Medicinal Chemistry Research
https://doi.org/10.1007/s00044-019-02310-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimycobacterial evaluation of new 5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-2-arylthiazole derivatives

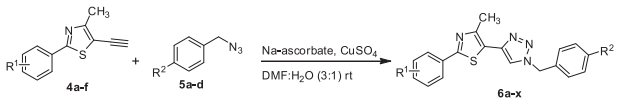
Vikas Shinde[1] · Pramod Mahulikar[1] · Pravin C. Mhaske[2] · Shakti Chakraborty[3] · Amit Choudhari[3] · Siddharth Phalle[4] · Prafulla Choudhari[4] · Dhiman Sarkar[3]

Received: 11 October 2018 / Accepted: 6 February 2019

Abstract

A new series of 5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-4-methyl-2-arylthiazole derivatives, **6a**−**w** have been synthesized by click reaction of substituted benzylazide, **5a**−**d** with 5-ethynyl-4-methyl-2-substituted phenylthiazole, **4a**−**f**. The starting compounds 4-ethynyl-2-substituted phenylthiazole (**4a**−**f**) were synthesized from the corresponding thiazole aldehyde by using the Ohira−Bestmann reagent. The structure of the synthesized compounds was determined by spectral analysis. All the synthesized compounds were screened for their preliminary antitubercular activity against *Mycobacterium tuberculosis* H37Ra (MTB, ATCC 25177). Most of the synthesized compounds reported good activity against *M. tuberculosis* H37Ra strain with IC_{50} range of 0.58−8.23 µg/mL. Compounds **6g** and **6k** reported good antitubercular activity with MIC_{90} values of 4.71 and 2.22 µg/mL, respectively. Potential antimycobacterial activity suggested that these compounds could serve as good lead compounds for further optimization and development of a newer antitubercular candidate.

Graphical Abstract



Keywords Thiazole · 1,2,3-Triazole · Ohira−Bestmann reagent · Antitubercular activity · Molecular docking

Introduction

Mycobacterium tuberculosis (MTB) is among the most challenging bacterial infections declared by the World Health Organization (WHO). In 2015, WHO estimated that globally 10.4 million people were diagnosed with TB and it was one of the top 10 causes of death worldwide (WHO Tuberculosis Fact Sheet 2016). In addition, *Mycobacterium bovis* BCG vaccination is also among the most commonly administered vaccines worldwide (Wang et al. 2013). The spontaneous mutations in genes of the pathogenic strains increase the number of multi-drug-resistant and extensively drug-resistant pathogens; therefore, a need for new classes of antimicrobial agents is warranted. The increase in antibiotic resistance has encouraged the researchers to search for new compounds, which are active against acute as well as chronic forms of tuberculosis (Shenoi and Friedland

Supplementary information The online version of this article (https://doi.org/10.1007/s00044-019-02310-y) contains supplementary material, which is available to authorized users.

✉ Pramod Mahulikar
mahulikarpp@rediffmail.com

✉ Pravin C. Mhaske
mhaskepc18@gmail.com

[1] School of Chemical Sciences, North Maharashtra University, Jalgaon, Maharashtra, India

[2] Post Graduate Department of Chemistry, S.P. Mandali's Sir Parashurambhau College, Savitribai Phule Pune University, Tilak Road, Pune, Maharashtra 411030, India

[3] CombiChemBio Resource Centre, CSIR-National Chemical Laboratory, Pune, Maharashtra 411008, India

[4] Department of Pharmaceutical Chemistry, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra 413016, India

Published online: 13 April 2019

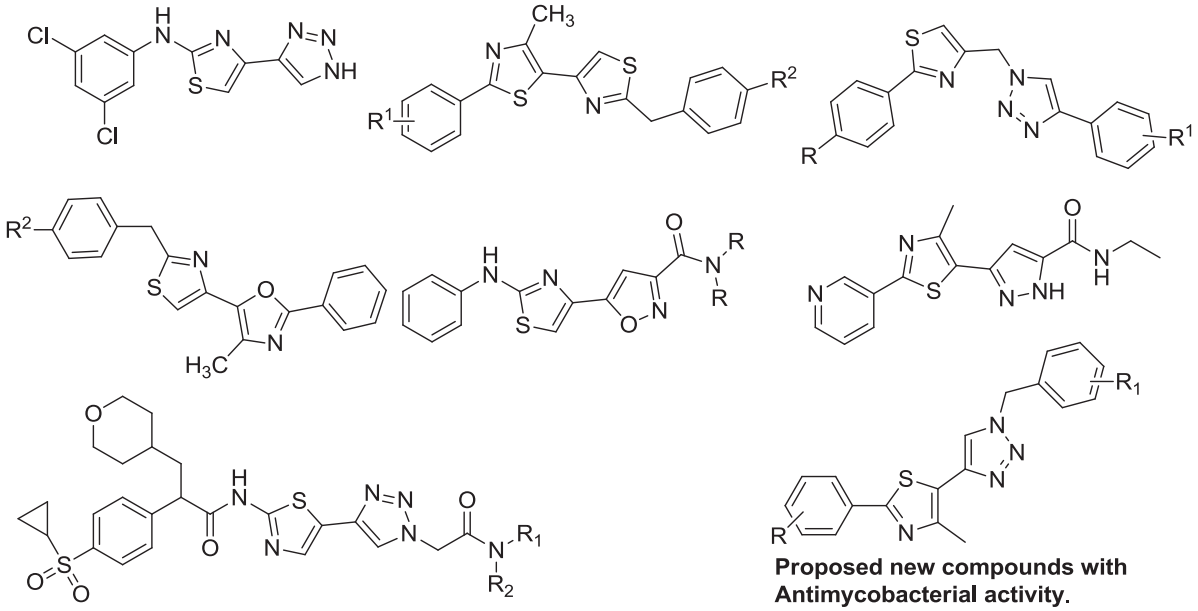


Fig. 1 Representative antitubercular active thiazolyl-triazole compounds and the new proposed analogs

2009, Ramesh et al. 2016, Jeankumar et al. 2016, Tantry et al. 2017).

The synthesis of a new hybrid architecture of two or more bioactive scaffolds is one of the powerful tools used in new drug discovery. The synthesis of triazole and thiazole pharmacophore units has received much attention due to their antitubercular activity (Fig. 1). 1,2,3-Triazole, 1,2,4-triazole, and their derivatives are an important class of bioactive molecules that exhibit significant pharmacological activities, such as antitubercular (Ramesh et al. 2016, Jeankumar et al. 2016, Patpi et al. 2012, Shaikh et al. 2015, Shanmugavelan et al. 2011, Keri et al. 2015, Gonzaga et al. 2013, Krishna et al. 2014, Foks et al. 2005, Jadhav et al. 2009, Shiradkar et al. 2007), antimicrobial (Chen et al. 2000, Holla et al. 2005, Dongamanti et al. 2014, Wang et al. 2017), analgesic, anti-inflammatory and ulcerogenic (Hafez et al. 2008), antineoplastic (Passannanti et al. 1998), anticonvulsant (Guan et al. 2007), antiproliferative (Dmitry et al. 2014), Alzheimer (Christian et al. 2008), antiviral activity (Farghaly et al. 2006), anticancer (Jeong et al. 2015, Reddy et al. 2015), antimalarial (Gujjar et al. 2009), β-lactamase inhibitors (Weide et al. 2010), fungicidal and antitubercular (Kathiravan et al. 2012, Shirude et al. 2013) activities, and many more.

Thiazole and its derivatives are an important structure in medicinal chemistry that could provide a rich spectrum of biological activities, such as antitubercular (Abhale et al. 2015, 2016, 2017, Jeankumar et al. 2012, Samala et al. 2016, Tomasic et al. 2015), antimicrobial (Davyt et al. 2010, Kashyap et al. 2012, Oniga et al. 2012, 2015, Shiran et al. 2013, Skedelj et al. 2013, Gaikwad et al. 2012a, b), anti-inflammatory (Rostom et al. 2009, Shelke et al. 2012, Kouatly et al. 2008, Giri et al. 2009), antiviral (Barradas et al. 2011), CNS-active agents (Mishra et al. 2015), and anticancer activities (Liu et al. 2009, Pandya et al. 2015). Thiazole clubbed with triazole reported antitubercular (Shiradkar et al. 2007, Shinde et al. 2018) and antimicrobial (Güzeldemirci and Küçükbasmac 2010, Karale et al. 2014) activities. Substituted 2-amino thiazole clubbed with 1,2,3-triazole was reported as inhibitors of leukemia stem cells (Li et al. 2018), glucokinase activators (Liu et al. 2011), and antitubercular activities (Azzali et al. 2017). These reports encouraged facilitating the structural diversity and biological importance of 1,2,3-triazole and thiazoles nucleus in medicinal chemistry, and have made them attractive targets for synthesis.

Mycobacterial fatty acid biosynthesis is a vital process for the growth of mycobacterium. Fatty acid biosynthesis results in the mycolic acid-rich cell wall, a major reason behind the generation of MDR and XDR types of tuberculosis. Fatty acid biosynthesis is an attractive target due to its conserved nature and its contribution in mycobacterium growth. *Enoyl acyl carrier protein reductase* (*INHA*) is a key enzyme involved in the type II fatty acid biosynthesis that regulates the reduction of 2-*trans*-enoyl-ACP (acyl carrier protein) to generate a reduced enoyl thioester–ACP substrate. This enoyl thioester–ACP substrate takes part in the mycolic acid synthesis to generate mycolic acid. Inhibition of *enoyl acyl carrier protein reductase* will lead to inhibition of the growth and survival of the *Mycobacterium* in the host (Martinelli et al. 2017, Shanthi and Ramanathan 2014, Patil et al. 2016).

Keeping in mind the biological significance of 1,2,3-triazole and thiazole derivatives, we report herein the synthesis of 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole, **6a**−**x** as potential antimycobacterial agents.

Materials and methods

Chemistry

All the reactions were monitored by thin-layer chromatography (TLC), performed on Merck 60 F-254 silica gel plates with visualization by UV light. The melting points were determined in capillary tubes in silicon oil bath using a Veego melting point apparatus and are uncorrected. ^{1}H NMR (500-MHz) and ^{13}C NMR (126-MHz) spectra were recorded on BRUKER AVANCE II 500 NMR spectrometer. Chemical shifts are reported from an internal tetramethylsilane standard and are given in δ units. All the target compounds were purified by column chromatography using silica gel (100–200 mesh). The starting compounds 4-methyl-2-arylthiazole-5-carbaldehyde (**3a**−**f**) were synthesized from a known literature method (Shinde et al. 2018).

General procedure for the synthesis of 5-ethynyl-4-methyl-2-phenylthiazole (4a)

To an ice-cold solution of freshly prepared diethyl (1-diazo-2-oxopropyl)phosphonate (13 mmol) and K_2CO_3 (20 mmol) in dry methanol (20 mL), a solution of 4-methyl-2-phenylthiazole-5-carbaldehyde (**3a**) (10 mmol) in methanol (20 mL) was added and the reaction mixture was stirred at room temperature for 24 h. After completion of the reaction (TLC), the solvent was distilled under vacuum and the residue was dissolved in water (80 mL), and the reaction mass was extracted by ethyl acetate (3 × 25 mL). The organic layer was washed with brine, dried over sodium sulfate, and evaporated on a rotary evaporator. The crude product purified by column chromatography using ethyl acetate:hexane (2:8) as an eluent gave 5-ethynyl-4-methyl-2-phenylthiazole (**4a**), yield 0.95 g, 45%.

5-ethynyl-4-methyl-2-phenylthiazole, 4a ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.90 (m, 2H), 7.60 (m, 2H), 7.45–7.41 (m, 1H), 3.55 (s, 1H), 2.55 (s, 3H); d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 3.59 (s, 1H), and 2.55 (s, 3H); LCMS *m/z*: 200.04 $(M+H)^+$.

2-(4-bromophenyl)-5-ethynyl-4-methylthiazole, 4b ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.6$ Hz, 2H), 7.56 (d, $J = 8.6$ Hz, 2H), 3.58 (s, 1H), and 2.56 (s, 3H); LCMS *m/z*: 278.01 $(M+H)^+$.

