Design and Synthesis Of Novel Urea / Thiourea Derivatives As Mycobacterium InhA Inhibitors

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1. **Abstract**

Many of the drugs available in the market for the treatment of tuberculosis have developed resistance by *Mycobacterium tuberculosis* and many nitrogen containing compounds have been reported to posse's relatively high toxicity compared to other derivatives therefore there is a need for the new Antitubercular agents to treat tuberculosis of resistant *Mycobacterium tuberculosis* infections. Based on the literature survey we planned to synthesize some novel thiourea compounds which are less toxic and more potent anti-tubercular agents.

2. Introduction

Tuberculosis (TB) is caused by bacteria *Mycobacterium tuberculosis* that most often affect the lungs. tuberculosis is curable and preventable. Tuberculosis (TB) remains the leading cause of morality due to a bacterial pathogen. Mycolic acids are long fatty acids found in the cell walls of bacteria that include *Mycobacterium tuberculosis*. The fatty acid long chain (C74-C90) alpha-alkyl beta-hydroxy fatty acids covalently linked to arabino-galactan. They are the major components of the mycobacterial cells envelope providing protection from commonly used antibiotics. They are also responsible for a great part of mycobacteria virulence. The enoyl acyl carrier protein reductase, InhA, is one of the enzymes that are employed in the mycobacterial fatty acid biosynthesis pathway. This enzyme is essential for the growth of *Mycobacterium tuberculosis* and has been also identified as the target of two anti-tubercular drugs; isoniazid and ethionamide. Therefore, InhA attracts great interest as a target for the development of new anti-tubercular agents.

3. Aim and objectives

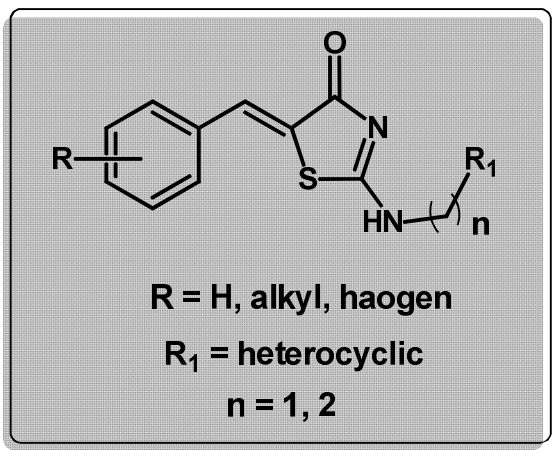
A growing number of immune compromised patients are as a result of cancer therapy, organ transplantation and HIV infections which are the measure factors contributing to this increase.The health problems demands to search and synthesize a new class of anti-microbial compounds effective against pathogenic micro organisms that developed resistance to the drugs used in the therapy. The therapeutic importance of aminothiazoles and fused

aminothiazoles is well documented. The N-bridged heterocyclics derived from them are found to be associated with diverse pharmacological activities. Substituted aminothiazoles with attachment of heterocyclic alkyl side chain are among the various heterocycles that have received the most attention during the last two decades as potential anti-microbial agents. Substituted aminothiazoles and heterocyclic alkyl side chain derivatives have been reported to possess wide spectrum of activities ranging from antibacterial, anti-inflammatory, anticonvulsant, antineoplastic, antimalarial, antiviral, anticancer, antitubercular, antiproliferative.

The present work is undertaken with the following objectives:

1. To achieve the synthesis of the title compounds adapting unambiguous synthetic routes.
2. Chemical characterization of the newly synthesized compounds by ^{1}H NMR, IR, and Mass spectral data.
3. Screening of newly synthesized compounds for antitubercular activity.
4. To arrive at the SAR in order to optimize the structures for further development of the lead molecule.

   The main objective of the present investigation is to explore newer molecules with potent biological activities such as antitubercular activity of newly synthesized compounds. The following type of compounds were designed and synthesized.



4. Methodology

General procedure for the preparation of 2-aminothiazol-4-one:

In a 100 ml clean and dry round bottom flask a mixture of thiourea (0.002 mol), 2-choro acetic acid (0.002 mol, 1.87gm) and glacial acetic acid (10 ml) was refluxed for 1 hour. During the reaction a solid separates. The obtained solid were filtered and washed with methyl alcohol. The solid dissolved in 5 ml water then basified with sodium bicarbonate (3%) solution to give white crystals of 2-aminothiazol-4-one (2-iminothiazolidin-4-one).

m.p. 243-245 ºC.

General procedure for synthesis of 2-amino-5-(substituted benzylidene)thiazol-4(5*H*)-one (K1-K10):

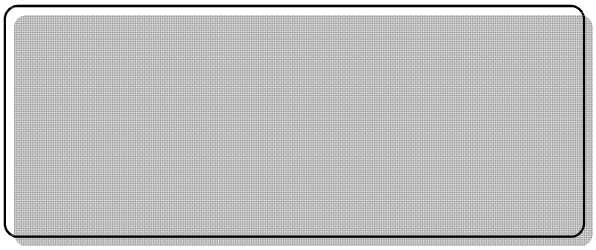
In a 100 ml clean and dry round bottom flask stir to dissolve equimolar quantities of 4-aminothiazol-2(5*H*)-one (0.01 mol), anhydrous sodium acetate (0.01 mol) in glacial acetic acid (10 ml) and to this add appropriate aldehyde (0.01 mol) and subject to reflux for 12-24 h. The progress of reaction was monitored by TLC by using solvents chloroform and n-hexane (1:1). After completion of the reaction, the reaction mixture is poured in a beaker and evaporated. The solid separates was filtered, dried and recrystallized using suitable solvent (ethanol).

