Synthesis and antimicrobial activity of new 2-phenoxy-[1,2,4]triazolo[1,5-*a*]quinazoline derivatives

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Abstract: This paper was aimed to synthesize a new group of 2-phenoxy[1,2,4]triazolo[1,5-*a*]quinazolin-5-one and their derivatives, then evaluate their antimicrobial activities. Antibacterial activity of the target molecules was tested against a variety of species from Gram positive bacteria (*Streptococcus pneumoniae* RCMB 010010 and *Bacillis subtilis* RCMB 010067), and Gram negative bacteria (*Pseudomonas aeroginosa* RCMB 010043 and *E. coli* RCMB 010052). In addition, their activities were screened against four fungi species *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotricum candidum* (RCMB 05097) and *Candida albicans* (RCMB 05036). The minimum inhibitory concentration (MIC) of the tested products has been determined by using broth double dilution method (Serially diluted technique) in proper nutrient. For comparison, compounds **2, 7, 14, 15, 16**, **31** and **32** were found to have the highest broad-spectrum antifungal and antibacterial activities in correspondence to amphotericin B, ampicillin, and gentamicin which were used as antifungal and antibacterial reference drugs. The present study revealed that compounds **2, 7, 14, 15, 16**, **31** and **32** have been disclosed as potential antimicrobial agents and could be useful as templates for further development to design more potent antimicrobial agents.
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1. Introduction

In our previous papers, we reported that certain groups of prepared triazoloquinazolines constitute a pharmacologically interesting class of compounds. For instance, the novel compounds 2-alkoxy(aralkoxy)-[1,2,4]triazolquinazolines are effective adenosine antagonist (Al-Salahi et al., 2011a; Al-Salahi & Geffken 2011b), whereas some of their derivatives have shown significant antifungal activity (Berezank et al., 2008; Al-Salahi & Geffken 2010a). Increase of communicable diseases caused by bacteria and viral affect millions of people worldwide. Hence, systematic and concerted research programs to discover and develop new antibiotics have been driven to a considerable extent by the development of resistance by these organisms to the commonly used drugs. In the field of triazoloquinazolines and their broad range of pharmacological properties (Kim et al., 1998; Ongini et al., 2001; Francis et al., 1991; Alagarsamy et al., 2007; 5-8], we have prepared some of interested 2-methylsulfanyl-[1,2,4]triazoloquinazolines that have been displayed potential antimicrobial activity against different microbial species (Al-Salahi et al., 2013a; Al-Salahi & Geffken, 2011c). Furthermore, a number of them have drawn much attention due to their antiviral activity (Al-Salahi et al., 2013b). Moreover, it was established that 9-chloro-5-morpholin-4-yl-3-(5-nitrothien-2-yl) [1,2,4]-triazolo[4,3-*c*]quinazoline was the most effective compound, which has caused growth inhibition of *B. subtilis*, *Staphylococcus aureus*, *Candida tropicalis* and *Rickettsia nigricans* (Jantova et al., 2005). Thus, considering the fact of anti-microbial activities existence among 1,2,4-triazoloquinazoline comounds, and as a part of our interest in the search for novel antimicrobial agents, we herein report the synthesis of 2-phenoxy-[1,2,4]triazoloqunizolines **(1-36)** and their biological evaluation at different bacterial strains and fungi media.

2. Experimental

2.1. Apparatus

Melting points were determined on open glass capillaries using a Mettler FP 62 apparatus and are uncorrected. The IR (KBr, ν, cm^{-1}) spectra were recorded on a Perkin Elmer FT-IR Spectrum BX system. NMR spectra were recorded on a Bruker AMX 500 spectrometer in DMSO-d_6 and reported as δ ppm values relative to TMS at 500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively. Mass spectra were measured on an Agilent 6410 TSQ system connected

to Agilent 1200 HPLC interface (samples were infused in MeOH). Follow up of the reactions and checking the purity of compounds was made by TLC on DC-Mikrokarten polygram SIL G/UV254, from the Macherey-Nagel Firm, Duren Thickness: 0.25 m. Column chromatography was conducted on silica gel (ICN Silica 100-200, active 60 Å).

The experimental data of compounds **2**, **3**, **5**, **8**, **23**, **25-28**, **30** and **32** were reported in our previous work (Al-Salahi et al., 2013c).

General procedure for synthesis of 3-22

To a solution of **1** or **2** (I mmol) in DMF (5 mL), potassium carbonate (1.2 mmol) was added portion wise over a period of 10 min at room temperature. After stirring for 20 min, the appropriate alkyl(hetero) halide (1.5 mmol) was added dropwise, and the reaction mixture was stirred for 18 h at room temperature. The mixture was poured into ice/water, the precipitate was filtered off, washed with water and dried. Analytically pure products **3-22** were obtained after recrystallization from THF.

4-Ethyl-8-methyl-2-phenoxy[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (4)

White amorphous powder; (yield: 70%), m.p. 140 °C IR (cm^{-1}): 1670 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.04 (1H, br s, H-9), 7.74 (2H, br s, H-6/7), 7.47 (2H, td, *J*= 8.5, 2 Hz, H-3'/5'), 7.36 (2H, br d, *J*= 8 Hz, H-2'/6'), 7.27 (1H, br t, *J*= 7.5 Hz, H-4'), 4.14 (2H, q, *J*= 7 Hz, -$\underline{CH_2}$-CH_3), 1.29 (3H, t, J= 7 Hz, -CH_2-$\underline{CH_3}$), 2.43 (3H, s, Ar-$C\underline{H_3}$); ^{13}C NMR (DMSO-d_6): δ_C ppm 165.3 (C-2), 158.2 (C-5), 154.3 (C-1'), 147.8 (C-9a), 136.2 (C-8), 135.5 (C-3a), 133.0 (C-5a), 129.8 (C-3'/5'), 128.0 (C-6), 124.9 (C-4'), 119.1 (C-2'/6'), 116.1 (C-7), 114.0 (C-9), 38.5 (-$\underline{CH_2}$-CH_3), 20.5 ($\underline{CH_3}$-Ar), 12.5 (-CH_2-$\underline{CH_3}$). EI-MS, *m/z* (%): 320 ($M^{+\bullet}$, 92). *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$ (320.13).

4-Allyl-2-phenoxy-8-methyl-[1,2,4]triazolo[1,5-*a*]-quinazolin-5-one (6)

White amorphous powder; (yield: 82%), m.p. 130 °C (DMF). IR 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ ppm 8.07 (1H, br s, H-9), 7.75 (2H, br s, H-6/7), 7.46 (2H, dt, *J*= 8.5, 1 Hz, H-3'/5'), 7.36 (2H, dd, *J*= 8.5, 1 Hz, H-2'/6'), 7.25 (1H, br t, *J*= 7.5 Hz, H-4'), 5.96 (1H, m, H-2"), 5.22 (1H, dd, *J*= 17.5, 1.5 Hz, H-3a"), 5.16 (1H, dd, *J*= 10.5, 1.5 Hz, H-3b"), 4.73 (2H, d, *J*= 5 Hz, H-1"), 2.45 (3H, s, $C\underline{H_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.3 (C-2), 158.4 (C-5), 154.2 (C-1'), 148.1 (C-9a), 135.3 (C-8), 135.2 (C-3a), 133.3 (C-5a), 131.5 (C-2"), 129.7 (C-3'/5'), 128.3 (C-6), 124.9 (C-4'), 119.1 (C-2'/6'), 117.4 (C-3"), 116.1 (C-7), 114.3 (C-9), 45.4 (C-1"), 20.5 ($\underline{CH_3}$-Ar). EI-MS *m/z* (%): 332 ($M^{+\bullet}$, 98). *Anal.* Calcd. for $C_{19}H_{16}N_4O_2$ (332.13).

2-Phenoxy-4-benzyl-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (7)

White amorphous powder; (yield: 65%), m.p. 134 °C IR (cm^{-1}): 1684 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.24 (1H, dd, J= 8, 1 Hz, H-9), 7.90 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.84 (1H, br d, J= 8 Hz, H-6), 7.56 (1H, td, J= 8, 1 Hz, H-7), 7.45 (4H, m, H-3'/5' & 3"/5"), 7.33 (4H, m, H-2'/6' & 2"/6"), 7.26 (2H, m, H-4' & 4"), 5.30 (2H, s, -$C\underline{H_2}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.3 (C-2), 158.5 (C-5), 154.1 (C-1'), 148.5 (C-9a), 135.7 (C-4"), 135.6 (C-8), 135.1 (C-3a), 129.8 (C-3'/5'), 128.6 (C-1"), 128.4 (C-3"/5"), 127.9 (C-2"/6"), 127.6 (C-6), 126.0 (C-5a), 125.0 (C-4'), 119.1 (C-2'/6'), 116.1 (C-7), 114.2 (C-9), 46.5 (-$\underline{CH_2}$-Ar). EI-MS, *m/z* (%): 413 ($M^{+\bullet}$, 92). *Anal.* Calcd. for $C_{22}H_{16}N_4O_2$ (368.13).

