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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Convenient synthesis, antimalarial and antimicrobial potential of thioethereal 1,4-disubstituted 1,2,3-triazoles with ester functionality

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Abstract This paper elicits the synthesis of twenty five 1,4-disubstituted 1,2,3-triazole analogs (**5a–5y**) comprising thioether and ester linkages from aryl(prop-2-yn-1-yl)sulfanes and benzyl 2-azidoacetates employing Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition. Structures of synthesized compounds were elucidated by spectroscopic techniques like FTIR, ^{1}H NMR, ^{13}C NMR, and HRMS. Newly synthesized compounds were screened for in vitro antimalarial evaluation against *P. falciparum* strain and microbicidal potential against *B. subtilis*, *S. epidermidis*, *E. coli*, *P. aeruginosa*, *C. albicans*, and *A. niger*. Some of synthesized triazoles displayed moderate antimalarial activity against tested strain, while, the compounds **5i** and **5n** were found to exhibit significant inhibitory activity against most of the tested microbial strains.

Keywords Antimalarial evaluation · Antimicrobial potential · Click chemistry · 1,4-Disubstituted 1,2,3-triazoles · Huisgen 1,3-dipolar cycloaddition

Introduction

Malaria is one of the common prevalent fatal diseases caused by infection of protozoans parasites. Among the several species of plasmodium protozoans, *P. falciparum* is the most virulent form responsible for death of millions of people across the world. *P. falciparum* causes cerebral malaria which leads to abnormal behavior, convulsions and impairment of consciousness, whereas, crucial symptoms include severe anemia due to destruction of infected red blood cells. During the past few years, microbial infections are also increasing at an alarming rate in society. Emergence of increasing drug resistance against malarial parasite like *P. falciparum* and microbial infections prompted the researchers to design and synthesize new molecules which may prove as significant antimalarial/antimicrobial agent. In this scenario, N-heterocyclic compounds, especially triazole derivatives received considerable attention of organic chemists to explore their medicinal potentials particularly for malarial and microbial infections (Balabadra et al. 2017; Kaushik et al. 2014a; Zhang et al. 2015). Because 1,2,3-triazole derivatives have been found to possess various therapeutic properties like antimicrobial (Lal et al. 2012; Kaushik et al. 2014b, 2015, 2016a), anticancer (He et al. 2010; Singh et al. 2012; Kumbhare et al. 2014), anti-inflammatory (Vasilevsky et al. 2014), anticonvulsant (Karakurt et al. 2006), antiviral (Zhou et al. 2005), antioxidant (Dubey et al. 2015; Dügdü et al. 2016), antimalarial (D'hooghe et al. 2011), antihistaminic (Buckle et al. 1986), antitubercular (Gilla et al. 2008; Kumar et al. 2013), antiproliferative (Nagesh et al. 2015), anti-HIV (Whiting et al. 2006) etc.

Stability of 1,2,3-triazoles against metabolic degradation, oxidation, reduction, acidic and basic conditions, capability of hydrogen bonding and solubility in biological system

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facilitates these moieties for effective binding with biomolecular targets. (Horne et al. 2004; Ferreira et al. 2010) Moreover, substituted 1,2,3-triazole scaffolds also serve as versatile building blocks in synthesis of nucleosides (Jørgensen et al. 2011) and nucleotides analogs (Głowacka et al. 2012). Substituted 1,2,3-triazoles can be synthesized by Huisgen's thermally induced 1,3-dipolar cycloaddition, is the earliest known method leads to mixture of 1,4 and 1,5 regioisomers (Huisgen et al. 1967). However, highly accelerated Cu(I) catalyzed cycloaddition between terminal alkynes and azides invented by Sharpless and Meldal exclusively yields 1,4 disubstituted 1,2,3-triazoles (Kolb et al. 2001; Tornøe et al. 2002; Friscourt and Boons 2010). This reaction emerged as one of the prime example of click chemistry as it is modular, selective, versatile, wide in scope and easy to perform. The click reaction has also found many applications in supramolecular chemistry and drug discovery (Banday et al. 2012).

In continuation to our previous work on synthesis and biological evaluation of 1,4-disubstituted 1,2,3-triazole derivatives (Kaushik et al. 2016b), we report herein also, a series of expedient synthesis of thioether-ester linked 1,4-disubstituted 1,2,3-triazoles (**5a–5y**) from aryl(prop-2-yn-1-yl)sulfanes and benzyl 2-azidoacetates via Cu(I) catalyzed click reaction. All the synthesized compounds were characterized by spectroscopic techniques Fourier transform infrared (FTIR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR spectroscopy, and high resolution mass spectrometry (HRMS). In vitro antimalarial potential against *Plasmodium falciparum* and antimicrobial potential against *Bacillus subtilis*, *Staphylococcus epidermidis, Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Aspergillus niger* of synthesized triazoles were also accessed.

Materials and methods

Chemistry

All the starting materials and solvents used in present work were procured from Hi-Media, Alfa-Aesar, Sigma-Aldrich and were used without any further purification. Nutrient broth and Sabouraud dextrose broth used in antimicrobial evaluation were purchased from Hi-Media, Mumbai. Thin layer chromatography (TLC) was performed on readymade silica gel plates (SIL G/UV254, ALUGRAM) to examine the completion of reaction and visualization was achieved under ultraviolet (UV) light. Melting points (°C) of the synthesized compounds were measured by open capillaries and are uncorrected. The infrared (IR) spectra were obtained on SHIMAZDU IR AFFINITY-I FT-IR spectrophotometer in potassium bromide (KBr) powder and values were represented in cm^{-1}. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively on BRUKER AVANCE II 400 MHz spectrophotometer (chemical shift in δ, ppm). Values of coupling constant (J) were recorded in Hz. HRMS were recorded on Bruker micro TOF Q-II spectrometer.

*General procedure for synthesis of thioether-ester linked 1–4 disubstituted 1,2,3-triazoles (**5a–5y**)*

Thioether linked terminal alkynes i.e., aryl(prop-2-yn-1-yl) sulfanes (Kaushik et al. 2017) (**2a–2e**) were synthesized by reaction of aromatic thiols (**1a–1e**) (1.0 mmol) and propargyl bromide (1.0 mmol) with potassium carbonate (3.0 mmol) as base using *N*,*N*-dimethylformamide as solvent at 10–25 °C temperature with constant stirring for 5–6 h. Reaction was monitored by TLC. Upon completion of reaction, dilute hydrochloric acid was added to reaction mixture and compound was extracted with ethyl acetate (3 × 30 mL). Organic layer was removed by evaporation under reduced pressure to get desired terminal alkynes (**2a–2e**).

