INTRODUCTION

Antimicrobial chemotherapy is a concern for many regions and centuries. The development of resistance against existing chemotherapeutics is still an important issue, although there are a large number and wide spectrum of antimicrobial drugs. In addition, disproportionate antibiotic use increases the associated problems, and prevents the treatment from reaching the desired outcome. Thus, there is an urgent need for new antimicrobial drugs (Tomasic et al., 2010; Zoumpoulakis et al., 2012; Perron et al., 2015; Blanco et al., 2016).

It is well-known that radicals such as superoxide anion and hydroxyl affect some pathological or physiological processes (Miliovsky et al., 2015). Organisms are suitable to provide the stability between the radicals and their antioxidant systems under normal conditions. However, in a pathological situation, endogenous antioxidants are not enough to cope with the raised levels of the radicals (Halliwell, 1996; Halliwell, 2001).

In the recent years, five-membered heterocyclic aromatic compounds were reported to possess various biological activities including antimicrobial and antioxidant activity (Pitucha, Pachuta-Stec, Kaczor, 2013; Padmavathi et al., 2008; Sahin et al., 2012; Ceylan et al., 2013; Baviskar et al., 2011). For example, triazoles are an important functionality of pharmaceutical agents with many diverse biological activities (Arfan et al., 2018; Patel, Khan, Rajani, 2010). Remarkably, the biological activity profile of the compounds contains azole antifungal drugs (Iqbal et al., 2020; Sekhar et al., 2019; Çavusoglu, Uyrttas, Cantürk, 2018; Yang L, Synthesis, antimicrobial and antioxidant activities of pyridyl substituted thiazolyl triazole derivatives

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In this present study, 63 different 5-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-yl]-4-substituted-3-substituted benzylthio-4H-1,2,4-triazole derivatives were synthesized, and evaluated for their in vitro antimicrobial activity against various human pathogenic microorganisms and antioxidant activity. The derivatives were synthesized in a multi-step synthesis procedure including triazole and thiazole ring closure reactions, respectively. The synthesized derivatives (A1-24; B1-39) were screened for their antibacterial, antifungal, and antioxidant activities compared to standard agents. The derivatives possessing 3-pyridyl moiety particularly exhibited relatively high antibacterial activity (MIC = < 3.09-500 µg/mL) against Gram-positive bacteria, and compounds possessing 4-pyridyl moiety showed remarkable antioxidant activity.

Keywords: Triazole. Thiazole. Pyridine. Antimicrobial activity. Antioxidant activity. DPPH radical scavenging.
Bao XP, 2017; Tumosienė et al., 2016; Mange et al., 2013; Panda, Jain, 2014). However, the widespread use of triazoles increased the resistance and hepatotoxicity formation, which is a current problem (Gaikwad, Patil, Bobade, 2012; Kharb, Sharma, Sharma, 2011). Therefore, it is necessary to design novel and activeazole compounds. The synergistic effect may be increased, and provide a broader antimicrobial spectrum, reduce the effective dose, and avoid the undesired side effects (Mentese et al., 2013). In previous studies, triazole-thiazoles (Login, 2019; Kumar, Prasad, Makrandi, 2013), triazole-pyridine (Dharavath, Boda, 2019; Singh et al., 2018; Bektas et al., 2010; Tiperciuc, 2012), thiazole-pyridine (Eryılmaz et al., 2020; Suryawanshia et al., 2019; Radulescu, Radulescu, 2009), and various heterocyclic rings containing triazole ring (Abdel-Wahab, Abdel-Aziz, Ahmed, 2009; Demirayak, Benkli, Güven, 1998; Cui et al., 2013) were proven derivatives with antimicrobial activity. Also, it was observed that sulfur linked 1,2,4-triazole compounds were relatively efficient antimicrobial agents without resistance (Turan-Zitouni et al., 2005; Shiradkar et al., 2007; Jalilian et al., 2000; Rostami, Manesh, Samiei, 2013; Sun et al., 2014). In addition, a large number of synthesized 1,2,4-triazole derivatives were reported and associated with significant antioxidant activities (Bindu, Vijayalakshmi, Manikandan, 2020; Kaddouri Y et al., 2020; Dorovic et al., 2019; Koparir, 2019; Tumosienė et al., 2019; Tumosienė et al., 2018; Behalo, Amine, Fouda, 2017; Tumosienė et al., 2016). The thiazole systems, which are known to have an antimicrobial activity are also effectiveazole rings.

It is also well known that there are various natural and synthetic compounds bearing thiazole ring processes in biological activities and in various pharmacological properties (Pricopie et al., 2019; Althagafi, El-Metwaly, Farghaly 2019; Yurttas et al., 2015; Prakash et al., 2014; Kashyap et al., 2012; Rauf, Farshori, 2012).

Pyridine compounds that bound to different azole rings are an important class of the heterocyclic system. The pyridine ring, which has many various biological effects, is present in more than 7000 drugs produced by the worldwide pharmaceutical industry (Hosseinzhadeh et al., 2020; Elkanzi, Bakr, Ghoneim 2019; Zaki, Al-Gendey, Abdelhamid 2018; El-Naggar 2018; Chaubey, Pandeya, 2011).

In continuation of our bioactive screenings, a series of new 5-[4-methyl-2-(pyridin-3/4-yl) thiazole-5-yl]-4-substituted-3-substituted benzylthio-4H-1,2,4-triazole derivatives were synthesized, and their broad in vitro antimicrobial and antioxidant activities were evaluated.

MATERIAL AND METHODS

Chemistry

All chemicals were used without further purification. All melting points were measured by using an Electrotherm 9300 digital melting points apparatus. Spectroscopic data were recorded on the following instruments: a Perkin Helmer FTIR 100 spectrophotometer; ¹H NMR (nuclear magnetic resonance) and ¹³C NMR spectra were recorded by a Bruker 500 MHz and 75 MHz NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d₆, respectively. Chemical shift values are given in δ scales; a mass spectrometry (MS) Agilent 1100 MSD spectrometer (Agilent Technologies, Palo Alto, CA); an elemental analysis was performed in a Thermo Finnigan Flash EA 1112 elemental analyzer. The completion of the reactions was checked by thin-layer chromatography (TLC) on silica gel coated aluminum sheets (silica gel 60 F₂₅₄, ethyl acetate/petroleum ether, 1:1). Derivatives of 4-methyl-2-(pyridin-3/4-yl)-5-carbethoxythiazole (I), 4-methyl-2-(pyridin-3/4-yl)thiazole-5-carboxyhydrazide (II), 4-substituted phenyl-1-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-carbonyl]thiosemicarbazide (III), and 5-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-yl]-4-substituted-2,3-dihydro-4H-1,2,4-triazole-3-thione (IV) series were synthesized, respectively, according to the methods described previously (Zia et al., 2012; Chao, Wang 2013; Tiperciuc, 2012), the general procedure for the synthesis of the compounds are given below.
General procedure for the synthesis of the compounds I-V

4-Methyl-2-(pyridin-3/4-yl)-5-carbethoxythiazole (I)

Pyridine-3/4-thiocarboxamide (15 g, 109 mmol) was dissolved in ethanol (200 mL), then ethyl 2-chloroacetoacetate (19.5 mL, 131 mmol) was added to this solution and the mixture was refluxed for 4 days. After TLC check, the solvent was evaporated and the residue was treated with water and neutralized with acetic acid. The precipitate was filtered, dried, and recrystallized using ethanol. The physical properties and spectral data of the final compounds are given below;

4-Methyl-2-(pyridin-3/4-yl)thiazole-5-carbohydrazide (II)

A mixture of 4-methyl-2-(pyridin-3/4-yl)-5-carbethoxythiazole I (20.82 g, 84 mmol) and hydrazine hydrate (10 mL, 175 mmol) was refluxed in ethanol (100 mL) for 1 day. After TLC check, precipitate was filtered, dried, and recrystallized from ethanol.

4-Substituted phenyl-1-[4-methyl-2-(pyridin-3/4-yl)thiazole-5-carbonyl] thiosemicarbazide (III)

A mixture of 4-methyl-2-(pyridin-3/4-yl)thiazole-5-carbohydrazide II (5 g, 21 mmol) and an appropriate aryl isothiocyanate derivative (22 mmol) was refluxed in ethanol (100 mL) for 2 days. After the TLC check, the mixture was kept in a cool place until a product precipitated. The obtained precipitate was filtered, washed with ethanol, and dried.

5-[4-Methyl-2-(pyridin-3-yl)-thiazole-5-yl]-4-phenyl-3-benzylthio-4H-1,2,4-triazole V(A1)

Yield 83%, m.p. 147-149 °C, \( \text{IR (KBr)} \nu_{\text{max}} (\text{cm}^{-1}) \): 3054 (aromatic CH), 2955, 2856 (aliphatic CH), 1634 (C=N), 1590 (C=C), 809 (mono substituted benzene), 772 and 728 (1,3-disubstituted benzene), 690 (C-S); \( ^1\text{H NMR} \) (500 MHz, DMSO-\( d_6 \)) \( \delta \) (ppm): 2.77 (3H, s, CH₃), 4.40 (2H, s, CH₂), 7.26-7.64 (10H, m, Ar-H), 8.33 (1H, t, \( J \): 8.0 Hz, pyridine C₅-H), 8.38 (1H, d, \( J \): 8.0 Hz, pyridine C₄-H), 8.75 (1H, d, \( J \): 4.7 Hz, pyridine C₆-H), 9.19 (1H, s, pyridine C₂-H); For C₂₄H₁₉N₅S₂ calculated: (%) C 65.28, H 4.34, N 15.86, found: (%) C 65.25, H 4.31 N 15.85; \( \text{MS(ES+)} [\text{M+1}]^+ \): m/z 442.

5-[4-Methyl-2-(pyridin-3-yl)-thiazole-5-yl]-4-phenyl-3-(2-methylbenzylthio)-4H-1,2,4-triazole V(A2)

Yield 72%, m.p. 87-89 °C, \( \text{IR (KBr)} \nu_{\text{max}} (\text{cm}^{-1}) \): 3051 (aromatic CH), 2952, 2922, 2856 (aliphatic CH), 1636 (C=N), 1590 (C=C), 809 (mono substituted benzene), 770 (1,2-disubstituted benzene), 690 (C-S); \( ^1\text{H NMR} \) (500 MHz, DMSO-\( d_6 \)) \( \delta \) (ppm): 2.25 (3H, s, CH₃), 2.45 (3H, s, CH₃), 4.43 (2H, s, S-CH₂), 7.14 (1H, d, \( J \): 7.3 Hz, Ar-H), 7.19-7.20 (2H, m, Ar-H), 7.25 (1H, d, \( J \): 7.4 Hz, Ar-H), 7.28-7.30 (2H, m, Ar-H), 7.51-7.56 (4H, m, Ar-H, pyridine C₅-H), 8.16 (1H, d, \( J \): 8.1 Hz, pyridine C₆-H), 8.67 (1H, d, \( J \): 4.8 Hz, pyridine C₄-H), 8.99 (1H, s, pyridine C₂-H); \( ^{13}\text{C} \)
Yield 78%, m.p. 134-137 °C, IR (KBr) νmax (cm⁻¹): 3054, 3028 (aromatic CH), 2972, 2925 (aliphatic CH), 1626 (C= N), 1596 (C=C), 809 (mono substituted benzene), 774 and 726 (1,3-disubstituted benzene), 690 (C= S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.30 (3H, s, CH₃), 2.50 (3H, s, CH₃), 4.40 (2H, s, S-CH₂), 7.11-7.35 (4H, m, Ar-H), 7.28 (2H, d, J: 7.4 Hz, Ar-H), 7.54 (4H, m, Ar-H, pyridine C₅-H), 8.13 (1H, d, J: 8.1 Hz, pyridine C₆-H), 8.70 (1H, d, J: 4.8 Hz, pyridine C₄-H), 9.10 (1H, s, pyridine C₂-H); for C₂₅H₂₁NS₂ calculated: (%) C 65.91, H 4.65, N 15.37, found: (%) C 65.90, H 4.62 N 15.34; MS (ES⁺) [M+1]⁺: m/z 457.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-phenyl-3-(3-methylbenzylthio)-4H-1,2,4-triazole V (A3)

