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RESEARCH ARTICLE

Synthesis, Cytotoxic Evaluation, and Molecular Docking Studies of New Oxadiazole Analogues

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Abstract: ***Background***: Cancer is one of the major health diseases worldwide with an approximately 14 million new cases of cancer and 8.2 million cancer related death tolls were reported in 2012. The major complications associated with chemotherapy are limited efficacy, selectivity, safety as well as higher cost, emergence of drug resistant cancer, and genotoxicity. Today we need more effective and safer cytotoxic agents to combat cancer.

Method: Two new series of *N*-(2,6-dimethylphenyl)-5-aryl-1,3,4-oxadiazol-2-amine (**4a–g**) and *N*-{[5-aryl-1,3,4-oxadiazol-2-yl]methyl}-2,6-dimethylaniline (**4h-n**) were designed and synthesized based on the structure of IMC-038525 (tubulin polymerization inhibitor) and NSC 777948 as cytotoxic agents. The cytotoxicity of eight compounds was carried out as per National Cancer Institute (NCI US) protocol on nearly 60 cancer cell lines, while the cytotoxicity of five compounds was carried out as per Sulforhodamine B assay on two breast cancer cell lines. The molecular docking studies implying tubulin inhibition were also carried out to observe the binding mode of new oxadiazoles.

Results: *N*-(2,6-Dimethylphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (**4b**) showed significant cytotoxicity with comparatively higher sensitivity towards colon cancer (HT29), melanoma (LOX IMVI), leukemia (RPMI-8226), and melanoma (M14), with percent growth inhibitions (% GIs) of 80.99, 75.05, 63.25, and 62.19 respectively. Compound **4b** showed better cytotoxicity than the standard drug imatinib. Further compound **4b** showed maximum docking score and was found to have different binding mode than the rest of the compounds at the colchicine binding site of tubulin enzyme with a hydrogen bonding between NH with carbonyl oxygen of Thr353 (bond length = 3.05Å). The hydrophilicity of compound **4b** was another parameter that might play a major role and made it most effective when compared to the rest of the compounds.

Conclusion: The oxadiazoles reported herein are cytotoxic agents. These findings may be helpful in future drug design of more potent cytotoxic agents.

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1. INTRODUCTION

Cancer, an uncontrolled cell growth and proliferation, is the leading cause of deaths worldwide. Nearly 14 million new cases and 8.2 million cancer related death tolls were reported in 2012. The conditions become worst with the new cancer cases that are expected to increase up to 22 million within the next two decades [1]. Limited efficacy, selectivity, safety, higher cost, emergence of drug resistant cancer, and genotoxicity are the major complications associated with chemotherapy, usually a major strategy of cancer treatment [2]. The scientist and researchers focused their research on

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the development of synthetic compounds with comparatively higher selectivity towards cancerous cells and relatively safe.

The oxadiazoles are good bioisosteres of amide and ester, participate with the receptor through hydrogen bonding and increase the biological profile to a large extent [3]. Five membered 1,3,4-oxadizole analogues are rich in potential activities [4]. Oxadiazole analogues are reported as anticancer [5], antitubercular [6], antimicrobial [7], anti-HIV [8], anti-inflammatory [9] agents and many more. We reported preparation, characterization and cytotoxic screening of the fourteen new oxadiazoles. The oxadiazoles linked with the aryl core of IMC-038525 (tubulin polymerization inhibitor; IC_{50} = 0.39 ± 0.06 µM) and NSC 777948 (cytotoxic agent with mean GP = 62.61, at 10 µM drug concentration) were taken into the consideration to design the oxadiazoles with (**4h-n**) and without (**4a-g**) methylene (-CH_2-) linkage (Fig. **1**) as cytotoxic agents [10,11]. The cytotoxic evaluation of eight compounds was tested on panels of nine different human cancer cell lines (60 NCI cancer cell lines). Today breast cancer has drawn much attention among the major causes of cancer related death in female globally, so breast cancer cell lines (MCF-7 and MDA-MB-231) were tested for cytotoxicity of the remaining five compounds.

