MICROWAVE ASSISTED SYNTHESIS, ANTIMICROBIAL ACTIVITY AND *IN SILICO* PHARMACOKINETIC STUDY OF SOME NOVEL 1', 3', 4'-OXADIAZOLE DERIVATIVES

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ABSTRACT

A novel series of 1', 3', 4' -oxadiazole derivatives were synthesized. The chemical structure of the synthesized compounds was established on the basis of spectral data and elemental analysis. Further, the synthesized compounds were tested for their antimicrobial activity by disk diffusion assay. The synthesized compounds exhibited significant activity against selected bacterial and fungal strains compared to the standard drugs. Lipinski's rule and *in silico* ADMET pharmacokinetic parameters were found to be within the acceptable range thereby indicating their potential as a drug-like molecule. Compounds 4c and 4d showed good drug-likeness score and bioactivity score, in comparison with the other compounds. The SAR study revealed that the hydroxy/chloro substituent at the para position of the phenyl ring on oxadiazole ring can improve the antimicrobial activity.

Keywords: 1', 3', 4'-Oxadiazole, benzimidazole, antimicrobial, drug-likeness, ADMET.

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INTRODUCTION

Heterocycles are important structural unit found in a wide range of biologically active compounds. Nitrogen and oxygen-containing heterocycles have received considerable attention due to their broad spectrum of biological activities. One of these compounds is oxadiazole which has been found to exhibit various pharmacological activities. Oxadiazole is a cyclic compound containing one oxygen and two nitrogen atoms in a five-membered ring and can undergo a variety of chemical reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical reaction. It exists in four isomeric forms. Out of its four isomers, 1,3,4-oxadiazole derivatives were found to possess a wide range of biological activities which includes antimicrobial, anticonvulsant, antitubercular, anti-inflammatory, anticancer, insecticidal, antitumor, antioxidant, analgesic, and herbicidal activity.¹⁻¹⁹ The potent biological activity of 1, 3, 4-oxadiazole is probably by the virtue of -N=C-O grouping. A large number of drugs used clinically have oxadiazole ring as the structural building block. On the other hand, benzimidazole nucleus has turned out to be a potential chemotherapeutic agent.²⁰⁻²⁵ Based on these findings and in continuation of the work on heterocycles, a present communication reports the synthesis of some 1', 3', 4'-oxadiazoles bearing benzimidazole moiety. Structure-activity relationships of 1', 3', 4'-oxadiazole derivatives were also studied to analyze the effect of various substituents on the biological activity. Pharmacokinetic profile of the synthesized compounds was also predicted with the aid of computer programs to select the best drug candidate.

EXPERIMENTAL

Material and Methods

Melting points were taken in open capillaries in a simple 'Neolab' electrical apparatus and are uncorrected. The infrared spectra were recorded on a Shimadzu 8101A spectrophotometer in KBr pellets. The Proton Magnetic Resonance (¹H NMR) spectra were recorded on a DPX 300 MHz Bruker

spectrophotometer in DMSO with a chemical shift in δ ppm. Mass spectra were recorded on JEOL SX 102/DA-6000 mass spectrometer data system using argon/Xenon (6 KV, 10 MA) as FAB gas. N-methyl phthalyl benzimidazole (1) was synthesized by the known method.²⁶

General Procedure

Synthesis of Ethyl (N-methyl phthalyl benzimidazolo) acetate (2)

A mixture of N-methyl phthalyl benzimidazole (0.1mol), ethyl chloro acetate (0.1mol) and potassium carbonate (0.15mol) in dry acetone (20 ml) was refluxed for 6 h. Completion of the reaction was monitored by thin layer chromatography (TLC). The reaction mixture was filtered. From the clear filtrate excess acetone was removed by distillation and then was added to water. The solid product separated was collected by filtration and dried. Further purification was done by crystallization from ethyl acetate to give ethyl (N-methyl phthalyl benzimidazolo) acetate (2). Yield 80%, mp 98-102°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1550 ($\text{C}=\text{N}$ str), 1650 ($\text{C}=\text{O}$), ^1H NMR (DMSO, δ ppm, 300 MHz): 4.12 (m, 2H, CH_2), 1.45 (m, 3H, CH_3), 6.95-7.63 (m, 8H, ArH); Anal calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4$: C, 66.11; H, 4.68; N, 11.57; O, 17.63. Found: C, 66.10; H, 4.69; N, 11.58; O, 17.61.

