Four Components One-Pot Synthesis of New Thiazoles and Their Biological Screening for Anti-Tuberculosis Activity

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ABSTRACT: *Multi heterocyclic ring system shows wide spectrum of pharmaceutical and biological activities. Novel series of 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester derivatives have been synthesized by one-pot condensation of 2-Benzyloxy-5-(2-bromo-acetyl)-benzoic acid methyl ester, thiosemicarbazide and 3-(substituted-phenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde using orthophosphoric acid as a catalyst under mild reaction condition. All the synthesized compounds were screened for their anti-tubercular activity against Mycobacterium tuberculosis H37Rv stains using the* Lowenstein-Jensen *(L. J.) medium conventional method. Most of these synthesized compounds are found to be actively potent against the Mycobacterium tuberculosis H_{37}Rv strain. Environmentally benign, multicomponent, rapid, high atom and step economy, and facile are the remarkable features of the present one-pot multicomponent protocol.*

KEYWORDS: *Thiazole, pyrazole, anti-tuberculosis, multicomponent reaction.*

INTRODUCTION

World Health Organization's 2020 TB reports indicate that 1.5 million people died of TB infection. Worldwide TB is the 13th largest death-causing disease. Rifampicin was the last discovered drug for the treatment of TB. With time duration development and gene modifications in bacteria, there is an urgent need to synthesize of more active and advanced drug candidates to treat tuberculosis [1]. This created a great deal of interest in designing novel antitubercular heterocyclic compounds. Heterocycles attracted a great deal of interest from organic researchers

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because of their broad spectrum of medicinal and pharmacological applications [2-4].

A literature survey revealed that thiazole derivatives are important components of some natural products such as of steroids, flavones, pigments, and alkaloids [5]. Compounds of thiazole show a broad range of bioactivities such as hypertension [6, 7], schizophrenia [8], hypotonic [9,10], inflammation [11], HIV infections [12,13], allergies [14], used as a pain reliever [15,16]. Pyrazole containing heterocycles exhibits various bioactivities such as anti-proliferative [17], anti-microbial [18], anti-depressant [19], anti-histaminic [20], and herbicidal [21].

The presence of an ester functional group on chemical moieties showed various drug-binding properties such as anti-inflammatory activity [22], anti-fungal activity [23], anti-bacterial activity [24] anti-cancer activity [25, 26].

Achievement of high levels of diversity is mainly due to multicomponent reactions (MCRs), as MCRs allow more than two reactants to be combined in chemical transformations [27]. MCRs reactions are time-saving pot operations, simultaneously formation of two or more bonds gives complex molecules according to the domino principle [28]. These reactions contribute to the requirement of eco-friendly processes by minimizing the synthetic steps, energy consumption, and waste production [29-33].

The spread of drug-resistant tuberculosis (TB) is one of the most desperate and difficult challenges facing the world. Thiazole, pyrazole, and ester pharmacophores exhibit enormous biological activities in the field of medicinal chemistry.

Hence, here we synthesized new derivatives of thiazoles and screened for their anti-tuberculosis activity and some of them were found active.

EXPERIMENTAL SECTION

Materials

All the raw materials were purchased from Sigma Aldrich, India, and used without further purification. ^{1}H NMR spectra were recorded on a Bruker Avance (100 MHz) spectrometer in DMSO using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectra were recorded at 100 MHz and chemical shifts were reported in parts per million relatives to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on an Agilent spectrometer. The melting points were determined on the Labstar melting point apparatus.

One pot synthesis of 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1H-pyrazol-4 ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester 5a-j:

A mixture of 5-acetyl-2-benzyloxy-benzoic acid methyl ester 1 (1 mmole) and bromine (1 mmole) in acetic acid (2 mL) was stirred at 10-15 ºC with purging of nitrogen gas to remove the HBr and the reaction mixture was concentrated under reduced pressure to obtained 2-benzyloxy-5-(2-bromo-acetyl)-benzoic acid methyl ester 2. Then after in-situ prepared 2-benzyloxy-5-(2-bromo-acetyl)-benzoic acid methyl ester 2 treated with thiosemicarbazide (1 mmole) 3 and 5 mL acetonitrile stirred for 30 min to obtain corresponding imine. Thereafter 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde 4a-j was added to the same reaction mixture in the presence of 2 drops of ortho-phosphoric acid and the reaction was stirred for 1-2 h at 50-60 ºC. Obtained solids were filtered, dried, and washed with water. Products 5a-j were purified by flash chromatography eluting with (mobile phase 8:2 heptane: ethyl acetate).

