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Research Article

Synthesis In Silico Estimation and Pharmacological Screening of Some Substituted Oxadiazole Derivatives

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ABSTRACT

Oxadiazole derivatives have emerged as a vital class of heterocyclic compounds in medicinal chemistry due to their diverse pharmacological activities and favorable drug-like properties. The present study focuses on the design, synthesis, in-silico analysis, and pharmacological evaluation of a series of novel substituted oxadiazole derivatives with the objective of identifying promising candidates for future therapeutic development. The structures of the synthesized derivatives were confirmed using spectral techniques such as FT-IR, ^{1}H-NMR, and mass spectrometry, ensuring purity and structural integrity. In-silico studies were performed to predict the biological behavior of the synthesized compounds, focusing on their molecular docking interactions with selected protein targets known to play key roles in microbial infection and inflammation. The docking results indicated strong binding affinities and stable interactions between several oxadiazole derivatives and the active sites of the target enzymes, suggesting potential for antimicrobial and anti-inflammatory activities.

INTRODUCTION

In the present study, a series of substituted 1,3,4-oxadiazoles were synthesized using microwave-assisted methods and evaluated for their antibacterial and antifungal activities. Microwave synthesis proved to be highly efficient, offering significantly higher yields in a shorter time compared to conventional methods. The synthesized compounds were recrystallized using various solvents, including ethanol, petroleum ether, n-hexane, methanol, butanol, and acetone, through a slow evaporation technique. Among these solvents, ethanol and acetone produced the most well-defined crystal structures, typically

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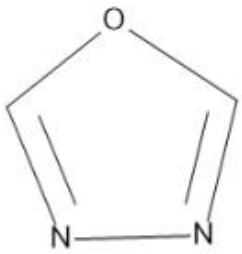
forming needle-like, cross-shaped, and clustered crystals. This is particularly important, as polymorphism can greatly influence the bioavailability of drugs—especially those with poor water solubility. The structural integrity of the synthesized compounds was confirmed by satisfactory results from IR, ^{1}H NMR, and mass spectroscopic analyses.

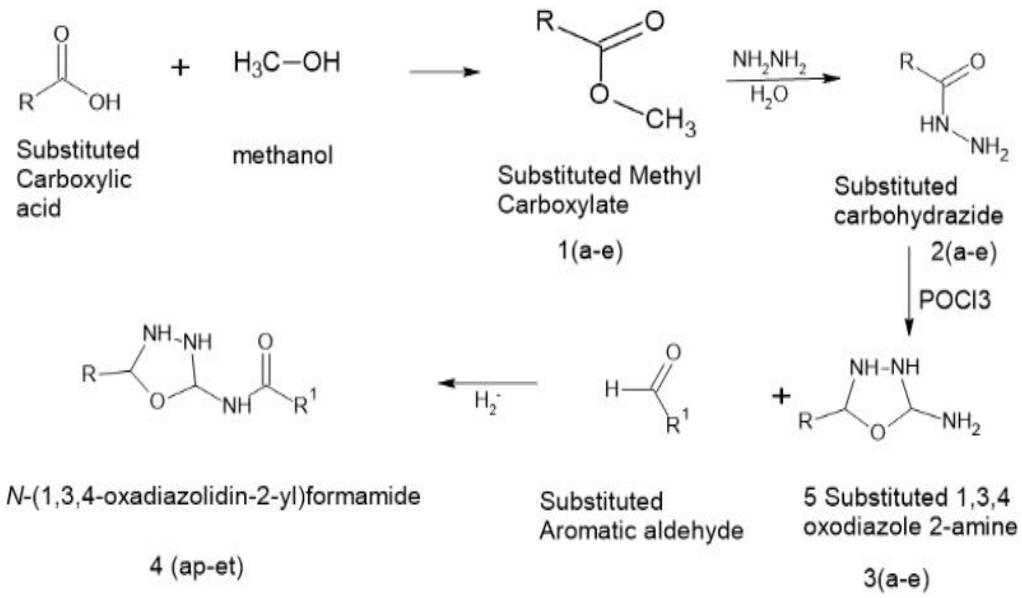
1,3,4-oxadiazole- An important Heterocycle[16-19]: -



1,3,4-oxadiazole

The five-membered oxadiazole nucleus is present in heterocyclic compounds with a wide range of health benefits. Oxadiazoles are cyclic compounds that include one oxygen and two nitrogen atoms in a five-membered ring. Oxadiazole is considered to be created by replacing two of the methane (-CH=) groups with two of the nitrogen (-N=) groups of the pyridine type in furan. Compounds with the 1,3,4-oxadiazole nucleus exhibit unique anti-inflammatory, analgesic, antibacterial, anticancer, anticonvulsant, anthelmintic, herbicidal, anti-mycobacterial, antioxidant, and anti-hepatitis B virus properties. Oxadiazole is a heterocyclic aromatic compound with five components, including one oxygen and two nitrogen atoms. In medicinal chemistry, they have also been studied as bioisosteres for carboxylic acids, esters, and carboxamides. It comes in a variety of isomeric forms, including 1,2,3, 1,2,4, 1,2,5, and 1,3,4-oxadiazole.