Synthesis of benzyl 2-bromoacetates (**4a–4e**) were carried out by dropwise addition of bromoacetyl bromide (1.2 mmol) in the stirred solution of benzyl alcohols (**3a–3e**) (1.0 mmol) in acetonitrile in the presence of sodium bicarbonate (1.5 mmol) as base at 0–4 °C and continued stirring for 45 min. When the reaction was completed, reaction mixture was extracted with dichloromethane (3 × 30 mL). Organic layer was evaporated under vaccum to obtain products (**4a–4e**) in good yield.

For the synthesis of triazole derivatives (**5a–5y**), benzyl 2-bromoacetates (1.0 mmol) (**4a–4e**) were dissolved in *N*,*N*-dimethylformamide in round bottom flask and aqueous sodium azide (3.0 mmol) was added at 25–40 °C under stirring which was continued for 1 h. Afterwards, aryl(prop-2-yn-1-yl)sulfanes (**2a–2e**) were added followed by aqueous copper sulfate pentahydrate (0.1 mmol) and sodium ascorbate (0.4 mmol), to above reaction mixture which was allowed to stirred for 8–18 h at same temperature. After the completion of reaction, ice cold water was added to the reaction contents and products were extracted with ethyl acetate (3 × 30 mL), followed by washing with aqueous ammonia solution and then with saturated brine solution. Thereafter, organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain crude solid which was further recrystallized from chloroform to furnish pure compounds (**5a–5y**) in good yields.

*Characterization of synthesized compounds (**5a–5y**)*

Benzyl 2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazol-1-yl) acetate (**5a**) White solid; yield: 82%; m.pt: 78–82 °C;

FT-IR (KBr): 3120 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2997 (C–H str., aliphatic), 1753 (C=O str., ester), 1639, 1457 (C=C str., aromatic ring), 1209 (C–O asym. str., ester), 1053 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.25$ (s, 2H, $\underline{SCH_2}$), 5.12 (s, 2H, $\underline{NCH_2}$), 5.20 (s, 2H, $\underline{OCH_2}$), 7.18–7.36 (m, 10H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.88$, 50.93, 68.01, 123.46 (C_5 triazole), 126.53, 128.56, 128.77, 128.86, 129.02, 129.61, 134.52, 135.45, 145.65 (C_4 triazole), 165.99 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{17}N_3O_2S$ $[M + H]^+$: 340.1075. Found: 340.1070.

4-Methoxybenzyl 2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5b**) White solid; yield: 93%; m.pt: 64–68 °C; FT-IR (KBr): 3120 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2952 (C–H str., aliphatic), 1759 (C=O str., ester), 1611, 1480 (C=C str., aromatic ring), 1212 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.82$ (s, 3H, $\underline{OCH_3}$), 4.25 (s, 2H, $\underline{SCH_2}$), 5.09 (s, 2H, $\underline{NCH_2}$), 5.14 (s, 2H, $\underline{OCH_2}$), 6.89 (d, 2H, Ar–H, $J = 8.0$Hz), 7.17–7.34 (m, 7H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.81$, 50.92, 55.33, 67.98, 114.14, 123.41 (C_5 triazole), 126.52, 126.64, 129.01, 129.52, 130.38, 135.32, 145.52 (C_4 triazole), 160.03, 166.07 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{19}N_3O_3S$ $[M + H]^+$: 370.1181. Found: 370.1177.

4-Nitrobenzyl 2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5c**) White solid; yield: 84%; m.pt: 72–76 °C; FT-IR (KBr): 3115 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2958 (C–H str., aliphatic), 1766 (C=O str., ester), 1603, 1480 (C=C str., aromatic ring), 1519 (N–O asym. str., NO_2), 1341 (N–O sym. str., NO_2), 1219 (C–O asym. str., ester), 1057 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.39$ (s, 2H, $\underline{SCH_2}$), 5.17 (s, 2H, $\underline{NCH_2}$), 5.25 (s, 2H, $\underline{OCH_2}$), 7.17–7.47 (m, 8H, Ar–H +C–H triazole), 8.21 (d, 2H, Ar–H, $J = 8.0$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.63$, 50.77, 66.26, 123.45 (C_5 triazole), 123.95, 126.65, 128.65, 129.01, 129.61, 135.45, 141.37, 145.73 (C_4 triazole), 147.97, 165.71 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{16}N_4O_4S$ $[M + H]^+$: 385.0926. Found: 385.0920.

4-Chlorobenzyl 2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5d**) White solid; yield: 93%; m.pt: 94–98 °C; FT-IR (KBr): 3137 (C–H str., triazole ring), 3087 (C–H str., aromatic ring), 2997 (C–H str., aliphatic), 1747 (C=O str., ester), 1616, 1469 (C=C str., aromatic ring), 1225 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.24$ (s, 2H, $\underline{SCH_2}$), 5.12 (s, 2H, $\underline{NCH_2}$), 5.15 (s, 2H, $\underline{OCH_2}$), 7.18–7.32 (m, 9H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.85$, 50.84, 67.12, 123.32 (C_5 triazole), 126.53, 128.98, 129.02, 129.57, 129.92, 132.99, 134.86, 135.45, 145.66 (C_4 triazole), 165.95 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{16}ClN_3O_2S$ $[M + H]^+$: 374.0730 (^{35}Cl), 376.0701 (^{37}Cl). Found: 374.0726 (^{35}Cl), 376.0696 (^{37}Cl).

4-Methylbenzyl 2-(4-((phenylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5e**) White solid; yield: 93%; m.pt: 98–102 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2991 (C–H str., aliphatic), 1758 (C=O str., ester), 1633, 1480 (C=C str., aromatic ring), 1200 (C–O asym. str., ester), 1057 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H, $\underline{CH_3}$), 4.27 (s, 2H, $\underline{SCH_2}$), 5.13 (s, 2H, $\underline{NCH_2}$), 5.19 (s, 2H, $\underline{OCH_2}$), 7.21–7.37 (m, 9H, Ar–H), 7.50 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.25$, 28.84, 50.90, 68.00, 123.41 (C_5 triazole), 126.52, 128.72, 129.00, 129.43, 129.64, 131.54, 135.48, 138.80, 145.63 (C_4 triazole), 166.03 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{19}N_3O_2S$ $[M + H]^+$: 354.1232. Found: 354.1224.

Benzyl 2-(4-(((4-bromophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5f**) White solid; yield: 79%; m.pt: 86–90 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2991 (C–H str., aliphatic), 1750 (C=O str., ester), 1636, 1472 (C=C str., aromatic ring), 1210 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.21$ (s, 2H, $\underline{SCH_2}$), 5.13 (s, 2H, $\underline{NCH_2}$), 5.21 (s, 2H, $\underline{OCH_2}$), 7.18 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.33–7.37 (m, 7H, Ar–H), 7.49 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 28.82, 50.89, 68.05, 120.57, 123.40 (C_5 triazole), 128.56, 128.78, 128.88, 131.23, 132.10, 134.50, 134.55, 145.23 (C_4 triazole), 166.01 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{16}BrN_3O_2S$ $[M + H]^+$: 418.0225 (^{79}Br), 420.0204. (^{81}Br). Found: 418.0220 (^{79}Br), 420.0200 (^{81}Br).

