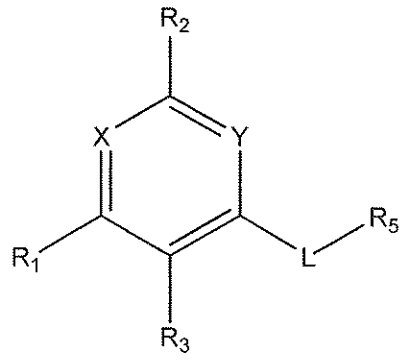
[0010] Previous studies have shown that agents able to increase brain KYNA content cause sedation, mild analgesia, increase in the convulsive threshold and neuroprotection against excitotoxic or ischemic damage. In addition to the above reported evidences, it has been recently demonstrated that a number of compounds able to increase brain KYNA formation may cause a robust decrease in glutamate (GLU) mediated neurotransmission by reducing GLU concentrations in brain extracellular spaces.

[0011] There remains a need for compounds that are effective inhibitors of KMO and may be used in treating neurodegenerative disorders.

Summary

[0011a] In one aspect, there is provided at least one chemical entity chosen from compounds of Formula I



Formula I

and pharmaceutically acceptable salts and prodrugs thereof wherein:

X and Y are independently chosen from –N– and –CH–, provided that at least one of X and Y is –N–;

R_1 is aryl or monocyclic heteroaryl, each of which is substituted with

a first group of the formula –Z-R_6 wherein

Z is chosen from –O–, –S–, –S(O)–, –$S(O)_2$–, –$CR_{11}R_{12}$–, –$OCR_{11}R_{12}$–, –NR_{13}–, –$NR_{13}CR_{11}R_{12}$–, –$CR_{11}R_{12}NR_{13}$–, and

–C(O)– where R_{11}, R_{12}, and R_{13} are independently chosen from hydrogen, lower alkyl, hydroxyl, and lower alkoxy,

R_6 is chosen from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally

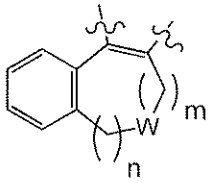
substituted heterocycloalkyl, provided that if Z is –O–, then R_6 is not optionally substituted benzyl or optionally substituted pyridylmethyl, or

R_6 and R_{13}, taken together with the nitrogen to which they are bound form an optionally substituted 5- to 7-membered heterocycloalkyl ring, and

a second group chosen from halo and lower alkyl optionally substituted with halo, or

R_1 is chosen from: 2,3-dihydrobenzofuran-5-yl, chroman-6-yl, 1,3-benzodioxol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1,3-benzoxazol-5-yl, 1,3-benzoxazol-6-yl, 2-oxo-2,3-dihydro-1,3-benzoxazol-5-yl, benzothiophen-5-yl, benzothiazol-5-yl, benzoimidazol-5-yl, benzofuran-5-yl, 1H-indol-5-yl, 1H-indazol-5-yl, isoindolin-5-yl, benzo[c][1,2,5]oxadiazol-5-yl, 1,2,3,4-tetrahydroquinolin-6-yl, imidazo[1,2-a]pyridin-6-yl, pyrazolo[1,5-a]pyridine-5-yl, quinolin-6-yl, quinazolin-6-yl, quinazolin-7-yl, and quinoxalin-6-yl, each of which is optionally substituted, or

R_1 and R_3, taken together with intervening atoms form a bicyclic ring of the formula



which is optionally substituted where m is 0 or 1 and n is 0 or 1, provided that at least one of m and n is 1 and W is –O-, or $–N(R_8)-$ where R_8 is hydrogen or lower alkyl;

R_2 is chosen from hydrogen and optionally substituted lower alkyl;

R_3 is chosen from hydrogen, halo, optionally substituted lower alkyl, hydroxyl, optionally substituted lower alkoxy, and optionally substituted amino;

L is chosen from $-C(O)-$, $-C(O)O-$, $-C(O)N(R_4)-$, $-C(O)N(OR_7)-$, $-N(R_4)S(O)_2-$, $-S(O)_2N(R_4)-$, and $-C(O)N(R_4)-S(O)_2-$;

R_4 is chosen from hydrogen and lower alkyl;

R_5 is chosen from hydrogen, optionally substituted lower alkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted

cycloalkyl, and optionally substituted heterocycloalkyl; provided that when L is $-N(R_4)S(O)_2-$, then R_5 is not hydrogen, or

R_4 and R_5 taken together with the nitrogen to which they are bound form an optionally substituted 4- to 7-membered heterocycloalkyl ring, which is optionally fused to an optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl or optionally substituted heteroaryl ring; or

R_3 and R_5, taken together with the intervening atoms, form an optionally substituted 5- to 7-membered ring; and

R_7 is chosen from hydrogen and lower alkyl;

provided that the compound of Formula I is not chosen from

6-(3-chloro-4-methyl-phenyl)-pyrimidine-4-carboxylic acid methyl ester;

6-(3-chloro-4-methyl-phenyl)-pyrimidine-4-carboxylic acid;

6-(3-chloro-4-methoxy-phenyl)-pyrimidine-4-carboxylic acid methyl ester; and

6-(3-chloro-4-methoxy-phenyl)-pyrimidine-4-carboxylic acid.

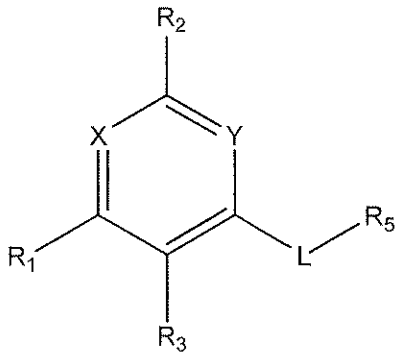
[0011b] In another aspect, there is provided a pharmaceutical composition comprising at least one chemical entity as defined herein and at least one pharmaceutically acceptable excipient.

[0011c] In yet another aspect, there is provided the use of a therapeutically effective amount of at least one chemical entity as defined herein in the manufacture of a medicament for treating a condition or disorder mediated by Kynurenine 3-mono-oxygenase activity in a subject in need of such a treatment.

[0011d] In yet another aspect, there is provided a packaged pharmaceutical composition comprising at least one pharmaceutical composition as defined herein and instructions for using the composition to treat a subject suffering from a condition or disorder mediated by Kynurenine 3-mono-oxygenase activity.

Description

[0012] Provided is at least one chemical entity chosen from compounds of Formula I



Formula I

and pharmaceutically acceptable salts and prodrugs thereof wherein:

X and Y are independently chosen from –N– and –CH–, provided that at least one of X and Y is –N–;

R_1 is aryl or monocyclic heteroaryl, each of which is substituted with a first group of the formula $–Z-R_6$ wherein

Z is chosen from –O–, –S–, –S(O)–, $–S(O)_2–$, $–CR_{11}R_{12}–$, $–OCR_{11}R_{12}–$, $–NR_{13}–$, $–NR_{13}CR_{11}R_{12}–$, $–CR_{11}R_{12}NR_{13}–$, and –C(O)– where R_{11}, R_{12}, and R_{13} are independently chosen from hydrogen, lower alkyl, hydroxyl, and lower alkoxy,

R_6 is chosen from hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkyl, provided that if Z is –O–, then