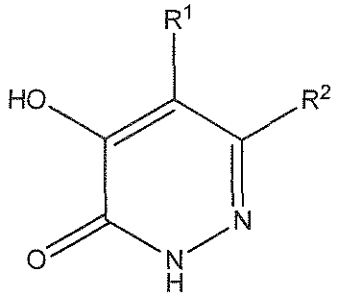
by Ferraris *et al.*, *J. Med. Chem.* **2008**, *51*, 3357–3359 and by Duplantier *et al.*, *J. Med. Chem.* **2009**, *52*, 3576–3585. A further series of carboxylic acid-containing DAAO enzyme inhibitors from Sepracore are described in WO 2008/089453.

Summary

In a first aspect of the present disclosure, there is provided a compound of formula (I)

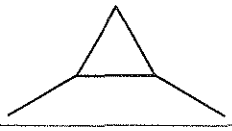
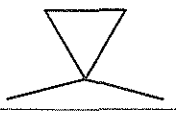


(I)

wherein

R^1 represents a hydrogen or fluorine atom or a trifluoromethyl group;

R^2 represents a group $-X-Y-R^3$;

X and Y each independently represent a bond, an oxygen atom or a group -C(O), $-S(O)_n-$, $-C(O)NR^4-$, $-S(O)_2NR^4-$, $-NR^4-$, ,  or $-CR^4R^5-$, provided that X and Y cannot both simultaneously represent a bond and provided that if X and Y are both other than a bond, then at least one of X and Y represents $-CR^4R^5-$;

n is 0, 1 or 2;

each R^4 independently represents a hydrogen atom or a C_1-C_6 alkyl or C_1-C_6 haloalkyl group;

each R^5 independently represents a hydrogen atom, a C_1-C_6 alkyl or C_1-C_6 haloalkyl group or =CH-;

R^3 represents a 3- to 10-membered saturated or unsaturated carbocyclic or heterocyclic ring system, the ring system itself being optionally substituted by at least one substituent selected from halogen, hydroxyl, cyano, oxo, C_1-C_6 alkyl, C_2-C_6

alkenyl, C_1-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulphinyl, C_1-C_6 alkylsulphonyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkoxycarbonyl, amino ($-NH_2$), $-CON(R^6)_2$, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkyloxy, C_3-C_6 cycloalkylmethyl, $-[O]_p-(CH_2)_q-O-R^7$ and a 4- to 6-membered saturated or unsaturated heterocyclic ring (optionally substituted with at least one substituent selected from C_1-C_4 alkyl and C_1-C_4 alkoxy);

each R^6 independently represents a hydrogen atom or a C_1-C_6 alkyl group;

p is 0 or 1;

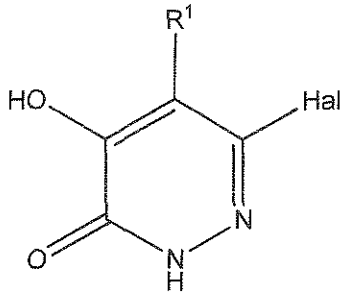
q is 1, 2, 3 or 4; and

R^7 represents a C_1-C_6 alkyl group;

or a pharmaceutically acceptable salt thereof.

In a second aspect of the present disclosure, there is provided a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof as defined in the first aspect which comprises

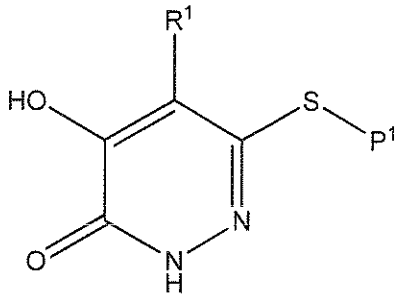
(i) when X represents a sulphur atom or when X is a bond and Y represents a sulphur atom, reacting a compound of formula (II)



(II)

in which Hal represents a halogen atom and R^1 is as defined in formula (I), with a compound of formula (III), $HS-[Y]_t-R^3$, where t is 0 or 1 and Y and R^3 are as defined in formula (I); or

(ii) when X represents SO or when X is a bond and Y represents SO, oxidising a compound of formula (IV)