2-(4-chlorophenyl)-5-ethynyl-4-methylthiazole, 4c ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, $J = 8.6$ Hz, 2H), 7.40 (d, $J = 8.6$ Hz, 2H), 3.59 (s, 1H), and 2.55 (s, 3H); LCMS *m/z:* 234.01 $(M+H)^+$.

5-ethynyl-2-(4-fluorophenyl)-4-methylthiazole, 4d ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, $J = 8.7$, 5.3 Hz, 2H), 7.11 (t, $J = 8.6$ Hz, 2H), 3.58 (s, 1H), and 2.54 (s, 3H); LCMS *m/z*: 218.04 $(M+H)^+$.

5-ethynyl-4-methyl-2-(p-tolyl)thiazole, 4e ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 3.56 (s, 1H), 2.54 (s, 3H), and 2.38 (s, 3 H); LCMS *m/z*: 214.07 $(M+H)^+$.

General procedure for the synthesis of 2-phenyl-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazole (6a)

A reaction mixture of 5-ethynyl-4-methyl-2-phenylthiazole, **4a** (0.2 g, 1 mmole), benzylazide, **5a** (0.14 g, 1 mmole), copper sulfate (0.040 g, 0.25 mmole), and sodium ascorbate (0.050 g, 0.22 mmole) in DMF:water (6 mL, 3:1) was stirred overnight. After completion of the reaction (TLC), the reaction mixture was quenched in water and extracted by ethyl acetate (3 × 15 mL). The organic layer was dried over sodium sulfate and evaporated on a rotary evaporator. The crude product was purified by column chromatography (ethyl acetate:hexane) and furnished the target compound 2-phenyl-4-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)thiazole (**6a**). Compounds **6b**−**w** were synthesized by a similar procedure.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole (6a) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, Thiazole−$C\underline{H}_3$), 5.60 (s, 2H, Ar−$C\underline{H}_2$−N), 7.32 (dd, $J = 7.7$, 1.7 Hz, 2H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.38–7.44 (m, 6H, Ar−H), and 7.93 (dd, $J = 7.9$, 1.7 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.12 (CH_3, Thiazole−$\underline{C}H_3$), 54.42 (CH_2, Ar−$\underline{C}H_2$−N), 120.10 (CH, Triazole−C-5), 121.68 (C, Thiazole–C-5), 127.86 (C, C-4′′), 127.94 (CH, C-2′′,-6′′), 128.15 (CH, C-3′′,-5′′), 129.42 (CH, C-3′,-5′), 129.52 (CH, C-2′,-6′), 130.14 (CH, C-4′), 130.96 (C, C-1′′), 134.96 (C, C-1′), 140.97 (C, Triazole−C-4), 149.95 (C, Thiazole−C-4), and 165.68 (C, Thiazole−C-2); Chemical formula: $C_{19}H_{16}N_4S$, Exact mass: 332.1096, HRMS: 333.1172 $(M+H)^+$, 355.0991 $(M+Na)^+$.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(4-bromophenyl)-4-methylthiazole(6b) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, Thiazole−$C\underline{H}_3$), 5.60 (s, 2H, Ar−$C\underline{H}_2$−N), 7.33 (d, $J = 7.8$, 2H, Ar−H), 7.38–7.44 (m, 5H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.93 (d, $J = 7.8$, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.08 (CH_3, Thiazole−$\underline{C}H_3$), 54.36 (CH_2,

Ar−CH$_2$−N), 120.10 (CH, Triazole−C-5), 121.70 (C, Thiazole−C-5), 127.90 (C, C-4′′), 128.12 (CH, C-2′′,-6′′), 127.35 (C, C-4′), 129.20 (CH, C-3′′,-5′′), 129.88 (CH, C-2′,-6′), 130.90 (CH, C-3′,-5′), 130.99 (C, C-1′′), 134.96 (C, C-1′), 140.92 (C, Triazole−C-4), 149.80 (C, Thiazole−C-4), 165.35 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{15}BrN_4S$, Exact mass: 410.0201, HRMS: 411.0269 (M+H)$^+$, 413.0249 (M+2+H)$^+$.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole(6c) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (s, 3H, Thiazole−CH$_3$), 5.60 (s, 2H, Ar−CH$_2$−N), 7.30–7.35 (m, 2H, Ar−H), 7.37–7.41 (m, 5H, Ar−H), 7.60 (s, 1H, Triazole−H), 7.86 (d, J = 8.6 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.21 (CH_3, Thiazole−CH$_3$), 54.38 (CH_2, Ar−CH$_2$−N), 120.10 (CH, Triazole−C-5), 122.03 (C, Thiazole−C-5), 127.82 (C, C-4′′), 127.86 (CH, C-2′′,-6′′), 129.10 (CH, C-3′′,-5′′), 129.38 (CH, C-2′,-6′), 129.45 (CH, C-3′,-5′), 130.92 (C, C-1′′), 135.00 (C, C-4′), 135.93 (C, C-1′), 140.84 (C, Triazole−C-4), 149.88 (C, Thiazole−C-4), 164.77 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{15}ClN_4S$, Exact mass: 366.0706, HRMS: 367.0786 (M+H)$^+$, 369.0758 (M+2+H)$^+$, and 389.0603 (M+Na)$^+$.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole(6c) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (s, 3H, Thiazole−CH$_3$), 5.60 (s, 2H, Ar−CH$_2$−N), 7.12 (t, J = 8.7 Hz, 2H, Ar−H), 7.30–7.36 (m, 2H, Ar−H), 7.40 (t, J = 4.9 Hz, 3H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.89–7.95 (m, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.96 (CH_3, Thiazole−CH$_3$), 54.42 (CH_2,Ar−CH$_2$−N), 116.05 (CH, C-3′, -5′), 120.13 (CH, Triazole−C-5), 121.86 (C, Thiazole−C-5), 128.08 (CH, C-3′′,-5′′), 128.30 (CH, C-2′, -6′), 128.99 (CH, C-4′′), 129.27 (CH, C-2′′,-6′′), 130.91 (C, C-1′′), 134.36 (C, C-1′), 140.77 (C, Triazole−C-4), 149.87 (C, Thiazole−C-4), 163.86 (C, C-4′), 164.39 (C, Thiazole−C-2), Chemical formula: $C_{19}H_{15}FN_4S$, Exact mass: 350.1001, HRMS: 351.1078 (M+H)$^+$, 373.0895 (M+Na)$^+$.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole(6e) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (s, 3H, Ar−CH$_3$), 2.58 (s, 3H, Thiazole−CH$_3$), 5.59 (s, 2H, Ar−CH$_2$−N), 7.22 (d, J = 7.5 Hz, 2H, Ar−H), 7.31 (d, J = 7.3 Hz, 3H, Ar−H), 7.36−7.40 (m, 3H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.70 (d, J = 7.0 Hz, 1H, Ar−H), 7.78 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.02 (CH_3, Thiazole−CH$_3$), 21.37 (CH_3, Ar−CH$_3$), 54.38 (CH_2, Ar−CH$_2$−N), 120.19 (CH, Triazole−C-5), 121.65 (C, Thiazole−C-5), 123.68 (CH, C-5′), 126.85 (CH, C-4′′), 128.07 (CH, C-2′′,-6′′), 128.88 (CH, C-2′), 128.95 (CH, C-4′), 129.25 (CH, C-3′′,-5′′), 130.88 (C, C-1′′), 133.36 (C, C-6′), 134.41 (C, C-1′), 138.77 (C, C-3′), 140.89 (C, Triazole−C-4), 149.81 (C, Thiazole−C-4), 165.87 (C, Thiazole−C-2), Chemical formula: $C_{20}H_{18}N_4S$, Exact mass: 346.1252, HRMS: 347.1334 (M+H)$^+$, 369.1153 (M+Na)$^+$.

5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-(p-tolyl)thiazole(6f) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.38 (s, 3H, Ar−CH$_3$), 2.57 (s, 3H, Thiazole−CH$_3$), 5.59 (s, 2H, Ar−CH$_2$−N), 7.23 (d, J = 8.0 Hz, 2H, Ar−H), 7.30–7.34 (m, 2H, Ar−H), 7.37−7.41 (m, 3H, Ar−H), 7. 7.58 (s, 1H, Triazole−H), 82 (d, J = 8.1 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.06 (CH_3, Thiazole−CH$_3$), 21.24 (CH_3, Ar−CH$_3$), 54.40 (CH_2, Ar−CH$_2$−N), 120.08 (CH, Triazole−C-5), 121.61 (C, Thiazole−C-5), 126.85 (CH, C-4′′), 128.07 (CH, C-2′′,-6′′), 129.37 (CH, C-3′,-5′), 129.28 (CH, C-3′′,-5′′), 129.68 (CH, C-2′,-6′), 130.88 (C, C-1′′), 134.96 (C, C-1′), 138.86 (C, C-4′), 141.08 (C, Triazole−C-4), 150.02 (C, Thiazole−C-4), 165.87 (C, Thiazole−C-2), Chemical formula: $C_{20}H_{18}N_4S$, Exact mass: 346.1252, HRMS: 347.1334 (M+H)$^+$, 369.1153 (M+Na)$^+$.

5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole (6g) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (s, 3H, Thiazole−CH$_3$), 5.57 (s, 2H, Ar−CH$_2$−N), 7.07–7.13 (m, 2H, Ar−H), 7.39–7.35 (m, 2H, Ar−H), 7.40–7.46 (m, 3H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.90–7.97 (m, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.03 (CH_3, Thiazole−CH$_3$), 53.65 (CH_2,Ar−CH$_2$−N), 116.30 (CH, C-3′,-5′′), 120.01 (CH, Triazole−C-5), 121.66 (C, Thiazole−C-5), 126.40 (CH, C-3′, -5′), 128.98 (CH, C-2′, -6′), 129.98 (CH, C-2′′,-6′′), 130.08 (CH, C-4′), 130.24 (C, C-1′′), 133.45 (C, C-1′), 141.00 (C, Triazole−C-4), 149.96 (C, Thiazole−C-4), 162.97 (C, C-4′′), 165.70 (C, Thiazole−C-2), Chemical formula: $C_{19}H_{15}FN_4S$, Exact mass: 350.1001, HRMS: 351.1078 (M+H)$^+$, 373.0895 (M+Na)$^+$.

2-(4-bromophenyl)-5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methylthiazole(6h) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H, Thiazole−CH$_3$), 5.57 (s, 2H, Ar−CH$_2$−N), 7.10 (t, J = 8.6 Hz, 2H, Ar−H), 7.33 (dd, J = 8.7, 5.2 Hz, 2H, Ar−H), 7.40 (d, J = 8.6 Hz, 2H, Ar−), 7.59 (s, 1H, Triazole−H), 7.86 (d, J = 8.6 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.99 (CH_3, Thiazole−CH$_3$), 53.67 (CH_2, Ar−CH$_2$−N), 116.31 (CH, C-3′′,-5′′), 120.04 (CH, Triazole−C-5), 122.08 (C, Thiazole−C-5), 127.56 (CH, C-2′, -6′), 129.19 (CH, C-3′, -5′), 130.0 (CH, C-2′′,-6′′), 130.20 (C, C-1′′), 131.95 (C, C-4′), 135.97 (C, C-1′), 140.81 (C, Triazole−C-4), 150.07 (C, Thiazole−C-4), 162.98 (C, C-4′′), 164.24 (C, Thiazole−C-2), Chemical formula: $C_{19}H_{14}BrFN_4S$, Exact mass: 428.0107, HRMS: 429.0187 (M+H)$^+$, 431.0168 (M+H)$^+$, and 453.9986 (M+Na)$^+$.

