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Review Article

SYNTHESIS OF SOME NOVEL BENZOPYRANES DERIVATIVES AND EVALUATION THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

Benzopyran (chromene) is one of the privileged medicinal pharmacophore, which appears as an important structural component in natural compounds and generated great attention because of their interesting biological activity. The derivatives of benzopyran moiety can be capable of interacting with a variety of cellular targets which leads to their wide ranging biological activities such as antitumor, antihepatotoxic, antioxidant, anti-inflammatory, diuretic, anticoagulant, antispasmolytic, estrogenic, antiviral, antifungal, antimicrobial, anti-helminthic, hypothermal, vasodilatory, anti-HIV, antitubercular, herbicidal, anticonvulsant and analgesic activity. In the present study the synthesis of substituted benzopyran derivatives have been reported as one-pot reaction by reaction of 2-chlororesorcinol with malononitrile in the presence and aldehydes or ketones. The produced products were led to react with formamide to produce pyrimidochromene. Aminochromene-2-carbonitrile was converted into the corresponding imidate, which in turn converted upon treatment withhydrazine or ammonia to the corresponding amidine. The produced amidines were cyclized into the pyrimidochromene derivatives. The synthesized compounds have been characterized by TLC, Elemental analysis, IR and 1H-NMR Spectroscopy. Some of the synthesized compounds in this work were chosen and screened in vitro for their antimicrobial and anti-fungal activity against some strains of bacteria and fungi. The antibacterial and anti-fungal activities of synthesized compounds were compared with antibacterial and anti-fungal activity of the standard antibiotics Chloramphenicol and Sertaconazol. The most of the tested compounds revealed antibacterial and antifungal properties. This review is summarized to know about the different pharmacological activities of chromene nucleus with the extended knowledge about its antimicrobial and antifungal activity.

Keywords: 2-Chlororesorcinol, Pyrimidochromene, Amidines, antimicrobial and antifungal activity.

INTRODUCTION

Benzopyrans are an important group of organic compounds that are used as bactericides [1-3], fungicides [4], anti-inflammatory [5], and anticancer agents [6]. Benzopyrans also called chromenes, in which benzene and pyran are fused together with various levels of saturation and oxidation; they are very common in nature [7]. Benzopyrans derivatives are an important class of compounds, widely present in plants, including edible vegetables and fruits [8]. Chromene constitutes the backbone of various types of polyphenols and is widely found in natural alkaloids, tocopherols, flavonoids, and anthocyanins [9]. The biological activity of some natural chromene-based structures led to the development of synthetic analogs, some of them displaying remarkable effects as pharmaceuticals [4,10-13], including antimicrobial agents [14]. These pharmacological properties make us thought in the synthesis of some benzopyran derivatives in hoping that maybe have a prospective pharamatheoutical importance.

RESULTS AND DISCUSSION

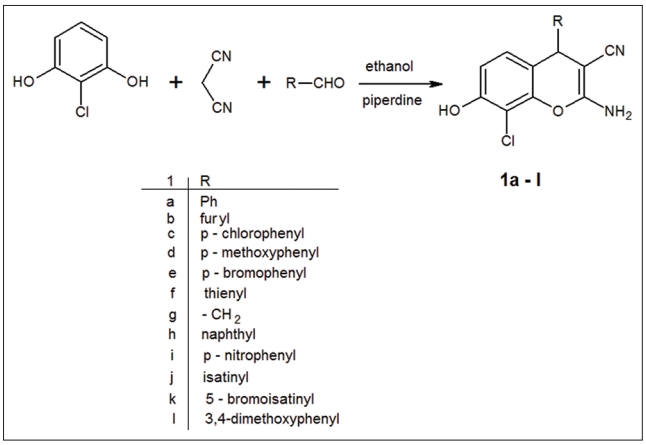
When 2-chlororesorcinol was made to react with arylidinemalononitriles in ethanol, 2-amino-8-chloro-7-hydroxy-4-aryl-4H-chromen-3-carbonitriles compounds 1a-l were produced as one pot reaction. The knoevenagel condensation of these aryl aldehydes with malononitrile were shown to proceed in water [15] or ethano [16] without other catalyst, and the reaction being driven toward completion by the precipitation of the product (Scheme 1).

