Canadian Chemical Transactions Year 2015 | Volume 3 | Issue 1 | Page 108-117

Research Article

DOI:10.13179/canchemtrans.2015.03.01.0173

Synthesis of New 1,2,4-Triazole Derivatives via 1,3-Dipolar Cycloaddition Reaction of Nitrilimines with Hydrazones

Hany M. Dalloul*

Chemistry Department, Faculty of Applied Science, Al-Aqsa University of Gaza, P. O. Box 4051, Gaza 76888, Palestine

Corresponding Author: Email: hmdalloul@yahoo.com

Received: *February 13, 2015* ***Revised:*** *March 18, 2015* ***Accepted:*** *March 20, 2015* ***Published:*** *March 20, 2015*

Abstract: A new series of 1,2,4-triazole derivatives (**4a-j, 6a-j**) have been synthesized by the 1,3-dipolar cycloaddition of a suitable nitrilimines **2** to pyruvaldehyde (2-oxopropanal) hydrazones having (COPh, COOMe, COOEt, Me/Me and Me/Ph) **3** and **5**. Both analytical and spectroscopical data of all the synthesized compounds are in full agreement with the proposed structures. The microbial features of the synthesized compounds were studied by a known method.

Keywords: nitrilimines, 1,3-dipolar cycloaddition, hydrazonoyl halide, pyruvaldehyde hydrazones, 4,5-dihydro-1,2,4-triazoles.

1. INTRODUCTION

There has been considerable interest in the development of nitrogen containing heterocyclic compounds in medicinal chemistry and pharmaceutical communities as these molecules have potent biological activities. Among them, azole derivatives are known to exhibit various pharmacological properties such as antifungal [1], antibacterial [2], anticonvulsant, antiviral, anti-inflammatory, anti-HIV [3], analgesic and antimalarial [4]. The azole derivatives, (e.g. imidazoles and triazoles) inhibit the biosynthesis of fungal sterols, through the inhibition of lanosterol 14 α-demethylase, are commonly used as first line drugs to treat Candida infections [5]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs, including H1/H2 histamine receptor blockers, CNS stimulants, anti-anxiety agents, and sedatives [6]. 1,2,4-Triazoles and their derivatives constitute an important class of organic compounds with diverse agricultural, industrial and biological activities [7-9] including anti-microbial [10,11] sedative, anticonvulsant [12], anti-HIV, antiviral, antifungal, antipro-liferative [13-15] and anti-inflammatory properties [16]. The synthesis of compounds containing 1,2,4-triazole rings in their structure has attracted widespread attention. 1,3-Dipolar cycloaddition is one of the most versatile methods for the construction of five-membered heterocycles [17,18]. Recently, we have described a versatile and efficient one-pot synthesis of dispiro-heterocycles containing 1,2,4-triazole moieties utilizing available keto oximes, hydrazones and hydrazonoyl halides [19].

Keeping this observation in view and in continuation of our study on the synthesis of biologically active nitrogen containing heterocycles [20,21], this paper describes the synthesis of a series of some new

substituted 1,2,4-triazoles via reaction of available nitrilimines **2** with different pyruvaldehyde hydrazones **3** and **5**, in anticipation of expected interesting biological activities.

2. EXPERIMENTAL SECTION

2.1 Instruments and reagents

Melting points were determined on an A. Krüss Melting Point Meter and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from internal TMS. Electron impact (EI) mass spectra were run on Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analysis was performed at the Microanalytical Center of Cairo University, Egypt.

The hydrazonoyl halides **1** [22,23] and pyruvaldehyde hydrazones **3** and **5** [24] were prepared according to literature procedures. Pyruvaldehyde, tetrahydrofuran (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

2.2 Reaction of nitrilimine 2 with pyruvaldehyde hydrazones 3 (general procedure)

Triethylamine (5g, 5 mmol) was added to the stirred mixture of pyruvaldehyde hydrazones **3** (7.5-10 mmol) and the appropriate hydrazonoyl halides **1** (5 mmol) in dioxane (50 mL) at room temperature and stirring was continued for 12-16h or refluxed for 2-4h. The precipitated salt was filtered off and the solvent was then evaporated. The solvent was then evaporated under reduced pressure and the residual solid was washed with water several times. The crude solid product was then collected and recrystallized from ethanol or methanol to give the desired compounds **4a-j** and **5a,b**. The following compounds were synthesized using this method:

4-Benzoylamino-3,5-diacetyl-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (4a):
Yield 64%; m.p. 163-165^{o}C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.70 (1H, s, NH), 7.76-7.14 (10H, m, arom. H), 4.61 (1H, s, C5-H), 2.61-2.58 (6H, s, 2COCH$_3$); ^{13}C NMR (DMSO-d_6) δ/ppm 193.6, 193.4 (2C=O acetyl), 168.8 (N-C=O), 147.4 (C=N), 143.7-117.9 (8 arom. C.), 85.6 (C-5), 24.2, 23.98 (2CH$_3$); IR (KBr) ν/cm^{-1} 3256 (NH), 1695, 1690 (2C=O), 1676 (N-C=O), 1622 (C=N); MS: m/z = 350 [M^{+}]; Analysis (% Calculated/ found) for $C_{19}H_{18}N_4O_3$ (Mw 350.38) C: 65.13/65.45, H: 5.18/4.90, N: 15.99/16.15.

1-(4-Chlorophenyl)-3,5-diacetyl-4-ethoxycarbonylamino-4,5-dihydro-1H-1,2,4-triazole (4b): Yield 65%; m.p. 146-148^{o}C; ^{1}H NMR (DMSO-d_6) δ/ppm 6.94 (1H, s, NH), 7.39-7.17 (4H, m, arom. H), 4.62 (1H, s, C5- H), 2.69 (2H, q, J 7.5, CH$_2$), 2.60-2.57 (6H, s, 2COCH$_3$), 1.90 (3H, s, CH$_3$), 1.08 (3H, t, J 7.5, CH$_3$); ^{13}C NMR (DMSO-d_6) δ/ppm 193.3, 193.1 (2C=O acetyl), 158.1 (O-C=O), 147.5 (C=N), 143.4-121.3 (4 arom. C.), 85.6 (C-5), 63.4 (CH$_2$), 24.2, 24.0 (2CH$_3$ acetyl), 15.1 (CH$_3$ ethyl); IR (KBr) ν/cm^{-1} 3255 (NH), 1730 (O-C=O), 1694, 1689 (2C=O), 1629 (C=N); MS: m/z = 352/354 [M^{+}]; Analysis (% Calculated/ found) for $C_{15}H_{17}ClN_4O_4$ (Mw 352.78) C: 51.07/50.85, H: 4.86/4.70, N: 15.88/16.05.