Yield 82%, m.p. 235-236 °C, IR (KBr) νmax (cm⁻¹): 3055 (aromatic CH), 2955, 2928, 2856 (aliphatic CH), 1636(C=N), 1590 (C=C), 809 (mono substituted benzene), 776 and 730 (1,3-disubstituted benzene), 690 (C=S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.46 (3H, s, CH₃), 4.41 (2H, s, S-CH₂), 6.99-7.27 (4H, m, Ar-H), 7.31 (2H, d, J: 7.4 Hz, Ar-H), 7.61 (4H, m, Ar-H, pyridine C₅-H), 8.14 (1H, d, J: 8.1 Hz, pyridine C₆-H), 8.74 (1H, d, J: 4.7 Hz, pyridine C₄-H), 9.14 (1H, s, pyridine C₂-H); for C₂₅H₂₃N₅S₂ calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.54, H 3.80, N 14.74; MS (ES⁺) [M+1]⁺: m/z 477.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-phenyl-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (A6)

Yield 84%, m.p. 234-235 °C, IR (KBr) νmax (cm⁻¹): 3056 (aromatic CH), 2954, 2855 (aliphatic CH), 1632 (C=N), 1590 (C=C), 809 (mono substituted benzene), 774 and 730 (1,3 disubstituted benzene), 690 (C=S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.55 (3H, s, CH₃), 4.43 (2H, s, S-CH₂), 7.18 (1H, d, J: 7.3 Hz, Ar-H), 7.24-7.26 (2H, m, Ar-H), 7.30 (1H, d, J: 7.2 Hz, Ar-H), 7.36 (2H, d, J: 7.3 Hz, Ar-H), 7.55-7.61 (4H, m, Ar-H, pyridine C₅-H), 8.11 (1H, d, J: 8.1 Hz, pyridine C₆-H), 8.72 (1H, d, J: 4.8 Hz, pyridine C₄-H), 9.11 (1H, s, pyridine C₂-H); for C₂₅H₁₈ClN₅S₂ calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.54, H 3.80, N 14.74; MS (ES⁺) [M+1]⁺: m/z 477.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-phenyl-3-(4-methoxybenzylthio)-4H-1,2,4-triazole V (A7)

Yield 84%, m.p. 234-235 °C, IR (KBr) νmax (cm⁻¹): 3056 (aromatic CH), 2954, 2855 (aliphatic CH), 1632 (C=N), 1590 (C=C), 809 (mono substituted benzene), 774 and 730 (1,3 disubstituted benzene), 690 (C=S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.55 (3H, s, CH₃), 3.80 (3H, s, OCH₃), 4.39 (2H, s, S-CH₂), 6.78-7.23 (4H, m, Ar-H), 7.29 (2H, d, J: 7.4 Hz, Ar-H), 7.58 (4H, m, Ar-H, pyridine C₅-H), 8.17 (1H, d, J: 8.1 Hz, pyridine C₆-H), 8.72 (1H, d, J: 4.8 Hz, pyridine C₄-H), 9.21 (1H, s, pyridine C₂-H); for C₂₅H₂₁O₄N₅S₂ calculated: (%) C 63.67, H 4.49, N 14.85, found: (%) C 63.65, H 4.47, N 14.89; MS (ES⁺) [M+1]⁺: m/z 473.
5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-benzylthio-4H-1,2,4-triazole V (A8)

Yield 74%, m.p. 132-134 °C, IR (KBr) v max (cm⁻¹): 3056 (aromatic CH), 2958, 2855 (aliphatic CH), 1607 (C=N), 1586 (C=C), 809 (mono substituted benzene), 772 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.80 (3H, s, CH₃), 2.55 (3H, s, CH₃), 4.41 (2H, s, S-CH₂), 7.10 (1H, s, Ar-H), 7.15 (1H, d, J: 7.3 Hz, Ar-H), 7.26-7.38 (3H, m, Ar-H), 7.48 (1H, t, J: 7.4 Hz, Ar-H), 7.49-7.51 (2H, m, Ar-H), 7.52 (1H, t, J: 8.4 Hz, Ar-H), 7.55 (1H, t, J: 8.4 Hz, Ar-H, pyridine C₅-H), 7.98 (1H, d, J: 8.0 Hz, pyridine C₄-H), 8.59 (1H, d, J: 4.8 Hz, pyridine C₄-H), 8.88 (1H, s, pyridine C₅-H); For C₂₅H₂₁N₅S₂ calculated: (%) C 65.91, H 4.65, N 15.37; found: (%) C 65.90, H 4.64, N 15.34; MS (ES+) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(2-methylbenzthio)-4H-1,2,4-triazole V (A9)

Yield 68%, m.p. 90-92 °C, IR (KBr) v max (cm⁻¹): 3058 (aromatic CH), 2962, 2857 (aliphatic CH), 1607 (C=N), 1586 (C=C), 774 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.84 (3H, s, CH₃), 2.29 (3H, s, CH₃), 2.69 (3H, s, CH₃), 4.48 (2H, s, S-CH₂), 7.15-7.21 (3H, m, Ar-H), 7.29-7.32 (2H, m, Ar-H), 7.47 (1H, t, J: 7.4 Hz, Ar-H), 7.49-7.52 (2H, m, Ar-H), 7.54 (1H, t, J: 8.4 Hz, Ar-H, pyridine C₅-H), 8.09 (1H, d, J: 8.0 Hz, pyridine C₆-H), 8.65 (1H, d, J: 4.8 Hz, pyridine C₄-H), 8.92 (1H, s, pyridine C₅-H); ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 164.17, 155.96, 151.86, 148.78, 147.10, 137.17, 136.31, 134.68, 134.37, 132.02, 131.91, 131.76, 131.32, 130.84, 130.39, 129.85, 129.39, 128.46, 128.21, 127.16, 126.49, 116.73, 35.20,19.06, 17.69, 17.11. For C₂₅H₂₁N₅S₂ calculated: (%) C 66.50, H 4.94, N 14.91; found: (%) C 66.47, H 4.94, N 14.93; MS (ES+) [M+1]: m/z 471.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(2-chlorobenzthio)-4H-1,2,4-triazole V (A10)

Yield 75%, m.p. 96-98 °C, IR (KBr) v max (cm⁻¹): 3032, 3014 (aromatic CH), 2946, 2856 (aliphatic CH), 1610 (C=N), 1590 (C=C), 770 (1,2 disubstituted benzene), 680 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.85 (3H, s, CH₃), 2.69 (3H, s, CH₃), 4.44 (2H, s, S-CH₂), 7.18-7.23 (3H, m, Ar-H), 7.30-7.34 (2H, m, Ar-H), 7.48 (1H, t, J: 7.4 Hz, Ar-H), 7.50-7.52 (2H, m, Ar-H), 7.55 (1H, t, J: 8.4 Hz, Ar-H, pyridine C₅-H), 7.81 (1H, d, J: 8.0 Hz, pyridine C₆-H), 8.67 (1H, d, J: 4.8 Hz, pyridine C₄-H), 8.91 (1H, s, pyridine C₅-H); For C₂₅H₂₁ClN₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29; found: (%) C 61.26, H 4.13, N 14.28; MS (ES+) [M+1]: m/z 496.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-benzylthio-4H-1,2,4-triazole V (A11)

Yield 84%, m.p. 160-162 °C, IR (KBr) v max (cm⁻¹): 3057 (aromatic CH), 2958, 2855 (aliphatic CH), 1607 (C=N), 1586 (C=C), 806 (mono substituted benzene), 770 and 740 (1,3 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 11.64 (1H, d, S-CH₃), 1.85 (3H, s, CH₃), 4.32 (2H, s, s-CH₂), 7.06-8.15 (10H, m, Ar-H), 8.14 (1H, d, J: 8.5 Hz, Ar-H, pyridine C₅-H), 8.65 (1H, d, J: 4.8 Hz, Ar-H, pyridine C₆-H), 8.96 (1H, s, Ar-H, pyridine C₅-H); ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 17.36, 21.14, 36.97, 124.81, 125.39, 128.02, 128.47, 128.57, 128.97, 129.51, 130.16, 131.68, 133.03, 134.12, 137.50, 140.21, 147.17, 148.60, 151.89, 152.16, 155.70, 164.50; For C₂₅H₂₁N₅S₂ calculated: (%) C 65.91, H 4.65, N 15.37; found: (%) C 65.89, H 4.63, N 15.41; MS (ES+) [M+1]: m/z 457.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(2-chlorobenzthio)-4H-1,2,4-triazole V (A12)

Yield 72%, m.p. 163-165 °C, IR (KBr) v max (cm⁻¹): 3054 (aromatic CH), 2962, 2852 (aliphatic CH), 1606 (C=N), 1586 (C=C), 783 (1,2 disubstituted benzene), 776 and 737 (1,3 disubstituted benzene), 697 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.30 (3H, s, CH₃), 2.48 (3H, s, CH₃), 4.50 (2H, s, S-CH₂), 7.08-7.14 (2H, m, Ar-H), 7.30-7.43 (6H, M, Ar-H), 7.46-7.52 (3H, m, Ar-H), 7.50-7.52 (2H, m, Ar-H), 8.14 (1H, d, J: 8.0 Hz, pyridine C₅-H), 8.65 (1H, d, J: 4.6 Hz, Ar-H, pyridine C₆-H), 8.97 (1H, s, Ar-H, pyridine C₅-H); ¹³C NMR (75 MHz, DMSO-d₆) δ (ppm): 17.35, 21.18, 35.24, 124.81, 125.39, 127.86, 128.44, 128.57,
130.0, 131.71, 131.98, 132.96, 134.13, 134.80, 140.21, 147.17, 148.80, 151.90, 164.89; For C\textsubscript{25}H\textsubscript{20}ClN\textsubscript{5}S\textsubscript{2} calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.24, H 4.08, N 14.26; MS (ES\textsuperscript{+}) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (A13)

Yield 79%, m.p. 98-100 °C, IR (KBr) v\textsubscript{max} (cm\textsuperscript{-1}): 3057 (aromatic CH), 2955, 2852 (aliphatic CH), 1606 (C=N), 1586 (C=C), 776 and 736 (1,3 disubstituted benzene), 694 (C=S), \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) δ (ppm): 2.30 (3H, s, CH\textsubscript{3}), 2.48 (3H, s, CH\textsubscript{3}), 4.42 (2H, s, S-CH\textsubscript{2}), 7.08-7.15 (2H, m, Ar-H), 7.31-7.52 (7H, m, Ar-H), 8.14 (1H, dt, J=8.1, 1.9 Hz, pyridine C\textsubscript{6}-H), 8.65 (1H, d, J= 4.9 Hz, pyridine C\textsubscript{5}-H), 8.96 (1H, s, pyridine C\textsubscript{2}-H); \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) δ (ppm): 17.41, 21.17, 35.97, 117.10, 124.81, 125.40, 128.44, 128.57, 128.89, 130.20, 131.41, 131.72, 132.5, 132.98, 134.11, 136.90, 140.25, 147.16, 148.69, 151.89, 152.0, 155.72, 164.49; For C\textsubscript{25}H\textsubscript{20}ClN\textsubscript{5}S\textsubscript{2} calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.27, H 4.09, N 14.28; MS (ES\textsuperscript{+}) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(2-chlorobenzylthio)-4H-1,2,4-triazole V (A15)

