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Synthesis and Antimicrobial Activity of Triazole-isothiazole Analogues

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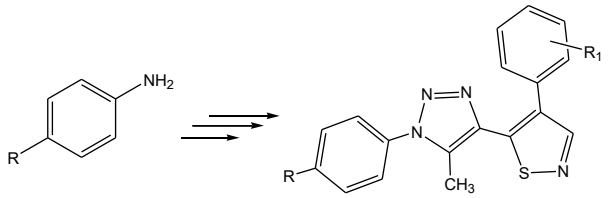
Abstract:
A new series of 5-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)-4-aryl-isothiazole ***8(a-i)*** *were synthesized by the reaction of 4-bromo-5-(5-methyl-1-aryl-1H-1,2,3-triazol-4-yl)isothiazole* ***7(a-c)*** *with aryl boronic acid, and evaluated for their antibacterial activity against Gram-positive bacteria viz. B. Subtilis, B. Sphaericus, S. Aureus and Gram-negative bacteria viz. P. Aeruginosa, K. Aerogenes, C. Violaceum and also screened for their antifungal activity against fungal strains viz. C. Albicans, A. Fumigatus, T. rubrum and T. Mentagrophytes. Compounds* ***8e*** *and* ***8f*** *showed significant antibacterial activity against all the tested strains. Similarly, compounds* ***8e*** *and* ***8d*** *also showed good antifungal activity, and emerged as potential molecules for further development.*



Keywords: Triazole, Isothiazole, Antibacterial Activity, Antifungal Activity.

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I. INTRODUCTION

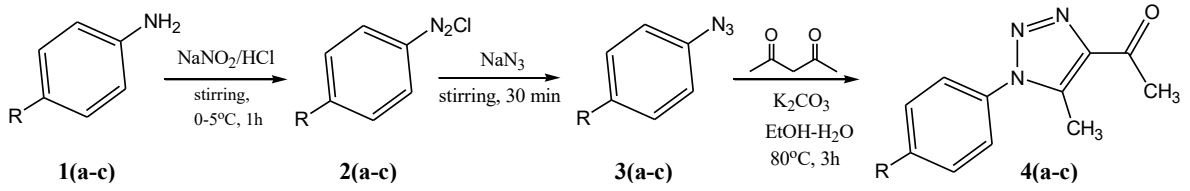
Because of antibiotic resistance, the prevalence of microbial infection has skyrocketed during the last few decades over the world [1-6]. Microbial infections are a rising problem in modern medicine, and antibiotics are widely used around the world. As a result, there is an urgent need to broaden the range of antimicrobial medicines that are effective against resistant microbes. The heterocyclic compounds, particularly those with nitrogen and sulphur atoms, are valuable in medicinal chemistry due to their many biological actions, such as antibacterial [7], anticancer [8], antiviral [9] and enzyme inhibition [10]. Incorporating nitrogen and sulphur atoms into heterocyclic frameworks improves their pharmacological profile, making them promising therapeutic candidates.

The 1,2,3-triazoles are nitrogen-containing heterocycles with three nitrogen atoms in the ring, making them more resistant to metabolic breakdown than other heterocycles [11]. The insertion of 1,2,3-triazole units into therapeutic structures has grown in favour due to their ability to build stable compounds with hydrogen bonding interactions, which improve drug solubility and efficacy [12]. As a result, medicines containing 1,2,3-trazole compounds have been created and shown to exhibit a variety of biological features, including anticancer [13,14], antibacterial [15], antiviral [16] and anti-HIV activity [17]. Similarly, the isothiazole derivatives are of tremendous interest since they have shown great potential in the design and synthesis of a variety of biologically active compounds. A variety of pharmacological activities were demonstrated by compounds with an isothiazole ring, including bioregulatory [18], prostaglandin release inhibitory [19], cytotoxicity [20], anti-poliovirus activity [21], anti-parkinson [22], anticancer [23-28], antidiabetic [29-30], antimicrobial [31] treatment of liver diseases [32], GABA receptor antagonist [33], plant growth regulatory [34] and fungicidal [35].

Following the successful introduction, inspired by the biological profile of triazole and isothiazole, and in the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame, may lead to compounds with interesting biological profiles, it was thought of interest to accommodate triazole and isothiazole rings in a single molecular framework. In the present investigation, driven by these observations, the synthesis and antimicrobial activity of new series of 5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-4-aryl-isothiazole **8(a-i)**.

