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Article

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.

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, Yurttas, Cantürk, 2018; Yang L,

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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 active azole 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, Chandrashekar, 2013; Kumar, Kumar, 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, Samie, 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 effective azole 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 (Hosseinzadeh *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 Electrothermal 9300 digital melting points apparatus. Spectroscopic data were recorded on the following instruments: a Perkin Helmer FTIR 100 spectrophotometer; ^{1}H NMR (nuclear magnetic resonance) and ^{13}C NMR spectra were recorded by a Bruker 500 MHz and 75 MHz NMR spectrometer (Bruker Bioscience, Billerica, MA, USA) in DMSO-d_6, 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 F_{254}, 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-carbohydrazide (**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 sodium acetate. The precipitate was filtered, washed with water, dried and recrystallized from 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-3/4-yl)thiazole-5-yl]-4-substituted-2,3-dihydro-*4H*-1,2,4-triazole-3-thione (IV)

A mixture of thiosemicarbazide derivative **III** (13 mmol), with potassium carbonate (65 mmol) and ethanol (50 mL) was refluxed for 2 hours. After the 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.

5-[4-Methyl-2-(pyridin-3/4-yl)thiazole-5-yl]-4-substituted-3-substituted benzylthio-*4H*-1,2,4-triazole V (A1-A24, B1-B39)

Compound **IV** (35 mmol), appropriate benzyl bromide derivative (36 mmol) and potassium carbonate (36 mmol) was stirred in acetone (50 mL) for 1 day at room temperature, and was evaluated by TLC. After finalizing the reaction, acetone was evaporated, the precipitate was treated with water, filtered, and then crystallized from ethanol. The physical properties and spectral data of the pure final compounds are given below.

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, **IR** (KBr) ν_{max} (cm^{-1}): 3054 (aromatic CH), 2955, 2928, 2856 (aliphatic CH), 1634 (C=N), 1590 (C=C), 809 (mono substituted benzene), 772 and 728 (1,3-disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.77 (3H, s, CH_3), 4.40 (2H, s, CH_2), 7.26-7.64 (10H, m, Ar-H), 8.33 (1H, t, *J*: 8.0 Hz, pyridine C_5-H), 8.38 (1H, d, *J*: 8.0 Hz, pyridine C_4-H), 8.75 (1H, d, *J*: 4.7 Hz, pyridine C_6-H), 9.19 (1H, s, pyridine C_2-H); For $C_{24}H_{19}N_5S_2$ calculated: (%) C 65.28, H 4.34, N 15.86, found: (%) C 65.25, H 4.31 N 15.85; **MS(ES+)** $[M+1]^+$: *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, **IR** (KBr) ν_{max} (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}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.45 (3H, s, CH_3), 4.43 (2H, s, S-CH_2), 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 C_5-H), 8.16 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.67 (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) δ (ppm): 17.22, 19.01, 35.82, 117.15, 124.78, 126.48, 127.16, 128.29, 128.45, 128.57, 129.30, 129.84, 130.33, 130.38, 130.86, 130.93, 131.32, 133.19,134.64, 137.23, 147.15, 148.59, 151.88, 155.70, 164.64; For $C_{25}H_{21}N_5S_2$ 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 78%, m.p. 134-137 °C, **IR** (KBr) ν_{max} (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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.30 (3H, s, CH_3), 2.50 (3H, s, CH_3), 4.40 (2H, s, S-CH_2), 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 C_5-H), 8.13 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.70 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 9.10 (1H, s, 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 4.64, N 15.38; **MS (ES+)** $[M+1]^+$: *m/z* 457.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-phenyl-3-(2-chlorobenzylthio)-*4H*-1,2,4-triazole V (A4)

Yield 82%, m.p. 245-247 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3054 (aromatic CH), 2952, 2926, 2866 (aliphatic CH), 1634 (C=N), 1590 (C=C), 809 (mono substituted benzene), 771 (1,2-disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 2.55 (3H, s, CH_3), 4.43 (2H, s, S-CH_2), 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 C_5-H), 8.11 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.72 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 9.11 (1H, s, pyridine C_2-H); For $C_{24}H_{18}ClN_5S_2$ 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-(3-chlorobenzylthio)-*4H*-1,2,4-triazole V (A5)

Yield 82%, m.p. 235-236 °C, **IR** (KBr) ν_{max} (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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.46 (3H, s, CH_3), 4.41 (2H, s, S-CH_2), 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 C_5-H), 8.14 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.74 (1H, d, *J*: 4.7 Hz, pyridine C_4-H), 9.14 (1H, s, pyridine C_2-H); For $C_{24}H_{18}ClN_5S_2$ 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 76%, m.p. 158-160 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3051 (aromatic CH), 2948, 2856 (aliphatic CH), 1636 (C=N), 1590 (C=C), 815 (1,4-disubstituted benzene), 807 (mono substituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.45 (3H, s, CH_3), 4.43 (2H, s, S-CH_2), 7.36-7.58 (10H, m, Ar-H), 8.12 (1H, d, *J*: 8.1 Hz, Ar-H, pyridine C_4-H), 8.65 (1H, d, *J*:4.9 Hz, Ar-H, pyridine C_6-H), 8.96 (1H, s, Ar-H, pyridine C_2-H); ^{13}**C NMR (75 MHz,** DMSO-d_6) δ (ppm): 17.28, 35.75, 117.10, 124.80, 128.29, 128.55, 128.87, 130.46, 131.07, 131.42, 132.58, 133.10, 134.08, 136.78, 147.14, 148.66, 151.89,152.03, 155.68, 164.5; For $C_{24}H_{18}ClN_5S_2$ calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.57, H 3.78, N 14.69; **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) ν_{max} (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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.55 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 4.39 (2H, s, S-CH_2), 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 C_5-H), 8.17 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.72 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 9.21 (1H, s, pyridine C_2-H); For $C_{25}H_{21}N_5OS_2$ 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) ν_{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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 1.80 (3H, s, CH_3), 2.55 (3H, s, CH_3), 4.41 (2H, s, S-CH_2), 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 C_5-H), 7.98 (1H, d, *J*: 8.0 Hz, pyridine C_6-H), 8.59 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 8.88 (1H, s, pyridine C_2-H); For $C_{25}H_{21}N_5S_2$ calculated: (%) C 65.91, H 4.65, N 15.37, found: (%) C 65.90, H 4.64, N 15. 34; **MS (ES+)** $[M+1]^+$: *m/z* 457.

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

Yield 68%, m.p. 90-92 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3058 (aromatic CH), 2962, 2857 (aliphatic CH), 1607 (C=N), 1586 (C=C), 774 (1,2 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 1.84 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.48 (2H, s, S-CH_2), 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 C_5-H), 8.09 (1H, d, *J*: 8.0 Hz, pyridine C_6-H), 8.65 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 8.92 (1H, s, pyridine C_2-H); ^{13}**C NMR** (75 MHz, DMSO-d_6) 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 $C_{26}H_{23}N_5S_2$ 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-chlorobenzylthio)-*4H*-1,2,4-triazole V (A10)

Yield 75%, m.p. 96-98 °C, **IR** (KBr) ν_{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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 1.85 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.44 (2H, s, S-CH_2), 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, ArH, pyridine C_5-H), 8.11 (1H, d, *J*: 8.0 Hz, pyridine C_6-H), 8.67 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 8.91 (1H, s, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ 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* 491.