Synthesis of (N-methyl phthalyl benzimidazolo) acetohydrazide (3)

A mixture of compound 2 (0.04 mol) in ethanol (15 ml) was mixed with hydrazine hydrate 99% (2.2 ml, 0.044 mol) and refluxed for 4 h. Completion of the reaction was monitored by TLC. The excess of solvent was removed by distillation and the contents were added to an excess of water. The solid product separated was collected by filtration and dried. The crude product was purified by recrystallization from ethanol. Yield 82%, mp 170-180°C, FTIR (KBr, Cm^{-1}): 1772, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1660 ($\text{C}=\text{N}$ str), 1666 ($\text{C}=\text{O}$), 1032(N-N), 3044 ($\text{CH}-\text{Ar}$), 3291 (NH), 3400 (NH_2). ^1H NMR (DMSO, δ ppm, 300 MHz): 2.54 (s, 2H, NH_2), 4.95 (s, 2H, CH_2), 6.94-7.66 (m, 8H, ArH), 9.50 (s, 1H, CONH); Anal calcd for $\text{C}_{18}\text{H}_{15}\text{N}_5\text{O}_3$: C, 61.89; H, 4.29; N, 20.05; O, 13.75. Found: C, 61.87; H, 4.30; N, 20.07; O, 13.76.

Synthesis of 2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-substituted phenyl)-1', 3', 4'-oxadiazoles (4a-h)

The mixture of compound 3 (0.002 mol), aromatic acid (0.003 mol) and phosphorous oxy chloride (1 ml) were ground to get a homogenous mixture and then heated in a beaker under microwave irradiation at 160 W for 5-10 min. The contents were cooled to room temperature and added to excess ice-cold water. The solid product separated was collected by filtration. Further purification was done by recrystallization from the ethanol-DMF mixture (2:1). The other derivatives were synthesized following the same procedure. Spectral details for the compounds 4a-h are given below.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-phenyl -1', 3', 4'-oxadiazoles (4a)

Yield 70%, mp 210°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1603 ($\text{C}=\text{N}$ str), 1035 (N-N), 1240 (C-O-C). ^1H NMR (DMSO, δ ppm, 300 MHz): 4.07 (s, 2H, CH_2), 7.20-7.81 (m, 13H, ArH); Anal calcd for $\text{C}_{25}\text{H}_{17}\text{N}_5\text{O}_3$: C, 68.96; H, 3.90; N, 16.09; O, 11.03. Found: C, 68.96; H, 3.87; N, 16.08; O, 11.04.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-methyl phenyl)-1', 3', 4'-oxadiazoles (4b)

Yield 65%, mp 220°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1616 ($\text{C}=\text{N}$ str), 1238 (N-N), 1242 (C-O-C). ^1H NMR (DMSO, δ ppm, 300 MHz): 2.38 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 6.94-7.72 (m, 12H, ArH); Anal calcd for $\text{C}_{26}\text{H}_{19}\text{N}_5\text{O}_3$: C, 69.48; H, 4.23; N, 15.59; O, 10.69. Found: C, 69.50; H, 4.22; N, 15.60; O, 10.68.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-hydroxy phenyl)-1', 3', 4'-oxadiazoles (4c)

