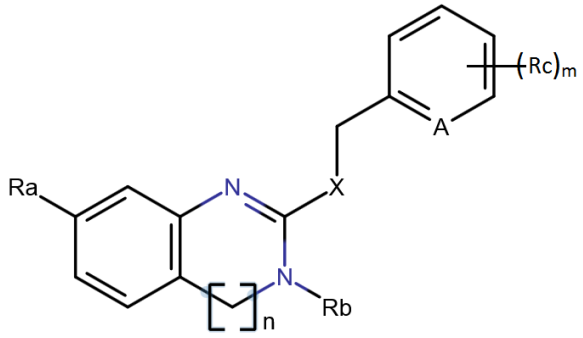
Claims

What is claimed is:

1. A compound of formula (I),



(I)

wherein n is 0 or 1,

X is –S–;

A is N;

R_a is –C(=O)OR_{a1}; wherein

R_{a1} is H or linear or branched C_{1-15}alkyl;

R_b is H, linear or branched C_{1-15}alkyl, linear or branched C_{2-15}alkenyl, C_{1-3}alkoxy-C_{1-15}alkyl-, -T'-C_{3-10}cycloalkyl, -T'-C_{3-10}cycloalkenyl, -T'-C_{6-10} aryl or -T'-C_{5-10}heteroaryl;

R_c each is independently linear or branched C_{1-15}alkyl, linear or branched C_{1-15}alkoxyl, hydroxyl, or –C_{1-10}alkylene-Y-C_{6-10}heteroaryl wherein -Y- is -CH_2-, -NH-, -O- or -S-;

m is an integer from 0 to 4;

-T- is absent, C_{1-3}alkylene or C_{2-3}alkenylene;

-T'- is C_{1-3}alkylene or C_{2-3}alkenylene; and

wherein the heteroaryl contains at least one heteroatom, each heteroatom being independently S, N or O;

wherein the alkyl, alkenyl, alkoxy, cycloalkyl, aryl, heteroaryl, alkylene and alkenylene are each independently unsubstituted or substituted with at least one substituent;

wherein the substituent is each independently a halogen, amino, nitro, nitroso, linear or branched C_{1-15} alkyl, or linear or branched C_{1-15} alkoxy or C_{3-10}cycloalkyl; and

when R_b is H, the tautomers are included,

or a pharmaceutically acceptable salt thereof,

provided that the compound is not

5-carbethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole,

5-carbmethoxy-2-[[(4,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole,

5-carbmethoxy-2-[[(3,5-dimethyl-2-pyridinyl)methyl]thio]-1H-benzimidazole,

5-carbmethoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole,

5-carbethoxy-2-[[(3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]thio]-1H-benzimidazole,

2-[2-pyridylmethylthio]-(5-carbethoxy)benzimidazole,

ethyl 1-ethyl-2-[(2-pyridinylmethyl)thio]-1H-benzimidazole-5-carboxylate, or

2-[(2-pyridinylmethyl)thio]-1H-benzimidazole-6-carboxylic acid.

2. The compound of Claim 1, wherein R_a is –C(=O)OH, or –C(=O)$OC_{1\text{-}4}$alkyl.

3. The compound of Claim 1, which is selected from the group consisting of:

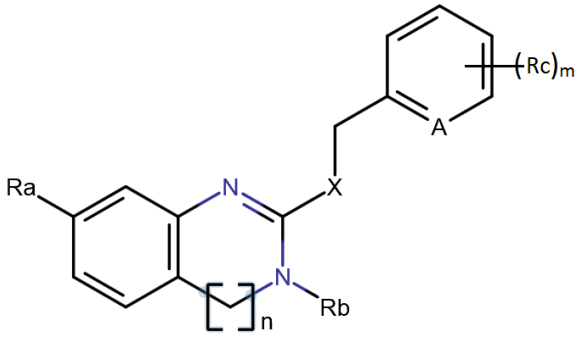
12082: Methyl 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole-5-carboxylate

12083: 1-(2-(cyclohex-1-en-1-yl)ethyl)-2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazole-5-carboxylic acid, and

12088: methyl 2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1-octyl-1H-benzo[d]imidazole-5-carboxylate,

or a pharmaceutically acceptable salt thereof.

4. A compound of formula (I),



(I)

wherein n is 0 or 1,

X is –S–; wherein

A is N;

R_a is–OR_{a2}, –O–C(=O)R_{a3} or –O–C(=O)-T-OR_{a4}; wherein

R_{a2} is phosphonate, or diarylphosphonate;

R_{a3} and R_{a4} are independently linear or branched C_{1-15}alkyl, linear or branched C_{2-15}alkenyl, -T-C_{3-10}cycloalkyl, -T-NHR_{a3p}, -T-C_{3-10}cycloalkenyl, -T-C_{6-10}aryl, -T-C_{5-10}heteroaryl, -T-NH-C(=O)-O-C_{1-10}alkyl, -T-adamantyl or -C_{1-3}alkylene-C_{6-10}aryl where the alkylene is substituted with -T-NHR_{a3p};

R_{a3p} is H, Fmoc, or Boc;