Yield 78%, m.p. 122-124 °C, IR (KBr) v\textsubscript{max} (cm\textsuperscript{-1}): 3051 (aromatic CH), 2971, 2909 (aliphatic CH), 1636 (C=N), 1593 (C=C), 816 (1,4 disubstituted benzene), 760 (1,2 disubstituted benzene), 690 (C-S); \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) δ (ppm): 2.37 (3H, s, CH\textsubscript{3}), 2.46 (3H, s, CH\textsubscript{3}), 4.50 (2H, s, S-CH\textsubscript{2}), 7.22 (1H, s, Ar-H), 7.25 (1H, s, Ar-H), 7.24 (1H, s, Ar-H), 7.32-7.36 (4H, m, Ar-H), 7.47-7.54 (2H, m, Ar-H), pyridine C\textsubscript{5}-H), 8.16 (1H, d, J= 8.1 Hz, pyridine C\textsubscript{6}-H), 8.67 (1H, d, J= 4.8 Hz, pyridine C\textsubscript{2}-H), 8.99 (1H, d, s, pyridine C\textsubscript{2}-H); \textsuperscript{13}C NMR (75 MHz, DMSO-d\textsubscript{6}) δ (ppm): 164.62, 155.69, 151.88, 148.80, 147.18, 140.88, 134.77, 134.13, 133.76, 132.01, 130.45, 130.17, 129.97, 128.86, 128.57, 127.95, 127.85, 124.79, 117.12, 134.92, 21.26, 17.26; For C\textsubscript{25}H\textsubscript{20}ClN\textsubscript{5}S\textsubscript{2} calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.27, H 4.12, N 14.32; MS (ES\textsuperscript{+}) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (A16)

Yield 68%, m.p. 121-123 °C, IR (KBr) v\textsubscript{max} (cm\textsuperscript{-1}): 3057 (aromatic CH), 2971, 2912 (aliphatic CH), 1626 (C=N), 1596 (C=C), 813 (1,4 disubstituted benzene), 694 (C=S); \textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) δ (ppm): 2.37 (3H, s, CH\textsubscript{3}), 2.51 (3H, s, CH\textsubscript{3}), 4.40 (2H, s, S-CH\textsubscript{2}), 6.85-7.24 (4H, m, Ar-H), 7.32-7.34 (5H, m, Ar-H), pyridine C\textsubscript{5}-H), 8.14 (1H, d, J= 8.1 Hz, pyridine C\textsubscript{6}-H), 8.66 (1H, d, J= 4.8 Hz, pyridine C\textsubscript{2}-H), 8.97 (1H, s, pyridine C\textsubscript{2}-H); For C\textsubscript{25}H\textsubscript{20}ClN\textsubscript{5}S\textsubscript{2} calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, H 4.08, N 14.30; MS (ES\textsuperscript{+}) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-methoxyphenyl)-3-(2-chlorobenzylthio)-4H-1,2,4-triazole V (A17)

Yield 82%, m.p. 98-100 °C, IR (KBr) v\textsubscript{max} (cm\textsuperscript{-1}): 3061, 3008 (aromatic CH), 2932, 2836 (aliphatic CH), 1636
Synthesis, antimicrobial and antioxidant activities of pyridyl substituted thiazolyl triazole derivatives

(C=N), 1586 (C=C), 819 (1,4 disubstituted benzene), 760 (1,2 disubstituted benzene), 690 (C-S); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.37 (3H, s, CH\(_3\)), 2.51 (3H, s, CH\(_3\)), 4.40 (2H, s, S-CH\(_2\)), 6.85-7.24 (4H, m, Ar-H), 7.32-7.34 (5H, m, Ar-H, pyridine C\(_5\)-H), 8.14 (1H, d, \(J = 8.1\) Hz, pyridine C\(_6\)-H), 8.66 (1H, d, \(J = 4.8\) Hz, pyridine C\(_4\)-H), 8.97 (1H, s, pyridine C\(_2\)-H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 17.41, 34.83, 56.04, 115.51, 124.80, 125.35, 127.85, 128.60, 129.43, 129.71, 129.98, 130.16, 130.49, 131.29, 131.76, 132.02, 132.67, 133.76, 134.11, 134.79, 143.31, 147.15, 149.13, 151.86, 152.14, 155.72, 160.94, 164.48; For C\(_{25}\)H\(_{20}\)ClN\(_5\)S\(_2\) calculated: (%) C 59.34, H 3.98, N 13.84, found: (%) C 59.32, H 3.99, N 13.84; MS (ES+) \([M+1]^+\): m/z 507.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-methoxyphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (A18)

Yield 88%, m.p. 179-180 °C, IR (KBr) \(v_{\text{max}}\) (cm\(^{-1}\)): 3057, 3005 (aromatic CH), 2975, 2928 (aliphatic CH), 1624 (C=N), 770 and 737 (1,3 disubstituted benzene), 690 (C-S); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.45 (3H, s, CH\(_3\)), 3.81 (3H, s, OCH\(_3\)), 4.42 (2H, s, S-CH\(_2\)), 7.31-7.36 (4H, m, Ar-H), 7.43-7.58 (3H, m, Ar-H), 7.66 (1H, d, \(J = 7.6\) Hz, Ar-H, pyridine C\(_5\)-H), 8.17 (1H, d, \(J = 8.2\) Hz, pyridine C\(_6\)-H), 8.66 (1H, d, \(J = 4.8\) Hz, pyridine C\(_4\)-H), 8.99 (1H, s, pyridine C\(_2\)-H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 160.96, 152.95, 147.17, 145.64, 142.96, 136.82, 132.77, 132.54, 131.47, 131.41, 129.72, 129.60, 128.85, 125.38, 125.28, 124.79, 115.61, 115.53, 115.35, 56.05, 35.57, 17.41; For C\(_{25}\)H\(_{20}\)ClN\(_5\)S\(_2\) calculated: (%) C 59.34, H 3.98, N 13.84, found: (%) C 59.32, H 3.99, N 13.84; MS (ES+) \([M+1]^+\): m/z 511.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-chlorophenyl)-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (A21)

Yield 76%, m.p. 137-139 °C, IR (KBr) \(v_{\text{max}}\) (cm\(^{-1}\)): 3057, 3028 (aromatic CH), 2975, 2928 (aliphatic CH), 1624 (C=N), 1596 (C=C), 770 and 737 (1,3 disubstituted benzene), 690 (C-S); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.46 (3H, s, CH\(_3\)), 4.42 (2H, s, S-CH\(_2\)), 7.31-7.34 (6H, m, Ar-H), 7.49-7.57 (3H, m, Ar-H), 7.28-7.41 (3H, m, Ar-H), 7.65 (1H, d, \(J = 8.8\) Hz, pyridine C\(_5\)-H), 8.17 (1H, d, \(J = 8.0-6\) Hz, pyridine C\(_4\)-H), 8.66 (1H, d, \(J = 4.8\) Hz, pyridine C\(_3\)-H), 8.99 (1H, s, pyridine C\(_2\)-H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 17.28, 37.28, 147.21, 151.95, 155.88; For C\(_{24}\)H\(_{18}\)ClN\(_5\)S\(_2\) calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.56, H 3.80, N 14.72; MS (ES+) \([M+1]^+\): m/z 477.
J: 8.2 Hz, pyridine C4-H), 8.70 (1H, d, J: 4.7 Hz, pyridine C4-H), 8.99 (1H, s, pyridine C2-H); 13C NMR (75 MHz, DMSO-d_6) δ (ppm): 17.31, 36.21, 116.85, 124.81, 127.37, 128.39, 128.54, 128.91, 131.17, 131.39, 131.98, 132.63, 134.18, 134.33, 134.44, 136.80, 147.21, 148.54, 151.18, 151.94, 155.87, 164.77; For C26H_{21}Cl2N5S2 calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.44, H 3.33, N 13.70; MS (ES+) [M+1]^+: m/z 511.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-chlorophenyl)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (A22)

Yield 83%, m.p. 132-134 °C, IR (KBr) ν_{max} (cm⁻¹): 3081, 3054, 3028 (aromatic CH), 2955, 2919, 2856 (aliphatic CH), 1626 (C=N), 1573 (C=C), 806 (1,4 disubstituted benzene), 776 (1,2 disubstituted benzene), 694 (C-S); 1H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH3), 2.51 (3H, s, CH3), 4.42 (2H, s, S-CH2), 7.25-7.32 (3H, m, Ar-H), 7.37-7.42 (4H, m, Ar-H), 7.66-7.71 (2H, m, Ar-H, pyridine C4-H), 8.16 (1H, d, J: 8.1 Hz, pyridine C6-H), 8.67 (1H, d, J: 4.7 Hz, pyridine C7-H), 8.99 (1H, s, pyridine C2-H); For C26H_{20}ClN5S2 calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.26, H 4.09, N 14.31; MS (ES+) [M+1]^+: m/z 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-chlorophenyl)-3-(3-methylbenzylthio)-4H-1,2,4-triazole V (A23)

Yield 74%, m.p. 89-90 °C, IR (KBr) ν_{max} (cm⁻¹): 3084, 3051, 3028 (aromatic CH), 2955, 2918, 2854 (aliphatic CH), 1626 (C=N), 1573 (C=C), 809 (1,4 disubstituted benzene), 770 and 737 (1,3 disubstituted benzene), 694 (C-S); 1H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.32 (3H, s, CH3), 2.52 (3H, s, CH3), 4.42 (2H, s, S-CH2), 7.21-7.34 (4H, m, Ar-H), 7.36-7.41 (2H, m, Ar-H), 7.66-7.71 (3H, m, Ar-H, pyridine C4-H), 8.13 (1H, d, J: 8.1 Hz, pyridine C6-H), 8.66 (1H, d, J: 4.7 Hz, pyridine C7-H), 8.97 (1H, s, pyridine C2-H); For C26H_{20}ClN5S2 calculated: (%) C 65.91, H 4.65, N 15.37, found: (%) C 65.87, H 4.63, N 15.40; MS (ES+) [M+1]^+: m/z 457.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-phenyl-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B1)

Yield 81%, m.p. 268-269 °C, IR (KBr) ν_{max} (cm⁻¹): 3041 (aromatic CH), 2970-2800 (aliphatic CH), 1626 (C=C), 1593 (C=C), 822 (mono substituted benzene), 776 (1,2-disubstituted benzene), 694 (C-S); 1H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.51 (3H, s, CH3), 2.80 (3H, s, CH3), 4.20 (2H, s, S-CH2), 7.05 (1H, t, ArH), 7.12 (1H, d, ArH), 7.19 (1H, t, ArH), 7.25 (1H, d, ArH), 7.29 (1H, t, ArH), 7.39 (2H, t, ArH), 7.63 (2H, d, ArH), 7.95 (2H, d, J: 5.7 Hz pyridine C4-H, C6-H), 8.75 (2H, d, J: 5.2 Hz, pyridine C2-H, C6-H); For C25H_{21}N5S2 calculated: (%) C 61.72, H 4.63, N 14.37; MS (ES+) [M+1]^+: m/z 457.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-phenyl-3-(4-methylbenzylthio)-4H-1,2,4-triazole V (B2)

Yield 87%, m.p. 271-272 °C, IR (KBr) ν_{max} (cm⁻¹): 3034 (aromatic CH), 2935-2800 (aliphatic CH), 1626 (C=C), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); 1H NMR (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH3), 2.68 (3H, s, CH3), 4.51 (2H, s, S-CH2), 7.00 (1H, t, ArH), 7.15 (2H, d, J: 8.1 Hz, pyridine C6-H), 8.70 (1H, d, J: 4.7 Hz, pyridine C7-H), 9.01 (1H, s, pyridine C2-H); For C25H_{21}N5S2 calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.26, H 4.15, N 14.33; MS (ES+) [M+1]^+: m/z 491.
7.9 Hz, ArH), 7.31 (2H, d, J: 8.0 Hz, ArH), 7.33 (2H, t, ArH), 7.58 (2H, d, ArH), 8.01 (2H, d, J: 5.9 Hz pyridine C_5-H, C_6-H), 8.76 (2H, d, J: 5.3 Hz, pyridine C_2-H, C_6-H); For C_{25}H_{21}N_5S_2 calculated: (%) C 65.91, H 4.65, N 15.37, found: (%) C 65.95, H 4.69, N 15.36; MS (ES+)[M+1]^+: m/z 457.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-phenyl-3-(2-chlorobenzylthio)-4H-1,2,4-triazole V (B3)