II. RESULTS AND DISCUSSION

Diazotization of corresponding arylamine **1(a-c)** with sodium nitrite in the presence of hydrochloric acid at 0-5 ºC under stirring for 1 h gave corresponding aryl diazonium chloride **2(a-c)** which on direct treatment with sodium azide in water under stirring for 30 min afforded the corresponding 1-arylazides **3(a-c)** in good yields. The cyclization of compound **3** with acetylacetone in ethanol-water in the presence of K_2CO_3 under heating at 80 ºC for 3 h, gave corresponding 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-1-ethanone **4(a-c)** in good to moderate yields (**Scheme 1**). The structures compounds were confirmed by IR, ^{1}H, ^{13}C NMR and MS spectral analysis.



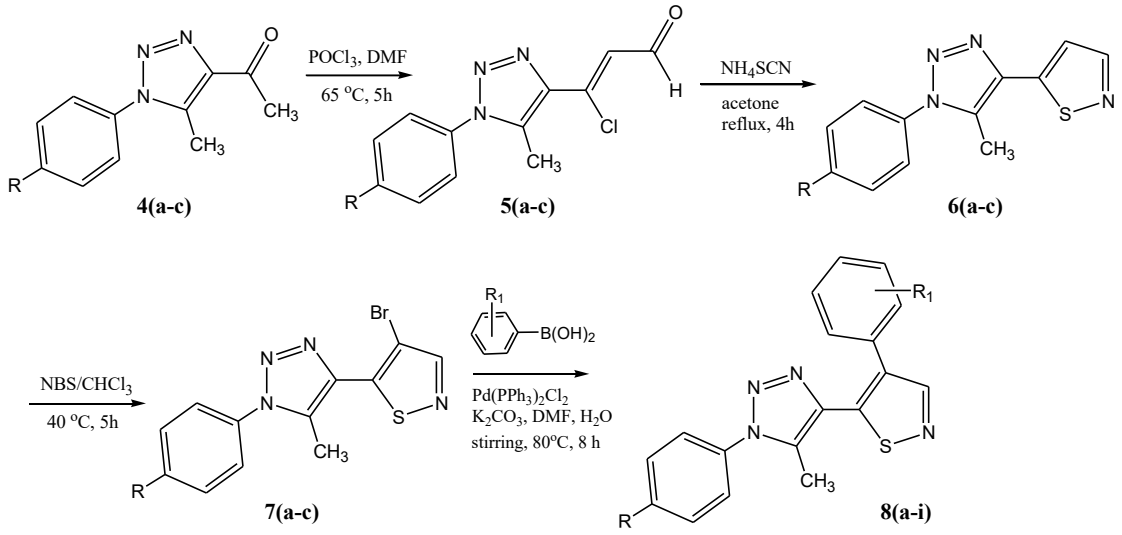
1/2/3/4: R = a) H; b) F c) Cl

Scheme 1

The IR spectrum of compound **3a** the stretching frequency observed at 2167, 1610 and 1277 cm^{-1} corresponding to N3, C=C and C-N groups. Its proton NMR spectra a multiplet at δ 7.10-7.20 ppm integrated for five protons is assigned for aromatic protons. The ^{13}C NMR spectra the signal corresponding to the phenyl ring observed between δ 120.4-140.6 ppm. The IR spectrum of compound **4a** the characteristic stretching frequency for C=O and N=N were appeared at 1710 and 1579 cm^{-1}. Its proton NMR spectrum showed the singlet signal at δ 2.17 ppm for three protons of methyl group and a singlet at δ 2.89 ppm assigned for methyl protons attached to carbonyl group, the aromatic protons signal appeared as multiplet at δ 7.35-7.40 ppm. The 13C NMR spectrum, the prominent signals corresponding to the carbons of triazole ring observed at δ 140.3 (C-4), 129.0 (C-5) ppm and the carbonyl carbon appear a 191.2 ppm.

The Vilsmeier-Hack reaction of compound **4(a-c)** with $POCl_3$ in the presence of dimethylformamide (DMF) under stirring at 65-70 ºC for 5 h yields the corresponding (*Z*)-3-chloro-3-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-2-propenal **5(a-c)** through the initial formation of chloro iminium salt followed by base hydrolysis. The cyclization of compound **5** with ammonium thiocyanate in acetone under reflux for 4 h, afforded the corresponding 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)isothiazole **6(a-c)** in good yields, which on bromination with *N*-bromosuccinamide (NBS) in chloroform under reflux at 40-45 ºC for 5 h to gave corresponding 4-bromo-5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)isothiazole **7(a-c)**. The treatment of mixture of corresponding compound **7** and corresponding boronic acid in DMF-water in the presence of $Pd(PPh_3)_2Cl_2$ and potassium carbonate under heated at 80°C for 8h, it gave the desired compound 5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-4-aryl-isothiazole **8(a-i)** in good yields (**Scheme 2**). The structures compounds were confirmed by IR, ^{1}H, ^{13}C NMR and MS spectral analysis.

