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HYDROGEN PEROXIDE SCAVENGING ACTIVITY OF OXAZOLE DERIVATIVES

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Keywords:

Oxazole, Evaluation, UV, *In-vitro* Anti-oxidant activity, Buffer

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ABSTRACT: The present study is reported the antioxidant activity of oxazole derivatives. Oxazole are five-member heterocyclic ring containing nitrogen and oxygen as a hetero atom. Due to binding with a wide spectrum of receptors and enzymes easily in biological systems through various non-covalent interactions, oxazole-based molecules are becoming a kind of significant heterocyclic nucleus, which have received attention from researchers globally, leading them to synthesize diverse oxazole derivatives. Oxazole have been reported to possess diverse biological activities like antimicrobial, antiviral, anti-inflammatory and anticancer activity. In this research work some heterocyclic like 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one with potent derivatives for 100 ug/ml are 4-(4-methylbenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-7), 4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl)oxazol-5(4*H*)-one (PA-13) and are 4-(5-Oxo)-2- (pyrazin-2-yl) 4(5*H*)-ylidene) methyl) benzonitrile (PA-15) and for 200 ug/ml 4-(4-fluoro benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-4), 4-(4-hydroxy-3-methoxy benzylidene)-2-(pyrazin-2-yl) oxazol-5 (4*H*)-one (PA-8) and 4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-13) shows promising anti-oxidant activities. The method mainly used as hydrogen peroxide radical scavenging activity. Antioxidant scavenging effect of synthesized derivatives also compared with standard Ascorbic acid.

INTRODUCTION: Oxazole is the parent compound for a vast class of heterocyclic compound. These are azoles with oxygen and nitrogen separated by one carbon. Oxazole is a clear colorless liquid. It is polar and weekly basics [1, 2]. Oxazole exhibit interesting chemical reactivity. It undergo reaction with electrophile particularly at nitrogen C_2 and C_5. Nucleophile also reacts with Oxazole at C_2, C_3 and C_5 position. Oxazole also dienophile in dials alder reaction to prepare substituted pyridines [3].

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Antioxidant is a molecule capable of inhibiting the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons from a substance to an oxidizing agent. Oxidation reactions can produce free radicals [4]. In turn; these radicals can start chain reactions. When a chain reaction occurs in a cell, it can cause damage or death. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions.

They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid, oxazole and polyphenols. Antioxidant property concerns with hydroxyl group in aromatic ring. The hydroxyl group gives the hydrogen atom to neutralize the free radical present in the body and shows the potent effect of drug [5, 7]. Thus, the present study was designed to evaluate

the antioxidant activity of oxazole derivatives by hydrogen peroxide method.

MATERIALS AND METHODS: All the reagents and solvents used in the present study were of analytical grade and procured from Loba chemie. Jasco UV Spectrophotometer determined the antioxidant activities and it mainly compared with standard as an ascorbic acid. Hydrogen peroxide radical scavenging method mainly used to determine the percentage scavenging effect.