Yield 84%, m.p. 259-260 °C, IR (KBr) ν_max (cm⁻¹): 3034 (aromatic CH), 2935-2800 (aliphatic CH), 1626 (C=N), 1590 (C=C), 822 (mono substituted benzene), 776 (1,2 disubstituted benzene), 694 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.77 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.07 (1H, t, ArH), 7.40 (2H, t, ArH), 7.48 (1H, d, ArH), 7.51 (1H, t, ArH), 7.53 (1H, t, ArH), 7.55 (1H, d, ArH), 7.64 (2H, d, ArH), 8.05 (2H, d, J: 6.1 Hz pyridine C_3-H, C_5-H), 8.81 (2H, d, J: 5.3 Hz, pyridine C_2-H, C_6-H); For C_{25}H_{18}ClN_5S_2 calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.53, H 3.78, N 14.69; MS (ES+)[M+1]^+: m/z 477.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-phenyl-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (B4)

Yield 87%, m.p. 270-271 °C, IR (KBr) ν_max (cm⁻¹): 3038 (aromatic CH), 2945-2800 (aliphatic CH), 1626 (C=N), 1593 (C=C), 824 (mono substituted benzene), 770 and 736 (1,3 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.78 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.00 (1H, t, ArH), 7.04 (1H, t, ArH), 7.10 (2H, d, ArH), 7.18 (1H, s, ArH), 7.37 (2H, t, ArH), 7.62 (2H, d, ArH), 8.07 (2H, d, J: 6.1 Hz pyridine C_3-H, C_5-H), 8.82 (2H, d, J: 5.4 Hz, pyridine C_2-H, C_6-H); For C_{24}H_{18}ClN_5S_2 calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.55, H 3.85, N 14.73; MS (ES+)[M+1]^+: m/z 477.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-phenyl-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B5)

Yield 80%, m.p. 278-279 °C, IR (KBr) ν_max (cm⁻¹): 3036 (aromatic CH), 2930-2800 (aliphatic CH), 1626 (C=N), 1590 (C=C), 822 (mono substituted benzene), 780 (1,2 disubstituted benzene), 694 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.77 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.07 (1H, t, ArH), 7.34 (2H, d, J: 8.0 Hz, ArH), 7.41 (2H, d, ArH), 7.46 (2H, d, J: 8.1 Hz, ArH), 7.65 (2H, d, ArH), 7.98 (2H, d, J: 6.1 Hz pyridine C_3-H, C_5-H), 8.79 (2H, d, J: 5.4 Hz, pyridine C_2-H, C_6-H); For C_{24}H_{18}ClN_5S_2 calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.52, H 3.79, N 14.68; MS (ES+)[M+1]^+: m/z 477.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-benzylthio-4H-1,2,4-triazole V (B6)

Yield 85%, m.p. 274-276 °C, IR (KBr) ν_max (cm⁻¹): 3037 (aromatic CH), 2945-2800 (aliphatic CH), 1626 (C=N), 1593 (C=C), 824 (mono substituted benzene), 770 and 736 (1,3 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.68 (3H, s, CH₃), 3.77 (3H, s, OCH₃), 4.28 (2H, s, S-CH₂), 6.61 (1H, d, ArH), 6.80 (1H, s, ArH), 6.82 (1H, d, ArH), 6.87 (1H, t, ArH), 7.05 (1H, t, ArH), 7.40 (2H, t, ArH), 7.63 (2H, d, ArH), 7.99 (2H, d, J: 6.2 Hz pyridine C_3-H, C_5-H), 8.80 (2H, d, J: 5.4 Hz, pyridine C_2-H, C_6-H); For C_{25}H_{21}N_5S_2 calculated: (%) C 63.67, H 4.49, N 14.85, found: (%) C 63.67, H 4.46, N 14.88; MS (ES+)[M+1]^+: m/z 473.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methoxybenzylthio)-4H-1,2,4-triazole V (B7)

Yield 83%, m.p. 200-201 °C, IR (KBr) ν_max (cm⁻¹): 3127, 3028 (aromatic CH), 2922-2850 (aliphatic CH), 1619 (C=N), 1586 (C=C), 819 (mono substituted benzene), 763 (1,2 disubstituted benzene), 697 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.08 (3H, s, CH₃), 2.77 (3H, s, CH₃), 4.40 (2H, s, S-CH₂), 7.06-7.23 (5H, m, ArH), 7.29 (1H, d, ArH), 7.37 (1H, t, ArH), 7.42 (1H, d, ArH), 7.45 (1H, d, J: 8.2 Hz, pyridine C_5-H), 7.50 (1H, t, ArH), 7.80 (1H, d, J: 6.1 Hz pyridine C_2-H, C_6-H), 8.45 (1H, d, J: 5.9 Hz, pyridine C_6-H), 8.80 (1H, d, J: 6.1 Hz, pyridine C_2-H); For C_{25}H_{21}N_5S_2 calculated: (%) C 65.91, H 4.65, N 15.37, found: (%) C 65.88, H 4.61, N 15.39; MS (ES+)[M+1]^+: m/z 457.
5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(2-methylbenzylthio) -4H-1,2,4-triazole V (B8)

Yield 75%, m.p. 197-198 °C, IR (KBr) ν max (cm⁻¹): 3033 (aromatic CH), 2928-2856 (aliphatic CH), 1624 (C=N), 1590 (C=C), 760 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.22 (3H, s, CH₃), 2.58 (3H, s, CH₃), 2.70 (3H, s, CH₃), 4.51 (2H, s, S-CH₂), 7.10 (1H, d, ArH), 7.17 (1H, t, ArH), 7.22 (1H, d, ArH), 7.26 (1H, t, ArH), 7.35 (1H, d, ArH), 7.39 (1H, t, ArH), 7.45 (1H, d, ArH), 7.53 (1H, t, ArH), 7.75 (1H, d, J: 8.0 Hz, pyridine C₅-H), 7.94 (1H, d, J: 5.7 Hz, pyridine C₂-H), 8.65 (1H, d, J: 5.7 Hz, pyridine C₆-H), 8.76 (1H, d, J: 5.7 Hz, pyridine C₇-H); For C₂₆H₂₃N₅S₂ calculated: (%) C 66.50, H 4.94, N 14.91; found: (%) C 66.51, H 4.91, N 14.92; MS (ES⁺) [M+I]⁺: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (B9)

Yield 78%, m.p. 180-181 °C, IR (KBr) ν max (cm⁻¹): 3035 (aromatic CH), 2925-2850 (aliphatic CH), 1621 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 762 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 1.82 (3H, s, CH₃), 2.27 (3H, s, CH₃), 2.69 (3H, s, CH₃), 4.50 (2H, s, S-CH₂), 7.13 (2H, d, J: 8.0 Hz, ArH), 7.28 (2H, d, J: 8.0 Hz, ArH), 7.38 (1H, d, ArH), 7.42 (1H, t, ArH), 7.47 (1H, d, ArH), 7.56 (1H, t, ArH), 7.78 (1H, d, J: 8.0 Hz, pyridine C₁-H), 7.96 (1H, d, J: 5.8 Hz, pyridine C₅-H), 8.67 (1H, d, J: 5.7 Hz, pyridine C₆-H), 8.78 (1H, d, J: 5.7 Hz, pyridine C₂-H); For C₂₆H₂₃N₅S₂ calculated: (%) C 66.50, H 4.94, N 14.91; found: (%) C 66.50, H 4.92, N 14.87; MS (ES⁺) [M+I]⁺: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B10)

Yield 82%, m.p. 176-178 °C, IR (KBr) ν max (cm⁻¹): 3034 (aromatic CH), 2925-2850 (aliphatic CH), 1624 (C=N), 1590 (C=C), 765 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.25 (3H, s, CH₃), 2.79 (3H, s, CH₃), 4.30 (2H, s, S-CH₂), 7.43 (1H, d, ArH), 7.44 (1H, t, ArH), 7.49 (1H, t, ArH), 7.51 (1H, d, ArH), 7.33 (1H, d, ArH), 7.37 (1H, t, ArH), 7.46 (1H, d, ArH), 7.54 (1H, t, ArH), 7.91 (2H, d, J: 7.9 Hz, pyridine C₂-H, C₅-H); For C₂₅H₂₀ClN₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29; found: (%) C 61.24, H 4.08, N 14.26; MS (ES⁺) [M+I]⁺: m/z 491.
5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(3-methoxybenzylthio)-4H-1,2,4-triazole V (B13)

Yield 86%, m.p. 183-184 °C, IR (KBr) v_{max} (cm^{-1}): 3028 (aromatic CH), 2925-2850 (aliphatic CH), 1621 (C=N), 1590 (C=C), 765 (1,2 disubstituted benzene), 770 and 737 (1,3 disubstituted benzene), 690 (C=S); ^1 H NMR (500 MHz, DMSO-d_{6}) δ (ppm): 2.25 (3H, s, CH), 2.66 (3H, s, CH), 3.67 (3H, s, OCH$_3$), 4.28 (2H, s, S-CH$_2$), 6.81 (1H, t, ArH), 6.89 (2H, d, ArH), 6.99 (1H, s, ArH), 7.06 (1H, d, ArH), 7.15 (1H, t, ArH), 7.19 (1H, d, ArH), 7.26 (1H, t, ArH), 7.80 (1H, d, J: 8.0 Hz, pyridine C$_3$-H), 8.40 (1H, d, J: 5.8 Hz, pyridine C$_2$-H), 8.79 (1H, d, J: 6.0 Hz pyridine C$_5$-H), 9.80 (1H, d, J: 5.8 Hz, pyridine C$_2$-H); For C$_{26}$H$_{23}$N$_5$S$_2$ calculated: (%) C 66.50, H 4.94, N 14.91, found: (%) C 66.53, H 4.91, N 14.88; MS (ES+) [M+1]^+: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(4-methylbenzylthio)-4H-1,2,4-triazole V (B14)

Yield 79%, m.p. 231-232 °C, IR (KBr) v_{max} (cm^{-1}): 3058 (aromatic CH), 2955-2850 (aliphatic CH), 1612 (C=N), 1586 (C=C), 806 (mono substituted benzene), 770 and 740 (1,3 disubstituted benzene), 690 (C=S); ^1 H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.45 (3H, s, CH), 2.76 (3H, s, CH$_3$), 4.40 (2H, s, S-CH$_2$), 7.14 (1H, d, ArH), 7.17-7.32 (5H, m, ArH), 7.27 (1H, d, ArH), 7.29 (1H, t, ArH), 7.45 (1H, d, J: 8.2 Hz, pyridine C$_2$-H), 7.49 (1H, s, ArH), 7.85 (1H, d, J: 6.3 Hz, pyridine C$_3$-H), 8.51 (1H, d, J: 5.9 Hz, pyridine C$_5$-H), 8.81 (1H, d, J: 6.1 Hz, pyridine C$_2$-H); For C$_{25}$H$_{20}$ClN$_5$S$_2$ calculated: (%) C 66.48, H 4.97, N 14.91; MS (ES+) [M+1]+: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B15)

