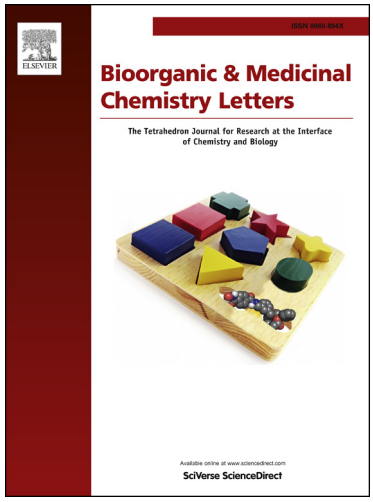


# Hybrids from 4-anilinoquinazoline and hydroxamic acid as dual inhibitors of vascular endothelial growth factor receptor-2 and histone deacetylase

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

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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].

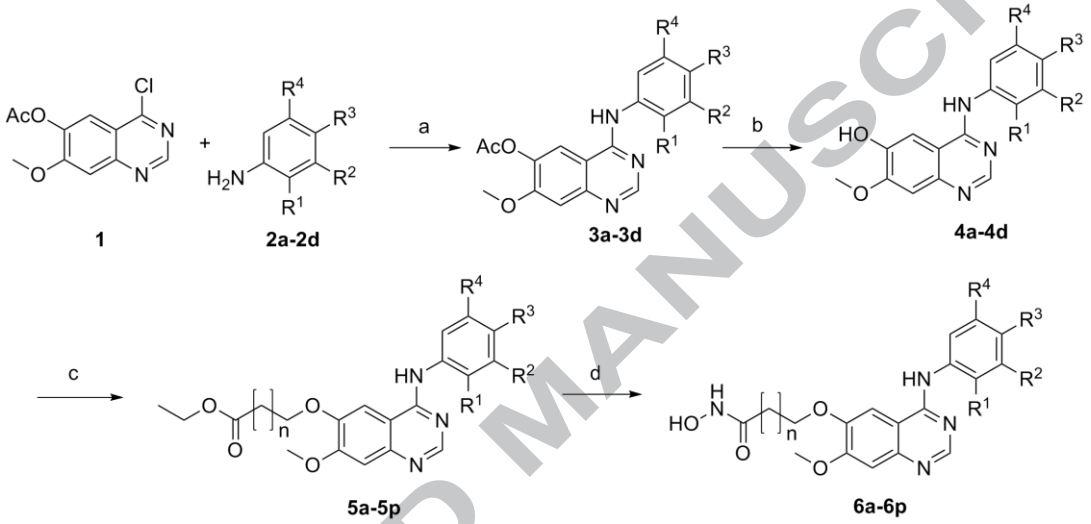
Histone deacetylases (HDACs) are a class of enzymes which catalyze the removal of acetyl groups from lysine residues in histone amino termini, leading to chromatin condensation and transcriptional repression [27,28]. The eighteen HDACs identified in humans are classified in four classes depending on 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-

ABL expressing CML cells [39, 40]. More importantly, HDACI in combination with imatinib was effective against imatinib-refractory CML, and both wild-type BCR-ABL and the T315I mutant form of BCR-ABL, which is resistant to imatinib, were equivalently degraded following combination treatment [39, 40].

Unlike combinations of TKI and HDACI, a single agent with VEGFR-2 and HDAC inhibitory activities offers some advantages, such as concurrent pharmacokinetics, decreasing drug-drug interactions caused by multiple drugs and off-target adverse effects, increasing patient compliance, and reducing drug cost. Recently, multi-acting inhibitors against HDAC and RTK have been reported as potent anticancer agent [41-44]. In this paper, a series of hybrids with 4-anilinoquinazoline and hydroxamic acid motifs were discovered as novel VEGFR-2/HDAC dual inhibitors.

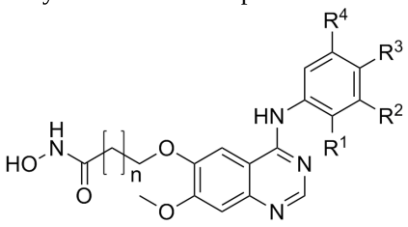
The preparation of target compounds followed the general reaction route outlined in Scheme 1 [41]. Compounds **3a**-**3d** were prepared through the coupling of 4-chloro-7-methoxyquinazolin-6-yl acetate (**1**) with substituted anilines (**2a**-**2d**). Hydrolysis of the acetyl group on compounds **3a**-**3d** using lithium hydroxide gave corresponding phenol intermediates **4a**-**4d**. Alkylation of the hydroxyl group on compounds **4a**-**4d** with various chain lengths of ethyl bromoalkanoate gave ethyl ester intermediates **5a**-**5p**. Conversion of ethyl esters **5a**-**5p** to hydroxamic acids using freshly prepared hydroxylamine furnished target hybrids **6a**-**6p**. The structures of all the synthesized intermediates and target compounds were confirmed by $^1$H-NMR, ESI-MS and elemental analyses.