The IR spectrum of compound **5a** the stretching frequencies observed at 2810 (CHO), 1722 (C=O), 1562 (C=C), 1543 (N=N), 696 (C-Cl) cm^{-1}. Its proton NMR spectra a multiplet at δ 7.30-7.50 ppm integrated for five protons is assigned for aromatic protons, the two doublet signals with J = 7.9 Hz integrating one proton in each at δ 7.62 and 9.98 ppm assigned to alkene and aldehyde protons respectively, the methyl proton signal appear at δ 2.71 as singlet. The ^{13}C NMR spectra the signal corresponding triazole ring appeared at δ 159.0 (C-4), 132.7 (C-5) ppm, the alkene carbon signals observed at δ 139.8 and 132.7 ppm, the carbonyl carbon is observed at δ 182.1 ppm. The IR spectrum of compound **6a** the stretching frequencies of triazole ring observed at 1607 (C=N), 1549 (N=N) and isothiazole ring at 1490 (N-S) cm^{-1}. Its proton NMR spectra a multiplet at δ 7.40-7.50 ppm integrated for five protons is assigned for aromatic protons, the two doublet signals with J = 1.6 Hz integrating one proton in each at δ 8.07 and 8.54 ppm assigned to isothiazole ring. The ^{13}C NMR spectra the prominent signals for triazole ring appeared at δ 149.8 (C-4), 135.9 (C-5) ppm, the carbons of isothiazole ring appeared at δ 155.6 (C-3), 128.7 (C-4) and 155.6 (C-5) ppm.



Comp.	R	R_1	Comp.	R	R_1	Comp.	R	R_1
8a	H	H	**8d**	F	H	**8g**	Cl	H
8b	H	4-Cl	**8e**	F	4-Cl	**8h**	Cl	4-Cl
8c	H	3-COOH	**8f**	F	3-COOH	**8i**	Cl	3-COOH

(Scheme 2)

The IR spectrum of compound **7a** the stretching frequencies of triazole ring observed at 1602 (C=N), 1581 (N=N) and isothiazole ring at 1487 (N-S) cm^{-1}. Its proton NMR spectra a multiplet at δ 7.35-7.40 ppm integrated for five protons is assigned for aromatic protons, the singlet signal at δ 8.22 for one proton is assigned to isothiazole ring, the methyl proton singlet appear at δ 2.52 ppm. The ^{13}C NMR spectra the prominent signals for triazole ring appeared at δ 153.1 (C-4), 129.0 (C-5) ppm, the carbons of isothiazole ring appeared at δ 156.3 (C-3), 109.3 (C-4) and 140.1 (C-5) ppm. The IR spectrum of compound **8a** the stretching frequencies of triazole ring observed at 1612 (C=N), 1564 (N=N) and isothiazole ring at 1485 (N-S) cm^{-1}. Its proton NMR spectra a multiplet at δ 7.35-7.40 ppm integrated for ten protons is assigned to aromatic protons, the singlet signal at δ 8.62 for one proton is assigned to isothiazole ring, the methyl proton singlet appear at δ 2.68 ppm. The ^{13}C NMR spectra the prominent signals for triazole ring appeared at δ 151.7 (C-4), 119.9 (C-5) ppm, the carbons of isothiazole ring appeared at δ 157.2 (C-3), 141.3 (C-4) and 147.0 (C-5) ppm.

ANTIBACTERIAL ACTIVITY

All the compounds **8(a-i)** were assayed for their antibacterial activity against Gram-positive bacteria *viz*. *Bacillus Subtilis* (MTCC 441), *Bacillus Sphaericus* (MTCC 11) and *Staphylococcus Aureus* (MTCC 96) and Gram-negative bacteria *viz*. *Pseudomonas Aeruginosa* (MTCC 741), *Klobsinella Aerogenes* (MTCC 39) and *Chromobacterium Violaceum* (MTCC 2656) by disc diffusion method [36,37] the mean zone of inhibition (MZI, mm) of the compounds were determined and presented in **Table 1**. In addition, the minimum inhibitory concentration (MIC, μg/ml, *i.e.* minimum concentration required to inhibiting the growth of bacteria) and the minimum bacterial concentration (MBC, μg/mL, *i.e.* the lowest concentration of the drug/compound at which 99.9% inoculums were killed) of all the compounds were determined by the broth dilution method [38] and presented in **Table 2**. All assays included the solvent and reference controls. Streptomycin was used as standard drugs.