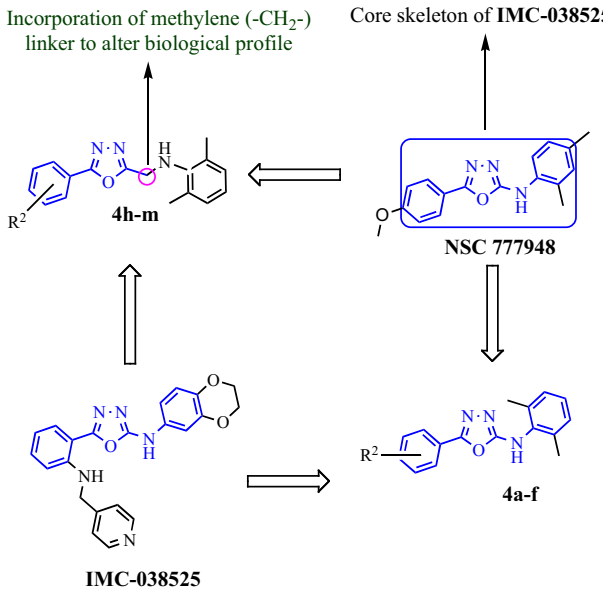


Fig. (1). Design of title compounds (**4a-n**) based on the structure IMC-038525 and NSC 777948 [10, 11].

