SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF POST HETEROCYCLIC DERIVATIVES OF 3-ACETYLCOUMARIN

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Abstract

Chalcones, 3-(3-(4-substituted cyclopenta-1,3-dien-1-yl)acryloyl)-2H-chromen-2-one **(3a-e)** were prepared by condensation of 3-acetylcoumarin **(1)** with 5- substituted-2-furaldehyde **(2a-e)**. These chalcones were reacted with Thiourea to yield 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen-2-one **(4a-e)**. The compounds **(4a-e)** further reacted respectively with Chloro acetic acid and anthranilic acid to formed 5-(5-substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-2H-thiazolo[3,2-a] pyrimidin -3(5H)-one **(5a-e)** and 4-(5- substituted furan-2-yl)-2-(2-oxo-2H-chromen-3-yl)-2H-pyrimido [2,1-b] quinazolin-6(11H)-one **(6a-e)**. All the synthesised compounds were characterized by IR, NMR and LC-MS spectroscopies and elemental analyses. All the produced compounds were evaluated for their antimicrobial activities.

Keywords: Chalcone, Coumarin, thiazolo-pyrimidine, pyrimido-quinazolinone, Spectral studies and Antimicrobial activity.

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INTRODUCTION

Coumarin is an important natural resource with various medicinal properties. Many biological properties of Coumarin derivatives have been documented like antimicrobial, diuretic, anticoagulant and antitumor activities [1-9]. It has also been reported that pyrimidine derivatives showed antimicrobial activity. Most of the derivatives are reported based on 3-acetyl coumarin [10].

Chalcone is an important sub segment broadly exhibit in many natural product which entail extraordinary biological properties [11,12]. The Chalcones based on 3-acetyl coumarin have been reported recently as an anticancer agent [13]. The review [14] also indicates many derivatives can be done from 3-cinnamoyl coumarin derivatives. The review indicates that the 3-cinnamoyl coumarin derivative into post heterocyclization has not been much developed except some instance [15-18]. Thus, the present author interested to synthesize new coumarin derivatives containing pyrimidine ring. The research scheme is shown below. The antimicrobial properties of all those derivatives also been studied.

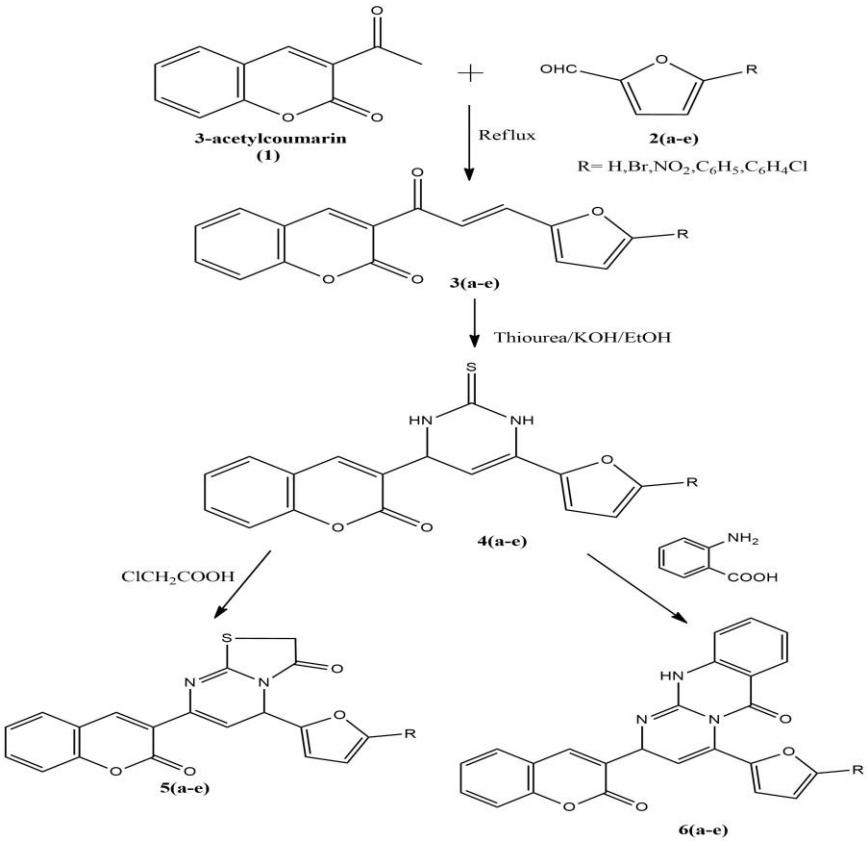
EXPERIMENTAL

Materials

All other chemicals used were of pure grade. 5-substituted -2-furaldehydes **(2a-e)** were prepared by method reported in literature [19,20].