(IV)

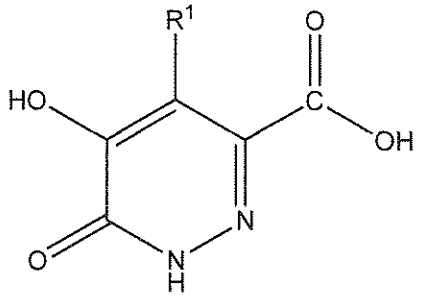
in which P^1 represents a protecting group and R^1 is as defined in formula (I), with a suitable oxidising agent, followed by reaction with a compound of formula (V), L^1-$[Y]_w$-R^3, where w is 0 or 1, L^1 represents a leaving group and Y and R^3 are as defined in formula (I); or

(iii) when X represents SO_2 or when X is a bond and Y represents SO_2, oxidising a compound of formula (IV) as defined in (ii) above with a suitable oxidising agent, followed by reaction with a compound of formula (V) as defined in (ii) above; or

(iv) when X represents an oxygen atom or when X is a bond and Y represents an oxygen atom, reacting a compound of formula (II) as defined in (i) above, with a compound of formula (VI), HO-$[Y]_z$-R^3, where z is 0 or 1 and Y and R^3 are as defined in formula (I); or

(v) when X represents C(O) or when X is a bond and Y represents C(O), reacting a compound of formula (II) as defined in (i) above with carbon dioxide, followed by addition of an activating agent and reaction with a compound of formula (Va), M-$[Y]_w$-R^3, where M is Li or MgR^{20}, R^{20} represents a halogen atom and w, Y and R^3 are as defined in formula (V) in (ii) above; or

(vi) when X represents -C(O)NR^4 or when X is a bond and Y represents -C(O)NR^4, reacting a compound of formula (VII)



(VII)

in which R^1 is as defined in formula (I), with a compound of formula (VIII), R^{4}HN-[Y]$_g$-R^3, where g is 0 or 1 and Y, R^3 and R^4 are as defined in formula (I); or

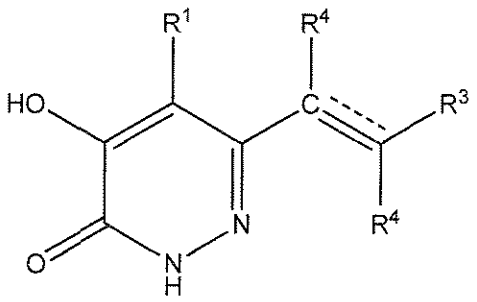
(vii) when X represents -S(O)$_2$NR^4 or when X is a bond and Y represents -S(O)$_2$NR^4, reacting a compound of formula (II) as defined in (i) above with sulphur dioxide, followed by addition of an oxidising-chlorinating agent and then reaction with a compound of formula (VIII) as defined in (vi) above; or

(viii) when X represents -NR^4 or when X is a bond and Y represents -NR^4, reacting a compound of formula (II) as defined in (i) above, with a compound of formula (VIII) as defined in (vi) above; or

(ix) when X represents -CR^{4}R^5- or when X is a bond and Y represents -CR^{4}R^5- and R^4 and R^5 each independently represent a C$_1$-C$_6$ alkyl group, reacting a compound of formula (II) as defined in (i) above with a compound of formula (IX), L^2-CR$^{4'}$R$^{5'}$-[Y]$_h$-R^3, where h is 0 or 1, L^2 represents a leaving group, R$^{4'}$ and R$^{5'}$ each independently represent a C$_1$-C$_6$ alkyl group and Y and R^3 are as defined in formula (I); or

(x) when X represents $-CR^4R^5-$ or when X is a bond and Y represents $-CR^4R^5-$ and R^4 and R^5 each independently represent a hydrogen atom or a C_1-C_6 alkyl group but do not both simultaneously represent a C_1-C_6 alkyl group, reacting a compound of formula (II) as defined in (i) above with a compound of formula (IXa), $R^4C(O)$-$[Y]_h$-R^3, wherein h, Y, and R^3 are as defined in formula (IX) in (ix) above and R^4 is as defined in formula (I) above, followed by a hydrogenation reaction; or