**Scheme 1.** Synthesis of compounds **6a**-**6p**. Reagents and conditions: (a) isopropanol, refiux; (b) LiOH.$H_2O$, $CH_3OH$, $H_2O$; (c) ethyl bromoalkanoate, $K_2CO_3$, DMF, 40 $^oC$; (d) $NH_2OH$, $CH_3OH$, 0 $^oC$.

The *in vitro* inhibitory activities of the target compounds against VEGFR-2 and HDAC were evaluated. VEGFR-2 kinase inhibitory activity was measured using HTScan VEGF Receptor 2 Kinase Assay Kit (Cell Signaling Technology, Inc.) by colorimetric ELISA assay according to the manufacturer's instructions [17]. HDAC inhibitory activity was measured using the Fluor de Lys HDAC fluorometric activity assay kit (Enzo Life Sciences, Inc.) [45]. Besides, the *in vitro* antiproliferative activities of the targeted hybrids against MCF-7 (a human breast adenocarcinoma cell line) were also evaluated by MTT assay [17]. The biological results were summarized in Table 1.

**Table 1.** *In vitro* enzyme inhibitory activities and antiproliferative activities of target compounds.




| Compouds | $R^1$ | $R^2$ | $R^3$ | $R^4$ | n | $IC_{50}$ | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | VEGFR-2 (nM) | HDAC (nM) | MCF-7 (μM) |
| **6a** | H | Cl | H | H | 2 | 476 | 645 | >100 |
| **6b** | H | Cl | H | H | 3 | 352 | 121 | 65.2 |
| **6c** | H | Cl | H | H | 4 | 613 | 17 | 8.6 |
| **6d** | H | Cl | H | H | 5 | 501 | 5.4 | 3.2 |
| **6e** | H | Br | H | H | 2 | 625 | 531 | >100 |
| **6f** | H | Br | H | H | 3 | 434 | 97 | 68.4 |
| **6g** | H | Br | H | H | 4 | 415 | 15 | 8.5 |
| **6h** | H | Br | H | H | 5 | 462 | 4.5 | 2.8 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **6i** | Cl | H | Cl | H | 2 | 370 | 215 | 95.0 |
| **6j** | Cl | H | Cl | H | 3 | 138 | 86 | 56.8 |
| **6k** | Cl | H | Cl | H | 4 | 115 | 14 | 6.4 |
| **6l** | Cl | H | Cl | H | 5 | 84 | 2.8 | 1.2 |
| **6m** | Cl | H | H | Cl | 2 | 1260 | 348 | >100 |
| **6n** | Cl | H | H | Cl | 3 | 2140 | 57 | 44.5 |
| **6o** | Cl | H | H | Cl | 4 | 5200 | 21 | 13.7 |
| **6p** | Cl | H | H | Cl | 5 | 2450 | 8.4 | 4.0 |
| **Vandetanib** | - | - | - | - | - | 62 | >10000 | 18.5 |
| **Vorinostat** | - | - | - | - | - | >10000 | 12 | 4.5 |

As shown in Table 1, the synthesized hybrids **6a-6p** showed moderate VEGFR-2 inhibitory activities. Among them, compound **6l** exhibited the most potent inhibitory activity against VEGFR-2 kinase with $IC_{50}$ of 84 nM, which was comparable to the reference VEGFR-2 TKI Vandetanib ($IC_{50}$ = 62 nM). Comparison of the VEGFR-2 inhibition of compounds **6i-6l** with the same substituents on the phenyl ring indicated that increasing the length of the hydroxamic acid side chain increases VEGFR-2 inhibitory activity. However, this rule did not exist in other compounds with the same substituents on the phenyl ring but different hydroxamic acid chains. On the other hand, the type, number and position of halogen substituent on the phenyl ring play key roles in the VEGFR-2 inhibition. Comparison of VEGFR-2 inhibition of compounds **6d** ($IC_{50}$ = 501 nM), **6h** ($IC_{50}$ = 462 nM), **6l** ($IC_{50}$ = 84 nM) and **6p** ($IC_{50}$ = 2450 nM) with the same length of hydroxamic acid side chain demonstrated that introduction of 2,4-dichloro substituents on the phenyl ring is preferred for the VEGFR-2 inhibition.

