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SYNTHESIS AND ANTI-MICROBIAL ACTIVITIES OF SOME NEW S-TRIAZINE CONTAINING CHALCONES

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Abstract:
Chalcone and Triazine are major structural core systems found in many pharmacologically active Compounds. Chalcones represent a group of compounds with fascinating biological activities, in the present research article chalcone is coupled with 4-hydroxy coumarin comprising S-triazine molecule which contributes to increase the biological importance of the chalcones. The literature has demonstrated that compounds with a 1,3,5-triazine moiety or chalcone bridge frequently exhibit noteworthy biological activity characteristics. The designed molecules were successfully synthesized in the laboratory using literature methods and structures were confirmed by ^{1}HNMR, IR and Mass Spectroscopy. All the synthesized compounds **(7a-j)** were screened for anti-bacterial and anti-fungal activities.

Keywords: Chalcones, 1,3,5-Triazine, 4-Hydroxy Coumarin, Disubstituted Triazine Derivatives. Anti-bacterial and Anti-fungal Activities.

Introduction:

Chalcone scaffolds are privileged chemical structures in the medicinal chemistry sector [i]. Chalcones are a class of biological active agents composed of an aromatic ketone and an enone [ii] are useful in the synthesis of a wide range of heterocyclic compounds and undergo a number of chemical reactions. Chalcones are active aromatic compounds which is a parent of various bioorganic precursors molecules in medicinal chemistry. Aldol condensation can be used to synthesize chalcones. These processes are crucial for generating C-C bonds and are frequently employed in synthetic organic chemistry [iii-v]. Naturally occurring Chalcones has the molecular formula 1,3- diphenyl-2-propene-1-one. It has a broad spectrum of biological actions,including immunoregulation, analgesic, antioxidant, antifungal,
anticancer, and antibacterial properties [vi-ix].

In medicine, heterocyclic chemistry is vital. It is made up of many kinds of chemical compounds that have a variety of pharmacological properties[x]. s-Triazine is also one of the significant biological active heterocyclic molecules. Triazine is a six-membered heterocyclic

ring compound having three nitrogens in its structure by replacing carbon-hydrogen atoms in the benzene ring with the general formula $C_3H_3N_3$. Triazines are reactive groups that can sustain a variety of synthetic changes [xi]. Certain s-triazine compounds exhibit herbicidal, antibacterial, and antimicrobial properties [xii-xiii], anti-HIV infection [xiv]. Additionally, the triazine compounds have antiviral, antidepressant, and anti- ulcer properties [xv]. All 1,3,5-triazine derivatives with a wide range of practical uses are compounds with diverse substituents that are 2,4,6-mono, di-, or tri-substituted, symmetrical, or nonsymmetric. Because chlorine atoms are reactive with nucleophiles, cyanuric chloride is the most crucial reagent for achieving these synthetic molecular changes [xvi].

Coumarin derivatives have played a pivotal role in medicinal chemistry due to their broad biological properties [xvii]. Among the various coumarin derivatives, 4-hydroxy coumarins are potential in therapeutic applications such as anticancer [xviii], antimalarial [xix], antifungal [xx], antiviral [xxi], anticoagulants [xxii]. We decided to use the s-triazine nucleus as a core scaffold after reviewing the research mentioned above. It has been revealed that molecular imprinting uses s-triazine derivatives as templates [xxiii] 4-hydroxy Coumarin shows promising biological activity [xxiv]. Some derivatives of 4 amino Chalcones show anti-inflammatory and anti-microbial activity [xxv]. Due to the enormous biological potential of cyanuric chloride, 4-hydroxy coumarin, and chalcones derivatives, we were therefore inspired to synthesize new s-triazine derivatives and investigate their biological activities.