8-Methyl-2-phenoxy-4-(p-nitrobenzyl)-[1,2,4]-triazolo[1,5-*a*]quinazolin-5-one (9)

White amorphous powder; (yield: 70%), m.p. 184 °C IR (cm^{-1}): 1679 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.18 (2H, d, J= 8.5 Hz, H-3"/5"), 8.05 (1H, br s, H-9), 7.77 (2H, br s, H-6/7), 7.69 (2H, d, J= 8.5 Hz, H-2"/6"), 7.46 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.33 (2H, br d, J= 8 Hz, H-2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 5.43 (2H, s, -$C\underline{H_2}$-Ar), 2.46 (3H, s, $C\underline{H_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.1 (C-2), 158.6 (C-5), 154.1 (C-1'), 148.0 (C-9a), 146.9 (C-4"), 143.5 (C-1"), 136.6 (C-8), 135.7 (C-3a), 133.2 (C-5a), 129.8 (C-3'/5'), 128.8 (C-2"/6"), 128.1 (C-6), 124.9 (C-4'), 123.5 (C-3"/5"), 119.1 (C-2'/6'), 116.2 (C-7), 114.2 (C-9), 46.0 (-$\underline{CH_2}$-Ar), 20.5 ($\underline{CH_3}$-Ar). EI-MS, *m/z* (%): 427 ($M^{+\bullet}$, 92). *Anal.* Calcd. for $C_{23}H_{17}N_5O_4$ (427.13).

2-Phenoxy-4-(2-propylisoindolin-1,3-dione)-[1,2,4]-triazolo[1,5-*a*]quinazolin-5-one (10)

White amorphous powder, (yield: 82%), m.p. 102 °C IR (cm^{-1}): 1681, 1764, 1702 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.17 (1H, dd, J= 8, 1 Hz, H-9), 7.89 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.83 (4H, br s, H-3"-6"), 7.80 (1H, br d, J= 8 Hz, H-6), 7.54 (1H, td, J= 8, 1 Hz, H-7), 7.44 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.31 (2H, br d, J= 8 Hz, H-2'/6'), 7.25 (1H, br t, J= 7.5 Hz, H-4'), 4.17 (2H, t, J= 7.5 Hz, -$CH_2CH_2C\underline{H_2}$-phthalic imide), 3.71 (2H, t, J= 7.5 Hz, -$\underline{CH_2}CH_2CH_2$-phthalic imide), 2.16 (2H, pentet, J= 7 Hz, -$CH_2\underline{CH_2}CH_2$-phthalic imide); ^{13}C NMR (DMSO-d_6): δ ppm 167.9 (C-2"/7"), 165.2 (C-2), 158.3 (C-5), 154.0 (C-1'), 148.6 (C-9a), 135.4 (C-8), 134.9 (C-3a), 134.3 (C-2a"/6a"), 131.5 (C-4"/5"), 129.7 (C-3'/5'), 128.5 (C-6), 125.9 (C-5a), 124.8 (C-4'), 122.9 (C-3"/6"), 119.0 (C-2'/6'), 116.0 (C-7), 114.1 (C-9), 40.1, 25.7, 35.2 (-$CH_2CH_2CH_2$-phthalic imide). EI-MS, *m/z* (%): 465 ($M^{+\bullet}$, 87). *Anal.* Calcd. for $C_{26}H_{19}N_5O_4$ (465.14).

8-Methyl-2-phenoxy-4-(2-propylisoindolin-1,3-dione)-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (11)

White amorphous powder, (yield: 80%), m.p. 148 °C IR (cm^{-1}): 1675, 1754, 1710 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 7.94 (1H, br s, H-9), 7.81 (4H, m, H-3"-6"), 7.71 (2H, m, H-6/7), 7.44 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.31 (2H, br d, J= 7.5 Hz, H-2'/6'), 7.24 (1H, br t, J= 7.5 Hz, H-4'), 4.16 (2H, t, J= 7 Hz, -$CH_2CH_2\underline{CH_2}$-phthalic imide), 3.67 (2H, t, J= 7 Hz, -$\underline{CH_2}CH_2CH_2$-phthalic imide), 2.44 (3H, s, CH_3-Ar), 2.15 (2H, pentet, J= 7 Hz, -$CH_2\underline{CH_2}CH_2$-phthalic imide); ^{13}C NMR (DMSO-d_6): δ ppm 167.8 (C-2"/7"), 165.5 (C-2), 158.5 (C-5), 153.4 (C-1'), 147.6 (C-9a), 136.7 (C-8), 134.8 (C-3a), 134.3 (C-2a"/6a"), 131.5 (C-4"/5"), 129.7 (C-3'/5'), 128.0 (C-6), 124.8 (C-4'), 124.1 (C-5a), 122.9 (C-3"/6"), 119.0 (C-2'/6'), 116.9 (C-7), 114.0 (C-9), 40.1, 25.6, 35.3 (-$CH_2CH_2CH_2$-phthalic imide), 20.5 (CH_3-Ar). EI-MS, *m/z* (%): 479 ($M^{+\bullet}$, 87). *Anal.* Calcd. for $C_{27}H_{21}N_5O_4$ (479.16).

8-methyl-2-phenoxy-4-piperidinoethyl-[1,2,4]-triazolo[1,5-*a*]quinazolin-5-one (12)

White amorphous powder, (yield: 55%), m.p. 157 °C IR (cm^{-1}): 1664 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.02 (1H, br s, H-9), 7.74 (2H, m, H-6/7), 7.45 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.34 (2H, br d, J= 7.5 Hz, H-2'/6'), 7.28 (1H, br t, J= 7.5 Hz, H-4'), 4.22 (2H, t, J= 7 Hz, -$\underline{CH_2}CH_2$-piperidyl), 2.66 (2H, t, J= 7 Hz, -$CH_2\underline{CH_2}$-piperidyl), 2.46 (3H, s, CH_3-Ar), 2.42 (4H, m, H-2"/6"), 1.42 (4H, m, H-3"/5"), 1.40 (2H, m, H-4"); ^{13}C NMR (DMSO-d_6): δ ppm 165.3 (C-2), 158.4 (C-5), 154.2 (C-1'), 148.4 (C-9a), 136.4 (C-8), 135.7 (C-3a), 129.8 (C-3'/5'), 128.0 (C-6), 124.8 (C-5a), 124.3 (C-4'), 119.1(C-2'/6'), 116.5 (C-7), 114.0 (C-9), 54.9 (-$CH_2\underline{CH_2}$-piperidyl), 54.0 (C-2"/6"), 40.7 (-$\underline{CH_2}CH_2$-piperidyl), 25.4 (C-3"/5"), 23.8 (C-4"), 20.5 (CH_3-Ar). EI-MS, *m/z* (%): 403 ($M^{+\bullet}$, 67). *Anal.* Calcd. for $C_{23}H_{25}N_5O_2$ (403.02).

2-Phenoxy-4-piperidinoethyl-[1,2,4]triazolo[1,5-*a*]-quinazolin-5-one (13)

White amorphous powder, (yield: 60%), m.p. 143 °C IR (cm^{-1}): 1670 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.22 (1H, dd, J= 8, 1 Hz, H-9), 7.92 (1H, td, *J*= 8.5, 1.5 Hz, H-8), 7.81 (1H, br d, *J*= 8 Hz, H-6), 7.56 (1H, td, *J*= 8, 1 Hz, H-7), 7.46 (2H, td, *J*= 8.5, 2 Hz, H-3'/5'), 7.34 (2H, br d, J= 8 Hz, H-2'/6'), 7.24 (1H, br t, *J*= 7.5 Hz, H-4'), 4.23 (2H, t, *J*= 7 Hz, -$\underline{CH_2}CH_2$-piperidyl), 2.69 (2H, t, J= 7 Hz, -$CH_2\underline{CH_2}$-piperidyl), 2.46 (4H, m, H-2"/6"), 1.44 (4H, m, H-3"/5"), 1.36 (2H, m, H-4"); ^{13}C NMR (DMSO-d_6): δ ppm 165.4 (C-2), 158.5 (C-5), 154.4 (C-1'), 148.4 (C-9a), 135.5 (C-8), 135.0 (C-3a), 130.0 (C-3'/5'), 129.0 (C-6), 125.9 (C-5a), 124.9 (C-4'), 119.3 (C-2'/6'), 116.1 (C-7), 114.1 (C-9), 54.8 (-$CH_2\underline{CH_2}$-piperidyl), 53.9 (C-2"/6"), 40.6 (-$\underline{CH_2}CH_2$-piperidyl), 25.3 (C-3"/5"), 23.9 (C-4"). EI-MS, *m/z* (%): 389 ($M^{+\bullet}$, 60). *Anal.* Calcd. for $C_{22}H_{23}N_5O_2$ (389.18).

