Table 6.1: Summary of publications

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Title of the Manuscript</th>
<th>Name of the Journal and details of the published issue</th>
<th>Name of the Publisher</th>
<th>Impact Factor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pharmacophore optimization and design of competitive inhibitors of Thymidine monophosphate kinase through molecular modeling studies</td>
<td>Chemical Biology and Drug Design</td>
<td>Scholarone Manuscripts</td>
<td>2.5</td>
<td>Accepted</td>
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<tr>
<td>2</td>
<td>Synthesis and antitubercular activity of some substituted pyrimidine derivatives</td>
<td>Journal of Pharmacy Research 2011, 4(6), 1882-1883</td>
<td>Online</td>
<td>Indexed Journal 1.0</td>
<td>Published</td>
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<tr>
<td>3</td>
<td>Design, synthesis, docking and antimycobacterial activity of some novel thiouracil derivatives as Thymidine monophosphate kinase (TMPKmt) inhibitors</td>
<td>International Journal of Research in Pharmaceuticals and Biomedical Sciences, Vol. 2(2) April-June 2011</td>
<td>Indexed Journal (USA)</td>
<td>Published</td>
<td></td>
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</table>
It is my pleasure to accept your manuscript entitled "Pharmacophore optimization and design of competitive inhibitors of Thymidine Monophosphate Kinase through molecular modeling studies." in its revised form for publication in Chemical Biology & Drug Design.

On behalf of the Editorial Team of Chemical Biology & Drug Design, congratulations and thank you for your contribution to and support of the Journal.

All the best,

Tomi

Tomi Sawyer, Editor-in-Chief
Chemical Biology & Drug Design
Editor@cbdd.org
Pyrimidinedione: Pharmacophore Optimization of Selective Thymidine Monophosphate Kinase inhibitors using Group QSAR Studies as Potential Antitubercular agents

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ABSTRACT

Tuberculosis (TB) is the second major cause of death from a single infectious agent among adults in developing countries, followed by HIV. The emergence of multi-drug resistant strains of Mycobacterium tuberculosis and revival of TB in the industrialized world due to HIV infections has rendered the quest for new drugs against TB a priority. In this work an effort is made to optimize the pharmacophore required for potent and selective inhibition of one essential enzyme of nucleotide metabolism, viz., thymidine monophosphate kinase (TMPKmt), by selecting reported series of TMPKmt inhibitors. A new Group-Based QSAR (G-QSAR) method which uses descriptors evaluated for the fragments of the molecules, generated using specific fragmentation rules for the selected dataset was carried out. G-QSAR was specifically done for knowing the structure activity relationship for carrying out variations in substitution at specific substitution sites. Also mathematical model for the prediction of activities of the new molecules was developed. G-QSAR studies were carried out using VLife Molecular Design Suite (V Life MDS) software.

Key Words: Pharmacophore Optimization, Thymidine monophosphate kinase of M. tuberculosis (TMPKmt), Simulating Annealing (SA), Genetic Algorithm (GA), G-QSAR.

INTRODUCTION

Mycobacterium tuberculosis is responsible for at least 2 million deaths globally per year. Due to demographic factors, socioeconomic trends, neglected tuberculosis control in many countries and HIV infection, this epidemic has been able to adopt such a huge proportion. A peculiar aspect of its pathogenicity comes from the fact that it can remain quiescent and become active decades ago.
Synthesis of some uracil derivatives using ionic liquid

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ABSTRACT

In the present study, some 3-(substituted phenyl)-2, 10-dihydro-10-oxo-1-thioxo-1Hpyrimido[6, 1-b] quinazoline-4-carbonitriles were prepared from 6-(substituted phenyl)-1,2,3,4-tetrahydro-4-oxo-2-thioxopyrimidine-5 carbonitriles. The synthesis involved three steps. The first step was one pot condensation of thiourea with substituted benzaldehydes in alcohol using potassium carbonate as catalyst to give uracils (TSI –TSIV). These uracils were then converted to the compounds, 4-chloro-1, 2-dihydro-6-substituted phenyl-2-thioxopyrimidine-3-carbonitrile (TSIa-TSIVa) by overnight stirring of with POCl₃ using DMF as solvent. Later on the title compounds, quinazoline derivatives (TI-T4) were prepared in one step by reacting (TSIa-TSIVa) with anthranilic acid in DMSO using catalytic amount of ionic liquid (1-n-butylimidazolium chloride). The structures of newly synthesized compounds (TI-T4) have been confirmed on the basis of spectral data.