The well accepted pharmacophore for HDACI, comprising the zinc binding group chelating the zinc atom in the active site (such as hydroxamic acid moiety), a linker that accommodate the tubular access of the active site, and a cap group for interactions with the external surface. Data in Table 1 illustrated that most of the target hybrids **6a-6p** exhibited potent HDAC inhibitory activities, which suggested that the quinazolin-4-aniline motif is a suitable cap group for HDAC inhibitor. It is noteworthy that, compound **6l** with the most potent VEGFR-2 inhibitory activity also exhibited the most potent HDAC inhibitory activity with $IC_{50}$ of 2.8 nM, which promoted the potency significantly by nearly 5-fold compared to that of reference HDACI Vorinostat ($IC_{50}$ = 12 nM). Increasing the length of the hydroxamic acid side chain increases HDAC inhibitory activity by comparing the HDAC inhibitory activity of compounds **6i-6l** with the same substituent on the phenyl ring. Compoud **6i** with the shortest chain (n = 2) showed the weakest HDAC inhibitory activity with $IC_{50}$ of 215 nM. Moderate HDAC inhibition was observed when the carbon chain length reached 4 carbons (n = 3, compound **6j**, $IC_{50}$ = 86 nM). The HDAC inhibitory activity further increased with the carbon chain length reached 5 carbons (n = 4, compound **6k**, $IC_{50}$ = 14 nM). The optimal carbon chain length is 6 carbons (n = 5, compound **6l**, $IC_{50}$ = 2.8 nM). This discipline was also found in other halogen substituted hybrids. Comparison of HDAC inhibition of compounds **6d** ($IC_{50}$ = 5.4 nM), **6h** ($IC_{50}$ = 4.5 nM), **6l** ($IC_{50}$ = 2.8 nM) and **6p** ($IC_{50}$ = 8.4 nM) with the same hydroxamic acid side chain suggested that the the length of the hydroxamic acid side chain rather than the halogen substituents on the phenyl ring is the dominating factor for the HDAC inhibition.

To further explore the antitumor effect of these hybrids, all the synthesized compounds **6a-6p** were evaluated for their *in vitro* anticancer activities against MCF-7 (a human breast cancer cell line) by MTT assay. The results were summarized in Table 1. Among these compounds, compound **6l** with the most potent VEGFR-2 and HDAC inhibitory activity also exhibited the most potent anticancer activities with the $IC_{50}$ of 1.2 μM against MCF-7, which showed greater potency than the reference compounds Vandetanib ($IC_{50}$ = 18.5 μM) and Vorinostat ($IC_{50}$ = 4.5 μM). It seemed that the SARs analysis result of antiproliferation activities of the target hybrids were more consistent with their HDAC inhibitory activities, probably due to their potent inhibitory activities against HDAC but moderate inhibitory activities against VEGFR-2.

To investigate the HDAC isoform selectivity, representative compound **6l** with the most potent HDAC inhibitory activity and highest antiproliferative activity against MCF-7 was chosen to conduct enzyme inhibitory assays against HDAC1, HDAC2, HDAC6 and HDAC8. Results in Table 2 showed that compound **6l** exhibited potent inhibition against HDAC1, HDAC2, HDAC6 and HDAC8, with $IC_{50}$ of 3.5 nM, 6.8 nM, 25.5 nM and 5.2 nM, respectively. The most potent compound **6l** was also selected to further test their antiproliferative activity against four types of human cancer cell lines, including a human breast cancer cell line MCF-7, a human liver cancer cell line HepG2, a human lung cancer cell line A549, and a human colon cancer cell line HCT-116 (Table 2). Results showed that **6l** exhibited potent antiproliferative activities in the tested cancer cell lines.

**Table 2.** *In vitro* inhibition of HDAC isoenzymes and inhibition of proliferation in selected human cancer cell lines by compound **6l**.

| HDAC isoenzyme | $IC_{50}$ (nM) | Cell line | $IC_{50}$ (μM) |
|---|---|---|---|
| HDAC1 | 3.5 | MCF-7 | 1.2 |
| HDAC2 | 6.8 | HepG2 | 2.7 |
| HDAC6 | 25.5 | A549 | 5.4 |
| HDAC8 | 5.2 | HCT-116 | 1.8 |