Reaction scheme:



Where,

R=

(a) 4-Nitrobenzoic acid

(b) 3 Chlorobenzoic acid

R1=

(a)- Benzaldehyde

(b)Formaldehyde
(c) 4 Choro benzaldehyde
(d) 4 Dimethyl amine benzaldehyde
(e) 3 Nitrobenzaldehyde

Synthesis:

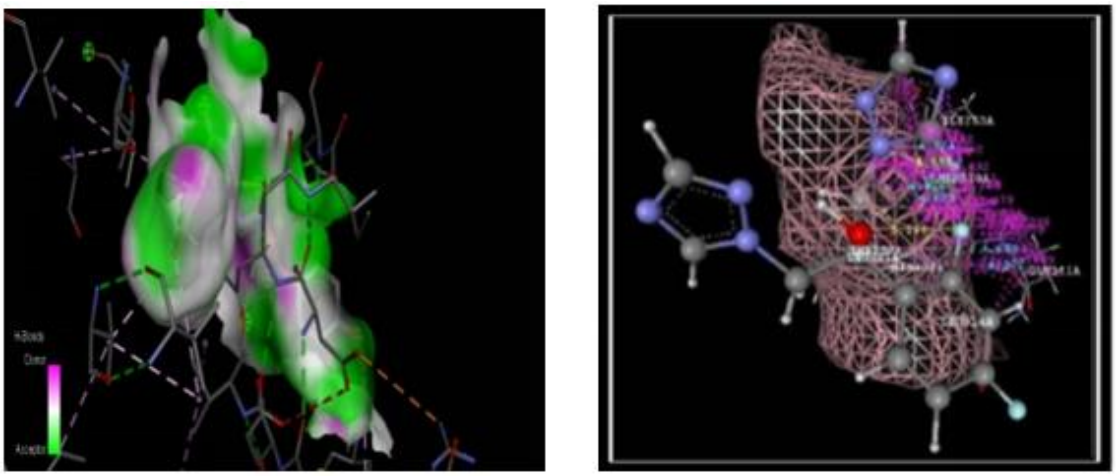
Synthesis by conventional method:

Table No. 5.1.1 Physicochemical data of 5 substituted 1,3,4 oxadiazolidin -2 yl formamide by Conventional and microwave methods

Sr. No.	Com-pound code	Molecular formula	Molecular weight g/mol	Melting Point °C	Percentage yield %		Rf Value	Mobile phase
					Conven-tional	Micro-wave		
1	**3a**	C16H11N5O9	417.29	120-124	88	90	0.74	Ethyl acetate :Ethanol (8:2)
2	**3b**	C16H11ClN4O7	406.74	130-134	84	80	0.80	Ethyl acetate :Ethanol (8:2)
3	**3c**	C16H12N4O7	372.29	122-128	74	88	0.66	Ethyl acetate :Ethanol (8:2)
4	**3d**	C18H17N5O7	415.36	120-126	86	92	0.82	Ethyl acetate :Ethanol (8:2)
5	**3e**	C11H8N4O7	324.21	165.5 – 167.5	79	88	0.76	Ethyl acetate :Ethanol (8:2)
6	**4a**	C16H11Cl2N3O5	396.18	240–245	86	94	0.77	Ethyl acetate :Ethanol (8:2)
7	**4b**	C16H11ClN4O7	406.74	122-126	78	85	0.81	Ethyl acetate :Ethanol (8:2)
8	**4c**	C18H17ClN4O5	420.81	130-138	69	78	0.84	Ethyl acetate :Ethanol (8:2)
9	**4d**	C11H8ClN3O5	297.65	128-134	74	88	0.76	Ethyl acetate :Ethanol (8:2)
10	**4e**	C16H12ClN3O5	361.74	331–333	70	80	0.63	Ethyl acetate :Ethanol (8:2)

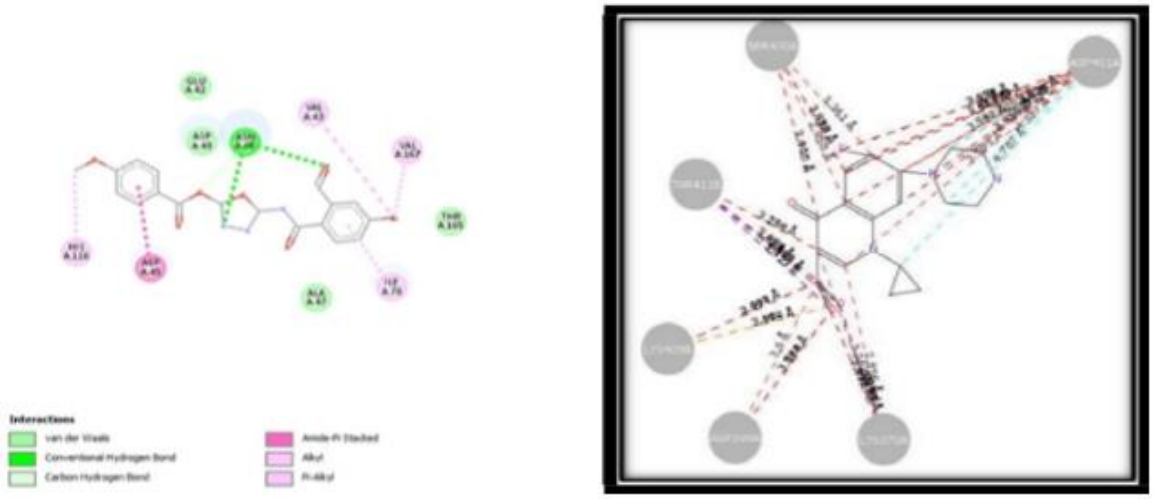
Antibacterial Activity Docking Result

When compared to other compounds, compounds 3a through 4e and compound 4a had the lowest dock scores (-62.60). When we compared the results of the molecule to the literature, this docking score indicated that the suggested compounds had a good binding affinity for hinding to receptors (PDB Code-4AA7). In the binding pocket, the suggested compounds all take on a very similar conformation, displaying van der Waals interactions with the ASP5SA, ARG56A, and TYR67A amino acids as well as hydrogen bond interactions with the ARG56A amino acid. A 2D image is used to depict it (figno.6.2.4.2). 4a chemical and receptor overlay in the figure. It was discovered that the popular drug ciprofloxacin had a dock score of -65.60.



