ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2020, Vol. 46, No. 6, pp. 1110–1116. © Pleiades Publishing, Ltd., 2020.

Microwave-Assisted Synthesis and Molecular Docking Studies of Fluorinated 1,3,4-Oxadiazole Derivatives as Antimicrobial Agent

B. K. Dhotre[a, 1], M. A. Patharia[b], A. U. Khandebharad[c], S. V. Raut[d], and M. A. Pathan[d]

[a] *Department of Chemistry, Swami Vivekanand Senior College, Mantha, Maharashtra, India*

[b] *Navin Research and Innovation Centre, NFIL Surat, Gujarat, India*

[c] *Department of Chemistry, JES College, Jalna, Maharashtra, India*

[d] *Department of Chemistry, Maulana Azad College, Aurangabad, Maharashtra, India*

Received March 28, 2020; revised April 14, 2020; accepted April 24, 2020

Abstract—A series of phenyl-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]-oxadiazole were prepared from 2,3,5,6-tetrafluoro-benzoic acid hydrazide by treatment with various substituted benzoic acid in the presence of phosphorus oxychloride using conventional as well as microwave-assisted methods. Evaluation of antibacterial activity of synthesized compound against *S. aures, S. pyogenes*, *S. typhi* and *Pseudomonas* species and antifungal activity against *C. albicans* and *A. niger* has been carried out. The compounds (**Vb**) and (**Ve**) showed significant activity against both bacteria and fungi. Some of the compounds has shown moderate activity against both the bacteria and fungi. The molecular docking studies also done which support the antimicrobial activity exhibited high inhibition constant and binding energy. The chemical structures of all the synthesized compounds were elucidated by their IR, ^{1}H NMR and mass spectra.

Keywords: 1,3,4-oxadiazoles, antibacterial activity, antifungal activity, molecular docking, microwave irradiation

DOI: 10.1134/S1068162020060059

INTRODUCTION

The heterocyclic compound play vital role in drug chemistry. They exhibit various biological activities against microorganisms. Specially 1,3,4-oxadiazole are very important nucleus in many drug molecules. Presence of fluorine atoms enhances its activity due to the increases the lipophilicity of molecules thus making more superior than non fluorinated compound. Also C–F bond is stronger than C–H which enlarges its bioavibility. Literature suggests that fluorine augments therapeutics efficiency, improves its pharmacological activity of 1,3,4-oxadiazole [1]. In recent days researcher are paying more attention on 1,3,4-oxadiazole due to its various medicinal, pesticidal, and polymer forming properties. 1,3,4-oxdiazole exhibits vast biological activity such anti-microbial [2–4], antitumor [5], antifungal [6, 7], anti-cancer [8–10], antiviral [11–13], anti-inflammatory [14–16], antibacterial [17, 18], anti-diabetic [19], antioxidant [20–22], antallergic [23], anti-tubercular [24], cytotoxic [25], and anti-HIV [26]. The considering this, it is decided to synthesize tetra fluorinated 1,3,4-oxadiazole as importantas pharmacore.

[1] Corresponding author: e-mail: bharatd219@gmail.com.

RESULTS AND DISCUSSION

Chemistry

We have synthesized series of phenyl-5-(2,3,5,6-tetrafluoro-phenyl)-[1, 3, 4]-oxadiazole (**Va–j**) using $POCl_3$ by the oxidative cyclization of 2,3,5,6-Tetrafluoro-benzoic acid hydrazide (**3**) and various substituted benzoic acid (**IVa–j**). Compound 2,3,5,6-Tetrafluoro-benzoic acid hydrazide (**III**) was obtained by the esterification followed by reaction with hydrazine hydrate. The structure of compound (**Va–j**) were established by spectroscopic method FTIR, ^{1}H NMR and LC-MS. The compound (**Va**) confirmed by disappearance of the peak at 4.70 for NH_2 and 10.30 (1 NH) in ^{1}H NMR spectrum. ^{1}H NMR peaks of aromatic proton appears at δ 7.27–8.91 as multiplet. IR absorption band appears at 1675 cm^{-1} indicates –C=N group while band at 1172 and 1066 cm^{-1} C–O–C bending vibration. LC-MS spectra shows peak at *m/z* 295.

