

# Design, One-pot Synthesis and Biological Evaluation of Imidazo[2,1-b] [1,3,4] Thiadiazole Derivatives for their Anti-Tubercular and Anti-Fungal Activity

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## ABSTRACT

In the present designed work, we have synthesized imidazo[2,1-b][1,3,4]thiadiazole derivatives (**6a1-a6 to 6d1-d6**) by reaction of compound **3** with appropriate  $\alpha$ -haloaryl ketones produce substituted imidazo thiadiazole derivatives (**4a-d**). In the next step, these compounds (**4a-d**) undergoes the Vilsmeier reaction to introduce formyl group on the substituted arylimidazo[2,1-b][1,3,4]thiadiazole derivatives to form carbaldehyde derivatives (**5a-d**) and finally in the last step of the reaction for the synthesis of designed molecules, a one-pot synthetic procedure was used. For this, the one-pot reaction of **5a-d**, thiosemicarbazide and substituted  $\alpha$ -haloaryl ketones were reacted together in different reaction condition in ethanol solvent at an optimum temperature around 80°C produces a corresponding derivatives (**6a1-a6 to 6d1-d6**) with a better yield. The IR, <sup>1</sup>H-NMR, and mass spectroscopy techniques were used to confirm the structure of final products and all synthesized molecules were tested for anti-TB and anti-fungal activity. The compounds **6a1**, **6a2**, **6a3**, **6c1**, **6c6** and **6d1** with MIC 1.6-6.25  $\mu$ g/ml displayed very good antitubercular and **6a1**, **6a4**, **6a5**, and **6d1** displayed very good antifungal activity with MIC 5  $\mu$ g/ml due to electron withdrawing groups at 4<sup>th</sup> position to both phenyl rings which are attached to the thiazole of the imidazo thiadiazole and imidazo thiadiazole ring.

## INTRODUCTION

Worldwide, Tuberculosis is utmost top ten causes of death, 1.72 million of people were died around the world in 2016, among them 0.42 million of people suffering from HIV along with TB especially in low and middle-class income countries like India, China, Indonesia, Nigeria, South Africa, Philippines, and Pakistan. The 96% of death occurred due to TB in the countries mentioned above among those India stands first with most deaths. In general, the main compliance of TB is a synergy with HIV, Multidrug-resistant strain development and patient non-compliance due to MTB has made the circumstance ever more

risk and it is extensively recognized that innovative intrusion tactics are required (Zheng and Blanchard, 2001). The basic imidazothiadiazole is an interesting and more demanding moiety with exciting biotic properties such as antimicrobial (Gwande *et al.*, 1987; Desai and Baxi, 1992; Mamolo *et al.*, 1996; Gadad *et al.*, 2000; Alireza *et al.*, 2003), antifungal (Alagawadi and Alegaon, 2011; Alagawadi and Alegaon, 2011), anti-tubercular (Manjoor *et al.*, 2013; Arya *et al.*, 1972; Gadad *et al.*, 2004), anti-inflammatory (Labanauskas *et al.*, 2001), antihyperlipidemic (Patel *et al.*, 2013), antihypertensive (Turner *et al.*, 1988; Turner *et al.*, 1988) and anticancer (Noolvi *et al.*, 2011; Noolvi *et al.*, 2012; Gireesh *et al.*, 2011; Gireesh *et al.*, 2013; Kumar *et al.*, 2014; Chou *et al.*, 2003). In the recent years, many antitubercular drugs reported which includes Rhodanine acetic acid carrying designed imidazothiadiazole moieties (Alegaon *et al.*, 2012), Scaffolds of imidazothiazole and thiadiazole (Romeo *et al.*, 2015), thiazole,

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imidazothiadiazole hybrids (Ramprasad *et al.*, 2015). In the present scenario, the compounds which has the imidazothiadiazole as a basic moiety have fascinated the attention of investigators in antitubercular agents. The study of the present work was to discover, advance the novel derivatives with upgraded potential for curing tuberculosis and anti-fungal assessment of various imidazothiadiazole molecules. We have designed, synthesized twenty-four derivatives of substituted imidazo[2,1-b][1,3,4]thiadiazole and they assessed for anti-tubercular and anti-fungal activity.

