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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL 1,3,4-OXADIAZOLYL ANILINE DERIVATIVES

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Abstract

Oxadiazoles represent a class of heterocyclic compounds with multiple isomeric forms, including 1,2,4-oxadiazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole, and 1,2,3-oxadiazole. These compounds consist of a five-membered ring containing two carbon atoms, two nitrogen atoms, and one oxygen atom. Among these isomers, 1,3,4-oxadiazole holds particular importance in medicinal chemistry. Synthesis: A systematic synthetic strategy was employed to access these derivatives, involving the careful selection of starting materials, reaction conditions, and purification techniques. The synthesis of these compounds was monitored and validated using a combination of thin-layer chromatography and various spectroscopic methods, including nuclear magnetic resonance (NMR), infrared (IR), and ultraviolet-visible (UV-Vis) spectroscopy. Characterization of the synthesized compounds was further confirmed through mass spectrometry and elemental analysis. Antimicrobial Evaluation: The synthesized compounds were subjected to rigorous antimicrobial evaluation against a diverse panel of microorganisms, including clinically relevant bacterial and fungal strains. Minimum inhibitory concentration (MIC) assays were employed to determine the potency of these compounds in inhibiting microbial growth. Control experiments utilizing established antimicrobial agents provided valuable benchmarks for comparison. 1,2,3-Oxadiazole exhibits slight instability and can transform into a diazoketone tautomer. Various synthesis methods are available for 1,3,4-oxadiazole, with one common approach involving the cyclodehydration of acid and hydrazide derivatives using dehydrating agents such as phosphorus oxychloride (POCl3), trifluoroacetic anhydride, thionyl chloride, or polyphosphoric acid. 1,3,4-

Oxadiazoles have been extensively investigated in medicinal chemistry due to their wide range of pharmacological activities, including anti-tubercular, analgesic, anti-inflammatory, antimicrobial, antimalarial, anti-oxidant, anticancer, antiviral properties, and more. This particular isomer is also a component of several commercially available medicinal agents used to treat various medical conditions.

Keywords; Synthesis, Antimicrobial, 1,3,4-Oxadiazolyl Aniline Derivatives, Novel Compounds, Microorganisms, Minimum Inhibitory Concentration (MIC), Antibacterial, Antifungal, Structure-Activity Relationships (SAR), Drug Discovery

INTRODUCTION

1.1 Oxadiazole

Oxadiazoles are five membered heterocyclic ring systems containing two carbons, two nitrogen and one oxygen atom. They are known to exist in different isomeric forms viz., 1,2,4-Oxadiazole, 1,3,4-oxadizole, 1,2,5-oxadiazole and 1,2,3-oxadiazole (Figure 1.1) [1]. Due to a broad spectrum of activities exhibited oxadiazole has a special position in medicinal chemistry [2]. The isomer 1,2,3-oxadiazole is a slightly unstable and gets converted into a diazoketone tautomer [3]. Amongst all the isomers, 1,3,4-oxadiazole has high significance in the area of research [4].

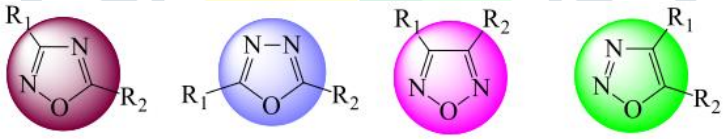


Figure 1.1 Isomers of Oxadiazole

Several methods can be reported in literature for preparation of 1,3,4-oxadiazole. Commonly used method involves cyclodehydration of acid and hydrazide derivatives in the presence of dehydrating agents like phosphorus oxychloride ($POCl_3$), trifluoroacetic anhydride, thionyl chloride, polyphosphoric acid [5] (figure 1.2).