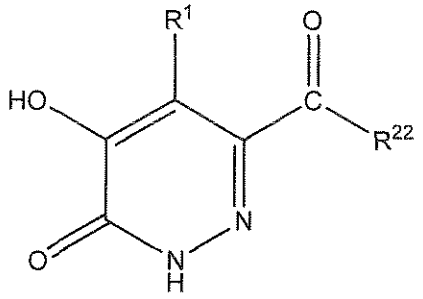
(xi) when X and Y each represent $-CHR^4$, hydrogenating a compound of formula (X)



(X)

wherein R^1, R^3 and R^4 are as defined in formula (I); or

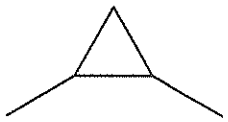
(xii) when X represents $-CR^4R^5-$ or when X is a bond and Y represents $-CR^4R^5-$ and R^5 is =CH, reacting a compound of formula (XI)

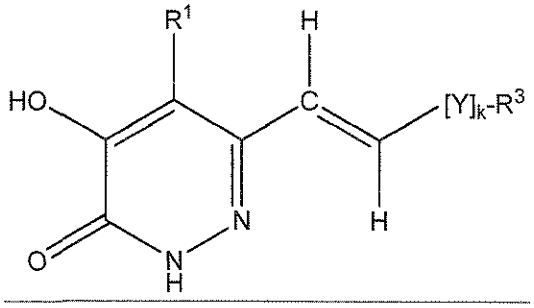


(XI)

wherein R^{22} represents a hydrogen atom or a C_1-C_6 alkyl group and R^1 is as defined in formula (I), with a compound of formula (IXb), R^{24}-$CH(R^{26})$-$[Y]_h$-R^3, wherein R^{24}

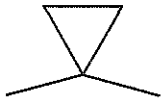
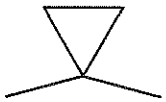
represents a phosphonate moiety, R^{26} represents a hydrogen atom or a C_1-C_6 alkyl group and h, Y and R^3 are as defined in formula (IX) in (ix) above; or

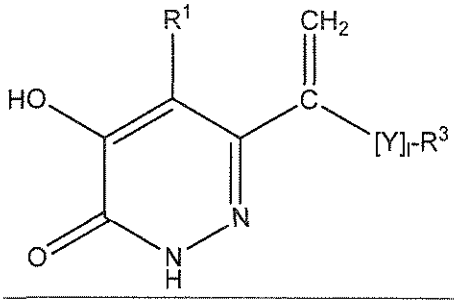
(xiii) when X represents a group  or when X is a bond and Y represents a group , reacting a compound of formula (XII)



(XII)

where k is 0 or 1 and Y, R^1 and R^3 are as defined in formula (I), with diiodomethane and zinc-copper couple; or

(xiv) when X represents a group  or when X is a bond and Y represents a group , reacting a compound of formula (XIII)



(XIII)

where l is 0 or 1 and Y, R^1 and R^3 are as defined in formula (I), with diiodomethane and zinc-copper couple;

and optionally thereafter carrying out one or more of the following procedures:

- converting a compound of formula (I) into another compound of formula (I)
- removing any protecting groups
- forming a pharmaceutically acceptable salt.

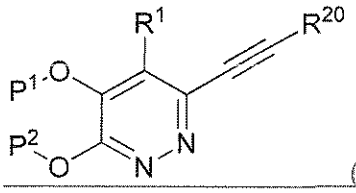
In a third aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein described, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

In a fourth aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein described for use in treating a condition whose development or symptoms are linked to D-amino acid oxidase (DAAO) enzyme activity.

In a fifth aspect of the present disclosure, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein described for use in treating schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive disorders or pain.

In a sixth aspect of the present disclosure, there is provided a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof as herein described and one or more agents selected from carbamazepine, olanzapine, quetiapine, verapamil, lamotrigine, oxcarbazepine, risperidone, aripiprazole, ziprasidone and lithium.