Characterization of synthesized thiazoles (5a-5j)

2-Benzyloxy-5-{2-[N'-(1,3-diphenyl-1H-pyrazol-4-ylmethylene)-hydrazino]-thiazol-4-yl}-benzoic acid methyl ester (5a).

Mp 210-212ºC, yield 64%, 1 hr; IR (KBr): 1566, 1764, 3376 ; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.92 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 7.22 (s, 1H, NH), 8.15 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.89 (s, 1H, N=CH), 7.38 (d, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 7.31-7.99 (m, 15H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 52.06, 69.83, 102.52, 114.45, 117.06, 118.79, 120.29, 126.97, 127.08, 127.45, 127.78, 128.33, 128.49, 128.59, 128.67, 129.70, 130.45, 132.37, 134.79, 136.95, 139.13, 149.19, 150.91, 156.82, 165.98, 168.19. Mass: [ES] $^{+}$ 586.70. calculated 585.67

2-Benzyloxy-5-(2-{N'-[3-(3-bromo-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5b).

Mp 204-206ºC, yield 70%, 30 min. IR (KBr): 1562, 1767, 3355 ; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.92 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 7.26 (s, 1H, NH), 8.22 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.15 (s, 1H, Ar-H), 8.92 (s, 1H, N=CH), 7.67 (s, 1H, Ar-H), 7.52 (d, 1H, Ar-H), 7.85

(d, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 7.99 (dd, 1H, Ar-H), 7.37 (d, 1H, Ar-H), 7.27-8.21 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 51.97, 69.745, 102.46, 114.39, 117.10, 118.77, 120.20, 121.83, 127.00, 127.36, 127.66, 128.24, 128.41, 128.56, 129.64, 130.34, 130.67, 130.79, 131.26, 134.29, 134.76, 136.89, 138.93, 148.98, 149.11, 156.74, 165.86, 167.99. Mass: $[ES]^+$ 664.65. calculate 664.70

2-Benzyloxy-5-(2-{N'-[3-(3-nitro-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5c).

Mp 215-216ºC, yield 60%, 90 min. IR (KBr): 1554, 1745, 3376; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.83 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 7.18 (s, 1H, NH), 8.17 (s, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.99 (s, 1H, N=CH), 7.57 (s, 1H, Ar-H), 7.51 (d, 1H, Ar-H), 7.86 (d, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.99 (dd, 1H, Ar-H), 7.40 (d, 1H, Ar-H), 7.01-8.34 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 52.01, 69.79, 102.42, 114.42, 117.25, 118.79, 120.22, 123.09, 127.04, 127.21, 127.33, 127.73, 128.30, 128.45, 129.74, 130.13, 130.40, 134.15, 134.22, 135.09, 136.93, 138.88, 147.91, 148.13, 149.13, 156.80, 165.90, 167.95. Mass: $[ES]^+$ 631.77 calculated 630.67

2-Benzyloxy-5-(2-{N'-[3-(4-methoxy-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5d).

Mp 239-240ºC, yield 68%, 30 min. IR (KBr): 1546, 1749, 3379; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.840 (s, 3H, -OCH_3), 3.843 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 7.07 (s, 1H, NH), 8.13 (s, 1H, Ar-H), 8.22 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.95 (s, 1H, N=CH), 8.00 (s, 1H, Ar-H), 7.27 (d, 1H, Ar-H), 7.73 (d, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.97 (d, 2H, Ar-H), 7.10-8.98 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 52.06, 55.36, 69.83, 102.53, 114.09, 114.49, 116.77, 118.70, 120.30, 124.77, 126.83, 127.09, 127.48, 127.70, 127.77, 128.31, 128.50, 129.68, 129.90, 130.44, 135.00, 136.99, 139.18, 149.18, 150.76, 156.82, 159.60, 165.97, 168.18. Mass: $[ES]^+$ 616.72. calculated 616.70

2-Benzyloxy-5-(2-{N'-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5e).

Mp 254-255ºC, yield 65%, 30 min. IR (KBr): 1548, 1776, 3359; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.84 (s, 3H, -OCH_3), 5.00 (s, 1H, -OH), 5.26 (s, 2H, -CH_2), 8.13 (s, 1H, Ar-H), 7.14 (s, 1H, NH), 8.23 (s, 1H, N=CH), 8.00 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.37 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.96 (d, 2H, Ar-H), 7.61 (d, 2H, Ar-H), 7.31-7.98 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 52.02, 69.80, 102.39, 114.41, 115.45, 116.61, 118.62, 120.26, 123.08, 126.70, 127.05, 127.36, 127.45, 127.73, 128.32, 128.45, 129.62, 129.89, 130.42, 135.19, 136.92, 139.18, 149.17, 151.19, 156.79, 157.93, 165.94, 168.16.

