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A Click Synthesis, Molecular Docking, Cytotoxicity on Breast Cancer (MDA-MB 231) and anti-HIV Activities of New 1,4-disubstituted-1,2,3-triazole Thymine Derivatives

Faeza Abdul Kareem Almashal[a], Hamsa Hussein Al-Hujaj[b], Ahmed Majeed Jassem[a, 1], and Najim Aboud Al-Masoudi[c]

[a] *College of Education for Pure Sciences, Department of Chemistry, Basrah University, Basrah, Iraq*
[b] *College of Pharmacy, University of Basrah, Basrah, Iraq*
[c] *College of Science, Department of Chemistry, Basrah University, Basrah, Iraq*

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Abstract—A new series of 1,4-disubstituted-1,2,3-triazolethymine derivatives (**VIa–e**) were synthesized and characterized by spectroscopic studies. The *in vitro* cytotoxic activities of selected compounds against human cancer cell line (MDA-MB 231) were evaluated by MTT assay. 4-Azido-*N*-substituted-benzenesulfonamides(**Vc–e**) and 4,4'-(4,4'-((5-methyl-2,4-dioxopyrimidine-1,3(2*H*,4*H*)-diyl)bis(methylene))-bis(1*H*-1,2,3-triazole-4,1-diyl))-bis(*N*-(4-methyl pyrimidin-2-yl)benzenesulfonamide) (**VIc**) displayed a significant cytotoxic activity with IC_{50} values of 1.61, 1.41, 1.61 and 1.81 μM, respectively. Molecular docking study of 4-azido-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (**Vd**) and4,4'-(4,4'-((5-methyl-2,4-dioxopyrimidine-1,3(2*H*,4*H*)-diyl)bis(methylene))-bis(1*H*-1,2,3-triazole-4,1-diyl))-bis (*N*-(4-methyl pyrimidin-2-yl)benzenesulfonamide) (**VIc**) showed hydrogen bonding with the amino acid residues of the receptors 1X7R and 1A53, respectively. These derivatives are useful as starting points for further study of new anticancer drugs and to confirm the potential of triazole-sulfonamide analogues as lead compounds in anticancer drug discovery. In addition, 1,4-disubstituted-1,2,3-triazolethymine derivatives (**VIa–e**) were evaluated *in vitro* for antiviral activity against the replication of HIV-1 and HIV-2 in MT-4 cells. The results showed that 1,4-disubstituted-1,2,3-triazolethymine derivatives (**VIc–e**) possess a potent activity against HIV-1 replication with IC_{50} values of 11.42, ≥15.25,and 14.36 μM, SI > 4, ≤6, >9, respectively.

Keywords: Breast cancer cell line (MDA-MB 231), anti-HIV activity, molecular docking, click reaction, 1,2,3-triazole thymine derivatives

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INTRODUCTION

Breast cancer or metastatic breast cancer is diagnosed as an incurable disease by current-cure strategies. The breast cancer is common as a malignant disease in United States, women, accounting for > 400 deaths each year [1, 2]. Mortality from this type of cancer remains high because the current cures are limited by the emergence of the treatment-resistant cancer cells [3]. Breast cancer's treatment normally involves healing strategies such as immunotherapy, surgery, radiotherapy, and chemotherapy [4]. The developed resistance toward the chemotherapeutic agents and combined with side effects are a major obstacle to restrict a chemotherapeutic treatment of breast cancer [5]. Therefore, the synthesis of effective anti-breast cancer compounds is the top way to overcome this obstacle and lead to an obvious clinical benefit with development of effective therapies [6].

[1] Corresponding author: e-mail: ahmed.majedd@uobasrah.edu.iq

Triazole derivatives have attracted a considerable attention for the past few decades due to their chemotherapeutic values such as antimalarial [7–9], antituberculosis agents [10], anticancer [11–20], antiviral [21–23], analgesic [24], fungicidal [25–27], antimicrobial [28], anticonvulsant activity [29], Src kinase [30], neuraminidase inhibitors [31], and protein tyrosine phosphatase inhibitors [32]. The synthesis of several inhibitors for the treatment of breast cancer (*e.g.*, MCF-7 cells) has since become an emerging field. Compound **A** (Fig. 1), a 1,2,3-triazole analogue as a potent antitumor agent, exhibited an IC_{50} values of 46 nM against MCF-7 cancer cell line [33]. A 1,2,3-triazol-dithiocarbamate-urea hybrid (compound **B**), showed IC_{50} vlaues of 1.62 and 1.86 μM against MGC-803 and MCF-7 cell line, respectively [34]. Jin et al. [35] have prepared novel derivatives of phenyl-substituted berberine triazolyls with a notable anticancer activity against MCF-7 cells compared with berberine, meanwhile, Bethala *et al.* [36] have demonstrated that methyl oleate with-CH_2OH as 1,2,3-tri-