The synthesis was initiated with the reaction between fluorinated benzoic acid hydrazide (**III**) with 2,3,5,6-tetrafluorobenzoic acid (**IVa**) suspended in phosphorus oxytrichloride was refluxed for 6 h and obtained yield 75%, while reaction under microwave radiation enhances the yield up to 92% (Table 1). Hence we conclude that the reaction under microwave

Table 1. Time and yield data of newly synthesized compounds (**Va–j**) using conventional and microwave irradiation method

Compound	R	Microwave irradiation		Conventional method		Mp, °C
		reaction time, min	yield, %	reaction time, h	yield, %	
(Va)	H	15	91	6	75	95
(Vb)	4-NO_2	15	92	6	74	208
(Vc)	3-NO_2	15	92	6	75	156
(Vd)	4-OCH_3	15	84	7	76	191
(Ve)	4-Cl	15	90	7	76	154
(Vf)	4-NH_2	15	85	7	76	97
(Vg)	4-CH_3	15	80	6	77	123
(Vh)	2-Cl	15	87	6	81	130
(Vi)	4-OH	15	85	7	76	294
(Vj)	3-OH	15	87	7	81	253

Table 2. Antimicrobial activity of compounds (**Va–j**) in zone of inhibition in mm

compound	Diameter of zone of inhibition, mm					
	GM +ve BACTERIA		GM –ve BACTERIA		FUNGUS	
	S. aureus	*S. pyogenes*	*S. typhi*	*Pseudomonas*	*C. albicans*	*A. niger*
(Va)	10	10	10	10	12	12
(Vb)	16	17	16	12	18	19
(Vc)	15	14	16	15	16	17
(Vd)	12	10	11	10	11	12
(Ve)	15	18	16	16	17	16
(Vf)	11	10	11	10	18	17
(Vg)	11	12	11	10	12	12
(Vh)	11	12	12	12	10	10
(Vi)	10	11	16	12	10	11
(Vj)	10	11	12	12	11	10
Ampicillin	20	23	22	22	–	–
Fluconazole	–	–	–	–	22	22

help to not only increase yield but also reduce the reaction time. Compound **(Vb)** and **(Vc)** containing the electron withdrawing group gave highest yield among all synthesized compound. While compound **(Vg)** containing electron donating group obtained lowest yield. Hence we observed that the effect of product substituent affect on reaction yield of product.

BIOLOGICAL ACTIVITY

Antimicrobial Activity

The synthesized targeted compounds were evaluated for their in vitro antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenes* as example of Gram-positive bacteria and *Salmonella typhi* and *Pseudomonas* as examples of Gram-negative bacteria. All bacterial strains were maintained on nutrient agar medium at ±37°C and fungi strains were maintained on potato dextrose agar (PDA) at ±27°C. The disc diffusion method was used for the screening of antimicrobial activity. The newly prepared compounds were screened for their antifungal activity against *Candida albicans* and *Aspergillus niger* in DMSO by agar dilution method. The lowest concentration (highest dilution) required to arrest the growth of fungus was regarded as minimum inhibitory concentra-

Table 3. In-vitro antibacterial, antifungal activity and molecular docking of synthesized compounds in the study

Compound	MIC values in μg/mL				MIC values in μg/mL		Free binding energy, kcal/mol
	S. aureus	*S. pyogenes*	*S. typhi*	*Pseudomonas*	*C. albicans*	*A. niger*	
(Va)	300	250	250	250	500	200	−4.23
(Vb)	100	100	100	200	125	62.5	−6.04
(Vc)	100	100	200	200	250	125	−4.24
(Vd)	250	250	250	250	250	500	−4.61
(Ve)	250	100	200	100	125	125	−5.56
(Vf)	500	200	200	250	250	125	−5.17
(Vg)	500	500	500	250	500	500	−4.24
(Vh)	500	500	500	250	500	250	−4.33
(Vi)	500	500	200	200	500	500	−4.81
(Vj)	500	500	200	500	500	250	−4.25
Ampicillin	250	100	100	100	–	–	
Fluconazole	–	–	–	–	125	62.5	

tion (MIC). The fungal activity of each compound was compared with fluconazole as standard drug.

Homology Modeling

The Homology modeling technique was employed to build 3D model structure of cytochrome P 450 lanosterol 14α-demethylase of *C. albicans* with help of V Life MD S 4.3 Promodel molecular modelling tool. The protein sequence was retrieved from Uniprot KB database (Accession no. P 10613). The homologue template sequencesearch was carried out against the Protein structure database (http://www.rcsb.org/) by using Blast P. The based on default parameters identity and positive criteria appropriate template crystal structure of human lanosterol 14α-demethylase (CYP 51) complexed with Ketocanazole (3 LD 6_B). The secondary structure assignment and sequence realignment was carried out to build final modeled structure of fungal CYP 51. The modeled structure was subjected to various checks like phi-psi, Z score and Cα deviation [27]. The model protein structure and 3D structure of sketched synthesized compound was prepared for molecular docking using Autodock Vina docking tool [28]. The modeled structure was subjected for various checks like phi-psi, Z score and Cα deviation compounds **(Va)** to **(Vj)** was carried out using final modeled structure of fungal CYP 51 to understand this mechanism of action of inhibitors molecular interactions were analyzed [29].

