Med Chem Res (2013) 22:4239–4252
DOI 10.1007/s00044-012-0431-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and pharmacological evaluation of some novel 4-isopropyl thiazole-based sulfonyl derivatives as potent antimicrobial and antitubercular agents

G. V. Suresh Kumar · Y. Rajendra Prasad · S. M. Chandrashekar

Received: 27 June 2012 / Accepted: 15 December 2012 / Published online: 3 January 2013

Abstract A series of novel sulfonyl derivatives 3-(substituted benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazoles **4a–4e,** isopropyl thiazole-derived schiff bases **8a–8l,** and 2-(substituted benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazoles **11a–11e** were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, elemental, and mass spectral analysis. All the compounds exhibited moderate to significant antibacterial and antifungal activities. Results of the antitubercular screening against *Mycobacterium tuberculosis* H37Rv ascertain compounds **4e**, **8b,** and **8f** as excellent antitubercular molecules, when compared with first line drug isoniazid (0.25 μg/mL).

Keywords: 4-Isopropylthiazole · Cytotoxicity · Antibacterial · Antifungal · Antitubercular activity

Electronic supplementary material The online version of this article (doi:10.1007/s00044-012-0431-1) contains supplementary material, which is available to authorized users.

G. V. Suresh Kumar (✉)
Department of Medicinal Chemistry, St. Johns Pharmacy College, 6, 2nd Stage Vijaynagar, R.P.C.Layout, Bangalore 560040, Karnataka, India
e-mail: gvsureshkumar@yahoo.com

Y. Rajendra Prasad
AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam 530003, Andhra Pradesh, India
e-mail: dryrp_au@rediffmail.com

S. M. Chandrashekar
Poornaprajna Institute of Scientific Research (PPISR), Poornaprajnapura, Bidalur, Devanahalli, Near Woodrich Resort, Bangalore 562110, Karnataka, India
e-mail: Chandra_jan25@yahoo.co.in

Introduction

Despite current multidrug therapy and ongoing drug development, tuberculosis (TB) continues to be a major health concern today. With more than 1.6 million deaths and 9.2 million new cases being reported each year, it is a leading infectious disease claiming millions of death globally *Mycobacterium tuberculosis* has ability to survive for extended periods of time in human host and thus requires prolonged drug treatment (6–9 months) and resulting in low compliance. Moreover, the evolution of multidrug-resistant (MDR), extremely drug-resistant (XDR) tuberculosis, and the AIDS epidemic further makes the situation more worsening (Goulding *et al*., 2002). In *M. tuberculosis*, drug resistance is not due to a common mechanism for all drugs, but different mechanisms for different class of drugs. Almost all conventional targets and drugs became inadequate to control resistant TB infection and therefore the discovery of novel, sensitive, and selective targets or new chemical entity is needed for the development of new generation of antitubercular drugs(Ballell *et al*., 2005); (Neu, 1992).

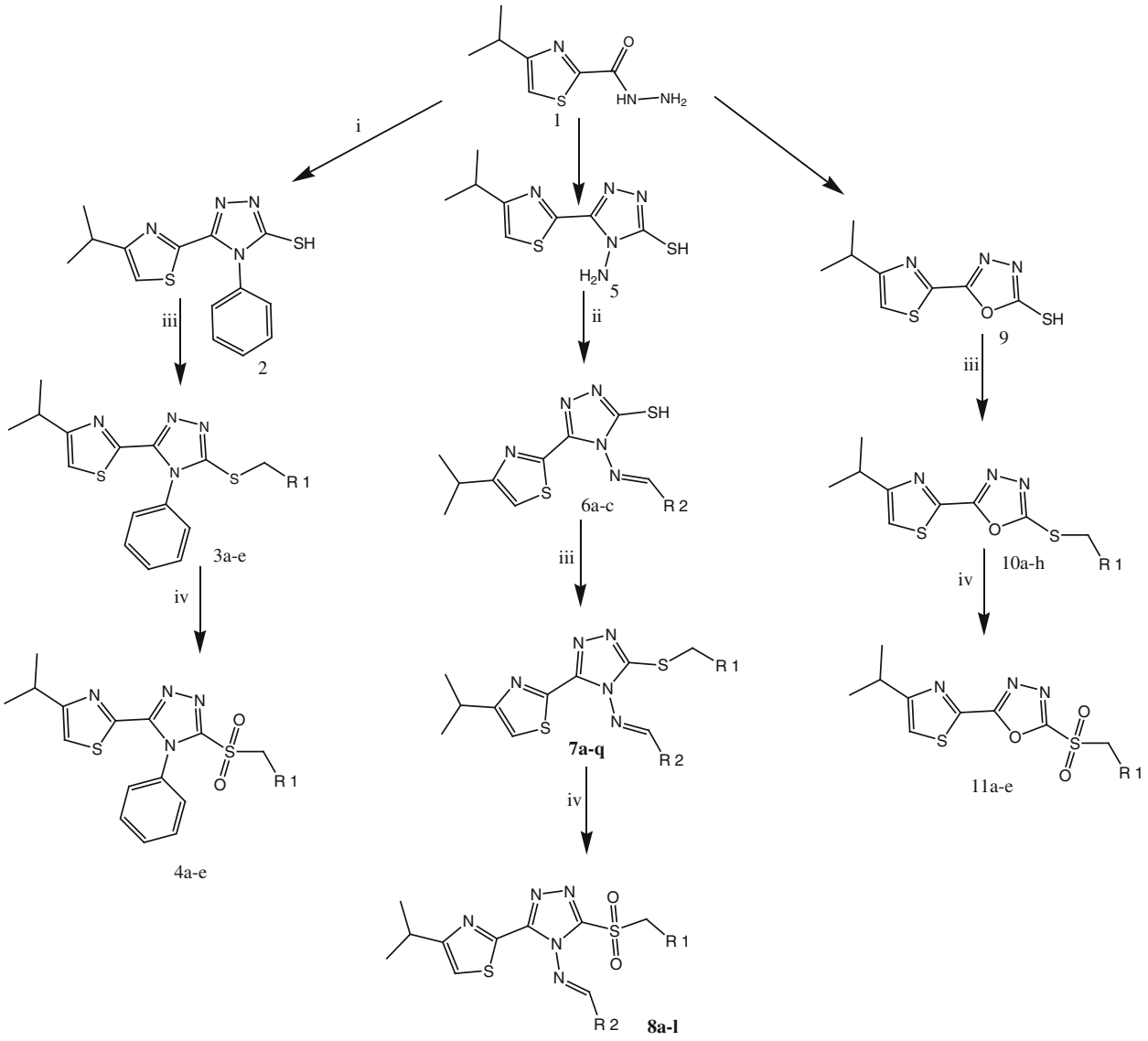
The development of inhibitors of Mycobacterial cell wall biosynthesis is one of the key strategies for designing effective antitubercular agents. The cell wall of Mycobacteria consists of a wide array of complex fatty acids, such as mycocerosic acid, mycolic acid, arabinogalactans (AGs), and peptidoglycans (PGs) (Spigelman, 2007); (Cegielski *et al*., 2002). Azole derivatives possess interesting antimycobacterial activity in addition to antimicrobial activity. It is established that these compounds reach target by transmembrane diffusion because of their lipophilic property. Azole derivatives target the sterol 14α-demethylase, a mixed-function oxidase involved in sterol synthesis in eukaryotic organisms (Walczak *et al*., 2004); (Babaoglu *et al*., 2003); (Khalaf *et al*., 2004).

