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Synthesis of Some New 1, 2, 4 – Triazolo [3, 4-B] [1, 3, 4] Thiadiazole Derivatives As Possible Antitubercular Agents

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ABSTRACT

In attempt to make significant pharmacologically active molecule, we report here the synthesis and in vitro antimicrobial activity of various series of 3 – (4 – fluorophenyl) - 6 – substituted phenyl [1, 2, 4] triazolo [3, 4 – b] [1, 3, 4] thiadiazole derivatives was prepared by the reaction of carbon disulfide, hydrazine hydrate. The compounds have been prepared by using P-toluene sulphonic acid, dimethyl formamide, 4-fluoro benzaldehyde, substituted benzaldehyde under conventional and microwave method. The products were found to be solid. The six compounds are characterized by analytical UV, IR, Mass, NMR. The compounds were screened for antitubercular activity against *Mycobacterium tuberculosis* species by using alamar blue assay method.

Keywords: Carbon disulfide, hydrazine hydrate, microwave oven, anti tubercular activity

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INTRODUCTION

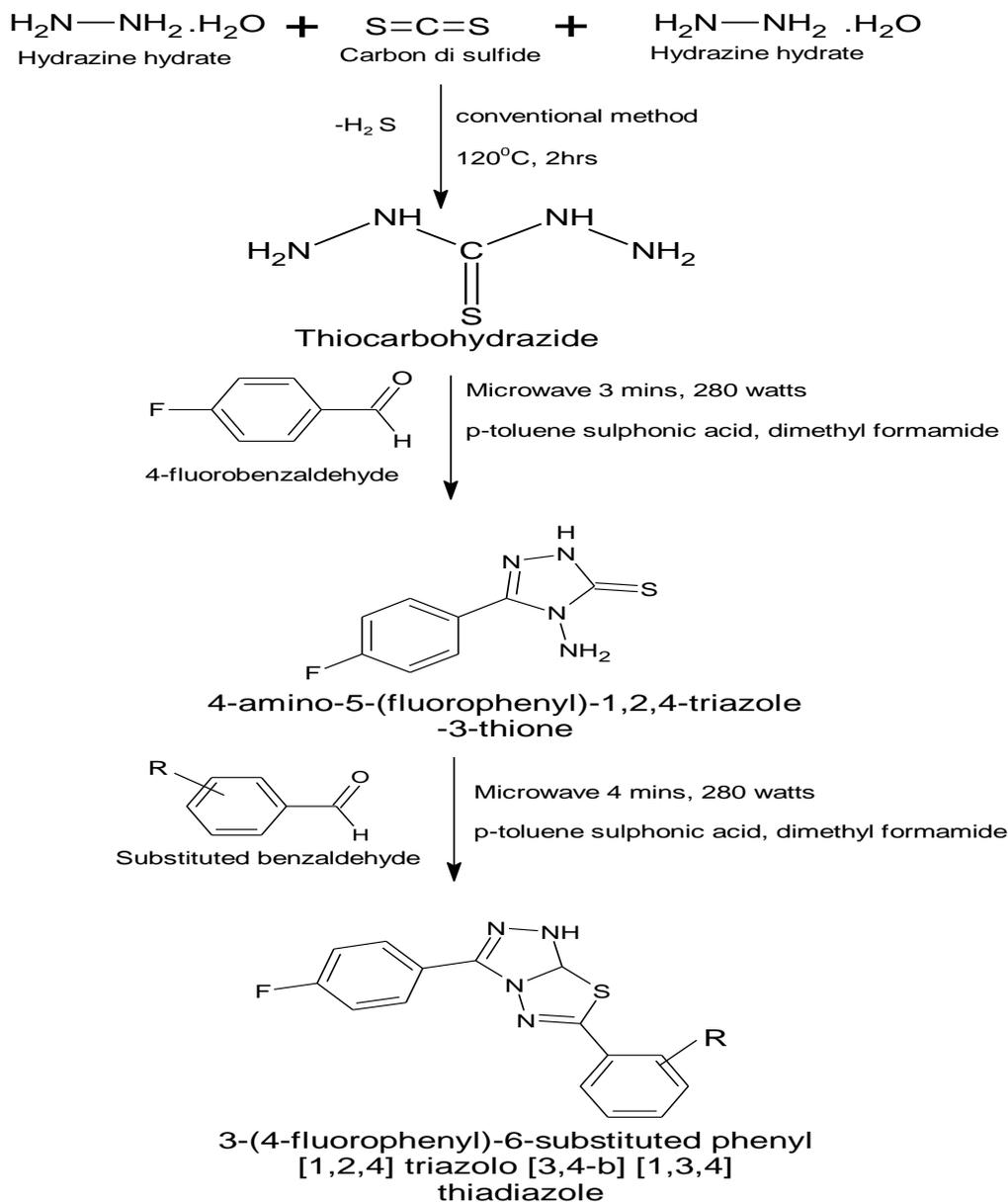
Recently, certain triazole based compounds were reported to possess antitubercular activity. Tuberculosis (TB) is the leading infectious cause of death in the world today, with ~3 million decreasing every year. An increase in the global burden of TB with the worldwide mortality rate of 23% is a major concern in the socioeconomic and health sectors. The synergy of this disease with HIV infection and the emergence of multidrug resistance and extensively drug resistance tuberculosis (MDRTB and XDRTB) pose a threatening global challenge. Although a number of lead molecules exist today to develop new drugs, no new chemical entity has emerged for clinical use for over the last 45 years in the treatment of this disease. Therefore, there is an urgent need to develop new drugs, acting through a novel mechanism of action for the chemotherapy of TB¹. A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Among them the derivatives of thiadiazole derivatives have been playing an important role in the medicinal chemistry. The 1,3,4 thiadiazole derivatives have been found to exhibit diverse biological activities such as antimicrobial², anti fungal³, anti viral⁴, antitubercular¹, anti-inflammatory⁴, anticonvulsant⁵, and antitumor⁶. The choice of 1,3,4-thiadiazole is due to its multiapplicability in the field of medicine. In the present study, some new 1,3,4-thiadiazoles T(1–6) have been synthesized and characterized by different spectral studies. All the new compounds were screened for their antitubercular activity studies.

