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SYNTHESIS, SPECTRAL STUDIES AND ANTIMICROBIAL SCREENING OF SOME NEW CHALCONE AND ISOXAZOLE DERIVATIVES BEARING FURAN NUCLEUS

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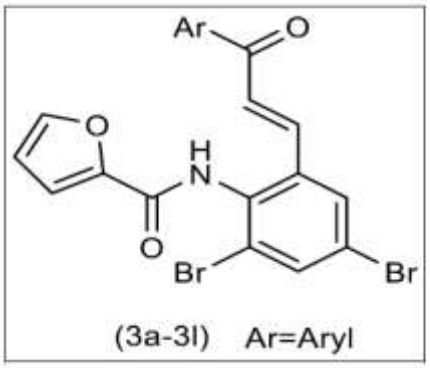
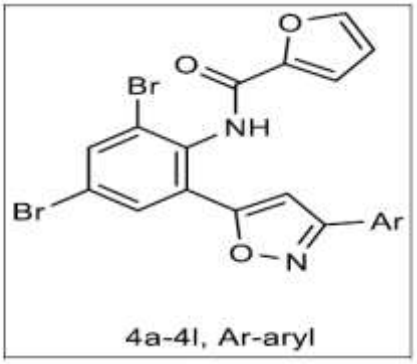
ABSTRACT

We have synthesized (E)-N-{2',4'-dibromo-6'-[3"-(aryl)-3"-oxoprop-1"-en-1"- yl]phenyl}furan-2-carboxamides (3a-3l) and N-{2',4'-Dibromo-6'-[3"-(aryl)isoxazol-5"- yl]phenyl}furan-2-carboxamides (4a-4l). The structure of the synthesized compounds proved by IR, ^{1}H-NMR, Mass spectra and TLC. The compounds (3a-3l) and (4a-4l) have been evaluated for their antimicrobial activity against Gram positive bacteria (*Staphylococcus aureus, Bacillus subtilis*), Gram negative bacteria (*Pseudomonas aeruginosa, Escherichia coli*) and Fungi (*Aspergillus Niger*). They are compared with known standard drugs.



(3a-3l) Ar=Aryl



4a-4l, Ar-aryl

KEYWORDS: Chalcones, Isoxazoles, Antimicrobial activity.

I. INTRODUCTION

Heterocyclic compounds are an important class of compounds from the point of view of providing biologically active compounds. There are many APIs that are heterocyclic compounds. One of the important heterocycles is furan ring. Furan nucleus containing

compounds tend to show biological activities like Antidepressant,[1] Anti anxiety,[2] Anti-inflammatory,[3] Analgesic activity,[4] Muscle relaxant,[5] Antihypertensive,[6] Antidiabetic,[6] antioxidative activity,[6] Antiarrhythmic,[7] Antimicrobial activity,[8] Anti-ulcer,[9] activity against UTIs,[10] Inhibition of sickle cell formation,[11] Anti Parkinson,[12] Antihistaminic,[13] Anticholinergic[14] Antineoplastic[15] etc. Compounds like Ranitidine.[16] that contain furan nucleus have shown biological activity. Other pharmacologically active compounds that possess furan nucleus are Firocoxib,[17] a nonsteroidal anti-inflammatory drug (NSAID) used to treat pain and inflammation in dogs and horses, Nitrofural,[18] shows antimicrobial activity. When it comes to biologically active substances, chalcones and isoxazoles are two significant classes of heterocyclic compounds that have demonstrated a variety of biological activities in addition to serving as essential building blocks for the synthesis of further compounds and their derivatives. The biological activity of chalcones is attributed to their reactive α, β-unsaturated keto group.[19] The heterocyclic molecule known as an isoxazole is five-member ring, with two heteroatoms: oxygen and nitrogen.

This work comprises a study on the biological activities of the chalcone derivatives 3a- 3l and the analogous isoxazole derivatives 4a-4l, as well as an outline of their synthesis. The cup plate method was used to measured the antibacterial activity at a 100µg/mL concentration while DMF was used as the solvent.[20][21]

II. MATERIALS AND METHOD

Analytical reagent-grade chemicals from Merck, Finar, and Loba Chemie were utilized for the synthesis; no additional purification was carried out. TLC plates with silica gel 60 F254 (Merck) were used to assess the purity of the synthesized compounds; using a solvent system of n-hexane: ethyl acetate. The TLC plates were visualized in UV Chamber at 254 nm. Melting points of the synthesized compounds were taken in open glass capillary tubes and are uncorrected. DMSO-d6 and $CDCl_3$ were utilized as a solvent and TMS (trimethylsilane) as an internal standard for the 1H-NMR spectra of the produced compounds, which were recorded on a Bruker-400 MHz NMR spectrometer. For the mass data, a GC-MS and a water mass spectrometer were utilized. The KBr pellet approach was utilized on the SHIMADZU-FTIR spectrophotometer to record the infrared spectra of the produced compounds. Using the cup- plate method, the antibacterial activity of the produced compounds 3a-3l and 4a-4l was measured and compared with recognized standard drugs.