Experimental section:

Melting points were determined in open capillaries. ^{1}H NMR spectra was recorded at 500 MHz (Bruker Avance) Cryo-magnet Spectrometer in $CDCl_3$ or DMSO Solvent using TMS as an internal standard. IR spectra were recorded on a FT Infra-Red Spectrophotometer Model RZX Perkin Elmer. The products were confirmed by the comparison of their Mass Spectra, IR, ^{1}HNMR.TLC was carried out on Silica gel G (Merk) plates with n-Hexane/Ethyl Acetate (8:2) system.

Synthesis of 2-(Coumarinyl-4-oxy)-4,6-dichloro-s-triazine(3)

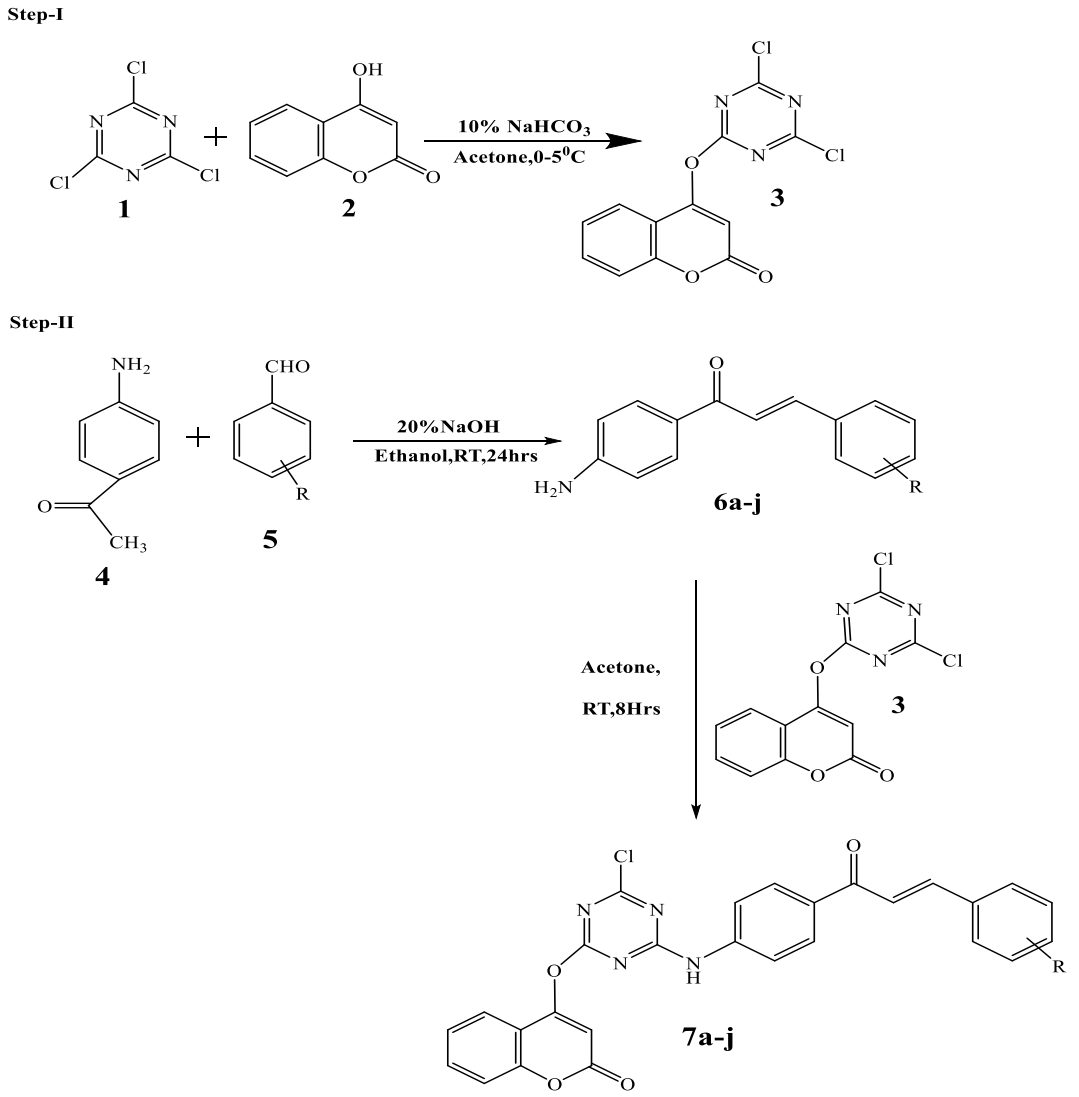
To a stirred solution of Cyanuric chloride (0.05 mol, 9.2 g) in acetone (50 ml) at 0-5°C, the solution of 4-hydroxy Coumarin (0.05 mol, 8.1 g) in 10% $NaHCO_3$ (45 ml) was added drop wise in two hours. The reaction was being monitored by TLC using n-Hexane/Ethyl Acetate (8:2) as eluent. After completion of reaction, the stirring was stopped and the reaction mixture was poured in to crushed ice. The product obtained was filtered and dried. The crude product was purified by recrystallization from acetone to give the title compound (3); yield 87%, M.P. 208-210°C.