## MATERIALS AND METHODS

### Chemicals and instruments

The majority of the chemicals required and solvents are found from marketable sources and they are used without additional purification. The Thin Layer Chromatography (Silica gel coated on aluminium plates) is used to monitor reaction condition of synthesized compounds. Bruker AM-400 and 100 MHz spectrometers were used to record the <sup>1</sup>H-NMR and <sup>13</sup>C-spectra of synthesized compounds. DMSO was used as a solvent for recording spectrum. The Mass spectrum of the compounds was recorded by Shimadzu, LCMS-2020 to determine the Molecular weight of the compounds by ESI-MS method.

### ANTIMICROBIAL ACTIVITY

H37Rv strain (ATCC No-27294) of *Mycobacterium Tuberculi* was used to perform an Anti-tubercular activity in BACTEC medium (Collins *et al.*, 1997; Franzblau *et al.*, 1998) using a broth microdilution assay (Yajko *et al.*, 1995; Suling *et al.*, 2000). The Microplate Alamar Blue Assay (MABA) used to determine the MIC (Minimum Inhibitory Concentration).

The two different fungal strains, *C. Albicans*, and *A. Fumigatus* were used to perform the Anti-fungal activity by using the standard drug Fluconazole with different series of dilutions (25, 10 and 5 microgram/mL) to read the MIC of the various compounds.

### Brief synthetic procedure for the synthesis of targeted molecules

The key starting material 5-amino-2-mercapto-1,3,4-thiadiazole (1) was synthesized from the reaction of Thiosemicarbazide and CS<sub>2</sub> (Carbon disulfide), compounds (2) was synthesized from the reaction of compound 1 against Hydrazine hydrate and compound 3 obtained by the reaction with Acetylacetone. The compound 3<sup>rd</sup> react with different  $\alpha$ -haloaryl ketones for refluxing about 8 hours to produce compound 4a-d. In the next step, 4a-d follows Vilsmeier reaction for the formylation to produce Carbaldehyde derivatives (5a-d). For the formation of final products one-pot synthetic reaction was used in that compound 5a-d,  $\alpha$ -haloaryl ketone and thiosemicarbazide were react together under different reaction conditions in solvent ethanol to produce the final products (6a1-a6 to 6d1-d6) and they were isolated in good yields. The physical data of the newly synthesized compounds (6a1-a6 to 6d1-d6) are given in Table 1. The detailed procedure for all synthesized compounds is as follows.

#### 1. Preparation of 5-amino-2-mercapto-1,3,4-thiadiazole

Potassium hydroxide (0.16 mole) was dissolved in

anhydrous ethanol (40 ml) and carbon disulfide (0.24 mole) and then add the thiosemicarbazide (0.15 mole) in anhydrous ethanol (40 ml) was added and the mixture was stirred and refluxed for 6 hrs. Under reduce pressure after removing excess of solvent, the residue was added to the water, dissolve and acidified with Conc. HCl with care. The final precipitate was filtered off to give 5-amino-2-mercapto-1,3,4-thiadiazole (Salih *et al.*, 2008).

Table 1: Physical data of the synthesized compounds.

