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Synthesis, characterization and biological activities of 1,3,4-oxadiazole derivatives of nalidixic acid and their copper complexes

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A series of novel 1, 3, 4-oxadiazole analogues was synthesized from cyclization of hydrazones of substituted 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carbohydrazides were prepared from nalidixic acid. The structures of synthesized oxadiazole derivatives and their copper complexes were elucidated on the basis of FTIR, elemental analyses, ^{1}H-NMR and atomic absorption spectral analysis. It was observed from spectral data that metal ligand ratio was 1:1 in all copper complexes and they were bidentate, coordination was found to be done through oxygen of 4-oxo group and nitrogen of oxadiazole ring. The synthesized compounds were further evaluated with biological activities and compared with parent hydrazones. Copper complexes possess antibacterial and antifungal activities better than the oxadiazoles while they have better antioxidant activity then copper complexes. Parent hydrazones were better in all biological activities than synthesized oxadiazoles.

Capsule Summary: A series of novel 1,3,4-oxadiazole analogues was synthesized from cyclization of hydrazone. The synthesized compounds showed considerable biological activities than synthesized oxadiazoles.

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INTRODUCTION

Nalidixic acid (1-ethyl-7-methy-1,8-naphthyridine-4-one-3-carboxylate, $C_{12}H_{12}N_2O_3$,) was the first developed compound of the family of quinolone and 1,8-naphthyridines. It was described by Lesher and his coworkers in (Lesher et al., 1962) and since then it has been used extensively in therapy (Aggarwal et al., 2010; Cotton et al., 1999; Miessler and Tarr, 1999). 1, 8-naphthyridine derivatives have been investigated for a long period of time to report complexation properties and medicinal uses e.g., possess antibacterial, anti-inflammatory, anti-hypertensive and anti-platelet activities.

After the discovery of first quinolone, nalidixic acid, medicinal and industrial chemists have made numerous structural modification and new quinolones (Chen et al., 2001; Roma et al., 2000) have continually been made, in the hope of incremental microbiological advantages over Nalidixic acid which displays remarkable potency against gram negative as well as gram positive and anaerobic organisms (Das, 1990).

Among derivatives of carbonyl compounds carboxylic acids, ketones, aldehydes, ester etc. hydrazones are important class, which often is found to be a constituent of biologically active compounds. They are obtained by the reaction of aromatic and heterocyclic hydrazide with mono and dialdehydes or ketones (Hughes, 1981). It was investigated that hydrazones have discovered to possess, antimicrobial, anticonvulsant, analgesic, anti-inflammatory, antiplatelet, antitubercular and antitumoral activities (Buu-Hoï et al., 1953; Dimmock et al., 2000; Rollas and Küçükgüzel, 2007; Sah and Peoples, 1954).

Derivatives of 1,3,4- Oxadiazoles are found to have remarkable pharmaceutical properties, they are shown to possess muscle relaxant, analgesic, anti-convulsive, anti-inflammatory, diuretic and anti-emetic properties. They also possess tranquilizing hypnotic, hypoglycemic herbicidal, antiviral, ameobicidal, insecticidal and sedative activites (Mukesh et al., 2011).

In continuation of preparing better therapeutic compounds ten 1,3,4- oxadiazole analogues from cyclization of hydrazones of Substituted 1-Ethyl-1,4-Dihydro-7-Methyl-4-Oxo-1,8-Naphthyridine-3-Carbohydrazides which we have prepared from Nalidixic acid and published earlier (Deeba et al., 2017; Deeba et al., 2013) from Nalidixic acid which have two fused pyridine rings (1,8-naphthyridines), hydrazone group -N-N=C- and ketone group in system. As literature reveals that these groups must have various biological activities due to lone pairs on nitrogen and oxygen atoms (Khalilullah et al., 2016; Shaharyar et al., 2017). So far, substituted, 8-naphthyridines along with their copper complexes and their biological activities are reported in studied in present investigation.

MATERIAL AND METHODS

Chemical, reagents and instruments

All the chemicals used in this study were purchased from E. Merck, BDH and Fluka. Melting points of all the compounds were taken on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained in KBr disc on a Hitachi FTIR-4300 and on a Thermo Nicolet FTIR-200 spectrometer in the 4000—400 cm^{-1} region. ^{1}H-NMR spectra were recorded on a Bruker DPX-400 NMR spectrometer in DMSO-d6 or $CDCl_3$ and chemical shifts are given in ppm downfield from tetramethylsilane (TMS) as the internal standard. The metal analyses were carried out on Atomic Absorption Spectrophotometers, Perkin Elmer Analyst 800 and Hitachi Polarized Zeeman, by using Flame technique on air-acetylene flame.

Synthesis procedure

Firstly, Nalidixic acid hydrazide was prepared then 1,8-naphthyridine hydrazones were synthesized by reacting it with different substituted benzaldehyde. In present work 1,3,4- oxadiazoles were prepared by cyclization of hydrazones (Lee et al., 2001). Copper complexes of oxadiazoles were prepared from $CuCl_2.2H_2O$ and they were evaluated for their antimicrobial activity and then comparison was done with parent series and their copper complexes.

