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Annals of Medicinal Chemistry and Research

Short Note

Anticancer Evaluation of S-Glycosylated Quinazolines

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Submitted: 14 July 2020

Accepted: 15 August 2020

Published: 17 August 2020

ISSN: 2378-9336

According to the world health organization (WHO), cancer is an important health problem that claims the level of more than 7 million people worldwide on an annual basis [1,2]. Because of the limitation of surgery and radiotherapy in effecting a cure for cancer, chemotherapy has been increasingly important [1,2]. Therefore, identification of novel potent, selective, and less toxic anticancer agents remains one of the most pressing health problems. In the vast cancer chemotherapeutic space, glycosides have played a very important role as established cancer chemotherapeutic agents, either in their nature, semi-synthetically, or synthetically forms [3-62]. As cited above, among the natural glycosides based antitumor the antibiotic doxorubicin, anthracycline O- glycoside, ranks among the most effective anticancer drug for acute myelocytic leukaemia [5-7]. Furthermore, many sugar modified nucleoside analogues are clinically useful chemotherapeutics [3]. For example, capecitabine [14], *N*-nucleoside and *C*-nucleoside, are applied in the treatment of metastatic breast cancer and hairy cell leukaemia, respectively. Recently, several *S*-glycosides, a new non-classical class of nucleosides, have been proved to be potential anticancer agents against many cell Lines [17-22]. Khodair et al., described the synthesis of a series of heterocyclic *S*-glycosides, thiohydantoins [31-47], rhodanines [48], thioquinazolines [49,50], thiopyridines (51-53), and thiopyrimidine [54], *S*-glycosides and revealed their potential antitumor activities.

Breast cancer is the most frequent malignancy in females. Due to its major impact on the population, this disease represents a critical public health problem that requires further research at the molecular level to define its prognosis and specific treatment. Basic research is required to accomplish this task and this involves cell lines as they can be widely used in many aspects of laboratory research and, particularly, as in vitro models in cancer research. MCF-7 is a commonly used breast cancer cell line, that has been promoted for more than 40 years by multiple research groups but its characteristics have never been gathered in a consistent review article. The current paper provides a broad description of the MCF-7 cell line, including the molecular profile, proliferation, migration, invasion, spheroid formation, its involvement in angiogenesis and lymphangiogenesis and its interaction with the mesenchymal stem cells [63].

Breast cancer is a commonly diagnosed cancer and a leading cause of cancer-related death in women worldwide [64]. It remains an area of active research both clinically and experimentally. Recent advances in metabolomics show that metabolic profiling can be useful for the identification of biomarkers in breast cancer. Metabolic profiles of human breast cancer show differences among breast cancer subtypes and offer a way to identify and develop strategies for precise prevention and treatment [65-67]. Obesity is a risk factor for breast cancer; its occurrence is positively associated with the risk of breast cancer [68,69]. Obesity is a modern disorder that has resulted, not just from changes in energy balance, but from changes in lifestyle that alter meal times and eating patterns [70,71]. These changes, as environmental factors, disrupt biological rhythms and contribute to metabolic dysfunction [72,73]. Laboratory studies have shown that the feeding timing modifies obesogenic in rodents. For example, mice fed a high-fat diet (HFD) during the light phase (rest phase for nocturnal animals) gain more weight than mice fed during the dark phase (active phase for nocturnal animals) [74]. Mice fed an HFD during both light and dark phases exhibit altered daily pattern of energy expenditure and gain body fat [75]. Time-restricted feeding (TRF) is an effective tool in obesity research in rodents. It reinforces the circadian rhythms of energy metabolism by temporal regulation of the feeding/fasting pattern to a fixed time during the dark phase of the day. Available studies have shown that TRF restores the diurnal rhythms of energy metabolism [73], and circadian gene expression [76], improves insulin sensitivity, and reduces body adiposity and inflammation in mice fed an HFD [75-77].