Our previous studies on clubbed triazolyl-thiazoles (Shiradkar *et al*., 2007a, b) proved that isopropyl thiazole moiety, on coupling with other heterocyclic rings, provides biologically active novel compounds that could be explored as potent antimicrobial and antitubercular agents (Mallikarjuna *et al*., 2009); (Suresh Kumar *et al*., 2010a, b, 2012, doi 10.1007/s00044-012-0092-0). The present study illustrates the design and synthesis of some novel 4- isopropyl thiazoles and link them with 1,3,4-oxadiazole and 1,2,4-triazoles by sulfone and study the use of an oxygen atom as a bioisosteric linker, which has a marginally smaller bond angle and much greater electronegativity, which results in an analog with increased potency as antimicrobial (bacterial and fungal) and antitubercular activity against *M. tuberculosis* H37Rv strain.

Chemistry

The reaction sequences employed for synthesis of target isopropyl thiazole derivatives are illustrated in Scheme 1 and their Physical properties are depicted in Table 1. The key isopropyl thiazole intermediates (**1**, **2**, and **5**) were synthesized as reported in the literature. (Mallikarjuna *et al*., 2009); (Suresh Kumar *et al*., 2010a, b, 2012, doi 10.1007/s00044-012-0092-0).

The important intermediate 3-(substituted benzylthio)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazoles **3a**–**3e** was prepared by condensation of compound **1** with phenylisothiocyanate in the presence of ethanol. Schiff bases **6a**–**6e** were obtained on reacting triazole **5** with various substituted benzaldehydes in the presence of catalytic amount



Scheme 1 Synthesis of 4-Isopropyl thiazole derived sulfonyl derivatives **4a**–**4e**, **8a**–**8l**, and **11a**–**11e**

Table 1 Analytical and physico-chemical data of synthesized sulfonyl derivatives **4a–4e**, **8a–8l**, and **11a–11e**

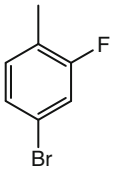
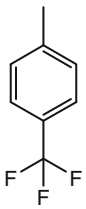
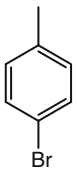
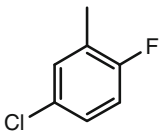
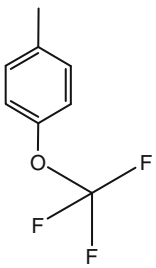
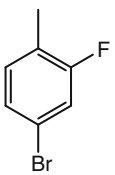
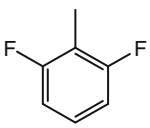
Compound	*R*1	*R*2	Solvent system	M.p (°C)[a]/crystallization solvent	Yield (%)	% Analysis of C, H, N found (Calc.)[b]		
						C	H	N
4a		–	$CHCl_3$:CH_3OH (9:2)	175–177 (ethanol)	84	C-48.37 (48.38)	H-3.48(3.47)	N-10.74(10.75)
4b		–	$CHCl_3$:CH_2OH (8:1)	164–166 (ethanol)	86	C-55.0(55.01)	H-4.24(4.28)	N-13.87(13.85)
4c		–	$CHCl_3$:CH_2OH (9:1)	161–163 (ethanol)	74	C-50.10(50.08)	H-3.80(3.83)	N-11.13(11.18)
4d		–	$CHCl_3$:CH_2OH (9:1)	189–191 (ethanol)	71	C-52.88(52.87)	H-3.80(3.84)	N-11.75(11.78)
4e		–	$CHCl_3$:CH_2OH (9:1)	203–205 (ethanol)	63	C-51.96(51.95)	H- 3.77(3.75)	N-11.02(11.06)
8a			$CHCl_3$:CH_3OH (9:1)	225–227 (ethanol)	84	C-45.21(45.24)	H-2.93(2.95)	N-11.98(11.95)

Table 1 continued

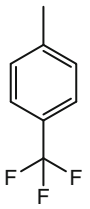
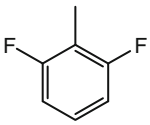
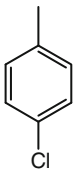
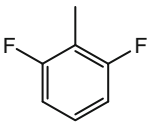
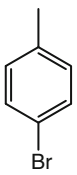
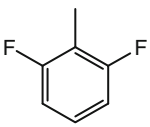
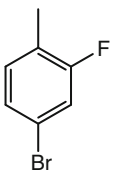
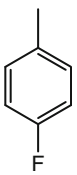
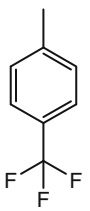
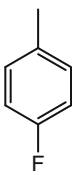
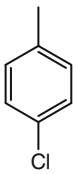
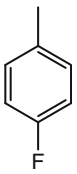
Compound	*R*1	*R*2	Solvent system	M.p (°C)[a]/crystallization solvent	Yield (%)	% Analysis of C, H, N found (Calc.)[b]		
						C	H	N
8b			$CHCl_3$:CH_3OH (8:2)	212–214 (ethanol)	76	C-49.73(49.75)	H-3.25(3.26)	N-12.61(12.62)
8c			$CHCl_3$:CH_2OH (9:1)	271–273 (ethanol)	86	C-50.62(50.65)	H- 3.48(3.45)	N-13.42(13.44)
8d			$CHCl_3$:CH_2OH (8:2)	208–211 (ethanol)	91	C-46.65(46.68)	H-3.20(3.24)	N-12.36(12.34)
8e			$CHCl_3$:CH_2OH (9:2)	224–226 (ethanol)	71	C-46.65(46.62)	H-3.20(3.24)	N-12.36(12.35)
8f			$CHCl_3$:CH_3OH (9:1)	202–204 (ethanol)	75	C-51.39(51.38)	H-3.56(3.58)	N-13.04(13.06)
8g			$CHCl_3$:CH_3OH (9:1)	195–197 (ethanol)	70	C-54.92(54.94)	H-4.01(4.05)	N-12.14(12.12)

Table 1 continued

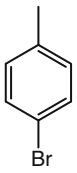
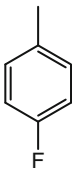
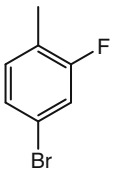
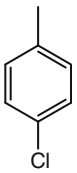
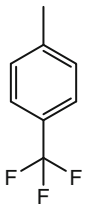
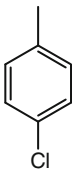
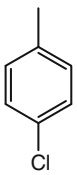
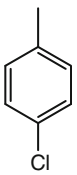
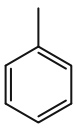
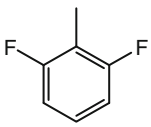
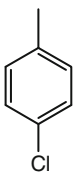
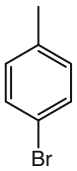
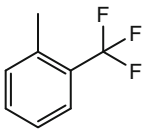
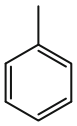
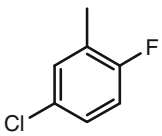
Compound	*R*1	*R*2	Solvent system	M.p (°C)[a]/crystallization solvent	Yield (%)	% Analysis of C, H, N found (Calc.)[b]		
						C	H	N
8h			$CHCl_3$:CH_2OH (9:2)	191–194 (ethanol)	65	C-48.18(49.68)	H-3.49(3.48)	N-12.77(12.80)
8i			$CHCl_3$:CH_2OH (9:2)	186–189 (ethanol)	69	C-45.33(45.35)	H-3.11(3.12)	N-12.01(12.05)
8j			$CHCl_3$:CH_3OH (9:1)	193–195 (ethanol)	91	C-49.86(49.85)	H-3.45 (3.42)	N-12.63(12.62)
8k			$CHCl_3$:CH_2OH (8:1)	187–189 (ethanol)	69	C-50.77(50.76)	H-3.68(3.65)	N-13.46(13.48)
8l			$CHCl_3$:CH_2OH (9:1)	194–196 (ethanol)	59	C-54.20(54.24)	H-3.93(3.95)	N-14.36(14.39)
11a		–	$CHCl_3$:CH_3OH (8:1)	180–182 (ethanol)	84	C-46.9(46.95)	H-3.68(3.66)	N-10.95(10.94)

