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Synthesis, spectral studies, and biological activity of novel 2-(substituted-phenyl)-6-phenylimidazo[2,1-b]1,3,4-oxadiazole

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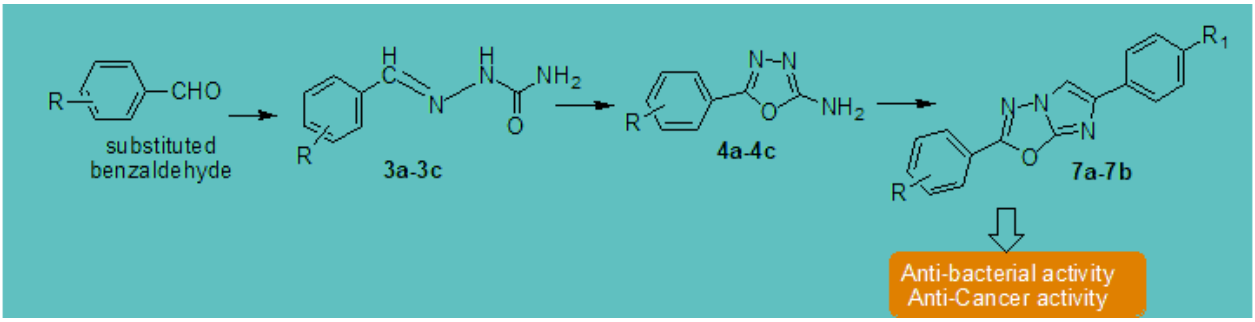
ABSTRACT



Diverse series of 2-(substituted phenyl)-6-phenylimidazo[2,1-b]1,3,4-oxadiazole were synthesized. Five of the synthesized compounds were evaluated for their anticancer activity on MCF-7 cancer cell lines. The recently synthesized compounds were illustrated by IR, ^{1}HNMR. The anticancer activity of the compounds was carried out at Anti-Cancer Drug Screening Facility (ACDSF), Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai. The anticancer activity would be evaluated by In vitro testing using SRB assay protocols. All the screened compounds showed good to moderate activity against the MCF-7 cancer cell line. Compounds 5b, 6c, 7a were found to be active with GI_{50}<10 µg/ml. All the synthesized compounds were screened against Gram-Positive and Gram-Negative bacteria *Streptococcus aureus, Bacillus subtilis*, and *E. coli* respectively.

Keywords: 1,3,4-oxadiazoles, Imidazole, Anti-cancer activity, Antimicrobial activity

INTRODUCTION

Cancer proves to be a serious health issue all around the world and is proved to be the major cause of death worldwide. Cancer is a group of different life-threatening diseases characterized by uncontrolled cell growth, leading to invasiveness in the surrounding tissues, and metastasizing to other parts of the body. Cancer is characterized to be the second most major cause of death after the cardiovascular disease reported in the statistics.[1–3] According to the report of the National Cancer Institute number of death due to cancer in different age groups was estimated to be 1960, in 2014 it was15, 780 and in 2017 it was increased to 1,688,780. The risk of developing cancer in an individual in his lifetime depends on factors like smoking, excessive alcohol consumption, sedentary lifestyle, lack of physical activity, and improper or unhealthy diet.[4,5] However, this can also be in association with transformation at the cellular level linked to viral infection radiation and chemical exposure.[6,7] Cancer treatment has been the major/foremost goal of pharmaceutical industries and R & D wings in research centers from the past decades.[8–11] The current therapeutic approaches used in the treatment of cancer involve Chemotherapy, immunotherapy, hormonal therapy, radiotherapy, monoclonal antibody therapy, targeted therapy.[12] But due to the invasive nature of cancerous cells to other cells or tissue, can cure 40% of individuals only and is thus associated with a high mortality rate. Chemotherapy is the major crossbow against the neoplasm but possesses some side effects to include alopecia, sore throat, diarrhea, fatigue, etc. The failure of chemotherapy is generally reported due to the development of multidrug-resistant, or the cancerous cells resist them against chemotherapeutic agents, poor patient compliance due to clinical systemic toxicity.[13] Mostly the clinical used antineoplastic

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molecules or drugs are synthetic in origin. These molecules act by a variety of molecular mechanics which include initiation inhibition, progression, promotion, and metastasis of cancerous cells but in the process also destroy the normal cells that lead to toxicity,[14] severe side effects of the drug entities, development of resistance against drugs, failure of antitumor drugs are the main obstacle in the successful development of anticancer drugs.[15,16] The incidence of cancer worldwide elevates the finding for new, safer, and efficient anticancer agents, aiming for the prevention or the cure of this disease. Research laboratories are still indulged deeply in the research of a new anticancer drug.[17]