Measurements

Elemental analysis was determined by Thermofinigen C,H,N analyser(Italy). Halogen was determined by Carius method. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded by a Perkin-Elmer 237 spectrophotometer and ^{1}H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker AM 400 instrument (at 400 MHz). LC-MS spectra of selected samples were recorded on M S route JMS 600-H. Antimicrobial activity of all compounds were evaluated by agar cup method [21].



Scheme-1 synthetic route

Synthesis of 3-(3-(4-substituted cyclopenta-1,3-dien-1-yl)acryloyl)-2H-chromen-2-one (3a-e):

An equimoler mixture of 3-acetylcoumarin **(1)** (0.001 mol) and 5-substituted-2-furaldehyde **(2a-e)** (0.001 mol), with few drops of TEA in 40 ml ethyl alcohol was refluxed for 3-6 hrs. The reaction mixture was cooled in ice bath and the solid was separated out, filtered it. The resulting solid was allowed to air dry and recrystallized from ethyl alcohol. The yields, melting points and other characterization data of these compounds designated as (2a-e) are given in Table -1.

Table:-1 Analysis of Chalcones 3(a-e)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.* 0C	Elemental Analysis							
				%C		% H		%N		%Halogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
3a	$C_{16}H_{10}O_4$ (266)	77	138-39	72.18	72.1	3.79	3.7	-	-	-	-
3b	$C_{16}H_9O_4Br$ (345)	75	132-33	55.68	55.6	2.63	2.6	-	-	23.15	23.1
3c	$C_{16}H_9NO_6$ (311)	73	136-37	61.74	61.7	2.91	2.9	4.50	4.4	-	-
3d	$C_{22}H_{14}O_4$ (342)	71	144-45	77.18	77.1	4.12	4.1	-	-	-	-
3e	$C_{22}H_{13}O_4Cl$ (376.5)	70	129-30	70.13	70.1	3.48	3.4	-	-	9.41	9.4

***** Uncorrected LC-MS peak 3a: 267.2 and 3e: 377.7

Synthesis of 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen-2-one (4a-e) :

Add thiourea (0.001mol) in a reaction mixture of 3-(3-(4- substituted cyclopenta-1,3–dien–1–yl) acryloyl) -2H-chromen-2-one **(3a-e)** (0.001 mol), aq.NaOH solution (2% w/v) and ethanol (20 ml). Refluxed this reaction mixture for 3-5 hrs then allowed to cool. The solid products obtained was filtered and crystallized from ethyl alcohol gave 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen-2-one **(4a-e)**.The details are given in Table-2.

Table:-2 Analysis of Coumarin-Pyrimidone derivatives 4(a-e)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.*0C	Elemental Analysis									
				%C		% H		%N		%S		%Halogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
4a	$C_{17}H_{12}N_2O_3S$ (324)	66	158-59	62.95	62.9	3.73	3.7	8.64	8.6	9.89	9.8	-	-
4b	$C_{17}H_{11}N_2O_3S$ (403)	69	162-63	50.63	50.6	2.75	2.7	6.95	6.9	7.95	7.9	19.82	19.8
4c	$C_{17}H_{11}N_3O_5S$ (369)	65	167-68	55.28	55.2	3.00	2.9	11.38	11.3	8.68	8.6	-	-
4d	$C_{23}H_{16}N_2O_3S$ (400)	67	160-61	68.98	68.9	4.03	4.0	7.00	6.39	8.01	8.0	-	-
4e	$C_{23}H_{15}N_2O_3SCl$ (434.5)	63	171-72	63.52	63.5	3.48	3.4	6.44	6.4	7.37	7.3	8.15	8.1

***** Uncorrected LC-MS peak 4a: 327.9 and 4e: 435.7

Synthesis of 5-(5-substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-2H-thiazolo3,2-a] pyrimidin-3(5H)-one (5a-e)

Refluxed a mixture of 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen- 2-one **(4a-e)** (0.001mol), chloroacetic acid (0.001mol), glacial acetic acid (35 ml) and acetic anhydride (15 ml) in the presence of anhydrous sodium acetate was for 6-7 hrs. The reaction mixture was cooled and poured onto ice cold water with constant stirring, the solid product formed was filtered off and crystallized from ethyl alcohol to give 5-(5- substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one **(5a-e)**. The details are presented in Table-4.