Synthesis of oxadiazoles from nalidixic acid through hydrazones

Firstly, Nalidixic acid hydrazide was prepared from reaction of Nalidixic acid, hydrazinium hydroxide and methanol. Then equimolar quantities of Nalidixic acid hydrazide and ten substituted benzaldehyde were refluxed in the presence of methyl alcohol for a period of 30 minutes. Then 3-5 drops of concentrated HCl was added and further refluxed for 4 hours. After completion of the reaction as indicated by TLC (Chloroform: methanol, 90:10) three fourth of the solvent was evaporated and contents were cooled down to room temperature. The synthesized Hydrazone ligand was filtered and washed 2-3 times with hot 1:1 ethanol: water quantity and dried in vacuum oven.

The synthesized hydrazone H-series, 0.025 mol were heated on hot plate with ortho phosphoric acid at 140 ^{o}C, for a period of 10 hours. Then reaction mixture was poured into ice breaker, then pH was neutralized by NaOH 10 % solution. The product oxadiazole was precipitated out as soon as pH was more than seven. The oxadiazoles prepared were extracted with chloroform, filtered it and washed precipitate 3-4 times with hot water and kept them in desiccator. The preparation of oxadiazoles from relevant oxidizole and Hydrazones are shown in Table 1.

Characterization of 1,3,4-oxadiazoles

Oxadiazole O- 1 form H-1 [1-ethyl-7-methyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1H)-one]

M.P. > 300^{o}C, yield: 3.34 g (40 %), colour: yellow, solubility: DMSO. E. analysis: ($C_{19}H_{16}N_4O_2$/332, found (calcd.) C=68.54 (68.67) H= 5.0 (4.81) N =16.69 (16.86). ^{1}H-NMR of O-1 (400 M *Hz* $CDCl_3$): δ : 1.5(3H,m,-1CH3) 2.69(3H,S,-7CH3) 4.56 (2H,m,-1CH2) 7.79 (1H,s,Ar-H) 7.31(4H,m,Ar-H-2,-5,) 7.80(1H,m, Ar- H,6) 7.8 (1H,s, Ar-H,2) 8.635(1H,m,Ar-H-5) 9.01(1H, s, -N=CH) 13.10 (1H,s,-NH) ppm. AAS studies: copper 12.10% and calculated: 12.33%.

Oxadiazole O-2 from H-2 [3-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one]

M.P. > 300 ^{o}C, yield: 5.98 g (65 %) colour: deep yellow, solubility: DMSO. E. analysis: ($C_{19}H_{14}N_4O_2$/ 366) C=61.77 (62.29) H=3.77(3.82) N=15.01(15.30). ^{1}H-NMR: (400 M *Hz* $CDCl_3$): δ: 1.50(3H,m,-1CH3), 2.70 (3H,S ,-7CH3) , 4.56 (2H,m ,-1CH_2), 8.63 (1H,m,Ar-H-5), 7.55 (1H,s,Ar-H-2) ,7.31 (4H,m ,Ar-H2',3',5',6'),7.23(1H,m,Ar-H-6), 9.00(1H,s,-N=CH), 13.14 (1H,s,-NH) ppm. AAS Studies: Found 11.67 % and calculated: 11.47%.

Oxadiazole/O-3 from H-3 [1-ethyl-3-(5-(3,4-dimethoxyphenyl)-1,3,4-oxadiazol-2-yl)-7-methyl-1,8-naphthyridin-4(1H)-one]

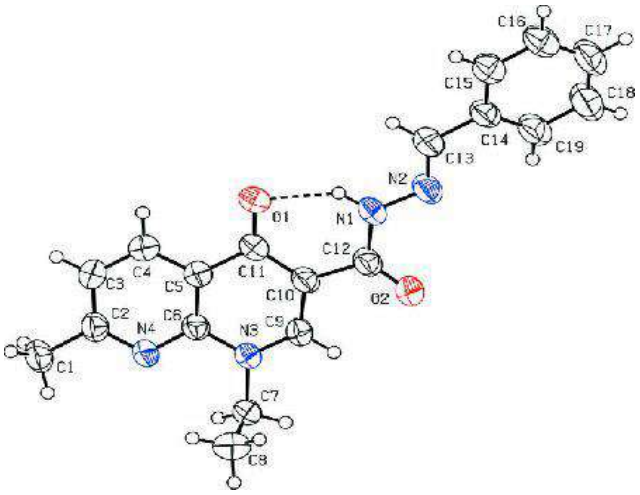


Fig. 1: X-rays Crystallographic picture of hyrazone ligand H-1 showing hydrogen bonding and positioning of oxygen atoms in red support IR data.

