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Research Article

SYNTHESIS AND ANTICANCER ACTIVITY OF 4-BENZYLIDENE-2- PHENYLOXAZOL-5(4*H*)-ONE DERIVATIVES

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ABSTRACT

A series of oxazolone derivatives (**1-14**) have been synthesized as potential anti cancer agent. The newly synthesized compounds were evaluated for cytotoxicity in the A549 cell line by SRB (Sulphorhodamine B) assay. Compound **1** was found to be most potent with 25 µg/ ml CTC_{50} value. Titled compounds have been prepared by the condensation of benzoylglycine with aromatic aldehydes in the presence of ethanol, acetic anhydride and sodium acetate. The newly synthesized compounds were characterized by FTIR, ^{1}HNMR, Mass spectroscopy and Elemental analysis.

Keywords:- Oxazolone, Cytotoxicity, A549 cell, SRB assay, Synthesis.

INTRODUCTION

4-Arylidene-2-phenyl-5(4*H*) oxazolones are important synthons for the synthesis of several biologically active molecules. Oxazolones that are internal anhydrides of acyl amino acids make an important class of five membered heterocycles. These are highly versatile intermediates used for the synthesis of several organic molecules including amino acids, peptides, antimicrobial[1], and antitumor[8-10] compounds.

These compounds exhibit a constellation of biological[13] activities e.g. analgesic[5], anti-inflammatory[7], antimicrobial, antibacterial[1-3], neuroleptic[12], anticancer, antifungal[4-5] etc. The tumor inhibiting properties of oxazolones pose special interest and have been found to arise from their effect on malignant cell proliferation, tumor angiogenesis and /or on the established neoplastic vasculature. In contrast to the majority of conventional cytotoxic agents the oxazolones are characterized by a low propensity to interact with DNA, which to a great extent eliminates the risk of mutagenicity and carcinogenicity common in various chemotherapeutics. This favorable toxicological profile has solicited intensive research with synthetic oxazolones in view of developing novel, patient friendly antineoplastic agent.

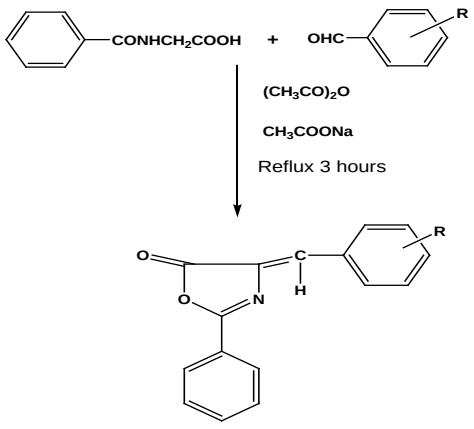
Anti cancer activity

All the newly synthesized compounds were evaluated for anticancer activity against A549 cell line. The anticancer activity was carried out by Sulforhodamine B (SRB) assay in which cell count adjusted to 1.0x 10^5 cells/ml using medium containing 10% new born calf serum. Determination of cell viability was performed by Sulforhodamine B which is a bright pink aminoxanthene dye with two sulfonic groups. Under mild acidic conditions, SRB binds to protein basic amino acid residues in Trichloro acetic acid (TCA) fixed cells to provide a sensitive index of cellular protein content that is linear over a cell density range of at least two orders of magnitude. Colour development in SRB assay is rapid, stable and visible. The developed colour was measured over a broad range of visible wavelength in either a spectrophotometer or a 96 well plate reader[13]. The results of anticancer screening against A549 cell line are shown in Table-1.

