American Journal of Biomedical Research, 2018, Vol. 6, No. 1, 25-32
Available online at http://pubs.sciepub.com/ajbr/6/1/4

DOI:10.12691/ajbr-6-1-4

Synthesis And Biological Activity of Some New 1,3,4-Oxadiazole Derivatives

Chhater Singh[1,*], Reeta Karal[2], Bijander Kumar[1]

[1]Mahaveer College of Pharmacy, Meerut
[2]OPJS University, Rajasthan
*Corresponding author: pharma_pharm@yahoo.com

Abstract Oxadiazole a heterocyclic nucleus has attracted a wide attention of the chemists in search for new therapeutic molecules. Compounds having a five membered ring containing one oxygen and two nitrogen atoms are called oxadiazoles or in older furadiazoles. Oxadiazole is considered to be derived from furan by replacement of two methane groups by two pyridine type nitrogen called as furadiazoles. The structures of the newly synthesized derivatives were established by the combined practice of UV, IR, 1H NMR, and 13C NMR. Further these synthesized derivatives were subjected to anticonvulsant, neurotoxicity, antibacterial and antifungal activity against all the selected microbial and antifungal strains in comparison with ofloxacin (antibacterial), Fluconazole (antifungal), Anticonvulsant and Neurotoxicity with Phentoin and Phenobarbital. The antibacterial activity of synthesized derivatives was correlated with their physicochemical and structural properties by QSAR analysis.

Keywords: *oxadiazole derivatives, heterocyclic nucleus, furadiazoles, antibacterial and antifungal activity*

Cite This Article: Chhater Singh, Reeta Karal, and Bijander Kumar, "Synthesis And Biological Activity of Some New 1,3,4-Oxadiazole Derivatives." *American Journal of Biomedical Research*, vol. 6, no. 1 (2018): 25-32. doi: 10.12691/ajbr-6-1-4.

1. Introduction

Oxadiazole a heterocyclic nucleus has attracted a wide attention of the chemists in search for new therapeutic molecules. Compounds having a five membered ring [1,2] containing one oxygen and two nitrogen atoms are called oxadiazoles or in older furadiazoles. Oxadiazole [3] is considered to be derived from furan by replacement of two methane groups by two pyridine type nitrogen called as furadiazoles. There are four possible isomers of oxadiazole depending on the position of nitrogen atom [4] in the ring namely 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4-oxadiazoles, out of these 1,3,4-oxadiazoles are found to be most potent biologically. [5-10]

A large number of 1, 3, 4-oxadiazole derivatives have been found to exhibit various biological activities such as Anti-Inflammatory, Antimicrobial, Anticancerous, Anticonvulsant, antihypertensive etc.

Researchers have already reported that gram positive bacteria are much more susceptible to antimicrobial agents [11,12] as compared to gram negative bacteria [13]. These differences may be attributed to the fact that the cell wall in gram positive bacteria is of single layer whereas the gram negative bacteria have multilayered cell wall. Gram negative bacteria possess an outer membrane and a unique periplasmic space which is not found in gram positive bacteria [14]. The resistance of gram negative bacteria towards antibacterial substances is due to more lipophilic nature of membrane, which acts as a barrier for various antimicrobial compounds. It was expected that hydrophilic compounds are unable to penetrate the cell membranes of these bacteria. Gram positive bacteria do not have such outer membrane and complex cell wall structure. Antibacterial substances can easily destroy the bacterial cell wall and cytoplasmic membrane of gram positive bacteria, which results in leakage of the cytoplasm [15].

2. Experimental Section

2.1. Material and Method

Reagent and solvents used were obtained from commercial sources. Thin layer chromatographic analysis of compounds was performed on silica gel G coated glass plates. The adsorbent silica gel G was coated to a thickness of about 0.3 mm on previously cleaned TLC plates of 20x5 cm using conventional spreader. The plates were placed in hot air oven at 105^{o}C for 30 min. The solution of compounds was applied as a spot on the activated plate about 2 cm above from the lower edge. The mobile phases were selected according to the polarity of compounds Benzene: Acetone, 1:3. The λmax was calculated by using double beam UV-Visible 1700 Shimadzu spectrophotometer and the values are given in Table 2. IR spectrum of the compounds was recorded on a FT-761 spectrophotometer (JASCO) by using potassium bromide pellets. ^{1}H-NMR Spectra of compounds was recorded on BRUKAR 500 ultra shield spectrophotometer either in DMSO or in $CDCl_3$ using TMS as internal standard (Chemical shift in δ ppm).

2.2. General Procedure for the Synthesis

2.2.1. STEP-1-Synthesis Benzotriazol-1-yl-acetic Acid Ester (A)

A mixture of Benzotriazol**(43)** (0.01 mole), and potassium carbonate 3gm in acetone 60ml was reflux at 50-60 c for 1/2 hours. Then add. (0.01 mole) ethyl chloro acetate. and was reflux at 50-60 c for 6-7 hours .After completion of reaction solvent was removed by distillation and the solid mass was obtained and extracted with ether (diethyl ether). The ether was removed to get needle shaped brown crystals to give a TLC of pure compound (Figure 1).

IR (KBr, cm^{-1}) υ: 2947(C-H), 2270(N=N), 1770(C=O), 1610(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 1.24(t, 3H, $-CH_3$), 3.5(s, 2H, $-CH_2$), 4.20(m, 2H, $-CH_2$-), 7.40(m, 2H, Ar-H), 7.99(d, 2H, Ar-H).

