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Research Article

ANTIMICROBIAL ACTIVITY AND DFT STUDIES OF SYNTHESIZED 3- (5-CYCLOHEXYL–1,3,4-OXADIAZOL-2-YL)-N- SUBSTITUTED ANILINE DERIVATIVES

S. Kavitha [1]*, N. Zulfareen [2], K. Kannan [1], S. Gnanavel [1]
[1]Department of Chemistry, Government College of Engineering, Salem-11, Tamilnadu, India
[2]Department of Chemistry, Mahendra Engineering College, Namakkal-637503, Tamilnadu, India
*Corresponding Author Email: kavisundar06@gmail.com

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ABSTRACT

In the present study, synthesized 3-(5-cyclohexyl -1,3,4-oxadiazol-2-yl)-N-substituted aniline derivatives were studied for their *in vitro* antibacterial activity against four bacterial strains like gram positive; *Staphylococcus aureus*, *Bacillus subtilis, gram negative bacteria : Escherichia coli, Pseudomonas aeruginosa* and antifungal strains like *Candida albicans, Aspergillus Niger.* All synthesized compound showed moderate to good antimicrobial activities. The fifteen synthesized compounds have been performed with DFT by using RB3LYP/ 311G (d, p) basis set.

Keywords: 1,3,4-oxadiazole, antimicrobial activity, DFT

INTRODUCTION

Heterocyclic compounds have diverse applications in many field like pharmaceutical, agriculture, fluorescent materials, and industries. 1,3,4-Oxadiazole are one of the main pharmacophore in nitrogen containing heterocyclic compounds. Heterocyclic compounds bearing 1,3,4-oxadiaozle scaffold showed a wide range of pharmaceutical applications such as antimicrobial [1-2], antiviral[3], antioxidant[4], antialthamic[5] anticancer[6-8], anti-inflammatory[9-10], tyrosinase inhibitors[10] , anti-HIV[11] etc. 1,3,4-oxadiazole exhibited potent bioactivities due to the presence of the –N=C-O- linkage in toxophoric in nature.
In previous work, a series of novel 2,5 disubtituted -1, 3, 4 oxadiazole derivatives were synthesized and also confirmed by spectral technique. The synthesized 1,3,4-oxadiazole compounds revealed that interesting biological activity[12]. In continuation, all the synthesized compounds were evaluated for antimicrobial activity and HOMO, LUMO and global chemical descriptors.

MATERIALS AND METHODS

Synthesized Compounds

The fifteen synthesized compounds are 1-[3-(5-Cyclohexyl-[1,3,4] oxadiazol-2-yl)-phenyl]-3-(4-fluoro-phenyl)-urea (1), 1-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-p-tolyl-urea (2), 1-[3-(5-Cyclohexyl-[1,3,4] oxadiazol-2-yl)-phenyl]-3-(3-methoxy-phenyl)-urea (3) , 4-Chloro-N-[3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzamide(4),N-[3-(5-Cyclohexyl [1,3,4]oxadiazol-2-yl)-phenyl]-4-methyl-benzamide (5), N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-2-(2-fluoro-phenyl)acetamide(6),N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3,5-difluoro-benzamide (7), Pyrazine-2-carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (8), N-[3-(5-Cyclohexyl-[1, 3, 4] oxadiazol-2-yl)-phenyl]-2-(1H-indol-3-yl)-Acetamide (9), Cyclopentane carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (10), Furan-2-carboxylic acid [3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-amide (11), N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-3-furan-2-yl-acrylamide (12), N-[3-(5-Cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-4-methyl-benzenesulfonamide(13), 4-tert-Butyl-N-[3-(5-cyclohexyl-[1,3, 4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide (14) , and 3,5-Dichloro-N-[3-(5-cyclohexyl-[1,3,4]oxadiazol-2-yl)-phenyl]-benzenesulfonamide **(15) .** The structures of the tested compounds are given Table 1.

Antibacterial Study

The antibacterial activities of all tested compounds were evaluated by disc diffusion method[13-14].
The concentrations of 100µg the synthesized compounds were dissolved in DMSO. The microorganisms were cultured in Mueller–Hinton broth (MHB). After 24 h the suspensions were adjusted to standard sub-culture dilution. The Petri dishes containing Muller Hinton Agar (MHA) medium were cultured with diluted bacterial strain. Disc made of Whatman No.1, diameter 6 mm was pre-sterilized and was maintained in aseptic chamber. Each concentration was injected to the sterile disc papers. Then the prepared discs were placed on the culture medium. Standard drug amikacin (30µg) was used as a positive reference standard to determine the sensitivity of each microbial species tested. Then the inoculated plates were incubated at 37 ºC for 24 h. The diameter of the clear zone around the disc was measured and expressed in millimeters as its anti-microbial activity.