1-(4-Chlorophenyl)-3,5-diacetyl-4-methoxycarbonylamino-4,5-dihydro-1H-1,2,4-triazole (4c): Yield 70%; m.p. 152-154^{o}C; ^{1}H NMR (DMSO-d_6) δ/ppm 6.91 (1H, s, NH), 7.30-7.12 (4H, m, arom. H), 4.62 (1H, s, C5- H), 3.68 (3H, s, OCH$_3$), 2.61-2.58 (6H, s, 2COCH$_3$), 1.91 (3H, s, CH3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.8, 193.6 (2C=O acetyl), 158.1 (O-C=O), 147.3 (C=N), 142.9-120.9 (4 arom. C.), 85.7 (C-5), 53.6 (OCH$_3$), 24.1, 23.9 (2CH$_3$); IR (KBr) ν/cm^{-1} 3275 (NH), 1735 (O-C=O), 1695, 1690 (2C=O), 1626 (C=N); MS: m/z = 338/340 [M^{+}]; Analysis (% Calculated/ found) for $C_{14}H_{15}ClN_4O_4$ (Mw 338.75) C: 49.64/49.40, H: 4.46/4.60, N: 16.54/16.40.

5-Acetyl-3-benzoyl-4-benzoylamino-1-(4-chlorophenyl)- 4,5-dihydro-1H-1,2,4-triazole (4d): Yield 56%; m.p. 199-201°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.56 (1H, s, NH), 8.12-7.15 (14H, m, arom. H), 4.62 (1H, s, C5-H), 2.56 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.6 (C=O acetyl), 184.3 (C=O benzoyl), 168.8 (N-C=O), 147.1 (C=N), 141.3-118.7 (8 arom. C.), 84.9 (C-5), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3257 (NH), 1692 (C=O), 1673 (N-C=O), 1656 (C=O), 1612 (C=N); MS: m/z = 446/448 [M$^+$]; Analysis (% Calculated/ found) for $C_{24}H_{19}ClN_4O_3$ (Mw 446.90) C: 64.50/64.25, H: 4.29/4.45, N: 12.54/12.40.

5-Acetyl-3-carbanilino-4-methoxycarbonylamino-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (4e): Yield 56%; m.p. 189-191°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.43 (1H, s, NH), 8.12-7.15 (10H, m, arom. H), 6.91 (1H, s, NH), 4.62 (1H, s, C5-H), 3.66 (3H, s, OCH_3), 2.64 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.4 (C=O acetyl), 184.3 (C=O benzoyl), 168.8 (N-C=O), 147.1 (C=N), 141.3-118.7 (8 arom. C.), 85.5 (C-5), 53.4 (OCH_3), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3362, 3257 (2NH), 1692 (C=O), 1673 (N-C=O), 1656 (C=O), 1612 (C=N); MS: m/z = 381 [M$^+$]; Analysis (% Calculated/ found) for $C_{19}H_{19}N_5O_4$ (Mw 381.39) C: 59.84/60.05, H: 5.02/4.90, N: 18.36/18.45.

5-Acetyl-1-(4-bromophenyl)-4-benzoylamino-3-carbanilino-4,5-dihydro-1H-1,2,4-triazole (4f): Yield 74%; m.p. 204-206°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.46 (1H, s, NH), 9.63 (1H, s, NH), 7.76-7.21 (14H, m, arom. H), 4.65 (1H, s, C5-H), 2.62 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.8 (C=O acetyl), 168.5 (N-C=O), 166.4 (PhNH-C=O), 147.3 (C=N), 143.1-120.7 (12 arom. C.), 85.3 (C-5), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3365, 3270 (2NH), 1691 (C=O), 1675 (N-C=O), 1650 (C=O), 1619 (C=N); MS: m/z = 506/508 [M$^+$]; Analysis (% Calculated/ found) for $C_{24}H_{20}BrN_5O_3$ (Mw 506.36) C: 56.93/57.20, H: 3.98/4.15, N: 13.83/13.70.

5-Acetyl-4-benzoylamino-3-carbanilino-1-(4-fluorophenyl)-4,5-dihydro-1H-1,2,4-triazole (4g): Yield 72%; m.p. 216-218°C; ^{1}H NMR (DMSO-d_6) δ/ppm 10.71 (1H, s, NH), 9.72 (1H, s, NH), 7.76-7.16 (14H, m, arom. H), 4.64 (1H, s, C5-H), 2.63 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.6 (C=O acetyl), 168.8 (N-C=O), 166.7 (PhNH-C=O), 147.5 (C=N), 143.4-115.7 (12 arom. C.), 85.2 (C-5), 24.5 (CH_3); IR (KBr) ν 3360, 3258 (NH), 1691 (C=O), 1678 (N-C=O), 1655 (C=O), 1622 (C=N); MS: m/z = 445/447 [M$^+$]; Analysis (% Calculated/ found) for $C_{24}H_{20}FN_5O_3$ (Mw 445.46) C: 64.71/64.45, H: 4.53/4.70, N: 15.72/15.55.

5-Acetyl-4-benzoylamino-1-(4-clorophenyl)-3-(2-furoyl)-4,5-dihydro-1H-1,2,4-triazole (4h):
Yield 65%; m.p. 165-167°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.55 (1H, s, NH), 8.31-7.20 (12H, m, arom. H), 4.54 (1H, s, C5-H), 2.56 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.5 (C=O acetyl), 173.7 (C=O furoyl), 169.0 (N-C=O), 146.8 (C=N), 144.4-115.4 (12 arom. C.), 84.6 (C-5), 24.1 (CH_3); IR (KBr) ν/cm^{-1} 3368, 3272 (NH), 1689 (C=O), 1676 (N-C=O), 1660 (C=O), 1609 (C=N); MS: m/z = 436/438 [M$^+$]; Analysis (% Calculated/ found) for $C_{22}H_{17}ClN_4O_4$ (Mw 436.86) C: 60.46/60.25, H: 3.92/4.10, N: 12.82/13.70.