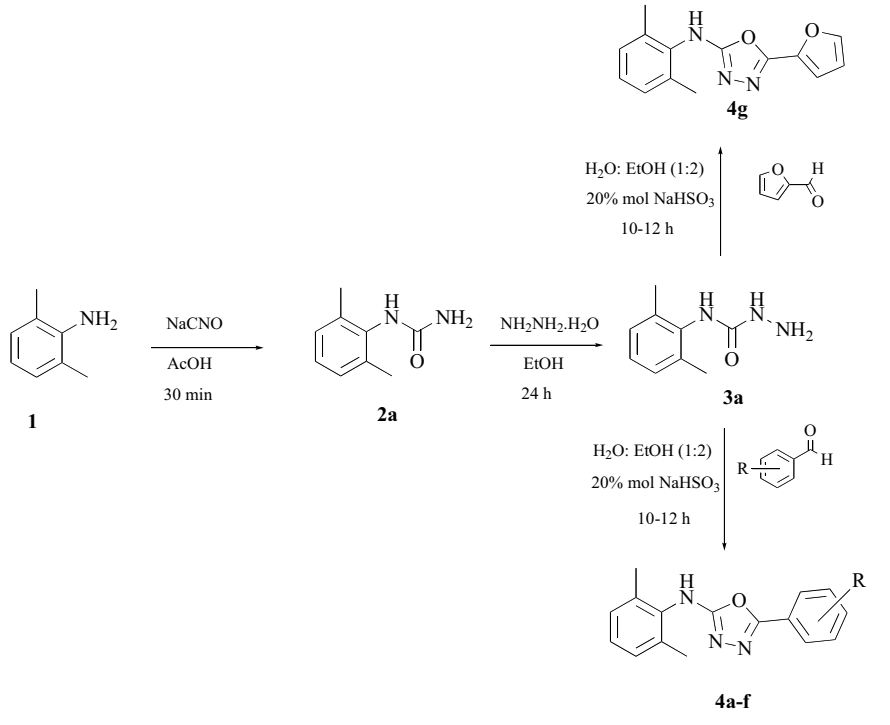
2. RESULTS AND DISCUSSION

2.1. Chemistry

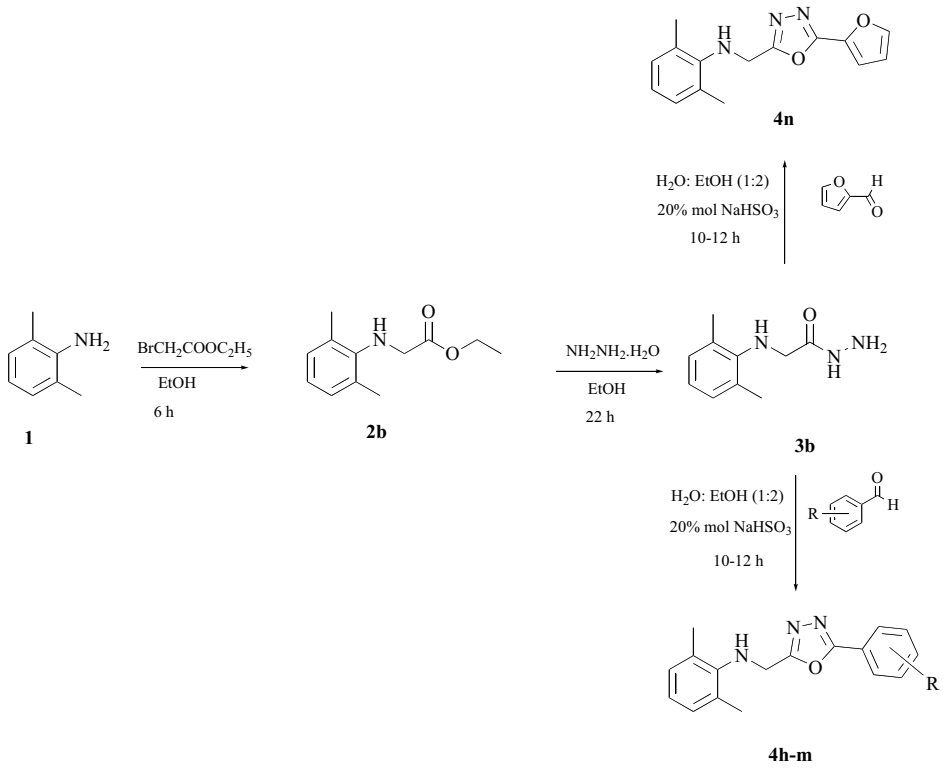
Methods for the synthesis of *N*-(2,6-dimethylphenyl)-5-aryl-1,3,4-oxadiazol-2-amine (**4a–g**) and *N*-{[5-aryl-1,3,4-oxadiazol-2-yl]methyl}-2,6-dimethylaniline (**4h-n**) are summarized in Scheme **1** and **2**, respectively. Both the series of oxadizoles were synthesized following two different route starting from 2,6-xylidine (**1**). For the synthesis of series one oxadiazoles (**4a-g**), the initial step involved in the synthesis of 2,6-dimethyl phenyl urea (**2a**) from 2,6-xylidine and sodium cyanate and in the subsequent step, 2,6-dimethyl phenyl semicarbazide (**3a**) was obtained by refluxing an equimolar mixture of intermediated, **2a** and hydrazine hydrate for 24 h in ethanol as per the reported method [12]. For the synthesis of series two oxadiazoles (**4h-n**,) the initial step involved the synthesis of ethyl[(2,6-dimethylphenyl)amino]-acetate (**2b**) by stirring a mixture of 2,6-xylidine (**1**) and ethylbromoacetate in ethanol and sodium acetate (trihydrate) for 6 h at 80°C, and in the subsequent step, an equimolar mixture of intermediate, **2b** and hydrazine hydrate was refluxed for 22 h in ethanol to afford the synthesis of 2-[(2,6-dimethylphenyl)amino]acetohydrazide (**3b**) [13]. The final compounds, *N*-(2,6-dimethylphenyl)-5-aryl-1,3,4-oxadiazol-2-amine analogues (**4a-g**)/*N*-(2,6-dimethylphenyl)[5-aryl-1,3,4-oxadiazol-2-yl]methyl amine analogues (**4h-n**) were synthesized by refluxing, an equimolar amount of 2,6-dimethyl phenyl semicarbazide (**3a**)/ 2-[(2,6-dimethylphenyl)-amino]acetohydrazide (**3b**) and aromatic aldehyde in water/ethanol (1: 2 v/v) system for 10-12 h with the addition of 20% mol solution of $NaHSO_3$ [14]. The progress of the reaction was monitored throughout by thin layer chromatography (TLC) using eluent n-hexane/ethylacetate/formic acid (5:4:1), benzene/acetone (8:2) and the spots were visualized in iodine vapour. All these compounds were obtained with satisfactory yields ranging between 58% and 86% after crystallization with ethanol and having sufficient purity as confirmed by microanalysis (elemental analysis). The title compounds (**4a-n**) were further characterized and confirmed by FT-IR, NMR (^{1}H NMR and ^{13}C NMR) and mass spectral data. The elemental analyses (microanalysis) confirmed the purity of the compounds. The FT-IR spectra of the compounds, oxadiazole stretching (C-O-C), C=N stretching and NH stretching was observed ranging between 1247-1259 cm^{-1}, 1509-1517 cm^{-1} and 3202-3219 cm^{-1}, respectively, while the phenolic (Ar-OH) stretching was observed ranging between 3412 and 3419 cm^{-1} bands. The nature and number of protons of the title compounds (**4a-n**) were verified and confirmed by proton nuclear magnetic resonance (^{1}H NMR) based on their chemical shifts, multiplicities (singlet, doublet, and multiplet *etc.*), and coupling constants (*J* values in Hz) in DMSO-d_6 using tetramethyl silane (TMS) as the standard. The ^{1}H NMR spectra of the compounds showed a singlet at δ 2.12-2.19, 3.71-3.85, and 4.09-4.42 ppm, corresponding to the methyl group (CH_3), methoxy group (OCH_3) and methylene (-CH_2-) linkage, respectively. The aromatic protons (ArH) were observed as singlet/doublet/ multiplet at δ 6.27-7.81 ppm. The peaks of aromatic NH (ArNH) and phenolic OH (ArOH) were observed as a singlet at δ 7.63-8.57 and 10.08-11.02 ppm respectively. The nature of carbon atoms was verified and characterized using ^{13}C NMR and the peak of the molecular ion peaks (M^+), and isotopomeric ion $(M+2)^+$ were prominent in the mass spectra.