4-Methoxybenzyl 2-(4-(((4-bromophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5g**) White solid; yield: 86%; m.pt: 108–112 °C; FT-IR (KBr): 3137 (C–H str., triazole ring), 3087 (C–H str., aromatic ring), 2935 (C–H str., aliphatic), 1744 (C=O str., ester), 1611, 1475 (C=C str., aromatic ring), 1222 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H, $\underline{OCH_3}$), 4.21 (s, 2H, $\underline{SCH_2}$), 5.10 (s, 2H, $\underline{NCH_2}$), 5.15 (s, 2H, $\underline{OCH_2}$), 6.89 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.18 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.27 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.37 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.48 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.09$, 51.14, 55.46, 68.18, 114.38, 120.80, 123.58 (C_5 triazole), 126.81, 130.73, 131.45, 132.28, 134.78, 145.37 (C_4 triazole), 160.44,

166.27 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}BrN_3O_3S$ $[M+H]^+$: 448.0330 (^{79}Br), 450.0310. (^{81}Br). Found: 448.0326 (^{79}Br), 450.0305 (^{81}Br).

4-Nitrobenzyl 2-(4-(((4-bromophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5h**) White solid; yield: 84%; m.pt: 116–120 °C; FT-IR (KBr): 3148 (C–H str., triazole ring), 3081 (C–H str., aromatic ring), 2991 (C–H str., aliphatic), 1755 (C=O str., ester), 1611, 1474 (C=C str., aromatic ring), 1516 (N–O asym. str., NO_2), 1343 (N–O sym. str., NO_2), 1227 (C–O asym. str., ester), 1052 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.23 (s, 2H, $\underline{SCH_2}$), 5.20 (s, 2H, $\underline{NCH_2}$), 5.30 (s, 2H, $\underline{OCH_2}$), 7.19 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.37 (d, 2H, Ar–H, $J = 8.0$ Hz) 7.47–7.49 (m, 3H, Ar–H+C–H triazole), 8.23 (d, 2H, Ar–H, $J = 8.0$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.72$, 50.65, 66.24, 120.50, 123.29 (C_5 triazole), 123.78, 128.61, 131.09, 131.82, 134.22, 141.28, 145.41 (C_4 triazole), 147.96, 165.66 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{15}BrN_4O_4S$ $[M+H]^+$: 463.0076 (^{79}Br), 465.0055. (^{81}Br). Found: 463.0081 (^{79}Br), 465.0062 (^{81}Br).

4-Chlorobenzyl 2-(4-(((4-bromophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5i**) White solid; yield: 79%; m.pt: 102–106 °C; FT-IR (KBr): 3154 (C–H str., triazole ring), 3077 (C–H str., aromatic ring), 2924 (C–H str., aliphatic), 1743 (C=O str., ester), 1625, 1471 (C=C str., aromatic ring), 1229 (C–O asym. str., ester), 1049 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.22$ (s, 2H, $\underline{SCH_2}$), 5.13 (s, 2H, $\underline{NCH_2}$), 5.17 (s, 2H, $\underline{OCH_2}$), 7.19 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.26 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.34–7.38 (m, 4H, Ar–H), 7.48 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.79$, 50.87, 67.20, 120.55, 123.42 (C_5 triazole), 128.95, 129.97, 131.27, 132.07, 132.94, 134.50, 134.86, 145.52 (C_4 triazole), 165.93 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{15}BrClN_3O_2S$ $[M+H]^+$: 451.9835 (^{79}Br and ^{35}Cl), 453.9806 (^{81}Br or ^{37}Cl), 455.9785 (^{81}Br and ^{37}Cl). Found: 451.9830 (^{79}Br and ^{35}Cl), 453.9801 (^{81}Br or ^{37}Cl), 455.9779 (^{81}Br and ^{37}Cl).

4-Methylbenzyl 2-(4-(((4-bromophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5j**) White solid; yield: 83%; m.pt: 104–108 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3059 (C–H str., aromatic ring), 2930 (C–H str., aliphatic), 1736 (C=O str., ester), 1625, 1474 (C=C str., aromatic ring), 1232 (C–O asym. str., ester), 1049 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H, $\underline{CH_3}$), 4.21 (s, 2H, $\underline{SCH_2}$), 5.11 (s, 2H, $\underline{NCH_2}$), 5.17 (s, 2H, $\underline{OCH_2}$), 7.17–7.23 (m, 6H, Ar–H), 7.37 (d, 2H, Ar–H, $J =$ 8.0 Hz), 7.48 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.46$, 29.16, 51.09, 68.28, 120.50, 123.54 (C_5 triazole), 128.98, 129.67, 131.52, 131.72, 132.28, 134.76, 139.06, 145.35 (C_4 triazole), 166.19 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}BrN_3O_2S$ $[M+H]^+$: 432.0381 (^{79}Br), 434.0361 (^{81}Br). Found: 432.0376 (^{79}Br), 434.0356 (^{81}Br).

Benzyl 2-(4-(((4-chlorophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5k**) White solid; yield: 76%; m.pt: 86–90 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2991 (C–H str., aliphatic), 1751 (C=O str., ester), 1625, 1477 (C=C str., aromatic ring), 1208 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.23$ (s, 2H, $\underline{SCH_2}$), 5.16 (s, 2H, $\underline{NCH_2}$), 5.23 (s, 2H, $\underline{OCH_2}$), 7.23–7.39 (m, 9H, Ar–H), 7.50 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.03$, 50.88, 68.01, 123.31 (C_5 triazole), 128.66, 128.73, 128.94, 129.02, 131.05, 132.74, 133.73, 134.31, 145.28 (C_4 triazole), 165.99 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{16}ClN_3O_2S$ $[M+H]^+$: 374.0730 (^{35}Cl), 376.0701. (^{37}Cl). Found: 374.0726 (^{35}Cl), 376.0699 (^{37}Cl).

4-Methoxybenzyl 2-(4-(((4-chlorophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5l**) White solid; yield: 75%; m.pt: 95–99 °C; FT-IR (KBr): 3148 (C–H str., triazole ring), 3081 (C–H str., aromatic ring), 2958 (C–H str., aliphatic), 1751 (C=O str., ester), 1614, 1475 (C=C str., aromatic ring), 1205 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.81$ (s, 3H, $\underline{OCH_3}$), 4.21 (s, 2H, $\underline{SCH_2}$), 5.10 (s, 2H, $\underline{NCH_2}$), 5.15 (s, 2H, $\underline{OCH_2}$), 6.89 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.21–7.28 (m, 6H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.03$, 50.80, 55.21, 67.84, 113.98, 123.21 (C_5 triazole), 126.45, 128.91, 130.41, 131.01, 132.51, 133.68, 145.12 (C_4 triazole), 160.00, 165.87 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}ClN_3O_3S$ $[M+H]^+$: 404.0836 (^{35}Cl), 406.0806. (^{37}Cl). Found: 404.0836 (^{35}Cl), 406.0806 (^{37}Cl).