8-Methyl-2-phenoxy-4-(2-(morphlinoethyl)-[1,2,4]-triazolo[1,5-*a*]quinazolin-5-one (14)

White amorphous powder, (yield: 64%), m.p. 185 °C IR (cm^{-1}): 1680 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 7.90 (1H, br s, H-9), 7.71 (2H, m, H-6/7), 7.47 (2H, td, *J*= 8.5, 2 Hz, H-3'/5'), 7.35 (2H, br d, *J*= 7.5 Hz, H-2'/6'), 7.25 (1H, br t, J= 7.5 Hz, H-4'), 4.22 (2H, t, *J*= 6.5 Hz, -$\underline{CH_2}CH_2$- morphlinyl), 3.48 (4H, m, H-3"/5"), 2.67 (2H, t, *J*= 6.5 Hz, -$CH_2\underline{CH_2}$-morphlinyl), 2.45 (4H, m, H-2"/6"), 2.44 (3H, s, CH_3-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.7 (C-2), 159.6 (C-5), 154.3 (C-1'), 148.0 (C-9a), 136.4 (C-8), 135.7 (C-3a), 129.8 (C-3'/5'), 128.0 (C-6), 124.9 (C-5a), 124.5 (C-4'), 119.4(C-2'/6'), 116.7 (C-7), 114.0 (C-9), 66.9 (C-3"/5"), 54.8 (-$CH_2\underline{CH_2}$- morphlinyl), 53.2 (C-2"/6"), 40.6 (-$\underline{CH_2}CH_2$-morphlinyl), 20.5 (CH_3-Ar). EI-MS, *m/z* (%): 405 ($M^{+\bullet}$, 70). *Anal.* Calcd. for $C_{22}H_{23}N_5O_3$ (405.18).

2-Phenoxy-4-(2-(morphlinoethyl)-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (15)

White amorphous powder, (yield: 58%), m.p. 179 °C IR (cm^{-1}): 1685 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.23 (1H, dd, J= 8, 1 Hz, H-9), 7.94 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.84 (1H, br d, J= 8 Hz, H-6), 7.58 (1H, td, J= 8, 1 Hz, H-7), 7.46 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.35 (2H, br d, J= 8 Hz, H-2'/6'), 7.28 (1H, br t, J= 7.5 Hz, H-4'), 4.23 (2H, t, J= 6.5 Hz, -$\underline{CH_2}CH_2$- morphlinyl), 3.48 (4H, m, H-3"/5"), 2.67 (2H, t, J= 6.5 Hz, -$CH_2\underline{CH_2}$-morphlinyl), 2.43 (4H, m, H-2"/6"); ^{13}C NMR (DMSO-d_6): δ ppm 166.3 (C-2), 158.5 (C-5), 154.9 (C-1'), 148.4 (C-9a), 135.6 (C-8), 135.0 (C-3a), 132.1 (C-3'/5'), 129.7 (C-6), 126.0 (C-5a), 123.9 (C-4'), 119.1 (C-2'/6'), 116.1 (C-7), 114.1 (C-9), 66.1 (C-3"/5") 54.8 (-$CH_2\underline{CH_2}$-morphlinyl), 53.2 (C-2"/6"), 40.5 (-$\underline{CH_2}CH_2$-morphlinyl). EI-MS, *m/z* (%): 391 ($M^{+\bullet}$, 78). *Anal.* Calcd. for $C_{21}H_{21}N_5O_3$ (391.16).

4-(1H-Benzoimidazol-2-ylmethyl)-2-phenoxy-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (16)

Brown amorphous powder, (yield: 45%), m.p. 192 °C IR (cm^{-1}): 1689 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 12.60 (1H, br s, -NH), 8.03 (1H, dd, J= 8, 1 Hz, H-9), 7.96 (2H, br s, H-2",5"), 7.90 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.81 (3H, m, H-6, 3"/4"), 7.48 (1H, td, J= 8, 1 Hz, H-7), 7.41 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.30 (2H, br d, J= 8 Hz, H-2'/6'), 7.23 (1H, br t, J= 7.5 Hz, H-4'), 5.54 (2H, br s, -$\underline{CH_2}$-imidazole); ^{13}C NMR (DMSO-d_6): δ ppm 165.2 (C-2), 158.6 (C-5), 154.0 (C-1'), 149.1 (C-7"), 148.2 (C-9a), 137.1 (C-1"a/5"a), 135.9 (C-8), 134.1 (C-3a), 133.2 (C-5a), 129.8 (C-3'/5'), 128.2 (C-6), 124.9 (C-4'), 119.5 (C-3"/4"), 119.1 (C-2'/6'), 116.0 (C-7), 114.3 (C-2"/5"), 114.1 (C-9), 62.9 (-$\underline{CH_2}$-imidazole). EI-MS, *m/z* (%): 408 ($M^{+\bullet}$, 75). *Anal.* Calcd. for $C_{23}H_{16}N_6O_2$ (408.13).

4-(1H-Benzoimidazol-2-ylmethyl)-8-methy-2-phenoxy-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (17)

Brown amorphous powder, (yield: 48%), m.p. 145 °C IR (cm^{-1}): 1680 (C=O). ^{1}H-NMR (DMSO-d_6, 700 MHz): δ ppm 12.47 (1H, br s, -NH), 8.02 (1H, br s, H-9), 7.96 (2H, br s, H-2",5"), 7.80 (4H, m, H-6/7 & 3"/4"), 7.40 (2H,

td, J= 8.5, 2 Hz, H-3'/5'), 7.30 (2H, br d, J= 7.5 Hz, H-2'/6'), 7.23 (1H, br t, J= 7.5 Hz, H-4'), 5.54 (2H, br s, -$\underline{CH_2}$-imidazole), 2.41 (3H, s, CH_3-Ar); ^{13}C NMR (DMSO-d_6, 176 MHz): δ ppm 165.7 (C-2), 162.2 (C-5), 154.4 (C-1'), 148.6 (C-7"), 148.4 (C-9a), 137.3 (C-1"a/5"a), 136.1 (C-8), 134.4 (C-3a), 133.5 (C-5a), 130.1 (C-3'/5'), 128.4 (C-6), 125.1 (C-4'), 119.9 (C-3"/4"), 119.6 (C-2'/6'), 116.4 (C-7), 114.7 (C-2"/5"), 114.5 (C-9), 63.4 (-$\underline{CH_2}$-imidazole). EI-MS, *m/z* (%): 422 ($M^{+\bullet}$, 70). *Anal.* Calcd. for $C_{24}H_{18}N_6O_2$ (422.15).

8-Methyl-2-phenoxy-4-(4-methylbenzonitrile)-[1,2,4]triazolo[1,5-*a*]quinazolin-5-one (18)

White amorphous powder; (yield: 83%), m.p. 183 °C IR (cm^{-1}): 1688 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.03 (1H, br s, H-9), 7.80 (2H, br d, J= 7.5 Hz, H-3"/5"), 7.76 (2H, br s, H-6/7), 7.61 (2H, br d, J= 7.5 Hz, H-2"/6"), 7.46 (2H, br t, J= 7.5 Hz, H-3'/5'), 7.33 (2H, br d, J= 8 Hz, H-2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 5.36 (2H, s, -$\underline{CH_2}$-Ar), 2.46 (3H, s, $\underline{CH_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.1 (C-2), 158.6 (C-5), 154.2 (C-1'), 148.0 (C-9a), 141.4 (C-1"), 136.5 (C-8), 135.7 (C-3a), 133.2 (C-5a), 132.3 (C-3"/5"), 129.8 (C-3'/5'), 128.5 (C-2"/6"), 128.1 (C-6), 125.0 (C-4'), 119.1 (C-2'/6'), 118.7 (C-CN), 115.9 (C-7), 114.1 (C-9), 110.3 (C-4"), 46.2 (-$\underline{CH_2}$-Ar). EI-MS, *m/z* (%): 407 ($M^{+\bullet}$, 78). *Anal.* Calcd. for $C_{24}H_{17}N_5O_2$ (407.14).

2-Phenoxy-4-(4-methylbenzonitrile)-[1,2,4]-triazolo[1,5-*a*]quinazolin-5-one (19)

White amorphous powder; (yield: 85%), m.p. 144 °C IR (cm^{-1}): 1677 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.23 (1H, dd, J= 8, 1 Hz, H-9), 7.94 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.86(1H, br d, J= 8.5 Hz, H-6), 7.81 (2H, d, J= 8 Hz, H-3"/5"), 7.63 (2H, d, J= 8 Hz, H-2"/6"), 7.57 (1H, td, J= 8, 1 Hz, H-7), 7.46 (2H, td, J= 8.5, 2 Hz, H-3'/5'), 7.33 (2H, dd, J= 8.5, 1 Hz, H-2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 5.38 (2H, s, -$\underline{CH_2}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.2 (C-2), 158.7 (C-5), 154.1 (C-1'), 148.5 (C-9a), 141.4 (C-1"), 135.7 (C-8), 135.3 (C-3a), 132.3 (C-3"/5"), 129.8 (C-3'/5'), 128.6 (C-6), 128.5 (C-2"/6"), 125.9 (C-5a), 124.9 (C-4'), 119.4 (C-2'/6'), 118.8 (C-CN), 116.2 (C-7), 114.2 (C-9), 110.2 (C-4"), 46.2 (-$\underline{CH_2}$-Ar). EI-MS, *m/z* (%): 393 ($M^{+\bullet}$, 85). *Anal.* Calcd. for $C_{23}H_{15}N_5O_2$ (393.12).

