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IN VITRO, EVALUATION OF ANTIOXIDANT AND ANTIBACTERIAL ACTIVITIES OF NEW 1,2,3-TRIAZOLE DERIVATIVES CONTAINING 1,2,4-TRIAOZLE RING

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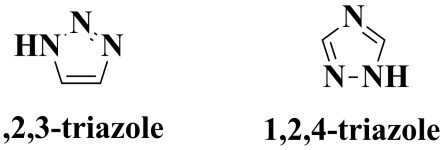
Abstract
A series of new heterocyclic compounds containing 1,2,3-triazole and 1,2,4-triazole moieties combined in the same matrix were synthesized via a multi-step synthetic pathway. The synthesized compounds and their precursors were screened for their in vitro antioxidant activity against DPPH and antibacterial activity against the negative bacterial strains of Helicobacter Pylori, Klebsiella pneumonia, Escherichia coli O157 and the positive bacterial strain of Staphylococcus aureus. Evaluation of antioxidant and antibacterial activities revealed that the combination of 1,2,3-traizole ring with 1,2,4-triazole ring together in the same matrix improved the antioxidant and bacterial activities.

Keywords: Heterocyclic compounds, 1,2,3-Triazole. 1,2,4-Triazole, Antioxidant activity, DPPH, Antibacterial activity.

INTRODUCTION

Nowadays, the rich nitrogen-containing heterocycles such as triazole structure occupy an unique position as a pharmacophore of different therapeutic agents in medicinal applications [1]. Triazole structure is an aromatic five-membered heterocyclic ring contains three nitrogen and two carbon atoms with the general formula $C_2H_2N_3$ [2]. Depending on the arrangement of the nitrogen atoms each other, triazole ring system is existed in two isomeric structures (Figure 1) named as 1,2,3-triazole [3] and 1,2,4-triazole [4].



1,2,3-triazole **1,2,4-triazole**

Figure 1: Chemical structure of 1,2,3-triazole and 1,2,4-triazole ring system.

Biologically, compounds containing 1,2,3-triazloe or 1,2,4-triazloe ring system are known to exhibit a wide range of biological activities such as antimicrobial [5][6], antimalarial [7][8], antitubercular [9][10], antifungal [11][12], anti-inflammatory [13][14], antiviral [15][16], anticancer [17][18], anti-diabetes [19][20], antioxidant [21][22], cytotoxic [23][24] and antiepileptic [25][26] agents. Moreover, it has been reported that the biological activity of heterocyclic compounds is increased by linking two or more heterocyclic systems in one molecular framework. Consequently, it is interested in the combination of 1,2,3-triazole and 1,2,4-triazole rings in the same matrix and study the antioxidant and antibacterial activities for the resulted compounds.

Chemicals and Instruments

All chemicals and solvents were supplied from available sources and directly used without further purification. The FT-IR spectra were recorded on a Shimadzu FT-IR 8400 spectrometer in KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 500 MHz and 125 MHz, respectively on Inova NMR spectrometer using DMSO-d6 as a solvent and TMS as the internal standard. The mass spectra (MS) were recorded using MS Model: 5973 Network Mass Selective Detector, with Ion source: Electron Impact (EI) 70_{ev}.

PROCEDURES

General procedure for the synthesis of 2-(5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-N-phenylhydrazinecarbothioamide derivatives (2a-d). A mixture of an appropriate derivative of carbohydrazides **1a-d** (10.0 mmol) and phenyl isothiocyanate (1.35 mL, 10.0 mmol) in ethanol (15 ml) was refluxed for one hour. The reaction mixture was allowed to cool into room temperature, filtered, recrystallized from ethanol and dried to obtain the target compounds **2a-d** in yield ranged 80-90%.

