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EVALUATION OF ANTI-TUBERCULAR ACTIVITY OF SOME 2-PHENYL OXAZOLINE DERIVATIVES

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ABSTRACT

A series of 2-phenyl oxazolone derivatives were synthesized by condensation of aldehydes with *N*-benzoyl glycine in the presence of sodium acetate and acetic anhydride. Reacting the various oxazolone derivatives with isoniazid in presence of methanol yields various Schiff's bases of oxazoline derivatives. The synthesis and characterization of 2-phenyl oxazoline derivatives has been published in WJPPS journal. The synthesized compounds were screened for *In-vitro* antitubercular activity by microplate Alamar Blue assay (MABA) method. The synthesized compounds were shown to exhibit antitubercular activity.

KEYWORDS: Antitubercular activity.

INTRODUCTION

Oxazolines have been known for many years, but in recent years the chemical literature shows considerable activity being pursued in this nucleus. Oxazoline derivatives exhibit several pharmaceutical activities such as antidiabetic, antitubercular, antihypertensive, antidepressive, anticancer, anti HIV-1, antitumor and antialzheimer activities.[1]

Tuberculosis, one of the most common infections, is caused by *Mycobacterium tuberculosis.* According to the World Health Organization (WHO), nearly one third of the world's population has been exposed to the tuberculosis pathogen.[2] The number of people who fell ill with TB dropped to 8.8 million in 2010, including 1.1 million cases among people with HIV. The number has been falling since 2005 as reported in the Global Strategy for Containment of Antimicrobial Resistance 2010 of the World Health Organization. However, it is estimated that between 2002 to 2020, approximately 1 billion people would be newly infected with the disease, more than 150 million people would get sick and 36 million would die of TB if new disease prevention and treatment measures are not developed.[3]

The limited effectiveness and long-term treatment lead to poor patient compliance, which often causes multi-drug resistant (MDR) and extensively-drug-resistant (XDR) tuberculosis. The emergence of new cases, the increased incidence of MDR strains of *M. tuberculosis*, the adverse effects of first-line anti-TB drugs isoniazid (INH) and rifampin (RIF) and the increased incidence of TB associated with HIV infections have led to renewed research interest in discovering novel anti-TB drugs.[4-5]

Several studies were conducted using different derivatives or analogues of INH to find activity against TB and MDR-TB recently. A study demonstrated that the antimycobacterial pharmacophore moiety of INH has been introduced in 510 moieties to improve their activity against *Mycobacteria* species, as well as their MDR strains. Many Schiff bases, hydrazones, hydrazides and metal complexes of INH have shown very good activity.[6-8]

MATERIAL AND METHODS

Antitubercular activity

The anti mycobacterial activity of compounds were assessed against *M. tuberculosis* using Microplate Alamar Blue Assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µL of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimize evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µL of the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/mL. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µL of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The MIC was defined as lowest drug concentration which prevented the color change from blue to pink.

RESULTS AND DISCUSSION

Antitubercular activity

The compounds were evaluated for their *in-vitro* anti-tubercular activity against *M.tuberculosis* H37Rv (ATCC 27294) using the Micro plate Alamar Blue assay (MABA) method. Compounds S1, S3, S4 and S5 were found to posses more potent activity against *M.tuberculosis* compared with standards namely INH, pyrazinamide, streptomycin and ciprofloxacin. The effective concentration for the compounds S1, S3, S4 and S5 were found to be 3.12 µg/mL which is as par with INH, pyrazinamide, streptomycin and ciprofloxacin. Compounds S2, S6 and S7 were found moderate activity against *M.tuberculosis.*

Table 1: Antitubercular activity of synthesized compounds.

S.NO	Samples	100 µg/mL	50 µg/mL	25 µg/mL	12.5 µg/mL	6.25 µg/mL	3.12 µg/mL	1.6 µg/mL	0.8 µg/mL
1.	S1	S	S	S	S	S	S	R	R
2	S2	S	S	S	S	S	R	R	R
3	S3	S	S	S	S	S	S	R	R
4	S4	S	S	S	S	S	S	R	R
5	S5	S	S	S	S	S	S	R	R
6	S6	S	S	S	S	S	R	R	R
7	S7	S	S	S	S	S	R	R	R
8	INH	S	S	S	S	S	S	R	R
9	PYRAZINAMIDE	S	S	S	S	S	S	R	R
10	STREPTOMYCIN	S	S	S	S	S	S	R	R
11	CIPROFLOXACIN	S	S	S	S	S	R	R	R

S - Sensitive
R - Resistant
Strain used: *M.tuberculosis* (H37 RV strain): ATCC No- 27294.

CONCLUSION

All the synthesized compounds exhibited activity against *Mycobacterium tuberculosis* H_{37}RV (ATCC27294) when compared with first line drugs such as isoniazid (INH), pyrazinamide, streptomycin and ciprofloxacin. The results of antitubercular activity indicate that compounds **S1, S3, S4 and S5** showed significant activity against *Mycobacterium tuberculosis.* Compounds **S2, S6** and **S7** showed moderate activity against *Mycobacterium tuberculosis.*

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