Preparation of 5-(substituted benzylidene)-2-((2-morpholinoethyl)amino)thiazol-4(5*H*)-one (KM1-KM10):

In a 100 ml clean and dry round bottom flask dissolve equimolar quantities of 2-amino-5-(substitutedbenzylidene)thiazol-4(5*H*)-one (K1-K10), 2-chloro ethyl morpholine (0.01 mol) in 20-30 ml of ethanol and catalytic amount of potassium hydroxide. Reflux the reaction mixture for 6-10 h. The progress of reaction was monitored by TLC by using solvents chloroform and n-hexane (1:1). After cooling the precipitated was filtered off, dried and recrystallized by using suitable solvent.

5. Results

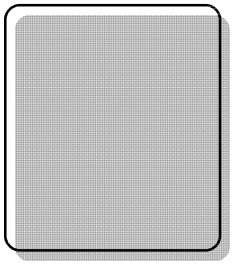
Physical characterization data of synthesized compounds (KM1-KM10).



S.No	Compound code	R	Molecular Formula	Molecular Weight	Melting Point ^{o}C	Yield (%)
01	K1	H	$C_{10}H_8N_2OS$	204	230-232	54.85
02	K2	2,3,4-tri OCH_3	$C_{13}H_{14}N_2O_4S$	294	232-234	66.31
03	K3	2-NO_2	$C_{10}H_7N_3O_3S$	249	260-262	70.21
04	K4	4-Cl	$C_{10}H_7ClN_2OS$	238	210-212	61.01
05	K5	4-$N(CH_3)_2$	$C_{12}H_{13}N_3OS$	247	260-262	64.56
06	K6	4-OH	$C_{10}H_8N_2O_2S$	220	265-267	68.37
07	K7	3-OCH_3, 4-OH	$C_{11}H_{10}N_2O_3S$	250	220-222	30.38
08	K8	3-OC_2H_5, 4-OH	$C_{12}H_{12}N_2O_3S$	264	264-266	40.10
09	K9	2-OC_2H_5	$C_{12}H_{12}N_2O_2S$	248	248-250	50.52
10	K10	2-F	$C_{10}H_7FN_2OS$	222	200-220	40.80

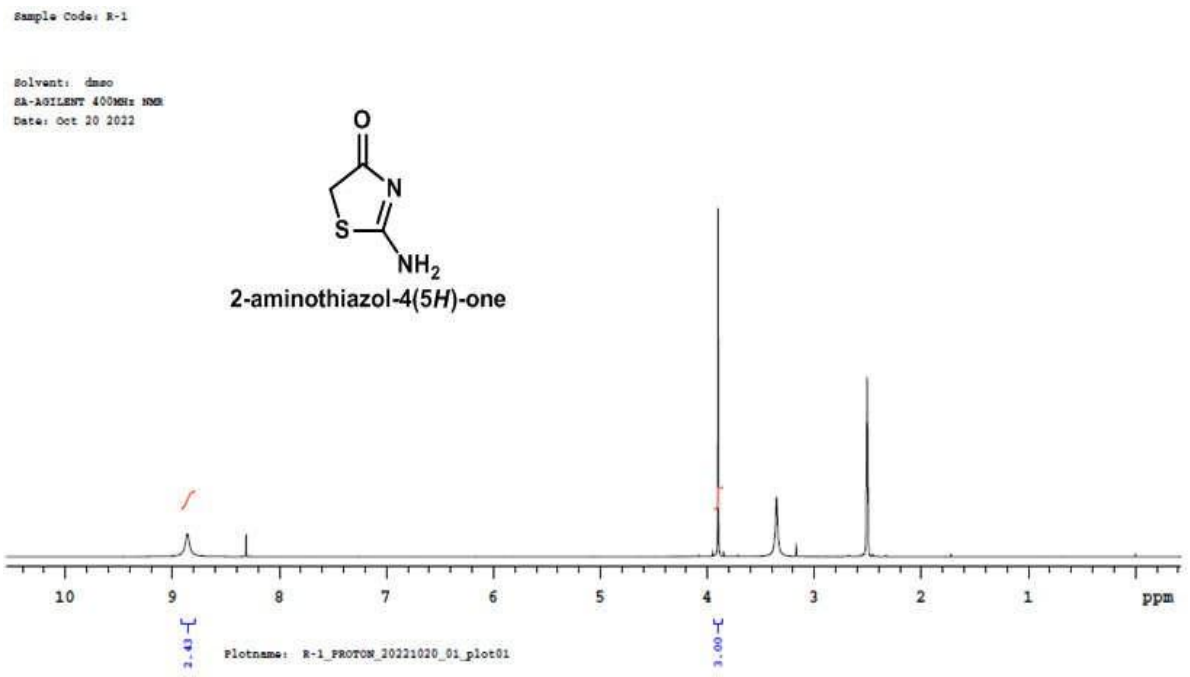
SPECTRAL DATA

2-aminothiazol-4(5*H*)-one



^{1}HNMR Spectra (DMSO-d_6, δ ppm):

Value (δ ppm)	Nature of segment	No of protons	Types of protons
8.8-9.0	Broad Singlet	2H	2H of NH_2
3.9-4.0	Singlet	2H	2H of CH_2



^{1}HNMR Spectrum of compound 2-aminothiazol-4(5*H*)-one

ANTI-TUBERCULAR ACTIVITY:

All the synthesised compounds herein (**KM1-KM10**) were screened for their anti tubercular activity. The anti tubercular activity was carried out against *M.tuberculosis* H37RV by micro plate alamar blue assay. The data for the anti tubercular activity screening revealed that all the compounds showed activity at 50 and 100 µg/ml where as some of the compounds are active at concentration 25 µg/ml compared to standard drugs employed for the study.