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Patent Highlight

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Toll-Like Receptor Agonists for Treatment of Viral Infections

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Title:	Quinazoline Derivatives for the Treatment of Viral Infections and Further Diseases		
Patent Application Number:	WO 2012/156498 A1	**Publication Date:**	November 22, 2012
Priority Application:	EP 11166538.6	**Priority Date:**	May18, 2011
Inventors:	McGowan, D.; Raboisson, P. J.-M. B.; Jonckers, T. H. M.; Last, S. J.; Embrechts, W.; Pieters, S. M. A.		
Assignee Company:	Janssen R&D Ireland; Eastgate Village, Eastgate, Little Island, Co Cork, Ireland		
Disease Area:	Treatment of viral infections and immune or inflammatory disorders	**Biological Target:**	Toll-like receptors (TLRs)

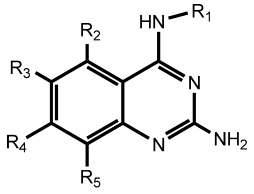
Summary:

The invention described in this patent application relates to quinazoline derivatives represented by formula (I). These compounds can modulate toll-like receptors and may potentially treat viral infections or immune or inflammatory disorders.

Toll-like receptors (TLRs) are primary trans-membrane proteins that play key roles in the innate immune system. There are 13 identified TLRs in humans and mammals named as TLR1 to TLR13, but they are not all presented in humans. TLRs expressed on the cell surface of certain types of immune cells recognize pathogen-associated molecular patterns and that activates the immune cell responses including production of cytokines and upregulation of costimulatory molecules on phagocytes.

Agonists of TLR7/8 are known to be IFN inducers; these agonists can act as vaccine adjuvants and promote T helper 1 (Th1) immune response against viral infections. Thus, the modulation of TLRs by small molecules is a promising therapeutic target and can potentially offer solutions to unmet clinical needs in treating viral infections and immune and inflammatory disorders.

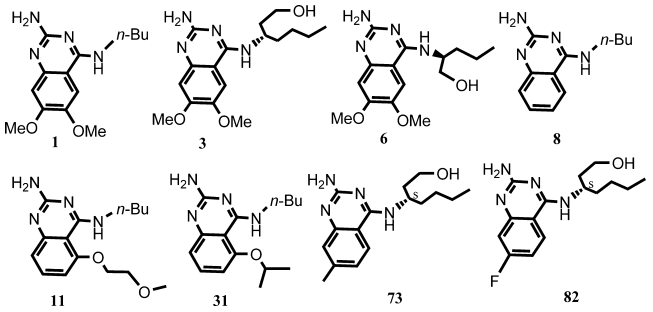
Important Compound Classes:



Formula (I)

Key Structures:

The patent application describes the synthesis and structures of 98 examples of the compounds of formula (I); 8 of these examples are shown below:



Biological Assay:

The biological activity of the compounds of formula (I) was determined by the following assays:

1. Assessment of TLR7 and TLR8 activity: The ability of compounds to activate human TLR7 and/or TLR8 was evaluated using HEK293 cells transiently transfected with a TLR7 or TLR8 expression vector and NF_KB-luc reporter construct. The lowest effective concentrations (LEC) values were determined for each compound.

2. The potential of compounds to induce interferon was evaluated in two assays:

   a. Suppression of HCV replicon replication: The antiviral activity in the HCV replicon system was determined upon incubation with conditioned media from peripheral blood mononuclear cells (PBMC). The inhibitory activity of each compound on the Huh7-luc/neo cells was reported as EC_{50} values.

   b. Activation of ISRE promoter elements: Measuring the activation of interferon-stimulated responsive elements (ISRE) by conditioned media from PBMC.

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Biological Data: Biological data were reported fully or partially for all 98 examples; the data for the above 8 compounds are shown in the following table:

Compound	TLR7-wt (LEC)	TLR8-wt (LEC)	HEK-ISRE luc (LEC)	PBMC-HUH7 (EC_{50})
1	5.0	1.1	NA	1.9
3	4.0	5.5	NA	0.6
6	NA	4.4	NA	3.0
8	0.1	0.1	NA	NA
11	0.08	0.17	0.12	NA
31	0.09	0.24	0.04	NA
73	0.03	0.06	0.02	NA
82	0.04	0.03	0.04	NA

Recent Review Articles:

1. Yuk, J.-M.; Jo, E.-K. *J. Bacteriol. Virol.* **2011**, *41* (4), 225−235.

2. Keogh, B.; Parker, A. E. *Trends Pharmacol. Sci.* **2011**, *32* (7), 435−442.

3. Hennessy, E. J.; Parker, A. E.; O'Neill, L. A. J. *Nat. Rev. Drug Discovery* **2010**, *9* (4), 293−307.

4. Gorden, K. B.; Gorski, K. S.; Gibson, S. J.; Kedl, R. M.; Kieper, W. C.; Qiu, X.; Tomai, M. A.; Alkan, S. S.; Vasilakos, J. P. *J. Immunol.* **2005**, *174* (3), 1259−1268.

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Notes

The author declares no competing financial interest.