Table 1 continued

Compound	*R*1	*R*2	Solvent system	M.p (°C)[a]/crystallization solvent	Yield (%)	% Analysis of C, H, N found (Calc.)[b]		
						C	H	N
11b		–	$CHCl_3$:CH_3OH (8:2)	169–172 (ethanol)	78	C-42.00(42.02)	H-3.29(3.27)	N-9.81(9.82)
11c		–	$CHCl_3$:CH_3OH (9:1)	182–184 (ethanol)	92	C-46.04(46.02)	H-3.38(3.36)	N-10.07(10.04)
11d		–	$CHCl_3$:CH_3OH (9:1)	191–195 (ethanol)	82	C-51.50(51.50)	H-4.33(4.31)	N-12.04(12.02)
11e		–	$CHCl_3$:CH_3OH (9:1)	199–201 (ethanol)	73	C-44.83(44.85)	H-3.26(3.25)	N-10.46 (10.45)

[a] Melting point range of the compounds

[b] Elemental analysis of C, H, and N were within ± 0.4 % of theoretic value

of concentrated sulfuric acid in ethanol (Mallikarjuna *et al*., 2009); (Suresh Kumar *et al*., 2010a, b, 2012, doi 10.1007/s00044-012-0092-0).

The key intermediate 5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole-2-thiol **9** was prepared by one pot procedure which involves reacting compound **1** with carbon disulfide under strong basic conditions followed by acidification with dilute hydrochloric acid. Condensation of isopropyl intermediates **2**, **6a–6c**, and **9** with substituted benzyl bromides in the presence of potassium hydroxide and methanol produced a series of thio benzyl derivatives **3a–3e**, **7a–7q**, and 2-(substituted benzylthio)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazoles **10a–10h** (Patil *et al*., 2010).

Further on, oxidation of isopropyl thiazole derivatives **3a–3e**, **7a–7q,** and **10a–10h** in the presence of 3-chloro per benzoic acid (*m*-CPBA) and MDC afforded target sulfonyl derivatives **4a–4e**, **8a–8l**, and 2-(substituted benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazoles **11a–11e** (John *et al*., 1994).

Biologic activity

The standard strains were procured from the American Type Culture Collection (ATCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India. The antibacterial activity of the synthesized target compounds (**4a–4e**, **8a–8l**, and **11a–11e**) was performed by broth dilution method (Eweiss *et al*., 1986) against the following standard bacterial strains: *Staphylococcus aureus* (ATCC 11632), *Streptococcus faecalis* (ATCC 14506), *Bacillus subtilis* (ATCC 60511), *Klebsiella pneumoniae* (ATCC 10031), *Escherichia*, and *Pseudomonas aeruginosa* (ATCC

10145), and antifungal activity against Yeasts: *Saccharomyces cerevisiae* (ATCC 9763, Sc) and *Candida tropicalis* (ATCC 1369, CT), mold: *Aspergillus niger* (ATCC 6275). MIC of compounds was determined against *M. tuberculosis* H37Rv strain by broth dilution assay method. The cytotoxicity of the synthesized compounds was evaluated for their cytotoxic potential using A549 (lung adenocarcinoma) cell lines in the presence of fetal bovine serum.

Results and discussion

Chemistry

The IR spectrum of series **4a**–**4e** illustrates stretching band at around 1,322 (assym), and 1,141 (sym) cm^{-1} due to SO_2 group. ^1H NMR spectrum of sulfones depicts the downfield shift of $–SO_2CH_2–$ protons compared with $–SCH_2$ derivatives **3a**–**3e** indicating the formation of oxidized derivatives. ^1H NMR of compound **4a** shows sharp singlet at δ 4.91 accountable for CH_2 group, doublet at δ 1.05 represent 6 protons of terminal isopropyl group. Further molecular ion peaks at 521 and 523 (1:1 isotopic peak for bromine) confirm the molecular weight of compound **4a**.

The ^1H NMR spectra of Schiff bases **8a**–**8l** display singlet between δ 9.53–9.71 ppm corresponding to one proton characteristic of N=CH group and stretching band around 1,324 (assym) and 1,142 (sym) cm^{-1} due to SO_2 group. Further, (M+2) peak at 586.00 in mass spectra is in agreement with molecular formula $C_{22}H_{17}BrF_3N_5O_2S_2$ of compound **8a**.

The ^1H NMR spectrum of compounds **11a**–**11e** illustrate singlet peak between δ 4.91 and 4.98 accounting for SCH_2

Table 2 Antibacterial and antifungal activity of compounds **4a**–**4e**, **8a**–**8l**, and **11a**–**11e** expressed as MIC (μg/mL)

Compounds	Gram-positive organisms[a]			Gram-negative organisms[b]			Fungi[c]		
	Sa	Sf	Bs	Kp	Ec	Pa	Sc	Ct	An
4a	31.25	31.25	16	16	8	16	16	31.25	16
4b	4	8	8	16	16	16	16	31.25	16
4c	8	16	16	16	16	8	16	16	16
4d	16	31.25	31.25	8	4	8	16	16	31.25
4e	31.25	8	8	4	2	8	16	16	31.25
8a	31.25	31.25	16	31.25	16	8	16	16	16
8b	8	16	8	16	4	8	16	4	8
8c	31.25	31.25	8	31.25	8	62.5	62.5	16	31.25
8d	31.25	16	16	8	8	8	62.5	8	8
8e	16	31.25	31.25	8	8	62.5	31.25	31.25	31.25
8f	4	8	8	4	8	8	4	16	4
8g	8	4	4	31.25	16	16	31.25	31.25	31.25
8h	62.5	62.5	8	8	8	62.5	31.25	31.25	125
8i	31.25	31.25	8	31.25	62.5	16	16	8	8
8j	4	8	4	16	8	4	4	8	4
8k	8	8	31.25	31.25	62.5	8	16	8	8
8l	4	8	62.5	31.25	31.25	4	8	16	8
11a	16	31.25	8	8	4	8	8	8	16
11b	8	31.25	31.25	8	4	8	62.5	31.25	31.25
11c	8	16	31.25	2	8	4	8	31.25	125
11d	62.5	16	31.25	8	8	8	4	8	16
11e	8	31.25	8	4	8	4	16	8	8
Ciprofloxacin	≤5	≤5	≤1	≤1	≤1	≤5	–	–	–
Norfloxacin	≤5	≤5	≤1	≤1	≤1	≤5	–	–	–
Flucanozole	–	–	–	–	–	–	≤1	≤1	≤1

[a] The screening organisms. Gram-positive bacteria: *Staphylococcus aureus* (ATCC 11632, Sa), *Streptococus faecalis* (ATCC 14506, Sf), and *Bacillus subtilis* (ATCC 60511, Bs)

[b] The screening organisms. Gram-negative bacteria: *Klebsiella penumoniae* (ATCC 10031, Kp), *Escherichia coli* (ATCC 10536, Ec), and *Pseudomonas aeruginosa* (ATCC 10145, Pa)

[c] The screening organisms. Yeasts: *Saccharomyces cerevisiae* (ATCC 9763, Sc) and *Candida tropicalis* (ATCC 1369, Ct), mold: *Aspergillus niger* (ATCC 6275, An)

group. Further, peaks at 164.25 (oxadiazole-C_2), 153.26 (oxadiazole-C_5) in ^{13}C NMR spectra and m/z at 417.05 in mass spectrum of compound **11c** were found to be in conformity with its molecular formula of the assigned structure.

