ejpmr, 2018,5(9), 277-282

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

SYNTHESIS, SPECTRAL STUDY AND BIOLOGICAL ACTIVITY OF SOME 2, 5–DISUBSTITUTED-1, 3, 4-OXADIAZOLE

Manpreet Kaur[1]*, Satvir Singh[1,2] and Mandeep Kaur[1]

[1]Department of Pharmaceutical Chemistry, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab 140111, India.

[2]University Institute of Pharmaceutical Sciences, Chandigarh University, Gharaun, Mohali, Punjab University.

***Corresponding Author: Manpreet Kaur**

Department of Pharmaceutical Chemistry, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab 140111, India.

Article Received on 12/07/2018 **Article Revised on 01/08/2018** **Article Accepted on 22/08/2018**

ABSTRACT

In the present article synthesis and evaluation for anticancer activity of a new series of 2,5-disubstituted-1,3,4-oxadiazole derivatives is described. 2,5-disubstituted-1,3,4-oxadiazole derivatives were synthesized by the reaction of Schiff bases derivatives with 2,5-disubstituted-1,3,4-oxadiazole. All the synthesized compounds were screened for their anticancer activity. 1,3,4-oxadiazoles are five membered heterocycles containing one oxygen and two nitrogen atoms at position 1, 3 and 4 position respectively. Five of the compounds possessed good to moderate anti-cancer activity. Three of the synthesized compounds *i.e.* 6a, 6f and 6g were found to possess maximum growth inhibition. The order for the % control growth inhibition of MCF-7 was found to be 6a>6f>6g>5b>6h as shown in Table no.6.1-6.7. The newly synthesized compounds were characterized on the basis of spectral (FT-IR, ^{1}H NMR) analyses. All the synthesized compounds were found to be active against both the bacterial strain that is Gram negative bacteria *Escherichia coli* (MTCC 40) and Gram positive bacteria *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC121). The zone of inhibition was observed in mm. Amongst all derivatives in series (5a-d), (6a-h) exhibited good antibacterial activity.

KEYWORDS: 1, 3, 4- oxadiazole, Anticancer activity, Antimicrobial activity, Schiff bases.

INTRODUCTION

Heterocyclic compounds are those cyclic compounds in which one or more of the ring carbons are replaced by another atom. The non-carbon atoms in such rings are referred to as hetero atoms. The most common hetero atoms are nitrogen, oxygen and sulphur, but other atoms such as boron, phosphorous, silicon can also be members of heterocyclic rings. A number of substances which are heterocyclic compounds according to the above definition are ethylene oxide, succinic anhydride, lactones and cyclic carbohydrates. These compounds are readily formed from open-chain substances and are easily converted into open-chain derivatives.[1] Heterocyclic compounds usually possess a stable ring structure which does not readily hydrolyses or depolymerises. In five membered heterocyclic rings, there is no ring strain and generally reactivity is similar to that of open chain analogues, however stearic hindrance at the hetero atom is reduced. Among different five membered heterocyclic systems pyrrole, oxadiazole, thiadiazole, triazole and their derivatives have gained importance as they constitute the structural features of many bioactive compounds. Among them 1,3,4-oxadiazoles are of significant interest in medicinal chemistry.[2]

Oxadiazole is a versatile heterocyclic nucleus, which has attracted a wide attention of the medicinal chemists for development of new drugs. Oxadiazole is a five-membered heterocyclic, aromatic chemical compound having two carbons, two nitrogens and one oxygen atom with two double bonds having general formula $C_2H_2ON_2$. There are four isomers of oxadiazole namely 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole and 1,3,4-oxadiazole. 1,3,4-oxadiazole was first prepared by Ainsworth in 1965 by the thermolysis of ethylformate, formally hydrazine, at atmospheric pressure and is liquid in nature.[3] 1,3,4-oxadiazole is a thermally stable molecule. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The 1,3,4-oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The electrophilic substitution in oxadiazole ring is extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawing effect of the nitrogen atom. If oxadiazole ring is substituted with electron releasing groups then the attack of electrophiles occurs at nitrogen. Also various route for the synthesis of 1,3,4-oxadiazole have been reported. Acid hydrazides have been in

general used as the starting materials in some 1,3,4-oxadiazole.[4]