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) ν_{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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.30 (3H, s, CH_3), 4.43 (2H, s, S-CH_2), 7.06-8.15 (10H, m, Ar-H), 8.14 (1H, d, *J*: 8.5 Hz, Ar-H, pyridine C_4-H), 8.65 (1H, d, *J*:4.8 Hz, Ar-H, pyridine C_6-H), 8.96 (1H, s, Ar-H, pyridine C_2-H); ^{13}**C NMR (75 MHz,** DMSO-d_6) 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 $C_{25}H_{21}N_5S_2$ 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-chlorobenzylthio)-*4H*-1,2,4-triazole V (A12)

Yield 72%, m.p. 163-165 °C, **IR** (KBr) ν_{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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 2.30 (3H, s, CH_3), 2.48 (3H, s, CH_3), 4.50 (2H, s, S-CH_2), 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, pyridine C_5-H), 8.14 (1H, d, *J*: 8.0 Hz, pyridine C_4-H), 8.65 (1H, d, *J*:4.6 Hz, Ar-H, pyridine C_6-H), 8.97 (1H, s, Ar-H, pyridine C_2-H); ^{13}**C NMR (75 MHz,** DMSO-d_6) 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 $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.24, H 4.08, N 14.26; **MS (ES+)** $[M+1]^+$: *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) ν_{max} (cm^{-1}): 3057 (aromatic CH), 2955, 2852 (aliphatic CH), 1606 (C=N), 1586 (C=C), 776 and 736 (1,3 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.30 (3H, s, CH_3), 2.48 (3H, s, CH_3), 4.42 (2H, s, S-CH_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_6-H), 8.65 (1H, d, *J*: 4.9 Hz, pyridine C_4-H), 8.96 (1H, s, pyridine C_2-H); ^{13}**C NMR (75 MHz,** DMSO-d_6) δ (ppm): 17.38, 21.17, 36.19, 117.09, 124.80, 125.39, 127.91, 128.23, 128.44, 128.56, 129.32, 130.18, 130.77, 131.72, 132.99, 133.38, 134.12, 140.24, 140.44, 147.16, 148.72, 151.89, 151.94, 155.73, 164.54; For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.27, H 4.09, N 14.28; **MS (ES+)** $[M+1]^+$: *m/z* 491.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(4-chlorobenzylthio)-*4H*-1,2,4-triazole V (A14)

Yield 71%, m.p. 126-128 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3058 (aromatic CH), 2955, 2852 (aliphatic CH), 1606 (C=N), 1586 (C=C), 817 (1,4 disubstituted benzene), 778 and 740 (1,3 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.31 (3H, s, CH_3), 2.48 (3H, s, CH_3), 4.42 (2H, s, S-CH_2), 7.08 (1H, brs, Ar-H), 7.16 (1H, d, *J*: 6.6 Hz, Ar-H), 7.36-7.39 (5H, m, Ar-H), 7.41-7.52 (2H, m, Ar-H), 8.13 (1H, d, *J*: 8.0 Hz, pyridine C_6-H), 8.65 (1H, d, *J*: 4.5 Hz, pyridine C_4-H), 8.96 (1H, s, pyridine C_2-H); ^{13}**C NMR (75 MHz,** DMSO-d_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 $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, H 4.08, N 14.30; **MS (ES+)** $[M+1]^+$: *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) ν_{max} (cm^{-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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.37 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.50 (2H, s, S-CH_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_5-H), 8.16 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.67 (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) δ (ppm): 164.62, 155.69, 151.88, 148.80, 147.18, 140.88, 134.77, 134.13, 133.76, 132.01, 130.87, 130.45, 130.17, 129.97, 128.86, 128.57, 127.95, 127.85, 124.79, 117.12, 34.92, 21.26, 17.26
For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.27, H 4.12, N 14.32; **MS (ES+)** $[M+1]^+$: *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) ν_{max} (cm^{-1}): 3057 (aromatic CH), 2971, 2912 (aliphatic CH), 1626 (C=N), 1596 (C=C), 813 (1,4 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (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); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, H 4.13, N 14.31; **MS (ES+)** $[M+1]^+$: *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) ν_{max} (cm^{-1}): 3061, 3008 (aromatic CH), 2932, 2836 (aliphatic CH), 1636

(C=N), 1586 (C=C), 819 (1,4 disubstituted benzene), 760 (1,2 di substituted benzene), 690 (C-S); **^{1}H NMR** (500 MHz, DMSO-d_6) δ (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) δ (ppm): 17.41, 34.83, 56.04, 115.51, 124.80, 125.23, 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, 134.74, 134.79, 143.31, 147.16, 149.13, 151.86, 152.14, 155.72, 160.94, 164.48; For $C_{25}H_{20}ClN_5OS_2$ calculated: (%) C 59.34, H 3.98, N 13.84, found: (%) C 59.33, H 3.99, N 13.87; **MS (ES+)** $[M+1]^+$: *m/z* 507.

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

Yield 88%, m.p. 102-103 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3058, 3005 (aromatic CH), 2932, 2832 (aliphatic CH), 1634 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.51 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.45 (2H, s, S-CH_2), 7.07 (1H, s, Ar-H), 7.08 (1H, s, Ar-H), 7.35-7.42 (3H, m, Ar-H), 7.65 (2H, d, *J*: 8.6 Hz, Ar-H), 7.62-7.63 (2H, m, Ar-H, pyridine C_5-H), 8.15 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.67 (1H, d, *J*: 4.8 Hz, pyridine C_4-H), 8.98 (1H, s, pyridine C_2-H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ (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 $C_{25}H_{20}ClN_5OS_2$ 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-chlorophenyl)-3-benzylthio-*4H*-1,2,4-triazole V (A19)

Yield 87%, m.p. 188-190 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3057, 3031 (aromatic CH), 2978, 2925 (aliphatic CH), 1623 (C=N), 1596 (C=C), 809 (mono substituted benzene), 770 and 727 (1,3 disubstituted benzene), 690 (C-S); **^{1}H NMR** (500 MHz, DMSO-d_6) δ (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), 7.44-7.51 (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_6-H), 8.99 (1H, s, pyridine C_2-H); **^{13}C NMR** (75 MHz, DMSO-d_6) δ (ppm): 17.28, 37.28, 124.82, 127.36, 128.07, 128.39, 128.53, 129.0, 129.49, 13113, 131.94, 134.19, 134.28, 134.47, 137.42, 147.21, 151.95, 155.85; For $C_{24}H_{18}ClN_5S_2$ 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.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(3-chlorophenyl)-3-(3-chlorobenzylthio)-*4H*-1,2,4-triazole V (A20)

Yield 72%, m.p. 179-180 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3057 (aromatic CH), 2928 (aliphatic CH), 1627 (C=N), 1596 (C=C), 770 and 740 (1,3 disubstituted benzene), 691 (C-S), **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.45 (3H, s, CH_3), 4.41 (2H, s, S-CH_2), 7.31-7.36 (4H, m, Ar-H), 7.43 (1H, brs, Ar-H), 7.48-7.58 (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) δ (ppm): 17.30, 36.40, 124.82, 127.34, 127.95, 128.22, 128.38, 128.52, 129.31, 130.79, 131.16, 131.96, 133.41, 134.19, 134.31, 134.42, 140.37, 147.21, 148.56, 151.83, 151.95, 155.87; For $C_{24}H_{17}Cl_2N_5S_2$ calculated: (%) C 56.47, H 3.36, N 13.72; found: (%) C 56.45, H 3.34, N 13.73; **MS (ES+)** $[M+1]^+$: *m/z* 511.