These compounds were further confirmed using microanalyses (Table 1) and spectral data (Table 2). The infrared (IR) spectra of compounds 1a-l showed two absorption bands at 2200-2170 and 3100-3407/cm corresponding to cyano (CN) and amino (NH_2) groups respectively. The ^{1}HNMR spectra of compounds 1a-i showed proton signal at δ 4.8-5.0 and 6.5-6.7 ppm for (C-H pyran) and (2H, NH_2) groups respectively. When 2-NH_2-8-chloro-7-hydroxy-4-phenyl-4*H*-chromene-3-carbonitrile 1a was refluxed in formamide, benzopyranopyrimidines 2 was produced. On reacting 1a with triethyl orthoformate in the presence of acetic anhydride, the reaction gave 2-ethyl chromeneimidate 3. The product compound 3 was used as versatile starting material for other heterocycles, whereas it reacted with different NH_2 compounds to afford benzopyranopyrimidines. When compound 3 stirred at 0°C in ethanolic solution of ammonia, amidine compound 4 was produced, which upon heating in ethanolic solution of sodium ethoxide, it was cyclized into pyrimidochromene 5, (Scheme 2). IR spectra for compound 2 showed the disappearance of an absorption band of the CN group as well as the presence of an absorption band at 3200-3350/cm for NH_2 group and proton signal at δ 5.1, 2.9 ppm for (C-H pyran and 2H, NH_2) respectively. The decreased chemical shift of NH_2 signal can be attributed to the shielding effect of the conjugation of the aryl π-electrons. Compound 3, showed disappearance of an absorption band of the NH_2 group, as well as for compound 4, there is an absorption band at 3350-3450/cm for NH_2 group. Similarly, attempt of condensation of amidate 3, the reaction with aniline under the same condition was failed. On treatment amidate compound 3 with aniline underwent –CH=N- fission to give the starting material 1a as shown in (Scheme 2).

When imidate compound 3 was allowed to react with hydrazines in ethanol at 0°C, condensation reaction occurred accompanied with the elimination of ethanol, followed by cycloaddition reaction to produce the corresponding pyrimidochromeine compound 6. On reacting pyrimidochromine 6 with triethyl orthoformate in the presence of catalytic drops of acetic acid, the reaction gave the pyrimidochromene compound 7, when, compound 6 condensed with aromatic aldehydes (p-chlorobenzaldehyde), followed by cyclization, compound 8 was given. Finally the reaction between compound 6 and chloroacetylchloride was succeeded, and triazinopyrimidino pyran component 9 was given, (Scheme 3).

BIOLOGICAL ACTIVITIES

Some of the synthesized compounds in this work were chosen and screened *in vitro* for their antimicrobial activity against some strains of bacteria and fungi. The antifungal activities of tested compounds were evaluated by reported method [17], using (2% concentration) of selected compounds in dimethyl sulfoxide (DMSO) as a solvent. The inhibition zone (mm) compared with sertaconazole as a reference. In case of antibacterial also the concentration of the tested compound is 2% and the inhibition zone in mm were compared with chloramphenicol as a reference. The most of the tested compounds revealed antibacterial properties. From the (Table 3), we are found that all the tested compounds inhibit the gross of all used strain of bacteria, whereas they inhibit the gross of *Serratia marcescens* more than the inhibition of antibiotic (chloramphenicol), which used as the blank. Also, they revealed antifungal activity against some species of used fungi, whereas all tested compounds revealed inhibition of *Candida clbicans* gross, and all of the tested compound are not show any activity against *Aspergillus niger*. However, they show activity against all the rest fungi species used except compounds, 1 h and 1 i (Table 4).



