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

¹Department of Chemistry, Government College of Engineering, Salem-11, Tamilnadu, India

²Department of Chemistry, Mahendra Engineering College, Namakkal-637503, Tamilnadu, India

*Corresponding Author Email: kavisundar06@gmail.com

Article Received on: 16/10/16 Revised on: 08/11/16 Approved for publication: 14/11/16

DOI: 10.7897/2230-8407.0711135

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-oxadiazole scaffold showed a wide range of pharmaceutical applications such as antimicrobial ¹⁻², antiviral³, antioxidant⁴, antialthamic⁵, anticancer⁶⁻⁸, anti-inflammatory⁹⁻¹⁰, tyrosinase inhibitors¹⁰, anti-HIV¹¹ 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 disubstituted -1, 3, 4 oxadiazole derivatives were synthesized and also confirmed by spectral technique. The synthesized 1,3,4-oxadiazole compounds revealed that interesting biological activity¹². 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 method¹³⁻¹⁴.

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 °C 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 Dextrose 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 09¹⁵⁻¹⁷ 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 decrease 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 100 μ g/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 100 μ g/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	

6		14
7		15
8

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	$\mu (D)$	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	11	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		
Ketoconazole					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.

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.

REFERENCES

1. Rajesh A, Rane, Shweta D Gutte, Niteshkumar U, Sahu. Synthesis and evaluation of novel 1,3,4-oxadiazole derivatives of marine bromopyrrole alkaloids as antimicrobial agent. *Bioorganic Medicinal Chemistry Letters* 2012; 22: 6429-6432.
2. B Chandrakanda, Prakash Shetty, Vijesh Nambiyar, Nishitha Isloor, Arun M Isloor. Synthesis, characterization and biological activity of some new 1, 3, 4-oxadiazole bearing 2-flouro-4-methoxy phenyl moiety. *European Journal of Medicinal Chemistry* 2010; 45: 1206-1210.
3. Theresa May Chin Tan, Yu Chen Kah Hoe Kong, Jing Bai, Yang Li, Seng Gee Lim, Thiam Hong Ang, Yulin Lam. Synthesis and the biological evaluation of 2-benzenesulfonylalkyl-5-substituted-sulfanyl-[1,3,4]-oxadiazoles as potential antihepatitis B virus agents. *Antiviral Research* 2006; 7: 17-14.
4. Y. Kotaiah, N. Harikrishna, K. Nagaraju C. Venkata Rao. Synthesis and antioxidant activity of 1,3,4-oxadiazole tagged thieno[2,3-d]pyrimidine derivatives. *European Journal of Medicinal Chemistry* 2012; 58: 340-345.
5. B, Naga sudha , C, Srithar, V, Girija Sastry, Y,S, R, Reddy, OWK Srividhya, S, Lavanya, V, Asha Jyothi, V, Nagesh, Saikat Sen, Raja Chakraborty. Synthesis, characterization, antihelmintic activity of 3-(4-acetyl -5-phenyl-4,5-dihydro oxadiazol-2-yl)-2H-chromen-2-one derivatives', *Indian Journal of Chemistry* 2013; 52B : 422-427.
6. M S R Murthy, B Ramalingeswara Rao, Maohana Rao katiki, Lekshmi R, Nath, Ruby John Anto. Synthesis of piperazinyl benzo[thiazole/benzoxazole derivatives coupled with 1,3,4-oxadiazole-2-thiol: novel hybrid heterocycles as anticancer agents. *Medicinal Chemistry Research* 2013; 22: 4980-4991.
7. Xiao-Min Zhang, Min Qiu, Juan Sun, Yan-Bin Zhang, Yu-Shun Yang, Xiao-Liang Wang, Jian-Feng Tang, Hai-Liang Zhu. Synthesis, biological evaluation and molecular docking studies of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan moiety as potential anticancer agents . *Bioorganic Medicinal Chemistry* 2011; 19: 6518-6524.
8. Gudipati R, Anreddy R, N, Manda S. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1,3,4-oxadiazole- 2-yl)phenylimino} indolin-2-one derivatives. *Saudi Pharmaceutical Journal* 2011; 19: 153-158.
9. Ali Almasirad, Zahra Mousavi, Mohammad Tajik, Mohammad Javad Assarzadeh and Abbas Shafiee. Synthesis, analgesic and anti-inflammatory activities of new methyl-imidazolyl-1,3,4-oxadiazoles and 1,2,4-triazoles. *Daru journal of pharmaceutical sciences* 2014; 22: 22.
10. Sadaf J, Gilani, Suroor A, Khan, Nadeem Siddqui. Synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted 1, 2,4-triazolo-[3,4-b]-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid .*Bioorganic Medicinal Chemistry Letters* 2010 ; 20: 4762-4765.
11. Z. Hajimahdi, A.Zarghi, R. Zabihollahi, M.R. Aghasadeghi. 2013. Synthesis, biological evaluation, and molecular modeling studies of new 1,3,4-oxadiazole-and 1,3,4-thiadiazole-substituted 4-oxo-4H-pyrido[1,2-a] pyrimidines as anti HIV-1 agents. *Medicinal Chemistry Research* 2013; 22: 2467-2475.
12. Kavitha Selvaraj, Kannan kulanthai, Sadhasivam Gnanavel, Synthesis, characterization and biological evaluation of novel 2, 5 substituted-1, 3, 4 oxadiazole derivatives. *Saudi Pharmaceutical Journal* 2016; doi.org/10.1016/j.jsps.2016.07.004.
13. Bauer AW, Kirby WM, Sherris JC, Turck M. Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology* 1966; 45: 493-6.
14. Zeba N Siddiqui, Farheen Farooq, T N Mohammed Musthafa Anis Ahmad Asad U Khan. synthesis, characterization and antimicrobial evaluation of novel halo pyrazole derivatives. *Jornal of Saudi Chemical Society* 2013; 17: 237-243.
15. Khan FA, Choudhury S. Synthesis and electrochemical properties of substituted para-benzoquinone derivatives. *Tetrahedron Letters* 2010 ; 51:2541.
16. Kosar B, Albayrak C. Spectroscopic investigations and quantum chemical computational study of (E)-4-methoxy-2-[(p-tolylimino)]phenol. *Spectrochimia Acta A* 2011; 78: 16.
17. Wahida Boufas, Nathalie Dupont, Malika Berredjem, Kamel Berrezag, Imene, Becheker, Hajira Berredjem, Nour-Eddine Aouf. Synthesis and antibacterial activity of sulphonamide. SAR and DFT studies, *Journal of Molecular Structure* 2014 ; doi.org/ 10.1016 /j.molstruc. 2014. 05.066.
18. N Zulfareen, K Kannan, T Venugopal, S Gnanavel. Synthesis, characterization and corrosion inhibition efficiency of N-4(4-(Morpholinomethyl