MATERIALS AND METHOD

Chemistry

All chemicals were of analytical grade and use directly. Micro wave synthesis was carried out using DAEWOO KOG-370A. All melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The completion of the reaction was checked by TLC using Merck silica gel G and spots were visualized using iodine as visualizing agent. UV spectra were recorded on JASCO-V-530. IR spectra were recorded on JASCO FT-IR-410 spectrophotometer in KBr (γ_{\max} in cm^{-1}). ¹H NMR spectra were recorded in CDCl₃ on a Bruker Avance II 400 NMR spectrometer (400 MHz) using TMS as internal standard (δ in ppm). The mass spectra were recorded on QTOF of micro (TOF MS ES+)^{10,11}. Substituted 3 – (4 – fluorophenyl) - 6 – substituted phenyl [1, 2, 4] triazolo [3, 4 – b] [1, 3, 4] thiadiazole derivatives (T₁₋₆) was prepared by the literature procedure.

Scheme of the study:



General procedure for synthesis of 3 – (4 – fluorophenyl) - 6 – substituted phenyl [1, 2, 4] triazolo [3, 4 – b] [1, 3, 4] thiadiazole derivatives (T 1-6)^{7,8,9}:

Thiocarbohydrazide was synthesized from hydrazine hydrate (24ml), carbon disulphide(13ml) in drop wise and water(75ml), stirred for 30mts at room temperature. Reflux the mixture for 2hrs. After the reaction completion, the mixture was cooled in an ice bath and filtered. A mixture of above prepared thiocarbohydrazide(0.002mol) and 4-fluoro benzaldehyde, P-toluene sulfonic acid(0.04g) and dimethy formamide(20ml) was zapped inside microwave oven for 3mts (280 watt, 40% microwave power). The reaction mixture was cooled and 4-amino-5-(4-fluorophenyl)-1,2,4-triazole -3-thione was filtered, washed with water and recrystallized from ethanol.

A mixture of 4-amino-5-(4-fluorophenyl)-1, 2, 4-triazole -3-thione (0.001mol), substituted benzaldehyde(0.001mol) and p-toluene sulfonic acid (0.08g) in dry dimethylformamide(5ml) and irradiated in a microwave oven for 4mts(280 watt,40% microwave power) the reaction mixture was cooled and poured into ice water. The reaction mixture was filtered and resulting precipitate was washed with distilled water. The resulting crude was crystallized from ethanol. The other compounds of the series were prepared by similar procedure.

2.1.3.(T₁). Yield 87%: m.p. 238°C. IR (KBr): 3129.9(C-H aromatic stretching), 1602.56 (C-N), 1400.07 (C-F), 831.16 (C-H bending), 1544.7 (thiazole) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.6–8.3 (m, 8H, Ar-H) ppm. Mass spectra 314.31 molecular weight. Molecular formula: C₁₅H₈F₂N₄S .

2.1.4.(T₂). Yield 85%: m.p. 119°C. IR (KBr): 3243.6(C-H aromatic stretching), 1728.5(C-N), 1398.2 (C-F), 821.1 (C-H bending), 1567.2 (thiazole), 1385.2(N-O) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.4-8.2 (m, 8H, Ar-H) ppm. Mass spectra 341.31 molecular weight. Molecular formula: C₁₅H₈FN₅O₂S.