General method of synthesis for 3,5-dibromo-(2-furfuralamido)benzaldehyde (3)

The method involves dissolving 2-amino-3,5-dibromo benzaldehyde (0.01 mole) in 1,4-Dioxane solvent, then after to this mixture, 2-furoyl chloride (0.01 mole) was added in a dropwise manner. After complete addition of 2-furoyl chloride; pyridine (0.7 mL) added to the mixture as catalyst. This reaction mixture is then refluxed for 9 hours at 120℃. Once the reaction was complete, it was poured in to crushed ice. For obtaining the resulting product excess water was filtered, the product was kept for drying at room temperature, crystallized in methanol.(Ochre yellow solid) Melting point-90-92℃, % Yield 95%.

Spectral analysis: IR Data: 3400 (N-H str.), 3065 (=C-H Str.), 2817 (-C-H str.), 1585 (C=C Str.), 1664 (C=O amide), 1689 (C=O aldehyde), 1469 (C-O-C), 1164 (C-H IP), 749 (CH OOP), 636 (C-Br Str.), ^{1}H-NMR ($CDCl_3$, 400 MHz) in δ ppm: 10.4 (Singlet, 1H-CHO), 9.9 (Singlet, 1H-N-H), 7.1-7.9 (Multiplet, 5H aromatic), 5.9 (Singlet, 1H-aromatic). MS at M/Z = 374.2, 372.2, 370.1, 318.9, 300.2, 195.0.

General method of synthesis for (E)-N-{2',4'-dibromo-6'-[3"-(4"'methoxyphenyl)-3"-oxoprop-1"-en-1"-yl]phenyl}furan-2-carboxamide (3j)

The method involves dissolving 3,5-dibromo-(2-furfuralamido)benzaldehyde (0.01 mole) in methanol and separately dissolving 4-methoxyacetophenone (0.01 mole) in methanol. Then both these solutions are mixed and to this mixture catalytic amount of 40% aq. NaOH is added. The solution is stirred continuously for 24 hours at room temperature, the completion of the reaction was confirmed by TLC. The reaction mixture was poured into crushed ice filtered, dried and crystallized in methanol. Melting point was 180-184℃, %Yield was 67%.

Spectral analysis: IR (KBr pellet) in CM:- 3356 (N-H str.), 3070 (C-H Str. Aromatic), 2962 (C-H Asym. Str. Alkane), 2839 (C-H sym. Alkane), 1666 (C=O Str. Ketone), 1597 (CH=CH Str. Vinyl), 1450 (C=C Str. Aromatic), 1357 (C-H bending sym.), 1257 (C-O-C Ether), 671 (C-Br Str.). ^{1}H-NMR ($CDCl_3$, 400 MHz) in δ ppm: 8.27 (Doublet, 2H-CH), 8.13 (Doublet, 1H-N-H), 8.07 (Doublet, 1H aromatic), 7.92 (Triplet, 2H-aromatic), 7.5 (Doublet, 2H -CH), 7.2 (Doublet, 2H aromatic), 7.06 (Doublet, 2H aromatic), 5.8 (Doublet, 2H aromatic), 5.2 (Doublet, 2H aromatic), 3.89 (Singlet, 3H-OCH_3). MS at M/Z = 504.3, 485.7, 420.8, 311.7, 222.3, 159.2.

Table 1: Physical data of (E)-N-{2',4'-dibromo-6'-[3"-(aryl)-3"-oxoprop-1"-en-1"-yl]phenyl}furan-2-carboxamides (3a-3l).

