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SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 6-(SUBSTITUTED BENZYLIDENE)-2-METHYLTHIAZOLO [2,3-b] OXAZOL-5(6H)-ONE AS POTENTIAL ANTICANCER AGENTS

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ABSTRACT: Heterocyclic systems are a part of a large number of drugs and biologically relevant molecules. The chemistry and biological study of heterocyclic compounds have been an interesting field for a long time, and oxazole is one such moiety that has gained attention in recent times due to its increasing importance in the field of medicinal chemistry. Oxazole is a doubly unsaturated five-membered ring having one oxygen atom at position 1 and nitrogen at position 3 separated by a carbon atom in between. The substituted pattern in oxazole derivatives play a vital role in delineating the biological activities like antimicrobial, antifungal, antitubercular, anticancer. The utility of oxazole as intermediates for the synthesis of new chemical entities in medicinal chemistry has been increased in the past few years. Oxazole is an important heterocyclic nucleus having a wide spectrum of biological activities, which drew the attention of researchers around the globe to synthesis various oxazole derivatives and screen them for their various pharmacological activities like antimicrobial activity, antitubercular activity, anticancer activity. 6-(substitutedbenzylidene)-2-methylthiazolo [2, 3-*b*] oxazol-5(6*H*)-one were prepared by dissolving 1- hydroxypropan-2-one and KSCN in ethanol and screened for anticancer activity. A series of 6-(substituted benzylidene)-2-methylthiazolo [2, 3-*b*] oxazol-5(6*H*)-one O13-24 were tested against anticancer activity. Their activity was evaluated by MTT assay method against cervical HeLa (ME 180) cells. The results of studies indicates that, among the compounds, O13, O14, O15, O16, O17, O21, O23, and O24 displayed significant activity. The purity of the compounds was characterized by means of IR, ^{1}HNMR mass spectral, and elemental analysis. Of these compounds, O14 and O24 showed enhanced activity.

INTRODUCTION: Heterocyclic chemistry is the branch of science which involves synthesis, properties, and applications of heterocycles. Heterocyclic systems containing mainly nitrogen, sulfur, and oxygen atom [1] constitute a huge set of compounds of biological and medicinal concern.

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A massive number of heterocyclic systems, which include mainly five and six-membered compounds, symbolize a different group of molecular scaffolds. All the heterocyclic compounds have a great interest in medicinal and Pharmaceutical chemistry.

Among the heterocyclic compounds, oxazole is a well-known privileged structure in medicinal chemistry [2], having various biological activities. Oxazole is an important pharmacophore in modern drug discovery, and one of the main resources for medicinal research and the nucleus contains a five-membered ring. Oxazole is heterocyclic compounds which contain a five-membered ring

and analogs can be suitably modified by the introduction of different aromatic and heterocyclic moieties to exhibit a wide variety of biological activities [3]. This nucleus is present in many marketed drugs as well as these nucleus substituted derivatives have long been regarded as possessing principal pharmacophore used in the treatment of various diseases [4]. Because of its excellent stability, bioavailability, biological activity it became a prime focus in the medicinal research field. They exemplify the biological significance and beneficial efficacy of some heterocyclic derivatives used as antiamoebic [5], anthelmintic, anticancer activity [6], antioxidant activity [7] anti-inflammatory [7], anti-microbial activity [8], antibacterial [9-11], antifungal [12] anti-infective agents [13], cytotoxic activity [14], protein-kinase [15], antiviral [16], analgesic and anticonvulsant [17], antiproliferative activity [18], anticancer activity [19]. Thus, the learning of chemistry and the biological importance of heterocyclic compounds has been an exciting area of research for an extended occasion.

Current literature has explored the biological consequence of an assortment of structural derivatives of heterocyclic compounds. Cancer is a serious worldwide health threat, killing almost seven million people a year. Human cancer comprises more than 200 different diseases together; they account for about one-fifth of all deaths worldwide. Apart from the already marketed drugs, there are many others being investigated for their promising activity against several malignancies. In particular, anticancer research has been capitalizing on the intrinsic versatility and dynamic core scaffold of these compounds. Nevertheless, as for any other promising anticancer drugs, heterocyclic compounds do not come without shortcomings. It is important to study heterocyclic active compounds and families and their main applications in medicine [20]. Carcinoma type of cancer largely manifests in the population than sarcoma [21].