4-Nitrobenzyl 2-(4-(((4-chlorophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5m**) White solid; yield: 88%; m.pt: 104–108 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3087 (C–H str., aromatic ring), 2984 (C–H str., aliphatic), 1761 (C=O str., ester), 1605, 1478 (C=C str., aromatic ring), 1517 (N–O asym. str., NO_2), 1347 (N–O sym. str., NO_2), 1204 (C–O asym. str., ester), 1052 (C–O sym. str., ester) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.22 (s, 2H, $\underline{SCH_2}$), 5.20 (s, 2H, $\underline{NCH_2}$), 5.30 (s, 2H, $\underline{OCH_2}$), 7.21–7.27 (m, 4H, Ar–H), 7.47–7.49 (m, 3H, Ar–H +C–H triazole), 8.23 (d, 2H, Ar–H, $J = 8.0$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 29.05$, 50.77, 66.36, 123.44 (C_5 triazole), 123.99, 128.74, 129.16, 131.13, 132.70, 133.66, 141.44, 145.43 (C_4 triazole), 148.01, 165.82 (C=O

ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{15}ClN_4O_4S$ $[M+H]^+$: 419.0581 (^{35}Cl), 421.0551 (^{37}Cl). Found: 419.0575 (^{35}Cl), 421.0545 (^{37}Cl).

4-Chlorobenzyl 2-(4-(((4-chlorophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5n**) White solid; yield: 83%; m.pt: 92–96 °C; FT-IR (KBr): 3149 (C–H str., triazole ring), 3087 (C–H str., aromatic ring), 2947 (C–H str., aliphatic), 1752 (C=O str., ester), 1611, 1477 (C=C str., aromatic ring), 1208 (C–O asym. str., ester), 1052 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.21$ (s, 2H, $\underline{SCH_2}$), 5.13 (s, 2H, $\underline{NCH_2}$), 5.16 (s, 2H, $\underline{OCH_2}$), 7.24–7.35 (m, 8H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.97$, 50.70, 67.04, 123.30 (C_5 triazole), 128.87, 129.02, 129.82, 131.06, 132.59, 132.83, 133.67, 134.76, 145.16 (C_4 triazole), 165.82 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{18}H_{15}Cl_2N_3O_2S$ $[M+H]^+$: 408.0340 (^{35}Cl and ^{35}Cl), 410.0311 (^{35}Cl or ^{37}Cl), 412.0282 (^{37}Cl and ^{37}Cl), Found: 408.0334 (^{35}Cl and ^{35}Cl), 410.0328 (^{35}Cl or ^{37}Cl), 412.0275 (^{37}Cl and ^{37}Cl).

4-Methylbenzyl 2-(4-(((4-chlorophenyl)thio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5o**) White solid; yield: 77%; m.pt: 98–102 °C; FT-IR (KBr): 3138 (C–H str., triazole ring), 3087 (C–H str., aromatic ring), 2930 (C–H str., aliphatic), 1749 (C=O str., ester), 1618, 1477 (C=C str., aromatic ring), 1227 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.36 (s, 3H, $\underline{CH_3}$), 4.20 (s, 2H, $\underline{SCH_2}$), 5.11 (s, 2H, $\underline{NCH_2}$), 5.16 (s, 2H, $\underline{OCH_2}$), 7.18–7.26 (m, 8H, Ar–H), 7.47 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 20.80, 29.01, 50.76, 67.48, 123.30 (C_5 triazole), 128.59, 128.99, 129.30, 131.08, 131.37, 132.56, 133.69, 138.42, 145.00 (C_4 triazole), 165.81 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}ClN_3O_2S$ $[M+H]^+$: 388.0887 (^{35}Cl), 390.0857 (^{37}Cl). Found: 388.0882 (^{35}Cl), 390.0852 (^{37}Cl).

Benzyl 2-(4-((p-tolylthio)methyl)-1*H*-1,2,3-triazol-1-yl) acetate (**5p**) White solid; yield: 91%; m.pt: 114–118 °C; FT-IR (KBr): 3120 (C–H str., triazole ring), 3070 (C–H str., aromatic ring), 2986 (C–H str., aliphatic), 1751 (C=O str., ester), 1607, 1475 (C=C str., aromatic ring), 1210 (C–O asym. str., ester), 1052 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, $\underline{CH_3}$), 4.20 (s, 2H, $\underline{SCH_2}$), 5.12 (s, 2H, $\underline{NCH_2}$), 5.20 (s, 2H, $\underline{OCH_2}$), 7.07 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.23 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.33–7.36 (m, 5H, Ar–H), 7.45 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.90$, 29.46, 50.75, 67.85, 123.38 (C_5 triazole), 128.40, 128.63, 128.71, 129.66, 130.38, 131.50, 134.34, 136.68, 145.63 (C_4 triazole), 165.90 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{19}N_3O_2S$ $[M+H]^+$: 354.1232. Found: 354.1226.

4-Methoxybenzyl 2-(4-((p-tolylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5q**) White solid; yield: 79%; m.pt: 88–92 °C; FT-IR (KBr): 3126 (C–H str., triazole ring), 3076 (C–H str., aromatic ring), 2935 (C–H str., aliphatic), 1756 (C=O str., ester), 1612, 1490 (C=C str., aromatic ring), 1212 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, $\underline{CH_3}$), 3.81 (s, 3H, $\underline{OCH_3}$), 4.19 (s, 2H, $\underline{SCH_2}$), 5.09 (s, 2H, $\underline{NCH_2}$), 5.14 (s, 2H, $\underline{OCH_2}$), 6.89 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.07 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.23–7.27 (m, 4H, Ar–H), 7.45 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.18$, 29.76, 51.04, 55.53, 68.08, 114.35, 123.59 (C_5 triazole), 126.92, 129.99, 130.69, 130.71, 131.79, 137.01, 146.05 (C_4 triazole), 160.31, 166.26 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{20}H_{21}N_3O_3S$ $[M+H]^+$: 384.1337. Found: 384.1333.