Yield 75%, mp 242°C, FTIR (KBr, Cm^{-1}): 1770, 1710 ($>\text{C}=\text{O}$, Phthalimido), 1620 ($\text{C}=\text{N}$ str), 1240 (N-N=C), 1242(C-O-C), 3509 (OH). ^1H NMR (DMSO, δ ppm, 300 MHz): 5.52 (s, 2H, CH_2), 7.32-7.82 (m, 12H, ArH), 9.07 (s, 1H, OH), EI-MS 451 (M^+); Anal calcd for $\text{C}_{25}\text{H}_{17}\text{N}_5\text{O}_4$: C, 66.51; H, 3.76; N, 15.52; O, 14.19. Found: C, 66.53; H, 3.77; N, 15.51; O, 14.20.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-chloro phenyl)-1', 3', 4'-oxadiazoles (4d)

Yield 65%, mp 250°C, FTIR (KBr, Cm^{-1}): 1770, 1710 ($>\text{C}=\text{O}$, Phthalimido), 1622 ($\text{C}=\text{N}$ str), 1094 ($\text{N}=\text{C}$), 1242 ($\text{C}-\text{O}-\text{C}$), 740 ($\text{C}-\text{Cl}$). ^1H NMR (DMSO, δ ppm, 300 MHz): 5.49 (s, 2H, CH_2), 6.88-7.80 (m, 12H, ArH); Anal calcd for $\text{C}_{25}\text{H}_{16}\text{N}_5\text{O}_3\text{Cl}$: C, 63.89; H, 3.40; N, 14.90; O, 10.22. Found: C, 63.90; H, 3.38; N, 14.91; O, 10.23.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-nitro phenyl)-1', 3', 4'-oxadiazoles (4e)

Yield 70%, mp 238°C, FTIR (KBr, Cm^{-1}): 1775, 1720 ($>\text{C}=\text{O}$, Phthalimido), 1625 ($\text{C}=\text{N}$ str), 1038 ($\text{N}=\text{C}$), 1242 ($\text{C}-\text{O}-\text{C}$), 1530 (NO_2). ^1H NMR (DMSO, δ ppm, 300 MHz): 5.50 (s, 2H, CH_2), 7.30-7.78 (m, 12H, ArH), EI-MS 480 (M^+); Anal calcd for $\text{C}_{25}\text{H}_{16}\text{N}_6\text{O}_5$: C, 62.50; H, 3.33; N, 17.50; O, 16.66. Found: C, 16.52; H, 3.34; N, 17.51; O, 16.65.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-methoxy phenyl)-1', 3', 4'-oxadiazoles (4f)

Yield 65%, mp 225°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1612 ($\text{C}=\text{N}$ str), 1030 ($\text{N}=\text{C}$), 1258 ($\text{C}-\text{O}-\text{C}$). ^1H NMR (DMSO, δ ppm, 300 MHz): 3.84 (s, 3H, OCH_3), 5.52 (s, 2H, CH_2), 6.96-7.76 (m, 12H, ArH); Anal calcd for $\text{C}_{26}\text{H}_{19}\text{N}_5\text{O}_4$: C, 67.09; H, 4.08; N, 15.05; O, 13.76. Found: C, 67.10; H, 4.06; N, 15.08; O, 13.77.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(3'',4''-dimethoxy phenyl)-1', 3', 4'-oxadiazoles (4g)

Yield 70%, mp 230°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1602 ($\text{C}=\text{N}$ str), 1026 ($\text{N}=\text{C}$), 1242 ($\text{C}-\text{O}-\text{C}$). ^1H NMR (DMSO, δ ppm, 300 MHz): 3.86 (s, 6H, OCH_3), 5.52 (s, 2H, CH_2), 6.94-7.76 (m, 11H, ArH); Anal calcd for $\text{C}_{27}\text{H}_{21}\text{N}_5\text{O}_5$: C, 65.45; H, 4.24; N, 14.14; O, 16.16. Found: C, 65.44; H, 4.22; N, 14.15; O, 16.17.