Mol. Formula: $C_{10}H_{11}N_3O_2$

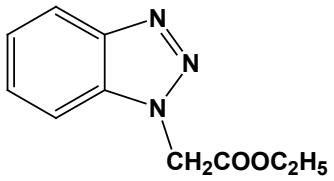


Figure 1. Benzotriazol-1-yl-acetic acid ester (A)

2.2.2. STEP-2-Synthesis of Benzotriazol-1yl-acetic Acid Hydrazide (B)

An ethanolic solution of Compound benzotriazol-1-yl-acetic acid ester (44) (0.01) and hydrazine hydrate (0.01) was stirred at room temperature for 5hour and refluxed on water bath for 3hours. The excess solvent was removed by distillation. Solid mass so obtained was filtered, washed with cold water and recrystalized from ethanol to give a TLC of pure compound **(45)**, m.p. 120-121°C.

IR (KBr, cm^{-1}) υ: 3389(NH_2), 2223(N=N), 1751(C=O), 1610(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 3.50(s, 2H, $-CH_2$), 3.10(s, 2H, $-NH_2$), 5.40(s, 1H, NH), 7.40(m, 2H, Ar-H), 7.99(d, 2H, Ar-H).

Mol. Formula: $C_8H_9N_5O$

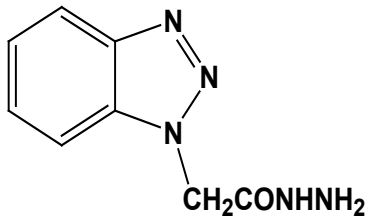
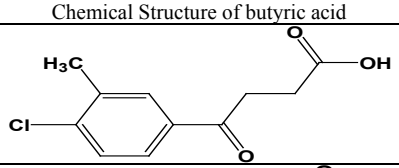
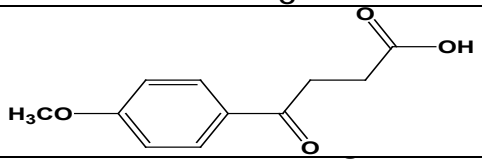
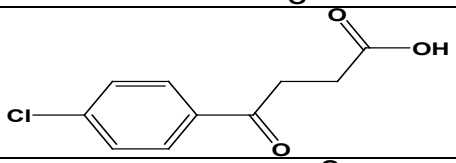
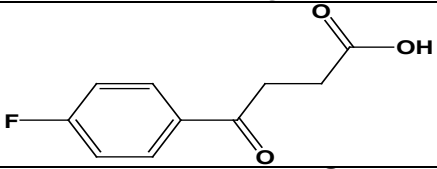
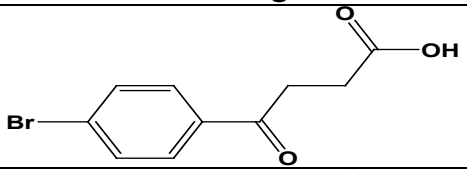
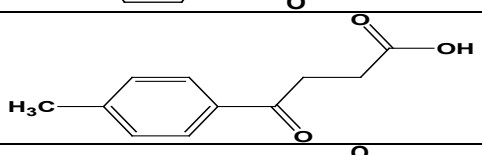
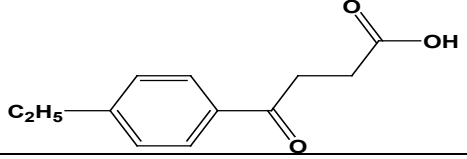


Figure 2. Benzotriazol-1yl-acetic acid hydrazide (B)

Table 1. Butyric acid

S. No.	Name of Butyric acid	Chemical Structure of butyric acid
(I)	**4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid**	
(II)	**4-(4-Methoxy-phenyl)-4-oxo-butyric acid**	
(III)	**4-(4-Chloro-phenyl)-4-oxo-butyric acid**	
(IV)	**4-(4-Fluoro-phenyl)-4-oxo-butyric acid**	
(V)	**4-(4-Bromo-phenyl)-4-oxo-butyric acid**	
(VI)	**4-Oxo-4-*p*-tolylbutyric acid**	
(VII)	**4-(4-Ethyl-phenyl)-4-oxo-butyric acid**	

2.1.3. Synthesis of 4-(substituted-phenyl)-4-oxo-butyric Acid

Succinic anhydride (0.01) was condensed with dry Substituted benzene (0.01) in presence of anhydrous aluminum chloride. A solid mass so obtained was filtered, washed with cold water, dried and crystallized from methanol to give colored needles, which gave effervescence with sodium bicarbonate solution, confirming presence of -COOH group.

2.1.4. STEP-3-Synthesis of Oxadiazole Derivatives

Compound **(B)** (0.01mole) was refluxed with Different aroyl acid (0.01 mole) is the presence of phosphoryl oxychloride (10 ml) for 6 hours. The content then were poured into ice- cold water and basified with sodium bi carbonate solution. The separated solid was filtered and recrystallised from ethanol to get solid compounds and get different derivatives **C1, C2, C3 ,C4, C5 ,C6, and C7** by the repetition of step 3 with different aryl acids respectively.

2.1.4.1. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-chloro-3-methyl-phenyl)-propan-1-one (C1):

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-chloro-3methyl-phenyl)-4-oxo- butyric acid **(I)** in phosphorous oxy chloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C1)**, m.p. 166-168°C

IR (KBr, cm^{-1}) υ: 2983(C-H), 2363(N=N), 1768(C=O), 1672(C=N), 1600(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.34(t, 3H, CH_3), 2.59, 2.89(t, each, 4H, -CH_2-), 4.89(s, 2H, -CH_2-), 7.12, 7.53, (d, each, 2H, Ar-H), 7.29(m, 2H, Ar-H), 7.48(s, 1H, Ar-H), 7.73(d, 2H, Ar-H).