- carbomoylphenyl)Furan-2-Carboxamide for brass for in HCl medium. *Arabian Journal of Chemistry* 2016; 9: 121-135.
19. Selma Spirtovic-Halilovic, Mirsada Salihovic, Huriya, Dzudzevic-Cancar, Snezana Trifunovic, Suncica roca, Dzenita Softics and Davorkazavrsnik, DFT study and microbial of some coumarin –based compounds containing a chalcone moiety, *Journal of the Serbian Chemical Society* 2014; 79: 435-443.
20. S Murugavel, N Manikandan, D Lakshmanan, Kanagaraj Naveen, Paramasivan Thirumalai Perumal. Synthesis, crystal structure, DFT and antibacterial activity studies of (E)-2-benzyl-3-furan-3yl)-6, 7-dimethoxy-4-(2-phenyl-1H-inden) 1,2,3,4-tetrahydroisoquinoline. *Journal of Chilean Chemical Society* 2015; 60: 3.

Cite this article as:

S. Kavitha, N. Zulfareen, K. Kannan, S. Gnanavel. Antimicrobial activity and DFT studies of synthesized 3- (5-cyclohexyl-1,3,4-oxadiazol-2-yl)-n- substituted aniline derivatives. *Int. Res. J. Pharm.* 2016;7(11):92-96
<http://dx.doi.org/10.7897/2230-8407.0711135>

Source of support: Nil, Conflict of interest: None Declared

Disclaimer: IRJP is solely owned by Moksha Publishing House - A non-profit publishing house, dedicated to publish quality research, while every effort has been taken to verify the accuracy of the content published in our Journal. IRJP cannot accept any responsibility or liability for the site content and articles published. The views expressed in articles by our contributing authors are not necessarily those of IRJP editor or editorial board members.