Table 1: Anticancer activity data of compound 1-14

Compound No.	CTC_{50} Value	Activity
1.	25 µg/ ml	+++
2.	80 µg/ ml	++
3.	33 µg/ ml	+++
4.	40 µg/ ml	+++
5.	156 µg/ ml	+
6.	179 µg/ ml	+
7.	140 µg/ ml	+
8.	38 µg/ ml	+++
9.	190 µg/ ml	+
10.	95 µg/ ml	++
11.	187 µg/ ml	+
12.	149 µg/ ml	+
13.	48 µg/ ml	+
14.	>200 µg/ ml	-

The cytotoxicity is classified a follows: very strong toxic ++++, CTC_{50} <10 µg/ml; strong +++, CTC_{50}11-40 µg/ml; moderate ++, CTC_{50} 41-100 µg/ml; weak +, CTC_{50}101-200 µg/ml and little or no activity, CTC_{50}>200 µg/ml.



Scheme 4: Benzylidene-2-phenyloxazol-5(4*H*)-one derivatives (1-14)

Table 2: Characterization data of compounds (1-14)

Comp. No.	R	M.P (°C)	R_f*value	Yield (%)	log P	Parachor (cm^3)
1.	H	165-166	0.88	72	3.37	552.3 ± 8.0 cm^3
2.	2-OH	138-139	0.85	69	2.98	557.9 ± 8.0 cm^3
3.	3-OH	144-145	0.80	77	2.98	557.9 ± 8.0 cm^3
4.	4-OH	172-173	0.72	58	2.98	557.9 ± 8.0 cm^3
5.	2-Cl	152-153	084	61	3.93	581.1 ± 8.0 cm^3
6.	3-Cl	158-159	0.86	65	3.93	581.1 ± 8.0 cm^3
7.	4-Cl	189-190	0.75	67	3.93	581.1 ± 8.0 cm^3
8.	3-OCH_3	101-102	0.82	73	3.25	602.5 ± 8.0 cm^3
9.	4-OCH_3	153-154	0.79	78	3.25	602.5 ± 8.0 cm^3
10.	2-NO_2	158-159	0.83	66	2.3	597.7 ± 8.0 cm^3
11.	3-NO_2	161-162	0.74	71	2.3	597.7 ± 8.0 cm^3
12.	4-NO_2	227-228	0.81	68	2.3	597.7 ± 8.0 cm^3
13.	4-F	179-180	0.71	73	3.53	552.4 ± 8.0 cm^3
14.	4-$N(CH_3)_2$	207-208	0.75	69	3.66	648.6 ± 8.0 cm^3

*Ethyl acetate: Pet. Ether (40-60 °C) (3:7)

MATERIALS AND METHODS

Melting points of all derivatives were recorded in open glass capillaries using paraffin bath and are uncorrected. Purity of the compounds were identified by performing Thin Layer Chromatography and visualized by exposure to iodine vapours. ^{1}H NMR spectra performed on a Bruker NMR spectrophotometer 300 MHz using TMS as an internal standard and $CDCl_3$ as a solvent, IR spectrum of compounds in KBr pellets were recorded on a FTIR-8400S spectrophotometer (SHIMADZU), ultraviolet (UV) spectra were recorded on a UV-Visible Spectrophotometer Pharma spec-1700 (SHIMADZU) for ($CHCl_3$), mass spectra were taken on a Shimadzu GC-MS QP-2010 and elemental analysis was performed using Elemental Vario EL III, Carlo-Erba 1108.

General Procedure for the synthesis of compounds (1-14)

Place a mixture of substituted benzaldehydes (0.0125 M), hippuric acid (0.0125 M), acetic anhydride (0.038 M) and anhydrous sodium acetate (0.0125 M) was refluxed with constant shaking for 3 hours. After reflux, the mixture was cooled and 20 ml of absolute ethanol was added slowly and allowed to stand for overnight. The crystallized crude product was filtered, washed with hot water and then with a small volume of ice cold water: methanol (1:1) dried and recrystallized with absolute ethanol. The purity of compounds was observed by TLC (30:70; ethyl acetate: petroleum ether).