Oxadiazole is from the major class of 5 membered aromatic heterocyclic compounds incorporating two nitrogen and one oxygen atom in the ring. 1,3,4-oxadiazole is thermally stable and exists in two forms 2,3-dihydro-,3,4-oxadiazole, and 2,5-dihydro-1,3,4-oxadiazole. Oxadiazole possesses four isomers 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-oxadiazole depending on the position of the nitrogen atom. Out of these four isomers, 1,3,4-oxadiazole possesses different pharmacological activities.[18]

Zibotentan is a marketed compound based upon 1,3,4-oxadiazole and possesses excellent anti-cancer activity. It is an endothelial receptor antagonist and is used for the treatment of prostate cancer.[19]

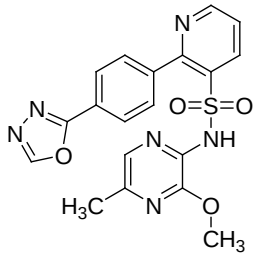

Figure 1. Chemical structure of Zibotenan

From the literature survey, we come to know that the 1,3,4-oxadiazole and its derivatives possess a wide range of pharmacological activities including antibacterial activity,[20,21] anti-mycobacterial,[22] antifungal[23,24] anti-HIV,[25–27] anti-inflammatory and analgesic,[28–30] hypoglycaemic,[31] anticonvulsant[32] and antitumor,[33] herbicidal properties,[34] Antihypertensive,[35] enzyme inhibition,[36] muscle relaxants[37] hypnotic, sedatives[38] and Anticancer activit[39,40] Oxadiazole possesses desirable charge transport and electronic properties, incorporation of different functional groups in the ring is easy. This resulted in the potential utilization of the oxadiazole derivatives in the field of medicinal chemistry. From the literature survey, it came to know that 1, 3, 4-oxadiazole acts as telomerase inhibitors. So, the researchers are interested to explore 1,3,4-oxadiazole because of its diverse pharmacological activities. In the present study, we report the synthesis of new series of 1,3,4-oxadiazole derivatives.

MATERIAL AND METHOD

Semicarbazide hydrochloride, substituted aromatic aldehyde, substituted phenacyl bromide, Sodium acetate, and solvents were purchased from LOBACHEM, India. The progress in the reaction was monitored by the thin layer chromatography technique using pre-coated TLC plates. The spots developed were seen in the iodine chamber. The melting point of the compounds reported was determined by the capillary method and was uncorrected. The infrared spectra (IR) were undergone on Bruker alpha-E FTIR-ATR at A.S.B.A.S.J.S.M. College of Pharmacy Bela, Ropar (Punjab). ^{1}HNMR was carried out from the Indian Institute of Technology (IIT) Ropar, (Punjab) using DMSO and chloroform as solvent and also at SAIF, Punjab University Chandigarh.

Chemistry

Preparation of 1-Benzylidenesemicarbazide derivatives (3a-3c):

Semicarbazide hydrochloride (1.12 g 0.01 mol) and sodium acetate (1.64 g 0.02mol) were mixed in 10-20 ml water. To this mixture substituted aromatic aldehyde (0.01 mol) was added slowly with continuous stirring to give a turbid solution. The solution was stirred for 10 h at room temperature. The reaction was monitored using TLC by hexane and ethyl acetate (2:1). Upon completion, the reaction mixture was kept overnight.

Preparation of 2-Amino-5-aryl-1, 3, 4-oxadiazole (4a-4c):

Semicarbazone (0.01 mol) and sodium acetate (1.64 g 0.02 mol) was dissolved in 30-40 ml of glacial acetic acid taken in a round bottom flask. Bromine (0.7 ml in 5 ml of glacial acetic acid) was added slowly to it while stirring magnetically. After 4 h of stirring, the solution was poured on crushed ice. The resulting solid was separated, dried, and recrystallized from ethanol.

Preparation of 2-(substituted phenyl)-6-phenylimidazo- [2, 1-b] 1, 3, 4- Oxadiazole (5-7)

A mixture of the equimolar quantity of 2-amino-5-aryl-1, 3, 4-oxadiazole (0.005 mol), and bromoacetyl compounds was refluxed with DMF for 16 h. The excess solvent was distilled off and the solid hydrobromide that separated was collected by filtration, suspended in water, and neutralized by sodium carbonate solution to get a free base. It was filtered washed with water, dried, and recrystallized from a suitable solvent.

2-(4-Bromophenyl)-6-phenylimidazo[2,1-b]-1.3.4-oxadiazole (**5a):** $C_{16}H_{10}BrN_3O$; Melting point 108-110ºC; Yield 47.33%; IR (γ cm^{-1}) C-Br stretch 686.19, Ar C-H stretch 3273.46, Ar C=C stretch 1478, C=N stretch 1656, C-N stretch 1351, C-O stretch 1063.^{1}HNMR ($CDCl_3$, 400MHz,) δ ppm 7.47-7.50 (m, 6H, Ar –CH),7.52-(s,1H, Ar –CH)7.61-7.69(m, 2H, Ar –CH), 9.07 (s,1H, imidazole).

