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SYNTHESIS, CHARACTERIZATION AND CYTOTOXIC EVALUATION OF 5-[4-(1H-IMIDAZOL-1-YL)PHENYL]-3-(2,4,6-TRIMETHYLPHENYL)-4,5-DIHYDRO-1,2-OXAZOLE DERIVATIVES BY USING MTT ASSAY METHOD

Gondu Eswara Rao[1,2]*, S. A. Rahaman[3] and A. Prameela Rani[4]

[1]Research Scholar, School of Pharmaceutical Sciences, JNTUK, Kakinada- 533003.
[2]Assistant Professor, Vignan Pharmacy College, Vadlamudi post, Chebrolu Mandal, Guntur District. AP. 522 213. India.
[3]Principal & Professor, Nirmala College of Pharmacy, Atmakur Village, Mangalagiri Mandal, Guntur Dt, A.P - 522 503.
[4]Principal & Professor, ANU College of Pharmaceutical Science, Nagarjuna Nagar, ANU, Guntur- 530 003, (A.P), India.

***Corresponding Author: Gondu Eswara Rao**

Research Scholar, School of Pharmaceutical Sciences, JNTUK, Kakinada- 533003.

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ABSTRACT

The isoxazoline derivatives were synthesized from chalcone as intermediate compound. the chalcones were reacted with hydroxyl amine in presence of glacial acetic acid and sodium acetate to form cyclic compound isoxazoline derivatives and the structures were confirmed by spectral evidence. The compounds were tested for cytotoxic evolution by MTT assay method. . In these test compounds, The compound IS-02, (45-[4-(1H-imidazol-1-yl)phenyl]-3-(3,4,5-trimethyl phenyl)- 4,5-dihydro-1,2-oxazole 15±2 µg/ml, 18±1 µg/ml,12±1 µg/ml against the Breast cancer (MDA MB, Colon cancer (HT-29), Prostate cancer(DU-145)

KEYWORDS: Isoxazoline derivatives, urea, cytotoxicity, MTT assay method.

INTRODUCTION

Heterocyclic compounds are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, and antibiotics.[1,2] Hence, they have attracted considerable attention in the design of biologically active molecules[3,4] and advanced organic chemistry.[5,6] Also in the family of heterocyclic compounds nitrogen containing Heterocyclic compounds are an important in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes.[7] However, the current review intends to focus on the significance of isoxazole class of antimicrobial agents, anti oxidant agents along with clinical and in vitro applications of this class of compounds to facilitate the development of more potent and effective antimicrobial agents, anti oxidant derivatives Isoxazole belongs to the class of 1, 2-oxazole having a remarkable number of applications and have been demonstrated to be very versatile building block in organic synthesis.[8] Various substituted isoxazoles were reported to possess a wide range of pharmacological activities such as anti-inflammatory, analgesic,[9-11] hypoglycemic,[12] antibacterial,[13] antiviral[14] and HIVinhibitory activity.[15] A group of antibiotics, containing isoxazole ring includes Oxacillin, Cloxacillin, Dicloxacillin and Flucloxacillin, Sulfamethaxazole and Sulfafurazole.

Experimental work

MATERIALS AND METHODS

2*E*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-one, hydroxyl amine, sodium acetate, glacial acetic acid conc. HCl , DMSO, all the reagents were purchased analytical grade. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded in the indicated solvent on Bruker WM 400 MHz spectrometer with TMS as internal standard. Infrared spectra were recorded in KBr on Perkin-Elmer AC-1 spectrophotometer. Column chromatography was performed on silica gel (Merck, 60-120 mesh).

General method of preparation[16]

A mixture of chalcone, (2*E*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-3-phenylprop-2-en-1-one (0.02 mol), hydroxylamine hydrochloride (0.02 mol) and catalytic amount of sodium acetate in ethanol (25 ml) was refluxed for 6 h. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed and recrystallized from ethanol. Finally the compound synthesized namely 5-[4-(1*H*-imidazol-1-

yl)phenyl]-3-(phenyl)-4,5-dihydro-1,2-oxazole derivatives. The completion of the reaction was monitored by TLC. Similarly various isoxazole derivatives IS 1-10were prepared.