5-Acetyl-4-benzoylamino-1-(4-clorophenyl)-3-(2-thenoyl)-4,5-dihydro-1H-1,2,4-triazole (4i): Yield 63%; m.p. 176-178°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.53 (1H, s, NH), 8.26-7.15 (12H, m, arom. H), 4.62 (1H, s, C5-H), 2.58 (3H, s, $COCH_3$); ^{13}C NMR (DMSO-d_6) δ/ppm 193.3 (C=O acetyl), 174.6 (C=O thenoyl), 168.7 (N-C=O), 146.6 (C=N), 144.6-114.9 (12 arom. C.), 84.7 (C-5), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 3275 (NH), 1687 (C=O), 1678 (N-C=O), 1665 (C=O), 1612 (C=N); MS: m/z = 452/454 [M$^+$]; Analysis (% Calculated/ found) for $C_{22}H_{17}ClN_4O_3S$ (Mw 452.92) C: 58.34/58.60, H: 3.78/3.65, N: 12.37/12.50.

5-Acetyl-4-benzoylamino-1-(4-clorophenyl)-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (4j): Yield 58%; m.p. 186-188°C; ^{1}H NMR (DMSO-d_6) δ/ppm 9.60 (1H, s, NH), 8.76-7.24 (16H, m, arom. H), 4.64 (1H, s, C5-H), 2.56 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.8 (C=O acetyl), 184.5 (C=O naphthoyl), 168.8 (N-C=O), 146.8 (C=N), 141.4-119.3 (18 arom. C.), 85.7 (C-5), 24.2 (CH_3); IR (KBr)

ν/cm^{-1} 3245 (NH), 1686 (C=O), 1675 (N-C=O), 1650 (C=O), 1621 (C=N); MS: m/z = 496/498 [M$^+$]; Analysis (% Calculated/ found) for $C_{28}H_{21}ClN_4O_3$ (Mw 496.96) C: 67.67/67.45, H: 4.26/4.45, N: 11.27/11.15.

1-(4-Chlorophenyl)-3,5-diacetyl-1,2,4-triazole (5a):

Yield 75%; m.p. 196-198^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 7.39-7.17 (4H, m, arom. H), 2.60-2.57 (6H, s, 2COCH$_3$); ^{13}C NMR (DMSO-d6) δ/ppm 193.3, 193.1 (2C=O acetyl), 154.6, 152.4 (2C=N), 143.4-121.3 (4 arom. C.), 24.2, 24.0 (2CH$_3$); IR (KBr) ν/cm^{-1} 1695, 1691 (2C=O), 1635, 1629 (2C=N); MS: m/z = 352/354 [M$^+$]; Analysis (% Calculated/ found) for $C_{15}H_{17}ClN_4O_4$ (Mw 352.78) C: 51.07/50.85, H: 4.86/4.70, N: 15.88/16.05.

5-Acetyl-3-carbanilino-1-phenyl-1,2,4-triazole (5b):

Yield 76%; m.p. 209-211^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 10.21 (1H, s, NH), 8.12-7.15 (10H, m, arom. H), 2.64 (3H, s, CH$_3$); ^{13}C NMR (DMSO-d6) δ/ppm 193.4 (C=O acetyl), 168.6 (C=O amide), 154.8, 152.3 (2C=N), 141.3-118.7 (8 arom. C.), 24.2 (CH$_3$); IR (KBr) ν/cm-1 3345 (NH), 1694 (C=O), 1655 (C=O), 1632, 1612 (2C=N); MS: m/z = 381 [M$^+$]; Analysis (% Calculated/ found) for $C_{19}H_{19}N_5O_4$ (Mw 381.39) C: 59.84/60.05, H: 5.02/4.90, N: 18.36/18.45.

2.3 Reaction of nitrilimine 2 with pyruvaldehyde hydrazones 5 (general procedure)

Triethylamine (10 mmol) in THF (10 mL) was dropwise added to the stirred mixture of pyruvaldehyde hydrazones **3** (5 mmol) and the appropriate hydrazonoyl halides **1** (5 mmol) in THF (50 mL) at -5-0 ^{o}C. The reaction temperature was allowed to rise slowly to room temperature and stirring was continued for 4-6 hours. The precipitated salt was filtered off, and the solvent was then evaporated under reduced pressure. The residue was washed with water (2x25 mL), and in few cases the oily or gummy products were triturated with ethanol or methanol (10 mL). The crude solid product was collected and recrystallized from ethanol to give the desired compounds. The following compounds were synthesized using this method:

3,5-Diacetyl-4-dimethylamino-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (6a):

Yield 77%; m.p. 133-135^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 7.76-7.14 (4H, m, arom. H), 3.25 (6H, s, 2CH$_3$) 2.56-2.52 (6H, s, 2COCH$_3$), 4.92 (1H, s, C$_5$-H); ^{13}C NMR (DMSO-d$_6$) δ/ppm 193.6, 193.4 (2C=O), 147.8 (C=N), 142.7-117.9 (4 arom. C.), 85.8 (C-5), 43.2 (2CH$_3$), 24.2, 23.9 (2CH$_3$ acetyl); IR (KBr) ν/cm^{-1} 1696, 1694 (2C=O), 1628 (C=N); MS: m/z = 274 [M$^+$]; Analysis (% Calculated/ found) for $C_{14}H_{18}N_4O_2$ (Mw 274.33) C: 61.30/61.45, H: 6.61/6.77, N: 20.42/20.25.

1-(4-Chlorophenyl)-3,5-diacetyl-4-dimethylamino-4,5-dihydro-1H-1,2,4-triazole (6b):

Yield 75%; m.p. 141-143^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 8.62 (1H, s, H-C=O), 7.39-7.17 (4H, m, arom. H), 3.25 (6H, s, 2CH$_3$), 2.54 (3H, s, COCH$_3$), 1.90 (3H, s, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm 193.3, 193.0 (2C=O), 148.0 (C=N), 142.4-120.9 (4 arom. C.), 85.3 (C-5), 43.2 (2NCH$_3$), 24.1, 23.8 (2CH$_3$ acetyl); IR (KBr) ν/cm^{-1} 1695, 1692 (2C=O), 1630 (C=N); MS: m/z = 308/310 [M$^+$]; Analysis (% Calculated/ found) for $C_{14}H_{17}ClN_4O_2$ (Mw 308.77) C: 54.46/54.75, H: 5.55/5.38, N: 18.15/18.05.

