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Original article

Synthesis and biological screening of 2′-aryl/benzyl-2-aryl-4-methyl-4′,5-bithiazolyls as possible anti-tubercular and antimicrobial agents

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ABSTRACT

A series of 2′-aryl/benzyl-2-aryl-4-methyl-4′,5-bithiazolyl derivatives, **25**–**64** were synthesized and evaluated for inhibitory activity against *Mycobacterium smegmatis* MC^2 155 strain and antimicrobial activities against four pathogenic bacteria *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli* and *Proteus vulgaris*. Among them, compounds **40**, **49**, **50**, and **54** exhibited moderate to good inhibition on the growth of the bacteria *Mycobacterium smegmatis* at the concentration of 30 μM. Compounds **26**, **40**, **44**, **54** and **56** exhibited moderate to good antibacterial activity. Compound 5-(2′-(4-fluorobenzyl)thiazol-4′-yl)-2-(4-fluorophenyl)-4-methyl-thiazole (**54**) exhibited both antitubercular as well as antimicrobial activity against all tested strains.

1. Introduction

Tuberculosis is a contagious disease with comparatively high mortality worldwide [1–3]. The last major clinical advance in tuberculosis chemotherapy was the introduction of Rifampicin in 1968 [4]. With the emergence of multidrug resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB) worldwide, WHO has declared TB as a global emergency [5–7].

Thiazole and its derivatives are important pharmacophore and coupled with other heterocyclic rings have furnished new biologically active compounds [8–10]. Thiazole containing compounds have exhibited a broad range of biological activities such as antitumor [11,12], anti-cancer [13], anti-inflammatory [13–17], antibacterial and antifungal [18–22], anti-tubercular [23–25] and antiviral [26] activity. Bithiazoles and directly linked polyazoles containing compounds are the backbone of bioactive natural products and thiopeptide antibiotics (Fig. 1) [27,28]. Bithiazoles (cystothiazoles A–F), isolated from the myxobacterium culture broth of *Cystobacter fuscus*, has demonstrated potent antifungal activity against the phytopathogenic fungus *Phytopathora capsici* [29,30]. Large numbers of bisazole have been synthesized by several groups and screened for their biological activities [31–38]. 2′-Alkyl/aryl-2-aryl-4-methyl-4′,5-bithiazolyls showed antiinflammatory activity [39] and thiazole linked with other azoles have exhibited anti-tubercular activity [23,24]. In view of these observations, we report herein the synthesis of 2′-aryl/benzyl-2-aryl-4-methyl-4′,5-bithiazolyls via Hantzsch cyclocondensation and their antimycobacterial activity.

2. Chemistry

The synthesis of 2′-aryl/benzyl-2-aryl-4-methyl-4′,5-bithiazolyls, **25**–**64** was achieved according to Scheme 1. Acetyl acetone **1** on reaction with *p*-toluene sulphonic acid and NBS in DCM:diethyl ether (1:1) gave 3-bromopentane-2,4-dione, **2**. Further, compound **2** on cyclocondensation with aryl thioamide **3**–**6** in dry ethanol gave 1-(4-methyl-2-arylthiazol-5-yl)ethanone, **7**–**10** [40,41]. Compounds **7**–**10** on bromination with bromine and *p*-toluene sulphonic acid as catalyst in DCM at room temperature

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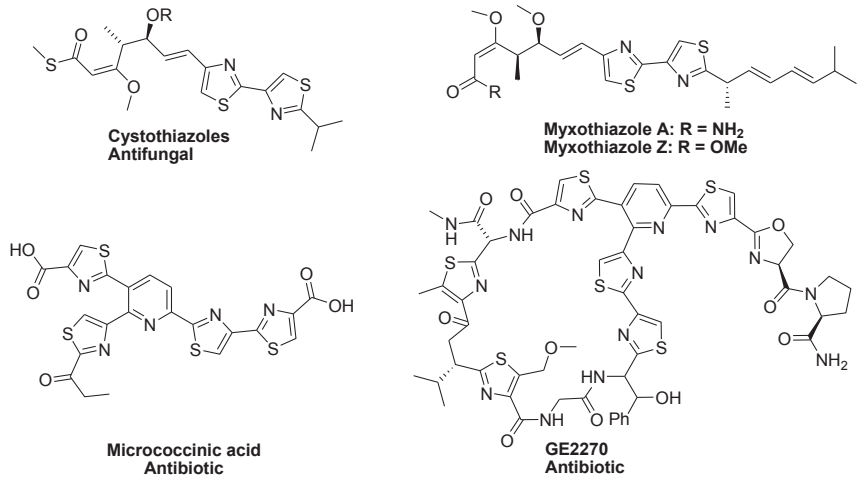
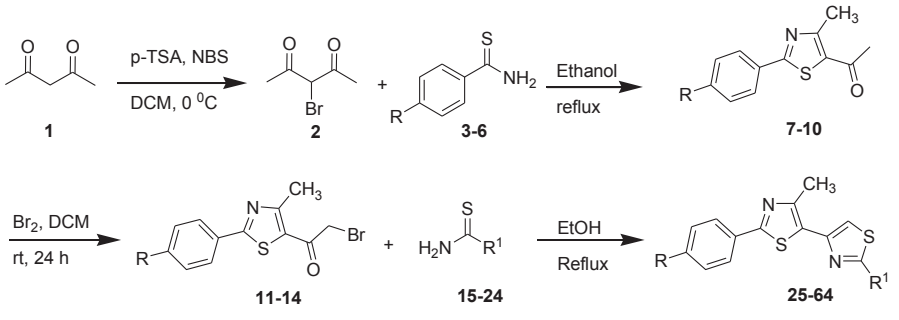


Fig. 1. Bithiazole natural products.



Comp	R	R^1	Comp	R	R^1	Comp	R	R^1	Comp	R	R^1
25	H	C_6H_5	**35**	Cl	C_6H_5	**45**	F	C_6H_5	**55**	CH_3	C_6H_5
26	H	4-BrC_6H_4	**36**	Cl	4-BrC_6H_4	**46**	F	4-BrC_6H_4	**56**	CH_3	4-BrC_6H_4
27	H	3-ClC_6H_4	**37**	Cl	3-ClC_6H_4	**47**	F	3-ClC_6H_4	**57**	CH_3	3-ClC_6H_4
28	H	4-ClC_6H_4	**38**	Cl	4-ClC_6H_4	**48**	F	4-ClC_6H_4	**58**	CH_3	4-ClC_6H_4
29	H	3-Cl,4-FC_6H_3	**39**	Cl	3-Cl,4-FC_6H_3	**49**	F	3-Cl,4-FC_6H_3	**59**	CH_3	3-Cl,4-FC_6H_3
30	H	4-FC_6H_4	**40**	Cl	4-FC_6H_4	**50**	F	4-FC_6H_4	**60**	CH_3	4-FC_6H_4
31	H	4-$CH_3C_6H_4$	**41**	Cl	4-$CH_3C_6H_4$	**51**	F	4-$CH_3C_6H_4$	**61**	CH_3	4-$CH_3C_6H_4$
32	H	$C_6H_5CH_2$	**42**	Cl	$C_6H_5CH_2$	**52**	F	$C_6H_5CH_2$	**62**	CH_3	$C_6H_5CH_2$
33	H	4-$ClC_6H_4CH_2$	**43**	Cl	4-$ClC_6H_4CH_2$	**53**	F	4-$ClC_6H_4CH_2$	**63**	CH_3	4-$ClC_6H_4CH_2$
34	H	4-$FC_6H_4CH_2$	**44**	Cl	4-$FC_6H_4CH_2$	**54**	F	4-$FC_6H_4CH_2$	**64**	CH_3	4-$FC_6H_4CH_2$

Scheme 1. Synthetic route of **25**–**64**.

resulted in the formation of 2-bromo-1-(4-methyl-2-arylthiazol-5-yl)ethanone **11**–**14** which on further cyclocondensation with aryl/benzyl thioamide, **15**–**24** furnished target compounds, **25**–**64**.