The aim is to develop research interest to develop new potent molecules that act against cancer with slightest side effects.

MATERIALS AND METHODS:

Materials: Synthetic starting material, reagents, and solvents were of analytical reagent grade or of the highest quality commercially available and were purchased from Aldrich Chemical Co., Merck Chemical Co., and were dried when necessary. The melting points were taken in an open capillary tube and are uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited Bengaluru, India). Proton (1H) NMR spectra (Bruker 400 NMR spectrometer Mumbai, India) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupol mass spectrometer (Shimadzu GC MS QP 5000, Chennai, India), and microanalyses were performed using a vario EL V300 elemental analyzer (Elemental Analysensysteme GmbH Chennai, India). The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF254, 200 mesh) aluminum plates (E. Merck) using ethyl acetate: benzene (1:3) and visualized in UV chamber. IR, 1H-NMR, mass spectral data and elemental analyses were consistent with the assigned structures.

Synthetic Procedure: Hydroxypropan-2-one (1.00 g,) and KSCN (1.07 g,) were dissolved in ethanol (30 mL). After cooling at -5 °C, 12M aqueous HCl (1.10 mL,) was carefully added, and the mixture was stirred under reflux for 24 h, and then it was cooled by using crushed ice. After extraction with ethyl acetate (3 × 25 mL), the combined organic phase was successively washed with saturated aqueous sodium bicarbonate, water, and finally, it was dried using Magnesium sulphate. After filtration and concentration under reduced pressure, the residue was collected to afford compound 1. A mixture of 5-methyloxazole-2(3H)-thione 1 chloro-acetic acid (0.006 mol), sodium acetate anhydrous (6 g) in glacial acetic acid and acetic acid anhydride (120 mL, 3:1) was refluxed for 12 min.

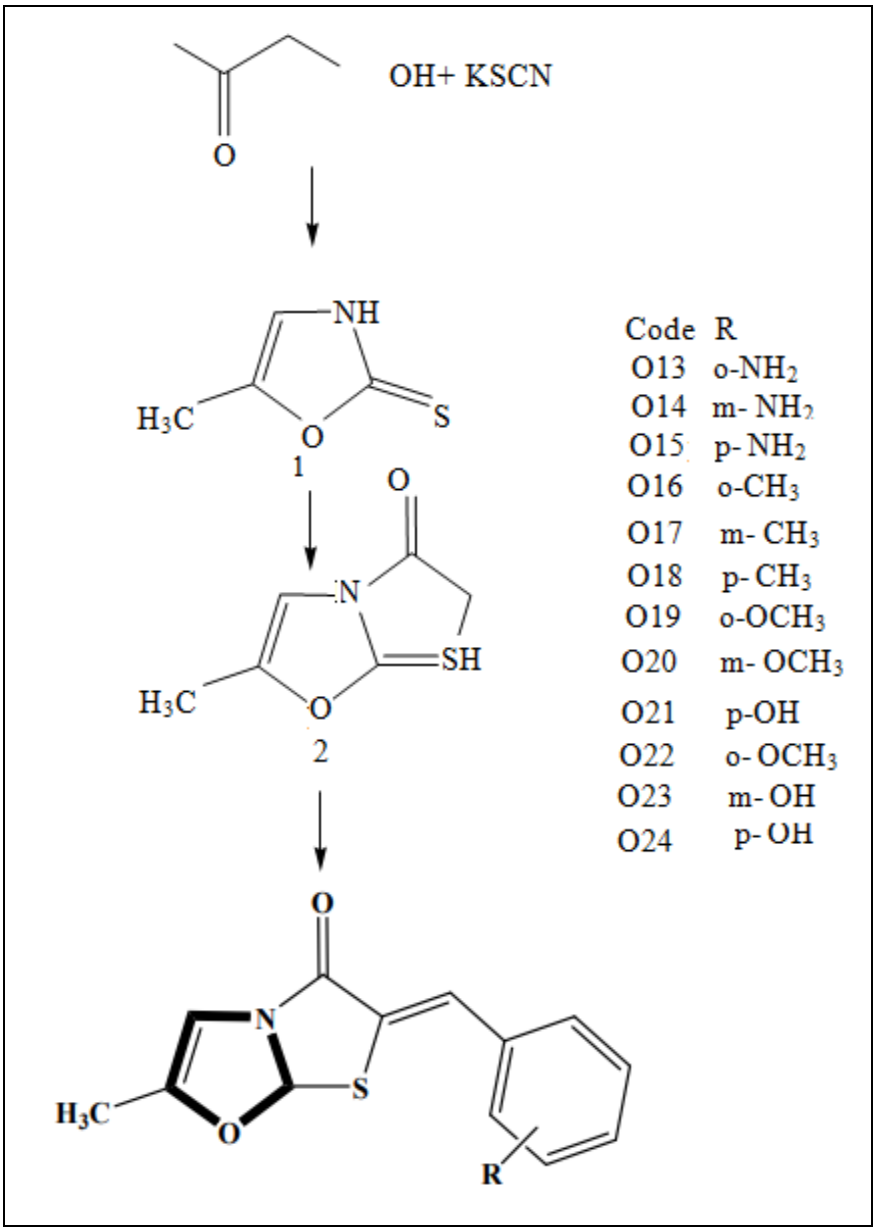
Further, an equimolecular amount (0.006 mol) of the appropriate aromatic aldehydes was added. The reaction mixture was refluxed for 2 h, allowed to cool and was poured into crushed ice water; the formed precipitate was filtered off, dried, and recrystallized by using ethanol to give the corresponding 6-(substitutedbenzylidene)-2-methylthiazolo [2,3-b]oxazol-5(6H)-one O13-24.