Product	R1	R2	Melting Point °C	Rf value (n-Hexane:Ethyl acetate) 3:2
6 a1	p-NO <sub>2</sub>	p-OCH <sub>3</sub>	210	0.28
6 a2	p-NO <sub>2</sub>	p-NO <sub>2</sub>	220	0.39
6 a3	p-NO <sub>2</sub>	p-CH <sub>3</sub>	190	0.41
6 a4	p-NO <sub>2</sub>	p-Cl	200	0.55
6 a5	p-NO <sub>2</sub>	p-Br	198	0.28
6 a6	p-NO <sub>2</sub>	m-NO <sub>2</sub>	218	0.57
6 b1	p-Br	p-NO <sub>2</sub>	214	0.22
6 b2	p-Br	p-OCH <sub>3</sub>	204	0.37
6 b3	p-Br	p-CH <sub>3</sub>	229	0.51
6 b4	p-Br	p-Cl	196	0.47
6 b5	p-Br	p-Br	242	0.36
6 b6	p-Br	m-NO <sub>2</sub>	236	0.28
6 c1	p-OCH <sub>3</sub>	p-NO <sub>2</sub>	177	0.42
6 c2	p-OCH <sub>3</sub>	p-OCH <sub>3</sub>	186	0.26
6 c3	p-OCH <sub>3</sub>	p-CH <sub>3</sub>	190	0.37
6 c4	p-OCH <sub>3</sub>	p-Cl	199	0.22
6 c5	p-OCH <sub>3</sub>	p-Br	165	0.59
6 c6	p-OCH <sub>3</sub>	m-NO <sub>2</sub>	209	0.47
6 d1	p-Cl	p-OCH <sub>3</sub>	155	0.41
6 d2	p-Cl	p-NO <sub>2</sub>	160	0.55
6 d3	p-Cl	p-CH <sub>3</sub>	172	0.47
6 d4	p-Cl	p-Cl	222	0.34
6 d5	p-Cl	p-Br	189	0.47
6 d6	p-Cl	m-NO <sub>2</sub>	193	0.37

#### 2. Preparation of the 2-amino-5-hydrazino-1,3,4-thiadiazole

Add the 0.02 moles of Hydrazine hydrate to 0.01 moles of 5-amino-2-mercapto-1,3,4-thiadiazole which is previously dissolved in absolute ethanol and reflux for 6 hours or until up to hydrogen sulfide gas was completely concluded (Salih *et al.*, 2008).

#### 3. Preparation of compound 3 [2-amino-5-(3,5-dimethyl-1H-pyrazolyl)-1,3,4-thiadiazole]

0.01 moles of 2-amino-5-hydrazino-1,3,4-thiadiazole was taken in absolute ethanol. Further added to the 0.01 moles of Acetyl acetone and refluxed for around 10 hours, concentrate the solution and allowed it to cool, to get the product and the solvent benzene was used to recrystallize the product (Salih *et al.*, 2008).

#### 4. General procedure for Preparation of 6-(3 or 4-substituted)-2-(3,5-dimethyl-1H-pyrazole-1yl)-imidazo(2,1-b)(1,3,4)-thiadiazole (4a-d)

The 0.01 mole of compound 3 and  $\alpha$ -haloaryl ketone





**1-((6-(4-bromophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (6b3)**

Brown solid, Yield: 86%, FT-IR: 3421 (NH), 2903 (C-H, aliphatic), 1616 (C=N), 1097 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.03 (s, NH), δ 5.91 (s, 1H, =CH), δ 3.18-3.79 (s, 3H, 2CH<sub>3</sub>), δ 6.91 (s, 1H, CH, thiazole), δ 7.72-7.77 (m, Ar-H, C2, C6) δ 7.85-8.12 (m, Ar-H, C3, C5); MS (ESI) m/z: 588.05 [M]<sup>+</sup>.

**1-((6-(4-bromophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (6b4)**

Brown solid, Yield: 87%, FT-IR: 3416 (NH), 2899 (C-H, aliphatic), 1611 (C=N), 1081 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.11 (s, NH), δ 5.90 (s, 1H, =CH), δ 3.68, 3.71 (s, 3H, CH<sub>3</sub>), δ 6.89 (s, 1H, CH, thiazole), δ 7.79-7.88 (m, Ar-H, C2, C6) δ 7.90-8.21 (m, Ar-H, C3, C5); MS (ESI) m/z: 607.99 [M]<sup>+</sup>.