2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-benzal-1', 3', 4'-oxadiazoles (4h)

Yield 70%, mp 240°C, FTIR (KBr, Cm^{-1}): 1770, 1715 ($>\text{C}=\text{O}$, Phthalimido), 1612 ($\text{C}=\text{N}$ str), 1036 ($\text{N}=\text{C}$), 1240 ($\text{C}-\text{O}-\text{C}$). ^1H NMR (DMSO, δ ppm, 300 MHz): 4.96 (s, 2H, CH_2), 6.98-7.68 (m, 13H, ArH); Anal calcd for $\text{C}_{26}\text{H}_{19}\text{N}_5\text{O}_3$: C, 69.48; H, 4.23; N, 15.59; O, 10.69. Found: C, 69.46; H, 4.22; N, 15.60; O, 10.68.

Antimicrobial Activity

The synthesized compounds 4a-h were screened *in vitro* for their antibacterial activity against two microorganisms i.e. *Escherichia coli* and *Staphylococcus aureus*, by cup-plate agar diffusion method.²⁷ Luria broth (20 gm, Hi-media M-575) and agar-agar (25gm) were taken in 1000 ml of distilled water and heated till it dissolved. Then, the mixture was sterilized by autoclaving at 15 atm pressure and 121°C for 15 minutes. The above-prepared mixture was then poured into Petri plates and 0.1 ml of activity growing culture was evenly spread onto the surface of the nutrient agar plate. Four well of 8 mm diameter were bored in each plate and 0.1 ml of testing solution was added into each well, having a concentration of 1000 ppm in DMF. A control was also established by using just the solvent in which each compound was dissolved. Ofloxacin was used as a standard drug for antibacterial activity. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37°C for overnight. After incubation, the degree of inhibition was observed by the formation of zones. The diameters of the zones were measured in mm. All the synthesized compounds showed good antibacterial activity. The compounds were tested *in vitro* for their antifungal activity against *Candida albicans* and *Aspergillus niger* by cup-plate agar diffusion method. Potato dextrose agar (Hi-media MU-096) was used as culture medium. The same procedure as above was followed for Antifungal activity. Ketoconazole was used as a standard drug for antifungal activity. After incubation for 48 hours at 37°C, the plates were examined for inhibition zones. The results of antibacterial and antifungal activities were represented in Table-1.

Molecular Descriptors

Molinspiration, a web-based software was used to obtain parameters such as Mi Log P (partition coefficient), TPSA, molecular weight, number of hydrogen acceptor, number of a hydrogen donor,

number of violation, number of rotatable bonds and volume (Table-2).²⁸ Using these parameters the compounds were checked for their compliance with the Lipinski's rule of five. ²⁹ Bioactivity of the synthesized compounds was checked by calculating the activity scores of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, a protease inhibitor, enzyme inhibitor using Molinspiration on-line tool (Table-3). OSIRIS Data Warrior programs were used to determine pharmacokinetic parameters such as toxicity potential, solubility and overall drug-Likeness (Table-4).³⁰

Table-1: Antimicrobial Activity of the Synthesized Compounds (4a-4h)

Compounds	Zone of Inhibition(mm)			
	Antibacterial activity		Antifungal activity	
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Candida albicans</i>	<i>Aspergillus niger</i>
4a	16	18	16	18
4b	15	14	12	13
4c	22	24	22	24
4d	20	22	20	21
4e	11	10	13	12
4f	12	11	16	17
4g	11	10	17	19
4h	18	18	16	14
Ofloxacin	25	26	-	-
Ketoconazole	-	-	26	28

Prediction of ADMET Properties

The ADMET (Absorption, Distribution, Metabolism, Excretion and Toxicity) properties of the synthesized compounds 4a-h were calculated using admetSAR prediction tool (<http://www.admetexp.org/predict/>) and results were tabulated in Table-5.³¹ BBB (Blood-Brain Barrier) penetration, HIA (Human Intestinal Absorption), Caco-2 cell permeability, Carcinogenicity and Ames toxicity were calculated for the evaluation of pharmacodynamics behavior of the synthesized compounds.