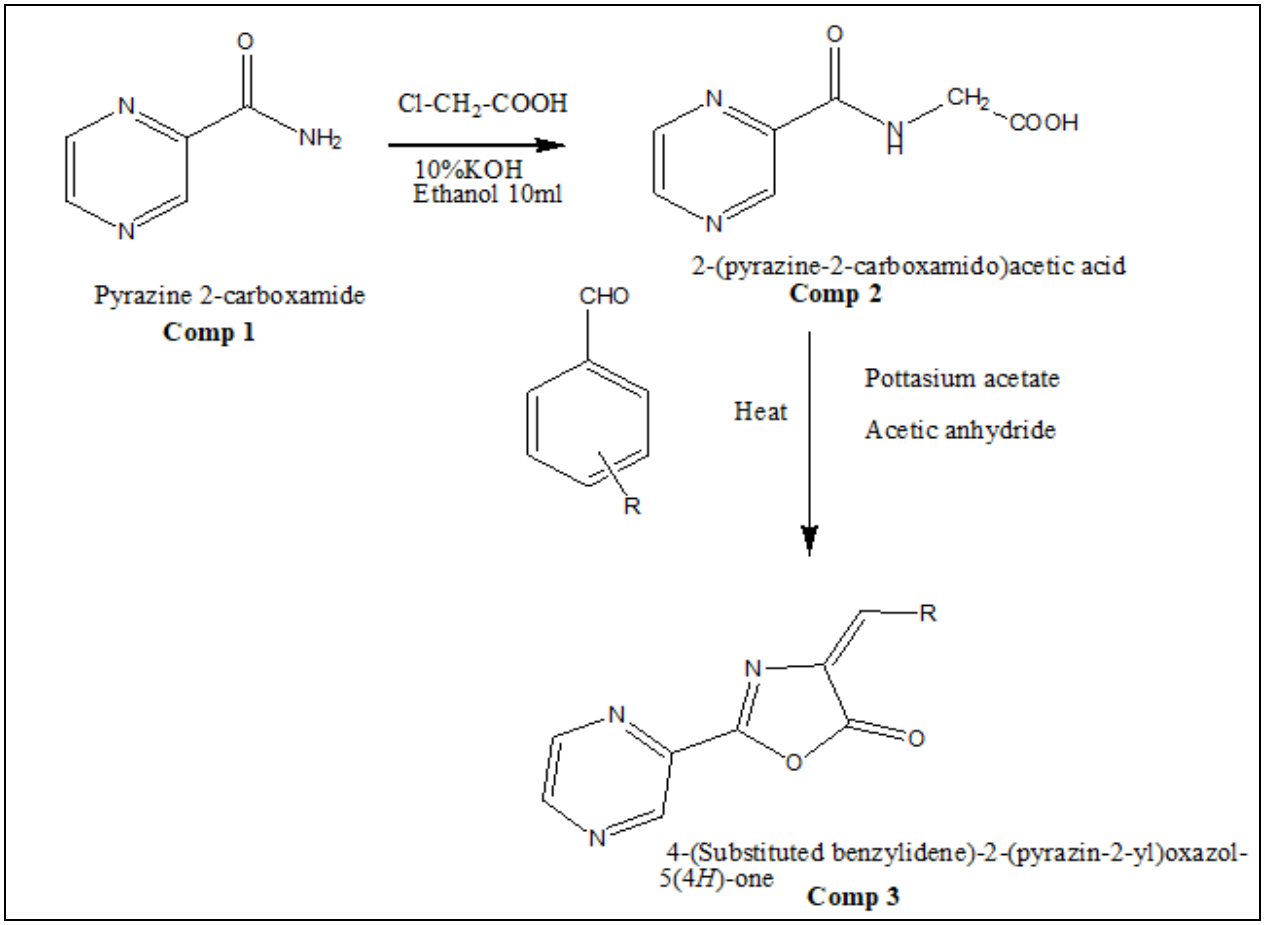


FIG. 1: SCHEME FOR SYNTHESIS OF 4-(SUBSTITUTED BENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4*H*)-ONE DERIVATIVES

Where, R= (PA-2) ph, (PA-3) 2-Cl-ph, (PA-4) 4-Fl-ph, (PA-5) 4-Br-ph, (PA-6) 4-Cl-ph, (PA-7) 4-CH3-ph, (PA-8) 4-OH, 3-OCH3-ph, (PA-9) furan, (PA-10) 4-OCH3-ph, (PA-11) 2-OH-ph, (PA-12) 4-OH-ph, (PA-13) 4-OH, 3-Br and 5-OCH3 ,(PA-14) 3-OH-ph, (PA-15) 4-CN-ph.

