Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2018, 10(10): 94-99
(http://www.derpharmachemica.com/archive.html)

Synthesis, Antibacterial and Antioxidant Activity of Novel Bis-1,3,4-oxadiazoles Carrying Pyrazole Moiety

Asma, Balakrishna Kalluraya*, Manju N

Department of Studies in Chemistry, Mangalore University, Mangalagangothri 574199, Karnataka, India

ABSTRACT

A series of new 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) derivatives were synthesized by the condensation of 1-(aryl)-1H-pyrazol-3,4-dicarbohydrazide with substituted aromatic acids. All the newly synthesized compounds were screened for their in vitro antibacterial and antioxidant activity. Among the tested compounds, bis-1,3,4-oxadiazole 3p exhibited excellent antioxidant activity. The structures of the newly synthesized compounds were confirmed by Proton Nuclear Magnetic Resonance (^{1}H-NMR), InfraRed (IR), Liquid Chromatography-Mass Spectrometry (LC-MS), X-Ray Diffraction (XRD) and elemental analysis.

Keywords: Bis-1,3,4-oxadiazole, Pyrazole, Sydnone, Antibacterial, Antioxidant.

INTRODUCTION

Sydnone is renowned for its propensity to undergo 1, 3-dipolar cycloaddition reactions with various dipolaropiles [1-3]. The 1,3-dipolar cycloaddition reaction of sydnone with Dimethylacetylene Dicarboxylate (DMAD) to give dimethyl-1-aryl-1*H*-pyrazole-3,4-dicarboxylates has been well utilized for the synthesis of various symmetrically substituted pyrazoles [4-7].

Meanwhile 1,3,4-oxadiazoles are the heterocyclic compounds containing two nitrogen and one oxygen atom in a five membered ring. Derivatives of 1,3,4-oxadiazoles have exhibited significant pharmacological activities such as, anticancer [8-10], anti-HIV [11], anti-inflammatory [12-13], antitubercular [14], antifungal [15], antiviral [16], antioxidant[17], muscle relaxants [18], antihypertensive [19], antimalarial [20], pesticides [21], antiproliferative [22] activity etc. Substituted 1,3,4-oxadiazoles have also been used as active layers in organic light emitting diodes [23], electron injection material [24], charge transport material [25], scintillators [26], corrosion inhibitors [27] etc.

There are many reports [28,29] involving the synthesis of bis-1,3,4-oxadiazoles *via* cycloaddition of sydnone and such reaction involves a four step process through the initial formation of hydrazones followed by cyclization. However in this study we report the synthesis of a novel series of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) in just three steps with minimal usage $POCl_3$ as cyclizing agent.

MATERIALS AND METHODS

Experimental

All the reagents and solvents were purchased from Sigma-Aldrich or Hi-Media and used after purification by distillation/recrystallization. Proton Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on Bruker Avance II NMR spectrometer operating at 400 MHz and all the chemical shift values were reported in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were acquired on a SHIMADZU Liquid Chromatography-Mass Spectrometry (LC-MS)-8030 mass spectrometer. Melting points of the synthesized compounds were determined in open capillary tubes in Innovative DTC-967A digital melting point apparatus. SHIMADZU Fourier Transform Infrared (FT-IR) 157 spectrophotometer was used for recording Infrared (IR) spectra. Antibacterial activity was tested against Gram-positive bacteria *S. aureus* (NCIM - 5021), *B. subtilis* (NCIM 2197) and Gram-negative bacteria *E. coli* (NCIM-2931), *P. aeruginosa* (NCIM-2036). Bacterial strains were purchased from National collection of industrial microorganisms, Pune, India. Elemental analysis was carried out on a Schimadzu Elementar Vario EL III model.

General procedure for the synthesis of 5,5'-(1-(Aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-3u)

1-(Aryl)-1H-pyrazol-3,4-dicarbohydrazide 1 (1 mmol) and aromatic acids (2 mmol) were taken in a round bottomed flask, phosphoryl chloride (5 ml) was added to it and heated in an oil bath for 6 hours at 90ºC. After cooling the contents to room temperature, the resulting reaction mass was poured into a beaker having ice flakes. The solid obtained was filtered, washed with sodium bicarbonate (5%) solution followed by water

and recrystallized from ethanol-dichloromethane mixture.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-thiophenyl-1,3,4-oxadiazole) (3a)

Yield 86%, mp 198ºC-200ºC. IR spectrum, ν, cm^{-1}: 2899 (C-H), 1675 (C=N) and 1268 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.45 (s, 3H, CH_3), 7.26 (d, 2H, J=8.84 Hz, o-protons of p-tolyl ring), 7.53(d, 2H, J=8.88 Hz, m-protons of p-tolyl ring), 7.21-7.89 (m, 4H, 4,4^1 and 3,3^1 protons of thiophene ring), 7.57 (d, 1H, J=4.04 Hz, 5,5^1 protons of thiophene ring), 7.75 (d, 1H, J=5.14 Hz, 5,5^1 protons of thiophene ring) 9.10 (s, 1H, H of pyrazole ring). Found, %: C 57.61; H 3.08; N 18.29. $C_{22}H_{14}N_6O_2S_2$. Calculated, %: C 57.63; H 3.08; N 18.33. *M* 459.20 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-thiophenyl-1,3,4-oxadiazole) (3b)