1	R
a	Ph
b	furyl
c	p - chlorophenyl
d	p - methoxyphenyl
e	p - bromophenyl
f	thienyl
g	- CH_2
h	naphthyl
i	p - nitrophenyl
j	isatinyl
k	5 - bromoisatinyl
l	3,4-dimethoxyphenyl

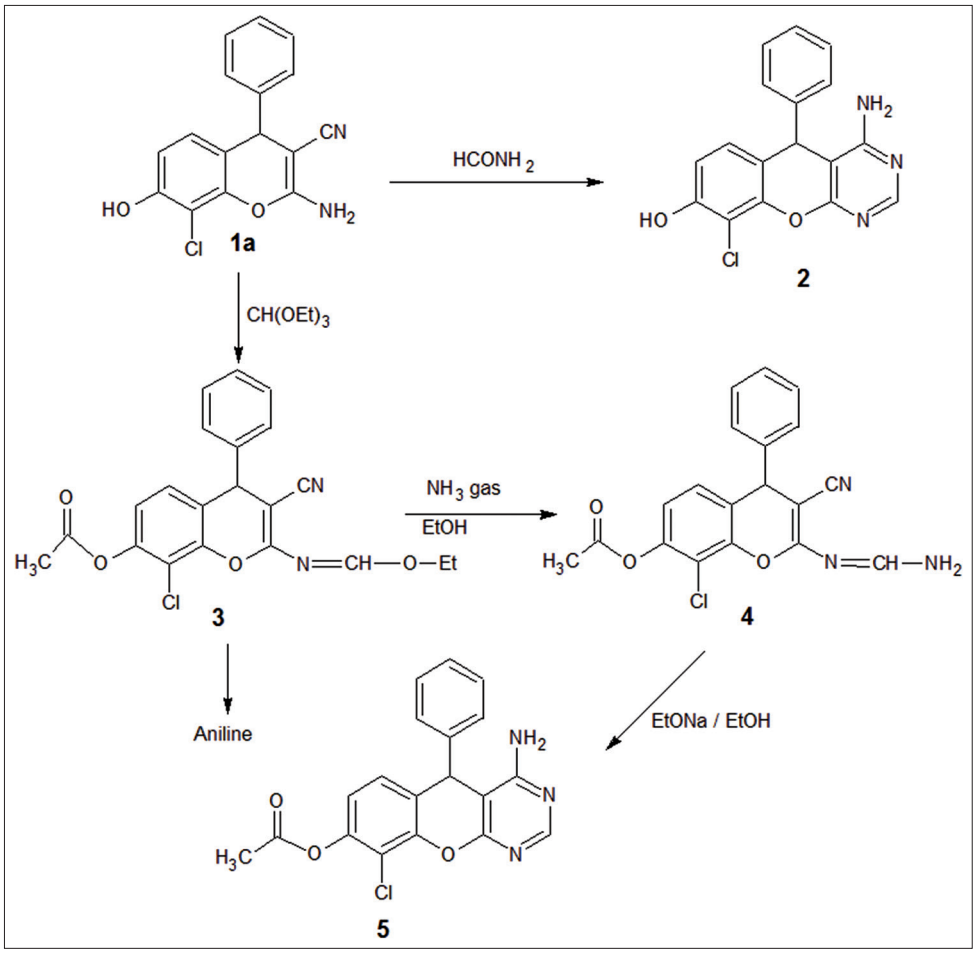
Scheme 1: Synthesis of 2-amino-8-chloro-7-hydroxy-4-aryl-4H-chromen-3-carbonitriles 1a-i.