Antifungal Study

Potato 0dextrose agar (PDA) was used for fungal cultures. The culture medium was inoculated with the fungal strains separately suspended in Potato dextrose broth. The synthesized compounds were applied on sterile disc. Standard antibiotic (ketoconazole 30µg) was used as positive control and fungal plates were incubated at 37°C for 72 h. The diameters of zone of inhibition observed were measured.

Computational Calculations

Quantum chemical parameter like, E_{HOMO} , E_{LUMO} and energy gap (ΔE), chemical potential(μ), Dipole moment, global hardness(η), Electrophilic index(ω) of the all titled molecules were fully optimized by using DFT by RB3LYP(2d, p) with electron basis set 6-311++G Gaussian 09 [15-17] and also Clog P were calculated using Chem draw ultra 7.0. The computed quantum parameters such as $E_{HOMO,}$ $E_{LUMO,}$ ΔE, chemical potential (μ), global hardness (η), electrophilicity index (ω) of were shown in Table 2

According to the frontier molecular orbital theory, HOMO and LUMO are the most important factors that affect the bioactivity. From the table it was observed that the large HOMO-LUMO energy gap displayed good stability and high chemical hardness of the molecules.[18-20] .The energy gaps increases in which decrese reactivity of the molecules and also biological activity of the compounds. The small chemical hardness for the compound has less stable and more reactive. Therefore, compound **12** is more reactive than others the tested compounds. Furthermore, the compound **15** has less hard. Electrophilic index (ω) is measured by using chemical potential and chemical hardness of the molecules. The results of electrophilic index showed that compound **3** is a strongest nucleophile and compound **15** act as strongest a electrophile. Chemical reactivity, energy gap Lipophilicity, and chemical hardness have significant properties on bioactive of the molecules. In general, the chemically reactive compounds showed less suitable for the biological activity. The compounds have the high values of C log P exhibited less antimicrobial activities and were calculated using Chem. Draw software 7.0. (Figure 1)

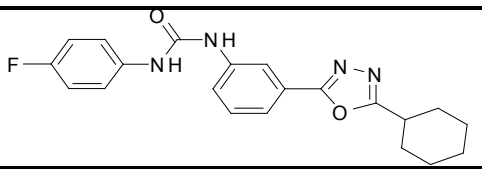
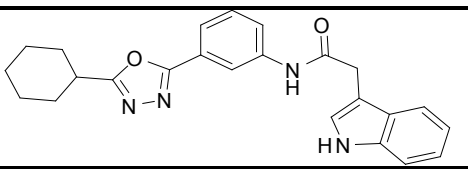
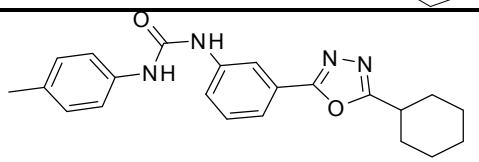
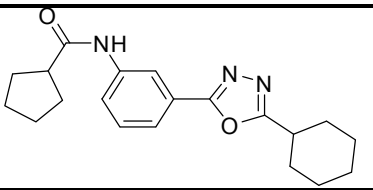
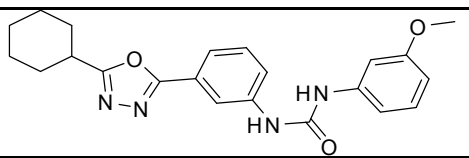
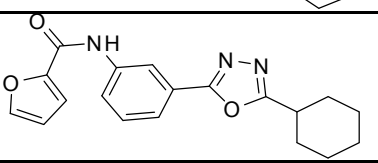
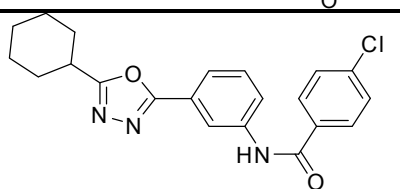
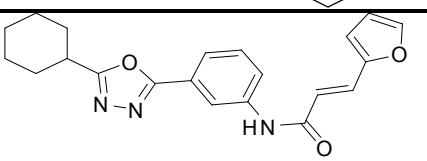
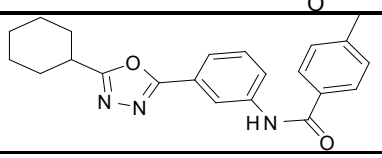
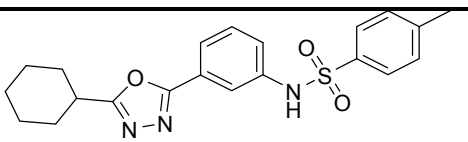
***In Vitro* Antibacterial Evaluation**