2-(4-Bromophenyl)-6-(4-methoxy)phenylimidazo[2,1-b]-1.3.4-oxadiazole (**5b**): $C_{16}H_{12}BrN_3O_2$; Melting point 78-80ºC; Yield 54.34%; IR (γ cm^{-1}) C-Br stretch 661, Ar C-H stretch 3183, Ar C=C stretch 1474, C=N stretch 1657, C-N stretch 1398, C-O stretch 1007. ^{1}HNMR ($CDCl_3$, 400MHz,) δ ppm3.03 (s, 3H, OCH_3), 7.11 (s,1H, imidazole),7.31(m, 2H, Ar –CH), 7.5-7.68 (m,4H, Ar –CH), 7.84 (s, 2H, Ar –CH).

2-(4-Bromophenyl)-6-*p*-tolylimidazo[2,1-b]-1.3.4-oxadiazole (**5c**): $C_{17}H_{12}BrN_3O$; Melting point 92-94ºC; Yield 35.42%; IR (γ cm^{-1}) C-Br stretch 636, Ar C=C stretch 1469, C=N stretch 1622, C-N stretch 1267, C-O stretch 1011, C-H stretch 2800. ^{1}HNMR ($CDCl_3$, 400MHz,) δ ppm2.9-3.0 (m, 3H, CH_3), 7.10 (s,1H, imidazole), 7.51-7.59 (m, 5H, Ar-CH), 7.67-7.69(m, 3H, Ar-CH),

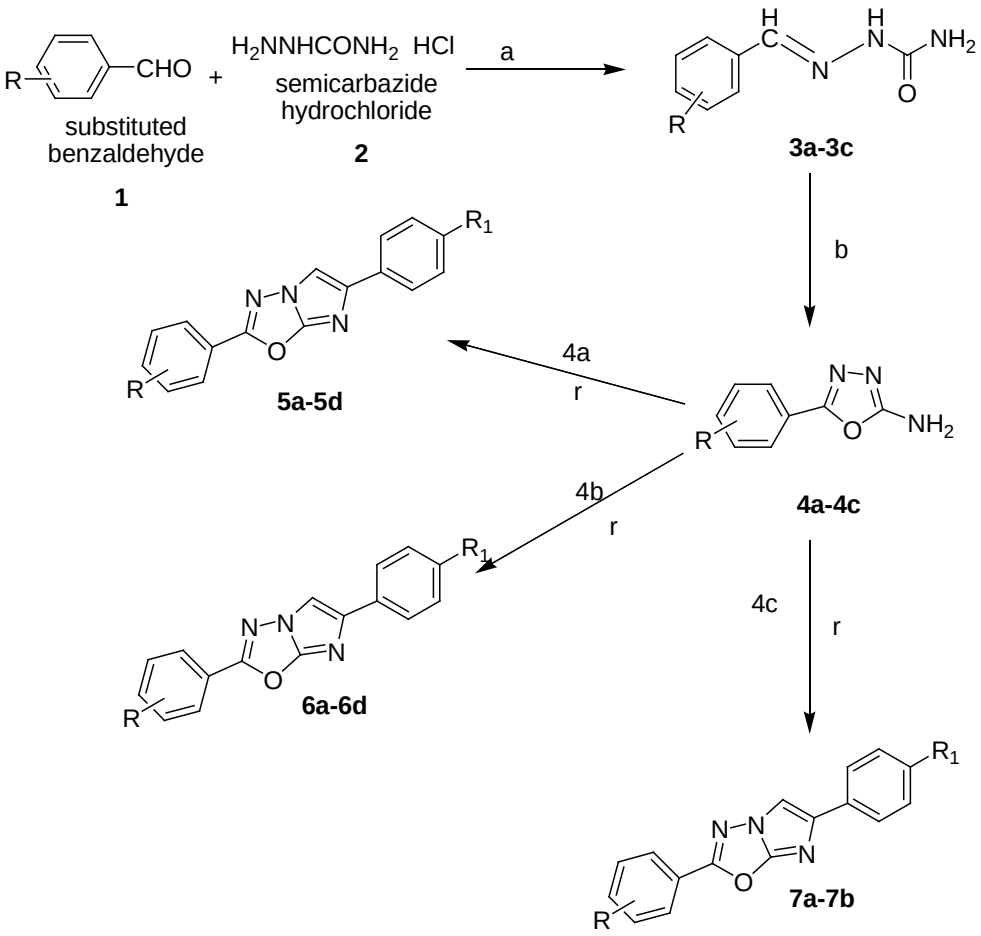

Figure 2. Reaction scheme for synthesis of compounds

Reagents and conditions: (a) CH_3COONa, Distilled water, stirring 10 h(b) CH_3COONa, CH_3COOH, Br_2 stirring 4 h (r) DMF, substituted Phenacylbromide, reflux 18 h.