Comparative Modeling

The sequence identity and atomic resolution are two key parameters during the selection of template structure. It was observed to be 44% and 2.8 Å which satisfy the basic criteria for comparative modeling. The final model was subjected for structure validations tool like Procheck, ProSA and SPDBV were 99.7% of residue followed in allowed region. Overall quality of model was evaluated using Prosa were Z-score = −3.2 and Cα deviation = 0.45 Å respectively. The Validation study of model suggested that it was perfect for further computation study.

The synthesized compounds **(Va–j)** docked in active site of modeled CACYP 51 using Autodock Vina docking tool. Results of docking are shown in Table 3. Analysis of docking interaction has been done and it was found that aryl substituted 1,3,4 oxadiazole are mainly responsible for interaction. The aryl substituted 1,3,4-oxadiazole derivatives **(Vb)**, **(Ve)** and **(Vf)** are most active agents. It also reproduced similar result as that of in vitro activity data. All active compounds efficiently bind in the active site residues like PRO104, PHE108, VAL130, SER414, MET413, CYS439, HIS504 and CYS50.

The Nitro phenyl substituted compound **(Vb)** has highest docking score with free energy of binding −6.04 kcal/mol. The positive charged polar Amino acid residue ARG417 forms conventional hydrogen bond interactions with oxygen atoms of Nitro group with the distance of 2.4 and 2.01Å respectively. Aliphatic amino acid VAL 130 form carbon hydrogen bond with one of the meta substituted fluorine atom with distance of 2.42 Å. The Non polar hydrophobic amino acid residues PRO 104 and PHE108 forms halogen fluoride bond interactions with another meta substituted fluorine atom with the distance of 3.15 and 2.25 Å respectively. The Non polar hydrophilic and hydrophobic amino acid residues CYS439, MET413 and SER414 forms Pi-sulfur, Pi-lone pair, Amide Pi stacked and Pi-alkyl interactions with 1,3,4-oxadizoline substituted phenyl and 1,3,4-oxadizoline with various distance shown in Fig. 1. The second most active derivative **(Ve)** have very good docking score

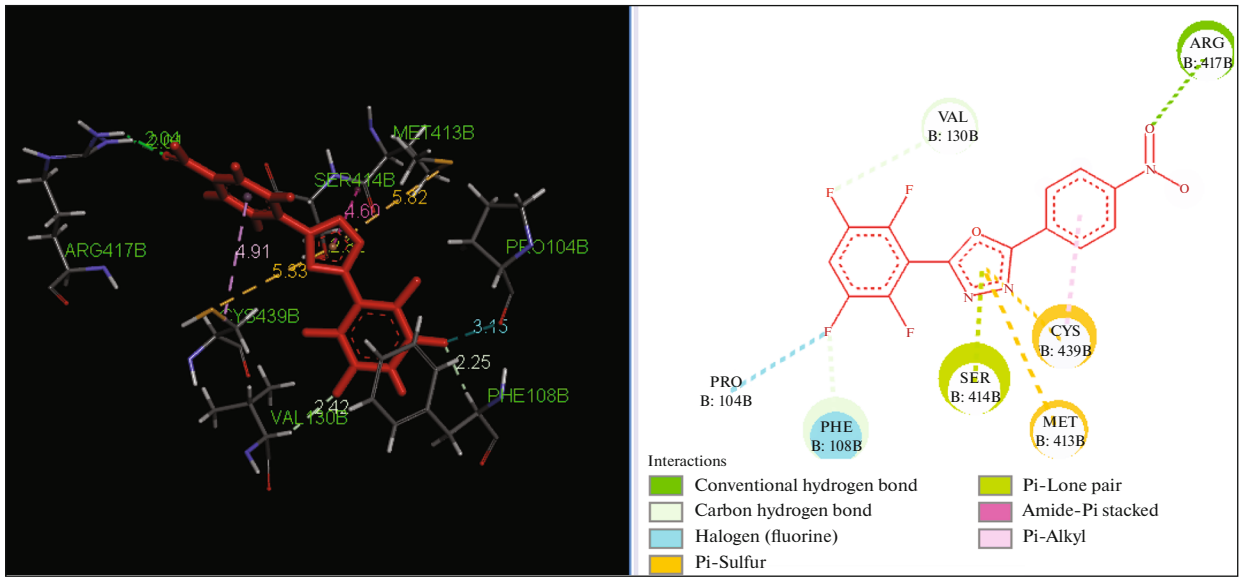


Fig. 1. Binding Pose and molecular interactions of **(Vb)** in the active site of cytochrome P450 lanosterol 14α-demethylase.