Synthesis of 2-(5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-*N*-phenylhydrazine-1-carbothioamide (2a): FT-IR (KBr disc, cm^{-1}), 3281 (NH), 3024 (=CH, aromatic), 2916 and 2847 (-CH, aliphatic), 1662 (C=O, amide), 1496 (N=N), 1317 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.55 (3H, s, CH_3), 7.12-7.66 (10H, m, Ar-H), 9.77 (2H, s, -NHCSNH-), 10.59 (1H, s, O=C-NH-NH). HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{16}N_6OS$= 352.1, Found= 352.3.

Synthesis of 2-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-*N*-phenylhydrazine-1-carbothioamide (2b): FT-IR (KBr disc, cm^{-1}), 3265 (NH), 3064 (=CH, aromatic), 2931 and 2848 (-CH, aliphatic), 1653 (C=O, amide), 1496 (N=N), 1317 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.56 (3H, s, CH_3), 7.12-7.74 (9H, m, Ar-H), 9.77 (2H, s, -NHCSNH-), 10.59 (1H, s, O=C-NH-NH). HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{15}ClN_6OS$= 386.07, Found= 386.2.

Synthesis of 2-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-*N*-phenylhydrazine-1-carbothioamide (2c): FT-IR (KBr disc, cm^{-1}), 3284 (NH), 3091 and 3026 (=CH, aromatic), 2924 and 2848 (-CH, aliphatic), 1651 (C=O,

amide), 1496 (N=N), 1321 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.56 (3H, s, CH_3), 7.12-7.87 (9H, m, Ar-H), 9.75 (2H, s, -NHCSNH-), 10.60 (1H, s, O=C-NH-NH). HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{15}BrN_6OS$= 430.02, Found= 430.2.

Synthesis of 2-(1-(4-nitrophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)-*N*-phenylhydrazine-1-carbothioamide (2d): FT-IR (KBr disc, cm^{-1}), 3281 (NH), 3088 and 3026 (=CH, aromatic), 2968 and 2854 (-CH, aliphatic), 1653 (C=O, amide), 1494 (N=N), 1319 (C=S). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.65 (3H, s, CH_3), 7.12-8.49 (9H, m, Ar-H), 9.78 (2H, s, -NHCSNH-), 10.67 (1H, s, O=C-NH-NH). HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{15}N_7O_3S$= 397.1, Found= 397.3.

General procedure for the synthesis of 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol derivatives 3a-d. A mixture of hydrazine-1-carbothioamide derivatives **2a-d** (5.0 mmol) and a solution of sodium hydroxide (2.0 N, 10 mL) was refluxed for three hours. The reaction mixture was then filtered, allowed to cool down and neutralized with a solution of HCl (10% v/v). The crude product was filtered and washed with water, dried and recrystallized from ethanol/methanol (1:1) to obtain the target compounds **3a-d** in yield (83-85%).

Synthesis of 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3a): FT-IR (KBr disc, cm^{-1}): 3099 and 3068 (=CH, aromatic), 2920 and 2829 (-CH, aliphatic), 2762 (SH), 1496 (N=N). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.43 (3H, s, CH_3), 7.39-7.63 (10H, m, Ar-H), 14.29 (1H, s, SH). ^{13}C-NMR (125 MHz, DMSO-d_6): 9.94, 129.16, 129.34, 129.63, 130.22, 130.47, 135.13, 135.66, 136.14, 144.21, 169.02, 182.03. HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{14}N_6S$= 334.1, Found= 334.2.

Synthesis of 5-(1-(4-chlorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3b): FT-IR (KBr disc, cm^{-1}): 3068 (=CH, aromatic), 2916 and 2829 (-CH, aliphatic), 2764 (SH), 1496 (N=N). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.46 (3H, s, CH_3), 7.40-7.70 (9H, m, Ar-H), 14.29 (1H, s, SH). ^{13}C-NMR (125 MHz, DMSO-d_6): 9.89, 127.39, 129.15, 129.35, 129.65, 130.25, 132.61, 134.49, 135.10, 136.37, 144.11, 169.06, 182.03. HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{13}ClN_6S$= 368.06, Found= 368.2.