2-Benzyloxy-5-(2-{N'-[3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5f).

Mp 231ºC, yield 66%, 60 min. IR (KBr): 1538, 1739, 3388; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.93 (s, 3H, -OCH_3), 5.26 (s, 2H, -CH_2), 8.14 (s, 1H, Ar-H), 7.26 (s, 1H, NH), 8.00 (s, 1H, N=CH), 8.21 (s, 1H, Ar-H), 7.72 (s, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.63 (d, 1H, Ar-H), 7.86 (d, 2H, Ar-H), 7.60 (d, 2H, Ar-H), 7.29-7.99 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 51.96, 69.73, 102.47, 114.35, 117.02, 118.68, 120.17, 126.98, 127.34, 127.67, 128.26, 128.39, 128.50, 129.62, 130.27, 130.35, 131.24, 133.18, 134.46, 136.86, 138.93, 149.09, 149.34, 156.74, 165.86, 168.05. Mass: $[ES]^+$ 620.70. calculated 620.67

2-Benzyloxy-5-(2-{N'-[3-(4-fluoro-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5g).

Mp 218-220ºC, yield 65%, 60 min. IR (KBr): 1556, 1769, 3343; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.84 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 8.13 (s, 1H, Ar-H), 7.24 (s, 1H, NH), 8.00 (s, 1H, N=CH), 8.22 (s, 1H, Ar-H), 7.57 (s, 1H, Ar-H), 7.36 (d, 1H, Ar-H), 7.55 (d, 1H, Ar-H), 7.86 (d, 2H, Ar-H), 7.89 (d, 2H, Ar-H), 7.25-7.99 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 51.98, 69.76, 102.49, 114.41, 115.32, 115.54, 116.90, 118.68, 120.22, 126.91, 127.01, 127.38, 127.70, 128.25, 128.42, 128.89, 129.64, 130.37, 130.69, 130.77, 134.56, 136.91, 139.01, 149.11, 149.72, 168.08, 165.89, 156.75. Mass: $[ES]^+$ 604.53 calculated 604.60

2-Benzyloxy-5-(2-{N'-[3-(4-nitro-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5h).

Mp 242-244ºC, yield 60%, 90 min. IR (KBr): 1542, 1742, 3372; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.84 (s, 3H, -OCH_3), 5.25 (s, 2H, -CH_2), 8.17 (s, 1H, Ar-H), 7.23 (s, 1H, NH), 8.99 (s, 1H, N=CH), 8.38 (s, 1H, Ar-H), 7.59

(s, 1H, Ar-H), 7.39 (d, 1H, Ar-H), 7.59 (d, 1H, Ar-H), 7.97 (d, 2H, Ar-H), 7.89 (d, 2H, Ar-H), 7.27-8.19 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 52.00, 69.79, 102.57, 114.39, 117.73, 118.84, 120.18, 123.62, 127.04, 127.29, 127.36, 127.73, 128.33, 128.45, 129.60, 129.70, 130.41, 134.11, 136.93, 138.84, 139.06, 147.06, 148.11, 149.16, 156.82, 165.90, 168.02. Mass: [ES] $^{+}$ 631.69. calculated 631.67

2-Benzyloxy-5-{2-[N'-(1-phenyl-3-p-tolyl-1H-pyrazol-4-ylmethylene)-hydrazino]-thiazol-4-yl}-benzoic acid methyl ester (5i).

Mp 231ºC, yield 68%, 30 min. IR (KBr): 1545, 1746, 3378; ^{1}H NMR (400 MHz, DMSO, δ ppm): 2.12 (s, 3H, -CH_3), 3.80 (s, 3H, -OCH_3), 5.22 (s, 2H, -CH_2), 7.10 (s, 1H, NH), 8.11 (s, 1H, Ar-H), 8.24 (s, 1H, Ar-H), 8.30 (s, 1H, Ar-H), 8.90 (s, 1H, N=CH), 8.00 (s, 1H, Ar-H), 7.28 (d, 1H, Ar-H), 7.56 (d, 1H, Ar-H), 7.52 (d, 1H, Ar-H), 7.97 (d, 2H, Ar-H), 7.00-8.40 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 51.06, 55.48, 69.80, 102.54, 114.10, 114.50, 116.80, 118.60, 120.20, 124.52, 126.50, 127.12, 127.50, 127.70, 127.77, 128.30, 128.50, 129.68, 129.90, 130.40, 135.00, 136.80, 139.20, 149.15, 150.52, 156.32, 159.52, 165.97, 168.20. Mass: [ES] $^{+}$ 600.05. calculated 600.13

2-Benzyloxy-5-(2-{N'-[3-(4-bromo-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5j).