**1-((6-(4-bromophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-bromophenyl)thiazol-2-yl)hydrazine (6b5)**

Dark green solid, Yield: 85%, FT-IR: 3416 (NH), 2899 (C-H, aliphatic), 1611 (C=N), 1081 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.15 δ 5.90 (s, 1H, =CH), δ 3.68, 3.71 (s, 3H, CH<sub>3</sub>), δ 6.89 (s, 1H, CH, thiazole), δ 7.79-7.88 (m, Ar-H, C2, C6) δ 7.90-8.21 (m, Ar-H, C3, C5); MS (ESI) m/z: 651.94 [M]<sup>+</sup>.

**1-((6-(4-bromophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(3-nitrophenyl)thiazol-2-yl)hydrazine (6b6)**

Brown solid, Yield: 86%, FT-IR: 3418 (NH), 2828 (C-H, aliphatic), 1650 (C=N), 1097 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.08 (S, NH), δ 5.93 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.99 (s, 1H, CH, thiazole), δ 7.77-7.79 (m, Ar-H, C2, C6) δ 8.10-8.32 (m, Ar-H, C4, C5); MS (ESI) m/z: 619.02 [M]<sup>+</sup>.

**1-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (6c1)**

Dark green solid, Yield: 85%, FT-IR: 3428 (NH), 2898 (C-H, aliphatic), 1639 (C=N), 1093 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ 12.14 (S, NH), δ 5.91 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.97 (s, 1H, CH, thiazole) δ 7.67-7.75 (m, Ar-H, C2, C6) δ 7.75-8.32 (m, Ar-H, C3, C5) δ 4.25 (S, OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO) d 172.8, 164.8, 160.2, 148.2, 147.2, 145.7, 139.2 (2C), 138.2, 137.2 (2C), 131.1, 129.5 (2C), 128.4 (3C), 127.2 (2C), 121.5 (2C), 104.3, 100.1, 56.1, 22.0, 13.8; MS (ESI) m/z: 571.12 [M]<sup>+</sup>.

**1-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine (6c2)**

Dark orange solid, Yield: 88%, FT-IR: 3428 (Secondary amine N-H), 2898 (C-H, aliphatic), 1639 (C=N), 1093 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.14 (S, NH), δ 5.91 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.97 (s, 1H, CH, thiazole) δ 7.67-7.75 (m, Ar-H, C2, C6) δ 7.75-8.32 (m, Ar-H, C3, C5) δ 4.36, 4.36 (S, OCH<sub>3</sub>); MS (ESI) m/z: 556.14 [M]<sup>+</sup>.

**1-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (6c3)**

Brown solid, Yield: 86%, FT-IR: 3411 (NH), 2901 (C-H, aliphatic), 1619 (C=N) 1101 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.14 (S, NH), δ 5.91 (s, 1H, =CH), δ 2.51, 2.55 (s, 3H, CH<sub>3</sub>), δ 6.98 (s, 1H, CH, thiazole) δ 7.22-7.30 (m, Ar-H, C2, C6) δ 7.42-7.68 (m, Ar-H, C3, C5) δ 3.88 (S, OCH<sub>3</sub>); MS (ESI) m/z: 540.15 [M]<sup>+</sup>.

**1-(4-(4-chlorophenyl)thiazol-2-yl)-2-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (6c4)**

Dark green solid, Yield: 86%, FT-IR: 3428 (NH), 2898 (C-H, aliphatic), 1639 (C=N), 1093 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.14 (S, NH), δ 5.86 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.97 (s, 1H, CH, thiazole) δ 7.82-7.96 (m, Ar-H, C2, C6) δ 8.00-8.24 (m, Ar-H, C3, C5) δ 4.27 (S, OCH<sub>3</sub>); MS (ESI) m/z: 560.09 [M]<sup>+</sup>.