Code No.	Ar-	Molecular formula	Molecular weight	Melting point ℃	%Yield
3a	3-Br-C6H4-	C20H12Br3NO3	550.84	190	97.5
3b	2-Cl-C6H4-	C20H12Br2ClNO3	506.89	216	71.7
3c	4-Cl-C6H4-	C20H12Br2ClNO3	506.89	208	70.6
3d	2,4-(Cl)2C6H3-	C20H11Br2Cl2NO3	540.85	96	71.7
3e	2-OH-C6H4-	C20H13Br2NO4	488.92	208	93.5
3f	3-OH-C6H4-	C20H13Br2NO4	488.92	186	90.0
3g	4-OH-C6H4-	C20H13Br2NO4	488.92	204	80.8
3h	2,4-(OH)2-C6H3-	C20H13Br2NO5	504.92	218	70.9
3i	H,3-OCH3- C6H3-	C21H15Br2NO5	518.93	200	71.9
3j	4-OCH3-C6H4-	C21H15Br2NO4	502.94	182	69.7
3k	4-CH3-C6H4-	C21H15Br2NO3	486.94	188	68.9
3l	3-NO2-C6H4-	C20H12Br2N2O5	517.91	214	67.7

General method of synthesis for N-{2',4'-dibromo-6'-[3"-(4'''-methoxyphenyl)isoxazol-5"-yl]phenyl}furan-2-carboxamide (4j)

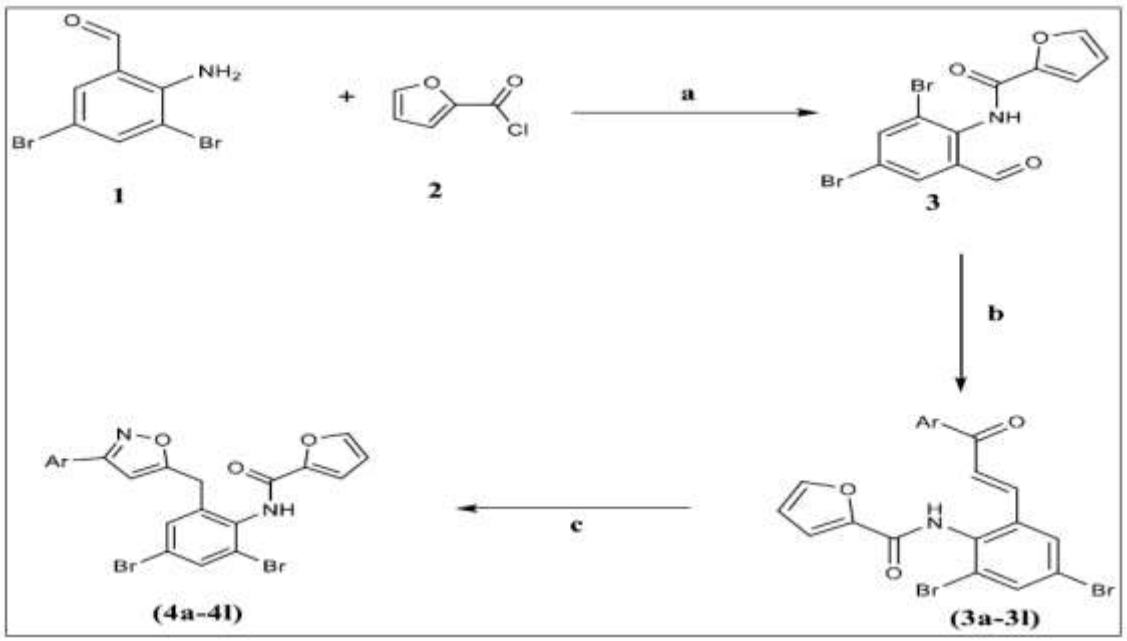
The (E)-N-{2',4'-dibromo-6'-[3"-(4'''methoxyacetophenone)-3"-oxoprop-1"-en-1"-yl]phenyl}furan-2-carboxamide (3j) (0.01 mole) was added to 20 mL of methanol. To this solution, hydroxylamine hydrochloride (0.02 mole) was added, and 10% alc. KOH was also added. This reaction mixture was then refluxed for 8 hours at 100℃. After the successful completion of the reaction, the reaction mixture was poured into crushed ice. The precipitated product was filtered and dried, then after crystallized in methanol. Melting point was 110-112℃ and %Yield was 79.9%.