2-Phenoxy-4-(3-methylbenzonitrile)-[1,2,-4]triazolo-[1,5-*a*]quinazolin-5-one (20)

White amorphous powder; (yield: 72%), m.p. 110 °C IR (cm^{-1}): 1670 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.24 (1H, dd, J= 8, 1 Hz, H-9), 7.94 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.92 (1H, br s, H-2"), 7.88 (1H, br d, J= 8.5 Hz, H-6), 7.81 (1H, br d, J= 8 Hz, H-4"), 7.77 (1H, br d, J= 8 Hz, H-6"), 7.58 (1H, td, J= 8, 1 Hz, H-7), 7.56 (1H, t-like, J= 8 Hz, H-5"), 7.46 (2H, br d, J= 7.5 Hz, H-3'/5'), 7.34 (2H, br d, J= 8.5 Hz, H-2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 5.35 (2H, s, -$\underline{CH_2}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.2 (C-2), 158.7 (C-5), 154.2 (C-1'), 148.5 (C-9a), 137.3 (C-1"), 135.6 (C-8), 135.3 (C-3a), 132.7 (C-6"), 131.3 (C-2"), 131.1 (C-4"), 129.8 (C-3'/5'), 129.6 (C-5"), 128.5 (C-6), 125.9 (C-5a), 124.9 (C-4'), 118.9 (C-2'/6'), 118.7 (C-CN), 116.3 (C-7), 114.2 (C-9), 111.4 (C-3"), 46.2 (-$\underline{CH_2}$-Ar). EI-MS, *m/z* (%): 393 ($M^{+\bullet}$, 80). *Anal.* Calcd. for $C_{23}H_{15}N_5O_2$ (393.12).

8-Methyl-2-phenoxy-4-(4-chlorobenzyl)-[1,2,-4]-triazolo[1,5-a]quinazolin-5-one (21)

White amorphous powder; (yield: 72%), m.p. 134 °C IR (cm^{-1}): 1677 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.03 (1H, br s, H-9), 7.74 (2H, br s, H-6/7), 7.46 (4H, m, H-3'/5' & 3"/5"), 7.39 (2H, d, J= 8 Hz, H-2"/6"), 7.34 (2H, br d, J= 8 Hz, H-2'/6'), 7.27 (1H, br t, J= 7.5 Hz, H-4'), 5.28 (2H, s, -$\underline{CH_2}$-Ar), 2.45 (3H, s, $\underline{CH_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.2 (C-2), 158.5 (C-5), 154.2 (C-1'), 148.0 (C-9a), 136.5 (C-8), 135.7 (C-3a), 134.8 (C-1"), 133.1 (C-5a), 132.2 (C-4"), 129.8 (C-3"/5"), 129.7 (C-3'/5'), 128.4 (C-2"/6"), 128.1 (C-6), 124.9 (C-4'), 119.1 (C-2'/6'), 116.0 (C-7), 114.1 (C-9), 45.8 (-$\underline{CH_2}$-Ar), 20.5 ($\underline{CH_3}$-Ar). EI-MS, *m/z* (%): 416 ($M^{+\bullet}$, 88). *Anal.* Calcd. for $C_{23}H_{17}ClN_4O_2$ (416.10).

2-phenoxy-4-(4-chlorobenzyl)-[1,2,-4]triazolo[1,5-*a*]-quinazolin-5-one (22)

White amorphous powder; (yield: 70%), m.p. 177 °C IR (cm^{-1}): 1679 (C=O). ^{1}H-NMR (DMSO-d_6): δ ppm 8.21 (1H, dd, J= 8, 1 Hz, H-9), 7.93 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.84 (1H, br d, J= 8.5 Hz, H-6), 7.55 (1H, td, J= 8, 1 Hz, H-7), 7.45 (4H, m, H-3'/5' & 3"/5"), 7.38 (2H, d, J= 8 Hz, H-2"/6"), 7.34 (2H, dd, J= 8.5, 1 Hz, H-2'/6'), 7.25 (1H, br t, J= 7.5 Hz, H-4'), 5.36 (2H, s, -$\underline{CH_2}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 165.3 (C-2), 158.6 (C-5), 154.2 (C-1'), 148.6 (C-9a), 135.7 (C-8), 135.3 (C-3a), 134.8 (C-1"), 132.2 (C-4"), 129.7 (C-3"/5"), 129.6 (C-3'/5'), 128.5 (C-2"/6"), 128.3 (C-6), 125.9 (C-5a), 124.9 (C-4'), 119.5 (C-2'/6'), 116.3 (C-7), 114.4 (C-9), 45.8 (-$\underline{CH_2}$-Ar) EI-MS, *m/z* (%): 402 ($M^{+\bullet}$, 88). *Anal.* Calcd. for $C_{22}H_{15}ClN_4O_2$ (402.09).

General proceure for synthesis of 23 and 24

Compounds **1** or **2** (1 mmol) were heated with phosphorous pentasulfide (1 mmol) in absolute pyridine (5 mL) for 2.5 h under reflux. Afterwards the reaction mixture was cooled and poured into ice/water, the yellow precipitate was separated by filtration and washed thoroughly with water. Recrystallization from aqueous dimethylformamide (DMF) furnished analytically pure compounds**.**

8-Methyl-2-phenoxy-4H-[1,2,4]triazolo[1,5-*a*]-quinazolin-5-thione (24)

Yellow amorphous powder; (yield: 85%), m.p. 187 °C IR (cm^{-1}): 1215 (C=S). ^{1}H-NMR (DMSO-d_6): δ ppm 13.03 (1H, s, -NH), 8.00 (1H, br s, H-9), 7.81 (2H, m, H-6/7), 7.46 (2H, m, H-3'/5'), 7.34 (2H, br d, J= 8 Hz, H-,2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 2.48 (3H, s, $\underline{CH_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 185.0 (C-5), 159.4 (C-2), 154.2 (C-1'), 149.5 (C-9a), 137.0 (C-8), 136.3 (C-3a), 131.3 (C-5a), 129.8 (C-3'/5'), 127.8 (C-6), 123.9 (C-4'), 119.4

(C-2'/6'), 116.9 (C-7), 114.5 (C-9), 20.5 ($\underline{CH_3}$-Ar). EI-MS, *m/z* (%): 308 ($M^{\bullet+}$, 89). *Anal.* Calcd. for $C_{16}H_{12}N_4OS$ (308.07).

General procedure for synthesis of compounds (25-27)

Compound **23** (1 mmol) was dissolved in 0.5 M sodium hydroxide solution (10 mL), alkyl halide (1.5 mmol) was added dropwise over a period of 2 min, the mixture was left to stir for 5-20 min at room temperature, and the obtained solid was separated by filtration, washed thoroughly with water and dried. Recrystallization of the crude products from ethanol afforded **25-27** as pure solids

General procedure for synthesis of compounds (28,29)

Compounds **1** or **2** (1 mmol) was heated with Phosphorous oxychloride (1 mL) in benzene (7 mL) for 2 h under reflux. The solvent was evaporated and the residue was treated with saturated solution of potassium carbonate. The solid was filtered, washed thoroughly with water, dried and recrystallized from tetrahydrofuran-hexane to give pure compound.

5-Chloro- 8-methyl-2-phenoxy-[1,2,4]triazolo[1,5-*a*]quinazoline (29)

White amorphous powder; (yield: 86%), m.p. 130 ^oC (THF). ^1H NMR (DMSO-d_6): δ ppm 8.05 (1H, br s, H-9), 7.65 (2H, br s, H-6/7), 7.42 (2H, dt, *J*= 8.5, 1 Hz, H-3'/5'), 7.27 (2H, dd, *J*= 8.5, 1 Hz, H-2'/6'), 7.22 (1H, br t, *J*= 8 Hz, H-4'), 2.50 (3H, s, $\underline{CH_3}$-Ar); ^{13}C NMR (DMSO-d_6): δ ppm 167.4 (C-2), 166.1 (C-5), 158.8 (C-9a), 155.2 (C-1'), 137.1 (C-3a),132.7(C-8), 129.2 (C-3'/5'), 126.8 (C-7), 123.7 (C-4'), 123.9 (C-6), 119.2 (C-2'/6'), 116.6 (C-5a), 111.5 (C-9), 20.5 ($\underline{CH_3}$-Ar). EI-MS, *m/z* (%): 296 ($M^{\bullet+}$, 100), *Anal.* Calcd. for $C_{15}H_9ClN_4O$ (310). MS: m/z (%): 310 ($M^{\bullet+}$, 100), *Anal.* Calcd. for $C_{16}H_{11}ClN_4O$ (310.06).

General procedure for synthesis of compounds (30, 31)

A freshly prepared sodium ethoxide solution (sodium 150 mg Na + 35 mL absolut ethanol) was reacted with 5-Chloro-2-phenoxy[1,2,4]triazolo[1,5-a]quinazoline**s 28, 29** (1 mmol) by stirring at room temperature for 30 min. Afterwards the solid was collected by filtration, air dried, and recrystallized from ethanol to give product as white solid.

5-Ethoxyl-8-methyl-2-phenoxy-[1,2,4]triazolo[1,5-*a*]quinazoline (31)

White amorphous powder; (yield: 52%), m.p. 210 ^oC. ^1H-NMR (DMSO-d_6): δ ppm 8.00 (1H, br s, H-9), 7.67 (2H, br s, H-6/7), 7.50 (2H, br t, J= 8.5, 2 Hz, H-3'/5'), 7.36 (2H, br d, J= 8 Hz, H-2'/6'), 7.27 (1H, br t, J= 7.5 Hz, H-4'), 4.40 (2H, q, J= 6.5 Hz, -$\underline{CH_2}$-CH_3), 2.61 (3H, s, $\underline{CH_3}$-Ar), 1.51 (3H, t, J= 6.5 Hz, -CH_2-$\underline{CH_3}$); ^{13}C NMR (DMSO-d_6): δ ppm 166.1 (C-2), 156.7 (C-5), 155.1 (C-1'), 150.1 (C-9a), 132.7 (C-8, 3a), 132.0 (C-5a), 129.4 (C-3'/5'), 127.6 (C-6), 123.8 (C-4'), 118.9 (C-2'/6'), 118.4 (C-7), 112.9 (C-9), 56.0 (-$\underline{CH_2}$-CH_3), 20.7 ($\underline{CH_3}$-Ar), 18.5 (-CH_2-$\underline{CH_3}$); EI-MS, *m/z* (%): 320 ($M^{\bullet+}$, 70). *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$ (320.12).