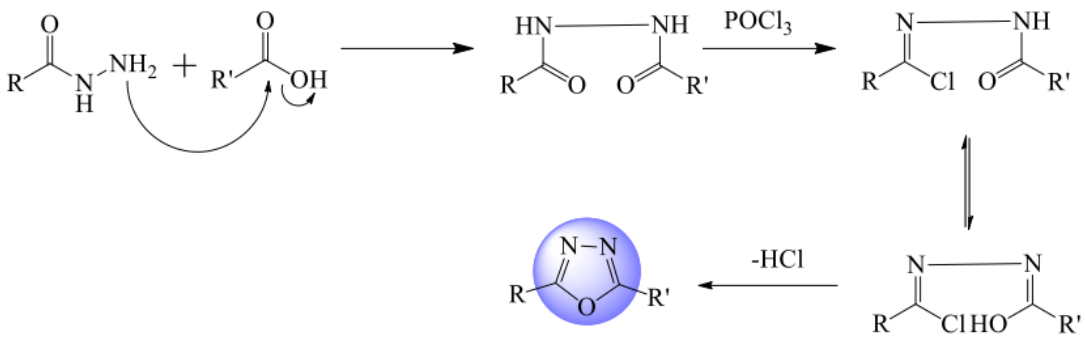
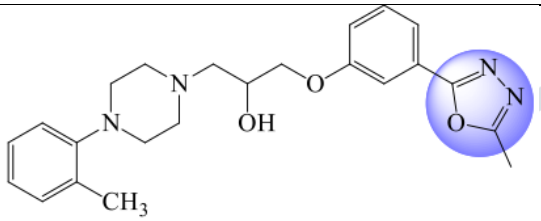
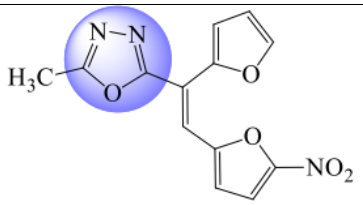
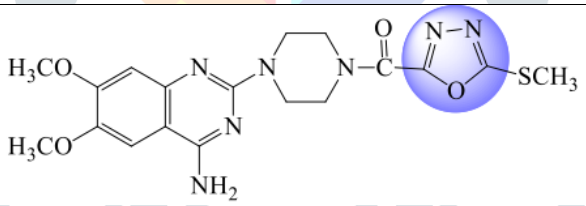
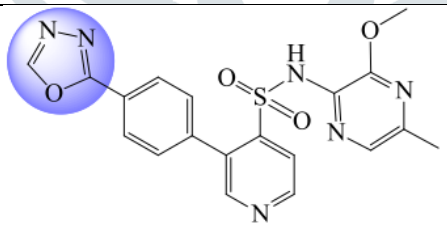
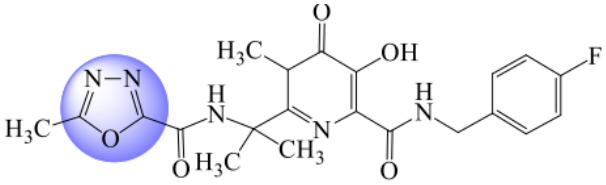


Figure 1.2 Mechanism of formation of oxadiazole

This moiety is well known to demonstrate a wide spectrum of pharmacological activities. This array includes antitubercular, analgesic, anti-inflammatory, antimicrobial, antimalarial, anti-oxidant, anticancer, antiviral and many more. This particular isoform is also found in a number of commercially available medicinal agents for treatment of several ailments (Table1).

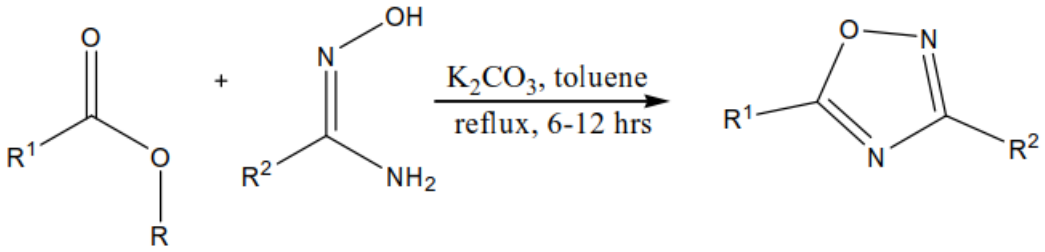
Table 1.1 Drugs containing oxadiazole nucleus

S.No.	Drug	Structure	Therapeutic Use
1	Nesapidil		Antihypertensive
2	Furamizole		Antibacterial
3	Tiodazosin		Antihypertensive
4	Zibotentan		Anticancer
5	Raltegravir		Antireteroviral

Apart from the presence of 1,3,4-oxadiazole in these commercially available drugs, researchers are actively involved in design and development of novel 1,3,4-oxadiazole based compounds.

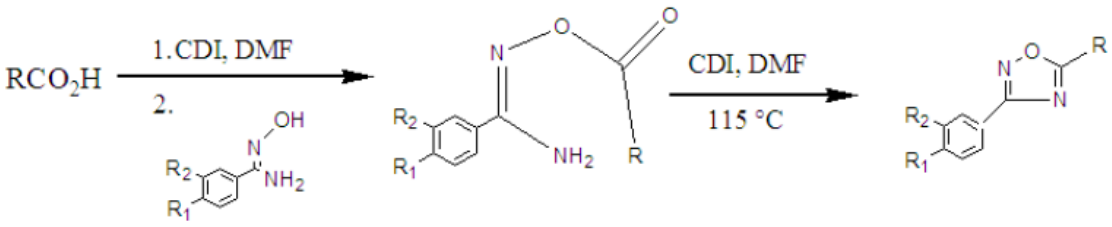
1.2 Approaches for synthesis of oxadiazole

One-pot synthesis of 1, 2, 4-oxadiazoles has been done using carboxylic acid esters and amidoxime implementing potassium carbonate and eventually reflux for 6-12 hrs.