The structure of the title compounds **25**–**64** was confirmed by elemental analysis, IR, NMR and MS.

As a representative analysis of compound **40**, the IR (KBr) spectrum showed C=C/C=N absorption bands at 1629–1475 cm^{-1}. The ^1H NMR spectrum of compound **40** displayed two singlets at δ 2.85 (CH_3) and δ 7.38 (thiazole CH). A triplet, J = 8.4 Hz, at δ 7.15 and a doublet of doublet, J = 8.4 and 3.0 Hz, 2H at δ 7.96 were attributed to protons of fluoro substituted phenyl ring, while doublets, J = 8.6 Hz, at δ 7.42 and δ 8.04 corresponds to protons of chloro substituted phenyl ring. The ^{13}C NMR spectrum of compound **40** revealed the methyl carbon signal at δ 16.3, while the aromatic carbons showed typical fluoro-coupling [$\underline{C}_1$-F, δ 165.5, 163.0 (^1J = 250 Hz), $\underline{C}_2$-F δ 116.4, 116.1 (^2J = 22 Hz), $\underline{C}_3$-F δ 128.7, 128.6 (^3J = 8 Hz)]. The structure of compound **40** was further confirmed by molecular ion peaks at m/z 387.1 $(M + H)^+$ and m/z 389.1 $(M + H+2)^+$ (3:1). Structures of all the derivatives were ascertained similarly.

3. Biology

3.1. Anti-tubercular activity

The synthesized compounds (**25**–**64**) were screened for their antitubercular activity against *Mycobacterium smegmatis*, which is a fast growing non-pathogenic strain to assess the activity of the compounds in primary screening. The literature revealed that *M. smegmatis* based screens show 100% specificity and 78% sensitivity in comparison to MDR *Mycobacterium tuberculosis* [42–45]. The percentage inhibition was determined against DMSO and compounds that showed inhibition at 30% or more were further subjected for MIC studies. Rifampicin and isoniazid were used as reference drugs. The results of antitubercular activity is reported in Table 1.

3.2. Antibacterial activity

The *in vitro* antibacterial activity of all the synthesized compounds was done by the disc diffusion method against the standard

Table 1
Antitubercular activity and cytotoxicity of compound **25**–**64**. These compounds showed good activity (comparable to the standard).

Compound	R	R[1]	*M. smegmatis*[a]	MIC μM	LC_{50}[b]	TGI[c]	GI_{50}[d] in μg/mL
25	H	C_6H_5	–	–	nd	nd	nd
26	H	4-Br C_6H_4	33.5	80.66	>80	>80	>80
27	H	3-Cl C_6H_4	39.1	69.02	>80	>80	>80
28	H	4-Cl C_6H_4	32.4	81.88	>80	>80	>80
29	H	3-Cl,4-F C_6H_3	37.9	71.1	>80	>80	>80
30	H	4-F- C_6H_4	38.8	62.51	>80	>80	>80
31	H	4-CH_3-C_6H_4	29.6	91.15	nd	nd	nd
32	H	$C_6H_5CH_2$	0.8	>100	nd	nd	nd
33	H	4-Cl-$C_6H_5CH_2$	6.1	>100	nd	nd	nd
34	H	4-F-$C_6H_5CH_2$	2.3	>100	nd	nd	nd
35	4-Cl	C_6H_5	nd	–	nd	nd	nd
36	4-Cl	4-Br C_6H_4	nd	–	nd	nd	nd
37	4-Cl	3-Cl C_6H_4	24.0	>100	nd	nd	nd
38	4-Cl	4-Cl C_6H_4	28.2	74.86	nd	nd	nd
39	4-Cl	3-Cl,4-F C_6H_3	–	–	nd	nd	nd
40	4-Cl	4-F- C_6H_4	66.3	**40.73**	>80	>80	>80
41	4-Cl	4-CH_3-C_6H_4	4.1	–	nd	nd	nd
42	4-Cl	$C_6H_5CH_2$	–	–	nd	nd	nd
43	4-Cl	4-Cl-$C_6H_5CH_2$	–	–	nd	nd	nd
44	4-Cl	4-F-$C_6H_5CH_2$	36.2	74.64	>80	>80	76.2
45	4-F	C_6H_5	4.4	>100	nd	nd	nd
46	4-F	4-Br C_6H_4	–	–	nd	nd	nd
47	4-F	3-Cl C_6H_4	13.3	–	nd	nd	nd
48	4-F	4-Cl C_6H_4	nd	–	nd	nd	nd
49	4-F	3-Cl,4-F C_6H_3	49.3	**54.71**	>80	>80	41.9
50	4-F	4-F- C_6H_4	56.0	**48.22**	>80	>80	>80
51	4-F	4-CH_3-C_6H_4	19.3	>100	nd	nd	nd
52	4-F	$C_6H_5CH_2$	21.6	>100	nd	nd	nd
53	4-F	4-Cl-$C_6H_5CH_2$	26.44	>100	nd	nd	nd
54	4-F	4-F-$C_6H_5CH_2$	88.9	**30.38**	nd	nd	nd
55	4-CH_3	C_6H_5	29.7	90.99	nd	nd	nd
56	4-CH_3	4-Br C_6H_4	33.4	80.81	>80	>80	>80
57	4-CH_3	3-Cl C_6H_4	–	–	nd	nd	nd
58	4-CH_3	4-Cl C_6H_4	nd	–	nd	nd	nd
59	4-CH_3	3-Cl,4-F C_6H_3	nd	–	nd	nd	nd
60	4-CH_3	4-F- C_6H_4	23.9	>100	nd	nd	nd
61	4-CH_3	4-CH_3-C_6H_4	–	–	nd	nd	nd
62	4-CH_3	$C_6H_5CH_2$	20.5	>100	nd	nd	nd
63	4-CH_3	4-Cl-$C_6H_5CH_2$	–	–	nd	nd	nd
64	4-CH_3	4-F-$C_6H_5CH_2$	28.0	96.32	nd	nd	nd
Rifampicin			98	9.72	>80	>80	>80
Isoniazid			97	36.46	>80	>80	>80

[a] % Inhibition; nd: Not determined.
[b] Concentration of the compound that kills 50% of the cells.
[c] Concentration of the compound that produces total inhibition of the cells.
[d] Concentration of the compound that produces 50% inhibition of the cells.

Table 2
Antibacterial activity of compound **25**–**64**. These compounds showed good activity (comparable to the standard).