Table 1. Inhibitory zone diameters (mm) of compounds 8(a-i)

Compound	Mean zone inhibition (MZI) in mm[a]					
	B. subtilis	***B. sphaericus***	***S. aureus***	***P. aeruginosa***	***K. aerogenes***	***C. violaceum***
8a	12	10	18	11	13	12
8b	21	17	14	10	16	10
8c	9	8	15	6	9	11
8d	13	9	10	8	10	8

8e	22	18	30	10	18	17
8f	24	16	29	11	16	16
8g	14	7	6	5	11	8
8h	23	17	32	9	13	15
8i	24	12	34	11	19	12
Streptomycin	30	20	41	15	25	20

Streptomycin (100 μg/disc) as positive reference and compounds 8(a-i) (300 μg/disc) were used.
[a]Values are mean (n = 3).

The investigation of antibacterial screening data reveal that almost all the compounds **8(a-i)** are active and showing moderate to good antibacterial activity. Compounds containing combination like 4-fluorophenyl on triazole, 4-chlorophenyl on isothiazole (**8e**) or 4-fluorophenyl on triazole, phenyl-3-carboxylic acid on isothiazole (**8f**) showed significant zone of inhibition against both gram-positive and gram-negative bacterial strains. Compounds with the combination of 4-chloropheny group on both triazole and isothiazole ring (**8h**) showed good inhibition but only against gram-positive bacterial strains. The compound (**8i**) showed the better inhibition against *B. Subtilis*, *S. Aureus and K. Aerogenes,* similarly compound (**8b**) also showed better activity against *B. Subtilis* and *B. Sphaericus* (**Table 1**). Most of the compounds exhibited good antibacterial activity almost equivalent to that of standard. The MBC of few compounds is the same as MIC but for many compounds it is two to four-folds higher than the corresponding MIC value (**Table 2**).

Table 2. Minimum inhibitory concentration (MIC) and minimum bacterial concentration (MBC) in μg/mL of compounds 8(a–i)

Compound	*B. subtilis*		*B. sphaericus*		*S. aureus*		*P. aeruginosa*		*K. aerogenes*		*C. violaceum*	
	MIC	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
8a	25.0	50.0	25.0	(—)	12.5	50.0	25.0	25.0	12.5	25.0	25.0	50.0
8b	12.5	25.0	12.5	25.0	25.0	(—)	25.0	50.0	12.5	25.0	25.0	50.0
8c	25.0	25.0	25.0	(—)	12.5	25.0	(—)	(—)	25.0	50.0	12.5	25.0
8d	50.0	(—)	25.0	50.0	25.0	50.0	12.5	25.0	(—)	(—)	25.0	(—)
8e	12.5	25.0	12.5	12.5	12.5	25.0	6.25	12.5	12.5	12.5	12.5	12.5
8f	12.5	25.0	6.25	12.5	12.5	12.5	3.12	12.5	6.25	12.5	12.5	25.0
8g	25.0	(—)	25.0	50.0	12.5	25.0	12.5	50.0	(—)	(—)	25.0	50.0
8h	12.5	25.0	12.5	25.0	12.5	25.0	25.0	25.0	12.5	25.0	25.0	25.0
8i	12.5	25.0	25.0	50.0	12.5	25.0	25.0	25.0	12.5	12.5	12.5	25.0
Streptomycin	6.25	12.5	6.25	25.0	6.25	12.5	1.56	6.25	1.56	6.25	3.12	6.25

(—) indicates bacterial strains are resistant to the compounds >100 μg/mL concentration.

ANTIFUNGAL ACTIVITY

The compounds **8(a-i)** were also screened for their antifungal activity against four fungal organisms *viz*. *Candida Albicans* (ATCC 10231), *Aspergillus Fumigatus* (HIC 6094), *Trichophyton rubrum* (IFO 9185) and *Trichophyton Mentagrophytes* (IFO 40996) in DMSO by agar diffusion method [39]. Amphotericin B was used as a standard drug and the zones of fungal inhibition values are reported in **Table 3**. In addition, the MIC and MFC (minimum fungicidal concentration, *i.e.* the lowest concentration of the compound at which 99.9% of inoculums were killed) values determined by the broth dilution method [38] and are presented in **Table 4**.

Table 3. Inhibitory zone diameters (mm) of compounds 8(a-i)

Compound	Mean zone inhibition (MZI) in mm[a]			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagrophytes*
8a	**(—)**	8	10	**(—)**
8b	12	10	**(—)**	9
8c	10	18	8	17
8d	21	19	16	15
8e	20	20	19	15
8f	9	**(—)**	7	5
8g	8	11	**(—)**	**(—)**
8h	22	18	8	6
8i	10	**(—)**	7	10
Amphotericin B	25	20	20	18

Amphotericin B (100 μg/disc) as positive reference and compounds 8(a-i) (300 μg/disc) were used.
[a]Values are mean (n = 3).
(—) indicates fungal are resistant to the compounds >100 μg/mL concentration.