**1-(4-(4-chlorophenyl)thiazol-2-yl)-2-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (6c5)**

Dark green solid, Yield: 86%, FT-IR: 3442 (NH), 2903 (C-H, aliphatic), 1640 (C=N), 1096 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.10 (S, NH), δ 5.97 (s, 1H, =CH), δ 3.83, 3.84 (s, 3H, CH<sub>3</sub>), δ 7.12 (s, 1H, CH, thiazol) δ 7.67-7.75 (m, Ar-H, C2, C6) δ 8.00-8.24 (m, Ar-H, C3, C5) δ 4.29 (S, OCH<sub>3</sub>); MS (ESI) m/z: 604.04 [M]<sup>+</sup>.

**1-((2-(3,5-dimethyl-1-H-pyrazol-1-yl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-1-yl)methylene)-2-(4-(3-nitrophenyl)thiazol-2-yl)hydrazine (6c6)**

Brown solid, Yield: 83%, FT-IR: 3418 (NH), 2828 (C-H, aliphatic), 1650 (C=N), 1097 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.08 (S, NH), δ 5.93 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.99 (s, 1H, CH, thiazole), δ 7.77-7.79 (m, Ar-H, C2, C6) δ 8.10-8.32 (m, Ar-H, C4, C5), δ 4.36 (S, OCH<sub>3</sub>); MS (ESI) m/z: 571.12 [M]<sup>+</sup>.

**1-((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazine (6d1)**

Light green solid, Yield: 85%, FT-IR: 3428 (NH), 2898 (C-H, aliphatic), 1639 (C=N), 1093 (C-N); <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.14 (S, NH), δ 5.58 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.96 (s, 1H, CH, thiazole), δ 7.11-7.63 (m, Ar-H, C2, C6) δ 7.80-7.88 (m, Ar-H, C3, C5) δ 4.25 (S, OCH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz, DMSO) d 171.7, 163.8, 160.2, 148.2, 145.2, 145.7, 144.2, 139.3 (2C), 136.2, 129.4 (2C), 128.9 (3C), 128.5 (2C), 127.3, 121.5, 114.8 (2C), 104.3, 100.1, 55.9, 17.6, 11.9; MS (ESI) m/z: 560.09 [M]<sup>+</sup>.

**1((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazine (6d2)**

Dark green solid, Yield: 86%, FT-IR: 3405 (NH), 2911 (C-H, aliphatic), 1618 (C=N), 1095 (C-N); <sup>1</sup>H-NMR (400 MHz,

DMSO-d<sub>6</sub>): δ 12.09 (s, NH), δ 6.06 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.71 (s, 1H, CH, thiazole), δ 7.72-7.85 (m, Ar-H, C2, C6) δ 8.02-8.11 (m, Ar-H, C3, C5); MS (ESI) m/z: 575.07 [M]<sup>+</sup>.

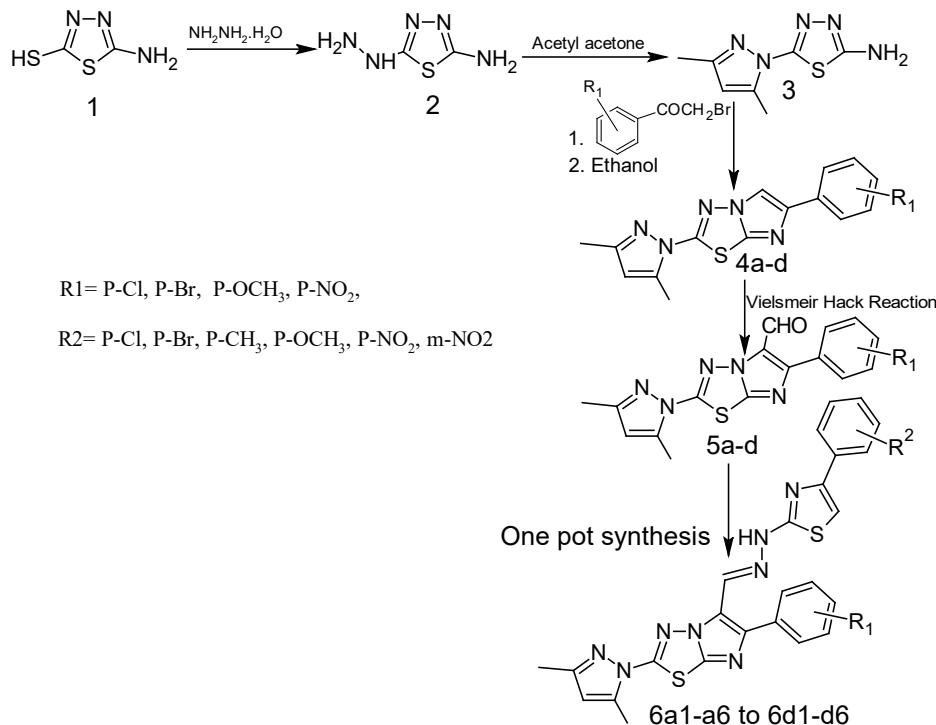
**1-((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-p-tolylthiazol-2-yl)hydrazine (6d3)**