R_b is H, linear or branched C_{1-15}alkyl, linear or branched C_{2-15}alkenyl, C_{1-3}alkoxy-C_{1-15}alkyl-, -T'-C_{3-10}cycloalkyl, -T'-C_{3-10}cycloalkenyl, -T'-C_{6-10} aryl or -T'-C_{5-10}heteroaryl;

R_c each is independently linear or branched C_{1-15}alkyl, linear or branched C_{1-15}alkoxyl, hydroxyl, or –C_{1-10}alkylene-Y-C_{6-10}heteroaryl wherein -Y- is -CH_2-, -NH-, -O- or -S-;

m is an integer from 0 to 4;

-T- is absent, C_{1-3}alkylene or C_{2-3}alkenylene;

-T'- is C_{1-3}alkylene or C_{2-3}alkenylene; and

wherein the heteroaryl contains at least one heteroatom, each heteroatom being independently S, N or O;

wherein the alkyl, alkenyl, alkoxy, cycloalkyl, aryl, heteroaryl, alkylene and alkenylene are each independently unsubstituted or substituted with at least one substituent;

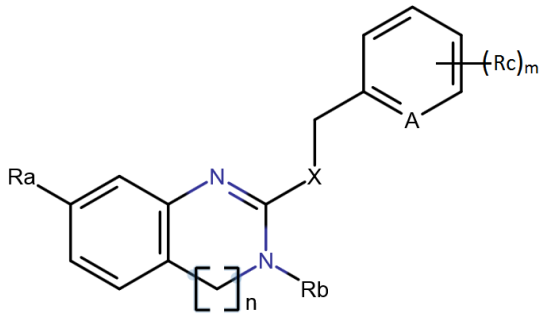
wherein the substituent is each independently a halogen, amino, nitro, nitroso, linear or branched C_{1-15} alkyl, or linear or branched C_{1-15} alkoxy or C_{3-10}cycloalkyl; and

when R_b is H, the tautomers are included,

or a pharmaceutically acceptable salt thereof,

with the proviso that the compound is not 6-phenylcarbonyloxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1Hbenzimidazole.

5. The compound of Claim 4, which is a compound of formula (I-a):



(I-a)

wherein n is 0 or 1,

X is –S–; wherein

A is N;

R_a is –O–C(=O)-T-OR_{a4}; wherein

R_{a4} is linear or branched C_{1-15}alkyl, linear or branched C_{2-15}alkenyl, -T-C_{3-10}cycloalkyl, -T-NHR_{a3p}, -T-C_{3-10}cycloalkenyl, -T-C_{6-10}aryl, -T-C_{5-10}heteroaryl, -T-NH-C(=O)-O-C_{1-10}alkyl or -T-adamantyl or -C_{1-3}alkylene-C_{6-10}aryl where the alkylene is substituted with -T-NHR_{a3p};

R_{a3p} is H, Fmoc, or Boc;

R_b is H, linear or branched C_{1-15}alkyl, linear or branched C_{2-15}alkenyl, C_{1-3}alkoxy-C_{1-15}alkyl-, -T'-C_{3-10}cycloalkyl, -T'-C_{3-10}cycloalkenyl, -T'-C_{6-10} aryl or -T'-C_{5-10}heteroaryl;

R_c each is independently linear or branched C_{1-15}alkyl, linear or branched C_{1-15}alkoxyl, hydroxyl, or –C_{1-10}alkylene-Y-C_{6-10}heteroaryl wherein -Y- is -CH_2-, -NH-, -O- or -S-;

m is an integer from 0 to 4;

-T- is absent, C_{1-3}alkylene or C_{2-3}alkenylene;

-T'- is C_{1-3}alkylene or C_{2-3}alkenylene; and

wherein the heteroaryl contains at least one heteroatom, each heteroatom being independently S, N or O;

wherein the alkyl, alkenyl, alkoxy, cycloalkyl, aryl, heteroaryl, alkylene and alkenylene are each independently unsubstituted or substituted with at least one substituent;

wherein the substituent is each independently a halogen, amino, nitro, nitroso, linear or branched C_{1-15} alkyl, linear or branched C_{1-15} alkoxy or C_{3-10}cycloalkyl and

when R_b is H, the tautomers are included,

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of Claims 1 to 5, wherein n is 0.

7. The compound of any one of Claims 1 to 5, wherein m is an integer from 0 to 3.

8. The compound of any one of Claims 4 to 5, wherein R_a is –O–C(=O)R_{a3} wherein R_{a3} is independently tert-butyl; linear or branched C_{1-10}alkyl unsubstituted or substituted by halogen, tert-butyl or NHFmoc or -NHBoc; linear or branched C_{2-10}alkenyl; C_{1-4}alkoxy; C_{3-10}cycloalkyl; -C_{1-3}alkylene-C_{3-10}cycloalkyl; -C_{3-10}cycloalkenyl; -C_{6-10}aryl unsubstituted or substituted by C_{1-10} alkyl, nitro, C_{1-15}alkoxy or halogen; -C_{5-10}heteroaryl unsubstituted or substituted by C_{1-10}alkoxy; C_{2-3}alkenylene-C_{6-10}aryl wherein C_{6-10}aryl is unsubstituted or substituted by halogen; -C_{1-3}alkylene-NH-C(=O)-O-C_{1-10}alkyl; or adamantly; or –O–C(=O)-O-C_{1-10}alkyl.