Chemical reaction

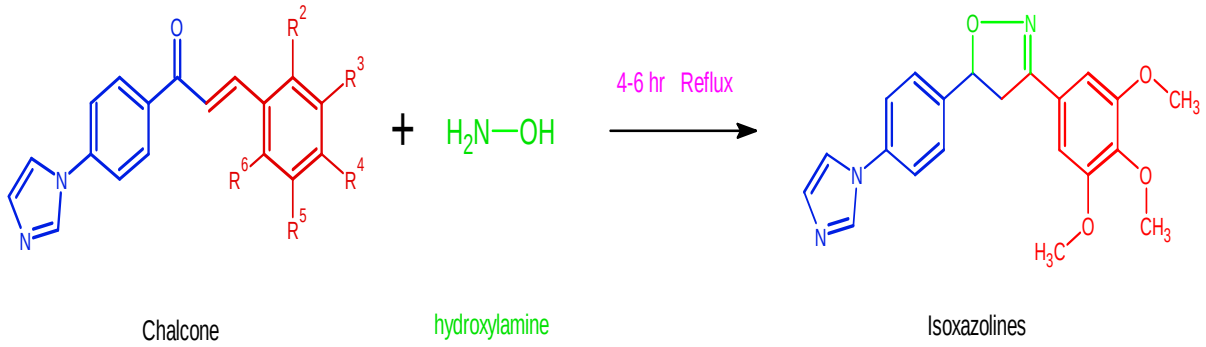
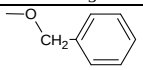
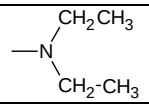


Table1: list of aldehydes.

Chalcone	Radicals				
	R_2	R_3	R_4	R_5	R_6
IS 01	-O-CH_3	-H	-O-CH_3	-H	-O-CH_3
IS 02	-H	-O-CH_3	-O-CH_3	-O-CH_3	-H
IS 03	-H	-H	-S-CH_3	-H	-H
IS 04	-H	-H	-CF_3	-H	-H
IS 05	-H	-H		-H	-H
IS 06	-CF_3	-H	-H	-H	-H
IS 07	-Cl	-H	-H	-H	-F
IS 08	-H	-H		-H	-H
IS 09	-H	-H	-C_2H_5	-H	-H
IS 10	-OH	-H	-H	-H	-H

Biological evolution of compounds

Based on the literature, chalcones were reported to possess antimicrobial activity, anti oxidant, anti inflammatory, analgesic, anti cancerous, etc. Therefore the present work performs the anti microbial, anti oxidant activities.

CYTOTOXICITY STUDIES[17]

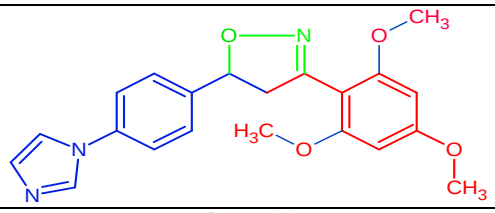
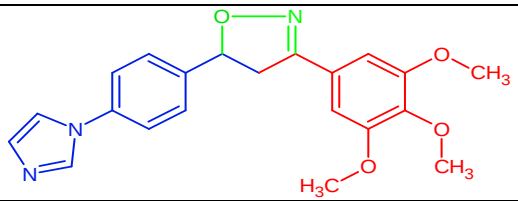
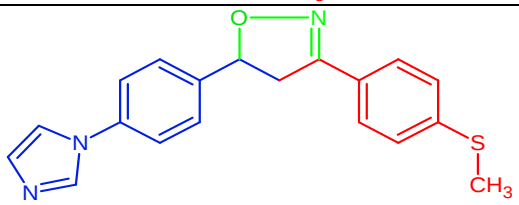
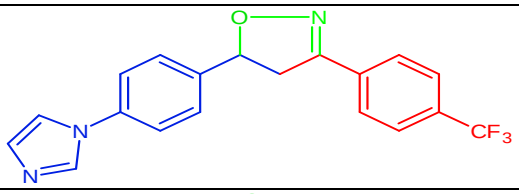
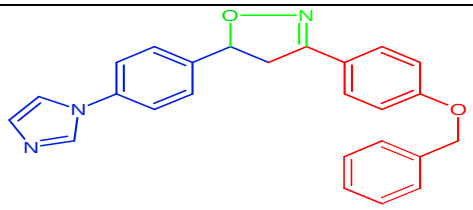
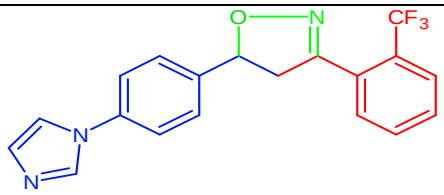
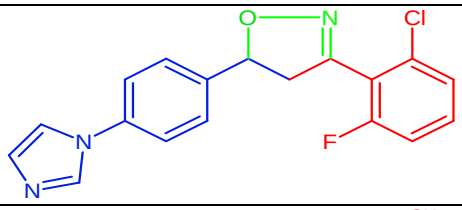
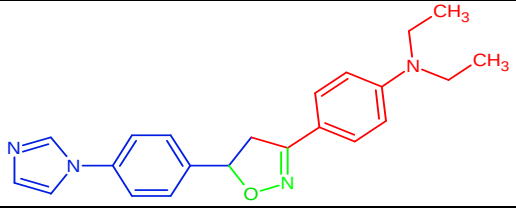
The *in vitro* cyto toxicity of the test compounds (**IS_1-IS_{10})** were performed based on MTT assay method on Breast cancer (MDA MB, Colon cancer (HT-29), Prostate cancer(DU-145). The cell lines were obtained from National Centre for Cell Science (NCCS), Pune, India. Methotrexate was used as reference drug for comparison. Assay was performed in triplicate for three independent determinations. The cytotoxicity was expressed as IC_{50} (µg/mL) which is the concentration of the compound that inhibited proliferation rate of the tumour cells by 50% as compared to the control untreated cells. IC_{50} values were determined from the plot: % inhibition versus concentration.