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

Yield 76%, m.p. 137-139 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3057, 3028 (aromatic CH), 2975, 2928 (aliphatic CH), 1624 (C=N), 1596 (C=C), 817 (1,4 disubstituted benzene), 774 and 737 (1,3 di substituted benzene), 690 (C-S); **^{1}H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.46 (3H, s, CH_3), 4.42 (2H, s, S-CH_2), 7.37-7.38 (5H, brs, Ar-H), 7.48-7.67 (4H, m, ArH), 8.16 (2H, m, Ar-H, pyridine C_5-H), 8.66 (1H, d,

J: 8.2 Hz, pyridine C_6-H), 8.70 (1H, d, *J*: 4.7 Hz, pyridine C_4-H), 8.99 (1H, s, pyridine C_2-H); ^{13}**C 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, 151.88, 151.94, 155.87, 164.77; For $C_{24}H_{17}Cl_2N_5S_2$ 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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 2.25 (3H, s, CH_3), 2.51 (3H, s, CH_3), 4.42 (2H, s, S-CH_2), 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 C_5-H), 8.16 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.67 (1H, d, *J*: 4.7 Hz, pyridine C_4-H), 8.99 (1H, s, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ 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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 2.32 (3H, s, CH_3), 2.52 (3H, s, CH_3), 4.42 (2H, s, S-CH_2), 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 C_5-H), 8.13 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.66 (1H, d, *J*: 4.7 Hz, pyridine C_4-H), 8.97 (1H, s, pyridine C_2-H); ^{13}**C NMR** (75 MHz, DMSO-d_6) δ (ppm): 164.85, 155.75, 152.11, 151.92, 148.44, 147.23, 138.17, 137.11, 135.61, 134.19, 132.10, 130.41, 130.18, 130.04, 129.81, 128.88, 128.70, 128.54, 126.56, 124.80, 116.92, 37.25, 21.38, 17.19. For $C_{25}H_{20}ClN_5S_2$ 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.

5-[4-Methyl-2-(pyridin-3-yl) thiazole-5-yl]-4-(4-chlorophenyl)-3-(4-chlorobenzylthio)-*4H*-1,2,4-triazole V (A24)

Yield 82%, m.p. 90-92 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3086, 3048, 3026 (aromatic CH), 2956, 2921, 2856 (aliphatic CH), 1626 (C=N), 1573 (C=C), 809 (1,4 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm)**:** 2.50 (3H, s, CH_3), 4.44 (2H, s, S-CH_2), 7.08 (1H, s, Ar-H), 7.38-7.44 (4H, m, Ar-H), 7.65-7.67 (4H, m, Ar-H, pyridine C_5-H), 8.13 (1H, d, *J*: 8.1 Hz, pyridine C_6-H), 8.66 (1H, d, *J*: 4.7 Hz, pyridine C_4-H), 8.97 (1H, s, pyridine C_2-H); For $C_{24}H_{17}Cl_2N_5S_2$ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.49, H 3.34, N 13.71; **MS (ES+)** $[M+1]^+$: *m/z* 511.

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) V_{max} (cm^{-1}): 3041 (aromatic CH), 2970-2800 (aliphatic CH), 1626 (C=N), 1593 (C=C), 822 (mono substituted benzene), 776 (1,2-disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.51 (3H, s, CH_3), 2.80 (3H, s, CH_3), 4.20 (2H, s, S-CH_2), 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 C_3-H, C_5-H), 8.75 (2H, d, *J*: 5.2 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 65.87, 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-(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=N), 1590 (C=C), 822 (mono substituted benzene), 819 (1,4 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.68 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 7.00 (1H, t, ArH), 7.15 (2H, d, *J*:

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_3-H, C_5-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); ^{1}**H 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), 7.40 (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 $C_{24}H_{18}ClN_5S_2$ 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 740 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.78 (3H, s, CH_3), 4.31 (2H, s, S-CH_2), 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); ^{1}**H 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), 7.34 (2H, d, *J*: 8.0 Hz, ArH), 7.41 (2H, t, 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-phenyl-3-(3-methoxybenzylthio)-*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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.68 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.28 (2H, s, S-CH_2), 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 $C_{25}H_{21}N_5OS_2$ 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-methylphenyl)-3-benzylthio-*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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.08 (3H, s, CH_3), 2.77 (3H, s, CH_3), 4.40 (2H, s, S-CH_2), 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_3-H), 7.50 (1H, t, ArH), 7.80 (1H, d, *J*: 6.1 Hz, pyridine C_5-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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.22 (3H, s, CH_3), 2.58 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 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 C_3-H), 7.94 (1H, d, *J*: 5.7 Hz, pyridine C_5-H), 8.65 (1H, d, *J*: 5.7 Hz, pyridine C_6-H), 8.76 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5S_2$ calculated: (%) C 66.50, H 4.94, N 14.91,; found: (%) C 66.51, H 4.91, N 14.92; **MS (ES+)** $[M+1]^+$: *m/z* 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(4-methylbenzylthio)-*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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 1.82 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.50 (2H, s, S-CH_2), 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 C_3-H), 7.96 (1H, d, *J*: 5.8 Hz, pyridine C_5-H), 8.67 (1H, d, *J*: 5.7 Hz, pyridine C_6-H), 8.78 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5S_2$ calculated: (%) C 66.50, H 4.94, N 14.91, found: (%) C 66.50, H 4.92, N 14.87; **MS (ES+)** $[M+1]^+$: *m/z* 471.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(2-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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 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 C_5-H, C_3-H), 8.81 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.24, H 4.08, N 14.26; **MS (ES+)** $[M+1]^+$: *m/z* 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(3-chlorobenzylthio)-*4H*-1,2,4-triazole V(B11)

Yield 87%, m.p. 187-188 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3031 (aromatic CH), 2930-2850 (aliphatic CH), 1624 (C=N), 1590 (C=C), 760 (1,2 disubstituted benzene), 770 and 737 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.22 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 7.07 (1H, t, ArH), 7.16 (2H, d, ArH), 7.26 (1H, s, ArH), 7.30 (1H, d, ArH), 7.34 (1H, t, ArH), 7.42 (1H, d, ArH), 7.50 (1H, t, ArH), 7.90 (2H, d, *J*: 7.9 Hz, pyridine C_5-H, C_3-H), 8.80 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.28, H 4.10, N 14.26; **MS (ES+)** $[M+1]^+$: *m/z* 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-methylphenyl)-3-(4-chlorobenzylthio)-*4H*-1,2,4-triazole V (B12)

Yield 89%, m.p. 234-237 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3127, 3031 (aromatic CH), 2920-2815 (aliphatic CH), 1624 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 761 (1,2 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.26 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 7.05 (1H, d, ArH), 7.16 (1H, t, ArH), 7.18 (1H, d, ArH), 7.26 (1H, t, ArH), 7.30 (2H, d, *J*: 8.1 Hz, ArH), 7.40 (2H, d, *J*: 8.1 Hz, ArH), 7.92 (2H, d, *J*: 8.0 Hz, pyridine C_5-H, C_3-H), 8.83 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, H 4.11, N 14.28; **MS (ES+)** $[M+1]^+$: *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) ν_{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_3), 2.66 (3H, s, CH_3), 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_5-H), 8.70 (1H, d, *J*: 6.0 Hz pyridine C_6-H), 9.80 (1H, d, *J*: 5.8 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5OS_2$ calculated: (%) C 64.31, H 4.77, N 14.42, found: (%) C 64.29, H 4.75, N 14.44; **MS (ES+)** $[M+1]^+$: *m/z* 487.

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

Yield 79%, m.p. 231-232 °C, **IR** (KBr) ν_{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_3), 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_3-H), 7.49 (1H, s, ArH), 7.85 (1H, d, *J*: 6.3 Hz, pyridine C_5-H), 8.51 (1H, d, *J*: 5.9 Hz, pyridine C_6-H), 8.81 (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 4.62, N 15.34; **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 (B15)

Yield 76%, m.p. 225-226 °C, **IR** (KBr) ν_{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), 2.55 (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_5-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 $C_{26}H_{23}N_5S_2$ 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 (B16)

Yield 77%, m.p. 173-174 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3056 (aromatic CH), 2960-2850 (aliphatic CH), 1606 (C=N), 1586 (C=C), 819 (1,4 disubstituted benzene), 778 and 740 (1,3 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.28 (3H, s, CH_3), 2.45 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.52 (2H, s, S-CH_2), 7.05 (1H, d, ArH), 7.11 (2H, d, *J*: 7.9 Hz, ArH), 7.17 (1H, d, ArH), 7.20 (1H, t, ArH), 7.25 (2H, d, *J*: 8.0 Hz, ArH), 7.40 (1H, s, ArH), 7.66 (1H, d, *J*: 8.1 Hz, pyridine C_3-H), 7.93 (1H, d, *J*: 5.8 Hz, pyridine C_5-H), 8.64 (1H, d, *J*: 5.7 Hz, pyridine C_6-H), 8.79 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5S_2$ calculated: (%) C 66.50, H 4.94, N 14.91, found: (%) 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-chlorobenzylthio)-*4H*-1,2,4-triazole V (B17)