Biologic activity

The results of the antimicrobial testing of the synthesized target compounds (**4a–4e**, **8a–8l**, and **11a–11e**) against selected Gram-positive, Gram-negative bacteria, yeasts, molds, and *M. tuberculosis* strain H37Rv are illustrated in Tables 2 and 3. The results exhibit interesting trends in structure activity relationship (SAR) studies based on various substitutions at the acidic –SH group.

The –SH proton of compound **2**, **5,** and **9** is acidic enough and substitution reaction could be achieved on this group in the presence of a base (Klimesova *et al*., 2004); (Pomarnacka and Kornicka, 2001). Several recent experiments indicate that incorporation of hydrophobic moieties into the framework of isopropyl thiazole enhance penetration of drug into tissues of mammalian host and into the waxy cell wall of bacterium. This strategy of drug design has been proposed as a vehicle for controlled study of growth cycle of pathogen as well as a means of augmenting fundamental drug activity (Mallikarjuna *et al*., 2009).

Structurally, modifications engendering desirable drug properties (enhanced penetration and decreased resistance) are optimally made at –SH group. Modifying the linkage between triazole/oxadiazole and isopropyl thiazole by SO_2 instead of –SH (i.e., by increasing the oxidation state of sulfur atom) would significantly augment the antimicrobial potency of the heterocycles (John *et al*., 1994) The enhanced antimicrobial ability of the sulphonyl derivatives instead of unsubstituted, or simple SCH_3 substitution is because of the inductive properties of the SO_2 group, which exhibit amphoteric behavior. This amphoteric behavior has been found to play an extremely important role in antibacterial activity by influencing dissociation constant.

In line with the above discussion, our rationale has been to prepare various sulphonyl derivatives (**4a–4e**, **8a–8l**, and **11a–11e**) with enhanced lipophilicity and to examine their efficacy against selected strains of Gram-positive, Gram-negative bacteria, yeasts, molds, and MTB H37Rv.

Evaluating the antimicrobial activity of the synthesized 3-(substituted benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazoles **4a–4e** revealed that compounds were more effective against the Gram-negative bacteria at MIC 2–16 μg/mL. Particularly, 4- triflouromethoxy-substituted compound **4e** exhibited excellent inhibition at MIC 2–8 μg/mL against tested Gram-negative bacteria and 1 μg/mL against *M. tuberculosis* H37Rv. In contradiction to compound **4b** comprising trifluoro methyl substitution which displays moderate to good inhibition against tested Gram-positive organisms. This excellent inhibition of compound **4e** is attributed to the participation of the free electron pairs on the oxygen of SO_2 group by resonance and increased electron density in the aromatic system.

Schiff bases **8a–8l** derived from 1, 2, 4-triazoles are reported to possess significant antimicrobial activity, particularly against *M. tuberculosis* H37Rv because of its increased ability to penetrate bacterial cell (Walczak *et al*., 2004). The SAR studies and antimicrobial activity of Schiff bases **8a–8l** illustrate compound **8b** comprising trifluoro methyl substitution exhibited excellent inhibition against *M. tuberculosis* H37Rv at MIC 0.5 μg/mL compared to its antifungal inhibition at MIC 4–16 μg/mL; this increased activity is attributed to the presence of fluorine atoms (highly electro negative) in the molecule which increases lipophilicity and affects the partitioning of a molecule into membranes and facilitates hydrophobic interactions of the molecule with specific binding sites on either receptor or enzymes (Bazile *et al*., 1992); (Bermejo *et al*., 1999). Compounds **8f** and **8j** also depict good antimicrobial activity and excellent antitubercular inhibition at MIC 2 and 4 μg/mL, respectively.

The antimicrobial activity of 2-(substituted benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazoles **11a–11e**

Table 3 Comparison of in vitro antimycobacterial activity of compounds **4a–4e**, **8a–8l**, and **11a–11e** against drug-sensitive *Mycobacterium tuberculosis* H37Rv strain

Compound	MIC values (μg/mL) of *M. tuberculosis* H37Rv
4a	8
4b	4
4c	8
4d	4
4e	1
8a	8
8b	0.5
8c	8
8d	8
8e	16
8f	2
8g	8
8h	8
8i	8
8j	4
8k	8
8l	4
11a	4
11b	4
11c	2
11d	4
11e	4
Isoniazid	0.25

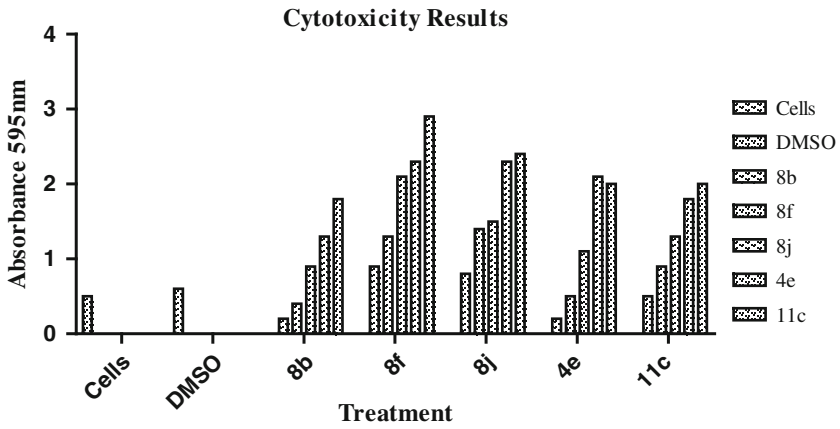


Fig. 1 Cytotoxic activity of compounds **8b**, **8f**, **8j**, **4e**, and **11c** tested in A549 cells by MTT assay. The *bars* reflect the viable cells in each treatment. Cells represent cells alone without any treatment, DMSO denotes the vehicle control. The experiment was done in duplicate with triplicate readings of each experiment

exhibit interesting SAR trends. In drug design, halogen atoms are used to improve penetration through lipid membranes and tissues. They may also present a significant reactivity depending on the structure of the molecule. Compound **11c** comprising 2-CF_3 on phenyl ring demonstrates improved antimicrobial activity against tested bacterial and fungal species and excellent inhibition against *M. tuberculosis* H37Rv at MIC 2 μg/mL. However, compounds **11a** and **11b** possessing 4-Cl and 4-Br substitution on phenyl ring exhibited moderate antimicrobial activity against Gram-positive species and good activity against tested Gram-negative species *K. pneumonia* and *E. coli* than *P. aeruginosa* at MIC 2-8 μg/mL. The SAR analysis indicates the volume of the halogen as a feasible restrictive factor since bromine, the largest halogen, is more deleterious to the antitubercular activity than chlorine or fluorine. Based on these data, we may infer that substituent (R) is a steric and/or restricted position which should be carefully considered in the future design of antitubercular targets.