Yield 88%, mp 216ºC. IR spectrum, ν, cm^{-1}: 2901 (C-H), 1686 (C=N) and 1275 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.87 (s, 3H, OCH_3), 7.04 (d, 2H, J=9 Hz, o-protons of p-anisyl ring), 7.75 (d, 2H, J=9Hz, m-protons of p-anisyl ring), 7.14-7.19 (m, 2H, 4,4^1 protons of thiophene ring), 7.82 (d, 1H, J=3.12 Hz, 3,3^1 protons of thiophene ring), 7.89 (d, 1H, J=3.68 Hz, 3,3^1 protons of thiophene ring), 7.54-7.59 (d, 2H, J=4.76 Hz and J=5.08 Hz, 5,5^1 protons of thiophene ring), 8.70 (s, 1H, H of pyrazole ring). Found, %: C 55.70; H 2.94; N 17.73. $C_{22}H_{14}N_6O_3S_2$. Calculated, %: C 55.69; H 2.97; N 17.71. *M* 475.00 [M^++1].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-thiophenyl-1,3,4-oxadiazole) (3c)

Yield 77%, mp 228ºC. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1678 (C=N) and 1269 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =7.15-7.20 (m, 2H, J=4.8Hz, protons of thiophene ring), 7.45 (t, 1H, J=7.4 Hz, proton of phenyl ring), 7.53-7.60 (m, 4H, protons of phenyl ring), 7.82-7.91 (m, 4H, 3,3^1 and 5,5^1 protons of thiophene ring), 8.78 (s, 1H, H of pyrazole ring). Found, %: C 55.71; H 2.73; N 18.89. $C_{21}H_{12}N_6O_2S_2$. Calculated, %: 56.74; H 2.72; N 18.91. *M 445.00 [M^++1]*.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-p-tolyl-1,3,4-oxadiazole) (3d)

Yield 86%, mp 231ºC. IR spectrum, ν, cm^{-1}: 2920 (C-H), 1605 (C=N) and 1231 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.42 (s, 6H, CH_3), 2.44 (s, 3H, CH_3), 7.34-7.40 (m, 6H, protons of p-tolyl ring), 7.93-7.97 (dd, 4H, J=8.12 Hz, protons of p-tolyl ring), 7.99 (d, 2H, J=8.2 Hz, protons of p-tolyl ring), 9.47 (s, 1H, H of pyrazole ring). Found, %: C 70.89; H 4.66; N 17.71. $C_{28}H_{22}N_6O_2$. Calculated, %: C 70.87; H 4.67; N 17.71. *M 475.15 [M^++1]*.

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-p-tolyl-1,3,4-oxadiazole) (3e)

Yield 85%, mp 178ºC-180ºC. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1612 (C=N) and 1248 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.89 (s, 3H, OCH_3), 7.04 (d, 2H, J=9 Hz, ortho protons of p-anisyl ring), 7.2-7.31 (m, 4H, meta-protons of p-tolyl ring), 7.76 (d, 2H, J=9 Hz, meta protons of p-anisyl ring), 7.99 (d, 2H, J=8.12 Hz, ortho-protons of p-tolyl ring), 8.06 (d, 2H, J=8.12 Hz, ortho-protons of p-tolyl ring), 8.69 (s, 1H, H of pyrazole ring). Found, %: C 68.53; H 4.50; N 17.14. $C_{28}H_{22}N_6O_3$. Calculated, %: C 68.56; H 4.52; N 17.13. *M 491.15 [M^++1]*.

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-p-tolyl-1,3,4-oxadiazole) (3f)

Yield 79%, mp 236ºC. IR spectrum, ν, cm^{-1}: 2905 (C-H), 1595 (C=N) and 1236 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.49 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 7.36-7.59 (m, 5H, protons of phenyl ring), 7.18-7.29 (m, 4H, meta-protons of p-tolyl ring), 7.83-7.99 (m, 4H, ortho-protons of p-tolyl ring), 8.56 (s, 1H, H of pyrazole ring). Found, %: C 70.45; H 4.36; N 18.23. $C_{27}H_{20}N_6O_2$. Calculated, %: C 70.42; H 4.38; N 18.25. *M 461.10 [M^++1]*.

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-p-anisyl-1,3,4-oxadiazole) (3g)

Yield 92%, mp 214ºC. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1611 (C=N) and 1265 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.44 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.96-7.01 (m, 4H, ortho-protons of p-anisyl ring), 7.34 (d, 2H, J=8.28 Hz, meta-protons of p-tolyl ring), 7.73 (d, 2H, J=8.44 Hz, ortho-protons of p-tolyl ring), 8.06 (d, 2H, J=8.84 Hz, meta-protons of p-anisyl ring), 8.11-8.13 (d, 2H, J=8.84 Hz, meta-protons of p-anisyl ring), 8.74 (s, 1H, H of pyrazole ring). Found, %: C 66.42; H 4.51; N 16.57. $C_{28}H_{22}N_6O_4$. Calculated, %: C 66.40; H 4.38; N 16.59. *M 507.10 [M^++1]*.