RESULTS AND DISCUSSION

The synthetic route followed for obtaining the title compounds is outlined in Fig.-1. N-methyl phthalyl benzimidazole (1) was synthesized by a known procedure. Compound 1 on treatment with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dry acetone gave ethyl (N-methyl phthalyl benzimidazolo) acetate (2), which on treatment with hydrazine hydrate resulted in the formation of (N-methyl phthalyl benzimidazolo) acetohydrazide (3). Compound 3 on reaction with various aromatic acids in the presence of phosphorous oxychloride resulted in the formation of 2'-[1-methyl-{N-methyl phthalyl benzimidazolo}]-5'-(4''-substituted phenyl)-1', 3', 4'-oxadiazoles (4a-h).

The synthesized compounds 4a-h were screened for their antibacterial activity against *E. Coli* and *S. Aureus* and antifungal activity against *C. albicans* and *A. niger* by agar diffusion technique. The diameter of the zone of inhibition exhibited by the compounds was measured. It was found that the compound 4c and 4d were highly active against both the bacterial strains. Compound 4a, 4b, and 4h were found to be moderately active whereas 4e, 4f and 4g were weakly active. Derivatives 4c and 4d were most active against both the fungal strains whereas derivatives 4a, 4f, 4g and 4h were moderately active. The results showed that the induction of hydroxyl and chloro group at the para position of phenyl ring on the

oxadiazole ring enhanced the antimicrobial activity. Figure-2 and 3 depict the comparative antibacterial and antifungal activities of the synthesized compounds respectively.

Fig.-1: Synthetic Route of Titled Compounds

Reagents: (a) Dry Acetone, K₂CO₃, ClCH₂COOC₂H₅; (b) NH₂NH₂.H₂O, C₂H₅OH; (c) POCl₃, RCOOH
 R= C₆H₅, 4-CH₃C₆H₄, 4-OHC₆H₄, 4-ClC₆H₄, 4-NO₂C₆H₄, 4-OCH₃C₆H₄, 3,4-diOCH₃C₆H₃, C₆H₅ CH₂

Fig.-2: Antibacterial Activity of the Synthesized Compounds (4a-4h)

Fig.-3: Antifungal Activity of the Synthesized Compounds (4a-4h)

Table-2: Prediction of Molecular Properties Descriptors of the Title Compounds (4a-4h)

Compounds	MiLogP	TPSA	% ABS	MW	nON	nOHNH	Nrotb	Nvio	Volume
4a	3.80	95.83	75.93	435.44	8	0	5	0	370.24
4b	4.25	95.83	75.93	449.47	8	0	5	0	386.80
4c	3.32	116.05	68.96	451.44	9	1	5	0	378.26
4d	4.48	95.83	75.93	469.89	8	0	5	0	383.77
4e	3.76	141.65	60.13	480.44	11	0	6	1	393.57
4f	3.86	105.06	72.75	465.47	9	0	6	0	395.79
4g	3.45	114.29	69.56	495.50	10	0	7	0	421.33
4h	3.40	95.83	75.93	449.47	8	0	6	0	387.04

MiLogP, the logarithm of compound partition coefficient between n-octanol and water; TPSA, topological polar surface area; % ABS, the percentage of absorption; MW, molecular weight; nON, number of hydrogen bond acceptors; nOHNH, number of hydrogen bond donors; Nrotb, number of rotatable bonds; Nvio, Number of violations