Light green solid, Yield: 86%, FT-IR: 3405 (NH), 2911 (C-H, aliphatic), 1618 (C=N), 1095 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.07 (s, NH), δ 5.99 (s, 1H, =CH), δ 3.58-3.74 (s, 3H, CH<sub>3</sub>), δ 6.71 (s, 1H, CH, thiazole), δ 7.75-7.85 (m, Ar-H, C2, C6), δ 7.85-8.32 (m, Ar-H, C3, C5); MS (ESI) m/z: 564.04 [M]<sup>+</sup>.

C6) δ 7.85-8.32 (m, Ar-H, C3, C5); MS (ESI) m/z: 544.10 [M]<sup>+</sup>.

**1-((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazine (6d4)**

Brown solid, Yield: 85%, FT-IR: 3405 (NH), 2911 (C-H, aliphatic), 1618 (C=N), 1095 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.09 (s, NH), δ 6.06 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.71 (s, 1H, CH, thiazole), δ 7.75-7.85 (m, Ar-H, C2, C6) δ 7.85-8.32 (m, Ar-H, C3, C5); MS (ESI) m/z: 564.04 [M]<sup>+</sup>.



SCHEME 1: Synthetic route for the preparation of imidazo-thiadiazole derivatives.

**1-(4-(4-bromophenyl)thiazol-2-yl)-2-((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)hydrazine (6d5)**

Dark brown solid, Yield: 84%, FT-IR: 3416 (NH), 2899 (C-H, aliphatic), 1611 (C=N), 1081 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.11 (s, NH), δ 5.90 (s, 1H, =CH), δ 3.68, 3.71 (s, 3H, CH<sub>3</sub>), δ 6.89 (s, 1H, CH, thiazole), δ 7.62-7.99 (m, Ar-H, C2, C6) δ 8.05-8.21 (m, Ar-H, C3, C5); MS (ESI) m/z: 607.99 [M]<sup>+</sup>.

**1-((6-(4-chlorophenyl)-2-(3,5-dimethyl-1-H-pyrazol-1-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-2-(4-(3-nitrophenyl)thiazol-2-yl) hydrazine (6d6)**

Brown solid, Yield: 86%, FT-IR: 3418 (NH), 2828 (C-H, aliphatic), 1650 (C=N), 1097 (C-N); <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>): δ 12.08 (s, NH), δ 5.93 (s, 1H, =CH), δ 3.78, 3.84 (s, 3H, CH<sub>3</sub>), δ 6.99 (s, 1H, CH, thiazole), δ 7.77-7.79 (m, Ar-H, C2, C6) δ 8.10-8.32 (m, Ar-H, C4, C5); MS (ESI) m/z: 575.07 [M]<sup>+</sup>.

