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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

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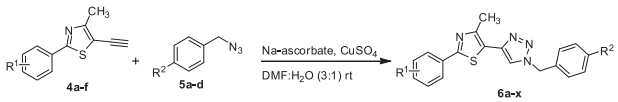
Abstract

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

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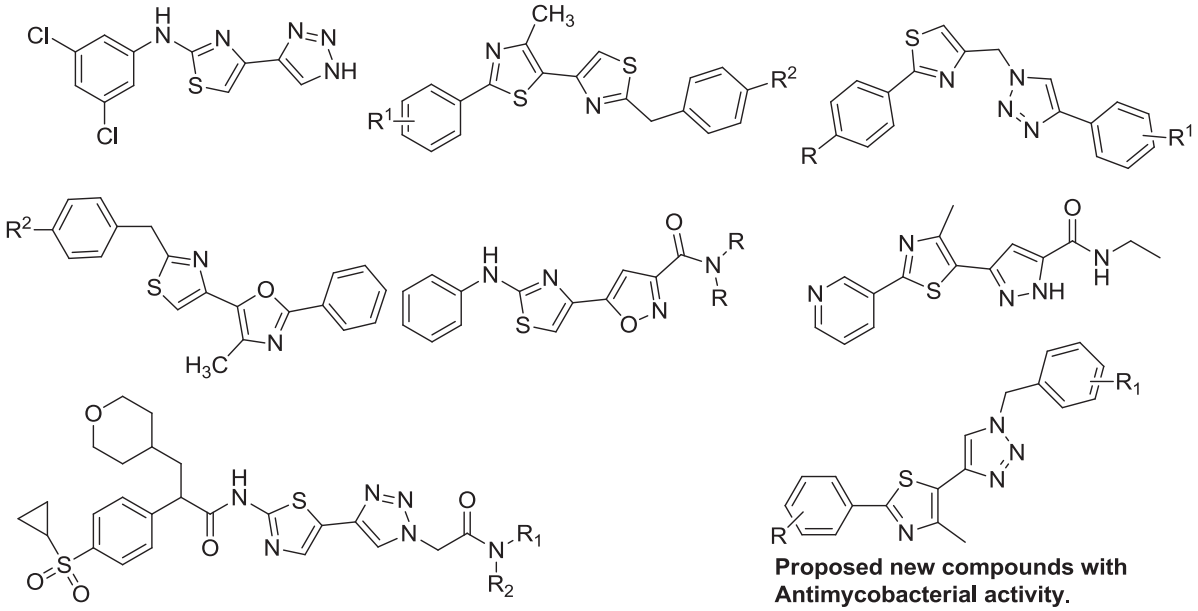


Fig. 1 Representative antitubercular active thiazolyl-triazole compounds and the new proposed analogs

