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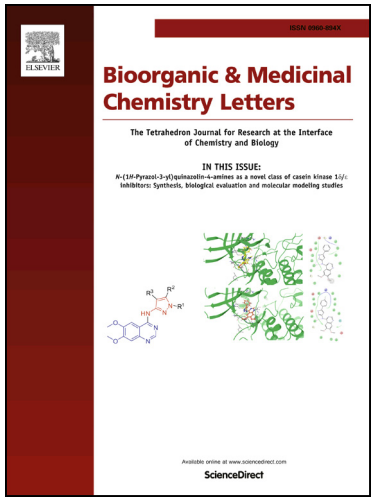

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PII: S0960-894X(17)30753-9
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.07.046
Reference: BMCL 25159

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 1 May 2017
Revised Date: 15 July 2017
Accepted Date: 18 July 2017

Please cite this article as: Hu, S., Yuan, L., Yan, H., Li, Z., Design, synthesis and biological evaluation of Lenalidomide derivatives as tumor angiogenesis inhibitor, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.07.046

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Design, synthesis and biological evaluation of Lenalidomide derivatives as tumor angiogenesis inhibitor

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Lenalidomide derivatives
Angiogenesis inhibitors
Molecular docking
Synthesis
CCK-8

ABSTRACT

Lenalidomide is a type of immunomodulatory agent with anti-tumor activity by mainly expressed in the anti-angiogenesis. In order to enhance the pharmacological activity of Lenalidomide, a series of Lenalidomide derivatives were designed as tumor angiogenesis inhibitors. The potential anti-angiogenesis targets of Lenalidomide derivatives were virtual screened on Auto-Dock 4.0 by using reverse docking method. The six target proteins, such as vascular endothelial growth factor receptor, epidermal growth factor receptor, fibroblast growth factor receptor, BCR-ABL tyrosine kinase, p38 mitogen activated protein kinase and metal protein kinase, were chosen as the targets. The Lenalidomide derivatives were synthesized by alkylated, acylated or sulfonylated Lenalidomide and verified by the ^{1}H-NMR, ^{13}C-NMR and LC-MS. Their anti-cancer activities were detected by using CCK-8 in the esophageal carcinoma cell line EC9706. The results indicate that the inhibitory activities of Lenalidomide derivatives were higher than that of Lenalidomide.

Angiogenesis, which is regulated by a host of growth factors in the microenvironment, plays an important role in the tumour growth, invasion and metastasis.[1,2] Inhibition of tumour angiogenesis, through small molecules acting on endothelial cell surface receptors to cut the signal downstream to block up blood vessels, has been widely used for treatment of malignant tumour.[3] The FDA has approved drugs that have anti-angiogenic activity, including Thalidomide and Erlotinib et al **(Fig. 1)**.[4]

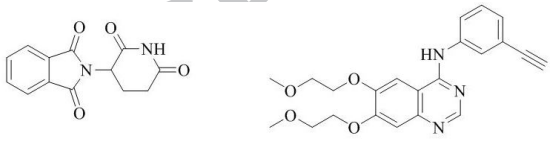
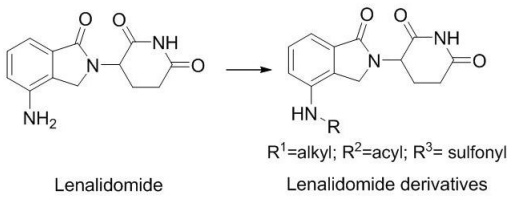


Fig. 1 Chemical structures of Thalidomide and Erlotinib

Lenalidomide, [3-(4-Amino-1-oxo-1,3-dihydro-2H-isoindol-2-yl)piperidine-2,6-dione], is a derivative of Thalidomide introduced in 2004. It was initially intended as a treatment for multiple myeloma. Now, it has been used to successfully treat for inflammatory disorders and tumors, such as myelodysplastic syndromes, Hodgkin's lymphoma and some solid cancers.[5] Lenalidomide has various activities, including direct anti-tumor effect, inhibition of angiogenesis and immunomodulatory role. It induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support.[6] Clinical studies have shown that Lenalidomide manifests fewer side effects and almost no neurological toxicity and teratogenicity, compared with Thalidomide.[7,8] It has been increasingly used in combination with other chemotherapy drugs in a variety of hematopathy and solid tumors.[9-14]

In order to enhance the pharmacological activity of Lenalidomide, a series of Lenalidomide derivatives **(Scheme 1)** were designed by the reverse virtual screening of the molecular targets of anti-angiogenesis on Auto-Dock 4.0. The Lenalidomide derivatives (**1**, **2** and **3**) were synthesized by the alkylation, acylation and sulfonylation of Lenalidomide. CCK-8 was used to detect the inhibitory activity in the esophageal carcinoma cell line EC9706.



Scheme 1 Lenalidomide and its derivatives

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