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-p-anisyl-1,3,4-oxadiazole) (3h)

Yield 83%, mp 213ºC. IR spectrum, ν, cm^{-1}: 2910 (C-H), 1626 (C=N) and 1273 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 7.03 (d, 2H, J=8.84Hz, ortho-protons of p-anisyl ring), 7.06 (d, 2H, J=8.46 Hz, meta-protons of p-tolyl ring), 7.72 (d, 2H, J=8.52 Hz, ortho-protons of p-tolyl ring), 7.78 (d, 2H, J=8.88 Hz, meta-protons of p-anisyl ring), 8.06 (d, 2H, J=8.90 Hz, meta-protons of p-anisyl ring), 8.69 (s, 1H, H of pyrazole ring). Found, %: C 64.39; H 4.24; N 16.10. $C_{28}H_{22}N_6O_5$. Calculated, %: C 64.36; H 4.24; N 16.08. *M 523.59 [M^++1]*.

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-p-anisyl-1,3,4-oxadiazole) (3i)

Yield 89%, mp 238ºC. IR spectrum, ν, cm^{-1}: 2885 (C-H), 1601 (C=N) and 1253 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.98 (d, 2H, J=8.82 Hz, ortho-protons of p-anisyl ring), 7.03 (d, 2H, J=8.82 Hz, ortho-protons of p-anisyl ring), 7.98-8.04 (m, 4H, meta-protons of p-tolyl ring), 7.53-7.59 (m, 3H, protons of phenyl ring), 8.16 (d, 2H, J=7.76 Hz, ortho-protons of phenyl ring) 8.60 (s, 1H, H of pyrazole ring). Found, %: C 65.86; H 4.06; N 17.03. $C_{27}H_{20}N_6O_4$. Calculated, %: C 65.85; H 4.09; N 17.06. M 493.20 [M^++1].

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-p-chlorophenyl-1,3,4-oxadiazole) (3j)

Yield 88%, mp 221ºC. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1605 (C=N) and 1233 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.52 (s, 3H, CH_3), 7.33-7.64 (m, 6H, Ar-H), 7.93 (d, 2H, J=8.44 Hz, Ar-H), 7.99 (dd, 1H, J=8.52 Hz, Ar-H), 8.06-8.14 (m, 3H, Ar-H), 9.49 (s, 1H, H of pyrazole ring). Found, %: C 60.56; H 3.11; N 16.33. $C_{26}H_{16}Cl_2N_6O_2$. Calculated, %: C 60.60; H 3.13; N 16.31. M 515.10 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-p-chlorophenyl-1,3,4-oxadiazole) (3k)

Yield 96%, mp 203ºC. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1603 (C=N) and 1246 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.89 (s, 3H, OCH_3), 7.04 (d, 2H, J=8.96 Hz, ortho-protons of p-anisyl ring), 7.47 (t, 4H, J=8.92 Hz, protons of p-chlorophenyl ring), 7.75 (d, 2H, J=8.96 Hz, meta-protons of p-anisyl ring), 8.06 (d, 2H, J=8.52 Hz, protons of p-chlorophenyl ring), 8.12 (d, 2H, J=8.56 Hz, protons of p-chlorophenyl ring), 8.69 (s, 1H, H of pyrazole ring). Found, %: C 58.74; H 3.01; N 15.81. $C_{26}H_{16}Cl_2N_6O_3$. Calculated, %: C 58.77; H 3.04; N 15.82. M 531.05, 533.05 and 535.05. [M^++1], [M^++3] and [M^++5].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-p-chlorophenyl-1,3,4-oxadiazole) (3l)

Yield 83%, mp 262ºC. IR spectrum, ν, cm^{-1}: 2610 (C-H), 1592 (C=N) and 1250 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =7.42 (m, 3H,Ar-H), 7.53 (m, 6H,Ar-H), 7.98 (d, 2H, J=8.48 Hz, protons of p-chlorophenyl ring), 8.06 (d, 2H, J=8.48 Hz, protons of p-chlorophenyl ring), 8.57 (s, 1H, H of pyrazole ring). Found, %: C 59.91; H 2.86; N 16.73. $C_{25}H_{14}Cl_2N_6O_2$. Calculated, %: C 59.89; H 2.81; N 16.76. M 502.10, 504.00 and 506.53. [M^++1], [M^++3] and [M^++5].