Anticancer Screening:

MTT Test: The MTT assay was performed by using human cervical carcinoma cell line (HeLa),

and it was obtained from the National Cancer Institute. The cells were cultured under the standard conditions in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS) 100 IU/ml of Penicillin and 100 mg/ml of Streptomycin. The cells were incubated at 37 °C under 5% CO for 24 h. The anticancer activity on HeLa cell line by sulforhodamine B assay as earlier reported method [22]. After the 1 × 04 cells were seeded into a 96-well plate and maintained in the DMEM medium at 37 °C under 5% CO for 24 h, the cells were treated with the synthesized compounds at various concentrations for 24 h. Cisplatin was used as a standard. The absorbance was measured at 570 nm by a microplate reader. The percentages of the growth inhibition (G) were determined by the following method [23, 24].

Scheme for- 6-benzylidene-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one:



SCHEME 1: Scheme for- 6-benzylidene-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one

Spectral Data of the Synthesized Data:

6-(2-aminobenzylidene)-2-methylthiazolo[2, 3-*b*] oxazol-5(6*H*)-one (O13): The compound was obtained as a solid; Yield: 61%; m.p. 162-164 °C.

IR cm^{-1}: 3447 (1^{o}N-H), 3027 (Ar-CH), 2911 (Alkane-CH), 1736 (C=O), 1338 (C-N), 1277 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.84 (s, 1H; Alkene-CH), 6.79-7.49 (m, 4H; Ar-H), 6.36 (s, 2H; Oxazole-CH), 5.47 (s, 2H; -NH_2), 2.27 (s, 3H; -CH_3).

EI-MS m/z (M+): 260 (calcd for $C_{13}H_{12}N_2O_2S$; 260.31).

Anal. calcd for $C_{13}H_{12}N_2O_2S$; C, 59.98; H, 4.65; N, 10.76; found: C, 59.94; H, 4.63; N, 10.72.

6- (3-aminobenzylidene)-2-methylthiazolo[2,3-*b*] oxazol-5(6*H*)-one (O14): The compound was obtained as a solid; Yield: 61%; m.p. 169-171 °C.

IR cm^{-1}: 3350 (1^{o}N-H), 3034 (Ar-CH), 2918 (Alkane-CH), 1662 (C=O), 1352 (C-N), 1294 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.81 (s, 1H; Alkene-CH), 6.72-7.41 (m, 4H; Ar-H), 6.31 (s, 2H; Oxazole-CH), 5.43 (s, 2H; -NH_2), 2.23 (s, 3H; -CH_3).

EI-MS m/z (M+): 260 (calcd for $C_{13}H_{12}N_2O_2S$; 260.31).

Anal. calcd for $C_{13}H_{12}N_2O_2S$; C, 59.98; H, 4.65; N, 10.76; found: C, 59.95; H, 4.64; N, 10.73.

