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SYNTHESIS OF 4-BENZYLIDENE-2-(4-NITRO- PHENYL) -4*H*-OXAZOL-5 -ONE DERIVATIVES WITH SUSPECTED BIOLOGICAL ACTIVITY

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ABSTRACT
Oxazolones are five membered heterocyclic compounds containing nitrogen and oxygen as heteroatoms.The C-2 and C-4 positions of the oxazolone are crucial for their various biological activities. A series of oxazolone derivatives (**1-11**) have been synthesized as potential antibacterial and fungal agent. The newly synthesized compounds were evaluated. compounds have been prepared by the condensation of 4-nitrobenzoylglycine or benzoyl glycine with aromatic aldehydes in the presence of ethanol, acetic anhydride and glacial acetic acid. The newly synthesized compounds were characterized by FTIR, ^{1}HNMR, C^{13}NMR.
Keywords:- Oxazolone, antibacterial and fungal agent, Synthesis.

1- NTRODUCTION

Oxazolon are considered as an important class of heterocyclic compounds since they are structural subunits of various biologically active natural products and are valuable synthetic precursors and pharmaceuticals. They can also be used as peptide mimetic or enzyme inhibitors . Various substituted analogues of oxazolon are reported to possess anti-inflammatory, antidiuretic, hemo regulatory, antimicrobial, blood platelet aggregation inhibiting properties and pesticides properties[4][3]. They plays a vital role in the manufacturing of various biologically active drugs as anti-depressants & analgesics and are also used in industries as pesticides, dyes, fluorescent brightening agent, textile auxiliaries& plastics. Various naturally occurring compounds also possess oxazolon-ring system in[5]their nucleus and are having useful biological properties. Various substituted derivatives of oxazoles have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity[6]. In medicinal chemistry oxazole derivatives have been very well known for their therapeutic applications. Oxazole is present as a base in various drugs like oxaprozin, sulfamethoxazole, trimethoprim **[7].** Oxazolones are heterocyclic compounds which perform an important role in the synthesis of several organic molecules including amino acids, amino alcohols, thiamine, amides, peptides [8] and polyfunctional compounds8. Certain natural and synthetic oxazolone also including benzoxazolone[9] derivatives possess important biological activities; such as antimicrobial[10],antiangiogenic,anticonvulsant,anti-inflammatory[11],antitumor, antagonisticanticancer, anti-HIV21,[12] , , sedative [13] and cardiotonic activity. These are used as synthons for the construction of various alkaloid skeletons, immunomodulators and biosensor or photosensitive composition devices for proteins. [14]

BIOLOGICAL AND MEDICINAL SIGNIFICANCE OF OXAZOLE

Although they have been known from long ago to be biologically active, their varied biological features are still of great scientific interest. Given below is a brief account of various alterations conducted oxazole ring and their associated biological activities.

1. Antimicrobial activity

Oxazolone derivatives by a convenient one-pot synthesis of fused steroidal oxazolone from ketones. The antimicrobial activities of these compounds were screened *in vitro* against Gram-positive bacteria, Gram-negative bacteria and fungi. Oxazolone derivatives showed potent antimicrobial activity. Antibacterial activity was assessed by the disc diffusion method against *B. subtilus, P.aeruginosa, S. aureus, pyrogenes, S. typhimurium,* and *E. coli*. Strains were inoculated in BHI medium and chloramphenicol was used as standard drug. For antifungal activity *C.albicans, C. glabrata, Penicillium spp., F. oxyporium, A.niger* were inoculated in Sabouraud Dextrose broth medium. Nystatin was used as standard drug. The *in vitro* study results demonstrate that the compound was found to be most active**.[15]**

2. Anticancer activity

The oxazolon moiety with some substitutions shows promising antitumor activity as there are large number of oxazolon based antimetabolites. The cytotoxicity of mono and di substituted oxazolon derivatives and their precursors were evaluated on macrophages and on tumer cell lines[9].Dalip *et al* [16].a very good yield, and studied their anticancer activity against six cancer cell lines. The anticancer activity was determined for each line using formazen dye (MTT) conversion assay. Substitution at C-2 position of oxazolon ring is important for the activity. Without any substitution the compounds exhibited very poor activity had been synthesized a series of 4-(3-indolyl) oxazolon in a very good yield, and studied their anticancer activity against six cancer cell lines. The anticancer activity was determined for each line using formazen dye (MTT) conversion assay. Substitution at C-2 position of oxazolon ring is important for the activity. Without any substitution the compounds exhibited very poor activity. oxazolon moieties is described by Joseph *et al*[17] . Selected compounds were evaluated for their ability for cytotoxic activity. An unexpected oxidative cleavage reaction afforded a macro cyclic imide that was also evaluated for G- quadruplex stabilizing and cytotoxic activity. The anticancer activity was found to be 85-90%.[18]