Yield 86%, m.p. 214-215 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3056 (aromatic CH), 2970-2850 (aliphatic CH), 1607 (C=N), 1586 (C=C), 786 (1,2 disubstituted benzene), 778 and 737 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.40 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.31 (2H, s, S-CH_2), 7.12 (1H, d, ArH), 7.25 (1H, d, ArH), 7.28 (1H, t, ArH), 7.48 (1H, s, ArH), 7.51 (1H, d, ArH), 7.55 (1H, t, ArH), 7.58 (1H, t, ArH), 7.60 (1H, d, ArH), 7.68 (1H, d, *J*: 8.1 Hz, pyridine C_3-H), 7.93 (1H, d, *J*: 5.8 Hz, pyridine C_5-H), 8.65 (1H, d, *J*: 5.7 Hz, pyridine C_6-H), 8.79 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, H 4.09, N 14.27; **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=N), 1586 (C=C), 774 and 737 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.43 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.31 (2H, s, S-CH_2), 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 C_3-H), 7.95 (1H, d, *J*: 5.8 Hz, pyridine C_5-H), 8.67 (1H, d, *J*: 5.8 Hz, pyridine C_6-H), 8.81 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.25, 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. 223-224 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3062 (aromatic CH), 2970-2850 (aliphatic CH), 1606 (C=N), 1586 (C=C), 816 (1,4 disubstituted benzene), 776 and 740 (1,3 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.46 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.31 (2H, s, S-CH_2), 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 C_3-H), 7.98 (1H, d, *J*: 5.9 Hz, pyridine C_5-H), 8.69 (1H, d, *J*: 5.8 Hz, pyridine C_6-H), 8.83 (1H, d, *J*: 5.8 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.24, H 4.14, N 14.29; **MS (ES+)** $[M+1]^+$: *m/z* 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-methylphenyl)-3-(3-methoxybenzylthio)-*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=N), 1586 (C=C), 776 and 737 (1,3 disubstituted benzene), 694 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.41 (3H, s, CH_3), 2.71 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.28 (2H, s, S-CH_2), 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 C_3-H), 7.97 (1H, d, *J*: 4.4 Hz, pyridine C_5-H), 8.66 (1H, d, *J*: 4.5 Hz, pyridine C_6-H), 8.79 (1H, d, *J*: 4.4 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5OS_2$ 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* 487.

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

Yield 69%, m.p. 226-227 °C, **IR** (KBr) V_{max} (cm^{-1}): 3037 (aromatic CH), 2915-2820 (aliphatic CH), 1626 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 806 (monosubstitüe benzen), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.27 (3H, s, CH_3), 2.77 (3H, s, CH_3), 4.40 (2H, s, S-CH_2), 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 C_3-H), 7.87 (1H, d, *J*: 6.3 Hz, pyridine C_5-H), 8.55 (1H, d, *J*: 6.0 Hz, pyridine C_6-H), 8.84 (1H, d, *J*: 6.2 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 4.63, N 15.40; **MS (ES+)** $[M+1]^+$: *m/z* 457.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-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=N), 1589 (C=C), 815 (1,4 disubstituted benzene), 767 (1,2 disubstituted benzene), 689 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.28 (3H, s, CH_3), 2.56 (3H, s, CH_3), 2.71 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 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 C_3-H), 7.88 (1H, d, *J*: 5.9 Hz, pyridine C_5-H), 8.58 (1H, d, *J*: 5.7 Hz, pyridine C_6-H), 8.80 (1H, d, *J*: 5.7 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5S_2$ 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=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.20 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.70 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 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 C_3-H, C_5-H), 8.82 (2H, d, *J*: 5.3 Hz, pyridine C_2-H, C_6-H); For $C_{26}H_{23}N_5S_2$ 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=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 806 (monosubstitüe benzen), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.35 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 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 C_5-H, C_3-H), 8.82 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.26, H 4.10, 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-chlorobenzylthio)-*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=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 774 and 737 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.28 (3H, s, CH_3), 2.81 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 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 C_5-H, C_3-H), 8.78 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ 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=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.35 (3H, s, CH_3), 2.79 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 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 C_5-H, C_3-H), 8.83 (2H, d, *J*: 6.1 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ 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=N), 1593 (C=C), 819 (1,4 disubstituted benzene), 776 and 737 (1,3 disubstituted benzene), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.37 (3H, s, CH_3), 2.74 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.32 (2H, s, S-CH_2), 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 C_3-H), 7.96 (1H, d, *J*: 4.4 Hz, pyridine C_5-H), 8.68 (1H, d, *J*: 4.6 Hz, pyridine C_6-H), 8.77 (1H, d, *J*: 4.3 Hz, pyridine C_2-H); For $C_{26}H_{23}N_5OS_2$ calculated: (%) C 64.31, H 4.77, N 14.42, found: (%) C 64.30, H 4.75, N14.43; **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) ν_{max} (cm^{-1}): 3142, 3008 (aromatic CH), 2825 (aliphatic CH), 1636 (C=N), 1590 (C=C), 770 (1,2 disubstituted benzene), 690 (C-S);[1]**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.54 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 7.09 (1H, d, ArH), 7.17 (1H, t, ArH), 7.21 (1H, d, ArH), 7.23 (1H, t, ArH), 7.25 (1H, t, ArH), 7.38 (1H, d, ArH), 7.57 (1H, t, ArH), 7.73 (1H, d, ArH), 7.92 (1H, d, *J*: 6.0 Hz, pyridine C_3-H), 8.54 (1H, d, *J*: 5.8 Hz, *J*: 6.1 Hz, pyridine C_5-H), 8.61 (1H, d, *J*: 6.1 Hz, pyridine C_6-H), 8.72 (1H, d, *J*: 1.5 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.28, H 4.10, N 14.29; **MS (ES+)** $[M+1]^+$: *m/z* 491.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(2-chlorophenyl)-3-(4-methylbenzylthio)-*4H*-1,2,4-triazole V (B29)

Yield 75%, m.p. 262-263 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3138, 3007 (aromatic CH), 2826 (aliphatic CH), 1634 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 771 (1,2 disubstituted benzene), 690 (C-S); [1]**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.25 (3H, s, CH_3), 2.68 (3H, s, CH_3), 4.50 (2H, s, S-CH_2), 7.12 (2H, d, *J*: 7.9 Hz, ArH), 7.17 (1H, t, ArH), 7.25 (2H, d, *J*: 8.0 Hz, ArH), 7.35 (1H, d, ArH), 7.53 (1H, t, ArH), 7.69 (1H, d, ArH), 7.95 (1H, d, *J*: 6.0 Hz, pyridine C_3-H), 8.58 (1H, d, *J*: 5.9 Hz, *J*: 6.2 Hz, pyridine C_5-H), 8.65 (1H, d, *J*: 6.1 Hz, pyridine C_6-H), 8.79 (1H, d, *J*: 1.5 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5S_2$ calculated: (%) C 61.28, H 4.11, N 14.29, found: (%) C 61.31, H 4.07, N 14.25; **MS (ES+)** $[M+1]^+$: *m/z* 491.

