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PATENT HIGHLIGHT

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Inhibitors of the PD-1/PD-L1 Pathway Can Mobilize the Immune System: An Innovative Potential Therapy for Cancer and Chronic Infections

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Title:	Compounds Useful as Immunomodulators		
Patent Application Number:	WO 2015/034820 Al	**Publication date:**	12 March 2015
Priority Application:	US 61/873,398	**Priority date:**	4 September 2013
Inventors:	Chupak, L. S.; Zheng, X.		
Assignee Company:	Bristol-Myers Squibb Company; Route 206 and Province Line Road, Princeton, NJ 08543, USA		
Disease Area:	Cancer and infectious diseases such as hepatitis C	**Biological Target:**	PD-1/PD-L1 pathway

Summary:

The invention in this patent application relates to compounds represented generally by formula (I), which possess activities as inhibitors of the PD-1/PD-L1 interactions and therefore may potentially be useful in the treatment of cancer as well as infectious diseases such as hepatitis C.

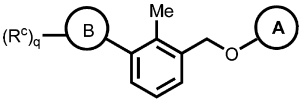
T-cells or lymphocytes are white blood cells that are essential for the immune system. They are capable of searching for and destroying infected and/or cancerous cells. Programmed death protein 1 (PD-1), also known as cluster of differentiation 279 (CD279), is a cell surface receptor on the T cells. The binding of PD-1 with either one of its two known ligands, programmed death-ligands 1 and 2 (PD-Ll or PD-L2), has been shown to suppress T cell receptor activating signals. The PD-l/PD-L1 pathway down regulates the immune responses during resolution of an infection or a tumor, or during the development of self-tolerance.

Studies have shown that blocking the PD-1/PD-Ll interactions using antibodies to the PD-Ll protein restores and augments T cell activation in many systems. A recent study has shown that therapy with a monoclonal antibody to PD-Ll benefited patients with advanced cancer. Blocking the PD-1/PD-Ll pathway by monoclonal antibodies enhanced the immune response and resulted in tumor rejection or control of infection in preclinical animal models. It can also restore *in vitro* antigen-specific functionality to T cells from HIV, HCV, or HBV patients. Other reports show that blocking the PD-1/PD-L1 interaction enhances T cell activity in chronic infection systems and may augment therapeutic immune response to a number of histologically distinct tumors. It also enhances the responses to vaccination, including therapeutic vaccination in chronic infections.

The term "T cell exhaustion" describes the conditions of the T cells resulting from chronic antigen stimulation that occurs during chronic infections and tumor disease. These cells are characterized by elevated levels of PD-1 and dysfunctional activities toward chronic antigen. Targeting PD-L1 protein to inhibit the PD-1/PD-L1 pathway has been shown to restore antigen-specific T cell immune functions *in vitro* and *in vivo*, including enhanced responses to vaccination in the setting of tumor or chronic infection.

The inhibition of the interaction of PD-Ll with PD-1 is thus a viable and promising therapeutic target for the treatment of cancer and/or chronic infections. The invention in this patent application presents compounds with activities as inhibitors of the PD-1/PD-Ll protein/protein interactions. These compounds may potentially be useful therapy to enhance immunity in patients with cancer or chronic infections.

Important Compound Classes:



Formula (I)

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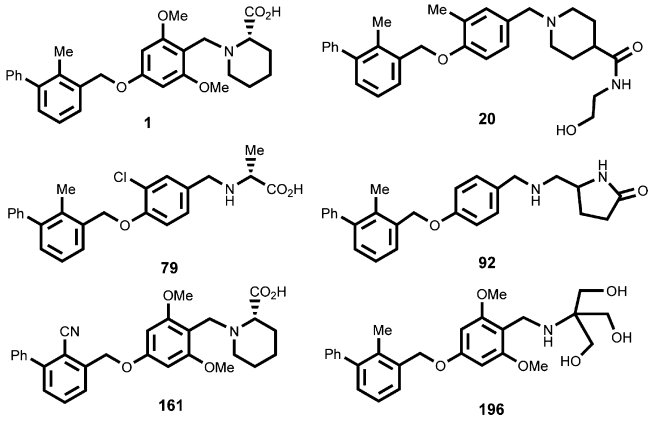
Key Structures: The inventors listed the structures of 297 examples of formula (I) including the following six representative examples:



Biological Assay:

- Homogenous Time-Resolved Fluorescence (HTRF) binding assay

Biological Data: The inventors listed the IC_{50} data from the HTRF binding assay for the 297 examples of formula (I). The following table contains the assay data for the above six representative examples:

Compound	PD1-L1 HTRF IC_{50} (μM)	Compound	PD1-L1 HTRF IC_{50} (μM)
1	A	**92**	C
20	B	**161**	A
79	A	**196**	A

Codes for IC_{50} values: A = 0.006−0.10 μM; B = 0.11−1.00 μM; C = 1.01−10 μM

Recent Review Articles:

1. Muenst, S.; Soysal, S. D.; Tzankov, A.; Hoeller, S. *Expert Opin. Ther. Targets* **2015**, *19* (2), 201−211.
2. Ohaegbulam, K. C.; Assal, A.; Lazar-Molnar, E.; Yao, Y.; Zang, X. *Trends Mol. Med.* **2015**, *21* (1), 24−33.
3. Saresella, M.; Rainone, V.; Al-Daghri, N. M.; Clerici, M.; Trabattoni, D. *Curr. Mol. Med.* **2012**, *12* (3), 259−267.
4. Larrubia, J. R.; Benito-Martinez, S.; Miquel, J.; Calvino, M.; Sanz-de-Villalobos, E.; Parra-Cid, T. *World J. Gastroenterol.* **2009**, *15* (41), 5129−5140.

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Notes

The authors declare no competing financial interest.