Compound	R	R[1]	*S. aureus*	*B. Subtilis*	*E. coli*	*P. Vulgaris*
25	H	C_6H_5	–	**24**	7	8
26	H	4-Br C_6H_4	14	**22**	13	14
27	H	3-Cl C_6H_4	10	9	8	8
28	H	4-Cl C_6H_4	12	8	–	8
29	H	3-Cl,4-F C_6H_3	11	10	–	–
30	H	4-F- C_6H_4	14	12	10	10
31	H	4-CH_3-C_6H_4	9	8	–	8
32	H	$C_6H_5CH_2$	–	10	–	–
33	H	4-Cl-$C_6H_5CH_2$	–	9	8	–
34	H	4-F-$C_6H_5CH_2$	–	18	–	–
35	4-Cl	C_6H_5	10	8	–	–
36	4-Cl	4-Br C_6H_4	–	–	7	–
37	4-Cl	3-Cl C_6H_4	0	8	10	7
38	4-Cl	4-Cl C_6H_4	11	–	8	–
39	4-Cl	3-Cl,4-F C_6H_3	8	11	–	–
40	4-Cl	4-F- C_6H_4	14	**21**	13	14
41	4-Cl	4-CH_3-C_6H_4	7	10	9	–
42	4-Cl	$C_6H_5CH_2$	–	12	–	–
43	4-Cl	4-Cl-$C_6H_5CH_2$	–	10	–	–
44	4-Cl	4-F-$C_6H_5CH_2$	14	**26**	**24**	12
45	4-F	C_6H_5	9	10	–	–
46	4-F	4-Br C_6H_4	–	9	–	–
47	4-F	3-Cl C_6H_4	13	**24**	**22**	16
48	4-F	4-Cl C_6H_4	–	–	8	18
49	4-F	3-Cl,4-F C_6H_3	10	–	8	8
50	4-F	4-F- C_6H_4	10	16	7	12
51	4-F	4-CH_3-C_6H_4	–	–	–	–
52	4-F	$C_6H_5CH_2$	10	14	10	13
53	4-F	4-Cl-$C_6H_5CH_2$	12	10	8	10
54	4-F	4-F-$C_6H_5CH_2$	**24**	**37**	**31**	**40**
55	4-CH_3	C_6H_5	–	8	8	–
56	4-CH_3	4-Br C_6H_4	14	**22**	12	16
57	4-CH_3	3-Cl C_6H_4	10	13	7	8
58	4-CH_3	4-Cl C_6H_4	9	–	9	8
59	4-CH_3	3-Cl,4-F C_6H_3	–	–	10	8
60	4-CH_3	4-F- C_6H_4	9	8	8	7
61	4-CH_3	4-CH_3-C_6H_4	9	**21**	10	10
62	4-CH_3	$C_6H_5CH_2$	10	10	8	7
63	4-CH_3	4-Cl-$C_6H_5CH_2$	8	9	–	7
64	4-CH_3	4-F-$C_6H_5CH_2$	10	12	–	9
Amoxycilin			42	28	24	40
Ciprofloxacin			28	26	27	31

Amoxycilin (100 μg/disc) and Ciprofloxacin (100 μg/disc were used as reference; synthesized compounds (100 μg/disc).

Gram-positive bacteria, *Bacillus subtilis* (NCIM 2162), *Staphylococcus aureus* (NCIM 2602) and Gram-negative bacteria, *Escherichia coli* (NCIM 2576), *Proteus vulgaris* (NCIM 2813). Ciprofloxacin and Amoxicillin which served as positive controls were obtained from their respective manufacturers. The *in vitro* preliminary screening results (zone of inhibition) against microorganisms tested are summarized in Table 2.

4. Result, discussion and conclusion

4.1. Antitubercular activity

The *in vitro* anti-tubercular activity against *M. smegmatis*, revealed that compounds **26**, **27**, **28**, **29**, **30**, **31**, **38**, **40**, **44**, **49**, **50**, **54**, **55**, **56**, and **64** exhibited moderate to good activity with inhibition in the range 28.0–88.9 %, at 30 μM concentration. The preliminary structure activity relationship study revealed that replacement of hydrogen atom of phenyl ring A and B (Fig. 2) by substituent groups like Br, Cl, F and CH_3 significantly increase the anti-tubercular activity.

Further, it was also noted that, the compounds**26**–**31**, with unsubstituted phenyl ring A and substituted phenyl ring B, all the compounds showed moderate activity whereas compounds **32**–**34** with substituted benzyl ring B were found to be less active. Among the compounds **35**–**41**with 4-chloro substituted phenyl ring A and chloro and fluoro substituted phenyl ring B, compounds **38** and **40** showed moderate and good activity respectively. Substitution of phenyl ring B by 4-fluoro benzyl ring in compound **44** showed moderate activity. Compounds **45**–**51**, with 4-fluorophenyl ring A and chloro or fluoro substituted phenyl ring B, exhibited good activity. Compound **54**, with 4-fluoro benzyl ring B, exhibited the best activity among all the synthesized derivatives. Among compounds **55**–**61**, with 4-methyl phenyl ring A and substituted phenyl ring B, only compounds **55** and **56** showed moderate activity. When the phenyl ring B was replaced by substituted benzyl, only compound **64** showed moderate activity.

It was noteworthy that chloro and fluoro substituents in both the rings A and B enhanced the antitubercular activity of the derivative, particularly compound 54 with fluoro substitution in both ring A and B was found to be the most activederivative.

The compounds that showed anti-tubercular activity (inhibition at 30% or more) were used for an *in vitro* cytotoxicity evaluation against Vero cell line. In general, the compounds tested did not

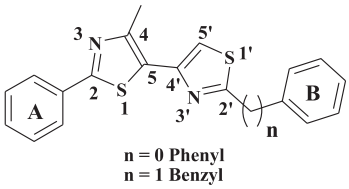


Fig. 2. Bithiazole **25**–**64**.

show cytotoxicity (IC_{50} > 80 μg/mL), confirming that the antitubercular activity does not arise from general toxicity of the compound class.

4.2. Antibacterial activity

Careful analysis of the antibacterial results presented in Table 2, provides some lead molecules with good antibacterial activity. Among the compounds **25**–**64** tested, it was observed that most of the derivatives with both substituted rings showed moderate to good activity. It was worthwhile to note that compounds **44** and **54** with chloro or fluoro substituted phenyl ring A and 4-fluorobenzyl ring B exhibited excellent activity comparable to the standard drug ciprofloxacin. It was observed that compound **54** exhibited excellent activity even better than the standard drugs Amoxicillin and ciprofloxacin.

5. Conclusion

In the present study, we have detailed the synthesis and evaluation of bithiazoles derivatives. It can be concluded that, most of the synthesized compounds with Br, Cl and F substituent on either or both phenyl rings showed moderate to good antibacterial activities. It is noteworthy that compound **54** can serve as a lead molecule as it exhibits good antitubercular as well as antimicrobial activity. Thus, these results warrant the need for synthesis of similar libraries with other substituents to ascertain the trend described in this work.

6. Experimental

6.1. Chemistry

All the reactions were monitored by thin layer chromatography (TLC). TLC was performed on Merck 60 F-254 silica gel plates. Melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H (300 MHz) NMR and ^{13}C (75 MHz) NMR spectra were recorded on Varian mercury XL-300 and Bruker at either 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR), spectrometer instruments. Chemical shifts are reported from internal tetramethyl silane standard and are given in δ units. Infrared spectra were recorded on Shimadzu FTIR (KBr) – 408 in KBr. The LC-MS spectra were recorded on a Shimadzu 2010 LC-MS. Elemental analysis was performed on a Hosli CH-analyzer. Column chromatography was performed on silica gel (100–200 mesh) supplied by Acme Chemical Co. The chemicals and solvents used were laboratory grade and were purified as per literature methods.

6.1.1. Synthesis of 3-bromopentane-2,4-dione(*2*)

A mixture of acetylacetone (10 mmol) and pTSA (5 mmol) in DCM: diethylether (50 mL, 1:1) was stirred at 0 °C for 10 min, followed by NBS (10 mmol). The reaction mixture was further stirred for 1 h at 0 °C (TLC). The reaction was quenched by sodium bicarbonate solution and stirred for 10 min. The aqueous layer was extracted with DCM and combined organic layers was washed with water, dried with sodium sulfate and distilled under vacuum. The product isolated was used for second step without purification.