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-p-fluorophenyl-1,3,4-oxadiazole) (3m)

Yield 91%, mp 230ºC. IR spectrum, ν, cm^{-1}: 2920 (C-H), 1620 (C=N) and 1252 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =2.45 (s, 3H, CH_3), 7.17-7.26 (m, 4H, ortho-protons of p-fluorophenyl ring), 7.35 (d, 2H, J=8.28 Hz, ortho-protons of p-tolyl ring), 7.73 (d, 2H, J=8.4 Hz, meta protons of p-tolyl ring), 8.13-8.16 (dd, 2H, J=8.84 Hz and J= 5.24 Hz, meta-protons of fluorophenyl ring), 8.19-8.23 (dd, 2H, J=8.88 Hz and J=5.2 Hz, meta-protons of fluorophenyl ring), 8.75 (s, 1H, H of pyrazole ring). Found, %: C 64.70; H 3.29; N 17.42. $C_{26}H_{16}F_2N_6O_2$. Calculated, %: C 64.73; H 3.34; N 17.42. M 483.10 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-p-fluorophenyl-1,3,4-oxadiazole) (3n)

Yield 84%, mp 217ºC. IR spectrum, ν, cm^{-1}: 2929 (C-H), 1615 (C=N) and 1265 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.78 (s, 3H, OCH_3), 7.09 (d, 2H, J=8.94 Hz, ortho protons of p-anisyl), 7.39-7.42 (m, 4H, ortho-protons of p-fluorophenyl ring), 7.80 (d, 2H, J=8.96 Hz, meta protons of p-anisyl), 7.96-8.02 (m, 4H, meta-protons of p-fluorophenyl ring), 8.81 (s, 1H, H of pyrazole ring). Found, %: C 62.59; H 3.23; N 16.88. $C_{26}H_{16}F_2N_6O_3$. Calculated, %: C 62.65; H 3.24; N 16.86. M 493.20 [M^++1].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-p-fluorophenyl-1,3,4-oxadiazole) (3o)

Yield 87%, mp 240ºC. IR spectrum, ν, cm^{-1}: 2926 (C-H), 1613 (C=N) and 1227 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) = 7.28-7.35 (m, 4H, protons of p-fluorophenyl ring), 7.48 (d, 1H, J=7.32 Hz, para-proton of phenyl ring), 7.58 (t, 2H, J=7.6 Hz, ortho-protons of phenyl ring), 8.04 (d, 2H, J=7.68, meta-protons of phenyl ring), 8.13-8.16 (dd, 2H, J=8.8 Hz and J=5.24 Hz, protons of fluorophenyl ring), 8.18-8.22 (d, 2H, J=8.8 Hz and J=5.28 Hz, protons of fluorophenyl ring), 9.42 (s, 1H, H of pyrazole ring). Found, %: C 64.08; H 3.04; N 17.91. $C_{25}H_{14}F_2N_6O_2$.. Calculated, %: C 64.10; H 3.01; N 17.94. M 469.10 [M^++1].

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-(2,4-dichlorophenyl)-1,3,4-oxadiazole) (3p)

Yield 89%, mp 198ºC. IR spectrum, ν, cm^{-1}: 2955 (C-H), 1620 (C=N) and 1263 (C-O-C); ^{1}H-NMR spectrum, δ (ppm)=2.59 (s, 3H, CH_3), 7.36 (d, 2H, J=8.44 Hz, ortho protons of p-tolyl), 7.39-7.42 (m, 2H, protons of 2,4-dichlorophenyl), 7.47-7.54 (m, 2H, protons of 2,4-dichlorophenyl), 7.87 (d, 2H, J=8.44 Hz, meta protons of p-tolyl), 7.90-7.92(m, 2H, protons of 2,4-dichlorophenyl), 8.57 (s, 1H, H of pyrazole ring). Found, %: C 53.49; H 2.49; N 14.36. $C_{26}H_{14}Cl_4N_6O_2$. Calculated, %: C 53.45; H 2.42; N 14.38. *M* 585.05, 587.47 and 589.10 [M^++1], [M^++3] and [M^++5].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-(2,4-dichlorophenyl)-1,3,4-oxadiazole) (3q)

Yield 83%, mp 190°C. IR spectrum, ν, cm^{-1}: 2918 (C-H), 1613 (C=N) and 1252 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) =3.87 (s, 3H, OCH_3), 7.03 (t, 2H, J= 9.04 Hz, Ar-H), 7.39-7.43 (m, 2H, Ar-H), 7.56-7.61 (m, 2H, Ar-H), 7.74 (d, 2H, J= 9.04 Hz, Ar-H), 8.06 (dd, 2H, J= 8.48 Hz, Ar-H), 8.69 (s, 1H, H of pyrazole ring). Found, %: C 52.03; H 2.38; N 14.02. $C_{26}H_{14}Cl_4N_6O_3$. Calculated, %: C 52.03; H 2.35; N 14.00. *M* 600.90, 603.00 and 605.00 [M^++1], [M^++3] and [M^++5].