1-(4-Chlorophenyl)-3,5-diacetyl-4-methylphenylamino-4,5-dihydro-1H-1,2,4-triazole (6c):

Yield 76%; m.p. 122-124^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 8.60 (1H, s, H-C=O), 7.30-7.12 (9H, m, arom. H), 3.18 (3H, s, CH$_3$), 2.56 (3H, s, COCH$_3$), 1.91 (3H, s, CH$_3$); ^{13}C NMR (DMSO-d$_6$) δ/ppm 193.8, 193.6 (2C=O), 147.9 (C=N), 142.6-120.5 (8 arom. C.), 85.6 (C-5), 43.4 (NCH$_3$), 24.3, 23.9 (2CH$_3$ acetyl); IR (KBr) ν/cm^{-1} 1695, 1693 (2C=O), 1628 (C=N); MS: m/z = 370/372 [M$^+$]; Analysis (% Calculated/ found) for $C_{19}H_{19}ClN_4O_2$ (Mw 370.84) C: 61.54/61.27, H: 5.16/4.98, N: 15.11/14.95.

5-Acetyl-3-benzoyl-1-(4-chlorophenyl)-4-dimethylamino-4,5-dihydro-1H-1,2,4-triazole (6d): Yield 71%; m.p. 159-161^{o}C; ^{1}H NMR (DMSO-d$_6$) δ/ppm 8.52 (1H, s, H-C=O), 8.12-7.15 (19H, m, arom. H),

3.21 (6H, s, $2CH_3$), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.8 (C=O acetyl), 184.3 (C=O benzoyl), 147.1 (C=N), 141.3-118.7 (8 arom. C.), 85.1 (C-5), 43.5 ($2NCH_3$), 24.2 (CH_3); IR (KBr) ν/cm^{-1} 1693 (C=O), 1660 (C=O), 1623 (C=N); MS: m/z = 370/372 [M^+]; Analysis (% Calculated/ found) for $C_{19}H_{19}ClN_4O_2$ (Mw 370.84) C: 61.54/61.35, H: 5.16/5.30, N: 15.11/15.25.

5-Acetyl-3-carbanilino-4-dimethylamino-1-phenyl-4,5-dihydro-1H-1,2,4-triazole (6e):
Yield 66%; m.p. 189-181°C; ^1H NMR (DMSO-d_6) δ/ppm 10.43 (1H, s, NH), 8.55 (1H, s, H-C=O), 8.12-7.15 (10H, m, arom. H), 3.12 (6H, s, $2CH_3$), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.6 (C=O acetyl), 167.8 (N-C=O), 147.1 (C=N), 142.3-118.7 (8 arom. C.), 84.7 (C-5), 43.0 ($2NCH_3$), 24.4 (CH_3); IR (KBr) ν/cm^{-1} 1687 (C=O), 1655 (C=O), 1622 (C=N); MS: m/z = 351 [M^+]; Analysis (% Calculated/ found) for $C_{19}H_{21}N_5O_2$ (Mw 351.41) C: 64.94/65.22, H: 6.02/5.92, N: 19.93/20.05.

5-Acetyl-1-(4-bromophenyl)-3-carbanilino-4-methylphenylamino-4,5-dihydro-1H-1,2,4-triazole (6f):
Yield 64%; m.p. 194-196°C; ^1H NMR (DMSO-d_6) δ/ppm 10.42 (1H, s, NH), 8.52 (1H, s, H-C=O), 7.76-7.21 (9H, m, arom. H), 3.14 (6H, s, $2CH_3$), 1.87(3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.6 (C=O acetyl), 162.6 (C=O), 147.6 (C=N), 143.1-120.9 (8 arom. C.), 84.8 (C-5), 43.1 (NCH_3), 24.5 (CH_3); IR (KBr) ν/cm^{-1} 1689 (C=O), 1650 (C=O), 1629 (C=N); MS: m/z = 392/394 [M^+]; Analysis (% Calculated/ found) for $C_{24}H_{22}BrN_5O_2$ (Mw 492.38) C: 58.55/58.37, H: 4.50/4.35, N: 14.22/14.30.

5-Acetyl-3-carbanilino-1-(4-flourophenyl)-4-methylphenylamino-4,5-dihydro-1H-1,2,4-triazole (6g):
Yield 68%; m.p. 176-178°C; ^1H NMR (DMSO-d_6) δ/ppm 10.35 (1H, s, NH), 8.57 (1H, s, H-C=O), 7.76-7.16 (14H, m, arom. H), 3.20 (3H, s, CH_3), 1.93 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 192.8 (C=O acetyl), 168.8 (N-C=O), 166.7 (PhNH-C=O), 148.7 (C=N), 143.8-116.1 (12 arom. C.), 84.8 (C-5), 43.7 (NCH_3), 24.6 (CH_3); IR (KBr) ν/cm^{-1} 1688 (C=O), 1650 (C=O), 1626 (C=N); MS: m/z = 431/433 [M^+]; Analysis (% Calculated/ found) for $C_{24}H_{22}FN_5O_2$ (Mw 431.47) C: 66.81/66.65, H: 5.14/5.05, N: 16.23/16.34.

5-Acetyl-1-(4-chlorophenyl)-4-dimethylamino-3-(2-furoyl)-4,5-dihydro-1H-1,2,4-triazole (6h): Yield 76%; m.p. 145-147°C; ^1H NMR (DMSO-d_6) δ/ppm 8.61 (1H, s, H-C=O), 8.31-7.20 (7H, m, arom. H), 3.28 (6H, s, $2CH_3$), 1.86 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.4 (C=O acetyl), 174.6 (C=O furoyl), 147.8 (C=N), 144.9-115.4 (8 arom. C.), 85.7 (C-5), 43.0 ($2NCH_3$), 24.7 (CH_3); IR (KBr) ν/cm^{-1} 1694 (C=O), 1655 (C=O), 1619 (C=N); MS: m/z = 360/362 [M^+]; Analysis (% Calculated/ found) for $C_{17}H_{17}ClN_4O_3$ (Mw 360.80) C: 56.59/56.33, H: 4.75/4.63, N: 15.53/15.70.