General Procedure for the Preparation of 1-(4-aminophenyl)-3-phenylprop-2-en-1-ones Compounds (6a-j):- Equimolar quantity (0.01M) of 4-amino acetophenone and respective aryl aldehyde were mix and dissolved in required amount of alcohol. To this add aqueous potassium hydroxide (KOH 20%) solution then reaction mixture was continuously stirred for 24 hours at room temperature and check reaction progress on TLC (n-Hexane/Ethyl Acetate, 8:2) after completion of reaction the reaction mixture was poured on crushed ice neutralized with dil. HCI and product was filtered and recrystallized from alcohol. The physical data is recorded and correlated with reference [xxv].

General Procedure for the Preparation of 4-((4-chloro-6-((4-cinnamoylphenyl)amino)-1,3,5-triazin-2-yl) oxy)-2H-chromen-2-ones Compounds(7a-j):- To the stirred solution of compound 3(0.001mol) in acetone 20 ml add substituted chalcones (0.001mol) , maintaining the temp 40^0C the pH was kept neutral by the addition of 10% $NaHCO_3$ solution. The temperature was gradually raised to 45^oC during 2 hours and further maintained for 2 hr. progress of reaction was monitored by TLC (n-Hexane/ethyl acetate, 8:2) after completion of reaction, and the reaction mixture was poured in ice-cold water. The solid product was

filtered and dried. The crude was purified and recrystallized from acetone.

Reaction scheme:



Scheme I. 4-((4-chloro-6-((4-cinnamoylphenyl)amino)-1,3,5-triazin-2-yl)oxy)- 2H-chromen-2-one .

Spectral Analysis and Physical Data of Synthesized Compound (7a-j):

4-((4-chloro-6-((4-cinnamoylphenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (7a) : Yield 60%, m.p.120-1220C**.** IR (KBr, νmax, cm-1): 3206 (-NH- stretch), 2926(-C-H- stretch in Ar),1717(-C=O stretch in Coumarin), 1620 (-C=O stretch), 1560(-CH=CH-), 1329 (-C-N- stretch), 1219(-C-O-C- stretch in Coumarin).^{1}H NMR (DMSO,500 MHz, δ ppm): 9.45 (s, 1H, -NH-, exchangeable with D2O), 8.10 (1H, d,), 7.80 (d,2H), 7.70 (d, 2H), 7.60 (d,2H), 7.52 (1H, d,), 7.40 (2H,), 7.30(m,1H), 7.35- 7.70(m,4H) 5.70(s,1H).Mass (m/z): 498 [m+1], Anal. Calcd. For C27H17ClN4O4, C:65.26, H:3.45, N:11.28, Found C:65.31, H: 3.49, N:11.30.