4-Nitrobenzyl 2-(4-((p-tolylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5r**) White solid; yield: 77%; m.pt: 110–114 °C; FT-IR (KBr): 3126 (C–H str., triazole ring), 3014 (C–H str., aromatic ring), 2919 (C–H str., aliphatic), 1751 (C=O str., ester), 1628, 1491 (C=C str., aromatic ring), 1518 (N–O asym. str., NO_2), 1345 (N–O sym. str., NO_2), 1222 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H, $\underline{CH_3}$), 4.13 (s, 2H, $\underline{SCH_2}$), 5.18 (s, 2H, $\underline{NCH_2}$), 5.29 (s, 2H, $\underline{OCH_2}$), 7.07–7.26 (m, 6H, Ar–H), 7.47 (s, 1H, C–H triazole), 8.23 (d, 2H, Ar–H, $J = 8.0$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.07$, 29.58, 50.75, 66.27, 123.37 (C_5 triazole), 124.00, 128.69, 129.89, 130.33, 130.95, 137.31, 141.25, 146.83 (C_4 triazole), 148.19, 165.81 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}N_4O_4S$ $[M+H]^+$: 399.1082. Found: 399.1075.

4-Chlorobenzyl 2-(4-((p-tolylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5s**) White solid; yield: 91%; m.pt: 104–108 °C; FT-IR (KBr): 3137 (C–H str., triazole ring), 3092 (C–H str., aromatic ring), 2952 (C–H str., aliphatic), 1752 (C=O str., ester), 1625, 1457 (C=C str., aromatic ring), 1223 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.30$ (s, 3H, $\underline{CH_3}$), 4.20 (s, 2H, $\underline{SCH_2}$), 5.12 (s, 2H, $\underline{NCH_2}$), 5.16 (s, 2H, $\underline{OCH_2}$), 7.07–7.34 (m, 8H, Ar–H), 7.45 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.98$, 29.41, 50.83, 67.11, 123.39 (C_5 triazole), 128.98, 129.80, 129.92, 130.42, 131.58, 132.97, 134.85, 136.81, 145.86 (C_4 triazole), 165.97 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{19}H_{18}ClN_3O_2S$ $[M+H]^+$: 388.0887 (^{35}Cl), 390.0857 (^{37}Cl). Found: 388.0882 (^{35}Cl), 390.0851 (^{37}Cl).

4-Methylbenzyl 2-(4-((p-tolylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5t**) White solid; yield: 88%; m.pt: 104–108 °C; FT-IR (KBr): 3120 (C–H str., triazole ring), 3070 (C–H

str., aromatic ring), 2919 (C–H str., aliphatic), 1759 (C=O str., ester), 1633, 1491 (C=C str., aromatic ring), 1199 (C–O asym. str., ester), 1057 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.33$ (s, 6H, $\underline{CH_3}$), 4.23 (s, 2H, $\underline{SCH_2}$), 5.13 (s, 2H, $\underline{NCH_2}$), 5.19 (s, 2H, $\underline{OCH_2}$), 7.11–7.25 (m, 8H, Ar–H), 7.48 (s, 1H, C–H triazole) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.25$, 29.58, 50.90, 67.99, 123.45 (C_5 triazole), 128.74, 129.43, 129.80, 130.50, 131.50, 131.59, 136.79, 138.84, 145.78 (C_4 triazole), 165.97 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{20}H_{21}N_3O_2S$ $[M + H]^+$: 368.1388. Found: 368.1381.

Benzyl 2-(4-((naphthalen-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5u**) White solid; yield: 79%; m.pt: 88–92 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3053 (C–H str., aromatic ring), 2952 (C–H str., aliphatic), 1754 (C=O str., ester), 1625, 1496 (C=C str., aromatic ring), 1208 (C–O asym. str., ester), 1052 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.34$ (s, 2H, $\underline{SCH_2}$), 5.07 (s, 2H, $\underline{NCH_2}$), 5.15 (s, 2H, $\underline{OCH_2}$), 7.29–7.47 (m, 9H, Ar–H+C–H triazole), 7.71–7.75 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.73$, 50.86, 67.92, 123.51 (C_5 triazole), 125.92, 126.60, 127.27, 127.37, 127.60, 127.70, 128.55, 128.58, 128.75, 128.84, 131.94, 132.87, 133.71, 134.50, 145.49 (C_4 triazole), 165.96 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{22}H_{19}N_3O_2S$ $[M + H]^+$: 390.1232. Found: 390.1225.

4-Methoxybenzyl 2-(4-((naphthalen-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5v**) White solid; yield: 83%; m.pt: 94–98 °C; FT-IR (KBr): 3143 (C–H str., triazole ring), 3053 (C–H str., aromatic ring), 2958 (C–H str., aliphatic), 1755 (C=O str., ester), 1611, 1492 (C=C str., aromatic ring), 1205 (C–O asym. str., ester), 1054 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.80$ (s, 3H, $\underline{OCH_3}$), 4.34 (s, 2H, $\underline{SCH_2}$), 5.05 (s, 2H, $\underline{NCH_2}$), 5.09 (s, 2H, $\underline{OCH_2}$), 6.89 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.23–7.44 (m, 6H, Ar–H+C–H triazole), 7.71–7.74 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.75$, 50.89, 55.32, 67.87, 114.11, 123.48 (C_5 triazole), 125.90, 126.59, 127.26, 127.37, 127.60, 127.69, 128.57, 130.44, 131.95, 132.88, 133.71, 134.50, 145.51 (C_4 triazole), 160.07, 166.06 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{23}H_{21}N_3O_3S$ $[M + H]^+$: 420.1337. Found: 420.1331.

4-Nitrobenzyl 2-(4-((naphthalen-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5w**) Light brown solid; yield: 79%; m.pt: 120–124 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3053 (C–H str., aromatic ring), 2924 (C–H str., aliphatic), 1754 (C=O str., ester), 1633, 1499 (C=C str., aromatic ring), 1521 (N–O asym. str., NO_2), 1347 (N–O sym. str., NO_2), 1222 (C–O asym. str., ester), 1057 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.38$ (s, 2H, $\underline{SCH_2}$), 5.17 (s, 2H, $\underline{NCH_2}$), 5.24 (s, 2H, $\underline{OCH_2}$), 7.29–7.51 (m, 6H, Ar–H+C–H triazole), 7.71–7.76 (m, 4H, Ar–H), 8.23 (d, 2H, Ar–H, $J = 8.0$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.61$, 50.75, 66.24, 123.47 (C_5 triazole), 123.93, 125.95, 126.64, 127.25, 127.44, 127.62, 127.70, 128.60, 128.64, 131.89, 132.77, 133.75, 141.39, 145.73 (C_4 triazole), 147.98, 165.74 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{22}H_{18}N_4O_4S$ $[M + H]^+$: 435.1082. Found: 435.1075.