$$\% \text{ inhibition at the given concentration} = \frac{1 - (\text{Absorbance average})}{(\text{Control absorbance average})} \times 100$$

IC_{50}=Inv. log(50-c) / m; c and m derived from y=mx+c of plot of % inhibition Vs log C. the results were tabulated.

RESULTS AND DISCUSSION

Table 2: Physical data of compounds.

Compound code	Compound Structure	Molecular Formula	Relative Molecular Mass (RMM)	Melting Point (°C)	Yield (%)
IS 01		$C_{21}H_{21}N_3O_4$	379.4	134-137	85
IS 02		$C_{21}H_{21}N_3O_4$	379.4	137-139	84
IS 03		$C_{19}H_{17}N_3OS$	335.4	133-136	78
IS 04		$C_{19}H_{14}F_3N_3O$	357.3	141-146	85
IS 05		$C_{25}H_{21}N_3O_2$	395.4	134-135	87
IS 06		$C_{19}H_{14}F_3N_3O$	357.3	155-157	94
IS 07		$C_{18}H_{13}ClFN_3O$	341.7	135-156	89
IS 08		$C_{22}H_{24}N_4O$	360.4	145-146	84

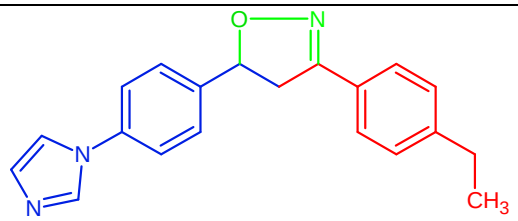
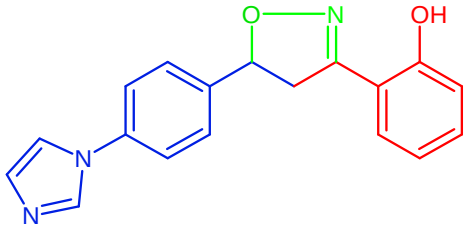
IS 09		$C_{20}H_{19}N_3O$	317.3	148-149	86
IS 10		**$C_{18}H_{15}N_3O_2$**	305.3	145-147	84

Table 3: Elemental Compositions.

