ejpmr, 2019,6(10), 520-528

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL OXADIAZOLE DERIVATIVES FROM PHTHALIMIDE MOIETY

Nidhi Dhama*

Assistant Professor (Pharmaceutical Chemistry), Translam Institute of Pharmaceutical Education and Research, Meerut, 250001, U.P. India.

***Corresponding Author: Prof. Nidhi Dhama**

Assistant Professor (Pharmaceutical Chemistry), Translam Institute of Pharmaceutical Education and Research, Meerut, 250001, U.P. India.

Article Received on 13/08/2019 **Article Revised on 03/09/2019** **Article Accepted on 23/09/2019**

ABSTRACT

Oxadiazole ring has two carbon, two nitrogen and one oxygen atom. There are four types of oxadiazole rings such as 1,2,3-oxadiazole 1,2,4-oxadiazole, 1,3,4-oxadiazole and 1,3,5-oxadiazole. While 1, 3, 4-oxadiazole has been known for about 80 yrs. it is first and foremost chemical molecule due to its highest useful characteristic in different areas. The further name of 1,3,4-oxadiazoles are furo diazole, biazole, oxybiazole. The 1, 3, 4-oxadiazole derivatives have been found to exhibit diverse biological activities such as anti-inflammatory, analgesic, anti-fungal and antibacterial activities. Apart from that it is also important for tuberculosis, cancer, HIV infection, low glucose levels and many other pathological conditions. In this research work we have synthesized and evaluated a number of derivatives having an oxadiazole moiety. Oxadiazole has an important role for this determination and this moiety may serve as new pattern for the synthesis of safer & prospective antimicrobial agents. In view of the broad spectrum of important biological activities including anti-inflammatory, antibacterial, antifungal and analgesics etc of oxadiazole derivatives, it has been well thought-out useful to work on this system i.e. oxadiazole skeleton. Oxadiazole derivative is synthesized by using the 3-nitro-phthalimide. The structures of the newly synthesized compounds have been established on the basis of spectral analytical data such as IR, ^{1}H-NMR, Mass and elemental analysis. 4-nitro-2-((5-propyl-1,3,4-oxadiazol-2-yl)methyl)isoindoline-1,3-dione shows broad spectrum activities of antibacterial and antifungal. All the synthesized compounds are evaluated for anti-bacterial activity by disc diffusion technique. The minimum inhibitory concentrations (MIC) are determined by using the twofold serial dilution technique.

KEYWORDS: Oxadiazole derivatives, Antibacterial and Antifungal.

INTRODUCTION

Medicinal chemistry is defined as a discipline which concerned with determination of the influence of chemical structure on biological activity. In medicinal chemistry one can synthesize new compound with the several modification in the main structure and then can identify their biological activity.[1,2]

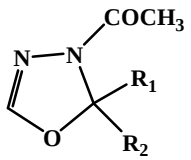
Medicinal chemistry or pharmaceutical chemistry is a regulation at the connection of chemistry. It includes the identification, synthesis and development of new chemical entities suitable for therapeutic use. It also involves the study of existing drugs, their biological properties and their quantitative structure-activity relationships (QSAR).Pharmaceutical chemistry focused on quality characteristics of medicines and aims to secure fitness for the intention of medicinal products.

It is well known that nitrogen and oxygen containing compounds are essentially used in medicine for the treatment of different types of fungal and bacterial infections along with the treatment of gastric ulcer, cancer etc.[7] Bacteria can live in virtually any kind of environment, from hot to super cold, some even in radioactive waste. A number of bacteria live in our bodies, on our skin, airway, mouth, digestive and urinary tracts- most of the time without causing any harm to the host. A relatively small number of bacteria cause diseases in humans. Some of the deadly diseases and devastating epidemics in human history have been caused by bacteria, including: Cholera, Diphtheria, Dysentery, pneumonia, tuberculosis and typhoid. Mycosis is a fungal infection in or on a part of the body, or a disease caused by a fungus. Some fungi reproduce through very small airborne spores which people either inhale or pick up on their skin – i.e. must fungal infections start in the lungs or the skin. Patients on long term strong antibiotics are at higher than normal risk of developing a fungal infection. Strong antibiotics can eventually reduce the population of good bacteria which help which help maintain the balance of microorganisms in the intestine, mouth, vagina and other parts of the body. If enough of these good bacteria are also destroyed, the fungi have an opportunity to grow and

cause health problems for the host. But we synthesized a oxadiazole derivative 4-nitro-2-((5-propyl-1,3,4-oxadiazol-2-yl)methyl) isoindoline-1,3-dione which shows the activity against the bacterial and fungal infections.