Mol. Formula: $C_{19}H_{16}ClN_5O_2$

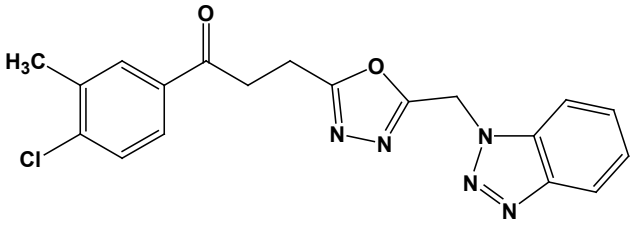


Figure 3. (C1)

2.1.4.2. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-methoxy-phenyl)-propan-1-one (C2)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-methoxy-phenyl)-4-oxo-butanoic acid **(II)** in phosphorous oxy chloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C2)**, m. p. 172-175°C.

IR (KBr, cm^{-1}) υ: 2987(C-H), 2363(N=N), 1770(C=O), 1676(C=N), 1610(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.60, 2.86(t, each, 4H, -CH_2-), 3.61(s, 3H, OCH_3), 4.90(s, 2H, -CH_2-), 6.82, 7.66, 7.82(d, each, 6H, Ar-H), 7.34(m, 2H, Ar-H).

Mol. Formula: $C_{19}H_{17}N_5O_3$

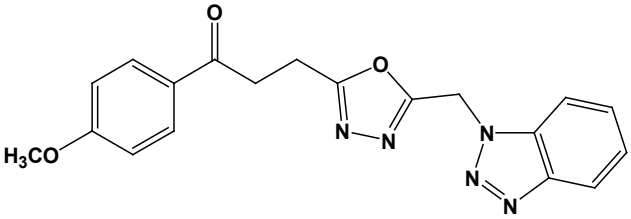


Figure 4. (C2)

2.1.4.3. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-chloro-phenyl)-propan-1-one (C3)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-chloro-phenyl)-4-oxo-butanoic acid (III) in phosphorous oxy chloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C3)**, m.p. 193-195º C

IR (KBr, cm^{-1}) υ: 2984(C-H), 2368(N=N), 1760(C=O), 1670(C=N), 1600(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.60, 2.86(t, each, 4H, -CH_2-), 4.90(s, 2H, -CH_2-), 7.03, 7.66, 7.82(d, each, 6H, Ar-H), 7.35(m, 2H, Ar-H).

Mol. Formula: $C_{18}H_{14}ClN_5O_2$

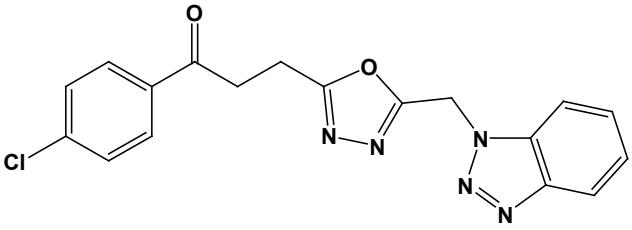


Figure 5. (C3)

2.4.4.4. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-fluoro-phenyl)-propan-1-one (C4)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-fluoro-phenyl)-4-oxo-butanoic acid **(IV)** in phosphorous oxy chloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C4)**, m.p. 151-153°C

IR (KBr, cm^{-1}) υ: 2983(C-H), 2365(N=N), 1766(C=O), 1673(C=N), 1610(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.65 2.87(t, each, 4H, -CH_2-), 4.89(s, 2H, -CH_2-), 7.03, 7.79, 7.92(d, each, 6H, Ar-H), 7.47(m, 2H, Ar-H).

Mol. Formula: $C_{18}H_{14}FN_5O_2$

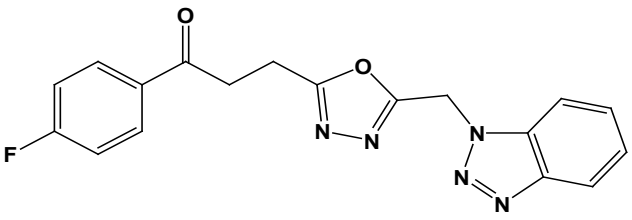


Figure 6. (C4)

2.1.4.5. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-bromo-phenyl)-propan-1-one (C5)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-bromo-phenyl)-4-oxo-butanoic acid **(V)** in phosphorous oxychloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C5)**, m.p. 166-167°C.

IR (KBr, cm^{-1}) υ: 2983(C-H), 2366(N=N), 1776(C=O), 1668(C=N), 1610(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.60 2.86(t, each, 4H, $-CH_2-$), 4.89(s, 2H, $-CH_2-$), 7.29(m, 2H, Ar-H), 7.48, 7.72, 7.90(d, each, 6H, Ar-H).

Mol. Formula: $C_{18}H_{14}BrN_5O_2$

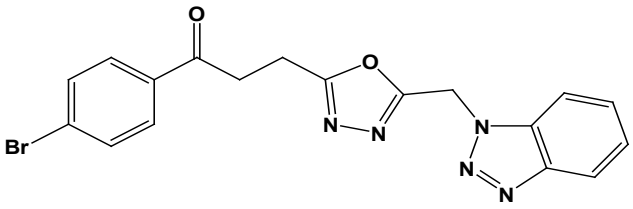


Figure 7. (C5)

2.1.4.6. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-methyl-phenyl)-propan-1-one (C6)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-methyl-phenyl)-4-oxo-butanoic acid **(VI)** in phosphorous oxychloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C6)**, m.p. 188-190°C

IR (KBr, cm^{-1}) υ: 2987(C-H), 2369(N=N), 1777(C=O), 1660(C=N), 1600(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 2.35(s, 3H, CH_3), 2.61 2.89(t, each, 4H, $-CH_2-$), 4.89(s, 2H, $-CH_2-$), 6.98, 7.70, 7.85(d, each, 6H, Ar-H), 7.30(m, 2H, Ar-H).