4-Chlorobenzyl 2-(4-((naphthalen-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5x**) Light brown solid; yield: 89%; m.pt: 108–112 °C; FT-IR (KBr): 3120 (C–H str., triazole ring), 3070 (C–H str., aromatic ring), 2935 (C–H str., aliphatic), 1755 (C=O str., ester), 1619, 1491 (C=C str., aromatic ring), 1218 (C–O asym. str., ester), 1060 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.35$ (s, 2H, $\underline{SCH_2}$), 5.09 (s, 2H, $\underline{NCH_2}$), 5.11 (s, 2H, $\underline{OCH_2}$), 7.21 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.32 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.41–7.47 (m, 4H, Ar–H+C–H triazole), 7.71–7.78 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.87$, 50.92, 67.19, 123.53 (C_5 triazole), 126.02, 126.70, 127.33, 127.43, 127.66, 127.79, 128.68, 129.06, 130.01, 132.04, 132.90, 133.04, 133.80, 134.94, 145.73 (C_4 triazole), 166.00 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{22}H_{18}ClN_3O_2S$ $[M + H]^+$: 424.0887 (^{35}Cl), 426.0857 (^{37}Cl). Found: 424.0885 (^{35}Cl), 426.0854 (^{37}Cl).

4-Methylbenzyl 2-(4-((naphthalen-2-ylthio)methyl)-1*H*-1,2,3-triazol-1-yl)acetate (**5y**) White solid; yield: 80%; m.pt: 82–86 °C; FT-IR (KBr): 3120 (C–H str., triazole ring), 3070 (C–H str., aromatic ring), 2941 (C–H str., aliphatic), 1756 (C=O str., ester), 1624, 1499 (C=C str., aromatic ring), 1212 (C–O asym. str., ester), 1059 (C–O sym. str., ester) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.34$ (s, 3H, $\underline{CH_3}$), 4.34 (s, 2H, $\underline{SCH_2}$), 5.05 (s, 2H, $\underline{NCH_2}$), 5.11 (s, 2H, $\underline{OCH_2}$), 7.16–7.25 (m, 4H, Ar–H), 7.42–7.47 (m, 4H, Ar–H +C–H triazole), 7.71–7.75 (m, 4H, Ar–H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.37$, 28.96, 51.11, 68.11, 123.72 (C_5 triazole), 126.13, 126.82, 127.49, 127.60, 127.82, 127.92, 128.80, 128.95, 129.61, 131.74, 132.17, 133.10, 133.94, 139.04, 145.72 (C_4 triazole), 166.27 (C=O ester) ppm; HRMS (*m/z*) calculated for $C_{23}H_{21}N_3O_2S$ $[M + H]^+$: 404.1388. Found: 404.1382.

General procedure for in vitro antimalarial evaluation

All the synthesized triazole derivatives (**5a–5y**) were screened for in vitro antimalarial activity in the Microcare laboratory & TRC, Surat, Gujarat.

The in vitro antimalarial assay was carried out in 96-well microtitre plates according to the micro assay protocol of

Rieckmann and co-workers with minor modifications. (Rieckmann et al. 1978) The cultures of *Plasmodium falciparum* strain were maintained in medium RPMI 1640 supplemented with 25 mm HEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat inactivated human serum. The asynchronous parasites of *Plasmodium falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8–1.5 at 3% hematocrit in a total volume of 200 µL of medium RPMI-1640 was determined by Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia(rings) and uniformly maintained with 50% RBCs(O^+). A stock solution of 5 mg/mL of each of the test samples was prepared in dimethyl sulphoxide (DMSO) and subsequent dilutions were prepared with culture medium. The diluted samples in 20 µL volume were added to the test wells so as to obtain final concentrations (at five fold dilutions) ranging between 0.4 and 100 µg/mL in duplicate well containing parasitized cell preparation. The culture plates were incubated at 37 °C in a candle jar. After 36–40 h incubation, thin blood smears from each well were prepared and stained with Jaswant Singh Bhattacharya stain. (Singh 1956; Trager and Jensen 1976; Lambros and Vanderberg 1979; Desjardins 1984; Panjarathinam 2007). The slides were microscopically observed to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the minimum inhibitory concentrations (MIC). Chloroquinine was used as the reference drug.

General procedure for in vitro antimicrobial evaluation

All the synthesized 1,4-disubstituted 1,2,3-triazole derivatives (**5a–5y**) were evaluated for their in vitro antimicrobial potential against two gram-positive bacterial strains [*B. subtilis* (MTCC 441) and *S. epidermidis* (MTCC 6880)], two gram-negative bacterial strains [*E. coli* (MTCC 1652) and *P. aeruginosa* (MTCC 424)] and two fungal strains [*C. albicans* (MTCC 183) and *A. niger* (MTCC 8189)] by the serial dilution technique (Kaushik et al. 2016c). Ciprofloxacin and Fluconazole were used as reference drugs for bacterial and fungal strains, respectively. Firstly, the stock solutions of test compounds were prepared (2.0 mg in 10 mL DMSO) to attain the final concentration of 200 µg/mL concentration. Nutrient broth and Sabouraud dextrose broth were used as culture media for bacterial strains and fungal strains, respectively. One milliliter of sterile culture media was added in each test tube aseptically. Stock solution of test compounds were then serially diluted in test tubes containing sterile culture media to prepare the concentrations of 100–6.25 µg/mL followed by inoculation of 0.1 mL of respective microorganisms in each tube. After that, these test tubes were incubated at 37 ± 1 °C for 24 h in case of bacteria, 37 ± 1 °C for 48 h in case of *C. albicans* and 25 ± 1 °C for 7 days in case of *A. niger*. Reference drugs were also accessed under similar experimental conditions for comparison with synthesized compounds. Results were recorded visually in terms of MIC (µmol/mL).

Results and discussion

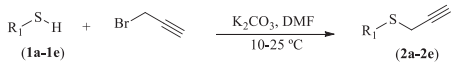
Chemistry

Synthesis of a series of thioether/ester linked 1,4-disubstituted 1,2,3-triazoles (**5a–5y**) has been outlined in Scheme 1. Firstly, the terminal alkynes i.e., aryl(prop-2-yn-1-yl)sulfanes (**2a–2e**) (Kaushik et al. 2017) were synthesized by treatment of aromatic thiols (**1a–1e**) with propargyl bromide in the presence of potassium carobonate using *N*,*N* dimethylformamide as solvent, while benzyl 2-bromoacetates (**4a–4e**) were prepared by the reaction of benzyl alcohols (**3a–3e**) and bromoacetyl bromide using sodium bicarbonate as base in acetonitrile.

Afterwards, 1,3-dipolar cycloaddition reaction was performed between aryl(prop-2-yn-1-yl)sulfanes (**2a–2e**) and benzyl 2-azidoacetates (which were generated in situ from the reaction of benzyl 2-bromoacetates (**4a–4e**) with sodium azide) employing catalytic amount of copper sulfate pentahydrate and sodium ascorbate in dimethylformamide: water to afford the desired final products (**5a–5y**).