1,3,4- oxadiazole is a versatile lead molecule for designing potential bioactive agents. These characteristic has attracted wide attention of the researcher in research of new therapeutic molecules in the field of medicinal chemistry. Oxadiazole are an important type of oxygen and nitrogen containing aromatic five membered heterocyclic compounds, possess desirable electronic and charge-transport properties and the various functional groups are easily introduced into the structurally rigid oxadiazole ring .

Literature review reveals that chemical modification of bioactive components is one of the most common approaches in drug discovery with improved therapeutic effect and the wide occurrence of nitrogen containing heterocycles in bioactive natural products and pharmaceuticals have made them important synthetic target.

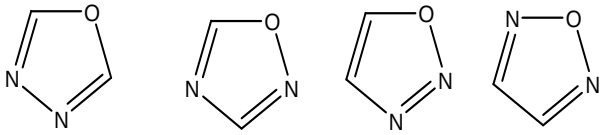


Structure of 1, 3, 4-oxadiazole.

The 1,3,4-oxadiazole derivatives have been found to exhibit diverse biological activities such as anti-inflammatory, analgesic, anti-fungal, antibacterial, antitubercular, anticancer, antiretroviral, hypoglycemic and other biological properties. Therefore, they have attracted growing concentration in the field of drug discovery.

Properties of Oxadiazole derivatives

Oxadiazoles are a class of heterocyclic aromatic chemical compound of the azoles family; with the molecular formula $C_2H_2N_2O$. Oxadiazole ring consist of two carbon atoms, two nitrogen atoms and one oxygen atom. There are four types of oxadiazole rings. They are 1,3,4-oxadiazole**(1)**, 1,2,4-oxadiazole**(2),** 1,2,3-oxadiazole**(3),** 1,2,5-oxadiazole **(4).**

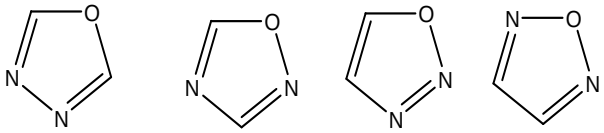


(1) (2) (3) (4)

Chemistry of oxadiazole

1, 3, 4-Oxadiazole is a heterocyclic compound consist of an oxygen atom and two nitrogen atoms in a five-membered ring. It is resulting from furan by substitution of two methylene groups (=CH_2) with two pyridine type nitrogen (-N=).[3,4] The three known isomers are:

1, 3, 4-oxadiazole **(1)**
1, 2, 4-oxadiazole **(2)**
1, 2, 3-oxadiazole **(3)**
1, 2, 5-oxadiazole **(4)**

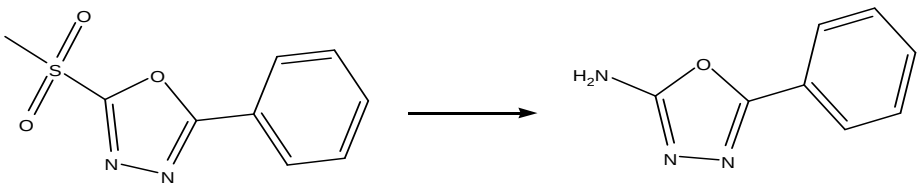


(1) (2) (3) (4)

Substitution Reaction Of 1, 3, 4-Oxadiazole

Direct Ring Substitution

The possibility of electrophilic attack in acidic medium is strongly hindered due to protonation of the nuclear nitrogen. Thus no nitration or sulphonation or halogenation of unsubstituted 1, 3, 4-oxadiazole has been reported. Nucleophilic substitution of substituted 1, 3, 4-oxadiazole with other functional group is also difficult. 2-phenyl-5-amino-1, 3, 4-oxadiazole is obtained by ammonolysis of 2-phenyl-5-methane sulphonyl-1, 3, 4-oxadiazole.[11]