The melting point of prepared derivatives was determined by open cup capillary method in a heavy liquid paraffin bath. The melting point shows the compound's purity and pure crystal's definite sharp melting point. After recrystallisation derivatives shows minute changes in melting point. Also the Rf value is characteristic of each compound. Percolated silica gel plates were used for checking the purity of the compound. The solvent system mainly used in specific proportion ethyl acetate: ethanol: acetone: drop of glacial acetic acid (2:1:1) 08, 13

Hydrogen Peroxide Radical Scavenging Activity: 1 ml of (100-200µg/ml) test drug/standard (Ascorbic acid) was added to 0.6 ml of hydrogen peroxide solution in phosphate buffer (pH- 7.4). After incubating for 10 minutes at 37°C the absorbance was measured at 230 nm. Corresponding blanks were taken. The experiment was performed in triplicate. The absorbance of hydrogen peroxide in phosphate buffer as control was measured at 230 nm. The scavenging effect (%) was measured using the following equation. Hydrogen peroxide produces hydroxyl radicals in cells. Scavenging of these radicals by the test drug is used as a test for antioxidant activity [14, 18].

RESULT AND DISCUSSION: All the compounds of 4- (Substituted benzylidene)-2-(pyrazin-2-yl) oxazole were screened for anti-oxidant activity by the Hydrogen peroxide free radical scavenging activity method. The results are expressed as mean ±SD (n = Compounds PA-7, PA-13 and PA-15 Have shown promising scavenging effect at 100 µgm/ml concentration, While PA-4, PA-8 and PA-13 show promising scavenging effects at the 200 µgm/ml Concentration. The derivatives PA-4, PA13 and PA-15 confirmed by IR, 1H-NMR and melting point prominent peak were observed and showed the proper melting point of all derivatives.

TABLE 1: LIST OF 4- (SUBSTITUTED BENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4H)-ONE DERIVATIVE WITH THEIR IUPAC NAMES AND STRUCTURE

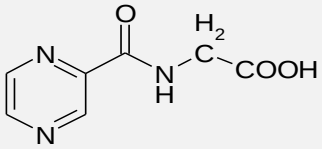
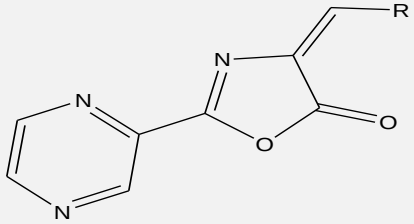
Compound	IUPAC Name	Structure
PA1	2-(pyrazine-2-carboxamido) acetic acid	
	4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (R)	
PA2	4-benzylidene-2-(pyrazin-2-yl)oxazol5-(4*H*)-one	ph
PA3	4-(2-chlorobenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	2-Cl-ph
PA4	4-(4-fluorobenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-Fl-ph
PA5	4-(4-bromobenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-Br-ph
PA6	4-(4-chlorobenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-Cl-ph
PA7	4-(4-methylbenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-CH_3-ph
PA8	4-(4-hydroxy-3-methoxybenzylidene)-2-(pyrazin-2-yl)oxazol-5(4*H*)-one	4-OH, 3-OCH_3-ph
PA9	4-(furan)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	furan
PA10	4-(4-methoxybenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-OCH_3-ph
PA11	4-(2-hydroxybenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	2-OH-ph
PA12	4-(4-hydroxybenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	4-OH-ph
PA13	4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl)oxazol-5(4*H*)-one	4-OH, 3-Br and 4-OCH_3
PA14	4-(3-hydroxybenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one	3-OH-ph
PA15	4-(5-Oxo)-2-(pyrazin-2-yl)4(5*H*)-ylidene) methyl) benzonitrile	4-CN-ph

TABLE 2: PHYSIOCHEMICAL DATA OF 4- (SUBSTITUTED BENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4H)-ONE DERIVATIVES