5-Acetyl-1-(4-chlorophenyl)-4-dimethylamino-3-(2-thenoyl)- 4,5-dihydro-1H-1,2,4-triazole (6i): Yield 73%; m.p. 156-158°C; ^1H NMR (DMSO-d_6) δ/ppm 8.58 (1H, s, H-C=O), 8.26-7.15 (7H, m, arom. H), 3.25 (6H, s, $2CH_3$), 1.88 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.2 (C=O acetyl), 176.2 (C=O thenoyl), 147.6 (C=N), 144.6-115.3 (8 arom. C.), 85.4 (C-5), 43.2 ($2NCH_3$), 24.8 (CH_3); IR (KBr) ν/cm^{-1} 1694 (C=O), 1660 (C=O), 1620 (C=N); MS: m/z = 376/378 [M^+]; Analysis (% Calculated/ found) for $C_{17}H_{17}ClN_4O_2S$ (Mw 376.87) C: 54.18/54.40, H: 4.55/4.65, N: 14.87/14.75.

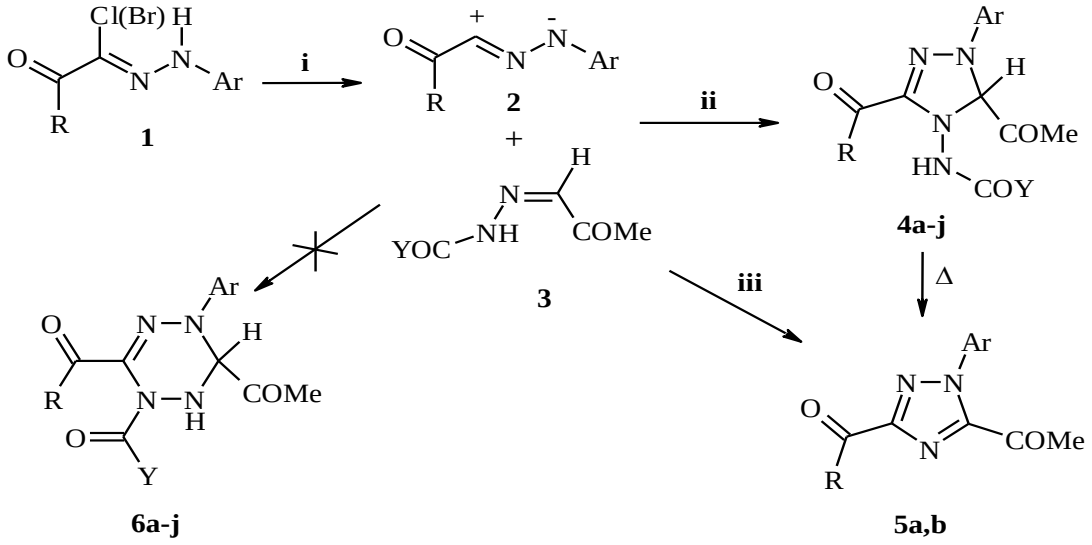
5-Acetyl-1-(4-chlorophenyl)-4-methylphenylamino-3-(2-naphthoyl)-4,5-dihydro-1H-1,2,4-triazole (6j):
Yield 68%; m.p. 202-204°C; ^1H NMR (DMSO-d_6) δ/ppm 8.60 (1H, s, H-C=O), 8.76-7.24 (16H, m, arom. H), 3.06 (3H, s, CH_3), 1.82 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ/ppm 193.6 (C=O acetyl), 183.9 (C=O naphthoyl), 146.8 (C=N), 142.4-120.3 (18 arom. C.), 84.7 (C-5), 42.9 (NCH_3), 24.8 (CH_3); IR (KBr) ν/cm^{-1} 1695 (C=O), 1645 (C=O), 1622 (C=N); MS: m/z = 482/486 [M^+]; Analysis (% Calculated/ found) for $C_{28}H_{23}ClN_4O_2$ (Mw 482.97) C: 69.63/69.40, H: 4.80/4.91, N: 11.60/11.48.

3. RESULTS AND DISCUSSION

3.1 Chemistry

1,3-Dipolar cycloaddition of nitrilimines 2, generated in situ from hydrazonoyl halides **1** in tetrahydrofuran or 1,4-dioxane in the presence of triethylamine, to 2-oxo-propanal hydrazones **3** (Y = COPh, COOMe, and COOEt) was carried out at room temperature for 12h, led to the formation of 4,5-dihydro-1,2,4-triazole derivatives **4a-j** as cycloaddition products rather than the cyclocondensation 1,2,4,5-tetrazines **6a-j** (Scheme 1). The later products **6a-j** were obtained from the reaction of hydrazonoyl halides with methyl hydrazones of aliphatic aldehydes and ketones [25]. This can be explained on the basis of the weak nucleophilicity of the nitrogen atom of the hydrazones carrying the electron withdrawing groups in comparison to that of the nitrogen atom carrying methyl group in methyl hydrazones. The purity of obtained compounds was controlled by TLC and elemental analyses. Both the analytical and spectral data (IR, ^{1}H NMR, ^{13}C NMR and mass spectra) of the synthesized dihydrotriazoles **4a-j** were in full agreement with the proposed structures and depicted in experimental section.

When the reaction was carried out under refluxing conditions the same dihydrotriazoles **4a,d,f-j** and aromatic triazoles **5a,b** were obtained (Scheme 1).

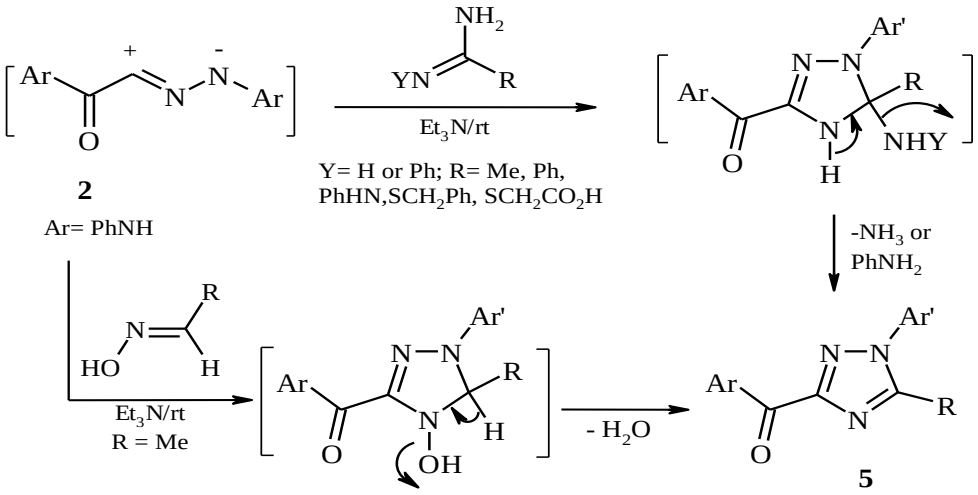


i) Et_3N, r.t.; **ii**) THFor Dioxane, r.t., 12h.; **iii**) Dioxane, Reflux, 2-4h.
Ar = 4-X-C_6H_4-
R/Y/X = **4a:** Me/Ph/H; **4b:** Me/OEt/Cl; **4c:**Me/OMe/Cl; **4d:** Ph/Ph/Cl;
4e: PhNH/OMe/H; **4f:** PhNH/Ph/Br;**4g:** PhNH/Ph/F;
4h: 2-C_4H_3O/Ph/Cl; **4i:** 2-C_4H_3S/Ph/Cl; **4j:** 2-$C_{10}H_7$/Ph/Cl;

