Synthesis, Characterization, and Antimicrobial Screening of 4″-methyl-2,2″-diaryl-4,2′:4′,5″-terthiazole Derivatives

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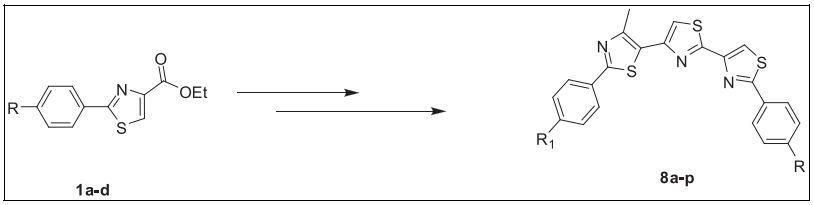


A series of novel 4″-methyl-2,2″-diaryl-4,2′:4′,5″-terthiazole (**8a-p**) derivatives has been synthesized and screened for antibacterial activity against four pathogenic bacteria, *Escherichia coli*, *Pseudomonas flurescence*, *Staphylococcus aureus*, and *Bacillus subtilis*. Among them, compounds **8a** and **8j** exhibited excellent antibacterial activity with minimum inhibitory concentration range of 1.0 to 5.3 μg/mL and compounds **8m** and **8p** exhibited moderate to good antibacterial activity with minimum inhibitory concentration range of 16.9 to 29.7 μg/mL against all tested strains. All the synthesized compounds were screened for their in vitro antifungal activity against *Cocinida candida*. Most of the compounds reported moderate antifungal activity. This study provides valuable directions to our ongoing endeavor of rationally designing more potent antimicrobial agent.

INTRODUCTION

In the 20th century, a large number of antibiotic and chemotherapeutic agents were developed for medicinal use. Due to emerging infectious diseases and increase in antibiotic resistant microbial pathogens, a need for new classes of antimicrobial agents is obligatory. One of the biggest challenges is the discovery of novel structures with high potency for a specific target. These factors have encouraged the search for new lead compounds that are active against multidrug resistant pathogens [1–4].

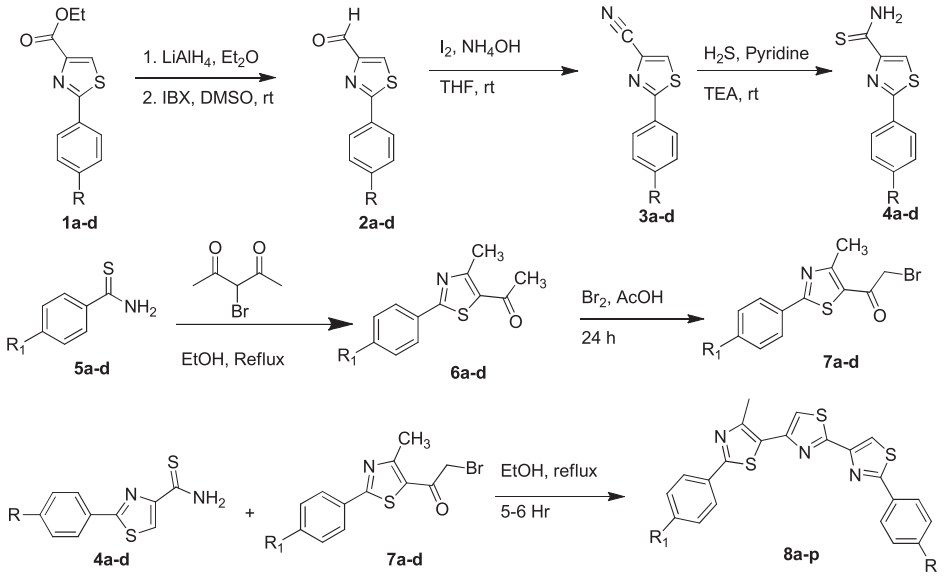
The thiazole ring containing compounds exhibited a wide spectrum of biological activities such as antimicrobial [5–10], antitubercular [11–13], antiviral [14], anti-inflammatory [15–18], anticonvulsant [19–21], and anticancer [22,23] activities. Polyazoles containing compounds are the backbone of bioactive natural products and thiopeptide antibiotics. Recently, many reports have been published on the biological activity of bisthiazole derivatives [24–28]. A thiopeptide antibiotic, urukthapelstatin A, isolated from a culture of *Thermoactinomycetaceae* bacterium *Mechercharimycesas porophorigenens*is an anticancer drug [29]. Bisthiazole glycopeptides, commonly known as Bleomycin [30], is antiviral, antibiotic, and antitumor drug isolated from the bacterium *Streptomyces verticillus*, Cystothiazole A antibiotic, inhibits fungi and human tumor cells [31], 2′-Alkyl/aryl-2-aryl-4-methyl-4′,5-bithiazolyls showed anti-inflammatory activity [27], aminoalkyl derivatives of 2,4′-bithiazole-4-carboxylic acid were shown to exhibit antitumor activity [32].

In our previous communication, 4,5′-bisthiazole, 2,5′-bisthiazole, thiazole substituted thiosemicarbazideand thiazolyl-oxazole derivatives were shown as potent antitubercular and antibacterial agents [33–35]. Encouraged by the observed biological activities of the various thiazole derivatives and as part of our ongoing search for compounds as potential antimicrobial agents, employing molecular simplification, the synthesis and antimicrobial screening of uncommon 4″-methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole derivatives is reported.

RESULTS AND DISCUSSION

Chemistry. The synthetic strategy adopted for the synthesis of title compounds **8a**–**p** is depicted in Scheme 1. The syntheses of compounds **1a**–**d** to **7a**–**d**

Scheme 1. Synthetic route of compounds **8a**–**p**.



Comp.	R	R_1	Comp.	R	R_1	Comp.	R	R_1	Comp.	R	R_1
8a	H	H	**8e**	4-Cl	H	**8i**	4-F	H	**8m**	4-CH_3	H
8b	H	4-Cl	**8f**	4-Cl	4-Cl	**8j**	4-F	4-Cl	**8n**	4-CH_3	4-Cl
8c	H	4-F	**8g**	4-Cl	4-F	**8k**	4-F	4-F	**8o**	4-CH_3	4-F
8d	H	4 -CH_3	**8h**	4-Cl	4-CH_3	**8l**	4-F	4-CH_3	**8p**	4-CH_3	4-CH_3

are reported in our previous papers. [33–36] Ethyl 2-arylthiazole-4-carboxylate, **1a**–**d** on reduction of carboethoxy group followed by selective oxidation using iodoxy benzoic acid furnished 2-arylthiazole-4-carbaldehyde **2a**–**d**. Aldehyde **2a**–**d** on reaction with iodine and ammonia in tetrahydrofuran gave 2-arylthiazole-4-carbonitrile **3a**–**d**. Carbonitrile **3a**–**d** on reaction with H_2S and catalytic amount of triethylamine in pyridine yielded 2-arylthiazole-4-carbothioamide **4a**–**d**. 1-(4-Methyl-2-phenylthiazol-5-yl) ethanone (**6a**–**d**) on reaction with bromine in acetic acid gave 2-bromo-1-(4-methyl-2-phenylthiazol-5-yl)ethanone, **7a**–**d**. Carbothioamide **4a**–**d** on cyclocondensation with 2-bromo-1-(4-methyl-2-phenylthiazol-5-yl)ethanone,

Table 1

Antibacterial activity, MIC_{90} in μg/mL of compounds **8a**–**p**.