(4-((4-chloro-6-((4-(3-(2-chlorophenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)- 2H-chromen-2-one (7b):

Yield 80%, m.p.137-1390C**.** IR (KBr, νmax, cm-1): 3220 (-NH- stretch), 2960(-C-H- stretch in Ar), 1730 (-C=O stretch in Coumarin), 1655 (-C=O stretch), 1587(-CH=CH-), 1340 (-C-N- stretch), 1220 (-C-O-C- stretch in Coumarin), 780 (C-Cl stretch).1H NMR (DMSO,500 MHz,

δ ppm): 9.40 (s, 1H, -NH-, exchangeable with D_2O),8.30 (d,1H), 7.60 (d,2H), 7.52 (d,1H), 7.50 (d,2H),7.45 (d,1H), 7.10(m,1H),7.35-7.70(m,4H),7.20-7.30 (d, 2H), 5.90(s,1H). Mass (m/z): 530.05 [m+1], Anal. Calcd. For $C_{27}H_{16}Cl_2N_4O_4$, C:61.04, H: 3.04, N:10.54, Found C:61.00, H: 3.00, N:10.45.

(4-((4-chloro-6-((4-(3-(4-chlorophenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one (7c):

Yield 85%, m.p.105-1070C**.** IR (KBr, νmax, cm-1): 3235 (-NH- stretch), 2980(-C-H- stretch in Ar), 1725 (-C=O stretch in Coumarin), 1650 (-C=O stretch), 1595(-CH=CH-), 1345(-C-N-stretch), 1221 (-C-O-C- stretch in Coumarin), 770 (C-Cl stretch).1H NMR (DMSO,500 MHz, δ ppm): 9.80 (s, 1H, -NH-, exchangeable with D_2O),7.80 (d,2H), 8.10 (d,1H), 7.72 (d,2H), 7.62(d, 2H), 7.60 (d,2H), 7.50 (d,1H), 7.35-7.70(m,4H,), 5.85(s,1H).Mass (m/z): 530.05 [m+1], Anal. Calcd. For $C_{27}H_{16}Cl_2N_4O_4$, C:61.04, H: 3.04, N:10.54, Found C:61.00, H: 3.00, N:10.45.

4-((4-chloro-6-((4-(3-(2,4-dichlorophenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2- yl)oxy)-2H-chromen-2-one(7d):

Yield 75%, m.p.140-1420C**.** IR (KBr, νmax, cm-1): 3255 (- NH- stretch), 2982(-C-H- stretch in Ar), 1725 (-C=O stretch in Coumarin), 1660 (-C=O stretch), 1590(-CH=CH-), 1342(-C-N-stretch), 1218 (-C-O-C- stretch in Coumarin), 785 (C- Cl stretch).1H NMR (DMSO,500 MHz, δ ppm): 9.42 (s, 1H, -NH-, exchangeable with D_2O),8.15 (d,1H), 7.80 (d,2H), 7.72 (d,2H), 7.63 (s,1H) , 7.65 (d,1H), 7.50 (d,1H), 7.40(d,1H),7.35-7.70 (m,4H), 5.85(s,1H).Mass (m/z): 564.02 [m+1], Anal. Calcd. For$C_{27}H_{15}Cl_3N_4O_4$, C:57.32, H: 2.67, N:9.90, Found C:57.27, H: 2.63, N:9.85.

4-((4-chloro-6-((4-(3-(2-fluorophenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)- 2H-chromen-2-one (7e):

Yield 65%, m.p.121-1230C**.** IR (KBr, νmax, cm-1): 3230 (-NH- stretch), 2980(-C-H- stretch in Ar), 1732 (-C=O stretch in Coumarin), 1650 (-C=O stretch), 1585(-CH=CH-), 1341 (-C-N-stretch), 1220 (-C-O-C- stretch in Coumarin), 860 (C-F stretch).1H NMR (DMSO,500 MHz, δ ppm): 9.43 (s, 1H, -NH-, exchangeable with D_2O),8.31 (d,1H), 7.60 (d,2H), 7.50 (d,2H,), 7.42 (d,1H,), 7.12(m,1H),7.14 (d,1H), 7.15-7.30 (d,2H), 7.35-7.70(m,4H), 5.90(s,1H).Mass (m/z): 514.08 [m+1], Anal. Calcd. For $C_{27}H_{16}ClFN_4O_4$, C:62.98, H: 3.13, N:10.88, Found C:62.91, H: 3.04, N:10.81.