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

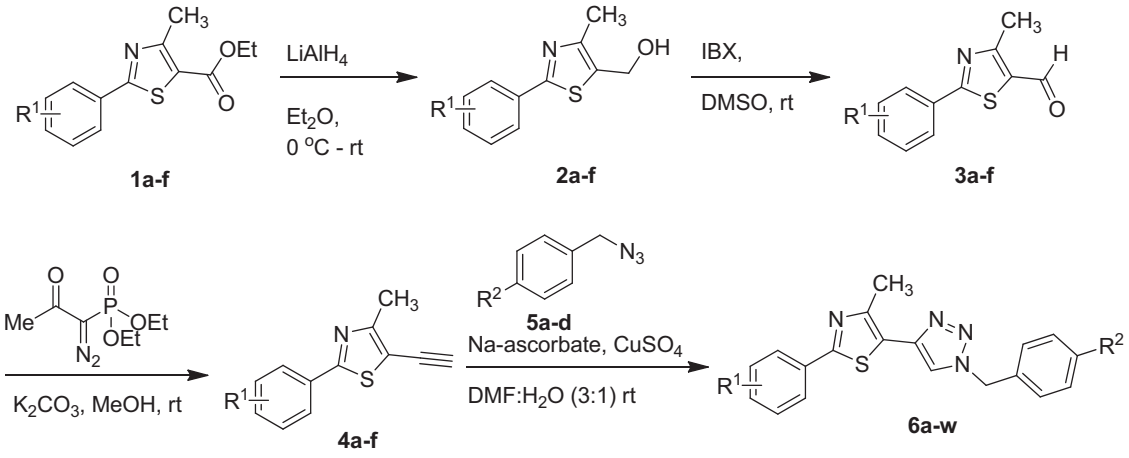
Chemistry

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**

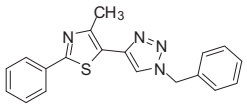
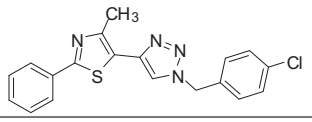
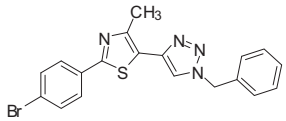
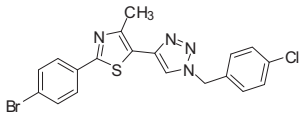
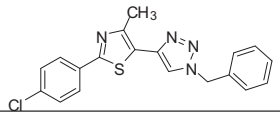
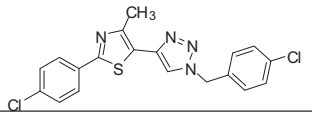
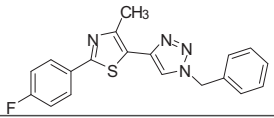
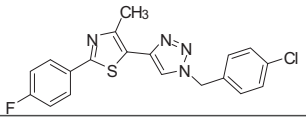
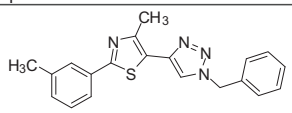
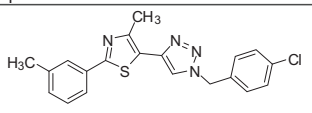
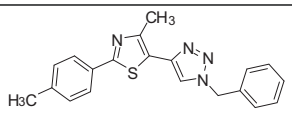
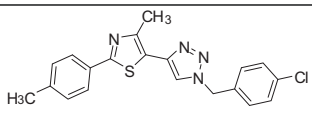
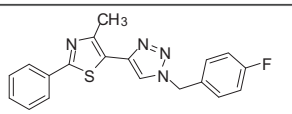
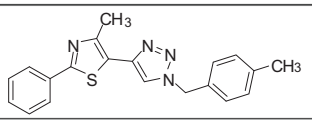
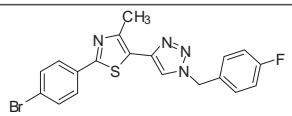
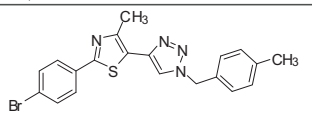
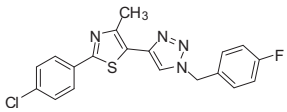
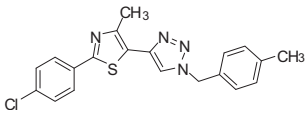
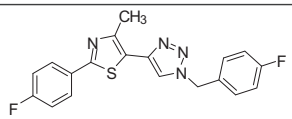
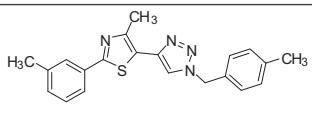
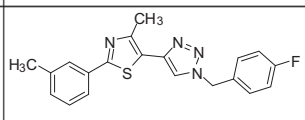
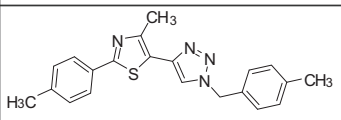
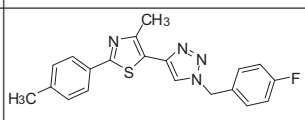
Comp.	Structure	m.p. °C	Yield %	Comp.	Structure	m.p. °C	Yield %
6a		168-170	84	**6m**		158-160	88
6b		149-150	80	**6n**		128-129	85
6c		176-178	75	**6o**		140-141	84
6d		168-170	80	**6p**		142-143	84
6e		136-137	88	**6q**		136-138	90
6f		139-140	86	**6r**		156-157	88
6g		136-138	72	**6s**		170-172	85
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

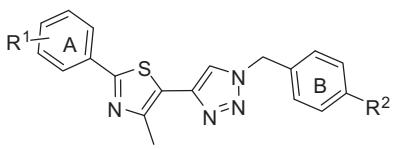


Fig. 2 Compounds **6a**–**w**

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

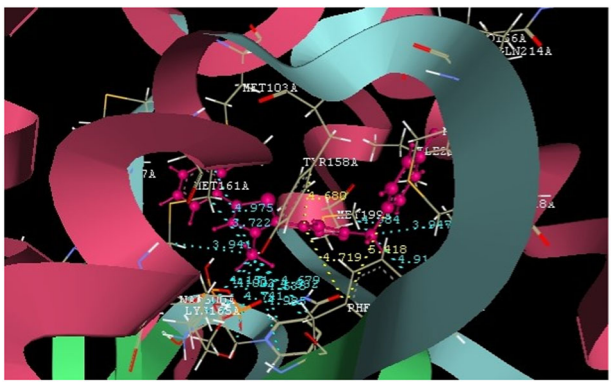


Fig. 3 Docking image of compound **6g** (5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-phenylthiazole)

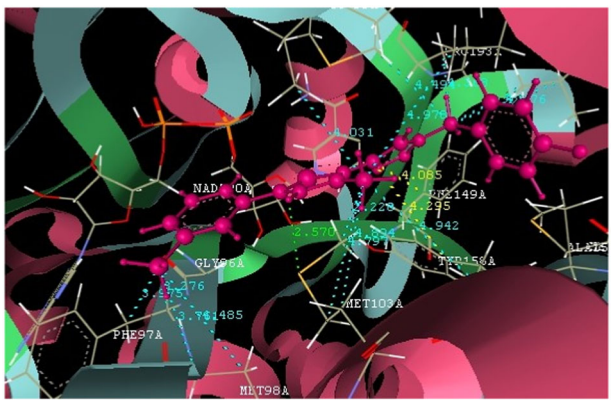


Fig. 4 Docking interactions of 5-(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)-4-methyl-2-(m-tolyl)thiazole (**6k**) (most active)

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.

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Compliance with ethical standards

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

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