9. The compound of any one of Claims 4 to 5, wherein R_a is–O–C(=O)R_{a3} wherein R_{a3} is a tert-butyl; adamantyl; linear or branched C_{1-10}alkyl unsubstituted or substituted by halogen or tert-butyl; C_{1-4}alkoxy; -C_{6-10}aryl unsubstituted or substituted by C_{1-10} alkyl, nitro, C_{1-15}alkoxy or halogen; C_{3-10}cycloalkyl; -C_{3-10}cycloalkenyl; linear or branched C_{2-10}alkenyl; -C_{5-10}heteroaryl; -C_{1-3}alkylene-C_{3-10}cycloalkyl; C_{2-3}alkenylene-C_{6-10}aryl wherein C_{6-10}aryl is unsubstituted or substituted by halogen; –O–C(=O)-O-C_{1-10}alkyl.

10. The compound of any one of Claims 4 to 5, wherein R_a is–O–C(=O)R_{a3} wherein R_{a3} is tert-butyl; adamantyl; linear or branched C_{1-8}alkyl unsubstituted or substituted by halogen or tert-butyl ; C_{1-4}alkoxy; -phenyl unsubstituted or substituted by C_{1-6} alkyl, nitro, C_{1-4}alkoxy or halogen; C_{3-6}cycloalkyl; -C_{3-6}cycloalkenyl; linear or branched C_{2-6}alkenyl; -C_{5-6}heteroaryl; -C_{1-3}alkylene-C_{3-6}cycloalkyl; C_{2-3}alkenylene-phenyl wherein phenyl is unsubstituted or substituted by halogen; –O–C(=O)-O-C_{1-4}alkyl.

11. The compound of any one of Claims 4 to 5, wherein R_a is -O-phosphate, or –O–C(=O)-C_{1-6}alkyl, –O–C(=O)-C_{1-4}alkylene-NH(Fmoc or Boc), or –O–C(=O)-NH-C(=O)-O-C_{1-10}alkyl.

12. The compound of any one of Claims 1 to 5, wherein R_c each is independently halogen, linear or branched C_{1-6}alkyl, linear or branched C_{1-6}alkoxyl, or –C_{1-10}alkenylene-Y-C_{6-10}heteroaryl; wherein Y is S and C_{6-10}heteroaryl is unsubstituted or substituted by C_{1-15}alkyl, C_{1-15}alkenyl, C_{1-15}alkoxy, -OH, -NH_2, -NO_2 or halogen.

13. The compound of Claim 4, which is selected from the group consisting of:

12092: 2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazol-5-yl (((9H-fluoren-9-yl)methoxy)carbonyl)glycinate

12093: 2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1H-benzo[d]imidazol-5-yl (tert-butoxycarbonyl)glycinate

12094: 2-(((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)thio)-1H benzo[d]-imidazole-5-yl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-2-phenylacetate

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition, comprising a compound of any one of Claims 1 to 13 or a pharmaceutically acceptable salt thereof.

15. An in vitro method of inhibiting a DAAO, comprising contacting a cell with a compound of any one of Claims 1 to 13 or a pharmaceutically acceptable salt thereof.

16. Use of a compound of any one of Claims 13 to 1 or a pharmaceutically acceptable salt thereof or the pharmaceutical composition of Claim 14 for the manufacture of a medicament effective in the treatment or prevention of a disease associated with DAAO inhibition in a subject.

17. Use of a compound of any one of Claims 1 to 13 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament effective in the treatment or prevention of a disease associated with DAAO inhibition, wherein the disease is symptom domains of schizophrenia and schizoaffective disorder, depression, Tourette Syndrome, Post-traumatic stress disorder (PTSD), Obsessive-compulsive disorder (OCD), analgesics, loss of memory and/or cognition associated with neurodegenerative diseases, loss of neuronal function characteristic of neurodegenerative diseases, mild cognitive impairment (MCI), Alzheimer's disease, Parkinson's disease or schizophrenia, pain, ataxia or convulsion.

18. The use of Claim 16 or 17, wherein the disease is symptom domains of schizophrenia and schizoaffective disorder, depression, Tourette Syndrome, Post-traumatic stress disorder (PTSD), Obsessive-compulsive disorder (OCD), analgesics, loss of memory and/or cognition associated with neurodegenerative diseases or loss of neuronal function characteristic of neurodegenerative diseases.

19. The use of Claim 16 or 17 wherein the symptom domains of schizophrenia and schizoaffective disorder include negative, cognitive, depressive, positive and general psychopathology symptom domains.

20. The use of Claim 16 or 17, wherein the disease is mild cognitive impairment (MCI), Alzheimer's disease, Parkinson's disease or schizophrenia.

21. The use of Claim 16 or 17, wherein the disease is pain, ataxia or convulsion.