6.1.2. General method for the synthesis of 4-methyl-2-phenylthiazole (*7*–*10*)

A mixture of thiobenzamide (6.62 mmol) and 3-bromopentane-2,4-dione, (6.62 mmol) was refluxed in ethanol. After completion of reaction (TLC), solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. Organic layer was washed with sodium bicarbonate and then water. Organic layer was dried over sodium sulfate and distilled under vacuum. The product obtained was purified by column chromatography using hexane: ethyl acetate (9:1) as eluant.

6.1.3. General method for the synthesis of 2-bromo-1-(4-methyl-2-(4-substituted phenyl)thiazol-5yl)ethanone (*11*–*14*)

A mixture of 1-(4-methyl-2-phenylthiazol-5-yl)ethanone (10 mmol) and pTSA (5 mmol) in 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 sulfate and distilled under vacuum.

6.1.4. General method for the synthesis of 4-methyl-2-aryl-5-(2-aryl/benzylthiazol-4-yl)thiazole (*25*–*64*)

A mixture of 2-bromo-1-(2-(4-phenyl)-4-methyl thiazol-5yl) ethanone (1 mmol) and substituted thioamide (1.1 mmol) was refluxed in dry ethanol (15 mL). The reaction was monitored on TLC. After completion of the reaction; reaction mixture was poured in ice water and extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water. The solvent was dried over sodium sulphate and removed under vacuum. The product was purified by crystallization from ethanol.

*6.1.4.1. 4-methyl-2-Phenyl-5-(2-phenylthiazol-4-yl)thiazole (**25**).* Yield: 64%; mp: 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.71 (s, 3H, CH_3), 7.46–7.54 (m, 7H, Ar-H and Thiazole-H), 7.95–8.01 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 115.5, 125.8, 126.2, 126.4, 126.8, 129.0, 130.0, 130.4, 132.4, 133.0, 147.1, 149.6, 163.7, 166.9; Anal. Calcd for: $C_{19}H_{14}N_2S_2$: C, 68.23; H, 4.22; N, 8.38; Found: C, 68.41; H, 4.39; N, 8.53; LC-MS, *m*/*z*: 335.1 $(M + H)^+$.

*6.1.4.2. 5-(2-(4-bromophenyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**26**).* Yield: 68%; mp: 204–206 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.18–7.49 (m, 6H, Ar-H, thiazole-H), 7.74–8.02 (m, 4H, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2, 115.7, 127.0, 128.4, 128.8, 129.2, 129.8, 130.6, 131.9, 133.1, 137.5, 145.8, 147.5, 165.4, 167.1; Anal. Calcd for: $C_{19}H_{13}BrN_2S_2$: C, 55.21; H, 3.17; N, 6.78; Found: C, 55.39; H, 3.10; N, 6.65; LC-MS, *m*/*z*: 413.0 $(M + H)^+$.

*6.1.4.3. 5-(2-(3-chlorophenyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**27**).* Yield: 70%; mp: 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.94 (s, 3H, CH_3), 7.41–7.61 (m, 6H, Ar-H, thiazole-H), 7.84 (d, J = 7.6 Hz, 1H, Ar-H), 8.00 (s, 1H, Ar-H), 8.20–8.22 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.9, 115.8, 124.8, 126.5, 127.4, 127.9, 129.4, 130.3, 130.6, 131.2, 132.2, 134.1, 135.1, 143.2, 146.2, 166.7, 167.9; Anal. Calcd for: $C_{19}H_{13}ClN_2S_2$: C, 61.86; H, 3.55; N, 7.59; Found: C, 61.97; H, 3.60; N, 7.70; LC-MS, *m*/*z*: 369.0 $(M + H)^+$.

*6.1.4.4. 5-(2-(4-chlorophenyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**28**).* Yield: 72%; mp: 176–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.89 (s, 3H, CH_3), 7.11–7.42 (m, 6H, Ar-H, thiazole-H), 7.91 (d, J = 8.6 Hz, 2H, Ar-H), 8.14–8.17 (m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1, 115.3, 127.2, 127.8, 128.2, 129.2, 129.3, 130.0, 131.1, 131.8, 136.7, 144.2, 146.5, 166.4, 167.0; Anal. Calcd for: $C_{19}H_{13}ClN_2S_2$: C, 61.86; H, 3.55; N, 7.59; Found: C, 62.00; H, 3.63; N, 7.51; LC-MS, m/z: 369.0 $(M + H)^+$.

*6.1.4.5. 5-(2-(3-chloro-4-fluorophenyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**29**).* Yield: 64%; mp: 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, CH_3), 7.47–7.57 (m, 4H, Ar-H, thiazole-H), 7.84–7.95 (m, 4H, Ar-H), 8.09 (d, J = 6.7 Hz, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.7, 118.5, 126.3, 127.6, 128.3, 129.1, 129.6, 130.5, 131.4, 133.2, 135.3, 138.2, 144.5, 147.4, 162.2, 164.8, 167.5; Anal. Calcd for: $C_{19}H_{12}ClFN_2S_2$: C, 58.98; H, 3.13; N, 7.24; Found: C, 59.08; H, 3.10; N, 7.39; LC-MS, m/z: 387.0 $(M + H)^+$.

*6.1.4.6. 5-(2-(4-fluorophenyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**30**).* Yield: 65%; mp: 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, CH_3), 7.18–7.31 (m, 6H, Ar-H, thiazole-H), 7.89–8.01 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 115.5, 125.8, 126.2, 126.4, 126.8, 129.0, 130.0, 130.4, 132.4, 133.0, 147.1, 149.6, 167.7, 168.9; Anal. Calcd for: $C_{19}H_{13}FN_2S_2$: C, 64.75; H, 3.72; N, 7.95; Found: C, 64.89; H, 3.77; N, 8.07; LC-MS, m/z: 353.1 $(M + H)^+$.

*6.1.4.7. 4-methyl-2-Phenyl-5-(2-p-tolylthiazol-4-yl)thiazole (**31**).* Yield: 74%; mp: 246 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.05–7.49 (m, 6H, Ar-H, thiazole-H), 7.87–8.19 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 20.9, 115.6, 125.9, 126.2, 129.2, 129.8, 130.3, 130.9, 132.6, 134.2, 140.5, 146.6, 149.3, 163.8, 167.1; Anal. Calcd for: $C_{20}H_{16}N_2S_2$: C, 68.93; H, 4.63; N, 8.04; Found: C, 69.07; H, 4.58; N, 8.13; LC-MS, m/z: 349.1 $(M + H)^+$.

*6.1.4.8. 5-(2-Benzylthiazol-4-yl)-4-methyl-2-phenylthiazole (**32**).* Yield: 60%; mp: 185–185 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.06 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.29–7.42 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole), 7.58–7.68 (m, 3H, Ar-H), 8.42 (d, J = 7.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 39.4, 117.7, 125.7, 127.6, 128.4, 129.0, 129.3, 130.0, 130.8, 134.2, 136.8, 141.5, 142.9, 167.8, 172.3; Anal. Calcd for: $C_{20}H_{16}N_2S_2$: C, 68.93; H, 4.63; N, 8.04; Found: C, 69.02; H, 4.69; N, 8.11; LC-MS, m/z: 349.1 $(M + H)^+$.