4-((4-chloro-6-((4-(3-(4-fluorophenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)- 2H-chromen-2-one (7f):

Yield 70%, m.p.126-1280C**.** IR (KBr, νmax, cm-1): 3240 (-NH- stretch), 2990(-C-H- stretch in Ar), 1700 (-C=O stretch in Coumarin), 1640 (-C=O stretch), 1570(-CH=CH-), 1345(-C-N-stretch), 1221 (-C-O-C- stretch in Coumarin), 882 (C-Fstretch).1H NMR (DMSO,500 MHz, δ ppm): 9.80 (s, 1H, -NH-, exchangeable with D_2O),8.02 (d,1H), 7.78 (d,2H), 7.68 (d,2H), 7.65(d, 2H), 7.52 (d,1H), 7.36 (d,2H), 7.35-7.70(m,4H), 5.85(s,1H). Mass (m/z): 514.08 [m+1], Anal. Calcd. For $C_{27}H_{16}ClFN_4O_4$, C:62.98, H: 3.13, N:10.88, Found C:62.91, H: 3.04, N:10.81.

4-((4-((4-(3-(4-bromophenyl)acryloyl)phenyl)amino)-6-chloro-1,3,5-triazin-2- yl)oxy)-2H-chromen-2-one (7g):

Yield 82%, m.p.111-1130C**.** IR (KBr, νmax, cm-1): 3215 (- NH- stretch), 2982(-C-H- stretch in Ar), 1710 (-C=O stretch in Coumarin), 1670 (-C=O stretch), 1605(-CH=CH-), 1310(-C-N-stretch), 1210 (-C-O-C- stretch in Coumarin), 850 (C- Br stretch).1H NMR (DMSO,500 MHz, δ ppm): 9.30 (s, 1H, -NH-, exchangeable with D_2O),8.00 (d,1H), 7.70(d, 2H,), 7.69 (d,2H), 7.61 (d,2H), 7.60 (d,2H), 7.50 (d,1H), 7.40-7.85(m,4H), 5.83(s,1H).Mass (m/z):

574.00 [m+1], Anal. Calcd. For $C_{27}H_{16}ClBrN_4O_4$, C:56.32, H: 2.80, N:9.73, Found C:56.25, H: 2.70, N:9.65.

4-((4-chloro-6-((4-(3-(o-tolyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H- chromen-2-one (7h):

Yield 80%, m.p.103-1050C**.** IR (KBr, ν_{max}, cm-1): 3205 (-NH- stretch), 3087(-C-H- stretch in Ar), 1720 (-C=O stretch in Coumarin), 1617 (-C=O stretch), 1562(- CH=CH-), 1320 (-C-N- stretch), 1220 (-C-O-C- stretch in Coumarin),.^{1}H NMR (DMSO,500 MHz, δ ppm): 9.20 (s, 1H, -NH-, exchangeable with D_2O), 8.15(d,1H), 7.60 (d,2H), 7.50 (d,2H), 7.34 (d,1H), 7.01 (d,1H), 6.92(m,1H), 7.25-7.32 (d, 2H), 7.40-7.82(m,4H) 5.70(s,1H),2.40 (s,3H).Mass (m/z): 510.11 [m+1], Anal. Calcd. For $C_{28}H_{19}ClN_4O_4$, C:65.82, H: 3.75, N:10.97, Found C:65.76, H: 3.69, N:10.91.