Comp	R	R_1	*Escherichia coli*	*Pseudomonas flurescence*	*Staphylococcus aureus*	*Bacillus subtilis*
8a	H	H	**2.2**	**1.4**	**2.9**	**5.3**
8b	H	4-Cl	[a]nd	nd	nd	nd
8c	H	4-F	>30	>30	>30	>30
8d	H	4-CH_3	>30	>30	>30	>30
8e	4-Cl	H	nd	nd	nd	nd
8f	4-Cl	4-Cl	>30	>30	>30	>30
8g	4-Cl	4-F	>30	>30	>30	>30
8h	4-Cl	4-CH_3	>30	>30	>30	>30
8i	4-F	H	>30	>30	>30	>30
8j	4-F	4-Cl	**1.0**	**1.5**	**2.3**	**3.2**
8k	4-F	4-F	>30	>30	>30	>30
8l	4-F	4-CH_3	>30	>30	>30	>30
8m	4-CH_3	H	**20.2**	**26.7**	**24.2**	**29.7**
8n	4-CH_3	4-Cl	>30	>30	>30	>30
8o	4-CH_3	4-F	>30	>30	>30	>30
8p	4-CH_3	4-CH_3	**16.9**	**25.8**	**19.6**	**23.6**
Ampicillin			1.46	4.36	1.0	10.32
Kanamycin			1.62	0.49	>30	1.35

[a]nd, Not determined.

The activity of active compounds are highlighted in bold.

7a–**d** afforded 4″-methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole, **8a**–**p**.

The structure of the synthesized compounds, **8a**–**p** was confirmed by IR, NMR, and MS. As a representative analysis of compound **8e**, the ^{1}H NMR spectrum of compound **8e** showed a singlet in aliphatic region at δ 2.72, for methyl group of thiazole ring. Two singlets in aromatic region at δ 7.47 and 8.00 integrated for one proton each corresponds to thiazole C─H. Five aromatic protons of one phenyl ring resonated between δ 7.38 and 7.45 as multiplet, while four aromatic protons for the second phenyl ring appeared at δ 7.90 and 8.00 as a set of two doublets. The ^{13}C NMR spectrum of compound **8e** revealed a signal at δ 16.93, which corresponds to thiazole-CH_3, whereas, the aromatic and thiazole carbons appeared between δ 115.87 and 167.29. The structure of compound **8e** was further confirmed by high-resolution mass spectrometry (HRMS) that showed molecular ion peak at *m*/*z*: 452.0112 $(M + H)^+$, *m*/*z*: 473.9933 $(M + Na)^+$.

Antibacterial activity evaluation. The antibacterial activity [37–39] of synthesized compounds was determined against the standard Gram-positive bacteria, *Staphylococcus aureus* (NCIM 2602), *Bacillus subtilis* (NCIM 2162) and Gram-negative bacteria, *Escherichia coli* (NCIM 2576), *Pseudomonas fluorescence* (NCIM 2059). Ampicillin and Kanamycin served as positive control for antibacterial activity. The in vitro preliminary screening values (% inhibition) against microorganisms tested are summarized in Tables S1. Compounds that showed more than 90% inhibition (Table S1) at 30 μg/mL were confirmed by carrying out dose-dependent effect with serial dilution of compounds in DMSO. The result of minimum inhibitory concentration (MIC) is shown in Table 1.

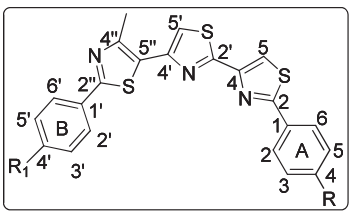


Figure 1. Compounds **8a**–**p**.

The in vitro antifungal activity of all the synthesized compounds was done by the disc diffusion method [40] against the *Candida albicans* (NCIM 3100). Fluconazole serves as positive control for antifungal activity.

The in vitro antibacterial activity results revealed that, most of the compounds showed moderate to good activity against *E. coli*, *P. flurescence*, *S. aureus* and *B. subtilis*. Among the synthesized compounds **8a**–**p**, the compounds **8a** and **8j** exhibited excellent activity with MIC in the range 1.0 to 5.3 μg/mL. The preliminary structure activity relationship study revealed that substitution at 4 or 4′ position of phenyl by Chloro, Fluoro, or methyl group affects the antibacterial activity (Fig. 1).

From structure activity relationship, it was noted that, compounds **8a**–**d**, with R═H and R_1═H/Cl/F/CH_3 substituted phenyl ring B, compound **8a** (R_1═H), reported excellent activity (MIC 1.4 to 5.3 μg/mL) against all Gram-positive and Gram-negative bacterial strains whereas, upon substitution at C-4 by Cl or F or CH_3, the activity decreases. Among the compounds **8e**–**h** with R = 4-Cl and substituted phenyl ring B, all the compounds showed moderate activity. Compounds **8i**–**l** with R = 4-F, and substituted phenyl ring B, compound **8j** (R_1 = 4-Cl) reported excellent activity (MIC 1.0 to 3.2 μg/mL) compared with standard drug ampicillin, against all tested strains. Among the compounds **8m**–**p** with R = 4-CH_3, and substituted phenyl ring B, compounds **8m** (R_1═H) and **8p** (R_1 = 4-CH_3) showed moderate to good activity against all strains.

From the antifungal activity result (Table 2), it was noticed that most of the synthesized compounds showed moderate activity against *C. albicans*.

It was noteworthy to mention that unsubstituted phenyl rings A and B or 4-fluoro substituent on phenyl ring A and 4-chloro on phenyl ring B enhances the antibacterial activity.

Table 2

Antifungal screening of synthesized compounds **8a**–**p** (zone of inhibition in mm).

Comp.	*Candida albicans*	Comp.	*Candida albicans*	Comp.	*Candida albicans*	Comp.	*Candida albicans*
8a	8	**8e**	8	**8i**	7	**8m**	9
8b	9	**8f**	9	**8j**	—	**8n**	9
8c	10	**8g**	—	**8k**	10	**8o**	12
8d	—	**8h**	9	**8l**	10	**8p**	11
Fluconazole 17							

Fluconazole (25 μg/disc) were used as reference; synthesized compounds (100 μg/disc).