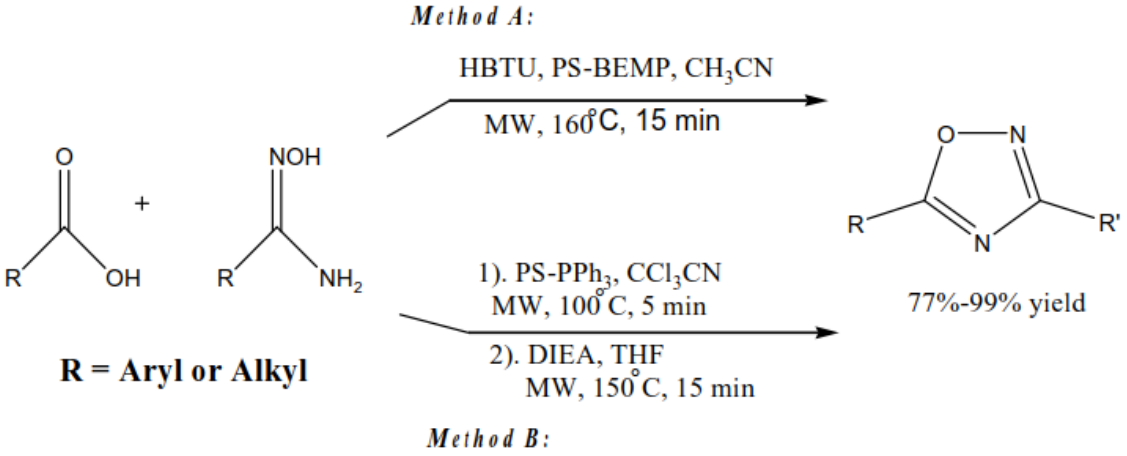


R = Me, Et

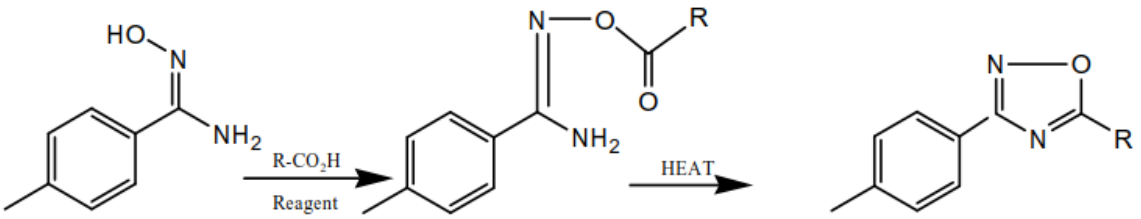
Parallel synthetic approach for 1, 2, 4-oxadiazoles has been reported employing CDI activation.



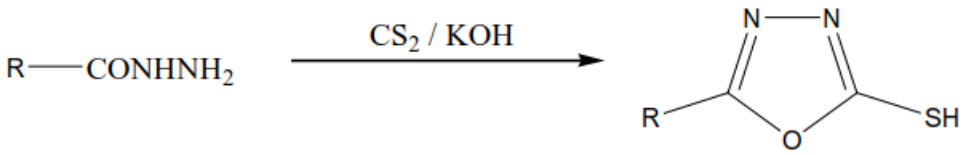
Swift Synthesis of 1,2,4-Oxadiazoles employing Polymer-Supported Reagents in Microwave Heating has also been reported.



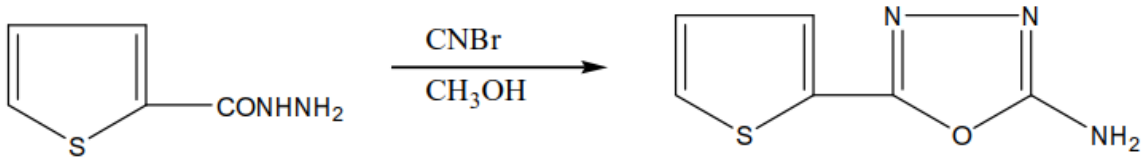
Synthesis of substituted 1,2,4-oxadiazoles in elevated yields in one pot method by condensing analogous amidoxime with carboxylic acids in the occurrence of peptide coupling reagent in diglyme & to heat the reaction mixture at about 100°C for numerous hours.