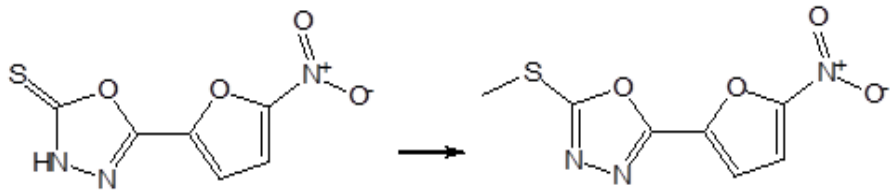


2-phenyl-5-methane sulphonyl-1,3,4-oxadiazole

2-phenyl-5-amino-1,3,4-oxadiazole

Alkylation

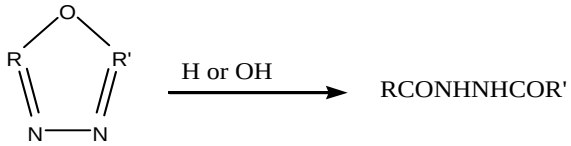
Due to mesomerism 1, 3, 4-oxadiazoline-5-thione, 1, 3, 4-oxadiazoline-5-one and 2-benzyl-5-aryl-1, 3, 4-oxadiazole may be alkylated. 2-(2-Nitro-5-furyl)-1, 3, 4-oxadiazole-5-thione is methylated by the action of methyl iodide in the presence of ethanolic potassium hydroxide to give 2-(2-Nitro-5-furyl)-5-methylthio-1, 3, 4-oxadiazole.[14]

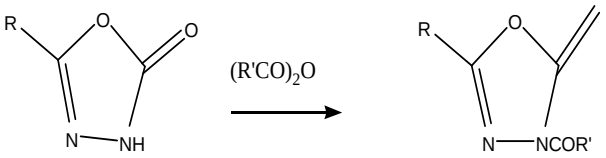


2-(2-Nitro-5-furyl)-1,3,4-oxadiazole-5-thione 2-(2-Nitro-5-furyl)-5-methylthio-1,3,4-oxadiazole

Hydrolysis

1, 3, 4-Oxadiazole are stable neutral substances. Their 2, 5-dialkyl derivatives are hydrolyzed by acid and alkali to give hydrazides. In contrast, diaryl derivatives are more resistance to hydrolysis.[15]



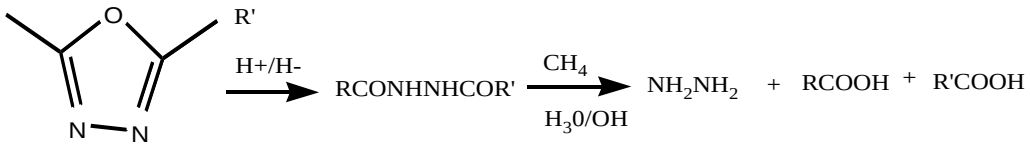


Reactions involving ring cleavage

Alkyl, aryl and heterocyclic substituted-1, 3, 4-oxadiazole ring undergo cleavage to 2,5-dialkyl-1,3,4-oxadiazole when attacked by acids or bases.[17]

Acylation

In 1, 3, 4-oxadiazoline-5-ones, acylation takes place at ring nitrogen.



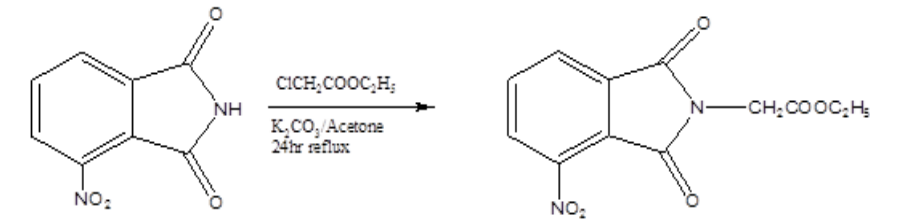
MATERIALS AND METHODS

The melting points of the synthesized derivatives were estimated by the capillaries method and are uncorrected. Spectral analysis of newly synthesized compounds was done. IR Spectra (KBr), ^{1}H NMR ($CDCl_3$) and the mass spectra (dry helium) of synthesized compounds were recorded from Shri Krishna Analytical Service (New Delhi).

GENERAL PROCEDURE

Step I

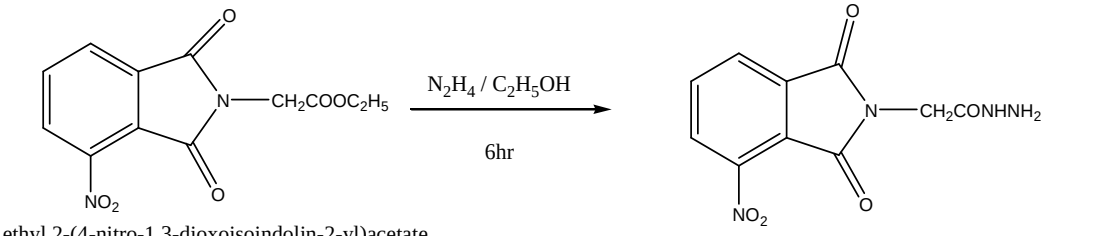
A mixture of 3-nitro-phthalimide (0.1mol), ethylchloroacetate (0.1 mol) and anhydrous potassium carbonate (19.5gm, 0.15mol) in dry acetone were refluxed on a water bath for 24 hours at 70^0c. The resultant reaction mixture was cooled and filtered. From the filtrate excess of acetone was removed by distillation. This reaction mixture of filtrate was then poured on to the ice cold water and stirred well. The organic layer was extracted with ether and further the ether layer was washed with 5% HCl and dried over anhydrous sodium sulphate. Ether layer was evaporated by drying on water bath. Finally the resultant collected liquid was purified under reduced pressure to give pure ethyl 2-(4-nitro-1, 3-dioxoisoindolin-2-yl) acetate.