Mol. Formula: $C_{19}H_{17}N_5O_2$

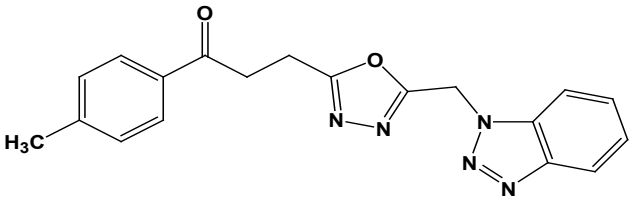


Figure 8. (C6)

2.1.4.7. 3-(5-Benzotriazole-1-ylmethyl-[1,3,4]-oxadiazole-2-yl)-1-(4-ethyl-phenyl)-propan-1-one (C7)

Benzotriazol-1-yl-acetic acid hydrazide **(B)** was refluxed with 4-(4-ethyl-phenyl)-4-oxo-butanoic acid **(VII)** in phosphorous oxychloride. The reaction mixture was cooled at room temperature and poured on to crushed ice and basified with sodium bi carbonate solution. The content was filtered and recrystalized from ethanol to give a TLC of pure compound **(C7)**, m.p. 195-197°C.

IR (KBr, cm^{-1}) υ: 2890(C-H), 2363(N=N), 1777(C=O), 1660(C=N), 1598(ArC=C)

^{1}HNMR ($CDCl_3$): δ, ppm 1.39(t, 3H, CH_3), 2.46(m, 2H, $-CH_2-$), 2.65 2.82(t, each, 4H, $-CH_2-$), 4.86(s, 2H, $-CH_2-$), 7.04, 7.70, 7.86(d, each, 6H, Ar-H), 7.28(m, 2H, Ar-H).

Mol. Formula: $C_{20}H_{19}N_5O_2$

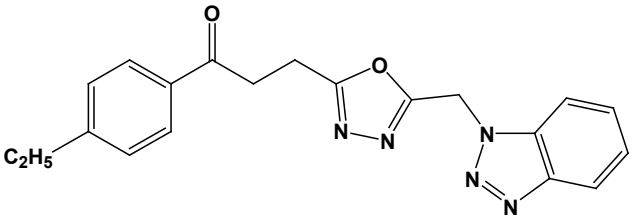


Figure 9. (C7)

2.2. Biological Evaluations

2.2.1. Antimicrobial Activity (Antibacterial and Antifungal activity)

The Antibacterial activity of the synthesized compounds C1-C7 was determined *in vitro* by using disc diffusion method against variety of pathogenic micro organisms like *Escherichia coli* (gram-negative), and *Bacillus subtilis* (gram-positive) at 50, 100 µg ml^{-1} concentrations, respectively, in the nutrient agar media by measuring the zone of inhibition in mm. The solutions of required concentrations (50, 100 µg ml^{-1}) of test compounds were prepared by dissolving the compounds in DMF. Under identical conditions the standard antibiotic ofloxacin at 100 µg ml^{-1} showed zone of inhibition 26.00mm for *E. coli*, 25.00mm for *Bacillus subtilis*. Antibacterial activity shown by the compounds towards various bacteria is recorded in Table 2. Similarly, the antifungal screening of the synthesized compounds C1-C7 was carried out *in vitro* by disc diffusion method against two fungi, *Aspergillus niger* and *Candida albicans* by using Fluconazole (100 µg ml^{-1}) as the standard, which had shown 23.00 and 25.00 mm zone of inhibition. Antifungal activity shown by the compounds towards fungi is recorded in Table 3. DMF was used, as the solvent control because the test compounds are freely soluble in DMF, for both antibacterial and antifungal activities.

Table 2. Antibacterial activity of compounds

COMPOUND CODE	Zone of inhibition in mm			
	B. subtilis (MTCC-441)		*E. coli (MTCC-11775)*	
	50 µg	100 µg	50 µg	100µg
C1	19	21	16	23
C2	13	14	13	14
C3	14	15	11	12
C4	16	17	12	15
C5	19	21	18	19
C6	18	20	17	19
C7	17	18	15	18
Ofloxacin	23	25	21	26
Control	-	-	-	-

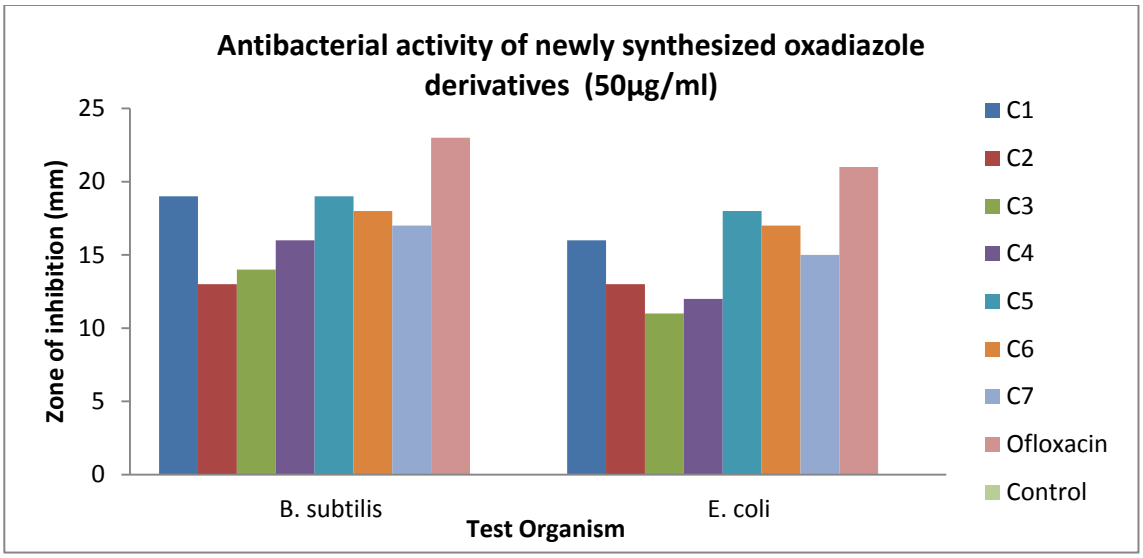


Figure 10. Antibacterial activities (50 µg/ ml)