Spectral analysis: IR Data (KBr Pellet) CM: 3356 (N-H Str.), 3078 (C-H Str. Aromatic), 2970 (C-H Str. Asym. Alkane), 2839 (C-H Str. Sym. Alkane), 1735, 1666 (C=O Str. Ketone), 1597 (C=C Str.), 1470 (C-H bending alkane), 1388 (C-H sym bending alkane), 1257 (C-O-C ether), 663 (C-Br Str.). ^{1}H-NMR (DMSO d6, 400 MHz): 8.44 (Singlet, 1H-N-H), 8.2 (Multiplet, 4H-aromatic), 7.8 (Doublet, 1H aromatic), 7.5 (doublet, 1H aromatic), 7.4 (Singlet, 1H aromatic), 7.2 (doublet, 2H aromatic), 5.9 (Singlet, 1H aromatic). MS. For M/Z: 520, 482, 449, 393, 391, 378, 350, 271, 249, 233, 218, 190, 164, 135.

Table 2: Physical data of N-{2',4'-dibromo-6'-[3"-(aryl)isoxazol-5"- yl]phenyl}furan-2-carboxamides (4a-4l).

Code No.	Ar-	Molecular formula	Molecular weight	Melting point ℃	%Yield
4a	3-Br-C6H4-	C20H11Br3N2O3	563.83	126	73.3
4b	2-Cl-C6H4-	C20H11Br2ClN2O3	519.88	133	78.0
4c	4-Cl-C6H4-	C20H11Br2ClN2O3	519.88	108	98.5
4d	2,4-(Cl)2C6H3-	C20H10Br2Cl2N2O3	533.84	136	91.2
4e	2-OH-C6H4-	C20H12Br2N2O4	501.92	110	77.0
4f	3-OH-C6H4-	C20H12Br2N2O4	501.92	158	68.2
4g	4-OH-C6H4-	C20H12Br2N2O4	501.92	186	70.1
4h	2,4-(OH)2-C6H3-	C20H12Br2N2O5	517.91	194	99.4
4i	H,3-OCH3- C6H3-	C21H14Br2N2O5	531.93	180	97.6
4j	4-OCH3-C6H4-	C21H14Br2N2O4	515.93	112	79.9
4k	4-CH3-C6H4-	C21H14Br2N2O3	499.94	196	98.4
4l	3-NO2-C6H4-	C20H11Br2N3O5	530.91	240	68.3

III. Reaction scheme



Scheme 1: The synthetic scheme for the preparation of Compounds (3a-3l) and (4a-4l).

Reagents and reaction conditions: (a)Pyridine, 1,4-Dioxane, 120℃, 9 hours; (b) Ar-COCH3, 40% aq. NaOH, Methanol, RT, 24 hours; (c) hydroxylamine hydrochloride, 10% alc. KOH, Methanol, 100℃, 8 hours.

IV. RESULTS AND DISCUSSION

Scheme 1 shows the reaction pathway for the synthesis of chalcone derivatives (3a-3l) and

their corresponding Isoxazole derivatives (4a-4l). The compound 3 was synthesized by condensation of 2-amino-3,5-dibromo benzaldehyde with 2-furoyl chloride in presence of pyridine catalyst in 1,4-Dioxane solvent at 120℃ for 9 hours. The chalcone derivatives (3a-3l) were prepared by the condensation of compound 3 with various aryl acetophenones in presence of 40% aq.NaOH in methanol at room temperature for 24 hours. All the chalcones were obtained in 67-97% Yield. The Isoxazole derivatives (4a-4l) were synthesized by the condensation of Chalcone derivatives (3a-3l) with hydroxylamine hydrochloride and 10% alcoholic KOH in methanol solvent at 100℃ for 8 hours. The isoxazoles were obtained in 68-98% Yield. Ethyl acetate: hexane TLC system was used for monitoring the reactions. The structures of all the newly synthesized compounds 3a-3l and 4a-4l were assigned based on the IR, Mass and ^{1}HNMR spectral data.

Antimicrobial activity

The antimicrobial activity was determined by cup plate method using 100µg/mL concentration using DMF as solvent. The activity was taken against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*; Gram negative bacteria *Escherichia Coli* and *Pseudomonas aeruginosa* and the anti-fungal activity was against *Aspergillus niger*. The zone of inhibition was measured in mm. The antibacterial activities were compared against standard drugs such as Gentamycin, Ampicillin and the anti-fungal activity was compared with standard drug Nystatin. The zone of inhibition and activity results are shown in Table 3 and Table 4 and the comparable antimicrobial activity is shown in Table 5.