Our research interest focused on design and synthesize new small heterocyclic nucleosides targeting cancer especially MCF-7 and HepG2 cell lines. The elaboration of quinazoline derivatives linked with ethoxy ethyl and glycopyranose sugars (Figure 1), to form the target nucleosides was our task [49,50]. The *in vitro* cytotoxic activity against MCF-7 and HepG2 cell lines showed effective anti-proliferative activity of the analyzed derivatives with lower IC_{50} values especially **9a** with IC_{50} = 2.09 and 2.08 µM against MCF-7 and HepG2, respectively, and their treatments were safe against the normal cell line Gingival mesenchymal stem cells (GMSC). Moreover, RT-PCR reaction investigated the apoptotic pathway for the compound **9a**, which activated the P53 genes and its related genes. So, further work is recommended for developing it as a chemotherapeutic drug. We found that anticancer activity of the promising derivatives **5, 8a,b** and **9a,b** was tested against breast (MCF-7), liver (HepG2) cell lines

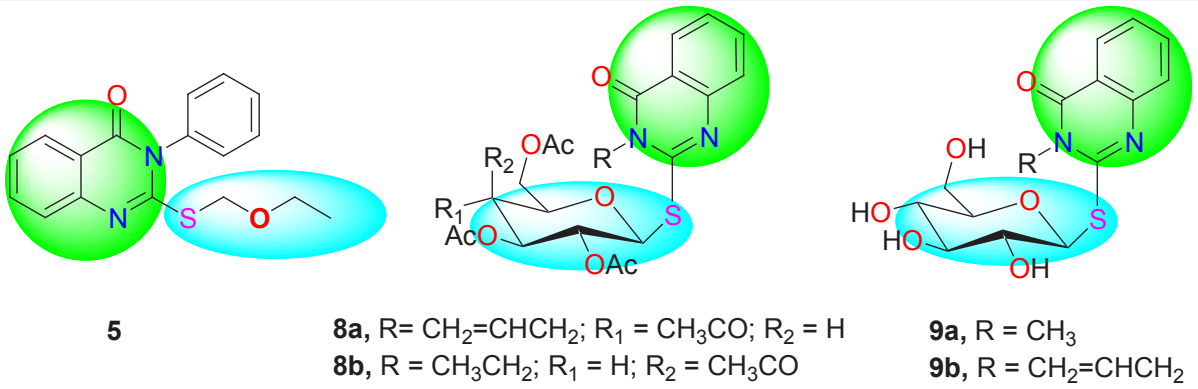

Figure 1 General structures of nucleoside drugs used in the MCF-7 and HepG2 cell lines.

Table 1: Summarized IC_{50} for the activity of the analyzed compounds against the MCF-7 and HepG2 cell lines.

	IC_{50} (µM)		
	MCF-7	**HepG2**	**GMSC**
5-FU	4.23	4.43	> 50
5	8.96	1.52	> 50
8a	5.93	3.79	> 50
8b	2.42	1.17	ND
9a	2.09	2.08	> 50
9b	2.04	2.09	> 50

ND= Not Determined

by measuring the percentage of cell survival against their serial dilutions (0.01, 0.1, 1, 10, and 100 µM) [50]. Moreover, they were screened against the GMSC as normal cell line to test their safety [50]. We conclude the incorporation of sugar portion to the nucleus, enhanced the cytotoxic activity against the MCF-7 and HepG2 cell lines by having lower IC_{50} values, as shown in **Table 1**. Although both compounds **9a** and **9b** have near IC_{50} values (**2.09** and **2.04µM**, respectively) against HepG2 cells, **9a** was considered as the lead compound in our study according to the molecular docking results. It has a higher binding affinity towards the EGFR tyrosine kinase receptor because it forms a larger number of hydrogen bonds with the key amino acid residue **Met 769** compared to other derivatives, so it was selected for further testing as the molecular mode of action. An attempt to study the structure-activity relationship using the molecular docking tool for elucidation the binding interactions of the nucleosides which might justify their higher potency [50]. Glycosides of structurally similar heterocyclic systems have been reported before [31-62].

The nucleoside bases 3-substituted 2-thioxo-2,3-dihydro-1H-quinazolin-4-ones and 3-substituted 2-thioxo-2,3-dihydro-1H-benzo[g]quinazolin-4-ones can be utilized as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides.

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Cite this article

Khodair AI, Alsafi MA (2020) Anticancer Evaluation of S-Glycosylated Quinazolines. Ann Med Chem Res 5(1): 1024.