Synthesis of 5-(1-(4-bromophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3c): FT-IR (KBr disc, cm^{-1}): 3070 (=CH, aromatic), 2916 and 2831 (-CH, aliphatic), 2766 (SH), 1494 (N=N). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.46 (3H, s, CH_3), 7.36-7.83 (9H, m, Ar-H), 14.30 (1H, s, SH). ^{13}C-NMR (125 MHz, DMSO-d_6): 9.90, 123.66, 127.59, 129.15, 129.35, 129.64, 132.64, 133.19, 134.91, 135.10, 136.33, 144.11, 169.06, 182.02. HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{13}BrN_6S$= 412.01, Found= 412.2.

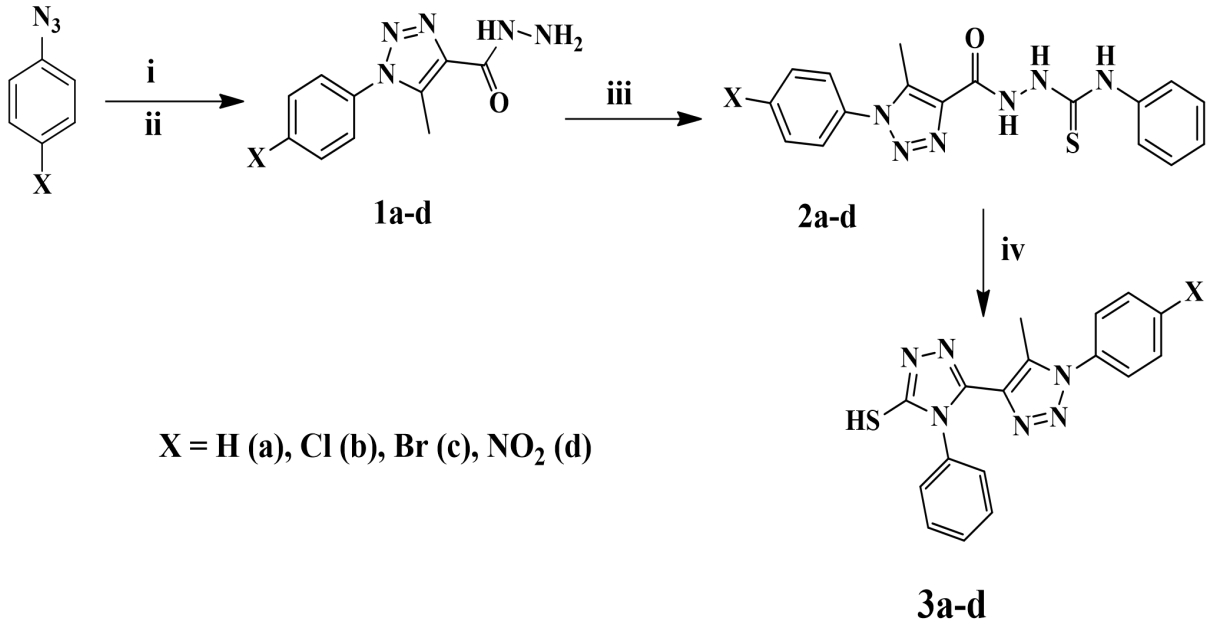
Synthesis of 5-(5-methyl-1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol (3d): FT-IR (KBr disc, cm^{-1}): 3082 (=CH, aromatic), 2926 and 2852 (-CH, aliphatic), 2758 (SH), 1498 (N=N). ^{1}H-NMR (500 MHz, DMSO-d_6): δ= 2.53 (3H, s, CH_3), 7.16-8.47 (9H, m, Ar-H), 14.33 (1H, s, SH). ^{13}C-NMR (125 MHz, DMSO-d_6): 10.44, 118.01, 122.59, 125.59, 126.65, 129.59, 133.72, 137.49, 140.58, 140.90, 148.26, 163.99, 182.03. HPMS-EI$^+$ (m/z): Calc. for $C_{17}H_{13}N_7O_2S$= 379.09, Found= 379.2.