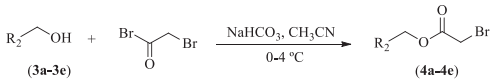
The structures of synthesized triazole derivatives (**5a–5y**) were well explicated by various spectroscopic techniques FTIR, ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. IR spectra of all these compounds reflects characteristic absorption bands in the region at 3115–3154 cm^{-1} (C–H, str., triazole ring) and 1736–1766 cm^{-1} (C=O str., ester). In ^{1}H NMR spectra of most of compounds, a characteristic singlet was observed in the region at δ 7.45–7.50 attributed to triazolyl proton, while the appearance of another singlets in the region at δ 4.13–4.39 (SCH_2), δ 5.05–5.20 (NCH_2) and 5.09–5.30 (OCH_2) also ensured the formation of target compounds. Other aliphatic and aromatic protons observed in expected regions. The salient feature of ^{13}C NMR spectra of thioethereal triazole derivatives with ester functionality was the signals observed in the region at δ 165.66–166.27, δ 145.00–146.83, and δ 123.21–123.72 due to carbonyl carbon, C_4 and C_5 of the triazole ring, respectively. Another characteristic signals resonated in the region at δ 28.61–29.76, δ 50.65–51.14, and δ 66.24–68.28 assigned to the aliphatic carbon attached to sulfur, nitrogen, and oxygen, respectively.

Further, the results obtained from high resolution mass spectral analysis were found in accordance to calculated values.



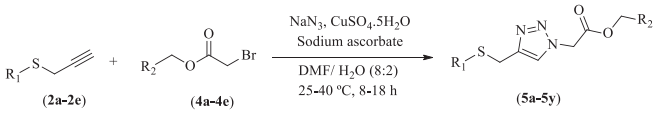
(**1a-1e**) (**2a-2e**)

R_1 = **1a**, **2a**: C_6H_5 R_1 = **1b**, **2b**: 4-BrC_6H_4
R_1 = **1c**, **2c**: 4-ClC_6H_4, R_1 = **1d**, **2d**: 4-$CH_3C_6H_4$
R_1 = **1e**, **2e**: $C_{10}H_7$



(**3a-3e**) (**4a-4e**)

R_2 = **3a**, **4a**: C_6H_5 R_2 = **3b**, **4b**: 4-$CH_3OC_6H_4$
R_2 = **3c**, **4c**: 4-$NO_2C_6H_4$, R_2 = **3d**, **4d**: 4-ClC_6H_4
R_2 = **3e**, **4e**: 4-$CH_3C_6H_4$



(**2a-2e**) (**4a-4e**) (**5a-5y**)

Compound	R_1	R_2
5a	C_6H_5	C_6H_5
5b	C_6H_5	4-$CH_3OC_6H_4$
5c	C_6H_5	4-$NO_2C_6H_4$
5d	C_6H_5	4-ClC_6H_4
5e	C_6H_5	4-$CH_3C_6H_4$
5f	4-BrC_6H_4	C_6H_5
5g	4-BrC_6H_4	4-$CH_3OC_6H_4$
5h	4-BrC_6H_4	4-$NO_2C_6H_4$
5i	4-BrC_6H_4	4-ClC_6H_4
5j	4-BrC_6H_4	4-$CH_3C_6H_4$
5k	4-ClC_6H_4	C_6H_5
5l	4-ClC_6H_4	4-$CH_3OC_6H_4$
5m	4-ClC_6H_4	4-$NO_2C_6H_4$
5n	4-ClC_6H_4	4-ClC_6H_4
5o	4-ClC_6H_4	4-$CH_3C_6H_4$
5p	4-$CH_3C_6H_4$	C_6H_5
5q	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$
5r	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$
5s	4-$CH_3C_6H_4$	4-ClC_6H_4
5t	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$
5u	$C_{10}H_7$	C_6H_5
5v	$C_{10}H_7$	4-$CH_3OC_6H_4$
5w	$C_{10}H_7$	4-$NO_2C_6H_4$
5x	$C_{10}H_7$	4-ClC_6H_4
5y	$C_{10}H_7$	4-$CH_3C_6H_4$

Scheme 1 Synthesis of thioether-ester linked 1,4-disubstituted 1,2,3-triazoles

Antimalarial evaluation

The synthesized 1,4-disubstituted 1,2,3-triazoles (**5a–5y**) were accessed for in vitro antimalarial activity against strain i.e., *Plasmodium falciparum* as per the micro assay protocol of Rieckmann and co-workers with minor modifications (Rieckmann et al. 1978). Results are presented in terms of MIC in μmol/mL. Mean IC_{50} values were calculated from experiments performed in duplicate. Chloroquinine and quinine were used as reference drugs. It has been observed that some of the synthesized triazoles displayed considerable antimalarial inhibitory activity as reflected in Table 1. The compounds **5g** (IC_{50}, 0.1784) and **5h** (IC_{50}, 0.1835) showed good activity against *P. falciparum*. While, compounds **5i** (IC_{50}, 0.2032), **5k** (IC_{50}, 0.2086), **5n** (IC_{50}, 0.2082), **5t** (IC_{50}, 0.2041), and **5w** (IC_{50}, 0.2072) possessed almost similar average inhibitory activity against tested malarial strain.

Table 1 In vitro antimalarial activity of 1,4-disubstituted 1,2,3-triazoles (**5a–5y**)

Compounds	Minimum inhibitory concentration (MIC, IC_{50}, μmol/mL × 10^{-2})
	P. falciparum
5a	0.3064
5b	0.2977
5c	0.2549
5d	0.3103
5e	0.2546
5f	0.2438
5g	0.1784
5h	0.1835
5i	0.2032
5j	0.2544
5k	0.2086
5l	0.2525
5m	0.2268
5n	0.2082
5o	0.2114
5p	0.2886
5q	0.2347
5r	0.3012
5s	0.2269
5t	0.2041
5u	0.2105
5v	0.2765
5w	0.2072
5x	0.2595
5y	0.2330
Chloroquinine	0.0062
Quinine	0.0826

Antimicrobial evaluation

All the synthesized triazole derivatives (**5a–5y**) were screened for in vitro antimicrobial activity against two gram-positive bacterial strains [*Bacillus subtilis* and *Staphylococcus epidermidis*], two gram-negative bacterial strains [*Escherichia coli* and *Pseudomonas aeruginosa*], and two fungal strains [*Candida albicans* and *Aspergillus niger*] by using serial dilution technique (Kaushik et al. 2016c). MIC were recorded in terms of μmol/mL. Ciprofloxacin and Fluconazole were used as reference drugs for antibacterial and antifungal activity, respectively.