1,3,4-oxadiazole rings have been introduced into drug discovery programs for several different purposes. For example, in some cases, they have been used as an essential part of the pharmacophore, favourably contributing to ligand binding, and in other cases, oxadiazole moieties have been shown to act as a flat, aromatic linker to place substituents in the appropriate orientation, as well as modulating molecular properties by positioning them in the periphery of the molecule.[5] The 1,2,4-oxadiazole, known as an ester isostere, is present in various biologically active compounds, such as benzodiazepine receptor ligands, muscarinic receptor agonists and 5-HT_3 receptor antagonists.[6] The 1,2,5-oxadiazole ring is a stable system and annular-group tautomerism is not favored. The 1,2,5-oxadiazole ring is inert to cycloaddition with singlet oxygen. It undergo thermal and photochemical ring cleavage at the O(1)-N(2) and C(3)-C(4) bonds to yield nitrile and nitrile oxide fragments, and products derived there from. In most cases the thermal reaction requires temperatures in excess of 200 °C, but for ring-strained analogues less forcing conditions are needed. 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological activities such as Anti-inflammatory[7], Analgesic[8], Antimicrobial[9], Anti-convulsant[10], Anti-proliferative[11], Anti-mycobacterial[12], Anti-protozoal[13], Anti-diabetic[14], Anticancer[15], CNS depressant and pesticidal property.[16] 1,3,4-oxadiazole is a very good bioisostere of amide and ester functional groups and is reported to contribute substantially to pharmacological activity by participating in hydrogen bonding interactions with various receptors.[17]

Bacterial infections are increasing worldwide and antibacterial agents are used for the treatment of these infectious diseases. Molecular modelling and pharmacokinetic studies have demonstrated that incorporating 1,3,4-oxadiazole moieties to drug molecules, change their polarity, flexibility as well as metabolic profile and ability to engage in hydrogen bonding.[18] 1,3,4-oxadiazole has become an important construction motive for the development of new drugs.[19]