Antioxidant Assay: The radical scavenging activity of the synthesized compounds **2a-d** and **3a-d** was evaluated against the stable free radicals of 1,1-diphenyl-2-picrylhydrazyl (DPPH) by spectrophotometric method. Practically, the tested compounds were prepared in five concentrations (12.5, 25, 50, 100 and 200 µg/mL) in methanol. To 1.0 ml of a solution of the tested compounds **2a-d** and **3a-d** of each concentration, a methanolic solution of DPPH (1.0 mL, 0.1 mM) was added. The resulted solution was incubated for 30 minutes in the dark at 37 °C and the absorbance was measured at 517 nm using UV-1650 Shimadzu Spectrophotometer. Absorbance of the DPPH radical without antioxidant was also measured as blank. All the determinations were performed in triplicate and ascorbic acid was used as positive reference. The capability of radical scavenging activity (*RSA*) % of the target compounds **2a-d** and **3a-d** was calculated by the equation: (RSA % = $\frac{A\,blank - A\,sample}{A\,balnk} \times 100$); where $A\,blank$ is the absorbance of (DPPH without an antioxidant) and $A\,sample$ is the absorbance of (DPPH + the tested sample). A calibration curve was plotted with % DPPH scavenged versus concentration of standard antioxidant ascorbic acid AA.

Antibacterial assay: The antibacterial activity of the synthesized compounds **2a-d** and **3a-d** were screened against the negative bacterial strains of *Helicobacter Pylori*, *Klebsiella pneumonia*, *Escherichia coli* O157 and the positive bacterial strain of *Staphylococcus aureus* using by well diffusion method. Practically, the nutrient agar and the nutrient broth cultures were prepared according to the manufactures' instructions, which were then incubated at 37 °C. After incubation for the required time, a suspension (50 µL) of each bacterium was added to the nutrient agar dishes. Using a sterilized glass tube, 5.0 mm cups were cut in the nutrient agar. Each cup in the agar well-received 30 µL of 1.0 mg/mL of the tested compounds in DMSO. The plates were incubated at 37 °C for 24 hours. Antibacterial activity was evaluated by measuring the inhibition zone against the tested organism and compared with tetracycline as the standard drug.

RESULTS AND DISCUSSION

Chemistry: In the current work, a combination of 1,2,3-triazole ring with 1,2,4-triazole ring system in one molecule was designed and achieved via a multi-step, versatile and efficient synthetic route as outlined in Scheme 1.



Scheme 1: i) Ethylacetoacetate, Et_3N, DMF; ii) hydrazine hydrate, ethanol; iii) PhSCN, ethanol, reflux; iv) NaOH (2.0 N) reflux.

The key starting materials 5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide derivatives **1a-d** were synthesized via two steps as described in the literatures [27][28]. In the current work, a series of *p*-substituted phenyl azide was used to investigate the effects of a structural variation of the substituent group on the chemical and biological activities of the target compounds. Reaction of compounds **1a-d** with phenyl isothiocyanate in ethanol under refluxing gave 2-(5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbonyl)-*N*-phenylhydrazinecarbothioamides derivatives **2a-d**. The structure of compounds **2a-d** was confirmed by appropriate spectroscopic methods such as FT-IR, ^{1}HNMR and mass spectroscopy. Mainly, along with the disappearance of the absorption band of the amino group (-NH_2) of the hydrazide group, FI-IR spectra showed the appearance of the stretching frequency of the formed (C=S) group at 1317-1321 cm^{-1}. In addition, their ^{1}HNMR spectra showed that all the signals are belonging to the starting materials combined with the correct integration of signals of the products. Thus, new single peak with two protons appeared at 7.5–7.8 ppm can be imputed to protons of (-NHCSNH-) group. Additional signals belonging to phenyl rings and CH_3 group were observed at their expected regions. Cyclization of compounds **2a-d** in the presence of an aqueous solution of NaOH (2.0 N) led to construct the 1,2,4-triazole ring system to obtain the target 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol derivatives **3a-d**. Clearly, FT-IR spectra showed the disappearance the absorption band of the carbonyl amide group (C=O), thiocarbonyl group (C=S) and three -NH group. Moreover, new absorption band was appeared 2741-2765 cm^{-1} that can be imputed to the thiol (SH) group attached to the formed 1,2,4-triazole ring. ^{1}HNMR spectra that were recorded for compounds **3a-d** displayed the appearance the signal belong to thiol group (SH) at 14.29-14.33 ppm associated with absence of the signals belong to protons of -NH groups. ^{13}C-NMR spectra indicates the appearance of two signals at 164-169 and 182-183 ppm to indicate forming new chemical environments of carbon in (-N=C-) and (HS-C=N) group, respectively to confirm formation of 1,2,4-triazle ring. Furthermore, GC-MS spectra showed that the calculated values of the ratio m/z of the final products being almost identical to the measured values.

