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Synthesis, molecular docking study and thymidine phosphorylase inhibitory activity of 3-formylcoumarin derivatives

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ABSTRACT

Thymidine phosphorylase (TP) over expression plays role in several pathological conditions, such as rheumatoid arthritis, chronic inflammatory diseases, psoriasis, and tumor angiogenesis. The inhibitor of this enzyme plays an important role in preventing the serious threat due to over expression of TP. In this regard, a series of seventeenanalogs of 3-formylcoumarin (**1–17**) were synthesized, characterized by ^{1}HNMR and EI-MS and screened for thymidine phosphorylaseinhibitory activity. All analogs showed a variable degree of thymidine phosphorylase inhibition with IC_{50} values ranging between 0.90 ± 0.01 and 53.50 ± 1.20 μM when compared with the standard inhibitor 7-Deazaxanthine having IC_{50} value 38.68 ± 1.12 μM. Among the series, fifteenanalogs such as **1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 16** and **17** showed excellent inhibition which is many folds better than the standard 7-Deazaxanthine whiletwo analogs **13** and **14** showed good inhibition. The structure activity relationship (SAR) was mainly based upon by bring about difference of substituents on phenyl ring. Molecular docking study was carried out to understand the binding interaction of the most active analogs.

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1. Introduction

Angiogenesis is the formation of new blood vessels from pre-existing vessels and it is essential for organ growth and repair. However, it is well known that this is a vital step in the process of cancer growth [1,2]. Thus, angiogenesis inhibitors are believed to be potential candidates for blocking cancer growth. In particular, thymidine phosphorylase (TP) is a pro-angiogenic factor which catalyzes the reversible phosphorolysis of thymidine into thymine and 2′-deoxy-D-ribose 1-phosphate [3,4]. The 2′-deoxy-D-ribose 1-phosphate undergoes further dephosphorylation to produce 2′-deoxy-D-ribose which stimulates the secretion of vascular endothelial growth factor (VEGF). VEGF activates a number of processes including endothelial cells for secretion of matrix metalloproteinase, proliferation, and migration of endothelial cells to tumor tissue. These actions result in fast generation of new blood vessels and cancer metastasis [5]. TP inhibitors affect the production of 2′-deoxy-D-ribose and in turn suppress tumor growth [6]. Therefore, there is an urgent need to develop new and potent thymidine phosphorylase inhibitors which have the ability to suppress the formation of new blood vessels and stop tumor growth. A number of efforts have been reported on the development of TP inhibitors [7–14]. The pyrimidine derivative 5-chloro-6-[1-(2-iminopyrrolidinyl)methyl] uracilhydrochloride (TPI) is the most potent inhibitor of human TP known till date and 7-deazaxanthine (7DX) is the first purine derivative identified as TP inhibitor (Fig. 1) [15–17].

Coumarin and their derivatives have attracted considerable attention from organic and medicinal chemists over the decades. They are widely used as additives in food, perfumes, agrochemicals, cosmetics, pharmaceuticals [18] and in the preparations of insecticides, optical brightening agents, dispersed fluorescent and tunable laser dye [19]. Coumarin and its derivatives have varied bioactivities such as antimicrobial [20–23], antidepressant [24],

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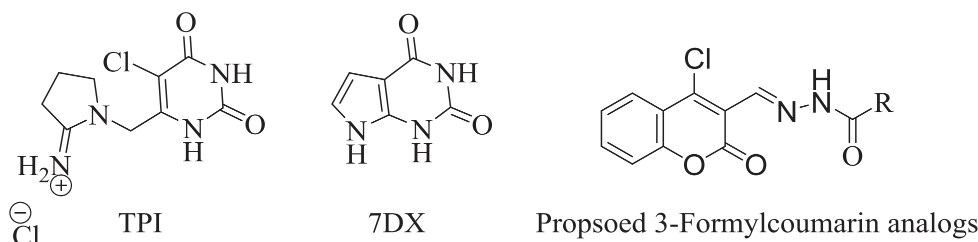

Fig. 1. Structure of known TP inhibitors- TPI and 7DX and proposed 3-formylcoumarin analogs as new class of thymidine phosphorylase inhibitor.

antioxidant [25], anti-inflammatory [26], antinociceptive [27], antitumor [28] activities. Coumarins also act as intermediates for the synthesis of furocoumarins, chromenes, coumarones and 2-acylresorcinols [29]. Our group is constantly working on enzymes inhibition study [30]. Keeping in view the basic skeleton of TP inhibitor having heterocyclic ring and number of nitrogen atoms, here in this paper we have plan to synthesize 3-formylcoumarin analogs and their evaluation for thymidine phosphorylase inhibitory potential.

2. Results and discussion

2.1. Chemistry

4-chloro-2-oxo-2H-chromene-3-carbohydrazones was mixed and refluxed with different substituted aryl-hydrazide in methanol in the presence of few drops of acetic acid to give us 4-chloro-2-oxo-2H-chromene-3-carbohydrazones (1–17). All the synthesized analogs were characterized by different spectroscopic techniques such as ^{1}HNMR, EI-MS.