Yield: 2.95 g (30 %), M.P: > 250°C, colour: yellow, solubility: DMSO. E. Analysis: $C_{21}H_{21}N_4O_4$/392, found (calcd.) C= 63.96(64.28) H=5.2(5.36) N=14.57(14.28). ^{1}H-NMR: (400 M *Hz* $CDCl_3$): δ : 1.48(3H,m,-1CH3) 2.69(3H,S,-7CH3) 3.82 (3H,s,-OCH_3,) 3.83 (3H,s,-OCH_3) 4.5 (2H,m, -$1CH_2$) 6.83 (1H,m,Ar-H-6) 7.29 (1H,m,Ar-H-5') 7.54 (1H,m,Ar-H-6') 8.14(1H,s,Ar-H-2') 8.62 (1H,m,Ar-H-5) 7.9(1H,S ,Ar-H-2) 9.01 (1H,s,-N=CH) 12.98(1H,s,-NH)ppm. AAS studies: found 10.88% and calculated: 10.94%.

Oxadiazole/O-4 from H-4 [1-ethyl-3-(5-(4-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)-7-methyl-1,8-naphthyridin-4(1H)-one]

M.P. > 270 °C, yield: 2.62 g (30%), colour: yellow, solubility: DMSO. E. analysis: $C_{19}H_{16}N_4O_3$/348, found (calcd.) C= 64.96(65.52) H=4.2(4.59) N=15.88(16.09). ^{1}H-NMR: (400 M Hz $CDCl_3$): δ 1.5 (3H, m, -1CH3) 2.70 (3H,S ,-7CH3) 4.56 (2H,m ,-$1CH_2$) 8.63 (1H,m,Ar-H-5) 79(1H,s,Ar-H-2) 7.31 (4H,m ,Ar-H 2',3',5',6') 7.23 (1H,d, J=8.39 Hz,Ar-H-6) 9.00(1H,s,-N=CH) 13.14 (1H,s,-NH) ppm. AAS studies: found 12.89% and calculated: 12.74%

Oxadiazole/O-5 from H-5 [N-(4-(5-(1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridin-3-yl)-1,3,4-oxadiazol-2-yl) phenyl) acetamide Oxadiazole]

M. P. > 250°C, yield: 6.34g (65%), colour: brown, solubility: DMSO. E. analysis: $C_{19}H_{18}N_4O_3$/388, found (calcd.) C=59.37(58.76) H=4.94(4.64) N=13.57(14.43). ^{1}H-NMR: (400 M Hz $CDCl_3$): δ 1.38 (3 H, m, -1CH3) 2.49 (3H,S ,-7CH3) 3.32 (3H,s,NCO-CH_3) 4.58 (2H,m,-$1CH_2$)8.58 (1H,m,Ar-H-5) 7.9(1H,s,Ar-H-2) 7.31 (4H,m ,Ar-H 2',3',5',6') 7.5 (1H,m,Ar-H-6) 10.13(1H,s,-N=CH) 13.01 (1H,s,-NH) ppm. AAS studies: found11.01% and calculated: 11.11%

Oxadiazole/O-6 from H-6 [3-(5-(4-(dimethylamino)phenyl)-1,3,4-oxadiazol-2-yl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one, oxadiazole]

M.P. > 300°C, yield: 3.77 g (40 %) colour: brown, solubility: DMSO. E. analysis:$C_{21}H_{21}N_5O_2$/375, found (calcd.) C=67.97(67.2) H=5.1(5.6) N=17.57(18.66). ^{1}H-NMR (400 M *Hz* $CDCl_3$): δ 1.50(3H,m,-1CH3) 1.67 (3H,S ,-7CH3) 2.68(3H-S-4'-NCH_3) 2.99 (3H-S-4'-NCH_3) 4.54 (2H,m,-$1CH_2$) 8.63 (1H,m,Ar-H-5) 7.8(1H,s,Ar-H-2) 6.66 (4H,m ,Ar-H 2',3',5',6') 7.66 (1H,m,Ar-H-6) 9.00(1H,s,-N=CH) 12.90 (1H,s,-NH) ppm. AAS studies: found 11.99% and calculated: 12.07%

Oxadiazole/O-7 from H-7 [1-ethyl-3-(5-(3-methoxy-4-phenoxyphenyl)-1,3,4-oxadiazol-2-yl)-7-methyl-1,8-naphthyridin-4(1H)-one]

M.P. > 250 °C, yield: 2.95 g (30%), colour: yellow, solubility: DMSO. E. analysis: $C_{26}H_{22}N_4O_4$/454, found (calcd.) C= 67.3(68.72) H=4.2(4.84) N=12.57(12.33). ^{1}H-NMR: (400 M *Hz* $CDCl_3$): δ 1.497(3H,m,-1CH3) 2.69(3H,S ,-7CH3) 3.96 (3H,s,-OCH_3) 4.56 (2H,m, -$1CH_2$) 7.24-7.42(5 H,-OC6H5) 7.56 (1H,m,Ar-H-6) 6.84 (1H,m,,Ar-H-5') 7.03 (1H,m,Ar-H-6') 5.17(1H,s,Ar-H-2') 8.63 (1H,m,Ar-H-5) 8.13(1H,S ,Ar-H-2) 9.00 (1H,s,-N=CH) 13.03(1H,s,-NH) ppm. **AAS studies**: found 9.98% and calculated: 9.93%