The most active antitubercular compounds **8b**, **8f**, **8j**, **4e,** and **11c** were tested for their cytotoxic potential using A549 (lung adenocarcinoma) cell lines in the presence of fetal bovine serum. As shown in Fig. 1, compound **8f** showed maximum cytotoxicity at the concentration of 250 mM. The other compounds **8b**, **8j**, **4e**, and **11c** showed appreciable cytotoxicity of about 50 % of the vehicle control at a concentration of 250 mM.

Conclusion

In conclusion, this work demonstrates the synthesis of series of novel clubbed Isopropylthiazole-derived sulphonyl derivatives and their in vitro evaluation of antimicrobial (bacterial and fungal) and antitubercular activity against *M. Tuberculosis* H37Rv strain. Antimicrobial study revealed that compounds **8b**, **8f**, and **11c** demonstrate significant activity against tested Gram-positive and Gram-negative bacteria and fungal species. The in vitro antituberculosis screening of these series showed that all the compounds were active; in particular, compounds **4e** and **8b** exhibited excellent antitubercular activity at MIC 1 and 0.5 μg/mL, respectively, when compared with first line drug such as Isoniazid. The promising in vitro antimicrobial activity and low-toxicity profile of the clubbed Isopropylthiazole class of compounds make them certain promising molecules for further lead optimization in the development of novel antimycobacterial agents.

Experimental

Chemical protocols

Melting points were determined in open capillary tubes in a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on Shimadzu FT-IR 157, ^{1}H NMR, and ^{13}C NMR spectra were recorded (in $CDCl_3$/DMSO-d6) on a Bruker spectrometer at 300/400 MHz using TMS as an internal standard. Mass spectra (EI) on (AMD-604) mass spectrometer operating at 70 eV. Elemental analysis was performed on Thermo Finnigan Flash (EA 1112 CHNS Analyzer).

*General procedure to synthesize sulfonyl derivatives **4a–4e**, **8a–8l,** and 2-(substituted benzylsulfonyl)-5-(4- isopropylthiazol-2-yl)-1,3,4-oxadiazoles **11a–11e***

To a solution of thio derivatives **3a–3e**, **7a–7q**, and **10a–10h** (2 mmol) in CH_2Cl_2 (5 mL) m-CPBA (*m*-chloroperbenzoic acid) (75 % purity, 6.8 mmol) was added at 0–5 °C. The mixture was stirred for 30 min, and the completion of the reaction was monitored through TLC. After the completion of the reaction, reaction mixture was quenched with 20 % aqueous $Na_2S_2O_3$ solution. The organic phase was separated and the aqueous phase was washed with 1 M NaOH solution and brine, dried over

anhydrous $Na_2S_2O_4$, filtered, and concentrated to afford target compounds in excellent yields.

Synthesis of 3-(4-bromo-2-fluorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole ***4a*** IR (KBr) ν_{max}, cm^{-1}: 1611 (C=N), 3057 (Ar C–H), 1322 (assym), 1141 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.89(m, 1H, isopropyl), 4.91(s, 2H, CH_2), 7.3–7.7 (m, 8H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 21.34 (terminal $2CH_3$-isopropyl), 24.44 (tertiary-1C- isopropyl), 53.43 (CH_2), 112.10 (thiazole-C5), 121–155 (Ar), 143.23 (triazole-C5), 160.61 (thiazole C2), 165.32 (thiazole C4).

m/e: 523.01 (M+2), 521.01 (100.0 %).

Synthesis of 3-(4-(trifluoromethyl)benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole ***4b*** IR (KBr) ν_{max}, cm^{-1}: 1611 (C=N),3054 (Ar C–H), 1325 (assym), 1146 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.02 (m, 1H, isopropyl), 4.98(s, 2H, CH_2), 7.2–7.6 (m, 9H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 11.16 (thiazole-C5), 22.11 (terminal $2CH_3$-isopropyl), 24.32 (tertiary-1C- isopropyl), 51.62(CH_2), 122–155 (Ar), 141.44 (triazole-C5), 160.24 (thiazole C2), 164.58 (thiazole C4).

m/e: 492.09 (100.0 %).

Synthesis of 3-(4-bromobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole ***4c*** IR (KBr) ν_{max}, cm^{-1}: 1611 (C=N), 3052 (Ar C–H), 1327 (assym), 1145 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.06 (d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.82 (m, 1H, isopropyl), 5.05(s, 2H, CH_2), 6.9–7.9 (m, 9H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 11.22 (thiazole-C5), 21.51 (terminal $2CH_3$-isopropyl), 23.11 (tertiary-1C- isopropyl), 51.62(CH_2), 122–165 (Ar), 164.51 (thiazole C4), 161.15 (thiazole C2), 142.59 (triazole-C5).

m/e: 505.01 (M+2), 503.02 (100.0 %).

Synthesis of 3-(5-chloro-2-fluorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole ***4d*** IR (KBr) ν_{max}, cm^{-1}: 1615 (C=N), 3057 (Ar C–H), 1329 (assym), 1152 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.82 (m, 1H, isopropyl), 4.96(s, 2H, CH_2), 7.3–7.6 (m, 8H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 11.27 (thiazole-C5), 21.53 (terminal $2CH_3$-isopropyl), 23.16 (tertiary-1C-isopropyl), 51.63(CH_2), 120–168 (Ar), 141.44 (triazole-C5), 162.73 (thiazole C4), 164.62 (thiazole C2).

m/e: 475.7 (100.0 %).

Synthesis of 3-(4-(trifluoromethoxy)benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4-phenyl-4H-1,2,4-triazole ***4e*** IR (KBr) ν_{max}, cm^{-1}: 1622 (C=N), 3053 (Ar C–H), 1325 (assym), 1147 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.32 (m, 1H, isopropyl), 5.04(s, 2H, CH_2), 7.1–7.6 (m, 9H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 11.65 (thiazole-C5), 21.14 (terminal $2CH_3$-isopropyl), 25.36 (tertiary-1C- isopropyl), 51.01(CH_2), 120–168 (Ar), 142.66 (triazole-C5), 161.58 (thiazole C4), 163.65 (thiazole C2).

m/e: 510.09 (M+2), 509.09 (M+1), 508.09 (100.0 %).

Synthesis of N-(2,6-difluorobenzylidene)-3-(4-bromo-2-fluorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazole-4-amine ***8a*** IR (KBr) ν_{max}, cm^{-1}: 3357 (NH), 1654 (C=N), 1326 (assym), 1144 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.32(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.98 (m, 1H, isopropyl), 5.09(s, 2H, CH_2), 7.3–7.9 (m, 6H, phenyl and 1H of thiazole-C5), 9.53 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 23.12 (terminal $2CH_3$-isopropyl), 30.123 (tertiary-1C- isopropyl), 52.14 (CH_2), 116.19 (thiazole-C5), 125–132 (Ar), 142.51 (triazole-C5), 153.14 (thiazole C2), 161.21 (thiazole C4), 164.44 (HC=N).

m/e: 586.00 (M+2, 84.3 %), 463.1 (3.8 %), 102.1 (11.8 %).

