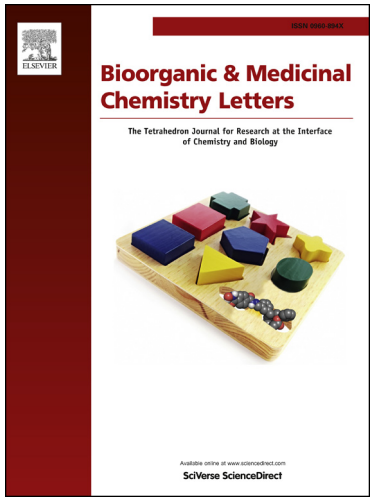


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PII: S0960-894X(15)30114-1
DOI: http://dx.doi.org/10.1016/j.bmcl.2015.10.006
Reference: BMCL 23162

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 1 September 2015
Revised Date: 29 September 2015
Accepted Date: 3 October 2015

Please cite this article as: Peng, F-W., Wu, T-T., Zeng, Z-W., Xue, J-Y., Shi, L., Hybrids from 4-anilinoquinazoline and hydroxamic acid as dual inhibitors of vascular endothelial growth factor receptor-2 and histone deacetylase, *Bioorganic & Medicinal Chemistry Letters* (2015), doi: http://dx.doi.org/10.1016/j.bmcl.2015.10.006

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

# Hybrids from 4-anilinoquinazoline and hydroxamic acid as dual inhibitors of vascular endothelial growth factor receptor-2 and histone deacetylase

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ARTICLE INFO

*Article history:*
Received
Revised
Accepted
Available online

*Keywords:*
Hybrid
4-Anilinoquinazoline
Hydroxamic acid
VEGFR-2
HDAC

ABSTRACT

A series of hybrids derived from 4-anilinoquinazoline and hydroxamic acid were designed, synthesized, and evaluated as dual inhibitors of vascular endothelia growth factor receptor-2 (VEGFR-2) tyrosine kinase and histone deacetylase (HDAC). Most of these compounds exhibited potent HDAC inhibition and moderate VEGFR-2 inhibition. Among them, compound **6l** exhibited the most potent inhibitory activities against VEGFR-2 ($IC_{50}$ = 84 nM ) and HDAC ($IC_{50}$ = 2.8 nM). It also showed the most potent antiproliferative ability against MCF-7, a human breast cancer line, with $IC_{50}$ of 1.2 μM. Docking simulation supported the initial pharmacophoric hypothesis and suggested a common mode of interaction of compound **6l** at the active binding sites of VEGFR-2 and HDAC.

Angiogenesis plays a pivotal role in the growth of most solid tumors and also contributes to the progression of tumor metastasis [1,2]. Vascular endothelial growth factor (VEGF) and its receptor tyrosine kinases VEGFR-2 or kinase insert domain receptor (KDR) are key regulators of angiogenesis [3-5]. Upon binding to VEGF, VEGFR-2 undergoes ligand-induced dimerization and autophosphorylation and initiates downstream signaling, ultimately leading to angiogenesis, tumor survival, proliferation, and migration [6-8]. The inhibition of the VEGF/VEGFR-2 pathway has become a valuable approach in the treatment of cancers. This is evident from the approval of the anti-VEGF monoclonal antibody Bevacizumab for the treatment of non-small-cell lung, colorectal, breast, kidney, and brain cancer by FDA [9,10]. Additionally, the small-molecule VEGFR-2 tyrosine kinase inhibitors such as sorafenib [11], sunitinib [12], vandetanib [13], and pazopanib [14] have been approved by FDA for treatment of diverse cancers. Recently, many researchers including us have been pursuing VEGFR-2 kinase domain inhibitors to discover novel anti-angiogenic drugs [15-19]. Unfortunately, a large number of patients do not respond to VEGF/VEGFR-2 targeted therapy. In addition, the duration of benefit from VEGF/VEGFR-2 targeted therapy can be relatively short. Ultimately, the majority of patients who initially respond to therapy will develop acquired resistance [20-22]. In order to overcome the acquired drug resistance to tyrosine kinase inhibitors (TKIs), including VEGFR-2 TKIs, a number of strategies have been tested, such as development of multi-targeted inhibitors and combination therapies [23-26].

Histone deacetylases (HDACs) are a class of enzymes which catalyze the removal of acetyl groups from lysine residues in histone amino termini, leading to chromatin condensation and transcriptional repression [27,28]. The eighteen HDACs identified in humans are classified in four classes depending on their sequence homology to yeast HDACs, their subcellular localization and their enzymatic activities [28]. Among them, Classes I (HDAC1, HDAC2, HDAC3, and HDAC8), II (HDAC4, HDAC5, HDAC6, HDAC7, HDAC9, and HDAC10) and IV (HDAC11) are zinc dependent metalloproteins [29]. It has been widely recognized that HDACs are diversely implied in cancer progression. HDAC inhibitors (HDACI) can affect tumour cell growth and survival by blocking the deacetylation of histone or nonhistone proteins (such as α-tubulin, Hsp90, and transcription factors p53 and NF-κB), inducing cell cycle arrest, angiogenesis suppression, tumor cell antigenicity enhancement, and apoptosis [30]. Recently immense efforts have been made to develop novel HDAC inhibitors [31-38].

Although HDACI show promise as single-agent anticancer drugs, given the range of molecular and biological responses that these agents can elicit and minimal toxicity to normal cells, their use in combination with other anticancer agents could prove to be their most useful application. Indeed, HDACI have been already shown to function synergistically with a host of structurally and functionally diverse chemical compounds [30]. For example, HDACI can function synergistically with imatinib, an ABL kinase inhibitor which can kill BCR-ABL positive chronic myeloid leukemia (CML) cells, to enhance apoptosis in BCR-