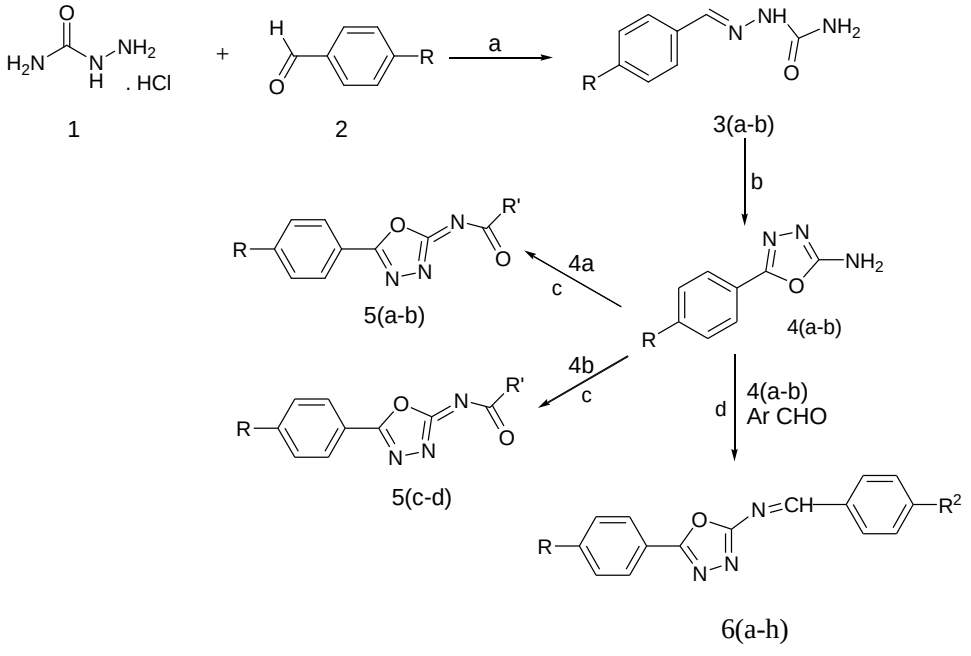
MATERIALS AND METHODS

The commercial chemicals employed for the present work were purchased from Sigma-Aldrich, Rankem and Loba Chem. All the solvents used were LR grade and were utilized in the reaction. The melting point was determined by open capillaries on Buchi-apparatus and was uncorrected. The reaction were monitored with the help of TLC using pre-coated aluminium sheets coated with $60F_{254}$ silica gel, 0.2 mm thickness from Merck. Various solvents systems used for developing chromatograms were (a) Hexane: ethyl acetate (7:3), (b) Ethyl acetate: benzene (6:4), (c) Hexane: ethyl acetate (6:4) and U.V light chamber were used for the visualization of the TLC spots. The IR Spectra were recorded on an FT-IR Perkin-Elmer spectrophotometer (4000-400 cm^{-1}). The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Avance Ⅱ 400 spectrometer where TMS was used as internal standard and chemical shifts are expressed as δ *ppm*.

RESULTS AND DISCUSSION

As per the proposed reaction scheme, the synthesis of 2,5-disubstituted-1,3,4-oxadiazole derivatives **5(a-d)** and schiff bases **6(a-h)** was carried out.

Reaction Scheme



3a: R= NO_2 **3b: R**= 3-OH-4-OCH_3
4a: R= NO_2 **4b: R**= 3-OH-4-OCH_3
5a: R= NO_2**, R'**= C_6H_5COCl **5b: R**= NO_2**, R'**= CH_2COCl
5c: R= 3-OH-4-OCH_3**, R'**= C_6H_5COCl **5d: R**= 3-OH-4-OCH_3**, R'**= CH_2COCl
6a: R^1= 4-NO_2**, R^3**= 4-NO_2 **6b: R^1**= 4-NO_2**, R^3**= 3-NO_2
6c: R^1= 4-NO_2**, R^3**= 2,5-$(OCH_3)_2$ **6d: R^1**= 4-NO_2**, R^3**= 4-$(N\text{-}CH_3)_2$
6e: R^1= 3-OH-4-OCH_3**, R^3**= 4-NO_2 **6f: R^1**= 3-OH-4-OCH_3**, R^3**= 3-NO_2
6g: R^1=3-OH-4-OCH_3, 2,5-$(OCH_3)_2$ **6h: R^1**=3-OH-4-OCH_3**, R^3**= 4-$(N\text{-}CH_3)_2$

Reagents and Conditions: a) Sodium acetate, stirring, rt, 2-4h **b)** Sodium acetate, Glacial acetic acid, Liquid Br_2, stirring, rt, 5h **c)** Pyridine, DMSO, Benzoyl chloride, Acetyl chloride, stirring, rt, 4-6h **d)** Ethanol, Substituted aldehyde, reflux, 6-8h.

Synthesis of Semicarbazones (3a-3b)
Semicarbazide hydrochloride (2.0g) (17.92 mmol) and sodium acetate (1.0g) (12.19 mmol) was dissolved in 50 ml water. The 4-Nitrobenzaldehyde and 3-hydroxy-4-methoxy benzaldehyde (1.0g) (6.08 mmol) was added with continuous stirring for 2-4 h. The mixture was left overnight, which gave semicarbazone as a solid.

Synthesis of 2-amino-5-substituted-1,3,4-oxadiazoles (4a-4b)
Semicarbazone (0.01M) and sodium acetate (0.02M) were dissolved in 30-40 ml of glacial acetic acid taken in a (100ml) round-bottomed flask equipped with a separating funnel for the addition of bromine. Bromine (0.7ml in 5ml glacial acetic acid) was added drop by drop, while stirring magnetically. After 5 hour stirring, the solution was poured on crushed ice. The resulting solid was separated.