Yield 76%, m.p. 225-226 °C, IR (KBr) v_{max} (cm^{-1}): 3052 (aromatic CH), 2958-2850 (aliphatic CH), 1606 (C=N), 1586 (C=C), 786 (1,2 disubstituted benzene), 776 and 737 (1,3 disubstituted benzene), 696 (C-S); ^1 H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.40 (3H, s, CH$_3$), 2.79 (3H, s, CH$_3$), 2.55 (3H, s, CH$_3$), 2.71 (3H, s, CH$_3$), 4.50 (2H, s, S-CH$_2$), 7.11 (1H, d, ArH), 7.14 (1H, d, ArH), 7.21 (1H, t, ArH), 7.23 (1H, d, ArH), 7.25 (1H, t, ArH), 7.28 (1H, d, ArH), 7.33 (1H, t, ArH), 7.46 (1H, s, ArH), 7.65 (1H, d, J: 8.1 Hz, pyridine C$_3$-H), 7.91 (1H, d, J: 5.8 Hz, pyridine C$_2$-H), 8.62 (1H, d, J: 5.7 Hz, pyridine C$_6$-H), 8.78 (1H, d, J: 5.7 Hz, pyridine C$_2$-H); For C$_{26}$H$_{23}$N$_5$S$_2$ calculated: (%) C 66.50, H 4.94, N 14.91, found: (%) C 66.53, H 4.91, N 14.88; MS (ES+) [M+1]^+: m/z 491.
5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (B18)

Yield 84%, m.p. 222-223 °C, IR (KBr) ν_max (cm⁻¹): 3058 (aromatic CH), 2960-2850 (aliphatic CH), 1606 (C=O), 1586 (C=C), 774 and 737 (1,3 disubstituted benzene), 690 (C-S); 1H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.43 (3H, s, CH₃), 2.79 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.08 (1H, t, ArH), 7.18 (2H, d, ArH), 7.10 (1H, d, ArH), 7.22 (1H, d, ArH), 7.25 (1H, t, ArH), 7.29 (1H, s, ArH), 7.45 (1H, s, ArH), 7.69 (1H, d, J: 8.1 Hz, pyridine C₅-H), 7.95 (1H, d, J: 5.8 Hz, pyridine C₃-H), 8.67 (1H, d, J: 8.1 Hz, pyridine C₅-H), 8.81 (1H, d, J: 5.7 Hz, pyridine C₆-H); For C_{25}H_{20}ClN_{5}S_{2} calculated: (%) C 61.28, H 4.11, N 14.29; found: (%) C 61.24, H 4.14, N 14.32; MS (ES⁺) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B19)

Yield 89%, m.p. 222-224 °C, IR (KBr) ν_max (cm⁻¹): 3062 (aromatic CH), 2970-2850 (aliphatic CH), 1606 (C=O), 1586 (C=C), 816 (1,4 disubstituted benzene), 776 and 740 (1,3 disubstituted benzene), 694 (C-S); 1H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.46 (3H, s, CH₃), 2.79 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.09 (1H, d, ArH), 7.20 (1H, d, ArH), 7.22 (1H, t, ArH), 7.32 (2H, d, J: 8.1 Hz, ArH), 7.42 (2H, d, J: 8.0 Hz, ArH), 7.46 (1H, s, ArH), 7.67 (1H, d, J: 8.2 Hz, pyridine C₅-H), 7.98 (1H, d, J: 5.9 Hz, pyridine C₃-H), 8.69 (1H, d, J: 5.8 Hz, pyridine C₆-H), 8.83 (1H, d, J: 5.8 Hz, pyridine C₂-H); For C_{25}H_{20}ClN_{5}S_{2} calculated: (%) C 64.31, H 4.77, N 14.42; found: (%) C 64.31, H 4.75, N 14.43; MS (ES⁺) [M+1]: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B20)

Yield 83%, m.p. 215-216 °C, IR (KBr) ν_max (cm⁻¹): 3057 (aromatic CH), 2960-2855 (aliphatic CH), 1606 (C=O), 1586 (C=C), 776 and 737 (1,3 disubstituted benzene), 694 (C-S); 1H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.41 (3H, s, CH₃), 2.71 (3H, s, CH₃), 3.81 (3H, s, OCH₃), 4.28 (2H, s, S-CH₂), 6.75 (1H, t, ArH), 6.85 (2H, d, ArH), 7.01 (1H, s, ArH), 7.10 (1H, d, ArH), 7.21 (1H, d, ArH), 7.23 (1H, t, ArH), 7.45 (1H, s, ArH), 7.74 (1H, d, J: 4.6 Hz, pyridine C₃-H), 7.97 (1H, d, J: 4.4 Hz, pyridine C₅-H), 8.66 (1H, d, J: 4.5 Hz, pyridine C₆-H), 8.79 (1H, d, J: 4.4 Hz, pyridine C₂-H); For C_{26}H_{23}N_{5}S_{2} calculated: (%) C 66.50, H 4.92, N 14.88; found: (%) C 66.51, H 4.89, N 14.88; MS (ES⁺) [M+1]: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-benzylthio-4H-1,2,4-triazole V (B21)

Yield 69%, m.p. 222-227 °C, IR (KBr) ν_max (cm⁻¹): 3037 (aromatic CH), 2915-2820 (aliphatic CH), 1626 (C=O), 1590 (C=C), 819 (1,4 disubstituted benzene), 806 (monosubstituted benzene), 690 (C-S); 1H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.27 (3H, s, CH₃), 2.77 (3H, s, CH₃), 4.40 (2H, s, S-CH₂), 7.10 (2H, d, J: 8.1 Hz, ArH), 7.20 (3H, m, ArH), 7.25 (2H, dd, ArH), 7.37 (2H, d, J: 8.1 Hz, ArH), 7.46 (1H, d, J: 8.2 Hz, pyridine C₅-H), 7.87 (1H, d, J: 6.3 Hz, pyridine C₆-H), 8.55 (1H, d, J: 6.0 Hz, pyridine C₂-H), 8.84 (1H, d, J: 6.2 Hz, pyridine C₃-H); For C_{25}H_{20}N_{4}S_{2} calculated: (%) C 65.91, H 4.65, N 15.37; found: (%) C 65.88, H 4.63, N 15.40; MS (ES⁺) [M+1]: m/z 457.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B22)

Yield 70%, m.p. 197-199 °C, IR (KBr) ν_max (cm⁻¹): 3032 (aromatic CH), 2923-2847 (aliphatic CH), 1620 (C=O), 1589 (C=C), 815 (1,4 disubstituted benzene), 767 (1,2 disubstituted benzene), 689 (C-S); 1H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.28 (3H, s, CH₃), 2.56 (3H, s, CH₃), 2.71 (3H, s, CH₃), 4.51 (2H, s, S-CH₂), 7.05 (2H, d, J: 8.2 Hz, ArH), 7.09 (1H, d, ArH), 7.11 (1H, t, ArH), 7.18 (1H, d, ArH), 7.21 (1H, t, ArH), 7.30 (2H, d, J: 8.2 Hz, ArH), 7.62 (1H, d, J: 8.0 Hz, pyridine C₅-H), 7.88 (1H, d, J: 5.9 Hz, pyridine C₆-H), 8.58 (1H, d, J: 5.7 Hz, pyridine C₂-H); For C_{26}H_{23}N_{5}S_{2} calculated: (%) C 66.50, H 4.94, N 14.91; found: (%) C 66.50, H 4.92, N 14.88; MS (ES⁺) [M+1]: m/z 471.
5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(4-methylbenzylthio)-4H-1,2,4-triazole V (B23)

Yield 79%, m.p. 244-245 °C, IR (KBr) ν_{max} (cm⁻¹): 3039 (aromatic CH), 2918-2836 (aliphatic CH), 1626 (C=O), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.20 (3H, s, CH₃), 2.36 (3H, s, CH₃), 2.70 (3H, s, CH₃), 4.51 (2H, s, S-CH₂), 7.14 (2H, d, J: 8.0 Hz, ArH), 7.15 (2H, d, J: 8.0 Hz, ArH), 7.27 (2H, d, J: 8.0 Hz, ArH), 7.40 (2H, d, J: 8.0 Hz, ArH), 8.38 (2H, d, J: 5.9 Hz, pyridine C₃-H, C₅-H), 8.82 (2H, d, J: 5.3 Hz, pyridine C₂-H, C₆-H); For C₂₆H₂₃N₅S₂ calculated: (%) C 66.50, H 4.94, N 14.91, found: (%) C 66.54, H 4.91 N 14.86; MS (ES⁺) [M+1]⁺: m/z 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(2-chlorobenzylthio)-4H-1,2,4-triazole V (B24)

Yield 77%, m.p. 233-234 °C, IR (KBr) ν_{max} (cm⁻¹): 3037 (aromatic CH), 2915-2820 (aliphatic CH), 1626 (C=O), 1590 (C=C), 819 (1,4 disubstituted benzene), 806 (monosubstituted benzenes), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.35 (3H, s, CH₃), 2.79 (3H, s, CH₃), 4.30 (2H, s, S-CH₂), 7.09 (2H, d, J: 8.0 Hz, ArH), 7.36 (2H, d, J: 8.1 Hz, ArH), 7.46 (1H, d, ArH), 7.50 (1H, t, ArH), 7.52 (1H, t, ArH), 7.54 (1H, d, ArH), 7.91 (2H, d, J: 7.9 Hz, pyridine C₅-H, C₃-H), 8.82 (2H, d, J: 6.1 Hz, pyridine C₂-H, C₆-H); For C₂₅H₂₀ClN₅S₂ calculated: (%) C 64.30, H 4.75, N 14.43; found: (%) C 64.32, H 4.68, N 14.42; MS (ES⁺) [M+1]⁺: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(3-methoxybenzylthio)-4H-1,2,4-triazole V (B25)

Yield 78%, m.p. 185-187 °C, IR (KBr) ν_{max} (cm⁻¹): 3032 (aromatic CH), 2920-2820 (aliphatic CH), 1626 (C=O), 1590 (C=C), 819 (1,4 disubstituted benzene), 774 and 737 (1,3 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.28 (3H, s, CH₃), 2.81 (3H, s, CH₃), 4.30 (2H, s, S-CH₂), 7.08 (1H, t, ArH), 7.11 (2H, d, J: 8.2 Hz, ArH), 7.15 (2H, d, ArH), 7.27 (1H, s, ArH), 7.32 (2H, d, J: 8.2 Hz, ArH), 7.89 (2H, d, J: 7.9 Hz, pyridine C₅-H, C₃-H), 8.78 (2H, d, J: 6.1 Hz, pyridine C₂-H, C₆-H); For C₂₆H₂₂N₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.29, H 4.08, N 14.32; MS (ES⁺) [M+1]⁺: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B26)

Yield 75%, m.p. 240-241 °C, IR (KBr) ν_{max} (cm⁻¹): 3036 (aromatic CH), 2924-2828 (aliphatic CH), 1626 (C=O), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.35 (3H, s, CH₃), 2.79 (3H, s, CH₃), 4.30 (2H, s, S-CH₂), 7.12 (2H, d, J: 8.2 Hz, ArH), 7.31 (2H, d, J: 8.1 Hz, ArH), 7.38 (2H, d, J: 8.1 Hz, ArH), 7.43 (2H, d, J: 8.2 Hz, ArH), 7.91 (2H, d, J: 7.9 Hz, pyridine C₅-H, C₃-H), 8.83 (2H, d, J: 6.1 Hz, pyridine C₂-H, C₆-H); For C₂₅H₂₀ClN₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.24, H 4.13, N 14.33; MS (ES⁺) [M+1]⁺: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-methylphenyl)-3-(3-methoxybenzylthio)-4H-1,2,4-triazole V (B27)

Yield 80%, m.p. 246-247 °C, IR (KBr) ν_{max} (cm⁻¹): 3034 (aromatic CH), 2915-2830 (aliphatic CH), 1623 (C=O), 1593 (C=C), 819 (1,4 disubstituted benzene), 776 and 737 (1,3 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.37 (3H, s, CH₃), 2.74 (3H, s, CH₃), 3.75 (3H, s, OCH₃), 4.32 (2H, s, S-CH₂), 6.67 (1H, d, ArH), 6.86 (1H, s, ArH), 6.89 (1H, d, ArH), 6.92 (1H, t, ArH), 7.07 (2H, d, J: 8.2 Hz, ArH), 7.33 (2H, d, J: 8.1 Hz, ArH), 7.74 (1H, d, J: 4.6 Hz, pyridine C₃-H), 7.96 (1H, d, J: 4.4 Hz, pyridine C₅-H), 8.68 (1H, d, J: 4.6 Hz, pyridine C₂-H), 8.77 (1H, d, J: 4.3 Hz, pyridine C₂-H); For C₂₆H₂₃N₅OS₂ calculated: (%) C 64.31, H 4.77, N 14.43; MS (ES⁺) [M+1]⁺: m/z 487.
5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-chlorophenyl)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B28)

Yield 70%, m.p. 177-180 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3142, 3008 (aromatic CH), 2826 (aliphatic CH), 1636 (C=N), 1590 (C=C), 1588 (1,3 disubstituted benzene), 730 (C-S); 3030 (aromatic CH), 2831 (aliphatic CH), 1635 (C=N), 1590 (C=C), 1589 (1,4 disubstituted benzene), 731 (1,2 disubstituted benzene), 693 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3142, 3030, 2826, 1635, 1590, 1589, 730, 731, 693.