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

Yield 77%, m.p. 180-181 °C, **IR** (KBr) ν_{max} (cm^{-1}): 3146, 3005 (aromatic CH), 2829 (aliphatic CH), 1639 (C=N), 1590 (C=C), 770 (1,2 disubstituted benzene), 690 (C-S); [1]**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.77 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 7.16 (1H, t, ArH), 7.34 (1H, d, ArH), 7.47 (1H, d, ArH), 7.51 (1H, t, ArH), 7.52 (1H, t, ArH), 7.55 (1H, t, ArH), 7.60 (1H, d, ArH), 7.68 (1H, d, ArH), 7.94 (1H, d, *J*: 6.0 Hz, pyridine C_3-H), 8.58 (1H, d, *J*: 5.9 Hz, *J*: 6.2 Hz, pyridine C_5-H), 8.64 (1H, d, *J*: 6.1 Hz, pyridine C_6-H), 8.76 (1H, d, *J*: 1.5 Hz, pyridine C_2-H); For $C_{24}H_{17}Cl_2N_5S_2$ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.47, H 3.34, N 13.76; **MS (ES+)** $[M+1]^+$: *m/z* 511.

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) ν_{max} (cm^{-1}): 3137, 3004 (aromatic CH), 2831 (aliphatic CH), 1635 (C=N), 1590 (C=C), 819 (1,4 disubstituted benzene), 770 (1,2 disubstituted benzene), 690 (C-S); [1]**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.78 (3H, s, CH_3), 4.30 (2H, s, S-CH_2), 7.31 (2H, d, *J*: 8.4 Hz, ArH), 7.42 (2H, d, *J*: 8.4 Hz, ArH), 7.18 (1H, t, ArH), 7.36 (1H, d, ArH), 7.55 (1H, t, ArH), 7.70 (1H, d, ArH), 7.96 (1H, d, *J*: 6.1 Hz, pyridine C_3-H), 8.60 (1H, d, *J*: 5.9 Hz, *J*: 6.2 Hz, pyridine C_5-H), 8.68 (1H, d, *J*: 6.2 Hz, pyridine C_6-H), 8.78 (1H, d, *J*: 1.5 Hz, pyridine C_2-H); For $C_{24}H_{17}Cl_2N_5S_2$ calculated: (%) C 56.47, H 3.36, N 13.72, found: (%) C 56.45, H 3.33, N 13.69; **MS (ES+)** $[M+1]^+$: *m/z* 511.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(3-chlorophenyl)-3-benzylthio-*4H*-1,2,4-triazole V (B32)

Yield 72%, m.p. 138-139 °C, **IR** (KBr) ν_{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); [1]**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.79 (3H, s, CH_3), 4.40 (2H, s, S-CH_2), 7.32 (1H, d, ArH), 7.35 (1H, t, ArH), 7.40 (3H, m, ArH), 7.44 (2H, dd, ArH), 7.46 (1H, d, ArH), 7.49 (1H, d, *J*: 8.2 Hz, pyridine C_3-H), 7.66 (1H, s, ArH), 7.88 (1H, d, *J*: 6.3 Hz, pyridine C_5-H), 8.52 (1H, d, *J*: 5.9 Hz, pyridine C_6-H), 8.82 (1H, d, *J*: 6.1 Hz, pyridine C_2-H); For $C_{24}H_{18}ClN_5S_2$ calculated: (%) C 60.56, H 3.81, N 14.71, found: (%) C 60.52, H 3.81, N 14.70; **MS (ES+)** $[M+1]^+$: *m/z* 477.

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), 2958-2853 (aliphatic CH), 1610 (C=N), 1590 (C=C), 777 and 739 (1,3 disubstituted benzene), 699 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.71 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 4.30 (2H, s, S-CH_2), 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), 7.43 (1H, d, ArH), 7.65 (1H, s, ArH), 7.72 (1H, d, *J*: 4.6 Hz, pyridine C_3-H), 7.96 (1H, d, *J*: 4.4 Hz, pyridine C_5-H), 8.63 (1H, d, *J*: 4.5 Hz, pyridine C_6-H), 8.76 (1H, d, *J*: 4.3 Hz, pyridine C_2-H); For $C_{25}H_{20}ClN_5OS_2$ 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-(4-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), 2955-2830 (aliphatic CH), 1626 (C=N), 1590 (C=C), 824 (1,4 disubstituted benzene), 819 (monosubstitüe benzen), 690 (C-S); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.79 (3H, s, CH_3), 4.40 (2H, s, S-CH_2), 7.35 (3H, m, ArH), 7.39 (2H, dd, 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 C_3-H, C_5-H), 8.81 (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 60.54, H 3.80, N 14.69; **MS (ES+)** $[M+1]^+$: *m/z* 477.

5-[4-Methyl-2-(pyridin-4-yl) thiazole-5-yl]-4-(4-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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.52 (3H, s, CH_3), 2.69 (3H, s, CH_3), 4.31 (2H, s, S-CH_2), 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 C_3-H, C_5-H), 8.78 (2H, d, *J*: 5.3 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ 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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.28 (3H, s, CH_3), 2.68 (3H, s, CH_3), 4.51 (2H, s, S-CH_2), 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 C_3-H, C_5-H), 8.79 (2H, d, *J*: 5.3 Hz, pyridine C_2-H, C_6-H); For $C_{25}H_{20}ClN_5S_2$ 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); ^{1}**H NMR** (500 MHz, DMSO-d_6) δ (ppm): 2.78 (3H, s, CH_3), 4.30 (2H, s, CH_2), 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 C_3-H, C_5-H), 8.81 (2H, d, *J*: 5.3 Hz, pyridine C_2-H, C_6-H); For $C_{24}H_{17}Cl_2N_5S_2$ 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); ^{1}**H 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_5-H, C_3-H), 8.78 (2H, d, *J*: 5.4 Hz, pyridine C_2-H, C_6-H); For $C_{24}H_{17}Cl_2N_5S_2$ 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); ^{1}**H 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_3-H, C_5-H), 8.82 (2H, d, *J*: 5.3 Hz, pyridine C_2-H, C_6-H); For $C_{24}H_{17}Cl_2N_5S_2$ 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 10^5cfu/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 turbitometer (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$^{\bullet}$ (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_{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 *et al*., 2007).

$$\text{Percentage Inhibition} = \left[\frac{(\text{Abs}_{\text{control}} - \text{Abs}_{\text{sample}})}{\text{Abs}_{\text{control}}}\right] x100 \quad \text{(Equation 1)}$$

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^{-1} and 3146-3004 cm^{-1}. C=N, C=C stretching bands were observed in the regions 1636-1573 cm^{-1}, and 1639-1586 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds **A1-A24** and **B1-B39**, exhibited singlet peaks owing to –S-CH_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,^{1}H NMR, and MS spectroscopic, and CHN analytical data, respectively. In ^{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_3 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.