2. Experimental

2.1. MATERIALS AND METHODS

Melting points were determined by capillary tube method on Banested (UK). The FTIR spectra were recorded on FTIR spectrophotometer, Shimadzu (Japan) at the colleges of pharmacy and Science (Baghdad University). H1NMR and C13NMR performed in the center laboratory of Esfahan University. Thin layer chromatography (TLC) was run on silica gel GF254 (60), Merck (Germany) to check both purity of compounds and their reactions progress.

2.2. General Procedure for the synthesis of compounds (1-11)

Synthesis 4-Nitro-hippuric acid or hippuric acid Glycine (10mmol) in 10ml of 1N sodium hydroxide was cooled at 0-5C and the cold solution was added dropwise to a solution of 10 mmol of an appropriate acid chlorides or in 15ml of chloroform. The reaction mixture was continued under stirring for an additional one hour. The aqueous layer was separated and acidified with 2N hydrochloric acid. The products were collected by filtration and recrystallized from 80% ethanol as colorless needles

To a stirring mixture of hippuric acid or 4-Nitro-hippuric acid (, 0.01 mol) acetic acid (5 ml) acetic anhydride (20 ml), aromatic aldehyde (0.01 mol) was added. Refluxed with temperature of reaction was reached to 80C° for 4hr., The mixture become almost solid, and then as the temperature rises, it gradually liquefies and turns deep yellow in color. After completion of the reaction monitored by TLC [Methanol : Ether: n-hexan (1: 3: 2)]the reaction is allowed to cool. , then the mixture was poured in to crushed ice and stirred for 30 min. the product was collected and recrystallized from suitable solvent to yield the desired compound

1- 4-(4-Bromo-benzylidene)-2-(4-nitro-phenyl)-4H-oxazol-5-one

(yield 85 %), (m.p, 115-117 C°,) , (FTIR (KBr) υ: 3093.82,3008.95 (C-H ar.=CH olf.), 1790 (-C=O lactone.), 1658.78 (-C=N, C=C olf.), 1598.99-1554.63 (C=C ar.), 1519.91asy.,1311.59 sy. of Ar-NO2 , str.), 1215.15 (-C-O.), 827.46 cm-1 (Ar-H def. of paradisubstituted benzene), 729.09 cm-1 (C-Br str.). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.49 – 8. 47 (m, Aromatic protons and C=CH- proton), C^{13}NMR (DMSO-d 6) ς (p p m), (165.04 , C=O), (164.96, C=N), (149.20, C=C), (122.99-139.10 Ar. Carbon and olifenic carbon)

2- 4-(4-Chloro-benzylidene)-2-(4-nitro-phenyl)-4H-oxazol-5-one:

(yield 83 %), (m.p, 155-197 C°) , (FTIR (KBr) υ : 3103.46,3009 (C-H ar.=CH olf.), 1789.94 (-C=O lactone.), 1656.85 (-C=N, C=C olf.), 1600.92,1552.7 (C=C ar.), 1521.84asy.,1313.52 sy. of Ar-NO2 , str.), 1253.73 (-C-O.), 825.53 cm-1 (Ar-H def. of paradisubstituted benzene), 729.09 cm-1 (C-Cl str.).. ^{1}HNMR (DMSO-d 6) ς (p p m), 7.54 – 8. 39 (m, Aromatic protons and C=CH-proton). C^{13}NMR (DMSO-d 6) ς (p p m), (168.63, C=O), (165.06, C=N), (149.20, C=C), (123.66-139.10 Ar. Carbon and olifenic carbon)

3- 4-(4-Nitro-benzylidene)-2-(4-nitro-phenyl)-4H-oxazol-5-one

(yield 80 %), (m.p, 275-277 C°) , (FTIR (KBr) υ: 3107.32,3009 (C-H ar.=CH olf.), 1774.51,1743.65 (-C=O lacton.), 1650 (-C=N, C=C olf.), 1600.92-1552.7 (C=C ar.), 1519.91asy.,1320 sy. of Ar-NO2 , str.), 1213.23 (-C-O.), 819.75 cm-1 (Ar-H def. of paradisubstituted benzene). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.66 – 9.17 (m, Aromatic protons and C=CH- proton). C^{13}NMR (DMSO-d 6) ς (p p m), (165.99, C=O), (162.74, C=N), (150.26, C=C), (123.73-149.53 Ar. Carbon and olifenic carbon)