Antioxidant assay: Although several methods are available to evaluate the antioxidant activity of antioxidant agents, DPPH is the common and fast method [29] [30]. In this method, the deep purple color solution of DPPH has a strong absorption at 515-520 nm and turns yellow color in the presence of an antioxidant which reacts with free radicals of 2,2-diphenyl-1-picrylhydrazyl (DPPH) by pairing the nitrogen centered single electron in DPPH with a hydrogen atom or by electronic donation. Thus, the reduction of DPPH absorption at 517 nm represents the ability of antioxidants to scavenge free radicals. In the current work, the free radical scavenging activity of the synthesized compounds **2a-d** and **3a-d** was achieved against the stable free radicals of (DPPH) and compared with ascorbic acid (AA) as a standard antioxidant agent. For more investigation, the antioxidant activity of the synthesized compounds **2a-d** and **3a-d** was evaluated in five different concentrations (12.5, 25, 50, 100 and 200 µg/mL) of each compound to determine the minimum active concentration. Based on the experimental results, compounds **3a-d** displayed very close a higher antioxidant activity against the free radicals of DPPH than their precursors **2a-d** and their values very close to the values belong to ascorbic acid as a standard antioxidant. In addition, it was noticed that antioxidant capacity is increased and the concentration as summarized in Figure 2.

