ACS Medicinal Chemistry Letters

PATENT HIGHLIGHT

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Indoleamine 2,3-Dioxygenase Inhibitors: Potential Treatment for Cancer, Sepsis, and More

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Title:	Compounds Useful as Inhibitors of Indoleamine 2,3-Dioxygenase		
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Priority Application:	US 61/728,333	**Priority Date:**	20 November 2012
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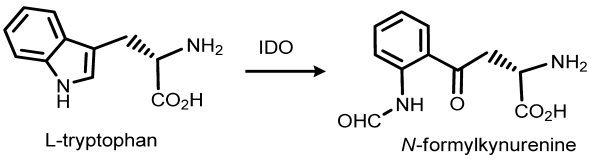
Assignee Company:	Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139, USA		
Disease Area:	Cancer, sepsis, and diseases linked to the activities of the IDO enzyme	**Biological Target:**	Indoleamine 2,3-dioxygenase (IDO)

Summary: The invention in this patent application relates to compounds represented generally by formula (I) that possess activities as IDO inhibitors and may be useful for treating or preventing a variety of diseases, disorders, or conditions including, but not limited to, cancer and sepsis.

Indoleamine 2,3-dioxygenase (IDO) is an enzyme that catalyzes the conversion of L-tryptophan (Trp) to *N*-formylkynurenine in a rate-limiting first step of Trp metabolism. It is an inducible enzyme that has a primary role in immune cell modulation. L-Tryptophan is an essential amino acid that is necessary for the biosynthesis of proteins, niacin, and serotonin. *N*-Formylkynurenine is a precursor in the biosynthesis of the immunomodulatory compounds kynurenines.



L-tryptophan *N*-formylkynurenine

The metabolic conversion of Trp to kynurenines may halt the growth of pathogens such as *Toxoplasma gondii* or *Chlamydia trachomatis*. It may also cause inhibition of effector immune cells and promote adaptive immune suppression through induction and maintenance of regulatory T cells. However, the increased metabolic conversion of Trp to kynurenines by IDO has been linked to a number of immune system disorders such as infection, malignancy, autoimmune diseases, trauma, and AIDS.

Several studies have provided evidence that linked IDO activities to cancer including the following:

- Upregulation of IDO serves as a mechanism in tumor cells to escape immune surveillance.
- IDO is widely expressed in solid tumors and was found in primary and metastatic cancer cells.
- Proinflammatory cytokines, including type I and type II interferons, induce IDO in tumors.
- Increased infiltration of gastrointestinal tumors by effector T cells is accompanied by reduction of IDO expression.
- IDO inhibitors reduce lymphocyte-dependent tumor growth.
- IDO inhibitors work in synergy with agents that promote tumor antigenicity like irradiation, chemotherapy, or vaccines.
- IDO expression was reported in antigen presenting cells including dendritic cells (DCs) that migrate to lymph nodes and induce anergy.
- IDO-positive DCs in tumor draining lymph nodes (TDLNs) of cancer-bearing mice block T-cell activation by preventing the conversion of regulatory T cells (Tregs) to inflammatory T-helper-17 (Th17)-like cells. Inhibition of IDO activity allows this conversion to occur.

Therefore, the inhibition of IDO enzyme may potentially be used as a cancer therapy.

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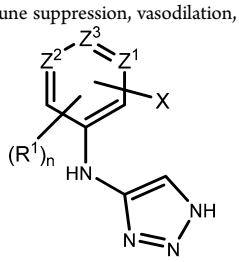
Studies have also shown that kynurenines can influence brain function. Kynurenine pathway metabolites may potentially cause several harmful brain diseases, and the fluctuations in their levels may lead to the occurrence of neurodegenerative diseases, schizophrenia, and depression. Vasodilation and shock in inflammation and sepsis may result from production of kynurenine in blood vessels. IDO activities were linked to dysregulated immune responses and impaired microvascular reactivity, as well as survival and disease severity in clinical studies on patients with sepsis and bacteremia. IDO activity correlates similarly with progression of sepsis severity in community-acquired pneumonia patients.

Therefore, the inhibition of the activity of the IDO enzyme may also provide a potential treatment for bacterial infections and sepsis.

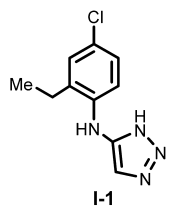
The inhibition of IDO can maintain desired physiological tryptophan levels and suppress the expression of harmful levels of kynurenines. Potent and selective inhibitors of the IDO enzyme may counteract a variety of diseases linked to the activities of this enzyme such as cancer, sepsis, bacteremia, immune suppression, vasodilation, neurotoxicity, and others.

Important Compound Classes:

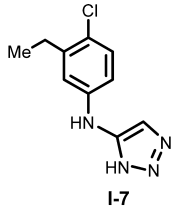


Formula (I)

Key Structures: The inventors disclosed the structures of 48 compounds of formula (I) including the following representative examples:



I-1



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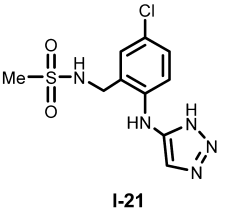

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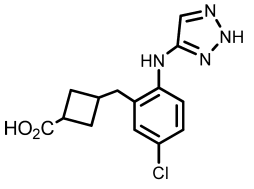

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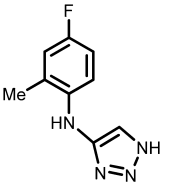

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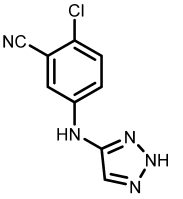

I-44

Biological Assay:

- Cellular IDO1 Inhibition Assay
- Cellular Viability Assay

Biological Data: The inventors reported IC_{50} data resulting from the cellular IDO1 assay for the 48 disclosed examples. The following table contains the IC_{50} values for the 6 representative examples displayed above:

Compound	Cellular IDO1 Assay IC_{50}	IC_{50} Classification
I-1	A	A: $IC_{50} < 0.1$ μM B: $IC_{50} = 0.1$ - 1 μM C: $IC_{50} = 1$ - 40 μM
I-7	B	
I-21	C	
I-28	C	
I-36	A	
I-44	B	

Recent Review Articles:

(1.) Dolusic, E.; Frederick, R. *Expert Opin. Ther. Pat.* **2013**, *23* (10), 1367−1381.
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Notes

The authors declare no competing financial interest.