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Research paper

Design, synthesis, anticancer, antimicrobial activities and molecular docking studies of theophylline containing acetylenes and theophylline containing 1,2,3-triazoles with variant nucleoside derivatives

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ABSTRACT

A new series of theophylline containing acetylene derivatives (**6a**–**6b** and **7**–**13**) and theophylline containing 1,2,3-triazoles with variant nucleoside derivatives (**20**–**32**) have been designed and synthesized. These compounds were screened for anticancer and antimicrobial activity. Further the computational docking and 2D QSAR were performed using MOE software to identify novel scaffolds. The results showed that compound **29** and **30** exhibit significant cytotoxic effect on all four cancer cells such as lung (A549), colon (HT-29), breast (MCF-7) and melanoma (A375) with IC_{50} values of 2.56, 2.19, 1.89, 4.89 μM and 3.57, 2.90, 2.10, 5.81 μM respectively. Whereas quite different results were observed for these compounds in antimicrobial studies. Compounds **11**, **21** and **26** have exhibited significant minimum inhibitory concentrations (MIC) against *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The docking studies demonstrate that compound **27**, **28**, **29** and **30** have good dock score and binding affinities with various therapeutic targets in cancer cell proliferation. In addition these compounds have shown acceptable correlation with bioassay results in the regression plots generated in 2D QSAR models. This is the first report to demonstrate the theophylline containing acetylene derivatives and theophylline containing 1,2,3-triazole nucleoside hybrids as potential anticancer and antimicrobial agents with comprehensive *in silico* analysis.

1. Introduction

Cancer is one of the most frequent causes of death in developed countries and the identification of new therapies is an area of ongoing importance in biomedical research [1,2]. Lung, colon, breast, and melanoma cancers are most common in the developing and under developed countries. For this purpose, chemotherapy is the most commonly used treatment worldwide to cure various types of cancers [3]. Currently, combination chemotherapy with different mechanisms of action is one of the methods that are being adopted to treat cancer.

Bacterial infection remains a serious threat to human lives because of its emerging resistance to existing antibiotics, which is an increasing public health problem. Consequently, there is a vital need for the development of new antimicrobial agents with potent activity against drug resistant microorganisms [4]. That is why anticancer and also antimicrobial agent investigations are very important and should be always up-to-date.

Theophylline, also known as 1,3-dimethylxanthine is a proven bronchodilator drug used in the therapy for respiratory diseases such as asthma or chronic pulmonary obstructive disease (COPD).

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[5–7]. One of the active mechanisms of theophylline is that of adenosine receptor antagonism. Theophylline is a non-specific adenosine antagonist, antagonizing A1, A2 and A3 receptors almost equally [8]. It is unclear if this mechanism is significant because, enprofylline has another methylxanthine drug which does not antagonize the adenosine receptors, is a more potent bronchodilator than theophylline [9,10]. Among theophylline derivatives, 7- and 8-positions have been investigated with respect to their bronchospasmolytic [11–14], anticancer [15], antimicrobial [16,17] and circulatory blood system activity [18]. Further nucleoside and their derivatives have emerged as molecules with potentially useful therapeutic properties that have gained considerable attention from both synthetic and medicinal chemists due to their versatile biological activities in various therapeutic areas. Over the past few years, several derivatives of the nucleosides are known to possess antimicrobial [19], anticancer [20], anti-inflammatory [21] and antiviral activities [22–25].

In addition, 1,2,3-triazole could also act as an attractive group to connect two pharmacophores and/or biologically beneficial fragments into one molecule to generate innovative multifunctional compounds [26]. The large dipole moment of 1,4-substituted 1,2,3-triazoles makes them to be served as hydrogen bond acceptor, which is a favor for binding to biological sites and improving solubility.

Based on the biological significance, it has been envisaged the integration of theophylline and nucleoside pharmacophore units with 1,2,3-triazole linkage in one molecular platform to generate a new theophylline containing 1,2,3-triazoles with variant nucleoside hybrids frame work with anticancer and antimicrobial properties. Some of theophylline, nucleoside and 1,2,3-triazole bioactive molecules are shown in Fig. 1.

The present work reports the synthesis, structure elucidation and characterization of theophylline acetylene and theophylline containing 1,2,3-triazole nucleoside derivatives and evaluation of anticancer properties using four different cell lines viz. lung, colon, breast and melanoma and also antimicrobial activity. Further, these studies augmented on the computational molecular docking with various therapeutic targets involved in cell proliferation and 2D QSAR analysis to screen novel anticancer target specific scaffolds.