The antifungal screening data reveal that most of the new compounds are active and having moderate to good antifungal activity. Among the screened compounds, the compound (**8e**) in which triazole moiety bearing 4-fluorophenyl and 4-chlorophenyl substituent on isothiazole and compound (**8d**) with 4-fluorophenyl on triazole ring showed highest inhibition against all the fungal strains. Compound (**8h**) showed significant inhibition against *C. Albicans*, *A. Fumigatus*, compound (**8c**) also showed better activity against *A. Fumigatu* and *T. Mentagrophytes*. The MFC of some compounds is the same as MIC but for many compounds it is two to four-folds higher than the corresponding MIC value.

Table 4. Minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC) in μg/mL of compounds 8(a-i)

Compound	*C. albicans*		*A. fumigatus*		*T. rubrum*		*T. mentagrophytes*	
	MIC	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**	**MIC**	**MBC**
8a	25.0	50.0	25.0	50.0	**(—)**	**(—)**	**(—)**	**(—)**
8b	**(—)**	**(—)**	25.0	50.0	**(—)**	**(—)**	12.5	25.0
8c	25.0	50.0	12.5	12.5	12.5	25.0	12.5	25.0
8d	12.5	12.5	6.25	12.5	12.5	25.0	12.5	25.0
8e	12.5	25.0	12.5	12.5	12.5	25.0	6.25	12.5
8f	25.0	50.0	12.5	25.0	**(—)**	**(—)**	12.5	25.0
8g	12.5	25.0	**(—)**	**(—)**	25.0	50.0	25.0	50.0
8h	12.5	25.0	6.25	12.5	12.5	25.0	**(—)**	**(—)**
8i	12.5	25.0	**(—)**	**(—)**	12.5	12.5	25.0	50.0
Amphotericin B	6.25	12.5	3.12	6.25	3.12	12.5	3.12	12.5

(—) indicates bacterial strains are resistant to the compounds >100 μg/mL concentration.

III. MATARIALS AND METHODS

All reagents are commercial grade and were used as supplied. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck, and compounds visualized by exposure to UV light. Chromatographic columns 70–230 mesh silica gel for separations were used. IR spectra were recorded using KBr disk on a Perkin–Elmer FTIR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in δ ppm units with respect to TMS as internal standard and coupling constants (*J*) are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer.

General procedure for the synthesis of 1-arylazides 3(a-c): To a cold solution of corresponding arylamine **1** (0.01 mol) in dil. hydrochloric acid (15 mL), sodium nitrite (1.1 mol) was added in small portions at 0-5 °C and stirred for one hour to afford the diazonium chloride **9**, then a solution of sodium azide (1.2 mol in 10 mL water) was added in drop wise manner and stirring was continued for 30 min and the resulting solid was filtered and recrystallized from ethanol to give pure compound **3(a-c)** in good yields.

1-Azidobenzene (3a): IR (KBr) ν_{max}: 3110 (C-H, ArH), 2167 (N_3), 1610 (C=C), 1277 (C-N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.10-7.20 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 120.4, 122.7, 128.4, 140.6; MS: *m/z* 119 (M^+).

1-Azido-4-fluorobenzene (3b): IR (KBr) ν_{max}: 3067, 2120, 1607, 1272, 1031 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.80 (d, J = 8.2 Hz, 2H, ArH), 6.98 (d, J = 8.2 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 114.7, 125.8, 139.9, 164.5; MS: *m/z* 137 (M^+).

1-Azido-4-chlorobenzene (3c): IR (KBr) ν_{max}: 3071, 2117, 1609, 1268, 687 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.20-7.25 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 122.8, 125.7, 136.8, 140.5; MS: *m/z* 153 (M^+).

General procedure for the synthesis of 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-1-ethanone 4(a-c): To a solution of corresponding compound **3(a-c)** (0.01 mol) in ethanol: water (1:1), acetylacetone (0.015 mol) and K_2CO_3 (0.02 mol) was added the resulting mixture was stirred in an oil bath at 80°C for 3 h. After completion of the reaction, as monitored by TLC, the reaction mixture was cooled to rt and poured into ice-cold water. The product that precipitated out was filtered, washed successively with ice-cold water, and purified column

chromatography on silica gel (60-120 mesh) with ethyl acetate-petroleum ether mixture (40:60) as the eluting solvent to obtain the corresponding compounds **4(a-c)**.

1-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-1-ethanone (4a): IR (KBr) ν_{max}: 3074, 1710, 1579, 1027 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.17 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 7.35-7.40 (m, 5H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.9, 29.1, 124.9, 128.1, 129.0, 130.5, 140.3, 144.7, 191.2; MS: *m/z* 202 (M^++1).

