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Synthesis, Characterisation and Biological Evaluation of Novel 1,2,4 Oxadiazole Derivatives

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A B S T R A C T

A series of 1,2,4 Oxa di azole derivatives5 (a-g) were prepared by reaction of P-Substituted Aldehydes(4) with hydroxyl amine hydro chloride in NMP & CDI ,DBU to get target compounds. The Structures of the Compounds are confirmed by IR, ^{1}H NMR &^{13}C NMR Spectral data, Elemental Analysis, Mass spectral data. The compounds are also evaluated for their anti microbial and antifungal activity, among them 5e& 5d are found as potent activity.

Keywords: Synthesis, Antimicrobial & Anti Fungal Activity, 1,2,4 oxa di Azoles, NMP,CDI,DBU

A R T I C L E I N F O

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1. Introduction

Heterocyclic compounds are organic compounds containing at least one carbon atom and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. The name comes from the Greek word “heteros” which means “different.” A variety of atoms, such as N, O, S, Se, P, Si, B can be incorporated in to ring structures.

Among heterocycles, nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis [1]. Nitrogen-containing heterocycles have been used as medicinal compounds for centuries, and form the basis for many common drugs such as Captopril [1] and Nitrogen containing hetero cycles occur in a diversity of natural products and drugs and are of great importance in a wide variety of applications. Aromatic nitrogen heterocycles may contain another heteroatom, such as the oxygen in isoxazoles, oxazoles, 1,3,4-oxadiazoles, and 1,2,4-oxadiazoles. Among the drugs containing aromatic five-membered nitrogen heterocycles are cholesterol-reducing Atorvastatin [2], anti-inflammatory Celecoxib [3], antifungal Fluconazole [4], and antihypertensive Losartan [5]. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, nucleic acids, ATP and serotonin [1]. Oxadiazole, a heterocyclic nucleus has attracted a wide attention for the chemist in search for the new therapeutic molecules. Oxadiazoles and their derivatives are considered as simple five membered heterocycles possessing one oxygen and two nitrogen atoms. The replacement of two -CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. There are 4 isomers of oxadiazole as shown in the figures below. [Fig.1]

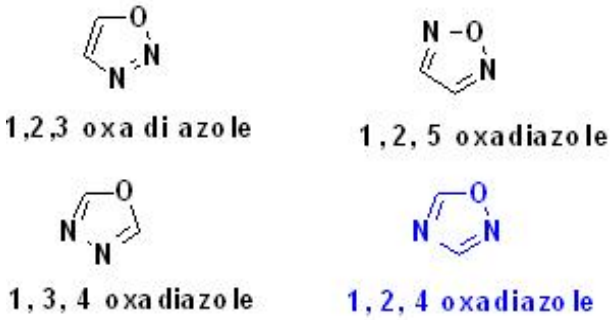


Figure 1

Electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom. Nitrogen-oxygen containing heterocycles are of synthetic interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities [2].

The interest in five-membered systems containing one oxygen and two nitrogen atoms (positions 1, 2, and 4) stems from the occurrence of saturated and partially saturated 1,2,4-oxadiazoles in biologically active compounds and natural products [3,4]. Oxadiazole rings have been introduced into drug discovery programs for several different purposes. In some cases, they have been used as an essential part of the pharmacophore, favorably contributing to ligand binding [5]. In other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker to place substituents in the appropriate orientation [6] as well as modulating molecular properties by positioning them in the periphery of the molecule [4]. It has also recently been shown that significant differences in thermodynamic properties can be achieved by influencing the water architecture within the aldose reductase active site by using two structurally related oxadiazole regioisomers [7]. Also, oxadiazoles have been used as replacements for carbonyl containing compounds such as esters, amides, carbamates, and hydroxamic esters [8]. In drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, including Zibotentan [1] as an anticancer agent [9] and Ataluren (2) for the treatment of cystic fibrosis [10]. So far, one oxadiazole containing compound, Raltegravir [11], an antiretroviral drug for the treatment of HIV infection, has been launched onto the market place. It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes, obesity [12], inflammation [13] cancer [14] and infection [15]. Aside from being biologically active themselves, 1,2,4- oxadiazoles also present an important linking site, for instance, for terminal amino groups of biologically important molecules. There are many drugs containing 1,2,4-oxadiazoles also many molecules are under development stages. Few drugs containing oxadiazole unit are mentioned below.

