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RESEARCH ARTICLE

SYNTHESIS AND STUDY OF ANTI-TUBERCULAR ACTIVITY OF SOME NEWLY SYNTHESISED4-THIAZOLIDINONE AND 2-AZETIDINONE DERIVATIVES

***Jyatinkumar. H. Solanki**

Department of Chemistry, Government College, Daman 396210

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ABSTRACT

A series of 2-azetidinone and 4- thiazolidinone derivatives having piperazine moiety have been prepared to evaluate the anti-tuberculosis activity. Various Schiff bases have been prepared from *N*-ethylpiperazine on condensation with *p*-chloroaniline in absolute alcohol in presence of K_2CO_3 and subsequent reaction with various aldehydes (4a-4j).These Schiff bases on cyclocondensation with thioglycolic acid in 1,4-dioaxne gave 4-thiozolidinones (5a-5j). Similarly, Schiff Bases (4a-4j) on cyclocondensation with chloroacetic acid in presence of triethyl amine gave the 2-azetidinones (6a-6j).

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INTRODUCTION

Tuberculosis is today amongst the worldwide health threats. As resistant strains of *Mycobacterium tuberculosis* have slowly emerged, treatment failure is too often a fact, especially in countries lacking the necessary health care organization to provide the long and costly treatment adapted to patients. Because of lack of treatment or lack of adapted treatment, at least two million people dies of tuberculosis each year. Due to this concern, this infectious disease was the focus of renewed scientific interest in the last decade. Despite the ready availability of effective treatments, tuberculosis remains a major public health threat worldwide. The emergence of drug-resistant strains of Mycobacterium tuberculosis, particularly multiple drug resistant strains (Rattan, 1998; Bastian, 1999; Loddenkemper, 2000; Janin, 2007), has complicated treatment protocols and raises the concern that tuberculosis may once again become an incurable disease. For this reason, it is critical to discover new drugs acting with a mechanism different from those presently used. Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties. 4-Thiazolidinones are the derivatives of thiazolidine with a carbonyl group at the 4 position. Considerable interest has been shown in the field of thiazolidinone chemistry due to their wide range of various important biological activities such as antibacterial (Khalil, 2009), antifungal (Hamdan, 2016), diuretic (Ahmad Khan, 2009), tuberculostatic (Karakus, 2002; Vermaand, 2008), anti-HIV (Ravichandran, 2009; Chen, 2011), antihistaminic (Previtera et al., 2014), anticancer (Szychowski, 2019; Asati et al., 2014), anticonvulsant (Faizi et al., 2017; Archana, 2003), anti-inflammatory (Vigorita, 2013; Bhati, 2008) and analgesic properties (Prabhu, 2010; Vigorita, 2001). 2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds (Singh, 2011). The activity of the famous antibiotics such as penicillin, cephalosporin and carbapenams are attributed to the presence of 2-azetidinone ring in them. The β-lactams also serve as synthons for many biologically important classes of organic compounds.The utility of azetidinones as synthons for various biologically active compounds, as well as their recognition as antibacterial (Kaura et al., 2011), anticonvulsant (Rajasekharan, 2010), antimicrobial (Basavaraj, 2011), anti-tubercular (Bhat, 2007), anti-inflammatory (Chavan, 2007), anthelmintic (Mathew, 2010), anesthetic (Ramalakshmi, 2008), antioxidant (Samadhiya, 2012). They also function as enzyme inhibitors (Kamble, 2011) and are effective on the central nervous system (Vibhute, 2013). Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists. In order to further assess the pharmacological profile of this class of these compounds, it was thought worthwhile to synthesize some new congeners of heterocycles by incorporatingpiperazine moiety in 4-thiazolidinones and 2-azetidinones and review the anti-tubercular activity of the same.

Corresponding author: **Jyatinkumar. H. Solanki,**
Department of Chemistry, Government College, Daman 396210.