1-[1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-1-ethanone (4b): IR (KBr) ν_{max}: 3069, 1698, 1581, 1302, 1033 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.15 (s, 3H, CH_3), 2.90 (s, 3H, CH_3), 7.50-7.55 (m, 4H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.3, 29.7, 118.9, 124.5, 128.2, 138.0, 143.3, 166.3, 190.7; MS: *m/z* 219 (M^+).

1-[1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-1-ethanone (4c): IR (KBr) ν_{max}: 3071, 1701, 1578, 1307, 1031 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.19 (s, 3H, CH_3), 2.92 (s, 3H, CH_3), 7.32 (d, J = 8.4 Hz, 2H, ArH), 7.94 (d, J = 8.4 Hz, 2H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.2, 29.4, 125.3, 129.5, 131.8, 134.2, 140.5, 143.3, 191.1; MS: *m/z* 235 (M^+).

General procedure for the synthesis of (*Z*)-3-chloro-3-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-2-propenal 5(a-c): N,N-dimethylformamide (20 mL) was added to a $POCl_3$ (0.02 mol) solution at 55 °C, and the reaction mixture was agitated for two hours at room temperature. After adding the corresponding compound **5** (0.01 mol), the reaction mixture was heated to 65-70 °C for five hours. Following the reaction's completion (which was observed using TLC in $CHCl_3$), the reaction mixture was cooled to room temperature, charged with 50 g of sodium acetate and 20 mL of water, agitated for five hours at room temperature, and then basified with an aqueous sodium carbonate solution. After filtering, the product was cleaned with water and dried. Dichloromethane-eluted column chromatography was used to purify the crude product to give pure compound **5(a-c)** in good yields.

(*Z*)-3-Chloro-3-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-2-propenal (5a): IR (KBr) ν_{max}: 3074, 2810, 1722, 1562, 1543, 1410, 696 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.71 (s, 3H, CH_3), 7.30-7.50 (m, 5H, ArH), 7.62 (d, J = 7.9 Hz, 1H, ethylene), 9.98 (d, J = 7.9 Hz, 1H, aldehyde); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.1, 128.2, 129.8, 130.4, 132.7, 139.8, 141.2, 142.1, 159.0, 182.1; MS: *m/z* 248 (M^++1).

(*Z*)-3-Chloro-3-[1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-2-propenal (5b): IR (KBr) ν_{max}: 3072, 2811, 1712, 1557, 1541, 1421, 1090, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.72 (s, 3H, CH_3), 7.30 (d, J = 8.3 Hz, 2H, ArH), 7.52 (d, J = 8.3 Hz, 2H, ArH), 7.57 (d, J = 7.8 Hz, 1H, ethylene), 9.99 (d, J = 7.9 Hz, 1H, aldehyde); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.9, 119.0, 127.1, 132.2, 139.1, 140.9, 141.0, 159.7, 164.5, 179.2; MS: *m/z* 265 (M^+).

(*Z*)-3-Chloro-3-[1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-2-propenal (5c): IR (KBr) ν_{max}: 3067, 2817, 1713, 1557, 1541, 1418, 694 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.62 (s, 3H, CH_3), 7.30-7.50 (m, 3H, ArH & ethylene), 8.42 (d, J = 8.8 Hz, 2H, ArH), 9.98 (d, J – 7.6 Hz, 1H, aldehyde); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.7, 126.0, 129.8, 131.5, 132.2, 139.3, 140.9, 141.1, 159.2, 181.5; MS: *m/z* 282 (M^+).

General procedure for the synthesis of 5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)isothiazole 6(a-c): Acetone (100 mL) was mixed with corresponding compound **5** (0.01 mol) and ammonium thiocyanate (0.015 mol) and the reaction mixture was refluxed for four hours. Following the reaction's completion (which was tracked using TLC in $CHCl_3$), the reaction mixture was allowed to cool to room temperature, washed with acetone, and dried. Ethyl acetate and petroleum ether were used in column chromatography to purify the crude product **6(a-c)** in good yields.

5-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)isothiazole (6a): IR (KBr) ν_{max}: 3091, 1607, 1562, 1549, 1490, 1410, 626 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.71 (s, 3H, CH_3), 7.40-7.50 (m, 5H, ArH), 8.07 (d, J = 1.6 Hz, 1H, ArH), 8.54 (d, J = 1.6 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 18.2, 125.9, 126.3, 128.7, 130.7, 131.1, 139.1, 149.8, 155.6, 159.2; MS: *m/z* 242 (M^+).