6- (4-aminobenzylidene)-2-methylthiazolo[2,3-*b*] oxazol-5(6*H*)-one (O15): The compound was obtained as a solid; Yield: 61%; m.p.197-199 °C.

IR cm^{-1}: 3446 (1^{o}N-H), 3025 (Ar-CH), 2916 (Alkane-CH), 1735 (C=O), 1336 (C-N), 1275 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H; Alkene-CH), 6.74-7.45 (m, 4H; Ar-H), 6.34 (s, 2H; Oxazole-CH), 5.45 (s, 2H; -NH_2), 2.24 (s, 3H; -CH_3).

EI-MS m/z (M+): 260 (calcd for $C_{13}H_{12}N_2O_2S$; 260.31).

Anal. calcd for $C_{13}H_{12}N_2O_2S$; C, 59.98; H, 4.65; N, 10.76; found: C, 59.97; H, 4.65; N, 10.74.

6-(2-methylbenzylidene)-2-methylthiazolo[2,3-*b*] oxazol-5(6*H*)-one (O16): The compound was obtained as a solid; Yield: 64%; m.p.142-144 °C.

IR cm^{-1}: 3027 (Ar-CH), 2911 (Alkane-CH), 1725 (C=O), 1331 (C-N), 1275 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.77 (s, 1H; Alkene-CH), 6.71-7.42 (m, 4H; Ar-H), 6.31 (s, 2H; Oxazole-CH), 2.29 (s, 6H; -CH_3).

EI-MS m/z (M+): 259 (calcd for $C_{14}H_{13}NO_2S$; 259.32).

Anal. calcd for $C_{14}H_{13}NO_2S$; C, 64.84; H, 5.05; N, 5.40; found: C, 64.88; H, 5.05; N, 5.43.

6-(3-methylbenzylidene)-2-methylthiazolo[2,3-*b*] oxazol-5(6*H*)-one (O17): The compound was obtained as a solid; Yield: 61%; m.p. 177-179 °C.

IR cm^{-1}: 3122 (Ar-CH), 3012 (Alkane-CH), 1654 (C=O), 1351 (C-N), 1250 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.79 (s, 1H; Alkene-CH), 6.71-7.41 (m, 4H; Ar-H), 6.31 (s, 2H; Oxazole-CH), 2.29 (s, 6H; -CH_3).

EI-MS m/z (M+): 259 (calcd for $C_{14}H_{13}NO_2S$; 259.32).

Anal. calcd for $C_{14}H_{13}NO_2S$; C, 64.84; H, 5.05; N, 5.40; Found: C, 64.86; H, 5.06; N, 5.42.

6-(4-methylbenzylidene)-2-methylthiazolo[2,3-*b*] oxazol-5(6*H*)-one (O18): The compound was obtained as a solid; Yield: 69%; m.p. 182-184 °C.

IR cm^{-1}: 3029 (Ar-CH), 2919 (Alkane-CH), 1737 (C=O), 1334 (C-N), 1271 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.87 (s, 1H; Alkene-CH), 6.94-7.47 (m, 4H; Ar-H), 6.54 (s, 2H; Oxazole-CH), 2.14 (s, 6H; -CH_3).

EI-MS m/z (M+): 259 (calcd for $C_{14}H_{13}NO_2S$; 259.32).

Anal. calcd for $C_{14}H_{13}NO_2S$; C, 64.84; H, 5.05; N, 5.40; found: C, 64.82; H, 5.02; N, 5.46.

6- (2-methoxybenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O19): The compound was obtained as a solid; Yield: 65%; m.p.147-149 °C

IR cm^{-1}: 3120 (Ar-CH), 2933 (Alkane-CH), 1726 (C=O), 1342 (C-N), 1271 (Ether C-O-C).

^{1}H NMR ($CDCl_3$) δ (ppm): 7.71 (s, 1H; Alkene-CH), 6.62-7.51 (m, 4H; Ar-H), 6.56 (s, 2H; Oxazole-CH), 4.29 (s, 3H; -OCH_3), 2.10 (s, 3H; -CH_3).

EI-MS m/z (M+): 275 (calcd for $C_{14}H_{13}NO_3S$; 275.32).