CONCLUSIONS

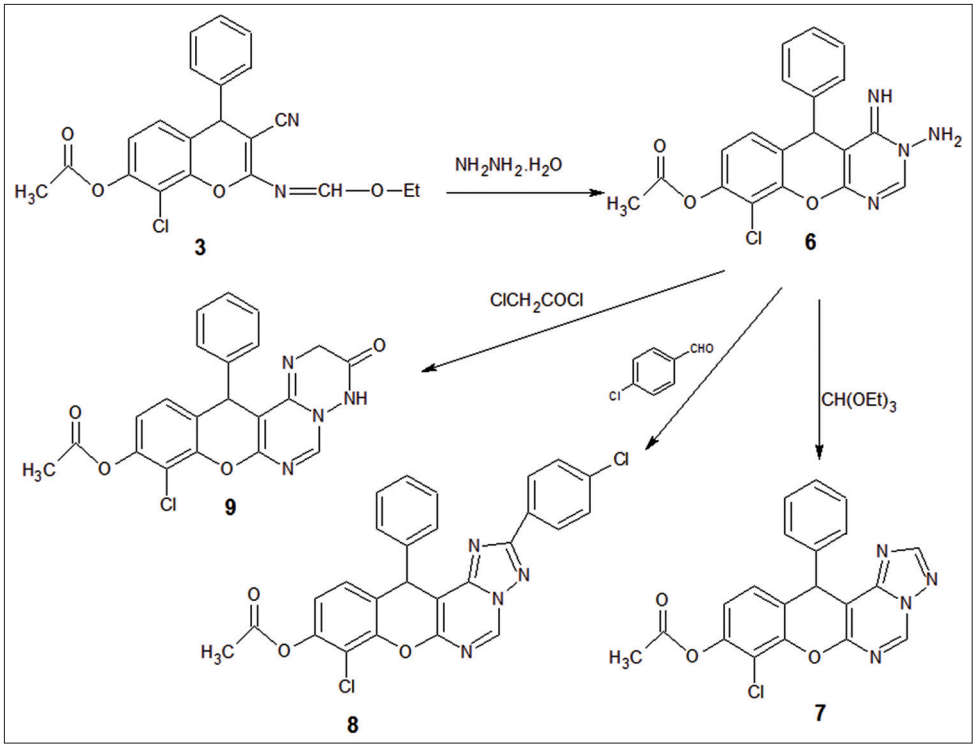
In this study, benzopyran derivatives were prepared in one-pot reaction and the resulting compound 1a react with formamid and orthoformate given pyrimidochromene 2, 3. When compound 3 react with ammonia, compound 4 was given, which convert to pyrimidochromene 5 when react with sodium ethoxide. Pyrimidochromeine compound produced when imidate compound 3 react with hydrazine which, the result compound convert to pyrimidochromene 7 and triazinopyrimidino pyran 9 when react with triethylorthoformate and chloroacetyl chloride respectively. Some of the synthesized compounds show activity against some strains of bacteria and fungi.

EXPERIMENTAL SECTION

Melting points were recorded on a Gallen–Kamp apparatus and were uncorrected. IR spectra were recorded on a Shimadzu- 470 IR-Spectrophotometer (KBr: ν_{max} in cm^{-1}). ^{1}HNMR Spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard or on a JEOL LA 400 MHz FT-NMR Spectrometer (δ in ppm). Elemental analyses were measured on a Perkin-Elmer 24°C elemental analyzer.



Scheme 2: Synthesis of compounds benzopyranopyrimidines 2, 2-ethyl chromeneimidate 3 which convert to amidine 4, which turned to pyrimidochromene 5



Scheme 3: Synthesis of compound pyrimidochromeine 6, which convert to corresponding compounds, pyrimidochromene 7, 8, triazinopyrimidino pyran 9

Table 1: Physical constants of compounds (1a-l)