Table:-3 Analysis Thiazolo-Coumarin-Pyrimidone derivatives 5(a-e)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.*0C	Elemental Analysis									
				%C		% H		%N		%S		%Halogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
5a	$C_{19}H_{12}N_2O_4S$ (364)	63	164-65	62.63	62.6	3.32	3.3	7.69	7.6	8.80	8.7	-	-
5b	$C_{19}H_{11}N_2O_4SBr$ (441)	60	170-71	51.48	51.4	2.50	2.4	6.32	6.3	7.23	7.2	18.03	18.0
5c	$C_{19}H_{11}N_3O_6S$ (409)	58	175-76	55.74	55.7	2.71	2.7	10.26	10.2	7.83	7.8	-	-
5d	$C_{25}H_{16}N_2O_4S$ (440)	62	169-70	68.17	68.1	3.66	3.6	6.36	6.3	7.28	7.2	-	-
5e	$C_{25}H_{15}N_2O_4SCl$ (474.5)	64	152-53	63.23	63.2	3.18	3.1	5.90	5.8	6.75	6.7	7.47	7.4

***** Uncorrected LC-MS peak 5a: 365.5 and 5e: 475.3

Synthesis of 4-(5- substituted furan-2-yl)-2-(2-oxo-2H-chromen-3-yl)-2H-pyrimido[2,1-b]quinazolin-6(11H)-one (6a-e)

Refluxed a mixture of 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen- 2-one **(4a-e)** (0.001mol), antharnilic acid (0.001mol) and glacial acetic acid (50 ml) for 5-7 hrs. Vaccum distilate this reaction mixture, the solid product formed was filtered off and crystallized from ethyl alcohol to give 4-(5-substituted furan-2-yl)-2-(2-oxo-2H-chromen-3-yl)-2H-pyrimido[2,1-b]quinazolin-6(11H)-one **(6a-e)**. The details are presented in Table-4.

Table:-4 Analysis of Pyrimido-Quinazolinone derivatives 6(a-e)

Compd.	Molecular formula (Mol.wt.)	Yield %	M.P.* ^{0}C	Elemental Analysis							
				%C		% H		%N		%Halogen	
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
6a	$C_{24}H_{15}N_3O_4$ (409)	60	160-61	70.41	70.4	3.69	3.6	10.26	10.2	-	-
6b	$C_{24}H_{14}N_3O_4Br$ (488)	65	172-73	59.03	59.0	2.89	2.8	8.61	8.6	16.36	16.3
6c	$C_{24}H_{14}N_4O_6$ (454)	62	168-69	63.44	63.4	3.11	3.1	12.33	12.3	-	-
6d	$C_{30}H_{19}N_3O_4$ (485)	63	176-77	74.22	74.2	3.94	3.9	8.66	8.6	-	-
6e	$C_{30}H_{18}N_3O_4Cl$ (519.5)	61	170-71	69.30	69.2	3.49	3.4	8.08	8.0	6.82	6.8