2. Results and discussion

2.1. Chemistry

A series of theophylline containing acetylene derivatives **6a**–**6b** and **7**–**13** were synthesized in Scheme 1 and Scheme 2. In the Scheme 1, the commercially available theophylline **1** alkylating with ethyl 2-bromoacetate and K_2CO_3 in DMF at 85 °C for 12 h gave **2a** with 84% yield and on the other hand **2b** was prepared by using mitsunobu reaction. Theophylline **1** reacted with ethyl 2-hydroxypropanoate by using the reagents TPP and DIAD at room temperature which gave 50% yield of **2b**. The ester compounds **2a**–**2b** were hydrolyzed with LiOH·H_2O in THF and H_2O at room temperature for 2 h to get **3a**–**3b** (91% and 98%). In the next stage, compound **3a** was coupled with glycine methyl ester hydrochloride and compound **3b** with alanine methyl ester hydrochloride by using HATU and DIPEA at room temperature for 16 h which yielded **4a** (81%) and **4b** (68%) and then followed by hydrolysis with LiOH·H_2O in THF. H_2O which gave compounds **5a**–**5b** with 80% and 74% yields respectively. Further, it was coupled with propargyl alcohol by using DCC and DMAP at room temperature which gave compounds **6a**–**6b** with yields of 86% and 74%. In the synthesis shown by Scheme 2, theophylline **1** was treated with propargyl bromide in the presence of K_2CO_3 in DMF heating at 85 °C for 2 h to get compound **7** (91%) and also in the same manner theophylline **1** treating with 5-bromo-1-pentyne gave compound **8** (84%) heating at 85 °C for 10 h. Later, expanding the acetylene chain with compound **3a** by using conditions alkylation and coupling methods, produced compound for **9** (**97%**) at room temperature by treating compound **3a** with propargyl bromide and K_2CO_3 in DMF, but compound **10** (90%) was obtained with 5-brmo-1-pentyne treating at 80 °C for 12 h. Compound **3a** was coupled with propargyl amine by using reagent HATU and DIPEA which gave compound **11** (92%) and with 3-butyn-1-ol with DCC and DMAP in DCM at room temperature resulted compound **12** (90%). Maintaining same condition with DCC and DMAP, compound **3b** coupled with propargyl alcohol

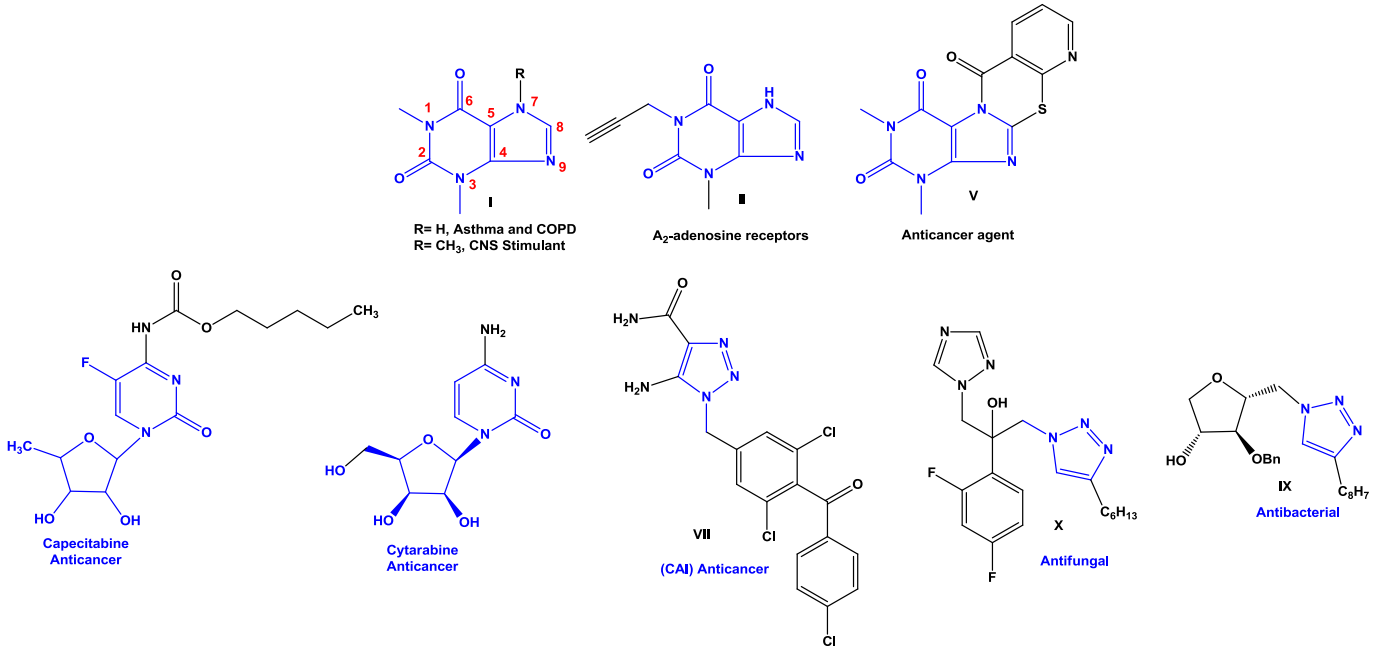

Fig. 1. Bioactive theophylline, nucleoside and 1,2,3-triazole moieties.