The 1, 2, 3-isomer is unstable and reverts to the di azo ketone tautomer [16]. Oxadiazoles were discovered against the schistosomiasis-causing fluke in the year 2008. It did not show any negative effects on humans. The stable oxadiazoles appear in a variety of pharmaceutical drugs including raltegravir (anti retroviral), butalamine, fasiplon, oxolamine and pleconaril. Tiodazosin, nosapidil, furamizole are other examples. The oxadiazoles were successfully tested against various diseases and hence are of importance in pharmaceutical chemistry due to their diverse medicinal potential. Nitrogen and oxygen containing compounds are always of synthetic interest. This is because there are large number of natural and synthetic compounds having nitrogen and oxygen with useful biological properties [17]. The five-membered heterocyclic 1,2,4-oxadiazole moitie is synthetic and pharmacological interest. It also forms an important constituent of biologically active compounds including natural products [18]. Sawyer et al. have

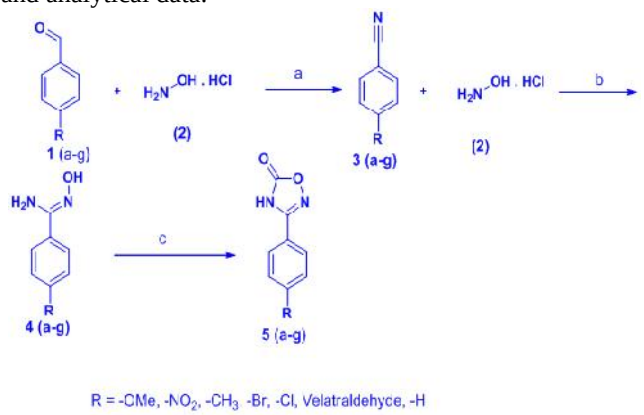
described such com- pounds as bioisosteres for amides and esters [19], with the 1,2,4-oxadiazoles showing higher hydrolytic and metabolic stability.

2. Materials and Methods

Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. ^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Elemental analyses of the newly synthesized compounds were carried out on Perkin Elmer model 2400 C H N analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values. All reactions were carried out under argon inoven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of CDCl3-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm ,DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

Scheme I:

The synthetic route was depicted in scheme **I.** The title compounds 5(a-g) were synthesised in three sequential steps using different reagents and reaction conditions, the 5(a-g) were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.



Scheme 1

Reagents and reaction conditions: (a) NMP, 120-130^{0}C (**b**) Ethanol, Reflux (**c**) CDI, DBU, 1, 4 DI oxane, Reflux.

Experimental Section:

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (60–120 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H, for ^{13}C, respectively, in $CDCl_3$ solution with tetra methyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents.

Synthesis of 4-(Methoxy/nitro/methyl/Bromo/Chloro) benzonitrile 3(a-e) & 3,4-dimethoxybenzo Nitrile (3f):

The mixture of P-substituted Aldehydes (1 a-f) (**0.1 m.mol**) in NMP (10v) and Hydroxylamine hydrochloride (2) (0.5m.mol) was stirred at 150^{0}C for 2hr. The reaction mixture was cooled to Room Temparature and then chilled water (50 ml) was added to quench the reaction. The crude product was obtained by filtration, and then washed with water (50 mlx3). After dried under vacuum condition, compound 3 (a-f) was obtained as solids.

Synthesis of N'-hydroxy benzimidamide(4g) & N'-hydroxy-4-(Methoxy/nitro/methyl/Bromo/Chloro) benzimidamide 4 (a-e) & N'-hydroxy-3,4-dimethoxy benzimidamide (4f) :

In a round-bottom flask, nitrile (0.1 m.mol), DIEA (2 m.mol), hydroxylamine hydrochloride (1.5 m.mol) and abs. EtOH (10 v) were added. The resulting mixture was stirred at 80°C. The reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). EtOH was removed under reduced pressure. The mixture in AcOEt was then extracted 3X20 ml with HCl (1N)., Na_2CO_3 1M solution was then added to the aqueous solution to p^H 9-10. If product precipitated, it was then filtered, washed with water and dried. The amidoxime was dried in a vacuum dessicator.