4-((4-chloro-6-((4-(3-(p-tolyl)acryloyl)phenyl)amino)-1,3,5-triazin-2-yl)oxy)-2H- chromen-2-one (7i) :

Yield 78%, m.p.100-1020C**.** IR (KBr, ν_{max}, cm-1): 3210 (-NH- stretch), 3013(-C-H- stretch in Ar), 1715 (-C=O stretch in Coumarin), 1694 (-C=O stretch), 1660(- CH=CH-), 1330 (-C-N- stretch), 1218 (-C-O-C- stretch in Coumarin).^{1}H NMR (DMSO,500 MHz, δ ppm): 9.25 (s, 1H, -NH-, exchangeable with D_2O), 8.02(d,1H), 7.82 (d,2H), 7.76 (d,2H), 7.55 (d, 2H), 7.30 (d,1H,),7.25 (d,2H), 7.45-7.86(m,4H), 5.75(s,1H),2.44 (s,3H).Mass (m/z): 510.11 [m+1], Anal. Calcd. For $C_{28}H_{19}ClN_4O_4$, C:65.82, H: 3.75, N:10.97, Found C:65.76, H: 3.69, N:10.91.

4-((4-chloro-6-((4-(3-(4-methoxyphenyl)acryloyl)phenyl)amino)-1,3,5-triazin-2- yl)oxy)-2H-chromen-2-one (7j):

Yield 78%, m.p.106-1080C**.** IR (KBr, ν_{max}, cm-1): 3200 (- NH- stretch), 2965(-C-H- stretch in Ar),1712 (-C=O stretch in Coumarin), 1642 (-C=O stretch), 1610(-CH=CH-), 1310 (-C-N- stretch), 1218 (-C-O-C- stretch in Coumarin),1030(- C-O-C-,Ar-OCH_3).1H NMR (DMSO,500 MHz, δ ppm): 9.15 (s, 1H, -NH-, exchangeable with D_2O), 8.05(d,1H), 7.80 (d,2H), 7.70 (d,2H), 7.52 (d, 2H), 7.06 (d,1H), 7.40 (d,2H), 7.45-7.86(m,4H), 5.75(s,1H), 2.44 (s,3H).Mass (m/z): 526.10 [m+1], Anal. Calcd. For $C_{28}H_{19}ClN_4O_5$, C:63.83, H: 3.63, N:10.63, Found C:65.78, H: 3.58, N:10.67.

Biological Activity.

Anti-bacteria and Anti-fungal Activities:

All the synthesized compounds from the series (**7a-j**) were screened for antibacterial activity against two Gram-Positive bacteria *viz. B licheniforims* and *B.subtilis*, and one Gram-Negative bacteria *viz. E.Coli* by disk diffusion assay [xxvi]. Using Chloramphenicol (100 µs/disk) the reference standard for comparing the results. The Anti-bacterial activity was screened by using nutrient agar obtained from Hi-media. Composition (gL^{-1}). Sodium chloride-5 : Beef extract-3: Penton 5.0 (P^H 7.2).The newly synthesized series of compounds (**7a-j**) were also screened for Anti-fungal activity against *C. albicans* by agar diffusion assay [xxvii] , using Amphotericin B (100 units /disk) as the reference standard. The Antifungal activity is screened by using Sabouraud Agar Media and DMSO as control solvent. The diameter of the Zone (mm) is measured by Vernier Caliper. The Antibacterial and Anti-fungal activity of the 4-((4-chloro-6-((4-cinnamoylphenyl) amino)-1,3,5-triazin-2-yl)oxy)-2H- chromen-2-one compound derivatives (**7a-j**) is shown in Table No.1.

TABLE NO 1.
Anti-bacterial and Anti-fungal Screening of Compounds (**7a-j**)

Compound		**Anti-bacterial Activity**			**Anti-Fungal Activity**
		B licheniforims	***B.subtilis***	***E.Coli***	***C. albicans***
7a	**H**	**-**	**-**	**9.6**	**11.91**
7b	**2-Cl**	**-**	**7.9**	**-**	**9.2**
7c	**4-Cl**	**9.6**	**10.2**	**10.4**	**22.9**
7d	**2,4-Cl**	**-**	**-**	**-**	**18.7**
7e	**2-F**	**-**	**-**	**-**	**10.5**
7f	**4-F**	**-**	**10.8**	**-**	**14.4**
7g	**4-Br**	**-**	**-**	**-**	**15.8**
7h	**2-Me**	**-**	**-**	**7.6**	**7.3**
7i	**4-Me**	**-**	**-**	**-**	**19.7**
7j	**4-OCH3**	**-**	**-**	**-**	**12.8**
Chloramphenicol		**17**	**19**	**27.1**	**NA**
Amphotericin B		**NA**	**NA**	**NA**	**10.11**