Mp 240ºC,yield 65%, 60 min. IR (KBr): 1549, 1743, 3356; ^{1}H NMR (400 MHz, DMSO, δ ppm): 3.82 (s, 3H, -OCH_3), 5.22 (s, 2H, -CH_2), 8.11 (s, 1H, Ar-H), 7.20 (s, 1H, NH), 8.02 (s, 1H, N=CH), 8.22 (s, 1H, Ar-H), 7.60 (s, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 7.86 (d, 2H, Ar-H), 7.89 (d, 2H, Ar-H), 7.15-7.94 (m, 10H, Ar-H). ^{13}C NMR (400 MHz, DMSO, δ ppm): 51.95, 69.74, 102.50, 114.52, 115.40, 115.50, 116.95, 118.61, 120.20, 126.90, 127.00, 127.40, 127.72, 128.25, 128.42, 128.90, 129.60, 130.37, 130.69, 130.80, 134.56, 136.90, 139.00, 149.11, 149.72, 168.10, 165.90, 156.90. Mass: [ES] $^{+}$ 664.58 calculated 664.67

In vitro anti-tuberculosis activity

In vitro, the anti-tuberculosis activity of the synthesized compounds was evaluated against *Mycobacterium tuberculosis* H_{37}Rv using L. J. medium conventional method. *Mycobacterium tuberculosis* strains were used for the determination of Minimum Inhibitory Concentration (MIC).

RESULTS AND DISCUSSION

Chemistry

Recently, multicomponent reactions (MCR) are well regarded as versatile techniques used for the synthesis of valuable chemicals. The present attempt was to design multi-heterocycles and active pharmacophores in a single molecular framework. Initially, 2-Benzyloxy-5-(2-bromo-acetyl)-benzoic acid methyl ester (2) was prepared in situ using molecular bromine in acetic acid. In-*situ* prepared 2-benzyloxy-5-(2-bromo-acetyl)-benzoic acid methyl ester (2) reacted with thiosemicarbazide (3) to afford thiazole derivatives which further condensed with substituted 3-(substituted-phenyl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (4a-j) in the presence of catalytic amount of ortho-phosphoric acid in acetonitrile as a reaction medium (Scheme 1). Liberated HBr during the bromination was removed by purging of Nitrogen gas. Similarly, acetic acid is also distilled out under reduced pressure.

2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1*H*-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5a-j) were filtered out and washed with maximum water and purified by flash chromatography eluting with 8:2 heptane: ethyl acetate.

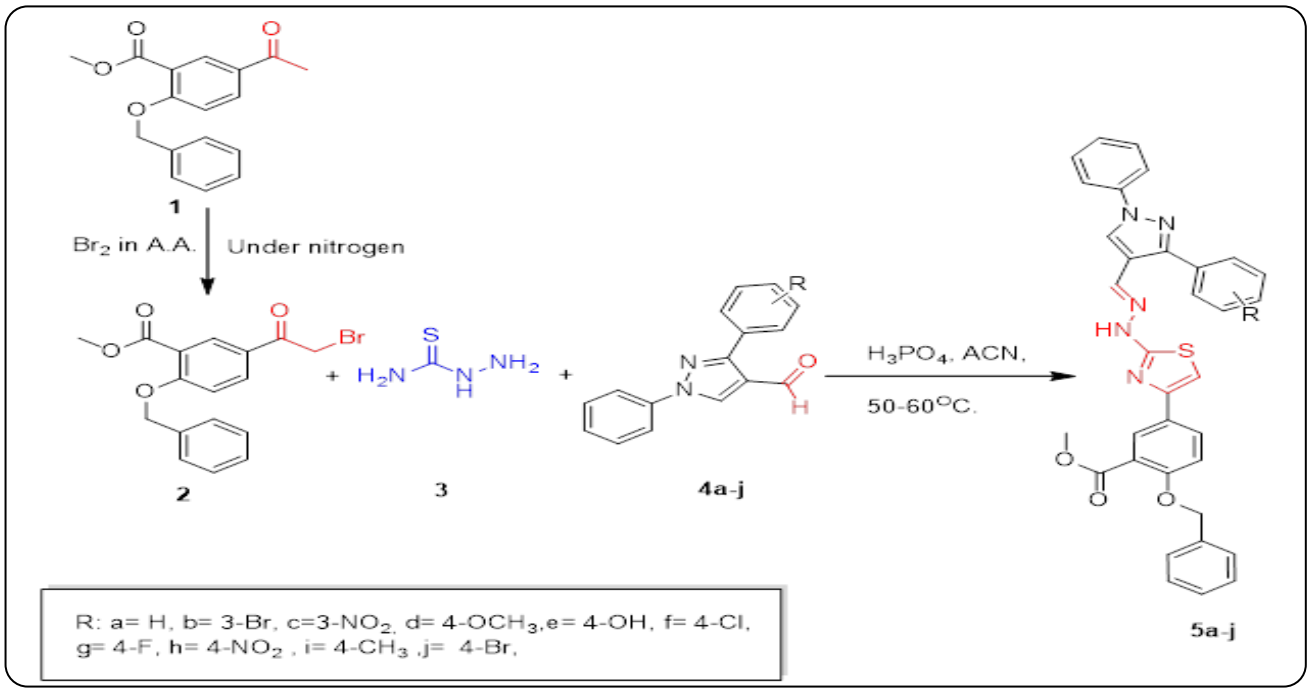
To generalize the scope of this multicomponent reaction differently substituted pyrazol-4-carbaldehydes containing electron-donating as well as electron-withdrawing substituents condensed to obtained 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1*H*- pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5a-j). Various substitutions and bulkiness of substitution adversely affect the percentage yields and reaction time. Electron-seeking groups –NO_2 require reasonable reaction time with a low percentage of yields. While electron-releasing groups –OCH_3, -CH_3 give satisfactory yield with minimum reaction time.