In a seventh aspect of the present disclosure, there is provided an intermediate compound of formula (XXX)



(XXX)

wherein P^1 and P^2 each independently represent a protecting group, R^{20} represents a hydrogen atom or a leaving group and R^1 is as defined in formula (I) as herein described.

In an eighth aspect of the present disclosure, there is provided 6-[2-(4-Fluorophenyl)ethyl]-4-hydroxypyridazin-3(2H)-one.

In a ninth aspect of the present disclosure, there is provided 6-[2-(4-Fluorophenyl)ethyl]-4-hydroxypyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof.

In a tenth aspect of the present disclosure, there is provided 4-Hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one.

In an eleventh aspect of the present disclosure, there is provided 4-Hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof.

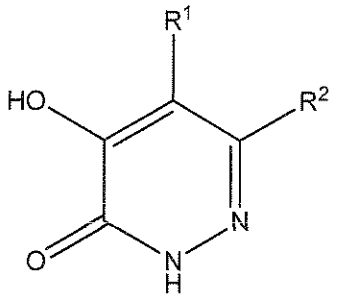
In a twelvth aspect of the present disclosure, there is provided 6-(4-Chlorobenzyl)-4-hydroxypyridazin-3(2H)-one.

In a thirteenth aspect of the present disclosure, there is provided 6-(4-Chlorobenzyl)-4-hydroxypyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof.

Description

We have now discovered a new class of compounds that are DAAO enzyme inhibitors which have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

In accordance with the present invention, there is therefore provided a compound of formula (I)

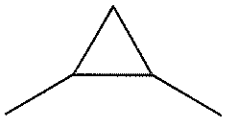
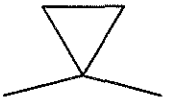


(I)

wherein

R^1 represents a hydrogen or fluorine atom or a trifluoromethyl group;

R^2 represents a group –X-Y-R^3;

X and Y each independently represent a bond, an oxygen atom or a group -C(O), -$S(O)_n$, -$C(O)NR^4$, -$S(O)_2NR^4$, -NR^4, ,  or -CR^4R^5-, provided that X and Y cannot both simultaneously represent a bond and provided that if X and Y are both other than a bond, then at least one of X and Y represents -CR^4R^5-;

n is 0, 1 or 2;

each R^4 independently represents a hydrogen atom or a C_1-C_6 alkyl or C_1-C_6 haloalkyl group;

each R^5 independently represents a hydrogen atom, a C_1-C_6 alkyl or C_1-C_6 haloalkyl group or =CH-;

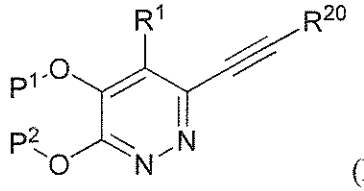
12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10 for use in treating a condition whose development or symptoms are linked to D-amino acid oxidase (DAAO) enzyme activity.

14. A compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10 for use in treating schizophrenia, schizophreniform disorder, schizoaffective disorder, cognitive disorders or pain.

15. A combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof as claimed in any one of claims 1 to 10 and one or more agents selected from carbamazepine, olanzapine, quetiapine, verapamil, lamotrigine, oxcarbazepine, risperidone, aripiprazole, ziprasidone and lithium.

16. An intermediate compound of formula (XXX)



(XXX)

wherein P^1 and P^2 each independently represent a protecting group, R^{20} represents a hydrogen atom or a leaving group and R^1 is as defined in formula (I) of claim 1.

17. 6-[2-(4-Fluorophenyl)ethyl]-4-hydroxypyridazin-3(2H)-one.

18. 6-[2-(4-Fluorophenyl)ethyl]-4-hydroxypyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof

19. 4-Hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one.

20. 4-Hydroxy-6-{2-[4-(trifluoromethyl)phenyl]ethyl}pyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof.

21. 6-(4-Chlorobenzyl)-4-hydroxypyridazin-3(2H)-one.

22. 6-(4-Chlorobenzyl)-4-hydroxypyridazin-3(2H)-one or a pharmaceutically acceptable salt thereof.