2-(4-chlorophenyl)-5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methylthiazole(6i) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.09 (t, $J = 8.6$ Hz, 2H, Ar−H), 7.32 (dd, $J = 8.7$, 5.2 Hz, 2H, Ar−H), 7.43 (d, $J = 8.0$ Hz, 2H), 7.59 (s, 1H, Triazole−H), 7.93 (d, $J = 8.0$ Hz, 2H, Ar−H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.02 (CH_3, Thiazole−$\underline{C}H_3$), 53.65 (CH_2, Ar−$\underline{C}H_2$−N), 116.30 (CH, C-3′′,-5′′), 120.02 (CH, Triazole−C-5), 121.67 (C, Thiazole−C-5), 126.40 (CH, C-2′, -6′), 128.98 (CH, C-3′, -5′), 129.99 (CH, C-2′′,-6′′), 130.25 (C, C-1′′), 132.15 (C, C-4′), 133.44 (C, C-1′), 140.99 (C, Triazole−C-4), 149.96 (C, Thiazole−C-4), 162.98 (C, C-4′′), 165.70 (C, Thiazole−C-2), Chemical formula: $C_{19}H_{14}ClFN_4S$, Exact mass: 384.0612, HRMS: 385.0683 $(M+H)^+$, 387.0655 $(M+2+H)^+$, and 407.0503 $(M+Na)^+$.

5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole(6j) ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.58 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.08−7.14 (m, 4 H, Ar−H), 7.33 (dd, $J = 8.7$, 5.2 Hz, 2H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.92 (dd, $J = 8.9$, 5.3 Hz, 2H, Ar−H), ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.98 (CH_3, Thiazole−$\underline{C}H_3$), 53.67 (CH_2, Ar−$\underline{C}H_2$−N), 116.06 (CH, C-3′′,-5′′), 116.41 (CH, C-3′, -5′), 119.97 (CH, Triazole−C-5), 121.72 (C, Thiazole−C-5), 128.31 (CH, C-2′′,-6′′), 129.83 (C, C-1′′), 129.99 (CH, C-2′, -6′), 130.21 (C, C-1′), 140.89 (C, Triazole−C-4), 149.94 (C, Thiazole−C-4), 162.98 (C, C-4′′), 163.88 (C, C-4′), 164.47 (C, Thiazole−C-2), Chemical formula: $C_{19}H_{14}F_2N_4S$, Exact mass: 368.0907, HRMS: 369.0990 $(M+H)^+$, 391.0809 $(M+Na)^+$.

5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole(6k) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H, C3′−C$\underline{H}_3$), 2.60 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.10 (t, $J = 8.6$ Hz, 2H, Ar−H), 7.23 (d, $J = 7.6$ Hz, 1H, Ar−H), 7.35–7.30 (m, 3H, Ar−H), 7.58 (s, 1H, Triazole−H), 7.71 (d, $J = 7.7$ Hz, 1H, Ar−H), 7.78 (s, 1H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.03 (CH_3, Thiazole−$\underline{C}H_3$), 21.37 (CH_3, C3′−$\underline{C}H_3$), 53.64 (CH_2, Ar−$\underline{C}H_2$−N), 116.30 (CH, C-3′′,-5′′), 120.00 (CH, Triazole−C-5), 121.49 (C, Thiazole−C-5), 123.69 (CH, C-6′), 126.86 (CH, C-4′), 128.88 (CH, C-5′), 129.99 (CH, C-2′′,-6′′), 130.25 (C, C-1′′), 130.91 (CH, C-2′), 133.34 (C, C-1′), 138.79 (C, C-3′), 141.04 (C, Triazole−C-4), 149.89 (C, Thiazole−C-4), 162.98 (C, C-4′′), 165.97 (C, Thiazole−C-2), Chemical formula: $C_{20}H_{17}FN_4S$, Exact mass: 364.1158, HRMS: 365.1238 $(M+H)^+$, 387.1056 $(M+Na)^+$.

5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(p-tolyl)thiazole(6l) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H, C3′−C$\underline{H}_3$), 2.58 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.09 (t, $J = 8.6$ Hz, 2H, Ar−H), 7.24 (d, $J = 8.0$ Hz, 2H, Ar−H), 7.32 (dd, $J = 8.6$, 5.2 Hz, 2H, Ar−H), 7.57 (s, 1H, Triazole−H), 7.82 (d, $J = 8.0$ Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.02 (CH_3, Thiazole−$\underline{C}H_3$), 21.45 (CH_3, C4′−$\underline{C}H_3$), 53.64 (CH_2, Ar−$\underline{C}H_2$−N), 116.29 (CH, C-3′′,-5′′), 119.94 (CH, Triazole−C-5), 121.10 (C, Thiazole−C-5), 126.32 (CH, C-2′,-6′), 129.66 (CH, C-3′,-5′), 129.98 (CH, C-2′′,-6′′), 130.26 (C, C-1′′), 130.81 (C, C-1′), 140.37 (C, C-4′), 141.09 (C, Triazole−C-4), 149.81 (C, Thiazole−C-4), 162.97 (C, C-4′′), 165.93 (C, Thiazole−C-2), Chemical formula: $C_{20}H_{17}FN_4S$, Exact mass: 364.1158, HRMS: 365.1238 $(M+H)^+$, 387.1056 $(M+Na)^+$.

5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole(6m) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.60 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.23–7.31 (m, 2H, Ar−H), 7.38 (d, $J = 8.4$ Hz, 2H, Ar−H), 7.41−7.45 (m, 3H, Ar−H), 7.60 (s, 1H, Triazole−H), 7.94 (dd, $J = 7.6$, 1.7 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.04 (CH_3, Thiazole−$\underline{C}H_3$), 53.65 (CH_2, Ar−$\underline{C}H_2$−N), 120.06 (CH, Triazole−C-5), 121.61 (C, Thiazole−C-5), 126.41 (CH, C-2′′,-6′′), 128.98 (CH, C-3′′,-5′′), 129.39 (CH, C-3′,-5′), 129.49 (CH, C-2′,-6′), 130.08 (CH, C-4′), 132.87 (C, C-4′′), 133.45 (C, C-1′′), 135.06 (C, C-1′), 141.07 (C, Triazole−C-4), 150.01 (C, Thiazole−C-4), 165.73 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{15}ClN_4S$, Exact mass: 366.0706, HRMS: 367.0786 $(M+H)^+$, 369.0758 $(M+2+H)^+$, and 389.0603 $(M+Na)^+$.

2-(4-bromophenyl)-5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methylthiazole(6n) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.25 (d, $J = 8.4$ Hz, 2H, Ar−H), 7.38 (d, $J = 8.4$ Hz, 2H, Ar−H), 7.43 (d, $J = 7.1$ Hz, 2H, Ar−H), 7.60 (s, 1H, Triazole−H), 7.93 (d, $J = 7.1$, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.12 (CH_3, Thiazole−$\underline{C}H_3$), 53.66 (CH_2, Ar−$\underline{C}H_2$−N), 120.08 (CH, Triazole−C-5), 121.76 (C, Thiazole−C-5), 127.12 (CH, C-2′′,-6′′), 127.39 (C, C-4′), 128.89 (CH, C-3′′,-5′′), 129.96 (CH, C-2′,-6′), 130.88 (CH, C-3′,-5′), 132.84 (C, C-4′′), 133.39 (C, C-1′′), 135.06 (C, C-1′), 141.01 (C, Triazole−C-4), 149.96 (C, Thiazole−C-4), 165.78 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{14}BrClN_4S$, Exact mass: 443.9811, HRMS: 444.9880 $(M+H)^+$, 446.9855 $(M+2+H)^+$, and 448.9848 $(M+4+H)^+$

5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-2-(4-chlorophenyl)-4-methylthiazole(6o) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.26 (d, $J = 8.0$ Hz, 2H, Ar−H), 7.38 (d, $J = 8.0$ Hz, 2H, Ar−H), 7.40 (d, $J = 8.5$ Hz, 2H, Ar−H), 7.60 (s, 1H, Triazole−H), 7.86 (d, $J = 8.5$ Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.21 (CH_3, Thiazole−$\underline{C}H_3$), 53.67 (CH_2, Ar−$\underline{C}H_2$−N), 120.10 (CH, Triazole−C-5), 122.03 (C, Thiazole−C-5), 127.56 (CH, C-2′′,-6′′), 129.20 (CH, C-3′′,-5′′),

129.40 (CH, C-2′,-6′), 129.49 (CH, C-3′,-5′), 131.94 (C, C-4′′), 132.82 (C, C-1′′), 135.08 (C, C-4′), 135.98 (C, C-1′), 140.87 (C, Triazole−C-4), 150.11 (C, Thiazole−C-4), 164.27 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{14}Cl_2N_4S$, Exact mass: 400.0316, HRMS: 401.0385 (M+H)$^+$, 403.0348 (M+2+H)$^+$, and 405.0335 (M+4+H)$^+$.

5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)-4-methylthiazole(6p) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.12 (t, J = 8.6 Hz, 2H, Ar−H), 7.26 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H, Triazole H), 7.88–7.95 (m, 2H, Ar−H);); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.10 (CH_3, Thiazole−C$\underline{H}_3$), 53.59 (CH_2, Ar−C$\underline{H}_2$−N), 116.32 (CH, C-3′, -5′), 120.16 (CH, Triazole−C-5), 121.94 (C, Thiazole−C-5), 127.56 (CH, C-2′′,-6′′), 129.20 (CH, C-3′′,-5′′), 129.94 (CH, C-2′, -6′), 130.21 (C, C-1′), 131.94 (C, C-4′′), 132.82 (C, C-1′′), 140.42 (C, Triazole−C-4), 149.65 (C, Thiazole−C-4), 163.94 (C, C-4′), 164.44 (C, Thiazole−C-2). Chemical formula: $C_{19}H_{14}ClFN_4S$, Exact mass: 384.0612, HRMS: 385.0683 (M+H)$^+$, 407.0503 (M+Na)$^+$

5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole(6q) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H, C3′−C$\underline{H}_3$), 2.60 (s, 3H, Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.21–7.28 (m, 3H, Ar−H), 7.32 (t, J = 7.6 Hz, 1H, Ar−H), 7.38 (d, J = 8.4 Hz, 2H, Ar−H), 7.59 (s, 1H, Triazole−H), 7.71 (d, J = 7.7 Hz, 1H, Ar−H), 7.78 (s, 1H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.10 (CH_3, Thiazole−C$\underline{H}_3$), 21.38 (CH_3, C3′−C$\underline{H}_3$), 53.59 (CH_2, Ar−C$\underline{H}_2$−N), 120.16 (CH, Triazole−C-5), 121.94 (C, Thiazole−C-5), 123.70 (CH, C-6′), 127.56 (CH, C-2′′,-6′′), 127.12 (CH, C-4′), 128.90 (CH, C-5′), 129.26 (CH, C-3′′,-5′′), 130.91 (CH, C-2′), 131.90 (C, C-4′′), 132.85 (C, C-1′′), 133.34 (C, C-1′), 138.79 (C, C-3′), 140.86 (C, Triazole−C-4), 149.85 (C, Thiazole−C-4), 165.87 (C, Thiazole−C-2); Chemical formula: $C_{20}H_{17}ClN_4S$, Exact mass: 380.0862, HRMS: 381.0935 (M+H)$^+$, 383.00912 (M+2+H)$^+$.

5-(1-(4-chlorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(p-tolyl)thiazole(6r) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H C4′−C$\underline{H}_3$), 2.60 (s, 3H Thiazole−C$\underline{H}_3$), 5.57 (s, 2H, Ar−C$\underline{H}_2$−N), 7.24 (d, J = 7.6 Hz, 2H, Ar−H), 7.25 (d, J = 7.6 Hz, 2H, Ar−H), 7.37 (d, J = 7.6 Hz, 2H, Ar−H), 7.58 (s, 1H, Triazole−H), 7.83 (d, J = 7.6 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.02 (CH_3, Thiazole−C$\underline{H}_3$), 21.44 (CH_3, C4′′−C$\underline{H}_3$), 53.61 (CH_2, Ar−C$\underline{H}_2$−N), 119.98 (CH, Triazole−C-5), 121.04 (C, Thiazole−C-5), 126.31 (CH, C-2′′,-6′′), 129.37 (CH, C-3′,-5′), 129.46 (CH, C-3′′,-5′′), 129.64 (CH, C-2′,-6′), 130.79 (C, C-1′′), 132.88 (C, C-4′′), 135.02 (C, C-1′), 140.36 (C, C-4′), 141.13 (C, Triazole−C-4), 149.84 (C, Thiazole−C-4), 165.94 (C, Thiazole−C-2); Chemical formula: $C_{20}H_{17}ClN_4S$, Exact mass: 380.0862, HRMS: 381.0935 (M+H)$^+$, 383.00912 (M+2+H)$^+$.