Synthesis of 3-(4- Methoxy/nitro/methyl/Bromo/Chloro phenyl)-1, 2, 4-oxadiazol-5(4H)-one 5 (a-e) & 3-(3, 4-dimethoxy phenyl)-1, 2, 4-oxadiazol-5(4H)-one 5(f) & 3-phenyl-1, 2, 4-oxadiazol-5(4H)-one 5 (g):

In a round-bottom flask, amidoxime (0.1 m.mol), DBU (0.5 m.mol), CDI (1 m.mol) and dioxane (5 ml) were added. The resulting mixture was stirred at 90°C (1-1.5 h). The reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl (1N), Organic layers were dried over Sodium Sulphate and filtered before evaporation in vacuo. The product was dried in a vacuum dessicator.

Biological Activity:

Antibacterial activity:

All the newly synthesized 1, 2, 4 Oxa diazole derivatives were screened for their antibacterial and antifungal activity. For antibacterial studies microorganisms employed were Staphylococcus aureus ATCC 9144, Bacillus Cereus ATCC 11778, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 2853. For antifungal, Aspergillus Niger ATCC 9029 and Aspergillus fumigatus ATCC 46645 were used as organism. Both microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. For this, the compound whose MIC has to be determined is dissolved in serially diluted DMSO Then a standard drop of the culture prepared for the assay is added to each of the dilutions, and incubated for 16–18 hrs at 37^0c. MIC is the highest dilution of the compound, which shows clear fluid with no development of turbidity. The results are shown in the table 13. The order of activity was **5e>5d>5b>5c>5a>5f>5g**

3. Results and Discussion

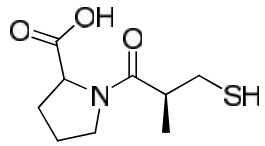
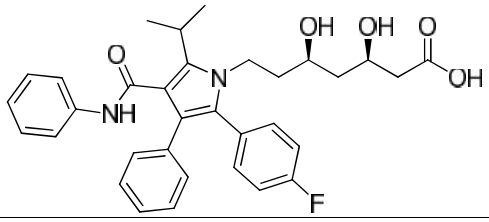
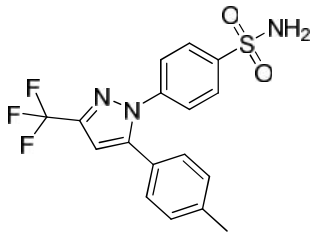
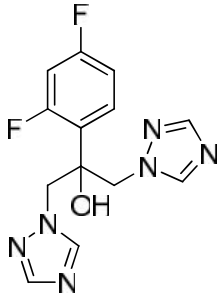
Characterization:

The IR spectrum of the title Compounds 5(a-g) has given stretching vibration at 3100cm^{-1}, due to the stretching vibration corresponding to Ar-H Stretching vibrations. The absorption peak at 2910 cm^{-1} is due to The stretching vibration corresponding to the SP^3 C-H (methyl gp).The strong Intensity absorption at 2250cm^{-1} is due to The stretching vibration of Nitrile, 550 cm^{-1} is due to The stretching vibration of C-Br bond. The weak Intensity absorption at 750 cm^{-1} corresponds to a C-Cl Stretching vibration.1150cm^{-1} corresponding to C-O Stretching. It has been observed from chemical structure of compound 5(a-g) that different pair of protons. The protons of methoxy group appeared as a singlet at δ =3.8 ppm, The protons of methyl group which is attached to benzene ring appeared as a Singlet at δ =2.3 ppm. The chemical shifts of the final compound carbon vary from δ = 165 to 23 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, the carbon chemical shift of the methoxy group at δ= 55ppm. The carbon chemical shift of the methyl group whichnis attached to benzene ring at δ= 25ppm.

Anti microbial screening:

The results of antimicrobial studies of newly synthesized compounds reveal that the compounds possess significant antibacterial and anti fungal activities. The results of these studies are given in (Table). From Anti bacterial screening results, it has been observed that compounds 5f and 5d possess good activity.