2.1.5.(T₃). Yield 86%: m.p. 116°C. IR (KBr): 3121.3(C-H aromatic stretching), 1635.4(C-N), 1414.3 (C-F), 812.1 (C-H bending), 1501.9 (thiazole), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.9-1.3 (m, 3H), δ 7.9-8.7 (m, 8H, Ar-H) ppm. Mass spectra 326.34 molecular weight. Molecular formula: C₁₆H₁₁FNO₅S.

2.1.6.(T₄). Yield 88%: m.p. 90°C. IR (KBr): 3125.3(C-H aromatic stretching), 1629.2(C-N), 1420.1 (C-F), 628.12 (C-H bending), 1510.2 (thiazole), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.8-1.7 (m, 3H), δ 7.0-8.8 (m, 8H, Ar-H) ppm. Mass spectra 326.34 molecular weight. Molecular formula: C₁₆H₁₁FNO₅S.

2.1.7.(T₅). Yield 84%: m.p. 116°C. IR (KBr): 3561.8(C-H aromatic stretching), 1588.3(C-N), 1420.1 (C-F), 785.4 (C-H bending), 1565.1 (thiazole), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.3-9.2 (m, 8H, Ar-H) ppm. Mass spectra 330.76 molecular weight. Molecular formula: C₁₅H₈FN₄S.

2.1.8.(T₆). Yield 87%: m.p. 113°C. IR (KBr): 3526.6(C-H aromatic stretching), 1560.3(C-N), 1486.4 (C-F), 734.5 (C-H bending), 1523.4 (thiazole), cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.4-8.2 (m, 8H, Ar-H) ppm. Mass spectra 330.76 molecular weight. Molecular formula: C₁₅H₈FN₄S.

Antitubercular Activity

Drug susceptibility and determination of MIC by the colour change from blue to pink of the test compounds against *M. tuberculosis* were performed by Alamar blue assay (MIC) method, where 100, 50, 25, 12.5, 6.25, 3.125, 1.6, 0.8, 0.4, 0.2 µg/mL concentration of compounds were prepared in DMSO dilutions of each test compound were added; Middlebrook 7H9 broth medium and then

media were sterilized by inspissation method. These tubes were then incubated at 37°C for 5 days. After this time 25µl of freshly prepared 1:1 mixture of alamar blue reagent and 10% tween 80 was added to the plate and incubated for 24hrs, followed by streaking of *M. tuberculosis* H₃₇Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37°C. Growth of bacilli was seen after of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis*. The concentration at which the colour change from blue to pink was taken as MIC concentration of test compound. The standard strain *M. tuberculosis* was tested with known drug isoniazid.

RESULTS AND DISCUSSION

Chemistry

3 – (4 – fluorophenyl) - 6 – substituted phenyl [1, 2, 4] triazolo [3, 4 – b] [1, 3, 4] thiadiazole derivatives was prepared by the reaction of carbon di sulfide, hydrazine hydrate. The structure of the newly synthesized compounds were characterized and conformed using spectral studies such as UV, IR, NMR, mass spectroscopy.

Antitubercular Activity

Screening of synthesized compounds against *M. tuberculosis* is summarized in Table 2. From the preliminary examination of the antitu-bercular activity results, compound **T₅ and T₆** containing chloro substituted thiadiazole derivatives showed better activity (100, 50, 25, 12.5, 6.25, 3.125 µg/mL) against *M. tuberculosis* While **T₃ and T₄** containing methoxy substituted thiadiazole derivatives showed moderate activity against *M. tuberculosis* as compared to the standard (isoniazid).

Table 1: MIC of synthesized compounds T1-T6 against *Mycobacterium tuberculosis*:

S.NO	Compounds	100	50	25	12.5	6.25	3.125	1.6	0.8	0.4	0.2
1.	T ₁	S	R	R	R	R	R	R	R	R	R
2.	T ₂	S	S	R	R	R	R	R	R	R	R
3.	T ₃	S	S	S	R	R	R	R	R	R	R
4.	T ₄	S	S	S	R	R	R	R	R	R	R
5.	T ₅	S	S	S	S	S	R	R	R	R	R
6.	T ₆	S	S	S	S	S	S	R	R	R	R
7.	Isoniazid	S	S	S	S	S	S	S	S	S	S

CONCLUSION

A series of newer analogues Substituted 3 – (4 – fluorophenyl) - 6 – substituted phenyl [1, 2, 4] triazolo [3, 4 – b] [1, 3, 4] thiadiazole derivatives were synthesized and accessed for antitubercular activity. Modification of substituents on thiadiazoles ring with various electron-releasing and

electron-withdrawing substituents improved the activity. The analogues of chloro and methoxy substituents emerged as promising antituberculars showing better to moderate activity. Specially, compound T5 and T6 due to their better activity against *M. tuberculosis* strain, is the best choice for the preparation of new derivatives in order to improve antitubercular activity in future.

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