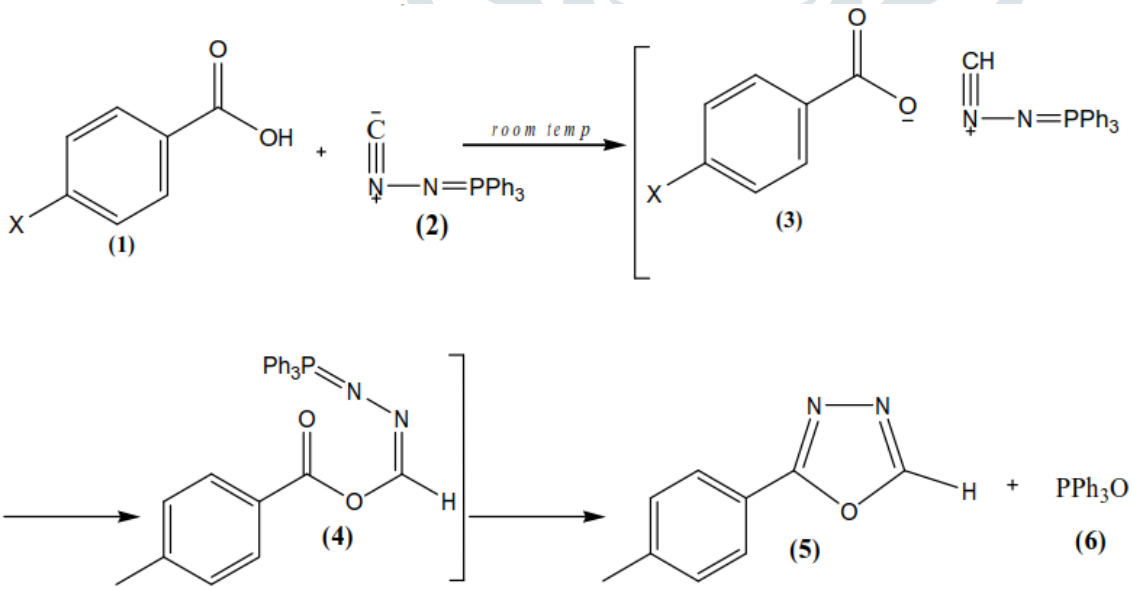
The synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazole has been performed from well substituted acid hydrazide in presence of CS2/KOH in alkaline media.



Preparation of 1, 3, 4-oxadiazole amine using cyanogen bromide is very easy for routine application and even takes shorter reaction time & gives better yields.



Iminophosphorane-facilitated one-pot synthesis of 1, 3, 4-oxadiazole derivatives has also been reported.



where X = I; CN; CO_2Me; OAc; Et

Experimental Work

4.1 Materials

N-Phenylanthranilic acid was purchased from Loba Chemie. All other reagents and chemicals used were of synthesis grade, purchased from Oxford Fine Chemicals, Mumbai and were used without further purification.

4.2 Methods

The scheme for the synthesis of the oxadiazole derivatives was adapted from the procedures reported by Amir et al [41] and Mishra et al [42] and the scheme is depicted in Figure 4.1. The scheme was modified for microwave assisted synthesis and validated for the reaction conditions.

General method for synthesis of substituted benzohydrazides

0.1 moles of substituted benzoic acid **(1a-e)** was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. The intermediate was reacted by hydrazine hydrate in presence of ethanol with catalytic amount of concentrated sulfuric acid. Briefly, 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2a-e**.

4.2.1.1 Synthesis of 2a

0.1 moles of coumaric acid was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2a**.

4.2.1.2 Synthesis of 2b

0.1 moles of cinnamic acid was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2b**.

4.2.1.3 Synthesis of 2c

0.1 moles of gallic acid was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2c**.

4.2.1.4 Synthesis of 2d

0.1 moles of 2,4-dintrobenzoic acid was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2d**.

4.2.1.5 Synthesis of 2e

0.1 moles of 2,5-dinitrobenzoic acid was dissolved in 25 ml ethanol and the mixture was irradiated using microwave for 7 min at 100 Watt in presence of 5 drops of concentrated H_2SO_4. On cooling, a solid separated which was filtered to give an intermediate. 0.1 mole of the intermediate in 20 ml ethanol, 0.1 mole of hydrazine hydrate was added. To the mixture, catalytic amount of concentrated sulfuric acid was added. The mixture was

irradiated at 100 Watt using microwave until the completion of the reaction (approximately 3 min). On cooling, a solid separated, which was recrystallized from ethanol to give the products **2e**.

4.2.2 Synthesis of N-phenyl-2-(5-phenyl-1,3,4-oxadiazol-2-yl)aniline derivatives

Compound **2a-e** (0.001 mol) and N-Phenylanthranilic acid, **3** (0.001 mol) were dissolved in phosphorus oxychloride and irradiated at 100 Watt using microwave for 25 min. The reaction mixture was slowly poured over crushed ice and kept overnight. The solid thus precipitated was filtered, washed with water, dried and recrystallized from ethanol to obtain compounds **4a-e.**

4.3 Chemical Characterization

All the synthesized compounds were characterized for melting point, solubility, yield and elucidation of the structure. The structure elucidation was performed by spectroscopic analysis (NMR, Mass and IR).