Table 1: Some of nitrogen containing heterocyclic drugs

	**Captopril (1)** (For treatment of hypertension)
	**Atorvastatin (2)** (Cholesterol-reducing)
	**Celecoxib (3)** (Anti-inflammatory)
	**Fluconazole (4)** (Antifungal)

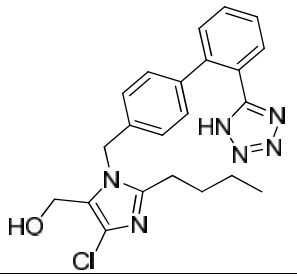
	**Losartan (5)** (Antihypertensive)

Table 2: Drugs containing oxadiazole core moiety

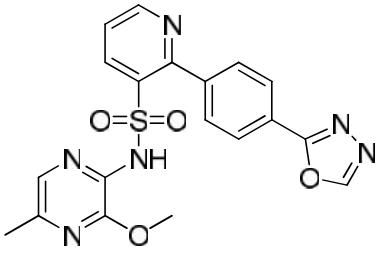
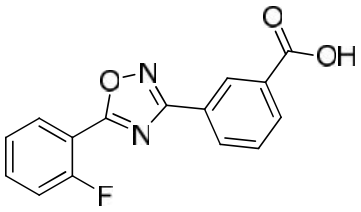
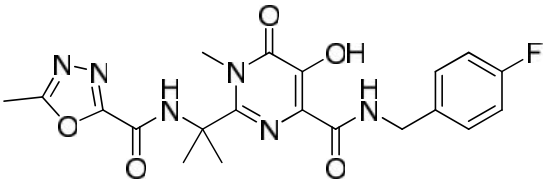
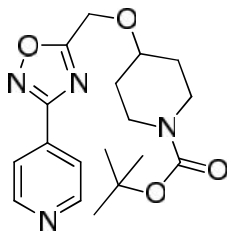
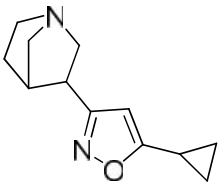
S.NO	Drug Name & Structure	Use
1	 **Zibotentan**	anticancer agent
2	 **Ataluren**	cystic fibrosis
3	 **Raltegravir**	antiretroviral
4		Anti parkinsonic
5		Anti glaucoma

Table 3: Melting points of P-Substituted benzo nitriles 3 (a-f)

Compound	Melting point	appearence	Yield (%)
3a	55-56^{0}C	White to off-white crystalline Powder.	75
3b	146-147^{0}C	Light yellow to light brown powder.	73
3c	At RT it is liquid, at 10^{0}c solid	liquid	76
3d	111-112^{0}C	Pale yellow powder	74
3e	90-92^{0}C	White crystals	78
3f	69-70^{0}C	Off white powder	80

Table 4: IR [KBr] Spectra of P-Substituted Benzo Nitriles 3 (a-f)

Compound	ν_{max} in cm^{-1}
3a	2250 cm^{-1}, 3100 cm^{-1}, 1150 cm^{-1}1620 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, C-O, Aromatic C=C, Stretching, wave numbers respectively.
3b	2270 cm^{-1}, 3090 cm^{-1}, 1530 & 1350cm^{-1} (doublet),1600 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, N-O(in nitro group), Aromatic C=C, Stretching, wave numbers respectively.
3c	2240 cm^{-1}, 3010 cm^{-1}, 2910cm^{-1},1610 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, SP^3 C-H(in Methyl group), Aromatic C=C, Stretching, wave numbers respectively.
3d	2255 cm^{-1}, 3013 cm^{-1}, 550cm^{-1},1600 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, C-Br, Aromatic C=C, Stretching, wave numbers respectively.
3e	2250 cm^{-1}, 3018 cm^{-1}, 750cm^{-1},1610 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, C-Cl, Aromatic C=C, Stretching, wave numbers respectively.
3f	2255 cm^{-1}, 3100 cm^{-1}, 1140 cm^{-1}1620 cm^{-1} due to stretching vibrations of Nitrile, Aromatic C-H, C-O, Aromatic C=C, Stretching, wave numbers respectively.