3.1.1 The antitubercular activity of 4-thiazolidinones are presented in Table.1

Table 1. Antitubercular activity of compounds 5a-5j

Compounds	R	MIC values (μg/mL) of *M. tuberculosis* $H_{37}Rv$	% Inhibition
5a	H	512	99%
5b	4-Cl	256	98%
5c	4-OCH_3	512	98%
5d	3-NO_2	256	99%
5e	3-OCH3	256	99%
5f	4-OH	64	98%
5g	2-Cl	512	98%
5h	2-OH	32	99%
5i	3,4,5-OCH_3	256	99%
5j	3,4-OCH_3	256	98%
Rifampicin	-	40	98%

3.1.2. The antitubercular activity of 2-azetidinonesare presented in Table.2

Table 2. Antitubercular activity of compounds 6a-6j

Compounds	R	MIC values (μg/ml) of *M. tuberculosis* $H_{37}Rv$	% Inhibition
6a	H	512	99%
6b	4-Cl	256	98%
6c	4-OCH_3	512	98%
6d	3-NO_2	256	99%
6e	3-OCH3	256	99%
6f	4-OH	32	98%
6g	2-Cl	512	98%
6h	2-OH	32	99%
6i	3,4,5-OCH_3	256	99%
6j	3,4-OCH_3	256	98%
Rifampicin		40	98%

EXPERIMENTAL

General: All chemicals used were from Sigma Aldrich, Merck and Fluka. Solvents used were of analytical grade. All reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F254 grade, Merck DC) with spots visualized by UV light. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr on a Shimadzu 8400S FTIR spectrophotometer. 1H NMR spectra were recorded on a Hitachi 300 MHz using TMS as an internal standard and elemental analysis had been carried out on Perkin-Elmer CHNS-2400.[32],[33]

Synthesis of 4-(4-ethylpiperazin-1-yl) benzenamine (3): A mixture of *N*-ethylpiperazine(1) (0.01mole) and *p*-chloroaniline(2) (0.01 mole) and anhydrous K2CO3 in absolute alcohol (20 mL) was refluxed for 4 hrs. The resultant mixture was cooled to room temperature and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystallized from absolute alcohol.

Synthesis of N-substitutedbenzylidene-4-(4-ethylpiperazin-1-yl) benzenamine (4a-4j): A mixture of 4-(4-ethylpiperazin-1-yl)benzenamine (3) (0.01 mole), aromatic aldehyde (0.01 mole) and 2-3 drops of glacial acetic acid in absolute alcohol (30 ml) was refluxed for 2 hrs. After the completion of reaction it was poured into ice-cold water with stirring. The solid product obtained was filtered, washed with water and recrystalized from absolute ethanol to give compound (4a).Similarly other compounds (4b-4j)were synthesized by above procedure.

Synthesis of2-(sustitutedphenyl)-3-(4-(4-ethylpiperazin-1-yl)phenyl)thiazolidin-4- one(5a-5j): A mixture of compound (4a)(0.01 mole) and thioglycolic acid (0.02 mole) was refluxed in the presence of 1, 4-dioxane for 12 hrs. After completion, reaction mass was dumped in ice cold water. The product formed was isolated, washed with water and recrystallized from ethanol to give compound(5a). Similarly other compounds (5b-5j)were synthesized by above procedure.

Synthesis of 3-chloro-1-(4-(4-ethylpiperazin-1-yl)phenyl)-4-(substituents phenyl)azetidin-2-one (6a-6j): To a stirred solution of substituted Schiff base(4a), (0.01 mole), triethylamine (0.02 mole) in dry1,4- dioxane (50ml), monochloroacetylchloride (0.02 mole) was added drop wise at room temperature. The reaction mixture was stirred for 30 min. and then refluxed for 12 hrs. After completion of reaction, it was poured into water. The separated solid was filtered, washed with water and recrystallized from ethanol.Similarly other compounds (6b-6j)were synthesized from 4b-4j using above procedure.

PHARMACOLOGY

Evaluation of anti-tubercular activity: The anti-mycobacterial activity of the synthesized compounds **(5a-5j)**and **(6a-6j)**were assessed against M. tuberculosis H37Rv (ATCC 2729411) using Lowenstein–Jensen (L. J. Slope).The activity was expressed as minimum inhibitory concentration (MIC) inμg/mL. The drug concentration tested were in the range 0.1 – 100.0 μg/mL

Conclusion

The results of antitubercular activity of all the synthesized analogs viz.. 4-thiazolidinones and 2-azetidinones can be

summarized as below. In case of 4-thiazolidinoes, compounds 5fand 5h were found to be active against *M. tuberculosis* $H_{37}Rv$ with 64 (98%) and 32 (99%)µg/mL MICs respectively while in case of 4-thiazolidinones compounds6f and 6hwere found to be active against the same strainwith 32(98%) and 32(99%).Remaining compounds of both the series were found to be inactive against tubercular strain. The present study reveals that presumably the presence of hydroxyl groups at ortho and para positions in 4-thiazolidinones and 2-azetidinonesdisplayed good activity (MIC 32 µg/ml) against *M.tuberculosis* comparable to Rifampicin.

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