Compound code 4a **Standard (Ciprofloxacin)**

Fig. no. 6.2.4.1 Docking poses of compound code 4a and standard drug

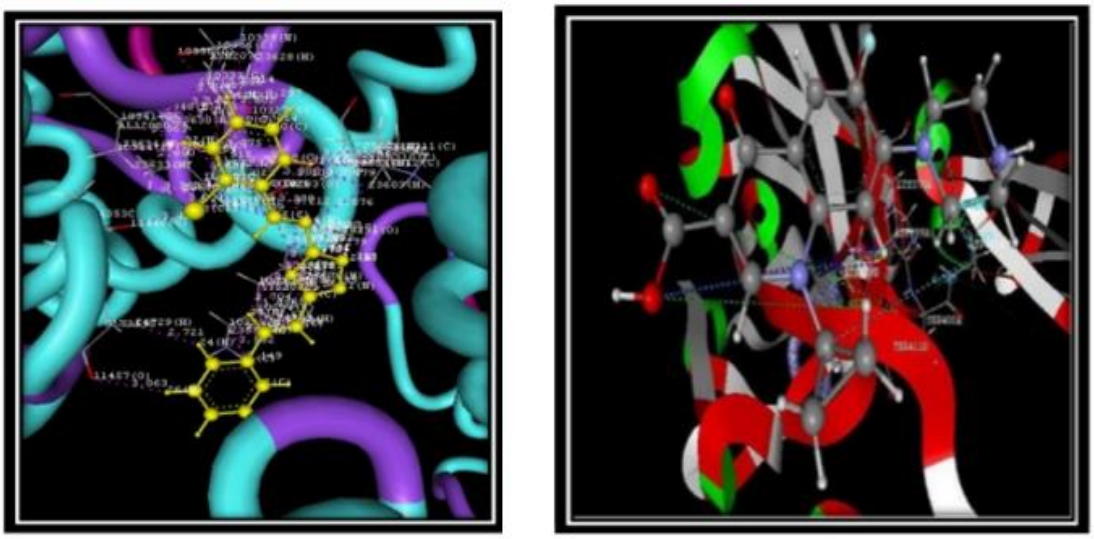


Compound code 4a **Standard (Ciprofloxacin)**

Fig. no. 6.2.4.2: 2D representation of Docking poses of compound code 4a and standard drug

Table 6.2.4.2: Data for interaction of compound code 4a with amino acid

Amino acid	Atom of ligand	Distance	Interaction type
TYR279B	1C	3.991	AROMATIC_INTERACTION
ARG56A	956H	2.982	VDW_INTERACTION
OH507C	17C	2.937	VDW_INTERACTION
ARG56A	957H	2.534	HYDROGENBOND_INTERACTION

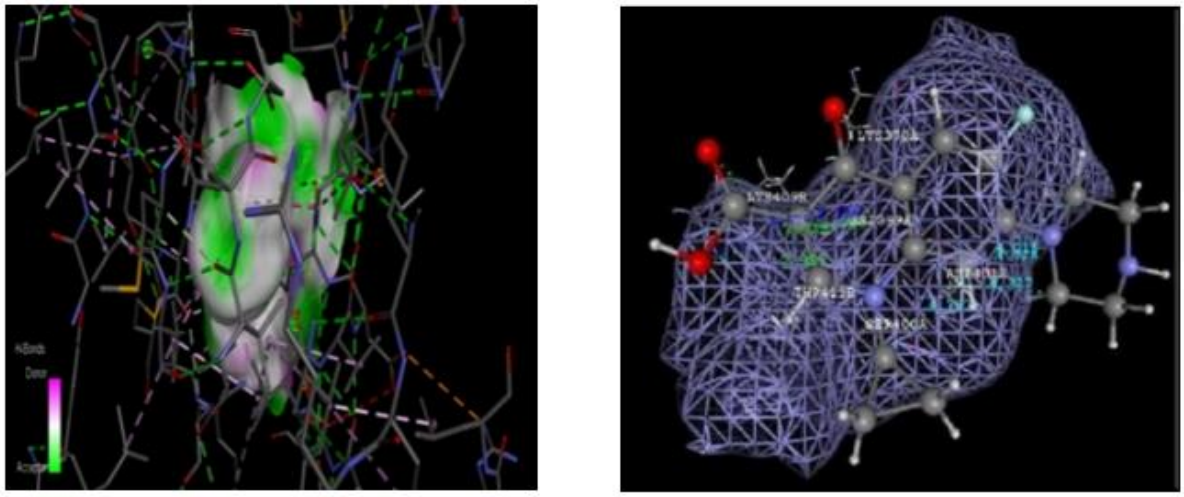


Compound code 4a **Standard (Ciprofloxacin)**

Fig. no. 6.2.4.3: Superimpose image representation of Docking poses of compound code 4a and standard drug