4.3.1 Melting point

The melting points were determined by open capillary method and are uncorrected using a electrically heated melting point determination apparatus.

4.3.2 Thin Layer Chromatography

The purity and homogeneity of the compounds was determined by thin layer chromatography, using silica gel G as the stationary phase on glass plates. Iodine vapors were used for development of the chromatogram. The solvent system used for performing the TLC of compounds was hexane: methanol in the ratio 7:3.

4.3.3 Solubility

The solubility of all the synthesized compounds was qualitatively determined in different solvents. A small amount of the sample was shaken in 1 mL of solvent in a test tube and was visually inspected for the absence of the solid particles in the test tube.

4.4 Antibacterial acivity

The compounds synthesized during the present investigation were screened for their antibacterial activity. The antibacterial tests were conducted on four common microorganisms viz. *Bacillus subtilis, Streptococcus aureus,*

Escherichia coli and Salmonella, which are the representative types of gram positive and gram-negative organisms respectively. The antibacterial activity of the compounds was assessed by disc diffusion.

4.4.4.1 Preparation of Nutrient broth:

- Nutrient broth powder – 37.2 g
- Distilled water - 1000 ml

Nutrient broth was prepared by dissolving all the ingredients and adjusting the pH adjusted to 7.2 and autoclaved at 15 lbs pressure for 20 min in an autoclave. One day before the testing, the microorganisms were subcultured into sterile nutrient broth and incubated at 37°C for 24 h. The culture growth thus obtained was used as inoculum for the antibacterial testing.

4.4.4.2 Preparation of nutrient agar media

The nutrient agar media was prepared by using the following ingredients.

- Nutrient agar – 28.6 g
- Distilled water - 1000 ml

The specified amount of nutrient agar powder was dissolved by heating on a water bath. and the volume of final solution is made up to 1000 ml with distilled water. The above prepared nutrient agar media was sterilized by autoclave at 121°C for 20 minutes at 15 lbs pressure.

4.4.4.3 Preparation of test solution

20 mg of the synthesized compounds were dissolved separately in 20 ml chloroform. 1 ml of this solution was diluted to 10 ml with chloroform. 0.5 ml (50 µg) and 1 ml (100 µg) of this solution was further diluted upto 2 ml by addition of chloroform to obtain a solution of 25 and 50 µg/ml strength. These sample solutions were sterilized test tubes. These test compounds (25, 50 and 100 µg/ml) were soaked on small circular disc of 5 mm.

4.4.4.4 Preparation of standard solution

Ciprofloxacin was used as the standard drug prepared in distilled water.

4.4.4.5 Procedure of antibacterial testing

The sterilized media (nutrient agar) was cooled to 45°C with gentle shaking for uniform cooling and then inoculated with 18-24 h old bacterial subculture under aseptic conditions in a laminar air flow bench and mixed well by gentle shaking. This was poured in to sterile Petri dishes and allowed to set. After solidification all the Petri dishes were transferred to laminar flow unit and the test sample discs were carefully kept on the solidified media by using sterilized forceps. These Petri dishes were kept in the laminar air flow unit undisturbed for one-hour diffusion at room temperature and then for incubation at 37°C for 24 h in an incubator. The extent diameter of inhibition after 24 h was measured as the zone of inhibition in millimeters (mm).

RESULTS AND DISCUSSION

The synthesis of all the compounds was achieved using the scheme depicted in Figure 5.1. The results of characterization of the synthesized compounds are presented in the present section.

Chemical Characterization

The synthesized compounds were subjected to determination of yield, melting point, solubility and structure elucidation. The physicochemical properties are shown in Table 5.1, 5.2 and 5.3.

Table 5.1 Yield and color

Compound code	Aromatic acid Used	Yield (%)	Color
4a	Coumaric acid	81	Yellow
4b	Cinnamic acid	75	Yellow
4c	Gallic acid	73	Yellow
4d	2,4-dihydroxy benzoic acid	77	Yellow
4e	2,5-dihydroxy benzoic acid	74	Brown

Table 5.2 Physical Properties of the synthesized compounds

Compound code	Molecular Formula	Molecular Weight	R_f Value	Melting point (°C)
4a	$C_{22}H_{17}N_3O_2$	355.39	0.67	247-249
4b	$C_{22}H_{17}N_3O$	339.14	0.63	236-238
4c	$C_{20}H_{15}N_3O_4$	361.15	0.69	225-227
4d	$C_{20}H_{15}N_3O_3$	345.35	0.64	233-235
4e	$C_{20}H_{15}N_3O_3$	345.35	0.66	234-236