Oxadiazole/O-8 from H-8 [3-(5-(benzo[d][1,3]dioxol-6-yl)-1,3,4-oxadiazol-2-yl)-1-ethyl-7-methyl-1,8-naphthyridin-4(1H)-one]

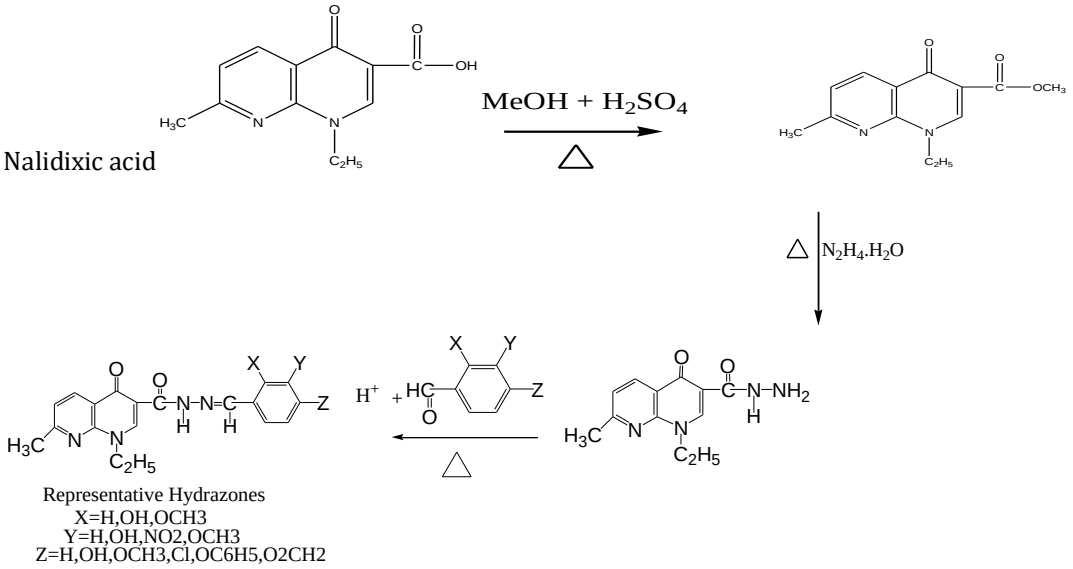
Yield: 2.83 g (30%), M.P. > 250°C, colour: yellow, solubility: DMSO. E. analysis$C_{20}H_{16}N_4O_4$/376, found (calcd.) C= 63.96(63.83) H=4.2(4.25) N=14.57(14.89). ^{1}H-NMR (400 M *Hz* $CDCl_3$): δ : 1.03(3H,m,-1CH3) 2.35(3H,S ,-7CH3) 3.32 (2H,s,NCO-CH_3) 4.59 (2H,m , -$1CH_2$) 7.51 (1H,m,Ar-H-6) 7.21 (1H,m,Ar-H-6') 8.38(1H,s,Ar-H-2') 8.58 (1H,m,Ar-H-5) 6.99 (1H,m,Ar-H-5') 7.8(1H,S, Ar-H-2) 10.51 (1H,s,-N=CH) 12.99(1H,s,-NH) ppm. AAS studies: found 11.40% and calculated: 11.34%.

Oxadiazole/O-9 from H-9 [1-ethyl-7-methyl-3-(5-p-tolyl-1,3,4-oxadiazol-2-yl)-1,8-naphthyridin-4(1H)-one]

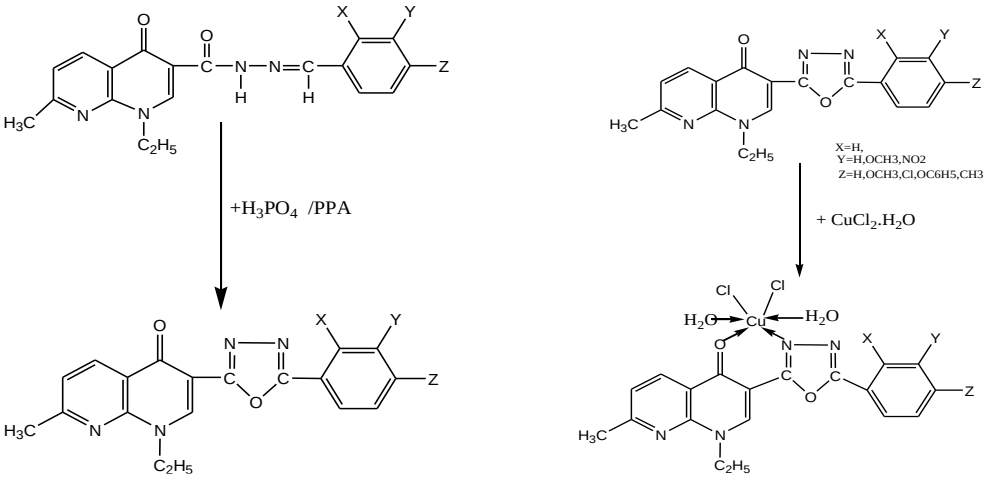
M.P. > 250 °C, yield: 3.8 g (40 %), solubility: DMSO. ^{1}H-NMR (400 M *Hz* $CDCl_3$): δ : 1.5(3H,m,-1CH3) 2.36 (3H,s,Ar-CH3, 4')2.7(3H,S ,-7CH3) 4.5 (2H,m ,-$1CH_2$) 8.63(1H,m,Ar-H-5) 7.88(1H,s,Ar-H-2) 7.18 (4H,m, Ar-H 2',3',5',6') 7.68(1H,m,Ar-H-6) 9.00(1H,s,-N=CH) 13.04 (1H,s,-NH) ppm. AAS studies: found 11.98% and calculated: 12.01%.