4-methyl-5-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)-2-phenylthiazole(6s) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, C4′′−C$\underline{H}_3$), 2.58 (s, 3H, Thiazole−C$\underline{H}_3$), 5.54 (s, 2H, Ar−C$\underline{H}_2$−N), 7.24–7.17 (m, 4H, Ar−H), 7.45–7.39 (m, 3H, Ar−H), 7.57 (s, 1H, Triazole−H), 7.95–7.91 (m, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.01 (CH_3, Thiazole−C$\underline{H}_3$), 21.21 (CH_3, C4′′−C$\underline{H}_3$), 54.22 (CH_2, Ar−C$\underline{H}_2$−N), 120.07 (CH, Triazole−C-5), 121.88 (C, Thiazole−C-5), 126.38 (CH, C-2′′,-6′′), 128.13 (CH, C-3′,-5′), 128.96 (CH, C-3′′,-5′′), 129.91 (CH, C-2′,-6′), 130.01 (CH, C-4′), 131.35 (C, C-1′′), 133.50 (C, C-1′), 138.93 (C, C-4′′), 140.78 (C, Triazole−C-4), 149.85 (C, Thiazole−C-4), 165.55 (C, Thiazole−C-2); Chemical formula: $C_{20}H_{18}N_4S$, Exact mass: 346.1252, HRMS: 347.1334 (M+H)$^+$, 369.1153 (M+Na)$^+$

2-(4-bromophenyl)-4-methyl-5-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)thiazole(6t) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, Ar−C$\underline{H}_3$), 2.57 (s, 3H, Thiazole−C$\underline{H}_3$), 5.55 (s, 2H, Ar−C$\underline{H}_2$−N), 7.24–7.18 (m, 4H, Ar−H), 7.43 (d, J = 7.8, 2H, Ar−H), 7.56 (s, 1H, Triazole−H), 7.93 (d, J = 7.8, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 17.01 (CH_3, Thiazole−C$\underline{H}_3$), 21.21 (CH_3, C4′′−C$\underline{H}_3$), 54.22 (CH_2, Ar−C$\underline{H}_2$−N), 120.07 (CH, Triazole−C-5), 121.88 (C, Thiazole−C-5), 126.36 (CH, C-2′′,-6′′), 128.94 (CH, C-3′′,-5′′), 129.96 (CH, C-2′,-6′), 130.86 (CH, C-3′,-5′), 132.80 (CH, C-4′), 131.34 (C, C-1′′), 135.02 (C, C-1′), 138.92 (C, C-4′′), 140.80 (C, Triazole−C-4), 149.84 (C, Thiazole−C-4), 165.49 (C, Thiazole−C-2); Chemical formula: $C_{20}H_{17}BrN_4S$, Exact mass: 424.0357, HRMS: 425.0419 (M+H)$^+$, 425.0403 (M+2+H)$^+$.

2-(4-chlorophenyl)-4-methyl-5-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)thiazole(6u) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, C4′′−C$\underline{H}_3$), 2.56 (s, 3H, Thiazole−C$\underline{H}_3$), 5.55 (s, 2H, Ar−C$\underline{H}_2$−N), 7.25–7.19 (m, 4H, Ar−H), 7.39 (d, J = 8.6 Hz, 2H, Ar−H), 7.57 (s, 1H, Triazole−H), 7.85 (d, J = 8.6 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 16.94 (CH_3, Thiazole−C$\underline{H}_3$), 21.19 (CH_3, C4′′−C$\underline{H}_3$), 54.22 (CH_2, Ar−C$\underline{H}_2$−N), 120.07 (CH, Triazole−C-5), 122.27 (C, Thiazole−C-5), 127.52 (CH, C-2′′,-6′′), 128.12 (CH, C-2′,-6′), 129.15 (CH C-3′′,-5′′), 129.90 (CH, C-3′,-5′), 131.27 (C, C-1′′), 131.98 (C, C-1′), 135.87 (C, C-4′), 138.95 (C, C-4′′), 140.58 (C, Triazole−C-4), 149.93 (C, Thiazole−C-4), 164.07 (C, Thiazole−C-2); Chemical formula: $C_{20}H_{17}ClN_4S$, Exact mass: 380.0862, HRMS: 381.0936 (M+H)$^+$, 383.00913 (M+2+H)$^+$.

4-methyl-5-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)-2-(m-tolyl)thiazole(6v) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H, C4′′−C$\underline{H}_3$), 2.40 (s, 3H, C3′−C$\underline{H}_3$), 2.56 (s, 3H, Thiazole−C$\underline{H}_3$), 5.56 (s, 2H, Ar−C$\underline{H}_2$−N), 7.20–7.27 (m, 3H, Ar−H), 7.32 (t, J = 7.6 Hz, 1H, Ar−H), 7.38 (d, J = 8.4 Hz, 2H, Ar−H), 7.60 (s, 1H, Triazole−H), 7.71 (d, J = 7.7 Hz, 1 H, Ar−H), 7.78 (s, 1H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.96 (CH_3, Thiazole−C$\underline{H}_3$), 21.20 (CH_3, C4′′−C$\underline{H}_3$), 21.35 (CH_3, C3′−C$\underline{H}_3$), 54.20 (CH_2, Ar−C$\underline{H}_2$−N), 120.10 (CH, Triazole−C-5), 121.94 (C, Thiazole−C-5), 123.68 (CH, C-6′), 127.10 (CH, C-4′), 127.23 (CH, C-2′′,-6′′), 128.88 (CH, C-5′), 129.02 (CH, C-3′′,-5′′), 130.90 (CH, C-2′), 132.90 (C, C-1′′), 135.02 (C, C-4′′), 133.32 (C, C-1′), 138.78 (C, C-3′), 140.85 (C, Triazole−C-4), 149.86 (C, Thiazole−C-4), 165.88 (C, Thiazole−C-2); Chemical formula: $C_{21}H_{20}N_4S$, Exact mass: 360.1409, HRMS: 319.1021 $(M+H)^+$, 341.0840 $(M+Na)^+$.

4-methyl-5-(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)-2-(p-tolyl)thiazol(6w) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H, C4′′−C$\underline{H}_3$), 2.38 (s, 3H, C4′−C$\underline{H}_3$), 2.57 (s, 3H, Thiazole−C$\underline{H}_3$), 5.54 (s, 2H, Ar−C$\underline{H}_2$−N), 7.19−7.23 (m, 6H, Ar−H), 7.55 (s, 1H, Triazole H), 7.82 (d, J = 8.1 Hz, 2H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 16.96 (CH_3, Thiazole−C$\underline{H}_3$), 21.20 (CH_3, C4′′−C$\underline{H}_3$), 21.22 (CH_3, C3′−C$\underline{H}_3$), 54.20 (CH_2, Ar−C$\underline{H}_2$−N), 120.08 (CH, Triazole−C-5), 121.94 (C, Thiazole−C-5), 127.23 (CH, C-2′′,-6′′), 127.58 (CH, C-2′, C-6′), 129.02 (CH, C-3′′,-5′′), 129.58 (CH, C-3′, C-5′), 132.38 (C, C-1′), 132.90 (C, C-1′′), 134.03 (C, C-4′), 135.02 (C, C-4′′), 140.84 (C, Triazole−C-4), 149.90 (C, Thiazole−C-4), 165.85 (C, Thiazole−C-2); Chemical formula: $C_{21}H_{20}N_4S$, Exact mass: 360.1409, HRMS: 319.1021 $(M+H)^+$, 341.0840 $(M+Na)^+$.

Biological activity

Antitubercular activity

In vitro antimycobacterial activity against *M. tuberculosis* H37Ra (dormant) was performed using the XTT reduction menadione assay (XRMA) (Khan and Sarkar 2008, Singh et al. 2015, Sarkar and Sarkar 2012). A compound solution (2.5 µL) was added in a total volume of 250 µL of *Mycobacterium* pheli medium consisting of the *M. tuberculosis* H37Ra, sealed with plate sealers and allowed to incubate for 12 days at 37 °C. The XRMA was then carried out to estimate viable cells present in different wells of the assay plate. To all wells, 200 µM XTT was added and incubated at 37 °C for another 20 min, followed by the addition of 60 µMmenadione, and incubated at 37 °C for a further 40 min. The optical density was measured using a microplate reader (SpectraMaxPlus 384 plate reader, Molecular Devices Inc.) at a 470-nm filter against a blank prepared from a well free of cells. Absorbance obtained from the cells treated with 1% DMSO alone was considered as 100% cell growth. The % inhibition in the presence of the test material is calculated by using the formula, % inhibition = (average of control − average of compound)/(average of control − average of blank) × 100), where control is the culture medium with cells and DMSO and blank is the culture medium without cells. For all samples, each compound concentration was tested in triplicate in a single experiment and the quantitative value was expressed as the mean ± standard deviation (SD).

Cytotoxic activity

Cell lines were obtained from NCCS, Pune, India, and maintained under standard cell culture conditions at 37 °C and 5% CO_2 in a humidified environment. The cytotoxic effect of the synthesized compounds was checked on cervix adenocarcinoma HeLa and human acute monocytic leukemia cell line THP-1 cancer cell lines using the concentrations ranging from 0.781 to 100 µg/mL to determine the growth inhibition (Alley et al. 1988). The log-phase cells were harvested using trypsin (0.05% trypsin and 0.02% ethylene diamine tetra-acetic acid in PBS) from tissue culture flasks and the suspension was diluted with appropriate culture medium to obtain a cell density of 105 cells/mL as determined by hemocytometry. An aliquot of 100 µL of each suspension was seeded in 96-well cell culture plates and was incubated at 37 °C in an atmosphere of 5% CO_2 and 95% relative humidity in a CO_2 incubator. After 24 h, synthesized compounds (1 µL/well) were added to the wells containing cells. The plates were further incubated for 48 h, then the solution containing the unattached cells was discarded, and the wells were washed three times with 1 mL of PBS followed by addition of 10 µL of MTT (5 mg/mL in PBS) to adherent cells in growth medium. After 4 h at 37 °C for MTT cleavage, the formazan product was solubilized by addition of 100 µL of 0.04 N HCl in isopropanol. Absorbance was measured on a SpectraMax® PLUS 384 plate reader (Molecular Devices, Sunnyvale, CA) at a wavelength of 570 nm. Percentage cytotoxicity was calculated using the formula: % cytotoxicity = (average of control − average of compound) / (average of control − average of blank) × 100). Each concentration was tested in triplicate in a single experiment and the quantitative value was expressed as the mean ± SD.

Docking analysis

Virtual docking analysis was performed on the biopredicta module of V life MDS 4.3. Docking simulations are utilized to predict the drug target interactions using the molecular structure of proteins or enzymes. Docking simulations were performed on *Enoyl acyl carrier protein reductase*.

Docking analysis was accrued out using the crystal structure of *Enoyl acyl carrier protein reductase* (PDB ID: 4tzk) downloaded from free protein database www.rcsb.org. Prior to docking simulations, the crystal structure of *Enoyl acyl carrier protein reductase* was cleaned for reducing experimental errors. All the ligand structures were first drawn in a molecular builder in V life MDS 4.3 and converted into 3D geometry via a 3D converter; these 3D structures of ligands were optimized via MMFF. These optimized ligands were utilized for grip-based docking analysis (Patil et al. 2016, Patravale et al. 2016, Bansode et al. 2016).