Molecular docking of the most potent compound **6l** into the three dimensional X-ray structure of VEGFR-2 (PDB code: 2QU5) [46] and HDLP (HDAC homologue, PDB code: 1C3S) [47] was carried out using the Discovery Studio 3.1 CDOCKER protocol.The three-dimensional structure of the compound **6l** was constructed using ChemBio 3D Ultra 11.0 software [Chemical Structure Drawing Standard; Cambridge Soft corporation, USA (2008)], then it was energetically minimized by using MMFF94 with 5000 iterations and minimum RMS gradient of 0.10. The crystal structures of VEGFR-2 kinase and HDLP were retrieved from the RCSB Protein Data Bank (http://www.rcsb.org/pdb/home/home.-do). All bound waters and ligands were eliminated and the polar hydrogen was added. The whole 2QU5 or 1C3S was defined as a receptor and the site sphere was selected based on the binding site of 2QU5 or 1C3S.

Compound **6l**were placed during the molecular docking procedure. Types of interactions of the docked protein with ligand were analyzed after the end of molecular docking.

Figure 1 shows the possible binding modes of compound **6l** into the ATP-binding cavity of VEGFR-2 kinase. In the binding model, the imine hydrogen atom of compound **6l** forms a hydrogen bond with the carbonyl oxygen atom of Asp1046 (O...H-N: 2.5 Å). In addition, the terminal hydroxyl oxygen atom of compound **6l** forms another hydrogen bond with the amino hydrogen atom of Cys919 (O...H-N: 2.0 Å). Apart from that, the phenyl ring of quinazoline moiety form a π-σ interaction with Leu889 (distance: 2.8 Å).

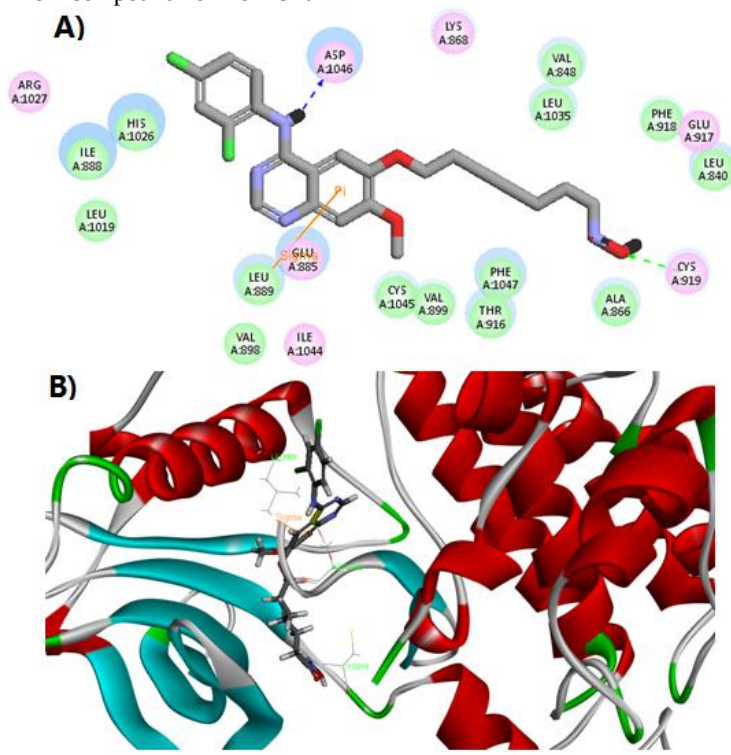



**Figure 1.** A) 2D molecular docking modeling of compound **6l** into VEGFR-2 ATP-binding cavity. The hydrogen bonds are displayed as green or blue dotted lines. The π-σ interactions are shown as yellow line. (B) 3D model of the interaction between compound **6l** and VEGFR-2 kinase ATP-binding site.

Figure 2 shows the possible binding modes of compound **6l** into the binding site of HDLP. In the binding model, the hydrogen atom in amide group of compound **6l** forms a hydrogen bond with the two carboxylic oxygen atoms of Asp168 (O...H-N: 2.4 Å). Besides, the terminal hydroxyl oxygen atom of compound **6l** forms a hydrogen bond with the amino hydrogen atom of Gly295 (O...H-N: 2.3 Å). Additionally, the terminal hydroxyl hydrogen atom of compound **6l** forms a hydrogen bond with the carbonyl oxygen atom of Gly295 (O...H-O: 2.4 Å) and also forms another hydrogen bond with the carbonyl oxygen atom of Gln254 (O...H-O: 2.4 Å). The nice binding model of compound **6l** with VEGFR-2 and HDLP suggests that compound **6l** might be a potent dual inhibitor against VEGFR-2 and HDAC.