Yield 77%, m.p. 180-181 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3146, 3005 (aromatic CH), 2829 (aliphatic CH), 1639 (C=N), 1590 (C=C), 730 (1,2 disubstituted benzene), 690 (C-S); 3007 (aromatic CH), 2826 (aliphatic CH), 1634 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 771 (1,2 disubstituted benzene), 691 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3058, 3138, 3137, 2826, 2823, 1636, 1635, 1590, 1589, 1588, 730, 731, 693.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-chlorophenyl)-3-(4-methylbenzylthio)-4H-1,2,4-triazole V (B30)

Yield 72%, m.p. 180-181 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3146, 3005 (aromatic CH), 2829 (aliphatic CH), 1639 (C=N), 1590 (C=C), 770 (1,2 disubstituted benzene), 690 (C-S); 3004 (aromatic CH), 2826 (aliphatic CH), 1635 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 770 (1,2 disubstituted benzene), 690 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3141, 3030, 2826, 1635, 1590, 1589, 730, 770, 690.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-chlorophenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B31)

Yield 80%, m.p. 169-170 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3137, 3004 (aromatic CH), 2821 (aliphatic CH), 1635 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 770 (1,2 disubstituted benzene), 690 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3137, 3004, 2821, 1635, 1590, 1589, 819, 770, 690.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-chlorobenzylthio)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B32)

Yield 72%, m.p. 138-139 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3058, 3030 (aromatic CH), 2976, 2923 (aliphatic CH), 1620 (C=N), 1598 (C=C), 810 (mono substituted benzene), 772 and 725 (1,3 disubstituted benzene), 691 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3058, 3030, 2976, 2923, 1620, 1598, 810, 772, 725, 691.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-chlorobenzylthio)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B33)

Yield 72%, m.p. 138-139 °C, IR (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3058, 3030 (aromatic CH), 2976, 2923 (aliphatic CH), 1620 (C=N), 1598 (C=C), 810 (mono substituted benzene), 772 and 725 (1,3 disubstituted benzene), 691 (C-S); IR \( \nu \text{max} \) (KBr) \( \nu \text{max} \) (cm\(^{-1}\)) = 3058, 3030, 2976, 2923, 1620, 1598, 810, 772, 725, 691.
5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(3-chlorophenyl)-3-(3-methoxybenzylthio)-4H-1,2,4-triazole V (B33)

Yield 90%, m.p. 256-258 °C, IR (KBr) ν max (cm⁻¹): 3050 (aromatic CH), 2958-2835 (aliphatic CH), 1610 (C=O), 1590 (C=C), 777 and 739 (1,3 disubstituted benzene), 699 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.71 (3H, s, CH₃), 3.75 (3H, s, OCH₃), 4.30 (2H, s, S-CH₂), 6.87 (1H, t, ArH), 6.97 (2H, d, ArH), 7.05 (1H, s, ArH), 7.29 (1H, d, ArH), 7.32 (1H, t, ArH), 7.44 (2H, d, J: 4.6 Hz, pyridine C₅-H), 7.96 (1H, d, J: 4.4 Hz, pyridine C₃-H), 8.63 (1H, d, J: 4.5 Hz, pyridine C₆-H), 8.76 (1H, d, J: 4.3 Hz, pyridine C₂-H); For C₅H₅NCl₂S₂ calculated: (%) C 59.34, H 3.98, N 13.84, found: (%) C 59.33, H 3.97, N 13.83; MS (ES⁺) [M+1]⁺: m/z 507.

5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(3-chlorophenyl)-3-benzylthio-4H-1,2,4-triazole V (B34)

Yield 88%, m.p. 247-248 °C, IR (KBr) ν max (cm⁻¹): 3041 (aromatic CH), 2950-2830 (aliphatic CH), 1626 (C=N), 1590 (C=C), 824 (1,4 disubstituted benzene), 819 (monosubstituted benzenes), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.79 (3H, s, CH₃), 4.40 (2H, s, S-CH₂), 7.35 (3H, m, ArH), 7.39 (2H, d, ArH), 7.46 (2H, d, J: 8.6 Hz, ArH), 7.67 (2H, d, J: 8.6 Hz, ArH), 8.48 (2H, d, J: 5.9 Hz, pyridine C₃-H, C₅-H), 8.81 (2H, d, J: 5.4 Hz, pyridine C₂-H, C₆-H); For C₂₅H₂₀ClN₅S₂ calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.54, H 3.80, N 14.69; MS (ES⁺) [M+1]⁺: m/z 477.

5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(3-chlorophenyl)-3-(2-methylbenzylthio)-4H-1,2,4-triazole V (B35)

Yield 80%, m.p. 147-148 °C, IR (KBr) ν max (cm⁻¹): 3083, 3052, 3026 (aromatic CH), 2953, 2922 (aliphatic CH), 1623 (C=N), 1570 (C=C), 809 (1,4 disubstituted benzene), 777 (1,2 disubstituted benzene), 695 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.52 (3H, s, CH₃), 2.69 (3H, s, CH₃), 4.31 (2H, s, S-CH₂), 7.16 (1H, d, ArH), 7.22 (1H, t, ArH), 7.29 (1H, d, ArH), 7.32 (1H, t, ArH), 7.44 (2H, d, J: 8.7 Hz, ArH), 7.64 (2H, d, J: 8.7 Hz, ArH), 8.41 (2H, d, J: 5.9 Hz, pyridine C₃-H, C₅-H), 8.78 (2H, d, J: 5.3 Hz, pyridine C₃-H, C₆-H); For C₂₅H₂₁Cl₂N₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.28, H 4.09, N 14.29; MS (ES⁺) [M+1]⁺: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(4-chlorophenyl)-3-(4-methylbenzylthio)-4H-1,2,4-triazole V (B36)

Yield 80%, m.p. 264-265 °C, IR (KBr) ν max (cm⁻¹): 3047 (aromatic CH), 2965-2820 (aliphatic CH), 1629 (C=N), 1593 (C=C), 826 (1,4 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.28 (3H, s, CH₃), 2.68 (3H, s, CH₃), 4.51 (2H, s, S-CH₂), 7.12 (2H, d, J: 8.0 Hz, ArH), 7.24 (2H, d, J: 8.1 Hz, ArH), 7.40 (2H, d, J: 8.7 Hz, ArH), 7.61 (2H, d, J: 8.7 Hz, ArH), 8.40 (2H, d, J: 5.9 Hz, pyridine C₃-H, C₅-H), 8.79 (2H, d, J: 5.3 Hz, pyridine C₃-H, C₆-H); For C₂₅H₂₁Cl₂N₅S₂ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.29, H 4.11, N 14.28; MS (ES⁺) [M+1]⁺: m/z 491.

5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(4-chlorophenyl)-3-(2-chlorobenzylthio)-4H-1,2,4-triazole V (B37)

Yield 80%, m.p. 219-220 °C, IR (KBr) ν max (cm⁻¹): 3045 (aromatic CH), 2958-2820 (aliphatic CH), 1626 (C=N), 1590 (C=C), 821 (1,4 disubstituted benzene), 770 (1,2 disubstituted benzene), 690 (C-S); ¹H NMR (500 MHz, DMSO-d₆) δ (ppm): 2.78 (3H, s, CH₃), 4.30 (2H, s, CH₂), 7.49 (1H, d, ArH), 7.50 (1H, t, ArH), 7.53 (1H, t, ArH), 7.47 (2H, d, J: 8.6 Hz, ArH), 7.54 (1H, d, ArH), 7.67 (2H, d, J: 8.6 Hz, ArH), 8.43 (2H, d, J: 6.1 Hz, pyridine C₃-H, C₅-H), 8.81 (2H, d, J: 5.3 Hz, pyridine C₃-H, C₆-H); For C₂₅H₂₁Cl₂N₅S₂ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.48, H 3.37, N 13.70; MS (ES⁺) [M+1]⁺: m/z 511.

5-[4-Methyl-2-(pyridin-4-yl)thiazole-5-yl]-4-(4-chlorophenyl)-3-(3-chlorobenzylthio)-4H-1,2,4-triazole V (B38)

Yield 91%, m.p. 266-267 °C, IR (KBr) ν max (cm⁻¹): 3035 (aromatic CH), 2955-2840 (aliphatic CH), 1624 (C=N),
1590 (C=C), 826 (1,4 disubstituted benzene), 770 and 737 (1,3 disubstituted benzene), 690 (C-S); 1H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.77 (3H, s, CH$_3$), 4.31 (2H, s, S-CH$_2$), 7.07 (1H, t, ArH), 7.16 (2H, d, ArH), 7.26 (1H, s, ArH), 7.46 (2H, d, J: 8.7 Hz, ArH), 7.66 (2H, d, J: 8.7 Hz, ArH), 8.44 (2H, d, J: 7.9 Hz, pyridine C$_2$-H, C$_6$-H), 8.78 (2H, d, J: 5.4 Hz, pyridine C$_2$-H, C$_6$-H); For C$_{24}$H$_{17}$Cl$_2$N$_5$S$_2$ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.44, H 3.34, N 13.70; MS (ES+) [M+1]$^+$: m/z 511.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-chlorophenyl)-3-(4-chlorobenzylthio)-4H-1,2,4-triazole V (B39)

Yield 74%, m.p. 232-233 °C, IR (KBr) ν$_{max}$ (cm$^{-1}$): 3038 (aromatic CH), 2965-2840 (aliphatic CH), 1629 (C=N), 1593 (C=C), 826 (1,4 disubstituted benzene), 687 (C-S); 1H NMR (500 MHz, DMSO-d$_6$) δ (ppm): 2.77 (3H, s, CH$_3$), 4.30 (2H, s, S-CH$_2$), 7.31 (2H, d, J: 8.3 Hz, ArH), 7.41 (2H, d, J: 8.7 Hz, ArH), 7.43 (2H, d, J: 8.3 Hz, ArH), 7.61 (2H, d, J: 8.7 Hz, ArH), 8.42 (2H, d, J: 5.9 Hz, pyridine C$_2$-H, C$_6$-H), 8.82 (2H, d, J: 5.3 Hz, pyridine C$_2$-H, C$_6$-H); For C$_{24}$H$_{17}$Cl$_2$N$_5$S$_2$ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.49, H 3.39, N 13.74; MS (ES+) [M+1]$^+$: m/z 511.

**Antimicrobial activity**

**General:** All antimicrobial agents, Mueller Hinton broth, Mueller Hinton II Broth and RPMI medium, BHT (Butylated hydroxytoluene), and 1,1-Diphenyl-2-picrylhydrazyl (DPPH) were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp. St. Louis, MO). Solvents used were analytical grade.