Synthesis of N-(2,6-difluorobenzylidene)-3-(4-(trifluoromethyl)benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8b*** IR (KBr) ν_{max}, cm^{-1}: 3342 (NH), 1621 (C=N), 1323 (assym), 1145 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.08(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.94 (m, 1H, isopropyl), 5.22(s, 2H, CH_2), 7.3–7.8 (m, 7H, phenyl and 1H of thiazole-C5), 9.65 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.55 (terminal $2CH_3$-isopropyl), 29.12 (tertiary-1C- isopropyl), 52.60 (CH_2), 116.24 (thiazole-C5), 124–138 (Ar), 141.54 (triazole-C5), 152.31 (thiazole C2), 161.12 (thiazole C4), 164.44 (HC=N).

m/e: 557.3 (M+2, 92 %), 556.3 (M+1), 417.3 (7.0 %), 432.3

Synthesis of N-(2,6-difluorobenzylidene)-3-(4-chlorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-

amine ***8c*** IR (KBr) ν_{max}, cm^{-1}: 3351 (NH), 1644 (C=N), 1329 (assym), 1146 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.95 (m, 1H, isopropyl), 5.05(s, 2H, CH_2), 7.1–7.7 (m, 7H, phenyl and 1H of thiazole-C5), 9.62 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.61 (terminal $2CH_3$-isopropyl), 29.16 (tertiary-1C- isopropyl), 53.42 (CH_2), 116.32 (thiazole-C5), 124–141 (Ar), 141.62 (triazole-C5), 152.51 (thiazole C2), 161.22 (thiazole C4), 164.31 (HC=N).

m/e: 523.87 (M+2), 522.06 (M+1), 521.96.

Synthesis of N-(2,6-difluorobenzylidene)-3-(4-bromobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8d*** IR (KBr) ν_{max}, cm^{-1}: 3353 (NH), 1648 (C=N),1322 (assym), 1143 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.91 (m, 1H, isopropyl), 5.12(s, 2H, CH_2), 7.3–7.8 (m, 7H, phenyl and 1H of thiazole-C5), 9.63 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.51 (terminal $2CH_3$-isopropyl), 29.44 (tertiary-1C- isopropyl), 54.46 (CH_2), 116.55 (thiazole-C5), 124–139 (Ar), 141.32 (triazole-C5), 152.69 (thiazole C2), 161.62 (thiazole C4), 164.58 (HC=N).

m/e: 566.01 (100.0 %).

Synthesis of 3-(4-bromo-2-fluorobenzylsulfonyl)-N-(4-fluorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8e*** IR (KBr) ν_{max}, cm^{-1}: 3332 (NH), 1654 (C=N), 1329 (assym), 1145 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.06(d, $J = 8.5$ Hz, 6H, $2CH_3$), 2.95 (m, 1H, isopropyl), 5.01(s, 2H, CH_2), 7.3–7.8 (m, 7H, phenyl and 1H of thiazole-C5), 9.62 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.61 (terminal $2CH_3$-isopropyl), 27.25 (tertiary-1C- isopropyl), 53.82 (CH_2), 112.54 (thiazole-C5), 124–141 (Ar), 141.21 (triazole-C5), 154.31 (thiazole C2), 161.32 (thiazole C4), 164.62 (HC=N).

m/e: 568.61 (M+2, 100.0 %). 566.01 (100.0 %).

Synthesis of 3-(4-(trifluoromethyl)benzylsulfonyl)-N-(4-fluorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazole-4-amine ***8f*** IR (KBr) ν_{max}, cm^{-1}: 3351 (NH), 1622 (C=N), 1325 (assym), 1143 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.03 (m, 1H, isopropyl), 4.98(s, 2H, CH_2), 7.3–7.8 (m, 8H, phenyl and 1H of thiazole-C5), 9.71 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.35 (terminal $2CH_3$-isopropyl), 27.21 (tertiary-1C- isopropyl), 53.14 (CH_2), 115.14 (thiazole-C5), 122–148 (Ar), 140.21 (triazole-C5), 154.22 (thiazole C2), 160.55 (thiazole C4), 165.67 (HC=N).

m/e: 537.10 (100.0 %), 538.10 (M+1).

Synthesis of 3-(4-chlorobenzylsulfonyl)-N-(4-fluorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8g*** IR (KBr) ν_{max}, cm^{-1}: 3325 (NH), 1636 (C=N), 1325 (assym), 1143 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.05 (d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.05 (m, 1H, isopropyl), 5.04(s, 2H, CH_2), 7.3–7.8 (m, 8H, phenyl and 1H of thiazole-C5), 9.65 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.68 (terminal $2CH_3$-isopropyl), 27.41 (tertiary-1C- isopropyl), 52.68 (CH_2), 115.24 (thiazole-C5), 124–156 (Ar), 140.21 (triazole-C5), 154.11 (thiazole C2), 160.32 (thiazole C4), 165.54 (HC=N).

m/e: 506.07 (M+2), 504.07 (100.0 %).

Synthesis of 3-(4-bromobenzylsulfonyl)-N-(4-fluorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8h*** IR (KBr) ν_{max}, cm^{-1}: 3354 (NH), 1625 (C=N), 1328 (assym), 1144 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.28(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.02 (m, 1H, isopropyl), 5.02(s, 2H, CH_2), 7.3–7.8 (m, 8H, phenyl and 1H of thiazole-C5), 9.62 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.66 (terminal $2CH_3$-isopropyl), 27.51 (tertiary-1C-isopropyl), 52.21 (CH_2), 115.91 (thiazole-C5), 124–155 (Ar), 140.21 (triazole-C5), 154.65 (thiazole C2), 160.11 (thiazole C4), 165.22 (HC=N).

m/e: 550.23 (M+2), 549.13 (M+2), 548.49 (100.0 %).

Synthesis of 3-(4-bromo-2-fluorobenzylsulfonyl)-N-(4-chlorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8i*** IR (KBr) ν_{max}, cm^{-1}: 3323(NH), 1651 (C=N), 1327 (assym), 1150 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.05(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.09 (m, 1H, isopropyl), 5.05(s, 2H, CH_2), 7.3–7.8 (m, 7H, phenyl and 1H of thiazole-C5), 9.63 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.41 (terminal $2CH_3$-isopropyl), 27.68 (tertiary-1C- isopropyl), 52.47 (CH_2), 115.61 (thiazole-C5), 124–158 (Ar), 140.61 (triazole-C5), 153.26 (thiazole C2), 161.62 (thiazole C4), 165.44 (HC=N).

m/e: 584.9 (M+2), 582.36 (100.0 %).

Synthesis of 3-(4-(trifluoromethyl)benzylsulfonyl)-N-(4-chlorobenzylidene)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8j*** IR (KBr) ν_{max}, cm^{-1}: 3352 (NH), 1623 (C=N), 1324 (assym), 1147 (sym) SO_2.

^1H NMR (DMSO-d6, 300 MHz) δ: 1.04(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.08 (m, 1H, isopropyl), 4.97(s, 2H, CH_2), 7.3–7.8 (m, 8H, phenyl and 1H of thiazole-C5), 9.62 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 23.19 (terminal $2CH_3$-isopropyl), 26.61 (tertiary-1C- isopropyl), 51.49 (CH_2), 114.61 (thiazole-C5), 122–158 (Ar), 144.33 (triazole-C5), 154.22 (thiazole C2), 160.55 (thiazole C4), 163.36 (HC=N).

m/e: 556.06 (M+2), 554.07 (100.0 %).

Synthesis of N-(4-chlorobenzylidene)-3-(4-chlorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8k*** IR (KBr) ν_{max}, cm^{-1}: 3361 (NH), 1611 (C=N), 1324 (assym), 1142 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.04(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.01 (m, 1H, isopropyl), 4.99(s, 2H, CH_2), 7.3–7.8 (m, 8H, phenyl and 1H of thiazole-C5), 9.64 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 23.44 (terminal $2CH_3$-isopropyl), 26.31 (tertiary-1C- isopropyl), 52.32 (CH_2), 115.60 (thiazole-C5), 121–155 (Ar), 143.53 (triazole-C5), 155.61 (thiazole C2), 161.32 (thiazole C4), 164.44 (HC=N).

m/e: 521.04 (M + 2), 519.04 (100.0 %).