Synthesis of 2-Phenoxy-3-phenyl-bis[1,2,4]triazolo-[1,5-*a*; 4,3-*c*]quinazoline (33)

A mixture of **32** (0.5 mmol) and $POCl_3$ (5 mL) was heated at 100 ^oC for 2 h under reflux. After cooling, the excess of $POCl_3$ was removed under reduced pressure and the residue was treated with saturated aqueous solution of K_2CO_3 under ice cooling. The resulting solid was collected by filtration and recrystallized from MeOH to afford **33** as white amorphous powder; (yield: 60%), m.p. 198 ^oC. ^1H-NMR (DMSO-d_6): δ ppm 8.25 (1H, dd, J= 8, 1 Hz, H-9), 7.90 (1H, td, J= 8.5, 1.5 Hz, H-8), 7.82 (1H, br d, J= 8 Hz, H-6), 7.59 (1H, td, J= 8, 1 Hz, H-7), 7.50-7.20 (10H, m, 2 X -Ar); ^{13}C NMR (DMSO-d_6): δ ppm 167.7 (C-2), 159.5 (C-5), 156.1 (C-7"), 154.1 (C-1'), 149.9 (C-9a), 135.7 (C-8), 135.4 (C-3a), 130.1 (C-1"), 129.8 (C-3'/5'), 128.1 (C-3"/5"), 127.9 (C-4"), 127.6 (C-6), 127.1 (C-2"/6"), 125.6 (C-5a), 124.9 (C-4'), 119.5 (C-2'/6'), 116.8 (C-7), 114.2 (C-9). EI-MS, *m/z* (%): 378 ($M^{+\bullet}$, 92). *Anal.* Calcd. for $C_{22}H_{14}N_6O$ (378.12).

General procedure for synthesis of compounds 34-36

Compound **23** (0.5 mmol) was dissolved under heating with appropriate secondary amines (1 mL) for 5 min.. After cooling, the solution was treatment with hydrogen peroxide, the solid obtained was collected by filtertion, dried and recrystallized by toluene to give pure products **34-36.**

5-Morphlino-2-phenoxy-[1,2,4]triazolo[1,5-*a*]-quinazoline (34)

Pale yellow amorphous powder; (yield: 62%), m.p. 146 ^oC. ^1H NMR (DMSO-d_6): δ ppm 8.17 (1H, br d, J= 8.5 Hz, H-9), 8.06 (1H, br d, J= 8 Hz, H-6), 7.96 (1H, t-like, J= 8.5 Hz, H-8), 7.89 (1H, t-like, J= 8 Hz, H-7), 7.46 (2H, br t, J= 8.5, 2 Hz, H-3'/5'), 7.33 (2H, br d, J= 8 Hz, H-2'/6'), 7.26 (1H, br t, J= 7.5 Hz, H-4'), 3.84 (4H, t-like, J= 4.5 Hz, H-3"/5"), 3.68 (4H, t-like, J= 4.5 Hz, H-2"/6"); ^{13}C NMR (DMSO-d_6): δ ppm 167.1 (C-2), 161.8 (C-5), 154.4 (C-1'), 151.5 (C-9a), 136.2 (C-3a), 134.4 (C-8), 129.7 (C-3'/5'), 127.6 (C-5a), 124.9 (C-4'), 124.6 (C-6), 119.5 (C-2'/6'), 115.0 (C-7), 112.1 (C-9), 65.8 (C-3"/5"), 50.6 (C-2"/6"),. EI-MS, *m/z* (%): 347 ($M^{\bullet+}$, 73). *Anal.* Calcd. for $C_{19}H_{17}N_5O_2$ (347.14).

5-Dimethylamino-2-phenoxy-[1,2,4]triazolo[1,5-*a*]-quinazoline (35)

White amorphous powder; (yield: 40%), m.p. 199 °C. ^{1}H-NMR (DMSO-d_6): δ ppm 8.18 (1H, br d, J= 8.5 Hz, H-9), 7.96 (1H, t-like, J= 8.5 Hz, H-8), 7.88 (1H, br d, J= 8 Hz, H-6), 7.57 (1H, t-like, J= 7.5 Hz, H-7), 7.45 (2H, br t, J= 8.5, 2 Hz, H-3'/5'), 7.33 (2H, br d, J= 8 Hz, H-2'/6'), 7.25 (1H, br t, J= 7.5 Hz, H-4'), 3.32 (6H, s, (-N($\underline{CH_3}$)$_2$); ^{13}C NMR (DMSO-d_6): δ ppm 165.6 (C-2), 159.8 (C-5), 154.3 (C-1'), 148.1 (C-9a), 135.7 (C-3a), 135.2 (C-8), 129.7 (C-3'/5'), 128.2 (C-5a), 125.5 (C-4'), 124.8 (C-6), 119.4 (C-2'/6'), 116.9 (C-7), 114.1 (C-9), 39.5 (C-N($\underline{CH_3}$)$_2$). EI-MS, *m/z* (%): 305 ($M^{\bullet+}$, 73). *Anal.* Calcd. for $C_{17}H_{15}N_5O$ (305.13).

2-Phenoxy-5-piperidino-[1,2,4]triazolo[1,5-*a*]-quinazoline (36)

White amorphous powder; (yield: 51%), m.p. 190 °C. ^{1}H-NMR (DMSO-d_6): δ ppm 8.17 (1H, br d, J= 8.5 Hz, H-9), 7.90 (1H, t-like, J= 8.5 Hz, H-8), 7.8 (1H, br d, J= 8 Hz, H-6), 7.50 (1H, t-like, J= 7.5 Hz, H-7), 7.40 (2H, br t, J= 8.5, 2 Hz, H-3'/5'), 7.32 (2H, br d, J= 8 Hz, H-2'/6'), 7.25 (1H, br t, J= 7.5 Hz, H-4'), 3.65 (4H, m, H-2"/6"), 1.75 (4H, m, H-3"/5"), 1.66 (2H, m, H-4"); ^{13}C NMR (DMSO-d_6): δ ppm 165.9 (C-2), 160.5 (C-5), 154.3 (C-1'), 149.2 (C-9a), 135.8 (C-3a), 134.9 (C-8), 129.7 (C-3'/5'), 127.7 (C-5a), 125.3 (C-6), 124.7 (C-4'), 119.5 (C-2'/6'), 117.8 (C-7), 114.9 (C-9), 51.2 (C-2"/6"), 25.3 (C-4"), 24.0 (C-3"/5"). EI-MS, *m/z* (%): 345 ($M^{\bullet+}$, 78). *Anal.* Calcd. for $C_{20}H_{19}N_5O$ (345.16).

2.2. Antimicrobial activity

The target molecules were individually examined against of different fungal and a panel of Gram positive and negative bacterial pathogens. Antimicrobial tests were carried out by the agar well diffusion method (Scott, 1989) using 100 µL of suspension containing 1 x10^8 CFU/mL of pathological tested bacteria, and 1 x 10^4 spore/mL of fungi spread on nutrient agar (NA), Sabourand dextrose agar (SDA), and potato dextrose agar (PDA) respectively (Scott, 1989). After the media had cooled and solidified, wells (6 mm in diameter) were made in the solidified agar and loaded with 100 µL of tested compound solution prepared by dissolving 5 mg of the chemical compound in 1 ml of dimethyl sulfoxide (DMSO). The inculcated plates were then incubated for 24 h at 37 °C for bacteria and 48 h at 28°C for fungi. Negative controls were prepared using DMSO employed for dissolving the tested compound. Ampicilin (50 µg/ml), Gentamicin (50 µg/ml) and Amphotericin (50 µg/ml) were used as standard drugs for Gram positive bacteria, Gram negative bacteria and fungi respectively. After incubation time, antimicrobial activity was evaluated by measuring the zone of inhibition against the test organisms and compared with that of the standard. Antimicrobial activities were expressed as inhibition diameter zones in millimeters (mm). The experiment was carried out in triplicate and the average zone of inhibition was calculated (Table 1).

Measurement of MIC

The bacteriostatic activity of the active molecules (having inhibition zones was evaluated using the two fold serial dilution technique (Perez C *et al*., 1990). The twofold serial dilutions of the tested compounds solutions were prepared using proper media broth. The final concentrations of the solutions were 500-0.007 µg/ml. The tubes were then inoculated with the test organisms, grown in their suitable broth for tested pathogenic bacteria (1 x 10^8 CFU/ml for bacteria and 1 x10^4 spore/ml for fungi); each 5 ml received 0.1 ml of the above inoculum and was incubated at 37°C for 24 h for bacteria and fungi at 28°C for 48 h. The lowest concentration showing no growth was taken as the minimum inhibitory concentration (MIC).