3-nitro-phthalimide ethyl 2-(4-nitro-1,3-dioxoisoindolin-2-yl)acetate

Step II.

A mixture of ethyl 2-(4-nitro-1, 3-dioxoisoindolin-2-yl) acetate (0.05mol), hydrazine hydrate (99% 0.07m0l) in ethanol (100ml) was refluxed for 6 hours. From the resultant mixture excess of ethanol was removed by distillation. On cooling, from the resultant mixture, white needle like 2-(4-nitro-1, 3-dioxoisoindolin-2-yl) acetohydrazide crystals of began to separate. It was collected and then recrystallized from ethanol.

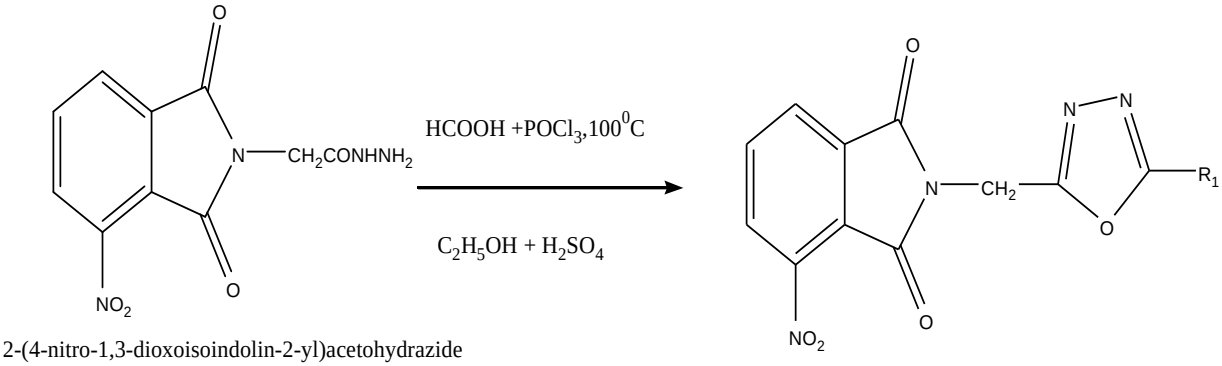


ethyl 2-(4-nitro-1,3-dioxoisoindolin-2-yl)acetate

2-(4-nitro-1,3-dioxoisoindolin-2-yl)acetohydrazide

Step III.

A equimolar mixture of 2-(4-nitro-1, 3-dioxoisoindolin-2-yl) acetohydrazide (0.01mol) with different aromatic carboxylic acid (0.01mol) was refluxed at 110^0c with phosphorous oxychloride (10vol) for 2-3 hours. The reaction mixture was cooled at room temperature, the excess of $POCl_3$ was concentrated through high vacuum, the residue was quenched with ice water and the solid separated was filtered and dried. Newly synthesized compound was wash with water and further purified by recrystallization with ethanol to afford 1, 3, 4-Oxadiazole derivative as white crystalline solid.