Synthesis of 2,5-disubstituted 1,3,4-oxadiazoles derivatives (5a-5d)
2-amino-5-substituted 1,3,4-oxadiazole (0.01M) were dissolved in sufficient amount of dimethyl sulphoxide (DMSO). To this solution, pyridine was added with continuous stirring for 30 min at 4ºC. To this solution, of benzoyl chloride or acetyl chloride, previously dissolved in dimethyl sulphoxide, was added slowely over a period of 4-6 h with continuous stirring. The reaction was monitored using TLC. The residue was washed with water and the product was recrystallized from ethanol to give **5a-5d**.

General procedure for the synthesis of 6a-6h
A solution of 2-amino-5-substituted 1,3,4-oxadiazole (0.01M) was taken in 20ml ethanol a round-bottomed flask. Subsitituted aldehyde 1.5g dissolved in 15ml ethanol was then added to it. The mixture was refluxed for 6-8 h. The volume of ethanol was reduced to half by distillation under reduced pressure. The resulting solution was poured on crushed ice. The precipitate was separated, dried and recrystallized from ethanol to give 6a-6h.

Synthesis of N-(4-nitrobenzylidene)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (6a)
IR (cm^{-1}): N=O(1339); C=N(1701); C-O-C(1097); C=C(1600); N=O(1523); ^{1}HNMR (DMSO, 400MHz, δ ppm): 8.11-8.39 (m, 7H, Ar-H); 6.6(s, 1H, CH); 10.1 (s, 1H, C-H).

Synthesis of N-(3-nitrobenzylidene)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (6b)
IR (cm^{-1}): N=O(1342); C=N(1692); C-O-C(1076); C=C(1524); N=O(1398); ^{1}HNMR (DMSO, 400MHz, δ ppm): 7.84-8.65 (m, 8H, Ar-H); 10.1 (s, 1H, C-H).

Synthesis of N-(2,5-dimethoxybenzylidene)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (6c)
(IR (cm^{-1}): N=O(1338); N=O(1426); C-H(3146); C=C(1579); C-O-C(1098); C=N(1675); CH_3,C-H(2842,2918); ^{1}HNMR (DMSO, 400MHz, δ ppm): 3.70-3.83 (m, 6H, OCH_3); 10.2 (s, 1H, C-H); 7.12-7.50 (m, 4H, Ar-H); 7.8-8.1 (m, 3H, Ar-H).

Synthesis of N-(4-(dimethylamino) benzylidene)-5-(4-nitrophenyl)-1,3,4-oxadiazol-2-amine (6d)
IR (cm^{-1}): C-N(1226), C=C(1514), C=N(1659), Ar-C-H(2911), N=O(1589); N=O(1333); ^{1}HNMR (DMSO, 400MHz, δ ppm): 3.00 (s, 3H, $N(CH_3)$; 3.30 (s, 3H, $N(CH_3)$; 9.62 (s, 1H, C-H); 6.73-6.76 (m, 2H, Ar-H); 7.63-8.15 (m, 6H, Ar-H).

Synthesis of 5-(5-(4-nitrobenzylideneamino) 1,3,4-oxadiazol-2-yl)-2-methoxy phenol (6e)
IR (cm^{-1}): N=O(1338); N=O(1519); C=C(1574); Ar-C-H(3189); C=N(1674); C-O-C(1098); O-H(3451); CH_3,C-H(2847,2918); ^{1}HNMR (DMSO, 400MHz, δ ppm): 3.74-3.83(m, 3H, OCH_3); 6.87(s, 1H, O-H); 8.10-8.13(m, 4H, Ar-H); 8.36-8.38 (m, 2H, Ar-H); 8.97(s, 1H, Ar-H); 10.1 (s, 1H, C-H).

Synthesis of 5-(5-(3-nitrobenzylideneamino) 1,3,4-oxadiazol-2-yl) 2-methoxy phenol (6f) IR (cm^{-1}): N=O(1523); N=O(1340); C=C(1582); C=N(1689); O-H(3456); CH_3,C-H(2843,2912); C-O-C (1074).