2.3. Statistical analysis

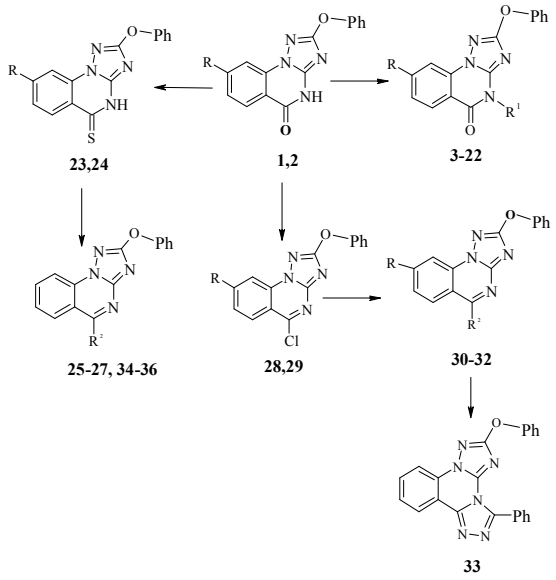
The experiment was carried out in triplicate and the data was expressed as mean ± SD. Difference in zone of inhibition between tested compounds and reference drugs were compared using Anova one way test with a difference being significant where $p < 0.001$ or $p < 0.05$.

3. Results and discussion

3.1. Chemistry

Taking into consideration scheme 1 and table 1, synthesis of our lead compounds were started with the preparation of main 2-phenoxy-4H-[1,2,4]triazolo[1,5-a]quinazolin-5-one (**1**) (Lolak, 2008; Al-Salahi et al., 2012) and its 8-methyl derivative (**2**) is prepared from condensation of 5-methyl-2-hydrazinobenzoic acid with diphenyl-N-cyanoimidocarbonate in presence of triethyl amine (Al-Salahi & Geffken, 2010b). The structures of **1** and **2** were characterized by MS and IR spectra, and have been unambiguously proven by NMR (see experimental data). Their regioselective *N*-alkylation of **1** and **2** with alkyl and hetero halides in a molar ratio of 1:1.5 in dry dimethyl formamide at room temperature in the presence of potassium carbonate, led to the formation of 4-alkyl(heteroalkyl)-[1,2,4] triazolo[1,5-*a*]quinazolin-5-ones (**3-22**) in about 45-85% yield (Al-Salahi & Geffken 2011b). Compounds **3-22** were obtained as coloress amorphous powder and characterized by IR spectra that displayed a strong (C=O) absorption band in the range of 1670-1690 cm^{-1} and confirmed by NMR. Equimolar molar reaction of triazoloquinazolin-5-ones (**1, 2**) with phosphorus pentasulfide in dry pyridine under reflux for 2.5 h,

produced the desired triazoloquinazolin-5-thiones (**23,24)** as yellow solid in excellent yield of 85 and 90% (Al-Salahi & Geffken, 2010b). Their IR spectra displayed a weak (C=S) absorption band at around 1197 and 1215 cm^{-1}. Reaction of the [1,2,4]triazolo-quinazolin-5-thione (**23)** with different alkyl halides in aqueous sodium hydroxide solution (2 M) afforded smoothly the expected thioethers **(25-27)** in 50-70% yield, whereas, its reaction with various secondary amines followed by treatment with hydrogen peroxide produced compounds **34-36** (Pfeiffer, *et al.*, 1999). The transformation of [1,2,4]triazoloquinazolin-5-ones (**1,2**) into their corresponding 5-chloro-[1,2,4]triazolo-[1,5-*a*]quinazolines (**28,29**) have been successfully performed by phosphorus oxychloride in boiling benzene for 2.5 h, followed by trituration with a saturated aqueous solution of potassium carbonate [15]. This transformation was noticed from the gradual disappearance of the characteristic (C=O) band in IR of **1** and **2** at 1711 and 1692 cm^{-1}. The 5-chloro-derivatives (**28,29**) were converted into the corresponding 5-ethoxytriazoloquinazolines (**30,31** in 52 and 57% yields) through the reaction with sodium ethoxide in the corresponding ethanol at ambient temperature. Finally, the reaction of **28** with phenyl-hydrazide in toluene, under reflux could be afforded the amidrazones **32** in good yield (75%) that can be subsequently treated with phosphorous oxychloride to produce the tetracyclic system **33.**



Scheme 1. Synthesis routes of compounds **1**–**36**

Basiclly, the structures of all prepared compounds (**2-36**) were tentatively characterized by recording of m.p. and study of their IR and MS data, as well (see experimental section). The confirmation of final accurate structures was acheived through detailed discussion of splitting pattern, δ- and *J*-values in their ^{1}H and ^{13}C NMR spectra; as well as comparison of their data with literature of structural related compounds (Al-Salahi & Geffken 2011b; Berezank et al., 2008; Al-Salahi & Geffken, 2010b).

Basiclly, the structures of all prepared compounds (**2-36**) were tentatively characterized by recording of m.p. and study of their IR and MS data, as well (see experimental section). The confirmation of final accurate structures was acheived through detailed discussion of splitting pattern, δ- and *J*-values in their ^{1}H and ^{13}C NMR spectra; as well as comparison of their data with literature of structural related compounds (Al-Salahi & Geffken 2011b; Berezank et al., 2008; Al-Salahi & Geffken, 2010b). In the ^{1}H NMR spectra of all compounds the parent tricyclic structure was proven by four 1H-signals, two of which are appeared as dd (or br d) resonances with J_{ortho} (7.5-8.5 Hz) and J_{meta} (1-2 Hz) assignable for H-9 and H-6 at about δ 8.2 and 7.8 ppm. The other two are described at about 7.9 and 7.5 ppm as td (or br t) resonances with J_{ortho} and J_{meta} for H-8 and H-7, respectively. In case of 8-methyl analuges, these aromatic protons were changed into an AMM'-spin coupling system at about 7.9 (br s) and 7.7 (br s) for H-9 and H-6/7 due to replacement of H-8 with a methyl group that is located at about δ ppm 2.5 (s) and 20.5 ppm in all ^{1}H and ^{13}C NMR spectra. A singlet signal was assigned at δ > 13 for the exchangeable NH-4 proton in case of 5-one (**1,2**) and 5-thione (**23**,**24**) derivatives that is disappeared in all other spectra of N-alkylation (**3-22**) or N-unsaturation (**25-36**) products. ^{13}C NMR spectra proved the main tricyclic moiety through characteristic nine resonances including the most downfield key signal of C-2 assigned at about 165-166 ppm due to the strong –R and –I (deshielding) effects of O-phenoxy. Another key ^{13}C-signal was C-5 that interpreted at about δ 158-160 ppm in 5-one (**1-22**), 167 in 5-Cl (**28**,**29**) and 185 in case of 5-thione (**23,24**) deriveatives**.**The intrensic three resonances that are located at about 7.45 (td, *J*= 8.5, 2), 7.33 (br d, *J*= 8) and 7.25 (br t, *J*= 7.5) were assignable for H-3'/5', H-2'/6' and H-4' of the 2-phenoxy function in all structures. As well as it was further confirmed through its four ^{13}C resonances at about δ ppm 154, 130, 124 and 119 interpretable for C-1', 3'/5', 4', and 2'/6', respectively. Insersion of a new functional structural part in all synthesized compounds was individually examined by its own ^{1}H- and ^{13}C-signals (splitting pattern, δ- and *J*-values) alongside anisotropic effects (up- and/or downfield shifts) on all neibours in their ^{1}H and ^{13}C NMR spectra. The *N*-ethyl function was observed as a typical A2X3-spin coupling system as a quartet (CH_2) and triplet (CH_3) at about 4.15 (q, *J*= 7) and 1.3 (t, *J*=