2.2. Cytotoxicity Evaluation

Eight oxadiazole analogues (**4a-e**, **4g**, **4l**, and **4n**) were evaluated for their cytotoxicity studies on nearly 60 cancer cell lines in one dose assay (10 µM concentration) as per the reported method [15-18]. The cytotoxicity of the tested compounds was calculated as growth percent (GP) and percent growth inhibition (GI) at single high dose at 10 µM drug concentrations. The average GP ranged between 71.97 and



Scheme (1). Synthetic protocol of *N*-(2,6-dimethylphenyl)-5-aryl-1,3,4-oxadiazol-2-amine (**4a–g**).



Scheme (2). Synthetic Protocol of *N*-{[5-aryl-1,3,4-oxadiazol-2-yl]methyl}-2,6-dimethylaniline (**4h-n**).

Table 1. The cytotoxicity activity of oxadiazole analogues (4a-n).

Compound/ NSC Code	Cytotoxicity Evaluation in One Dose Assay at Molar Concentration (10 µM)				
	Mean GP	**Range of GP**	**The Most Sensitive Cell Lines**	**GP**	**% GI**
4a NSC Code 791186	101.89	80.16 to 118.96	SNB 75 (CNS Cancer)	80.16	18.84
			UO-31 (Renal Cancer)	88.80	11.20
			KM12 (Colon Cancer)	89.16	10.84
			NCI-H23 (Non-Small Cell Lung Cancer)	92.40	7.60
4b NSC Code 791183	71.97	19.01 to 111.49	HT29 (Colon Cancer)	**19.01**	**80.99**
			LOX IMVI (Melanoma)	**24.95**	**75.05**
			RPMI-8226 (Leukemia)	36.75	63.25
			M14 (Melanoma)	37.81	62.19
			HCT-15 (Colon Cancer)	39.38	60.62
			SK-MEL-5 (Melanoma)	44.04	55.96
			MDA-MB-231/ATCC (Breast Cancer)	47.03	52.97
			NCI-H460 (Non-Small Cell Lung Cancer)	48.90	51.10
			DU-145 (Prostate Cancer)	52.01	47.99
			NCI/ADR-RES (Ovarian Cancer)	52.88	47.12
			BT-549 (Breast Cancer)	53.43	46.57
			NCI-H226 (Non-Small Cell Lung Cancer)	58.36	41.64
			HOP-62 (Non-Small Cell Lung Cancer)	59.39	40.61
			OVCAR-4 (Ovarian Cancer)	63.06	36.94
			SR (Leukemia)	64.54	35.46
			PC-3 (Prostate Cancer)	65.02	34.98
			A549/ATCC (Non-Small Cell Lung Cancer)	65.63	34.37
			MCF-7 (Breast Cancer)	66.27	33.73
			HOP-92 (Non-Small Cell Lung Cancer)	67.78	32.22
4c NSC Code 791184	98.62	82.05 to 112.70	MDA-MB-231/ATCC (Breast Cancer)	82.05	17.95
			BT-549 (Breast Cancer)	85.07	14.93
			SNB-75 (CNS Cancer)	85.33	14.67
			UACC-62 (Melanoma)	88.53	11.47
4d NSC Code 791185	101.30	83.25 to 127.76	SNB-75 (CNS Cancer)	83.25	16.75
			UO-31 (Renal Cancer)	87.09	12.91
			HOP-92 (Non-Small Cell Lung Cancer)	87.41	12.59
			KM12 (Colon Cancer)	91.29	8.71
4e NSC Code 791187	99.69	82.86 to 123.64	KM12 (Colon Cancer)	82.86	17.14
			OVCAR-5 (Ovarian Cancer)	85.99	14.01
			BT-549 (Breast Cancer)	86.12	13.88
			MDA-MB-231/ATCC (Breast Cancer)	86.49	13.51
4g NSC Code 791188	101.50	91.41 to 120.00	UO-31 (Renal Cancer)	91.41	8.59
			SF-268 (CNS Cancer)	91.73	8.27
			PC-3 (Prostate cancer)	92.78	7.22
			T-47D (Breast Cancer)	93.03	6.97
4h	93.45	89.90 to 97.00	MCF-7 (Breast Cancer)	89.90	10.10
			MDA-MB-231 (Breast Cancer)	97.00	3.00
4i	86.65	67.50 to 105.80	MCF-7 (Breast Cancer)	67.50	32.50
			MDA-MB-231 (Breast Cancer)	105.80	-5.80
4j	78.50	50.90 to 106.10	MCF-7 (Breast Cancer)	50.90	49.10
			MDA-MB-231 (Breast Cancer)	106.10	-6.10
4k	76.30	55.80 to 96.80	MCF-7 (Breast Cancer)	55.80	44.20
			MDA-MB-231 (Breast Cancer)	96.80	3.20
4l NSC Code 791189	98.71	-4.35 to 125.80	HS 578T (Breast Cancer)	**-4.35**	**104.35**
			SNB-75 (CNS Cancer)	77.82	22.18
			UO-31 (Renal Cancer)	85.47	14.53
			HOP-92 (Non-Small Cell Lung Cancer)	88.27	11.73
4m	60.45	36.20 to 84.70	MCF-7 (Breast Cancer)	36.20	63.80
			MDA-MB-231 (Breast Cancer)	84.70	15.30
4n NSC Code 791190	93.02	65.11 to 122.78	UO-31 (Renal Cancer)	65.11	34.89
			NCI-H522 (Non-Small Cell Lung Cancer)	72.77	27.23
			RPMI-8226 (Leukemia)	77.90	22.10
			MDA-MB-231/ATCC (Breast Cancer)	79.70	20.30