Compound	R	M.p.°C	Yield %	Mol. Formula (Mol.W)	Analytical Data: Calcd./Found				
						C	H	N	Cl
1a	C_6H_5	279	89	$C_{16}H_{11}ClN_2O_2$	Calcd	64.33	3.72	9.38	11.87
				(298.73)	Found	64.07	3.92	9.54	12.06
1b	C_4H_3O-2-furyl	>360	70	$C_{14}H_9ClN_2O_3$	Calcd	58.25	3.14	9.70	12.28
				(288.69)	Found	58.12	2.92	9.86	12.44
1c	P-ClC_6H_4	240	75	$C_{16}H_{10}Cl_2N_2O_2$	Calcd	57.68	3.03	8.41	21.28
				(333.18)	Found	57.47	2.83	8.64	21.46
1d	O-$MeOC_6H_4$	280	80	$C_{17}H_{13}ClN_2O_3$	Calcd	62.11	3.99	8.52	10.78
				(328.76)	Found	61.89	4.25	8.81	11.02
1e*	P-BrC_6H_4	220	65	$C_{16}H_{10}BrClN_2O_2$	Calcd	50.89	2.67	7.42	9.39
				(377.63)	Found	51.18	2.83	7.69	9.22
1f**	2-Thienyl	265	75	$C_{14}H_9ClN_2O_2S$	Calcd	55.18	2.98	11.63	9.19
				(304.76)	Found	54.97	3.32	11.90	9.46
1g	-$(CH_2)_5$	255-57	70	$C_{15}H_{15}ClN_2O_2$	Calcd	61.97	5.20	9.63	12.19
				(290.75)	Found	62.23	5.03	9.38	12.44
1h	1-naphthyl	275-77	80	$C_{20}H_{13}ClN_2O_2$	Calcd	68.87	3.76	10.16	8.03
				(348.79)	Found	69.12	3.97	9.94	7.84
1i	P-$NO_2C_6H_4$	268	85	$C_{16}H_{10}ClN_3O_4$	Calcd	55.91	2.93	12.22	10.31
				(343.73)	Found	56.26	3.28	12.33	10.55
1j	Isatinyl	285	75	$C_{17}H_{10}ClN_3O_3$	Calcd	60.10	2.97	12.37	10.44
				(339.74)	Found	60.28	3.12	12.09	10.42
1k***	Bromoisatinyl	236	70	$C_{17}H_9BrClN_3O_3$	Calcd	48.77	2.17	10.04	8.47
				(418.64)	Found	48.94	2.35	9.82	8.25
1l	Dimethoxyphenyl	275	85	$C_{18}H_{15}ClN_2O_4$	Calcd	60.26	4.21	7.81	9.88
				(358.78)	Found	60.10	4.01	8.04	10.02

*Br: Calc.: 21.16; Found: 21.78%, **S: Calc.: 10.52; Found: 10.44%, ***Br: Calc.: 19.09; Found: 18.77%

General methods

2-NH_2-8-chloro-7-hydroxy-4-aryl-4H-chromene-3-carbonitrile (1a-l)

A mixture of appropriate aromatic aldehydes (0.01 mol), malononitril (0.01 mol, 660 mg) and 2-chlororesorcinol (0.01 mol, 1445 mg) in ethanol (10 ml) was heated under reflux for 10 minutes, the solid products was filtered, washed with ethanol and recrystallized by the

Table 2: Spectral data of compounds 1a-l

Compd	IR	^{1}H NMR
1a*	3485 (OH), 3280-3407 (NH_2), 2170 (CN), 1630 (C=C)	4.8 (s, 1H, CH pyran), 6.6 (s, 2H, NH_2), 6.8-7.6 (m, 7H, Ar-H), 10.3 (s, 1H, OH)
1b*	3500 (OH), 3200-3350 (NH_2), 2200 (CN), 1620 (C=C)	4.8 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 6.8-7.5 (m, 6H, Ar-H), 10.5 (s, 1H, OH)
1c*	3490 (OH), 3200-3350 (NH_2), 2200 (CN) ,1610 (C=C)	4.9 (s, 1H, CH-pyran), 6.6 (s, 2H, NH_2), 6.8-7.9 (m, 6H, CH-arom), 10.5 (s, 1H, OH)
1d*	3400 (OH), 3180-3340 (NH_2), 2190 (CN) , 1630 (C=C)	3.8 (s, 3H, CH3), 5.0 (s, 1H, CH-pyran), 6.7 (s, 2H, NH_2), 6.8-7.8 (m, 6H, CH-arom), 10.5 (s, 1H, OH)
1e*	3450 (OH), 3200-3350 (NH_2), 2200 (CN), 1630 (C=C)	4.8 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 6.8-8.0 (m, 6H, Ar-H), 10.4 (s, 1H, OH)
1f*	3400 (OH), 3200, 3350 (NH_2), 2200 (CN) , 1630 (C=C)	4.8 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 4.9 (s, 1H, CH pyran), 6.8-7.2 (m, 5H, Ar-H, thiophene-ring-H), 10.3 (s, 1H, OH)
1g*	3350 (OH), 3300-3100 (NH_2), 2200 (CN), 1620 (C=C)	1.3-1.5 (m, 6H, $3CH_2$), 1.7-1.9 (m, 4H, $2CH_2$), 4.8 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 6.8-7.0 (2s, 2H, Ar-H), 10.4 (s, 1H, OH)
1h**	3420 (OH), 3200-3350 (NH_2), 2200 (CN), 1610 (C=C)	4.8 (s, 1H, CH pyran), 6.5 (s, 2H, NH_2), 6.8-7.8 (m, 9H, Ar-H), 10.3 (s, 1H, OH)
1i**	3490 (OH), 3200-3350 (NH_2), 2200 (CN), 1630 (C=C)	5.0 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 6.8-8.0 (m, 6H, Ar-H), 10.5 (s, 1H, OH)
1j**	3480 (OH), 3210-3250 (NH_2), 2200 (CN), 1630 (C=C)	4.8 (s, 1H, CH pyran), 6.7 (s, 2H, NH_2), 6.8-8.0 (m, 5H, Ar-H), 10.5-11.0 (2s, 1H, OH, NH)
1k**	3500 (OH), 3200-3350 (NH_2), 3200 (NH), 2200 (CN), 1620 (C=C)	4.9 (s, 1H, CH pyran), 6.8 (s, 2H, NH_2), 6.8-8.0 (m, 6H, Ar-H), 10.5-11.2 (2s, 1H, OH, NH)
1l*	3400 (OH), 3200-3350 (NH_2), 2200 (CN), 1620 (C=C)	3.5-3.6 (2s, 6H, OCH3), 4.8 (s, 1H, CH pyran), 6.6 (s, 2H, NH_2), 6.7-7.1 (m, 5H, Ar-H), 10.3 (s, 1H, OH)