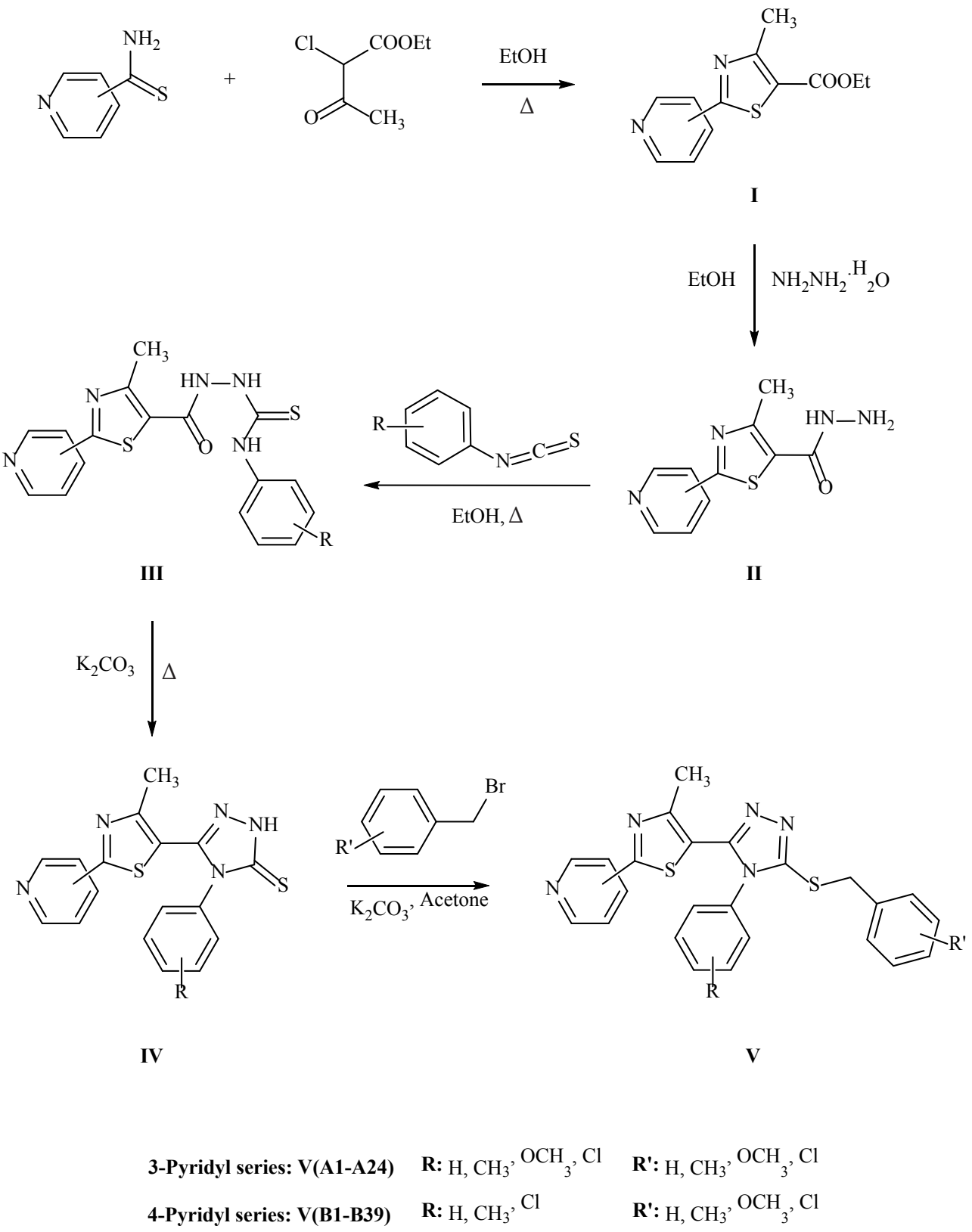
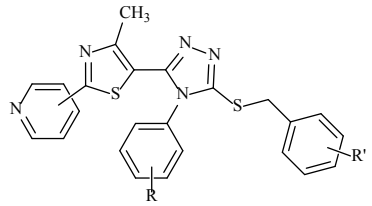


Figure 1 - The synthesis of the compound series V (A1-A24, B1-B39)

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

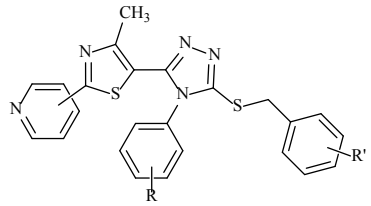


3-Pyridyl series: V(A1-A24)；4-Pyridyl series: V(B1-B39)

Compound	R	R'	Compound	R	R'
A1	H	H	B1	H	2-CH_3
A2	H	2-CH_3	B2	H	4-CH_3
A3	H	3-CH_3	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-OCH_3
A7	H	3-OCH_3	B7	2-CH_3	H
A8	2-CH_3	H	B8	2-CH_3	2-CH_3
A9	2-CH_3	2-CH_3	B9	2-CH_3	4-CH_3
A10	2-CH_3	2-Cl	B10	2-CH_3	2-Cl
A11	3-CH_3	H	B11	2-CH_3	3-Cl
A12	3-CH_3	2-Cl	B12	2-CH_3	4-Cl
A13	3-CH_3	3-Cl	B13	2-CH_3	3-OCH_3
A14	3-CH_3	4-Cl	B14	3-CH_3	H
A15	4-CH_3	2-Cl	B15	3-CH_3	2-CH_3
A16	4-CH_3	4-Cl	B16	3-CH_3	4-CH_3
A17	4-OCH_3	2-Cl	B17	3-CH_3	2-Cl
A18	4-OCH_3	4-Cl	B18	3-CH_3	3-Cl
A19	3-Cl	H	B19	3-CH_3	4-Cl
A20	3-Cl	3-Cl	B20	3-CH_3	3-OCH_3
A21	3-Cl	4-Cl	B21	4-CH_3	H
A22	4-Cl	2-CH_3	B22	4-CH_3	2-CH_3
A23	4-Cl	3-CH_3	B23	4-CH_3	4-CH_3
A24	4-Cl	4-Cl	B24	4-CH_3	2-Cl
			B25	4-CH_3	3-Cl
			B26	4-CH_3	4-Cl
			B27	4-CH_3	3-CH_3O
			B28	2-Cl	2-CH_3

(continues on the next page...)

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



3-Pyridyl series: V(A1-A24) ; 4-Pyridyl series: V(B1-B39)

Compound	R	R'	Compound	R	R'
			B29	2-Cl	4-CH_3
			B30	2-Cl	2-Cl
			B31	2-Cl	4-Cl
			B32	3-Cl	H
			B33	3-Cl	3-CH_3O
			B34	4-Cl	H
			B35	4-Cl	2-CH_3
			B36	4-Cl	4-CH_3
			B37	4-Cl	2-Cl
			B38	4-Cl	3-Cl
			B39	4-Cl	4-Cl

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

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	-	-	-

(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*
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	250	250	125
B5	250	250	125	125	125
B6	250	250	250	250	125
B7	250	250	250	250	125
B8	250	250	250	250	125
B9	250	250	125	125	125
B10	250	250	125	125	62.50
B11	250	250	250	250	125
B12	250	250	125	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	125	125	125
B22	250	250	250	125	125
B23	250	250	250	125	125
B24	250	250	31.25	31.25	62.50
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: Ampicilin 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...)

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
A18	< 3.09	< 3.09	<15.62	31.25	< 3.09	< 3.09
A23	< 3.09	15.62	<15.62	31.25	< 3.09	< 3.09
A24	< 3.09	15.62	<15.62	<15.62	< 3.09	< 3.09
Ref. 1	4	32	8	2	8	8
Ref. 2	< 0.25	0.5	0.25	0.06	8	0.5

Ref. 1: Chloramphenicol Ref. 2: Ampicilin

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

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

REFERENCES

Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM. Synthesis and antimicrobial evaluation of some 1,3-thiazole, 1,3,4-thiadiazole, 1,2,4-triazole, and 1,2,4-triazolo[3,4-b][1,3,4]-thiadiazine derivatives including a 5-(benzofuran-2-yl)-1-phenylpyrazole moiety. Monatsh Chem. 2009;140(6):601-605.

Althagafi I, El-Metwaly N, Farghaly TA. New series of thiazole derivatives: synthesis, structural elucidation, antimicrobial Activity, molecular modeling and MOE docking. Molecules. 2019;24(9):1741.

Arfan M, Siddiqui SZ, Abbasi MA, Rehman A, Shah Syed AA, Ashraf M, et al. Synthesis, in vitro and in silico studies of s-alkylated 5-(4-methoxyphenyl)-4-phenyl-4H-1,2,4-triazole-3-thiols as cholinesterase inhibitors. Pak J Pharm Sci. 2018;31(6):2697-2708.

Baviskar BA, Shiradkar MR, Khadabadi SS, Deore SL, Bothara KG. Synthesis of thiazolyltriazole substituted azetidinones as antimicrobial agents. Indian J Chem B. 2011;50(3):321-325.

Bayomi SM, El-Kashef HA, El-Ashmawy MB, Nasr MNA, El-Sherbeny MA, Abdel-Aziz N I, et al. Synthesis and biological evaluation of new curcumin analogues as antioxidant and antitumor agents: molecular modeling study. Eur J Med Chem. 2015;101:584-594.