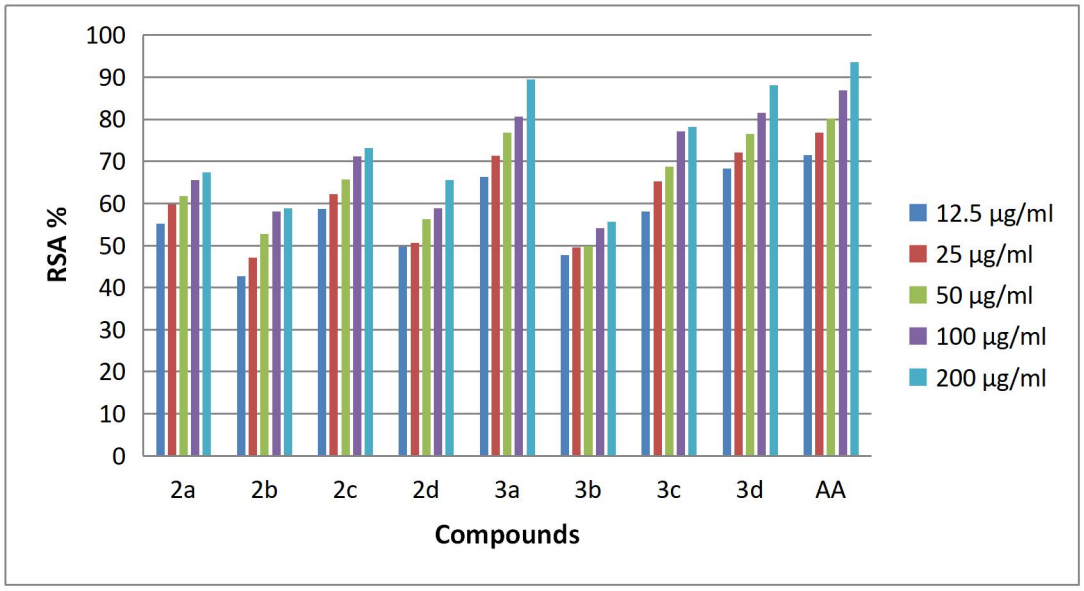


Figure 2: Antioxidant activity of DPPH scavenger radical for compounds **2a-d** and **3a-d**.

Based on structure-antioxidant activity relationship, activity was associated with the type of substituent, it was found that compound **3a, 3c** and **3d** displayed very close values of antioxidants. In addition, compound **3a** where there is substituted group attached to the phenyl group displayed an antioxidant activity very close to compound **3d**. In general, the antioxidant activity of 5-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)-4-phenyl-4H-1,2,4-triazole-3-thiol derivatives **3a-d** can be demonstrated by the presence of the thiourea segment (C=S) which illustrates the stability of nitrogen atoms as free radicals by conjugation further to the association between the free radicals of the nitrogen atom and the aromatic ring π electrons. Interestingly, the results indicated that the combination of 1,2,3-triazole and 1,2,4-triazole structures led to improve the antioxidant activity of compounds **3a-d** in spite of compounds **2a-d** containing carbohydrazidecarbothioamide (C=ONHNHC=SNH-Ph) that can be considered as a strong scavenger group for free radicals.

Antibacterial assay: The antibacterial action of the newly synthesized compounds **3a-d** and its precursors **2a-d** were screened for its *in vitro* antibacterial activity by determining the minimum inhibiton zone using well diffusion method against the Gram-negative strains *Helicobacter Pylori*, *Klebsiella pneumonia*, *Escherichia coli* O157 and the Gram-positive strain *Staphylococcus aureus via* comparing with tetracycline as a standard antibiotic. In general, the results showed that the combination of 1,2,4-traizole ring with 1,2,3-triaozle ring improved the antibacterial activity of compounds **3a-d** compered to their precursors **2a-d** as summarized in Table 1. The optimum activity was obtained with compound **3a** against all tested bacterial strains where the phenyl group attached to 1,2,3-triaozle ring system is not substituted. Although compounds **3b** and **3c** displayed an activity against the tested strain of *K. pneumonia* and the positive *strain* of *S. aureau*s, they were not active against the tested strain of *Helicobacter Pylori* and *Escherichia coli* O157. In spite of, compound **3d** is not active towards the tested strain of *K. pneumonia*, it displayed a moderate to good antibacterial activity against the other tested strains of bacteria.

Table 1. Antibacterial Activity of the synthesized compounds **2a–d** and **3a–d**.

Zone of inhibition (mm)				
Gram-positive Bacterial strain	Gram-negative Bacterial strains			
S. aureaus	E. Coli	K. pneumonia	H. pylori	No.
8	-	10	-a	2a
-	-	7	-	2b
-	-	8	-	2c
9	-	-	-	2d
12	10	10	13	3a
8	-	10	-	3b
9	-	12	-	3c
10	8	-	7	3d
14	20	12	14	Control b
-	-	-	-	Control c

[a] (-) Inactive (no inhibition zone)
[b] Tetracycline (positive control)
[c] DMSO (negative control)

CONCLUSIONS

A combination of 1,2,3-triazole and 1,2,3-triazole ring systems was achieved a multiple-step synthetic pathway to obtain compounds **3a-d**. Furthermore, their antioxidant and anti-bacterial activities were also elevated. All compounds **3a-d** displayed a promising activity as antioxidants agent

against the stable free radicals of DPPH. The antibacterial tests indicated that only compound **3a** showed a an activity against all the tested strains of bacteria, while the other compounds displayed an activity ranged from weak to good.

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