Result and Discussion:

Literature survey reveals that there is no reports of 4-((4-chloro-6-((4-cinnamoylphenyl) amino)- 1,3,5-triazin-2-yl) oxy)-2H-chromen-2-one Compound **(7a-7j)** hence it was planned to synthesis these compounds. In the present study step-I, 1,3,5-triazine **(1)** is reacted with 4-hydroxy Coumarin **(2)** in the presence of aq. $NaHCO_3$ in acetone to the yield 2-(Coumarinyl-4- oxy)-4,6-dichloro-s-triazine **(3)** in good yield**.** In the step-II, 4-Amino acetophenone **(4)** is reacted with the substituted aryl aldehydes **(5)** in the presence of NaOH followed by condensation reaction to yield 1-(4-aminophenyl)-3-phenylprop-2-en-1-one compound **(6a-6j)** with good yield. Further synthesis, Compounds **(6a-6j)** reacted with the compound **(3)** in the presence of aq. $NaHCO_3$ and Acetone as solvent to Yield **(7a-7j)** with excellent yield. The IR spectra of **(7c)** show strong absorption band at 3235cm^{-1} indicated the Stretching frequency of -NH- functional group. 1725cm^{-1} is stretching of (-C=O) in Coumarin ring, 1650cm^{-1} is the value for (-C=O) functional group in Chalcones and
1725cm^{-1} is for (-CH=CH-), 1345(-C-N-) stretching confirm the synthesis of coupling of Chalcone with s-triazine. ^{1}H NMR Spectrum of **(7c)** show that, Singlet at δ 9.80 ppm for (–NH-) gives confirmation of secondary amine, again singlet at δ 5.85 ppm for (-C-O-C-) confirm that the coupling of s-triazine and 4-hydroxy Coumarin. The Mass Spectra shows the molecular ion peak at 530.05 [m+1]. All these Spectral analyses shows that the Confirmation of synthesis of **(7a-7j)** compounds.

Screening of the biological activities of synthesized compounds revealed that, compound **7c** electron withdrawing chlorine group show good antibacterial activity against Gram Positive bacteria i.e. *B licheniforims.* Compounds **7b, 7c, 7f** having electron withdrawing chlorine and fluorine show good antibacterial activity against Gram-Positive bacteria i.e. *B.subtilis.* Compounds **7a,7c,7h,** show good antibacterial activity against Gram-Negative bacteria i.e. *E.Coli.*

The Investigation of Anti-fungal activity data revealed that, the compound which having Para substituent attached to the phenyl ring shows a very high zone of inhibition as compared to

ortho substituent against *C. albicans.* Fungal strain compared with the standard Amphotericin B drug.

Conclusion:

In the present study, we have reported the synthesis of new series of 4-((4-chloro-6-((4-cinnamoylphenyl) amino)-1,3,5-triazin-2-yl)oxy)-2H-chromen-2-one derivatives. The synthesized compound contains two heterocyclic i.e.4-Hydroxy Coumarin and s-Triazine moieties which couple with the biological active Chalcones which are evaluated for Anti-bacterial and Anti-fungal activities. The Compound with electron withdrawing group shows good Anti-bacterial activities compared to the standard Chloramphenicol drug. Para substituent shows more potent Anti- fungal activities against standard Amphotericin B. drug, than Ortho substituted derivatives. All the synthesized series of compound shows excellent to moderate activity against the Pathogens and are very promising core molecule as potent Antifungal agents, further investigation is needed.

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Conflict of Interest:

The Authors declare that there is no conflict of interest regarding the Publication of these Articles.

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