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New *N*-ribosides and *N*-mannosides of Rhodamine Derivatives for Suppressing Leukemia Cell Line Growth

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Introduction

Leukemia is a tumor of the primary blood-forming cells. leukemia is not only a cancer of the white blood cells but also it originates in other blood cell types. Types of leukemia are categorized based on the rate of growth to acute (fast-growing) or chronic (slower growing), and whether it arises in myeloid cells or lymphoid cells. Different types of leukemia have a different line of treatment and prognosis.

Nucleoside drugs have high clinical efficacy in alleviating cancer. Currently, different drugs are prescribed in the treatment of Leukemia [1-4]. For examples, Fludarabine, Cladribine, Clofarabine, Troxacitabine, and Pentostatin (Figure 1). Pentostatin is a deoxy sugar of imidazolodiazepine architecture. Pentostatin is an antimetabolite drug used in hairy cell leukemia. Cytarabine is an antimetabolite drug which arrests cell in the S phase. It should be activated intracellular to the nucleotide metabolite ara-CTP. It is used in different types of Leukemia such as acute or chronic in addition to non-Hodgkin lymphoma. Liposomal cytarabine is prescribed in the cancer of the lymph system that has spread to the brain. Nucleosides, as small molecule drug candidates especially *N*-ribosylation and *N*-mannosylation compounds have a great role in anticancer activity.

Our research interest focused on design and synthesize new small heterocyclic nucleosides targeting cancer especially leukemia [5]. The elaboration of rhodanine derivatives linked with ribofuranose and mannopyranose sugars (Figure 1) to form the target nucleosides was our task [6]. Judging from drugs chemical structure, we can conclude that these drugs contain two moieties: a) glycoside part either sugar, deoxy sugar or dioxane. the second moiety is the aglycone part which complement different varieties of the heterocyclic core. In this regard, our compounds were designed and synthesized to target Leukemia. All compounds were synthesized and confirmed by different analyses methods and were screened against leukaemia 1210. These compounds were found to be considerably less potent (Ic50% 1.4-10.6 μM) than doxorubicin (Ic50% 0.02 μM). Compounds Id and IIb, with ribose moiety, have better activity than those with mannose sugar. DFT

Compound	IC_5 [a] (μM) cellules L-1210 0
Ia	12
Ib	5.2
Ic	10.6
Id	1.4
IIa	1.6
IIb	6.3
IIIa	4.5
IIIb	2.3
Doxorubicin	0.02

[a]50% Inhibitory concentration: molar concentration of compound that cause 50% inhibition for cell growth.

Table 1: Antitumor activity of 5-((Z)-arylidene)-3-(β-D-ribofuranosyl)-2-thioxo-4- thiazolidinones (**Ia-d, IIa,b**), and 5-((Z)-arylidene)-3-(β-D-mannopyranos-yl)-2-thioxo-4-thiazolidinones (**IIIa,b**) against leukaemia-1210.

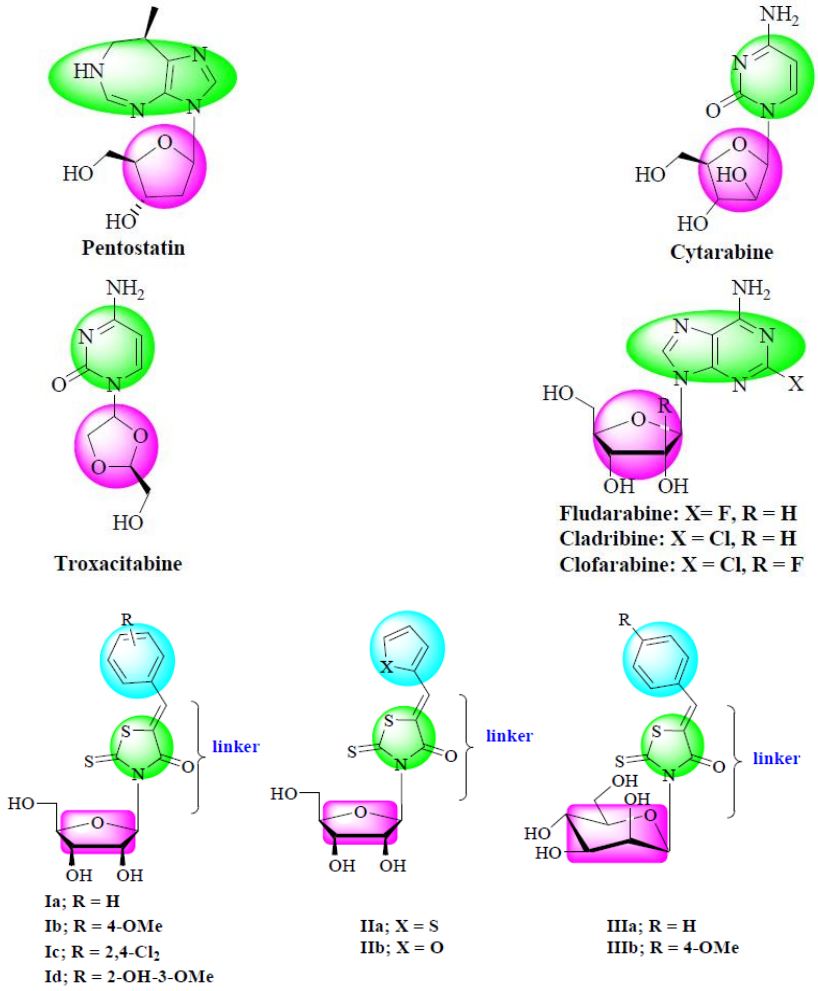

Figure 1: General structures of nucleoside drugs used in leukemia and our tested compounds.

calculations with B3LYP/6-31+G (d) level were used to analyze the electronic and geometric characteristics deduced from the stable structure of the compounds. The principal quantum chemical descriptors showed a good correlation with the experimental observations. Rapid Overlay Chemical Similarity (ROCS) study was operated to explain the similarity of the compounds and to figure out the most important pharmacophoric features. Glycosides of structurally similar heterocyclic systems have been reported before [7-15].

The electronic and geometric structures [16-25] were deduced from DFT calculations with B3LYP/6-31 + G (d) level to analyze the stable structure of the compounds. The quantum chemical parameters obtained from the calculations showed a good correlation with the experimental observations. ROCS analysis [26-28] showed that the sugar part is an important molecular descriptor. 3D-QSAR showed ribose (furanose skeleton) has better inactivity than mannose (hexoses). The aryl part has EDG capability to form HB with receptors. The antiviral and the antitumor activities of the newly prepared compounds are under investigation and will be reported in the due time. The nucleoside bases I, II and III can be utilized as starting materials for the synthesis of other carbohydrate derivatives as deoxy, amino and azido nucleosides.

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