$CDCl_3$*, DMSO-d_6**, DMSO: Dimethyl sulfoxide

Table 3: Antibacterial activity of compounds 1a-l

Compound	*Bacillus cereus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Micrococcus Luteus*	*Serratia marcescens*
1a	9	11	8	12	11	12
1c	17	7	22	17	19	14
1d	8	13	8	14	14	12
1f	21	7	22	16	24	11
1h	16	16	14	18	17	13
1i	0	10	12	13	13	16
3	12	12	8	10	13	13
Chloramphenicol	12	15	12	12	12	10

Table 4: Antifungal activities of compounds 1a-l

Compound	*Aspergillus flavus*	*Aspergillus niger*	*Candida albicans*	*Geotrichum candidum*	*Scopulairopsis brevicaulis*	*Fusaium oxysporum*	*Trichophyton rubrum*
1a	1	1	8	7	9	1	2
1c	8	3	7	11	7	0	9
1d	2	0	8	1	1	1	1
1f	1	4	7	2	8	0	8
1h	7	2	7	13	9	8	7
1i	0	1	8	1	1	0	1
3	3	0	8	1	0	1	0
Sertaconazol	23	18	12	6	23	10	15

same solvent, compounds (1a-l), were produced (Scheme 3). The physical constants and spectral data of these compounds were listed in (Tables 1 and 2).

4-NH_2-9-chloro-5-phenyl-5H-chromeno [2, 3-d] pyrimidin-8-ol (2a)

When a mixture of compound (1a) (299 mg, 0.001 mol) and formamide (5 ml), was heated under reflux for 3 h, and allowed to cool. The crude product was filtered, and recrystallized from methanol, to yield (2a) as black solid (194 mg, 65%). Mp > 360°C: ν_{max} (KBr) 3410 (OH), 3200-3350 (NH_2), 1600, (C=C) cm^{-1};^{1}HNMR (DMSO) 2.9 (b, 2H, NH_2), 5.1 (s, 1H, CH-pyran), 7.0 -7.5 (m, 7H, Ar-H), 8.5 (s, 1H, OH); Anal. Calcd. $C_{17}H_{12}ClN_3O_2$ (325.74): C, 62.68; H, 3.71; Cl, 10.88; N, 12.90; O, 9.82%; Found: C, 62.89; H, 3.96; Cl, 11.15; N, 12.96; O, 9.99%.