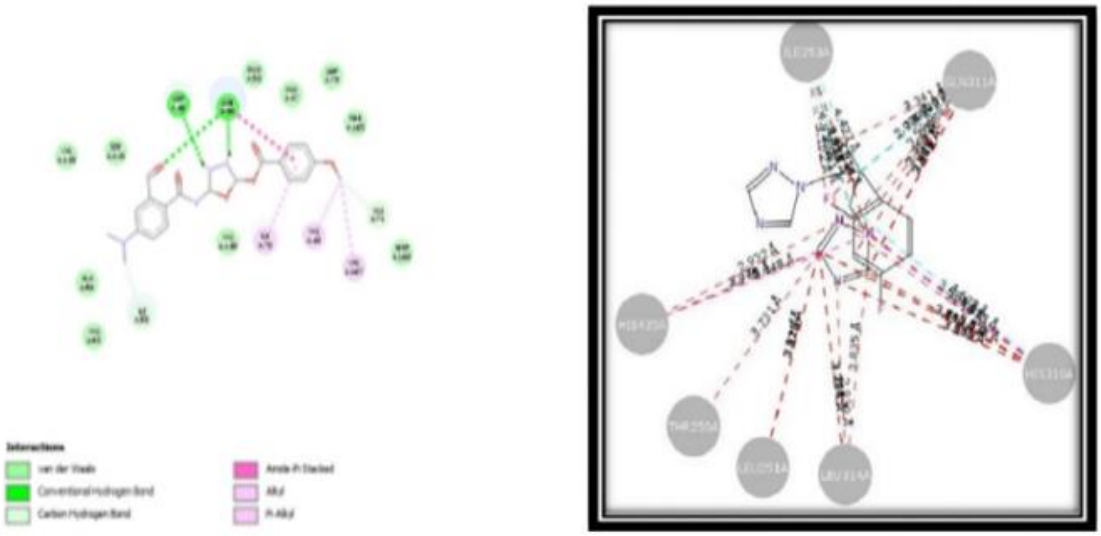
Anti-Fungal Activity Docking Result

Compounds 3a through 4e have dock scores ranging from - 48.121, with compound 3a having the minimum dock value compared to the remaining compounds. This docking score showed that the developed compounds have a strong binding affinity for binding to the receptor (PDB Code-1kZN) when we compared the results of compound 3a to the literature. The optimal position derived from the docking findings is shown in figure no.6.2.4.4. At the binding pocket, every proposed molecule takes on a fairly similar shape. This includes hydrogen bonding with the amino acid of TYR80A, vanderwal interaction binding LEU83A, hydrophobic interaction binding LEU83A, and aromatic interaction showing with the amino acid of HIS72A. This is depicted in the 2D representation diagram (fig. 6.2.4.5). Superimpose the 3a compound picture with the receptor depicted in the diagram (fig. 6.2.4.6).



Compound code 3a **Standard (Fluconazole)**

Fig. no. 6.2.4.4: Docking poses of compound code 3a and standard drug

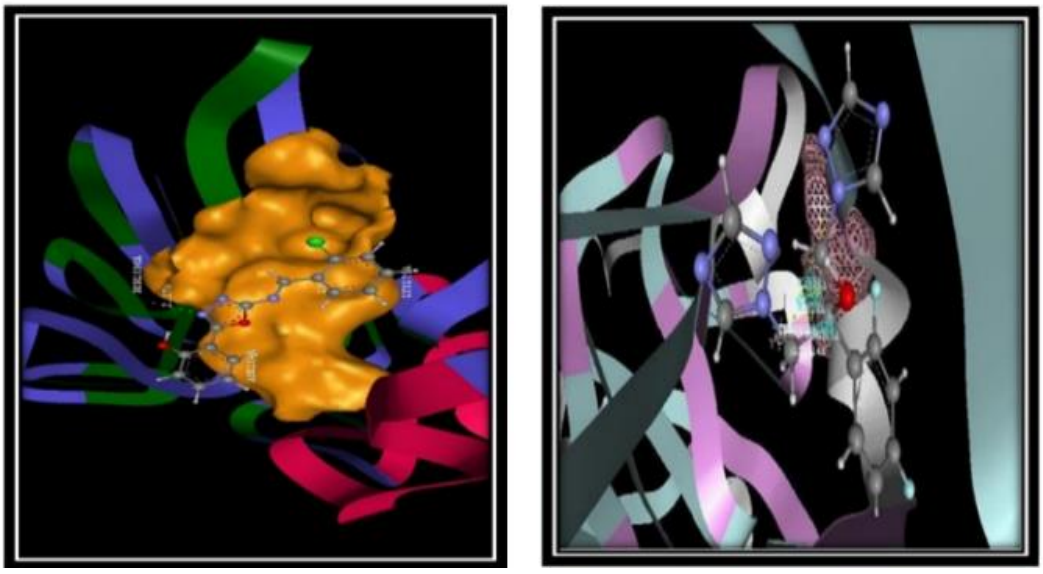


Compound code 3a **Standard (Fluconazole)**

Fig. no. 6.2.4.5: 2D representation of Docking poses of compound code 3a and standard drug

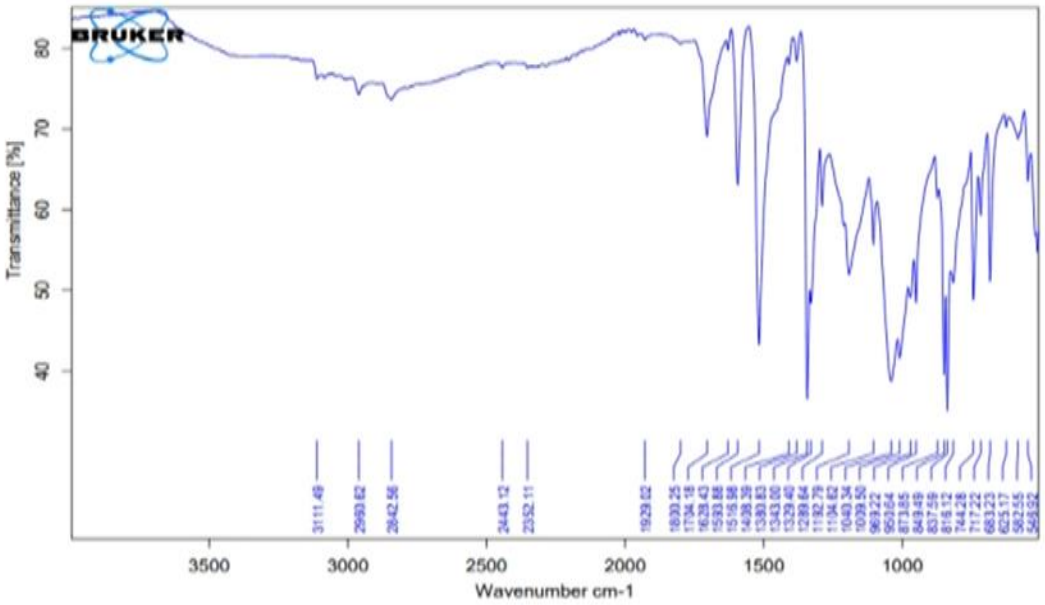
Table 6.2.4.4: Data for interaction of compound code 3a with amino acid