Oxadiazole/O-10 from H-10 [1-ethyl-3-(5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-7-methyl-1,8-naphthyridin-4(1H)-one]

M.P. >270°C, yield: 3.65 g (40 %), colour: orang, solubility: DMSO. E. analysis: $C_{20}H_{18}N_4O_3$/363, found (calcd.) C, 64.96(66.11) H,4.6(4.95) N,15.57(15.43). ^{1}H-NMR (400 M Hz $CDCl_3$): δ 1.5(3H, t, m, -1CH3) 2.69 (3H,s ,-7CH3) 3.82(3H,s,-OCH3,4') 4.54 (2H,m ,-$1CH_2$) 8.62 (1H,m,Ar-H-5) 8.16(1H,s,Ar-H-2) 6.88 (4H,m ,Ar-H 2',3',5',6') 7.72(1H,m,Ar-



Scheme 1: Basic scheme for preparation of hydrazones from nalidixic acid



Scheme 2: Basic scheme for preparation of all 1,3,4-oxadiazoles from hydrazones

[Synthesis of 1,3,4- Oxadiazole from hydrazones and their copper complexes, supposed structure of copper complex have arrow lines showing coordinate covalent bond and straight lines showing covalent bonds].

H-6) 9.00(1H,s,-N=CH) 13.01 (1H, s, -NH) ppm. AAS studies: found 12.48% and calculated: 12.36%.

Antibacterial activities by turbidimetric method

E. coli was selected for testing of antibacterial activity (Li et al., 2007) of oxadiazoles and their copper complexes, at concentration of 1 mg/5mL in nutrient broth. Their solutions were first prepared in DMSO then added to nutrient broth, Nalidixic acid was taken as reference to measure the comparative inhibition. After autoclaving of test tubes having test solution, an inoculum of E. Coli (20 µl) prepared in saline solution was added to each test tube. Initial absorbance of each tested solution was taken at 600 nm (Fotadar et al., 2005; Warrell, 2003), afterwards placed them in shaking incubator at 37 °C. After 24 hours other readings were taken at 600 nm and % age inhibition of ligands and their complexes were calculated.