CONCLUSIONS

In conclusion, a series of new 4″-methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole (**8a**–**p**) derivatives have been synthesized and screened for antimicrobial activity. From these results, it is concluded that 4-methyl-2-phenyl-5-(2-(2-phenylthiazol-4-yl)thiazol-4-yl)thiazole (**8a**) 2-(4-chlorophenyl)-5-(2-(2-(4-fluorophenyl)thiazol-4-yl)thiazol-4-yl)-4-methylthiazole (**8j**) displayed excellent antibacterial activity against all tested strains. However, the antifungal results were not very encouraging. Thus, these results warrant the need for synthesis of similar libraries with other substituent's to ascertain the trend described in this work.

EXPERIMENTAL

Chemistry. Melting points of synthesized compounds were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian mercury XL-300 and Bruker at either 400/500 MHz (^{1}H NMR) and 100/126 MHz (^{13}C NMR), spectrometer instruments. Chemical shifts are reported from internal tetramethylsilane standard and are given in δ units. HRMS spectra were recorded on Bruker Compass Data Analysis 4.2. The chemicals and solvents used were laboratory grade and were purified as per literature methods.

General procedure for synthesis of 4-methyl-2-phenylthiazole-5-carbonitrile (3a–d). To a solution of 4-methyl-2-phenylthiazol-5-carbaldehyde (2.0 gm, 9.8 mmol) in tetrahydofuran (15 mL) and ammonia (20 mL), iodine (3.73 gm, 29.4 mmol) was added and reaction mixture was stirred at ambient temp for 6 h. The progress of reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate (30 mL × 3), the organic layer was washed with water, dried (Na_2CO_3), solvent removed under vacuum to give 4-methyl-2-phenylthiazole-5-carbonitrile, (yield 78%). The nitrile was used further without purification.

2-Phenylthiazole-4-carbonitrile (3a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.35 (m, 3H, Ar─H), 7.87 (d, J = 8.4 Hz, 2H, Ar─H), 7.94 (s, 1H, Thiazole-H); LCMS: m/z = 187.0 $(M + H)^+$.

2-(4-Chlorophenyl)thiazole-4-carbonitrile (3b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.5 Hz, 2H, Ar─H), 7.90 (d, J = 8.5 Hz, 2H, Ar─H), 7.99 (s, 1H, Thiazole-H); LCMS: m/z = 221.0 $(M + H)^+$.

2-(4-Fluorophenyl)thiazole-4-carbonitrile (3c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (t, J = 8.5 Hz, 2H, Ar─H), 7.93–7.97 (m, 2H, Ar─H), 8.63 (s, 1H, Thiazole-H); LCMS: m/z = 205.1 $(M + H)^+$.

2-(p-Tolyl)thiazole-4-carbonitrile (3d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H, Ar─CH_3), 7.28 (d, J = 8.0 Hz, 2H, Ar─H), 7.85 (d, J = 8.1 Hz, 2H, Ar─H), 7.93 (s, 1H, Thiazole-H); LCMS: m/z = 200.9 $(M + H)^+$.

General procedure for synthesis of 4-methyl-2-phenylthiazole-5-carbothioamide (4a–d). In a solution of 4-methyl-2-phenylthiazole-5-carbonitrile (7.5 mmol), triethyl amine (2 mL) in pyridine (15 mL), H_2S gas was for 2 h at room temperature. After completion of the reaction (TLC), the reaction mixture was quenched in ice cold water and neutralized by dilute HCl. The product was filtered and washed with water and dried in air afforded thioamide, (yield 80%).

2-Phenylthiazole-4-carbothioamide (4a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.36 (m, 3H, Ar─H), 7.74 (s, 1H, NH), 7.91 (d, J = 8.4 Hz, 2H, Ar─H), 8.42 (s, 1H, Thiazole-H), 8.75 (s, 1H, NH); LCMS: m/z = 221.0 $(M + H)^+$.

2-(4-Chlorophenyl)thiazole-4-carbothioamide (4b). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H, Ar─H), 7.76 (s, 1H, NH), 7.88 (d, J = 8.4 Hz, 2H, Ar─H), 8.45 (s, 1H, Thiazole-H), 8.74 (s, 1H, NH); LCMS: m/z = 254.8 $(M + H)^+$.

2-(4-Fluorophenyl)thiazole-4-carbothioamide (4c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (t, J = 8.6 Hz, 2H, Ar─H), 7.71 (s, 1H, NH), 7.94 (dd, J = 8.7, 5.2 Hz, 2H, Ar─H), 8.44 (s, 1H, Thiazole-H), 8.74 (s, 1H, NH); LCMS: m/z = 238.8 $(M + H)^+$.

2-(p-Tolyl)thiazole-4-carbothioamide (4d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H, Ar─CH_3), 7.26 (d, 2H, J = 8.1 Hz, Ar─H), 7.72 (s, 1H, NH), 7.82 (d, J = 8.1 Hz, 2H, Ar─H), 8.41 (s, 1H, Thiazole-H), 8.79 (s, 1H, NH); LCMS: m/z = 235.7 $(M + H)^+$.

General procedure for synthesis of 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (6a–d). A mixture of benzothioamide (10 mmol) and 3-bromopentane-2,4-dione (10 mmol) in absolute ethanol was refluxed for 2 h. After completion of the reaction (TLC), solvent was distilled under vacuum. The residue was dissolved in sodium bicarbonate solution (30 mL) and stirred for 10 min. The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and combined organic layer was washed with water, dried over sodium sulphate, and distilled under vacuum. The product was purified by column chromatography using ethyl acetate:hexane (2:8) as elute.

1-(4-Methyl-2-phenylthiazol-5-yl)ethanone (6a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.50 (s, 3H, Thiazole-CH_3), 2.71 (s, 3H, $COCH_3$), 7.43–7.35 (m, 3H, Ar─H), 7.92–7.88 (m, 2H, Ar─H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.49 (CH_3,

Thiazole-CH_3), 30.80 (CH_3, CO—CH_3), 126.90 (CH, Ar—C-4), 129.10 (CH, Ar—C-3, C-5), 131.20 (CH, Ar—C-2, C-6), 131.27 (C, Ar—C-1), 132.79 (C, Thiazole-C-5), 159.52 (C, Thiazole-C-4), 169.44 (C, Thiazole-C-2), 190.55 (C, C═O).