Ethyl (8-chloro-3-CN-7-[2-oxopropyl]-4-phenyl-4H-chromen-2-yl)imidoformate (3)

A mixture of compound (1a) (299 mg, 0.001 mol) and (0.0135 mol) triethyl orthoformate, 2 ml) in acetic anhydride (5 ml) was refluxed for 7 hrs, then allowed to cool and poured into cold water. The solid product was filtered off and recrystallized from methanol to yield (3) as white solid (227 mg, 76%). Mp 170°C; ν_{max} (KBr) 3109 (CH -arom), 2950 (CH-aliphatic), 2220 (CN), 1710 (C=O) cm^{-1}; ^{1}HNMR (DMSO) 1.3 (t, 3H, CH_3), 2.9 (s, 3H, CH_3), 4.4 (q, 2H, CH_2),

4.8 (s, 1H, CH pyran), 6.9-7.0 (s – CH arom), 7.1-7.3 (s, 6H, phenyl-H and –CH-N-); Anal. Calcd., $C_{22}H_{19}ClN_2O_3$ (394.85): C, 66.92; H, 4.85; Cl, 8.98; N, 7.09; O, 12.16%; Found: C, 66.76; H, 4.54; Cl, 9.15; N; 6.84; O, 12.01%.

2-([aminomethylidene]NH_2)-8-chloro-3-CN-4-phenyl-4H-chromen-7-yl acetate(4)

Ammonia gas was bubbled to a stirred solution of compound (3) (397 mg, 0.001 mol) in ethanol for 30 minutes, then bubbling of ammonia was stopped and stirring was continued for 4 hrs. The solid product filtered off to yield (4) as white solid (313 mg, 79%). Mp.230°C; ν_{max} (KBr) 3450-3350 (NH_2), 3109 (arom-CH), 2220 (CN), 1710 (C=O) cm^{-1}; ^{1}HNMR (DMSO) 2.5 (s, 3H, CH_3), 5.2 (s,1H, CH pyran), 6.8-7.2 (broad, 2H, NH_2), 7.0-7.3 (s, 5H, phenyl), 7.5 (s, 1H, CH-N); Anal. Calcd., $C_{19}H_{14}ClN_3O_3$ (367.79): C, 62.05; H, 3.84; Cl, 9.64; N, 11.43; O, 13.05%; C, 61.73; H, 4.05; Cl, 9.76; N, 11.16; O, 12.99%.

4- amino -9-chloro-5-phenyl-5H-chromeno [2, 3-d] pyrimidin-8-yl acetate (5)

A mixture of compound (4) (368 mg, 0.001 mol) in absolute ethanol (10 ml) containing sodium ethoxide (68 mg, 0.001 mol) was refluxed for 2 hrs, then allowed to cool and poured into cold water (50 ml). The solid product was collected and recrystallized from ethanol to yield (5) as white crystals (312 mg, 85%). Mp >360°C; ν_{max} (KBr) 3450-3350 (NH_2), 3110 (arom-CH), 1710 (C=O) cm^{-1}; ^{1}HNMR (DMSO) 2.5 (s, 3H, CH_3), 3.4 (broad, 2H, NH_2), 5.1 (s, 1H, CH–pyran), 7.1-7.4 (m, 8H, CH–arom, CH–pyrimidine); Anal. Calcd., $C_{19}H_{14}ClN_3O_3$ (367.79): C, 62.05; H, 3.84; Cl, 9.64; N, 11.43; O, 13.05%; C, 62.36; H, 4.04; Cl, 9.46; N, 11.26; O, 12.99%.

3-amino-9-chloro-4-imino-5-phenyl-3, 5-dihydro-4H-chromeno [2, 3-pyrimidin -8-yl acetate (6)

To a cooled stirred solution of compound (3) (368 mg, 0.001 mol) in absolute ethanol (10 mL), was added to ethanolic solution of hydrazine hydrate (0.001 mol) and 5 mL of ethanol was added drop wise during 10 minutes. The stirring was continued and the reaction temperature was raised to room temperature gradually during 1 hr. The solid product was collected and recrystallized from ethanol to yield (6) as yellow crystal (317 mg, 86%). Mp 273°C; ν_{max} (KBr) 3350-3500 (NH_2), 3200 (NH), 1710 (C=O) cm^{-1}; ^{1}HNMR(DMSO) 2.3 (s, 3H, CH_3), 3.4 (broad, 2H, NH_2), 5.1 (s, 1H, CH–pyran), 5.7 (s, 1H, NH), 7.2-6.8 (m, 7H, CH–arom), 7.4 (s, 5H, phenyl), 8.1 (s, 1H, CH–pyrimidine); Anal. Calcd. $C_{19}H_{15}ClN_4O_3$ (382.80): C, 59.61; H, 3.95; Cl, 9.26; N, 14.64; O, 12.54%; Found: C, 60.70; H, 4.04; Cl, 9.36; N, 14.02; O, 12.49%.

