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Design, synthesis and molecular docking of novel indole derivatives as VEGFR-2 inhibitors

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The vascular endothelial growth factor receptor-2 (VEGFR-2) is considered as the most important transducer of VEGF-dependent angiogenesis. VEGFR-2 is highly up-regulated in several solid tumors and plays a critical role in the process of tumor angiogenesis; therefore, VEGFR-2 inhibition emerged as a prime approach for discovering new therapies for many human angiogenesis-dependent malignancies. A novel series of indole derivatives was synthesized and tested for their cytotoxic activities against a panel of 60 cancer cell lines. A molecular docking study was also carried out to determine their binding modes and binding affinities in the VEGFR-2 active site using a reference VEGFR-2 inhibitor, sorafenib (Figure 1). The synthesized compounds exhibited a broad spectrum antiproliferative activity on 60 cell lines with growth inhibition percent (GI)% ranging from 31 to 82.5%. An indoloimidazolone derivative was found the most potent VEGFR-2 inhibitor with IC50 of 0.07 μM more potent than that of sorafenib (0.09 μM). The molecular docking study attributed the promising inhibitory activity on VEGFR-2 of this series to their hydrophobic interaction with the VEGFR-2 binding site hydrophobic side chains and their hydrogen bonding interaction with the key amino acids Glu885 and Asp1046.

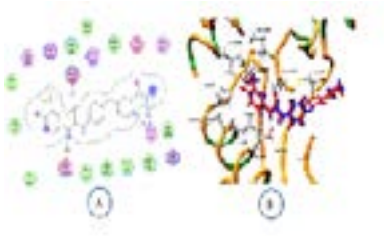

Fig.1 (A) Superimposition of the docking pose (red) and the co-crystallized (blue) of sorafenib in the VEGFR-2 active site with RMSD of 0.47Å. (B) 2D interaction diagram showing sorafenib docking pose interactions with the key amino acids (hot spots) in the VEGFR-2 active site. (Distances in Å).

Recent publications

1. H M Roaiah, I A Y Ghannam, Islam H Ali, A M El Kerdawy, M M Ali, et al. (2018) Design, synthesis, and molecular docking of novel indole scaffold-based VEGFR-2 inhibitors as targeted anticancer agents, Arch. Pharm. Chem. Life Sci. 351:e1700299.
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3. F M Awadallah, T A El-Waei, M M Hanna, S E Abbas, M Ceruso, et al. (2015) Synthesis, carbonic anhydrase inhibition and cytotoxic activity of novel chromone-based sulfonamide derivatives. Eur. J. Med. Chem. 96:425-435.
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5. S S El-Nakkady, M M Hanna, H M Roaiah and I A Y Ghannam (2012) Synthesis, molecular docking study and antitumor activity of novel 2-phenylindole derivatives. Eur. J. Med. Chem. 47:387-398.

Biography

Iman A Y Ghannam has her expertise in design and synthesis of structural mimics of drug candidates using molecular docking techniques. She is Researcher of Pharmaceutical Chemistry at Chemistry of Natural and Microbial Products Department, Pharmaceutical and Drug Industries Research Division, National Research Centre (NRC), Cairo, Egypt.

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