4-Benzylidene-2-phenyloxazol-5(4*H*)-one (1):- UV λ_{max} (chloroform): 215 nm (log ε: 4.13). FTIR (KBr) ν: 3080.05 (aromatic C-H str.), 1793.68 (-C=O str.), 1652.88 (-C=N str.), 1550.66 (C=C str.), 1292.22 (C-N str.), 1159.14 (-C-O str.), 690.47 cm^{-1} (Ar-H def. of monosubstituted benzene). ^{1}HNMR ($CDCl_3$) δ : 7.151 (s, 1H, =CH-), 7.260-7.903 ppm (m, 10H, Ar-H). EIMS: m/z (%): 250 (18) $[M+1]^+$, 249 (M^+,100), 221 (15), 116 (9), 105 (27), 89 (21), 77 (37), 63 (11), 51 (32). Elemental analysis: Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62, Found: C, 77.21; H, 4.35; N, 5.60 %.

4-(*o*-Hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one (2):- UV λ_{max} (chloroform): 227 nm (log ε: 4.35). FTIR (KBr) ν: 3565.55 (O-H str.), 3076.25 (aromatic C-H str.), 1793.68 (-C=O str.), 1660.60 (-C=N str.), 1596.95 (C=C str.), 1361.65 (C-O str.) of Ar-OH, 1294.15 (C-N str.), 1159.14 (-C-O str.), 759.90 cm^{-1} (Ar-H def. of ortho disubstituted benzene). ^{1}HNMR ($CDCl_3$) δ : 7.074 (s, 1H, =CH-), 7.231-7.785 (m, 9H, Ar-H), 8.945 ppm (s, 1H, OH) D_2O exchangeable. EIMS: m/z (%): 266 (16) $[M+1]^+$, 265 (M^+, 100), 237 (20), 132 (23), 105 (38), 104 (18), 77 (29), 51 (26). Elemental analysis: Calcd for $C_{16}H_{11}NO_3$: C,72.45; H, 4.18; N, 5.28, Found: C, 77.21; H, 4.15; N, 5.20 %.

4-(*m*-Hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one (3):- UV λ_{max} (chloroform): 231nm (log ε: 4.65). FTIR (KBr) ν: 3548.92 (O-H str.), 3047.32 (aromatic C-H str.), 1797.53 (-C=O str.), 1654.81 (-C=N str.), 1564.31 (C=C str.), 1375.15 (C-O str.) of Ar-OH, 1328.86 (C-N str.), 1161.07 (-C-O str.), 806.19 cm^{-1} (Ar-H def. of meta disubstituted benzene). ^{1}HNMR ($CDCl_3$) δ : 6.891 (s, 1H, =CH-), 7.210-7.738 (m, 9H, Ar-H), 8.831 ppm (s, 1H, OH) D_2O exchangeable. EIMS: m/z (%): 266 (13) $[M+1]^+$, 265 (M^+, 100), 237 (18), 132 (26), 105 (38), 104 (21), 77 (30), 51 (23). Elemental analysis: Calcd for $C_{16}H_{11}NO_3$: C,72.45; H, 4.18; N, 5.28, Found: C, 77.21; H, 4.31; N, 5.50 %.

4-(*p*-Hydroxybenzylidene)-2-phenyloxazol-5(4*H*)-one (4):- UV λ_{max} (chloroform): 236 nm (log ε: 4.19). FTIR (KBr) υ: 3560.05 (O-H str.), 3045.39 (aromatic C-H str.), 1793.68 (-C=O str.), 1654.81 (-C=N str.), 1562.25 (C=C str.), 1363.58 (C-O str.) of Ar-OH, 1325.01 (C-N str.), 1164.92 (-C-O str.), 808.12 cm^{-1} (Ar-H def. of para disubstituted benzene). ^{1}HNMR ($CDCl_3$) δ: 7.081 (s, 1H, =CH-), 7.249-7.681 (m, 9H, Ar-H), 8.851 ppm (s, 1H, OH) D_2O exchangeable. EIMS m/z (%): 266 (18) $[M+1]^+$, 265 (M^+, 100), 237 (25), 132 (20), 105 (44), 104 (14), 77 (31), 51 (22). Elemental analysis: Calcd for $C_{16}H_{11}NO_3$: C,72.45; H, 4.18; N, 5.28, Found: C, 77.29; H, 4.26; N, 5.39 %.