Table 5: ^{1}H NMR Spectra of P-Substituted Benzo Nitriles 3 (a-f)

Compound	^{1}HNMR (CDCl$_3$, 400 M.Hz) (δ ppm)
3a	3.9 (3H,S,-OC**H**$_3$), 7 (2H,d,Ar-H,ortho to –OCH$_3$), 7.8(2H,d,Ar-H,ortho to nitrile group)
3b	8(2H,d,Ar-H,ortho to Nitrile group), 8.5(2H,d,Ar-H,ortho to nitro group).
3c	2.3 (3H,S,- methyl protons which is attached to benzene ring), 7.4 (2H,d,Ar-H,ortho to –CH$_3$ group), 7.6(2H,d,Ar-H,ortho to nitrile group)
3d	7.8 (2H,d,Ar-H,ortho to –Br group), 7.6(2H,d,Ar-H,ortho to nitrile group)
3e	7.6 (2H,d,Ar-H,ortho to –Cl group), 7.55(2H,d,Ar-H,ortho to nitrile group)
3f	3.9 (6H,S,-OC**H**$_3$×2), 7 (1H,d,Ar-H,ortho to –OCH$_3$), 7.3(1H,d,Ar-H,ortho to nitrile group), 7.5(1H,S,ortho to methoxy & nitrile group)

Table 6: Melting points of Compounds 4 (a-g)

Compound	Melting point	Appearence	Yield (%)
4a	125-126^{0}C	off-white crystalline powder.	65
4b	140-142^{0}C	Light yellow powder.	62
4c	95-96^{0}C	liquid	66
4d	-	Pale yellow liquid	64
4e	180-182^{0}C	White crystals	68
4f	134-136^{0}C	Off white powder	60
4g	-	liquid	70

Table 7: IR [KBr] Spectra of Compounds 4(a-g)

Compound	ν_{max} in cm^{-1}
4a	3320 & 3400 cm^{-1}, 3550 cm^{-1}, 3100 cm^{-1}, 1150 cm^{-}1, 1620 cm^{-1} due to stretching vibrations of –NH (in –NH$_2$), -OH, Aromatic C-H, C-O, Aromatic C=C, Stretching, wave numbers respectively.

4b	3300 & 3420 cm^{-1}, 3550 cm^{-1}, 3090 cm^{-1}, 1530 & 1350cm^{-1} (doublet),1600 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, N-O(in nitro group), Aromatic C=C, Stretching, wave numbers respectively.
4c	3320 & 3400 cm^{-1}, 3550 cm^{-1}, 3010 cm^{-1}, 2910cm^{-1},1610 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, SP^3 C-H(in Methyl group), Aromatic C=C, Stretching, wave numbers respectively.
4d	3300 & 3420 cm^{-1}, 3550 cm^{-1}, 3110 cm^{-1}, 550cm^{-1},1600 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, C-Br, Aromatic C=C, Stretching, wave numbers respectively.
4e	3320 & 3420 cm^{-1}, 3560 cm^{-1}, 3018 cm^{-1}, 750cm^{-1},1610 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, C-Cl, Aromatic C=C, Stretching, wave numbers respectively.
4f	3310 & 3440 cm^{-1}, 3530 cm^{-1}, 3100 cm^{-1}, 1140 cm^{-1}1620 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, C-O, Aromatic C=C, Stretching, wave numbers respectively.
4g	3320 & 3400 cm^{-1}, 3550 cm^{-1}, 3100 cm^{-1}, 1600 cm^{-1} due to stretching vibrations of –NH (in $–NH_2$), -OH, Aromatic C-H, C-O, Aromatic C=C, Stretching, wave numbers respectively.

Table 8: ^{1}H NMR Spectra of Compounds 4 (a-g)