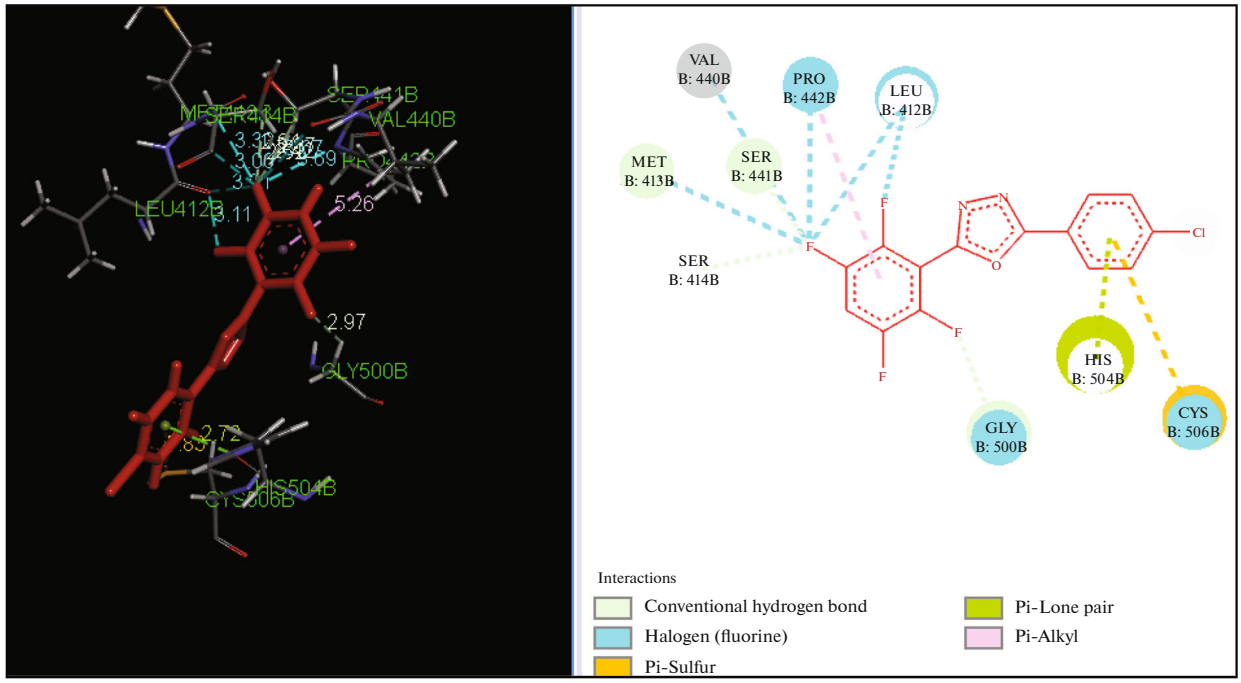


Fig. 2. Binding Pose and molecular interactions of **(Ve)** in the active site of cytochrome P 450 lanosterol 14α-demethylase of **(Ve)** in the active site of cytochrome P450 lanosterol 14α-demethylase.

with free energy of binding of –5.17 kcal/mol. The aliphatic Amino acid residue GLY500 forms carbon hydrogen bond interactions with ortho substituted fluorine atoms with the distance of 2.51 Å. The Non Polar and Polar amino acid LEU 412, MET413, PRO 442, SER 441 and SER 414 forms fluoride bond interaction with ortho and meta substituted fluorine atom with various distance. Non charged and charged amino acid residues HI S504 and CYS506 forms Pi bond interaction with Pi electron cloud of phenyl ring such as Pi-line pair and Pi-alkyl interactions of 2.72 and 5.83Å respectively shown in Fig. 2.

EXPERIMENTAL

Materials and Methods

All the solvents and reagents used were of AR grade from Aldrich and used without further purification.

The NMR spectra were recorded on a Bruker DPX 400 (1H at 400.13 MHz and (^{13}C at 100.63 MHz) spectrometer, 5 mm sample tubs, 298 K, digital resolution of ±0.01 ppm, 0.5 M in $CDCl_3$, containing TMS as internal standard. Mass spectra were achieved using an HP 6890 GC connected to HP 5973 MSD and interfaced by a Pentium PC.