4-(*o*-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (5):- UV λ_{max} (chloroform): 241nm (log ε 4.87). FTIR (KBr) υ: 3055.03 (aromatic C-H str.), 1795.06 (-C=O str.), 1650.95 (-C=N str.), 1550.66 (C=C str.), 1292.22 (C-N str.), 1166.85 (-C-O str.), 756.04 cm^{-1} (Ar-H def. of ortho disubstituted benzene), 692.40 (C-Cl str.). ^{1}HNMR ($CDCl_3$) δ : 6.836 (s, 1H, =CH-), 7.238-7.985 ppm (m, 9H, Ar-H). EIMS: m/z (%): 285 (31), 284 (13) $[M+1]^+$, 283 (M^+, 100), 256 (4), 255 (12), 150 (10), 115 (14), 105 (38), 89 (18), 77 (33), 63 (12), 51 (28). Elemental analysis: Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94, Found: C, 67.71; H, 3.47; Cl, 12.45; N, 4.87 %.

4-(*m*-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (6):- UV λ_{max} (chloroform): 245 nm (log ε: 4.21). FTIR (KBr) υ: 3060.05 (aromatic C-H str.), 1795.60 (-C=O str.), 1650.52 (-C=N str.), 1454.52 (C=C str.), 1290.29 (C-N str.), 1157.21 (-C-O str.), 783.05 cm^{-1} (Ar-H def. of meta disubstituted benzene), 675. 04 (C-Cl str.). ^{1}HNMR($CDCl_3$) δ: 6.904 (s, 1H, =CH-), 7.219-7.923 ppm (m, 9H, Ar-H). EIMS m/z (%): 285 (33), 284 (11) $[M+1]^+$, 283 (M^+, 100), 256 (6), 255 (17), 151 (3), 150 (10), 115 (21), 105 (45), 89 (15), 77 (39), 63 (9), 51 (28). Elemental analysis: Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94, Found: C, 67.67; H, 3.48; Cl, 12.55; N, 4.91 %.

4-(*p*-chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (7):- UV λ_{max} (chloroform): 247 nm (log ε: 4.26). FTIR (KBr) υ: 3030.13 (aromatic C-H str.), 1793.68 (-C=O str.), 1652.88 (-C=N str.), 1552.59 (C=C str.), 1301.86 (C-N str.), 1159.14 (-C-O str.), 827.41 (Ar-H def. of para disubstituted benzene), 692.40 cm^{-1} (C-Cl str.). ^{1}HNMR($CDCl_3$) δ: 7.061 (s, 1H, =CH-), 7.260-7.892 ppm (m, 9H, Ar-H). EIMS m/z (%): 285 (33), 284 (18) $[M+1]^+$, 283 (M^+, 100), 256 (6), 255 (17), 150 (9), 115 (12), 105 (47), 89 (14), 77 (33), 63 (17), 51 (38). Elemental analysis: Calcd for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; Cl, 12.50; N, 4.94, Found: C, 67.69; H, 3.53; Cl, 12.41; N, 4.95 %.

4-(*m*-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (8):- UV λ_{max} (chloroform): 254 nm (log ε: 4.57). FTIR (KBr) υ: 3031.89 (aromatic C-H str.), 1799.46 (-C=O str.), 1652.88 (-C=N str.), 1485.09 (C=C str.), 1282.57 (C-N str.), 1166.85 (-C-O str.), 1041.49 (-C-O str.) of Ar-OCH_3, 773.40 cm^{-1} (Ar-H def. of meta disubstituted benzene).