Synthesis of 5-(5-(2,5-dimethoxybenzylideneamino)-1,3,4-oxadiazol-2-yl) 2-methoxy phenol (6g)
IR (cm^{-1}): C-O-C(1091); CH_3,C-H(2842,2918); C=C(1577); C=N(1677); O-H(3407).

Synthesis of 5-(5-(4-(dimethylamino) benzylideneamino)-1,3,4-oxadiazol-2-yl)-2-methoxy phenol (6h)

IR (cm^{-1}): C-N(1314); C=C(1472); C=N(1660); O-H(3552); CH_3,C-H(2848,2914).

Table 6.1: Physical Characteristics of synthesized compounds 5(a-d), 6(a-h).

Comp. No.	Molecular Formula	Molecular Weight (g)	Melting point (ºC)	R_f^*	Yield (%)
5a	$C_{16}H_9ClN_4O_5$	372	135-137	0.6	55
5b	$C_{11}H_7ClN_4O_5$	310	195-197	0.7	90
5c	$C_{17}H_{12}ClN_3O_5$	373	183-185	0.5	33
5d	$C_{12}H_{10}ClN_3O_5$	311	191-193	0.7	33
6a	$C_{15}H_9N_5O_5$	339	90-92	0.6	32
6b	$C_{15}H_9N_5O_5$	339	60-62	0.7	82
6c	$C_{17}H_{14}N_4O_5$	354	150-152	0.5	82
6d	$C_{17}H_{15}N_4O_3$	337	57-59	0.5	76
6e	$C_{16}H_{12}N_4O_5$	340	127-129	0.6	72
6f	$C_{16}H_{12}N_4O_5$	340	105-107	0.5	89
6g	$C_{16}H_{12}N_4O_5$	355	52-54	0.5	90
6h	$C_{18}H_{18}N_4O_3$	338	82-84	0.6	92

ANTICANCER DRUG SCREENING

Five compounds from the synthesized compounds were screened against MCF-7 cell line to determine the growth inhibitory effect of compounds. *In vitro* testing was done using SRB assay protocol, each derivative was tested at 4 dose levels (10 µg/ml, 20 µg/ml, 40 µg/ml, 80 µg/ml).

Table 6.2: *In vitro* percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 1).

C. No.	% Control growth (MCF-7)			
	Compound concentration (µg/mL)			
	10	20	40	80
5b	72.1	60.0	43.6	48.7
6a	67.9	32.6	26.3	4.6
6f	30.7	32.3	34.0	24.9
6g	33.3	50.0	51.0	39.5
6h	92.6	108.5	81.0	59.1
ADR	-6.2	-11.0	-16.0	-16.5

Table 6.3: *In vitro* percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 2).

C. No.	% Control growth (MCF-7)			
	Compound concentration (µg/mL)			
	10	20	40	80
5b	75.5	63.0	40.8	40.6
6a	71.3	29.4	11.9	-6.0
6f	32.0	26.7	16.9	12.5
6g	35.2	34.6	28.3	15.9
6h	103.2	96.0	65.1	40.5
ADR	0.0	-11.6	-22.9	-28.7

Table 6.4: *In vitro* percentage control growth of MCF-7 cell line at different concentrations of compounds (Experiment 3).

C. No.	% Control growth (MCF-7)			
	Compound concentration (µg/mL)			
	10	20	40	80
5b	75.2	66.0	45.1	33.7
6a	56.6	28.4	8.7	-0.2
6f	29.9	31.8	18.5	15.3
6g	39.1	38.7	29.6	25.1
6h	81.8	87.8	64.1	46.4
ADR	-5.9	-14.6	-27.4	-23.7

Table 6.5: Average values of percentage control growth of MCF-7 cell line at different drug concentrations.