Anal. calcd for $C_{14}H_{13}NO_3S$; C, 61.07; H, 4.76; N, 5.09; found: C, 61.05; H, 4.75; N, 5.07.

6- (3-methoxybenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O20): The compound was obtained as a solid; Yield: 66%; m.p. 151-153 °C.

IR cm^{-1}: 3011 (Ar-CH), 2911 (Alkane-CH), 1722 (C=O), 1333 (C-N), 1276 (Ether C-O-C).

^1H NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H; Alkene-CH), 6.64-7.57 (m, 4H; Ar-H), 6.54 (s, 2H; Oxazole-CH), 4.27 (s, 3H; -OCH_3), 2.17 (s, 3H; -CH_3).

EI-MS m/z (M+): 275 (calcd for $C_{14}H_{13}NO_3S$; 275.32).

Anal. calcd for $C_{14}H_{13}NO_3S$; C, 61.07; H, 4.76; N, 5.09; found: C, 61.07; H, 4.73; N, 5.05.

6- (4-methoxybenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O21): The compound was obtained as a solid; Yield: 71%; m.p. 167-169 °C.

IR cm^{-1}: 3029 (Ar-CH), 2917 (Alkane-CH), 1739 (C=O), 1331 (C-N), 1277 (Ether C-O-C).

^1H NMR ($CDCl_3$) δ (ppm): 7.84 (s, 1H; Alkene-CH), 6.69-7.59 (m, 4H; Ar-H), 6.59 (s, 2H; Oxazole-CH), 4.34 (s, 3H; -OCH_3), 2.29 (s, 3H; -CH_3).

EI-MS m/z (M+): 275 (calcd for $C_{14}H_{13}NO_3S$; 275.32).

Anal. calcd for $C_{14}H_{13}NO_3S$; C, 61.07; H, 4.76; N, 5.09; found: C, 61.04; H, 4.71; N, 5.01.

6- (2-hydroxybenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O22): The compound was obtained as a solid; Yield: 64%; m.p. 171-173 °C.

IR cm^{-1}: 3634 (Phenolic O-H), 3013 (Ar-CH), 2921 (Alkane-CH), 1726 (C=O), 1329 (C-N), 1262 (Ether C-O-C).

^1H NMR ($CDCl_3$) δ (ppm): 8.42 (s, 1H; Phenolic-OH), 7.61 (s, 1H; Alkene-CH), 6.47-7.25 (m, 4H; Ar-H), 6.32 (s, 2H; Oxazole-CH), 2.27 (s, 3H; -CH_3).

EI-MS m/z (M+): 261 (calcd for $C_{13}H_{11}NO_3S$; 261.3).

Anal. calcd for $C_{13}H_{11}NO_3S$; C, 59.76; H, 4.24; N, 5.36; found: C, 59.73; H, 4.22; N, 5.33.

6- (3-hydroxybenzylidene)-2-methylthiazolo[2,3-*b*]oxazol-5(6*H*)-one (O23): The compound was obtained as a solid; Yield: 71%; m.p. 162-164 °C.

IR cm^{-1}: 3385 (Phenolic O-H), 3176 (Ar-CH), 2901 (Alkane-CH), 1668 (C=O), 1321 (C-N), 1227 (Ether C-O-C).

^1H NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H; Phenolic-OH), 7.32 (s, 1H; Alkene-CH), 6.61-7.27 (m, 4H; Ar-H), 6.37 (s, 2H; Oxazole-CH), 2.21 (s, 3H; -CH_3).

EI-MS m/z (M+): 261 (calcd for $C_{13}H_{11}NO_3S$; 261.3).

Anal. calcd for $C_{13}H_{11}NO_3S$; C, 59.76; H, 4.24; N, 5.36; found: C, 59.76; H, 4.24; N, 5.34.

6-(4-hydroxybenzylidene)-2-methylthiazolo[2, 3-*b*]oxazol-5(6*H*)-one (O24): The compound was obtained as a solid; Yield: 64%; m.p. 171-173 °C.

IR cm^{-1}: 3612 (Phenolic O-H), 3015 (Ar-CH), 2927 (Alkane-CH), 1729(C=O), 1321 (C-N), 1263 (Ether C-O-C).