10-Acetoxy -11- chloro-7- [H] -7- phenyl – triazolo [5, 1:1′, 6′] lpyrimido [4,5-b]chromene (7)

When a few drops of acetic anhydride was added to a mixture of compound (6) (383 mg, 0.001 mol) and triethyl orthoformate (3 mL), under reflux for 2 hrs, and then allowed to cool, the solid product was collected and recrystallized from ethanol to yield (7) as brown solid (229 mg, 60%). Mp. 317°C; ν_{max} (KBr) 1710 (C=O), 1600 (C=C) cm^{-1}; ^{1}HNMR (DMSO) 2.5 (s, 3H, CH_3), 5.5 (s, 1H, CH– pyran), 7.5-7.2 (m, 7H, CH–arom), 8.5 (s, 1H, CH–pyrimidine), 9.6 (s, 1H, CH triazol). Anal. Calcd $C_{20}H_{13}ClN_4O_3$ (392.80): C, 61.16; H, 3.34; Cl, 9.03; N, 14.26; O, 12.22%; Found: C, 60.96; H, 3.58; Cl, 9.18; N, 14.12; O, 12.03%.

10- Acetoxy -11- chloro -5- p - chlorophenyl -7- [H] -7- phenyl - [1,2,4] triazolo [5,1:1′,6′] pyrimido [4,5-b] chromene (8)

To a mixture of compound (6) (383 mg, 0.001 mol) and *p*-chlorobenzaldehyde (140 mg, 0.001 mol) in ethanol (20 ml), was added to a few drops of piperidine, and refluxed for 3 hrs, and allowed to cool. The product was collected and recrystallized from ethanol to yield (8) as brownish yellow solid (306 mg, 80%). Mp.220°C; ν_{max} (KBr) 2932 (arom-CH), 1710 (C=O), 1600 (C=C) cm^{-1}; ^{1}HNMR (DMSO) 2.3 (s, 3H, CH_3), 5.2 (s, 1H, CH–pyran), 7.2-7.5 (m, 11H, CH–arom), 8.5 (s, 1H, CH–pyrimidine); Anal. Calcd. $C_{26}H_{16}Cl_2N_4O_3$ (503.34); C, 62.04; H, 3.20; Cl, 14.09; N, 11.13; O, 9.54%.

11-Acetoxy – 12 – chloro – 8 - [H] – 8 – pheny - [1, 2, 4] triazino [6, 1:1′, 6′] lpyrimido [4, 5-b] chromene (9)

When chloroacetyl chloride (112 mg, 0.001 mol) was added drop wise to a stirred solution mixture of compound (6) (383 mg, 0.001 mol) in pyridine (10 mL). The stirring was continued for 30 minutes, then heated on steam bath for 3 hrs, allowed to cool and poured into cold water (100 mL). The product was collected and recrystallized from ethanol to yield (9) as brown crystals (218 mg, 70 %). Mp. 249°C; ν_{max} (KBr) 3250 (NH), 1710 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR (DMSO) 2.5 (s, 3H, $CH_{3)}$, 4.1 (m, 2H, CH_2), 5.1 (s, 1H, CH–pyran), 5.6 (br, 1H, NH), 7.5-7.2 (m, 7H, CH–arom), 8.3 (s, 1H, CH–pyrimidine); Anal. Calcd. $C_{21}H_{15}ClN_4O_4$ (422.83): C, 59.65; H, 3.58; Cl, 8.38; N, 13.25; O, 15.14%; Found: C, 59.72; H, 3.80; Cl, 8.56; N, 13.08%.

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