GP = Growth percent; GI = Growth inhibition; The compound **4f** was not evaluated for cytotoxicity; The compound having GP ≤32%, against particular cell lines is supposed to be active and marked as bold figure.

101.89 percent. The cytotoxicity of compounds **4a** (mean GP = 101.89), **4c** (mean GP = 98.62), **4d** (mean GP = 101.03), **4e** (mean GP = 99.69) and **4g** (mean GP = 101.50) was less and inconsequential. Similarly the cytotoxicity of compounds **4l** (mean GP = 98.71) and **4n** (mean GP = 93.02) is inconsequential, however compound **4l** showed lethal effect on HS 578T (breast cancer) with percent GI of 104.35 while compound **4n** showed higher sensitivity towards UO-31 (renal cancer) with percent GI of 34.89. Compound **4b** showed significant cytotoxicity and was found to have highly sensitivity towards colon cancer (HT29 and HCT-15; %GI 80.99 and 60.62 respectively), melanoma (LOX IMVI, M14, and SK-MEL-5; %GI 75.05, 62.19 and 55.96 respectively), leukemia (RPMI-8226 and SR; %GI 63.25 and 35.46 respectively), breast cancer (MDA-MB-231/ATCC, BT-549, and MCF-7; %GI 52.97, 46.57 and 33.73 respectively), non-small cell lung cancer (NCI-H460, NCI-H226, HOP-62, A549/ATCC and HOP-92; %GI 51.10, 41.64, 40.61, 34.37 and 32.22 respectively), prostate cancer (DU-145, and PC-3; %GI 47.99 and 34.98 respectively), and ovarian cancer (NCI/ADR-RES and OVCAR-4; %GI 47.12 and 36.94 respectively). Five oxadiazole analogues (**4h-k** and **4m**) were evaluated for their cytotoxicity on two breast cancer cell lines (MCF-7 and MDA-MB-231) according to sulforhodamine B assay as per the reported method [19, 20]. The compounds **4i**, **4j**, **4k**, and **4m** showed significant anticancer activity against MCF-7 (breast cancer cell line) with GIs of 32.50, 49.10, 44.20, and 63.80 at 10 μM drug concentrations, respectively. The compound having GP ≤32% (*i.e.* GIs ≥68%) was considered to be significant in terms of cytotoxicity towards that particular human cancer cell line and this is marked in bold figures in Table **1** [21]. The growth curve of five compounds at four different drug concentrations (0.1, 1.0, 10.0 and 100.0 μM) is shown in Fig. (**2a**) (MCF-7) and Fig. (**2b**) (MDA-MB-231). Further three dose related parameters LC_{50}, TGI and GI_{50} were calculated for five compounds. The compounds **4k** and **4m** showed significant cytotoxicity with GI_{50} of 35.9 and 34.5 μM, respectively against MCF-7 and GI_{50} of 73.0 and 72.4 μM, respectively against MDA-MB-231 (Table **2**). The LC_{50} and TGI for all these compounds (**4h-j**, **4l** and **4m**) were found to be >100 μM. The imagery of growth control on breast cancer cell lines for some of the compounds (**4k** and **4m**) having significant cytotoxicity among the five compounds is shown in Fig. (**3**). The cytotoxicity of compound **4b** and standard drug Imatinib on different cancer cell lines in the form of percent GIs was comparatively studied. The cytotoxicity data of imatinib was taken from the NCI database compound ID NSC 759854 for comparison study [22]. Compound **4b** showed superior cytotoxicity than that of the imatinib on nearly 45 human cancers cell lines out of 52 cell lines in common (Fig. **4**). In the present report, the cytotoxicity of compound **4n** (mean GP = 93.02) having methylene linkage (-CH_2-) was found to be slightly more than compound, **4g** (mean GP = 101.50). Similarly, the percent GIs compounds, **4b** and **4h** on MCF-7 (breast cancer cell line) were found to be 33.73 and 10.10 percent, respectively [23]. It was found that the introduction of methylene (-CH_2-) linkage altered the biological profile, however not necessarily increased the biological activity. Further investigation is required by adding more methylene linkage (-CH_2-) and comparing more cytotoxic data to establish this fact. The structure activity relationship (SAR) was established with the cytotoxicity screening results showing the significance of 4-chloro substitution on phenyl ring attached to the oxadiazole ring, followed by 4-methoxy, 4-hydroxy-3-methoxy, and 3,4-dimethoxy, substitutions on phenyl ring. The order of cytotoxicity was observed as 4-Cl > 4-OCH_3 > 4-OH-3-OCH_3 >3,4-$(OCH_3)_2$.