Results and discussion

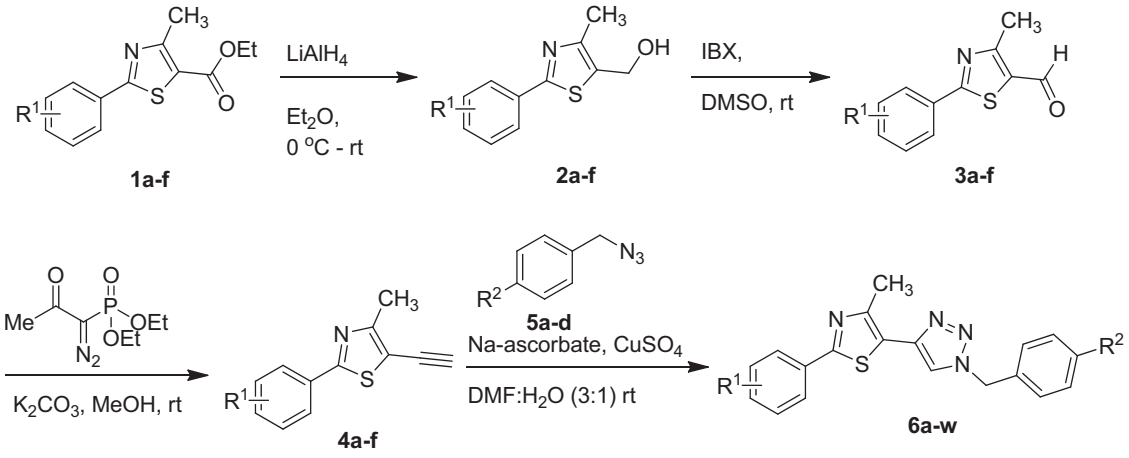
Chemistry

A series of 4-(1-substituted benzyl-1*H*-1,2,3-triazol-4-yl)-2-arylthiazole derivatives, **6a**−**w** were synthesized according to Scheme 1. Ethyl 4-methyl-2-arylthiazole-5-carboxylate **1a**−**f** on reduction with lithium aluminum hydride in diethyl ether gave (4-methyl-2-arylthiazol-5-yl)methanol, **2a**−**f**. Alcohol **2a**−**f** on selective oxidation with iodoxybenzoic acid (IBX) furnished 4-methyl-2-arylthiazole-5-carbaldehyde, **3a**−**f**. Aldehyde **3a**−**f** on reaction with diethyl (1-diazo-2-oxopropyl)phosphonate and K_2CO_3 in methanol gave 5-ethynyl-4-methyl-2-phenylthiazole, **4a**−**f**. Alkyne **4a**−**f** on click reaction with substituted benzylazide, **5a**−**d** furnished target compounds 4-(1-substituted benzyl-1H-1,2,3-triazol-4-yl)-2-arylthiazole, **6a**−**w** (Table 1).

The structure of the title compounds, **6a**−**w** was confirmed by NMR and HRMS. As a representative analysis of compound 4-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-(4-fluorophenyl)thiazole, (**6d**), the ^{1}H NMR spectrum that displayed two singlets in the aliphatic region at δ 2.57 and 5.59 corresponds to thiazole−CH_3 and thiazole−CH_2–triazole, respectively. A triplet at δ 7.12 and a multiplate at δ 7.89–7.95 were attributed to protons of a fluoro-substituted phenyl ring, while a multiplate at δ 7.30−7.36 and a triplet at δ 7.40 corresponds to protons of the phenyl ring. Triazole proton was resonated as a singlet at δ 7.59. The ^{13}C NMR spectrum of compound **6d** showed two signals of thiazole −$\underline{C}H_3$ at δ 16.96 and phenyl−$\underline{C}H_2$−N carbon at δ 54.33. Aromatic carbons of fluoro-substituted phenyl reported typical fluoro-coupling ($\underline{C}_1$-F δ 164.86, 162.86 ($^1J = 252$ Hz), $\underline{C}_2$-F δ 116.14, 115.96 ($^2J = 21.42$ Hz), and $\underline{C}_3$-F δ 128.33, 128.26 ($^3J = 8.82$ Hz)). The structure of compound **6d** was further confirmed by HRMS, *m/z* 337.0930 $(M+H)^+$, 359.0748 $(M+Na)^+$. The structure of all the derivatives was ascertained similarly.

Antitubercular activity evaluation: primary screening

The antitubercular activity for each synthesized compound was determined by measuring the inhibition of growth



Comp.	R^1	R^2	Comp.	R^1	R^2	Comp.	R^1	R^2	Comp.	R^1	R^2
6a	H	H	**6g**	H	F	**6m**	H	Cl	**6s**	H	CH_3
6b	4-Br	H	**6h**	4-Br	F	**6n**	4-Br	Cl	**6t**	4-Br	CH_3
6c	4-Cl	H	**6i**	4-Cl	F	**6o**	4-Cl	Cl	**6u**	4-Cl	CH_3
6d	4-F	H	**6j**	4-F	F	**6p**	4-F	Cl	**6v**	3-CH_3	CH_3
6e	3-CH_3	H	**6k**	3-CH_3	F	**6q**	3-CH_3	Cl	**6w**	4-CH_3	CH_3
6f	4-CH_3	H	**6l**	4-CH_3	F	**6r**	4-CH_3	Cl			

Scheme 1 Synthetic route of 4-(1-substituted benzyl-1H-1,2,3-triazol-4-yl)-2-arylthiazole derivatives, **6a**−**w**

Table 1 Structure and physical properties of compounds **6a**–**w**

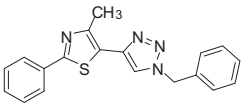
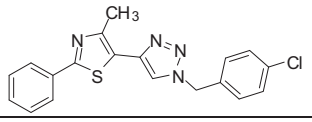
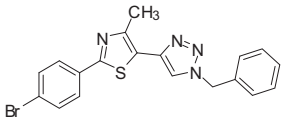
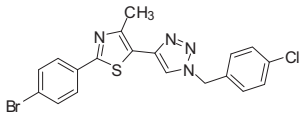
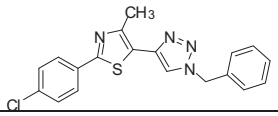
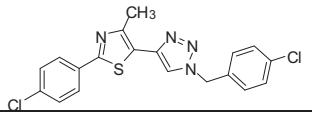
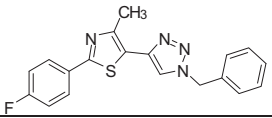
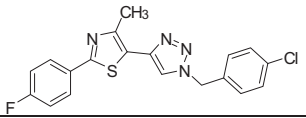
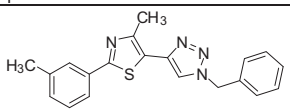
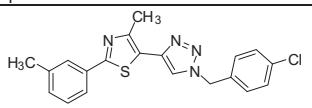
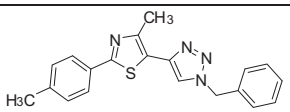
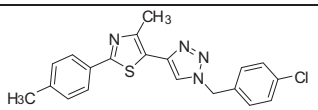
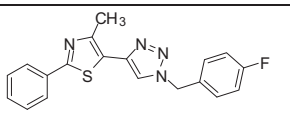
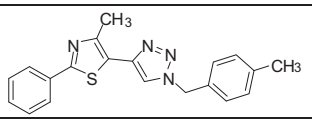
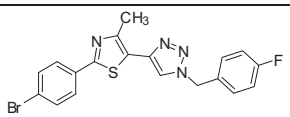
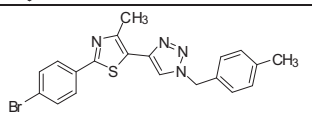
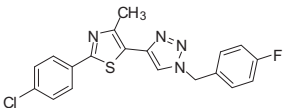
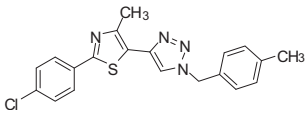
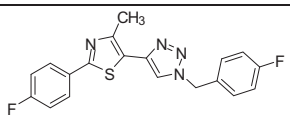
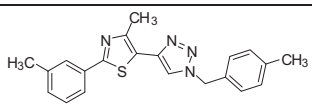
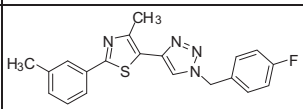
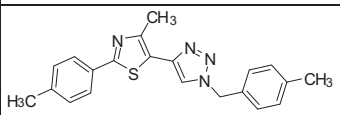
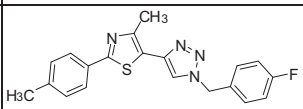
Comp.	Structure	m.p. °C	Yield %	Comp.	Structure	m.p. °C	Yield %
6a		168-170	84	**6m**		158-160	88
6b		149-150	80	**6n**		128-129	85
6c		176-178	75	**6o**		140-141	84
6d		168-170	80	**6p**		142-143	84
6e		136-137	88	**6q**		136-138	90
6f		139-140	86	**6r**		156-157	88
6g		136-138	72	**6s**		170-172	85
6h		160-161	78	**6t**		134-135	80
6i		166-168	72	**6v**		136-138	84
6j		138-139	76	**6v**		160-162	78
6k		130-131	78	**6w**		150-152	84
6l		168-170	82				

Table 2 Antitubercular activity in % inhibition at 30, 10, 3, and 1 μg/mL concentration of compounds **6a**−**p** against *M. tuberculosis* H37Ra

Comp.	% inhibition			
	30 μg/mL	10 μg/mL	3 μg/mL	1 μg/mL
6a	81.56 ± 8.23	86.71 ± 0.08	70.91 ± 2.08	49.85 ± 2.79
6b	88.89 ± 3.60	88.35 ± 0.16	76.00 ± 5.10	58.60 ± 2.37
6c	44.10 ± 5.62	39.91 ± 5.84	38.55 ± 1.09	35.41 ± 6.66
6d	44.75 ± 5.13	44.74 ± 0.90	45.40 ± 4.22	42.90 ± 8.82
6e	85.41 ± 0.85	87.24 ± 2.58	85.67 ± 5.12	72.88 ± 6.93
6f	81.44 ± 0.94	81.78 ± 0.15	67.63 ± 4.76	59.17 ± 13.72
6g	90.38 ± 4.09	90.46 ± 3.33	91.08 ± 0.68	80.74 ± 3.47
6h	43.01 ± 6.07	62.75 ± 1.84	71.00 ± 2.52	72.43 ± 6.77
6i	83.30 ± 2.84	79.54 ± 0.42	73.43 ± 8.65	75.70 ± 5.22
6j	69.87 ± 3.67	64.31 ± 3.09	71.51 ± 11.00	71.58 ± 5.22
6k	92.40 ± 0.04	91.90 ± 0.94	91.47 ± 0.44	91.22 ± 1.35
6l	81.33 ± 0.02	84.04 ± 5.72	85.36 ± 3.18	84.27 ± 5.05
6m	84.11 ± 5.04	86.36 ± 0.95	86.06 ± 5.36	83.65 ± 5.80
6n	63.32 ± 8.81	81.07 ± 0.65	85.67 ± 1.58	79.52 ± 6.56
6o	65.64 ± 6.09	67.65 ± 9.79	59.81 ± 0.67	49.57 ± 6.17
6p	19.43 ± 3.06	23.40 ± 10.79	37.63 ± 12.71	0.09 ± 8.15
6q	17.99 ± 2.27	27.90 ± 10.31	27.62 ± 2.46	9.85 ± 6.93
6r	64.33 ± 4.41	71.02 ± 2.88	70.32 ± 3.83	61.30 ± 11.49
6s	56.22 ± 9.17	49.59 ± 9.68	29.08 ± 10.86	24.53 ± 7.79
6t	62.07 ± 11.18	57.32 ± 12.48	43.81 ± 4.54	47.04 ± 2.30
6u	37.38 ± 10.49	31.53 ± 4.70	23.72 ± 4.00	7.93 ± 5.68
6v	53.23 ± 2.96	57.64 ± 7.09	38.49 ± 7.06	29.18 ± 12.00
6w	57.32 ± 2.24	68.25 ± 4.98	57.74 ± 3.58	48.77 ± 1.07

against the avirulent strain of *M. tuberculosis* H37Ra (MTB, ATCC 25177) in liquid medium. In vitro activity studies against MTB were performed using the XRMA (Khan and Sarkar 2008, Singh et al. 2015, Sarkar and Sarkar 2012). In a preliminary screening, the anti-mycobacterial activity of these compounds was assessed at 30, 10, and 3 μg/mL concentration; the results of % inhibition are shown in Table 2. All the compounds were further screened for minimum inhibition concentration (MIC_{90}). The results of antitubercular activity are reported in Table 3. The first-line antitubercular drug rifampicin was used as the reference standard.

