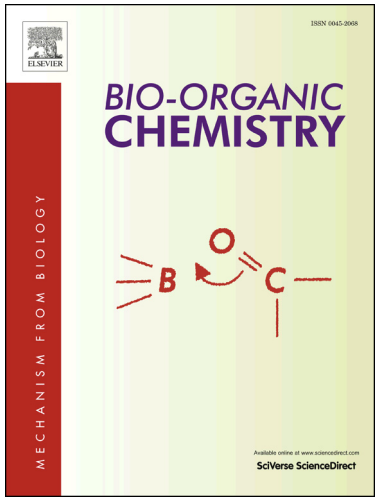

Molecular docking simulation and anticancer assessment on human breast carcinoma cell line using novel bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) and bis(1,4-dihydropyrazolo[4',3':5,6]pyrano[2,3-*b*]pyridine-6-carbonitrile) derivatives

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ABSTRACT: An efficient route for the synthesis of novel bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) derivatives is reported. The synthetic pathway involves one pot, synthesis of bis-aldehydes, malononitrile, and pyrazolone in the presence of pyridine. The anticancer activity of the synthesized products against MCF7, HEPG2, and A549 cell lines was assessed. Docking studies were performed and indicated the best binding mode compared to the standard ligand sorafenib.

KEYWORDS: Bis-aldehydes; Malononitrile; Bis-arylidenemalononitriles; Multicomponent reactions; Bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile), Docking studies, cytotoxic assay, MTT.

1. Introduction

Dihydropyrano[2,3-*c*]pyrazole scaffolds are important class of heterocycles with a wide range of biological properties such as molluscicidal activities[1,2], antimicrobial[3], anti-inflammatory[4] and anticancer[5]. They have also been identified as promising human Chk1 kinase inhibitors in computer-based screening and kinase-inhibition assays[6]. Cancer angiogenesis is a fundamental process for the tumor growth through the development of new blood vessels, potentially causing cancer progression and metastasis[7]. VEGF and its receptor are highly expressed in many tumor types, including breast cancer[8]. Therefore, they may represent potential targets for anticancer therapy. Environmental factors like hypoxia, as well as the silencing of specific tumor suppressor genes (*PTEN, p53, VHL*) or the activation of oncogenes (e.g., *RAS, SRC, EGFR, HER2*) resulted in an increased VEGF production[9]. VEGFR2 (a type II transmembrane TK receptor) is the principal mediator of the VEGF-induced angiogenic signaling. This receptor contains three different parts, including an Ig-like domain extracellular region, a hydrophobic transmembrane region containing the TK domain and the carboxyl terminal tail. VEGFR2 binds all VEGF-A isoforms, VEGF-C and VEGF-D. Contrarily, VEGFR1 is a selective ligand for VEGF-B and PlGFs peptides. Also the binding affinity of VEGF ligands to their receptors is increased by the presence of the two non-enzymatic co-receptors neuropilin (NRP)-1 and NRP-2[10]. Since NRP receptors expression correlates with tumor aggressiveness and poor prognosis, these molecules are currently studied as potential antiangiogenic targets[11]. The binding of VEGF-A to VEGFR2 induces a cascade of different signaling pathways. The dimerization of the receptor and the following autophosphorylation of the intracellular TK domains lead to the simultaneous activation of PLC-γ-Raf kinase-MEK-MAP kinase and PI3K-AKT pathways, causing cellular proliferation and endothelial-cell survival. In conjunction of our efforts the synthesis of bis-heterocycles[12–27] as well as our contribution in *C-C* bond formation through atom economically approaches as the Michael addition reactions with cinnamonitriles, enamines and azaenamines,[24,28–39] we report herein on the synthesis of bis(1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile) derivatives each linked to aliphatic, or arene core through an oxyphenyl bridge as a new class of bis(heterocycles). In ddition, as VEGFR is overexpressed on breast carcinoma and induced a cascade pathway, so the target of our studies is to find strategies for blocking these pathways using of our novels as expected anticancer agents, which may bind with the active domains of VEGFRTK and to understand their possible mechanism of action.