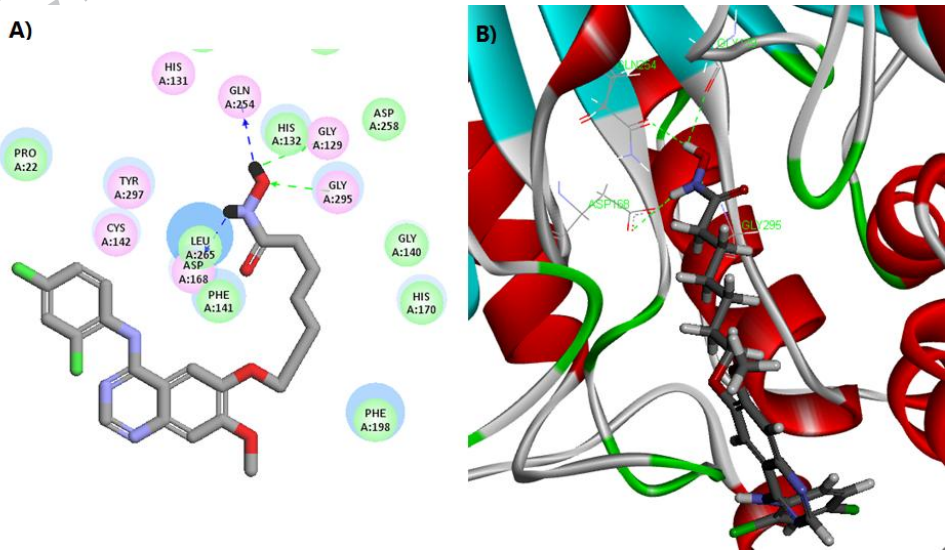



Figure 2. (A) 2D molecular docking modeling of compound **6l** into the binding site of HDLP. The hydrogen bonds are displayed as green or blue dotted lines. (B) 3D model of the interaction between compound **6l** and the active site of HDLP.

In summary, a series of hybrids combined by 4-anilinoquinazoline and hydroxamic acid moity were discovered as dual inhibitors against VEGFR-2 and HDAC. Some of these hybrids also displayed great antiproliferation potency against a human breast cancer cell line MCF-7. Compound **6l** exhibited the most potent inhibitory activity against VEGFR-2 and HDAC. Besides, it showed excellent inhibition against HDAC1, HDAC2, HDAC6 and HDAC8, which revealed its pan-HDAC inhibitory activity. It also exhibited great inhibitory potency against human cancer cell lines MCF-7, HepG2, A549, and HCT-116. Molecular docking of the compound **6l** into the active binding sites of VEGFR-2 and HDLP was performed and the result indicated that compound **6l** could be a potential dual VEGFR-2/HDAC inhibitor.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version.

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## Graphical Abstract

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

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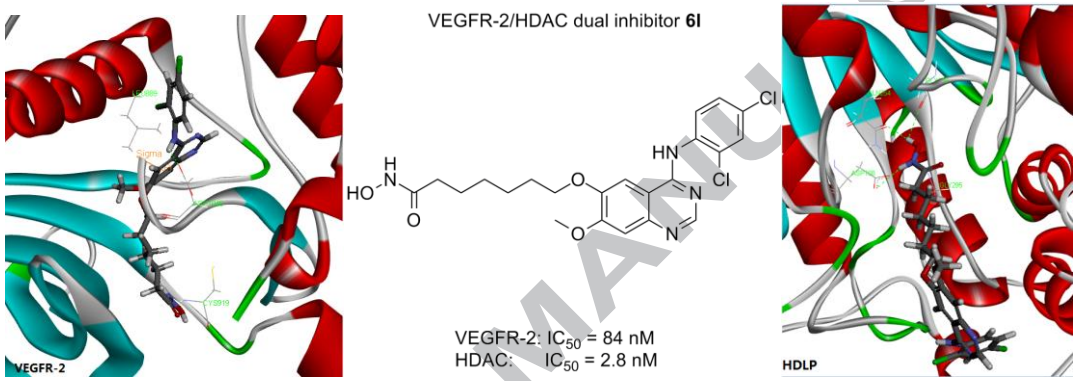
Fan-Wei Peng [a], Ting-Ting Wu [a], Zi-Wei Zeng [a], Jia-Yu Xue [b], Lei Shi [a]*




A series of hybrids from 4-anilinoquinazoline and hydroxamic acid were discovered as potent dual inhibitors of VEGFR-2 and HDAC. Compound **6l** exhibited the most potent inhibitory activities with $IC_{50}$ value of 84 nM and 2.8 nM against VEGFR-2 and HDAC, respectively.