C. No.	% Control growth (MCF-7)			
	Compound concentration (µg/mL)			
	10	20	40	80
5b	74.3	63.0	43.2	41.0
6a	65.3	30.1	15.7	-0.6
6f	30.9	30.3	23.1	17.5
6g	35.9	41.1	36.3	26.9
6h	92.5	97.4	70.1	48.7
ADR	-4.0	-12.4	-22.1	-22.9

Table 6.6: Synthesized compound (5b-6h) concentrations (µg/mL) as TGI, LC_{50} and GI_{50} for MCF-7 cell line

	Drug concentrations (µg/ml) calculated from graph[#]		
MCF-7	LC_{50}	TGI	GI_{50}*
5b	NE	NE	49.4
6a	NE	71.9	<10
6f	NE	NE	<10
6g	NE	NE	<10
6h	NE	NE	76.4
ADR	NE	<10	<10

[#]calculated from graph; LC_{50} = Concentration of drug causing 50% cell kill; GI_{50} = Concentration of drug causing 50% inhibition of cell growth; TGI = Concentration of drug causing total inhibition of cell growth; ADR = Adriamycin, Positive control compound; GI_{50} value of $\leq 10^{-6}$ molar (1 µmolar) or $\leq$ 10µg/ml is considered to demonstrate activity in case of pure compounds; Yellow highlighted values under GI_{50} column indicate activity: NE=Non-evaluable data. Experiment needs to be repeated using different set of drug concentrations.

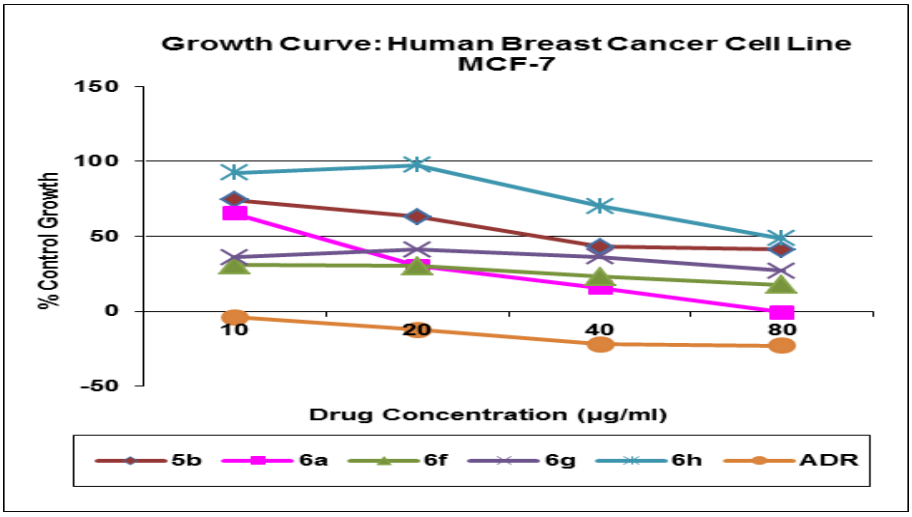


Figure 6.1. Variation of percentage control growth with increase in the compounds concentration (µg/ml).

6.3 ANTIMICROBIAL ACTIVITY

All the synthesized compounds were subjected to antibacterial activity against Gram negative *Escherichia coli* (MTCC 40) and Gram positive *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121). The zone of inhibition was observed in mm.

Table No. 6.7 *In vitro* antibacterial activity of synthesized compounds

Compounds	Bacterial Strains		
	Gram –ve bacteria *Escherichia coli* (MTCC 40)	Gram +ve bacteria *Bacillus subtilis* (MTCC121)	Gram +ve bacteria *Staphylococcus aureus* (MTCC87)
5a	-	+	+
5b	-	-	-
5c	+	-	-
5d	-	-	-
6a	+	+	+
6b	+	+	+
6c	+	+	+
6d	+	+	+
6e	+	+	+
6f	+	+	+
6g	+	+	+
6h	+	+	-

(-) no active
(+) active

All the synthesized compounds were found to be active against both the bacterial strain that is Gram negative bacteria *Escherichia coli* (MTCC 40) and Gram positive bacteria *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC121). The zone of inhibition was observed in mm. Amongst all derivatives in series (5a-d), (6a-h) exhibited good antibacterial activity. The synthesized derivatives can be further explored for better antimicrobial activity by studying their structure activity relationship.

