ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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D-Amino Acid Oxidase Inhibitors: Potential Therapy for Schizophrenia

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Title:	Pyridazinones as DAAO Enzyme Inhibitors		
Patent/Patent Application Number:	WO 2014/096757 Al	**Publication Date:**	26 June 2014
Priority Application:	GB 1222711.2	**Priority Date:**	17 December 2012
Inventors:	Farnaby, W.; Fieldhouse, C.; Hazel, K.; Kerr, C.; Kinsella, N.; Livermore, D.; Merchant, K.; Miller, D.		
Assignee Company:	(*for all designated States except MG*): Takeda Pharmaceutical Company Limited; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 5410045, Japn (*for MG only*): Takeda Cambridge Limited; 418 Cambridge Science Park, Cambridge CB4 OPA, U.K.		
Disease Area:	Schizophrenia	**Biological Target:**	D-amino acid oxidase enzyme (DAAO)

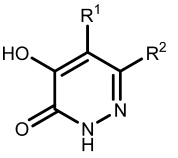
Summary:

The invention in this patent application relates to pyridazinone derivatives represented generally by formula (I). These compounds are inhibitors of the D-amino acid oxidase enzyme and may be useful for the treatment of schizophrenia.

One approach to treat schizophrenia is to target the levels of glycine or D-serine (D-SER), the coagonists of the *N*-methyl-D-aspartate (NMDA) receptor. There is an evidence that links NMDA receptor dysfunction to the positive (psychotic), negative, and cognitive symptoms in schizophrenia. Attempts to enhance NMDA receptor activity through the use of glycine transporter inhibitors have not been successful in producing any marketed drugs to-date. D-SER is more potent than glycine as a coagonist of NMDA receptor, and therefore, the modulation of D-SER may potentially provide an effective alternative approach for treating schizophrenia. D-Amino acid oxidase (DAAO) is a flavoenzyme that regulates the levels of D-amino acids (including D-SER) through their degradation via an oxidative deamination process. Increased expression and activity of DAAO have been associated with the progress of schizophrenia. Increasing the levels of D-SER in the blood and brain may be achieved through inhibition of the activity of DAAO enzyme.

Some research groups have reported the structures of several small heterocyclic ring compounds that can inhibit the DAAO enzyme. The inventors of this patent application introduce a series of pyridazinone compounds that are DAAO enzyme inhibitors. They are described as having desirable activity profiles regarding potency, selectivity, and/or pharmacokinetic properties.

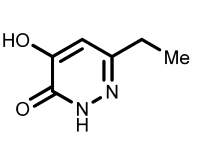
Important Compound Classes:



Formula (I)

Key Structures:

The inventors reported the structures of 14 examples of compounds of formula (I) including the following four representative examples:



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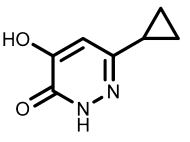

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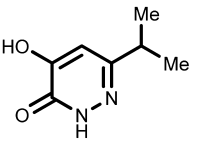

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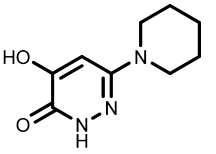

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Biological Assay: In Vitro DAAO Enzyme Assay

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Biological Data: The inventors determined the IC_{50} values for the 14 reported examples using the above assay based on ten-point half log scale dose response studies. The IC_{50} values of the above four representative examples are listed in the following table:

DAAO Enzyme Assay			
Example	**Mean IC_{50} (nM)**	**Example**	**Mean IC_{50} (nM)**
1	11	**8**	36
3	40	**13**	3600

Recent Review Articles:

1. Muthuraman, A.; Singh, N.; Jaggi, A. S.; Ramesh, M. *Curr. Drug Targets* **2014**, *15* (2), 210−253.
2. Sacchi, S.; Rosini, E.; Pollegioni, L.; Molla, G. *Curr. Pharm. Des.* **2013**, *19* (14), 2499−2511.
3. Ferraris, D. V.; Tsukamoto, T. *Curr. Pharm. Des.* **2011**, *17* (2), 103−111.
4. Smith, S. M.; Uslaner, J. M.; Hutson, P. H. *Open Med. Chem. J.* **2010**, *4*, 3−9.

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Notes

The authors declare no competing financial interest.