The result of the antitubercular activity against *M. tuberculosis* H37Ra revealed that most of the compounds exhibited good activity. The preliminary structure−activity relationship study revealed that substitution of the hydrogen atom of phenyl rings A and B (Fig. 2) by substituent groups like Br, Cl, F, and CH_3 affects the antitubercular activity.

The analysis of antitubercular activity revealed that, among the compounds **6a**−**f** with an unsubstituted phenyl ring A and a substituted phenyl ring B, compounds **6a** ($R^1 = H$), **6b** ($R^1 = Br$), **6e** ($R^1 = H$), and **6f** ($R^1 = H$) showed good activity against *M. tuberculosis* H37Ra with IC_{50} values of 0.84 −1.28 μg/mL. Compounds **6c** ($R^1 = Cl$) and **6d** ($R^1 = F$) were found less active. Among the compounds **6g**−**l** with a substituted phenyl ring A and 4-fluro-substituted phenyl ring B, all these compounds showed excellent activity with IC_{50} values of 0.58−0.83 μg/mL. Among the compounds **6g**−**l**,

Table 3 Antitubercular activity (IC_{50} and MIC_{90}) in μg/mL of compounds **6a**−**w** against *M. tuberculosis* H37Ra and cytotoxicity activity (IC_{50}) of compounds **6g** and **6k** in μg/mL

Comp.	R^1	R^2	IC_{50} (μM)	MIC_{90} (μM)	Hela IC_{50}	THP-1 IC_{50}
6a	H	H	**1.28** (**3.85**)	>30	n.d.	n.d.
6b	4-Br	H	**1.09** (**2.65**)	>30	n.d.	n.d.
6c	4-Cl	H	>30	>30	n.d.	n.d.
6d	4-F	H	>30	>30	n.d.	n.d.
6e	3-CH_3	H	**0.84** (**2.42**)	>30	n.d.	n.d.
6f	4-CH_3	H	**1.06** (**3.05**)	>30	n.d.	n.d.
6g		F	**0.69** (**1.96**)	**4.71** (**13.44**)	>80	>80
6h	4-Br	F	**0.83** (**1.93**)	>30	n.d.	n.d.
6i	4-Cl	F	**0.77** (**2.00**)	>30	n.d.	n.d.
6j	4-F	F	**0.75** (**2.03**)	>30	n.d.	n.d.
6k	3-CH_3	F	**0.58** (**1.59**)	**2.22** (**6.09**)	>80	>80
6l	4-CH_3	F	**0.68** (**1.86**)	>30	n.d.	n.d.
6m		Cl	**0.71** (**1.93**) >30	n.d.	n.d.	
6n	4-Br	Cl	**0.74** (**1.66**)	>30	n.d.	n.d.
6o	4-Cl	Cl	**1.65** (**4.11**)	>30	n.d.	n.d.
6p	4-F	Cl	>30	>30	n.d.	n.d.
6q	3-CH_3	Cl	>30	>30	n.d.	n.d.
6r	4-CH_3	Cl	**1.07** (**2.80**)	>30	n.d.	n.d.
6s	H	CH_3	>30	>30	n.d.	n.d.
6t	4-Br	CH_3	**6.3** (**14.81**)	>30	n.d.	n.d.
6u	4-Cl	CH_3	>30	>30	n.d.	n.d.
6v	3-CH_3	CH_3	**8.23** (**22.83**)	>30	n.d.	n.d.
6w	4-CH_3	CH_3	**1.74** (**4.82**)	>30	n.d.	n.d.
Rifampicin			**0.002** (**0.0024**)	**0.75** (**0.91**)	>80	>80

n.d. not determined

The active compounds are presented in the bold values

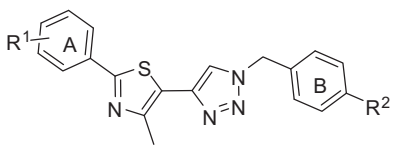


Fig. 2 Compounds **6a**−**w**

compounds **6g** ($R^1 = H$) and **6k** ($R^1 = 3\text{-}CH_3$) were found most active with MIC_{90} values of 4.71 and 2.22 µg/mL. It is worth mentioning that, as compared to the standard drug Rifampicin, compounds **6g** and **6k** were found sixfold and threefold less potent, respectively.

Among the compounds **6m**−**k** with a substituted phenyl ring A and 4-chloro-substituted phenyl ring B, compounds **6m** ($R^1 = H$), **6n** ($R^1 = 4\text{-}Br$), **6o** ($R^1 = 4\text{-}Cl$), and **6r** ($R^1 = 4\text{-}CH_3$) reported good activity with IC_{50} values of 0.71−1.65 µg/mL, whereas compounds **6p** ($R^1 = 3\text{-}CH_3$) and **6q** ($R^1 = 3\text{-}CH_3$) were found less active. Among the compounds **6a**−**w** with a substituted phenyl ring A and 4-methyl-substituted phenyl ring B, compound **6w** ($R^1 = 3\text{-}CH_3$) exhibited good activity with an IC_{50} value of 1.74 µg/mL, compounds **6t** ($R^1 = 3\text{-}CH_3$) and **6v** ($R^1 = 3\text{-}CH_3$) reported moderate activity with IC_{50} values of 6.3 and 8.23 µg/mL, respectively. Compounds **6s** ($R^1 = H$) and **6u** ($R^1 = 4\text{-}Cl$) were found less active. It was notable that 4-fluoro-substituted benzyl (ring B) on 1,2,3-triazole and a substituted phenyl (ring A) at 2-position of thiazole, all the compounds reported good-to-excellent activity. Also, 4-bromo- or 4-methyl-substituted phenyl (ring A) at 2-position of thiazole and an unsubstituted, 4-fluoro-, 4-chloro-, or 4-methyl-substituted benzyl ring (ring B) at 1,2,3-triazole showed good antitubercular activity against *M. tuberculosis H37Ra*.

Cytotoxicity activity

Active thiazolyl-triazole **6g** and **6k** were further evaluated against two human cancer cell lines (HeLa and THP-1) to check the toxicity of these compounds (Table 4). The IC_{50} values of compounds **6g** and **6k** against both cell lines are >80 µg/mL, indicating that these compounds are potent and specific inhibitors against MTB. Compounds **6g** and **6k** were relatively nontoxic against HeLa and THP-1 cell lines.

Docking analysis

Docking analysis was performed to evaluate the possible mode of action of synthesized derivatives for antimycobacterial potential. *Enoyl acyl carrier protein reductase* is a key enzyme involved in the metabolic and many conservative processes in mycobacterium. Docking analysis was performed using the crystal structure of *Enoyl acyl carrier protein reductase* (PDB ID: 4TZK) downloaded from the free protein database www.rcsb.org. Derivative **6a** showed aromatic interaction with amino acids like PHE149 and TYR158 and hydrophobic interactions with PHE97, MET98, MET103, and MET161 and van der Waals interactions with amino acid residues like PHE97, MET98, GLN100, MET103, PHE149, and TYR158 (Fig. S1). 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-2-(4-bromophenyl)-4-methylthiazole (**6b**) showed aromatic binding interaction with TYR158, PHE149, and PHE97 and hydrophobic interactions with GLY96, PHE97, and MET199 and van der Waals interactions with amino acid residues like GLY96, PHE97, MET98, MET103, PHE149, MET155, PRO156, and TYR158 (Fig. S2). 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole (**6e**) is another active derivative that showed binding interaction via the formation of hydrophobic bonds with amino acid residues like ALA206, ALA201, ALA198, MET161, PHE97, and GLY96. Compound **6e** also showed van der Waals interactions with amino acid residues like GLY96, PHE97, MET103, TYR158, MET161, ALA198, ALA201, ILE202, ALA206, and LEU207 (Fig. S3). Derivative **6f** showed hydrophobic interactions with LEU207, ALA206, GLY205, ILE202, ALA201, ALA198, and PHE97 and van der Waals interactions with amino acid residues like GLY96, PHE97, MET161, ALA198, ALA201, ILE202, and GLY204 (Fig. S4). Compound **6g** showed aromatic binding interaction with TYR158 and PHE149 and hydrophobic interaction with PHE149, MET161, LYS165, PRO193, MET199, and LEU218 and van der Waals interactions with GLY96, PHE97, MET98, MET103, PHE149, MET155, PRO156, TYR158, MET161, MET199, GLN214, and LEU218 (Fig. 3). Compound **6h** interacted with *Enoyl acyl carrier protein reductase* via the formation of hydrogen bond interaction with ALA198, TYR158, and MET98 and aromatic interaction with TYR158 and van der Waals interactions with GLY96, PHE97, MET98, MET103, PHE149, MET155, PRO156, TYR158, MET161, and MET199 (Fig. S5). Compound **6i** showed interactions with MET199 via the formation of a hydrogen bond and TYR158 via the formation of an aromatic bond; it also showed hydrophobic interaction with PHE97, ALA198, and MET199 and van der Waals interactions with GLY96, PHE97, MET98, MET103, and PHE149 (Fig. S6). Compound **6j** is another active molecule found to show hydrogen bond interactions with TYR158 and hydrophobic interactions with ALA201 and ALA206 and van der Waals interactions with GLY96, PHE97, MET103, TYR158, MET161, and ALA201 (Fig. S7). Compound **6k** showed hydrogen bond interaction with MET103 and aromatic interactions with PHE149 and TYR158 and hydrophobic interaction with LEU218, ILE215, ILE202, MET199, PRO193, and TYR158 and van der Waals interactions with GLY96, PHE97, MET103, TYR158, and MET161 (Fig. 4). Compound **6l** showed hydrogen bond interactions with TYR158, hydrophobic interaction with PHE97, LEU197, ALA198, ALA201, and GLY205, and van der Waals interactions with GLY96, PHE97, MET98, MET103, PHE149, MET155, and PRO156 (Fig. S8). Compound **6n** is also an active derivative that showed hydrogen bond interaction with TYR158 and

Table 4 ADME prediction of compounds **6a**–**w**

Comp.	MW	#Rotatable bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	M LogP	GI absorption	BBB permeate	Bioavailability score
6a	332.42	4	3	0	97.28	71.84	3.02	High	Yes	0.55
6b	411.32	4	3	0	104.98	71.84	3.63	High	No	0.55
6c	366.87	4	3	0	102.29	71.84	3.52	High	No	0.55
6d	350.41	4	4	0	97.24	71.84	3.4	High	No	0.55
6e	346.45	4	3	0	102.25	71.84	3.25	High	No	0.55
6f	346.45	4	3	0	102.25	71.84	3.25	High	No	0.55
6g	350.41	4	4	0	97.24	71.84	3.4	High	No	0.55
6h	429.31	4	4	0	104.94	71.84	4.01	High	No	0.55
6i	384.86	4	4	0	102.25	71.84	3.9	High	No	0.55
6j	368.4	4	5	0	97.2	71.84	3.78	High	No	0.55
6k	364.44	4	4	0	102.2	71.84	3.63	High	No	0.55
6l	364.44	4	4	0	102.2	71.84	3.63	High	No	0.55
6m	364.44	4	4	0	102.2	71.84	3.63	High	No	0.55
6n	445.76	4	3	0	109.99	71.84	4.12	High	No	0.55
6o	401.31	4	3	0	107.3	71.84	4.01	High	No	0.55
6p	384.86	4	4	0	102.25	71.84	3.9	High	No	0.55
6q	380.89	4	3	0	107.26	71.84	3.74	High	No	0.55
6r	380.89	4	3	0	107.26	71.84	3.74	High	No	0.55
6s	346.45	4	3	0	102.25	71.84	3.25	High	No	0.55
6t	425.34	4	3	0	109.95	71.84	3.85	High	No	0.55
6u	380.89	4	3	0	107.26	71.84	3.74	High	No	0.55
6v	364.44	4	4	0	102.2	71.84	3.63	High	No	0.55
6w	360.48	4	3	0	107.21	71.84	3.47	High	No	0.55