*6.1.4.9. 5-(2-(4-chlorobenzyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**33**).* Yield: 65%; mp: 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.05 (s, 3H, CH_3), 4.34 (s, 2H, CH_2), 7.28–7.37 (m, 5H, Ar-H), 7.50 (s, 1H, thiazole), 7.57–7.65 (m, 2H, Ar-H), 8.40 (d, J = 7.2 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 38.6, 117.3, 126.1, 128.3, 129.1, 128.8, 129.9, 130.3, 133.5, 134.0, 135.2, 143.3, 144.2, 167.8, 171.3; Anal. Calcd for: $C_{20}H_{15}ClN_2S_2$: C, 62.73; H, 3.95; N, 7.32; Found: C, 62.85; H, 3.87; N, 7.43; LC-MS, m/z: 383.1 $(M + H)^+$.

*6.1.4.10. 5-(2-(4-fluorobenzyl)thiazol-4-yl)-4-methyl-2-phenylthiazole (**34**).* Yield: 68%; mp: 200–202 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.03 (s, 3H, CH_3), 4.31 (s, 2H, CH_2), 7.23 (t, J = 8.2 Hz, 2H, Ar-H), 7.26–7.31 (m, 2H, Ar-H), 7.49 (s, 1H, thiazole), 7.52–7.61 (m, 3H, Ar-H), 8.38 (d, J = 7.6 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 38.4, 115.8, 117.7, 125.5, 128.3, 129.1, 129.9, 130.6, 132.4, 134.1, 141.4, 142.8, 161.5, 167.8, 171.9; Anal. Calcd for: $C_{20}H_{15}FN_2S_2$: C, 65.55; H, 4.13; N, 7.64; Found: C, 65.63; H, 4.07; N, 7.78; LC-MS, m/z: 367.1 $(M + H)^+$.

*6.1.4.11. 2-(4-chlorophenyl)-4-methyl-5-(2-phenylthiazol-4-yl)thiazole (**35**).* Yield: 70%; mp: 150–152 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.70 (s, 3H, CH_3), 7.49–7.53 (m, 5H), Ar-H, 7.83 (s, 1H, thiazole), 7.94–8.08 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): 16.0, 115.7, 127.7, 128.6, 128.9, 129.2, 129.5, 130.8, 133.9, 139.0, 141.8, 147.6, 149.5, 166.1, 167.0; Anal. Calcd for: $C_{19}H_{13}ClN_2S_2$: C, 61.86; H, 3.55; N, 7.59; Found: C, 61.98; H, 3.49; N, 7.71; LC-MS, m/z: 369.0 $(M + H)^+$.

*6.1.4.12. 5-(2-(4-bromophenyl)thiazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole (**36**).* Yield: 70%; mp: 164–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.75 (s, 3H, CH_3), 7.45 (d, J = 8 Hz, 2H, Ar-H), 7.59 (d, J = 8 Hz, 2H, Ar-H), 7.82 (s, 1H, thiazole), 7.99 (d, J = 8 Hz, 2H, Ar-H), 8.12 (d, J = 8 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.2, 114.4, 127.3, 127.6, 128.9, 129.0, 130.2, 131.3, 132.9, 135.4, 136.0, 147.7, 150.0, 163.2, 166.1; Anal. Calcd for: $C_{19}H_{12}BrClN_2S_2$: C, 50.96; H, 2.70; N, 6.26; Found: C, 51.10; H, 2.74; N, 6.31; LC-MS, m/z: 447.0 $(M + H)^+$.

*6.1.4.13. 2-(4-chlorophenyl)-5-(2-(3-chlorophenyl)thiazol-4-yl)-4-methylthiazole (**37**).* Yield: 66%; mp: 224–226 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.71 (s, 3H, CH_3), 7.38–7.46 (m, 4H, Ar-H), 7.68 (s, 1H, thiazole) 7.89–8.00 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 115.8, 127.5, 128.8, 128.9, 129.2, 129.4, 129.8, 130.5, 131.7, 133.5, 134.6, 137.0, 147.6, 150.0, 163.1166.0 Anal. Calcd for: $C_{19}H_{12}Cl_2N_2S_2$: C, 56.58; H, 3.00; N, 6.95; Found: C, 56.73; H, 3.08; N, 6.90; LC-MS, m/z: 403.0 $(M + H)^+$.

*6.1.4.14. 2-(4-chlorophenyl)-5-(2-(4-chlorophenyl)thiazol-4-yl)-4-methylthiazole (**38**).* Yield: 68%; mp: 196–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.72 (s, 3H, CH_3), 7.44 (d, J = 8 Hz, 2H, Ar-H), 7.51 (d, J = 8 Hz, 2H, Ar-H), 7.68 (s, 1H, thiazole), 7.96 (d, J = 8 Hz, 2H, Ar-H), 8.08 (d, J = 8 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 115.9, 127.6, 128.9, 129.5, 129.8, 130.2, 130.6, 131.8, 133.9, 134.8, 147.5, 149.8, 163.0166.1; Anal. Calcd for: $C_{19}H_{12}Cl_2N_2S_2$: C, 56.58; H, 3.00; N, 6.95; Found: C, 56.69; H, 3.11; N, 7.08; LC-MS, m/z: 403.0 $(M + H)^+$.

*6.1.4.15. 5-(2-(3-chloro-4-fluorophenyl)thiazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole (**39**).* Yield: 74%; mp: 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.69 (s, 3H, CH_3), 7.45–7.55 (m, 3H, Ar-H), 7.69 (m, 1H, Ar-H), 7.76 (s, 1H, thiazole), 8.05 (d, J = 8.4 Hz, 2H, Ar-H), 8.11 (m, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.5, 116.1, 118.1, 125.7, 126.2, 127.8, 128.6, 129.4, 130.7, 133.4, 134.2, 134.5, 138.3, 148.0, 161.8, 162.4, 165.1; Anal. Calcd for: $C_{19}H_{11}Cl_2FN_2S_2$: C, 54.16; H, 2.63; N, 6.65; Found: C, 54.29; H, 2.59; N, 6.73; LC-MS, m/z: 421.0 $(M + H)^+$.

*6.1.4.16. 2-(4-chlorophenyl)-5-(2-(4-fluorophenyl)thiazol-4-yl)-4-methylthiazole (**40**).* Yield: 70%; mp: 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (s, 3H, CH_3), 7.15 (t, J = 8.4 Hz, 2H, Ar-H), 7.38 (s, 1H, thiazole), 7.42 (d, J = 8.4 Hz, 2H, Ar-H), 7.96 (dd, J = 8.4 and 3.0 Hz, 2H, Ar-H), 8.04 (d, J = 8.6 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 115.1, 116.2, 128.3, 128.6, 128.7, 129.0, 129.6, 132.0, 135.7, 146.4, 147.0, 164.5, 164.7, 167.2; LCMS:387.1 $(M + H)^+$ Anal. Calcd for: $C_{19}H_{12}ClFN_2S_2$: C, 58.98; H, 3.13; N, 7.24; Found: C, 59.11; H, 3.17; N, 7.31; LC-MS, m/z: 387.1 $(M + H)^+$.