5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-(2,4-dichlorophenyl)-1,3,4-oxadiazole) (3r)

Yield 85%, mp 235°C. IR spectrum, ν, cm^{-1}: 2898 (C-H), 1610 (C=N) and 1255 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) = 6.98-7.33 (m, 4H, Ar-H), 7.52-7.68 (m, 3H, Ar-H), 7.82 (d, 2H, J=8.98 Hz, Ar-H), 7.99 (d, 2H, J=8.94 Hz, Ar-H), 8.56 (s, 1H, H of pyrazole ring). Found, %: C 52.65; H 2.16; N 14.75. $C_{25}H_{12}Cl_4N_6O_2$. Calculated, %: C 52.66; H 2.12; N 14.74. *M* 571.00, 573.20 and 575.00 [M^++1], [M^++3] and [M^++5].

5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole) (3s)

Yield 88%, mp 227°C. IR spectrum, ν, cm^{-1}: 2943 (C-H), 1598 (C=N) and 1225 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) = 2.45 (s, 3H, CH_3), 3.87 (s, 12H, OCH_3), 3.91 (d, 6H, OCH_3), 7.34 (m, 6H, Ar-H), 7.74 (d, 2H, J=7.84 Hz, Ar-H), 8.77 (s, 1H, H of pyrazole ring). Found, %: C 61.31; H 4.87; N 13.46. $C_{32}H_{30}N_6O_8$. Calculated, %: C 61.34; H 4.83; N 13.41. M 627.20 [M^++1].

5,5'-(1-(p-Anisyl)-1H-pyrazole-3,4-diyl)bis-(2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole) (3t)

Yield 82%, mp 225°C. IR spectrum, ν, cm^{-1}: 2922 (C-H), 1611 (C=N) and 1227 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) = 3.87 (s, 10H, OCH_3), 3.89 (s, 5H, OCH_3), 3.91 (d, 6H, OCH_3), 7.05 (d, 2H, J=8.96 Hz, ortho protons of p-anisyl ring), 7.34 (d, 4H, Ar-H), 7.77 (d, 2H, J=8.92 Hz, meta protons of p-anisyl ring), 8.72 (s, 1H, H of pyrazole ring). Found, %: C 59.86; H 4.73; N 13.01. $C_{32}H_{30}N_6O_9$. Calculated, %: C 59.81; H 4.71; N 13.08. M 643.20 [M^++1].

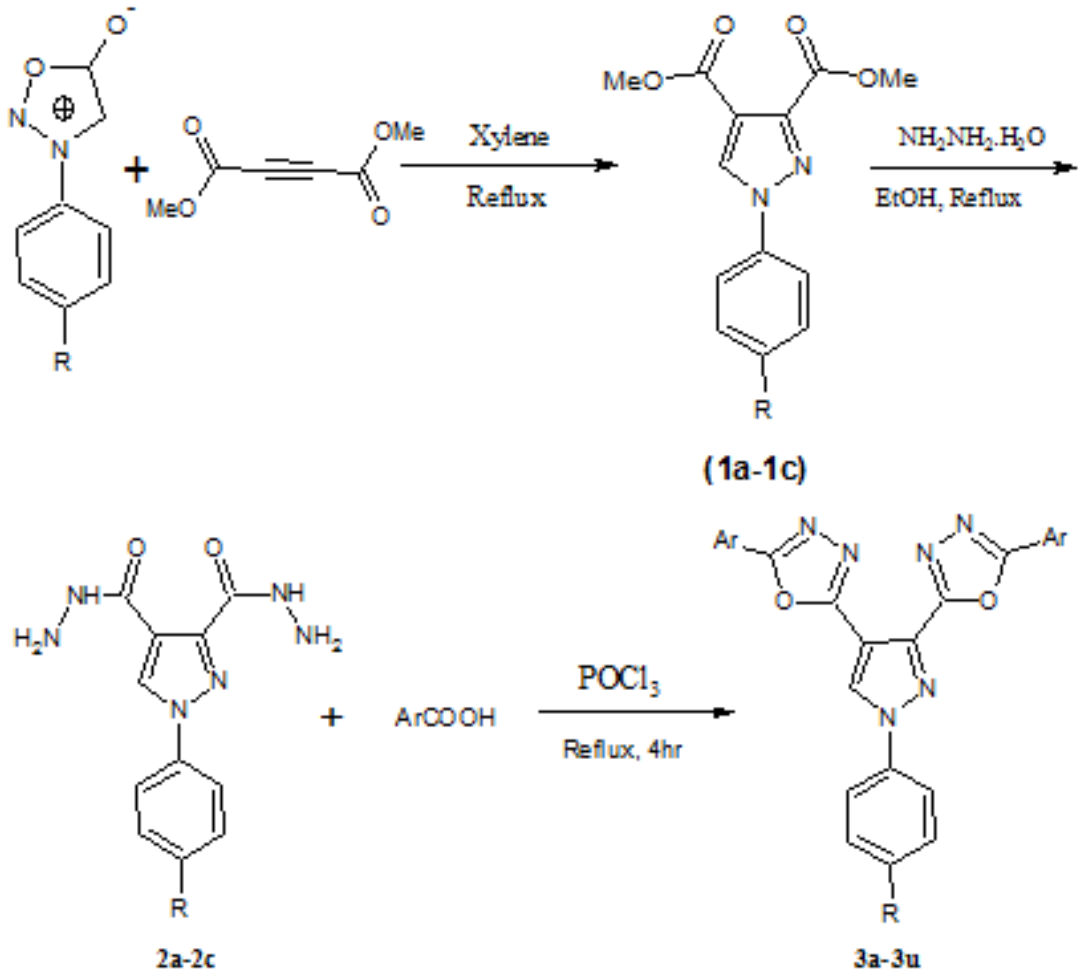
5,5'-(1-(Phenyl)-1H-pyrazole-3,4-diyl)bis-(2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole) (3u)