Amino acid	Atom of ligand	Distance	Interaction type
TYR80A	9O	1.690	HYDROGENBOND_INTERACTION
TYR80A	15N	3.750	VDW_INTERACTION
HIS72A	8C	4.310	AROMATIC_INTERACTION
LEU83A	17C	3.408	VDW_INTERACTION



Compound code 3a **Standard (Ciprofloxacin)**

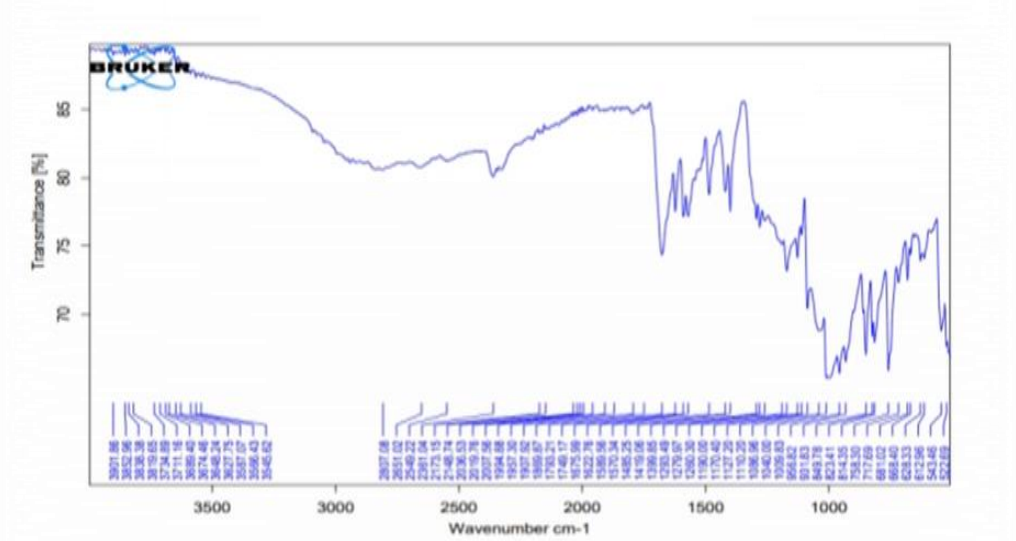
Fig. no. 6.2.4.6: Superimpose image representation of Docking poses of compound code 3a and standard drug



Graph No.5.2.1: IR Spectrum of 3a 5-(2 -formyl-4-nitrobenzamido)-1,3,4-oxadiaazolidin-2-yl-4-nitrobenzoate

Table. No.5.2.1: IR Spectrum of 3a 5-(2 -formyl-4-nitrobenzamido)-1,3,4-oxadiaazolidin-2-yl-4-nitrobenzoate

Sr. No.	Assignment	Functional groups	Wavenumber (cm^{-1})
1	C-H Stretching	Aromatic and alkyl C-H	3111-2924
2	C=O Stretching	Ester and amide carbonyls	1729-1702
3	C=C Aromatic stretching	Aromatic rings	1600-1500
4	NO2 Stretching	Nitro group	1350-1300
5	C-O Stretching	Ester or ether	1250-1000

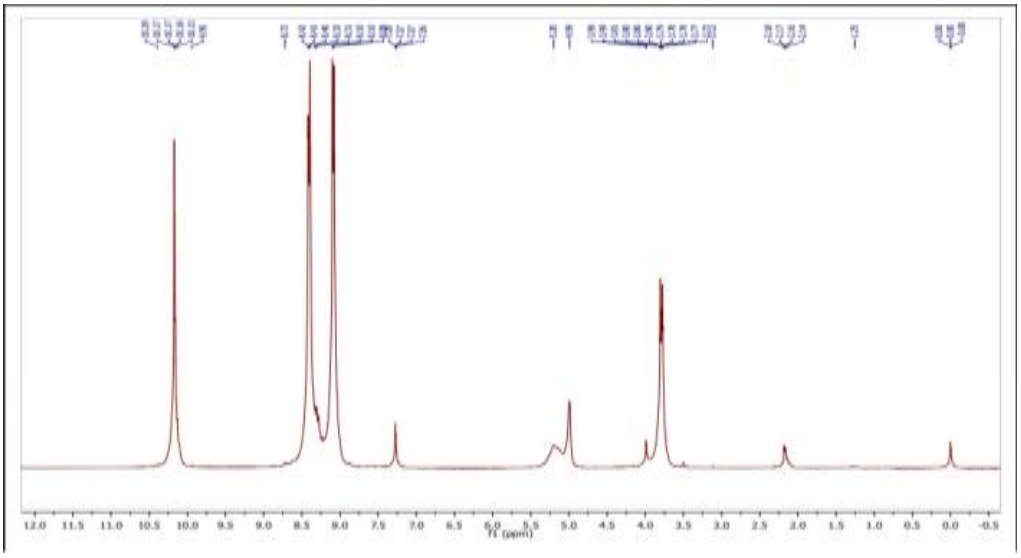


Graph No.5.2.6: IR Spectrum of 4a 5 (5 -chloro-2-formylbenzamido)-1,3,4-oxadiazolidin-2-yl-4-chlorobenzoate

Table. No.5.2.6: IR Spectrum of 4a 5 (5 -chloro-2-formylbenzamido)-1,3,4-oxadiazolidin-2-yl-4-chlorobenzoate.