Compound		C	H	N	O	S	Cl	F
IS 01	%Calculated	66.48	5.58	11.08	16.87	-	-	-
	%Found	66.47	5.54	11.10	16.85	-	-	-
IS 02	%Calculated	66.48	5.58	11.08	16.87	-	-	-
	%Found	66.45	5.61	11.11	16.83	-	-	-
IS 03	%Calculated	68.03	5.11	12.53	4.77	9.56	-	-
	%Found	68.07	5.09	12.51	4.75	9.52	-	-
IS 04	%Calculated	63.86	3.95	11.76	4.48	-	-	15.95
	%Found	63.82	3.94	11.77	4.51	-	-	15.93
IS 05	%Calculated	75.93	5.35	10.63	8.09	-	-	
	%Found	75.95	5.37	10.60	8.11	-	-	-
IS 06	%Calculated	63.86	3.95	11.76	4.48	-	-	15.95
	%Found	63.82	3.94	11.75	4.50	-	-	15.92
IS 07	%Calculated	63.26	3.83	12.29	4.68	-	10.37	5.56
	%Found	63.29	3.81	12.31	4.70	-	10.39	5.53
IS 08	%Calculated	73.31	6.71	15.54	4.44	-	-	-
	%Found	73.30	6.74	15.51	4.47	-	-	-
IS 09	%Calculated	75.69	6.03	13.24	5.04	-	-	-
	%Found	75.71	6.07	13.21	5.03	-	-	-
IS 10	%Calculated	70.81	4.95	13.76	10.48	-	-	-
	%Found	70.80	4.97	13.79	10.45	-	-	

Table 4: Spectral data of compounds.

Compound	IR, NMR data
PR-01	C=O,str. – 1660.76cm^{-1} ;C=C, str. – 1602.33cm^{-1}; C-O-N- 1246 cm^{-1} ;C=N 1605 cm^{-1} ; N-H stretching :3365.01 cm^{-1} , C-H stretching: 3105 cm^{-1} ,C-H stretching:3048.5 cm^{-1} , C-H stretching: 2936.16 cm^{-1}, C-C stretching:1583.83 cm^{-1},C-N stretching: 1461.77cm^{-1} C-N stretching: 1371.05 cm^{-1}, C-N stretching:1318.09 cm^{-1} :(H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 6.08-7.57 (6H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 3.83 (9H, s, 3-OCH_3)
PR-02	C=O,str. – 1661.12cm-1 ,C=C str. – 1588.75cm-1 C-O str. – 828.23cm-1; C-O-N- 1248cm^{-1} ;C=N1610 cm^{-1} ; N-H stretching : 3364.71 cm^{-1} , C-H stretching:3364 cm^{-1} C-H stretching: 3119.04 cm^{-1} , C-H stretching: 2937.74 cm^{-1} C-C stretching: 2834.04 cm^{-1} ,C-N stretching: 1587.08 cm^{-1} ,C-N stretching: 1486.59 cm^{-1} ,C-N stretching: 1420.91 cm^{-1}:H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 6.95-7.36 (6H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 3.83 (9H, s, 3-OCH_3)
PR-03	C=O: str. – 1657.87cm-1 C=C str. – 1600.46 cm-1 C-S str. – 1333.18 cm-1; C-O-N- 1252 cm^{-1} ;C=N 1610 cm^{-1} ; N-H stretching :3404 cm^{-1} , C-H stretching: 3144.43 cm^{-1} C-H stretching :3051.37 cm^{-1} , C-H stretching : 2926.41 cm^{-1}, C-C stretching:1588.82 cm^{-1} ,C-N stretching: 1491.32 cm^{-1} ,C-N stretching: 1491.32 cm^{-1},C-N stretching:1426.08 cm^{-1} H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.29-7.73 (8H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 2.53 (3H, s, -CH_3)