**Microbials strains:** The antimicrobial activities of compounds were tested against Gram-negative bacteria such as, *Escherichia coli* NRRLY B 3008 and *Pseudomonas aeruginosa* ATCC 10145, and against Gram-positive bacteria such as, *Staphylococcus aureus* ATCC BAA-1026 and *Bacillus cereus* NRRLY B 3711, as well as yeast *Candida albicans* ATCC 24443. According to the test results, some active compounds were also tested against different Gram-positive bacteria, such as ampicillin-resistant clinical isolate *S. aureus* and methicillin resistant-clinical isolate *S. aureus* (MRSA), *Streptococcus pyogenes* ATCC 19615, and *Streptococcus sanguinis* ATCC 10556, respectively.

**Minimum inhibitory concentration (MIC):** The minimum inhibitory concentration (MIC) values were determined by broth microdilution methods (CLSI, 2006; CLSI, 2008). The results here were compared with standard antimicrobial agents.

Test Compounds were diluted between [2000-3.9 µg/mL for minimum inhibitory concentrations, and the antimicrobial standard agents comprised of ampicillin, chloramphenicol, ketoconazole, and oxiconazole (64-0.125 µg/mL) were prepared in dimethyl sulfoxide (DMSO) and water. The compounds (100 µL) were added to wells of row A, while the remaining wells in rows B to H received 50 µL of Mueller-Hinton Broth. Bacterial suspensions were grown overnight in double strength broth and standardized to 10$^5$cfu/mL for bacteria. Each bacterial suspension (50 µL) was added to the appropriate well. *Candida* strain was inoculated on Potato Dextrose Agar (PDA) prior to the experiments at 35 °C. After incubation had grown, the microorganism was inoculated with sterile saline of 0.85%. Subsequently, it was standardized using a turbidimeter (Biosan) (McFarland No: 0.5) to 5 x 10$^3$ cfu per well in RPMI medium inoculated under sterile conditions. Serial dilution series were prepared in 100 µl RPMI medium with an equal amount of the test compounds. After serial dilution, 100 µL microorganism suspension was pipetted into each well and then incubated at 35°C for 24 h. Positive growth controls (to assess the presence of turbidity) were performed in wells without standard antimicrobial agents. After incubation at 35°C for 24 h, the first well without turbidity was determined as the minimal inhibitory concentration (MIC, µg/mL). All experiments were repeated in triplicates, and mean values were reported.

**1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity:** Serial dilutions were prepared from the stock solutions (4 mg/mL) of the test compounds to get the half concentrations of the previous one. To diluted solutions, DPPH (equal amounts) was added.
After 30 min, UV absorbance was recorded at 517 nm. The experiment was performed in triplicate for extract and positive standard control, BHT (Butylated hydroxytoluene). The average of the absorptions was noted for each concentration. The percentage inhibition of triplicate experiments was calculated using Equation 1. The IC\textsubscript{50} value, which is the concentration of the test compound that inhibits 50% of the free radical concentration, was calculated as mg/mL using Sigma Plot statistical software (Kumarasamy \textit{et al}., 2007).

\[
\text{Percentage Inhibition} = \left(\frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}}\right) \times 100
\]

\text{(Equation 1)}

RESULTS AND DISCUSSION

Chemistry

Final compounds listed in Table I were synthesized using the sequence of reactions depicted in Figure 1. In the first step, compound I derivatives were prepared via the reaction of pyridine-3/4-thiocarboxamide with ethyl 2-chloroacetoacetate. The resulting thiazole derivatives substituted with pyridyl moiety I, were treated with hydrazine hydrate to produce the hydrazide derivatives II, and then with appropriate aryl isothiocyanate derivative III, respectively. The obtained thiosemicarbazide derivatives were treated with potassium carbonate to form 1,2,4-triazole-3-thione compounds IV. Finally, compounds V (A1-A24 and B1-B39) were synthesized by the reaction of 1,2,4-triazole-3-thiones IV, and various benzyl bromide derivatives. The structures of the final compounds were elucidated by using spectral data, listed in the experiment. In the IR spectra of compounds A1-A24 and B1-B39, the aromatic C-H stretching vibrations gave rise to bands at 3086-3005 cm\textsuperscript{-1} and 3146-3004 cm\textsuperscript{-1}. C=N, C=C stretching bands were observed in the regions 1636-1573 cm\textsuperscript{-1}, and 1639-1586 cm\textsuperscript{-1}, respectively. The \textsuperscript{1}H NMR spectra of compounds A1-A24 and B1-B39, exhibited singlet peaks owing to –S-CH\textsubscript{2} protons at 4.50-4.39 ppm, and 4.51-4.20 ppm upfield. Resonances of other aliphatic protons and aromatic protons were observed at the expected regions. Formation of different 1,2,4-triazoles linked with substituted benzyl groups through the thio linkage, derivatives were confirmed by their IR,\textsuperscript{1}H NMR, and MS spectroscopic, and CHN analytical data, respectively. In \textsuperscript{13}C NMR spectrum of the compound A2, carbon resonance of methylene carbon bridge between sulfur and phenyl appeared in the region 35.82 ppm. The thiazole and phenyl connected CH\textsubscript{2} carbons resonated at 17.22 and 19.01 ppm, respectively. The signals of thiazole, triazole, pyridine and phenyl ring systems were observed at 164.64-155.70, 151.88-137.23, 148.59-117.15, 134.65-124.78 ppm, respectively (for more details evaluate the experimental section, and supplementary data).

In the MS spectra of the synthesized compounds, the M+1 base peak was observed.
3-Pyridyl series: V(A1-A24)  \( R: H, \text{CH}_3\text{OCH}_3\text{Cl} \)  

4-Pyridyl series: V(B1-B39)  \( R: H, \text{CH}_3\text{Cl} \)
### Table I - Structures of the synthesized compound series V (A1-A24, B1-B39)

| Compound | R   | R’  | Compound | R   | R’   |
|----------|-----|-----|----------|-----|------|
| A1       | H   | H   | B1       | H   | 2-CH₃|
| A2       | H   | 2-CH₃| B2       | H   | 4-CH₃|
| A3       | H   | 3-CH₃| B3       | H   | 2-Cl |
| A4       | H   | 2-Cl | B4       | H   | 3-Cl |
| A5       | H   | 3-Cl | B5       | H   | 4-Cl |
| A6       | H   | 4-Cl | B6       | H   | 3-OCH₃|
| A7       | H   | 3-OCH₃| B7      | 2-CH₃| H    |
| A8       | 2-CH₃| H   | B8       | 2-CH₃| 2-CH₃|
| A9       | 2-CH₃| 2-CH₃| B9       | 2-CH₃| 4-CH₃|
| A10      | 2-CH₃| 2-Cl | B10      | 2-CH₃| 2-Cl |
| A11      | 3-CH₃| H   | B11      | 2-CH₃| 3-Cl |
| A12      | 3-CH₃| 2-Cl | B12      | 2-CH₃| 4-Cl |
| A13      | 3-CH₃| 3-Cl | B13      | 2-CH₃| 3-OCH₃|
| A14      | 3-CH₃| 4-Cl | B14      | 3-CH₃| H    |
| A15      | 4-CH₃| 2-Cl | B15      | 3-CH₃| 2-CH₃|
| A16      | 4-CH₃| 4-Cl | B16      | 3-CH₃| 4-CH₃|
| A17      | 4-OCH₃| 2-Cl | B17      | 3-CH₃| 2-Cl |
| A18      | 4-OCH₃| 4-Cl | B18      | 3-CH₃| 3-Cl |
| A19      | 3-Cl | H   | B19      | 3-CH₃| 4-Cl |
| A20      | 3-Cl | 3-Cl | B20      | 3-CH₃| 3-OCH₃|
| A21      | 3-Cl | 4-Cl | B21      | 4-CH₃| H    |
| A22      | 4-Cl | 2-CH₃| B22      | 4-CH₃| 2-CH₃|
| A23      | 4-Cl | 3-CH₃| B23      | 4-CH₃| 4-CH₃|
| A24      | 4-Cl | 4-Cl | B24      | 4-CH₃| 2-Cl |
|          |     |     | B25      | 4-CH₃| 3-Cl |
|          |     |     | B26      | 4-CH₃| 4-Cl |
|          |     |     | B27      | 4-CH₃| 3-CH₃O|
|          |     |     | B28      | 2-Cl | 2-CH₃ |

(continues on the next page...)
Bioactivity

Antimicrobial activity

All compounds (A1-14, B1-39) were screened for their in vitro antimicrobial activity against E. coli (NRRLY B 3008), P. aeruginosa (ATCC 10145), S. aureus (ATCC BAA-1026), B. Cereus (NRRLY B 3711) and C. albicans (ATCC 24443) using the microbroth dilution method. Chloramphenicol, ampicillin, ketoconazole and oxiconazole were used as standard drugs, and positive control group was also studied for comparing the microbial growth. MIC (minimum inhibitory concentration) was determined for all compounds, and standard drugs, as the lowest inhibition concentration that killed all tested microorganisms after overnight incubation. Tested compounds were active mainly between 500-31.25 µg/mL, as seen in Table II. Among the tested compounds, most of them showed high antimicrobial activity, particularly against Gram-positive bacteria and serial dilution was continued to 3.09 µg/mL as the second stage for antibacterial activity evaluation for the selected potent derivatives (see Table III). Compounds A2, A3, A8, A9, A10, A15, A16, A17, A18, A23, and A24, which exhibited relatively high inhibition against two Gram-positive bacteria, and Candida albicans, were tested at lower three concentrations (15.62, 7.81 and 3.09 µg/mL), against six Gram-positive bacteria; ampicillin-resistant clinical isolate S. aureus and methicillin-resistant clinical isolate S. aureus (MRSA), S. pyogenes ATCC 19615 and S. sanguinis ATCC 10556 along with S. Aureus (ATCC BAA-1026) and B. Cereus (NRRLY B 3711). Apart from the mentioned compounds from the A series, compounds B10, B24, B25, B26, B27, B35, and B37 also exhibited good inhibitory activity against S. aureus, B. cereus and C. albicans compared to standard antimicrobial control.

TABLE I - Structures of the synthesized compound series V (A1-A24, B1-B39)

| Compound | R  | R’  | Compound | R  | R’  |
|----------|----|-----|----------|----|-----|
| B29      | 2-Cl | 4-CH₃ | B30      | 2-Cl | 2-Cl |
| B31      | 2-Cl | 4-Cl  | B32      | 3-Cl | H    |
| B33      | 3-Cl | 3-CH₃O| B34      | 4-Cl | H    |
| B35      | 4-Cl | 2-CH₃ | B36      | 4-Cl | 4-CH₃|
| B37      | 4-Cl | 2-Cl  | B38      | 4-Cl | 3-Cl |
| B39      | 4-Cl | 4-Cl  |          |     |      |
agents. All synthesized compounds failed to exhibit antibacterial activity against the two Gram-negative pathogenic microorganisms, namely against *E. coli* and *P. aeruginosa*, respectively. As an outcome of the continued second-panel antibacterial activity evaluation studies, among eleven tested compounds, all of them inhibited ampicillin-resistant clinical isolate *S. aureus* and methicillin resistant-clinical isolate *S. aureus* (MRSA) at the lowest tested concentration, i.e. MIC values of these compounds against the bacteria were lower than <3.09 µg/mL, whereas, MIC values of the standard drugs chloramphenicol and ampicillin were 8 and 0.5 µg/mL, respectively. Similarly, compounds A2, A9, A16, A17, A18, A23, and A24 showed remarkable antibacterial activity against *Staphylococcus* ATCC BAA-1026 with MIC values lower than 3.09 µg/mL, which was a better outcome than the one with a standard agent of ampicillin. The rest of the eleven compounds also showed high activity against the same microorganism with MIC values of 7.81 and 15.62 µg/mL. Compounds A9, A17, and A18 exhibited high antibacterial activity against *B. cereus* and certain MIC values could not be even calculated as the lowest tested concentration (3.09 µg/mL). Other MIC values were detected between the tested concentrations as 7.81 and 15.62 µg/mL against these bacteria, whereas the MIC value of chloramphenicol was 32 µg/mL. Regarding activity evaluation of the synthesized compounds against *Streptococcus species*, the compounds inhibited the growth of two *spp.* (*S. pyogenes* ATCC 19615, and *S. sanguinis* ATCC 10556) at 250-15.62 µg/mL concentrations. Except for compounds A2 and A9, the others exhibited satisfying MIC values, which varied lower than 15.62 and 31.25 µg/mL against *S. pyogenes*. Similar results were observed against *S. sanguinis* as most of the compounds exhibited remarkable activity results.