Synthesis of methyl 2,3,5,6-tetrafluorobenzoate (II). The Fluorinated benzoic acid (0.01 mol) was dissolved in 20 mL absolute methanol followed by the addition of 3.0 mL concentrated sulphuric acid in a 100 mL round bottom (RB) flask. The mixture was refluxed for 3h. Reaction progress was monitored on TLC (ethyl acetate : *n*-hexane, 30 : 70), after conformation product formation the reaction mixture was poured into a 500 mL separating funnel. Then 100 mL distilled water and 10% sodium bicarbonate solution was added that to remove unreacted carboxylic acid. 100 mL diethyl ether was added and ether layer containing compound isolated. The solvent was distilled off to afford the transparent esters, with yields 74%.

Synthesis of 2,3,5,6-tetra fluoro benzo hydrazide (III). Fluorinated methyl ester of benzoic acid **(II)** (0.01 mol) was added to 25 mL methanol in 100 mL RB flask followed by 4.0 mL of 80% hydrazine hydrate. The mixture was refluxed consequently for 5h till the completion of reaction, supervised by TLC (ethyl acetate : *n*-hexane, 30 : 70). The precipitates of solid products was generated after addition of excess of distilled water which was filtered and washed with distilled water to afford **(III)** with yields 73%.

Conventional synthesis of 1,3,4-oxadiazoles from Fluorinated benzoic acid hydrazide (Va–j). A mixture of fluorinated benzoic acid hydrazide **(III)** (0.01 mol) with substituted benzoic acid **(IV)** (0.01 mol) suspended in phosphorus oxytrichloride (10 mL) was refluxed. The progress of reaction was monitored by TLC. After completion of reaction the reaction mass was cooled and poured on to crushed ice with continuous stirring. The separated solid mass was neutralized with Sodium bicarbonate. The mixture was left overnight for Room temperature. The resulting solid **(Va–j)** thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

Microwave assisted synthesis of 1,3,4-oxadiazoles from fluorinated benzoic acid hydrazide (Va–j). A mixture of fluorinated benzoic acid hydrazide (3) (0.01 mol) with substituted benzoic acid **(IV)** (0.01 mol) suspended in phosphorus oxytrichloride (10 mL) was irradiated at 110°C for 15 min. The completion of the reaction was monitored by TLC. After completion of the reaction the RBF was removed from the oven. The reaction mixture was poured on to crushed ice with continuous stirring. The separate was left overnight at Room temperature. The resulting solid **(Va–j)** thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from absolute ethanol.

Phenyl-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Va). Yield 91%, mp 95°C; IR (KBr, cm^{-1}): 1675 (C=N stretching), 1172 (C–O–C stretching), 1549 (C=C stretching, aromatic ring), 1066 (C=N stretching). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (s, 1H), 7.53 (dd, J = 8.6 , 6.0 Hz, 1H), 7.58 (dd, J = 6.0, 8.6 Hz, 2H), 8.14 (d, J = 8.24 Hz, 2H), ESI-MS: m/z 295 (M + 1).

2-(4-Nitro-phenyl)-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Vb). Yield 92%, mp 208°C; IR (KBr, cm^{-1}): 1606 (C=N stretching), 1176 (C–O–C stretching), 1507 (C=C stretching, aromatic ring), 1440 (N–O stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.3 (s, 1H), 8.35 (d, J = 8.88 Hz, 2H) 8.44 (d, J = 8.88 Hz, 2H). ESI-MS: m/z 340 (M + 1).

2-(3-Nitro-phenyl)-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Vc). Yield 92%, mp 156°C; IR (KBr, cm^{-1}): 1588 (C=N stretching), 1174 (C–O–C stretching), 1506 (C=C stretching aromatic ring), 1421 (N–O stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (s, 1H), 7.78 (dd, J = 8.08 Hz), 8.45 (d, J = 6.8 Hz, 1H), 8.51 (d, J = 7.8 Hz, 1H), 8.98 (s, 1H), ESI-MS: m/z 340 (M + 1).

2-(4-Methoxy-phenyl)-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Vd). Yield 84%, mp 191°C; IR (KBr, cm^{-1}): 1609 (C=N stretching), 1015 (C–O–C stretching), 1551 (C=C stretching, aromatic ring), 2896 (C–OCH_3 stretching); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.9 (s, 3H, OCH_3), 7.054 (s, 1H, Ar–H), 7.055 (d, J = 8.4 Hz, 2H, Ar–H), 8.081 (d, J = 8.4 Hz, 2H, Ar–H). ESI-MS: m/z 325 (M + 1).