Table 5.3 Physical Properties of the synthesized compounds

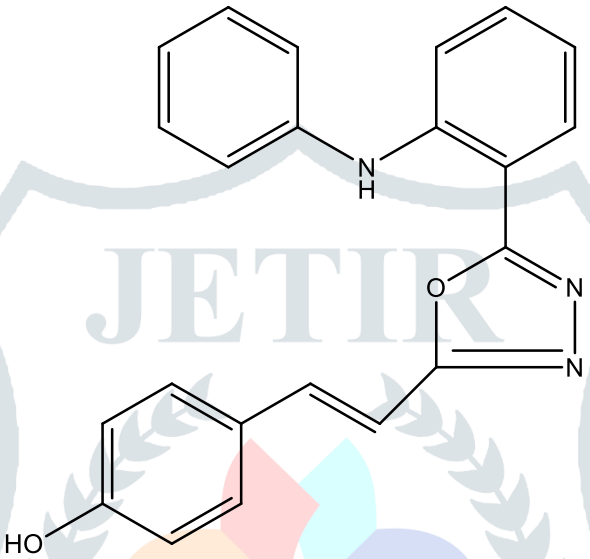
Compound code	Water	Methanol	Chloroform	DMSO
4a	Insoluble	Insoluble	Soluble	Soluble
4b	Insoluble	Insoluble	Soluble	Soluble
4c	Insoluble	Insoluble	Soluble	Soluble
4d	Insoluble	Insoluble	Soluble	Soluble
4e	Insoluble	Insoluble	Soluble	Soluble

Structure Elucidation

The structure elucidation of the synthesized compounds was confirmed by interpretation of the IR, ^{1}HNMR and Mass spectra of the compounds. The IR spectra were observed for the characteristic peaks obtained due to the presence of the functional groups. All the compounds exhibited the peaks of aromatic C=C stretching, C-H stretching, C-N and C=N

stretching and C-O stretching. The occurrence of absorption bands for C-O and C=N may occur at the same frequency and Fermi resonance peaks may be the diagnostic of a carbonyl group in the compounds. The ^{1}HNMR spectra of all the compounds exhibited chemical shifts of aromatic hydrogen. They also exhibited any peak that may arise due to certain functional groups like –OH and NH protons. The mass spectra of the compounds were examined for the presence of molecular ion peak or the isotopic peaks to confirm the formation of the compounds.

Elucidation of 4a



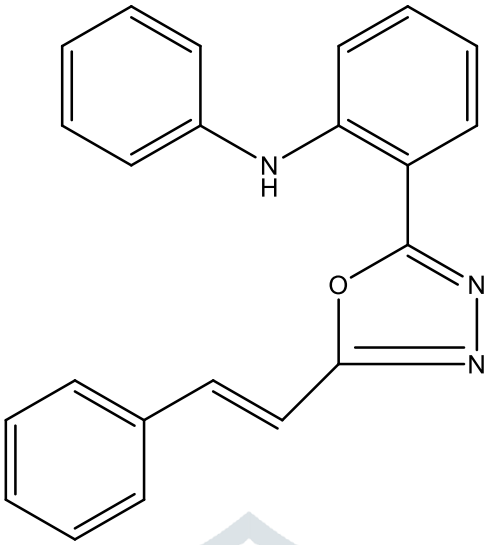
IUPAC Name - (E)-4-(2-(5-(2-(phenylamino)phenyl)-1,3,4-oxadiazol-2-yl)vinyl)phenol

Table 5.4 IR and 1H NMR data of 4a

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.9-6.8 Ar H, 2.996 CH_3, 3.969 NH	3104.67	Ar/Het C-H Str
2		2970.38	Ar C-C Str
3		1639.00	C=N Str
4		1417.36	C-N Str

MS – 356.1 (M^+ + 1)

Elucidation of 4b



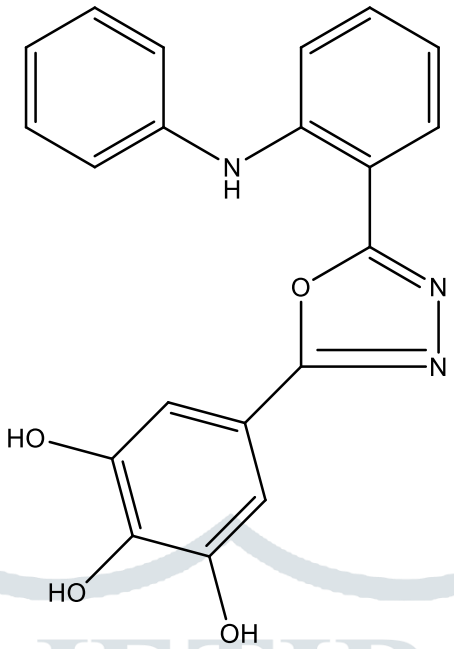
IUPAC Name - (E)-N-phenyl-2-(5-styryl-1,3,4-oxadiazol-2-yl)aniline