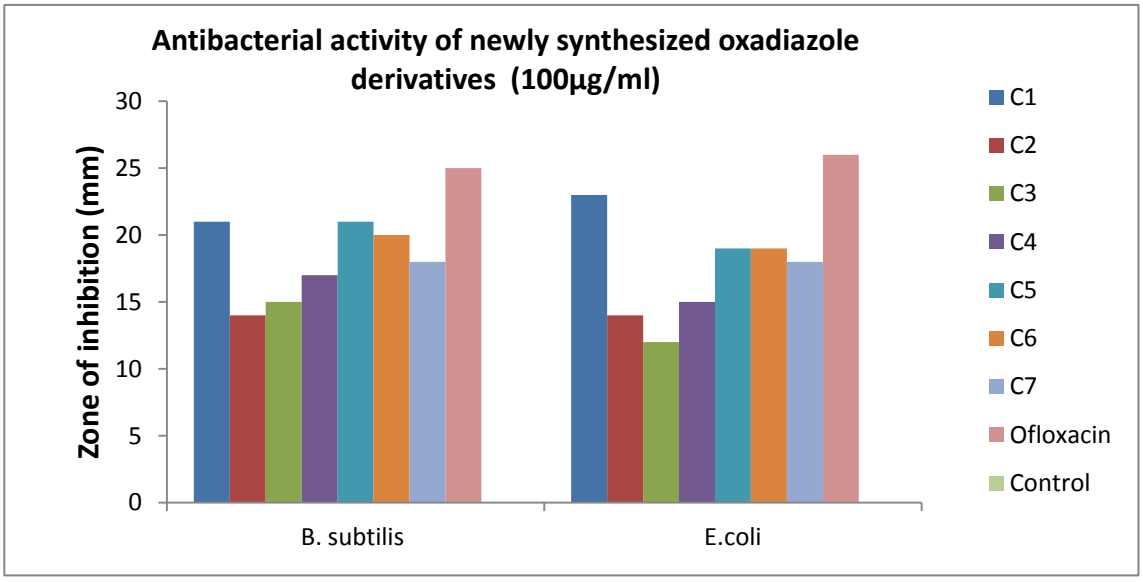


Figure 11. Antibacterial activities (100 µg/ ml)

Antibacterial activity of newly synthesized oxadiazole derivatives (50µg/ml)

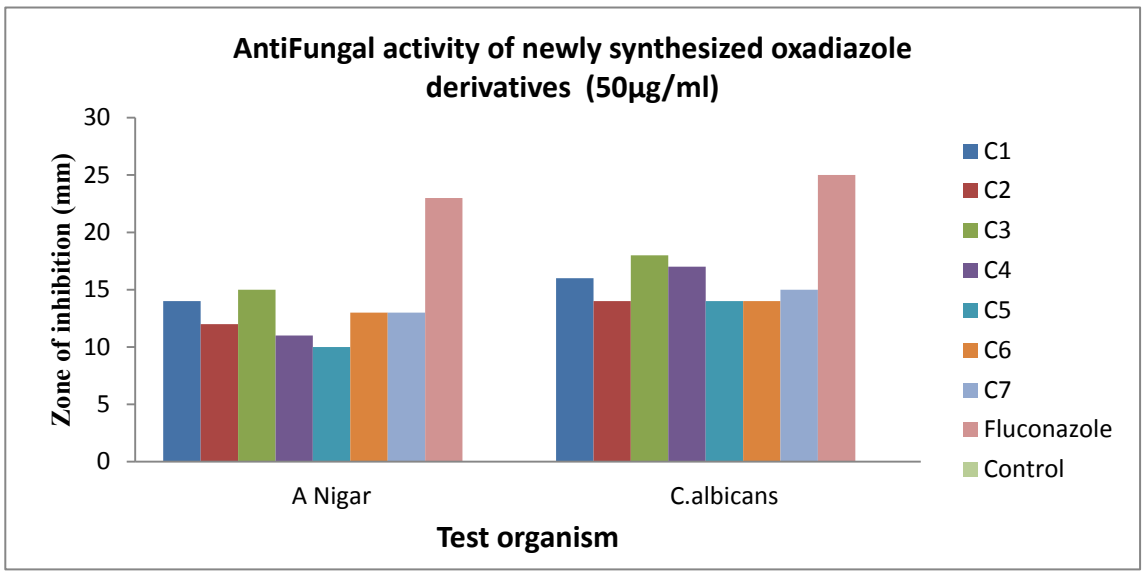


Figure 12. Antifungal activities (50 µg/ml)