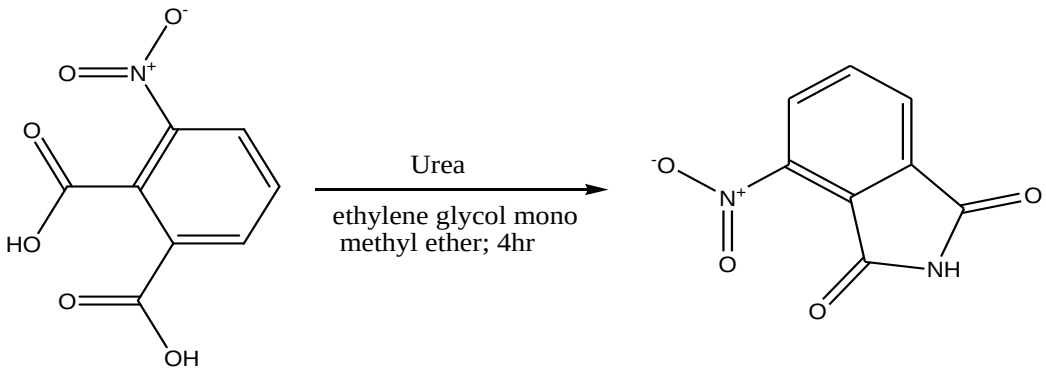


2-(4-nitro-1,3-dioxoisoindolin-2-yl)acetohydrazide

1,3,4-Oxadiazole derivative

Preparation of 3-Nitro-Phthalimide

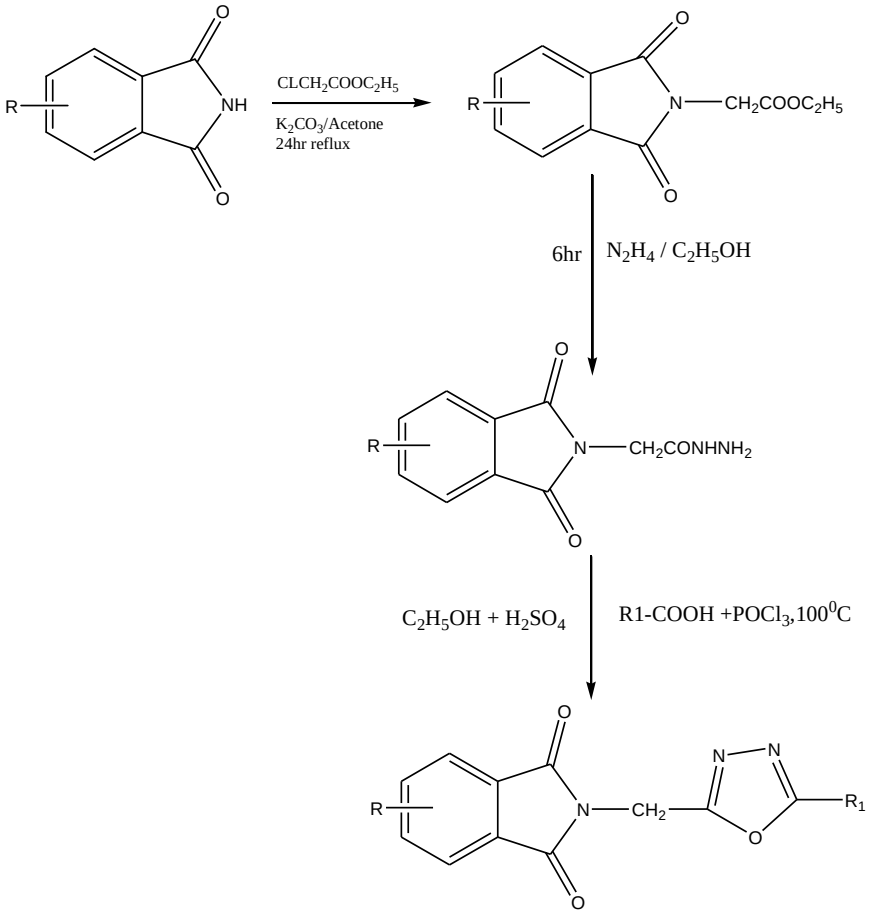
A mixture of 3-nitro phthalic acid (21.1g, 0.01 mol) and urea (6 g, 0.1 mol) was refluxed in ethylene glycol mono methyl ether (40 ml) for 4hr. The resulting mixture of 3-nitro-phthalimide was obtained; the crude nitration products was filtered and wash with ice cold water repeatedly for four to five time. This product was purified by recrystalization from 95% ethyl alcohol. This furnished 3-nitro-phthalimide was obtained as white crystal (0.4 g, 42.27%) of melting point 137-139 ^{0}C.



3-nitro-phthalicacid

3-nitro-phthalimide

REACTION SCHEME



Oxadiazole derivarives

Physical data of newly synthesized oxadiazole derivatives

Compounds	Molecular formula	Molecular weight	Physical state	R^f value	Melting point (^OC)	% Yield
4a	$C_{11}H_6N_4O_5$	274.19	White crystalline solid	0.67	205-252	60.3
4b	$C_{12}H_8N_4O_5$	288.22	Light yellow solid	0.69	208-210	56.6
4c	$C_{14}H_{12}N_4O_5$	316.28	Light yellow solid	0.82	260-262	65
4d	$C_{28}H_{40}N_4O_5$	512.64	Yellow solid	0.86	210-212	59.3
4e	$C_{20}H_{24}N_4O_5$	400.43	White crystalline solid	0.93	218-220	43.2
4f	$C_{18}H_{12}N_4O_6$	380.31	Yellow solid	0.72	238-240	58.7
4g	$C_{17}H_9ClN_4O_5$	384.73	Yellow crystalline solid	0.83	260-262	65.3

Spectral Chracterization of Synthesized Compounds

The IR spectra of all the derivatives **4a-g** showed absorption band at 3010-3024 cm-^{1} due to CH stretching, 1679-1697 cm-^{1} due to C=O stretching, 1545-1563 cm-^{1} due to Aromatic NO_2 stretching, 1617-1621 cm-^{1}due to C=N stretching, 1517 cm-^{1}due to N-N stretching, 1486-1504 cm-^{1}due to C=C stretching and 1095 cm-^{1} due to C-O-C stretching.