Synthesized 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1*H*-pyrazol-4-ylmethylene]-hydrazino} -thiazol-4-yl)-benzoic acid methyl ester 5a-j were confirmed by spectral analysis. ^{1}H NMR of compounds at δ 3.92 singlet was characteristic values of ester -OCH_3 group, δ 5.25 singlet for -CH_2 group, singlet at δ 7.22 for NH, singlet at δ 8.89 for Schiff base N=CH group and δ 7.31-7.99 were observed for aromatic hydrogen. ^{13}C NMR and mass spectra also support the formation of desired compounds.

The present synthesis was carried out by one-pot multicomponent reactions (MCRs), a protocol that

Table 1: Anti-tuberculosis activity of synthesized compounds (5a-j)

Anti-Tuberculosis Activity		
mMethod		L L. J. Medium [Conventional Method]
B Bacteria		H H_{37}RV
Standard drug		Is isoniazid, rifampicin
Entry	MIC µg/ml	--
5a	100	Is isooniazid = 0.20 µg/ml
5b	50	R rifampicin = 0.25 µg/ml
5c	125	--
5d	62.5	--
5e	100	--
5f	250	--
5g	100	--
5h	62.5	--
5i	65.5	--
5j	82.5	--



Scheme 1: Synthesis of 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-hydrazino}-thiazol-4-yl)-benzoic acid methyl ester (5a-j)

achieves high levels of diversity which allows more than two reactants to be combined in chemical transformations. Such reactions are rapid with one-pot operations; simultaneously formation of two or more bonds gives complex molecules according to the domino principle with an eco-friendly process by minimizing the energy consumption, synthetic step, and waste production.

Biological activity A total 10 new derivatives of thiazole were synthesized and evaluated for their antimycobacterial activities against *mycobacterium tuberculosis* h_{37}rv. results are shown with the standard drugs isoniazid and rifampicin (Table 1). we synthesized compounds with a wide range of substitutes by an electron-

donating and electron-withdrawing nature. electron-withdrawing substituent like 4–NO_2 entry 5h show good anti-mycobacterial activity. compound 5b, 5d, 5i and 5j show good activity (Table 1).

CONCLUSIONS

In present investigation, new series of 2-Benzyloxy-5-(2-{N'-[3-(substituted-phenyl)-1-phenyl-1*H*-pyrazol-4-ylmethylene]-hydrazino}-Thiazol-4-Yl)-Benzoic Acid Methyl Ester Derivatives Synthesized By One-Pot Synthetic Protocol. The Remarkable features of This Protocol Such As High Energy Efficiency, High Atom Economy, Rapid Synthetic Pathway, metal-free, and the isolation of lacrimetric α-bromo ketones. Synthesized compounds showed good anti-tuberculosis activity. Thus, this designed multi-component protocol would be a worthwhile addition to the present methodologies.

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Abbreviations

TB**:**	tuberculosis
MCR:	multicomponent reactions
mp**:**	melting points
MIC**:**	minimum inhibitory concentration

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