Compound	Mol. Formula	Mol. Wt.	M.P °C	R_f Value	Yield %	Color
PA1	$C_7H_7N_3O_3$	181.15	210-212	0.55	75	White crystal
PA2	$C_{14}H_9N_3O_2$	251.24	153-154	0.60	75	Yellowish
PA3	$C_{14}H_8N_3O_2$ Cl	285.69	175-176	0.65	68	Yellowish
PA4	$C_{14}H_8N_3O_2F$	269.23	156-157	0.63	77	Brown
PA5	$C_{14}H_8N_3O_2Br$	330.14	170-171	0.52	67	Yellow
PA6	$C_{14}H_8N_3O_2$ Cl	285.69	165-166	0.65	72	Yellowish
PA7	$C_{15}H_{11}N_3O_2$	265.27	120-122	0.70	65	Brown
PA8	$C_{15}H_{11}N_3O_4$	297.27	163-164	0.50	69	Yellowish
PA9	$C_{12}H_7N_3O_3$	241.20	180-181	0.60	76	Brown
PA10	$C_{15}H_{11}N_3O_3$	281.27	135-136	0.56	80	Faint yellow
PA11	$C_{14}H_9N_3O_3$	267.24	90-91	0.53	81	Yellow
PA12	$C_{14}H_9N_3O_3$	267.24	140-141	0.65	72	Yellowish
PA13	$C_{15}H_{10}N_3O_4Br$	376.16	146-147	0.50	68	Brown
PA14	$C_{14}H_9N_3O_3$	267.24	105-106	0.65	65	Brownish
PA15	$C_{15}H_8N_4O_2$	276.25	149-150	0.56	72	Dark yellow

TABLE 3: SCAVENGING EFFECT OF 4- (SUBSTITUTED BENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4H)-ONE DERIVATIVE FOR 100 AND 200 UG/ML CONCENTRATION

Sample code	Absorbance (Mean) (Mean±SD*)		Scavenging effect (%)	
	100 µgm/ml	200 µgm/ml	100 µgm/ml	200 µgm/ml
PA-2	0.3620±2.9692	0.2223±0.00133	51.40	70.16
PA-3	0.3816±0.000593	0.2029±0.0106	48.77	72.76
PA-4	0.3040±0.000103	0.1813±0.1813	59.19	75.66
PA-5	0.2513±0.000587	0.2050±0.000637	66.26	72.48
PA-6	0.2512±0.000244	0.2254±0.00115	66.28	69.74
PA-7	0.2510±0.000103	0.2071±0.000163	66.30	72.20
PA-8	0.4051±0.000258	0.1840±0.000132	45.62	75.30
PA-9	0.3934±0.000271	0.2039±0.000972	47.19	72.63
PA-10	0.3852±0.000103	0.2151±0.000204	48.29	71.12
PA-11	0.3815±0.000109	0.2260±0.000121	48.79	69.66
PA-12	0.3576±0.000427	0.2548±0.000512	52	65.79
PA-13	0.2271±0.000109	0.1360±0.000103	69.51	81.74
PA-14	0.4211±0.000285	0.2731±0.000204	43.47	63.34
PA-15	0.2287±0.000109	0.2840±0.000103	69.30	61.87
Ascorbic acid	0.470±2.582	0.385±2.236	36.91	48.32

Where, *n=3 Control-0.7450.