All these compounds (**4a-n**) were docked at colchicine binding site of tubulin enzyme considered as an attractive active site for the above class of compounds [24, 25]. The anticancer effect of the oxadiazole analogues (**4a-n**) correlated with molecular docking studies. The hydrophobic active site of colchicine binding site includes Lys254, Cys241, Asn248, Lys352, Ala316, Val315, Meth259, Leu248, Ala250 and Ala317 residues. Binding mode analysis through Glide XP protocol suggested a few key points about the present study [26]. A careful analysis of the study provided essential information that the binding mode of compound **4b** was found to be entirely opposite to that all other compounds. A hydrogen bond was found between the NH of compound, **4b** and carbonyl oxygen of Thr353 (bond length = 3.05Å). The van der Waals (vdw) score of all other compounds was found to be higher than compound **4b**. Simultaneously, the H-bond effect exhibited by compound **4b** was found to be greater than that of the remaining compounds (**4a** and **4c-n**). The hydrophilicity of compound **4b** was another

Table 2. LC_{50}, TGI, and GI_{50} of oxadiazole analogues against MCF-7 and MDA-MB-231 cancer cell lines.

Compound	Cytotoxicity Activity (μM)					
	MCF-7			MDA-MB-231		
	LC_{50}	TGI	GI_{50}	LC_{50}	TGI	GI_{50}
4h	>100	>100	61.9	>100	>100	>100
4i	>100	>100	53.1	>100	>100	>100
4j	>100	>100	49.3	>100	>100	>100
4l	>100	85.2	35.9	>100	>100	73.0
4m	>100	>100	34.5	>100	>100	72.4
ADR	82.9	2.7	<0.1	>100	39.6	<0.1

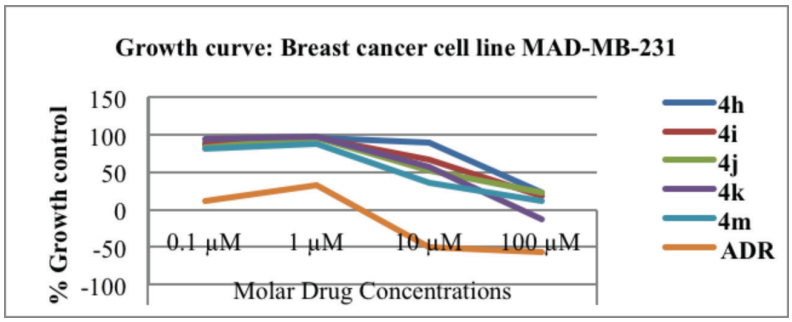


Fig. (2a). Growth control of oxadiazoles on MCF-7 at molar drug concentrations.