The molecular descriptors of 1', 3', 4'-oxadiazoles derivatives (4a-h) were calculated using Molinspiration Cheminformatics software and were presented in Table-2. Lipinski's "rule of five" is commonly used to predict oral bioavailability of potential drug molecule. The rule states that a candidate molecule will likely to be active if i) $\log P \leq 5$, ii) molecular weight ≤ 500 , iii) a number of hydrogen bond acceptors ≤ 10 and iv) a number of hydrogen bond donors ≤ 5 . The synthesized compounds did not violate any of the Lipinski's rules of five, however, one violation was observed for the compound 4e. All the compounds except 4e fulfill Lipinski's rule and show good drug-likeness score (Table-2). Mi Log P values of the synthesized compounds were found to be below 5, which showed good permeability across the cell membrane. In respect of TPSA, all the compounds were found to be within the limit, i.e. 160 Å, which implies that the molecules fulfilled the optimal requirement for drug absorption. TPSA was used to calculate the percentage of absorption (% ABS) following the equation: $\% \text{ ABS} = 109 - (0.345 \times \text{TPSA})$.³² Synthesized compounds exhibited a moderate % ABS ranging from 60.13% to 75.93%. The molecular weights of the compounds were less than 500 Daltons. The compounds in the series possessed a high number of rotatable bonds (5 -7) and therefore, exhibited conformational flexibility.

Table-3: Prediction of Bioactivity Scores of the Synthesized Compounds (4a-4h)

Compounds	GPCR	ICM	KI	NRL	PI	EI
4a	-0.14	-0.46	-0.26	-0.36	-0.22	-0.10
4b	-0.17	-0.50	-0.29	-0.37	-0.26	-0.14
4c	-0.11	-0.42	-0.22	-0.25	-0.21	-0.06
4d	-0.14	-0.45	-0.27	-0.37	-0.25	-0.12
4e	-0.24	-0.50	-0.34	-0.41	-0.31	-0.18
4f	-0.17	-0.50	-0.27	-0.35	-0.26	-0.13
4g	-0.17	-0.53	-0.23	-0.36	-0.27	-0.12
4h	-0.11	-0.46	-0.40	-0.32	-0.13	-0.05
Ofloxacin	0.23	-0.14	-0.06	-0.13	-0.26	0.35
Ketoconazole	0.26	-0.14	-0.17	-0.32	-0.21	0.15

GPCR, G-protein-coupled receptor ligand; ICM, Ion channel modulator; KI, Kinase inhibitor; NRL, Nuclear receptor ligand; PI, Protease inhibitor; EI, Enzyme inhibitor

Table-4: Drug-Likeness and Toxicity Prediction

Compds	Clog P	CLogS	Drug Likeness	Mutagenic	Tumorigenic	Reproductive Effect	Irritant
4a	3.1057	-3.909	3.8313	None	None	None	None
4b	3.4496	-4.253	3.7723	None	None	None	None
4c	2.76	-3.613	3.8271	None	None	None	None
4d	3.7117	-4.645	3.8725	None	None	None	None
4e	2.0137	-4.367	-1.2718	None	None	None	None
4f	3.0357	-3.927	3.8565	None	None	None	None
4g	2.9657	-3.945	3.8565	None	None	None	None
4h	3.1681	-2.759	3.8026	None	None	None	None
Ofloxacin	-0.3426	-2.736	5.7723	None	None	None	None
Ketoconazole	3.3639	-2.995	8.14	None	None	None	None

The bioactivity scores of the compound 4a-h were predicted by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor and enzyme inhibitor by Molinspiration and were presented in Table-3. A molecule having bioactivity score more than 0.00 is most likely to possess considerable biological activities, while values -0.50 to 0.00 are expected to be moderately active and if the score is less than -0.50 it is presumed to be inactive.³³ Results of the present study demonstrated that the investigated compounds were moderately active compared to the

standard drugs. On the basis of the bioactivity scores compound, 4c was identified as the most promising compound in the series.