Bektas H, Karaali N, Sahin D, Demirbas A, Karaoglu SA, Demirbas N. Synthesis and antimicrobial activities of some new 1,2,4-triazole derivatives. Molecules. 2010;15(4):2427-2438.

Bindu B, Vijayalakshmi S, Manikandan A. Synthesis and discovery of triazolo-pyridazine-6-yl-substituted piperazines as effective anti-diabetic drugs; evaluated over dipeptidyl peptidase-4 inhibition mechanism and insulinotropic activities. Eur J Med Chem. 2020;187:111912.

Behalo MS, Amine MS, Fouda IM. Regioselective synthesis, antitumor and antioxidant activities of some 1,2,4-triazole derivatives based on 4-phenyl-5-(quinolin-8-yloxy) methyl-4H-1,2,4-triazole-3-thiol. Phosphorus Sulfur. 2017;192(4):410–417

Blanco P, Hernando-Amado S, Reales-Calderon JA, Corona F, Lira F, Alcalde-Rico M, et al. Bacterial multidrug efflux pumps: much more than antibiotic resistance determinants. Microorganisms. 2016;4(1):1-19.

Ceylan S, Bektas H, Bayrak H, Demirbas N, Alpay-Karaoglu S, Ulker S. Synthesis and biological activities of new hybrid molecules containing different heterocyclic moieties. Arch Pharm. 2013;346(10):743-756.

Chao S, Wang Y. Synthesis of novel s-glucosides containing 5-methylisoxazole

substituted 1,2,4-triazole. J Chem. 2013:Article ID 568907.

Chaubey A, Pandeya SN. Pyridine a versatile nucleuse in pharmaceutical field. Asian J Pharm Clin Res. 2011;4(4):5-8.

Clinical and Laboratory Standards Institute (CLSI). Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, CLSI M7-A7, Clinical and Laboratory Standards Institue, 940 West Valley Road,Wayne, PA, USA 2006.

Clinical and Laboratory Standards Institute (CLSI) Reference Method for Broth Dilution Antifungal SusceptibilityTesting of Yeast, Approved Standard, CLSI 27-A3, 3rd ed., PA, USA 2008.

Cui SF, Ren Y, Zhang SL, Peng XM, Damu GL, Geng RX, et al. Synthesis and biological evaluation of a class of quinolone triazoles as potential antimicrobial agents and their interactions with calf thymus DNA. Bioorg Med Chem Lett. 2013;23(11):3267-3272.

Çavusoglu Kaya B, Yurttas L, Cantürk Z. The synthesis, antifungal and apoptotic effects of triazole-oxadiazoles against Candida species. Eur J Med Chem. 2018;144:255-261.

Demirayak Ş, Benkli K, Güven K. Synthesis of some 3-arylamino-5-aryloxymethyl [1,2,4]triazole derivatives and their antimicrobial activity. Pharm Acta Helv. 1998;72(5):285-290.

Dharavath R, Boda S. A synthesis and biological screening of newly substituted 9-methyl-6-aryl-[1,2,4] triazolo[4,3-a] [1,8]naphthyridines using chloranil. Synth Commun. 2019;49(14):1741–1749.

Dorovic J, Milenkovic D, Joksovic L, Joksovic M, Markovic Z. Study of influence of free radical species on antioxidant activity of selected 1,2,4-Triazole-3-thiones. ChemistrySelect. 2019;4(25):7476–7485.

Elkanzi NAA, Bakr RB, Ghoneim AA. Design, synthesis, molecular modeling study, and antimicrobial activity of some novel pyrano[2,3-*b*]pyridine and pyrrolo[2,3-*b*] pyrano[2.3-*d*]pyridine derivatives. J Heterocycl Chem. 2019;56(2):406-416.

El-Naggar M, Almahli H, Ibrahim HS, Eldehna WM, Hatem AAA. Pyridine-ureas as potential anticancer agents: Synthesis and in vitro biological evaluation. Molecules. 2018;23(6):1459.

Eryılmaz S, Türk Çelikoğlu E, İdil Ö, İnkaya E, Kozak Z, Mısır E, et al. Derivatives of pyridine and thiazole hybrid: synthesis, DFT, biological evaluation *via* **antimicrobial and DNA cleavage activity.** Bioorg Chem. 2020;95:103476.

Gaikwad ND, Patil SV, Bobade VD. Hybrids of ravuconazole: synthesis and biological evaluation. Eur J Med Chem. 2012;54:295-302.

Halliwell B. Antioxidants in human health and disease. Annu Rev Nutr. 1996;16:33-50.

Halliwell B. Role of free radicals in the neurodegenerative diseases - therapeutic implications for antioxidant treatment. Drug Aging. 2001;18(9):685-716.

Hosseinzadeh Z, Razzaghi-Asl N, Ramazani A, Aghahosseini H, Ramazani A. Synthesis, cytotoxic assessment, and molecular docking studies of 2,6-diaryl-substituted pyridine and 3,4- dihydropyrimidine-2(1H)-one scaffolds. Turk J Chem. 2020;44(1):194–213.

Iqbal J, Rehman AR, Abbas MA, Siddiqui SZ, Khalid H, Laulloo SJ, et al. BSA binding, molecular docking and in vitro biological screening of some new 1, 2, 4-triazole heterocycles bearing azinane nucleus. Pak J Pharm Sci. 2020;33(1):149-160.

Jalilian AR, Sattari S, Bineshmarvasti M, Shafiee A, Daneshtalab M. Synthesis and in vitro antifungal and cytotoxicity evaluation of thiazolo-4H-1,2,4-triazoles and 1,2,3-thiadiazolo-4H-1,2,4-triazoles. Arch Pharm. 2000;333(10):347-354.

Kaddouri Y, Abrigach F, Yousfi EB, Kodadi ME, Touzani R. New thiazole, pyridine and pyrazole derivatives as antioxidant candidates: synthesis, DFT calculations and molecular docking study. Heliyon. 2020;6(1):e03185.

Kashyap SJ, Garg VK, Sharma PK, Kumar N, Dudhe R, Gupta JK. Thiazoles: having diverse biological activities. Med Chem Res. 2012;21(8):2123-2132.

Koparir P. Synthesis, antioxidant and antitumor activities of some of new cyclobutane

containing triazoles derivatives. Phosphorus Sulfur. 2019;194(11):1028–1034.

Kharb R, Sharma PC, Yar MS. Pharmacological significance of triazole scaffold. J Enzyme Inhib Med Chem. 2011;26(1):1-21.

Kumarasamy Y, Byres M, Cox PJ, Jaspars M, Nahar L, Sarker SD. Screening seeds of some scottish plants for free radical scavenging activity. Phytother Res. 2007;21(7):615-621.

Kumar GVS, Prasad YR, Chandrashekar SM. Synthesis and pharmacological evaluation of some novel 4-isopropyl thiazole-based sulfonyl derivatives as potent antimicrobial and antitubercular agents. Med Chem Res. 2013;22(9):4239-4252.

Kumar P, Kumar A, Makrandi JK. Synthesis and evaluation of bioactivity of thiazolo[3,2-b]-[1,2,4]-triazoles and isomeric thiazolo[2,3-c]-[1,2,4]-triazoles. J Heterocyclic Chem. 2013;50(5):1223-1229.

Li QY, Chen J, Luo SY, Xu JL, Huang QX, Liu TY. Synthesis and assessment of the antioxidant and antitumor properties of asymmetric curcumin analogues. Eur J Med Chem. 2015;93:461-469.

Login CC, Bâldea I, Tiperciuc B, Benedec D, Vodnar DC, Decea N, et al. A novel thiazolyl schiff base: antibacterial and antifungal effects and in vitro oxidative stress modulation on human endothelial cells. Oxid Med Cell Longev. 2019;Article ID 1607903.

Mange YJ, Isloor AM, Malladi S, Isloor S, Fun HK, Synthesis and antimicrobial activities of some novel 1,2,4-triazole derivatives. Arab J Chem. 2013;6(2):177-181.

