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PATENT HIGHLIGHT

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Kynurenine Monooxygenase (KMO) Inhibitors for the Treatment of Acute Pancreatitis and Neurodegenerative Disorders

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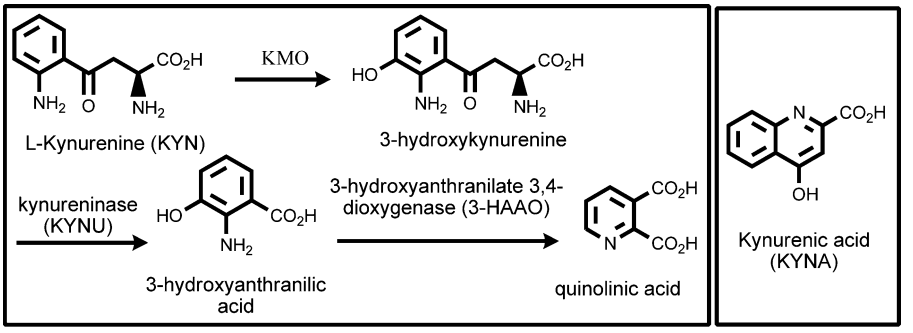
Title:	3-(5-Chloro-2-oxobenzo[*d*]oxazol-3(2*H*)-yl)propanoic Acid Derivatives as KMO Inhibitors		
Patent Application Number:	WO 2015/091647 A1	**Publication date:**	25 June 2015
Priority Application:	GB 1322512.3	**Priority date:**	19 December 2013
Inventors:	Bouillot, A. M. J.; Mirguet, O.; Liddle, J.; Walker, A. L.		
Assignee Company:	GlaxoSmithkline Intellectual Property Development Limited; 980 Great West Road, Brentford Middlesex TW8 9GS (GB)		
Disease Area:	Acute pancreatitis and acute conditions associated with systemic inflammatory response syndrome (SIRS)	**Biological Target:**	Kynurenine monooxygenase (KMO)

Summary: The invention in this patent application relates to 5-chlorobenzo[*d*]oxazol-2(3*H*)-one derivatives represented generally by formula (I). The compounds possess activities as KMO inhibitors and may be useful as a treatment of acute pancreatitis and other acute conditions associated with systemic inflammatory response syndrome (SIRS).

Kynurenine monooxygenase (KMO) is a flavin adenine dinucleotide (FAD) dependent monooxygenase located on the outer mitochondrial membrane. It is highly expressed in the liver, placenta, kidney endothelial cells, and monocytes. It is also expressed at lower levels in microglia and macrophages in the brain. KMO participates in the major route of catabolism of tryptophan by oxidizing L-kynurenine (KYN) to 3-hydroxykynurenine (3HK). 3HK is subsequently transformed to 3-hydroxyanthranilic acid and quinolinic acid by the action of kynureninase (KYNU) and 3-hydroxyanthranilate 3,4-dioxygenase (3-HAAO) as illustrated in the scheme below. L-Kynurenine is also converted to kynurenic acid (KYNA), through an alternative pathway.



Studies have implicated increased levels of 3HK and quinolinic acid as well as reduced levels of KYNA in several diseases including Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and acute pancreatitis. Also, 3-HK and quinolinic acid have shown neurotoxic effects, while KYNA displayed neuroprotective effects in the CNS. Inhibition of KMO oxidative activity would therefore be expected to result in reduced levels of 3-HK and quinolinic acid and increased levels of KYNA, which may potentially provide beneficial treatment for these diseases.

Strong evidence shows that tryptophan metabolism is altered in a range of acute injury settings. Thus, increased kynurenine level has been linked to the development of sepsis following trauma, and increased levels of kynurenine and 3-HK is associated with the development of organ failure in acute pancreatitis. The dysregulation of tryptophan metabolism is explained partly by the induction of indolamine 2,3-dioxygenase (IDO), which converts tryptophan to *N*-formyl kynurenine as part of the inflammatory cascade.

Acute pancreatitis (AP) is driven by factors such as excessive alcohol consumption or gallstones and causes severe abdominal pain that usually requires emergency hospitalization. The disease is self-limiting in most cases, and the pain resolves within 24−36 h. However, a systemic inflammatory response occurs in about 20−30% of the patients resulting in rapid progression to multiple organ dysfunction (MOD). This leads to prolonged stays in ICU (averaging 17 days), with a mortality rate of over 30%. Despite the seriousness of this disease, the current standard of care is purely supportive, and there are no available effective treatments.

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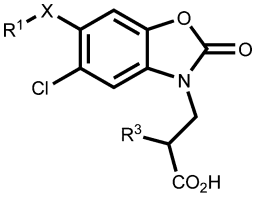
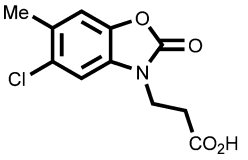
Several recent patent applications have described KMO inhibitors to treat neurodegenerative disorders and inflammatory conditions. However, there remains a need for the discovery of effective KMO inhibitors suitable for intravenous administration to treat acute pancreatitis and other conditions associated with systemic inflammatory response syndrome (SIRS). The inhibitors of KMO described in this patent application may potentially provide useful treatments for these conditions.

Important Compound Classes:



Formula (I)

Key Structures: The inventors described the structures and synthetic methods of 72 examples of formula (I). The compounds are presented as free acids or as salts; several of the reported compounds are different salts of the same molecule. The following representative examples are shown as free acids:



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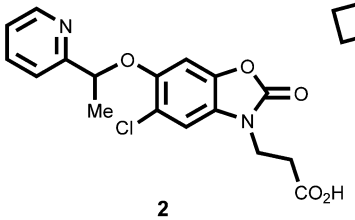

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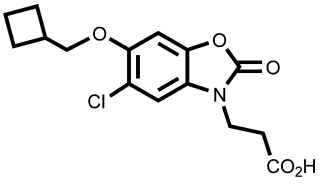

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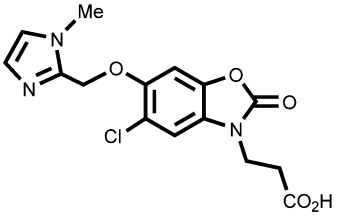

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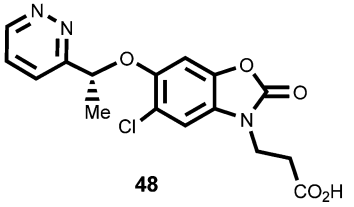

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Biological Assay:

- KMO MS Rapidfire assay protocol

Biological Data: The inventors reported that the tested compounds have median pIC_{50} values of >6.1 in the MS Rapidfire assay. Specific values were mentioned for two compounds: compound **1** median pIC_{50} = 7.9 and compound **2** median pIC_{50} = 8.4

Recent Review Articles:

1. Amaral, M.; Outeiro, T. F.; Scrutton, N. S.; Giorgini, F. *J. Mol. Med.* 2013, 91 (6), 705−713.
2. Thevandavakkam, M. A.; Schwarcz, R.; Muchowski, P. J.; Giorgini, F. *CNS Neurol. Disord.: Drug Targets* **2010**, *9* (6), 791−800.
3. Moroni, F.; Carpenedo, R.; Cozzi, A.; Meli, E.; Chiarugi, A.; Pellegrini-Giampietro, D. E. *Adv. Exp. Med. Biol.* **2003**, *527*, 127−136.

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Notes

The authors declare no competing financial interest.