1-(2-(4-Chlorophenyl)-4-methylthiazol-5-yl)ethanone (6b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.57 (s, 3H, Thiazole-CH_3),2.78 (s, 3H, $COCH_3$), 7.43 (d, *J* = 8.7 Hz, 2H, Ar—H), 7.91 (d, *J* = 8.7 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.45 (CH_3, Thiazole-CH_3), 30.78 (CH_3, CO—CH_3), 128.09 (CH, Ar—C-3, C-5), 129.37 (CH, Ar—C-2, C-6), 131.29 (C, Ar—C-1), 131.58 (C, Thiazole-C-5), 137.28 (C, Ar—C-4), 159.56 (C, Thiazole-C-4), 168.00 (C, Thiazole-C-2), 190.46 (C, C═O).

1-(2-(4-Fluorophenyl)-4-methylthiazol-5-yl)ethanone (6c). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.49 (s, 3H, Thiazole-CH_3), 2.70 (s, 3H, $COCH_3$), 7.07 (t, *J* = 8.6 Hz, 2H, Ar—H), 7.89 (dd, *J* = 8.9, 5.3 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.44 (CH_3, Thiazole-CH_3), 30.75 (CH_3, CO—CH_3), 116.18 and 116.35 (CH, Ar—C-3, C-5), 128.92 and 128.99 (CH, Ar—C-2, C-6), 129.16 and 129.18 (C, Ar—C-1), 131.41 (C, Thiazole-C-5), 159.48 (C, Thiazole-C-4), 163.54 and 165.55 (C, Ar—C-4), 168.18 (C, Thiazole-C-2), 190.47 (C, C═O).

1-(4-Methyl-2-(p-tolyl)thiazol-5-yl)ethanone (6d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H, Thiazole-CH_3), 2.49 (s, 3H, Ar—CH_3), 2.70 (s, 3H, $COCH_3$), 7.19–7.16 (m, 2H, Ar—H), 7.79 (d, *J* = 8.2 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.49 (CH_3, Thiazole-CH_3), 21.54 (CH_3, Ar—CH_3), 30.79 (CH_3, CO—CH_3), 126.85 (CH, Ar—C-3, C-5), 129.79 (CH, Ar—C-2, C-6), 130.16 (C, Ar—C-1), 130.82 (C, Thiazole-C-5), 141.76 (C, Ar—C-4), 159.50 (C, Thiazole-C-4), 169.72(C, Thiazole-C-2), 190.56(C, C═O).

General procedure for synthesis of 2-bromo-1-(4-methyl-2-(4-substituted phenyl)thiazol-5-yl)ethanone (7a–d). A mixture of 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (10 mmol) and pTSA (5 mmol) in dichloromethane (DCM) (50 mL) was stirred at 0°C for 10 min. Bromine (10 mmol) in DCM (20 mL) was then added dropwise to the reaction mixture and was further stirred for 12 h at room temperature. After completion of the reaction, sodium bicarbonate solution was added in reaction mixture and stirred for 10 min. The aqueous layer was extracted with DCM, and combined organic layer was washed with water, dried over sodium sulphate, and distilled under vacuum.

2-Bromo-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (7a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.82 (s, 3H, Thiazole-CH_3), 4.30 (s, 2H, $COCH_2$—Br), 7.50 (m, 3H, Ar—H), 8.00 (dd, *J* = 8.1, 1.4 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.67 (CH_3, Thiazole-CH_3), 33.92 (CH_2, $COCH_2$—Br), 126.91 (C, Ar—C-4), 127.08 (CH, Ar—C-3, C-5), 129.20 (CH, Ar—C-2, C-6), 131.60 (C, Thiazole-C-5), 132.47 (C, Ar—C-1), 162.39 (C, Thiazole-C-4), 170.47 (C, Thiazole-C-2), 184.11 (C, C═O).

2-Bromo-1-(2-(4-chlorophenyl)-4-methylthiazol-5-yl) ethanone (7b). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.73 (s, 3H, Thiazole-CH_3), 4.21 (s, 2H, $COCH_2$—Br), 7.38 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.86 (d, *J* = 8.6 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.64 (CH_3, Thiazole-CH_3), 33.74 (CH_2, $COCH_2$—Br), 127.34 (C, Ar—C-1), 128.27 (CH, Ar—C-3, C-5), 129.48 (CH, Ar—C-2, C-6), 130.97 (C, Thiazole-C-5), 137.73 (C, Ar—C-4), 162.44 (C, Thiazole-C-4), 169.00 (C, Thiazole-C-2), 184.09 (C, C═O).

2-Bromo-1-(2-(4-fluorophenyl)-4-methylthiazol-5-yl) ethanone (7c). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (s, 3H, Thiazole-CH_3), 4.20 (s, 2H, $COCH_2$—Br), 7.08 (t, *J* = 8.6 Hz, 2H, Ar—H), 7.92 (dd, *J* = 8.9, 5.2 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.64 (CH_3, Thiazole-CH_3), 33.78 (CH_2, $COCH_2$—Br), 116.33 and 116.50 (CH, Ar—C-2, C-6), 127.17 (C, Thiazole-C-5), 128.85 and 128.88 (C, Ar—C-1), 129.16 and 129.23 (CH, Ar—C-2, C-6), 162.40 (C, Thiazole-C-4), 163.77 and 165.78 (C, Ar—C-4), 169.17 (C, Thiazole-C-2), 184.08(C, C═O).

2-Bromo-1-(4-methyl-2-(p-tolyl)thiazol-5-yl)ethanone (7d). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H, Ar—CH_3), 2.73 (s, 3H, Thiazole-CH_3), 4.20 (s, 2H, $COCH_2$—Br), 7.19 (d, *J* = 7.9 Hz, 2H, Ar—H), 7.81 (d, *J* = 7.9 Hz, 2H, Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.68 (CH_3, Thiazole-CH_3), 21.61 (CH_3, Ar—CH_3), 33.95 (CH_2, $COCH_2$—Br), 126.86 (C, Ar—C-1), 127.04 (CH, Ar—C-2, C-6), 129.80 (C, Thiazole-C-5), 129.89 (CH, Ar—C-3, C-5), 142.27 (C, Ar—C-4), 162.43(C, Thiazole-C-4), 170.74 (C, Thiazole-C-2), 184.06(C, C═O).

General procedure for synthesis of 4″-methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole, (8a–p). To a solution of 4-methyl-2-phenylthiazol-5-carbothiomide (0.85 mmol) in 8 mL ethanol, 2-bromo-1-(4-methyl-2-(4-substituted phenyl)thiazol-5yl)ethanone (0.71 mmol) was added and reaction mixture was reflux for 2 h. After completion of reaction (TLC), the solid product was obtained. The product was filtered and washed with ethanol, dried in air afforded 4″-methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole. Yield 65%, mp: 158–160°C. Compounds **8a–p** were synthesized by the similar method.