Antifungal activities by turbidimetric method

Table 1: Preparation of oxadiazoles from relevant hydrazones

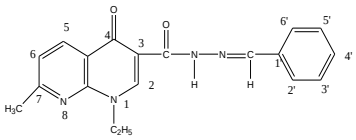
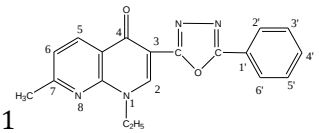
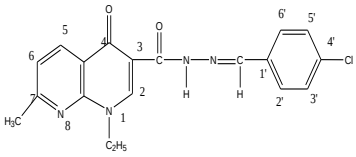
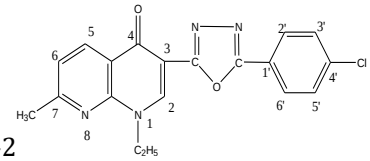
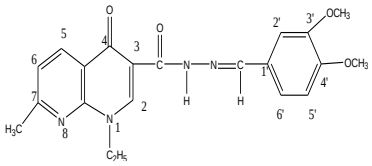
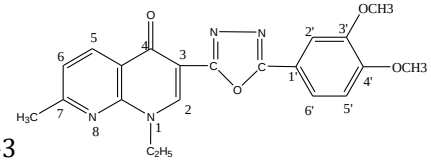
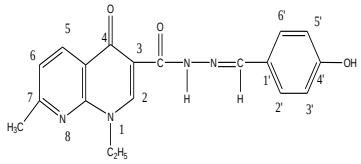
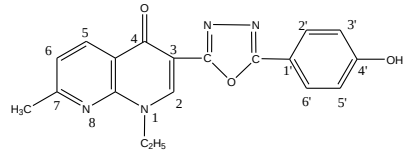
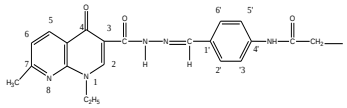
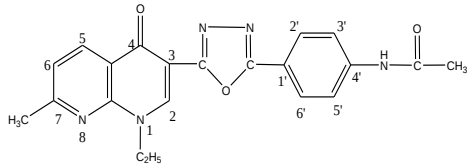
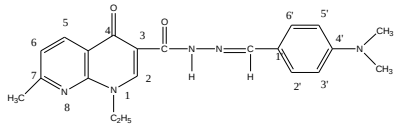
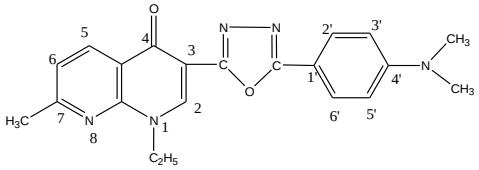
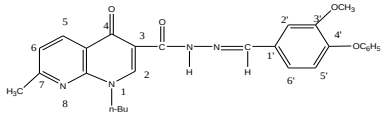
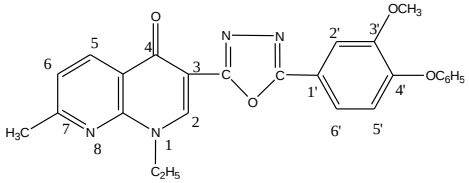
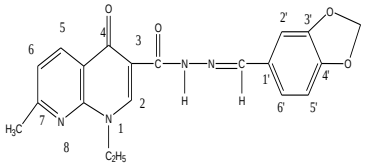
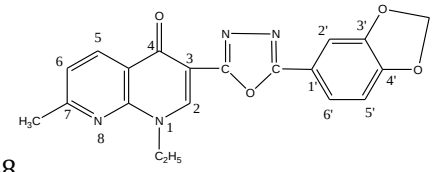
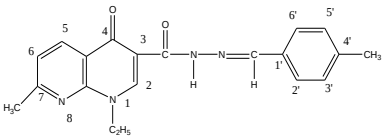
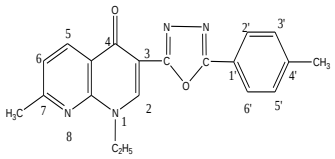
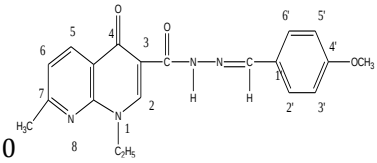
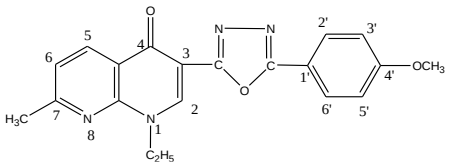
Sr.#	From Hydrazone	To Oxadiazole
1-	H-1 	O-1 
2-	H-2 	O-2 
3-	H-3 	O-3 
4-	H-4 	O-4 
5-	H-5 	O-5 
6-	H-6 	O-6 
7-	H-7 	O-7 

Table 1: Continue…

8-	 H-8	 O-8
9-	H-9 	 O-9
10	 H-10	 O-10

Aspergillus niger was selected for the antifungal activity of seven hydrazone ligands and their respective complexes at concentration of 1 mg/5mL in nutrient broth. The solutions of hydrazones and complexes were first prepared in DMSO as concentration of 1mg/mL in test tubes, then added 4 mL nutrient broth in each test tube with concentration of 200 µg/mL, Nalidixic acid was taken as reference to measure the comparative inhibition. After autoclaving of test tubes having test solution, an inoculum of *Espergillus niger* (20 µl) prepared on slant of agar was added to each test tube. Take initial absorbance at 550 nm, then keep test tube in shaking incubator at 26 ± 2 ^{o}C. After 72 hours readings at 550 nm were taken (Faida et al., 1997) and noted the % inhibition of ligands and their complexes.

Determination of antioxidant capacity

Samples of Oxadiazoles and reagent solution (0.6 M sulfuric acid, 28 milli-mole sodium phosphate and 4 milli-mole ammonium molybdate) were incubated at 95 °C for 90 minutes. After the mixture had cooled to room temperature, the absorbance of each solution was measured at 695 nm against a blank. The antioxidant capacity was expressed as mg of ascorbic acid/g of polysaccharide, described as an ascorbic acid equivalent (Mangal et al., 2013; Pal et al., 2012).

RESULTS AND DISCUSSION

Ten 1,3,4-oxadiazoles were prepared from 1,8-naphthyridine hydrazones (H-series) after cyclization in the presence of ortho phosphoric acid. Synthesis of Oxadiazoles were confirmed by comparing IR, ^{1}H-NMR Spectra and CHNS/Elemental analysis. Then copper complexes of these Oxadiazoles were prepared and analyzed through Atomic Absorption Spectrophotometer. Schemes 1 and 2 represent overall reactions to prepare Hydrazones from Nalidixic acid and 1,3,4-Oxadiazoles from Hydrazones and their copper complexes. Figure 1 shows X-rays Crystallographic picture of one of the hydrazone showing hydrogen bonding and positioning of oxygen atoms which support structures of Hydrazones and Oxadiazoles.

IR spectra

The IR spectral data of oxadiazoles, Hydrazone and copper complexes of Oxadiazoles and their tentative assignments are shown in Table 2. The IR spectral data showed that two very strong distinct peaks were found in all Hydrazone ligands, one at ~ 1680cm-^{1}, and other at ~ 1610 cm-1, attributed to ketone at 4th position (oxo-group) and carbonyl at 3rd position respectively, also a strong IR absorption peak is also observed at ~ 1498cm-^{1} in all hydrazone H-series, assigned to (NCO-) (Kriza Angela, 2002) but not observed in Oxadiazole.