3a: R= 4-Br	**3b:R=**4-NO_2	**3c:R=**2,5-diOCH_3
4a: R=4-Br	**4b:R=**4-NO_2	**4c:R=**2,5-diOCH_3
5a: R=4-Br R_1=H	**6a: R=**4-NO_2 R_1=H	**7a:R=**2,5-diOCH_3 R_1=OCH_3
5b:R=4-BrR_1=OCH_3	**6b: R=**4-NO_2 R_1=OCH_3	**7b: R=**2,5-diOCH_3 R_1=CH_3
5c:R=2,5-diOCH_3 R_1=CH_3	**6c: R=**4-NO_2 R_1=CH_3	
5d:R=2,5-diOCH_3 R_1=Cl	**6d: R=**4-NO_2 R_1=Cl	

2-(4-Bromophenyl)-6-(4-Chloro)phenylimidazo[2,1-b]-1.3.4-oxadiazole (**5d**): $C_{16}H_9BrN_3OCl$; Melting point 151-153ºC; Yield 52.97%; IR (γ cm^{-1}) C-Br stretch 628, Ar C-H stretch 3052, Ar C=C stretch 1480, C=N stretch 1659,C-N stretch 1267, C-O stretch 1002, C-Cl stretch 742.

2-(4-Nitrophenyl)-6-phenylimidazo[2,1-b]-1.3.4-oxadiazole (**6a**): $C_{16}H_{10}N_4O_3$; Melting point 88-90ºC; Yield 30%; IR (γ cm^{-1}) N=O stretch 1518, 1338, Ar C-H stretch 3061, Ar C=C stretch 1450, C=N stretch 1677, C-N stretch 1171, C-O stretch 1018.

2-(4-Nitrophenyl)-6-(4-methoxy)-phenylimidazo[2,1-b]-1.3.4-oxadiazole (**6b**): $C_{17}H_{12}N_4O_4$; Melting point 74-76ºC; Yield 42.76%; IR (γ cm^{-1}) N=O stretch 1504, 1335, Ar C-H stretch 3065, Ar C=C stretch 1456, C=N stretch 1662, C-N stretch 1243, C-O stretch 1018, C-H stretch 2923, 2838. ^{1}HNMR (DMSO, 400MHz) δ ppm 3.90 (m, 3H,-OCH_3), 6.9-8.2 (m, 8H, Ar –CH), 7.7 (imidazole C-H).

2-(4-Nitrophenyl)-6-*p*-tolylimidazo[2,1-b]-1.3.4-oxadiazole (**6c**): $C_{17}H_{12}N_4O_3$; Melting point 78-80ºC; Yield 34.52%; IR (γ cm^{-1}) N=O stretch 1510, 1334, Ar C-H stretch 3030, Ar C=C stretch 1595, C=N stretch 1665, C-N stretch 1071, C-O stretch 1013, C-H stretch 2921, 2859.

2-(4-Nitrophenyl)-6-(4-chloro)-phenylimidazo[2,1-b]-1.3.4-oxadiazole (**6d**): $C_{16}H_9ClN_4O_3$; Melting point 75-77ºC; Yield 50%; IR (γ cm^{-1}) N=O stretch 1524, 1398, Ar C-H stretch 3048, Ar C=C stretch 1585, C=N stretch 1661, C-N stretch 1267, C-O stretch 1002, C-Cl stretch 741.

2-(2,5-dimethoxyphenyl)-6-(4-methoxy)phenylimidazo[2,1-b]-1.3.4-oxadiazole (7a): $C_{19}H_{17}N_3O_4$; Melting point 80-82ºC; Yield 40%; IR (γ cm^{-1}) Ar C-H stretch 3067, C=N stretch 1667, Ar C=C stretch 1499, C-N stretch 1244, C-O stretch 1018, C-H stretch 2920, 2844.^{1}HNMR (DMSO, 400MHz, δ ppm)δ 3.73 (m, 1H,-OCH_3), δ 3.73 (o, 1H,-OCH_3), δ 3.73 (p, 1H,-OCH_3), δ 6.9 (m, 4H, Ar –CH), δ 7.0-7.3 (m, 3H, Ar –CH), δ 7.1 (imidazole C-H).

2-(2,5-dimethoxyphenyl)-6-*p*-tolylimidazo[2,1-b]-1.3.4-oxadiazole (**7b**): $C_{19}H_{17}N_3O_3$; Melting point 60-62ºC; Yield 48%; IR (γ cm^{-1}) Ar C-H stretch 3030, Ar C=C stretch 1595, C=N stretch 1665, C-N stretch 1334, C-O stretch 1013, C-H stretch 2921, 2859.