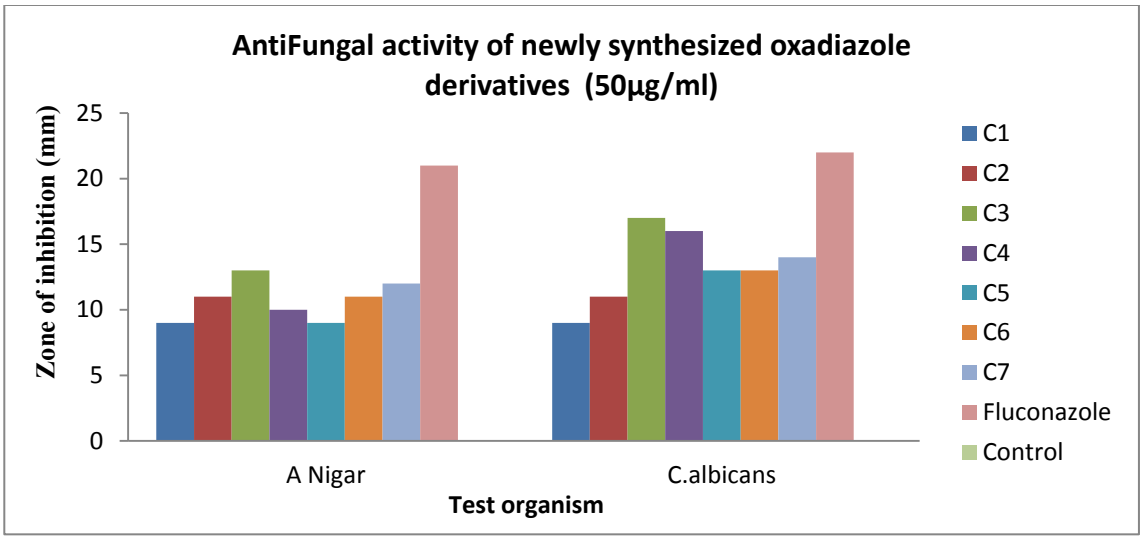


Figure 13. Antifungal activity (100 µg/ml)

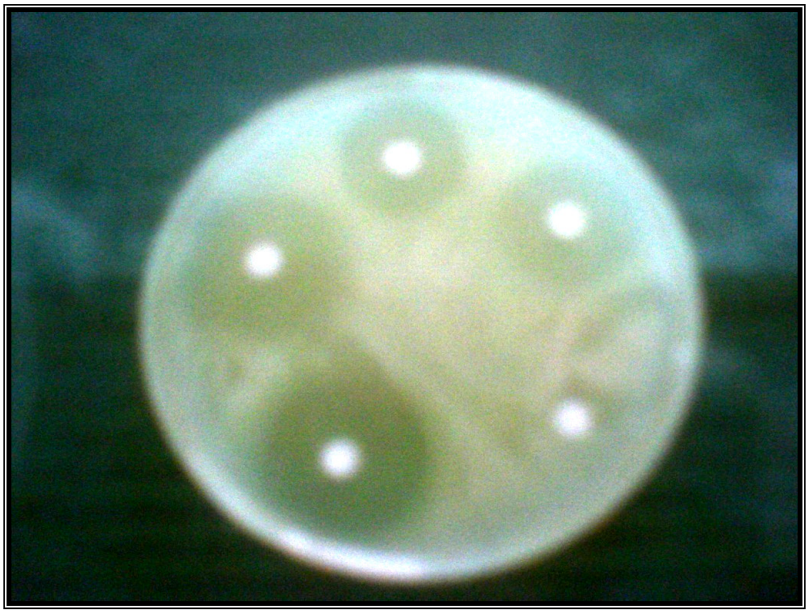


Figure 14. Zone of inhibition in antibacterial activity

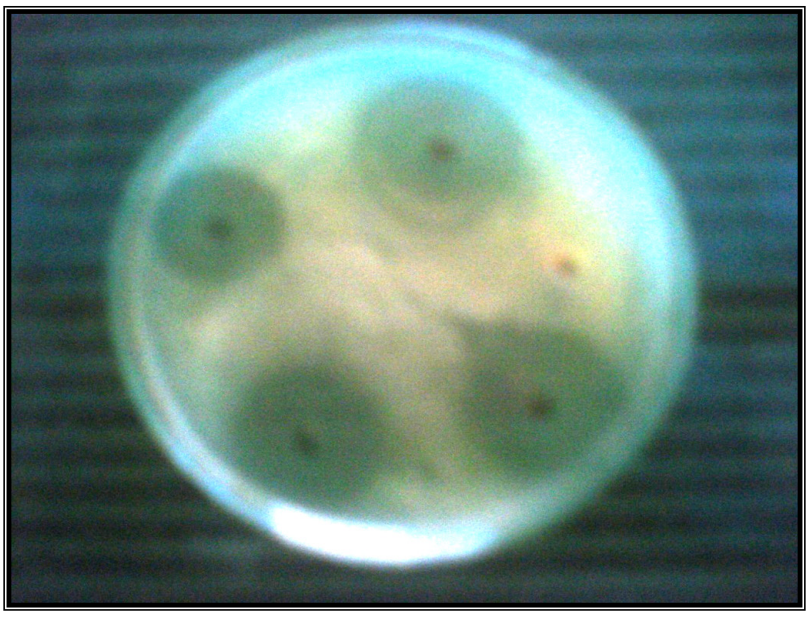


Figure 15. Zone of inhibition in antifungal activity

Table 3. Antifungal activity of synthesized compound

COMPOUND CODE	Zone of inhibition in mm			
	A. niger		*C.albicans*	
	50 µg	100 µg	50 µg	100 µg
C1	9	14	9	16
C2	11	12	11	14
C3	13	15	17	18
C4	10	11	16	17
C5	9	10	13	14
C6	11	13	13	14
C7	12	13	14	15
Fluconazole	21	23	22	25
Control	-	-	-	-

2.2.2. Anticonvulsant activity:

2.2.2.1. Maxeimal Electroshock-induced Seizures (MES test)

Albino mice (20-25g) were used in this test. Animals were divided in groups of six and were stimulated through corneal electrodes to 50mA current at a pulse of 60 Hz alternating current for 2s. The mice were previously administered *i.p.* with the test drug solution in polyethylene glycol at three dose levels (50,150 and 350 mg/kg), the anticonvulsant activity was assessed after 30 minutes and 4h intervals of administration. The abolition of hind limb tonic extensor spasm was recorded as a measure of anticonvulsant activity.