Table-5: ADMET Profile of the Synthesized Compounds (4a-4h)

Compds	Blood-Brain Barrier	Human Intestinal Absorption	Caco-2 Permeability	CYP Inhibitory Promiscuity	AMES toxicity	Carcinogenicity	Rat Acute Toxicity LD50, mol/kg
4a	0.9953	1.0000	0.5000	High	Nontoxic	Non-carcinogenic	2.1944
4b	0.9917	1.000	0.5237	High	Nontoxic	Non-carcinogenic	2.2400
4c	0.9596	1.000	0.5810	Low	Nontoxic	Non-carcinogenic	2.2490
4d	0.9909	1.000	0.5119	High	Nontoxic	Non-carcinogenic	2.1706
4e	0.9793	0.9970	0.5689	High	Toxic	Non-carcinogenic	2.3768
4f	0.9736	1.000	0.5096	High	Nontoxic	Non-carcinogenic	2.3132
4g	0.9576	1.000	0.5096	High	Nontoxic	Non-carcinogenic	2.3417
4h	0.9940	1.000	0.5120	High	Nontoxic	Non-carcinogenic	2.1752
Ofloxacin	0.9659	0.9545	0.8867	Low	Toxic	Non-carcinogenic	2.1639
Ketoconazole	0.6704	0.9156	0.8866	High	Nontoxic	Non-carcinogenic	3.4739

In silico drug-likeness prediction helps in accelerating the discovery of new drug candidates. Table-4 depicts the drug-likeness properties of the synthesized compounds predicted using OSIRIS Data Warrior programs. The OSIRIS tools measure the ClogP value (logarithm of compound's partition coefficient between n-octanol and water) which is a well-established measure of the compound's hydrophilicity. Higher ClogP value indicates lower hydrophilicity and, thus, poor absorption and permeation. The logS value indicates solubility, the lesser the logS value, the higher the solubility which would enhance the absorption. Of all the toxicological features predicted like mutagenicity, tumorigenicity, reproductive toxicity and irritability, none of the compounds was found to be toxic. Drug-likeness prediction study revealed that the compound 4c and 4d to be the best with these properties.

ADMET prediction was done using admetSAR and the results were summarized in Table5. The compounds showed high probability score in terms of Blood-Brain Barrier (BBB) penetration and Human Intestinal Absorption (HIA) compared to the standard drugs. CYP450 substrates and inhibitors hold a key role in drug metabolism. The results revealed that the Compound 4c showed low CYP Inhibitory Promiscuity as it was found to be non-inhibitor for most of the CYP450 enzymes i.e. 1A2, 2D6, 2C19 and 3A4 and non-substrate for two CYP450 substrates (2C9, 2D6). The compound 4c showed highest Caco-2 permeability score (0.5810) in the series. The tested compounds were found to be non-toxic in AMES toxicity test except compound 4e, which showed that the compounds were nonmutagenic. The carcinogenic profile also revealed that the compounds were non-carcinogenic. The computed LD50 dose in rat model revealed that the compound 4d had almost the same LD50, compared to the standard drug Ofloxacin. Highest LD50 of 2.3768 was observed for the compound 4e among the other derivatives.

CONCLUSION

The present work reports the synthesis of some novel 1', 3', 4'-oxadiazole derivatives bearing benzimidazole moiety. The synthesized compounds were characterized by the spectral techniques and tested for their antimicrobial activity. The synthesized compounds showed significant activity and were found to be active against all the selected bacterial and fungal strains. It was observed that the synthesized compounds conformed to the Lipinski's rule of five and had good bioavailability. A good correlation was

obtained between the theoretical predictions and experimental verification. It was observed that the compounds bearing hydroxyl and chloro group (compound 4c and 4d respectively) at the phenyl ring of oxadiazole showed maximum drug-likeness score among the series. The compound 4c and 4d emerged as the potent molecules in the series and can be considered for further *in vivo* evaluation. The results provided an insight for the construction of hybrid compounds for the generation of efficient leads.

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