Synthesis of N-(2,6-difluorobenzylidene)-3-(benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-4H-1,2,4-triazol-4-amine ***8l*** IR (KBr) ν_{max}, cm^{-1}: 3351 (NH), 1644 (C=N), 1329 (assym), 1146 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.02(d, $J = 8.5$ Hz, 6H, $2CH_3$) 2.99 (m, 1H, isopropyl), 4.98(s, 2H, CH_2), 7.3–7.7 (m, 8H, phenyl and 1H of thiazole-C5), 9.62 (s, 1H, N=CH).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 24.61 (terminal $2CH_3$-isopropyl), 29.16 (tertiary-1C-isopropyl), 53.42 (CH_2), 116.32 (thiazole-C5), 124–141 (Ar), 141.62 (triazole-C5), 152.51 (thiazole C2), 161.22 (thiazole C4), 164.31 (HC=N).

m/e: 488.10 (M+1), 349.1, 250.2.

Synthesis of 2-(4-chlorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole ***11a*** IR (KBr) ν_{max}, cm^{-1}: 1671 (C=N), 3057 (Ar C–H), 1326 (assym), 1144 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.02(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.03 (m, 1H, isopropyl), 4.94(s, 2H, CH_2), 7.2–7.7 (m, 4H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.41 (terminal $2CH_3$-isopropyl), 32.07 (tertiary-1C-isopropyl), 50.25(CH_2), 115.32 (thiazole-C5), 122–165 (Ar), 151.21 (thiazole-C2), 154.54 (oxadiazole-C5), 161.95 (thiazole C4), 165.71 (oxadiazole-C2).

m/e: 385.82 (M+2), 383.91 (100.0 %).

Synthesis of 2-(4-bromobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole ***11b*** IR (KBr) ν_{max}, cm^{-1}: 1671 (C=N), 3057 (Ar C–H), 1325 (assym), 1142 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.31(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.05 (m, 1H, isopropyl), 4.98(s, 2H, CH_2), 7.2–7.7 (m, 4H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 21.36 (terminal $2CH_3$-isopropyl), 31.36 (tertiary-1C-isopropyl), 51.44(CH_2), 114.12 (thiazole-C5), 122–175 (Ar), 154.25 (oxadiazole-C5), 159.05 (thiazole-C2), 161.55 (thiazole C4), 164.25 (oxadiazole-C2).

m/e: 428.97 (M+2), 427.97 (M+1), 425.97 (93.1 %).

Synthesis of 2-(2-(trifluoromethyl)benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole ***11c*** IR (KBr) ν_{max}, cm^{-1}: 1632 (C=N), 3059 (Ar C–H), 1325 (assym), 1148 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.35(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.14 (m, 1H, isopropyl), 4.91(s, 2H, CH_2), 7.4–7.9 (m, 4H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.25 (terminal $2CH_3$-isopropyl), 32.55 (tertiary-1C-isopropyl), 52.15(CH_2), 113.25 (thiazole-C5), 122–175 (Ar), 153.26 (oxadiazole-C5), 158.36(thiazole-C2), 160.55 (thiazole C4), 164.25 (oxadiazole-C2).

m/e: 418.05 (M+1), 417.05 (100.0 %).

Synthesis of 2-(benzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole ***11d*** IR (KBr) ν_{max}, cm^{-1}: 1628 (C=N), 3052 (Ar C–H), 1327 (assym), 1151 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.22(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.04 (m, 1H, isopropyl), 4.92(s, 2H, CH_2), 7.2–7.8 (m, 5H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 22.25 (terminal $2CH_3$-isopropyl), 32.55 (tertiary-1C-isopropyl), 52.15(CH_2), 113.25 (thiazole-C5), 122–175 (Ar), 157.54(thiazole-C2), 152.25 (oxadiazole-C5), 161.25 (thiazole C4), 165.22 (oxadiazole-C2).

m/e: 351.06 (M+2),350.06 (M+1), 349.06 (100.0 %).

Synthesis of 2-(5-chloro-2-fluorobenzylsulfonyl)-5-(4-isopropylthiazol-2-yl)-1,3,4-oxadiazole ***11e*** IR (KBr) ν_{max}, cm^{-1}: 1622 (C=N), 3056 (Ar C–H), 1324 (assym), 1157 (sym) SO_2.

^{1}H NMR (DMSO-d6, 300 MHz) δ: 1.32(d, $J = 8.5$ Hz, 6H, $2CH_3$), 3.11 (m, 1H, isopropyl), 4.94(s, 2H, CH_2), 7.2–7.8 (m, 3H, phenyl and 1H of thiazole-C5).

^{13}C NMR (DMSO-d6, 300 MHz) δ: 21.36 (terminal $2CH_3$-isopropyl), 32.44 (tertiary-1C-isopropyl), 51.74(CH_2), 112.65 (thiazole-C5), 122–168 (Ar), 152.11(thiazole-C2), 154.38 (oxadiazole-C5), 164.32 (thiazole C4), 165.15 (oxadiazole-C2).

m/e: 400.91 (100.0 %).

Biologic protocol

Antimicrobial activity

The antimicrobial susceptibility testing was performed in vitro by broth microdilution method (Hassan *et al*., 1983);

(Khalil *et al*., 1993). The MIC determination of the synthesized compounds was carried out in side-by-side comparison with ciprofloxacin and norfloxacin against Gram-positive bacteria (*S. aureus*, *S. faecalis*, *B. subtilis*) and Gram-negative bacteria (*K. penumoniae*, *E. coli*, *P. aeruginosa*). The antifungal activity was assayed against yeasts (*C. tropicalis*, *S. cerevisiae*) and molds (*A. niger*). The minimal inhibitory concentrations (MIC, μg/mL) were defined as the lowest concentrations of a compound that completely inhibited the growth of each strain. Test compounds (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL) and then diluted in culture medium (Mueller–Hinton Broth for bacteria and Sabouraud Liquid Medium for fungi) to obtain final concentrations of 0.5, 1, 2, 4, 8, 16, 31.25, 62.5, 125, 250, and 500 μg/mL. DMSO never exceeded 1 % v/v. The tubes were inoculated with 105 cfu mL^{-1} (colony-forming unit/mL) and incubated at 37 °C for 24 h. The growth control consisting of media (positive control) and media with DMSO (negative control) at same dilutions as used in the experiments were employed.

Antitubercular activity

The preliminary antitubercular screening for the test compounds were obtained for MTB H37Rv; MIC of each drug was determined by broth dilution assay (Goto *et al*., 1981) and is defined as the lowest concentration of drug that inhibits ≤99 % of bacterial population present at beginning of assay. A frozen culture in Middlebrook 7H9 broth supplemented with 10 % albumin-dextrosecatalase and 0.2 % glycerol was thawed and diluted in broth to 105 cfu mL^{-1} (colony-forming unit/mL) dilutions. Each test compound was dissolved in DMSO and then diluted in broth twice at desired concentration. The final concentration of DMSO in assay medium was 1.3 %. Each U-tube was then inoculated with 0.05 mL of standardized culture and then incubated at 37 °C for 21 days. The growth in U-tubes was compared with visibility against positive control (without drug), negative control (without drug and inoculum), and with standard isoniazid.