4″-Methyl-2,2″-diphenyl-4,2′:4′,5″-terthiazole (8a). Yield: 72%, mp: 136–138°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.70 (s, 3H, Thiazole-CH_3), 7.46–7.52 (m, 6H, Ar—H), 7.79 (s, 1H, Thiazole-H), 7.93–8.00 (s, 4H, Ar—H), 8.23 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.72 (CH_3, Thiazole-C-5″-CH_3), 116.62 (CH, Thiazole-C-5′), 117.78 (CH, Thiazole-C-5), 126.29 (CH, Ar—C-3, C-5), 126.72 (CH, Ar—C-3′,C-5′), 127.19 (C, Thiazole-C-5″), 129.43 (CH, Ar—C-2, C-6), 129.54 (CH, Ar—C-2′, C-6′), 130.39 (CH, Ar—C-4), 131.05

(CH, Ar—C-4′), 132.73 (C, Ar—C-1), 133.49 (C, Ar—C-1′), 147.79 (C, Thiazole-C-4′), 149.24 (C, Thiazole-C-4), 150.13 (C, Thiazole-C-4″), 162.16 (C, Thiazole-C-2′), 164.30 (C, Thiazole-C-2), 168.57 (C, Thiazole-C-2″); HRMS *m*/*z*: 418.0508 $(M + H)^+$, *m*/*z*: 440.0329 $(M + Na)^+$.

2″-(4-Chlorophenyl)-4″-methyl-2-phenyl-4,2′:4′,5″-terthiazole (8b). Yield: 72%, mp: 158–160°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.77 (s, 3H, Thiazole-CH_3), 7.42 (s, 1H, Thiazole-H), 7.44 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.50–7.52 (m, 3H, Ar—H), 7.93 (d, *J* = 8.6 Hz, 2H, Ar—H), 8.03–8.08 (m, 3H, Thiazole-H and Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.47 (CH_3, Thiazole-C-5″-CH_3), 115.87 (CH, Thiazole-C-5′), 116.80 (CH, Thiazole-C-5), 126.57 (CH, Ar—C-3, C-5), 127.48 (C, Thiazole-C-5″), 127.55 (CH, Ar—C-2′, C-6′), 129.07 (CH, Ar—C-3′, C-5′), 129.18 (CH, Ar—C-2, C-6), 130.62 (CH, Ar—C-4), 132.18 (C, Ar—C-1′), 132.93 (C, Ar—C-1), 135.84 (C, Ar—C-4′), 148.17 (C, Thiazole-C-4′), 149.69 (C, Thiazole-C-4), 150.22 (C, Thiazole-C-4″), 162.54 (C, Thiazole-C-2′), 163.77 (C, Thiazole-C-2), 168.76 (C, Thiazole-C-2″); HRMS *m*/*z*: 452.0112 $(M + H)^+$, *m*/*z*: 473.9933 $(M + Na)^+$.

2″-(4-Fluorophenyl)-4″-methyl-2-phenyl-4,2′:4′,5″-terthiazole (8c). Yield: 72%, mp: 136–138°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.78 (s, 3H, Thiazole-CH_3), 7.16 (t, *J* = 8.7 Hz, 2H, Ar—H), 7.41 (s, 1H, Thiazole-H), 7.50–7.52 (m, 3H, Ar—H), 8.00 (dd, *J* = 7.9, 1.6 Hz, 2H, Ar—H), 8.04–8.06 (m, 2H, Ar—H), 8.07 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.42 (CH_3, Thiazole-C-5″-CH_3), 115.08 (CH, Thiazole-C-5′), 115.96 and 116.13 (CH, Ar—C-3′, C-5′), 116.25 (CH, Thiazole-C-5), 126.72 (CH, Ar—C-3, C-5), 127.19 (C, Thiazole-C-5″), 128.27 and 128.34 (CH, Ar—C-2′, C-6′), 129.07 (CH, Ar—C-2, C-6), 132.05 (C, Ar—C-1′), 130.62 (CH, Ar—C-4), 132.94 (C, Ar—C-1), 148.21 (C, Thiazole-C-4′), 149.71 (C, Thiazole-C-4), 149.71 (C, Thiazole-C-4″), 162.53 54 (C, Thiazole-C-2′), 164.03 (C, Thiazole-C-2), 162.87 and 164.86 (C, Ar—C-4′), 168.76 (C, Thiazole-C-2″); HRMS *m*/*z*: 436.0407 $(M + H)^+$, *m*/*z*: 458.0227 $(M + Na)^+$.

4″-Methyl-2-phenyl-2″-(p-tolyl)-4,2′:4′,5″-terthiazole (8d). Yield: 72%, mp: 192–194°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.44 (s, 3H, Ar—CH_3), 2.92 (s, 3H, Thiazole-CH_3), 7.34 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.48 (s, 1H, Thiazole-H), 7.50–7.52 (m, 3H, Ar—H), 8.04–8.07 (m, 4H, Ar—H), 8.09 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 16.17 (CH_3, Thiazole-C-5″-CH_3), 21.72 (CH_3, Ar—CH_3), 116.66 (CH, Thiazole-C-5′), 117.21 (CH, Thiazole-C-5), 126.65 (CH, Ar—C-2′, C-6′), 126.78 (CH, Ar—C-3, C-5), 127.30 (C, Thiazole-C-5″), 128.99 (CH, Ar—C-3′, C-5′), 129.21 (CH, Ar—C-2, C-6), 129.99 (CH, Ar—C-4), 130.71 (C, Ar—C-1′), 132.82 (C, Ar—C-1), 140.10 (C, Ar—C-4′), 147.62 (C, Thiazole-C-4′), 149.16 (C, Thiazole-C-4), 150.12 (C, Thiazole-C-4″), 163.01 (C, Thiazole-C-2′), 166.65 (C, Thiazole-C-2), 168.66 (C, Thiazole-C-2″); HRMS *m*/*z*: 432.0665 $(M + H)^+$, *m*/*z*: 454.0481 $(M + Na)^+$.

2-(4-Chlorophenyl)-4″-methyl-2″-phenyl-4,2′:4′,5″-terthiazole (8e). Yield: 72%, mp: 212–214°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.72 (s, 3H, Thiazole-CH_3), 7.38–7.45 (m, 5H, Ar—H), 7.47 (s, 1H, Thiazole-H), 7.90 (d, *J* = 8.1 Hz, 2H, Ar—H), 7.94 (d, *J* = 8.7 Hz, 2H, Ar—H), 8.00 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.93 (CH_3, Thiazole-C-5″-CH_3), 115.87 (CH, Thiazole-C-5′), 116.80 (CH, Thiazole-C-5), 126.57 (CH, Ar—C-2, C-6), 127.48 (C, Thiazole-C-5″), 127.89 (CH, Ar—C-3′, C-5′), 129.16 (CH, Ar—C-3, C-5), 129.27 (CH, Ar—C-2′, C-6′), 130.76 (CH, Ar—C-4′), 131.30 (C, Ar—C-1), 132.13 (C, Ar—C-1′), 136.44 (C, Ar—C-4), 147.41 (C, Thiazole-C-4′), 148.46 (C, Thiazole-C-4), 149.54 (C, Thiazole-C-4″), 162.29 (C, Thiazole-C-2′), 165.38 (C, Thiazole-C-2), 167.29 (C, Thiazole-C-2″); HRMS *m*/*z*: 452.0112 $(M + H)^+$, *m*/*z*: 473.9933 $(M + Na)^+$.