2-(4-Chloro-phenyl)-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Ve). Yield 90%, mp 154°C; IR (KBr, cm^{-1}): 1638 (C=N stretching), 1151 (C–O–C stretching), 1499 (C=C C stretching, aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56 (s, 1H, Ar–H), 7.8 (d, J = 6.12 Hz, 2H, Ar–H), 8.8 (d, J = 6.12 Hz, 2H, Ar–H), ESI-MS: m/z 329 (M + 1).

4-[5-(2,3,5,6-Tetrafluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenylamine (Vf). Yield 85%, mp 97°C IR (KBr, cm^{-1}): 1605 (C=N stretching), 1171 (C–O–C stretching), 1492 (C=C stretching); 3415 (NH_2 stretching): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73 (s, 2H, Ar–NH_2), 6.78 (s, H, Ar–H), 7.32 (d, J = 7.8 Hz, 2H, Ar–H), 7.87 (d, J = 9 Hz, 2H, Ar–H). ESI-MS: m/z 310 (M + 1).

2-(2,3,5,6-Tetrafluoro-phenyl)-5-p-tolyl-[1,3,4]oxadiazole (Vg). Yield 80%, mp 123°C, IR (KBr, cm^{-1}): 1601 (C=N stretching), 1173 (C–O–C stretching), 1492 (CH stretching, CH_3 group), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (s, 3H, Ar–CH_3), 7.26 (s, H, Ar–H), 7.34 (d, J = 8.4 Hz, 2H, Ar–H), 8.01 (d, J = 6 Hz, 2H, Ar–H). ESI-MS: m/z 309 (M + 1).

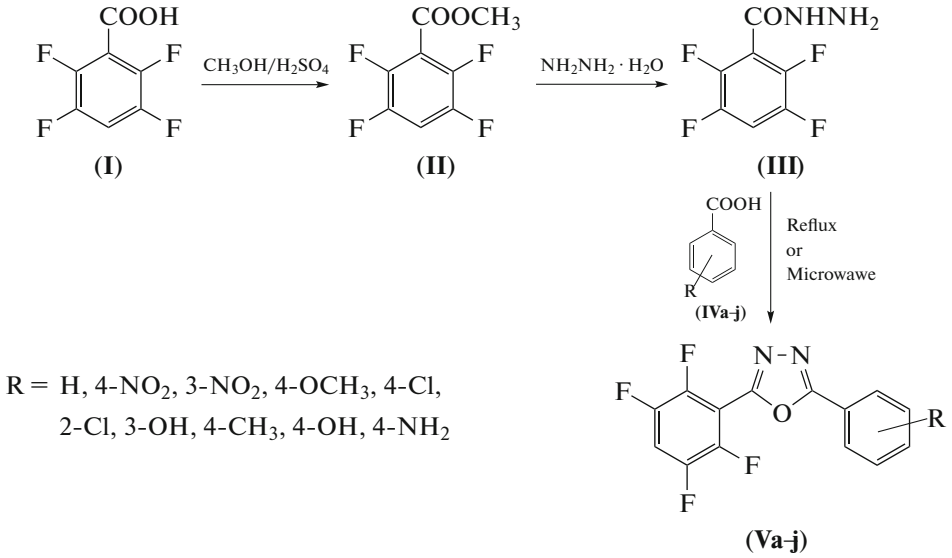
2-(2-Chloro-phenyl)-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]oxadiazole (Vh). Yield 87%, mp 130°C; IR (KBr, cm^{-1}): 1600 (C=N), 1171 (C–O–C), 1497 (C=C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (s, H, Ar–H), 7.44 (dd, J = 6.04 Hz, H, Ar–H), 7.52 (dd J = 7.3 Hz, 1H, Ar–H), 7.61 (d, J = 8.04 Hz, 1H, Ar–H), 8.1 (d, J = 6 Hz, 1H, Ar–H),), ESI-MS: m/z 329 (M + 1).

3-3-[5-(2,3,5,6-Tetrafluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol (Vi). Yield 85%, mp 294°C; IR (KBr) cm^{-1}: 1608 (C=N), 1171 (C–O–C), 1467 (C=C); (O–H stretching aromatic): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (s, 1H, Ar–OH), 7.27 (s, 1H, Ar–H), 7.8 (d, J = 9.0 Hz, 2H, Ar–H),7.1 (d, J = 9.0 Hz, 2H, Ar–H). ESI-MS: m/z 311 (M + 1).