Results of antibacterial activity are revealed in Table 2. The synthesized triazole derivatives displayed moderate to good bactericidal activity against all tested bacterial strains. Some of the compounds like **5m** (MIC, 0.0149), **5n** (MIC, 0.0153), **5u** (MIC, 0.0160), and **5w** (MIC, 0.0144) against *B.subtilis*; **5h** (MIC, 0.0135), **5i** (MIC, 0.0138), **5n** (MIC,

Table 2 In vitro antibacterial activity of 1,4-disubstituted 1,2,3-triazoles (**5a–5y**)

Compounds	Minimum inhibitory concentration (MIC, μmol/mL)			
	Gram positive bacteria		Gram negative bacteria	
	B. subtilis	*S. epidermidis*	*E. coli*	*P. aeruginosa*
5a	0.0737	0.0368	0.0737	0.0737
5b	0.0677	0.0338	0.1353	0.0677
5c	0.0650	0.0325	0.0325	0.0163
5d	0.0669	0.0334	0.0167	0.0334
5e	0.0707	0.0707	0.0707	0.0707
5f	0.0299	0.0299	0.0149	0.0598
5g	0.0558	0.0558	0.0139	0.0279
5h	0.0540	0.0135	0.0270	0.0135
5i	0.0276	0.0138	0.0138	0.0138
5j	0.0578	0.0289	0.0578	0.0289
5k	0.0669	0.0334	0.0669	0.0669
5l	0.0619	0.0309	0.0619	0.0155
5m	0.0149	0.0298	0.0149	0.0298
5n	0.0153	0.0153	0.0153	0.0153
5o	0.0322	0.0322	0.0322	0.0322
5p	0.0707	0.0707	0.0707	0.0707
5q	0.0326	0.0326	0.0652	0.0652
5r	0.0627	0.0314	0.0314	0.0157
5s	0.0645	0.0161	0.0645	0.0645
5t	0.0340	0.0680	0.0680	0.0680
5u	0.0160	0.0321	0.0321	0.0321
5v	0.1192	0.0298	0.0149	0.0596
5w	0.0144	0.0575	0.0575	0.0575
5x	0.0590	0.0147	0.0295	0.0295
5y	0.0620	0.0620	0.0620	0.0620
Ciprofloxacin	0.0189	0.0189	0.0189	0.0189

Table 3 In vitro antifungal activity of 1,4-disubstituted 1,2,3-triazoles (**5a–5y**)

Compounds	Minimum inhibitory concentration (MIC, μmol/mL)	
	C. albicans	*A. niger*
5a	0.0368	0.0368
5b	0.0677	0.0338
5c	0.0163	0.0163
5d	0.0334	0.0334
5e	0.0707	0.0354
5f	0.0149	0.0598
5g	0.0279	0.0139
5h	0.0270	0.0540
5i	0.0138	0.0276
5j	0.0578	0.0578
5k	0.0334	0.0669
5l	0.0619	0.0309
5m	0.0298	0.0298
5n	0.0153	0.0306
5o	0.0322	0.0645
5p	0.0707	0.0354
5q	0.0326	0.0652
5r	0.0627	0.0314
5s	0.0322	0.0645
5t	0.0680	0.0680
5u	0.0642	0.0321
5v	0.0596	0.0596
5w	0.0288	0.0575
5x	0.0147	0.0590
5y	0.0310	0.0620
Fluconazole	0.0204	0.0204

0.0153), **5s** (MIC, 0.0161), and **5x** (MIC, 0.0147) against *S. epidermidis*; **5d** (MIC, 0.0167), **5f** (MIC, 0.0149), **5g** (MIC, 0.0139), **5i** (MIC, 0.0138), **5m** (MIC, 0.0149), **5n** (MIC, 0.0153), and **5v** (MIC, 0.0149) against *E. coli*; **5c** (MIC, 0.0163), **5h** (MIC, 0.0135), **5i** (MIC, 0.0138), **5l** (MIC, 0.0155), **5n** (MIC, 0.0153), and **5r** (MIC, 0.0157) against *P. aeruginosa* displayed appreciable bactericidal efficiency in comparison to reference drug used. Interstingly, compound **5n** found to possess better antibacterial activity against all tested bacterial strains.

Results of antifungal evaluation are represented in Table 3. Most of the tested compounds exhibited average to good antifungal efficacy. Some of the compounds like **5c** (MIC, 0.0163), **5f** (MIC, 0.0149), **5i** (MIC, 0.0138), **5n** (MIC, 0.0153), and **5x** (MIC, 0.0147) against *C. albicans*; **5c** (MIC, 0.0163) and **5g** (MIC, 0.0139) against *A. niger* found to possess better inhibitory activity as compared to standard drug. Moreover, antifungal evaluation is less prolific than antibacterial evaluation.

Structure–activity relationships (SAR)

From the antimalarial and antimicrobial results, following SAR may be inferred-

Antimalarial activity:

- Compounds with 4-bromo/4-chloro substituted thiophenyl moiety exhibited better antimalarial activity in comparison to compounds having unsubstituted thiophenyl moiety.
- Triazoles with thionapthyl moieties possess better inhibitory activity as compared to thiophenyl moiety.
- Compounds having halogen group on thiophenyl as well as on benzyl moiety behave as better antimalarial agent.

Antimicrobial activity:

- In most of cases, compounds containing electron withdrawing nitro group on benzyl ring displayed the improved bactericidal potency as compared to the compound without any substitution or substituted with electron releasing methoxy and methyl group on benzyl moiety.
- Moreover, presence of halogen groups on thiophenyl/benzyl moiety of compounds enhanced inhibitory activity against tested bacterial strain.
- In most of cases, triazoles having thionapthyl moieties displayed better antibacterial activity as compared to thiophenyl moiety.
- Generally, synthesized compounds having methyl group on thiophenyl moiety exhibited better inhibitory activity against unsubstituted one among the tested bacterial strains.
- In most of cases, presence of bromo group on thiophenyl moiety showed improved bactericidal activity than compounds with chloro substituted thiophenyl moiety.
- Presence of halogen group on thiophenyl/benzyl moiety enhanced activity of some of compounds against *C. albicans*.
- In most of cases, triazole derivatives with nitro group were found to be more potency against *A. niger*.
- In case of *A. niger*, methoxy group present on benzyl group enhanced inhibitory activity than compounds with unsubstituted benzyl moiety, in most of cases.

Conclusion

Conclusively, we have synthesized twenty five thioethereal 1,4-disubstituted 1,2,3-triazole analogs with ester

functionality (**5a–5y**) through expedient and facile strategy of Cu(I) catalyzed 1,3-dipolar cycloaddition reaction between aryl(prop-2-yn-1-yl)sulfanes and benzyl 2-azidoacetates in good yields. All the synthesized compounds were investigated for in vitro antimalarial and antimicrobial evaluation. Most of the synthesized triazole derivatives found to possess moderate antimalarial potential against *Plasmodium falciparum* strain. Whereas, the synthesized compound **5n** exhibited overall encouraging efficiency against all tested microbial strains except *A. niger*. The compound **5i** displayed better antimicrobial potency against all microbial strains except *B. subtilis* and *A. niger*.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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