4- 4-(4-Hydroxy-benzylidene)-2-(4-nitro-phenyl)-4H-oxazol-5-one

(yield 65 %), (m.p, 197-199C°) , (FTIR (KBr) υ: 3390(,OH ar.). , 3113.11,3000 (C-H ar.=CH olf.),

1793.8,1766.8 (-C=O lacton.), 1651.07 (-C=N, C=C olf.), 1597.06 (C=C r.),1519.91asy.,1315.45 sy. of Ar-NO2 , str.), 1292.31 (-C-O.), 856.96 cm-1 (Ar-H def. of paradisubstituted benzene ^{1}HNMR (DMSO-d 6) ς (p p m), 6.98 (s, 1H, =CH-),7.15 – 8. 44 (m, Aromatic protons). 3.37(b,s, 1H, OH), C^{13}NMR (DMSO-d 6) ς (p p m), (165.68, C=O), (16151, C=N), (152.82, C=C), (115.72-150.01 Ar. Carbon and olifenic carbon)

5- 4- (3-Nitro-benzylidene)-2-(4-nitro-phenyl)-4H-oxazol-5-one

(yield 89 %), (m.p, 258-260 C°) , (FTIR (KBr) υ: 3093.82,3001.24 (C-H ar.=CH olf.), 789.94,1759.08 (-C=O lacton.), 1658.78 (-C=N, C=C olf.), 1598.99,1558.48 (C=C ar.), 1529.55asy.,1350.17 sy. of Ar-NO2, str.), 1294.24 (-C-O.), 823.6 cm-1 (Ar-H def. of meta disubstituted benzene). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.63-8.76 (m, Aromatic protons and C=CH- proton). (171.28, C=O), (165.88, C=N), (162.74, C=C), (123.8-150.26 Ar. Carbon and olifenic carbon)

6- 4-(4-Bromo-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 85 %), (m.p, 174-176C°) , (FTIR (KBr) υ: 3150.03, 3037.89 (C-H ar.=CH olf.), 1793.80,1766.8 (- C=O lacton.), 1651.07 (-C=N, C=C olf.), 1581.63,1556.55 (C=C ar.), 1236.37 (-C-O.), 819.75 cm-1 (Ar-H def. of paradisubstituted benzene), 775.38 cm-1, (C-Br str.). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.05 – 8. 60 (m, Aromatic protons and C=CH- proton). C^{13}NMR (DMSO-d 6) ς (p p m), 166.72, C=O), (163.39, C=N), (163.39, C=C), (122.57-139.57 Ar. Carbon and olifenic carbon)

7- (4-Chloro-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 80 %), (m.p, 209-211C°) , (FTIR (KBr) υ: 3068.75,3043.67 (C-H ar.=CH olf.), 1795.73,1766.8 (-C=O lactone.), 1654.92, (-C=N, C=C olf.), 1590,1554.63 (C=C ar.), 1234.44 (-C-O.), 825.53 cm-1 (Ar-H def. of paradisubstituted benzene). 77.31 cm-1 (C-Cl str.). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.18 – 8. 53 (m, Aromatic protons and C=CH- proton). C^{13}NMR (DMSO-d 6) ς (p p m), (166.72, C=O), (163.37, C=N), (163.37, C=C), (124.99-135.81 Ar. Carbon and olifenic carbon)

8- 4-(4-Nitro-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 90 %), (m.p, 198-200C°) , (FTIR (KBr) υ: 3103.46, 3043.67 (C-H ar.=CH olf.), 1797.66,1761 (-C=O lacton.), 1654.92 (-C=N, C=C olf.), 1598.99,1558.48 (C=C ar.), 1519.91asy.,1325.110 sy. of Ar-NO2 , str.), 1224.80 (-C-O.), 820 cm-1 (Ar-H def. of para disubstituted benzene). Elemental analysis: Calcd for C16H10N2O4: C, 65.31; H, 3.43; N, 9.52, Found:C, 65.32; H, 3.48; N, 9.53 %. ^{1}HNMR (DMSO-d 6) ς (p p m), 7.48-8.57 (m, Aromatic protons and C=CH- proton), C^{13}NMR (DMSO-d 6) ς (p p m), (166.25, C=O), (164.84, C=N), (147.78, C=C), (123.47-139.58 Ar. Carbon and olifenic carbon)