Keywords: Uracil, quinazoline, ionic liquid, one pot.

INTRODUCTION

The uracil is reported to possess various possess biological activities attributed to various modifications at the ring nitrogen’s, N1 and N3 as well as modifications at position 2, 5 and 6 like enzyme inhibition[1], inhibition of DNA synthesis [2], antiretroviral[3-6], antineoplastic agents [7] as well as antimycobacterial[8-12].

Also, the quinazoline nucleus is reported to possess various biological activities from antimicrobial [13], antihypertensive [14] and anticancer [15] to name a few.

Ionic liquids (ILs) have attracted increasing interest recently in the context of green organic synthesis. Actual mechanism of IL as a catalyst is not exactly known [16].
Design, Synthesis, Docking and Anti-mycobacterial activity of some novel thiouracil derivatives as thymidine monophosphate kinase (TMPKmt) inhibitors


Shri Shivaji Memorial Society’s College of Pharmacy, Near RTO office, Kennedy road, Pune, Maharashtra, India.

ABSTRACT

In the present study, a novel series of 5-cyano 4, 6-disubstituted, 2-thiouracil derivatives were synthesized. Docking study was performed to rationalize the possible interactions between test compounds and active site of TMPKmt. The test compounds were screened for antimycobacterial activity using Micro plate Alamar Blue assay (MABA) against M. tuberculosis H37Rv (ATCC 27294) as well as INH resistant clinical strain. Among the series 3c & 3d were found to be potent (susceptible). The SAR study reveals the importance of presence of electronegative group for better activity.

Key Words: Tuberculosis, thymidine monophosphate kinase (TMPKmt), thiouracil, MABA.

INTRODUCTION

Tuberculosis (TB) is caused by the most infectious agent, Mycobacterium tuberculosis. Tuberculosis is the leading cause of death among HIV positive patients because of less immunity in these patients. One most important factor responsible for rise in TB infections & increase in number of deaths is multiple drug resistance (MDR). M. tuberculosis thymidine monophosphate kinase ( TMPKmt) phosphorylates deoxy thymidine monophosphate (dTMP) to deoxy thymidine diphosphate (dTDP), is believed to be an attractive potential target for chemotherapeutic intervention.

In recent years, several dTMP derivatives were synthesized and studied for their effect on the TMPKmt. Nucleotide analogue, 3'-azido-3'-deoxythymidine monophosphate (AZTMP) was identified as a competitive inhibitor of TMPKmt. The TMPKmt represents the first reported TMPK that does not phosphorylate AZTMP. In addition, nucleoside analogues like 3'-azido-3'-deoxythymidine (AZT) and 5-bromo-2'-deoxyuridine (5 Br-DU) are reported to be inhibitors of TMPKmt as potent as their nonphosphorylated 5'-modified derivatives.

Literature survey revealed different methods of synthesis for substituted 2-thiouracils such as conventional cyclisation, solvent free one-pot condensation and ultrasound irradiation. Various Thiouracil derivatives were synthesized & its biological activities were determined. Recently we have reported a series of 1, 3, 4-(thiadiazol-2-ylamino) methyl-5-(pyridine-4-yl)-1, 3, 4-oxadiazol-2-thione as antimycobacterial agent. In continuation of our earlier work of antitubercular activity, docking of these derivatives was done into the active site of TMPKmt in order to analyze the probable mode of action. We have synthesized a series of the Thiouracil derivatives & tested for antitubercular activity using MABA method. The docking study was also performed to rationalize the possible interactions between the synthesized compounds and the active site of TMPKmt.

MATERIALS AND METHOD

The synthetic route used to synthesize the title compounds is outlined in scheme 1. The compounds1,2,3,4-tetrahydro-4-oxo-6-substitute diphosphoric-2-thiopyrimidine-5-carbonitrile (1a-1b) were prepared using one pot condensation of chloro/fluro benazaldehydes with ethylcyaac acid and thiourea in presence catalytic amount of a base (K2CO3) at 450w for 10-12min. The
Mycobacterium tuberculosis.