Yield 85%, mp 201ºC-203°C. IR spectrum, ν, cm^{-1}: 2940 (C-H), 1613 (C=N) and 1227 (C-O-C); ^{1}H-NMR spectrum, δ (ppm) = 3.89 (s, 12H, OCH_3), 7.28-7.35 (m, 9H, Ar-H), 8.80 (s, 1H, H of pyrazole ring). Found, %: C 60.79; H 4.58; N 13.69. $C_{31}H_{28}N_6O_8$. Calculated, %: C 60.78; H 4.61; N 13.72. M 613.10 [M^++1].

RESULTS AND DISCUSSION

Chemistry

A series of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) 3a-3u were synthesized by the cyclocondensation of 1-(aryl)-1H-pyrazol-3,4-dicarbohydrazide 2a-2c with various aryl acids employing phosphoryl chloride as condensing agent (Scheme 1). The intermediate, 1-(aryl)-1H-pyrazol-3,4-dicarbohydrazide 2a-2c was synthesized by the hydrozinolysis of respective ester (1a-1c). The 1,3-dipolar cycloaddition of sydnones with dimethylacetylene dicarboxylate (DMAD) in xylene medium resulted in the formation of 1-(ary)-1H-pyrazole-3,4-dimethylcarboxylate (1a-1c) [30].



R= CH_3, Ar= 2-thiophenyl (**3a**); R= OCH_3, Ar= 2-thiophenyl (**3b**); R= H, Ar= 2-thiophenyl (**3c**); R= CH_3, Ar= 4- tolyl (**3d**); R= OCH_3, Ar= 4- tolyl (**3e**); R= H, Ar= 4- tolyl (**3f**); R= CH_3, Ar= 4- anisyl (**3g**); R= OCH_3, Ar= 4- anisyl (**3h**); R= H, Ar= 4- anisyl (**3i**); R= CH_3, Ar= 4- chloro phenyl (**3j**); R= OCH_3, Ar= 4- chloro phenyl (**3k**); R= H, Ar= 4- chloro phenyl (**3l**); R= CH_3, Ar= 4- fluoro phenyl (**3m**); R= OCH_3, Ar= 4- fluoro phenyl (**3n**); R= H, Ar= 4- fluoro phenyl (**3o**); R= CH_3, Ar= 2,4- dichloro phenyl (**3p**); R= OCH_3, Ar= 2,4- dichloro phenyl (**3q**); R= H, Ar= 2,4- dichloro phenyl (**3r**); R= CH_3, Ar= 3,4,5- trimethoxy phenyl (**3s**); R= OCH_3, Ar= 3,4,5- trimethoxy phenyl (**3t**); R= H, Ar= 3,4,5- trimethoxy phenyl (**3u**).

Scheme 1: Cyclocondensation of 1-(aryl)-1H-pyrazol-3,4-dicarbohydrazide 2a-2c

Antibacterial studies

Newly synthesized 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-3u) were tested for their antibacterial activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillus subtilis* and Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa* at concentration of 100 µg/ml using the agar-diffusion method [31,32]. Compound 3a, 3f, 3h, 3i, 3m and 3r showed moderate activity against *S. aureus*, while compound 3b, 3k, 3o and 3t displayed moderate activity against *B. subtilis.* Compound 3u was found to be moderately active against *E. coli*, further compound 3a and 3i showed descent activity against *P. aeruginosa* (Table 1).

Table 1: Antibacterial activity 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-3u)

Compounds	Diameter of zone of inhibition (in mm) at 100 µg/ml			
	Staphylococcus aureus	*Bacillus subtilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
3a	13 ± 1	11.5 ± 0.5	10.5 ± 0.5	14.5 ± 0.5
3b	11 ± 1	13.5 ± 0.5	12 ± 1	10.5 ± 0.5
3c	9.5 ± 0.5	11 ± 1	10 ± 0	12 ± 0
3d	10 ± 0	10 ± 0	10 ± 0	11.5 ± 0.5
3e	11.5 ± 0.5	12.5 ± 0.5	12.5 ± 0.5	12 ± 0