The ^{1}HNMR spectrum of the compounds appeared as singlet in the region of δ.4.87-4.89 for CH_2 proton, δ.7.95-8.62 appeared as multiplet due to CH-isoindoline, and showed singlet in the region δ.2.39 due to methyl proton,δ.2.5 appeared as triplet due to CH_2 proton where as δ 1.96 showed quartet and δ 1.02 showed triplet in case of **4c** compound.

The mass spectra of the compounds were showed molecular ion peak corresponding to their molecular formula.

Pharmacological Evaluation of Synthesized Compounds

Antimicrobial activity

All the newly synthesized compounds are screened for their antibacterial activity against some multidrug resistant strains like Gram-negative *Escherichia coli*, and Gram-positive *Stephylococcus aureus* and *Bacillus subtilis*. In addition, these compounds were also screened for their antifungal activity against *Candida albicans*. The compounds were tested at 50 µg/mL and 100 µg/mL. Antimicrobial activity of the compounds has been evaluated using agar plate diffusion technique.

Antibacterial and Antifungal Activities

All the synthesized compounds were also tested for their antibacterial and antifungal activities. It was observed that none of the compounds exhibited marked antibacterial or antifungal activity against different strains. Results of the antimicrobial activity are reported in tables.

Antibacterial Activity

The antibacterial activity of the synthesized compounds was evaluated by the cup plate method. The compounds were tested on gram positive *S.aureus*, *B. subtilis* and gram negative, *E. coli* bacterial strains respectively. The standard solution of and the solutions of test compounds were prepared in dimethyl sulfoxide (DMSO) in the concentration of 50 µg /ml and 100 µg/ml respectively. The first generation flouroquinolone ciprofloxacin was used as standard for comparison. The plates were incubated at 37±0.5^{0}C for 24 hr and the zone of inhibition formed around the cups was measured and the percentage inhibition of test compounds was evaluated with reference to the standard drug.

The nutrient agar medium was prepared and autoclaved at 15.1 lbs pressure for 20 min. This medium was poured into petri plates and allowed to solidify. On the surface of media microbial suspension was spread with the help of sterilized cotton swab. Cups were made by boring into agar surface with a previously sterilized cork borer and scooping out the punched part of agar. Four cups were made in each petri plate. To two of these cups was added the solution of the test compounds (conc. 50 µg/mL and 100 µg/mL), third was filled with the standard drug and fourth was filled with the control (DMSO).

The plates were kept in cold for one hour to allow the diffusion of test compounds and then incubated at 37±0.5°C for 24 h for antibacterial activity. The zone of inhibition formed around the cups after respective incubation was measured. These results were repeated three times and standard error was also calculated. Finally, percentage inhibitions of the compounds were calculated.

All the newly synthesized compounds were tested for *in vitro* antibacterial activities against Gram -ve (*E. coli*) and Gram -ve (*S. aureus*, *B. subtilis*, and *E. faecalis*) bacterial strains. Results are described as zone of inhibition and percentage inhibition at the conc. of 50µg/mL and 100µg/mL. Results of the antibacterial activity are reported in Table as zone of inhibition.

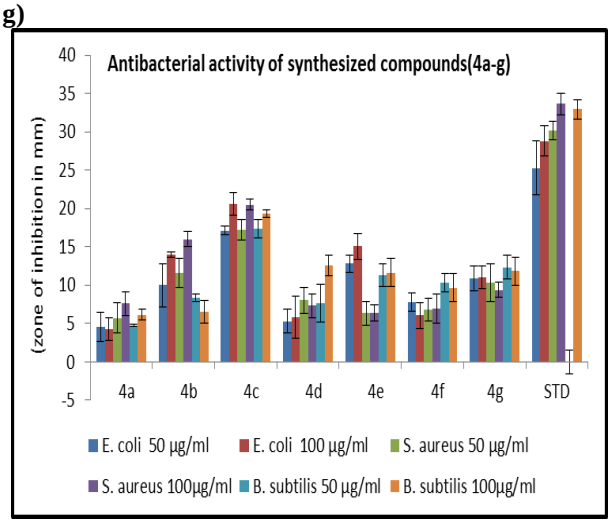
The most active compound of Schem -1 was found **4c** which is oxadiazole derivative of 3-bromo-4-chloro-benzoic acid containing *p*-fluoro substituted phenyl ring. It was showed MIC as 3.25, 7.25 and 5.75 µg/mL against *E. coli*, *S. aureus* and *B. subtilis* respectively. Compound **4c,** which is oxadiazole derivative of chlorofelbinac containing *o*-chloro substituted phenyl ring was showed MIC 6.12, 4.54 and 4.56 µg/mL against *E. coli*, *S. aureus* and *B. subtilis* respectively when compared with Cipro-floxacin.