*6.1.4.17. 2-(4-chlorophenyl)-4-methyl-5-(2-p-tolylthiazol-4-yl)thiazole (**41ß**).* Yield: 75%; mp: 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.40 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 7.24 (d, J = 8.1 Hz, 2H, Ar-H), 7.25 (s, 1H, thiazole), 7.42 (d, J = 8.1 Hz, 2H, Ar-H), 7.87–7.90 (m, 4H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.5, 21.5, 113.5, 126.5, 127.5, 129.1, 129.6, 129.9, 130.4, 132.1, 135.7, 140.7, 147.9, 150.0, 163.6, 167.9 Anal. Calcd for $C_{20}H_{15}ClN_2S_2$: C, 62.73; H, 3.95; N, 7.32; Found: C, 62.82;

H, 4.01; N, 7.27; LC-MS, *m/z*: 383.0 $(M + H)^+$.

*6.1.4.18. 5-(2-Benzylthiazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole (**42**).* Yield: 65%; mp: 100–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 7.10 (s, 1H), 7.17–7.8 (m, 5H, Ar-H, thiazole-H), 7.30 (d, J = 8.4 Hz, 2H, Ar-H), 7.79 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 39.6, 114.4, 127.3, 127.5, 128.1, 128.8, 129.1, 131.3, 132.1, 135.7, 137.4, 146.9, 149.8, 163.5, 170.7; Anal. Calcd for: $C_{20}H_{15}ClN_2S_2$: C, 62.73; H, 3.95; N, 7.32; Found: C, 62.79; H, 4.00; N, 7.38; LC-MS, *m/z*: 383.0 $(M + H)^+$.

*6.1.4.19. 5-(2-(4-chlorobenzyl)thiazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole (**43**).* Yield: 75%; mp: 148–150 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.67 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.21–7.43 (m, 5H, Ar-H, thiazole-H), 7.39 (d, J = 8.5 Hz, 2H, Ar-H), 7.91 (d, J = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 38.8, 114.4, 115.6, 127.4, 129.1, 129.9, 130.6, 132.1, 133.2, 135.8, 147.1, 149.9, 163.6, 168.6, 169.7; Anal. Calcd for: $C_{20}H_{14}Cl_2N_2S_2$: C, 57.55; H, 3.38; N, 6.71; Found: C, 57.61; H, 3.44; N, 6.80; LC-MS, *m/z*: 417.1 $(M + H)^+$.

*6.1.4.20. 5-(2-(4-fluorobenzyl)thiazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole (**44**).* Yield: 68%; mp: 136–137 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 2.66 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 7.04 (t, J = 8.5 Hz, 2H, Ar-H), 7.21 (s, 1H, thiazole), 7.32 (dd J = 8.5 and 2 Hz, 2H, Ar-H), 7.39 (d, J = 8.5 Hz, 2H, Ar-H), 7.78 (d, J = 8.5 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 38.7, 114.4, 115.7, 127.4, 129.2, 130.6, 131.5, 132.1, 133.2, 135.8, 147.1, 149.8, 161.5, 163.6, 170.8; Anal. Calcd for: $C_{20}H_{14}ClFN_2S_2$: C, 59.92; H, 3.52; N, 6.99; Found: C, 60.01; H, 3.47; N, 7.10; LC-MS, *m/z*: 401.0 $(M + H)^+$.

*6.1.4.21. 2-(4-fluorophenyl)-4-methyl-5-(2-phenylthiazol-4-yl)thiazole (**45**).* Yield: 70%; mp: 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 2.66 (s, 3H, CH_3), 7.29 (t, J = 9.1 Hz, 2H, Ar-H), 7.52–7.59 (m, 3H, Ar-H), 7.97–8.07 (m, 5H, Ar-H, thiazole-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 113.9, 116.0, 123.4, 126.6, 128.1, 128.9, 129.9, 130.3, 134.5, 148.1, 149.9, 162.2, 163.9, 167.7; Anal. Calcd for: $C_{19}H_{13}FN_2S_2$: C, 64.75; H, 3.72; N, 7.95; Found: C, 64.87; H, 3.79; N, 7.99; LC-MS, *m/z*: 353.0 $(M + H)^+$.

*6.1.4.22. 5-(2-(4-bromophenyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**46**).* Yield: 76%; mp: 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.18 (t, J = 9.1 Hz, 2H, Ar-H), 7.48 (d, J = 8.4 Hz, 2H, Ar-H), 7.68 (s, 1H, thiazole), 7.88 (m, 2H, Ar-H), 8.02 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 115.5, 115.7, 116.1, 126.4, 127.3, 127.7, 129.2, 129.4, 131.2, 135.1, 147.6, 149.2, 162.5, 165.3; Anal. Calcd for: $C_{19}H_{12}BrFN_2S_2$: C, 52.91; H, 2.80; N, 6.49; Found: C, 53.01; H, 2.88; N, 6.55; LC-MS, *m/z*: 431.0 $(M + H)^+$.

*6.1.4.23. 5-(2-(3-chlorophenyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**47**).* Yield: 66%; mp: 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H, CH_3), 7.16 (t, J = 8.8 Hz, 2H, Ar-H), 7.44–7.50 (m, 2H, Ar-H), 7.61 (s, 1H, thiazole), 7.89–7.94 (m, 3H, Ar-H), 8.04 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0, 115.9, 116.1, 127.5, 128.7, 129.0, 129.2, 129.5, 130.0, 131.1, 133.9, 136.4, 144.3, 147.8, 162.2, 166.5, 167.1; Anal. Calcd for: $C_{19}H_{12}ClFN_2S_2$: C, 58.98; H, 3.13; N, 7.24; Found: C, 59.10; H, 3.10; N, 7.33; LC-MS, *m/z*: 387.1 $(M + H)^+$.

*6.1.4.24. 5-(2-(4-chlorophenyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**48**).* Yield: 70%; mp: 208–210 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, CH_3), 7.16 (t, J = 9.1 Hz, 2H, Ar-H), 7.44 (d, J = 8.4 Hz, 2H, Ar-H), 7.66 (s, 1H, thiazole), 7.89 (m, 2H, Ar-H), 8.00 (d, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1, 115.6, 116.0, 126.6, 127.6, 127.8, 127.9, 129.1, 129.5, 131.1, 135.3, 147.2, 149.6, 162.6, 165.5; Anal. Calcd for: $C_{19}H_{12}ClFN_2S_2$: C, 58.98; H, 3.13; N, 7.24; Found: C, 59.13; H, 3.19; N, 7.35; LC-MS, *m/z*: 387.1 $(M + H)^+$.

*6.1.4.25. 5-(2-(3-chloro-4-fluorophenyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**49**).* Yield: 68%; mp: 192–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.72 (s, 3H, CH_3), 7.24 (t, J = 8.4 Hz, 2H, Ar-H) 7.45 (t, J = 8.44 Hz, 1H, Ar-H), 7.78 (s, 1H, thiazole), 7.95–8.02 (m, 3H, Ar-H), 8.13 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.5, 116.1, 116.4, 118.0, 125.5, 126.2, 127.7, 128.8, 129.3, 129.9, 130.6, 138.1, 147.6, 161.8, 162.3, 163.1, 165.6; Anal. Calcd for: $C_{19}H_{11}ClF_2N_2S_2$: C, 56.36; H, 2.74; N, 6.92; Found: C, 56.38; H, 2.71; N, 7.01; LC-MS, *m/z*: 405.1 $(M + H)^+$.

*6.1.4.26. 2-(4-fluorophenyl)-5-(2-(4-fluorophenyl)thiazol-4-yl)-4-methylthiazole (**50**).* Yield: 66%; mp: 165–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.70 (s, 3H, CH_3), 7.27–7.36 (m, 4H, Ar-H), 7.86 (s, 1H, thiazole),7.99–8.06 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 115.7, 116.0, 116.2, 128.0, 128.4, 128.5, 129.2, 130.3, 147.0, 149.6, 161.9, 162.2, 164.4, 165.0; Anal. Calcd for: $C_{19}H_{12}F_2N_2S_2$: C, 61.60; H, 3.27; N, 7.56; Found: C, 61.78; H, 3.22; N, 7.67; LC-MS, *m/z*: 371.1 $(M + H)^+$.