2,2″-Bis(4-chlorophenyl)-4″-methyl-4,2′:4′,5″-terthiazole (8f). Yield: 72%, mp: 216–218°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.70 (s, 3H, Thiazole-CH_3), 7.38 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.44 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.47 (s, 1H, Thiazole-H), 7.90 (d, *J* = 8.6 Hz, 2H, Ar—H), 7.94 (d, *J* = 8.6 Hz, 2H, Ar—H), 8.04 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.30 (CH_3, Thiazole-C-5″-CH_3), 115.68 (CH, Thiazole-C-5′), 116.65 (CH, Thiazole-C-5), 126.60 (CH, Ar—C-2, C-6), 127.52 (C, Thiazole-C-5″), 127.69 (CH, Ar—C-2′, C-6′), 129.27 (CH, Ar—C-3, C-5), 130.76 (CH, Ar—C-3′, C-5′), 131.30 (C, Ar—C-1), 132.13 (C, Ar—C-1′), 135.85 (C, Ar—C-4), 136.44 (C, Ar—C-4′), 147.45 (C, Thiazole-C-4′), 148.54 (C, Thiazole-C-4), 149.89 (C, Thiazole-C-4″), 162.30 (C, Thiazole-C-2′), 165.40 (C, Thiazole-C-2), 168.50 (C, Thiazole-C-2″); HRMS *m*/*z*: 485.9721 $(M + H)^+$, *m*/*z*: 507.9545 $(M + Na)^+$.

2-(4-Chlorophenyl)-2″-(4-fluorophenyl)-4″-methyl-4,2′:4′,5″-terthiazole (8g). Yield: 72%, mp: 212–214°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.68 (s, 3H, Thiazole-CH_3), 7.19 (m, 2H, Ar—H), 7.49 (d, *J* = 8.0 Hz, 2H, Ar—H), 7.70 (s, 1H, Thiazole-H), 7.92–7.98 (m, 4H, Ar—H), 8.18 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.59 (CH_3, Thiazole-C-5″-CH_3), 116.33 (CH, Thiazole-C-5′), 116.23 and 116.41 (CH, Ar—C-3′, C-5′), 117.75 (CH, Thiazole-C-5), 127.21 (C, Thiazole-C-5″), 128.18 (CH, Ar—C-2, C-6), 128.35 and 128.42 (CH, Ar—C-2′, C-6′), 129.55 (CH, Ar—C-3, C-5), 130.03 and 130.05 (C, Ar—C-1′), 131.43 (C, Ar—C-1), 136.01 (C, Ar—C-4), 147.81 (C, Thiazole-C-4′), 149.39 (C, Thiazole-C-4), 150.06 (C, Thiazole-C-4″), 161.97 (C, Thiazole-C-2′), 163.18 (C, Thiazole-C-2), 162.65 and 164.63 (C, Ar—C-4′), 167.21 (C, Thiazole-C-2″); HRMS *m*/*z*: 470.0018 $(M + H)^+$, *m*/*z*: 491.9839 $(M + Na)^+$.

2-(4-Chlorophenyl)-4″-methyl-2″-(p-tolyl)-4,2′:4′,5″-terthiazole (8h). Yield: 72%, mp: 218–220°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.39 (s, 3H, Ar—CH_3), 2.69 (s,

3H, Thiazole-CH_3), 7.32 (d, J = 8.0 Hz, 2H, Ar—H), 7.47 (d, J = 7.5 Hz, 2H, Ar—H), 7.78 (s, 1H, Thiazole-H), 7.89 (d, J = 8.0 Hz, 2H, Ar—H), 7.93 (d, J = 7.5 Hz, 2H, Ar—H), 8.18 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.64 (CH_3, Thiazole-C-5″-CH_3), 21.50 (CH_3, Ar—CH_3), 116.50 (CH, Thiazole-C-5′), 117.21 (CH, Thiazole-C-5), 126.30 (CH, Ar—C-2′, C-6′), 126.66 (CH, Ar—C-2, C-6), 127.28 (C, Thiazole-C-5″), 129.47 (CH, Ar—C-3, C-5), 129.85 (CH, Ar—C-3′, C-5′), 130.10 (C, Ar—C-1), 130.45 (C, Ar—C-1′), 133.42 (C, Ar—C-4), 141.09 (C, Ar—C-4′), 147.73 (C, Thiazole-C-4′), 149.09 (C, Thiazole-C-4), 150.03 (C, Thiazole-C-4″), 162.23 (C, Thiazole-C-2), 164.33 (CH, Ar—C-4′), 168.50 (C, Thiazole-C-2″); HRMS m/z: 466.0270 $(M + H)^+$, m/z: 488.0086 $(M + Na)$.$^+$

2-(4-Fluorophenyl)-4″-methyl-2″-phenyl-4,2′:4′,5″-terthiazole (8i). Yield: 72%, mp: 250°C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.78 (s, 3H, Thiazole-CH_3), 7.16 (t, J = 8.7 Hz, 2H, Ar—H), 7.41 (s, 1H, Thiazole-H), 7.52–7.49 (m, 3H, Ar—H), 7.99 (dd, J = 8.7, 5.1 Hz, 2H, Ar—H), 8.06 (m, 3H, Thiazole-H and Ar—H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.67 (CH_3, Thiazole-C-5″-CH_3), 116.57 and 116.75 (CH, Ar—C-3, C-5), 116.75 (CH, Thiazole-C-5′), 117.94 (CH, Thiazole-C-5), 126.33 (CH, Ar—C-3′, C-5′), 127.22 (C, Thiazole-C-5″), 129.00 and 129.07 (CH, Ar—C-2, C-6), 129.30 and 129.33 (C, Ar—C-1), 129.46 (CH, Ar—C-2′, C-6′), 130.50 (CH, Ar—C-4′), 133.35 (C, Ar—C-1′), 147.70 (C, Thiazole-C-4′), 149.15 (C, Thiazole-C-4), 150.01 (C, Thiazole-C-4″), 162.08 (C, Thiazole-C-2′), 163.02 and 165.01 (C, Ar—C-4), 164.34 (C, Thiazole-C-2), 167.42 (C, Thiazole-C-2″); HRMS m/z: 436.0411 $(M + H)^+$, m/z: 458.0227 $(M + Na)^+$.