Figure 1 showed the crystal structure of H-1 confirmed NCO^{-} enolic exhibition of bond before cyclization. Due to participation in ring formation peak ~1608 cm-^{1} at 3rd position in Oxadiazoles has disappeared. The absorption peak at 1680 cm-^{1} found in all Hydrazone ligands of H-series, due to participation of carbonyl at position 4th oxo-group, has shifted to lower frequency ~1620 cm- ^{1} in all oxadiazoles of O-series.

Table 2: IR spectral data of ligands of hydrazones, 1,3,4-oxadiazoles and their copper complexes in cm^{-1}

Compounds	υ(C=O)4th	υ(C=O)3rd	υ (C=N)	υ(C-N)	υ(N-N)	υ(NCO^-)	υ (M-N)
Nalidixic acid	1710	1615	1517	1444	----	---	---
H-1	1673	1618	1525	1445	1145	1495	---
O-1	1660	---	1521	1436	1129	--	
O-1-Cu	1620	---	1520w	1421w	1114	--	508
H-2	1680	1608	1526	1440	1145	1489	
O-2	1661	---	1520	1437	1130	---	
O-2-Cu	1620	---	1523w	1421w	1056	---	507
H-3	1680	1607	1532	1440	1145	1498	
O-3	1621	----	1531	1438	1128		
O-3-Cu	1628	----	1530w	1435w	1055		505
H-4	1680	1615	1537	1440	1155	1498	---
O-4	1620	----	1534	1442	1120	---	---
O-4-Cu	1630	-----	1530w	1435w	1054	---	506
H-5	1680	1610	1531	1442	1126	1489	----
O-5	1620	----	1531	1442	1109	---	---
O-5-Cu	1635	----	1530w	1420w	1056	---	509
H-6	1680	1610	1530	1442	1156	1493	--
O-6	1621	----	1532	1436	1125	---	---
O-6-Cu	1636	-----	1540w	1435w	1026	---	506
H-7	1680	1604	1537	1443	1138	1498	--
O-7	1620	----	1532	1440	1110	----	----
O-7-Cu	1636	----	1529w	1435w	1054	--	508
H-8	1680	1610	1537	1444	1140	1498	---
O-8	1620	----	1532	1440	1109	---	---
O-8-Cu	1630	----	1530w	1435w	1050	---	509
H-9	1680	1608	1530	1439	1155	1495	---
O-9	1621	---	1532	1438	1129	--	---
O-9-Cu	1636	---	1530w	1439w	1098	--	509
H-10	1680	1610	1532	1440	1210	1498	--
O-10	1621	----	1533	1440	1128	--	--
O-10-Cu	1638	---	1530w	1420w	1056	---	505

M=metal copper, W=wide

There is a distinct peak at ~ 1129 cm- [1] attributed to-N-N stretching in all oxadiazoles and hydrazones and band for -C =N and –C-N ring was almost same in all spectra for hydrazone H-series and oxadiazoles O-series, at ~ 1444cm-[1]and ~ 1520 cm-[1] respectively. Metal and Nitrogen bond has peak ~ 508cm-[1] in all copper complexes of Oxadiazoles.

[1]H-NMR spectra

The [1]H-NMR Spectra of oxadiazole ligands show signals due to exhibition of protons of ethyl $–CH_3$ appeared as triplet, and quartet for $–CH_2$ of carbon at 1st position in all ligands. The [1]H-NMR Spectra exhibited Ar-CH_3 protons as singlet for all hydrazones at 7th position of naphthyridine nucleus. As far as exhibition of naphthyridine protons in all hydrazones by **[1]**H-NMR Spectra, is concerned, a very small difference in δ values was observed. The [1]H-NMR Spectra exhibited the –OH proton in hydrazone O-4 at δ 13. 12. Two protons (-HN-N=CH) in all synthesized oxadiazoles were absent. The two –OCH_3 protons in case of O-3 appeared as singlet at δ 3.82 and 3.83 and in O-10 at 3.82. Most of the signals were found within expected range, however the signal due to methylene CH= and NH had disappeared after cyclization in all prepared 1,3,4-Oxadiazoles.

Elemental analysis

Elemental analytical data gave carbon, hydrogen and nitrogen percentage of Oxadiazoles. The C, H and N percentage for oxadiazoles were very close to calculated ratios derived from structural formula.

Atomic absorption spectrophotometric (AAS) studies

The synthesis of copper complexes of oxadiazoles was confirmed by atomic absorption spectrophotometry. Pre-weighed and oven dried samples were digested in nitric acid and then volume was made up to 100 mL then it was subjected to AAS technique for determination of copper percentage in complexes. all copper complexes gave AAS analysis of percentage of copper in very near to calculated value. Proposed diagram of copper complex is shown in scheme 2.