Compound	**^{1}HNMR (DMSO-d_6, 400 M.Hz) (δ ppm)**
4a	3.9 (3H,S,-OC**H**$_3$), 7 (2H,d,Ar-H,ortho to $–OCH_3$), 7.5(2H,d,Ar-H, ortho to benzimidamide group), 6.6 (2H,bs, $-NH_2$), 2(1H,bs)
4b	8(2H,d,Ar-H,ortho to benzimidamide group), 8.3(2H,d,Ar-H,ortho to nitro group), 6.2 (2H,bs, $-NH_2$), 1.4(1H,bs)
4c	2.34 (3H,S,- methyl protons which is attached to benzene ring), 7.3(2H,d,Ar-H,ortho to $–CH_3$ group), 7.8(2H,d,Ar-H,ortho to benzimidamide), 7.4 (2H,bs, $-NH_2$), 2.2 (1H,bs)
4d	7.5 (2H,d,Ar-H,ortho to –Br group), 7.8(2H,d,Ar-H,ortho to benzimidamide group), 6.6 (2H,bs, $-NH_2$), 2.1(1H,bs)
4e	7.6 (2H,d,Ar-H,ortho to –Cl group), 7.45(2H,d,Ar-H,ortho to benzimidamide group), 6.4 (2H,bs, $-NH_2$), 2(1H,bs)
4f	3.9 (6H,S,-OC**H**$_3$×2), 7 (1H,d,Ar-H,ortho to $–OCH_3$), 7.1(1H,d,Ar-H,ortho to benzimidamide group), 6.7(1H,S,ortho to methoxy & benzimidamide), 6.6 (2H,bs, $-NH_2$), 2(1H,bs)
4g	7.5-7.8(5H.m,Ar-H), 6.5 (2H,bs, $-NH_2$), 2(1H,bs)

Table 9: Melting points of Compounds 5 (a-g)

Compound	Melting point	Appearance	Yield (%)
5a	110-111^{0}C	Off-white crystalline powder.	57
5b	123-125^{0}C	Light yellow powder.	62
5c	65-66^{0}C	liquid	66
5d	-	Pale yellow liquid	64
5e	154-155^{0}C	White crystals	68
5f	124-126^{0}C	Off white powder	60
5g	89-90^{0}C	White solid	67

Table 10: IR [KBr] spectra of Compounds 5 (a-g)

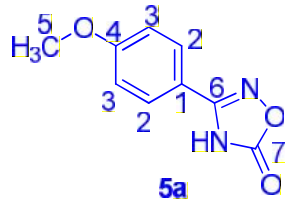
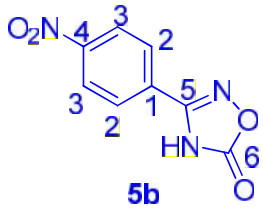
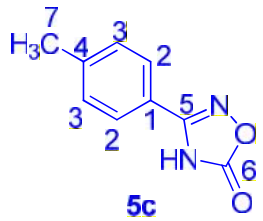
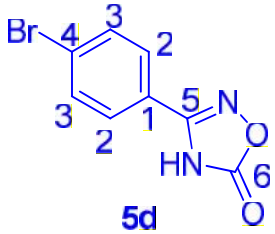
Compound	**ν_{max} in cm^{-1}**
5a	3400 cm^{-1}, 3100 cm^{-1}, 1720 cm^{-1} 1150 cm^{-1}, 1620 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, carbonyl(**C=O**), C-O, Aromatic C=C, Stretching, wave numbers respectively.
5b	3420 cm^{-1}, 3090 cm^{-1}, 1530 & 1350cm^{-1} (doublet),1600 cm^{-1}, 1710 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, N-O(in nitro group), Aromatic C=C, carbonyl(**C=O**) Stretching, wave numbers respectively.
5c	3320 cm^{-1}, 3010 cm^{-1}, 2910cm^{-1},1610 cm^{-1}, 1711 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, SP^3 C-H(in Methyl group), Aromatic C=C, carbonyl(**C=O**) Stretching wave numbers respectively.

5d	3320 cm^{-1}, 3110 cm^{-1}, 550cm^{-1},1600 cm^{-1}, 1715 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, C-Br, Aromatic C=C, Carbonyl(**C=O**) Stretching, wave numbers respectively.
5e	3340, 3018 cm^{-1}, 750cm^{-1},1610 cm^{-1} , 1715 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, C-Cl, Aromatic C=C, carbonyl(**C=O**) Stretching, wave numbers respectively.
5f	3320 cm^{-1}, 3100 cm^{-1}, 1140 cm^{-1}, 1620 cm^{-1}, 1715 cm^{-1} due to stretching vibrations of –NH Aromatic C-H, C-O, Aromatic C=C, Carbonyl(**C=O**) Stretching, wave numbers respectively.
5g	3330 cm^{-1}, 3100 cm^{-1}, 1600 cm^{-1}, 1711 cm^{-1} due to stretching vibrations of –NH, Aromatic C-H, C-O, Aromatic C=C, Carbonyl(**C=O**) Stretching wave numbers respectively.