^1H NMR ($CDCl_3$) δ (ppm): 8.31 (s, 1H; Phenolic-OH), 7.66 (s, 1H; Alkene-CH), 6.41-7.21 (m, 4H; Ar-H), 6.33 (s, 2H; Oxazole-CH), 2.24 (s, 3H; -CH_3).

EI-MS m/z (M+): 261 (calcd for $C_{13}H_{11}NO_3S$; 261.3).

Anal. calcd for $C_{13}H_{11}NO_3S$; C, 59.76; H, 4.24; N, 5.36; found: C, 59.75; H, 4.23; N, 5.35.

RESULTS AND DISCUSSION:

Chemistry: The chemical structure of chlorogenic acid was confirmed by IR, 1H-NMR, 13C-NMR, and mass spectroscopy. In 6-(substituted-benzylidene)-2-methylthiazolo[2,3-b]oxazol-5(6H) one O1-12, Ar- CH stretching band appears in the range of 3150-3050 cm^{-1} and the appearance of a strong intensity band in the IR spectra of Alkane-CH in the range of 3000-2850 cm^{-1}. The appearance of 1740-1705, 1300-1000 cm^{-1} range was attributable to ester C=O, Ether C-O-CH, respectively.

Anticancer Screening:

Results of anti-cancer screening of 6-benzylidene-2- methylthiazolo [2,3-b] oxazol-5(6*h*)-one:

TABLE 1: ANTI-CANCER SCREENING OF THE SYNTHESIZED COMPOUNDS O13-O24

Compound	Cell line	Compound Concentration (µ mol L^{-1}) % Growth Inhibition				IC_{50}
		5	12.5	25	40	
O13		51.55	69.43	79.63	90.16	19.46
O14		62.22	79.36	89.11	97.18	13.42
O15		52.25	74.23	86.32	92.42	19.23
O16		56.25	78.32	89.42	96.42	19.15
O17		54.2	66.42	78.31	89.13	16.34
O18		9.4	12.12	18.32	19.42	>100
O19	HeLa	8.22	9.34	14.21	16.42	>100
O20		6.43	8.21	12.51	15.22	>100
O21		44.12	64.11	74.26	88.42	19.46
O22		2.41	4.12	6.21	10.24	>100
O23		51.22	71.36	83.34	89.41	15.12
O24		54.11	62.12	71.37	90.28	11.37
Cisplatin		69.21	79.42	86.32	99.31	24.13

Anticancer Screening:

Discussion of Anti-cancer Screening of– 6-benzylidene- 2- methylthiazolo [2, 3-b] oxazol-5(6h)-one: The title compounds 6-(substituted benzylidene)- 2- methylthiazolo [2, 3-*b*] oxazol-5(6*H*)-one O13- 24 were screened for their Anti-cancer activity against cervical HeLa (ME 180) cells and this activity is done at the Karnataka college of pharmacy by using the MTT assay which was determined by previously reported methods. The different concentrations (5, 12.5, 25, and 40 µmol L^{-1}) were used to test Anti-cancer activity. The concentration required for 50% inhibition of cell viability (IC) was calculated and compared with the reference drug Cisplatin, and the results are given in **Table 1**.

The data from **Table 1** reveals that the compounds O18, O19, O20, and O22 were inactive at all the concentrations used. The compounds O13, O14, O15, O16, O17, O21, O23, and O24 show significant activity towards the HeLa (ME 180) cell lines and also showed equipotent activity with the control Cisplatin. Of these, the compounds O24, O14, which has a *para*-substituted hydroxyl group and *meta* substituted amino group, showed enhanced activity. It was considered the most potent analog and found to have significant Anti-cancer activity. It is also observed that the derivatives having the hydroxyl group at either the *meta* or the *para* positions were active, while, those derivatives having the methyl group at either of these positions were inactive.

The result revealed that substituted compounds of benzylidene ring, except the methyl-substituted compound, showed significant anticancer activity.

CONCLUSION: The compounds O24, O14, which has a para-substituted hydroxyl group and meta substituted amino group, were considered as the most potent analog and found to have significant anticancer activity.

The synthesized analogs will generate a good impact to the chemists and research scholars for further investigation in this field of oxazole and selectively being the influence of electronic effects as well as the change in basic nucleus possessing significant activity.

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CONFLICTS OF INTEREST: The authors declare that there is no conflicts of interest.

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