9- 4-(4-Hydroxy-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 75 %), (m.p, 93-95C°) , (FTIR (KBr) υ: 3271.27 (O-H str.), 3074,3000 (C-H ar.=CH olf.), 1795.73,1759.08 (-C=O lactone.), 1656.85 (-C=N, C=C olf.), 1602.85,1558.48 (C=C ar.), 1240.23 (-C-O.), 835.18 cm-1 (Ar-H def. of para disubstituted benzene). ^{1}HNMR (DMSO-d 6) ς (p p m), 7.32-8.36 (m, Aromatic protons and C=CH- proton).
C^{13}NMR (DMSO-d 6) ς (p p m), (166.77, C=O), (152.43, C=N), (151.31 , C=C), (121.90-139.58 Ar. Carbon and olifenic carbon)

10- 4-(3-Nitro-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 80 %), (m.p, 157-159C°) , (FTIR (KBr) 3089.96,3000 (C-H ar.=CH olf.), 1793.8,1762.94 (-C=O lactone.), 1658.78 (-C=N, C=C olf.), 1600,1558.48 (C=C ar.), 1531.46asy.,1323.17 sy. of Ar-NO2 str.), 1226.73 (-C-O.), 806.25 cm-1, (Ar-H def. of meta disubstituted benzene).. ^{1}HNMR (DMSO-d 6) ς (p p m) 6.84(s, 1H, =CH-), 7.4-7,96 (m, 7H, Ar-H), 8.04-8.69 ppm (dd, 2H, 2 and 4 Ar-H), C^{13}NMR (DMSO-d 6) ς (p p m), (191.83, C=O), (166.40, C=N), (164.27, C=C), (124.04-148.12 Ar. Carbon and olifenic carbon)

11- 4-(4-Dimethylamino-benzylidene)-2-phenyl-4H-oxazol-5-one

(yield 73 %), (m.p, 204-206C°) , (FTIR (KBr) 3105.39 (C-H ar.=CH olf.), 1764..87 (-C=O lactone.), 1641.42 (-C=N, C=C olf.), 1585.49,1527.62 (C=C ar.), 1438.9asy.,1327.03 sy. of (Ar-NO2), 1265.3 (-C-O.), 815.89 cm-1 (Ar-H def. of paradisubstituted benzene), 754.17 cm^{-1} of υp-N(Me)$_2$ ^{1}HNMR (DMSO-d 6) ς (p p m), 2.848 (s, 6H, -N(CH3)2) 7.32-8.36 (m, Aromatic protons and C=CH- proton).

3. Results and Discussion

Oxazolone derivatives were synthesized by Erlenmeyer's synthesis and identify on the basis of melting point range, Rf values, solubility, FTIR, ^{1}HNMR, C13NMR., All the compounds were evaluated for their

antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, Bacilluse Spp and S aureus, using disc diffusion method. Selected of some newly synthesized oxazolons derivatives were screened *in vitro* for their antibacterial activity against four types of pathogenic bacterial isolates and for antifungal activity against one type of Candida albicans. DMSO as a blank exhibited no antimicrobial activity against any of the tested microorganisms used. The bacterial isolates were more susceptible to the synthesized compounds than isolated fungal. The recorded inhibition zones are summarized in Table (1). We observed some important results from the data of inhibition zone: Most of the synthesized compounds showed antibacterial and/or antifungal activities. All compounds at concentration (1 mg/ml) were highly active against *Staphylococcus aureus* except (2,3,4,7,8,10) showed resistance. Most compounds at concentration (1 mg/ml) were highly active against *Bacillus subtilis* whereas (4,7) showed moderate activity against this microorganism. All compounds at concentration (1 mg/ml) except (11, 17) showed highly active against *E. Coli*. Gram (-ve) type *Pseudomonas aeuroginosa* showed resistance to compound (6) all Compounds acts moderate activity as antifungal agents towards *Candida Albicans*. While Compounds*(7,8,10)* show good activity as antifungal agents towards *Candida Albicans*. Therefore oxazolons derivatives compounds (7,8,10) can be recommended for further studies.