3f	14 ± 1	9.5 ± 0.5	12 ± 0	10.5 ± 0.5
3g	9.5 ± 0.5	10.5 ± 0.5	10.5 ± 0.5	10 ± 0
3h	13.5 ± 0.5	10 ± 0	10.5 ± 0.5	11 ± 1
3i	14 ± 1	10 ± 1	11.5 ± 0.5	13 ± 1
3j	12.5 ± 0.5	10.5 ± 0.5	12 ± 0	12 ± 0
3k	10 ± 0	15.5 ± 0.5	9.5 ± 0.5	10.5 ± 0.5
3l	11.5 ± 0.5	10 ± 0	12.5 ± 0.5	12.5 ± 0.5
3m	14 ± 1	11 ± 1	10 ± 0	12 ± 0
3n	10.5 ± 0.5	10 ± 0	11.5 ± 0.5	9.5 ± 0.5
3o	11.5 ± 0.5	13.5 ± 0.5	11 ± 0	11.5 ± 1.5
3p	12 ± 1	10 ± 0	10.5 ± 0.5	10 ± 0
3q	11.5 ± 1.5	11 ± 1	9.5 ± 0.5	12 ± 0
3r	14 ± 1	10.5 ± 0.5	12 ± 1	11 ± 1
3s	11.5 ± 0.5	10 ± 0	11.5 ± 0.5	10 ± 1
3t	12 ± 0	13.5 ± 0.5	10.5 ± 0.5	11 ± 1
3u	17.5 ± 0.5	10.5 ± 0.5	14.5 ± 0.5	10.5 ± 0.5
Ciprofloxacin (Std)	24.5 ± 0.50	22.5 ± 0.50	23.5 ± 0.50	23.5 ± 0.50

Assay of *in vitro* antibacterial activity

The sterilized nutrient agar medium was distributed 100 ml each in two 250 ml conical flasks and allowed to cool to room temperature. To these media, 18-24 h grown bacterial/fungal sub-cultures were added and shaken thoroughly to ensure uniform distribution of organisms throughout the medium. Then, agar medium was distributed in equal portions, in sterilized Petri dishes, ensuring that each Petri dish contains about 45-50 ml of the medium. The medium was then allowed for solidification. The cups were made with the help of a sterile cork borer (6 mm diameter) punching into the set of agar media. The solutions of required concentrations (100 µg/ml) of test compounds were prepared by dissolving the compounds in DMSO were filled into the cups with 1 ml of respective solution. Then, the Petri dishes were kept for incubation in an inverted position for 24-48 h at 37ºC in an incubator. When growth inhibition zones were developed surrounding each cup, their diameter in mm was measured and compared with that of the standard drugs. Each experiment was made in triplicate using DMSO as a control.

Antioxidant studies

The novel series of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-3u) were evaluated for their antioxidant property at the concentration of 100 µg/ml of each sample in dimethyl sulfoxide (DMSO). Butylated hydroxy anisole (BHA) was taken as standard. Free radical scavenging assay of the compounds was carried out based on the scavenging activity of stable DPPH according to Mensor et al. [32].

5,5'-(1-(Aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-3u) exhibited DPPH scavenging activity varying from 98.27% to 2.11%, whereas standard drug BHA showed 90% inhibition. 5,5'-(1-(p-Tolyl)-1H-pyrazole-3,4-diyl)bis-(2-(2,4-dichlorophenyl)-1,3,4-oxadiazole) (3p) showed 98.27% DPPH scavenging activity higher than the standard, while 5,5'-(1-(p-tolyl)-1H-pyrazole-3,4-diyl)bis-(2-p-fluorophenyl-1,3,4-oxadiazole) (3m) displayed least DPPH scavenging activity of 2.11%. The percentage radical scavenging activity of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-u) has been described in Table 2.

Table 2: DPPH scavenging activity of 5,5'-(1-(aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-u)

Compound	DPPH Assay in %
3a	76.61
3b	7.11
3c	2.3
3d	2.71
3e	17.81
3f	14.23
3g	46.81
3h	12
3i	18.94
3j	18.81
3k	55.51
3l	22.01
3m	2.11
3n	16.61
3o	20.03
3p	98.27

3q	17.71
3r	6.31
3s	14.01
3t	6.21
3u	15.81
Standard BHA	90

CONCLUSION

A series of 5,5'-(1-(Aryl)-1H-pyrazole-3,4-diyl)bis-(2-aryl-1,3,4-oxadiazole) (3a-u) were synthesized by the cyclocondensation of 1-(Aryl)-1H-pyrazol-3,4-dicarbohydrazide (3a-c) with substituted aromatic acids. The newly synthesized compounds were further evaluated for their *in vitro* antibacterial and antioxidant studies. Compound 5,5'-(1-(p-tolyl)-1H-pyrazole-3,4-diyl)bis-(2-(2,4-dichlorophenyl)-1,3,4-oxadiazole) (3p) showed 98.27% radical scavenging activity.