^{1}HNMR($CDCl_3$) δ : 3.462 (s, 3H, -OCH_3), 6.841 (s, 1H, =CH-), 7.247-7.681 ppm (m, 9H, Ar-H). EIMS m/z (%): 280 (14) $[M+1]^+$, 279 (M^+,100), 251 (15), 146 (22), 116 (19) 105 (58), 89 (28), 77 (48), 63 (18), 51 (37). Elemental analysis: Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.62; N, 5.02, Found: C, 73.20; H, 4.56; N, 5.10 %.

4-(*p*-methoxybenzylidene)-2-phenyloxazol-5(4*H*)-one (9):- UV λ_{max} (chloroform): 252 nm (log ε 4.87). FTIR (KBr) υ: 3039.60 (aromatic C-H str.), 1780.17 (-C=O str.), 1650.95 (-C=N str.), 1512.03 (C=C str.), 1263.29 (C-N str.), 1159.14 (-C-O str.), 1105.14 (-C-O str.) Ar-OCH_3, 830.13 cm^{-1} (Ar-H def. of meta disubstituted benzene). ^{1}HNMR($CDCl_3$) δ : 3.755 (s, 3H, -OCH_3), 6.914 (s, 1H, =CH-), 7.161-7.649 ppm (m, 9H, Ar-H). EIMS m/z (%): 280 (17) $[M+1]^+$, 279 (M^+,100), 251 (18), 146 (17), 116 (22) 105 (51), 89 (28), 77 (48), 63 (14), 51 (35). Elemental analysis: Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02, Found: C, 73.18; H, 4.65; N, 5.08 %.

4-(*o*-nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (10):- UV λ_{max} (chloroform): 249 nm (log ε: 4.51). FTIR (KBr) υ: 3033.22 (aromatic C-H str.), 1794.02 (-C=O str.), 1652.95 (-C=N str.), 1563.33 (C=C str.), 1515.22 (N=O str.) of Ar-NO_2, 1292.29 (C-N str.), 1167.77 (-C-O str.), 775.33 cm^{-1} (Ar-H def. of ortho disubstituted benzene). ^{1}HNMR($CDCl_3$) δ : 7.107 (s, 1H, =CH-), 7.209-7.672 (m, 8H, Ar-H), 8.591-8.728 ppm (d,1H, Ar-H). EIMS m/z (%): 295 (25) $[M+1]^+$, 294 (M^+, 100), 266 (15), 115 (12), 105 (28), 89 (18), 77 (37), 63 (13), 51 (32). Elemental analysis: Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.50, Found: C, 65.35; H, 3.47; N, 9.42 %.

4-(*m*-nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (11):- UV λ_{max} (chloroform): 251 nm (log ε: 3.56). FTIR (KBr) υ: 3050.82 (aromatic C-H str.), 1795.60 (-C=O str.), 1650.95 (-C=N str.), 1562.23 (C=C str.), 1514.02 (N=O str.) of Ar-NO_2, 1292.22 (C-N str.), 1168.78 (-C-O str.), 773.33 cm^{-1} (Ar-H def. of meta disubstituted benzene). ^{1}HNMR($CDCl_3$) δ : 6.971 (s, 1H, =CH-), 7.230-7.621 (m, 7H, Ar-H), 8.201-8.224 ppm (dd, 2H, 2 and 4 Ar-H). EIMS m/z (%): 295 (22) $[M+1]^+$, 294 (M^+, 100), 266 (18), 116 (15), 105 (47), 89 (14), 77 (39), 63 (10), 51 (30). Elemental analysis: Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.48; N, 9.52; O, 21.51, Found: C, 65.37; H, 3.52; N, 9.49; O, 21.45%.