Antibacterial activity of the synthesized compounds (4a-g) as zone of inhibition.

S.No.	Compounds	*E. coli* (MTCC-1687)		*S. aureus* (MTCC-2940)		*B. subtilis* (MTCC- 441)	
		50 µg/ml ± SD	100µg/ml ± SD	50 µg/ml ± SD	100µg/ml ± SD	50 µg/ml ± SD	100µg/ml ± SD
1	4a	4.60±1.92	4.30±1.48	5.73±1.93	7.60±1.52	4.73±0.17	6.13±0.71
2	4b	10.02±2.82	14.01±0.31	11.61±1.87	16.01±0.97	8.31±0.51	6.55±1.51
3	4c	17.11±0.57	20.61±1.51	17.21±12.33	20.51±0.74	17.31 ±1.21	19.31±0.51
4	4d	5.31±1.53	5.81±2.76	8.01±1.68	7.31±1.54	7.63±2.51	12.57±1.31
5	4e	12.81±1.16	15.04±1.70	6.33±1.51	6.37±1.02	11.33±1.52	11.63±1.83
6	4f	7.81±1.16	6.04±1.70	6.83±1.51	6.97±1.92	10.33±1.00	9.63±1.83
7	4g	10.87±1.60	11.04±1.50	10.33±2.51	9.38±1.02	12.33±1.52	11.83±1.83
8	Cipro Floxa-cin	25.31±3.51	28.81±2.02	30.15±1.19	33.63±1.46	29.6`±1.57	32.93±1.23

Zone of inhibition in millimeter, SD = standard deviation

Antibacterial activity of synthesized compounds (4a-g)



Antifungal Activity

For antifungal screening, Sabourauds agar medium was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distill water (100 mL) and adjusting pH to 5.7. Normal saline was used to make a suspension of spore of fungal strain for lawing. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar medium was poured into each petri dish. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h. Using an agar punch, wells were made and each well was labeled. A control was also prepared in triplicate and maintained at 37°C for 3-4 days. The fungal activity of each compound was compared with fluconazole as a standard drug at the conc. of 50 µg/mL and 100 µg/mL. These petri dishes were incubated at 37±1°C for 48 h. The zone of inhibition of growth was considered as an indicator for the antifungal activity. These results were repeated three times and standard error was also calculated. Finally, percentage inhibitions of the compounds were calculated.

All the newly synthesized compounds were tested for their *in-vitro* antifungal activities against *C. albican* sand *A. niger*. Fluconazole was used as reference drug. Results are described as zone of inhibition and percentage inhibition at the concentrations of 50µg/mL and 100µg/mL. Maximum inhibition was observed at 100µg/mL, therefore this was made the basis of discussion. Results of the antifungal activity are reported in Table as zone of inhibition.

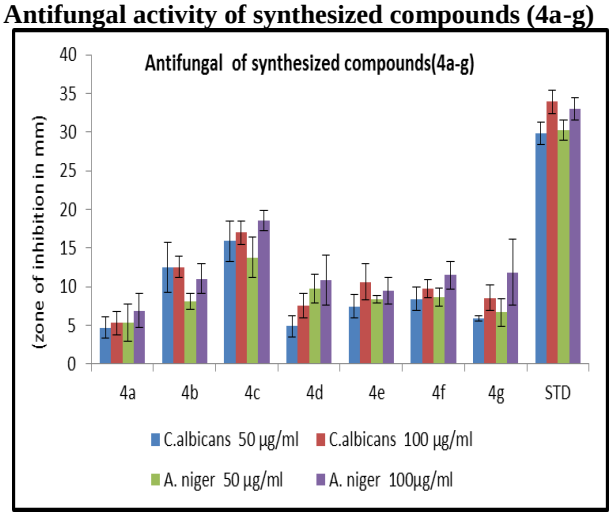
It was observed that none of the compound showed significant activity. Compound **4c** showed the highest activity against *C. albicans* and *A. niger* respectively, when compared with fluconazole.

Antifungal activity of the synthesized compounds (4a-g) as zone of inhibition.