Sr. No.	Assignment	Functional groups	Wavenumber (cm^{-1})
1	N–H or O–H stretch	amide N–H stretch or phenolic O–H	3300–3400
2	C–H stretch	Alkyl or aromatic C–H	2900
3	C=O stretch	Ester or amide carbonyl group	1700–1730
4	C=C or C=N stretch	Aromatic ring or oxadiazole C=N	1600–1620
5	C–O stretch	Ester	1200–1300
6	C–Cl stretch or aromatic C–H bending	Chlorine-substituted aromatic ring	700–800

NMR Spectrum of 3a 5-(2 -formyl-4-nitrobenzamido)-1,3,4-oxadiaazolidin-2-yl-4-nitrobenzoate

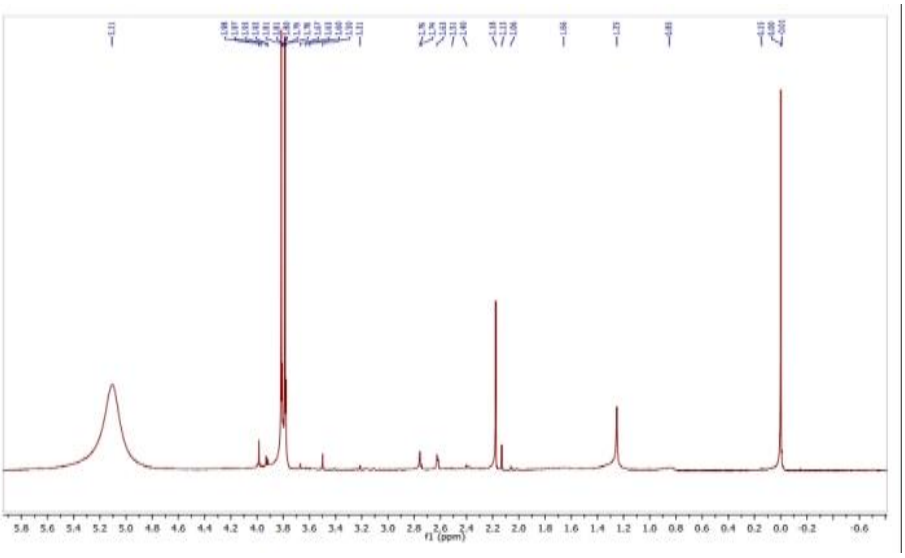


Graph no 5.2.11: NMR Spectrum of compound 3a

Table no. 5.2.11: NMR Spectrum value of compound 3a

Sr. No.	Chemical Shift (δ)	Assignment
1	10.39	Aldehyde (-CHO) proton
2	10.17	Amide NH proton
3	9.72	Aromatic H ortho to NO_2 group
4	8.46	Aromatic protons on substituted benzene rings
5	4.99	CH/CH_2 attached to oxadiazole or ester group
6	2.18	Minor aliphatic protons

NMR Spectrum of 4a 5 (5 -chloro-2-formylbenzamido)-1,3,4-oxadiazolidin-2-yl-4-chlorobenzoate