REFERENCES

[1] R. Huisgen, *Angew. Chem. Int. Ed. Engl.*, **1963**, 2, 565-598.
[2] S.N. Rai, B. Kalluraya, B. Lingappa, B. Shenoy, G.P. Vedavati, *Eur. J. Med. Chem.*, **2008**, 43, 1715-1720.
[3] C.H. Jyothi, G. Rai, V.G. Puranik, B. Kalluraya, *Synth. Commun.*, **2005**, 36, 1285-1290.
[4] G. Coispeau, J. Elguero, R. Jacquier, Bul. Soc. Chi. Fr., 206-2063, Badami BV, Puranik GS, 1982- Reactions of sydnone, *Romanian J. Chem.*, **1969**, 27, 281-284.
[5] D.B. Dambal, B.V. Badami, G.S. Puranik, *Indian J. Chem.*, **1982**, 21B, 865-868.
[6] R.K. Tikare, B.V. Badami, G.S. Puranik, *Indian. J. Chem.*, **1983**, 22B, 673-677.
[7] K.A. Jessen, N.M. English, J.Y. Wang, S.K. Maliartenou, S.P. Archer, *Mol. Cancer. Ther.*, **2005**, 4, 761-771.
[8] Z. Kai, W. Peng, X. Li-Na, Y.F. Xiao, J. Fen, *Bioorg. Med. Chem. Lett.*, **2014**, 24, 5154-5156.
[9] A. Almasirad, S.A. Tabatabai, M. Faizi, A. Kebriaeezadeh, N. Mehrabi, *Bioorg. Med. Chem. Lett.*, **2004**, 14, 6057-6059.
[10] A. El-Emam, O.A. Al-Deeb, M. Al-Omar, *Bioorg. Med. Chem. Lett.*, **2004**, 12, 5107-5113.
[11] B. Sumit, B. Manju, K.S. Sharad, C. Shivani, B. Shoumyo, *Eur. J. Med. Chem.*, **2014**, 80, 167-174.
[12] M.D. Mullican, C.R. Kostlan, D.J. Schrier, R. Dyer, *J. Med. Chem.*, **1993**, 36, 1090-1099.
[13] S.G. Kucukguzel, E.E. Oruc, S. Rollas, F. Sahin, A. Ozbek, *Eur. J. Med. Chem.*, **2002**, 37, 197-206.
[14] A.O. Maslat, M. Abussaud, H. Tashtoush, M. Al-Talib, *Polish J. Pharmacol.*, **2002**, 54, 55-59.
[15] Z. Li, P. Zhan, X. Liu, *Mini. Rev. Med. Chem.*, **2011**, 11, 1130-1142.
[16] M. Liang, X. Yu, L. Cong, X. Zheng-Lu, L. Dong-Dong, *Med. Chem. Lett.*, **2013**, 21, 6763-6770.
[17] H.I. Yale, K. Losee, *J. Med. Chem.*, **1966**, 9, 478-483.
[18] G.R. Bankar, K. Nandakumar, P.G. Nayak, A. Thakur, M.R. Chamallamudi, *Chem. Bio. Interact.*, **2009**, 181, 377-382.
[19] P.R. Kagthara, N.S. Shah, R.K. Doshi, H.H. Parekh, *Indian J. Chem.*, **1999**, 38B, 572-576**.**
[20] X. Zheng, Z. Li, Y. Wang, W. Chen, Q. Huang, *Fluorine. Chem.*, **2003**, 123, 163-169.
[21] Salahuddin, M. Shaharyar, A. Mazumder, M.M. Abdullah, *Arab. J. Chem.*, **2017**, 10, S503-S508.
[22] B. Schulz, I. Orgzall, A. Freydank, C. Xu, *Adv. Colloid. Interface. Sci.*, **2005**, 116, 143-164.
[23] C. Zhang, H.V. Seggern, K. Pakbaz, B. Kraabel, H.W. Schmidt, *Synth. Met.*, **1994**, 62, 35-40.
[24] H. Antoniadis, M. Inbasekaran, E.P. Woo, *Appl. Phys. Lett.*, **1998**, 73, 3055-3057.
[25] I.H. Campbell, B.K. Crone, *App. Phys. Lett.*, **2007**, 90, 012117.
[26] M. Bouklah, B. Hammouti, M. Lagrenée, F. Bentiss, *Corros. Sci.*, **2006**, 48, 2831-2842.
[27] L.Y. Wang, E.C. Chang, M.Y. Yeh, Y.H. Chung, J.J. Huang, *Heteroatom. Chem.*, **2014**, 25, 172-177.
[28] E.M. Chang, C.J. Lin, F.F. Wong, M.Y. Yeh, *Heterocycl.*, **2006**, 68, 733-748.
[29] R. Sanyal, B.V. Badami, *J. Heterocyclic. Chem.*, **2006**, 43, 827-834.
[30] H.W. Seeley, P.J. Van Denmark, A laboratory manual of Microbiology, 2nd (Edn.), D.B. Taraporewala Sons and Co Microbes in action, Bombay, **1975**, 55-80.
[31] A.L. Banty, The antimicrobial susceptibility test: principle and practice, Edited by Illus, Lea and Febiger, Philadelphia, PA, USA, **1976**, Pp 180.
[32] L.I. Mensor, F.S. Menezes, G.G. Lietao, A.S. Reis, T. Don Santos, *Phytother. Res.*, **2001**, 15, 127-130.