Table 5.5 IR and 1H NMR data of 4b

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.9-6.8 Ar H, 2.641 CH_3, 4.063 NH	3554.90	N-H stretching
2		3107.54	Ar/Het C-H Str
3		3039.13	Ar C-C Str
4		1653.56	C=N Str
5		1393.03	C-N Str

MS – 341.2 (M^++2)

Elucidation of 4c



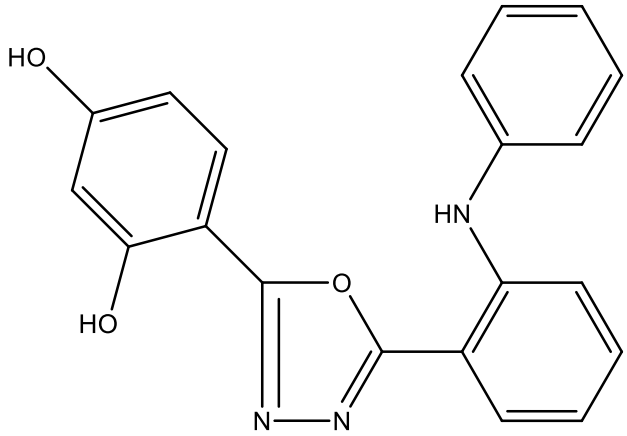
IUPAC Name - 5-(5-(2-(phenylamino)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

Table 5.6 IR and 1H NMR data of 4c

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.9-6.8 Ar H, 2.993 CH_3, 3.974 NH, 5.008 OH	3100.40	Ar/Het C-H Str
2		2970.97	Ar C-C Str
3		1639.54	C=N Str
4		1289.17	C-N Str

MS – 361.3 (M^+)

Elucidation of 4d



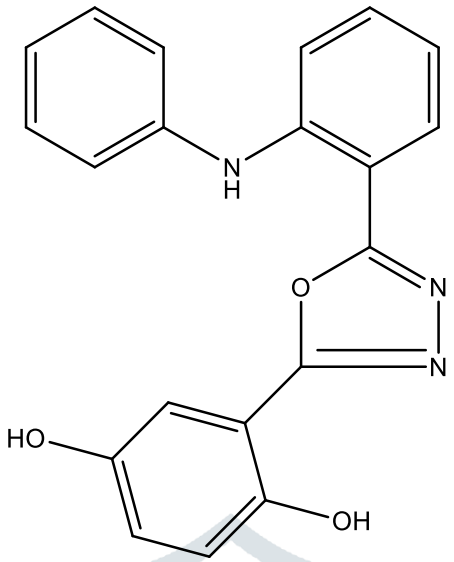
IUPAC Name - 4-(5-(2-(phenylamino)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,3-diol

Table 5.7 IR and 1H NMR data of 4d

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	8.001-8.025 Ar, 7.9-6.8 Ar H, 2.991 CH_3, 3.974 NH,	3705.25	O-H str
2		3104.67	Ar/Het C-H Str
3		2970.38	Ar C-C Str
4		1639.00	C=N Str
5		1289.63	C-N Str
6		1082.70	C-O Str

MS – 345.1 (M^+)

Elucidation of 4e



IUPAC Name - 2-(5-(2-(phenylamino)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,4-diol

Table 5.8 IR and 1H NMR data of 4e

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.9-6.8 Ar H, 2.993 CH_3, 3.974 NH	3099.37	Ar/Het C-H
2		2992.19	Ar C-C
3		1687.76	C=N
4		1299.77	C-N

MS – 345.1 (M^+)

Antibacterial Action

The antibacterial activity of the synthesized oxadiazole derivatives was determined measuring the zone of inhibition in the agar plate. Three concentrations of the synthesized compounds were tested for antibacterial action against ciprofloxacin as the standard drug for antibacterial action. The zone of inhibition of the test compounds is presented in table 5.9.

Table 5.9 Zone of Inhibition of synthesized compounds

Compound Code	Zone of Inhibition (mm)*											
	B. subtilis			***S. auerus***			***E.coli***			***Salmonella***		
	25µg	50µg	100µg	25µg	50µg	100µg	25µg	50µg	100µg	25µg	50µg	100µg
4a	7	9	14	6	8	15	11	16	**23**	10	16	**24**
4b	5	5	7	5	7	9	5	8	11	6	11	13
4c	6	9	13	6	8	13	9	15	**24**	8	16	**25**
4d	10	16	**25**	9	16	**24**	6	9	13	5	9	14
4e	11	14	**23**	10	15	**23**	6	8	12	6	10	13
Ciprofloxacin	21	**26**	**31**	20	**24**	**28**	18	**25**	**36**	20	**27**	**36**

* Below 12 mm – poor activity; 13-18 mm – moderate activity & above 18 mm – good activity

The results revealed that the antibacterial action of the synthesized compounds was dose dependent. The compounds were mild to moderately antibacterial. The presence of hydroxy group at para position in the phenyl ring attached to oxadiazole in the compounds favored antibacterial activity against gram negative bacteria (**4a, & 4c**) whereas hydroxyl group on meta or ortho position of the phenyl ring attached to oxadiazole favored activity against gram positive bacteria (**4d, 4e**). Compound 4b did not exhibit significant antibacterial action as compared to the control suggesting the importance of the hydroxyl substitution in the compounds for antibacterial potency.