REFERENCES

1. Bhal BS, Bhal A, Advanced organic chemistry, 1977; 1: 1201.
2. Katrizky AR, Pozharski AF. Handbook of heterocyclic chemistry. Elsevier Huntington, 2000; 2: 4-5.
3. Sharma PK, Kumar D, Sharma R. Pharm Chem, 2010; 2: 253–263.
4. Somani RR, Shirodka PY, Der Pharma Chemica, 2009; 1(1): 130-140.

5. Aydogan F et al. Synthesis and electronic structure of new aryl- and alkyl-substituted 1,3,4-Oxadiazole-2-thione derivatives. Turk J Chem, 2002; 26: 159-69.
6. Orlek BS, Blaney FE. Comparison of azbicyclic esters and oxadiazole as ligands for the muscarinic receptors. P J Med Chem, 1991; 34: 2726.
7. Aziz-ur-Rehman A, Fatima N, Abbas AM, Abbasi KM, Khan M, Ashraf IA. Synthesis, characterization and biological screening of 5-substituted-1,3,4-oxadiazole-2yl-N-(2-methoxy-5-chlorophenyl)-2-sulfanyl acetamide. Pak J Pharm Sci, 2013; 26: 345–352.
8. Aziz-ur-Rehman SZ, Siddiqu N, Abbas MA, Abbasi KM, Khan M, Mahmood SY. Synthesis, antibacterial screening and hemolytic acitvity of S-substituted derivatives of 5-benzyl-1,3,4-oxadiazole-2-thiol. Int J Pharm Sci, 2012; 4: 676–680.
9. Shivi B, Gupta M, 1, 3, 4-oxadiazole as antimicrobial agents. Jour Chem Pharma Res, 2011; 3(3): 137-147.
10. Ahmed MO, Mahmud A, Hasan, Mahmoud T. Synthesis, antibacterial, antifungal and genotoxic activity of bis-1,3,4-oxadiazole derivatives. Polish Jour Pharma, 2002; 54: 55-59.
11. Rakesh C, Anshu A, Manoj KP, Prabodh CS, Sukuma M, Thengungal KR. Synthesis of novel 1,3,4-oxadiazole derivatives as potential antimicrobial agents. Act Poloniae Pharmaceutica-Drug Res, 2010; 3(67): 247-253.
12. Farshori NN, Banday MR, Ahmad A, Khan AU, Rauf A. Synthesis, characterization, and in vitro antimicrobial activities of 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-oxadiazoles and thiadiazoles. Bioorg Med Chem Lett, 2010; 20: 1933-1938.
13. Bhardwaj N, Saraf P, Sharma SK, Kumar P. Synthesis, evaluation and characterization of 1,3,4oxadiazoles as antimicrobial agents. Eur J Chem, 2009; 6(4): 1133-38.
14. Yathirajan HS, Anil MN, Narayana B, Sarojini BK, Kumari Suchetha. Synthesis and antimicrobial studies on new substituted 1,3,4-oxadiazole derivatives bearing 6-bromonaphthalene moiety. Int J Chem, 2010; 2(1): 38-54.
15. Parkash O, Kumar M, Sharma C, Aneja KR. Hypervalent iodine (III) mediated, synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4-oxadiazoles as antibacterial and antifungal agents. Eur J Med Chem, 2010; 45(9): 4252-4257.
16. Jakubkiene V, Burbuliene MM, Mekuskiene G. Synthesis and anti-inflammatory activity of 5-(6-methyl-2substituted 4-pyrimidinyloxymethyl)-1,3,4-oxadiazole 2thiones and their 3-morpholinomethyl derivatives. Farmaco II, 2003; 58(4): 323.
17. Amir M, Shikha K. Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of some new 2-[(2,6-dichloroanilino) phenyl]acetic acid. Int Jour Pharma Sci Res, 2014; 5(4): 1124-1137.
18. Jakopin, Ziga. Molecules, 2012; 17: 10192.
19. Kucukguzel SG, Oruc EE, Rollas S, Sahin F, Ozbek A. Synthesis, characterization and biological activity of 4-thiozolidinones, 1,3,4-oxadiazoles and some related compounds. Eur J Med Chem, 2002; 37: 197-206.