PR-04	C=O,str. – 1661.12cm-1 ,C=C str. – 1588.75cm-1 C-O str. – 828.23cm-1; C-O-N- 1258 cm^{-1} ;C=N 1610 cm^{-1} ; N-H stretching : 3379.04 cm^{-1} , C-H stretching:2971.04 cm^{-1} C-H stretching : 2922.0 cm^{-1} , C-H stretching: 2866.04 cm^{-1} C-C stretching: 1603.2 cm^{-1} ,C-N stretching: 1455.99 cm^{-1} ,C-N stretching: 1325.03 cm^{-1} : H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.29-7.96 (8H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline)
PR-05	C=O: str. – 1657.87cm-1 C=C str. – 1600.46 cm-1 C-O str. – 1333.18 cm-1; C-O-N- 1256 cm^{-1} ;C=N 1610 cm^{-1} ; N-H stretching : 3330.60 cm^{-1} , C-H stretching: 3115.98 cm^{-1} C-H stretching: 3034 cm^{-1} , C-H stretching: 2931.65 cm^{-1} C-C stretching: 1595.88 cm^{-1} ,C-N stretching: 1451.59 cm^{-1} ,C-N stretching: 1422.70 cm^{-1} ,C-N stretching: 1347.88 cm^{-1}, H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.06-7.91 (13H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 5.16 (2H, s, -OCH_2-)
PR-06	C=O: str.- 1649.38cm-1 C=C str. – 1598.05cm-1 C-O str.- 1376.52cm-1; C-O-N- 1260cm^{-1} ;C=N 1600 cm^{-1} ; N-H stretching :3368.84 cm^{-1} , C-H stretching: 2971.98 cm^{-1} C-H stretching: 2834.04 cm^{-1} , C-H stretching: 11587.08 cm^{-1},C-C stretching: 1486.59 cm^{-1},C-N stretching: 1420.91 cm^{-1} ,C-N stretching: 1370.02 cm^{-1} ,C-N stretching:1326.02 cm^{-1}, H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.29-7.26 (8H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline)
PR-07	C=O: str.- 1649.38cm-1 C=C str. – 1598.05cm-1 C-O str.- 1376.52cm-1; C-O-N- 1255 cm^{-1} ;C=N 1608 cm^{-1} ; N-H stretching : 3077.88 cm^{-1} , C-H stretching: 3116.5 cm^{-1} C-H stretching: 3025.22 cm^{-1} , C-H stretching: 2969.61 cm^{-1} C-C stretching: 1599.52 cm^{-1} ,C-N stretching: 1479.27 cm^{-1} ,C-N stretching: 1370.88 cm^{-1} ,C-N stretching: 1308.03 cm^{-1} H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.24-7.36 (7H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline)
PR-08	C=O,str. – 1661.12cm-1 ,C=C str. – 1588.75cm-1 C-O str. – 828.23cm-1; C-O-N- 1250 cm^{-1} ;C=N 1600 cm^{-1} ; N-H stretching : 3364.71 cm^{-1} , C-H stretching:3364 cm^{-1} C-H stretching: 3119.04 cm^{-1} , C-H stretching: 2937.74 cm^{-1} C-C stretching: 2834.04 cm^{-1} ,C-N stretching: 1587.08 cm^{-1} ,C-N stretching: 1486.59 cm^{-1} ,C-N stretching: 1420.91 cm^{-1}:H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 6.81-7.65 (8H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 1.15 (6H, t, 2-CH_3), 3.41 (4H, q, 2-CH_2-)
PR-09	C=O: str. – 1657.87cm-1 C=C str. – 1600.46 cm-1 C-O str. – 1333.18 cm-1; C-O-N- 1260 cm^{-1} ;C=N 1600 cm^{-1} ; N-H stretching :3404 cm^{-1} , C-H stretching: 3144.43 cm^{-1} C-H stretching :3051.37 cm^{-1} , C-H stretching :2926.41 cm^{-1}, C-C stretching:1588.82 cm^{-1} ,C-N stretching: 1491.32 cm^{-1} ,C-N stretching: 1491.32 cm^{-1},C-N stretching:1426.08 cm^{-1} H^1 NMR(CHCl3): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 7.29-7.78 (8H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 1.25 (3H, t, -CH_3), 2.60 (2H, q, -CH_2-)
PR-10	C=O: str.- 1658.95cm-1 C=Cs tr.- 1594.05cm-1 C-O str.- 756.23cm^{-1}; C-O-N- 1260 cm^{-1} ;C=N 1600 cm^{-1} ; N-H stretching : 3392.75 cm^{-1} , C-H stretching: 3123.41 cm^{-1} C-H stretching: 2942.19 cm^{-1} , C-H stretching: 2829.8 cm^{-1} C-C stretching: 1602.2 cm^{-1} ,C-N stretching: 1486.58 cm^{-1},C-N stretching :1587.10 cm^{-1} :H^1 NMR($CHCl_3$): 7.15 (1H, s, C-2 of imidazole), 7.16 (1H, d, C-4 of imidazole), 6.92-7.52 (7H, m, Ar-H), 3.85 (2H, d, C-4 of isoxazoline), 5.93 (1H, t, C-5 of isoxazoline), 5.35 (1H, s, -OH)