2″-(4-Chlorophenyl)-2-(4-fluorophenyl)-4″-methyl-4,2′:4′,5″-terthiazole (8j). Yield: 72%, mp: 204–204°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.78 (s, 3H, Thiazole-CH_3), 7.20 (t, J = 8.6 Hz, 2H, Ar—H), 7.42 (s, 1H, Thiazole-H), 7.44 (d, J = 8.0 Hz, 2H, Ar—H), 7.92–7.96 (m, 2H, Ar—H), 8.02–8.07 (m, 3H, Thiazole-H and Ar—H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.39 (CH_3, Thiazole-C-5″-CH_3), 115.24 (CH, Thiazole-C-5′), 116.11 and 116.29 (CH, Ar—C-3, C-5), 116.23 (CH, Thiazole-C-5), 127.53 (C, Thiazole-C-5″), 127.61 (CH, Ar—C-2′, C-6′), 128.67 and 128.73 (CH, Ar—C-2, C-6), 129.22 (CH, Ar—C-3′, C-5′), 129.88 (C, Ar—C-1′), 131.92 (C, Ar—C-1), 136.01 (C, Ar—C-4′), 148.10 (C, Thiazole-C-4′), 149.68 (C, Thiazole-C-4), 149.99 (C, Thiazole-C-4″), 162.41 (C, Thiazole-C-2′), 163.21 and 163.20 (C, Ar—C-4), 163.88 (C, Thiazole-C-2), 167.54 (C, Thiazole-C-2″); HRMS m/z: 470.0018 $(M + H)^+$, m/z: 491.9839 $(M + Na)^+$.

2,2″-Bis(4-fluorophenyl)-4″-methyl-4,2′:4′,5″-terthiazole (8k). Yield: 72%, mp: 138–140°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.68 (s, 3H, Thiazole-CH_3), 7.22 (t, J = 8.6 Hz, 2H, Ar—H), 7.28 (t, J = 8.6 Hz, 2H, Ar—H), 7.77 (s, 1H, Thiazole-H), 7.96 (dd, J = 8.2, 5.6 Hz, 2H, Ar—H), 8.03 (dd, J = 8.3, 5.4 Hz, 2H, Ar—H), 8.20 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.66 (CH_3, Thiazole-C-5″-CH_3), 116.26 (CH, Thiazole-C-5′), 116.31 and 116.49 (CH, Ar—C-3, C-5), 116.49 and 116.67 (CH, Ar—C-3′, C-5′), 117.66 (CH, Thiazole-C-5), 127.25 (C, Thiazole-C-5″), 128.41 and 128.48 (CH, Ar—C-2, C-6), 128.94 and 129.01 (CH, Ar—C-2′, C-6′), 129.29 and 129.31 (C, Ar—C-1), 130.04 and 130.07 (C, Ar—C-1′), 147.74 (C, Thiazole-C-4′), 149.23 (C, Thiazole-C-4), 150.09 (C, Thiazole-C-4″), 162.07 (C, Thiazole-C-2′), 163.15 (C, Thiazole-C-2), 162.66 and 164.64 (C, Ar—C-4′), 163.03 and 165.01 (C, Ar—C-4), 167.39 (C, Thiazole-C-2″); HRMS m/z: 454.0320 $(M + H)^+$, m/z: 476.0142 $(M + Na)^+$.

2-(4-Fluorophenyl)-4″-methyl-2″-(p-tolyl)-4,2′:4′,5″-terthiazole (8l). Yield: 72%, mp: 192–194°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H, Ar—CH_3), 2.69 (s, 3H, Thiazole-CH_3), 7.28 (d, J = 8.0 Hz, 2H, Ar—H), 7.32 (t, J = 8.8 Hz, 2H, Ar—H), 7.83 (d, J = 8.0 Hz, 2H, Ar—H), 7.84 (s, 1H, Thiazole-H), 8.05 (dd, J = 8.8, 5.3 Hz, 2H, Ar—H), 8.25 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.68 (CH_3, Thiazole-C-5″-CH_3), 21.46 (CH_3, Ar—CH_3), 116.56 (CH, Thiazole-C-5′), 116.60 and 116.78 (CH, Ar—C-3, C-5), 117.98 (CH, Thiazole-C-5), 126.27 (CH, Ar—C-2′, C-6′), 126.64 (C, Thiazole-C-5″), 129.02 and 129.09 (CH, Ar—C-2, C-6), 129.33 (C, Ar—C-1), 130.05 (CH, Ar—C-3′, C-5′), 130.83 (C, Ar—C-1′), 140.39 (C, Ar—C-4′), 147.83 (C, Thiazole-C-4′), 149.16 (C, Thiazole-C-4), 150.38 (C, Thiazole-C-4″), 162.03 (C, Thiazole-C-2′), 163.02 and 165.01 (C, Ar—C-4), 164.49 (C, Thiazole-C-2), 167.42 (C, Thiazole-C-2″); HRMS m/z: 450.0571 $(M + H)^+$, m/z: 472.0393 $(M + Na)^+$.

4″-Methyl-2″-phenyl-2-(p-tolyl)-4,2′:4′,5″-terthiazole (8m). Yield: 72%, mp: 190–192°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H, Ar—CH_3), 2.69 (s, 3H, Thiazole-CH_3), 7.30 (d, J = 7.9 Hz, 2H, Ar—H), 7.45–7.49 (m, 3H, Ar—H), 7.77 (s, 1H, Thiazole-H), 7.88 (d, J = 8.1 Hz, 2H, Ar—H), 7.90–7.95 (m, 2H, Ar—H), 8.16 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.67 (CH_3, Thiazole-C-5″-CH_3), 21.53 (CH_3, Ar—C-4-CH_3), 116.58 (CH, Thiazole-C-5′), 117.20 (CH, Thiazole-C-5), 126.64 (CH, Ar—C-2,C-6), 127.68 (C, Thiazole-C-5″), 127.78 (CH, Ar—C-3′, C-5′), 129.45 (CH, Ar—C-3, C-5), 130.07 (CH, Ar—C-2′, C-6′), 130.15 (CH, Ar—C-4′), 131.49 (C, Ar—C-1), 135.02 (C, Ar—C-1′), 140.07 (C, Ar—C-4), 147.64 (C, Thiazole-C-4′), 149.11 (C, Thiazole-C-4), 150.23 (C, Thiazole-C-4″), 162.92 (C, Thiazole-C-2′), 164.28 (C, Thiazole-C-2), 168.66 (C, Thiazole-C-2″); HRMS m/z: 432.0665 $(M + H)^+$, m/z: 454.0481 $(M + Na)^+$.