Biological Activity

***In vitro* Anti-cancer screening**

Five of the synthesized compounds were submitted to Anti-Cancer Drug Screening Facility (ACDSF), Advanced Centre for Treatment, Research & Education in Cancer (ACTREC), Tata Memorial Centre, Kharghar, Navi Mumbai. The source of cell lines

was NCI USA. *In vitro* testing was done using SRB assay protocol, each derivative was tested at 4 dose levels 1×10^{-7} M, 1×10^{-6} M, 1×10^{-5} M, 1×10^{-4}). The compounds were screened against MCF-7 (breast cancer) cell line.

***In vitro* Antimicrobial screening**

All the synthesized compounds were evaluated for antibacterial activity against Gram-Negative bacteria *E-coli* (MTCC), Gram-Positive bacteria *Staphylococcus aureus* (MTCC), *Bacillus subtilis* (MTCC) at Microbiological lab in Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela (Ropar).

Results and Discussion

The synthesis, spectral studies, and biological activity of some 2-(substituted phenyl)-6-phenylimidazo[2,1-b]1,3,4-oxadiazole was carried out as per the proposed protocol.[41]

Anticancer Screening Results

All the screened compounds showed good to moderate activity against the MCF-7 Human cancer cell line. The compounds 5b, 6c, 7a possess good growth inhibition activity whereas compound 5a, 6b shows moderate growth activity. The compounds 5b, 6c, 7a have GI_{50} <10 µg/ml which is equal to the standard used in the screening [42,43] The order for the % control growth inhibition of MCF-7 was found to be 6b<7a<5b<6c<5a as shown in (Table: 1-4)

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

C. No.	% Control growth (MCF-7) Compound concentration (µg/mL)			
	10	**20**	**40**	**80**
5a	63.8	65.3	32.7	12.4
5b	26.3	25.1	22.8	20.9
6b	88.7	84.3	71.6	52.2
6c	48.3	42.2	21.2	8.5
7a	34.0	28.6	29.1	21.6
ADR	-4.3	-10.7	-14.7	-47.7

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

C. No.	% Control growth (MCF-7) Compound concentration (µg/mL)			
	10	**20**	**40**	**80**
5a	74.7	60.6	37.6	12.7
5b	29.1	25.4	30.5	29.1
6b	87.0	84.6	77.7	62.9
6c	49.9	32.5	21.5	14.6
7a	38.0	31.9	34.3	30.3
ADR	-1.8	-3.9	-18.5	-40.9

Table: 3 *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**
5a	73.8	60.0	39.2	16.1
5b	28.4	28.1	31.4	30.3
6b	86.5	78.7	74.9	67.4
6c	48.5	31.5	25.5	21.2
7a	35.0	34.1	31.7	36.6
ADR	-8.4	-10.4	-27.4	-39.7

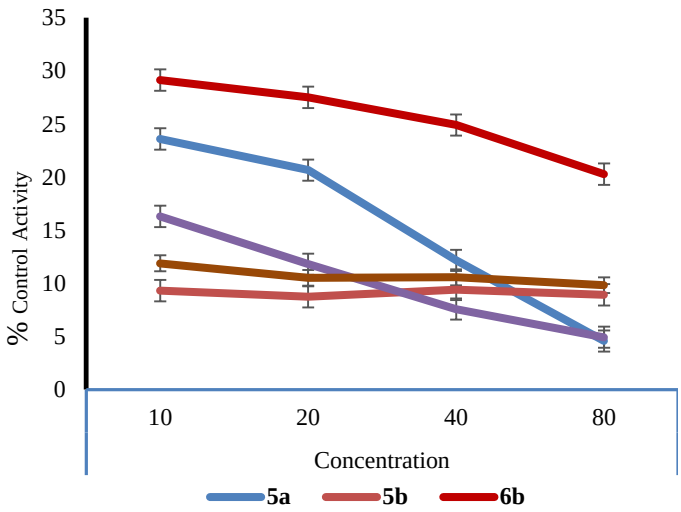

Figure 3. Anticancer activity graph with Standard deviation of compound 5a, 5b and 6b.

Table: 4 Screened compound concentrations (µg/mL) as TGI, LC_{50}, and GI_{50} for MCF-7 cell line.

C. No.	Compound concentration(µg/mL)		
	LC_{50}	**TGI**	**GI_{50}**
5a	NE	NE	32.3
5b	NE	NE	<10
6b	NE	NE	>80
6c	NE	NE	<10
7a	NE	NE	<10
ADR	NE	<10	<10

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 ≤ 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. The

experiment needs to be repeated using a different set of drug concentrations.