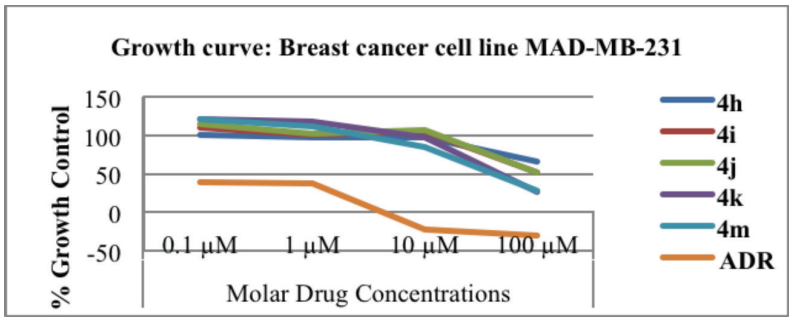
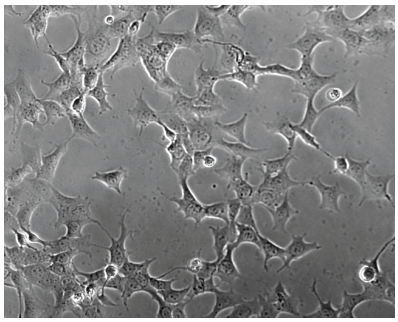
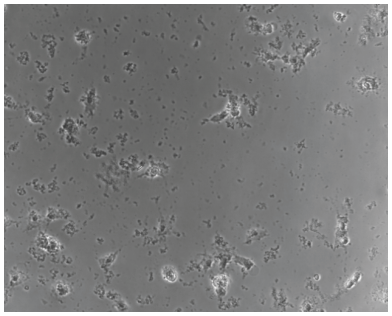


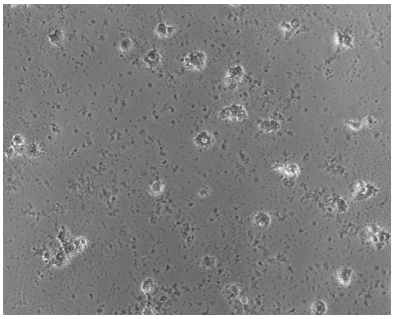
Fig. (2b). Growth control of oxadiazoles on MDA-MB-231 at molar drug concentrations.



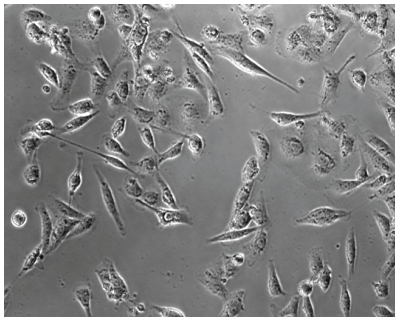
MCF-7 (Control)



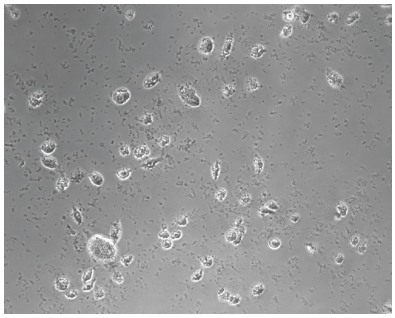
MCF-7; Compound **4j** (GI_{50} = 35.9 µM)



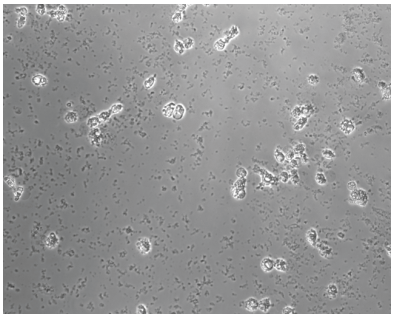
MCF-7; Compound **4l** (GI_{50} = 34.5 µM)



MDA-MB-231 (Control)



MDA-MB-231; Compound **4j** (GI_{50} = 73.0 µM)



MDA-MB-231; Compound **4l** (GI_{50} = 72.4 µM)

Fig. (3). The images of growth control on cancer cell lines (MCF-7 and MDA-MB-231).

parameter that might play a major role and made it most effective when compared to the rest of the compounds (**4a** and **4c-n**). Compound **4n** exhibited similar H-bond interaction to that of the compound **4b**, but the binding mode was found to be diverse from active one (**4b**). The binding mode of compound **4b** is shown in Fig. (**5**).