2.2.2.2. Anticonvulsant Screening

In the preliminary screening, each compound was administered as i.p. injection at three dose levels (50, 150 and 350 mg/kg), the anticonvulsant activity was assessed after 30 min and 4 h intervals of administration. The anticonvulsant efficacy was evaluated by maximal electroshock-induced seizure (MES) using reported procedure [88] and the data are presented in Table below.

2.2.2.3. Neurotoxicity Screen

Minimal motor impairment was measured in mice by the rotarod test. The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions /min. The rod diameter was 3.2 cm. Trained animals were given i.p. injection of the test compounds 50, 150 and 350 mg/kg. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min. in each of the trials. All the animal experimental protocols have met with the approval of the Institutional Animal Ethics Committee (IAEC).

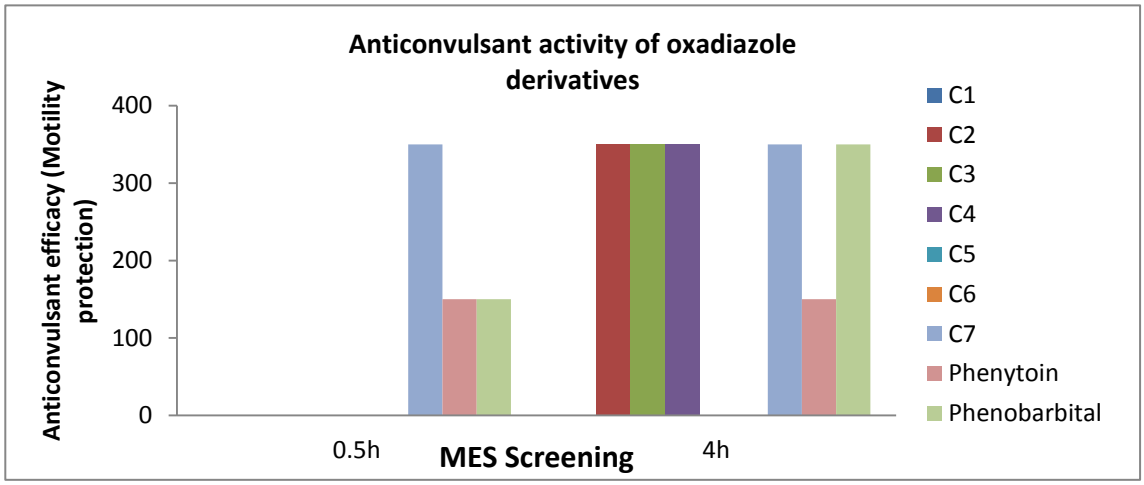


Figure 16. Anticonvulsant activity

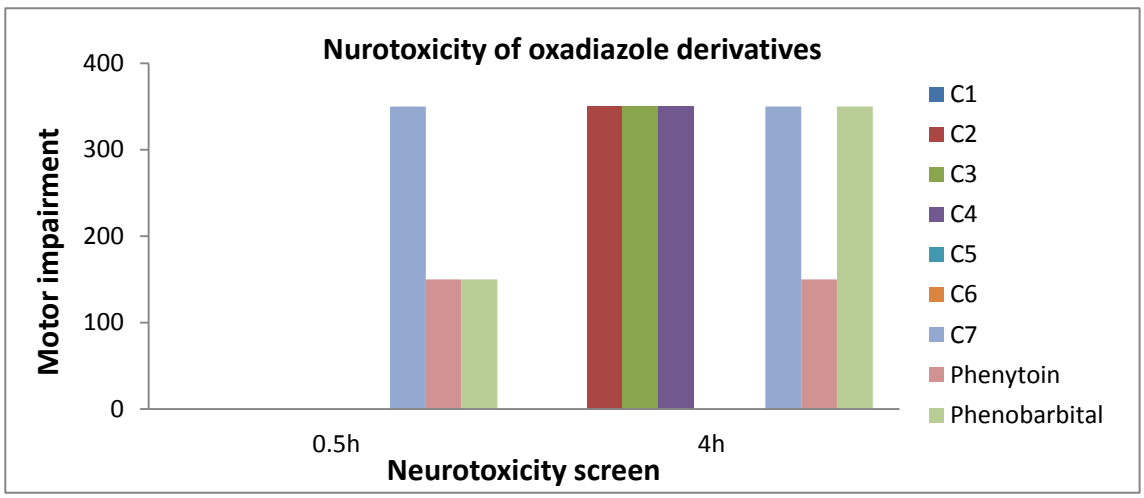


Figure 17. Neurotoxicity

Table 4. Anticonvulsant and neurotoxicity results of compounds

Compound No.	Intraperitonial injection in mice			
	MES screen		Toxicity screen	
	0.5h	4h	0.5h	4h
C1	350	-	-	-
C2	350	350	-	350
C3	350	-	-	350
C4	-	350	-	350
C5	350	350	-	-
C6	-	-	-	-
C7	150	350	350	350
Phenytoin	50	50	150	150
Phenobarbital	150	50	150	350

Doses of 50, 150 and 350 mg/kg were administered. The figure in the Table indicates the minimum dose whereby bioactivity was demonstrated in half or more of the animals. The animals were examined 0.5 and 4 h after administration. (-) indicates an absence of activity at the maximal dose administered (350 mg/kg).

3. Results and Discussion

The structures of all the newly synthesized derivatives were confirmed by chromatographic and spectroscopic (IR, 1H-NMR, 13C NMR, and mass) methods. Both analytical and spectral data of all the synthesized derivatives were in full agreement with the proposed structures.