Cytotoxic results

S.No	Compound code	Cell line		
		Breast cnacer (MDA MB)	Colon cancer (HT-29)	Prostate cancer(DU-145)
1	IS-01	24±1	38±2	28±2
2	IS-02	18±2	23±1	20±1
3	IS-03	76±1	84±2	54±2
4	IS-04	178±1	156±1	117±1
5	IS-05	32±1	40±1	36±2
6	IS-06	195±2	174±1	154±1
7	IS-07	150±1	138±2	97±1
8	IS-08	44±1	62±1	46±2
9	IS-09	122±2	124±2	73±1

10	IS-10	108±1	106±1	65±2
11	Methothrexate	12 ± 1	9 ± 1	5 ± 1

Data presented as mean ± SD (n=3). All the compounds and the standard dissolved in DMSO, diluted with culture medium containing 0.1% DMSO. The control cells were treated with culture medium containing 0.1% DMSO. NA- No Activity (i.e $IC_{50} > 200$ µg/mL)

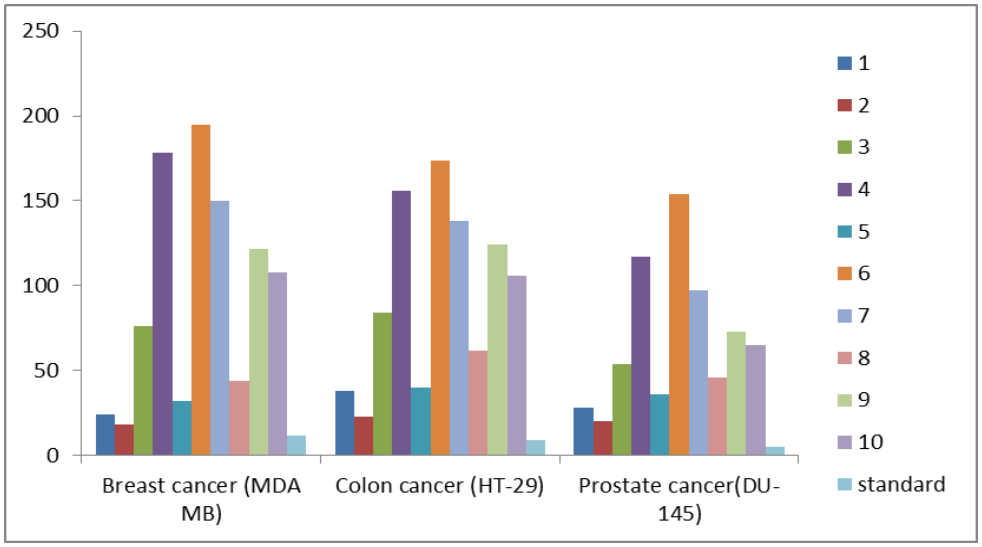


Fig: 1: Graphical representation of the cancerous activity.

DISCUSSION

Based on the results conclude that the compounds shows better anti cancerous activity different cell lines like Breast cancer (MDA MB, Colon cancer (HT-29), Prostate cancer(DU-145). In all of these compounds, compound-02,1-[-[4-(1H-imidazol-1-yl)phenyl]-3-(3,4,5-trimethyl phenyl)- 4,5-dihydro-1,2-oxazole was found to be 18±2 µg/ml, ,23±1 µg/ml,20±1 µg/ml respectively and compound - 01, 5-[4-(1H-imidazol-1-yl)phenyl]-3-(2,4,6-trimethylphenyl)-4,5-dihydro-1,2-oxazolewas found to be 24±1 µg/ml,, 38±2 µg/ml,28±2 µg/ml respectively.

CONCLUSION

The compound IS-02, 5-[4-(1H-imidazol-1-yl)phenyl]-3-(3,4,5-trimethyl phenyl)- 4,5-dihydro-1,2-oxazole was found to be 18±2 µg/ml, ,23±1 µg/ml,20±1 µg/ml against the Breast cancer (MDA MB, Colon cancer (HT-29), Prostate cancer(DU-145).

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