3-3-[5-(2,3,5,6-Tetrafluoro-phenyl)-[1,3,4]oxadiazol-2-yl]-phenol (Vj). Yield 87%, mp 253°C; IR (KBr) cm^{-1}: 1605 (C=N), 1159 (C–O–C), 1430 (C=C); 3260 (O–H stretching aromatic), ^{1}H NMR (400 MHz, DMSO, dppm): δ: 7.05 (s, 1H, Ar–H), 7.3 (s, 1H, Ar–H), 7.31 (d, J = 7.84, 1H), 7.37 (d, J = 7.84 Hz, 1H, Ar–H) 7.48 (dd, J = 7.84, 6.68 Hz, 1H, Ar–H), 7.70 (d, J = 6.8 Hz, 1 H, Ar–H). ESI-MS: m/z 311 (M + 1).

CONCLUSION

A series of phenyl-5-(2,3,5,6-tetrafluoro-phenyl)-[1,3,4]-oxadiazole derivatives was synthesized by using conventional as well as microwave-assisted technique and evaluated for the antimicrobial activity. In vitro antimicrobial screening revealed that **(Vb)**, and **(Ve)** can serve as important lead moiety as they replicating in vitro activity in the inhibition assay and in silico molecular docking study. They can be used in scaffold hoping for the design and development of new lead as antibacterial and antifungal agents.



Scheme 1.

ACKNOWLEDGMENTS

We are thankful to Principal, Maulana Azad College, Aurangabad, and Principal, Swami Vivekanand College Mantha for providing research facilities. We also thank SAIF Punjab University, Chandigarh and SAIF Shillong for providing the spectral and analytical data.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies involving human & animals participants performed by any of the authors.

Conflict of Interests

The authors declare that they have no conflicts of interest.

REFERENCES

1. Mori, T., Ujihara, K., Matsumoto, O., Yanagi, K., and Matsuo, N., *J. Fluor. Chem.,* 2007, vol. 128, pp. 1174–1181. https://doi.org/10.1016/j.jfluchem.2007.07.016
2. Vodela, S., Mekala, R.V.R., Danda, R.R., and Kodhati, V., *Chin. Chem. Lett.,* 2013, vol. 24, pp. 625–628. https://doi.org/10.1016/j.cclet.2013.04.005
3. Padmavathi, V., Reddy, G.S., Reddy, G.D., and Payani, T., *Synth. Commun.*, 2010, vol. 40, pp. 482–493. https://doi.org/10.1080/00397910902985531
4. Khalilullah, H., Khan, S., Nomani, M.S., and Ahmed, B., *Arab. J. Chem.,* 2016, vol. 9, pp. S1029–S1035. https://doi.org/10.1016/j.arabjc.2011.11.009