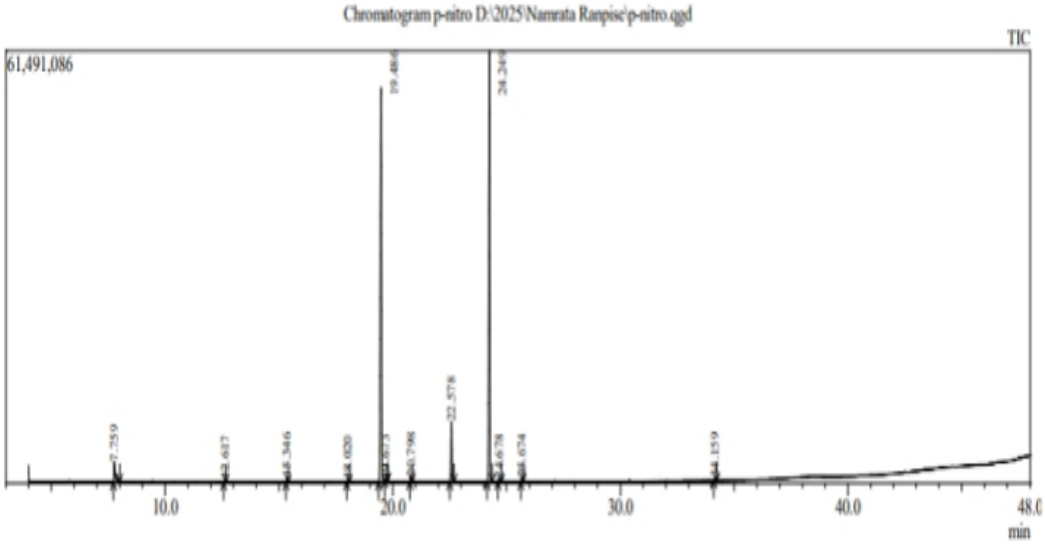


Graph no 5.2.12: NMR Spectrum of compound 4a

Table no.5.2.12: NMR Spectrum value of compound 4a

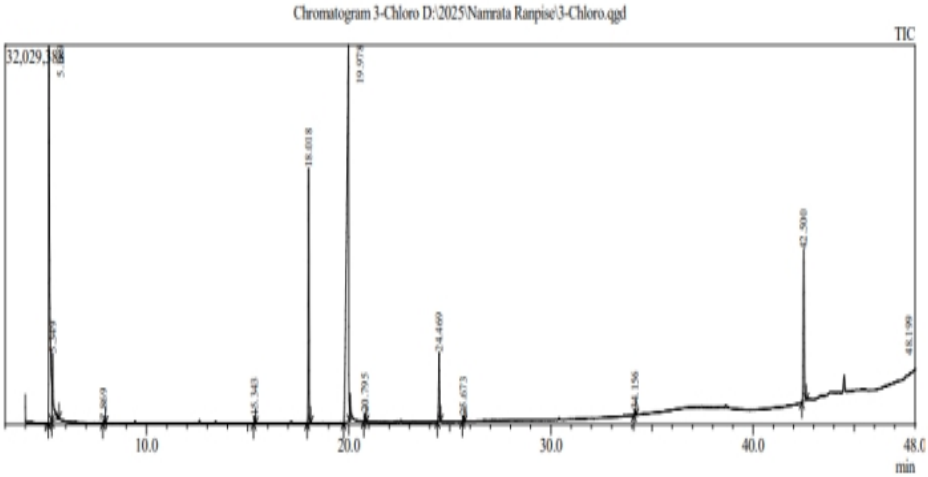
Sr. No.	Chemical Shift (δ)	Assignment
1	10.38	Aldehyde proton (-CHO)
2	10.16	Amide NH
3	8.4	Aromatic protons
4	5.11	amide NH
5	3.90	CH near oxadiazole or solvent
6	2.76	trace impurities
7	1.25	aliphatic solvent

MASS Spectrum of 3a 5-(2 -formyl-4-nitrobenzamido)-1,3,4-oxadiaazolidin-2-yl-4-nitrobenzoate



Graph no. 5.2.13: MASS Spectrum of compound 3a

MASS Spectrum of 4a 5 (5 -chloro-2-formylbenzamido)-1,3,4-oxadiazolidin-2-yl-4-chlorobenzoate



Graph no 5.2.14: MASS Spectrum of compound 4a

Antimicrobial Activity **Observations:**

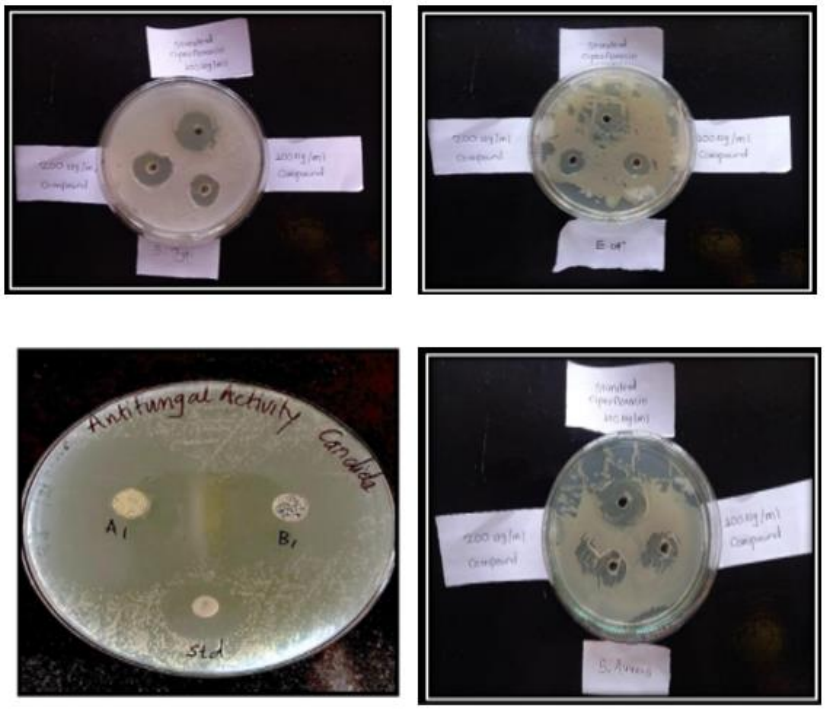


Fig no.7.7.1: Antimicrobial properties of synthesized compound

Table.no. 7.7.1 Antibacterial screening of synthesized compound (3a-4e) measuring the zone of inhibition in millimeters.

Sr.No.	Compound code	Zone of inhibition in mm					
		E. Coli		P.aeruginosa		S.aureus	
		100µg/ml	200µg/ml	100µg/ml	200µg/ml	100µg/ml	200µg/ml
1	3a	**10**	**13**	**9**	**15**	**13**	**17**
2	3b	7	10	5	7	7	9
3	3c	5	9	6	9	7	12

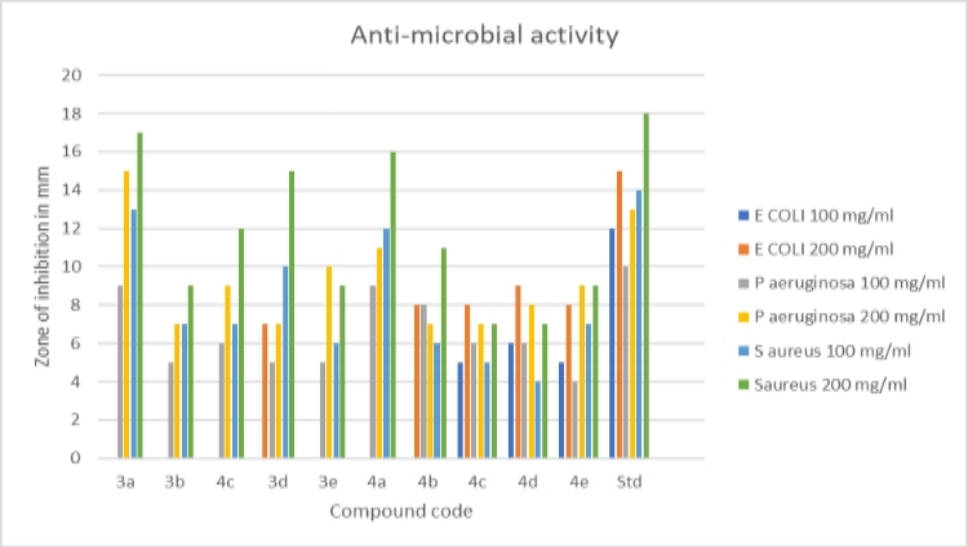
4	3d	4	7	5	7	10	15
5	3e	6	10	5	10	6	9
6	4a	**11**	**14**	**9**	**11**	**12**	**16**
7	4b	7	8	8	7	6	11
8	4c	5	8	6	7	5	7
9	4d	6	9	6	8	4	7
10	4e	5	8	4	9	7	9
11	**Std (Ciprofloxacin)**	**12**	**15**	**10**	**13**	**14**	**18**

Table.no. 7.7.2 Antifungal screening of synthesized compound (3a-4e) measuring the zone of inhibition in millimeters.