5-[1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (6b): IR (KBr) ν_{max}: 3087, 1610, 1557, 1545, 1489, 1407, 1089, 632 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 7.25-7.30 (m, 4H, ArH), 8.12 (d, J = 1.7 Hz, 1H, ArH), 8.57 (d, J = 1.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.9, 116.5, 125.9, 126.7, 130.1, 138.2, 149.2, 155.5, 159.7, 166.7; MS: *m/z* 261 (M^++1).

5-[1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (6c): IR (KBr) ν_{max}: 3078, 1611, 1561, 1548, 1487, 1405, 689, 633 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 7.54 (d, J = 8.4 Hz, 2H, ArH), 8.00-8.10 (m, 3H, ArH), 8.57 (d, J = 1.7 Hz, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.1, 126.4, 128.1, 129.8, 130.6, 132.9, 138.9, 149.2, 155.1, 159.3; MS: *m/z* 276 (M^+).

General procedure for the synthesis of 4-bromo-5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)isothiazole 7(a-c): Chloroform (50 mL) was mixed with corresponding compound 6 (0.01 mol) and *N*-bromosuccinamide (0.015 mol). For four hours, the reaction mixture was heated to 40–45 °C while being agitated. Following the reaction's completion (which was tracked using TLC in $CHCl_3$), the reaction mixture was allowed to cool to room temperature, washed with chloroform, and dried. Petroleum ether and ethylacetate were used in column chromatography to purify the crude product.

4-Bromo-5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)isothiazole (7a): IR (KBr) ν_{max}: 3110, 1602, 1581, 1552, 1487, 1417, 686, 617 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.52 (s, 3H, CH_3), 7.35-7.40 (m, 5H, ArH), 8.22 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.3, 109.3, 125.4, 128.7, 129.0, 130.9, 140.1, 142.8, 153.1, 156.3; MS: *m/z* 321 (M^+).

4-Bromo-5-[1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (7b): IR (KBr) ν_{max}: 3089, 1611, 1578, 1549, 1482, 1412, 689, 622 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.61 (s, 3H, CH_3), 7.30-7.40 (m, 4H, ArH), 8.17 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.1, 118.0, 109.7, 125.5, 133.9, 139.4, 142.2, 153.5, 155.2, 158.9, 162.1; MS: *m/z* 339 (M^+).

4-Bromo-5-[1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (7c): IR (KBr) ν_{max}: 3102, 1609, 1587, 1552, 1481, 1425, 1039, 682, 619 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.67 (s, 3H, CH_3), 7.57 (d, J = 8.5 Hz, 2H, ArH), 8.02 (d, J = 8.5 Hz, 2H, ArH), 8.29 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.6, 108.7, 126.9, 130.9, 131.8, 135.6, 138.7, 141.2, 153.4, 155.1; MS: *m/z* 355 (M^+).

General procedure for the synthesis 5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-4-aryl- isothiazole 8(a-i): To a mixture of solvent DMF (5 mL) and water (5 mL), corresponding compound **7** (0.01 mol) was added, to this mixture corresponding boronic acid (0.015 mol) and K_2CO_3 (0.02 mol) were added and then the mixture was degassed with nitrogen bubbling and charged with $Pd(PPh_3)_2Cl_2$ (0.001 mol) and stirred at 80 °C for 8 h. After completion of the reaction (monitored through TLC in $CHCl_3$), the reaction mixture was cooled to room temperature, and the reaction mass was filtered and partitioned between ethyl acetate and water; the organic layer was collected, and the solvent was removed under reduced pressure. The crude material was purified by column chromatography eluted with ethyl acetate and petroleum ether to get corresponding compounds **8(a-i)**.

5-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-4-phenylisothiazole (8a): IR (KBr) ν_{max}: 3089, 1612, 1564, 1551, 1485, 1427, 619 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.68 (s, 3H, CH_3), 7.35-7.40 (m, 10H, ArH), 8.62 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.5, 119.9, 126.9, 127.4, 128.2, 129.0, 129.7, 135.1, 136.2, 139.6, 141.3, 147.0, 151.7, 157.2 ; MS: *m/z* 318 (M^+).

4-(4-Chlorophenyl)-5-(5-methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)isothiazole (8b): IR (KBr) ν_{max}: 3091, 1602, 1571, 1547, 1488, 1429, 697, 621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.68 (s, 3H, CH_3), 7.35-7.40 (m, 5H, ArH), 7.50-7.55 (m, 4H, ArH), 8.57 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.7, 119.2, 126.3, 127.8, 128.5, 129.6, 133.9, 134.1, 136.1, 138.4, 139.1, 147.2, 151.3, 157.1; MS: *m/z* 352 (M^+).