***** Uncorrected LC-MS peak 5a: 410.3 and 5e: 519.8

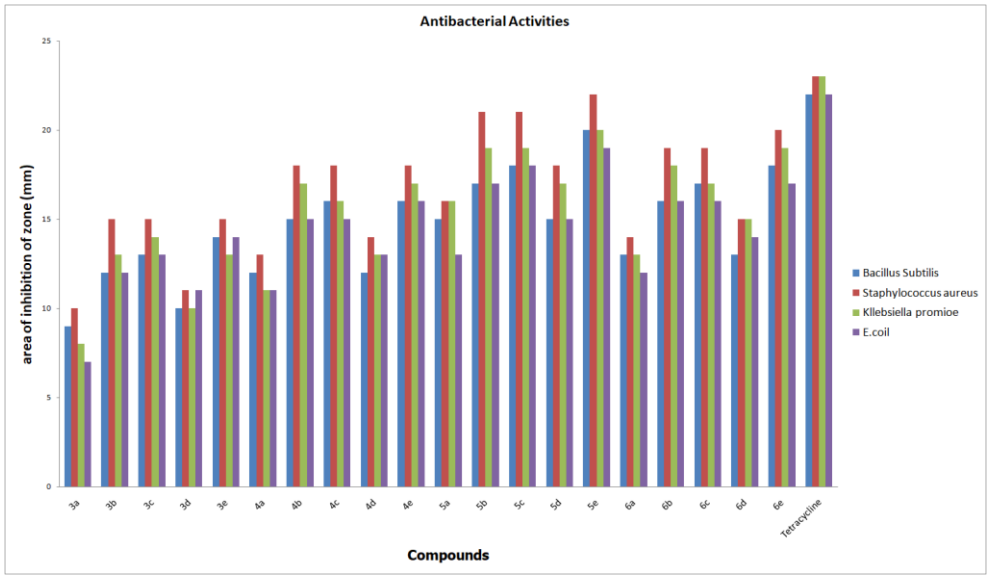
BIOLOGICAL SCREENING

Antibacterial activities

The antibacterial activities of all the compounds of three series were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used as standard for comparison. The area of inhibition of zone was measured in mm. The data are shown in Tables -5.

Table: - 5 Antibacterial Activity of Compounds 3(a-e), 4(a-e) , 5(a-e) and 6(a-e)

Compounds	Gram +Ve		Gram –Ve	
	Bacillus subtilis	***Staphylococcus aureus***	***Klebsiella promioe***	***E. coli***
3a	09	10	08	07
3b	12	15	13	12
3c	13	15	14	13
3d	10	11	10	11
3e	14	15	13	14
4a	12	13	11	11
4b	15	18	17	15
4c	16	18	16	15
4d	12	14	13	13
4e	16	18	17	16
5a	15	16	16	13
5b	17	21	19	17
5c	18	21	19	18
5d	15	18	17	15
5e	20	22	20	19
6a	13	14	13	12
6b	16	19	18	16
6c	17	19	17	16
6d	13	15	15	14
6e	18	20	19	17
Tetracycline	22	23	23	22



Antifungal Activities

The fungicidal activity of all the compounds of three series was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Aspergillus niger*, *Botrydepladia thiobromine*, *Nigrospora Sp, and Fusarium oxyporium*. The antifungal activities of all the compounds were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120°C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. Flucanozol was used as standard. The percentage inhibition for fungi was calculated after five days using the formula given below:

Percentage of inhibition = 100(X-Y) / X

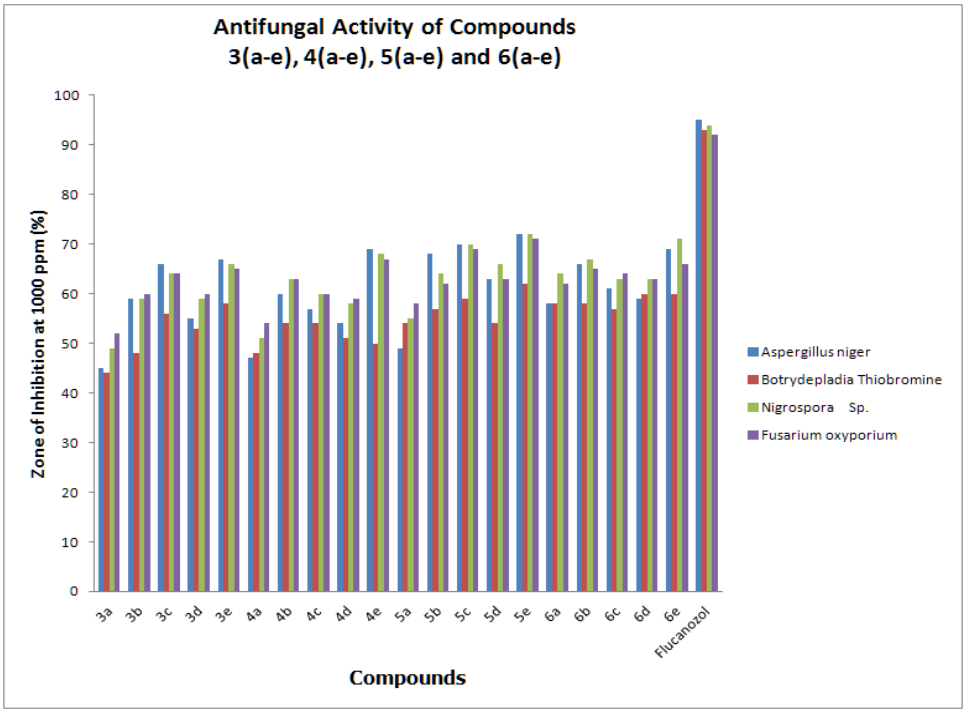
Where, X = Area of colony in control plate

Y = Area of colony in test plate

The fungicidal activities displayed by all three series are shown in Tables-6.