Scheme 1. Synthetic pathway for the preparation of 1,2,4-triazoles **4a-j**

The formation of compounds **5a,b** involve the elimination of ethyl and methyl carbamate from dihydrotriazoles **4b,c,e** as shown in Scheme 1. It is worth mentioning that different aromatic triazoles were obtained from the reaction of similar nitrilimines with acetaldoxime, acetamidine, benzamidine, benzylthioformamidine, and guanidines through the elimination of water, ammonia or amine molecules as shown in Scheme 2 [16,26].

The electron impact (EI) mass spectra of dihydrotriazoles **4a-j** displayed the correct molecular ions in accordance with the suggested structures. Their IR spectra showed absorption bands in the region 3275-3245 cm^{-1}, 1695-1685 cm^{-1} and 1620-1610 cm^{-1} assignable to NH, acetyl and C=N groups, respectively. Their ^{1}H NMR spectra revealed, besides aromatic protons at 8.4-7.0 ppm and singlet signal at 5.9-5.8 ppm assigned to the proton at C-5 and singlet signal in the region 2.6-2.5 ppm assignable to acetyl protons. The detailed ^{1}H NMR data is shown in the experimental section. Their ^{13}C NMR spectra showed all the signals corresponding to the proposed structures, especially C-5 was found to resonate at about 85-84 ppm.



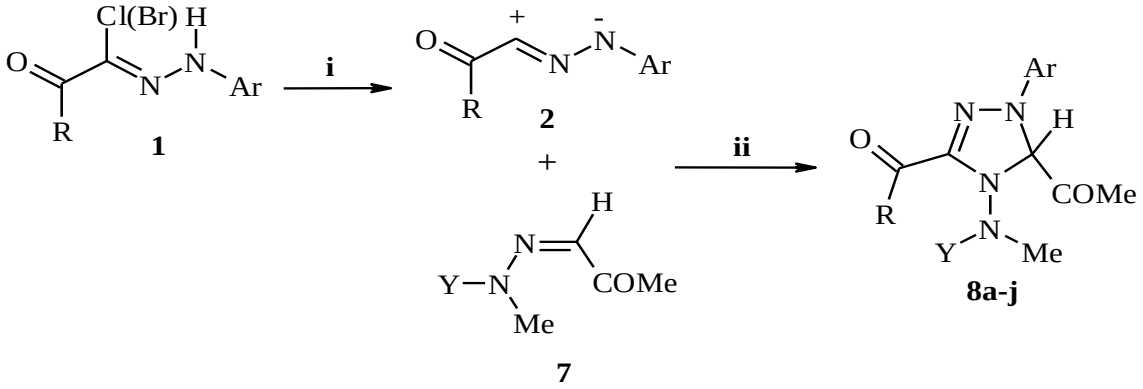
Scheme 2. Synthetic pathway of aromatic triazoles **5**

This is similar to reported values of carbon flanked by two nitrogen atoms in five-membered heterocycles [25-28], which provide strong evidence in support of the structures 4a-j rather than the six-membered heterocyclic structure 6a-j which is expected to have a C-6 signal at about 70-65 ppm. The complete 13C NMR data are presented in experimental section.

The structures of the triazole compounds **5a,b** were deduced from their elemental analyses and spectroscopic data. Their mass spectra displayed the correct molecular ion peaks and showed the disappearance of ethyl and methyl carbamate molecule. The IR spectra of all compounds confirm the absence of stretching NH band of dihydrotriazoles ring in the region 3260-3250 cm^{-1}, and display the characteristic stretching absorption band of the C=O bond of acetyl moieties near 1695 cm^{-1}. The ^{1}H NMR spectra don't display the signal due to NH triazole ring which appears in the spectra of 4,5-dihydrotriazoles **4b,c,e** at 6.90 ppm, and also, don't display the signal of C5-H which appear at 5.8 ppm. In addition, the signals of ethyl and methyl ester groups were disappeared. A characteristic singlet signal also appeared at 2.6-2.5 ppm due to acetyl protons. The ^{13}C NMR spectra exhibit a signal at about 152 ppm due to C=N formed and the C-5 signal of dihydrotriazoles at about 84 ppm was disappeared.

On the other hand, the reaction of the same nitrilimines **2** with 2-oxopropnal hydrazones **7** having N, N-dimethyl or N-methyl-N-phenyl substituents, under ambient temperature afford only one isolable product in each case. On the bases of their spectroscopical data, the structure of the reaction products were identified as 1,3,4,5-substituted-1,2,4-triazoles **8a-j** (Scheme 3) in good yields. The synthesized compounds **8a-j** gave satisfactory analysis for the proposed structures which are confirmed on the bases of their spectroscopical data. The electron impact (EI) mass spectra displayed the correct molecular ions (M^{+}) in accordance with the suggested structures. Their IR spectra showed absorption bands in the region

1695-1950 cm^{-1} assignable to acetyl and carbonyl group. The absorption band of C=N appeared in 1630-1620 cm^{-1} region. Their ^{1}H NMR spectrum revealed characteristic signals for the N-CH_3 at about δ 3.4-3.1 ppm in addition to the signals resulting from acetyl and aromatic hydrogens. The ^{13}C NMR spectrum exhibited the characteristic signals of the suggested structures. The signal for triazole carbon (C-5) appeared around δ 85 ppm. The signal at δ 37.8-37.2 ppm is attributed to the N-CH_3 carbon. The entire ^{13}C NMR data are presented in the experimental section.