7) and confirmed by their corresponding ^{13}C-resonances at δ ppm 38.5 and 12.5 (**3**,**4**). In case of compounds **27**, **30** and **31,** *S*-ethyl and *O*-ethyl functions showed the same splitting pattern of *N*-ethyl but with slightly different δ-values in both ^{1}H and ^{13}C NMR spectra due to the stronger downfield shift by stronger –I efeect of S- and O-atoms. However, alkylation with allyl moiety was proved by its four characteristic ^{1}H-resonances with intrinsic splitting pattern at about 5.9 (m), 5.25 (dd, *J*= 17.5, 1.5), 5.20 (dd, *J*= 10.5, 1.5) and 4.72 (d, *J*= 5) assignable for olefinic methine and methylene and CH_2-saturated types (**5**,**6**). The corresponding three ^{13}C-resonances were interpreted at δ ppm 131.2, 117.5 and 45.2 for C-2, C-3 and C-1 of allyl group, respectively. In compound **25**, 5-*S*-allyl protons were interpreted with the same splitting pattern but more deshielded at 6.04, 5.42, 5.20 and 4.09 by higher electronegativity of *S*-atom and their ^{13}C-signals were reported at 129.6 (C-2"), 115.1 (C-3"), and 32.1 (C-1"). Moreover, *N*-benzyl group was indicated by its three types of protons at 7.45 (3"/5"), 7.33 (2"/6"), and 7.26 (4") together with a singlet for CH_2-group at about 5.30 (s) in all ^{1}H NMR spectra of all benzyl derivatives (**7-9, 18-22**). The corresponding ^{13}C-resonances were assigned at 135.7 (C-4"), 128.6 (C-1"), 128.4 (C-3"/5") and 127.9 (C-2"/6") together with $\underline{CH_2}$-Ar group at 46.5 ppm. Whereas, *p*-substitution with $–NO_2$ (**7**,**8**), -CN (**18**,**19**) or –Cl (**21**,**22**) was unambiguously reflected as A2M2-spin coupling system of two *ortho*-doublets assignable for H-3"/5" and H-2"/6" together with the downfield located CH_2-singlet at about 5.4 and its ^{13}C-signal at 46 ppm. In case of the products **10** and **11**, insersion of the *N*-propylphthalimide function was proved by the three characteristic aliphatic methylene resonances at 4.16 (t, J= 7), 3.67 (t, J= 7) and 2.15 (pentet, J= 7) together with their own ^{13}C-signals at 40.1, 25.7 and 35.2 and the two equivalent carbonyl carbons at 167.8 (C-2"/7") of imide ring. The identity of piperidinoethyl group (**12**,**13**) was deduced due to their resonances at 4.23 (t, J= 7) and 2.69 (t, J= 7) for two methylenes and 2.46 (m, H-2"/6"), 1.44 (m, H-3"/5") and 1.36 (m, H-4") for piperidinyl group along with their corresponding ^{13}C resonances at 54.8, 53.9, 25.3 and 23.9. Formation of morpholinoethyl derivatives (**14**,**15**) was followed from the two charcteristic spin coupling systems; the first one is A2X2 in the form of two triplets at 4.23 and 2.67 (J= 6.5), assignable for two methylenes and the second A4X4 at 3.48 and 2.43 (m) for H-3"/5" and H-2"/6" of morpholinyl moiety. Further confirmation of this structural feature was performed from corresponding ^{13}C resonances (see experimental data). The characteristic ^{1}H and ^{13}C resonances at 3.32 (6H, s) and 39.5 led us to deduce the formation of N-dimethyl group at C-5 in case of **35**. Like in *O*-phenyl functional group of all compounds, *S*-phenyl function in **26** showed the same splitting pattern but with slightly different δ-values in both ^{1}H and ^{13}C NMR spectra. In compound **32**, phenylhydrazide moiety was clearly concluded due to its intrinsic ^{1}H and ^{13}C resonances specially a broad singlet at 9.78 (2H) was interpretable for -NH-NH- group and hydrazide carbonyl carbon at 165.6 ppm. The transformation of the tricyclic nuclus into tetracyclic structure was simply followed from the characteristic ^{1}H and ^{13}C-resonances of an extra phenyltriazolo[4,3-c] fused ring (see NMR data of **33**). All other ^{1}H and ^{13}C-resonances of all structures were finally assigned on the basis of comparison with literature data of structure related compounds (Al-Salahi & Geffken 2011b; Berezank et al., 2008; Al-Salahi & Geffken, 2010b) and according to application of substitution additive rules of ^{13}C NMR.

3.2. Antimicrobial Activity

The prepared products **(1-36)** were assayed *in vitro* for their antimicrobial activity against *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922), *Geotricum candidum* (RCMB 05097), *Candida albicans* (RCMB 05036) *Streptococcus pneumoniae* (RCMB 010010), *Bacillis subtilis* (RCMB 010067), *Pseudomonas aeruginosa* (RCMB 010043) and *Escherichia coli* (RCMB 010052). Examination of the results listed in tables **2** and **3** revealed that, the alkyl(hetero)halides, ethoxy, and phenyl hydrazide groups are of particular importance, showing considerable impact on the antibacterial and antifungal activities among all structural modifications **(1-36)** on the 4 and 5- positions of the triazoloquinazoline systems **1** and **2.** Furthermore, it seems that lipophilicity plays an essential role in the diffusion of target molecules into bacterial cells and produces a remarkable change of the antimicrobial activity profile in terms of inhibition and selectivity. Many of the prepared molecules demonstrated significant comparable antimicrobial activities with respect to the control drugs. Compounds **2, 7, 14, 15, 16, 31, 32, 33** and **35** exhibited the highest potency against *Aspergillus fumigatus* (RCMB 02568), *Syncephalastrum racemosum* (RCMB 05922 *Geotricum candidum* (RCMB 05097), *Candida albicans* (RCMB 05036) in regards to the reference drug (Amphotericin B). Whereas, the products **2, 15, 16, 31, 32, 33** and **36** were more potent against *Bacillis subtilis* (RCMB 010067), and similarely **7, 15**, **16** and **32** showed the highest activity against *Streptococcus pneumoniae* (RCMB 010010). However, compounds **15, 16, 22** and **31** have emerged almost the same behavior with respect to the reference drug (Gentamicin). Furthermore, compounds **2, 4, 6, 7, 8, 12, 14, 15, 16, 17** and **22** displayed the highest

activity against *Escherichia coli* (RCMB 010052) with the lowest MIC value ranged between 0.007 to 7.81 µg/ml in comparision with reference drug (15.63 µg/ml). In addition, compounds **31, 32**, and **35** were demonstrated similar activity with respect to the reference drug against *Escherichia coli*. On the other hand, compounds **15, 16,** and **22** are highly active towards Gram negative bacteria *Streptococcus pneumoniae* (RCMB 010010) with the lowest MIC (0.06-0.24 µg/ml) in regard to the reference drug (0.98 µg/ml). Moreover, compounds **15** and **16** represent the most active compounds obtained during this study and were found to display the highest activity against all the tested species of fungi and bacteria that mentioned above.

As well as, the *Geotricum candidum* (RCMB 05097) was found to be more sensitive towards compounds **2, 14, 31, 33** and 3**5,** but compound **14** was active against *Candida albicans* (RCMB 05036). Furthermore, compound **32** demonstrated the same MIC values in comparable to the referenc drug against fungal pathogens.

Throughout this study, we have noticed that the parent **2** was found to possess the highest activity against *Geotricum candidum* (RCMB 05097), *Bacillis subtilis* (RCMB 010067), *Escherichia coli* (RCMB 010052), and *Candida albicans* (RCMB 05036) followed from the lowest MIC values of 0.007 µg/ml and 0.12 µg/ml, respectively.

Taken together, structure modifications in the parent compounds **(1** and **2)** have led to various antimicrobial activity depending on the structure change and examined microbial species. In compounds **3-22**, N-alkylation / heteroalkylation of lactam have demonstrated remarkable activity such as compound **15, 16** and **14** that displayed a significant MIC values **(**Table 2). However, **15** and **16** represent the most populated set of compounds obtained during this study. Within our work, conversion of the lactam moiety into an imidoyl chloride function **(28, 29)** has not influenced positively effect on the activity profiles; however its further chemical transformation into **31** and **32** has offer advantageous in the activity in regard to their parent. Moreover, the transformation of the tricyclic system **32** into tetracyclcic system **33** has shown the highest activity against *Geotricum candidum* (RCMB 05097) and a good effect against *Bacillis subtilis* (RCMB 010067). This result indicates that the presence of fused ring is well tolerated and plays an important role in the activity.

Finally, the thionation products **23** and **24** did not showed remarkable antimicrobial activity; despite these compounds possess enhanced lipophilicity comparable to those parent compounds **1** and **2**.

Table 1. Substitution pattern in compounds **1-36**

Cpd	R	R^1	R^2
1	H	-	-
2	CH_3	-	-
3	H	$-CH_2CH_3$	-
4	CH_3	$-CH_2CH_3$	-
5	H	$-CH_2CH=CH_2$	-
6	CH_3	$-CH_2CH=CH_2$	-
7	H	*p*-Nitrobenzyl	-
8	CH_3	*p*-Nitrobenzyl	
9	H	-Benzyl	-
10	H	2-Pr-isoindole-1,3-dione	-
11	CH_3	2-Pr-isoindole-1,3-dione	-
12	CH_3	Et-piperidinyl	-
13	H	Et-piperidinyl	-
14	CH_3	Et-morphlinyl	-
15	H	Et-morphlinyl	-
16	H	2-Me-benzoimidazole	-
17	CH_3	2-Me-benzoimidazole	-
18	CH_3	4-Me-Benzonitile	-
19	H	4-Me-Benzonitile	-
20	H	3-Me-Benzonitile	-
21	CH_3	*p*-Chlorobenzyl	-
22	H	*p*-Chlorobenzyl	-
23	H	-	-
24	CH_3	-	-
25	H	-	*S*-allyl
26	H	-	*S*-phenyl
27	H	-	*S*-ethyl
28	H	-	-
29	CH_3	-	-
30	H	-	*O*-ethyl
31	CH_3		*O*-ethyl
32	H	-	Phenylhydrazide
33	H	-	-
34	H	-	Morphlino
35	H	-	Dimethylamino
36	H	-	Piperidino

Pr= propyl; Et= Ethyl; Me= Methyl

Conclusion

The present study revealed that compounds **2, 7, 14, 15, 16**, **31** and **31** have been disclosed as potent antimicrobial agents and could be useful as templates for further development to design more potent antimicrobial agents.