Table:-6 Antifungal Activity of Compounds 3(a-e), 4(a-e), 5(a-e) and 6(a-e)

Zone of Inhibition at 1000 ppm (%)				
Fungus → Compounds ↓	***Aspergillus Niger***	***Botrydepladia Thiobromine***	***Nigrospora Sp.***	***Fusarium oxyporium***
3a	45	44	49	52
3b	59	48	59	60
3c	66	56	64	64
3d	55	53	59	60
3e	67	58	66	65
4a	47	48	51	54
4b	60	54	63	63
4c	57	54	60	60
4d	54	51	58	59
4e	69	50	68	67
5a	49	54	55	58
5b	68	57	64	62
5c	70	59	70	69
5d	63	54	66	63
5e	72	62	72	71
6a	58	58	64	62
6b	66	58	67	65
6c	61	57	63	64
6d	59	60	63	63
6e	69	60	71	66
Flucanozol	95	93	94	92



RESULTS AND DISCUSSION

The condensation of 3-acetylcoumarin **(1)** with 5-substituted-2-furaldehyde **(2a-e)**, yields Chalcones namely, 3-(3-(4-substituted cyclopenta-1,3-dien-1-yl)acryloyl)-2H-chromen -2-one **(3a-e)**. The structures of **(3a-e)** were confirmed by elemental analysis and IR spectra showing an absorption band at 3030-3075 cm^{-1}(C-H, of Ar.),1670-1630 cm^{-1}(ketones), 1600-1550cm^{-1} (conjugated C=C), 1275(C-O),1120(C-O-C),1350(NO_2), 1050(C-Cl),590 (C-Br).^{1}H NMR: (3a) 7.45–8.60(5H,m,Ar-H),7.43-8.20(3H,m,CH of furan) and 6.95, 7.70 (2H,d,CH=CH), (3b) 7.45–8.60(5H,m,Ar-H),7.45-7.54(2H,m,CH of furan) and 6.95,7.70 (2H, d, CH=CH), (3c) 7.45–8.60(5H,m,Ar-H),7.60-7.95 (2H,m,CH of furan) and 6.94,7.70 (2H, d, CH=CH), (3d) 7.40–8.60(10H,m,Ar-H),7.43-7.54 (2H,m, CH of furan) and 6.94,7.70 (2H,d,CH=CH) and (3e) 7.45–8.60(9H,m,Ar-H),7.45-7.56(2H,m, CH of furan) and 6.94,7.70 (2H, d, CH=CH). The C, H, N analysis data of all compounds are presented in Table -1.

The **(3a-e)** were reacted with Thiourea to form 3-(6-(5- substituted furan-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-yl)-2H-chromen-2-one **(4a-e)**. The structures **(4a-e)** were supported by the elemental analysis and IR spectra showing an absorption bands at 3350-3300 (N-H),1220(C=S),3030-3080 cm^{-1}(C-H of Ar.), 1650-1630 cm^{-1}(ketones), 1580-1550cm^{-1} (C=C), 1275(C-O),1120 (C-O-C),1350(NO_2), 1050 (C-Cl), 590 (C-Br). ^{1}H NMR: (4a) 7.45–8.00(5H,m,Ar-H),7.43-8.22(3H,m,CH of furan), 6.50 (1H,s, =CH), 4.15(1H,t, Ar-H) and 12.08-9.10(2H,s,NH), (4b) 7.45–8.05(5H,m,Ar-H),7.45-7.54(2H,m,CH of furan), 6.50 (1H,s,= CH), 4.15(1H,t,Ar-H) and 12.08-9.10(2H,s,NH), (4c) 7.45–8.60 (5H,m,Ar-H),7.15-7.65(2H,m, CH of furan) 6.50 (1H,s, =CH), 4.15(1H,t,Ar-H) and 12.08-9.10 (2H,s,NH), (4d) 7.40–8.60(10H,m, Ar-H),7.40-7.54 (2H,m, CH of furan), 6.50 (1H,s, =CH), 4.15(1H,t,Ar-H) and 12.08-9.10(2H,s,NH), and (4e) 7.45–8.60(9H,m,Ar-H),7.40-7.56(2H,m, CH of furan), 6.50 (1H,s, =CH), 4.15(1H,t,Ar-H) and 12.08-9.10(2H,s,NH). All these are agreed with the structure expected. All these are agreed with the reaction products of 3(a-e) with thiourea. The C, H, N analysis data of all compounds are presented in Table-2.