i) Et_3N, r.t.; **ii**) THFor Dioxane, r.t., 12h.
Ar = 4-X-C_6H_4-
R/Y/X = **8a:** Me/Me/H; **8b:** Me/Me/Cl; **8c:**Me/Ph/Cl; **8d:** Ph/Me/Cl;
8e: PhNH/Me/H; **8f:** PhNH/Ph/Br;**8g:** PhNH/Ph/F;
8h: 2-C_4H_3O/Me/Cl; **8i:** 2-C_4H_3S/Me/Cl; **8j:** 2-$C_{10}H_7$/Ph/Cl;

Scheme 3. Synthetic pathway for the preparation of triazoles **8a-j.**

3.3 Antimicrobial activity

Some of the synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *Euterococci*, *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp*, *Proteus spp*, and fungi such as *Aspergillus niger*, *Candida albicans*, employing the nutrient agar disc diffusion method [29-30] at 10 mg/ml concentration in dimethyl formamide (DMF) by measuring the average diameter of the inhibition zone in mm. The results showed that all the tested compounds exhibited a marked degree of activity against bacteria and fungi compared with well-known antibacterial and antifungal substances such as tetracycline and fluconazole. According to National Committee for Clinical Laboratory Standards (NCCLS) [31], zones of inhibition for tetracycline and fluconazole < 14 mm were considered resistant, between 15 and 18 mm were considered weakly sensitive and > 19 mm were considered sensitive. Also, the results showed the degree of inhibition varied with the tested compounds.

4. CONCLUSION

In conclusion, the reaction of several nitrilimines with pyruvaldehyde hydrazones having electron withdrawing or electron releasing groups leads to formation of substituted 4,5-dihydro-1,2,4-triazoles **4,8** and aromatic triazoles **5**. Some of them proved to have potent antibacterial and antifungal activity. The results confirm that, the antimicrobial activity is strongly dependent on the nature of the substituents on triazole rings.

REFERENCES

[1] Aher, N. G., Pore, V. S., Mishra, N. N., Kumar, A., Shukla, P. K., Sharma, A., Bhat, M. K. Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. *Bioorg. Med. Chem. Lett.* **2009**, ***19***, 759-763.

[2] Mochalkin, I., Miller, J. R., Narasimhan, L., Thanabal, V., Erdman, P., Cox, P. B., Prasad, J. V., Lightle, S., Huband, M .D., Stover, C. K. *ACS Chem. Biol.* **2009**, *4*, 473-483

[3] Jordão, A. K., Ferreira, V. F., Souza, T. M., Faria, G. G., Machado, V., Abrantes, J. L., de Souza, M. C., Cunha, A. C. Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives. *Bioorg. Med. Chem.* **2011**, *19*, 1860-1865.

[4] Aher, N. G., Pore, V. S., Mishra, N. N., Kumar, A., Shukla, P. K., Sharma, A., Bhat, M. K. Synthesis and antifungal activity of 1,2,3-triazole containing fluconazole analogues. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 759-763.

[5] Agalave, S. G., Maujan, S. R., Pore, V,. S. Click Chemistry: 1,2,3-Triazoles as Pharmacophores. *Chem. Asian. J.* **2011**, *6*, 2696-2718.

[6] Whiting, M., Tripp, J. C., Lin, Y. C., Lindstrom, W., Olson, A .J., Elder, J. H., Sharpless, K. B., Fokin, V. V. Rapid Discovery and Structure−Activity Profiling of Novel Inhibitors of Human Immunodeficiency Virus Type 1 Protease Enabled by the Copper(I)-Catalyzed Synthesis of 1,2,3-Triazoles and Their Further Functionalization. *J. Med. Chem.***2006**, *4*, 7697-7710.

[7] Ikízler, A.; Gümüs, F.; Ozden, S.; Abbasoğlu, U., Biological activities of some 1,2,4-triazoles and 1,2,4-triazolin-5-ones. *Pharmazie* **1989**, *44*, 506-507.

[8] Vinícius, R.C.; Paula, A.A.; Helena, C.C.; Carlos, R.R.; Alessandro, K.J.; Vitor, F.F.; Maria, C.B.V.S.; Fernanda da, C.S.; Laura, A.M.; Thaisa, S.D.; Carla, C.; Eládio, F. S.; André, L. F.; Anna, C. C., Synthesis, biological, and theoretical evaluations of new 1,2,3-triazolesagainst the hemolytic profile of the Lachesis muta snake venom. *Bioorg. Med.Chem.* **2009**, *17*, 7429-7434.

[9] Prasad, A.; Ramalingam, R. J.; Rao, A. B.; Diwan, P. V.; Sattur, P. B., A convenient synthesis and biological activities of novel 6-aryl-3-(1,2,3,4-tetrahydroxybutan-1-yl)-7 H -1,2,4-triazolo-[3,4- b][1,3,4]thiadiazines. *Eur. J. Med. Chem.* **1989**, *24*, 199-201.

[10] El-masry, A. H.; Fahmy, H. H.; Ali, S. H.; Waheed, A., Synthesis and Antimicrobial Activity of Some New Benzimidazole Derivatives. *Molecules* **2000**, *5*, 1429-1438.

[11] Orabi, A.S.; Moneim, M. A.; El-Din Salem, E.; El-Din Abdel-Fattah, M., Synthesis and physicochemical studies of some antimicrobial active triazole metal complexes. *Polish J. Chem.* **2000**, *74*, 1675-1683.

[12] Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A., Synthesis and anticonvulsant activity of new 2-substituted-5- [2-(2-fluorophenoxy)phenyl]-1,3,4-oxadiazoles and 1,2,4-triazoles. *Bioorg. Med. Chem Lett.* **2004**, *14*, 6057-6059.

[13] George, T.; Mehta, D. V.; Tahilramani, R.; Davvid, J.; Talwalker, P. K., Synthesis of some s-triazoles with potential analgesic and antiinflammatory activities *J. Med. Chem.* **1971**, *14*, 335-338.

[14] Padwa, A., Intramolecular 1,3-Dipolar Cycloaddition. Trost, B. M., Flemin, I., Eds., Pergamon, Oxford, **1991**, Vol. 4, p 1069.

[15] Caramella, P.; Grunanger, P.; in 1,3-Dipolar Cycloaddition Chemistry; A. Padwa, Ed., Wiely Interscience, New York, **1984**, pp. 291-319.