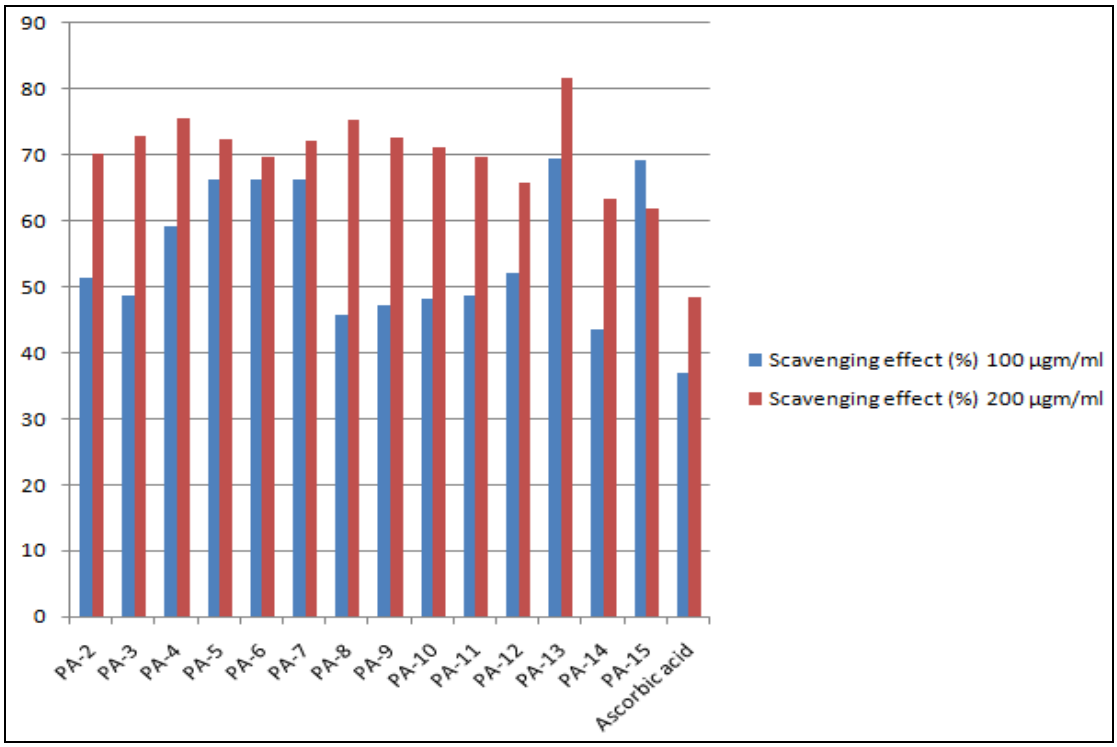


FIG. 2: GRAPHICAL REPRESENTATION OF SCAVENGING EFFECT 100 AND 200 UG/ML CONCENTRATION STANDARD AS ASCORBIC ACID AND TEST COMPARISON

Spectral Data: IR and ^{1}H-NMR spectra of synthesized 4-(substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4H)-one. The compound is identified by FT-IR and ^{1}H-NMR spectroscopy.

IR gives information about the functional group present in structure detected at a wavelength of 4000 cm^{-1}-250 cm^{-1} IR spectra recorded on BRUKER FT-IR spectrophotometer. ^{1}H-NMR of derivatives recorded on BRUKER ADVANCE II 400 NMR spectrometer. TMS is the internal standard, and DMSO is the solvent.

PA4: FT-IR v max (KBr,cm^{-1}) of 4-(4 Fluoro benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one - 3080.66 (C-H_{Str}, Aromatic), 2917.78 (CH_{Str}, Alkane), 1156.87 (C-O-C_{Str} ring), 1603.17 (C=N_{Str}, Ring), 1679.74 (C=O_{Str}, Ring), 1510.98 (C=C_{Str}, Ring), 1051.39 (C-$F_{Str.}$ Aromatic).

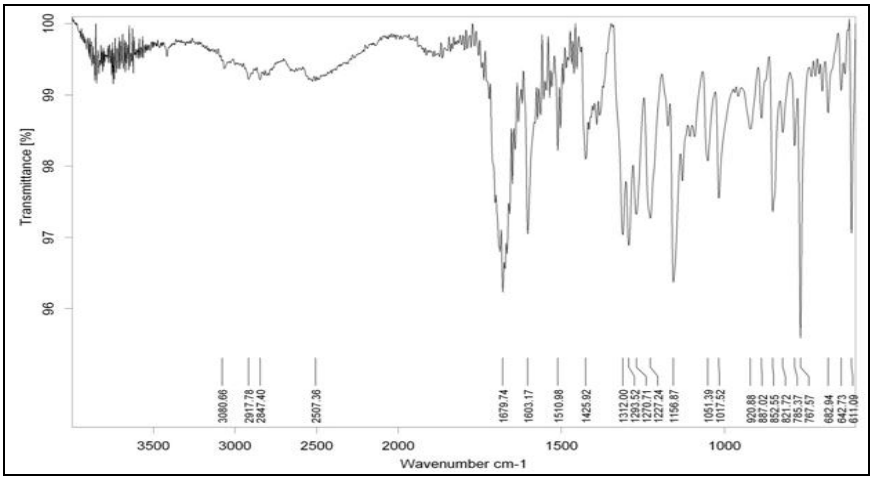


FIG. 3: IR SPECTRA OF 4-(4 FLUORO BENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4*H*)-ONE (PA4)