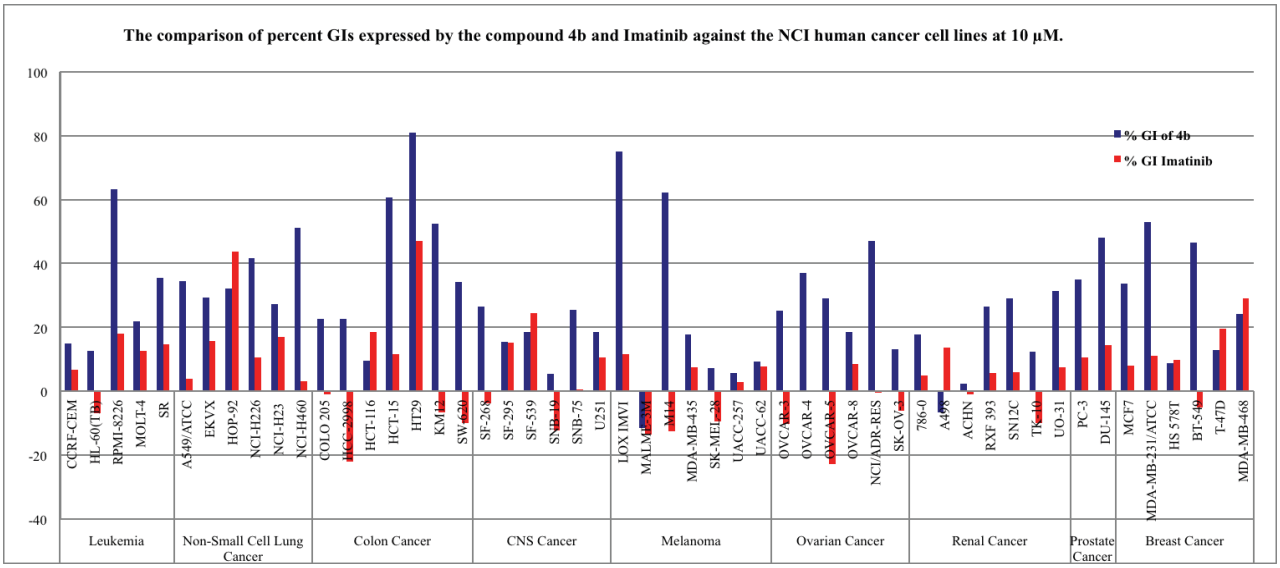


Fig. (4). The comparative study of cytotoxicity of compound **4b** and Imatinib in terms of percent GIs at 10 µM.

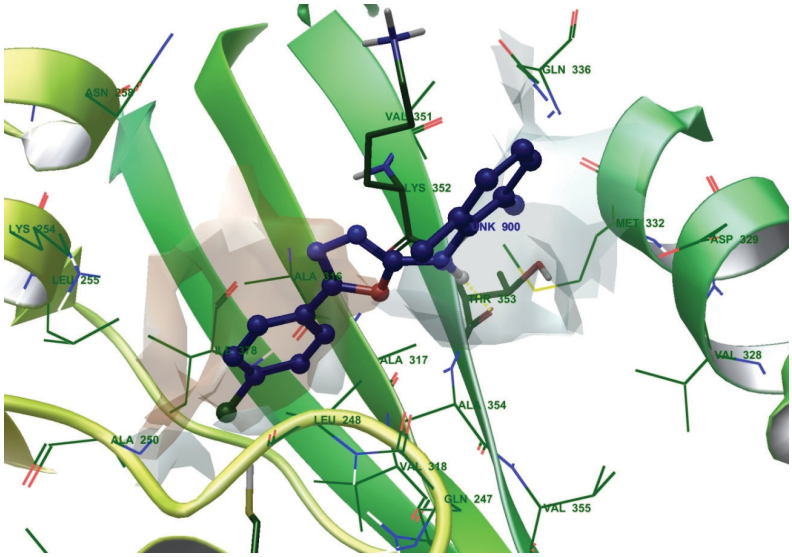


Fig. (5). The molecular docking pose of the compound **4b** at the colchicine binding site.

CONCLUSION

Two new series of fourteen oxadiazole analogues were prepared in satisfactory yields. All these compounds were confirmed by modern analytical techniques using FT-IR, NMR and mass spectral data followed by their cytotoxicity studies as per the standard protocol (NCI US protocol and sulforhodamine B assay) reported elsewhere. *N*-(2,6-Dimethylphenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazol-2-amine (**4b**) showed promising cytotoxic activity on cancer cell lines. The cytotoxicity of the compound, **4b** was found to be significantly better than that of the standard drug imatinib. The information conveyed herein could be significant in further design and discovery of cytotoxic drugs with improved efficacy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article. Supplementary information contains full experimental detail, ^{1}H NMR, ^{13}C NMR spectra, mass spectra and cytotoxicity data.

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