Antimicrobial screening results

All the synthesized compounds were tested against Gram-Positive and Gram-Negative bacteria *Streptococcus aureus*, *Bacillus subtilis*, and *E.coli* respectively. The cup plate agar diffusion method was used to perform its antimicrobial activity. The compounds active against Gram-Positive bacterial strains *Streptococcus aureus* were 5c, 5d, 6c, 6d, and compounds against *Bacillus subtilis* were 5a, 5c, 5d, 6a, 6c, 7a, 7b. Complete series of compounds were inactive against Gram-Negative[44]. (Table: 5)

Table: 5 Showing Antimicrobial activity

Compound no.	Activity		
	Gram-Positive bacteria		Gram Negative bacteria
	S.aureus	*B. subtilis*	*E. coli*
5a	_	+	_
5b	_	_	_
5c	+	+	_
5d	+	+	_
6a	_	+	_
6b	_	_	_
6c	+	+	_
6d	+	_	_
7a	_	+	_
7b	_	+	_

(-) Not active, (+) Active

CONCLUSION

In conclusion, a series of compounds such as 2-(substituted phenyl)-6-phenylimidazo[2,1-b]1,3,4-oxadiazole were synthesized and tested for anti-cancer and antimicrobial activity. Five compounds from the synthesized compounds were tested against the 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). All the selected synthesized compounds possess good to moderate anticancer activity. Compounds **5b, 6c, 7a** were found to be active with GI_{50} <10 µg/ml. The order for the % control growth inhibition of MCF-7 was found to be 6b<7a<5b<6c<5a. All the synthesized compounds were screened against Gram-Positive and Gram-Negative bacterias *Streptococcus aureus*, *Bacillus subtilis*, and *E.coli* respectively[45–47]. It is concluded that the compounds with electron-withdrawing group/ electronegative groups possess good activity.

REFERENCES

1. S. Eckhardt. Recent progress in the development of anticancer agents. *Curr. Med. Chem. agents* **2002**, 2 (3), 419–439.
2. D. Belpomme, P. Irigaray, A.J. Sasco, et al. The growing incidence of cancer: role of lifestyle and screening detection. *Int. J. Oncol.* **2007**, 30 (5), 1037–1049.
3. R. Gudipati, R.N.R. Anreddy, S. Manda. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1, 3, 4-oxadiazole-2-yl) phenylimino} indolin-2-one derivatives. *Saudi Pharm. J.* **2011**, 19 (3), 153–158.
4. B.W. Stewart, P. Kleihues. World cancer report; IARC press Lyon, **2003**; Vol. 57.
5. I. Khanna. Drug discovery in pharmaceutical industry: productivity challenges and trends. *Drug Discov. Today* **2012**, 17 (19–20), 1088–1102.
6. E. Han, B. Kwon, D. Yoo, et al. Dual stimuli-activatable oxidative stress amplifying agent as a hybrid anticancer prodrug. *Bioconjug. Chem.* **2017**, 28 (4), 968–978.
7. G. Verma, G. Chashoo, A. Ali, et al. Synthesis of pyrazole acrylic acid based oxadiazole and amide derivatives as antimalarial and anticancer agents. *Bioorg. Chem.* **2018**, 77, 106–124.
8. B.S. Chhikara, B. Rathi, K. Parang. Critical evaluation of pharmaceutical rational design of Nano-Delivery systems for Doxorubicin in Cancer therapy. *J. Mater. Nanosci.* **2019**, 6 (2), 47–66.
9. B.S. Chhikara, D. Mandal, K. Parang. Synthesis, anticancer activities, and cellular uptake studies of lipophilic derivatives of doxorubicin succinate. *J. Med. Chem.* **2012**, 55 (4), 1500–1510.
10. B.S. Chhikara, N.S. Jean, D. Mandal, et al. Fatty acyl amide derivatives of doxorubicin: Synthesis and in vitro anticancer activities. *Eur. J. Med. Chem.* **2011**, 46 (6), 2037–2042.
11. B.S. Chhikara, K. Parang. Development of cytarabine prodrugs and delivery systems for leukemia treatment. *Expert Opin. Drug Deliv.* **2010**, 7 (12), 1399–1414.
12. D. Coskun, M. Erkisa, E. Ulukaya, M.F. Coskun, F. Ari. Novel 1-(7-ethoxy-1-benzofuran-2-yl) substituted chalcone derivatives: synthesis, characterization and anticancer activity. *Eur. J. Med. Chem.* **2017**, 136, 212–222.
13. M.J. Ahsan, J. Sharma, M. Singh, S.S. Jadav, S. Yasmin. Synthesis and anticancer activity of N-aryl-5-substituted-1, 3, 4-oxadiazol-2-amine analogues. *Biomed Res. Int.* **2014**, 2014.
14. M. Rashid, A. Husain, R. Mishra, et al. Design and synthesis of benzimidazoles containing substituted oxadiazole, thiadiazole and triazolo-thiadiazines as a source of new anticancer agents. *Arab. J. Chem.* **2019**, 12 (8), 3202–3224.
15. G. Moghaddam, S.A. Ebrahimi, N. Rahbar-Roshandel, A. Foroumadi. Antiproliferative activity of flavonoids: influence of the sequential methoxylation state of the flavonoid structure. *Phyther. Res.* **2012**, 26 (7), 1023–1028.
16. S.X. Cai, B. Nguyen, S. Jia, et al. Discovery of substituted N-phenyl nicotinamides as potent inducers of apoptosis using a cell-and caspase-based high throughput screening assay. *J. Med. Chem.* **2003**, 46 (12), 2474–2481.
17. M. Shaharyar, A. Mazumder, M.J. Ahsan. Synthesis, characterization and anticancer evaluation of 2-(naphthalen-1-ylmethyl/naphthalen-2-yloxymethyl)-1-[5-(substituted phenyl)-[1, 3, 4] oxadiazol-2-ylmethyl]-1H-benzimidazole. *Arab. J. Chem.* **2014**, 7 (4), 418–424.
18. D. Dewangan, A. Pandey, T. Sivakumar, R. Rajavel, R.D. Dubey. Synthesis of some novel 2, 5-disubstituted 1, 3, 4-oxadiazole and its analgesic, anti-inflammatory, anti-bacterial and anti-tubercular activity. *Int. J. Chem. Tech. Res* **2010**, 2 (3), 1397–1412.
19. N. James, J.W. Growcott. Zibotentan endothelin ETA receptor antagonist oncolytic. *Drugs Future* **2009**, 34 (8), 624–633.
20. B.S. Holla, R. Gonsalves, S. Shenoy. Synthesis and antibacterial studies of a new series of 1, 2-bis (1, 3, 4-oxadiazol-2-yl) ethanes and 1, 2-bis (4-amino-1, 2, 4-triazol-3-yl) ethanes. *Eur. J. Med. Chem.* **2000**, 35 (2), 267–271.