PA13: FT-IR v max (KBr,cm^{-1}) of 4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl)oxazol-5(4*H*)-one -2915.91(C-H_{Str}, Aromatic), 2847.01 (CH_{Str}, Alkane), 1058.11 (C-O-C_{Str} ring), 1585.36(C=N_{Str}, Ring), 1668.86 (C=O_{Str}, Ring), 1557.10(C=C_{Str}, Ring), 3266.28 (OH_{Str}), 675.38(Br_{Str}).

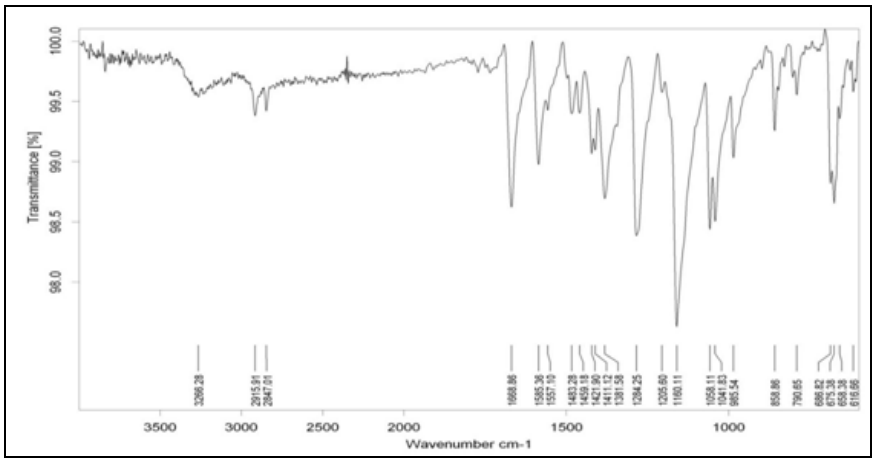


FIG. 4: IR SPECTRA OF 4-(3-BROMO-4-HYDROXY-5 METHOXYBENZYLIDENE)-2-(PYRAZIN-2-YL)OXAZOL-5(4*H*)-ONE (PA13)

PA15: FT-IR v max (KBr,cm^{-1}) of 4-(5-Oxo)-2-(pyrazin-2-yl)4(5*H*)-ylidene) methyl) benzonitrile IR-2916.35 (C-H_{Str}, Aromatic), 2848.27 (C-H_{Str}, Alkane), 1649.07 (C=N_{Str}, Ring), 1741.74 (C=O_{Str}, Ring), 2229.10 (C---N_{Str}) , 1563.69 (C=C_{Str}, Ring), 1097.21 (C-O-C_{Str}, Ring).