Mentese MY, Bayrak H, Uygun Y, Mermer A, Ulker S, Karaoglu SA, et al. Microwave assisted synthesis of some hybrid molecules derived from norfloxacin and investigation of their biological activities. Eur J Med Chem. 2013;67:230-242.

Miliovsky M, Svinyarov I, Prokopova E, Batovska D, Stoyanov S, Bogdanov MG. Synthesis and antioxidant activity of polyhydroxylated trans-restricted 2-arylcinnamic Acids. Molecules. 2015;20(2):2555-2575.

Padmavathi V, Mohan AVN, Mahesh K, Padmaja A. Aroylethenesulfonylacetic acid methyl ester - A synthon for novel sulfone linked bis heterocycles. Chem Pharm Bull. 2008;56(6):815-820.

Panda SS, Jain SC. Synthesis and QSAR studies of some novel disubstituted 1,2,4-triazoles as antimicrobial agents. Med Chem Res. 2014;23(2):848-861.

Patel NB, Khan IH, Rajani SD, Pharmacological evaluation and characterizations of newly synthesized 1,2,4-triazoles. Eur J Med Chem. 2010;45(9):4293-4299.

Perron GG, Inglis RF, Pennings PS, Cobey S. Fighting microbial drug resistance: a primer on the role of evolutionary biology in public health. Evol Appl. 2015;8(3):211-222.

Pitucha M, Pachuta-Stec A, Kaczor AA. New five-membered ring heterocyclic compounds with antibacterial and antifungal activity. In: Méndez-Vilas A, ed. microbial pathogens and strategies for combating them: Science, Technology and Education. Badajoz: Formatex Research Center. 562-573 p, 2013.

Prakash TB, Reddy GD, Padmaja A, Padmavathi V. Synthesis and antimicrobial activity of amine linked bis- and tris-heterocycles. Eur J Med Chem. 2014;82:347-354.

Pricopie AI, Ionut I, Marc G, Arseniu A, Vlase L, Grozav A, et al. Design and synthesis of novel 1,3-thiazole and 2-hydrazinyl-1,3-thiazole derivatives as anti-candida agents: in vitro antifungal screening, molecular docking study, and spectroscopic investigation of their binding interaction with bovine serum albumin. Molecules. 2019;24(19):3435.

Radulescu C, Stihi C. Biological activity of new heterocyclic systems containing thiazolic ring. Rev Chim-Bucharest. 2009;60(11):1164-1168.

Rauf A, Farshori NN. Microwave-induced synthesis of aromatic heterocycles. Berlin: Springer Press; 2012. 15p.

Rostami Z, Manesh AA, Samie L. QSAR modeling of antimicrobial activity with some novel 1,2,4-triazole derivatives, comparison with experimental study. Iran J Math Chem. 2013;4(1):91-109.

Sahin D, Bayrak H, Demirbas A, Demirbas N, Alpay-Karaoglu S. Design and synthesis of some azole derivatives as potential antimicrobial agents. Med Chem Res. 2012;21(12):4485-4498.

Sekhar MM, Yamini G, Gari Divya KR, Padmavathi V, Padmaja A. Synthesis and bioassay of a new class of disubstituted 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. Med Chem Res. 2019;28:1049–1062.

Singh R, Kashaw SK, Mishra VK, Mishra M, Rajoriya V, Kashaw V. Design and synthesis of new bioactive 1,2,4-triazoles, potential antitubercular and antimicrobial agents. Indian J Pharm Sci. 2018;80(1):36-45.

Shiradkar MR, Murahari KK, Gangadasu HR, Suresh T, Kalyan CA, Panchal D, et al. Synthesis of new s-derivatives of clubbed triazolyl thiazole as anti-Mycobacterium tuberculosis agents. Bioorgan Med Chem. 2007;15(12):3997-4008.

Sun GX, Yang MY, Shi YX, Sun ZH, Liu XH, Wu HK, et al. Microwave assistant synthesis, antifungal activity and DFT theoretical study of some novel 1,2,4-triazole Derivatives containing pyridine moiety. Int J Mol Sci. 2014;15(5):8075-8090.

Suryawanshia M, Gujarb V, Ottoorb D, Bobade V. Synthesis, characterization and photophysical properties of novel thiazole substituted pyridine derivatives. Indian J Chem Sect B. 2019;58:1361-1374.

Tiperciuc B, Zaharia V, Colosi I, Moldovan C, Crisan O, Pirnau A, et al. Synthesis and evaluation of antimicrobial activity of some new hetaryl-azoles derivatives obtained from 2-Aryl-4-methylthiazol-5-carbohydrazides and isonicotinic acid hydrazide. J Heterocyclic Chem. 2012;49(6):1407-1414.

Tomasic T, Zidar N, Mueller-Premru M, Kikelj D, Masic LP. Synthesis and antibacterial activity of 5-ylidenethiazolidin-4-ones and 5-benzylidene-4,6-pyrimidinediones. Eur J Med Chem. 2010;45(4):1667-1672.

Tumosienė I, Kantminienė K, Jonuškienė I, Peleckis A, Belyakov S, Mickevičius V. Synthesis of 1-(5-Chloro-2-hydroxyphenyl)-5-oxopyrrolidine-3-carboxylic acid derivatives and their antioxidant activity. Molecules. 2019;24(5):971.

Tumosienė I, Peleckis A, Jonuškienė I, Vaickelioniene R, Kantminiene K, Šiugždaitė J, et al. Synthesis of novel 1,2- and 2-substituted benzimidazoles with high antibacterial and antioxidant activity. Monatsh Chem. 2018;149:577–594.

Tumosienė I, Jonuškienė I, Kantminienė K, Šiugždaitė J, Mickevičius V, Beresnevičius ZJ. Synthesis and biological activity of 1,3,4-oxa(thia)diazole, 1,2,4-triazole-5-(thio)one and *s*-substituted derivatives of 3-((2-carboxyethyl)phenylamino)propanoic acid. Res Chem Intermed. 2016;42:4459–4477.

Turan-Zitouni G, Kaplancikli ZA, Yildiz MT, Chevallet P, Kaya D. Synthesis and antimicrobial activity of 4-phenyl/cyclohexyl-5-(1-phenoxyethyl)-3-[N-(2-thiazolyl) acetamido]thio-4H-1,2,4-triazole derivatives. Eur J Med Chem. 2005;40(6):607-613.

Yang L, Bao XP. Synthesis of novel 1,2,4-triazole derivatives containing the quinazolinyl piperidinyl moiety and N-(substituted phenyl)acetamide group as efficient bactericides against the phytopathogenic bacterium Xanthomonas oryzae pv. oryzae. RSC Adv. 2017;7:34005.

Yurttas L, Özkay Y, Karaca Gençer H, Acar U. Synthesis of some new thiazole derivatives and their biological activity evaluation. J Chem. 2015; Article ID 464379.

Zaki Y H, Al-Gendey MS, Abdelhamid AO. A facile synthesis, and antimicrobial and anticancer activities of some pyridines, thioamides, thiazole, urea, quinazoline, β-naphthyl carbamate, and pyrano[2,3-*d*]thiazole derivatives. Chem Cent J. 2018;12(1):70.

Zia M, Akhtar T, Hameed S, Al-Masoudic N. New aryl-1,3-thiazole-4-carbohydrazides, their 1,3,4-oxadiazole-2-thione, 1,2,4-triazole, isatin-3-ylidene and carboxamide derivatives.

Synthesis and anti-HIV activity. Z Naturforsch. 2012;67b(7):747–758.

Zoumpoulakis P, Camoutsis C, Pairas G, Sokovic M, Glamoclija J, Potamitis C, et al. Synthesis of novel sulfonamide-1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles, as potential antibacterial and antifungal agents. Biological evaluation and conformational analysis studies. Bioorgan Med Chem. 2012;20(4):1569-1583.

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