Sr. No.	Compound code	Zone of inhibition in mm			
		C. albicans		A. niger	
		100µg/ml	200µg/ml	100µg/ml	200µg/ml
1	3a	14	16	17	20
2	3b	7	8	11	12
3	3c	10	9	9	7
4	3d	12	13	15	10
5	3e	6	6	8	9
6	4a	13	16	18	20
7	4b	5	7	8	9
8	4c	7	8	7	10
9	4d	5	6	8	7
10	4e	6	7	9	12
11	Std (Fluconazole)	15	17	20	22

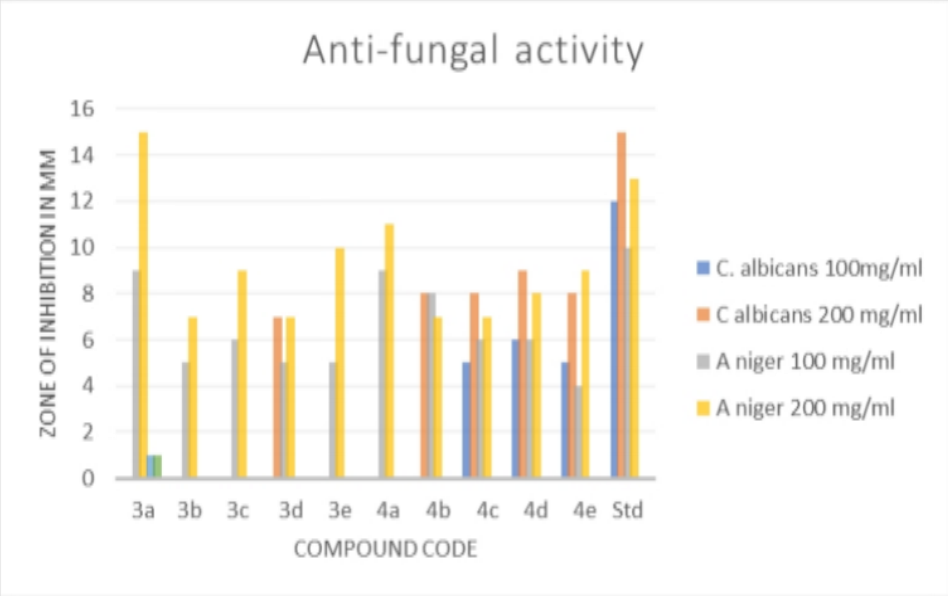
RESULT AND DISCUSSION

Antimicrobial action: The cup-and-plate method was used to investigate the antibacterial activity of a synthesised chemical. It has been demonstrated that the test sample (3a–4e) shows significant action and a comparable percentage of inhibition to the reference drug.



Graph no. 8.3.1 Antibacterial activity on synthesized compound. (3a-4e).

Antifungal activity: To test the synthesized compound's antifungal qualities, the cup-plate method was employed. The test sample (3a–4e) has been seen to have strong activity and a comparable proportion of inhibition to the conventional medication.



Graph no. 8.3.2 Antifungal activity on synthesized compound. (3a-4e)

SUMMARY AND CONCLUSION

A set of ten synthesized compounds were subjected to molecular docking studies to evaluate their antibacterial and antifungal potential. Compound 4a showed strong binding affinity and significant activity against the *E. coli* receptor and *E. coli* GLMU (PDB ID: 4AA7), particularly when combined with an antibacterial inhibitor. Meanwhile, compound 3a demonstrated notable antifungal activity by targeting the receptor DNA gyrase, which contains five disulfide bridges (PDB ID: 1KZN). In the present study, a series of substituted 1,3,4-oxadiazoles were synthesized using microwave-assisted methods and evaluated for their antibacterial and antifungal activities. Microwave synthesis proved to be highly efficient, offering significantly higher yields in a shorter time compared to conventional methods. The synthesized compounds were recrystallized using various solvents, including ethanol, petroleum ether, n-hexane, methanol, butanol, and acetone, through a slow evaporation technique. Among these solvents, ethanol and acetone produced the most well-defined crystal structures, typically forming needle-like, cross-shaped, and clustered crystals. This is particularly important, as polymorphism can greatly influence the bioavailability of drugs—especially those with poor water solubility. The structural integrity of the synthesized compounds was confirmed by satisfactory results from IR, ^{1}H NMR, and mass spectroscopic analyses. In this study, a group of new oxadiazole compounds was made and tested using both computer-based methods and laboratory experiments. The in-silico (computer) studies showed that some of the compounds could strongly bind to proteins of harmful microbes, suggesting they might work as drugs. Laboratory tests confirmed that a few of these compounds had good antibacterial and antifungal activity. In comparison to ciprofloxacin, compound 4a exhibits substantial antibacterial activity, and In comparison to Fluconazole, compound 3a exhibits

similar antifungal activity. Overall, the results suggest that the synthesized oxadiazole derivatives have the potential to be developed into effective medicines for treating infections.

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