2.2. In vitro thymidine phosphorylase inhibitory activity

We have synthesized seventeen analogs of 3-formylcoumarin (**1**–**17**) and screened for thymidine phosphorylaseinhibitory activity. Among the series, all analogs showed a variable degree of thymidine phosphorylase inhibition with IC_{50} values ranging between 0.90 ± 0.01 and 53.50 ± 1.20 μM when compared with standard 7-Deazaxanthine having IC_{50} value 38.68 ± 1.12 μM. Out of seventeen analogs, fifteenanalogs **1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11,12, 15, 16** and **17** showed outstanding inhibition with IC_{50} values 13.40 ± 0.1, 29.30 ± 0.60, 23.50 ± 0.20, 3.50 ± 0.1, 01.20 ± 0.01, 4.50 ± 0.01, 29.30 ± 0.80, 1.30 ± 0.10, 24.40 ± 0.50, 31.20 ± 0.90, 34.50 ± 0. 1, 38.30 ± 0.90, 13.20 ± 0.20, 0.90 ± 0.01 and 16.30 ± 0.20 μM respectively, which is many folds better than the standard 7-Deazaxanthine. Two analogs **13** and **14** showed moderate inhibition with IC_{50} values 41.60 ± 1.10 and 53.50 ± 1.20 μM respectively. The structure activity relationship was mainly based upon by bring about difference of substituents on phenyl ring.

The most active analog among the series is analog **16**having quinolone moiety directly attached to the phenyl ring.

If we compare analog **3** having IC_{50} value 23.50 ± 0.20 μM with analog **9** having IC_{50} value 24.40 ± 0.50 μM and analog **13** with IC_{50} value 41.60 ± 1.10 μM, all three analogs have methoxy groups at the phenyl ring but position of the methoxy groups are different. In analog **3,** the methoxy group is present at 3,4-positions on the phenyl ring while in analog **9,** the methoxy group is present at 2,4-positions on the phenyl ring and in analog **13,** the methoxy group is present at 3,5-positions. The difference in the activity of these three analogs may be due to the different position of the substituents on the phenyl ring.

By comparing analog **11** having IC_{50} value 34.50 ± 0.1 μM with analog **12** having IC_{50} value 38.30 ± 0.90 μM, both analogs have methoxy group, but the arrangement of methoxy group is different in them which confirm that the difference in position of substituents greatly affect the inhibitory potentials of the compounds.

All those analogs having hydroxyl group on phenyl ring like analog **4, 8** and **15** showed greater potential among the series. The analog **8**, a 3,4,5-tri-hydroxy analog (IC_{50} value 1.30 ± 0.10 μ M) show greater potential as compare to 2,3-di-hydroxy analog **4** (IC_{50} value 3.50 ± 0.1 μM) and 2-hydroxy analog **15** (IC_{50} value 13 .20 ± 0.20 μM). This show that increasing the number of hydroxyl group correspondingly increase the inhibitory potential which might be due to greater number of hydrogen bonding with active site of enzyme.

Among the halogenated analogs, the chloro analog like analog **17**(IC_{50} value 16.30 ± 0.20) showed greater potential as compare to the bromo analog like analog **2**(IC_{50} value 29.30 ± 0.60) which might be due the greater electronegativity of the chloro group.

In this study, we observed that either EWG or EDG on phenyl ring showed potential but the slight difference in potential was mainly effected by the position of the substituent as well as in some cases the number of substituent also play a role. To understand the binding interaction of the most active analogs molecular docking study was performed.

2.3. Molecular docking

Molecular docking had been performed on all coumarins (**1**–**17**) to identify plausible binding mode that is able to explain their inhibitory activity. The docking studies had been performed with reference to Taha et al. (2016) [31]. In this study, cluster analysis provides the data on binding position having the highest probability with reference to stability of the ligand-substrate complex. Docking for the most active derivative, compound **16**, showed that it interacts with enzyme through a number of hydrogen bonds and hydrophobic interactions (Fig. 2). The docking results showed that compound **16** occupies the phosphate binding site with a total of four hydrogen bond interactions. Oxygen on carbonyl (C=O) of coumarin ring forms a hydrogen bond with the backbone (N) of Gly118 at a distance of 2.87 Å. On the other hand, amino (NH) on the hydrazone linkage was found to interact with the backbone (O) of hydrophobic residue Leu117 (2.88 Å), preventing the enzyme from binding pyrimidine ribonucleosides. Carbonyl oxygen of quinolinone ring is able to form hydrogen bonds with important amino acids Gly114 (3.13 Å) and Ser113(2.96 Å). These interactions are believed to be important in decreasing the nucleophilic properties of the phosphate thus preventing any phosphorolysis from taking place. On the other hand, His85, which plays an important role in regulating the nucleophilicity of the phosphate through the donation or acception of a proton in the consequent steps of the reaction, forms a π-π *T*-shaped interaction with the hydropyridinone moiety of quinolinone. Other hydrogen bond for compound **16** includes carbonyl (C=O) of the hydrazone linkage interacting with Thr87 (O) at a distance of 2.48 Å and carbonyl of quinoline interacting with Ser113 (O) at 2.96 Å. Residues in hydrophobic pocket, Phe210 and His119, were observed to provide

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