5. Bondock, S., Adel, S., Etman, H.A., and Badria, F.A., *Eur. J. Med. Chem.,* 2011, vol. 21, pp. 444–448. https://doi.org/10.1016/j.ejmech.2011.12.013
6. Sangshetti, J.N., Chabukswar, A.R., and Shinde, D.B., *Bioorgan. Med. Chem. Lett.,* 2011, vol. 21, pp. 444–448. https://doi.org/10.1016/j.bmcl.2010.10.120
7. Sharma, L.K., Saraswat, A., Singh, S., Srivastav, M.K., and Singh, R.K.P., *Proc. Natl. Acad. Sci. India Sect. A. Phys. Sci.*, 2015, vol. 85, pp. 29–34. https://doi.org/10.1007/s40010-0140175-z
8. Kumar, D., Sundaree, S., Johnson, E.O., and Shah, K., *Bioorgan. Med. Chem. Lett.*, 2009, vol. 19, pp. 4492–4494. https://doi.org/10.1016/j.bmc.2011.08.013
9. Zhang, X., Qiu, M., Sun, J., Zhang, Y., Yang, Y., Wang, X., Tang, J., and Zhu, H., *Bioorgan. Med. Chem.* 2011, vol. 19, pp. 6518–6524. https://doi.org/10.1016/j.bmc.2011.08.013
10. Roy, P.P., Singh, J., and Pratim, P., *Comp. Bio. Chem.,* 2012, vol. 48, pp. 192–199. https://doi.org/10.1016/j.compbiolchem.2018.05.013
11. Gan, X., Hu, D., Chen, Z., Wang, Y., and Song, B., *Bioorgan. Med. Chem. Lett.*, 2017, vol. 27, pp. 4298–4301. doi.org/ https://doi.org/10.1016/j.bmcl.2017.08.038
12. Wang, P.Y., Shao, W. Bin, Xue, H.T., Fang, H.S., Zhou, J., Wu, Z.B., Song, B.A., and Yang, S., *Res. Chem. Intermed.,* 2017, vol. 43, pp. 6115–6130. https://doi.org/10.1007/s11164-017-2980-x
13. El-Sayed, W.A., El-Essawy, F.A., Ali, O.M., Nasr, B.S., Abdalla, M.M., and Abdel-Rahman, A. A.H., *Monatshefte fur Chemie,* 2007, vol. 42. pp. 1021–1028. https://doi.org/10.1007/s00706-010-0360-y
14. Ibrahim, T.M., and El-emam, A.A., *Eur. J.Med. Chem.,* 2007, vol. 42, pp. 235–242. https://doi.org/10.1016/j.ejmech.2006.10.003
15. Kumar, H., Javed, S.A., Khan, S.A., and Amir, M., *Eur. J. Med. Chem.*, 2008, vol. 43, pp. 2688–2698. https://doi.org/10.1016/j.ejmech.2008.01.039
16. Abd-ellah, H.S., Abdel-aziz, M., Shoman, M.E., Beshr, E.A.M., Kaoud, T., and Ahmed, A.F., *Bioorg. Chem.,* 2017, vol. 74, pp. 15–29. https://doi.org/10.1016/j.bioorg.2017.06.003
17. Aziz-ur-Rehman, Siddiqa, A., Abbasi, M.A., Rasool, S., Siddiqui, S.Z., Ahmad, I., and Afzal, S., *Bull. Fac. Pharmacy, Cairo Univ.*, 2014, vol. 53, pp. 37–43. https://doi.org/10.1016/j.bfopcu.2014.10.001
18. Song, X., Li, P., Li, M., Yang, A., Yu, L., Luo, L., Hu, D., and Song, B., *Pestic. Biochem. Physiol.*, 2018, vol. 147, pp. 11–19. https://doi.org/10.1016/j.pestbp.2017.10.01119
19. Selvaraj, K., Kulanthai, K., and Sadhasivam, G., *Saudi Pharm. J.*, 2017, pp. 337–345. https://doi.org/10.1016/j.jsps.2016.07.004
20. Kotaiah, Y., Harikrishna, N., Nagaraju, K., and Rao, C.V., *Eur. J. Med. Chem.,* 2012, vol. 58, pp. 340–345. https://doi.org/10.1016/j.ejmech.2012.10.007
21. Malhotra, M., Rawal, R.K., Malhotra, D., Dhingra, R., Deep, A., and Chander, P. *Arab. J. Chem.*, vol. 013, pp. 1022–1031. https://doi.org/10.1016/j.arabjc.2013.01.005
22. Sindhe, M.A., Bodke, Y.D., Kenchappa, R., Telkar, S., and Chandrashekar, A., *J. Chem. Biol.,* 2016, vol. 9, pp. 79–90. https://doi.org/10.1007/s12154-016-0153-9
23. Akhter, M., Husain, A., Azad, B., and Ajmal, M., *Eur. J. Med. Chem.,* 2009, vol. 44, pp. 2372–2378. https://doi.org/10.1016/j.ejmech.2008.09.005
24. Rane, R.A., Bangalore, P., Borhade, S.D., and Khandare, P.K., *Eur. J. Med. Chem.*, 2013, vol. 25, pp. 49–58. https://doi.org/10.1016/j.ejmech.2013.09.039
25. Padmavathi, V., Reddy, G.S. Padmaja, A., and Kondaiah, P., *Eur. J. Med. Chem.,* 2009, vol. 44, pp. 2106–2112. https://doi.org/10.1016/j.ejmech.2008.10.012
26. El-Emam, A.A., Al-Deeb, O.A., Al-Omar, M., and Lehmann, J., *Bioorgan. Med. Chem.,* 2004, vol. 12, pp. 5107–5113. https://doi.org/10.1016/j.ejmech.2008.10.012
27. Wiederstein, M., Sippl, M.J., *Nucleic Acids Res.,* 2007, vol. 35, p. 407. https://doi.org/10.1093/nar/gkm290
28. Hashmi, S., Al-Salam, S., *Int. J. Clin. Exp. Pathol.,* 2015, vol. 8, pp. 8786–8796. https://doi.org/10.1002/jcc
29. Mohmmad, Y.W., Aijaz A., Rayees, A.S., Khalaf J.A., Abilio J.F.N., *Bioorgan. Med. Chem.,* 2015, vol. 23, pp. 4172–4180. https://doi.org/10.1016/j.bmc.2015.06.053