The antibacterial activity of the all the title compounds were carried out by using disc diffusion technique at concentration of 100μg/mL and compared with that known standard amikacin.. From the resulted data, all synthesized 1,3,4-oxdaizole derivatives displayed poor to high activity against all the tested strains. Interestingly, Compounds **3** and **4** exhibited significant activity against positive gram positive bacteria; *S. aureus, B. subtilis*.. The most of the synthetic compounds showed moderate activity against *P.aeruginosa* and *E.coli*. The zone of inhibition of the all compounds is summarized in table 3.

***In Vitro* Antifungal Evaluation**

The antifungal activities of the compounds were tested by using the disc diffusion method at concentration of 100μg/mL. The results revealed that majority of the tested compounds have shown excellent activity against two fungal strains *Candida albicans*, *Aspergillus Niger*. Among the series, Compounds **3, 4, 11** and **12** were found to be most active antifungal agents, while comparing with the standard Ketaconazole. The zone of inhibition of the all compounds is summarized in Table 3.

Table 1: The structure of the tested compounds

Compound no.	Structure		Structure
1		9	
2		10	
3		11	
4		12	
5		13	

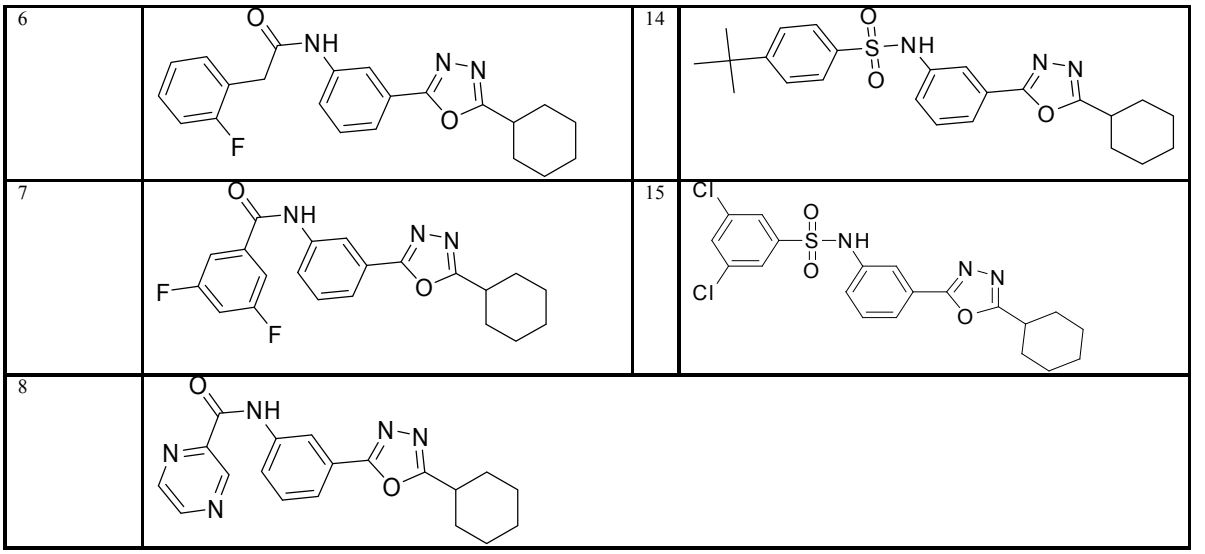


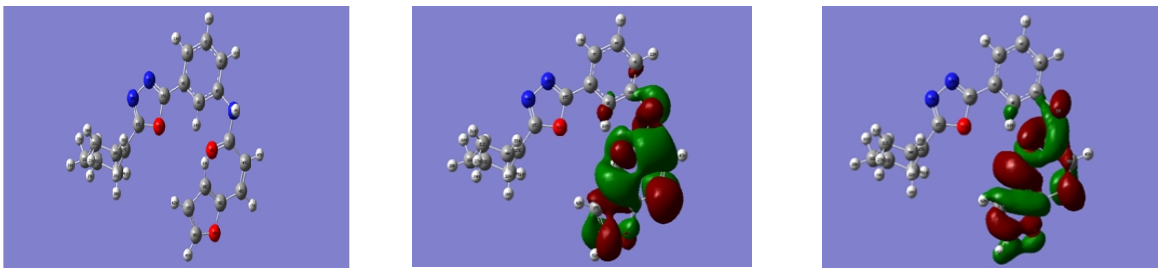
Table 2: Quantum chemical descriptor for synthesized compounds calculated using RB3LYP/6-311G (d, p) and values in a.u unit

Compound	E_{HOMO}	E_{LUMO}	ΔE	μ	μ (D)	η	ω	C log P
1	-0.13833	-0.04838	-0.08995	0.09335	11.170	0.04497	0.0969	4.35
2	-0.14547	-0.05821	-0.08726	0.10184	5.7955	0.04363	0.1188	4.59
3	-0.14592	-0.05846	-0.08746	0.04373	5.2705	0.04373	0.0219	4.030
4	-0.14495	-0.07529	-0.06966	0.11012	6.2685	0.03483	0.1741	4.441
5	-0.14350	-0.06543	-0.07807	0.10446	7.8755	0.03903	0.1398	4.187
6	-0.14177	-0.07960	-0.06217	0.11068	7.3303	0.03108	0.1970	3.880
7	-0.14546	-0.07921	-0.06625	0.11233	6.8077	0.03312	0.1905	4.028
8	-0.22895	-0.08412	-0.14483	0.15653	5.4537	0.07241	0.1692	2.284