### TABLE II – MIC (µg/mL) of the compounds series V(A1-A24, B1-B39)

| Comp | *E. coli* NRRLY B 3008 | *P. aeruginosa* ATCC 10145 | *S. aureus* ATCC BAA-1026 | *B. cereus* NRRLY B 3711 | *C. albicans* ATCC 24443 |
|------|------------------------|-----------------------------|---------------------------|--------------------------|--------------------------|
| A1   | 250                    | 250                         | 250                       | 250                      | 125                      |
| A2   | 500                    | 250                         | -                         | -                        | 125                      |
| A3   | 500                    | 250                         | -                         | -                        | 62.5                     |
| A4   | 500                    | 250                         | 500                       | 500                      | 250                      |
| A5   | 250                    | 250                         | 250                       | 250                      | 125                      |
| A6   | 500                    | 250                         | 500                       | 500                      | 250                      |
| A7   | 250                    | 250                         | 250                       | 250                      | 125                      |
| A8   | 500                    | 250                         | -                         | -                        | -                        |
| A9   | 500                    | 250                         | -                         | -                        | 250                      |
| A10  | 250                    | 250                         | -                         | -                        | 250                      |
| A11  | 500                    | 250                         | 500                       | 500                      | 250                      |
| A12  | 500                    | 250                         | 500                       | 500                      | 250                      |
| A13  | 500                    | 250                         | 125                       | 125                      | 250                      |
| A14  | 500                    | 250                         | 500                       | 500                      | -                        |
| A15  | 500                    | 250                         | -                         | -                        | -                        |
| A16  | 500                    | 250                         | -                         | -                        | -                        |

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### TABLE II – MIC (µg/mL) of the compounds series V(A1-A24, B1-B39)

| Comp | E. coli NRRLY B 3008 | P. aeruginosa ATCC 10145 | S. aureus ATCC BAA-1026 | B. cereus NRRLY B 3711 | C. albicans ATCC 24443 |
|------|---------------------|--------------------------|--------------------------|------------------------|------------------------|
| A17  | 500                 | 250                      | -                        | -                      | -                      |
| A18  | 500                 | 250                      | -                        | -                      | -                      |
| A19  | 500                 | 250                      | 500                      | 250                    | 250                    |
| A20  | 500                 | 250                      | 250                      | 250                    | 250                    |
| A21  | 500                 | 250                      | 500                      | 250                    | 250                    |
| A22  | 500                 | 250                      | 125                      | 125                    | 250                    |
| A23  | 500                 | 250                      | -                        | -                      | 125                    |
| A24  | 500                 | 250                      | -                        | -                      | 62.5                   |
| B1   | 250                 | 125                      | 250                      | 250                    | 125                    |
| B2   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B3   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B4   | 250                 | 250                      | 125                      | 250                    | 125                    |
| B5   | 250                 | 250                      | 125                      | 125                    | 62.5                   |
| B6   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B7   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B8   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B9   | 250                 | 250                      | 250                      | 250                    | 125                    |
| B10  | 250                 | 250                      | 250                      | 125                    | 62.5                   |
| B11  | 250                 | 250                      | 125                      | 250                    | 62.5                   |
| B12  | 250                 | 250                      | 250                      | 125                    | 125                    |
| B13  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B14  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B15  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B16  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B17  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B18  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B19  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B20  | 250                 | 250                      | 250                      | 250                    | 125                    |
| B21  | 250                 | 250                      | 250                      | 125                    | 125                    |
| B22  | 250                 | 250                      | 250                      | 125                    | 125                    |
| B23  | 250                 | 250                      | 250                      | 125                    | 125                    |
| B24  | 250                 | 250                      | 31.25                    | 31.25                  | 62.5                   |
| B25  | 250                 | 250                      | 62.5                     | 15.62                  | 125                    |
| B26  | 250                 | 250                      | 125                      | 31.25                  | 125                    |

(continues on the next page...)

TABLE II – MIC (µg/mL) of the compounds series V(A1-A24, B1-B39)

| Comp | E. coli NRRLY B 3008 | P. aeruginosa ATCC 10145 | S. aureus ATCC BAA-1026 | B. cereus NRRLY B 3711 | C. albicans ATCC 24443 |
|------|----------------------|---------------------------|---------------------------|-------------------------|------------------------|
| B27  | 250                  | 250                       | 250                       | 62.5                    | 125                    |
| B28  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B29  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B30  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B31  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B32  | 250                  | 250                       | 250                       | 500                     | 125                    |
| B33  | 250                  | 250                       | 250                       | 500                     | 125                    |
| B34  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B35  | 250                  | 250                       | 15.62                     | 15.62                   | 31.25                  |
| B36  | 250                  | 250                       | 125                       | 125                     | 125                    |
| B37  | 250                  | 250                       | 62.5                      | 62.5                    | 125                    |
| B38  | 250                  | 250                       | 250                       | 250                     | 125                    |
| B39  | 125                  | 250                       | 125                       | 125                     | 125                    |
| Ref. 1 | 1                   | 32                        | 8                         | 8                       | X                      |
| Ref. 2 | 8                   | 2                         | <0.25                     | 2                       | X                      |
| Ref. 3 | X                   | X                         | X                         | X                       | 1                      |
| Ref. 4 | X                   | X                         | X                         | X                       | 0.125                  |
| Contr. | +                   | +                         | +                         | +                       | +                      |

Ref. 1: Chloramphenicol Ref. 2: Ampicillin Ref. 3: Ketoconazole Ref. 4: Oxiconazole; Contr.; Positive control
(-): Highly active. These compounds were tested with increasing dilution series.
(X): Not tested.
(+) : Good development in microbial growth.

TABLE III – Antimicrobial (MIC µg/mL) effect of compound V(A2,A3,A8,A9,A10,A15,A16,A17,A18,A23 and A24)

| Comp. | S. aureus ATCC BAA-1026 | B. cereus NRRLY B 3711 | S. pyogenes ATCC 19615 | S. sanguinis ATCC 10556 | S. aureus Clin.isolate (ampicillin resist.) | Methicillin-resist. S. aureus-MRSA clin.isolate |
|-------|-------------------------|------------------------|-----------------------|------------------------|--------------------------------------------|-----------------------------------------------|
| A2    | < 3.09                  | 15.62                  | 62.5                  | 31.25                  | < 3.09                                     | < 3.09                                       |
| A3    | 15.62                   | 7.81                   | 31.25                 | 62.5                   | < 3.09                                     | < 3.09                                       |
| A8    | 7.81                    | 7.81                   | <15.62                | <15.62                 | < 3.09                                     | < 3.09                                       |
| A9    | < 3.09                  | < 3.09                 | 62.5                  | 250                    | < 3.09                                     | < 3.09                                       |
| A10   | 7.81                    | 15.62                  | <15.62                | <15.62                 | < 3.09                                     | < 3.09                                       |
| A15   | 7.81                    | 15.62                  | 31.25                 | <15.62                 | < 3.09                                     | < 3.09                                       |
| A16   | < 3.09                  | 7.81                   | <15.62                | <15.62                 | < 3.09                                     | < 3.09                                       |
| A17   | < 3.09                  | < 3.09                 | <15.62                | <15.62                 | < 3.09                                     | < 3.09                                       |

(continues on the next page...)
The structure-activity relationship analysis of the triazole derivatives revealed that compounds differ from each other with 3-pyridyl-, 4-pyridyl-moieties, and with substituents on both phenyl rings. The substituents were varied as methyl-, methoxy-, and chloro- functions on ortho-, meta- and, para- positions of the phenyl rings. Compounds from series A possessing 3-pyridyl-residue - were remarkable due to their antimicrobial activity. Also, compounds bearing ortho-, and para- substituents on phenyl rings stand out with high antibacterial activity, especially against Gram-positive pathogens.

**Antioxidant activity**

All final test compounds (A1-24, B1-39) were screened for their antioxidant activity using *in vitro* DPPH radical scavenging assay, which is one of the assays that depend on measuring the consumption of stable free radicals (Bayomi *et al*., 2015; Li *et al*., 2015). The obtained results are presented in Table IV, reported in IC$_{50}$ values (the concentration of the tested compounds which inhibited half percentage of free radicals) for compounds B7, B8, B10, B11, B13, B28, B30, B32, B33, and B34. The IC$_{50}$ value could not be calculated for the other compounds at the highest tested concentration (> 4 mg/mL). Interestingly, the antioxidant property was not found for the compounds in A1-A24 series, including 4-pyridyl moiety, contrary to their relatively high antimicrobial activity.

**TABLE IV - Antioxidant activity of the compounds (μg/mL) V(B7, B8, B10, B11, B13, B28, B30, B32, B33 and B34)**

| Compounds | IC$_{50}$  |
|-----------|------------|
| B7        | 17.10 ± 1.10 |
| B8        | 18.40 ± 2.00 |
| B10       | 34.70 ± 5.70 |
| B11       | 20.70 ± 1.40 |
| B13       | 20.00 ± 1.60 |
| B28       | 22.80 ± 1.30 |
| B30       | 23.60 ± 1.60 |
| B32       | 21.10 ± 1.50 |
| B33       | 54.30 ± 8.10 |
| B34       | 22.70 ± 1.60 |
| Ref. 1    | 3.50 ± 0.80 |
| Ref. 2    | 10.40 ± 0.40 |

Ref. 1: Gallic acid; Ref. 2: BHT (Butylated Hydroxytoluene).

IC$_{50}$ > 4 mg/mL for all other compounds. The calculated IC$_{50}$ values for the certain compounds were determined between the range of 17.10-54.30 μg/mL, whereas the IC$_{50}$ values were defined as 3.50 and 10.40 μg/mL for standard compounds of gallic acid and butylated hydroxytoluene (BHT), respectively. Among the specified ten compounds, B7 and B8 exhibited the highest antioxidant activity with the...
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lowest IC_{50} which were as low as 17.10 and 17.40 µg/mL. Compounds B7, B8, B10, B11, and B13, including 2-methyl phenyl moiety at fourth position of triazole ring, have attracted attention with antioxidant activity potential. Additionally, other indicated compounds contain chloro substituted phenyl moiety at triazole ring. The remaining parts of the molecules differ from each other with the substituents on benzyl residue at the third position of triazole ring linked to the sulfur atom. Among them, 2-chloro, 2-methyl, 3-chloro and 3-methoxy substituents have come into prominence with the presence of repetitive antioxidant activity.

**CONCLUSION**

To the best of our knowledge, the new compounds were tested for the first time for their biological and pharmacological potential. Thus, in this present study, 63 new triazole derivatives were synthesized, and evaluated for their *in vitro* antimicrobial, and antioxidant activities, respectively. The antibacterial screening revealed that compounds from series A possessing 3-pyridyl-residue showed relatively high antibacterial activity against Gram-positive bacteria. In addition, compound; B7 and B8 exhibited the highest antioxidant activity, which can be further evaluated *in vitro* for potential drug development. According to the present findings, further detailed biological and pharmacological investigations are worthwhile for the synthesized heterocyclic compounds.

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**DECLARATION OF INTEREST**

The authors have declared no conflict of interest

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