## RESULTS AND DISCUSSION

In this work, we have successfully synthesized twenty-

four new moieties presented in the scheme and their structures were analyzed with the help of various spectroscopic techniques. The <sup>1</sup>H-NMR for 6a1-a6 to 6d1-d6 showed a singlet of -NH proton with a broad peak around δ 12 ppm and one more proton of the (C=N-) imine linkage shows a singlet of -CH at around δ 8 ppm.

The <sup>13</sup>C-NMR of compound 6a1-a6 to 6d1-d6 showed a carbon frequency around 172 ppm due to the presence of secondary nitrogen either side of the carbon of thiazole at a second position which is attached to imine (CH=N-) linkage and the other carbon frequencies around 10 and 20 ppm for methyl groups on the pyrazole ring.

All synthesized compounds (6a1-a6 to 6d1-d6) were tested for anti-TB activity, compounds 6a1, 6a2, 6a3, 6c1, 6c6 and 6d1 have shown promising antitubercular activity since the results showed that amongst all the tested compounds, the compounds 6a1, 6a2, 6a3, 6c1, and 6d1 with methoxy/nitro substitution at 4<sup>th</sup> position of phenyl ring at 4<sup>th</sup> position of thiazole ring of the condensed imidazo[2,1-b][1,3,4]-thiadiazoles moiety and nitro or chloro or methoxy substitution on the 4<sup>th</sup> position of the phenyl ring at 6<sup>th</sup> position of the condensed imidazothiadiazole moiety was

shown good anti-tubercular activity (1.6 to 6.25 mcg/ml) against *Mycobacterium tuberculosis* H37Rv strain and Streptomycin (6.25 mcg/mL), Ciprofloxacin (3.125 mcg/mL) along with pyrazinamide (3.25 mcg/mL) as standard.

**Table 2:** Anti-Tubercular and Anti-fungal activity.

Product	MIC values ( $\mu\text{g}/\text{ml}$ )		
	Anti-Tubercular activity	Anti-fungal activity	
	<i>M. tuberculosis</i>	<i>Candida Albicans</i>	<i>A. Flavus</i>
6a1	1.6	5	25
6a2	6.25	10	25
6a3	6.25	10	50
6a4	12.5	5	10
6a5	12.5	5	50
6a6	12.5	50	75
6b1	25	25	25
6b2	12.5	10	25
6b3	12.5	25	50
6b4	25	25	25
6b5	12.5	25	50
6b6	12.5	50	75
6c1	6.25	75	75
6c2	12.5	75	75
6c3	6.25	25	75
6c4	12.5	25	50
6c5	12.5	25	50
6c6	6.25	50	75
6d1	6.25	5	25
6d2	25	25	25
6d3	25	25	50
6d4	25	10	25
6d5	25	25	50
6d6	25	75	75
		Standard values	
Pyrazinamide	3.125		
Streptomycin	6.25	Fluconazole	30
Ciprofloxacin	3.125		

All synthesized compound (6a1-a6 to 6d1-d6) were tested for antifungal activity and Fluconazole as a standard drug (MIC 30  $\mu\text{g}/\text{ml}$ ). The compounds 6a1, 6a4, 6a5, and 6d1 have shown promising antifungal activity (MIC 5  $\mu\text{g}/\text{ml}$ ) due to the presence of methoxy/chloro/bromo substitution at 4<sup>th</sup> position of phenyl ring at 4<sup>th</sup> position of thiazole ring of the basic imidazothiadiazole ring and presence of nitro/chloro groups on to the 4<sup>th</sup> position of phenyl ring attached to 6<sup>th</sup> position of basic ring moiety. But in the presence of electron donating groups in the same position are less reactive along with the substitution at the third position to the phenyl ring. The results are given in Table 2.

## CONCLUSION

The present study on the substituted derivatives of imidazo[2,1-b][1,3,4]thiadiazole showed a moderate to finest activity against *Mycobacterium tuberculosis* and fungal species.

There is a scope with a slight modification on the basic moiety can produce excellent derivatives with better activity and enhanced pharmacokinetic property.

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