21. K. Rajneesh, R. Singh, P. Ahlawat, P. Kaushik, K. Singh. Contemporary advances in therapeutic portfolio of 2-Azetidinones. *Chem. Biol. Lett.* **2020**, 7 (1), 13–26.
22. F. Macaev, G. Rusu, S. Pogrebnoi, et al. Synthesis of novel 5-aryl-2-thio-1, 3, 4-oxadiazoles and the study of their structure–anti-mycobacterial activities. *Bioorg. Med. Chem.* **2005**, 13 (16), 4842–4850.
23. F. Liu, X.-Q. Luo, B.-A. Song, et al. Synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1, 3, 4-thiadiazole and 1, 3, 4-oxadiazole moiety. *Bioorg. Med. Chem.* **2008**, 16 (7), 3632–3640.
24. N. Singh, S. Satpute, N. Polkam, et al. Design, synthesis and evaluation of 4H-Chromene-4-one analogues as potential Anti-bacterial and Anti-fungal agents. *Chem. Biol. Lett.* **2020**, 7 (1), 27–40.
25. A.A. El-Emam, O.A. Al-Deeb, M. Al-Omar, J. Lehmann. Synthesis, antimicrobial, and anti-HIV-1 activity of certain 5-(1-adamantyl)-2-substituted thio-1, 3, 4-oxadiazoles and 5-(1-adamantyl)-3-substituted aminomethyl-1, 3, 4-oxadiazoline-2-thiones. *Bioorg. Med. Chem.* **2004**, 12 (19), 5107–5113.
26. J. Singh, B.S. Chhikara. Comparative global epidemiology of HIV infections and status of current progress in treatment. *Chem. Biol. Lett.* **2014**, 1 (1), 14–32.
27. B.S. Chhikara, B. Rathi. Organic molecular drugs designing for inhibition of cellular multiplication biocycle of virus for anti-HIV therapy development: A recent advances review. *Adv. Org. Chem. Lett.* **2015**, 2 (1), 1–14.
28. M.M. Burbuliene, V. Jakubkiene, G. Mekuskiene, et al. Synthesis and anti-inflammatory activity of derivatives of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3H-1, 3, 4-oxadiazole-2-thiones. *Farm.* **2004**, 59 (10), 767–774.
29. E. Palaska, G. Şahin, P. Kelicen, N.T. Durlu, G. Altinok. Synthesis and anti-inflammatory activity of 1-acylthiosemicarbazides, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazole-3-thiones. *Farm.* **2002**, 57 (2), 101–107.
30. M. Akhter, A. Husain, B. Azad, M. Ajmal. Aroylpropionic acid based 2, 5-disubstituted-1, 3, 4-oxadiazoles: Synthesis and their anti-inflammatory and analgesic activities. *Eur. J. Med. Chem.* **2009**, 44 (6), 2372–2378.
31. K.G. Liu, J.S. Smith, A.H. Ayscue, et al. Identification of a series of oxadiazole-substituted α-isopropoxy phenylpropanoic acids with activity on PPARα, PPARγ, and PPARδ. *Bioorg. Med. Chem. Lett.* **2001**, 11 (17), 2385–2388.
32. A. Zarghi, S.A. Tabatabai, M. Faizi, et al. Synthesis and anticonvulsant activity of new 2-substituted-5-(2-benzyloxyphenyl)-1, 3, 4-oxadiazoles. *Bioorg. Med. Chem. Lett.* **2005**, 15 (7), 1863–1865.
33. H.B. Park, H.C. Kwon, C.-H. Lee, H.O. Yang. Glionitrin A, an antibiotic–antitumor metabolite derived from competitive interaction between abandoned mine microbes. *J. Nat. Prod.* **2009**, 72 (2), 248–252.