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Table 2. Antimicrobial activity expressed as the average zone of inhibition mm ± SD for compounds **1**–**36**

Cp. No.	Fungi				Gram positive Bacteria		Gram negitive Bacteria	
	Aspergillus fumigatus (RCMB 02568)	*Syncephal-strum racemosum* (RCMB 05922)	*Geotricum candidum* (RCMB 05097)	*Candida albicans* (RCMB 05036)	*Streptococ-cus pneumonia* (RCMB 010010)	*Bacillis subtilis* (RCMB 010067)	*Pseudomonas aeruginosa* (RCMB01004)	*Escherichia coli* (RCMB 010052)
1	9.3 ± 0.58	10.4 ± 0.36	10.9± 0.44	11.2± 0.58	NA	NA	NA	NA
2	23.7± 0.1	19.7± 0.2	28.7± 0.2	25.4± 0.1	23.8± 0.2	32.4± 0.3	17.3± 0.1	19.9± 0.3
3	14.9± 0.25	13.6± 0.25	12.8± 0.19	14.7 ± 0.58	13.3 ± 0.19	13.5± 0.36	NA	11.4± 0.36
4	19.3 ± 0.62	19.4 ± 0.34	17.6± 0.64	14.2 ± 0.53	20.6 ± 0.52	20.2 ± 0.63	14.0± 0.34	19.3 ± 0.62
5	12.3 ± 0.25	12.6± 0.37	12.6± 0.37	13.1± 0.34	13.1 ± 0.53	13.7 ± 0.58	NA	14.5± 0.28
6	19.8± 0.44	18.7± 0.24	17.3± 0.28	18.7± 0.19	20.2± 0.19	21.7± 0.24	11.7± 0.58	22.1± 0.24
7	22.6 ± 0.36	21.4 ± 0.25	20.8± 0.44	20.9 ± 0.73	21.9 ± 0.25	22.3 ± 0.58	17.3± 0.36	23.9± 0.44
8	18.6 ± 0.36	17.3 ± 0.35	16.5 ± 0.44	13.6 ± 0.58	19.2 ± 0.55	19.4 ± 0.52	13.6± 0.33	18.9 ± 0.58
9	15.4 ± 0.44	14.6 ± 0.25	13.1± 0.58	15.2 ± 0.73	15.4 ± 0.19	16.0 ± 0.58	NA	13.5± 0.44
10	NA	NA	NA	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA	NA	NA
12	17.1± 0.19	19.9± 0.22	18.3± 0.28	19.1± 0.58	19.3± 0.44	20.1± 0.58	16.4± 0.58	21.2± 0.19
13	9.3 ± 0.58	11.4 ± 0.44	8.2± 0.44	10.1 ± 0.58	NA	NA	NA	NA
14	21.6± 0.19	20.3± 0.58	20.4± 0.28	20.8± 0.44	21.3± 0.44	22.1± 0.28	16.8± 0.28	21.4± 0.44
15	24.2± 0.32	23.1± 0.25	21.2± 0.19	22.1 ± 0.58	24.3± 0.37	24.9± 0.37	18.9± 0.28	24.8± 0.24
16	25.8 ± 0.32	23.4 ± 0.25	22.6± 0.19	24.9 ± 0.58	25.8 ± 0.19	26.0 ± 0.37	19.2± 0.28	28.7± 0.24
17	18.6 ± 0.36	17.3 ± 0.35	16.5 ± 0.44	14.9 ± 0.58	20.6 ± 0.55	20.5 ± 0.52	14.3 ± 0.33	19.3± 0.58
18	10.3± 0.63	12.1± 0.43	NA	11.3± 0.58	NA	NA	NA	NA
19	13.7 ± 0.36	14.5± 0.25	NA	13.6± 0.44	13.9 ± 0.29	14.4 ± 0.38	NA	15.0± 0.25
20	13.6 ± 0.36	12.6± 0.19	NA	10.4± 0.25	NA	NA	NA	NA
21	14.2 ± 0.63	14.8± 0.58	14.3± 0.19	14.0± 0.19	14.5 ± 0.44	14.9 ± 0.31	NA	15.6± 0.19
22	17.8 ± 0.36	18.3 ± 0.35	14.9± 0.58	19.4 ± 0.44	20.3 ± 0.37	21.3 ± 0.25	19.4± 0.16	20.6± 0.37
23	15.7± 0.19	13.8± 0.19	16.9± 0.37	17.2± 0.44	17.9± 0.37	18.5± 0.28	NA	19.1± 0.44
24	15.6 ± 0.53	12.7± 0.36	16.3± 0.44	15.8± 0.54	18.9 ± 0.44	19.4 ± 0.53	NA	16.4± 0.23
25	14.2 ± 0.25	12.7 ± 0.42	11.6± 0.44	13.6 ± 0.22	16.7 ± 0.36	17.0 ± 0.58	NA	14.2 ± 0.68
26	15.6± 0.63	13.9 ± 0.54	12.2 ± 0.36	16.4 ± 0.77	17.3 ± 0.56	17.8 ± 0.67	NA	18.4 ± 0.38
27	NA	NA	NA	NA	NA	NA	NA	NA
28	16.7± 0.23	14.8 ± 0.28	13.6 ± 0.55	18.3 ± 0.27	19.9 ± 0.38	18.8 ± 0.17	NA	19.6 ± 0.42
29	16.8 ± 0.36	15.6± 0.19	14.4± 0.44	16.2 ± 0.19	16.2 ± 0.25	16.9 ± 0.44	NA	12.5± 0.19
30	NA	NA	NA	NA	NA	NA	NA	NA
31	12.6 ± 0.58	16.7± 0.14	22.6 ± 0.58	20.2 ± 0.58	20.3± 0.44	25.6± 0.63	NA	11.4± 0.17
32	23.9± 0.19	22.4± 0.19	17.9± 0.19	19.8± 0.37	21.9± 0.12	25.4± 0.16	19.4± 0.22	18.4± 0.19
33	13.4 ± 0.20	17.2 ± 0.29	20.3± 0.35	19.2± 0.58	20.6 ± 0.34	23.7± 0.25	NA	13.1 ± 0.14
34	NA	NA	15.8 ± 0.58	12.3 ± 0.44	15.1 ± 0.44	19.8± 0.58	NA	NA
35	17.2 ± 0.44	19.4 ± 0.23	21.3 ± 0.38	17.5 ± 0.72	20.0 ± 0.43	21.4± 0.53	NA	17.9± 0.37
36	12.6 ± 0.58	16.7± 0.14	17.2 ± 0.58	17.9 ± 0.65	19.6 ± 0.44	23.7± 0.63	NA	11.4± 0.17
Rf-1	**23.7± 0.1**	**19.7± 0.2**	**28.7± 0.2**	**25.4± 0.1**	-	-	-	-
Rf-2	-	-	-	-	**23.8± 0.2**	**32.4± 0.3**	-	-
Rf-3	-	-	-	-	-	-	**17.3± 0.1**	**19.9± 0.3**

Mean zone of inhibition in mm ± SD beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (5mg/ml) concentration of tested samples. The test was done using the diffusion agar technique, Well diameter: 6.0 mm…… …… (100 µl was tested), *NA: No activity, data are expressed in the form of mean ± SD**;** Rf-1= Amphotericin B; Rf-2= Ampicillin(+Ve); Rf-3= Gentamicin (-Ve)

Table 3. MIC values (µg/mL) of the most active compounds based on two-fold serial dilutions technique

Cpd No.	Fungi				Gram positive Bacteria		Gram negitive Bacteria	
	Aspergillus fumigatus (RCMB 02568)	*Syncephala-strum racemosum* (RCMB 05922)	*Geotricum candidum* (RCMB 05097)	*Candida albicans* (RCMB 05036)	*Streptococcus pneumonia* (RCMB 010010)	*Bacillis subtilis* (RCMB010067)	*Pseudomonas aeruginosa* (RCMB 010043)	*Escherichia coli* (RCMB 010052)
2	0.24	15.63	0.007	0.12	0.24	0.007	31.25	0.007
4	3.9	3.9	31.25	1.95	1.95	1.95	125	3.9
6	3.9	15.63	31.25	7.81	3.9	0.98	125	0.98
7	0.49	1.95	1.95	1.95	0.98	0.98	31.25	0.24
8	7.81	31.25	31.25	125	3.9	3.9	125	7.81
12	31.25	3.9	15.63	7.81	7.81	3.9	62.5	1.95
14	0.98	3.9	3.9	1.95	1.95	0.98	31.25	1.95
15	0.24	0.49	1.95	0.98	0.24	0.12	7.81	0.12
16	0.06	0.49	0.49	0.12	0.06	0.06	7.81	0.007
17	7.81	31.25	31.25	62.5	1.95	1.95	125	7.81
22	15.63	15.63	62.5	7.81	3.9	1.95	7.81	1.95
31	125	31.25	0.98	3.9	3.9	0.06	7.81	15.63
32	0.24	0.98	15.63	3.9	0.98	0.06	NA	15.63
33	125	31.25	3.9	7.81	1.95	0.24	NA	125
35	31.25	7.81	1.95	15.63	3.9	1.95	NA	15.63
36	125	31.25	31.25	15.63	3.9	0.24	0.24	125
Rf-1	**0.24**	**0.98**	**15.63**	**3.9**	-	–	–	–
Rf-2	–	–	–	–	**0.98**	**0.12**	-	–
Rf-3	–	–	–	–	–	–	**7.81**	**15.63**

Rf-1= Amphotericin B; Rf-2= *Ampicillin(+Ve)*; Rf-3= *Gentamicin (-Ve)*.

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