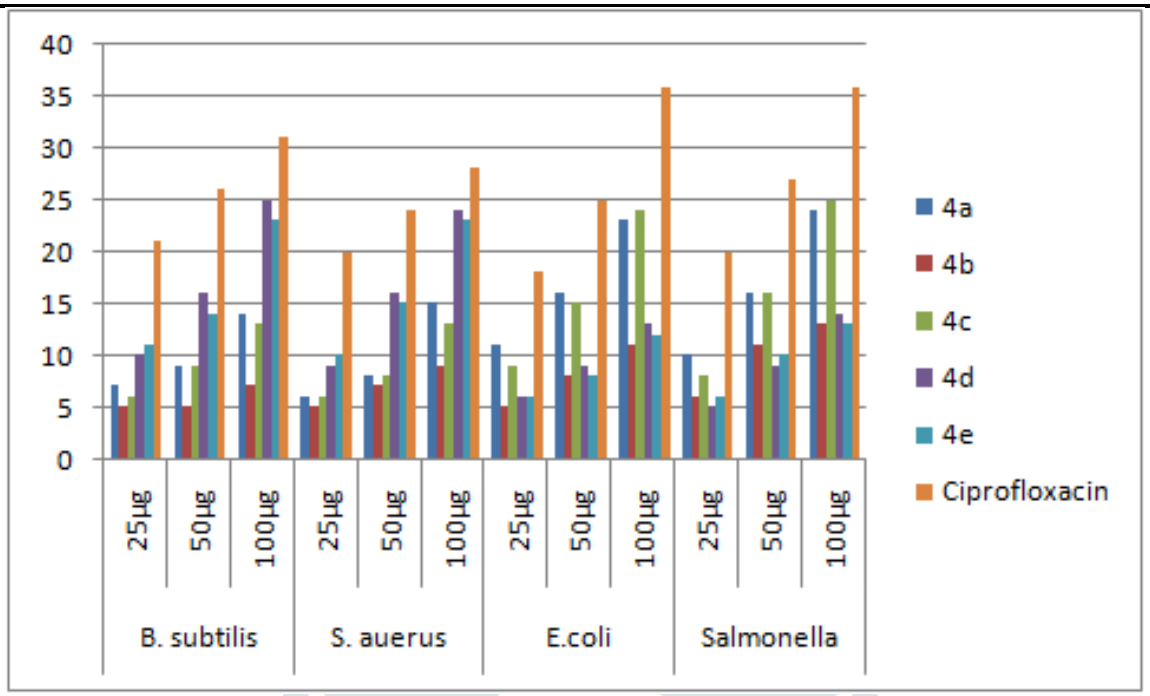


Figure 5.1 Zone of Inhibition of the tested compounds

Summary and conclusions

Summary

The pursuit of development of newer treatments for existing diseases has been the doorstep for the present research work. In the present work newer antibacterial agents based on 1,3,4-oxadiazole nucleus were synthesized using microwave irradiation and evaluated.

The synthesized compounds were characterized for the physicochemical properties such as melting point, colour and solubility. All the compounds were yellowish to brown in colour and were obtained in 73-81% yields using the optimized reaction conditions. The compounds were insoluble in water, methanol, soluble in chloroform and DMSO.

The confirmation of the structure of the synthesized compounds was done by IR, ^{1}HNMR and mass spectral studies. All the compounds exhibited the absorption bands of C=O, C=N, C-H, C=C stretching in the IR spectra. The ^{1}HNMR spectra of all the compounds exhibited chemical shifts of aromatic protons and characteristic proton of the functional groups. The mass spectra of the compounds were examined for the presence of molecular ion peak or the isotopic peaks to confirm the formation of the compounds.

The compounds were evaluated for anti-bacterial potential using disc diffusion method (*in vitro*). The results obtained led to the conclusion that the antibacterial activity of the oxadiazole derivatives as depends on position of the hydroxyl substitution present in the scaffold.

Conclusion

The objective of the present investigation was to synthesize anti-microbial molecules based on oxadiazole scaffold using microwave irradiation method. It was accomplished by converting the carboxyl group of substituted aromatic acids N-phenylanthranilic acid to 1,3,4-oxadiazole ring while conjugating it with the N-phenylanthranilic acid group. The synthesized compounds presented good yield and antibacterial activity comparable to that of the standard drug.

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