MW molecular weight; *MR* molar refraction; *TPSA* total polar surface area; *M LogP* logarithm of participation coefficient; *GI absorption* gastrointestinal tract absorption; *BBB* blood–brain barrier

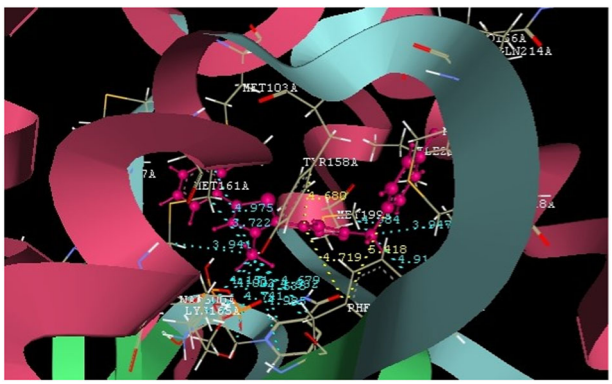


Fig. 3 Docking image of compound **6g** (5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole)

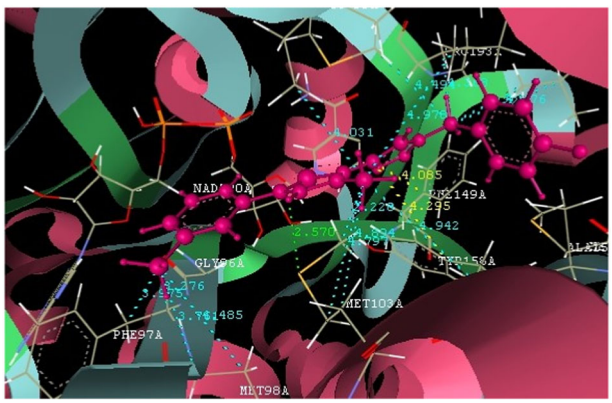


Fig. 4 Docking interactions of 5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole (**6k**) (most active)

aromatic interaction with TYR158 and PHE149, and hydrophobic interactions with GLY96, PHE97, MET161, and MET199 and van der Waals interactions with GLY96, PHE97, MET98, MET103, PHE149, MET155, and PRO156 (Fig. S9).

ADME prediction

ADME of all the synthesized molecules was predicted using the online free portal www.swissadme.ch to check the

possible violation of any drug-like properties (SwissADME 2017, iLOGP 2014). The synthesized derivatives are found to have good drug-like properties for oral use. All the molecules showed good GI absorption and nonpermeation in the BBB, which is an ideal property; they also showed a good bioavailability score of 0.55 (Table 4).

Conclusions

In the present study, we have detailed the synthesis and biological screening of 5-(1-benzyl-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole derivatives, **6a**−**w**. It can be concluded that most of the synthesized compounds showed good-to-excellent antitubercular activity against *M. tuberculosis H37Ra*. It is worth mentioning that 4-fluoro-substituted benzyl on 1-position of 1,2,3-triazole and a substituted phenyl at 2-position of thiazole reported good-to-excellent activity. Also, 4-bromo- or 4-methyl-substituted phenyl (ring A) at 2-position of thiazole and an unsubstituted or a substituted benzyl ring at 1,2,3-triazole showed good antitubercular activity. Among the synthesized compounds, compounds 5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole (**6g**) and 5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole (**6k**) reported excellent activity. Thus, these results warrant the need for further synthesis of similar libraries with other substituents to ascertain the trend described in this work.

Acknowledgements The authors would like to thank CSIR-NCL, Pune for supporting the biological activity. Central Analysis facility, Savitribai Phule Pune University, Pune is also acknowledged for the spectral analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abhale YK, Sasane AV, Chavan AP, Deshmukh KK, Kotapalli SS, Ummanni R, Sayyad SF, Mhaske PC (2015) Synthesis and biological screening of 20-aryl/benzyl-2-aryl-4-methyl-4,5-bithiazolyls as possible anti-tubercular and antimicrobial agents. Eur J Med Chem 94:340

Abhale YK, Deshmukh KK, Sasane AV, Chavan AP, Mhaske PC (2016) Synthesis and antitubercular activity of novel 6-substituted-2-(4-methyl-2-substituted phenylthiazol-5-yl)H-imidazo [1,2-a]pyridine. J Heterocycl Chem 53:229

Abhale YK, Sasane AV, Chavan AP, Shekh SH, Deshmukh KK, Bhansali S, Nawale L, Sarkar D, Mhaske PC (2017) Synthesis and antimycobacterial screening of new thiazolyl-oxazole derivatives. Eur J Med Chem 132:333

Alley MC, Scudiere DA, Monks A, Hursey ML, Czerwinski MJ, Fine DL, Abbott BJ, Mayo JG, Shoemaker RH, Boyd MR (1988) Feasibility of drug screening with panels of human tumor cell lines using a microculture tetrazolium assay. Cancer Res 48 (3):589–601

Azzali E, Machado D, Kaushik A, Vacondio F, Flisi S, Cabassi C, Lamichhane G, Viveiros M, Costantino G, Pieroni M (2017) Substituted *N*-phenyl-5-(2-(phenylamino)thiazol-4-yl)isoxazole-3-carboxamides are valuable antitubercular candidates that evade innate efflux machinery. J Med Chem 60:7108

Bansode P, Jadhav J, Kurane R, Choudhari P, Bhatia M, Khanapure S, Salunkhe R, Rashinkar G (2016) Potentially antibreast cancer enamidines via azide– alkyne–amine coupling and their molecular docking studies. RSC Adv 6:90597

Barradas JS, Errea MI, D'Accorso NB, Sepulveda CS, Damonte EB (2011) Imidazo[2,1-*b*]thiazole carbohydrate derivatives: Synthesis and antiviral activity against *Junin* virus, agent of Argentine hemorrhagic fever. Eur J Med Chem 46:259–264

Chen MD, Lu SJ, Yuag GP, Yang SY, Du XL (2000) Synthesis and antibacterial activity of some heterocyclic beta-enamino ester derivatives with 1, 2, 3-triazole. Heterocycl Comm 6:421

Christian F, Ben M, Susan Z, Joey M, Hua Z, Colby BW (2008) Preparation of triazole derivatives for treating Alzheimer's disease and related conditions, WIPO patent, WO2008156580A1

Davyt D, Serra G (2010) Thiazole and oxazole alkaloids: isolation and synthesis. Mar Drugs 8:2755

Dmitry V, Demchuk AV, Samet NB, Chernysheva VI, Ushkarov GA, Stashina LD, Konyushkin MM, Raihstat SI, Firgang AA, Philchenkov MP, Zavelevich LM, Kuiava VF, Chekhun DY, Blokhin AS, Kiselyov MN, Semenova VV (2014) Synthesis and antiproliferative activity of conformationally restricted 1,2,3-triazole analogues of combretastatins in the sea urchin embryo model and against human cancer cell lines. Bioorg Med Chem 22:738

Dongamanti A, Arram G, Bommidi V, Sidda R, Banoth R (2014) Microwave assisted synthesis and antimicrobial activity of novel 1-[1/2-(1-Benzyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-naphthalen-2/1-yl]-3-(1-phenyl-3-aryl-1*H*-pyrazol-4-yl)-propenones. Org Commun 8:24

Farghaly A. R, El-Kashef H (2006) Synthesis of some new azoles with antiviral potential ARKIVOC xi_76

Foks H, Janowiec M, Zwolska Z, Augustynowicz-Kopeć E (2005) Synthesis and tuberculostatic activity of some 2-Piperazinmethylene derivatives 1,2,4-Triazole-3-Thiones. Phosphorus Sulfur Silicon Relat Elem 180:537

Gaikwad ND, Patil SV, Bobade VD (2012a) Synthesis and biological evaluation of some novel thiazole substituted benzotriazole derivatives. Bioorg & Med Chem Lett 22:3449

Gaikwad ND, Patil SV, Bobade VD (2012b) Hybrids of ravuconazole: Synthesis and biological evaluation. Eur J Med Chem 54:295

Giri RS, Thaker HM, Giordano T, Williams J, Rogers D, Sudersanam V, Vasu KK (2009) Synthesis and characterization of novel 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3H-quinazoline-4-one derivatives as inhibitors of NF-kB and AP-1 mediated transcription activation and as potential anti-inflammatory agents. Eur J Med Chem 44:2184

Gonzaga DT, da Rocha DR, da Silva FC, Ferreira VF (2013) Recent advances in the synthesis of new antimycobacterial agents based on the 1H-1,2,3-triazoles. Curr Top Med Chem 13:2850

Guan LP, Jin QH, Tian GR, Chai KY, Quan ZS (2007) Synthesis of some quinoline-2(1*H*)-one and 1,2,4-triazolo [4,3-*a*]quinoline derivatives as potent anticonvulsants. J Pharm Sci 10:254

Gujjar R, Marwaha A, White J, White L, Creason S, Shackleford DM, Baldwin J, Charman WN, Buckner FS, Charman S, Rathod PK, Phillips MA (2009) Identification of a metabolically stable

triazolopyrimidine-based dihydroorotate dehydrogenase inhibitor with antimalarial activity in mice. J Med Chem 52:1864

Güzeldemirci NU, Küçükbasmac Ö (2010) Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole moiety. Eur J Med Chem 45:63

Hafez HN, Abbas HA, El-Gazzar AR (2008) Synthesis and evaluation of analgesic, anti-inflammatory and ulcerogenic activities of some triazolo- and 2-pyrazolyl-pyrido[2,3-*d*]-pyrimidines. Acta Pharm 58:359

Holla BS, Mahalinga M, Karthikeyen MS, Poojary B, Akberali PM, Kumari NS (2005) Synthesis, characterization and antimicrobial activity of some substituted 1,2,3-triazoles. Eur J Med Chem 40:1173

Jadhav GR, Shaikh MU, Kale RP, Shiradkar MR, Gill CH (2009) SAR study of clubbed [1,2,4]-triazolyl with fluorobenzimidazoles as antimicrobial and antituberculosis agents. Eur J Med Chem 44:2930

Jeankumar VU, Chandran M, Samala G, Alvala M, Koushik PV, Yogeeswari P, Salina EG, Sriram D (2012) Development of 5-nitrothiazole derivatives: Identification of leads against both replicative and latent *Mycobacterium tuberculosis*. Bioorg & Med Chem Lett 22:7414

Jeankumar VU, Rudraraju SR, Vats R, Janupally R, Saxena S, Yogeeswari P, Sriram D (2016) Engineering another class of anti-tubercular lead: Hit to lead optimization of an intriguing class of gyrase ATPase inhibitors. Eur J Med Chem 122:216

Jeong K, Lee J, Park S, Choi J, Jeong D, Choi D, Nam Y, Park J, Lee K, Kim S, Ku J (2015) Synthesis and in-vitro evaluation of 2-amino-4-arylthiazole as inhibitor of 3D polymerase against foot-and-mouth disease (FMD). Eur J Med Chem 102:375

iLOGP (2014) a simple, robust, and efficient description of n-octanol/water partition coefficient for drug design using the GB/SA approach. J Chem Inf Model 54:3284

Karale BK, Takate SJ, Salve SP, Zaware BH, Jadhav SS (2014) Synthesis and biological screening of thiazolyl triazoles and thiazoles. Indian J Chem 53B:339

Kashyap SJ, Garg VK, Sharma PK, Kumar N, Dudhe R, Gupta JK (2012) Thiazoles: having diverse biological activities. Med Chem Res 21:2123

Kathiravan MK, Salake A, Chothe AS, Dudhe PB, Watode RP, Mukta MS, Gadhwe S (2012) The biology and chemistry of antifungal agents: a review. Bioorg & Med Chem 20:5678