Table 11: ^{1}H NMR Spectra of Compounds 5(a-g)

Compound	^{1}**HNMR (DMSO-d_6, 400 M.Hz) (δ ppm)**
5a	3.9 (3H,S,-OC**H**$_3$), 7 (2H,d,Ar-H), 7.5(2H,d,Ar-H,), 8 (bs,-NH)
5b	8(2H,d,Ar-H), 8.3(2H,d,Ar-H), 8 (bs,-NH)
5c	2.3 (3H,S,- methyl protons which is attached to benzene ring), 7.3(2H,d,Ar-H), 7.8(2H,d,Ar-H), 8 (bs,-NH)
5d	7.4 (2H,d), 7.8(2H,d,Ar-H,) , 8 (bs,-NH)
5e	7.6 (2H,d), 7.4(2H,d,Ar-H), 8 (bs,-NH)
5f	3.9 (6H,S,-OC**H**$_3$×2),7(1H,d), 7.11H,d,Ar-H,), 6.7 (1H,S)8 (bs,-NH)
5g	7.5-7.9(5H.m,Ar-H), 8 (bs,-NH)

Table 12: ^{13}C –NMR data of Compounds 5(a-g)

Structure of the compound(With numbering)	**^{13}CNMR (100 M.HZ, DMSO-d_6, δ ppm)**
 **5a**	120,130,115,165,55,160,155The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 respectively.
 **5b**	135,130,125,150, 157,165The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 respectively.
 **5c**	125,130,128,140, 158,165, 22The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_7 respectively.
 **5d**	125,128,131,125, 157,165The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 respectively.

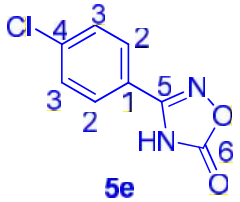
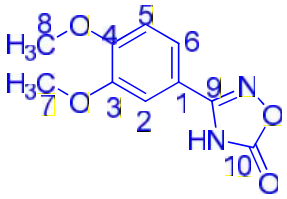
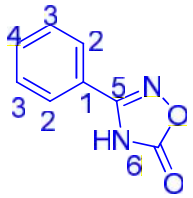
 **5e**	127,130, 128,135,155, 157 The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 respectively.
 **5f**	121,113, 148,151,111, 123, 55, 157,160,The signals are due to C_1 , C_2 , C_3 , C_4 , C_5 , C_6 C_7 &C_8, C_9,C_{10} respectively.
 **5g**	128-130 (Ar-C),158,160155 The signals are due to C_1 -C_4 , C_5 , C_6 respectively.

Table 13: Anti microbial Activity of Novel 1,2,4 oxa diazole derivatives 5 (a-g)

Compound	Antibacterial data in MIC(µg/ml)				Antifungal data in MIC (µg/ml)	
	Gram +ve Bacteria		Gram -ve Bacteria		A.niger	A.fumigatus
	S. aureus	B.cereus	P.aeruginosa	E.coli		
5a	8	7	5	7	14	15
5b	9	9	10	9	15	16
5c	8	8	9	9	15	15
5d	10	11	10	10	16	16
5e	12	12	11	10	18	18
5f	7	6	4	6	13	14
5g	7	5	4	6	12	13

4. Conclusion

Hetero cyclic compound containing oxa diazole nucleus plays most important role in the the field of clinical therapeutics. It shows wide range of activities for medication purpose. Vast number of oxa di azole containing compounds have been synthesized and evaluated for their biological activity. The various substituted oxadiazoles are having significant anti hypertensive activity, significant antineoplastic, antidepressant, Antipsychotic.

Whereas some of the derivatives of oxadiazoles are found to be effective as analgesic, antipsychotic, Antiarrhythmic, sedative hypnotics. Recently it was proven that, some of the important marketed oxa di azole nucleus containing drug having different biological or pharmacological activity were discussed in Table 1. In conclusion a series of new oxa di azole derivatives 5(a-g) were synthesized in good yield, characterized by different spectral studies and their biological activity have been evaluated. Various derivatives of oxa di azole derivatives showed potent anti fungal activity. Among the synthesised compounds 5e, 5d showed excellent anti bacterial and antifungal activity [Table 13].

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