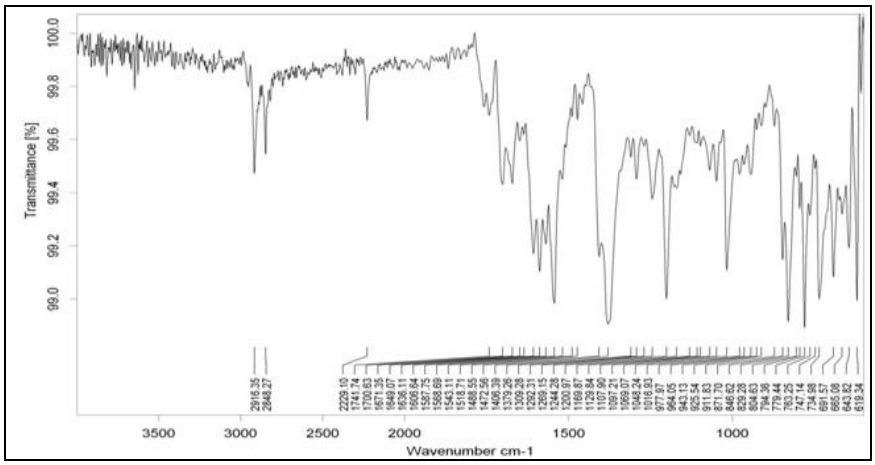


FIG. 5: IR SPECTRA OF 4-(5-OXO)-2-(PYRAZIN-2-YL) 4(5*H*)-YLIDENE) METHYL) BENZONITRILE (PA15)

PA4: [1]H-NMR (DMSO 400 MHz) -δ Values in ppm of *4*-(4Fluorobenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one 7.18-7.34 (s, 1H, ethylene), 7.21-8.68 (m, 4H, aromatic), 8.80-9.31 (m,3H, Pyrazine)

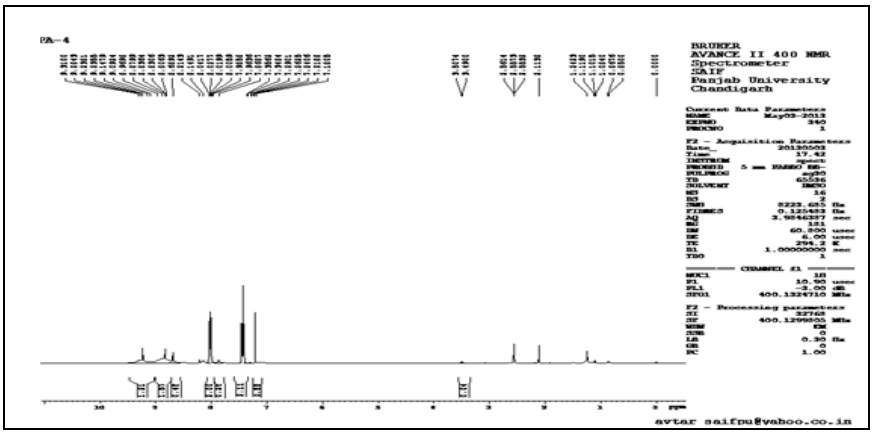


FIG. 6: [1]H-NMR SPECTRA OF *4*-(4FLUOROBENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4*H*)-ONE (PA4)

PA13: [1]H-NMR (DMSO 400 MHz) -δ Values in ppm 4-(3-bromo-4-hydroxy-5 methoxy-benzylidene) -2-(pyrazin-2-yl) oxazol-5(4*H*)-one 7.22 (s, 1H, ethylene), 7.36-8.12 (m, 2H, aromatic), 9.78-10.1 (m, 3H, Pyrazine), 10.1-10.8 (s,1H, hydroxyl), 3.88-3.94 (t,3H- methoxy).

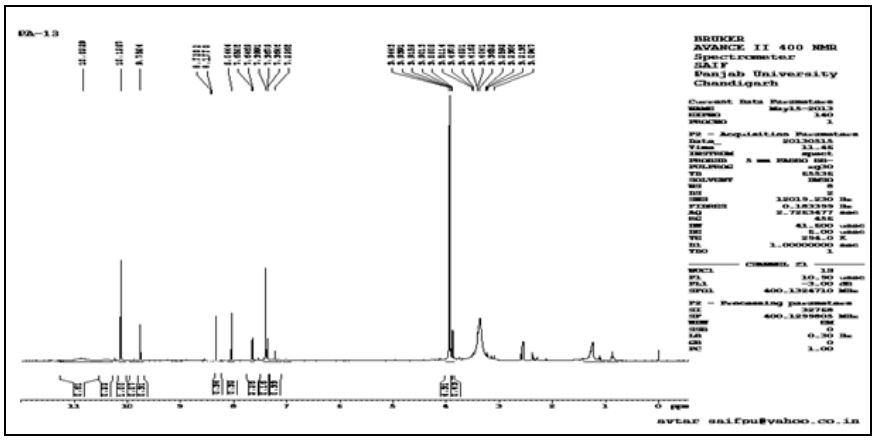


FIG. 7: [1]H-NMR SPECTRA OF 4-(3-BROMO-4-HYDROXY-5 METHOXYBENZYLIDENE)-2-(PYRAZIN-2-YL) OXAZOL-5(4*H*)-ONE (PA13)