MTT assay for cell viability

Toxicity of compounds **8b**, **8f**, **8j**, **4e**, and **11c** in A549 cell lines in the presence of 10 and 0.2 % FBS was determined by 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide reduction assay (MTT) (Mosmann, 1983). The compounds were dissolved in DMSO at 10 mM concentration and stored at −20 °C. The dilutions were made in culture medium before treatment.

Acknowledgments We thank the management of St. Johns Pharmacy College, Bangalore, for providing necessary facilities. We are grateful to Dr. K.G. Bhat, Maratha Mandal's Dental College, Hospital and Research Centre, Belgaum, India, for providing the facilities to determine the antibacterial and antitubercular activities. We also wish to thank IISC, Bangalore, India, for providing IR, NMR, mass spectra, and elemental analysis data.

References

Babaoglu K, Page MA, Jones VC, McNeil MR, Dong C, Naismith JH, Lee RE (2003) Novel inhibitors of an emerging target in Mycobacterium tuberculosis; substituted thiazolidinones as inhibitors of dTDP-rhamnose synthesis. Bioorg Med Chem Lett 13:3227–3230

Ballell L, Field RA, Duncan K, Young RJ (2005) New small-molecule synthetic antimycobacterials. Antimicrob Agents Chemother 49:2153–2163

Bazile S, Moreau N, Bouzard D, Essiz M (1992) Relationships among antibacterial activity, inhibition of DNA gyrase, and intracellular accumulation of 11 fluoroquinolones. Antimicrob Agents Chemother 36:2622–2627

Bermejo M, Merino V, Garrigues TM, Pla Delfina JM, Mulet A, Vizet P, Trouiller G, Mercier C (1999) Validation of a biophysical drug absorption model by the PATQSAR system. J Pharm Sci 88:398–405

Cegielski JP, Chin DP, Espinal MA, Frieden TR, Rodriquez Cruz R, Talbot EA, Weil DE, Zaleskis R, Raviglione MC (2002) The global tuberculosis situation. Progress and problems in the 20th century, prospects for the 21st century. Infect Dis Clin North Am 161:1–58

Eweiss NF, Bahajaj AA, Elsherbini EA (1986) Synthesis of heterocycles. Part VI. Synthesis and antimicrobial activity of some 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives. J Heterocycl Chem 23:1451–1458

Goto S, Jo K, Kawakita T, Misuhashi S, Nishino T, Ohasawa N, Tanami H (1981) Determination method for minimum inhibitory concentration. Jpn J Chemother 29:76–79

Goulding CW, Apostol M, Anderson DH, Gill HS, Smith CV, Kuo MR, Yang JK, Waldo GS, Suh SW, Chauhan R, Kale A, Bachhawat N, Mande SC, Johnston JM, Lott JS, Baker EN, Arcus VL, Leys D, McLean KJ, Munro AW, Berendzen J, Sharma V, Park MS, Eisenberg D, Sacchettini J, Alber T, Rupp B, Jacobs W Jr, Terwilliger TC (2002) The TB structural genomics consortium: providing a structural foundation for drug discovery. Curr Drug Targets Infect Disord 2:121–141

Hassan E, Al-Ashmawi MI, Abdel-Fattah B (1983) Synthesis and antimicrobial testing of certain oxadiazoline and triazole derivatives. Pharmazie 38:833–835

John MK, Michael AS, Christopher RD, Francis PM, Mark WD, Ann Marie LO, John HK, Herbert JK, Timothy CM (1994) 5-Aryl-3-(alkylthio)-4H-1,2,4-triazoles as selective antagonists of strychnine-induced convulsions and potential antispastic agents. J Med Chem 37:125–132

Khalaf AI, Waigh RD, Drummond AJ, Pringle B, McGroarty I, Skellern GG, Suckling CJ (2004) Distamycin analogues with enhanced lipophilicity: synthesis and antimicrobial activity. J Med Chem 47:2133–2156

Khalil MA, El-Sayed OA, El-Shamny HA (1993) Synthesis and antimicrobial evaluation of novel oxa(thia)diazolylquinolines and oxa(thia)diazepino[7,6-b] quinolines. Arch Pharm 326: 489–492

Klimesova V, Zahajska L, Waisser K, Kaustova J, Mollmann U (2004) Synthesis and antimycobacterial activity of 1,2,4-triazole 3-benzylsulfanyl derivatives. IL Farmaco 59:279–288

Mallikarjuna BP, Sastry BS, Suresh Kumar GV, Rajendra Prasad Y, Chandrashekar SM, Sathisha K (2009) Synthesis of new 4-isopropylthiazole hydrazide analogs and some derived clubbed triazole, oxadiazole ring systems—a novel class of potential antibacterial, antifungal and antitubercular agents. Eur J Med Chem 44:4739–4746

Mosmann T (1983) Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxic assays. J Immunol Methods 65:55–63

Neu HC (1992) The crisis in antibiotic resistance. Science 257:1064–1072

Patil BS, Krishnamurthy G, Bhojya Naik HS, Latthe PR, Ghate M (2010) Synthesis, characterization and antimicrobial studies of 2-(4-methoxy-phenyl)-5-methyl-4-(2-arylsulfanyl-ethyl)-2,4-dihydro-[1,2,4] triazolo-3-ones and their corresponding sulfones. Eur J Med Chem 45:3329–3334

Pomarnacka E, Kornicka A (2001) Synthesis and in vitro anticancer and anti-HIV evaluation of new 2-mercaptobenzenesulfonamides. IL Farmaco 56:571–577

Shiradkar MR, Suresh Kumar GV, Dasari V, Tatikonda S, Akula KC, Shah R (2007a) Clubbed triazoles: a novel approach to antitubercular drugs. Eur J Med Chem 42:807–816

Shiradkar MR, Mallikarjun BP, Bhetalabhotala S, Akula KC, Tupe DA, Pinninti RR, Thummanagoti S (2007b) A novel approach to cyclin-dependent kinase 5/p25 inhibitors: a potential treatment for Alzheimer's disease. Bioorg Med Chem Lett 15:6397–6406

Spigelman MK (2007) New tuberculosis therapeutics: a growing pipeline. J Infect Dis 196:828–834

Suresh Kumar GV, Rajendraprasad Y, Mallikarjuna BP, Chandrashekar SM, Kistayya C (2010a) Synthesis of some novel 2-substituted-5-[isopropylthiazole] clubbed 1,2,4-triazole and 1,3,4-oxadiazoles as potential antimicrobial and antitubercular agents. Eur J Med Chem 45:2063–2074

Suresh Kumar GV, Rajendra Prasad Y, Mallikarjuna BP, Chandrashekar SM (2010b) Synthesis and pharmacological evaluation of clubbed isopropylthiazole derived triazolothiadiazoles, triazolothiadiazines and mannich bases as potential antimicrobial and antitubercular agents. Eur J Med Chem 45:5120–5129

Suresh Kumar GV, Rajendra Prasad Y, Chandrashekar SM (2012) Synthesis and pharmacological evaluation of novel 4-isopropylthiazole-4-phenyl-1,2,4-triazole derivatives as potential antimicrobial and antitubercular agents. Med Chem Res. doi:10.1007/s00044-012-0092-0

Walczak K, Gondela A, Suwinski J (2004) Synthesis and antituberculosis activity of *N*-aryl-*C*-nitroazoles. Eur J Med Chem 39:849–853