2″-(4-Chlorophenyl)-4″-methyl-2-(p-tolyl)-4,2′:4′,5″-terthiazole (8n). Yield: 72%, mp >240°C (dec.); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.38 (s, 3H, Ar—CH_3), 2.70 (s, 3H, Thiazole-CH_3), 7.31 (d, J = 8.0 Hz, 2H, Ar—H), 7.46 (d, J = 7.5 Hz, 2H, Ar—H), 7.80 (s, 1H, Thiazole-H), 7.88 (d, J = 8.0 Hz, 2H, Ar—H), 7.93 (d, J = 7.5 Hz, 2H,

Ar—H), 8.19 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.68 (CH_3, Thiazole-C-5″-CH_3), 21.52 (CH_3, Ar—C-4—CH_3), 116.55 (CH, Thiazole-C-5′), 117.24 (CH, Thiazole-C-5), 126.31 (CH, Ar—C-2, C-6), 126.65 (CH, Ar—C-3′, C-5′), 127.24 (C, Thiazole-C-5″), 129.41 (CH, Ar—C-2′, C-6′), 130.11 (CH, Ar—C-3, C-5), 130.13 (C, Ar—C-1′), 130.43 (C, Ar—C-1), 133.42 (C, Ar—C-4′), 141.09 (C, Ar—C-4), 147.73 (C, Thiazole-C-4′), 149.09 (C, Thiazole-C-4), 150.03 (C, Thiazole-C-4″), 162.23 (C, Thiazole-C-2′), 164.32 (C, Thiazole-C-2), 168.71 (C, Thiazole-C-2″); HRMS *m*/*z*: 466.0270 (M + H)$^+$, *m*/*z*: 488.0086 (M + Na+)$^+$.

2″-(4-Fluorophenyl)-4″-methyl-2-(*p*-tolyl) – +4,2′:4′,5″-terthiazole (8o). Yield: 72%, mp: 174–176°C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.45 (s, 3H, Ar—CH_3), 2.77 (s, 3H, Thiazole-CH_3), 7.16 (t, *J* = 8.6 Hz, 2H, Ar—H), 7.31 (d, *J* = 7.9 Hz, 2H, Ar—H), 7.40 (s, 1H, Thiazole-H), 7.95 (d, *J* = 7.9 Hz, 2H, Ar—H), 7.97–8.00 (m, 2H, Ar—H), 8.03 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6) δ: 17.44 (CH_3, Thiazole-C-5″-CH_3), 21.51 (CH_3, Ar—C-4-CH_3), 114.99 (CH, Thiazole-C-5′), 115.81 (CH, Thiazole-C-5), 115.94 and 116.11 (CH, Ar—C-3′, C-5′), 126.64 (CH, Ar—C-2, C-6), 127.21 (C, Thiazole-C-5″), 128.24 and 128.30 (CH, Ar—C-2′, C-6′), 129.73 (CH, Ar—C-3, C-5), 130.07 (C, Ar—C-1′), 130.33 (C, Ar—C-1), 140.97 (C, Ar—C-4), 148.21 (C, Thiazole-C-4′), 149.55 (C, Thiazole-C-4), 150.07 (C, Thiazole-C-4″), 162.61 (C, Thiazole-C-2′), 162.84 and 164.83 (C, Ar—C-4′), 163.97 (C, Thiazole-C-2), 168.93 (C, Thiazole-C-2″); HRMS *m*/*z*: 450.0572 (M + H)$^+$, *m*/*z*: 472.0394 (M + Na)$^+$.

4″-Methyl-2,2″-di-*p*-tolyl-4,2′:4′,5″-terthiazole (8p). Yield: 72%, mp: 194–196°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.38 (s, 3H, Ar—CH_3), 2.68 (s, 3H, Ar—CH_3), 2.70 (s, 3H, Thiazole-CH_3), 7.30–7.45 (m, 4H, Ar—H), 7.78 (s, 1H, Thiazole-H), 7.86–7.94 (m, 4H, Ar—H), 8.19 (s, 1H, Thiazole-H); ^{13}C NMR (126 MHz, DMSO-d_6): δ 17.62 (CH_3, Thiazole-C-5″-CH_3), 21.42 (CH_3, Ar—CH_3), 21.52 (CH_3, Ar—CH_3), 116.54 (CH, Thiazole-C-5′), 117.22 (CH, Thiazole-C-5), 126.35 (CH, Ar—C-2, C-6), 126.70 (CH, Ar—C-2′, C-6′), 127.28 (C, Thiazole-C-5″), 129.50 (CH, Ar—C-3, C-5), 130.20 (CH, Ar—C-3′, C-5′), 130.40 (C, Ar—C-1), 133.46 (C, Ar—C-1′), 140.08 (C, Ar—C-4), 141.1 (C, Ar—C-4′), 147.72 (C, Thiazole-C-4′), 149.10 (C, Thiazole-C-4), 150.06 (C, Thiazole-C-4″), 162.22 (C, Thiazole-C-2′), 164.34 (C, Thiazole-C-2), 168.68 (C, Thiazole-C-2″); HRMS *m*/*z*: 446.0815 (M + H)$^+$, *m*/*z*: 468.0630 (M + Na)$^+$.

ANTIBACTERIAL ACTIVITY

Bacterial cultures were first grown in Luria-Bertani media at 37°C at 180 rpm. Once the culture reaches 1 O. D., it is used for antibacterial assay. Gram-negative bacterial strains *E. coli* (NCIM 2576), *P. flurescence* (NCIM 2059) and Gram-positive bacterial strains *S. aureus* (NCIM 2602) and *B. subtilis* (NCIM 2162) were obtained from NCIM (NCL, Pune) and were grown in Luria-Bertani medium from Hi Media, India. The assay was performed in 96-well plates after 8 and 12 h for Gram-negative and Gram-positive bacteria, respectively [38–40]. A total of 0.1% of 1 O.D. culture at 620 nm was used for screening inoculated culture was added into each well of 96-well plates containing the compounds to be tested. Optical density for each plate was measured at 620 nm after 8 h for Gram-negative bacteria and after 12 h for Gram-positive bacteria.

ANTIFUNGAL ACTIVITY

The in vitro antifungal activity of all the synthesized compounds was done by the disc diffusion method [40] against the *C. albicans* (NCIM 3100) obtained from National Chemical Laboratory Pune, India. A standard disc containing Fluconazole (25 μg/disc) was used as positive control. The plates were left for 30 min at room temperature to allow the diffusion of synthesized compounds and then incubated at 37°C for 24 h. The antifungal activity was evaluated by measuring the zone of inhibition against the test microorganism. All experiments were carried in triplicates.

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