The characteristic C=N band (1680–1520 cm^{-1}) of medium intensity and a medium-strong band at 1300-1050 cm^{-1} were identified in each IR spectra;

The synthesized compounds **(C1-C7)** were initially screened at 50, 150 and 350 mg/kg intra-peritoneally in mice for anticonvulsant activity (Table 4). All the compounds except **(C6)** exhibit anticonvulsant activity. In the MES test compounds **(C7)** with substituents at position 5 of oxadiazole ring, respectively, showed activity at 150 mg/kg after 0.5 h. On the other hand, compounds **C1, C2, C3, and C5** showed protection in mice at the dose level of 350 mg/kg after 0.5 h. Some compounds like **C2, C4, C5** and **C7** were also active after 4 h extended period of time. Compound **(C4)** with 4-(4-fluoro-phenyl)-4-oxo-butanoic acid substitution at position 5 of oxadiazole ring was active at lower dose of 50 mg/kg after 4 h. Thus compound **(C4)** showing activity at lower dose of 50 mg/kg seems to be potent in anticonvulsant MES screening.

In the rotarod neurotoxicity screening compounds **C1, C2, C3, C4 and C5** were devoid of toxicity at the dose of 350 mg/kg at 0.5 h. Compounds **C2, C3** and **C4** were toxic at the dose of 350 mg/kg after 4 h. Compounds **C7** were toxic after 0.5 h and 4 h. However, all the compounds were less toxic than phenytoin (150 mg/kg).

4. Conclusion

In general, Most of the oxidiazole derivatives showed antimicrobial activity. The oxidiazole derivatives, Substitution of p-F, p-Br, p-Ch3, at a phenyl ring showed potent antimicrobial activity and Substitution of p-Cl, and p-C2h5 showed the potent anti fungal activity Substitution of p-Cl, p-H3CO, P-F, p-Br and p-C2H5 at phenyl ring showed potent anticonvulsant activity against MES test. All derivatives not showed neurotoxicity at short period of time. The methyl substitution not showed the anticonvulsant activity against MES test.

References

[1] P. Sengupta, M. Mal, S. Mandal, J. Singh, and T. K. Maity, "Evaluation of antibacterial and antifungal activity of some 1, 3, 4 oxadiazoles," Iranian Journal of Pharmacology and Therapeutics, vol. 7, no. 2, pp. 165-167, 2008.

[2] N. Bhardwaj, S. K. Saraf, P. Sharma, and P. Kumar, "Syntheses, evaluation and characterization of some 1, 3, 4-oxadiazoles as antimicrobial agents," E-Journal of Chemistry, vol. 6, no. 4, pp.1133-1138, 2009.

[3] Hui, X. P.; Chang-Hu, C.; Zhang, Z. Y., Ind. J. Chem., 2000, 41(B), 2176-2179.

[4] Mulichen, N. D.; Wilson, M. W.; Connor, D. T., J. Med. Chem., 1993, 1090-1099.

[5] Garudachari, B.; Isloor, A.M.; Satyanaraya, M.; Ananda, K.; Fun, H-K. Synthesis, characterization and antimicrobial studies of some new trifluoromethyl quinoline-3-carbohydrazide and 1, 3, 4-oxadiazoles. RSC Adv,- **2014**, 4(58), 30864-30875.

[6] Chandrakantha, B.; Shetty, P.; Nambiyar, V.; Isloor, N.; Isloor, A.M. Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety. Eur. J. Med. Chem., **2010**, 45(3), 1206-1210.

[7] Rane, R.A.; Bangalore, P.; Borhade, S.D.; Khandare, P.K. Synthesis and evaluation of novel 4-nitropyrrole-based 1,3,4-oxadiazole derivatives as antimicrobial and anti-tubercular agents. Eur. J. Med. Chem., **2013**, 70, 49-58.

[8] Khalilullah, H.; Khan, S.; Nomani, M.S.; Ahmed, B. Synthesis, characterization and antimicrobial activity of benzodioxane ring containing 1, 3, 4-oxadiazole derivatives. Arabian. J. Chem., **2016**, 9(2), 1029-1035.

[9] Masciocchi, D.; Villa, S.; Meneghetti, F.; Pedretti, A.; Barlocco, D.; Legnani, L.; Toma, L.; Kwon, B.M.; Nakano, S.; Asai, A. Biological and computational evaluation of an oxadiazole derivative (MD77) as a new lead for direct STAT3 inhibitors. MedChemComm, **2012**, 3, 592-599.

[10] Shin, D.S.; Masciocchi, D.; Gelain, A.; Villa, S.; Barlocco, D.; Meneghetti, F.; Pedretti, A.; Han, Y.M.; Han, D.C.; Kwon, B.M. Synthesis, modeling, and crystallographic study of 3, 4-disubstituted-1, 2, 5-oxadiazoles and evaluation of their ability to decrease STAT3 activity. MedChemComm, **2010**, 1, 156-164.

[11] Desai, N.; Dodiya, A.M.; Rajpara, K.M.; Rupala, Y.M. Synthesis and antimicrobial screening of 1, 3, 4-oxadiazole and clubbed thiophene derivatives. J. Saudi Chem. Soc., **2014**, 18(3), 255-261.

[12] Karthikeyan, M.S.; Prasad, D.J.; Mahalinga, M.; Holla, B.S.; Kumari, N.S. Antimicrobial studies of 2,4-dichloro-5-fluorophenyl containing oxadiazoles. Eur. J. Med. Chem., **2008**, 43(1), 25-31.

[13] R. Fra´nski, "Biological activities of the compounds bearing 1,3,4-oxa(thia)diazole ring," Asian Journal of Chemistry, vol. 17, no. 4, pp. 2063-2075, 2005.

[14] J. Parekh and S.Chanda, "In vitro antimicrobial activity of Trapa natans L. fruit rind extracted in different solvents," African Journal of Biotechnology, vol. 6, no. 6, pp. 766–770, 2007.

[15] X. Yao, M. Jericho, D. Pink, and T. Beveridge, "Thickness and elasticity of gram-negative murein sacculi measured by atomic force microscopy," Journal of Bacteriology, vol. 181, no. 22, pp. 6865-6875, 1999.