Melting point /solubility

Table 3: Comparison of biological activities of H-series and O-series along with nalidixic acid

S.No.	Oxadiazoles and Hydrazones compounds	% Inhibition Antibacterial *E. Coli* at 60 0nm	% Inhibition Antifungal *A. Niger* at 550 nm	Total Antioxidant Activity at 694 nm
	Nalidixic acid Standard for antibacterial& Antifungal activities	76.06 %	60.12%	CITRIC ACID as standard reading 1.820 (100%)
1-	H-1	13.05%	12.05%	1.674 (91.9%)
	O-1	9.45%	11.45%	1.542(84.7%)
	O-1- Cu	9.98%	11.89%	1.483(81.48%)
2-	H-2	10.22%	0.0	1.432(78.68%)
	O-2	8.23%	0.0	1.401(76.97%)
	O-2- Cu	8.90%	0.0	1.408(77.36%)
3-	H-3	17.24%	16.34%	1.032(56.70%)
	O-3	15.11%	14.87%	0.968(53.18%)
	O-3- Cu	15.54%	14.99%	0.978(53.73%)
4-	H-4	10.10%	0.0	0.923(50.71%)
	O-4	7.87%	0.0	0.877(48.18%)
	O-4- Cu	8.01%	0.0	0.865(47.52%)
5-	H-5	10.22%	0.0	0.821(45.10%)
	O-5	9.54%	0.0	0.784(43.07%)
	O-5- Cu	9.99%	0.0	0.712(39.12%)
6-	H-6	63.70%	53.64%	1.690(92.85%)
	O-6	60.12%	52.77%	1.514(83.18%)
	O-6- Cu	60.88%	52.89%	1.343(73.79%)
7-	H-7	9.35%	0.0	1.010 (55.49%)
	O-7	8.09%	0.0	0.956(52.52%)
	O-7- Cu	8.75%	0.0	0.857(47.08%)
8-	H-8	9.63%	0.0	0.788(43.29%)
	O-8	9.89%	0.0	0.658(36.15%)
	O-8- Cu	10.01%	0.0	0.601(33.02%)

Table 3: Continue…

9-	H-9	11.88%	---	0.876(48.13%)
	O-9	10.44%	----	0.843(46.31%)
	O-9- Cu	10.79%	4.53%	0.786(43.18%)
10-	H-10	10.38%	9.17%	0.856(47.03%)
	O-10	9.03%	8.65%	0.8124(44.63%)
	O-10- Cu	9.45%	8.99%	0.8009(44.00%)

Almost all Oxadiazoles have melting points above 250 °C and their copper complexes have above 300 °C**.** All Oxadiazole and copper complexes were soluble in DMSO.

Biological activities

The investigation of antimicrobial screening revealed that synthesized compounds showed some promising antibacterial, antitubercular and antifungal activity. The result in Table 3 shows biological activities of Hydrazones and Oxadiazoles along with comparison with Nalidixic acid which was our starting compound. Citric acid was taken as standard in total antioxidant activity and Nalidixic acid was used as standard in antibacterial and antifungal activities. It was cleared that all Oxadiazoles have less antibacterial and antifungal activities as compares to their respective parent Hydrazones. Oxadiazole-6 has shown maximum all biological activities, antibacterial, antibacterial and total antioxidant activities. The copper complexes of Oxadiazoles have better antibacterial and antifungal activities as compared to their respective Oxadiazoles and Oxadiazoles have much better antioxidant activity than their copper complexes. Nalidixic acid our starting compound has better antibacterial and antifungal activities than synthesized Hydrazones, Oxadiazoles and their respective copper complexes. Our result are close agreement with results of Popiołek and Gawrońska-Grzywacz (2015) and Salahuddin et al. (2017).

CONCLUSIONS

The oxadiazole copper complexes are bidentate having 1:1 metal ligand ratio and formed stable complexes with copper chloride. They are coordinated with metal ions by one oxygen of 4-oxo group of naphthyridines and nitrogen of 1,3.4-oxadiazole ring in their complexes. The copper complexes of oxadiazoles are intensively colored (mostly dark green) and have better antibacterial and antifungal activities as compared to their respective oxadiazoles, which have much better antioxidant activity than their copper complexes. All oxadiazoles have less antibacterial and anti-fungal activities as compared to parent hydrazones of H-series. Oxadiazole O-6 has maximum of all biological activities than other synthesized compounds and near to Nalidixic acid, may be due to N-$(CH_3)_2$ group present in its molecules. Nalidixic acid our starting compound for series H & O, has better biological activities than synthesized hydrazones, oxadiazoles and their copper complexes. The reported ten 1,3,4-oxadiazole derivatives are unique, innovative, spectroscopic characterized and synthesized from Nalidixic acid which is potent antibiotic for Urinary tract infection. In literature 1,3,4-oxadiazoles are found to be pharmaceutical more active than 1,2,5-oxadiazole analogs and have a wide range of biological activities e. g., anticoagulant, antitubercular, anti-inflammatory, analgesic, ulcerogenic, anticancer activities etc. In future our compounds can be evaluated for other pharmaceutically biological activities.

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