3-[5-(5-Methyl-1-phenyl-1*H*-1,2,3-triazol-4-yl)-4-isothiazolyl]benzoic acid (8c): IR (KBr) ν_{max}: 3398, 3113, 1721, 1615, 1569, 1555, 1487, 1422, 1215, 621 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.68 (s, 3H, CH_3), 7.35-7.40 (m, 7H, ArH), 8.30-8.35 (m, 2H, ArH), 8.48 (s, 1H, ArH), 10.89 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 16.4, 119.1, 126.0, 128.0, 128.3, 128.9, 129.5, 130.2, 131.9, 132.7, 139.1, 140..0, 145.2, 147.7, 150.5, 156.1, 164.1; MS: *m/z* 362 (M^+).

5-[1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-phenylisothiazole (8d): IR (KBr) ν_{max}: 3082, 1617, 1558, 15512, 1479, 1432, 1031, 622 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 7.30-7.35 (m, 9H, ArH), 8.62 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.4, 118.4, 124.7, 127.0, 128.1, 134.9, 135.7, 136.0, 136.9, 137.4, 141.0, 148.1, 153.2, 154.3, 154.9, 166.2; MS: *m/z* 336 (M^+).

4-(4-chlorophenyl)-5-[1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (8e): IR (KBr) ν_{max}: 3067, 1609, 1582, 1549, 1481, 1422, 1032, 695, 623 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.65 (s, 3H, CH_3), 7.30-7.35 (m, 4H, ArH), 7.50-7.55 (m, 4H, ArH), 8.51 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.3, 118.6, 124.2, 127.1, 127.9, 132.9, 133.8, 134.6, 137.2, 138.4, 148.7, 153.4, 154.6, 154.8, 166.0; MS: *m/z* 370 (M^+).

3-5-[1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-isothiazolylbenzoic acid (8f): IR (KBr) ν_{max}: 3387, 3101, 1717, 1613, 1571, 1551, 1482, 1424, 1211, 628 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.64 (s, 3H, CH_3), 7.40-7.45 (m, 6H, ArH), 8.30-8.35 (m, 2H, ArH), 8.49 (s, 1H, ArH), 10.81 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.1, 118.5, 124.3, 127.4, 127.9, 128.8, 129.7, 130.5, 134.0, 137.1, 138.7, 143.8, 148.0, 153.1, 154.5, 154.9, 161.4, 166.1; MS: *m/z* 380 (M^+).

5-[1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-phenylisothiazole (8g): IR (KBr) ν_{max}: 3097, 1612, 1543, 1509, 1481, 1431, 697, 622 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.71 (s, 3H, CH_3), 7.20-7.25 (m, 5H, ArH), 7.59 (d, J = 8.6 Hz, 2H, ArH), 8.31 (d, J = 8.6 Hz, 2H, ArH), 8.54 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.2, 121.9, 127.8, 128.7, 131.6, 132.5, 133.5, 134.2, 136.1, 138.8, 139.0, 147.0, 153.7, 158.1; MS: *m/z* 352 (M^+).

4-(4-Chlorophenyl)-5-[1-(4-chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]isothiazole (8h): 3110, 1621, 1591, 1554, 1487, 1417, 699, 619 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.69 (s, 3H, CH_3), 7.40-7.50 (m, 6H, ArH), 8.32 (d, J = 8.8 Hz, 2H, ArH), 8.53 (s, 1H, ArH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.2, 121.9, 127.8, 128.7, 131.6, 132.5, 132.9, 133.9, 136.7, 138.7, 139.0, 147.0, 153.7, 158.1; MS: *m/z* 387 (M^+).

3-5-[1-(4-Chlorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]-4-isothiazolylbenzoic acid (8i): IR (KBr) ν_{max}: 3405, 3098, 1714, 1602, 1567, 1544, 1481, 1427, 1212, 622 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.59 (s, 3H, CH_3), 7.40-7.45 (m, 4H, ArH), 8.30-8.35 (m, 6H, ArH), 8.52 (s, 1H, ArH), 10.79 (s, 1H, COOH); ^{13}C NMR (DMSO-d_6, 300 MHz): δ 17.2, 121.9, 128.7, 129.8, 130.1, 130.9, 131.6, 132.5, 133.0, 134.1, 139.0, 139.7, 145.1, 147.0, 153.7, 158.1, 163.5; MS: *m/z* 396 (M^+).

IV. CONCLUSION

A new series of 5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)-4-aryl-isothiazole **8(a-i)** were synthesized by the reaction of 4-bromo-5-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)isothiazole **7(a-c)** with aryl boronic acid, and evaluated for their antibacterial activity against Gram-positive, Gram-negative bacteria and also screened for their antifungal activity against fungal strainsCompounds **8e** and **8f** showed significant antibacterial activity against all the tested strains. Similarly, compounds **8e** and **8d** also showed good antifungal activity, and emerged as potential molecules for further development.

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