CONCLUSION

A large number of oxazolons have been discovered and reflected significant biological activities with appreciably wider spectrum. The versatile synthetic applicability & biological activity of these heterocycles will help the medicinal chemists to plan, organize & implement new approaches towards discovery of novel drugs. Further combinatorial libraries of these compounds can be generated which can be screened optimal pharmacological activities by optimization techniques using QSAR investigation.

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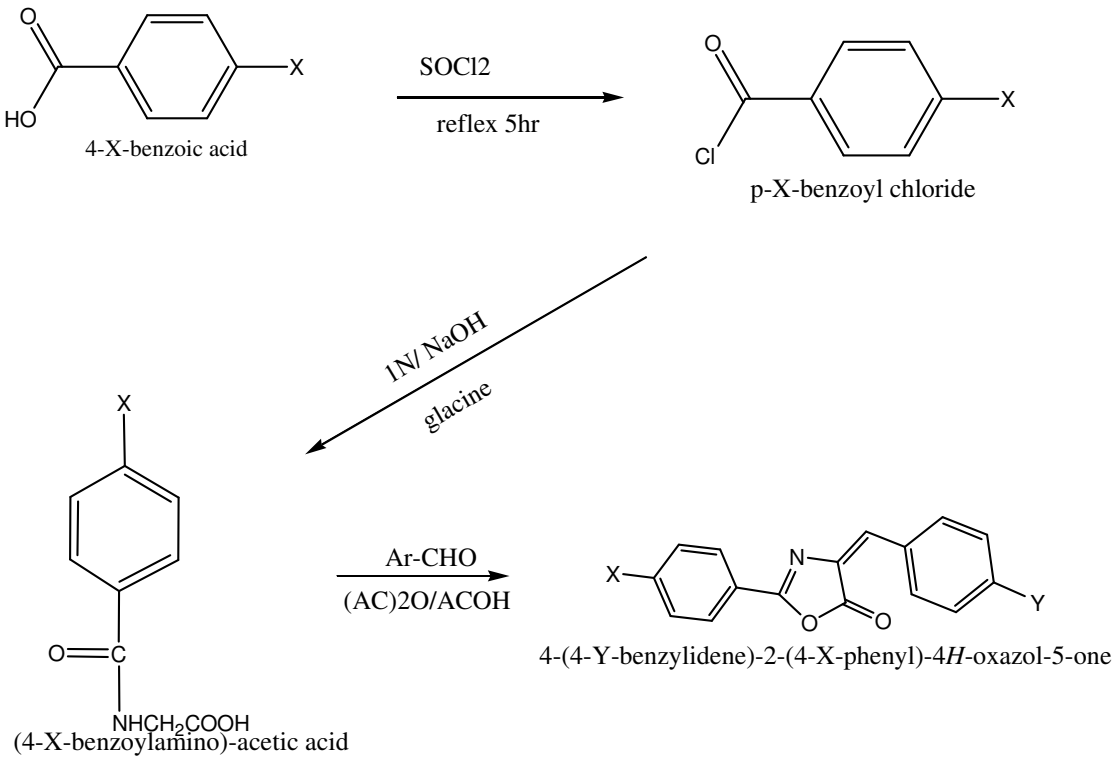
Table (1): The antimicrobial activity of the tested compounds.

Compound		Zone of Inhibition in mm				
		Bacillus Spp.	***Staph. aureus***	***E.coli***	***Pseudo-monas aeruginosa***	***Candida albicans***
1	*1mg/ml*	18	**20**	**25**	**14**	**13**
2	*1mg/ml*	20	**-**	**21**	**12**	12
3	*1mg/ml*	18	**-**	**21**	**14**	**12**
4	*1mg/ml*	10	**-**	**26**	**17**	**12**
5	*1mg/ml*	20	**20**	**23**	**17**	**14**
6	*1mg/ml*	22	**24**	**22**	**-**	**13**
7	*1mg/ml*	13	**-**	**14**	**15**	**16**
8	*1mg/ml*	21	**-**	**22**	**13**	**26.7**
9	*1mg/ml*	22	**20**	**23**	**12**	**17**
10	*1mg/ml*	20	**-**	**19**	**15**	**18**
11	*1mg/ml*	21	18	16	17	**13**
sulfamethaxazole	*1mg/ml*	34	32	**31**	29	-
miconozole	*1mg/ml*	-	-	-	-	16



X= -NO2, -H Y= -Br, -Cl, -NO2, -OH, -N(CH3)2

Figure 1, scheme for synthesis of targets compounds

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