The compounds **(4a-e)** also reacted chloro acetic acid and anthranilic acid to formed 5-(5-substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-2H-thiazolo[3,2-a]pyrimidin-3(5H)-one **(5a-e).** The **(5a-e)** structures were supported by the elemental analysis and IR spectra showing an absorption bands at 1620-1656 (C=N), 3030-3080 cm^{-1}(C-H of Ar.),1680-1650 (CO), 840(C-S), 1275(C-O),1120 (C-O-C),1350(NO_2),1050(C-Cl), 840(C-S),590 (C-Br). ^{1}H NMR: (5a) 7.45–8.00 (5H,m,Ar-H),7.43-8.22(3H,m,CH of furan), 6.50-5.80 (2H,d,CH) and 4.10(2H,s,CH_2) (5b) 7.45–8.05(5H,m,Ar-H),7.45-7.54(2H,m,CH of furan), 6.55-5.80 (2H,d,CH) and 4.10(2H,s,CH_2), (5c) 7.45–8.60 (5H,m,Ar-H),7.15-7.65(2H,m,CH of furan), 6.55-5.70 (2H,d,CH) and 4.15(2H,s,CH_2) (5d) 7.45–8.60(10H,m,Ar-H),7.40-7.55 (2H,m, CH of furan), 6.55-5.80 (2H,d,CH) and 4.10(2H,s,CH_2) and (5e) 7.45–8.60(9H,m,Ar-H),7.40-7.58(2H,m, CH of furan), 6.50-5.83 (2H,d,CH) and 4.12(2H,s, CH_2). The C, H, N analysis data of all compounds are presented in Table-3.

The compounds **(4a-e)** further react anthranilic acid to formed 4-(5- substituted furan-2-yl)-2-(2-oxo-2H-chromen-3-yl)-2H-pyrimido[2,1-b] quinazolin-6(11H)-one **(6a-e).** The **(6a-e)** were supported by the elemental analysis and IR spectra showing an absorption bands at 3350-3300(NH),1620-1655 (C=N), 3030-3080 cm^{-1}(C-H of Ar.),1680-1650 (CO), 1275(C-O),1120 (C-O-C),1350(NO_2),1050(C-Cl), 590 (C-Br). ^{1}H NMR: (6a) 7.25–8.00 (9H,m,Ar-H),7.43-8.22(3H,m,CH of furan), 6.50-3.30 (2H,d,CH) and 5.10(1H,s,NH) (6b) 7.25–8.05(9H,m,Ar-H),7.45-7.54(2H,m,CH of furan), 6.50-3.25 (2H,d,CH) and 5.05(1H,s,NH), (6c) 7.20–8.60 (9H,m,Ar-H),7.15-7.65(2H,m,CH of furan), 6.50-3.35 (2H,d,CH) and 5.12(1H,s,NH), (6d) 7.25–8.60(14H,m,Ar-H),7.40-7.55 (2H,m, CH of furan), 6.50-3.32 (2H,d,CH) and 5.08(1H,s,NH) and (6e) 7.25–8.60(13H,m,Ar-H),7.40-7.58(2H,m, CH of furan), 6.50-3.25 (2H,d,CH) and 5.15(1H,s, NH). The C, H, N analysis data of all compounds are presented in Table-4.

The examination of elemental analytical data for all three series of compounds reveals that the elemental contents are consistent with the predicted structure shown in Scheme-1. The IR/NMR data also direct the assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS peak value of selected compounds. These indicate the molecular weight of compound which assigned the predicted structure.

Antibacterial activity of all series of **(3a-e),(4a-e),(5a-e)** and **(6a-e)** compounds are presented in Table-5. The results show that all compounds are more or less toxic for bacteria depending upon the molecular structure of compounds. The results show the trend of activity as : e> c > b> d > a compounds of each series . It was also observed

that e and c series of compounds are more toxic as the presence of chlorine atoms in their structures.
Antifungal activity of all series of **(3a-e),(4a-e),(5a-e)** and **(6a-e)** compounds are presented in Table-6. The results show that all compounds are more or less toxic for fungi depending upon the molecular structure of compounds. The results show the trend of activity as : e> c > b> d > a compounds of each series . It was also observed that e and c series of compounds are more toxic as expected the presence of chlorine atoms in their structures.

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