Table 3: Antimicrobial activity of (E)-N-{2',4'-dibromo-6'-[3"-(aryl)-3"-oxoprop-1"-en-1"-yl]phenyl}furan-2-carboxamides (3a-3l)

Compound	Ar-	Antibacterial Activity				Anti- fungal activity
		Gram +ve bacteria		Gram -ve bacteria		
		B.subtilis	***S.aureus***	***E.coli***	***P.aeruginosa***	***A.niger***
3a	3-Br-C6H4-	4	3	2	7	-
3b	2-Cl-C6H4-	8	4	3	6	-
3c	4-Cl-C6H4-	12	6	2	6	-
3d	2,4-(Cl)2C6H3-	2	3	2	6	-
3e	2-OH-C6H4-	4	3	2	-	3
3f	3-OH-C6H4-	3	3	1	2	-
3g	4-OH-C6H4-	4	3	1	4	-
3h	2,4-(OH)2-C6H3-	7	7	2	7	11
3i	4-OH,3-OCH3-C6H3-	2	2	1	8	-
3j	4-OCH3-C6H4-	2	2	1	8	-
3k	4-CH3-C6H4-	2	2	-	8	-

3l	3-NO_2-C_6H_4-	2	7	-	6	-
Zone of Inhibition measured in mm						

Table 4: Antimicrobial activity of N-{2',4'-dibromo-6'-[3"-(aryl)isoxazol-5"-yl]phenyl}furan-2-carboxamides (4a-4l).

Compound	Ar-	Antibacterial Activity				Anti- fungal activity
		Gram +ve bacteria		Gram -ve bacteria		
		B.subtilis	***S.aureus***	***E.coli***	***P.aeruginosa***	***A.niger***
4a	3-Br-C_6H_4-	4	2	-	2	-
4b	2-Cl-C_6H_4-	4	8	-	2	-
4c	4-Cl-C_6H_4-	3	4	1	3	-
4d	2,4-$(Cl)_2C_6H_3$-	2	2	-	2	-
4e	2-OH-C_6H_4-	6	2	-	2	-
4f	3-OH-C_6H_4-	7	7	2	2	-
4g	4-OH-C_6H_4-	5	8	2	2	4
4h	2,4-$(OH)_2$-C_6H_3-	6	-	2	2	-
4i	4-OH,3-OCH_3-C_6H_3-	5	4	2	4	-
4j	4-OCH_3-C_6H_4-	7	2	2	4	-
4k	4-CH_3-C_6H_4-	6	4	3	7	-
4l	3-NO_2-C_6H_4-	4	2	-	8	-
Zone of Inhibition measured in mm						

Table 5: Synthesized compounds (3a-3l) and (4a-4l) showing antimicrobial activity and it's comparison to standard drugs.

Compound	Antibacterial Activity				Anti- fungal activity
	Gram +ve bacteria		Gram -ve bacteria		
	B.subtilis	***S.aureus***	***E.coli***	***P.aeruginosa***	***A.niger***
(3a-3l)	3b,3c,3h	3b,3c,3h,3l	3b	3a,3h,3i,3j,3k	3e,3h
(4a-4l)	4e,4f,4h,4j,4k	4b,4f,4g	4k	4i,4j,4k,4l	4g
Activity of known standard drugs					
Gentamycin (100µg/mL)	30	20	14	16	-
Ampicilin (100µg/mL)	24	22	-	-	-
Nystatin (100µg/mL)	-	-	-	-	22
Zone of Inhibition measured in mm					

V. CONCLUSION

To summarize the work done, we have synthesized 3,5-dibromo-(2- furfuralamido) benzaldehyde (3), (E)-N-{2',4'-dibromo-6'-[3"-(aryl)-3"-oxoprop-1"-en-1"-yl]phenyl}furan-2-carboxamides (3a-3l) and N-{2',4'-dibromo-6'-[3"-(aryl)isoxazol-5"-yl]phenyl}furan-2-carboxamides (4a-4l) and characterized them based on their physical and spectral data. Most of the synthesized compounds showed presence of antimicrobial activity

but some of the compounds from (3a-3l) like 3b,3c,3h,3l showed antibacterial activity against gram positive bacteria and 3a,3h,3i,3j,3k showed antibacterial activity against gram negative bacteria and 3e,3h showed presence of antifungal activity. From 4a-4l like 4b,4e,4f,4g,4h,4j,4k showed presence of antibacterial activity against gram positive bacteria and 4i,4j,4k,4l showed presence of antibacterial activity against gram negative bacteria and 4g showed presence of antifungal activity which are compared with standard drugs like Gentamycin, Ampicilin and Nystatin at concentration 100µg/mL as represented in Table 5.

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