PA15: [1]H-NMR (DMSO 400 MHz) -δ Values in ppm *4*-(5-Oxo)-2-(pyrazin-2-yl) 4(5*H*)-ylidene) methyl) benzonitrile 7.62 (s, 1H, ethylene), 7.62-8.14(m, 4H, aromatic), 8.09-9.34 (m,3H, Pyrazine)

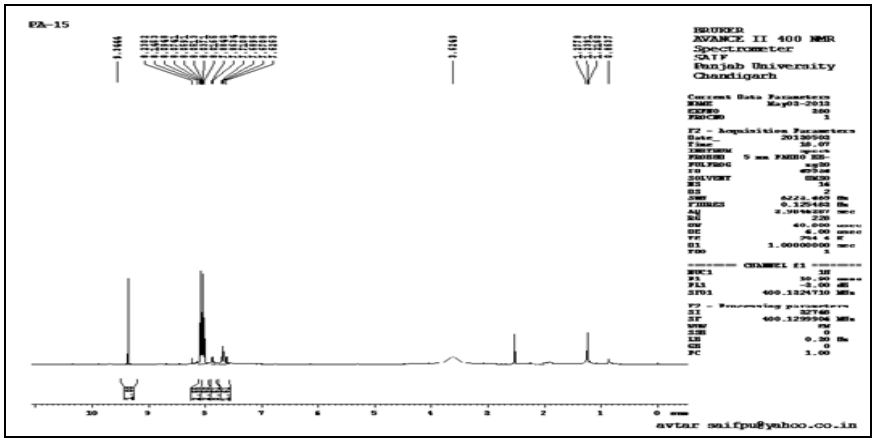


FIG. 8: [1]H-NMR SPECTRA OF *4*-(5-OXO)-2-(PYRAZIN-2-YL) 4(5*H*)-YLIDENE) METHYL) BENZONITRILE (PA15)

CONCLUSION: In conclusion, 4-(Substituted benzylidene)-2-(pyrazin-2-yl) oxazol-5(4H)-one were the proposed compounds were screened for antioxidant activity. Also it shows the promising

antioxidant activity of oxazole derivatives for 100 ug/ml are 4-(4-methylbenzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-7), 4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl)oxazol-5(4*H*)-one (PA-13) and are 4-(5-Oxo)-2- (pyrazin-2-yl) 4(5*H*)-ylidene) methyl) benzonitrile (PA-15) and for 200 ug/ml 4-(4-fluoro benzylidene)-2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-4), 4-(4-hydroxy-3-methoxy benzylidene)-2- (pyrazin-2-yl) oxazol-5 (4*H*)-one (PA-8) and 4-(3-bromo-4-hydroxy-5 methoxybenzylidene) -2-(pyrazin-2-yl)oxazol-5(4*H*)-one (PA-13) respectively shows promising anti-oxidant activities. The compound 4 - (3-bromo – 4 – hydroxyl - 5 methoxybenzylidene) -2-(pyrazin-2-yl) oxazol-5(4*H*)-one (PA-13) having hydroxyl group at Para position due to this for 100 ug/ml and for 200 ug/ml it shows highest scavenging effect. These compounds with suitable modification can be explored better for their therapeutic activities in the future like antiviral, anti-inflammatory and anticancer. The promising biological activities of these compounds are taken into consideration for drug development and drug discovery. The toxic studies of these compounds will be carried out to find an effective therapeutic index.

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