9	-0.14790	-0.07899	-0.06891	0.11344	3.8134	0.03445	0.1867	3.273
10	-0.18089	-0.05541	-0.12548	0.11815	3.5758	0.06274	0.1112	3.671
11	-0. 22003	-0.05789	-0.16214	0.13896	5.7668	0.08107	0.1191	2.864
12	-0.24051	-0.06628	-0.17423	0.15339	7.0152	0.08712	0.1350	3.878
13	-0.18381	-0.13035	0.05346	0.15708	4.0436	0.02673	0.4615	4.058
14	-0.16882	-0.11074	0.05808	0.13978	5.1184	0.02904	0.3364	5.385
15	-0.19436	-0.15709	-0.03727	0.17572	3.0385	0.01863	0.8248	5.227

Table 3: The zone of inhibition of the all tested compounds against antimicrobial activity

Compound Code	Diameter of Zone of Inhibition in mm					
	Gram positive	**Bacteria**	**Gram positive**	**Bacteria**	**Antifungal**	
	SA	**BS**	**EC**	**PA**	**CA**	**AN**
1	11	13	11	13	24	20
2	14	13	8	10	14	16
3	22	20	12	14	18	19
4	19	18	8	13	19	23
5	14	12	13	10	21	20
6	8	10	15	17	21	22
7	8	9	12	12	24	26
8	12	9	12	16	22	20
9	13	12	11	9	23	23
10	13	13	8	12	9	08
11	16	10	7	11	22	23
12	17	18	10	14	26	28
13	13	11	12	9	21	24
14	11	15	12	15	18	17
15	9	8	10	11	16	14
Amikacin	**22**	**26**	**26**	**22**		
Ketaconazole					**21**	**23**

SA = *Staphylococcus aureus* ATCC 9144, BS = *Bacillus subtilis* ATCC 6051, EA = *Escherichia coli* ATCC 25922, PA= *Pseudomonas aeruginosa* ATCC-2853, CA= *Candida albicans,* MTCC-227, AN = *Aspergillus Niger* MTCC-281.



Optimized structure of Compound 12 HOMO LUMO

Figure 1: Optimized structure and HOMO and LUMO energies of compound 12

CONCLUSION

In summary, a series of the fifteen synthesized compounds were evaluated for their in vitro antimicrobial activity. The most of the compounds showed good activity against antifungal activity than that of antibacterial activity. The biological data showed that some of the compounds showed good antimicrobial activity. Furthermore, Compound **12** was found to be effective an effective antifungal agent. The frontier orbital energy like HOMO, LUMO and the global reactivity descriptors were calculated using RB3LYP/ 311G (d, p) methods with Gaussian 09 and correlates with their anti microbial activities.

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