S.No.	Compound	*C.albicans* MTCC-3617		*A. niger* MTCC-281	
		50 µg/ml ± SDb	100 µg/ml ± SDb	50 µg/ml ± SDb	100µg/ml± SDb
1	4a	4.71±1.36	5.31±1.54	5.35±2.39	6.92±2.15
2	4b	12.51±3.24	12.56±1.41	8.10± 1.02	11.01±1.94
3	4c	15.91±2.63	17.01±1.52	13.80 ±2.67	18.53±1.31
4	4d	4.91±1.37	7.53±1.62	9.72±1.87	10.85±3.25
5	4e	7.45±1.52	10.61±2.34	8.35±0.51	9.42±1.73
6	4f	8.41±1.53	9.77±1.15	8.67±1.15	11.50±1.80
7	4g	5.91±0.37	8.53±1.67	6.67±1.78	11.85±4.25
8	Fluconazole	29.89±1.45	33.91±1.51	30.23±1.32	32.96±1.47

Zone of inhibition in millimeter, SD = standard deviation.

Antifungal activity of synthesized compounds (4a-g)



Determination of MICs

The minimum inhibitory concentrations (MIC) were determined using the twofold serial dilution technique. A control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in experiments and found inactive in the culture medium. For this study, the compounds and standard drug were dissolved in DMSO (0.8 mg/mL). Further dilutions of these solutions to the required conc. i.e. 100, 50, 25, 12.5, 6.25, 3.12 and 1.56 µg/mL was done with Mueller-Hinton broth or Sabouraud dextrose broth.

The selected compounds were tested for their in vitro growth inhibitory activity against different bacterial and fungal strains which was decided on the basis of previous studies. Cipro-floxacin and Fluconazole were used as

standard drugs for antibacterial and antifungal activity, respectively.

The data generated from this study is presented. It shows that compound **4c** displayed good antibacterial activity against *E. Coli* and *B. subtilis*. Compound **4c** exhibited good antifungal activity against A. niger.

The *in-vitro* antimicrobial activity of the selected compounds and the control drugs (MIC in µg/mL).

Compound	*E. coli* (MTCC-1687)	*S. aureus* (MTCC-2940)	*B. subtilis* (MTCC- 441)	*C.albicans* (MTCC-3617)	*A. niger* (MTCC-281)
4a	3.55	7.25	5.85	7.09	5.82
4b	12.96	---	---	--	--
4c	06.12	4.78	4.76	5.25	4.55
4d	---	6.25	---	---	6.41
4e	4.10	---	5.06	0.25	6.59
4f	---	2.50	---	---	---
4g	02.28	7.11	---	---	---
Ofloxacin	2.15	3.50	3.76	---	---
Fluconazole	---	---	---	3.99	3.76

--- = not tested for the same.

RESULT AND DISCUSSION

Newly synthesized oxadiazole derivatives are found good antimicrobial activity and anti bacterial activity by Turbidimetric, cylinder plate method and Serial disc diffusion method respectively. For antibacterial activity they treated against *S. aureus, Escherschia coli* and *B. subtilis* bacterial strains. It is found to be effective to exhibit anticonvulsant potency and toxicity.

^{1}HNMR spectra of all the compounds and mass spectrum of selected compounds were recorded and found in full agreements with the assigned structures.

All the synthesized compounds were evaluated for anti-bacterial activity by disc diffusion technique. The test drugs were evaluated at 50 and 100 µg/ml concentrations. The zone of inhibition was measured in "mm" and percentage. single concentration of 50 µg/ml.

Synthesized compounds were tested for their *in-vitro* antifungal activities against *C. albicans* and *A. niger*. Fluconazole was used as reference drug. Results are described as zone of inhibition at the concentrations of 50µg/mL and 100µg/mL. Maximum inhibition was observed at 100µg/mL, therefore this was made the bpasis of discussion.

The minimum inhibitory concentrations (MIC) were determined using the twofold serial dilution technique. A control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in experiments and found inactive in the culture medium.

As we consider all results obtained from antibacterial and antifungal tests together we can say that all oxadiazole derivatives tested are active against bacteria and fungi.

CONCLUSION

In conclusion, we have synthesized new biologically significant heterocycles 1,3,4-Oxadiazole moiety and evaluated their antimicrobial, anti-inflammatory and antifungal activities. Results indicated that most of the synthesized Oxadiazole derivatives exhibited good to excellent antimicrobial activity. From this work, compounds proved to be the most promising active molecules which are capable of inhibiting the growth of microbes.

ACKNOWLEDGMENT

We gratefully acknowledge the financial support from Translam institute of pharmaceutical education and research.

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