4-(*p*-nitrobenzylidene)-2-phenyloxazol-5(4*H*)-one (12):- UV λ_{max} (chloroform): 246 nm (log ε: 4.36). FTIR (KBr) υ: 3015.15 (aromatic C-H str.), 1789.82 (-C=O str.), 1649.02 (-C=N str.), 1552.59 (C=C str.), 1517.87 (N=O str.) of Ar-NO_2, 1292.15 (C-N str.), 1166.85 (-C-O str.), 771.47 cm^{-1} (Ar-H def. of para disubstituted benzene). ^{1}HNMR($CDCl_3$) δ : 6.884 (s, 1H, =CH-), 7.205-7.629 (m, 7H, Ar-H), 8.201-8.224 ppm (dd, 2H, 3 and 5 Ar-H). EIMS m/z (%): 295 (27) $[M+1]^+$, 294 (M^+, 100), 266 (21), 116 (16), 105 (51), 89 (13), 77 (46), 63 (7), 51 (32). Elemental analysis: Calcd for $C_{16}H_{10}N_2O_4$: C, 65.31; H, 3.43; N, 9.52, Found: C, 65.32; H, 3.48; N, 9.53 %.

4-(*p*-fluorobenzylidene)-2-phenyloxazol-5(4*H*)-one (13):- UV λ_{max} (chloroform): 257 nm (log ε: 4.53). FTIR (KBr) υ: 3058.89 (aromatic C-H str.), 1793.68 (-C=O str.), 1656.74 (-C=N str.), 1593.09 (C=C str.), 1296.08 (C-N str.), 1236.29 (C-F str.), 1159.14 (-C-O str.), 777.26 cm^{-1} (Ar-H def. of para disubstituted benzene). ^{1}HNMR($CDCl_3$) δ : 6.902 (s, 1H, =CH-), 7.278-8.039 ppm (m, 9H, Ar-H). EIMS m/z (%): 268 (21) $[M+1]^+$, 267 (M^+, 100), 239 (22), 134 (18), 116 (16), 105 (54), 89 (13), 77 (48), 63 (21), 51 (37). Elemental analysis: Calcd for $C_{16}H_{10}FNO_2$ C, 71.91; H, 3.77; F, 7.11; N, 5.24, Found: C, 71.89; H, 3.79; F, 7.08; N, 5.27 %.

4-(*p*-dimethylaminobenzylidene)-2-phenyloxazol-5(4*H*)-one (14):- UV λ_{max} (chloroform): 265 nm (log ε: 4.22). FTIR (KBr) υ: 3015.58 (aromatic C-H str.), 2885.09 (-C-H str.) of CH_3, 1760.89 (-C=O str.), 1645.17 (-C=N str.), 1529.45 (C=C str.), 1323.08 (C-N str.), 1161.07 (-C-O str.), 813.90 cm^{-1} (Ar-H def. of meta disubstituted benzene). ^{1}HNMR ($CDCl_3$) δ: 2.848 (s, 6H, -$N(CH_3)_2$), 6.514-6.561 (dd,2H, 3 and 5 Ar-H), 6.901 (s, 1H, =CH-), 7.238-7.614 ppm (m, 7H, Ar-H). Elemental analysis: Calcd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62, Found: C, 77.21; H, 4.35; N, 5.60 %.

CONCLUSION

Oxazolone derivatives were synthesized by Erlenmeyer's synthesis and identify on the basis of melting point range, R_f values, solubility, elemental analysis, UV, FTIR, ^{1}HNMR, MASS spectral data. On the basis of sulforhodamine B (SRB) assay, the anticancer activity is depended upon structure of the compounds. The strong anticancer activity have given by 1, 3, 4, 8 and moderate activity is given by 2, 3. Further weak activity is given by 5, 6, 7, 9, 11, 12, 13 and little activity by 14. When substitution of R with 3-OH, 3-OCH_3, 4-F were produced good anticancer activity as compare to other compounds. While substitution of R with -Cl, -NO_2 and -N $(CH_3)_2$ at different position were decreased the activity. On the basis of study we concluded that benzene ring without substitution is important for anticancer activity.

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