*6.1.4.27. 2-(4-fluorophenyl)-4-methyl-5-(2-p-tolylthiazol-4-yl)thiazole (**51**).* Yield: 68%; mp: 168–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 7.32 (t, J = 8.8 Hz, 2H, Ar-H), 7.34 (d, J = 8.2 Hz, 2H, Ar-H), 7.88 (d, J = 8.2 Hz, 2H, Ar-H), 7.89 (s, 1H, thiazole), 8.00–8.03 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.2, 21.0, 115.4, 116.2, 126.2, 127.0, 128.1, 129.8, 130.5, 132.2, 140.5, 146.7, 149.6, 162.6, 164.3, 167.1; Anal. Calcd for: $C_{20}H_{15}FN_2S_2$: C, 65.55; H, 4.13; N, 7.64; Found: C, 65.67; H, 4.10; N, 7.77; LC-MS, *m/z*: 367.1 $(M + H)^+$.

*6.1.4.28. 5-(2-Benzylthiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**52**).* Yield: 66%; mp: 110–112 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.30–7.39 (m, 7H, Ar-H), 7.72 (s, 1H, thiazole), 7.99 (dd, J = 8.4 Hz and 2.0 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.2, 39.4, 115.6, 116.1, 126.8, 128.7, 129.0, 129.3, 129.6, 134.7, 137.5, 146.5, 149.9, 162.2, 163.9, 167.6; Anal. Calcd for: $C_{20}H_{15}FN_2S_2$: C, 65.55; H, 4.13; N, 7.64; Found: C, 65.68; H, 4.08; N, 7.71; LC-MS, *m/z*: 367.0 $(M + H)^+$.

*6.1.4.29. 5-(2-(4-chlorobenzyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**53**).* Yield: 65%; mp: 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.09 (t, J = 8.6 Hz, 2H, Ar-H),7.17 (s, 1H, thiazole), 7.34 (d, J = 4.4 Hz, 4H, Ar-H), 7.90–7.93 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 39.7, 114.4, 116.0, 127.3, 127.4, 128.3, 128.9, 129.1, 130.0, 137.5, 147.1, 149.7, 163.8, 164.0, 170.7; Anal. Calcd for: $C_{20}H_{14}ClFN_2S_2$: C, 59.92; H, 3.52; N, 6.99; Found: C, 60.01; H, 3.59; N, 7.10; LC-MS, *m/z*: 400.0 $(M + H)^+$.

*6.1.4.30. 5-(2-(4-fluorobenzyl)thiazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole (**54**).* Yield: 68%; mp:108–110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.62 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.21 (t, J = 9.8 Hz, 2H, Ar-H), 7.33 (t, J = 9.4 Hz, 2H, Ar-H),7.45 (dd, J = 8.4 Hz and 3.1 Hz, 2H, Ar-H), 7.75 (s, 1H, thiazole),7.99 (dd, J = 8.4 Hz and 2.0 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.4, 38.9, 114.3, 115.7, 116.0, 127.2, 128.3, 129.0, 130.7, 133.2, 147.2, 149.8, 162.6, 163.3, 134.2, 170.4; Anal. Calcd for: $C_{20}H_{14}F_2N_2S_2$: C, 62.48; H, 3.67; N, 7.29; Found: C, 62.51; H, 3.65; N, 7.33; LC-MS, *m/z*: 385.0 $(M + H)^+$.

*6.1.4.31. 4-methyl-5-(2-phenylthiazol-4-yl)-2-p-tolylthiazole (**55**).* Yield: 72%; mp: 156–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.32 (d, J = 8.4 Hz, 2H), 7.55–7.57 (m, 3H,

Ar-H),7.86 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.97 (s, 1H, thiazole), 8.00–8.02 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.5, 21.5, 113.8, 126.3, 126.6, 126.7, 129.1, 129.6, 130.4, 131.0, 133.2, 140.2, 148.5, 149.9, 165.4, 167.7; Anal. Calcd for: $C_{20}H_{16}N_2S_2$: C, 68.93; H, 4.63; N, 8.04; Found: C, 69.02; H, 4.59; N, 8.18; LC-MS, *m*/*z*: 349.0 $(M + H)^+$.

*6.1.4.32. 5-(2-(4-bromophenyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**56**).* Yield: 72%; mp: 200 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.32 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.75 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.86 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.94 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.00 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.9, 21.7, 115.5, 125.2, 127.4, 127.5, 128.1, 130.2, 131.5, 132.3, 133.2, 140.2, 148.5, 149.9, 167.1, 167.3; Anal. Calcd for: $C_{20}H_{15}BrN_2S_2$: C, 56.21; H, 3.54; N, 6.55; Found: C, 56.30; H, 3.50; N, 6.47; LC-MS, *m*/*z*: 426.9 $(M + H)^+$.

*6.1.4.33. 5-(2-(3-chlorophenyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**57**).* Yield: 66%; mp: 228–230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.28–7.33 (m, 2H, Ar-H), 7.57–7.60 (m, 4H, Ar-H), 7.87 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.03 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): 16.0, 21.6, 115.8, 127.3, 127.5, 128.4, 129.0, 129.3, 129.8, 130.0, 131.5, 131.8, 134.7, 139.5, 147.9, 149.6, 167.1, 167.5 δ Anal. Calcd for: $C_{20}H_{15}ClN_2S_2$: C, 62.73; H, 3.95; N, 7.32; Found: C, 62.83; H, 3.99; N, 7.21; LC-MS, *m*/*z*: 383.0 $(M + H)^+$.

*6.1.4.34. 5-(2-(4-chlorophenyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**58**).* Yield: 68%; mp: 150–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.30 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.52 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.88 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.95 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.00 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.1, 21.5, 116.0, 127.5, 128.5, 128.8, 129.5129.9, 132.0, 134.5, 139.8, 141.5, 147.8, 149.5, 166.9, 167.4; Anal. Calcd for: $C_{20}H_{15}ClN_2S_2$: C, 62.73; H, 3.95; N, 7.32; Found: C, 62.81; H, 4.00; N, 7.25; LC-MS, *m*/*z*: 383.1 $(M + H)^+$.

*6.1.4.35. 5-(2-(3-chloro-4-fluorophenyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**59**).* Yield: 65%; mp: 162–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.70 (s, 3H, CH_3), 7.28–7.32 (m, 3H, Ar-H), 7.88–7.93 (m, 2H, Ar-H), 7.97–8.00 (m, 2H, Ar-H), 8.03 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.0, 21.5, 116.0, 117.4, 123.5, 126.9, 127.4, 127.6, 128.5, 129.1129.8, 131.9, 139.5, 147.2, 149.8, 160.8, 167.0, 167.7; Anal. Calcd for: $C_{20}H_{14}ClFN_2S_2$: C, 59.92; H, 3.52; N, 6.99; Found: C, 60.02; H, 3.44; N, 6.88; LC-MS, *m*/*z*: 400.0 $(M + H)^+$.