**MATERIALS AND METHODS:**

heterocycle (Table 1) exhibited promising antitubercular activities against (Scheme 1) and screened for antitubercular activity. The newly synthesized TMPKmt.'*'' In this work, some substituted pyrimidine derivatives were synthesized and evaluated. Several pyrimidine derivatives have shown good inhibitory activity against Mycobacterium tuberculosis. They can be designed for the development of new and potent antitubercular drugs. The structures of these compounds were established on the basis of preliminary analytical studies and spectral data. Then all these compounds were screened for antimycobacterial activity. These results make novel pyrimidine derivatives interesting lead molecules for further synthetic and biological evaluation.

**Key words:** Pyrimidines, TMPKmt inhibitors, MABA assay, Acetal.

**INTRODUCTION**

Thymidine monophosphate kinase is one of the important targets for the treatment of Mycobacterium tuberculosis as biochemical and physico-chemical characterization of TMPKmt revealed distinct structural and catalytic features. Also it is involved in DNA synthesis of mycobacteria. ""So, TMPKmt inhibitors are designed and synthesized (Scheme 1) and screened for antitubercular activity. The newly synthesized heterocycle (Table 1) exhibited promising antitubercular activities against Mycobacterium tuberculosis.

**MATERIALS AND METHODS:**

**Chemicals and equipments:**

KOH, Dimethyl formamide (DMF), Ethyl cyanoacetate, Malononitrile, Carbon disulphide, (CS2), Dimethyl Sulphoxide (DMS), Aromatic amines, Absolute alcohol, Sodium metal, Anhydrous guanidine hydrochloride, Magnetic stirrer, Hot plate and Heating mantle.

**Methods:**

**General Procedure:**

**STEP I Synthesis of 2-methyl-3,3-bis(methylthio)acrylonitrile:**

Potassium hydroxide (KOH) (2 mol) was dissolved in 10 ml water. DMF was added to KOH solution and was stirred maintaining the temperature at 0-5°C for 20 minutes. Ethyl cyanoacetate (1 mol) or malononitrile (1 mol) was added to the above reaction mixture, which was stirred for 20 minutes. After complete addition, the reaction mixture was brought to room temperature (RT) and then stirred for 1 hour. The reaction mixture was filtered and the filtrate was kept at room temperature for 48 hours. The crude product was subjected for subsequent washing with ice cold water. The completion of reaction was monitored by TLC.

**STEP II Synthesis of 2-methyl-3-(methylthio)but-2-enenitrile:**

The product of step I (1 mol) was taken along with the appropriate amine (1 mol) along with absolute alcohol. Reflux the reaction mixture at 100°C for 12hr by keeping the guard tube on the reaction mixture. The completion of reaction was monitored by TLC. The workup was done by simple filtration and further washings were given by absolute alcohol.

**STEP III Synthesis of 2-amino-4,6-dimethylpyrimidine-5-carbonitrile:**

Sodium metal (1 mol) was dissolved in absolute alcohol maintaining 0-5°C and stirred for 15 minutes. To this solution of anhydrous guanidine hydrochloride (1 mol) was added under chilled condition and then stirred for 20 minutes maintaining temperature at 0-5°C. The resulting suspension was filtered and the filtrate was taken for further reaction. The second step product, 2-formyl-3-(methylthio)but-2-enenitrile (1 mol) was taken with the above filtrate and the reaction mixture was refluxed for 24 hours at 125°C. The reaction was monitored by TLC. The reaction mixture was refrigerated overnight and was filtered to obtain crystalline product, which was dried and weighed.

**ABSTRACT**

In this manuscript substituted pyrimidines were designed as inhibitors of Thymidine Monophosphate Kinase of Mycobacterium tuberculosis (TMPKmt). A mixture of sodium metal and guanidine hydrochloride was stirred in absolute alcohol and was then refluxed with synthesized S, N-acetal to yield pyrimidine derivatives. The structures of these compounds were established on the basis of preliminary analytical studies and spectral data. Then all these compounds were screened for antitubercular activity. These results make novel pyrimidine derivatives interesting lead molecules for further synthetic and biological evaluation.

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