Keri RS, Patil SA, Budagumpi S, M.Nagaraja B (2015) Triazole: a promising antitubercular agent. Chem Biol Drug Des 86:410

Khan A, Sarkar D (2008) A simple whole cell based high throughput screening protocol using Mycobacterium bovis BCG for inhibitors against dormant and active tubercle bacilli. J Microbiol Methods 73:62

Kouatly O, Geronikaki A, Kamoutsis C, Hadjipavlou-Litina D, Eleftheriou P (2008) Adamantane derivatives of thiazolyl-N-substituted amide, as possible non-steroidal anti-inflammatory agents. Eur J Med Chem 44:1198

Krishna KM, Inturi B, Pujar GV, Purohit MN, Vijaykumar GS (2014) Design, synthesis and 3D-QSAR studies of new diphenylamine containing 1,2,4-triazoles as potential antitubercular agents. Eur J Med Chem 84:516

Li H, He D, Zhao X, Sun T, Zhang Q, Bai C, Chen Y (2018) Design and synthesis of novel dasatinib derivatives as inhibitors of leukemia stem cells. Bio-Org Med Chem Lett 28:700

Liu ZY, Wang YM, Li ZR, Jiang JD, Boykin DW (2009) Synthesis and anticancer activity of novel 3,4-diarylthiazol-2(3H)-ones (imines). Bioorg Med Chem 19:5661

Liu Z, Zhu Q, Li F, Zhang L, Leng Y, Zhang A (2011) N-(5-substituted thiazol-2-yl)-2-aryl-3-(tetrahydro-2H-pyran-4-yl)propanamides as glucokinase activators. Med Chem Commun 2:531

Martinelli LKB, Rotta M, Villela AD, Rodrigues-Junior VS, Abbadi BL, Trindade RV, Petersen GO, Danesi GM, Nery LR, Pauli I, Campos MM, Bonan CD, de Souza ON, Basso LA, Santos DS (2017) Functional, thermodynamics, structural and biological studies of *in silico*-identified inhibitors of *Mycobacterium tuberculosis* enoyl-ACP(CoA) reductase enzyme. Sci Rep 7:46696

Mishra CB, Kumari S, Tiwari M (2015) Thiazole: A promising heterocycle for the development of potent CNS active agents. Eur J Med Chem 92:1

Oniga O, Ndongo JT, Moldovan C, Tiperciuc B, Oniga S, Pirnau A, Vlase L, Verite P (2012) Synthesis and antimicrobial activity of some new 2- hydrazone-thiazoline-4-ones. Farmacia 60:6785

Oniga S, Duma M, Oniga O, Tiperciuc B, Pirnau A, Araniciu C, Palage M (2015) Synthesis of some new 4-methyl-2-(4-pyridyl)-thiazole-5-yl-azoles as potential antimicrobial agents. Farmacia 63:2

Pandya DH, Sharma JA, Jalani HB, Pandya AN, Sudarsanam V, Kachler S, NorbertKlotz K, Vasu KK (2015) Novel thiazole–thiophene conjugates as adenosine receptor antagonists: Synthesis, biological evaluation and docking studies. Bioorg & Med Chem Lett 25:1306

Passannanti A, Diana P, Barraja P, Mingooia F, Lauria A, Cirrincine G (1998) Pyrrolo[2,3-d][1,2,3]triazoles as potential antineoplastic agents. Heterocycles 48:1229

Patil KT, Walekar LS, Undare SS, Kolekar GB, Deshmukh MB, Choudhari PB, Anbhule PV (2016) Selective synthesis of 10,11-dihydrochromeno[4,3-b]chromene-6,8(7H,9H)-dione using copper oxide nanoparticles for potential inhibitors of β-ketoacyl-[acyl-carrier-protein]synthase III of Mycobacterium tuberculosis. Indian J Chem Sect B 55B:1151

Patpi SR, Pulipati L, Yogeeswari P, Sriram D, Jain N, Sridhar B, Murthy R, Devi AT, Kalivendi SV, Kantevari S (2012) Design, synthesis, and structure–activity correlations of novel dibenzo[*b*,*d*]furan, dibenzo[*b*,*d*]thiophene, and *N*-methylcarbazole clubbed 1,2,3-triazoles as potent inhibitors of *Mycobacterium tuberculosis*. J Med Chem 55:3911

Patravale AA, Gore AH, Kolekar GB, Deshmukh MB, Choudhari PB, Bhatia MS, Prabhu S, Jamdhade MD, Patole MS, Anbhule PV (2016) Synthesis, biological evaluation and molecular docking studies of some novel indenospiro derivatives as anticancer agents. J Taiwan Inst Chem Eng 68:105

Ramesh R, Shingare RD, Kumar V, Anand A, Swetha B, Veeraraghavan S, Viswanadha S, Ummanni R, Gokhale R, Reddy DS (2016) Repurposing of a drug scaffold: Identification of novel sila analogues of rimonabant as potent antitubercular agents. Eur J Med Chem 122:723

Reddy T, Kulhari H, Reddy V, Rao AVS, Bansal V, Kamal A, Shukla R (2015) Synthesis and biological evaluation of pyrazolo-triazole hybrids as cytotoxic and apoptosis inducing agents. Organic & Biomol Chem 13:10136

Rostom SAF, El-Ashmawy IM, Abd El Razik HA, Badr MH, Ashour HMA (2009) Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents. Bioorg Med Chem 17:882

Samala G, Devi PB, Saxena S, Meda N, Yogeeswari P, Sriram D (2016) Design, synthesis and biological evaluation of imidazo[2,1-*b*]thiazole and benzo[*d*]imidazo[2,1-*b*]thiazole derivatives as *Mycobacterium tuberculosis* pantothenate synthetase inhibitors. Bioorg & Med Chem 24:1298

Sarkar S, Sarkar D (2012) Potential use of nitrate reductase as a biomarker for the identification of active and dormant inhibitors of Mycobacterium tuberculosis in a THP1 infection model. J Biomol Screen 17:966

Shaikh MH, Subhedar DD, Nawale L, Sarkar D, Khan FAK, Sangshetti JN, Shingate BB (2015) 1,2,3-Triazole derivatives as

antitubercular agents: synthesis, biological evaluation and molecular docking study. Med Chem Comm 6:1104

Shanmugavelan P, Nagarajan S, Sathishkumar M, Ponnuswamy A, Yogeeswari P, Sriram D (2011) Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of *Mycobacterium tuberculosis*. Bioorg Med Chem Lett 21:7273

Shanthi V, Ramanathan K (2014) Identification of potential inhibitor targeting enoyl-acyl carrier protein reductase (InhA) in Mycobacterium tuberculosis: a computational approach. Biotech 4:253

Shelke SH, Mhaske PC, Nandave M, Narkhade S, Walhekar NM, Bobade VD (2012) Synthesis and pharmacological evaluation of a novel series of 3-aryl-2-(2-substituted-4-methylthiazole-5-yl) thiazolidin-4-one as possible anti-inflammatory and antimicrobial agents. Bioorg Med Chem Lett 22:6373

Shinde V, Mahulikar P, Mhaske PC, Nawale L, Sarkar D (2018) Synthesis and biological evaluation of new 2-aryl-4-((4-aryl-1*H*-1,2,3-triazol-1-yl)methyl)thiazole derivatives. Res Chem Intermed 44:1247

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

Shiradkar MR, Murahari KK, Reddy GH, Tatikonda S, Chakravarthy AK, Dolly P, Kaur R, Burange P, Ghogare J, Mokalec V, Rautc M (2007) Synthesis of new S-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents. Bioorg Med Chem 15:3997

Shiran JA, Yahyazadeh A, Mamaghani M, Rassa M (2013) Regioselective synthesis of novel 3-allyl-2-(substituted imino)-4-phenyl-3*H*-thiazole and 2,2′-(1,3-phenylene)bis(3-substituted-2-imino-4-phenyl-3*H*-thiazole) derivatives as antibacterial agents. J Mol Struct 1039:113

Shenoi S, Friedland G (2009) Extensively drug-resistant tuberculosis: a new face to an old pathogen. Annu Rev Med 60:307

Shirude PS, Madhavapeddi P, Naik M, Murugan K, Shinde V, Nandishaiah R, Bhat J, Kumar A, Hameed S, Holdgate G, Davies G, McMiken H, Hegde N, Ambady A, Venkatraman J, Panda M, Bandodkar B, Sambandamurthy VK, Read JA (2013) Methyl-Thiazoles: a novel mode of inhibition with the potential to develop novel inhibitors targeting InhA in mycobacterium tuberculosis. J Med Chem 56:8533

Singh R, Nawale L, Arkile M, Shedbalkar U, Wadhwani S, Sarkar D, Chopade B (2015) Chemical and biological metal nanoparticles as antimycobacterialagents: a comparative study. Int J Antimicrob Agents 46:183

Skedelj V, Perdih A, Brvar M, Kroflic A, Dubbée V, Savage V, O'Neill AJ, Solmajer T, Bester-Rogac M, Blanot D, Hugonnet JE, Magnet S, Arthur M, Mainardi JL, Stojan J, Zega A (2013) Discovery of the first inhibitors of bacterial enzyme D-aspartate ligase from Enterococcus faecium (Asl_{fm}). Eur J Med Chem 67:208

SwissADME (2017) a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 7:42717

Tantry SJ, Markad SD, Shinde V, Bhat J, Balakrishnan G, Gupta AK, Ambady A, Raichurkar A, Kedari C, Sharma S, Mudugal NV, Narayan A, Naveen Kumar CN, Nanduri R, Bharath S, Reddy J, Panduga V, Prabhakar KR, Kandaswamy K, Saralaya R, Kaur P, Dinesh N, Guptha S, Rich K, Murray D, Plant H, Preston M, Ashton H, Plant D, Walsh J, Alcock P, Naylor K, Collier M, Whiteaker J, McLaughlin RE, Mallya M, Panda M, Rudrapatna S, Ramachandran V, Shandil R, Sambandamurthy VK, Mdluli K, Cooper CB, Rubin H, Yano T, Iyer P, Narayanan S, Kavanagh S, Mukherjee K, Balasubramanian V, Hosagrahara VP, Solapure S, Ravishankar S, Shahul HP (2017) Discovery of Imidazo[1,2-a]pyridine ethers and squaramides as selective and potent inhibitors of mycobacterial adenosine triphosphate (ATP) synthesis. J Med Chem 60:1379

Tomasic T, Katsamakas S, Hodnik Z, Ilas J, Brvar M, Solmajer T, Montalvao S, Tammela P, Banjanac M, Ergovic G, Anderluh M, Masic LP, Kikelj D (2015) Discovery of 4,5,6,7-Tetrahydrobenzo[1,2-*d*]thiazoles as novel DNA gyrase inhibitors targeting the ATP-binding site. J Med Chem 58:5501

Wang Q, Song F, Xiao X, Huang P, Li L, Monte A, Abdel-Mageed WM, Wang J, Guo H, He W, Xie F, Dai H, Liu M, Chen C, Xu H, Liu M, Piggott AM, Liu X, Capon RJ, Zhang L (2013) Abyssomicins from the South China Sea deep-sea sediment Verrucosispora sp.: natural thioether Michael addition adducts as antitubercular prodrugs. Angew Chem Int Ed 52:1231

Wang X, Dai Z, Chen Y, Cao L, Yan W, Li S, Wang J, Zhang Z, Ye Y (2017) Synthesis of 1,2,3-triazole hydrazide derivatives exhibiting anti-phytopathogenic activity. Eur J Med Chem 126:171

Weide T, Saldanha SA, Minond D, Spicer TP, Fotsing JR, Spaargaren M, Frere J, Bebrone C, Sharpless KB, Hodder PS, Fokin VV (2010) NH-1,2,3-Triazole inhibitors of the VIM-2 metallo-β-lactamase. ACS Med Chem Lett 1:150

World Health Organization (2016) Tuberculosis Fact Sheet. http://www.who.int/news-room/fact-sheets/detail/tuberculosis.