*6.1.4.36. 5-(2-(4-fluorophenyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**60**).* Yield: 68%; mp: 154–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.32 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.40 (t, $J = 8.4$ Hz, 2H, Ar-H), 7.86 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.97 (s, 1H, thiazole), 8.04–8.08 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.0, 21.5, 115.9, 116.1, 127.5, 128.8, 129.2129.7, 131.7, 137.8, 139.6, 147.3, 149.7, 162.5, 166.9, 167.6; Anal. Calcd for: $C_{20}H_{15}FN_2S_2$: C, 65.55; H, 4.13; N, 7.64; Found: C, 65.67; H, 4.18; N, 7.55; LC-MS, *m*/*z*: 367.0 $(M + H)^+$.

*6.1.4.37. 4-methyl-2-p-Tolyl-5-(2-p-tolylthiazol-4-yl)thiazole (**61**).* Yield: 70%; mp: 202–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.32 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.36 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.87 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.89 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.92 (s, 1H, thiazole); ^{13}C NMR (100 MHz, DMSO-d_6): δ 16.0, 21.4, 21.5, 116.0, 127.5, 127.7, 128.8, 129.5129.6, 131.9, 132.0, 138.8, 138.9, 147.5, 149.5, 166.9, 167.4; Anal. Calcd for: $C_{21}H_{18}N_2S_2$: C, 69.58; H, 5.00; N, 7.73; Found: C, 69.55; H, 5.08; N, 7.81; LC-MS, *m*/*z*: 363.0$(M + H)^+$.

*6.1.4.38. 5-(2-Benzylthiazol-4-yl)-4-methyl-2-p-tolylthiazole (**62**).* Yield: 60%; mp: 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.15 (s, 1H, thiazole), 7.23–7.39 (m, 7H, Ar-H), 7.84 (d, $J = 7.6$ Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.4, 21.8, 38.6, 116.8, 125.9, 127.7, 128.6, 128.8, 129.1, 129.7, 131.9, 136.0, 141.2, 143.6147.3, 167.9, 169.4; Anal. Calcd for: $C_{21}H_{18}N_2S_2$: C, 69.58; H, 5.00; N, 7.73; Found: C, 69.71; H, 4.94; N, 7.65; LC-MS, *m*/*z*: 363.0 $(M + H)^+$.

*6.1.4.39. 5-(2-(4-chlorobenzyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**63**).* Yield: 66%; mp: 186–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.43 (s, 2H, CH_2), 7.20–7.49 (m, 6H, Ar-H), 7.77 (s, 1H, thiazole), 7.84 (d, $J = 8.0$ Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.8, 21.8, 38.7, 116.9, 126.7, 128.4, 128.7, 129.3, 131.8, 131.9, 132.2, 134.8, 140.8, 143.1, 146.1, 168.3, 169.7; Anal. Calcd for: $C_{21}H_{17}ClN_2S_2$: C, 63.54; H, 4.32; N, 7.06; Found: C, 63.68; H, 4.24; N, 7.00; LC-MS, *m*/*z*: 397.0 $(M + H)^+$.

*6.1.4.40. 5-(2-(4-fluorobenzyl)thiazol-4-yl)-4-methyl-2-p-tolylthiazole (**64**).* Yield: 66%; mp: 216 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.21 (t, $J = 8.8$ Hz, 2H, Ar-H), 7.30–7.32 (m, 2H, Ar-H), 7.43–7.46 (m, 2H, Ar-H), 7.76 (s, 1H, thiazole), 7.84 (d, $J = 8.0$ Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.7 21.9, 38.6, 115.9, 116.8, 127.0, 128.4, 129.3, 130.5131.8, 132.0, 140.6, 143.2146.2, 161.5, 168.1, 169.6; Anal. Calcd for: $C_{21}H_{17}FN_2S_2$: C, 66.29; H, 4.50; N, 7.36; Found: C, 66.22; H, 4.43; N, 7.51; LC-MS, *m*/*z*: 381.0 $(M + H)^+$.

6.2. Biological method

6.2.1. Anti-tubercular activity

The compounds listed in Table 1 were screened for their antibacterial activity against *M. smegmatis* MC^2 155 strain [46]. The series of compounds were obtained in 10 mM stock concentrations. Further, each compound was diluted with the required 100% (v/v) DMSO to achieve a working concentration of 1.5 mM. The inoculum for the assay was prepared by reviving a glycerol stock in Middlebrook 7H9 broth supplemented with 0.1% Tween 80 and 0.5% glycerol. At the time of inoculation, 10% ADS was added to the media and the culture was incubated in a shaker incubator at 37 °C and 200 rpm. The O.D. of the inoculum reached to 0.8–1 approximately, a secondary inoculum was inoculated and subsequently incubated. This was incubated overnight till the O.D. of the inoculum reached 0.4 approx., following which the inoculum was diluted 1:1000 times. In a 96 well microtiter plate, a 2 μL aliquot of the 1.5 mM dilution of compound was added to each well in triplicate, to which 98 μL of inoculum dilution was added, making the final concentration of compound 30 μM. To each plate, a set of controls was added to better ascertain the activity of the compounds. These included DMSO, which was taken as a growth control, and media control (Blank) and Rifampicin and Isoniazid, which were taken as positive controls of inhibition of *M. smegmatis*. After the completion of the period of 32 h, the absorbance of the inoculum in wells was measured at 600 nm using a Multi Mode Reader. Absorbance is considered directly proportional to the increase in growth of bacteria. Thus, it gives a measure of the growth of bacteria in each well. Percentage inhibition was determined against DMSO and those compounds which showed inhibition at 30% or more were further analyzed to determine their MIC values. In order to attain this objective, the inhibition was tested at an increasing concentrations of compound from 6.25 μM to 100 μM. After a period of 30 h incubation, the absorbance of the inoculum was observed at 600 nm using a Multi Mode Reader and the MIC values were calculated for the respective compounds. As internal

standards for assay, Rifampicin (MIC value ranges from 0.06 μg/mL) and Isoniazid (MIC value ranges from 0.03 μg/mL).

6.2.2. Cytotoxicity activity

Vero cells were used for an *in vitro* cytotoxicity evaluation for the compounds using SRB assay protocols [47], each compound was tested at 4 dose levels (10, 20, 40, 80 μg/ml). Appropriate positive controls are run in each experiment and each experiment is repeated thrice. Results are given in terms of GI50, TGI and LC50 values.

6.2.3. Antibacterial activity

The *in vitro* antibacterial activity of all the synthesized compounds were done by the disc diffusion method [48,49] against the standard strains Gram-positive bacteria, *B. subtilis* (NCIM 2162), *S. aureus* (NCIM 2602) and Gram-negative bacteria, *E. coli* (NCIM 2576), *P. vulgaris* (NCIM 2813). All the strains were obtained from National Chemical Laboratory, Pune, India. All cultures were maintained at 4 °C over nutrient agar slants throughout the experiment. The cultures were incubated overnight at 37 °C in nutrient broth before using for antibacterial activity. Five hundred microliters of overnight old bacterial suspension was spread over the nutrient agar plates using a sterile cotton swab in order to get a uniform microbial growth. The synthesized compounds were dissolved in DMSO. Under aseptic conditions, empty sterilized discs (Whatman no. 5, 6 mm diameter) were impregnated with different concentrations (25 μg/disc, 50 μg/disc, 75 μg/disc, 100 μg/disc) of respective synthesized compounds and placed on the agar surface. Paper disc moistened with aqueous DMSO was placed on seeded petriplates as a vehicle control. A standard disc containing Amoxycillin and Ciprofloxacin used as positive controls were obtained from their respective manufacturers. 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 antimicrobial activity was evaluated by measuring the zone of inhibition against the test of microorganism. All experiments were carried out in triplicates.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.03.016.

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