34. Z.-S. Li, W.-M. Wang, W. Lu, et al. Synthesis and biological evaluation of nonsymmetrical aromatic disulfides as novel inhibitors of acetohydroxyacid synthase. *Bioorg. Med. Chem. Lett.* **2013**, 23 (13), 3723–3727.
35. K. Sudeesh, R. Gururaja. Facile synthesis of some novel derivatives of 1, 3, 4-oxadiazole derivatives associated with quinolone moiety as cytotoxic and antibacterial agents. *Org Chem Curr Res* **2017**, 6 (2), 2–5.
36. S. K, G. R. Facile Synthesis of Some Novel Derivatives of 1,3,4,-Oxadiazole Derivatives Associated with Quinolone Moiety as Cytotoxic and Antibacterial Agents. *Org. Chem. Curr. Res.* **2017**, 6 (2), 1–5.
37. H.L. Yale, K. Losee. 2-Amino-5-substituted 1, 3, 4-oxadiazoles and 5-imino-2-substituted Δ2-1, 3, 4-oxadiazolines. A group of novel muscle relaxants. *J. Med. Chem.* **1966**, 9 (4), 478–483.
38. G.W. Adelstein, C.H. Yen, E.Z. Dajani, R.G. Bianchi. 3, 3-Diphenyl-3-(2-alkyl-1, 3, 4-oxadiazol-5-yl) propylcycloalkylamines, a novel series of antidiarrheal agents. *J. Med. Chem.* **1976**, 19 (10), 1221–1225.
39. T. Glomb, K. Szymankiewicz, P. Świątek. Anti-cancer activity of derivatives of 1, 3, 4-oxadiazole. *Molecules* **2018**, 23 (12), 3361.
40. A. Bharwal, M. Gupta. 1,3,4 Oxadiazole: An emerging scaffold to target different growth factors and kinases. *Chem. Biol. Lett.* **2020**, 7 (4 SE-Review Articles), 225–235.
41. F. Tok, Z. Uğraş, B.N. Sağlık, et al. Novel 2, 5-disubstituted-1, 3, 4-oxadiazole derivatives as MAO-B inhibitors: Synthesis, biological evaluation and molecular modeling studies. *Bioorg. Chem.* **2021**, 112, 104917.
42. M.M. Alam. 1, 3, 4-Oxadiazole as a Potential Anti-Cancer Scaffold: A. **2021**.
43. Y.L. Tamhankar, A.P. Gharote. Effect of Puta on in vitro anticancer activity of Shataputi AbhrakBhasma on lung, leukemia and prostate cancer cell lines. *J. Ayurveda Integr. Med.* **2020**, 11 (2), 118–123.
44. C.D. Mohan, N.C. Anilkumar, S. Rangappa, et al. Novel 1, 3, 4-oxadiazole induces anticancer activity by targeting NF-κB in hepatocellular carcinoma cells. *Front. Oncol.* **2018**, 8, 42.
45. A.A. Othman, M. Kihel, S. Amara. 1,3,4-Oxadiazole, 1,3,4-thiadiazole and 1,2,4-triazole derivatives as potential antibacterial agents. *Arab. J. Chem.* **2019**, 12 (7), 1660–1675.
46. R. Ningegowda, S. Chandrashekharappa, V. Singh, V. Mohanlall, K.N. Venugopala. Design, synthesis and characterization of novel 2-(2, 3-dichlorophenyl)-5-aryl-1, 3, 4-oxadiazole derivatives for their anti-tubercular activity against Mycobacterium tuberculosis. *Chem. Data Collect.* **2020**, 28, 100431.
47. M.M. Alam, A.S.A. Almalki, T. Neamatallah, et al. Synthesis of New 1, 3, 4-oxadiazole-incorporated 1, 2, 3-triazole moieties as potential anticancer agents targeting thymidylate synthase and their docking studies. *Pharmaceuticals* **2020**, 13 (11), 390.