[16] Dalloul, H. M., El-Abadla, N. S., Abu Samaha, A. S., Heterocyclic Synthesis Using Nitrilimines, Part 8: Synthesis of Aromatic 1,2,4-Triazoles. *J. Islamic Univ. (Ser. Nat. Stud. Eng.)* **2008**, 16, 87-95; Dalloul, H. M., Heterocyclic Synthesis Using Nitrilimines, Part 12: Synthesis and Bioactivity of 5-Carboxymethylthio-1,2,4-triazoles. *Synthetic Commun.* **2009**, 39(10), 1847-1856; Dalloul, H. M., Abu Samaha, A. S., Synthesis of nitrogen-containing dispiroheterocyles (II) using nitrilimines. *J. Serb. Chem. Soc.*, **2010**, *75* (*11*), 1473-1479.

[17] Demirbas, S. N., Ugurluoglu, R., Demirbas, A., Synthesis of 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro-1H-1,2,4-triazol-5-ones and 3-alkyl-4-alkylamino-4,5-dihydro-1H-1,2,4-triazol-5-ones as antitumor agents. *Bioorg. Med. Chem.*, **2002**, *10*, 3717-3723; Demirbas, S. N., Ugurluoglu, R., Synthesis of novel 4-alkylidene- and 4-alkylamino-5-oxo-4,5-dihydro-[1,2,4]triazole derivatives and investigation of their antitumor activities. *Turk. J.*

Chem., **2004**, *28*, 679-690; 559-571; Demirbas, S. N., Demirbas, A., Alpay-Karaoglu, S., Synthesis and biological activities of new 1,2,4-

triazol-3-one derivatives. *Russian J. Bioorg. Chem.*, **2005**, *31*, 430-440; Bayrak, H., Demirbas, A., Alpay-Karaoglu, S., Demirbas, N. Synthesis of some new 1,2,4-triazoles, their Mannich and Schiff bases and evaluation of their antimicrobial activities. *Eur. J. Med. Chem.*, **2009**, *44*, 1057-1066.

[18] Ikizler, A. A., Uzunali, E., Demirbas, A., Synthesis Of Some 1,2,4-Triazole Derivatives As Potential Antitumor Agents. *Indian J. Pharm. Sci.*, **2000**, *62(5)*, 371-375; Yuksek, H., Demirbas, A., Ikizler, A., Johansson, C. B., Celik, C., Ikizler, A.A., Synthesis and antibacterial activities of some 4,5-dihydro-1H-1,2,4-triazol-5-ones. *Arzneim. Forsh. Drug Res.*, **1997**, *47*, 405-409.

[19] Frohberg, P.; Drutkowski, G.; Wagner, C.; Synthesis and structural assignment of oxanilo-N-arylhydrazonoyl chlorides. *Eur. J. Org. Chem.* **2002**, 1654-1663.

[20] Hutt, M. P., Elstager, E. F., Werbet, L. M. 2-Phenyl-5-(trichloromethyl)-1,3,4-oxadiazoles, A new class of antimalarial substances. *J. Heterocycl. Chem.* **1970**, *7*, 511–518.

[21] Aoyama, Y., Yoshida, Y., Sato, R. Metabolism of 32-hydroxy-24,25-dihydrolanosterol by purified cytochrome P-45014DM from yeast. Evidence for contribution of the cytochrome to whole process of lanosterol 14 alpha-demethylation. *J. Biol. Chem.* **1984**, *259*, 1661–1666.

[22] Zhou, C. H., Wang, Y. Recent researches in triazole compounds as medicinal drugs. *Curr. Med. Chem.* **2012**, *19(2)*, 239-280.

[23] Shawali, A. S.; Hassaneen, H. M.; Shetta, A.; Osman, A.; Abdel-Galil, F.; Regioselectivity of reactions of furoyl-N-aryl nitrile imine with some dipolarophiles. *Heterocycles* **1982**, *19*, 57-62; A. M. Farag, M. S. Algharib, Org. Prep. Proced. Int. 1988, 20, 521-526; M. M. El-Abadelah, A. Q. Hussein, M. R. Kamal, K. H. Al-Adhami, Heterocycles from nitrile imines. Part I. 1,2,3,4-Tetrahydro-1,2,4,5-tetrazines. *Heterocycles* **1988**, *27*, 917-924.

[24] Begtrup, M.; Nytoft, H. P., Reactions of glyoxals with hydrazones: a new route to 4-hydroxypyrazoles. *J. Chem. Soc. Perkin Trans. I*, **1985**, 81-86.

[25] El-Sawi, E. A.: Awadallah, A. M.: Ferwanah, A. S.: Dalloul, H. M. Reaction of C-Aroyl-N-Aryl Nitrilimines with Selected Aliphatic Keto-Hydrazones and Keto-Methylhydrazones. *Asian J. Chem.* **2002**, *14*, 1225-1229.

[26] H.M. Dalloul, Heterocyclic synthesis using nitrilimines: Part 19. Synthesis of novel 1,3,5-trisubstituted-1,2,4-triazoles. *Arab. J. Chem.* **2014**, *7*, 604–608

[27] Awadallah, A. M.: El-Sawi, E. A.: Ferwanah, A. S.: Dalloul, H. M. 1,2,4-Triazoles from 1,3-Dipolar Cycloaddition Reaction of Nitrilimines with Aliphatic Ketohydrazones Carrying Electron Withdrawing Groups. *Asian J. Chem.* **2002**, *14*, 1230-1234.

[28] Ferwanah, A. S. 1,3-Dipolar Cycloaddition Reaction of C-Acetyl-N-arylnitrilimines with Selected Aliphatic Benzoylhydrazones. *Syn. Commun.*, **2003**, *33(2)*, 241-249.

[29] Collins, C. H., Lyne, P. M., Granga, J. M., *Microbiological Methods; 6th Edition*, Butterworths Co. Ltd., London, 1989, 410.

[30] Irob, O. N., Moo-Yung M., Anderson, W. A., Antimicrobial Activity of Annatto Extract. *Int J Pharm.*, **1996**, *34*, 87-90; Grayer, R. J., Harborne, J. B. A., A survey of antifungal compounds from higher plants, *Phytochemistry* **1994**, *37*, 19-42.

[31] National Committee for Clinical Laboratory Standards, "Performance Standards for Antimicrobial Disk Susceptibility Tests," Approved Standard NCCLS. M2-A5, 13, 24, NCCLS, Villanova, **2004**.

The authors declare no conflict of interest